Organisms

Journal of Biological Sciences

Vol. 4, No. 2(2020)

SAPIENZA
UNIVERSITÀ DI ROMA

ISSN: 2532-5876

CONTENTS

Editorial

Letters

Commentaries

Experimental Studies

Research Highligths

Sapienza Università di Roma

Feature

History and Science

Special Section: COVID-19 Pandemic

Books

Cover image: *Galaxy M51 in the constellation Canes Venatici and Nautilus, cephalopod*. Digital art by Ferruccio Piterà (2002), courtesy of Edizioni Nova Scripta S.r.l., Genoa, Italy, 2002. This image was originally used for the cover of the Italian translation of Lima-de-Faria A 1988, *Evolution without Selection: Form and Function by Autoevolution*, Amsterdam, New York, Oxford: Elsevier Science (Lima-de-Faria A 2003, *Evoluzione senza selezione. Autoevoluzione di forma e funzione*, Genova: Nova Scripta).

Editorial

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17322

Inattentional Blindness in Biology

Citation: "Inattentional Blindness in Biology" [editorial], *Organisms: Journal of Biological Sciences*, vol. 4, no. 2 (2020), pp. 5-7. DOI: 10.13133/2532-5876/17322

Our mind can trick us into ignoring the obvious if we focus too much on something in particular. This phenomenon, known as inattentional blindness, is illustrated by Simons & Chabris (1999) in their experiment, where participants are asked to count the number of passes made by players in a recorded ball game. While most viewers excel at counting the number of passes, only a minority notice a person dressed as a gorilla who is slowly walking among the players.

Scientists are not immune to inattentional blindness and, unfortunately, this blindness could cost human lives. A historical example of this blindness is the centuries-long dominance of the theory that infectious diseases were caused by miasma. This term indicated invisible vapors, detectable by their smell, and supposed to be produced by sick people, swamps, and the pools of human waste in cities. Fighting miasma by draining swamps, constructing urban sewers, and prescribing plenty of fresh air to patients led to improvements in public health, reinforcing the belief in the theory and the consequent implication to follow its prescriptions and stomp out miasma dissidents.

As we now know, miasma was a figment of scholarly imagination, which for centuries favored fiction to actual culprits, i.e., bacteria. Indeed, Marcus Varro in the 1st century BC speculated that "tiny creatures" invisible to the naked eye grow in swamps and, if swallowed or inhaled, caused disease. Girolamo Fracastoro, the physician that coined the word syphilis, furthered this idea in 1546 and named the pathogenic creatures "germs" (*seminaria*). However, evidence for the existence of "tiny creatures" was lacking until Antoni van Leeuwenhoek, using the microscopes he crafted, described unicellular organisms, including bacteria, in 1676. It took two additional centuries to reach the point when a disease could be attributed to a microorganism; indeed, in 1854 Filippo Pacini (Pacini 1866) and Joaquim Balcells i Pascual (Esteva de Sagrera 2018) independently identified the bacterium that causes cholera. Their discovery, however, was ignored for several decades because most scholars and physicians still firmly believed that infectious diseases were caused by miasma. It took the insight, energy, and public prominence of Pasteur and Koch to make them see the "gorilla" lurking in their midst.

Is this story relevant today? As human nature evolves slowly also for scientists, the possibility that we are still inattentionally blind to something even within our area of expertise is not negligible. As the story of miasma illustrates, a symptom of inattentional blindness is the persistent failure to solve a problem completely while having some success in alleviating it.

This symptom leads us to cancer research, a prospering field that has failed to noticeably reduce cancer mortality despite the unprecedented research effort and astronomical financial resources it has consumed. A recent article in *Cancer Cell* can be used as a case study. This article attempts to answer a fascinating, puzzling, and clinically relevant phenomenon, i.e., the existence of *exceptional responders* (ER), that is, "patients for whom a complete or partial response was expected in less than 10% of similarly treated patients or whose duration of response lasted three times the published median or longer". The term "exceptional" underscores once again that the response of most cancer patients to therapy is unexceptionally poor, which gives additional urgency to finding the mechanisms underlying ER.

In search of these mechanisms, the authors assembled an unprecedented collection of ER cases (111 in total) and attempted to define what was common among them. The analysis used several approaches but, overall, was based on the somatic mutation theory of carcinogenesis (SMT), which underlies most of the current cancer research. The SMT posits that cancers are cell-based diseases caused by mutations in certain genes. After analyzing the collected data, the authors concluded that "[a] final important observation is that the majority of ER cases could not have been "solved" by analysis of DNA mutations alone, emphasizing the need for multi-platform genomic analyses of additional ER cases in the future. Such analyses may solidify, modify, or reject the hypotheses [about specific molecular mechanisms] we have proffered, arguing for an international effort to study large cohorts of these fascinating patients" (Wheeler *et al*. 2020).

This conclusion adds to the growing list of observations that the SMT fails to explain. For example, not all carcinogens cause mutations, which implies alternative mechanisms of carcinogenesis, as does the observation that some cancer cells have no detectable alleged cancer-causing mutations at all. Likewise, the causal role of mutations is also challenged by the presence of presumed carcinogenic mutations in normal tissues and benign tumors and by the fact that no known mutations or their combinations directly cause cancer. Equally puzzling for this theory are observations that normal cells transplanted into organs treated with carcinogens give rise to cancers, that mouse teratocarcinoma cells inserted in normal blastocysts can generate normal mice, that cells from a carcinoma are normalized when placed into healthy orthotopic tissues, and that many cancers can regress spontaneously.

Given this evidence, an unbiased observer may wonder whether continuing to focus on cancer genomics comes at the cost of ignoring the "gorilla" that can account for those otherwise puzzling observations. For example, the Tissue Organization Field Theory (TOFT) explains these observations by positing that the initiation and progression of cancer is due to the disruption of the normal interaction of cells and tissues, and that proliferation is the default state of all cells (Sonnenschein & Soto 2020). An increasing number of observations suggest that cancer initiation and its progression, or regression, are not primarily caused by intracellular processes but should be considered, instead, relational phenomena occurring in tissues, involving the entire organism and its environment.

If alternative theories can explain the observations at which SMT fails, why then cancer research continues to focus on a theory that has lesser explanatory power? If SMT is *the* solution for cancer, why do physicians still continue treating cancer patients with drugs that are deemed by this very theory as carcinogenic?

As past and current accounts of science suggest, answers may lie not only in the realm of data and facts, but in conceptual, social, economic, and ideological currents that influence science as a human activity and, together, make it easier to overlook "gorillas". Indeed, oncology is a profitable and growing business, with positive outcomes so negligible that they require large cohorts to detect them.

Viewing cancer as a part of an organism would help experimental and clinical cancer researchers to consider empirical evidence and the explanatory power of theories, rather than ranking them by how popular, prevailing, or remunerating these theories are. This approach may help those in this field to notice "gorillas" which may be walking around research laboratories and cancer wards in plain sight, while researchers and clinicians are busy counting and cataloguing genomic abnormalities.

References

Esteva de Sagrera J 2018, "Joaquín Balcells y Pasqual", in *Real Academia de la Historia, Diccionario Biográfico electrónico*. Available from: http://dbe.rah.es/biografias/18541/joaquin-balcells-y-pasqual. [20 December 2020].

Pacini F 1866, "Microscopic observations and pathological deductions on Asiatic cholera", *The British and Foreign Medico-chirurgical Review*, vol. 38, July. (English translation of "Osservazioni microscopiche e deduzioni patologiche sul cholera asiatico", *Gazzetta Medica Italiana:*

Toscana, 2nd series, vol. 4, no. 50, pp. 397–401 and vol. 4, no. 51, pp. 405–412. Available from: https://books.google.com/books?id=PXw6AQAAMAAJ&pg=PA167. [20 December 2010].

Simons DJ & Chabris CF 1999, “Gorillas in our midst: Sustained inattentional blindness for dynamic events”, *Perception*, vol. 28, no. 9, pp. 1059–74. Available from: doi: 10.1068/p281059. [20 December 2010].

Sonnenschein C & Soto AM 2020, “Over a century of cancer research: Inconvenient truths and promising leads”, *PLoS Biol*, vol. 18, no. 4: e3000670. Available from: doi: 10.1371/journal.pbio.3000670.

Wheeler DA *et al.* 2020, “Molecular features of cancers exhibiting exceptional responses to treatment”, *Cancer Cell*, November 16, In press, Corrected proof, Nov 16:S1535-6108(20)30546-8. Available from: doi: 10.1016/j.ccell.2020.10.015. Epub ahead of print. PMID: 33217343.

Letters

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17349

The Great Problem Raised by the Pandemic

Roberto Verna [a]*

[a] *Professor of Clinical Pathology, In Unam Sapientiam University of Rome; Systems Biology Group; Saint Camillus International University of Health Sciences; President and Representative at the World Health Organization (WHO), World Association of Societies of Pathology and Laboratory Medicine; President, World Pathology Foundation; Past President, National College of Clinical Pathology Professors; Member of the Executive Board of the Council for International Organizations of Medical Science (CIOMS)*

***Corresponding author:** Roberto Verna, Email roberto.verna@fondazione.uniroma1.it

Citation: Verna, R 2020, “The Great Problem Raised by the Pandemic”, *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 9-10. DOI: x 10.13133/2532-5876/17349

The COVID-19 pandemic has raised many relevant questions, some of which have been thoroughly discussed in a previous issue of *Organisms* (Bizzarri 2020; Mascia 2020).

Further, it has shed light on a big problem in Italy (and let us hope that the same mistakes will not be repeated in the future): the attempt to hide a shameful inefficiency and planning failure by involving incongruous professional figures.

I am referring to swabs in particular. I personally know many people who have lined up for hours to take a swab and who have not been able to get the result for tens of days. Consequently, they had to remain quarantined, even if asymptomatic, for an indefinite time. The cause of the problem started long ago. People did not want to understand that laboratory diagnostics are essential for prevention and early detection of diseases—at low price. In fact, the cost of inadequate hospitalizations makes for 15% of healthcare expense compared to just 2–3% of laboratory tests.

Notwithstanding, cuts have been always and only made in laboratories by reducing the tests and, above all, the staff. This is why state-run laboratories are now unable to swiftly test, as needed, hundreds of thousands of swabs. If university and hospital public laboratories had been enabled during the past years—or even just months—then we would not witness such a disaster.

Instead and unfortunately, the government and the health department of the Lazio region (followed by the rest of Italy) welcomed and adopted a different, seemingly great idea by the President of the Federation of the Orders of Pharmacists: it let pharmacies perform rapid (not molecular) swab tests. You could say that the idea is brilliant because it takes the pressure off public laboratories. However, who will perform swab tests in the pharmacy if not pharmacists? Now, pharmacists are trained for dispensing drugs but have no idea about how to swab and its potential problems. What if a patient faints? What if he or she bleeds? And what if the pharmacist performs a wrong swabbing procedure, leading to a false negative? These are just a few examples and many others could be listed, but the most noticeable is the following: reporting is not the pharmacists’ job. Attesting that a patient is COVID-positive or -negative is not the same as providing a pregnancy or diabetes self-test, where the patient carries out the procedure independently and receives a figure in response. Reporting is a professional task that does not belong to pharmacists which, in fact and in most cases, are not even legally covered from any negative consequences.

It seems that the Federation aims more at increasing clients and revenue rather than caring for pharmacists. The latter have had outdated job contracts with inadequate pay for their professional services for years. Now, they are also requested to fulfill this task while pharmacy owners adorn themselves with the frieze of health workers and saviors of the National Health System. It goes without saying that these tests have a cost (22–24 euros) and are not covered by the NHS.

Then, the Order of Biologists came into play to support pharmacies by selecting those who have swabbing experience from among its members. Indeed, there would be no objection of such an offer, except for the request for compensation, i.e., allowing all the private laboratories to test for COVID. We come full circle.

Someone may think that I have an agenda against pharmacists and biologists. This is not the case. I deeply respect those valuable professionals who do well what they have been trained and qualified to do.

Rather, the target is public service management. This management does not invest in universities, hospitals, and local health units. It does not support its physicians, pharmacists, biologists, nurses, and laboratory technicians—all highly skilled health workers, nor hire more of them. It does not reinforce the national research to find a solution to the pandemic. Rather, it limits itself to finance private vaccine research and outsources its activities to individuals with no qualification. It even foreshadows a future in which pharmacists will administer vaccines.

Important managers of the Order of Pharmacists have declared that, so far, pharmacists cannot perform swab testing. However, the Trentino Health Councilor has submitted a request for authorization to the Ministry of Health. If such a request will be approved, then a simple circular letter from the Ministry will transform professional qualifications out of the blue without any change in the university curricula and with no legal base. Such a situation is not justified by the emergency, which would instead require the hiring of qualified personnel. This adds to the release of some tutorials on how to perform swab tests and administrate vaccines. These tutorials lasting a few minutes overcome years of study and practice by physicians and nurses…

I see here the outcome of a long-running attempt to misappropriate actions that have always been attributed to physicians.

The medical profession stemmed from minor activities (such as barber) to then stand out, at the beginning. A whole series of related activities, including laboratory diagnostics, followed. These used to be based on manual skills and were often not easily repeatable, while high technology and reliability characterize them today. Science has then grown pharmacy, biology, genetics, and all their branches.

In most cases, Physicians are satisfied with their own clinical activity while laboratory medicine is rather seen as a second choice. On the other hand, pharmacists, biologists, and chemists access activities that used to be typical of the physicians of the past and where the relationship with the patient still has a relevant role. This is why a physician prescribes but does not dispense drugs as others will take care of such a task. Accordingly, some pharmacists see swabbing as a professional step ahead.

No tutorial or webinar can make someone able to perform any activity. Even driving cannot be taught by mere verbal teaching, because it requires example and practice.

We think we know a lot about this virus: how it is made, how it enters cells, and the damage it causes. However, we may need to think twice. More than 15 million have been infected in the world, over a million in Italy as far as we know. Therefore, it seems we have enough material for an accurate epidemiological investigation to explain why some people are asymptomatic while others are affected by a different degree of severity, including death. Maybe the virus has variant forms, or the clinical outcome depends on age, lifestyle, or something else. Could we get adequate information from the autopsies of those who died because of (not just with) the virus? We all may carry important information about risk factors and correlations with, as a mere example, our body size, which could lead us to more responsible behavior. Indeed, though, research is expensive. Therefore, one might expect that a system governed by a capitalist ultra-right refuse to invest in it. Yet, our government pretends to be leftist, and it is supported by a pure party that would never defund research… but in fact does it.

References

Bizzarri M 2020, “Chronicle of a Pandemic Foretold”, *Organisms: Journal of Biological Sciences*, vol. 4, no. 1, pp. 102-112. Available from: doi: 10.13133/2532-5876/16966.

Mascia C *et al.* 2020, “COVID-19 Calls for Mathematics, Part 1: Neuraminidase Inhibitors, Chloroquine and Hydroxychloroquine”, *Organisms: Journal of Biological Sciences*, vol. 4, no. 1, pp. 115-127. Available from: doi: 10.13133/2532-5876/16968.

Commentaries

Vol. 4. No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17350

Force Matters in Canalizing Cell Differentiating Paths

Mariano Bizzarri [a]*

[a] *Department of Experimental Medicine, Systems Biology Group Lab, University Sapienza, Rome, Italy – Via Scarpa 16, 00160, Rome, Italy*

***Corresponding author:** Mariano Bizzarri, Email mariano.bizzarri@uniroma1.it

Commentary on: Panciera T, Citron A, Di Biagio D, Battilana G, Gandin A, Giulitti S, Forcato M, Bicciato S, Panzetta V, Fusco S, Azzolin L, Totaro A, Tos APD, Fassan M, Vindigni V, Bassetto F, Rosato A, Brusatin G, Cordenonsi M, & Piccolo S 2020, "Publisher Correction: Reprogramming normal cells into tumour precursors requires ECM stiffness and oncogene-mediated changes of cell mechanical properties", *Nature Materials*, vol. 19, no. 4, p. 475. Available from DOI: 10.1038/s41563-020-0644-5.

Citation: Bizzarri, A, 2020, "Force matters in canalizing cell differentiating paths", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2 pp. 11-13. DOI: x 10.13133/2532-5876/17350

When cells meet an adhesive matrix, they begin to spread and migrate with a speed that depends on the stiffness of the extracellular matrix. On a flat surface, migration speed decreases with matrix stiffness mainly due to an increased stability of focal adhesions. Noticeably, 3-dimensional (3D) cell invasion is enhanced by higher matrix stiffness, opposite to cell behavior in two dimensions, as long as the pore size does not fall below a critical value where it causes excessive steric hindrance (Lang *et al*. 2015). Indeed, non-transformed, premalignant, and transformed cancer cells not only invade in greater numbers but also migrate more persistently within a stiffer 3D type I collagen gel (Haage & Schneider 2014). In this respect, ECM density and composition can impose physical constraints to restrict cell movement by reducing pore size, necessitating a requirement for the cells to degrade the matrix or undergo transdifferentiation (epithelial–mesenchymal transition) to be able to invade and migrate. Conversely, it is of relevance that inhibiting ECM stiffening effectively impairs exogenous and resident cell invasion and migration, eventually promoting the reversion of the inflammatory phenotype and, in some circumstances, even the cancerous transformation (Kenny & Bissell 2003). Overall, this evidence prompted to consider the micro-environment and the mechanotransduction process as new, testable targets in the management of inflammatory-derived diseases, including cancer and age-associated comorbidities. Indeed, amazing examples of the reversion of cancer cells have been obtained by culturing cancer cell in 3D cultures. Those models composed by ECM of stroma cells (myoepithelial and stroma cells) have shown to reproduce the structure as well as the organization of the normal tissue *in vivo* (Speroni *et al*. 2014). Indeed, cells cultured in 3D display several differences regarding those traditionally conditioned in a 2D medium, so much so that the era of 2D studies should now be regarded as definitely waned (Bissell *et al*. 2017). Overall, these studies allowed for appreciating how critical the interaction among the different components of the micro-environment (collagen fibers, cells, soluble factors, ECM) is in shaping critical biological processes in which a causative role is clearly sustained by biophysical factors and forces (Tracqui, 2009).

Recently, Piccolo and colleagues (Panciera *et al.* 2020) found that a specific receptor tyrosine kinase (RTK)–Ras axis is activated in a process requiring increased force transmission between oncogene-expressing cells and their surrounding extracellular matrix. Noticeably, microenvironments approximating the normal softness of healthy tissues, or blunting cellular mechanotransduction, prevent oncogene-mediated cell reprogramming and tumor emergence. It is worth noting that RTK–Ras pathway empowers a disproportional cellular response to the mechanical properties emerging from the cell/micro-environment cross talk, such that when cells experience even subtle supra-physiological extracellular-matrix rigidity, they are converted into tumor-initiating cells. These regulations rely on YAP/TAZ mechanotransduction, and YAP/TAZ target genes account for a large fraction of the transcriptional responses downstream of oncogenic signaling. Conclusively, these results pave the way to see the mechanobiological machinery as a potential "target", which can be exploited to favor reversion of pre-neoplastic or even neoplastic conditions. Moreover, they vindicate several studies carried out in the last two decades highlighting the biological role sustained by biophysical factors and structural constraints (Bizzarri *et al.*, 2018) originating from bio-electromagnetic fields (Levin *et al.* 2011), or mechanical stresses emerging from the cell-stroma interplay and henceforth transmitted through the cytoskeleton (CSK) (Brock *et al.* 2015) to the nucleoskeleton (NSK) (Poh *et al.* 2012). In turn, mechanical transduction induces adaptive changes in CSK/NSK configuration and in cell shape with subsequent modulation of chromatin structure that constitutes an indispensable premise of any epigenetic reprogramming. These models allow for appreciating significant changes in gene expression patterns (Luo *et al.* 2013) and enzymatic activities which, overall, cooperate in inducing the reversion of the malignant phenotype throughout the physical cue that triggers the entire process (Su *et al.* 2013; Willhauck *et al.* 2007; Paszek *et al.* 2005). Noticeably, even mild "manipulations"—as seen in the report from Piccolo's team—are instrumental in influencing the natural history of cancerous diseases. This is especially true for a few substances that interfere with collagen biosynthesis and ECM composition. Ascorbic acid (Philips *et al.* 2009), hyaluronidase (Benitez *et al.* 2011), and Lysyl-Oxidase (Santhanam *et al.* 2010) inhibitors, as well as polyphenols (extracted from green tea or red wine) (Zlotogorski *et al.* 2013), modify tissue stiffness and collagen structure, contributing to reshaping the micro-environment architecture and exerting a significant clinical activity through this, both in the field of chemoprevention and as treatment (Sagar *et al.* 2006).

Therefore, as aptly asserted in the study, the gathered results "may inform research on potential routes to exploit oncogenic mechanosignalling as a vulnerability at the onset of tumorigenesis, including tumor prevention strategies akin to those used by normal tissues to prevent cancer emergence."

References

Benitez A, Yates TJ, Lopez LE, Cerwinka WH, Bakkar A, Lokeshwar VB 2011, "Targeting hyaluronidase for cancer therapy: Antitumor activity of sulfated hyaluronic acid in prostate cancer cells", *Cancer Res*, vol. 71, no. 4085, p. 95.

Bissell MJ 2017, "Goodbye flat biology – time for the 3rd and the 4th dimensions", *Cell Sci.*, vol. 130, no. 1, pp. 3-5. Available from: doi: 10.1242/jcs.200550.

Bizzarri M, Masiello MG, Giuliani A, Cucina A 2018, "Gravity constraints drive biological systems toward specific organization patterns: Commitment of cell specification is constrained by physical cues", *Bioessays*, vol. 40, no. 1.

Brock A, Krause S, Ingber DE 2015, "Control of cancer formation by intrinsic genetic noise and microenvironmental cues", *Nat. Rev. Cancer*, vol. 15, pp. 499-509.

Kenny PA & Bissell MJ 2003, "Tumor reversion: correction of malignant behavior by microenvironmental cues", *International Journal of Cancer*, vol. 107, no. 5, pp. 688–695.

Haage A & Schneider IC 2014, "Cellular contractility and extracellular matrix stiffness regulate matrix metalloproteinase activity in pancreatic cancer cells", *FASEB J.*, vol. 28, pp. 3589–3599.

Lang NR, Skodzek K, Hurst S, Mainka A, Steinwachs J, Schneider J, Aifantis KE, Fabry B. 2015, "Biphasic response of cell invasion to matrix stiffness in three-dimensional biopolymer networks", *Acta Biomaterialia*, vol. 13, pp. 61-67. Available from doi: 10.1016/j.actbio.2014.11.003.

Levin M 2011, "Endogenous bioelectric signals as morphogenetic controls of development, regeneration, and neoplasm", pp. 39-89 in: Pullar CE (ed.), *The Physiology of*

Bioelectricity in Development, Tissue Regeneration, and Cancer, Boca Raton: CRC Press.

Luo T, Mohan K, Iglesias PA, Robinson DN 2013, "Molecular mechanisms of cellular mechanosensing", *Nature Materials*, vol. 12, pp. 1064-1071.

Panciera T *et al*. 2020, "Publisher correction: Reprogramming normal cells into tumour precursors requires ECM stiffness and oncogene-mediated changes of cell mechanical properties". *Nature Materials*, vol. 19, no. 4, p. 475. Available from doi: 10.1038/s41563-020-0644-5.

Paszek MJ *et al*. 2005, "Tensional homeostasis and the malignant phenotype", *Cancer Cell*, vol. 8, pp. 241-254.

Philips N, Dulaj L, Upadhya T, 2009, "Cancer cell growth and extracellular matrix remodeling mechanism of ascorbate; beneficial modulation by P. leucotomos", *Anticancer Research*, vol. 29, pp. 3233-3238.

Poh YC *et al*. 2012, "Dynamic force-induced direct dissociation of protein complexes in a nuclear body in living cells", *Nature Communications*, vol. 3, p. 866.

Sagar SM, Yance D, Wong RK 2006, "Natural health products that inhibit angiogenesis: A potential source for investigational new agents to treat cancer—Part 2", *Current Oncology*, vol. 13, no. 3, pp. 99-107.

Santhanam AN, Baker AR, Hegamyer G, Kirschmann DA, Colburn NH 2010, "Pdcd4 repression of lysyl oxidase inhibits hypoxia-induced breast cancer cell invasion", *Oncogene*, vol. 29, pp. 3921-3932.

Speroni L, et al. 2014, "Hormonal regulation of epithelial organization in a three-dimensional breast tissue culture model", *Tissue Engineering. Part C, Methods*, vol. 20, pp. 42-51.

Su G, Zhao et al. 2013, "Direct conversion of fibroblasts into neural progenitor-like cells by forced growth into 3D spheres on low attachment surfaces", *Biomaterials*, vol. 34, pp. 5897-5906.

Tracqui P. "Biophysical model of tumor growth", *Reports on Progress in Physics*, vol. 72, no. 5, pp. 51-30. Available from: doi: 10.1088/0034-4885/72/5/056701

Zlotogorski A, Dayan A, Dayan D, Chaushu G, Salo T, Vered M 2013, "Nutraceuticals as new treatment approaches for oral cancer: II. Green tea extracts and resveratrol", *Oral Oncology*, vol. 49, pp. 502-506.

Willhauck MJ et al. 2007, "Reversion of tumor phenotype in surface transplants of skin SCC cells by scaffold-induced stroma modulation", *Carcinogenesis*, vol. 28, no. 3, pp. 595-610.

SAPIENZA
UNIVERSITÀ DI ROMA

Commentaries

Vol. 4. No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17269

The COVID-19 Epidemic as a Dynamic System: A Robust, Hypothesis-Free Approach

Alessandro Giuliani [a]*

[a] *Environment and Health Department, Istituto Superiore di Sanità, Roma, Italy*

***Corresponding author:** Alessandro Giuliani Email: alessandro.giuliani@iss.it

Commentary on: Bizzarri, M, Di Traglia, M, Giuliani, A, Vestri A, Fedeli V, & Prestininzi A. 2020, “New statistical RI index allows to better track the dynamics of COVID-19 outbreak in Italy”, *Scientific Reports*, vol. 10, no. 22365. Available from DOI: https://doi.org/10.1038/s41598-020-79039-x.

Citation: Giuliani, A 2020 “The COVID-19 Epidemic as a Dynamic System: A Robust, Hypothesis-Free Approach”, *Organisms: Journal of Biological Sciences*, vol. 4, no. 2 pp. 15-16. DOI: 10.13133/2532-5876/17269

The global diffusion of COVID-19 made apparent the many points of friction between scientific modelling (at both the mathematical and the biological levels) and the social and clinical ‘empirical’ consequences of the crisis. As aptly stressed by Mazzocchi (2020) in referring to the COVID-19 pandemic: “These crises are the result of multiple causes, which interact at different scales and across different domains. Therefore, investigating their proximate causes is not enough to fully understand them.”

The need to face the COVID-19 pandemic’s economic, political, and psychological consequences requires simple, albeit informative, estimates of the entity of the problem along both space and time dimensions. The classical SEIR (Susceptible, Exposed, Infected, Recovery) compartmental models with the consequent estimation of the Basic Reproduction Number (R) has been proven to generate severely biased estimates of epidemic spreading. The use of R in both popular media and governmental communication has led to misunderstandings and distortions of the real state of affairs. These distortions derive from many ‘anomalies’ with respect to the ideal case from where the SEIR model stems. These anomalies encompass the lack of ergodicity (the presence of ‘super-spreaders’, the marked spatial heterogeneity of the disease, the uncertainty of initial data) and the simple fact that R can only register the ‘increase of new cases’ without explicitly considering the ‘healed’ compartment, i.e., the ‘exit’ from the ‘infectious basin’. This situation can be equated to the estimate of the level of a hydrographic basin, taking into consideration the in-fluxes without considering the out-fluxes constituted by the emissaries. The situation turns out to be more critical due to the relatively low lethality and morbidity of the virus with a great majority of asymptomatic cases that (especially in the initial period of the epidemic) get unnoticed with a consequent bias in the estimation of both the actual number of infected persons and lethality of the disease.

Italy is a paradigmatic case of such problems that present a marked spatial and temporal heterogeneity of the epidemic with the much larger number of both fatalities and infections concentrated in Lombardy and, more in general, in the northern part of the country.

The authors thus shifted the attention from the actual number of infected persons (from where classical R-like statistics depend) to the dH/dI ratio (RI) being dH and dI the daily variation of healed and infected numbers. This index was demonstrated to correctly 'catch' the tipping-point of the epidemic, i.e., the discrete time points preceding the transitions of the epidemic going thru initial growth, exponential rise, plateau, and decline phases. Two very simple albeit powerful features of the index allow for reaching this result: 1. The daily differential is much less affected than the absolute number by the uncertainty and fatally non-random sampling of the population, and 2. The 'healed' status is acquired after three negative tests, then is fatally delayed with respect to acquiring the 'infected' condition, so giving to the dH/dI ratio the meaning of an 'acceleration' (positive or negative), acting as a 'second order' derivative of the dynamics catching the inflection-points of the time series.

The authors demonstrate the sensitivity of the RI index to such inflection-points (transitions) that go completely unnoticed by the R index.

On the other hand, the recognition of a strict linear relation between the number of accesses to intensive care units (ICUs) and fatalities (both the indexes known without any relevant uncertainty) and their ability to follow the epidemic dynamics allows for simultaneously getting a cross-check of the epidemic dynamics and of the stress on the nation's health system. Finally, yet importantly, a simple logistic model fed with the initial epidemic figures allowed for correctly predicting the timing of the plateau phase of infection. This demonstrated that even largely biased and preliminary evidence permits a reliable forecasting for the subsequent evolution of the crisis.

The authors know very well the difficulty of the task to go from science to the acquisition of the new perspective by regulators. At the same time, however, the huge social consequences of such a crisis asks for a correct assessment of the situation for both regulators and public opinion.

References

Mazzocchi, F 2020, "Tackling modern-day crises: Why understanding multilevel interconnectivity is vital", *BioEssays*, 2000294. Available from: doi: 10.1002/bies.202000294

Organisms

SAPIENZA UNIVERSITÀ DI ROMA

Experimental Studies

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/16997

pH, Electric Conductivity, and Delayed Luminescence Changes in Human Sera of Subjects Undergoing the Relaxation Response: A Preliminary Study and Theoretical Considerations

Carlo Dal Lin,[a]° Rosaria Grasso,[b] Agata Scordino,[b] Antonio Triglia,[b] Francesco Tona,[a] Sabino Iliceto,[a] Giuseppe Vitiello,[c]° Vittorio Elia[d], Elena Napoli[d], Roberto Germano[d], & Francesco Musumeci,[b]°*

[a] Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Medical School, Padua, Italy; [b] Department of Physics and Astronomy "Ettore Majorana", University of Catania, Catania, Italy; [c] Physics Department "E. R. Caianiello", Salerno University, Fisciano (Salerno), Italy; [d] Promete S.r.l. - Spin-off company, Consiglio Nazionale delle Ricerche (CNR), Naples, Italy

° Carlo Dal Lin, Francesco Musumeci and Giuseppe Vitiello equally contributed to this work.

***Corresponding author:** Carlo Dal Lin, MD, Department of Cardiac, Thoracic and Vascular Sciences, Padua University School of Medicine, Via Giustiniani 2, 35100 Padua, Italy. Fax: +39-049 8211802 Phone: +39-0498218642 Email: carlodallin@libero.it

Abstract In our recent works we reported that physical and chemical characteristics of serum can vary in relation to the psychic activity of an individual depending on whether it is oriented to stress or relaxation. We wandered if these observations could be accompanied by an appreciable modification of the pH, electric conductivity and Delayed Luminescence of the same serum samples. Our preliminary data may suggest that the serum pH could significantly increase during a Relaxation Response intervention while electric conductivity seems to decrease. Moreover, Delayed Luminescense could vary in the same subject according to the Relaxation Response practice. According to our preliminary data, we postulate the appearance of a *coherent* system within the blood samples analyzed after the Relaxation Response. Further researches and some technical development are needed to support our preliminary findings.

Keywords: Relaxation Response; pH; electric conductivity; delayed luminescence; fractals; coherent states; self-similarity

Citation: Dal Lin C *et al.* 2020, "pH, electric conductivity, and delayed luminescence changes in human sera of subjects undergoing the relaxation response: A preliminary study and theoretical considerations", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 15–29. DOI: 10.13133/2532-5876/16997

Introduction

The serum represents the liquid, non-cellular part of the blood; it contains water, proteins, electrolytes, ionic radicals, antibodies, antigens, hormones, and is the main biological material for the screening and diagnosis of many diseases (Harrison 2012).

In some recent works (Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018; Dal Lin, Brugnolo, *et al.* 2020) we have described how the characteristics of serum can vary in relation to the psychic activity of an individual depending on whether it is oriented to stress or relaxation. In fact, after about 20 minutes of relaxation through meditation or music appreciation, the physical appearance of the serum changes, becoming clearer and less viscous (Dal Lin, Gola, *et al.* 2018). This is accompanied by a decrease in serum lipid levels, inflammatory molecules, stress hormones, oxidative stress markers and by a change in gene expression (NfKB network) in white blood cell precursors (Dal Lin, Marinova, *et al.* 2018). Furthermore, body temperature seems to decrease with relaxation (Dal Lin, Marinova, *et al.* 2018).

Research carried out in the 1990s and subsequent years established the property of animal and plant tissues to generate relatively strong transient non ionizing radiations (NIR) wave in the electromagnetic range (electromagnetic waves, infrared radiation, thermal radiation, bioluminescence) due to mechanical stresses and temperature changes in biological structure (Chang 2008). These radiations are mainly due to the piezoelectric and pyroelectric voltage and electric polarization of natural biological structures (water, ions, proteic molecules etc.). Owing to cell metabolism, polarization domains due to molecular electric dipoles are continuously destroyed and restored in a non-equilibrium polarization (Del Giudice *et al.* 1985, 1986, 1988; Jiin-Ju, 2008) dynamical regime. Such type of non-equilibrium electric polarization is known as a main characteristic of electrets (Del Giudice *et al.* 1985, 1986, 1988; Jiin-Ju, 2008). Electrets are generated under certain conditions, e.g. under the influence of an electrostatic or electromagnetic field or ionizing radiation, light and other factors, and their polarization slowly diminishes in time (Cohen & Popp 2003; Popp 2003).

Starting from the works of Gurwitsch in the 20s of the last century and of F.A. Popp in the 70s, more and more researches have documented the emission of biophotons from living organisms (Jursinic 1986; Niggli 1993; Van Wijk *et al.* 1993), with a possible role in cell growth and differentiation and intra- or inter-cellular communication processes (Scordino *et al.* 1996; Lanzanò *et al.* 2007).

The emission of biophotons is responsible for the Delayed Luminescence (DL), the phenomenon of ultra-weak photo-induced light emission that persists up to a few minutes after a light source has stimulated the studied material (Jursinic 1986; Niggli 1993; Van Wijk *et al.* 1993).

DL seems to be closely correlated with the functional status of different biological systems studied to date (Scordino *et al.* 1996; Lanzanò *et al.* 2007; Scordino *et al.* 2008; Costanzo *et al.* 2008; Scordino *et al.* 2014; Yagura *et al.* 2019). It has been possible to reveal DL from liquid solutions of biological interest (Gulino *et al.* 2010; Musumeci *et al.* 2012; Colleoni *et al.* 2016; Grasso *et al.* 2018; Sun *et al.* 2019) and, although the precise origin of the DL is still a subject of debate (Brizhik *et al.* 2001; Sławinski, 2003; Scordino *et al.* 2010; Alvermann *et al.* 2015; Cifra *et al.* 2015; Scholz, Dědic, & Hála, 2017), these observations suggest it may vary depending on the REDOX state of the analyzed biological system and according to its degree of homeostatic stress (Sławinski 2003) .

These premises given and having documented the physical and biochemical change of the serum of the same human subject after 20 minutes of relaxation with reduction of oxidative stress markers, we wondered if these observed changes could be accompanied by an appreciable modification of the pH, electric conductivity and DL of the same serum samples previously analyzed (Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018). This paper contains a first answer to this question, reporting, as a pilot study, the response of a limited number of subjects. The chosen parameters are indeed the ones directly related (Gulino *et al.* 2005; Kubera-Nowakowska, Lichszteld and Kruk, 2007; Nagare,

Figure 1: The study design (explanation in the text). RR: Relaxation Response. RR 20 min: after 4 days of training, each subject relaxes through meditation or music appreciation for 20 minutes. A blood sample is taken immediately before and immediately after. The acute variation of the studied parameters can be attributed to the practice of relaxation according to the used methods because the precise timing of blood sampling (before and immediately after the end of the session) prevents any other influence. All groups were subjected to the same environmental conditions: in particular, also the control patients were taken in our classroom for 20 minutes and were not subjected to any intervention. We simply asked them to relax and most of them sat down with eyes closed. For more details please see our previous works (Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018). Modified from (Dal Lin, Brugnolo, *et al.* 2020).

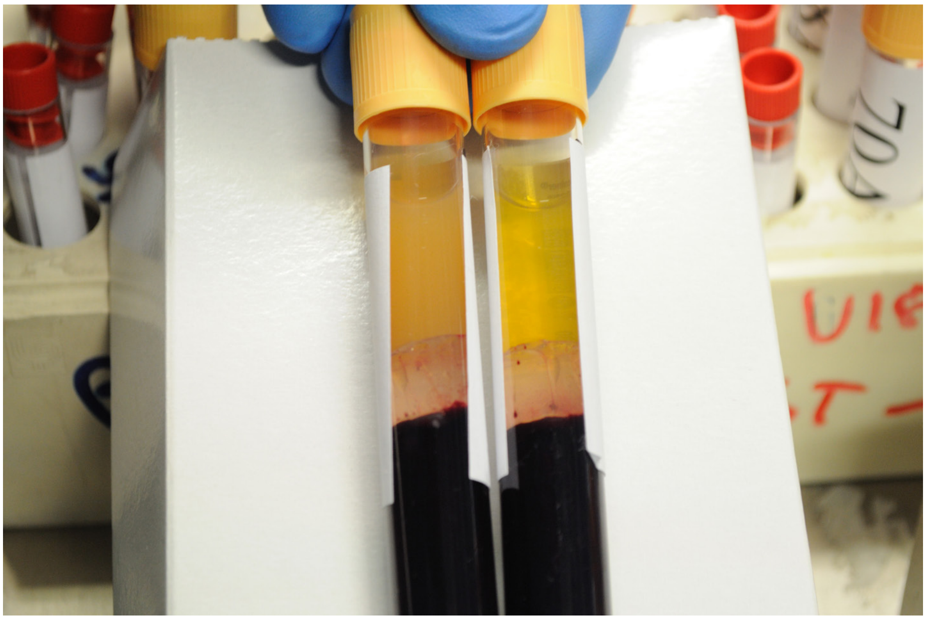


Figure 2: Variation of the physical characteristics of the plasma of the same patient during 20 min of meditation. On the left: the blood sample (after 4 min of centrifugation at 5000 rpm) before meditation is opalescent. On the right, the blood sample immediately after meditation is clearer. The patient was fasting for more than 5 h before meditating.

2013; Ho, 2015; Hansen, Nilsson and Rossmeisl, 2017; Chaplin, 2020) to the changes of the polarization densities and optical properties of the serum samples and their changes may contribute to explain the difference visible in Figure 2.

1. Material and methods

1.1. Biological samples

In this work we analyzed the serum samples collected in our previous study (Dal Lin, Marinova, *et al.* 2018), approved by our institutional review board (Comitato Etico per la Sperimentazione Clinica - Azienda Sanitaria di Padova, protocol number 3487/AO/15 - 13/7/2015 updated number 4895/AT/20 - 23/7/20). Briefly, we enrolled 40 subjects: 30 consecutive patients after myocardial infarction and 10 healthy controls. 10 patients were taught to meditate, 10 to appreciate music and 10 did not carry out any intervention and served as controls. As stated, in order to rule out that the disease state could interfere with the relaxation effect, we enrolled 10 healthy volunteers (5 were trained to meditate and 5 had music appreciation). The practices of meditation and music appreciation are able to produce the so called Relaxation Response (RR) in the same way (Benson & Klipper 1975; Dal Lin *et al.* 2015; Dal Lin, Marinova, *et al.* 2018). The details of the RR techniques that we used and the description of their pathophysiological mechanism is described in our previous works (Dal Lin *et al.* 2015; Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018; Dal Lin, Brugnolo, *et al.* 2020).

After the initial four-day training, after 6 and 12 months of RR practice, we collected a blood sample immediately before and after the relaxation session (according to the scheme reported in Figure 1) in order to study any modification of the pH, electric conductivity and DL of the same serum sample.

A clear variation of the physical characteristics of the serum samples (Figure 2), was observed.

According to Benson's researches (Benson & Klipper 1975) and to our previous study (Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018), there are no significant differences between relaxation techniques. Therefore, we merged into a single "intervention" group (called "RELAXATION RESPONSE") all patients treated with meditation and music and into a single "intervention healthy controls" group (called "RELAXATION RESPONSE HEALTHY CONTROLS") all healthy subjects. Finally, the patients that did not carry out any intervention constituted the "CONTROLS" group.

We emphasize that in our work we observed the RR using two conditioning techniques, meditation and music, which have to be considered as two ways leading to the same relaxation effect (Dal Lin *et al.* 2015). Therefore, even from a strictly methodological point of view, we used a unique technique—precisely the RR—from which also the need to unite in a single "intervention group" the treated subjects.

Indeed, all subjects enrolled in the study have continued the practice at home, twice a day, as they had been taught. During the follow-up period, each subject reported to have pleasantly performed more than 80% of the meditation or music listening sessions.

1.2. pH-metry measurement

The pH were monitored using a pH-meter model micropH2002 by CRISON, equipped with a pH electrode for microsamples, model 52 09. The electrode specifications are: asymmetry potential < ±15 mV, pH sensitivity 4…7 (at 25° C) > 98%.

1.3 Conductivity measurements

Systematic measurements of specific conductivity were performed on the samples, using an YSI 3200 conductometer with a conductivity cell having a constant of 1.0 cm^{-1}. The cell was periodically calibrated by determining the cell constant K (cm^{-1}). The specific conductivity, χ ($\mu S\ cm^{-1}$), was then obtained as the product of the cell constant and the conductivity of the solution. For a given conductivity measuring cell, the cell constant was determined by measuring the conductivity of a KCl solution with specific conductivity known with great accuracy, at several concentrations and temperatures. All conductivities were measured in a room at controlled temperature of 25±1°C and temperature-corrected to 25°C, using a pre-stored temperature compensation for pure water.

1.4. DL measurement set up

The DL extends over a rather large time scale: from about 10^{-7} seconds to more than 10^{2} seconds. It requires, therefore, a measurement system with a high dynamic capacity. The signal intensity is also very weak (from a few million to a few tens of photons per second, compared with about $3 * 10^{17}$ phonons per cm^2 per second of sunlight) and thus it is necessary to use a single photon detection system and a total optical isolation of the sample from the surrounding environment.

The measurement of DL is even more difficult when one studies samples without photosystem. As compared to plant cells, the DL intensity of the other systems is considerably reduced and the time decay is faster. In addition, the excitation spectrum shifts towards ultraviolet. This entails the risk that the DL spectrum overlaps the excitation spectrum of the materials used as specimen holders as plastic or quartz cuvettes.

To solve these problems, a specific equipment has been developed. Here we give a brief description of this set up, more information can be found in the literature (Tudisco *et al.* 2003; Scordino *et al.* 2014).

The equipment is based on the use of a photomultiplier (PMT) enhanced to count single photons. The excitation source is a high intensity pulsed nitrogen laser that illuminates the sample through an optical fiber. During the laser pulse, an electronic shutter switches off the PMT in order to prevent damage resulting from the large amount of photons diffused by the sample. We use an electronic shutter instead of a mechanic one because the former has the ability to reduce the delay between the laser pulse and the start of data acquisition.

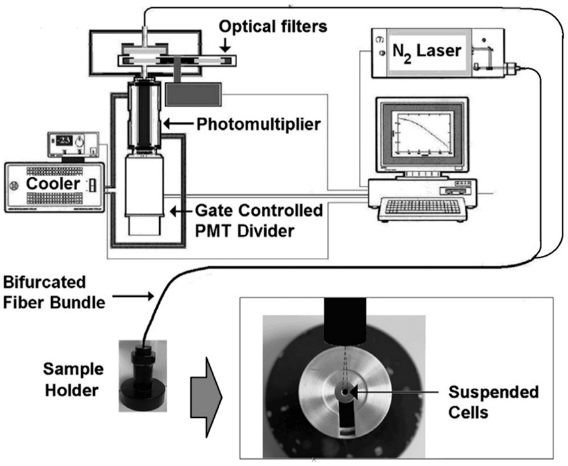


Figure 3: Drawing of the set-up. Schematic view of the sample configuration (for the sake of clarity the distances and sizes are not in scale).

The DL was measured in a time window that starts from about 10 µs after the illumination switching off and lasted until the signal is well distinct from the background. The entire data acquisition process is managed by a personal computer equipped with a special multichannel scaler. It records the number of photons collected in a time window as a function of time. To reduce the noise, a smoothing procedure was performed: the experimental points were sampled and averaged in such a way that final data are equally spaced on a logarithmic temporal axis.

The low intensity emitted by the DL signal does not allow to obtain a high spectral resolution. Therefore, to evaluate the spectrum we used three broadband interference filters (50 nm FWHM) placed between the sample and the photomultiplier. The central wavelength of the filter was 450 nm, 550 nm and 650 nm, respectively.

To reduce its background noise the photomultiplier was cooled down to -30 ° C. The most important background source in these measurements is represented by the DL emitted by parts of the same apparatus, such as the sample support.

With the objective of both reduce the quantity of serum sample required and eliminate any background signals deriving from the excitation of the sample containers, a specific support for the sample was developed. It consists of a hollow cylinder covered by a closing disc with a small 3.5 mm diameter hole (see photo in the insert in Figure 3).

The sample consisted of a "drop" (volume 20–25 μL) supported only by contact with the edge of the circular hole. This eliminated the presence of any material behind the sample and therefore the presence of spurious components due to support.

A bifurcated optical fiber was positioned just above the "drop" so that only the sample, not the support, fell inside its solid collection corner. In this way, the fiber, connected to both the laser and the PMT, was used both to illuminate the sample and to collect the DL.

To avoid contamination problems, the pierced metal disk that closed the sample holder and held up the "drop" was replaced at every measurement.

Due to the low level of the signal, for every sample the values of 100 runs were added in order to reduce the measurement error and increase the signal to noise ratio. In addition, two technical replicates of every sample were performed. The results presented here are average values from two to eight measurements, depending on the evaluated DL parameter (see Results).

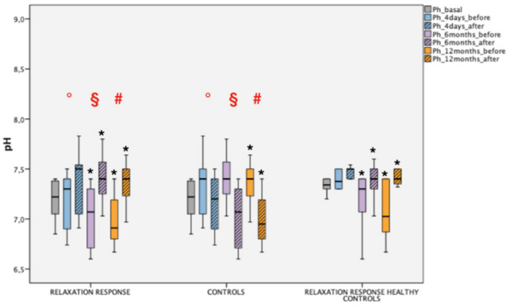
2. Results

2.1 pH and Electric Conductivity

The results of pH and electric conductivity evaluations are reported in Table I, Table II and in Figure 4 and 5 for different blood sampling timepoints (BST). The pH seems to significantly increase in the RR groups at 6 and 12 months while decreases in controls at 12

	Basal	4 days of RR training Before relaxation session	4 days After 20 min of RR session	6 months Before relaxation session	6 months After 20 min of RR session	12 months Before relaxation session	12 months After 20 min of RR session
RELAXATION RESPONSE	**7,22 (7,05-7,38)**	**7,3 (6,9-7,4)**	**7,5 (7,05-7,54)**	**7,07 (6,71-7,3)**	**7,4 (7,25-7,57)**	**6,91 (6,8-7,19)**	**7,4 (7,23-7,5)**
CONTROLS	**7,22 (7,05-7,38)**	**7,4 (7,05-7,5)**	**7,2 (6,9-7,4)**	**7,4 (7,25-7,57)**	**7,07 (6,71-7,3)**	**7,4 (7,23-7,49)**	**6,95 (6,8-7,19)**
RELAXATION RESPONSE HEALTHY CONTROLS	**7,34 (7,3-7,4)**	**7,38 (7,3-7,5)**	**7,5 (7,4-7,5)**	**7,3 (7,07-7,4)**	**7,4 (7,3-7,5)**	**7,03 (6,87-7,4)**	**7,4 (7,35-7,5)**

Table I: Serum pH at different BST. Median and interquartile range.



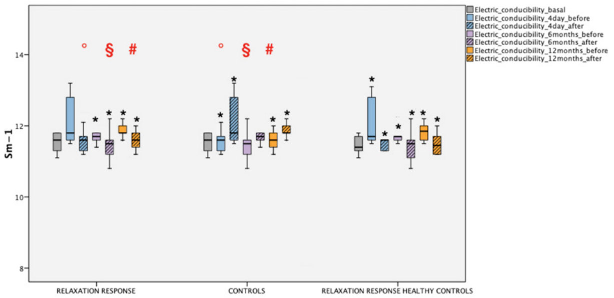
* p<0.01 Wilcoxon

° § # p<0.001 Mann-Whitney, delta comparison RR and controls (no differences of variations for RR groups)

Figure 4: pH at different BST. Graph with statistical analysis of the data reported in table I.

	Basal	4 days of RR training Before relaxation session	4 days After 20 min of RR session	6 months Before relaxation session	6 months After 20 min of RR session	12 months Before relaxation session	12 months After 20 min of RR session
RELAXATION RESPONSE	**11,6 (11,3-11,8)**	**11,8 (11,6-12,8)**	**11,6 (11,3-11,7)**	**11,7 (11,6-11,8)**	**11,5 (11,2-11,6)**	**11,8 (11,8-12)**	**11,6 (11,4-11,8)**
CONTROLS	**11,6 (11,3-11,8)**	**11,6 (11,33-11,7)**	**11,8 (11,6-12,78)**	**11,6 (11,23-11,7)**	**11,7 (11,6-11,8)**	**11,6 (11,4-11,8)**	**11,8 (11,8-12)**
RELAXATION RESPONSE HEALTHY CONTROLS	**11,4 (11,3-11,7)**	**11,7 (11,6-12,8)**	**11,6 (11,3-11,6)**	**11,7 (11,6-11,7)**	**11,5 (11,1-11,6)**	**11,85 (11,6-12)**	**11,45 (11,2-11,7)**

Table II: Serum conductivity at different BST. Median and interquartile range.



* p<0.01 Wilcoxon

° § # p<0.001 Mann-Whitney, delta comparison RR and controls (no differences of variations for RR groups)

Figure 5: Conductivity at different BST. Graph with statistical analysis of the data reported in table II.

months. Electric conductivity seems to decrease in the RR groups at 6 and 12 months while increases in controls at 12 moths and after the initial 4 days of training. Data are expressed as median and interquartile range (variables do not have a normal distribution as assessed by the Shapiro-Wilk test). The comparison between the pre-post intervention changes was performed by means of Wilcoxon test. In particular, we compared the extent of the percentage changes of each parameter occurring during each relaxation session by means of the Mann-Whitney test. An initial comparison between groups was performed by means of Kruskal-Wallis test for independent samples or by Friedman test for paired data. Bivariate correlation was performed by Spearman test. Statistical significance was assumed if the null hypothesis could be rejected at $p=0.05$. The statistical analysis was performed using software SPSS version 22.0 (Chicago, SPSS, Inc., Chicago, IL).

2.2 Delayed Luminescence

Figure 6 shows DL time trends from basal serum samples of one patient from the RELAXATION RESPONSE group. Generally speaking, DL data, both in the total number of photons re-emitted and in the time trend, differ at the different blood sampling times we considered.

First of all we tried to investigate possible difference in DL response before and after the relaxation session at each blood sampling times (BST). Starting from the DL decay intensity I(t), we evaluated the total number N_{tot} of emitted photons, that is

$$N_{tot} = \int_{t_i}^{t_f} I(t)dt$$

where t_i and t_f represent the initial and final acquisition times, respectively. Figure 7 shows the results at different BST in the case of a patient from the RELAXATION RESPONSE group.

Actually N_{tot} is an extensive parameter and it is subject to variations whose causes are not always controllable. The data reported in Figure 7, even when some (minimal) differences could be seen by comparing data before and after RR session, show that these differences do not manifest themselves always in the same direction. Precisely, sometimes the data before RR session are greater than the ones after, sometimes it is the opposite. This result was observed in all the samples analyzed.

Measuring DL, the intensive parameters are often more stable and therefore provide useful information on the system even when the extensive parameters present significant oscillations.

In our case a simple intensive parameter is linked to the dynamics of the time decay trend *I(t)*. A relatively simple way to analyze changes in the dynamics of two measurements is to compare the two time trends via a log-log graph.

In this case, if the dynamics are the same, the log-log graph will have a slope of 1, otherwise it is possible to obtain other useful information about the evolution of the system.

Concretely, looking for an intensive parameter to compare the measures immediately before and immediately after the relaxation session at the various BSTs, we studied the relationship:

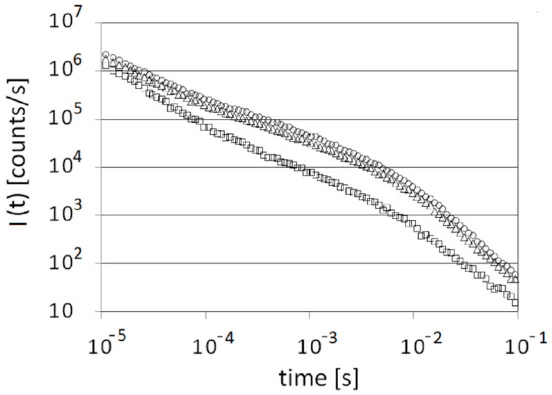


Figure 6: Delayed luminescence time trends of serum samples from one RELAXATION RESPONSE HEALTHY CONTROLS group patient, at different BST. (□) at first 4-days session, (△) after 6 months and(○) after 12 months of RR practice

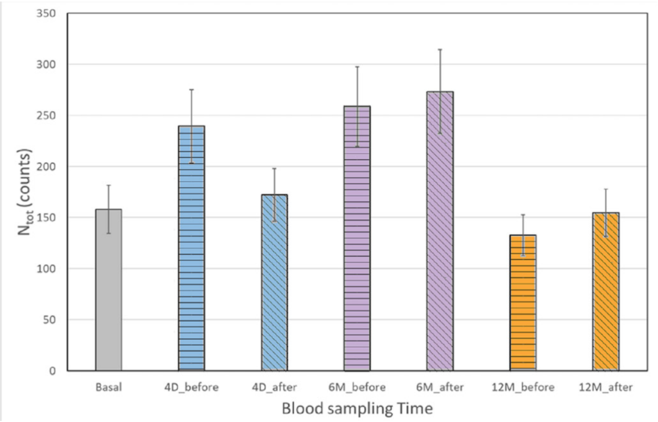


Figure 7: Total number of photon emitted (N_{tot}) at different BST in the case of a patient of the RELAXATION RESPONSE group. "Before" and "after" refer to the relaxation session. Average value and standard deviation of two measurements are reported.

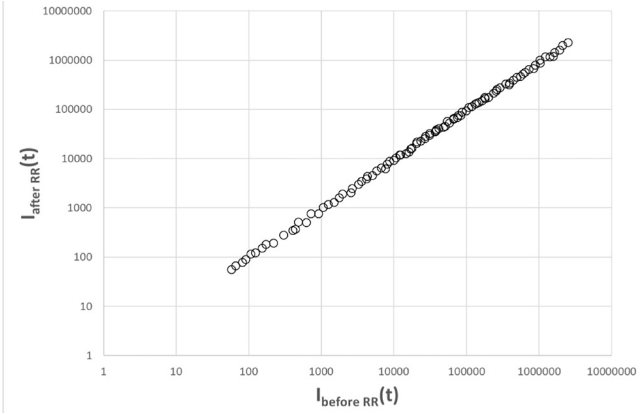


Figure 8: DL intensity after RR session as a function of the corresponding (at the same time) intensity before RR session. Data refer to blood samples from the same patient of Figure 7 at six months of RR practice..

$$I_{after}(t) = k\, I_{before}(t)^m \qquad (1)$$

and determined the parameter m, i.e. the slope of the curves like that drown in Figure 8, where the DL intensities, as the one reported in Figure 6, are compared point by point, that is at the same time from the beginning of the decay.

The average of the 90 evaluated values (20 RELAXATION RESPONSE GROUP and 10 RELAXATION RESPONSE HEALTHY CONTROLS, 3 BSTs each patient) we obtained was $m = 0.99 \pm 0.01$ with $R^2 > 0.991$. This means that there is not a change in the slope of the DL time decay from blood samples collected before and after relaxation session.

As a consequence, differently from the visual inspection shown in Figure 2, no significant difference can be ascribed to DL measurements performed at each BST before and after the relaxation session. Thanks to this result in the following the average value of the two was considered.

Interestingly, a change in the slope of the DL time decay was observed at different BSTs, that is on increasing the time that patient dedicated to RR practice. To point out this aspect we compared the DL time decay $I_{BST}(t)$ at each BST with the corresponding $I_B(t)$ at the basal condition (B) by considering again a log-log plot described by the relationship:

$$I_{BST}(t) = C\, I_B(t)^a \qquad (2)$$

As a result, no change in the slope was observed at the different BST for samples from the CONTROLS (no RR practice), getting as average value, with $R^2 > 0.997$

$$\bar{a}_{control} = 0.999 \pm 0.003$$

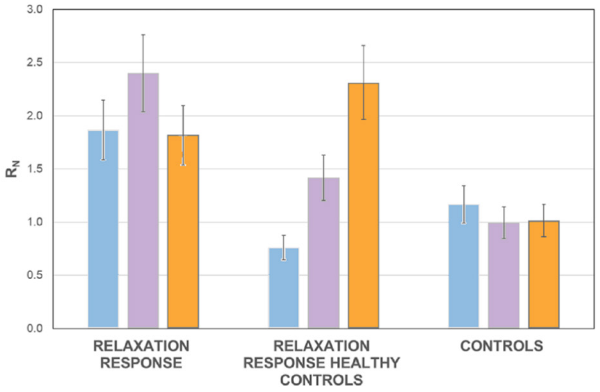


Figure 9. Values of the *a* parameter Equation 2 at different BST. (Light blue bar) the first four days session 4D, (violet bar) after 6 months (6M) and (orange bar) 12 months (12M) of RR practice. (colour with net) RELAXATION RESPONSE group, (colour) RELAXATION RESPONSE HEALTHY CONTROLS group, (solid tick line) CONTROLS. Mean and standard error of samples of the same group.

Significant differences were instead observed as a consequence of RR practice, as shown in Figure 9, where the parameter a is reported as a function of the BSTs. Data from patients of the same group were averaged.

It appears that for all subjects who have undergone RR practice, however, there is a significant variation in the parameter *a* of Equation 2 starting from the samples of the first BST, i.e. 4D. The most significant variations with respect to the CONTROLS occur in the samples from patients of the intervention group. In this case values of *a* less than 1 indicates that DL intensity I(t) from samples collected at different BSTs decays in time more slowly than the one from samples collected before the RR practice. Worth to note that it was previously observed (Scordino *et al.* 2014) that the DL trends from normal cells decay more slowly than in the case of DL from tumor cells.

We explored the possibility of considering also the total number of photon emitted N_{tot} at the different BSTs and comparing them. Above we have already argued on the extensive characteristics of this parameter, so in order to compare the response of the different samples we evaluated, for every patient at each BST, the dimensionless parameter R_N so defined:

$$R_N = N_{BST}/N_B \qquad (3)$$

where N_{BST} is the total number of photon emitted at the settled blood sampling time, evaluated as average value between samples collected before and after the relaxation session, and the corresponding value N_B evaluated on samples collected before starting the training to relaxation practice.

Average values within the group of R_N is reported in Figure 10. It appears, as expected, that the error bars are very large. Nevertheless, we can assess that R_N does not change at the different BSTs in the case of the CONTROLS (no RR practice) assuming the value 1, within the error. In contrast, for the two groups the behavior of R_N at different BSTs, i.e. on increasing the time during which the RR is practiced, not only is different from the CONTROLS but also between the two groups. More precisely, in the case of healthy people which experienced RR practice (RELAXATION RESPONSE HEALTHY CONTROLS), the parameter R_N increase with time; in the case of patients which experienced RR practice after myocardial infarction (RELAXATION RESPONSE group), R_N takes on much larger values than the CONTROLS, with an increase up to six months, followed by a decrease to the same value corresponding to the first four-day session.

In addition, results reported in Figure 10 are in accordance with that reported in Figure 9. Indeed, an increase of the total number of counts corresponds to a better capacity of the system to store and transmit the excited levels inside its structures and the decrease of slope in the intensity time decay (slow decay) corresponds to a decrease of the decay probability of these excited states.

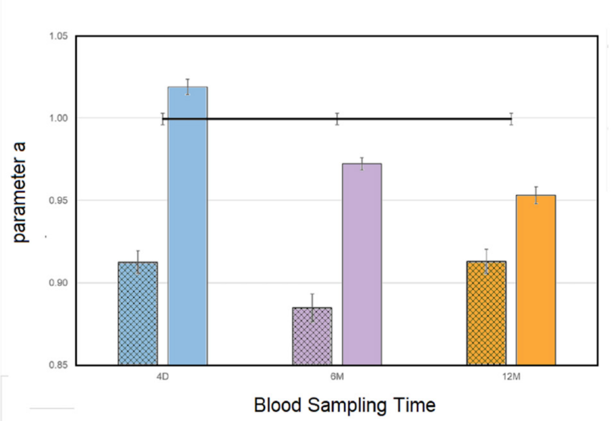


Figure 10: RN ratio between the total number of photon emitted at the settled blood sampling time and the corresponding value evaluated before starting the training to relaxation practice. (Light blue bar) the first four days session 4D, (violet bar) after 6 months (6M) and (orange bar) 12 months (12M) of RR practice. Average values and standard errors of the measurements on the whole group.

Up to now we have considered DL emission in the wavelength range (400–850 nm) of the acquisition system. A spectral analysis was performed by considering DL emission in three spectral intervals, centered at wavelengths 450 nm, 550 nm and 650 nm respectively, where important natural biomarkers, as for instance nicotinamide adenine dinucleotide, flavins, lipopigments, protoporphyrin, singlet oxygen, emit.

Figure 11 reports the DL emission spectrum relative to samples from the same patient (the one of Figure 6). It results that each spectral component is affected by a rather high error so no significant difference in the spectrum can characterize DL data at different BSTs. The same occurred for all the patients. Nevertheless, if one considers the contribution of these spectral components to the total emission some differences can be pointed out. More precisely, by denoting DL_{vis} the total number of photon emitted in the wavelength range (400–850 nm) of the acquisition system, and DL_{450}, DL_{550} and DL_{650} the total number of photons emitted when filters centered at wavelengths 450 nm, 550 nm and 650 nm, respectively, were used, the portion Q of the total emission within spectral range we observe can be evaluated as

$$Q = (DL_{450} + DL_{550} + DL_{650}) / DL_{vis} . \qquad (4)$$

To point out difference at different BSTs with respect the initial Basal condition, the ratio Q_{BST}/Q_B

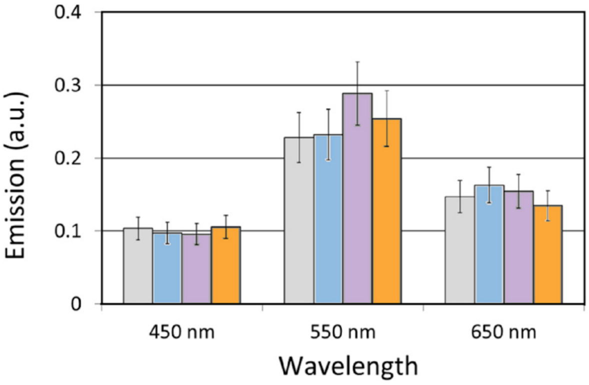


Figure 11: DL emission spectrum for samples from one pa-tient of the RELAXATION RESPONSE HEALTHY CONTROLS Group (the same as in Figure 6) at different BST. (light grey bar) Basal condition, (light blue bar) at the first four days session (4D), (violet bar) after 6 months (6M) and (orange bar) 12 months (12M) of RR practice.

between such portion, as defined in Equation 4, at a fixed BST and the corresponding value before beginning the training to relaxation practice was evaluated. Variance from the unitary value indicates a shifting of the spectrum out of the spectral emission range monitored by the used filters.

Figure 12 shows the values of the ratio Q_{BST}/Q_B, evaluated as average within each group, at the different BSTs. A significant change as a consequence of the RR practice can be observed. This change can be interpreted as due to a red shift of the sample spectra after the RR practice and could be useful in the design of further set-ups.

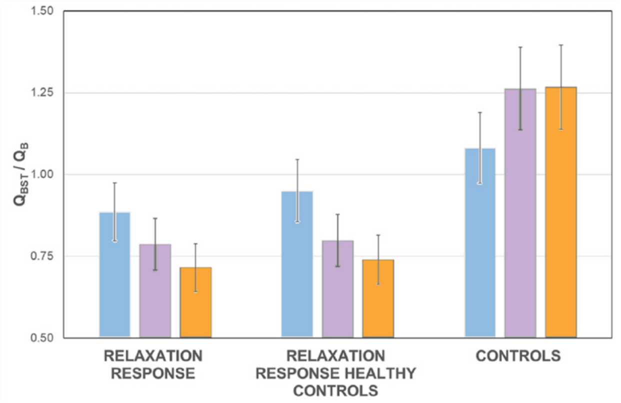


Figure 12: Ratio of the Q portion of the total emission within spectral observed range with respect the corresponding value evaluated before starting the training to relaxation practice at different BST. (Light blue bar) at the first four days session (4D), (violet bar) after 6 months (6M) and (orange bar) 12 months (12M) of RR practice. Average values and standard errors of the measurements on the whole group.

4. Discussion

In this paper we have presented some results of an exploratory study. In fact, during the study reported in our previous works (Dal Lin, Gola, *et al.* 2018; Dal Lin, Marinova, *et al.* 2018; Dal Lin, Brugnolo, *et al.* 2020) we have noticed an evident, visible change in the physical characteristics of the plasma of the subjects who undergo a Relaxation Response practice (Figure 2). Aiming to explain this observation, we analyzed some physical parameters characterizing the behaviour of human serum, i.e. of its main component, the water, in equilibrium with many proteins and ionic molecules.

Summing up, our preliminary data may suggest that the serum pH could significantly increase during a Relaxation Response intervention while electric conductivity decreases.

Regarding the evaluation of the DL on a complex medium such as human serum, more precise methods will have to be developed in order to bypass the background noise due to the huge chaotic balance of molecules contained in it. However, our preliminary results seem to indicate that a DL modification could be present according to the Relaxation Response practice. In fact we noticed a modification of the slope of the DL time decay with the Relaxation Response, namely that, in the same subject, DL may decay in time more slowly in blood samples collected after the RR practice than before. Worth to note that it was previously observed (Scordino *et al.* 2014) that the DL trends from normal cells decay more slowly than in the case of DL from tumor cells. Moreover, after the RR practice a red shift of the sample spectra may occur. Interestingly this would be in line with the brain activity during the techniques that lead to Relaxation Response (Wang *et al.* 2016; Dal Lin, Brugnolo, *et al.* 2020).

From the theoretical analysis standpoint, Figure 2 and these preliminary observations suggest the appearance of a coherent molecular dynamics within the blood samples analyzed after the Relaxation Response.

The available theoretical modeling (Del Giudice *et al.* 1985, 1986, 1988) in terms of many-body physics suggests indeed that a diffused coherent dynamics at intra- and inter-cellular level is at work in healthy biological systems and provides the conditions favorable to an efficient metabolic activity. Some technical and mathematical details of the theoretical analysis are presented in the Appendix. Here we briefly mention (cfr. the Appendix) that the coherent molecular dynamics is negatively affected by functional or chemical, oxidative stress. The theoretical model agrees with the observed red shift of light in the DL emission and the measured temperature decrease (Dal Lin, Marinova, *et al.* 2018). Coherence also accounts for the storage of energy in a convenient lapse of time, so that its radiation may be “delayed” till a convenient threshold is reached. Moreover, the theory predicts that biophoton emission occurs in the presence of dynamical singularities, in agreement with the observation that DL occurs in stressing situations.

In the Appendix we also comment on the linear log-log plot (Figure 8) of the measurements, which may expresses fractal self-similarity properties of the coherent molecular dynamics and relate them to equations (1) and (2) (see the Appendix for details).

Finally, theoretical and invitro experimental results show that higher pH corresponds to lower electric conductivity (and *vice versa*) for water in the presence of hydrophilic polymers (for example nafion (Capolupo *et al.* 2014)), where the formation of domains, called EZ (exclusion zones), is observed, which suggest that biological fluids may present similar properties of pH and electrical conductivity, consistently with the measurements mentioned above in the RR practice.

In conclusion, the theoretical modeling of a coherent dynamics within the blood samples analyzed after the Relaxation Response appears to be in agreement with the preliminary data reported above. Our analysis is also inspired by the finding of coherent responses of cells submitted to sound wave stimulation (Dal Lin, Radu, *et al.* 2021). Further researches and technical developments are needed to support our preliminary findings.

Appendix: Theoretical modelling

The electric dipoles characterizing macromolecules and the molecules of the water bath in which they are embedded offer the possibility of a molecular dynamics rich of phenomenological aspects. The theoretical model describes indeed the formation of the electret domains (already mentioned in the text, cfr. section 1) of coherent dipole oscillations and the generation of nonvanishing polarization density $P(x,t)$ arising from dynamically generated longrange correlation modes among the system microscopic components (Goldston, Salam, & Weinberg 1962; Del Giudice *et al.* 1985, 1986, 1988; Umezawa 1993; Blasone, Jizba, & Vitiello 2011; Vitiello 2012). The energetic feeding of the system at molecular level, by ATP hydrolysis or by other external or endogenous sources, is used for its coherent ordering (organizational activity). The quanta of the collective dipole waves (the dipole wave quanta, dwq) are condensed in the system ground state, out of which they may be excited under the action of some external input. The coherent ordering is negatively affected when the system undergoes mechanical or electromagnetic stress, or else, as already mentioned in the text, by functional or chemical, oxidative stress or other kind of stressing occurrences.

The coherent condensation of dwq provides the change of scale, from the system microscopic activity to its macroscopic behavior at the cellular and multicellular levels.

Due to boundary effects from the system finite size an effective nonzero mass m_{eff} is dynamically acquired by the dwq. Their propagation is in fact limited to the linear size $L = \hbar/(c\ m_{eff})$ (Gulino *et al.* 2005; Hansen, Nilsson, & Rossmeisl 2017). In stationary conditions the wavelength λ of the coherent dipole vibrational waves is related to L by $L = n\ \lambda/2$, with n integer. We thus see that larger coherent domains correspond to smaller m_{eff} and larger λ. This agrees with the *red shift* of light in the DL emission of treated subjects. Their RR practice consists indeed in the enhancement of the system coherent ordering at microscopic cellular and intercellular levels, i.e. in the increase of the linear extension L of coherent domains, thus shifting toward larger λ (toward the red band spectrum).

One also finds that $L = (\pi hc/6k_B)n^2\ /T$, with T the temperature and k_B the Boltzmann constant, which shows that more extended coherent domains, i.e. larger L consequent to RR practice, leads to temperature decrease, in agreement with measurements reported in previous observations (Dal Lin, Marinova, *et al.* 2018).

The fact that luminescence is *delayed* also finds its origin in the coherent dynamics. Indeed we recall that an electromagnetic (e.m.) field finds its way through the ordered medium of polarization density $P(x,t)$ by selffocusing propagation. According to general results of quantum field theory (QFT), the so-called AndersonHiggsKibble (AHK) mechanism predicts that the e.m. field in its filamentary propagation acquires a mass M_V, proportional to $P(x,t)$ (Del Giudice *et al.* 1986, 1988). For M_V = 13.60 eV, the hydrogen ionization energy, the diameter of the filament (channel) is $d = \hbar/(c\ M_V) = 125$ Å. This means that photons of energy $h\ \nu > 13.60$ eV may produce destructive effects on the coherent dipole ordered region and destruction of the e.m. filamentary propagation. Photons of energy $h\ \nu < 13.60$ eV instead may not be able to penetrate the ordering. However, small energy photons may themselves contribute to the system polarization and in this way they may be ‘stored’ within the system. The energy so accumulated in a convenient lapse of time may reach the threshold necessary to trigger a chemical reaction, or else it may be radiated under convenient stimuli, thus generating the “delayed” luminescence whose red shift signals its low energy (recall that the spectrum between $1/7$ and $1/8$ of 13.60 eV covers the red band spectrum). The radiated energy also carries the imprint of the long-range dwq coherent correlation in the system ground state. This is consistent with the discussion on the log-log plot (cfr. Figure 8) of the measurements reported above. It is in fact known (Zheng & Pollack 2003; Vitiello 2012) that the linear log-log plot generated form self-similarity relations, like $(q\alpha)^n = 1$, signals a coherent state structure in the system. In our case it is $q\alpha = I_{after}(t)/I_{before}(t)^m$, or $q\alpha = I_{BST}(t)/I_B(t)^a$, from equations (1) and (2), with k and C equal to 1, respectively. The strength of the coherence in the coherent state expression (Zheng & Pollack 2003; Vitiello 2012) is given by the quantity $q\alpha$, with q related to the slope m or a of the straight line in the log-log plot; m and a are the self-similarity, or fractal dimension.

It can be shown that biophotons can be emitted in the self-focusing regime (i.e. for non-zero M_V) (Del Giudice *et al.* 1988) and in the presence of topological singularities in the dwq condensate (Goldstone, Salam, & Weinberg 1962; Del Giudice *et al.* 1988; Blasone, Jizba, & Vitiello 2011; Vitiello, 2012). These singularities in the space-time non-homogeneous condensation are described by the condensation distribution $f(x,t)$. Moreover, singularities of $f(x,t)$ are only allowed (Goldstone, Salam, & Weinberg S 1962; Blasone, Jizba, & Vitiello, 2011; Vitiello, 2012) when dwq have vanishingly small effective mass, $m_{eff} \rightarrow 0$, i.e. for quite large size L of the ordered domain, which determines the scale for the (delayed) luminescence wavelength.

The theory prediction that biophotons are emitted in the presence of singularities of the condensation distribution $f(x,t)$ is consistent with the observation that DL occurs when the system undergoes stressing situations, like those indeed induced by illuminating the system with the high intensity pulsed nitrogen laser used in the experiments, exciting condensate modes, or by other endogen functional stress regimes, like during cell growth and differentiation.

The theoretical model seems to be consistent also with the observed behavior of pH and electrical conductivity reported above. This can be seen by considering that sources of singularities for $f(x,t)$ also come from surface boundaries in the biological structure, e.g. cell membranes, veins and arteries surfaces, etc., or surfaces due to the presence of impurities or any ionic aggregates in biological fluids, or surfaces dynamically generated by turbulent fluid circulation, e.g. by vortices (Vitiello 2012). In order for the coherent condensation to survive to the presence of these surfaces singularities, the correlation length modes dynamically respond propagating to enough large L so to have vanishingly small m_{eff} compatible with the existence of the $f(x,t)$ singularities. This means that a coherent stratum of biological fluids (serum, blood), will form near the surfaces. This is similar to what commonly observed (Vitiello 2012) in laboratory, where strata of coherent water molecular dipoles extending for a hundred of microns of thickness are observed adjacent to hydrophilic polymers (for example nafion). These strata are called EZ (exclusion zones) since their coherent organization expels present particle and is impenetrable by them or other impurities. The strata are polarized so that charges of sign opposite to the one of the charges of the material surface (negative in the case of nafion) are pushed out of the strata. A gradient of the pH orthogonal to the surface is thus produced (in the nafion case, pH is lowering moving far away from the surface). It is also known that the splitting of water molecules into OH^- and H^+ in the EZ region (Zheng & Pollack 2003; Zheng *et al.* 2006; Zheng, Wexler, & Pollack 2009; Del Giudice *et al.* 2015) is energetically advantageous, with consequent effects in the electrical conductivity (Del Giudice *et al.* 2015). Measurements have shown that higher pH corresponds to lower electric conductivity (and *vice versa*) for water in the presence of nafion (Capolupo *et al.* 2014). The conclusion is that theoretical and experimental results suggest that biological fluids in the cells or flowing in veins or arteries may present properties of charge distribution, pH and electrical conductivity of the kind just described, which may be consistent with the measurements described in the text according to Relaxation Response practice.

Conflict of interest statement: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ackowledgements: we thank the Pneumomeditazione teachers and the Entolé staff for the recording of audio files used for meditation and their support; the meditation music used in this study was composed by Paolo Spoladore.

Author contributions: conceptualization, CDL, FM and GV; methodology CDL, FM and GV; formal analysis, CDL, FM, GV, RG, AS, AT, VE, EN, RG; resources FM, FT, SI; data curation CDL, FM, AS; writing—original draft preparation, CDL, FM, GV.; writing—review and editing, CDL, FM, AS, GV, RG, FT; funding acquisition, FT, SI.

References

Alvermann M *et al.* 2015, "Biological electric fields and rate equations for biophotons", *European Biophysics Journal*, vol. 44, no. 3, pp. 165–170, DOI: 10.1007/s00249-015-1011-3.

Benson H & Klipper M Z 1975, *The Relaxation Response*, New York: William Morrow and Co.

Blasone M, Jizba P, & Vitiello G 2011, *Quantum Field Theory and its Macroscopic Manifestations*, London: Imperial College Press.

Brizhik L *et al.* 2001, "Delayed luminescence of biological systems arising from correlated many-soliton states", *Physical Review E*, vol. 64, no. 3, p. 031902, DOI: 10.1103/PhysRevE.64.031902.

Capolupo A. *et al.* 2014, "Self similarity properties of nafionized and filtered water and deformed coherent states", *International Journal of Modern Physics B*, 28(03), p. 1450007, DOI: 10.1142/S0217979214500076.

Chang J J 2008, "Studies and discussion of properties of biophotons and their functions", *NeuroQuantology*, vol. 6, no. 4, pp. 420–430.

Chaplin M 2020, *Water structure and science*, http://www1.lsbu.ac.uk/water/water_dissociation.html.

Cifra M *et al.* 2015, "Biophotons, coherence and photocount statistics: A critical review", *Journal of Luminescence*, vol. 164, pp. 38–51, DOI: 10.1016/j.jlumin.2015.03.020.

Cohen S & Popp F A 2003, "Biophoton emission of human body", *Indian Journal of Experimental Biology*, vol. 41, no. 5, pp. 440–445, DOI: 10.1016/S1011-1344(97)00050-X.

Colleoni C *et al.* 2016, "Delayed luminescence induced by complex domains in water and in TEOS aqueous solutions", *Physical Chemistry Chemical Physics*, vol. 18, no. 2, pp. 772–780, DOI: 10.1039/C5CP03420E.

Costanzo E *et al.* 2008 "Single seed viability checked by delayed luminescence", *European Biophysics Journal*, vol. 37, no. 2, pp. 235–238, DOI: 10.1007/s00249-007-0221-8.

Dal Lin C *et al.* 2015, "Coronary microvascular and endothelial function regulation: Crossroads of psychoneuroendocrine immunitary signals and quantum physics [Part A-B and C]", *Journal of Integrative Cardiology*, vol. 1 no. 5, pp. 132–209, OI: 10.15761/JIC.1000135.

Dal Lin C, Gola E, *et al.* 2018, "miRNAs may change rapidly with thoughts: The Relaxation Response after myocardial infarction", *European Journal of Integrative Medicine*, vol. 20 (March), pp. 63–72, DOI: 10.1016/j.eujim.2018.03.009.

Dal Lin C, Marinova M, *et al.* 2018, "Thoughts modulate the expression of inflammatory genes and may improve the coronary blood flow in patients after a myocardial infarction", *Journal of Traditional and Complementary Medicine*, vol. 8, no. 1, pp. 150–163. DOI: 10.1016/j.jtcme.2017.04.011.

Dal Lin C, Radu C M, *et al.* 2021, "Sounds stimulation on in vitro HL1 cells: A pilot study and a theoretical physical model", *International Journal of Molecular Sciences*, vol. 22, no. 1, p. 156, DOI:: 10.3390/ijms22010156.

Dal Lin C, Brugnolo L, *et al.* 2020, "Toward a unified view of cognitive and biochemical activity: Meditation and linguistic self-reconstructing may lead to inflammation and oxidative stress improvement", *Entropy. Multidisciplinary Digital Publishing Institute*, vol. 22, no. 8, p. 818, DOI: 10.3390/e22080818.

Del Giudice E *et al.* 1985, "A quantum field theoretical approach to the collective behavior of biological systems", *Nuclear Physics B*, vol. 251 (FS 13), pp. 375–400.

Del Giudice E *et al.* 1986, "Electromagnetic field and spontaneous symmetry breakdown in biological matter", *Nuclear Physics B*, 275 (FS 17), pp. 185–199.

Del Giudice E *et al.* 1988, 'Structure, correlations and electromagnetic interactions in living matter: Theory and applications.", in: Fröhlich H (ed.) *Biological Coherence and Response to External Stimuli*, Berlin: Springer-Verlag, pp. 49–64.

Del Giudice E *et al.* 2015, "The origin and the special role of coherent water in living systems", in: Fels D, Cifra M, & Scholkmann F (eds.), *Fields of the Cell*, pp. 95–111.

Goldstone J, Salam A, & Weinberg S (1962) "Broken Symmetries", *Physical Review*, vol. 127, pp. 965 – 970.

Grasso R *et al.* (2018) "Exploring the behaviour of water in glycerol solutions by using delayed luminescence", *PLoS ONE*, vol. 13, no. 1 (ed. Khodarahmi R). Available from: p. e0191861. doi: 10.1371/journal.pone.0191861.

Gulino M *et al.* 2005, "Role of water content in dielectric properties and delayed luminescence of bovine Achilles' tendon", *FEBS Letters*, vol. 579, no. 27, pp. 6101–6104, DOI: 10.1016/j.febslet.2005.09.077.

Gulino M *et al.* 2010, "Lifetime of low-density water domains in salt solutions by time-resolved Delayed Luminescence", *Chemical Physics Letters*, vol. 497, no. 1–3, pp. 99–102, DOI: 10.1016/j.cplett.2010.07.100.

Hansen M H, Nilsson A, & Rossmeisl J 2017, "Modelling pH and potential in dynamic structures of the water/Pt(111) interface on the atomic scale", *Physical Chemistry Chemical Physics*, vol. 19, no. 34, pp. 23505–23514, DOI: 10.1039/C7CP03576D.

Harrison R W 2012, *Principi di Medicina Interna*, 18th edition, Milan: Casa Editrice Ambrosiana.

Ho M-W 2015, "Illuminating water and life: Emilio Del Giudice", *Electromagnetic Biology and Medicine*, vol. 34, no. 2, pp. 113–122, DOI: 10.3109/15368378.2015.1036079.

Jiin-Ju C 2008, "Physical properties of biophotons and their biological functions", *Indian Journal of Experimental Biology*, vol. 46 (May), pp. 371–377.

Jursinic P 1986, "Delayed fluorescence: Current concepts and status" in: Govindjee I, Amesz J, Fork DC (eds.), *Light Emission by Plants and Bacteria*, New York: Academic Press, pp. 291–328.

Kubera-Nowakowska L, Lichszteld K, & Kruk I 2007, "Delayed luminescence of solid polymers", *Reviews on Advanced Materials Science*, vol. 14, pp. 90–96.

Lanzanò L *et al.* 2007, "Spectral analysis of Delayed Luminescence from human skin as a possible non-invasive diagnostic tool", *European Biophysics Journal*, vol. 36, no. 7, pp. 823–829, DOI: 10.1007/s00249-007-0156-0.

Musumeci F *et al.* 2012, "Delayed luminescence: A novel technique to obtain new insights into water structure", *Journal of Biological Physics*, vol. 38, pp. 181–195, DOI: 10.1007/s10867-011-9245-5.

Nagare A 2013, *Re: Relationship between pH and conductivity?* [forum post] https://www.researchgate.net/post/Relationship_between_pH_and_conductivity2/529eacc7d3df3e617c8b46b4/citation/download.

Niggli H 1993, "Artificial sunlight irradiation induces ultraweak photon emission in human skin fibroblasts", *Journal of Photochemistry and Photobiology B*, vol. 18, pp. 281–285.

Popp F-A 2003, "Properties of biophotons and their theoretical implications", *Indian Journal of Experimental Biology*, vol. 41 no. 5, pp. 391–402.

Scholz M, Dědic R, & Hála J 2017, "Microscopic time-resolved imaging of singlet oxygen by delayed fluorescence in living cells", *Photochemical & Photobiological Sciences*, vol. 16, no. 11, pp. 1643–1653, DOI: 10.1039/C7PP00132K.

Scordino A *et al.* 1996, "Influence of the presence of atrazine in water on the in-vivo delayed luminescence of Acetabularia acetabulum", *Journal of Photochemistry and Photobiology B: Biology*, vol. 32, no. 1–2, pp. 11–17, DOI: 10.1016/1011-1344(95)07213-6.

Scordino A *et al.* 2008, "Delayed luminescence of microalgae as an indicator of metal toxicity", *Journal of Physics D: Applied Physics*, vol. 41, no. 15, p. 155507, DOI: 10.1088/0022-3727/41/15/155507.

Scordino A *et al.* 2010, "Delayed luminescence from collagen as arising from soliton and small polaron states", *International Journal of Quantum Chemistry*, vol. 110, no. 1, pp. 221–229, DOI: 10.1002/qua.22010.

Scordino A. *et al.* 2014, "Ultra-weak Delayed Luminescence in cancer research: A review of the results by the ARETUSA equipment", *Journal of Photochemistry and Photobiology B: Biology*. vol. 139, pp. 76–84, DOI: 10.1016/J.JPHOTOBIOL.2014.03.027.

Sławinski J 2003, "Biophotons from stressed and dying organisms: Toxicological aspects", *Indian Journal of Experimental Biology*, vol. 41, no. 5, pp. 483–493.

Sun M *et al.* 2019, "Characterization of ginsenoside extracts by delayed luminescence, high-performance liquid chromatography, and bioactivity tests", *Photochemical & Photobiological Sciences*, vol. 18, no. 5, pp. 1138–1146, DOI: 10.1039/C8PP00533H.

Tudisco S *et al.* 2003 "Advanced research equipment for fast ultraweak luminescence analysis", *Review of Scientific Instruments*, vol. 74, no. 10, pp. 4485–4490, DOI: 10.1063/1.1611997.

Umezawa H 1993, *Advanced Field Theory: Micro, Macro, and Thermal Physics*, New York: AIP.

Vitiello G 2012, "Fractals, coherent states and self-similarity induced noncommutative geometry", *Physics Letteras A*, vol. 376, pp. 2527–2532.

Wang Z *et al.* 2016, "Human high intelligence is involved in spectral redshift of biophotonic activities in the brain", *Proceedings of the National Academy of Sciences*, vol. 113, no. 31, DOI: 10.1073/pnas.1604855113.

Van Wijk R *et al.* 1993, "Light-induced photon emission by mammalian cells", *Journal of Photochemistry and Photobiology B*, vol. 18, pp. 75–79.

Yagura R *et al.* 2019, "Delayed fluorescence as a new screening method of plant species for urban greening: An experimental study using four bryophytes", *Landscape and Ecological Engineering*, vol. 15, no. 4, pp. 437–445, DOI: 10.1007/s11355-019-00393-8.

Zheng J *et al.* 2006, "Surfaces and interfacial water: Evidence that hydrophilic surfaces have long-range impact", *Advances in Colloid and Interface Science*, vol. 23, pp. 19–27.

Zheng J & Pollack G 2003, "Long range forces extending from polymer surfaces", *Physical Review E*, vol. 68, p. 031408.10.1103.

Zheng J, Wexler A, & Pollack G 2009, "Effect of buffers on aqueous solute-exclusion zones around ion-exchange resins", *Journal of Colloid and Interface Science*, vol. 332, pp. 511–514.

Research Highlights

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17351

Environmental Epigenetics: Myth and Reality

Andrea Fuso [a*] *& Aron M. Troen* [b*]

[a]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy [b]Nutrition and Brain Health Laboratory, the Institute of Biochemistry Food and Nutrition Science, the Robert H. Smith Faculty of Agriculture Food and the Environment, The Hebrew University of Jerusalem, Rehovot, Israel

***Corresponding authors:** Andrea Fuso, Email andrea.fuso@uniroma1.it; Aron M. Troen, Email aron.troen@mail.huji.ac.il

Abstract

The field of epigenetics is primarily interested in the epigenetic basis of development and disease, the transgenerational transmission of epigenetically controlled traits, and the role of the environment in modulating epigenetic traits. The term "epigenetics" itself has evolved. Initially it designated that a limited number of molecular modifications to DNA can influence gene expression as one of the mechanisms controlling cellular differentiation and divergent phenotype despite containing the same genetic code. Today, a broad and imprecise classification of many other cellular regulatory processes that can influence gene expression and which may or may not be heritable are commonly referred to as "epigenetic". Two recent papers, one by Ute Deichmann and the other by Corrado Spadafora, expose the overly broad use of the term. Accepting their challenge to redefine epigenetics in a more precise and rigorous way could have significant consequences. It could help us avoid attributing alterations in an offspring's phenotype due to environmental stresses experienced by its parents to epigenetic mechanisms, and misuse of the term outside the narrow confines of scientific discourse in the life sciences. Moreover, such precision would ensure setting an appropriately high bar for testing whether newly identified aspects of DNA methylation and micro RNA transmission could be transmissible from parent to offspring through the germline, and more stringently verifying as yet unfounded claims for the transgenerational heritability of environmentally acquired traits that could discredit this important field of inquiry.

Keywords: epigenetics, DNA methylation, histone modifications, miRNAs, environmental epigenetics, transgenerational epigenetics

Citation: Fuso A & Troen A M 2020, "Environmental Epigenetics: Myth and Reality", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 31-34 DOI: 10.13133/2532-5876/17351

Epigenetics, which may be defined as "the study of mitotically and meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Waddington 1942; Riggs *et al.* 1996; Deichmann 2015), has become a very popular topic in the biomedical sciences. Emerging from early studies in the fields of cellular differentiation and embryonic development, which showed how DNA methylation and histone modifications could alter the phenotype of cells (Nakao 2001), Epigenetics garnered broad interest after the discovery that it was involved in carcinogenesis (Sugimura & Ushijima 2001). Paradoxically, insight into the association of epigenetics and cancer raised doubts regarding the role of epigenetic mechanisms in regulating cellular processes. A proliferation of studies showing that tumors could carry different, contrasting epigenetic profiles, led to questioning whether epigenetic changes observed in cancer might also reflect normal regulatory processes (Jones & Buckley 1990). The significance of epigenetics has been ambiguated by the gradual loosening of the above-mentioned definition of "epigenetic traits". Initially, the term "epigenetic" was limited to DNA methylation and histone modifications, however today, the term means different things to different scientists who commonly use it to refer to many other cell molecular events. This has led to confusion in interpreting epigenetic studies. A common joke among biologists illustrates this point: "If they ask you anything you don't know, just say it's due to epigenetic modifications".

Nevertheless, the field of epigenetics continues to attract considerable interest. This is due to its apparent involvement in many diseases (Feinberg 2018; Tollefsbol 2018) and to the intriguing notion that some sort of yet unidentified "epigenetic" process might be a mechanism that allows acquired traits to be inherited. This would mean environmentally determined parental phenotypes could be stably transmitted to offspring without a change in the germline's DNA sequence (Casas & Vavouri 2020; Senaldi & Smith-Raska 2020). *If* such a mechanism were revealed, it would have important implications for understanding health and disease, and would fundamentally change our understanding of evolution. Nevertheless, the value of the burgeoning research into these questions is limited by widespread and inaccurate use of the term, and by the tendency to mislabel a wide variety of cellular regulatory processes as "epigenetic".

The scientific problem and its broader implications are superbly discussed by science historian Ute Deichmann, in her insightful and incisive review "The social construction of the social epigenome and the larger biological context" (Deichman 2020, p. 37). She surveys the foundations of epigenetic science, highlighting the milestones and discoveries that we can rely on, and criticizing the misuse and over-interpretation of the biological epigenetic discourse by the social sciences. These have often ignored the narrow bio-molecular context of the findings, relying on flawed studies and limited findings to draw overarching inferences. It bears repeating that few phenomena in fact meet the strict definition of epigenetic traits, stipulating that such modifications 1) must not alter the DNA sequence and 2) must be transmittable from parent to progeny, at least during somatic cellular proliferation or gametogenesis. To date, DNA methylation and covalent histone modifications, which together can determine nucleosomal occupancy, are the only phenomena proven to meet these essential criteria.

Whether microRNAs (miRNA), commonly referred to in the biological literature as somehow being epigenetic also meet these criteria is still very much an open question. MicroRNAs can be transmitted, but given the apparently stochastic mode of their transmission, it is not evident they can indeed give rise to stably inherited traits not encoded by the offspring DNA (Gapp & Bohacek 2018; Fuso *et al.* 2020). In another recent review, Corrado Spadafora offers an intriguing hypothetical model, whereby miRNAs might be transmitted from the parental germlines to the developing embryo by circulating vesicles, and then stably acquired (Spadafora 2020).

The crucial questions raised by these reviews concern if and how the environment can modulate epigenetic traits in such a way that acquired traits could be transmitted across generations. Although as Deichmann cogently argues, it is abundantly evident that a wide range of environmental factors including chemical agents, nutrition, pollutants, physical activity, and even behavioral stress, can induce changes in the epigenome, the evidence is a far cry from the "revenge of Lamarkism" (Deichmann 2016). Deichmann extensively documents the fact that to date we have no credible evidence for transgenerational epigenetic inheritance in humans, and even in other species the evidence is exceptionally rare and has no permanent impact on the epigenetic marks. Furthermore, there is scant evidence of extensive environmentally induced demethylation of CpG islands in differentiated tissue.

In this regard, it should be noted that most studies of mammalian DNA methylation to date have focused on highly stable CpG methylation in CpG islands. Much less is understood about more dynamic changes that are increasingly documented in gene promoters outside of dense CpG regions. It is indeed difficult to imagine that a CpG-dense, heavily methylated promoter could be easily demethylated in a differentiated tissue. However, emerging evidence suggests that environmental-dependent differential methylation may play a functional role in promoters with low CpG density, even in non-proliferating tissues (Lee *et al.* 2020). We have demonstrated, for example, that B vitamin imbalances can induce differential non-CpG methylation in the promoter of the PSEN1 gene (related to amyloid processing) in adult mice, modulating gene expression and eventually exacerbating their Alzheimer-like phenotype (Fuso *et al.* 2012). Similar non-CpG differential methylation has been observed in the post-mortem brain from Alzheimer's patients and healthy controls (Monti *et al.* 2020; Nicolia *et al.* 2017). Such environmental modulation of non-CpG epigenetic patterns in tandem with altered gene expression, even in non-proliferating tissues, might shift the organism between health and disease. Further research into environmental effects on non-CpG methylation is warranted, and remains to be explored both in quiescent and proliferating somatic cells. Nevertheless, this type of environmental influence on what is generally regarded as an epigenetic marker, does not meet the essential criterion of being a heritable change. It would be of considerably greater interest if such adaptive or maladaptive changes were also observed in meiosis, because as far as we know, epigenetic modifications to non-mutated DNA would have to occur in the germ-line in order to stably influence the phenotype of the progeny without changing their inherited DNA sequence (Jawaid *et al.* 2020).

Spadafora proposes an alternative potential mechanism for transmitting acquired environmental traits involving miRNA in his review. He postulates that miRNAs released from parental somatic tissues that have been exposed to stress, can be taken up in vesicles by the gametes and transmitted as "epigenetic information" to somatic tissues in the developing embryos, potentially establishing stably inherited traits. It is difficult to see how vesicle-transported miRNAs could resolve the critical issues addressed in Diechmann's review since no evidence has yet been found for stable epigenetic inheritance in humans and scant evidence supports it in mammals. Another problem is the stochastic way the developing embryo would have to take up circulating miRNAs to ensure the offspring would preferentially express the parents' acquired phenotype. It is difficult to reconcile what we know of evolutionary selection with such "environmental epigenetics". Indeed, in the few documented mammalian models, transgenerational changes have never been observed to last beyond three generations (Heard & Martienssen 2014).

Until environmentally acquired phenotypes can be shown to be stably transmitted to offspring across multiple generations, independent of their inherited DNA sequence, the field of epigenetics would benefit from a renewed consensus on precise criteria for "epigenetic" traits and for designating newly discovered phenomena as epigenetic. It is clear that DNA methylation, histone modification, and non-coding RNAs represent different molecular species with different functional characteristics. Therefore, any new molecule or process can only be termed epigenetic through its functional epigenetic effects. In order to uphold the hypothesis that environmental conditions can produce a stably heritable, acquired phenotypic response, without altering the DNA sequence, we need a more precise understanding of how an organism might adapt to environmental conditions by specifically modifying the expression of relevant target genes and pathways in a beneficial manner to enhance evolutionary fitness. Until such evidence is available, we can advance the field by not using the term epigenetic indiscriminately. Overreaching inferences rooted in social and disciplinary arguments over the relative importance of nature and nurture are unlikely to carry us forward. We will do more to advance the field of epigenetics along with all the life sciences by testing novel hypotheses that can identify, deepen and refine our understanding of the master commands that direct the adaptive cellular response of target genes to environmental cues, without changing the gene sequence.

Acknowledgements

The authors are sincerely grateful to Dr. Carol Troen for constructive editorial comments.

References

Casas E & Vavouri T 2020, "Mechanisms of epigenetic inheritance of variable traits through the germline", *Reproduction*, vol. 159, no. 6, pp. R251–R263, DOI: 10.1530/REP-19-0340. PMID: 32302967.

Deichmann U 2015, "Chromatin: Its history, current research, and the seminal researchers and their philosophy", *Perspectives in Biology and Medicine*, vol. 58, no. 2, pp. 143–64, DOI: 10.1353/pbm.2015.0024. PMID: 26750599.

Deichmann U 2016, "Why epigenetics is not a vindication of Lamarckism—and why that matters. *Studies in History and Philosophy of Biological and Biomedical Sciences*, vol. 57, pp. 80–2, DOI: 10.1016/j.shpsc.2016.04.004. PMID: 27139147.

Deichmann U 2020, "The social construction of the social epigenome and the larger biological context", *Epigenetics Chromatin*, vol. 13, no. 1, p. 37, DOI: 10.1186/s13072-020-00360-w. PMID: 32967714; PMCID: PMC7510271.

Feinberg A P 2018, "The key role of epigenetics in human disease prevention and mitigation", *New England Journal of Medicine*, vol. 378, no. 14, pp. 1323-1334, DOI: 10.1056/NEJMra1402513. PMID: 29617578.

Fuso A *et al.* 2012, "S-adenosylmethionine reduces the progress of the Alzheimer-like features induced by B-vitamin deficiency in mice", *Neurobiology of Aging*, vol. 33, no. 7, p. 1482.e1-16, DOI: 10.1016/j.neurobiolaging.2011.12.013. PMID: 22221883.

Fuso A, Raia T, Orticello M, & Lucarelli M 2020, "The complex interplay between DNA methylation and miRNAs in gene expression regulation", *Biochimie*, vol. 173, pp. 12–16, DOI: 10.1016/j.biochi.2020.02.006. PMID: 32061806.

Gapp K & Bohacek J. 2018, "Epigenetic germline inheritance in mammals: Looking to the past to understand the future", *Genes, Brain and Behavior*, vol. 17, no. 3, p. e12407, DOI: 10.1111/gbb.12407. PMID: 28782190.

Heard E, Martienssen R A 2014, "Transgenerational epigenetic inheritance: Myths and mechanisms", *Cell*, vol. 157, no. 1, pp. 95–109, DOI: 10.1016/j.cell.2014.02.045. PMID: 24679529; PMCID: PMC4020004.

Jawaid A, Jehle K L, Mansuy I M. 2020, "Impact of parental exposure on offspring health in humans", *Trends in Genetics*, Nov 11:S0168-9525(20)30295-X. doi: 10.1016/j.tig.2020.10.006. Epub ahead of print. PMID: 33189388.

Jones P A, Buckley J D 1990, "The role of DNA methylation in cancer", *Advances in Cancer Research*, vol. 54, pp. 1–23, DOI: 10.1016/s0065-230x(08)60806-4. PMID: 2404377.

Lee J H, Saito Y, Park S J, Nakai K 2020, "Existence and possible roles of independent non-CpG methylation in the mammalian brain", *DNA Research*, vol. 27, no. 4, p. dsaa020, DOI: 10.1093/dnares/dsaa020. PMID: 32970817.

Monti N *et al.* 2020, "CpG and non-CpG Presenilin1 methylation pattern in course of neurodevelopment and neurodegeneration is associated with gene expression in human and murine brain", *Epigenetics*, vol. 15, no. 8, pp. 781–799, DOI: 10.1080/15592294.2020.1722917. PMID: 32019393; PMCID: PMC7518704.

Nakao M 2001, "Epigenetics: Interaction of DNA methylation and chromatin", *Gene*, vol. 278, no. 1–2, pp. 25-31, DOI: 10.1016/s0378-1119(01)00721-1. PMID: 11707319.

Nicolia V *et al.* 2017, "DNA methylation profiles of selected pro-inflammatory cytokines in Alzheimer disease", *Journal of Neuropathology & Experimental Neurology*, vol. 76, no. 1, pp. 27–31, DOI: 10.1093/jnen/nlw099. PMID: 28053004.

Riggs A D, Russo V E A, & Martienssen R A 1996, *Epigenetic Mechanisms of Gene Regulation*, Plainview: Cold Spring Harbor Laboratory Press.

Senaldi L & Smith-Raska M 2020, "Evidence for germline non-genetic inheritance of human phenotypes and diseases", *Clininical Epigenetics*, vol. 12, no. 1, p. 136, DOI: 10.1186/s13148-020-00929-y. PMID: 32917273; PMCID: PMC7488552.

Sugimura T & Ushijima T 2000, "Genetic and epigenetic alterations in carcinogenesis", *Mutation Research*, vol. 462, no. 2–3, pp. 235–46, DOI: 10.1016/s1383-5742(00)00005-3. PMID: 10767635.

Tollefsbol T (Ed.) 2018, *Epigenetics in Human Disease*, vol. 6, 2nd edition, Cambridge: Academic Press.

Waddington C H 1942, "The epigenotype", *Endeavor*, vol. 1, pp. 18–20.

Organisms

SAPIENZA
UNIVERSITÀ DI ROMA

Feature

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17352

Biological Periodicity's Atomic Mechanism Disposes of the "Current Theory" of Evolution

Antonio Lima-de-Faria,[a]*

[a] *Emeritus Professor of Molecular Cytogenetics, Lund University, Lund, Sweden*

***Corresponding author:** Antonio Lima-de-Faria, Trumslagaregränden 10, SE-226 39 Lund, Sweden
Email: johanessenmoller@icloud.com

Abstract

Physics led the way in the creation of Molecular Biology by employing X-ray crystallography in the elucidation of the atomic structure of proteins and DNA. Now it is physics again, by using large accelerators of electrons and neutrons, that is transforming molecular biology into Atomic Biology. This transformation process is guided by the establishment of periodicity, a phenomenon that can now be shown to start with elementary particles, to extend to atoms and macromolecules, and to occur equally among living organisms including humans. Biological periodicity was established in the following properties: vision, regeneration, luminescence, flight, placenta, penis, plant carnivory and mental ability. Significant is that three of these properties do not start at the cell or the organism, as previously thought, but emerge already in crystals and minerals which have no genes, and where organization is decided by atomic and electronic interactions. The punctuated reappearance of a given property, which leads to periodicity, is based on its own evolution of DNA. This is demonstrated by the formation of the placenta, which in plants and in humans, is decided by the same DNA sequences. Also, vision, which appears in the simplest invertebrates as well as in humans results from the action of the same gene *Pax6*. It is this DNA homology which allows the reappearance of the same pattern, in the most different organisms. The law of periodicity which has been enunciated at the atomic level holds equally well for the periodicity found in living organisms allowing predictions.

Keywords: biological periodicity, periodicity of elementary particles, periodicity of chemical elements, atomic biology, vision, regeneration, luminescence, flight, placenta, penis, plant carnivory, mental ability, crystals, minerals, accelerators of electrons and neutrons, periodicity of universe

Citation: Lima-de-Faria, A, 2020, "Biological Periodicity's Atomic Mechanism Disposes of the "Current Theory" of Evolution", Organisms: Journal of Biological Sciences, vol. 4, no. 2, pp. 35-68. DOI: 10.13133/2532-5876/17352

PART 1. It was Physics Which Led to the Emergence of Molecular Biology

1.1. X-Ray Crystallography Opened the Way to the Atomic Structure of Proteins and DNA

Molecular biology was born from the interaction of physics with microbiology and genetics. The original impulse did not come from biological disciplines, as could have been expected, but from experimental physics.

The pioneers were: Max von Laue (1879-1960), William Bragg (1862-1942) and Lawrence Bragg (1890-1971). All three were physicists. von Laue demonstrated that X-rays were electromagnetic waves, like light, but of very short wavelength. He then realized that the atoms in a crystal were in an ordered array, in accord with their external regularity. He passed a narrow beam of X-rays through a crystal of a copper compound and obtained a diffraction pattern of spots on a photographic film.

This experiment became the basis on which the Braggs later created X-ray crystallography. The atomic layers of a crystal acted as mirrors, reflecting X-rays, with interference resulting from reflexions at different layers. It allowed them to measure the interatomic distance in crystals of diamond, copper and salts, such as KCl. The ordered atomic interior of crystals became a reality.

Subsequently John D. Bernal, after taking a degree in physics, joined W.H. Bragg in London in 1923. Bernal published works on the position of carbon atoms in graphite and on a simple method of interpreting X-ray diffraction pictures that was widely adopted. Later, at Cambridge, Bernal discovered the rich X-ray diffraction patterns of protein crystals and of viruses. He opened a new field of research at the cellular level.

Biologists tend to think in terms of complexity and, by 1936 genetics had advanced so far, that the gene was considered to consist of proteins. Nucleic acids were too simple to carry the genetic material: "The riddle of life was in the structure of proteins".

It was at that time that Max Perutz joined Bernal at his laboratory and who after 30 years of intense labor, produced the three-dimensional map of haemoglobin (Perutz 2003).

Following World War II another student of Bernal was Rosalind Franklin a physical chemist (1920-1958) who collaborated with M. Wilkins. She produced the X-ray diffraction pattern of a thread of DNA. The bold cross-like pattern that emerged was characteristic of a helical structure and this led James Watson and Francis Crick to make a double-helical model of DNA in 1953.

Figure 1: Aerial view of MAX IV accelerator laboratory which started operating in June 2016 at Lund University, Lund, Sweden.

1.2. The Contribution of Genetics and Microbiology

In the meantime, George Beadle joined Edward L. Tatum who worked with the fungus *Neurospora*. The mutations obtained, by X-rays, led them to the concept of "one gene — one enzyme".

But it was from France, that microbiologists would give a major explanation of the genetic events occurring in the cell. Jacques Monod, Francois Jacob and André Lwoff studied mutant bacteria. They were led to introduce the idea of *operons*, groups of genes with related functions, which were controlled by an *operator*. They also developed the idea of messenger RNA, which carries information from DNA to the ribosomes, where protein synthesis occurs. All their predictions were fully confirmed, not only in bacteria, but in other living organisms from plants to humans.

By the 1960s Molecular Biology came of age.

1.3. Physics is Now Transforming Molecular Biology into Atomic Biology

New technologies are now allowing to go deeper than the atom.

Over 900 scientists have been performing experiments since 2013 using synchrotron radiation of the MAX II AND MAX III accelerators from Lund University in Sweden and a still more efficient laboratory MAX IV, has been completed in June 2016 (Figure 1).

Synchrotron radiation is obtained when electrons are accelerated to a speed close to that of light. At the same time a magnetic field curves their trajectory.

X-rays may damage the materials studied. As a consequence new laboratories are being created to use instead neutron scattering to probe the structures but in addition the behavior of large molecules. For this purpose the European Spallation Source is now under construction at Lund University and is expected to open in 2023 with 3,000 scientists working per year.

Neutrons probe structure, but most important, also motion. Measurement of structure extends from micrometers to one-hundred-thousandth of a micrometer and motion is recorded from milliseconds to ten-million-millionths of a millisecond (Eriksson 2015, Andersson 2020).

PART 2. Periodicity is a Phenomenon Inherent to Matter and Energy that will Guide Physics into Novel Areas of Research

2.1. Periodicity is Already Present in Elementary Particles

Padamsee (2003) described the present view of the evolution and periodicity of elementary particles as follows.

By 1963 physicists had identified 41 new particles. By 1970 the list exploded to several hundred. Most particles were unstable and there was a bewildering array, with various masses, charges and spin.

However, further research revealed that the initial plethora of particles could be reduced to two fundamental ones: quarks and leptons, which by combination produced all the others. This result led also to the establishment of their periodicity in the form of a Periodic Table of Elementary Particles. Murray Gell-Mann (1929-2019) succeeded in elucidating from the chaotic subnuclear landscape certain underlying patterns well hidden among the new properties. As Padamsee (2003) points out: "Order does exist, although at a deeper level than immediately recognizable".

This quark model predicted new particles with very specific properties which were later found experimentally. There are six quarks altogether in three genera-

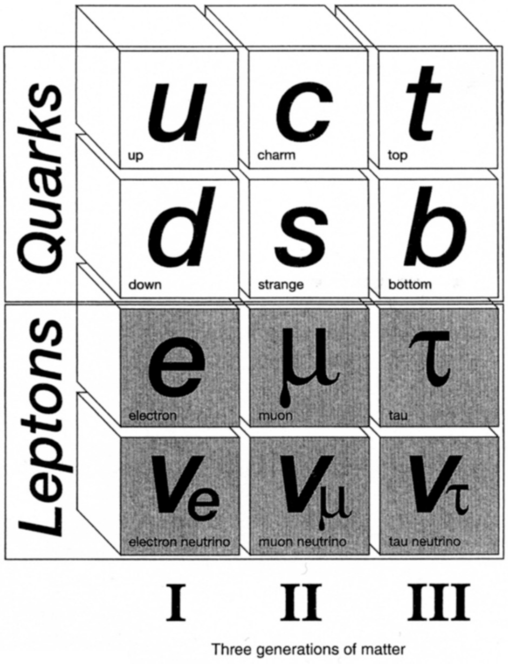


Figure 2: Periodic Table of quarks and leptons showing the three generations of matter derived from leptons and quarks.

tions of pairs: *up, down*; *charm, strange*; and *top, bottom*; and quark mass increases with generation. Each quark has an anti-quark partner. The leptons also span three generations in pairs: *electron, electron neutrino*; *muon, muon neutrino*; and *tau, tau neutrino*.

The evolution of the elementary particles results from the finding that all are derived from only two: a quark and a lepton. This is the same situation that happens later at the atomic level in which all the 118 chemical elements are derived from a single atom: hydrogen.

The periodicity is revealed by elementary particles which happen to have the same property. There are 3 types of neutrinos: electron neutrino, muon neutrino and tau neutrino with increasing mass (Figure 2). This is also the same situation that happens at the atomic level where atoms with increasing mass have the same basic properties, such as the noble gases.

Significant is that quarks and leptons are considered to have no structure — we are at the very core of matter and energy.

2.2. DNA has no Information for Iron, Zinc or Magnesium — The Importance of Single Atoms

Hemoglobin is a protein that functions as a respiratory pigment by binding oxygen reversibly. Its function is not located on the amino acid sequences which were formed, following instructions from DNA, but is carried by the four atoms of iron which occupy exact positions in the macromolecule. The ability to oxidize existed in iron before the cell was formed. It is the speed of the process that was enormously improved by the novel location within the edifice of amino acid residues.

Zinc finger is a protein motif associated with DNA-binding proteins. It consists of a loop of 12 amino acids that directly coordinates a zinc atom. These proteins intercalate directly into the DNA helix, but the main function lies in the zinc atom and not in the amino acid sequences.

Chlorophyll is responsible for light capture in the photosynthesis of plants. Each molecule comprises a porphyrin group containing magnesium. It is the magnesium atom which is responsible for its main function.

The simple atoms of iron, zinc and magnesium, are those that have the key to the functions of these vital macromolecules but DNA has no information for these atoms.

All this novel evidence points to the extreme importance of single atoms.

2.3. The Physical Rules that Predict the Atomic Behavior of DNA and Proteins Remain Elusive

At present there is a most detailed and coherent picture of the structure and function of DNA, RNA and proteins elucidating the biochemical activity of the cell. However, what are the physical rules that direct the evolution of these macromolecules? This question had been asked earlier for proteins because they are so many and diversified.

Concerning DNA and RNA we are mostly in the dark but physicists are now helping in this direction. Computer graphics and nuclear magnetic resonance have allowed a better resolution of their three-dimensional structure and function. But the picture is still far from satisfactory. As C. Branden and J. Tooze (1991) already pointed out "We shall not unravel the chemistry of life in molecular detail without knowing at atomic or close to atomic resolution the structure of biological macromolecules, especially proteins". This still applies to our present state of knowledge in proteins as well as in DNA and RNA, in which the behavior, as well as the movement of single atoms, remains to be elucitated.

2.4. The Iconic Table of the Chemical Elements Contains Many Irregularities —Biological Tables are Expected to be More Irregular but to Carry the Same Underlying Order

Scerri (2007) writes "There is a fundamental relationship between the elements" and he adds: "The periodic law states that after regular but varying intervals the chemical elements show an approximate repetition of their properties". But he also points out that "Periodicity among the elements is neither constant nor exact".

No phenomenon at the physical, chemical or biological level reveals total regularity. Already the periodicity of the movements of the planets in the Solar System contains irregularities. The eccentricity of some planetary orbits, such as that of Mercury, is not negligible (Weinberg 2015).

The Periodic Table of the Elements is accordingly irregular. Hydrogen (H) can be placed close to lithium on the extreme left side of the table, but may also occupy a position at the extreme right at the side of the noble gases. Helium (He) is an element with an anomalous position in the periodic table. The same is true of europium (Eu) and ytterbium (Yb) that belong to the lanthanide series. Other irregularities include chromium (Cr) and copper (Cu) atoms that carry 1 rather than 2 electrons on their outer orbitals.

"There is a clear line between radioactive and stable elements: everything below bismuth (No 83) is stable; everything above it is radioactive — except technetium (Tc) and promethium (Pm), which stick out like sore thumbs" (Gray 2009).

Not less than 700 different graphic representations of the Periodic Table of the Elements, with quite different configurations, have been published exposing the variety of interpretations of periodicity among elements (Mazurs 1974) (Figure 3).

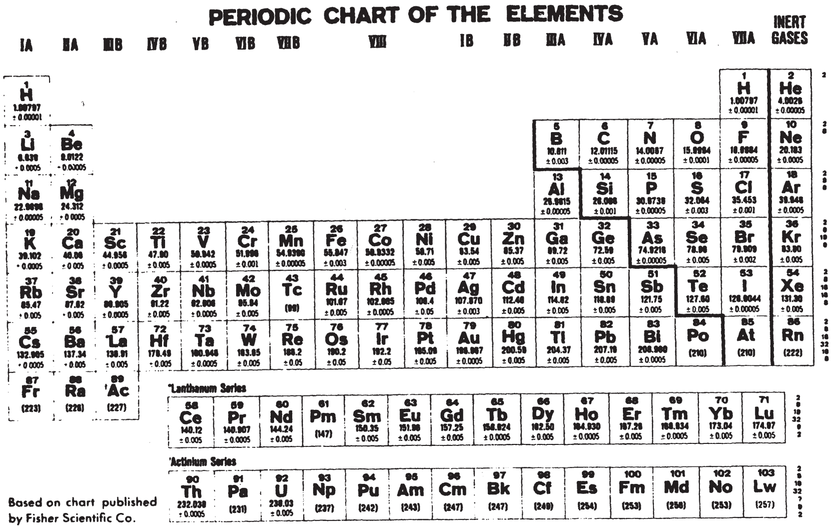
As Gray points out "Chemistry is too complicated for any rule to be absolutely hard and fast".

Biology is still more complicated and as such rules are expected to be even less rigid. But this does not exclude, as is the case of the chemical elements, that there is a fundamental underlying order that pervades biological phenomena.

2.5. The Periodicity of the Chemical Elements has Determined that of Minerals

That the periodicity of the chemical elements has determined the periodicity of the minerals is evidenced by the fact that: arsenic, antimony and bismuth are considered as both minerals and chemical elements (As) (Sb)

1



2

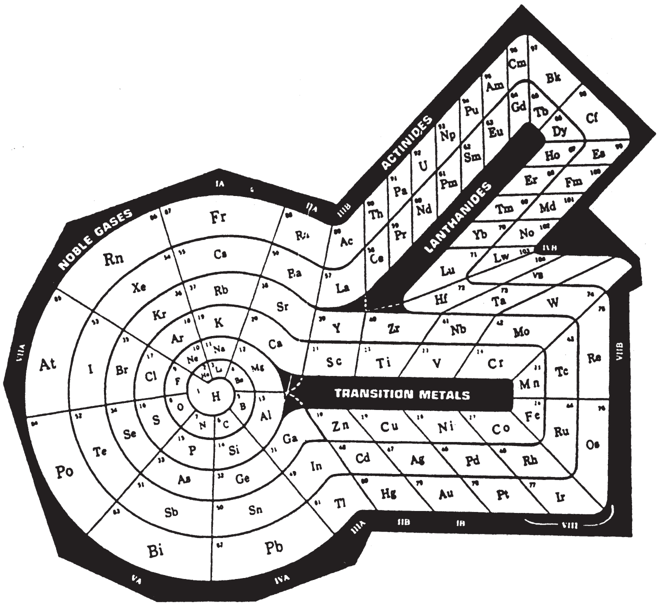


Figure 3: **(1)** The periodic chart is based on the original table of Mendeleev from 1869. Since then many other chemical elements have been added according to Mendeleev's prediction (in this chart 103). The vertical columns tend to have elements with the same properties. **(2)** In this spiral representation of periodicity, hydrogen occupies the origin of the spiral, because all other atoms are known to be derived from this chemical element. Within the spiral there is full regularity but the transition metals stick out of it building a separate block. Besides, the Actinides and Lanthanides cannot be easily compressed into any representation: be it the conventional chart where they build two separate rows or this one where they protrude distinctly from the spiral. Inert gases are also called noble gases.

(Bi). Another example is the group of elements consisting of gold, silver and copper (Au, Ag and Cu) that belong to the same group in the periodic table and which are at the same time minerals. Their common properties are known to be the result of the metallic bond of their atoms. As Jaffe (1988) remarks: "Electrons govern chemical behavior of atoms, and how they may be packed into minerals"

Significant, is that the chemical elements did not change their properties as they built the cell, a fact that we tend to overlook.

2.6. Periodicity Governing the Construction of DNA and Proteins

Ohno (1988) has described in detail the occurrence of periodicity among macromolecules. They represent an intermediate stage between chemical elements and living organisms.

Ohno states "It is a mistake to regard any coding sequence as unique implying the descent from random assemblages of four bases. Instead each coding sequence is comprised of primordial and derived repeating units." The DNA periodicity is evident in segments of the human X chromosome where a 419 long coding sequence consists of four widely separated segments (phosphoglycerate kinase coding sequence) (Ohno & Ohno 1986).

In the case of proteins, with transmembrane α-helices, the primordial repeating units of their coding sequences were base heptamers.

PART 3.

The Periodicity in Living Organisms is Displayed by their Fundamental Properties

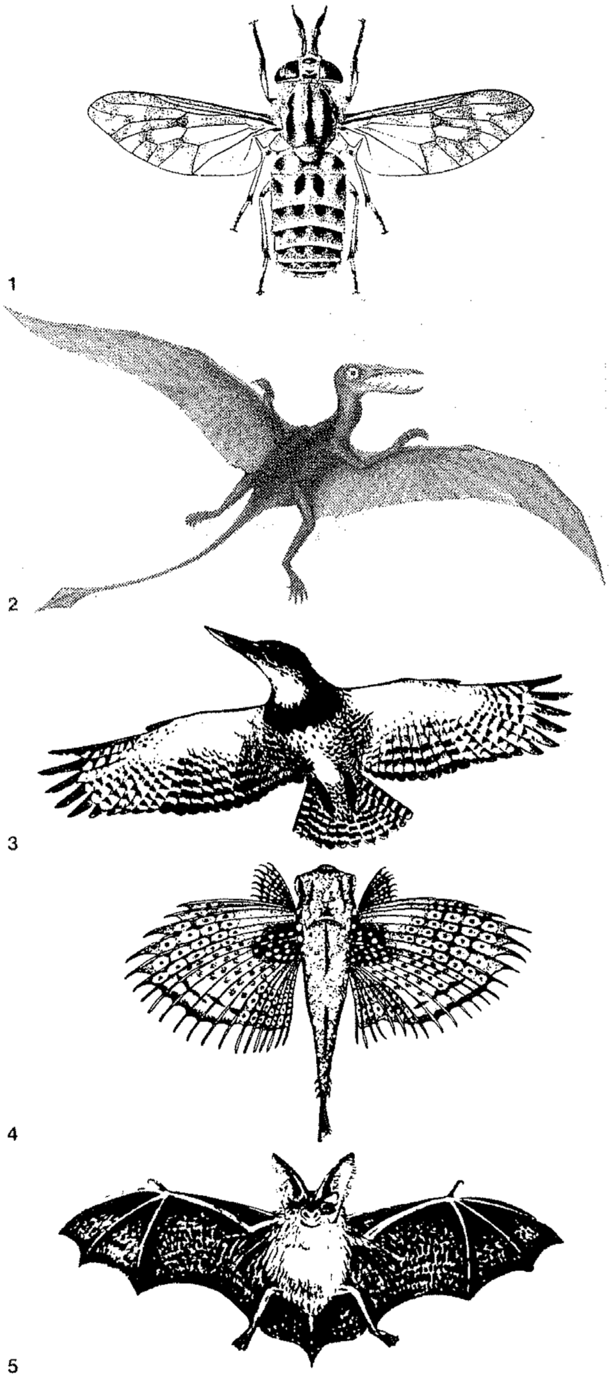
Periodicity in living organisms was established by Lima-de-Faria (1995), but the development of molecular biology, that occurred since then, allowed to treat this phenomenon more extensively and to establish it on a firm basis (Lima-de-Faria 2017). It led to the production of a *Periodic Table of Living Organisms* that covered 8 biological properties: vision, regeneration, luminescence, placenta, penis, flight, plant carnivory and mental ability.

All these properties were investigated at the molecular level, and the genes involved in them, as well as the RNA sequences that participated in their expression were included.

In this article the occurrence of biological periodicity will not be described in detail but only the main results are mentioned. The reader is referred to the above cited works for a comprehensive treatment of the subject.

3.1. Flight — Is a Punctuated Event which Arises from Species Without Wings

Flight is one of the periodic processes that is most easy to exemplify. It occurs in air in: insects, squids, fish, pterosaurs (fossil reptiles), birds and bats (Figure 4).



Increasing grade of complexity	ABSENCE OF FLIGHT IN AIR	FLIGHT IN AIR OR WATER	GLIDING: REGULAR AND OPTIONAL
1	INVERTEBRATES ALL PHYLA WINGLESS EXCEPT THE ARTHROPODA	INVERTEBRATES INSECTS FLYING Most species in air but some in water SQUIDS water and air	INVERTEBRATES INSECTS Some species Optional
2	INSECTS (ARTHROPODA) Some species wingless Silverfish Fleas	FISH Most species in water Flying rays	FISH Regular *Exocoetus* AMPHIBIANS Regular *Rhacophorus*
3	FISH Most species flightless in air AMPHIBIANS All species flightless in air	FISH Flying in water and air Bony fish	REPTILES Regular *Draco* BIRDS Some species Optional
4	EXTANT REPTILES All species flightless in air	FOSSIL REPTILES Flying in air Pterosaurs	MARSUPIALS Regular *Petaurus*
5	BIRDS which have wings but are flightless Kiwis Ostriches	BIRDS Most species in air	PLACENTALS DERMOPTERA Regular *Cynocephalus*
6	MAMMALS Many species flightless in air and water	MAMMALS BATS All species in air CETACEANS SEALS Most species in water	PLACENTALS RODENTIA Regular *Petaurista*

Table 1: PERIODIC TABLE OF FLIGHT AND GLIDING Flight in air and in water, both represent active movements, by the use of wings and fins, in different media. The periodicity is revealed by the sudden eruption of flight in the most unrelated groups of animals. The expression or repression of flight capacity is known to be decided by genes that control wing development. Gliding turns out to be also a periodic event re-emerging after periods of latency. It became of general occurrence in mammals, yet at the side of gliding species "there are extremely similar ones" that do not glide.

Figure 4 (*previous page*): Periodicity of flight. (1) Insect *Chrysops discalis*. (2) Extinct flying reptile *Rhamphorhymque*. (3) The bird giant kingfisher *Megaceryle maxima*. (4) Flying fish *Dactylopterus orientalis*. (5) A bat (flying mammal).

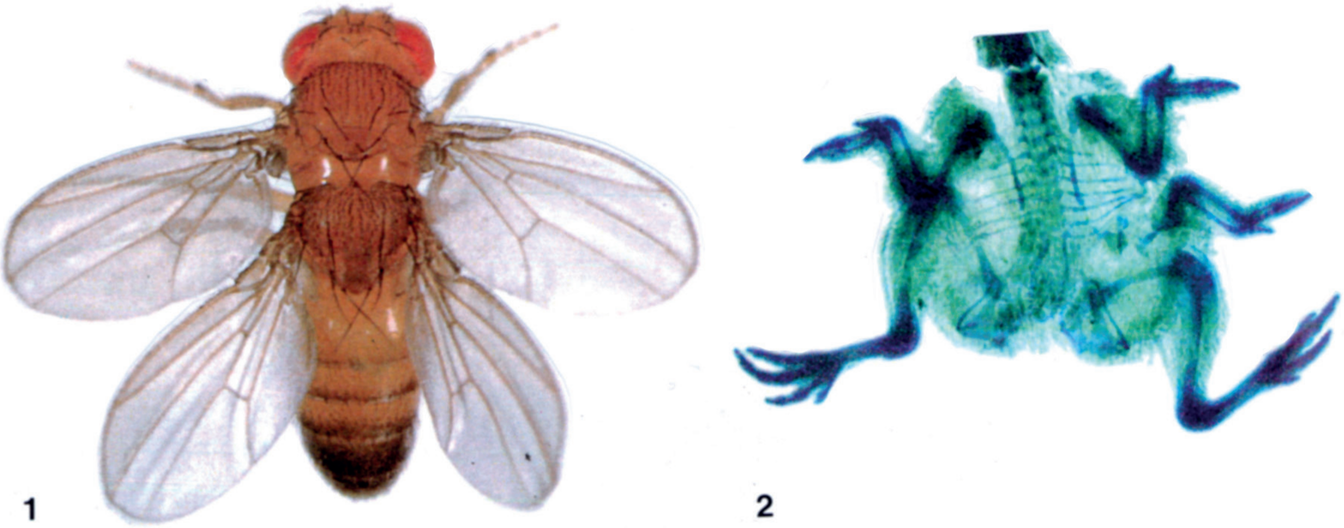


Figure 5: Production in the laboratory of flies with four wings (instead of two) and of birds with four wings (also instead of two) by genetic manipulation of DNA sequences. This was possible due to the gene similarity between invertebrates and vertebrates. (1) *Drosophila melanogaster* four-winged fruit fly produced by combining the gene mutations bithorax and post-bithorax. (2) *Gallus gallus*, chicken, genetic intervention leads to the production of a bird with four wings by modifying the location of a growth gene in the bird embryo.

It is a punctuated event, but moreover it occurs in animal species that are not related directly to the previous possessor of this property. Insects start flying without predecessors (the first insects had no wings). Moreover all other invertebrates which evolved for millions of years do not fly. Much later appeared flying reptiles that had no direct relation to insects. The birds evolved from non flying reptiles, and later the bats, had no direct relation to birds, but came from small terrestrial mammals. Some species of squids and fishes are able to move out of water and fly in air in a most advanced way. Flight is an evasion from gravity. It occurs in water, in the water-air interface, and in air. Not only marine mammals, but most fish, fly in water. Active flying is particularly evident in manta rays (a fish measuring up to 7 meters across) "swimming like a large bird on flapping wings" (Burnie 2004). Zoologists have not hesitated to call the swimming of these fish as "underwater flight" which is achieved by their large pectoral fins (Table 1).

The emergence of flight has been difficult to explain.

The hypotheses on the origin of bird flight do not apply to the origin of flight in insects and bats. Also authors agree that selection is impotent to furnish an explanation.

Instead the genetic evidence clarifies the situation. *Hox* genes are known to decide the formation of wings, as well as their suppression, and a fly with 4 wings (instead of 2) can be produced by genetic intervention without selection or successive random mutations. Also birds with four wings, instead of two, have been obtained in the laboratory (Affolter *et al.* 1990, McGinnis & Kuziora 1994, Cohn *et al.* 1997) (Figure 5). It also turns out that the same genes (*Hox*) determine the formation of insect and bird wings. Periodicity could hardly be conceived if the wings of insects and birds had different genetic origins.

What characterizes flight periodicity is the re-emergence of coherent flight capacity following long periods of latency. Gliding, which occurs from insects to mammals, is also a periodic event (Figure 6).

3.2. Placenta—Occurs in Humans but is Equally Well Developed in Flowering Plants

The placenta is a structure that interlocks the fetal and maternal tissue in animals, and in plants, is the place in the ovary where the ovules develop and are provided by nutrients (Figure 7). The placenta occurs in the most complex as well as the simplest living organisms be they animals or plants. It is found in mosses and ferns and reappears in flowering plants. It is independent of

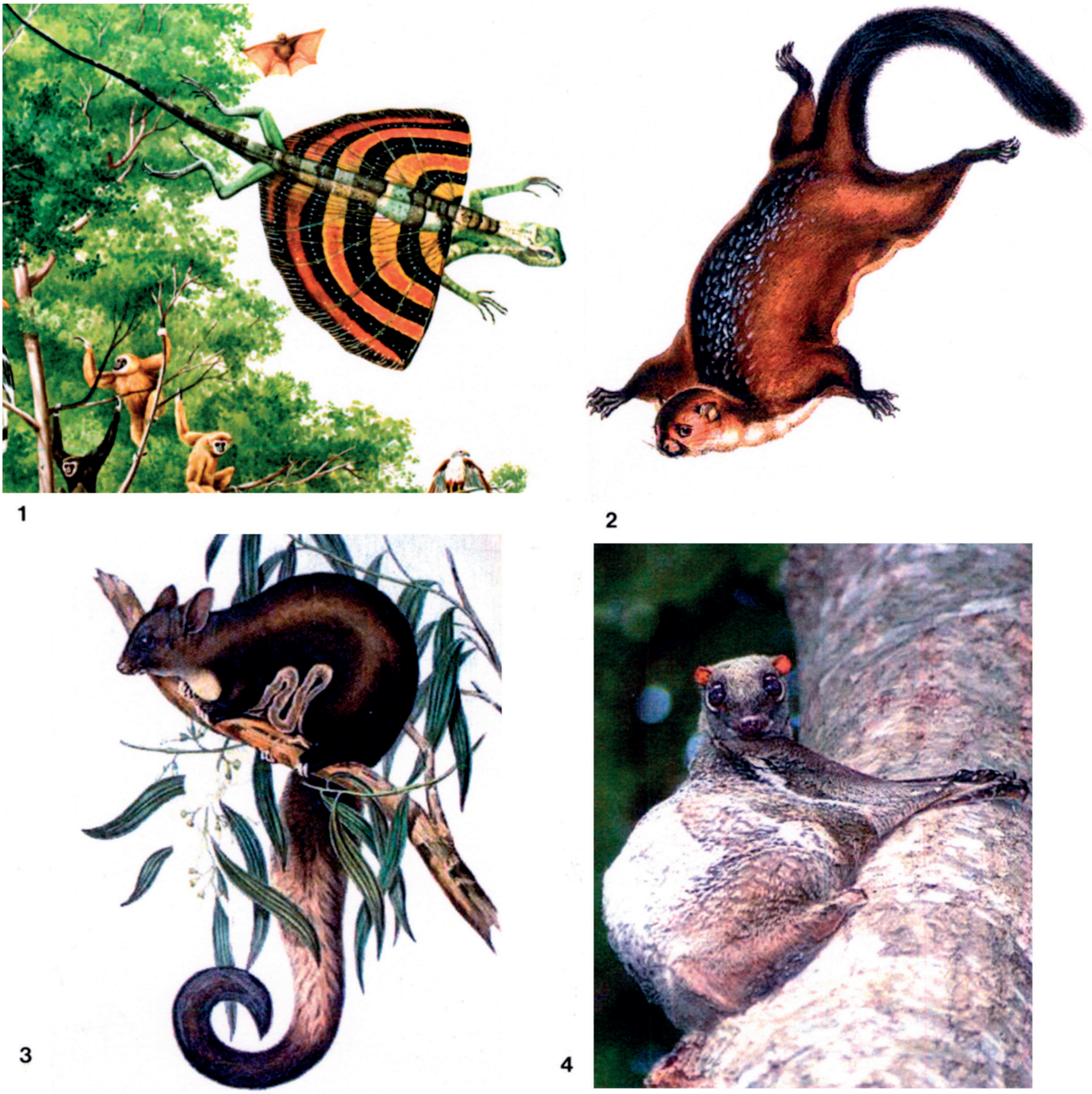


Figure 6: Gliding. (1) *Draco volans* (a reptile) glides by expanding its ribs that can be folded down. (2) Giant flying squirrel (placental mammal). (3) *Petaurus australis* (marsupial). (4) *Cynocephalus variegatus* (placental mammal).

organism complexity a feature that is evident in all properties that exhibit periodicity. It is well developed in the simplest animals (onychophorans and sponges) as well as in fish (sharks, rays and sea horses) (Table 2).

Not less than 94 human genes are highly expressed in the placenta. Remarkable is that the punctuated emergence of this organ is decided by common genes in plants and animals (Spielman *et al.* 2001). Its periodicity is evident in reptiles where it has evolved on more than 100 separate occasions (Flemming & Blackburn 2003) which is also a demonstration of its sudden emergence. This very high reappearance of the placenta is in agreement with the "hypermutation" found in vertebrates, including humans, where there is a sudden increase of the mutation rate at specific genes. An example is the immunoglobulin gene in which the mutation rate is 6 to 7 orders of magnitude greater than that of background mutations (Brown 1999).

3.3. Penis — Re-Emerges, without Previous Announcement, in Flatworms and Mammals

The penis would seem to be an organ characteristic of vertebrates, such as humans, but it occurs equally well formed already in worms (Figure 8).

It has an equally punctuated appearance neither related to the environment nor to nearly connected species.

Most birds have no penis. The genetic events leading to the elimination of the penis have been found to be dependent on the activity of the gene *Bmp4* which induces cell death in genitalia.

The penis is absent in whole groups of invertebrates (22 phyla) but it appears, without previous announcement, in marsupials and placental animals where it becomes well established (Table 3).

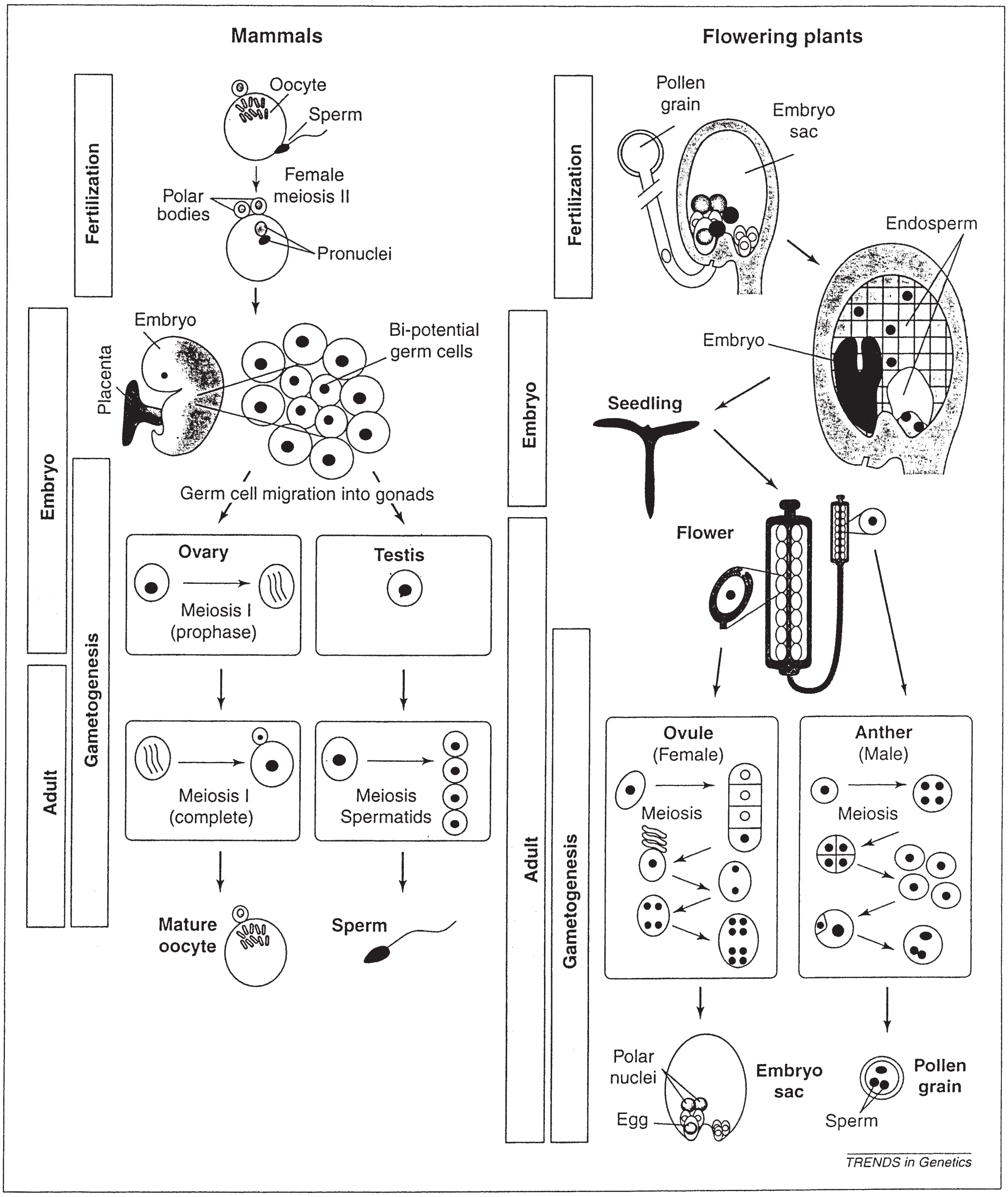


Figure 7: Comparison of the development of the placenta and other organs in mammals and flowering plants. The similarity is due to similar genes in the two unrelated groups. From Spielman et al. (2001) with permission.

Increasing grade of complexity	PRESENCE IN INVERTEBRATES	PRESENCE IN VERTEBRATES	PRESENCE AND ABSENCE IN PLANTS
1	ONYCHOPHORANS ENTOPROCTS BRYOZOANS	CARTILAGINOUS FISH SHARKS RAYS TELEOST FISH SEA HORSE	ALGAE Absent
2	SPONGES CNIDARIANS	AMPHIBIANS SURINAM TOAD BLACK SALAMANDER	MOSSES Present
3	RIBBONWORMS FLATWORMS ROUNDWORMS SEGMENTED WORMS	REPTILES AFRICAN SKINKS LIZARDS SNAKES	FERNS Present
4	SCORPIONS FRESH WATER CLAMS	MARSUPIALS BANDICOOTS	CYCADALES No indication
5	COCKROACHES WASPS FLIES	EARLY PLACENTAL MAMMALS LOWER PRIMATES	CONIFERS Present
6	ASCIDIANS SALPS Lower chordates	LATE PLACENTAL MAMMALS HUMANS	FLOWERING PLANTS Present

Table 2: PERIODIC TABLE OF THE PLACENTA. The placenta is such an important organ that it characterizes a whole animal group — the placental mammals. It interlocks foetal and maternal tissues in the uterus of animals. Surprisingly it appears equally well advanced in plants, where it is "the ovule part of the carpel and a sporangium bearing area". The periodicity is revealed by its emergence in many invertebrate species, and in vertebrates, such as the sharks, where it attained a development that rivals that of mammals. Besides, in reptiles, it emerged on more than 100 separate occasions whereas in sharks it reappeared 11 times.

3.4. Vision — is Decided by the Same Gene from the Simplest to the Most Complex Animals

Three properties are of special importance because they do not start at the organism level but appear before DNA and the cell emerged in evolution. Vision, regeneration and luminescence are already evident in crystals and minerals.

The ability to direct light to specific sites is present in crystals. The phenomenon is called double refraction. The light is divided into two polarized rays as seen in the minerals calcite and tourmaline (Wenk & Bulakh

Increasing grade of complexity	ABSENCE IN INVERTEBRATES	PRESENCE IN INVERTEBRATES	ABSENCE IN VERTEBRATES	PRESENCE IN VERTEBRATES	PRESENCE OF DOUBLE OR BILOBED PENIS
1	CNIDARIA CTENOPHORA MESOZOA NEMERTINA	FLATWORMS FLUKES	BONY FISH *Most species*	FISH SHARKS RAYS Modified fin	CRUSTACEANS Double
2	ROTIFERA KINORHYNCHA ENTOPROCTA NEMATODA	GNATHOSTOMULIDA *Problognathia*	AMPHIBIANS FROGS	AMPHIBIANS CAECILIANS Penis-like organ	MOLLUSCS Double
3	NEMATOMORPHA ECTOPROCTA PHORONIDA BRACHIOPODA	GASTROTRICHA *Dactylopodola*	AMPHIBIANS TOADS	REPTILES LIZARDS SNAKES	INSECTS Double
4	PRIAPULIDA SIPUNCULA ECHIURA ANNELIDA	ACANTHOCEPHALA Spiny-headed worms	REPTILES TURTLES	BIRDS OSTRICHES DUCKS	REPTILES LIZARDS SNAKES Double
5	PENTASTOMA ONYCHOPHORA POGNOPHORA	MOLLUSCS *Buccinum* CRUSTACEANS *Balanus*	REPTILES CROCODILIANS	MARSUPIALS Most species	MARSUPIALS Bilobed
6	ECHINODERMATA CHAETOGNATHA HEMICHORDATA	INSECTS Many species with additional structures	BIRDS Most species	PLACENTALS Most species	PLACENTALS Single

Table 3: PERIODIC TABLE OF THE PENIS. The penis is absent in a large number of invertebrate phyla as well as in most groups of vertebrates. It emerges suddenly in totally unrelated groups of simple as well as complex organisms. It establishes itself as a permanent organ in mammals. A double penis also occurs in a punctuated way among crustaceans, molluscs, insects and reptiles.

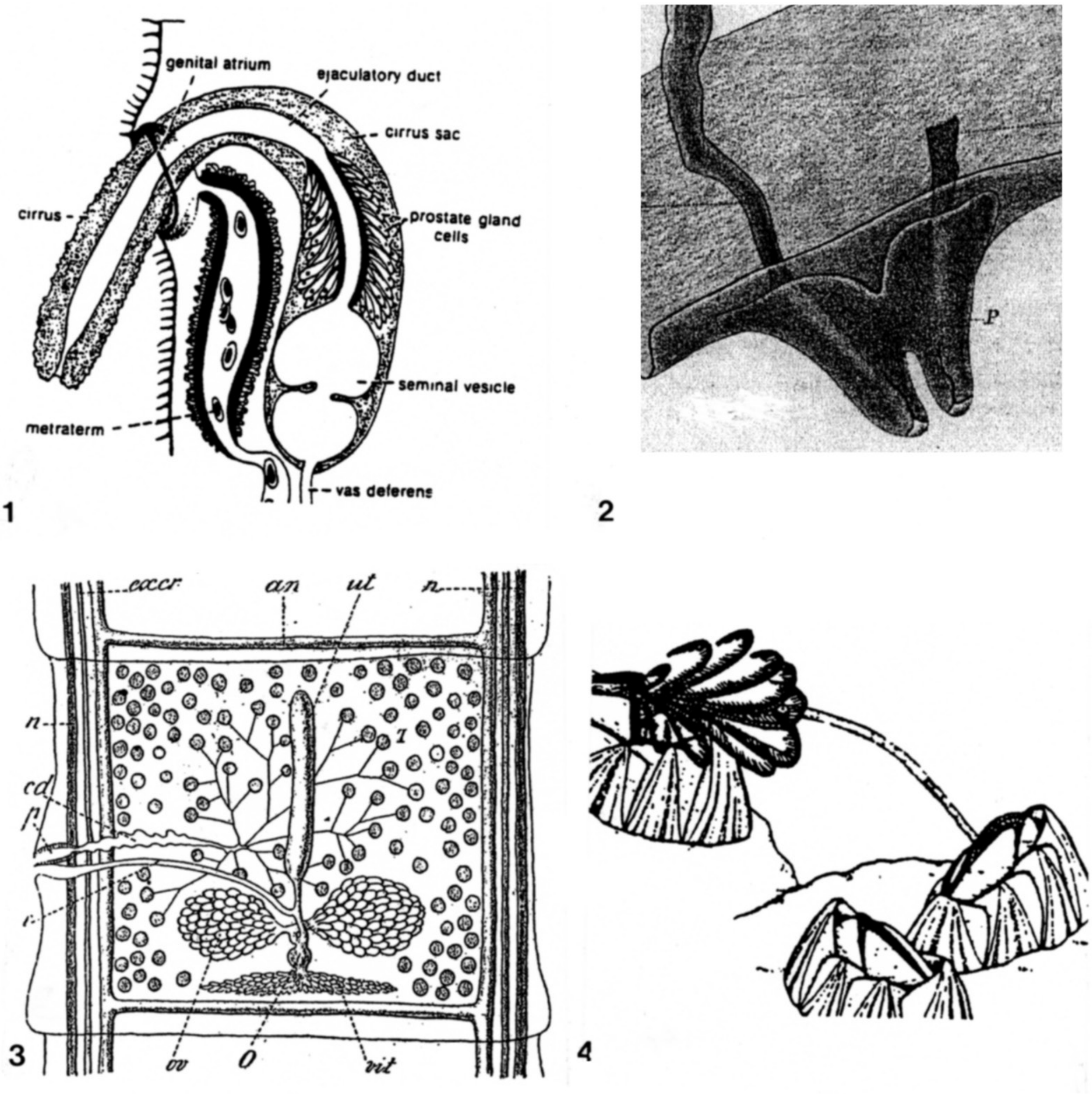


Figure 8: Penis in worms and crustaceans. (1) Flatworm, *Fasciola hepatica*, the penis has a seminal vesicle, a prostate gland and an ejaculatory duct. (2) Crustacean, *Cymathoa aestroides*, penis and part of ventral wall. (3) Flatworm, *Taenia saginata*, body segment showing ovaries (ov) and penis (p). (4) Crustacean, copulating Barnacles. The long penis of the individual on the left is inserted on the individual on the right (based on a photograph by R. Sisson).

2004). The cornea and the lens of the animal eye are the two structures that bend light rays to focus images on the retina. It turns out that in the eye of living brittle stars (echinoderms) the lens is made of calcite (Björn 2015), and in the mollusc chiton the eye lens is made of the mineral aragonite. This means that vision is anchored in the mineral world (Figure 8).

Typical of periodicity is that the complexity of the eye is not related to organism complexity. Bacterial cells act as spherical lenses and their vision is considered similar to that of the human eye (Schuergers *et al.* 2016). Moreover in molluscs eye organization becomes close to that of the human eye (Table 4).

Repression and expression of the same genes appear as the source of eye absence and reappearance. Larvae and adults of Annelid worms have the same genes yet larvae have eyes whereas adults lack them.

Ubiquitous genes and identical regulatory molecular cascades have shaped the eye throughout its evolution. Gehring and collaborators (2014) have shown that most animals "share the same master control gene, Pax6, and the same retinal and pigment cell determination genes". The loss of *Pax6* gene function, led to animals without eyes, in both mammals and insects, revealing again the identity of the genetic pathways which are at the basis of the periodicity (Figure 10).

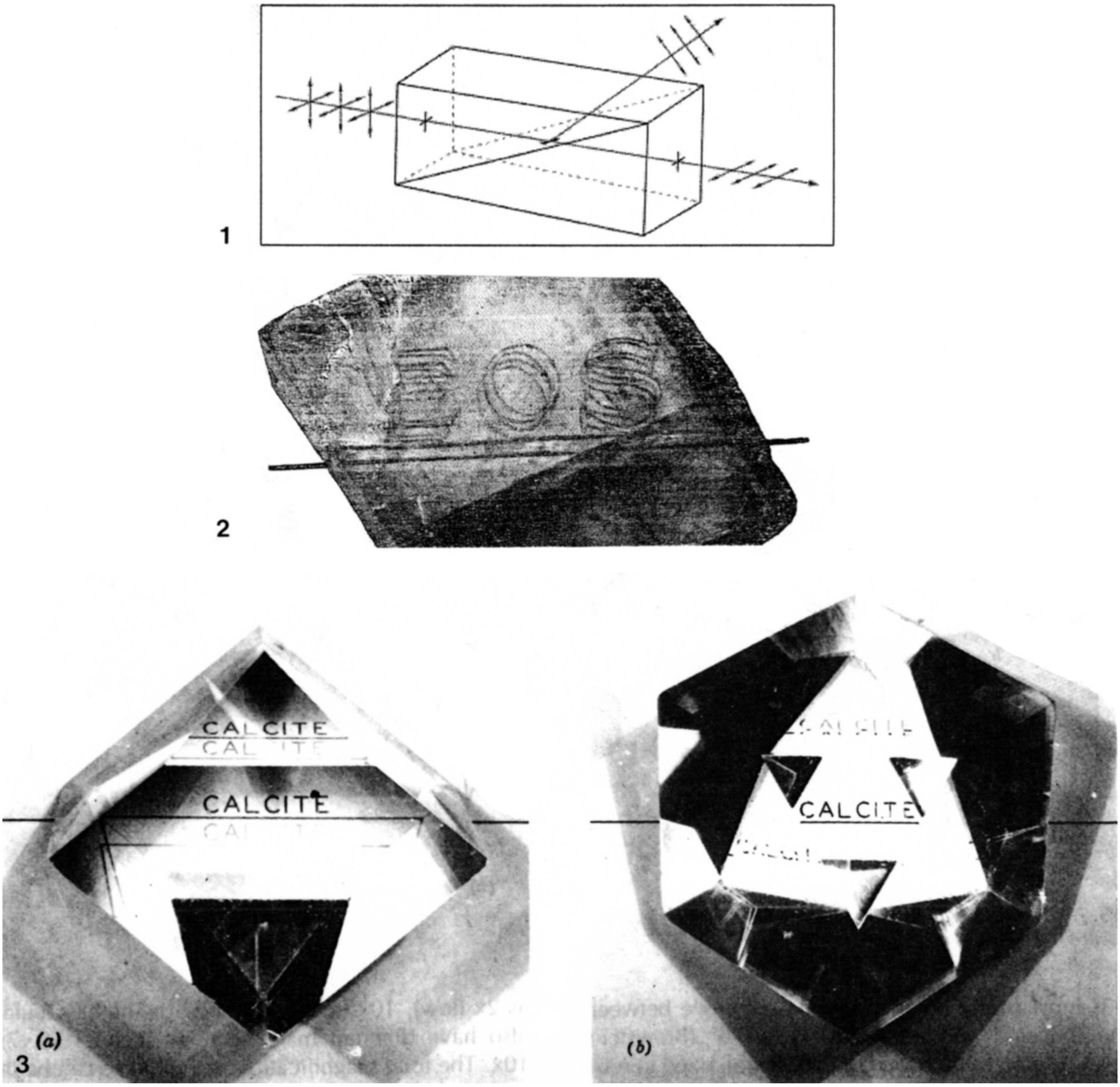


Figure 9: Mineral crystals deviated light before eye lenses did it. (1) Double refraction in calcite showing the splitting of the light into an ordinary and an extraordinary ray. (2) Transparent crystal of calcite in which one sees clearly the double refraction of the letters *EOS*. (3a) Calcite, viewed normal to the rhombohedron face. (3b) Calcite showing no double refraction, viewed parallel to the c axis.

Increasing grade of complexity	ABSENCE OF EYES	RUDIMENTARY EYES	COMPLEX EYES
1	MINERALS EUBACTERIA PROTOZOA Most species CNIDARIANS *Hydra*	CYANOBACTERIA PLANT CELLS PROTOZOA *Euglena* CNIDARIANS *Aurelia*	CNIDARIANS *Tripedalia* ANNELIDS *Vanadis*
2	PLACOZOA PORIFERA EUMETAZOA MESOZOA GASTROTRICHA ACANTHOCEPHALA	RHYNCHOCOELA ROTIFERA KINORHYNCHA NEMATODA	CRUSTACEANS *Homarus* Most species INSECTS Most species
3	GNATHOSTOMULIDA POGONOPHORA ECHIURA PRIAPULIDA PENTASTOMIDA	SIPUNCULA TARDIGRADA	MOLLUSCS SQUIDS CUTTLEFISH OCTOPODS
4	PHORONIDA BRYOZOA ENTOPROCTA BRACHIOPODA	FLATWORMS *Planaria* ANNELIDS MARINE WORMS	FISHES AMPHIBIANS
5	MYRIAPODS Many species ANNELIDS EARTHWORMS Most species	CRUSTACEANS Some species MYRIAPODS Some species SPIDERS	REPTILES BIRDS
6	FLATWORMS CESTODA Some species ECHINODERMS Sea urchins	MOLLUSCS *Patella* ASCIDIANS	MARSUPIALS PLACENTALS

Table 4: PERIODIC TABLE OF VISION. Thousands of species in invertebrates have existed, for millions of years and survived efficiently, without eyes. At the same time the eye attained a high degree of complexity even in the simplest invertebrates. There is an increase in eye complexity that tends to follow the organism's phylogenetic position. After being a punctuated event in invertebrates, the eye became a permanent feature of vertebrates. Periodicity is elucidated by the finding that the *Pax6* gene is present in all species that have eyes and even in those that lack eyes. This indicates that gene expression and repression are responsible for its periodic emergence.

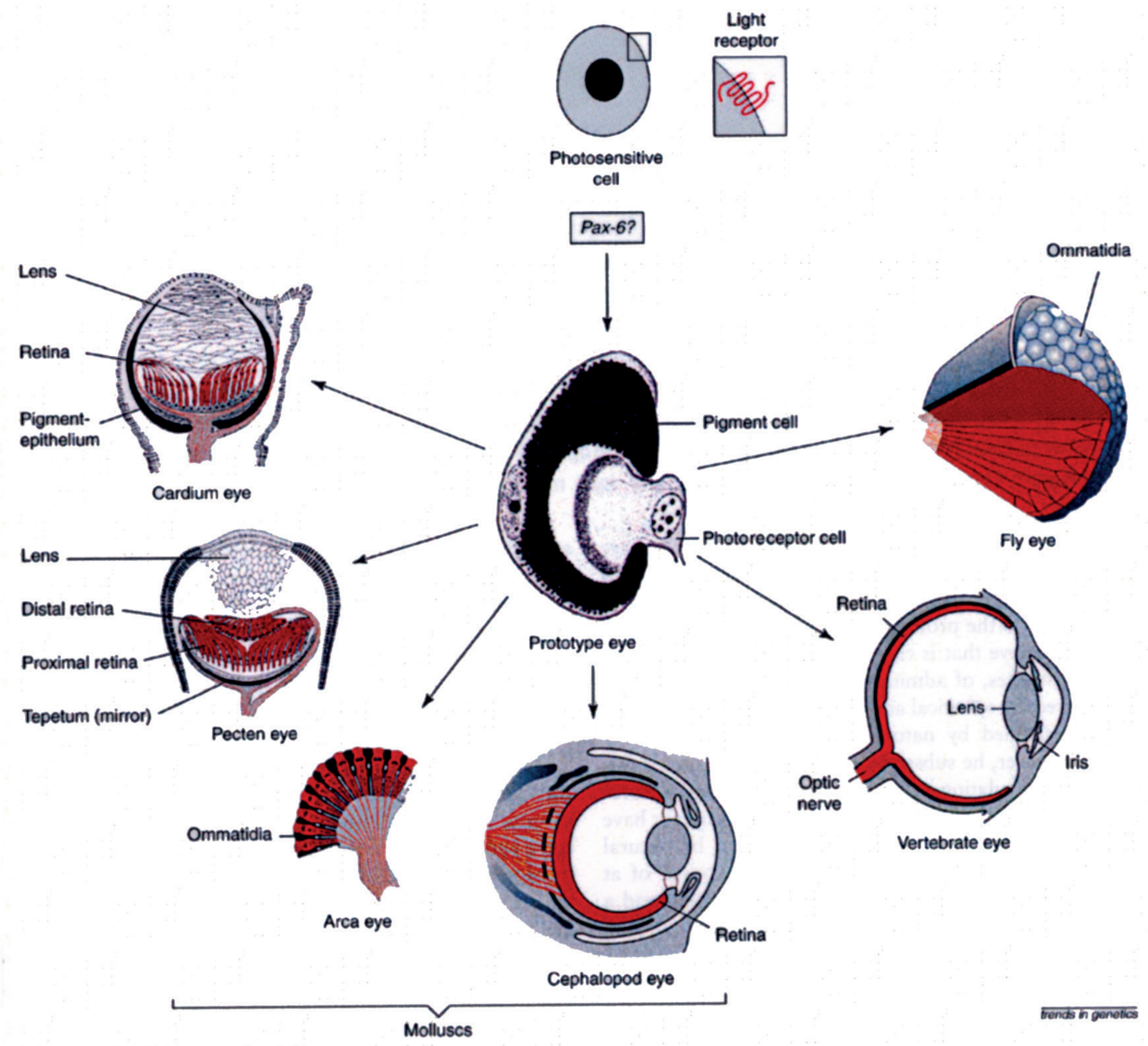


Figure 10: General scheme of eye evolution. Evolution of various eye-types from a common ancestral prototype. Under the control of the Pax6 gene the photosensitive cell assembles with a pigment cell to form an organ, the prototype eye. This generates the various eye-types from the eye of simple molluscs (Cardium, *Pecten*) to insect eyes, the complex eye of Cephalops (advanced *molluscs*) and the vertebrate eye (including humans).

3.5. Regeneration — Starts in Crystals, Expands in Plants, but Slows Down in Vertebrates

Regeneration is characterized by the ability to produce, without external intervention, the original pattern. It is actually based on atomic and cellular order.

Regeneration started in crystals before biological evolution arrived. It occurs in ammonium bimalate and ammonium oleate crystals as well as in minerals. If they get broken regeneration ensues the addition of identical atoms which lead to the restoration of the identical pattern (Bonner 1952).

Research on atomic configuration, taking place during crystal formation, shows that disorder is transformed into order depending on temperature. In the mineral feldspar low temperatures lead to an ordered assembly of novel atoms (Wenk & Bulakh 2004).

In living organisms the appropriate genes are called to action, and the cells only develop a preprogrammed cellular order that does not deviate from the original configuration of the organism. This program is actually a memory which remembers the whole organization — without it no identical pattern could be recreated.

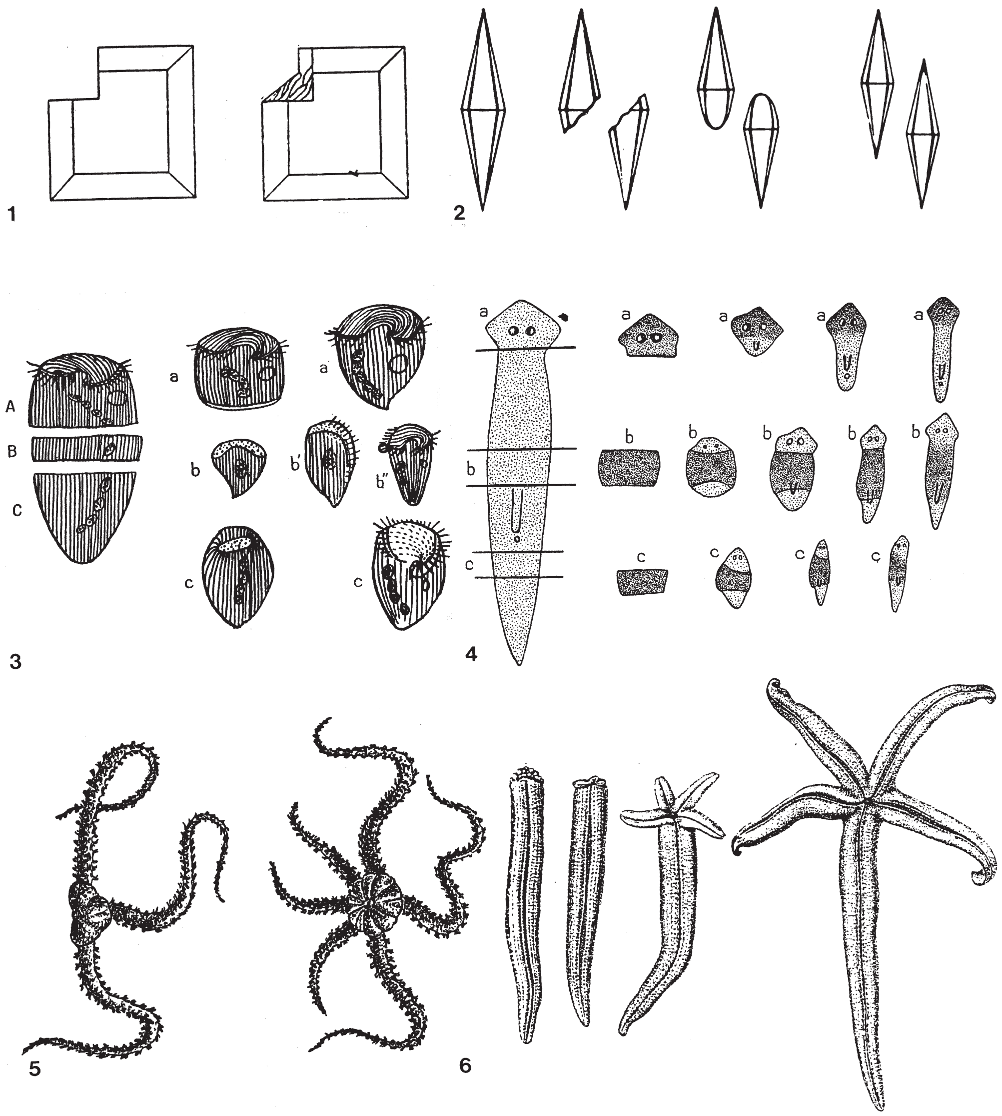


Figure 11: Regeneration in crystals, protozoa and invertebrates. (1) Crystals of ammonium bimalate. Crystal with its end broken (left) and under regeneration which leads to the restoration of the original pattern (right). (2) Liquid crystals of ammonium oleate. Following breakage the crystals regenerate building the original pattern. (3) Protozoa, *Stentor*, stages of regeneration from three separate fragments. (4) Flatworms, *Planaria*, regeneration of complete individuals from three separate fragments. (5) Echinoderm, an ophiuroid after being divided into two parts (left). Shortly after, one half regenerates building the original pattern (right). (6) Echinoderm, starfish, *Linckia*, three successive stages of the regeneration of the whole body from the end of a single arm.

Protozoa and algae rebuild their body from isolated fragments by releasing chemicals that determine the pattern. Hydras have body memory and the ability to sense structure size. These properties extend also to higher organisms (Figure 11).

The genes participating in regeneration have been identified in flatworms (Turbellaria). The *Wnt 3* genes induce a wave of proliferation in neighboring cells. As many as 694 genes decide ordered regrowth of organs in brittle stars when they regenerate the whole body from a single arm (Purushothaman *et al.* 2015).

As one reaches the vertebrates, fish rebuilt the: tail fin, kidney, heart and brain, when a battery of genes is activated.

The ability to reestablish the body pattern diminishes in vertebrates, becoming reduced to the mammalian heart, pancreas and other organs. Birds show an absence of regeneration, except for their feathers, that are replaced continuously. On the contrary mosses and ferns know their body plan and in flowering plants a single somatic cell can give rise to a whole plant (Haberlandt 1902) (Table 5).

Increasing grade of complexity	**ABSENCE OF MEMORY**	**CRYSTAL AND CELL MEMORY**	**ORGAN MEMORY**	**WHOLE BODY MEMORY**
1	CTENOPHORES MESOZOANS GNATHOSTOMULIDS GASTROTRICHS	CRYSTALS MOSSES *Sphagnum* FERNS *Pteris* CONIFERS *Pinus*	RIBBON WORMS ECHIURANS Proboscis PRIAPULIDS Appendages ANNELIDS Lost parts INSECTS Antennae	PROTOZOA *Stentor* PLACOZOA *Trycholax* ALGAE *Acetabularia*
2	ROTIFERS KINORHYNCHS ACANTHOCEPHALANS ENTOPROCTS	FISH Scales	CRUSTACEANS Limbs FISH Tail Teeth Brain Heart	SPONGES Ameboid cells
3	NEMATODES NEMATOMORPHA ECTOPROCTS PHORONIDS	AMPHIBIANS Skin	AMPHIBIANS Limbs	CNIDARIANS *Hydra*
4	BRACHIOPODS MOLLUSCS SIPUNCULANS TARDIGRADES	REPTILES Scales	REPTILES Tail	FLATWORMS *Planaria*
5	PENTASTOMA ONYCHOPHORANS POGONOPHORANS CHAETOGNATHS	BIRDS Feathers	BIRDS No indication of regeneration capacity	ECHINODERMS Starfish and others
6	BIRDS Absence of memory (except feathers)	MAMMALS Skin Hair Fibroblasts	MAMMALS Teeth Antlers Heart	FLOWERING PLANTS Many species

Table 5: PERIODIC TABLE OF REGENERATION. Biological memory is the capacity to copy preexisting patterns. Regeneration is a form of memory which started in the crystal world and expanded into cells, organs and whole bodies. The periodicity is shown by the absence of regeneration in many invertebrate phyla which is accompanied by a high ability of whole body memory in other species. This occurred in simple invertebrates and flowering plants. As organism complexity increased organ memory tended to decrease.

3.6. Luminescence — Is Found in Many Minerals and Has Become a Main Property in Bacteria, Insects and Fish, but Was Precluded in Later Evolution

Bioluminescence has been described as a "random and spasmodic phenomenon" and selection has also been evoked and denied. Luminescence occurs from minerals to fish, but like regeneration is a limited process. It is both an electronic event, resulting from changes in atomic energy states, and at the same time a genetic process.

Luminescence was widespread in minerals before it arose in living organisms. It was found even earlier in chemical elements, which are considered to be color activators in minerals, such as Europium and Uranium. No less than 21 minerals are luminescent and the colors emitted by living organisms are the same that are emitted by minerals (Figure 12).

All luminous bacteria have a common DNA sequence, they share the *lux operon*, that encodes for the biosynthesis of luciferase and its substrates (Dunlap *et al.* 2007) (Figure 13).

There are luminous and non-luminous algae and a large number of invertebrates were not allowed to develop luminosity. However, in some families of insects luminescence attained extreme intensity. Among the molluscs, the Cephalopods, are covered by hundreds of luminescent organs that glow in the ocean water. The number of photophores is as high as 687. Fishes, look also like Christmas trees with their long lines of luminous organs that "Are extraordinarily elaborate", but marine mammals are not luminous, yet they live at

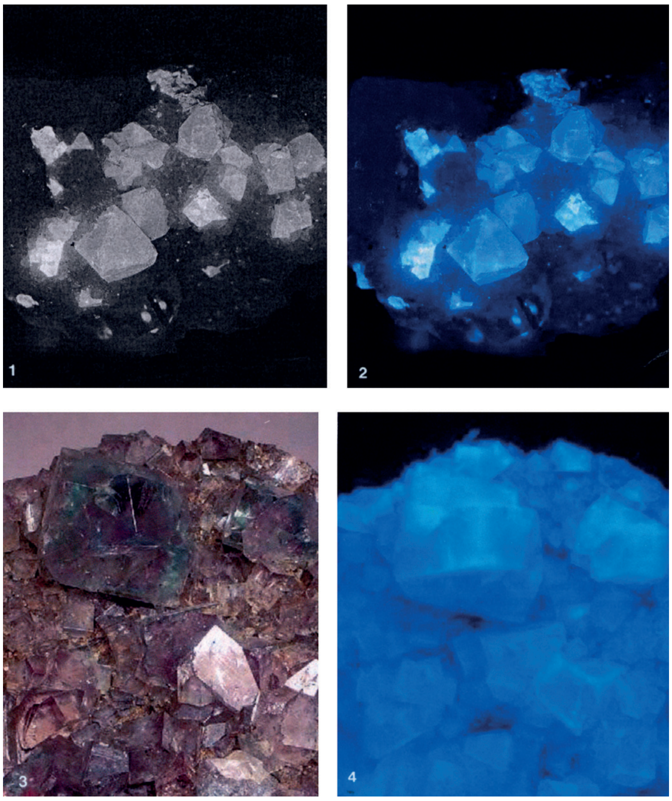


Figure 12: Luminescence in minerals. (1) Crystals of scheelite ($CaWO_4$) seen under daylight. (2) Luminescence in crystals of scheelite submitted to ultraviolet radiation. (3) Crystals of fluorite (CaF_2) seen under daylight. The large cubes have a blue-green color dispersion (natural fluorescence). (4) Luminescence in crystals of fluorite submitted to ultraviolet radiation.

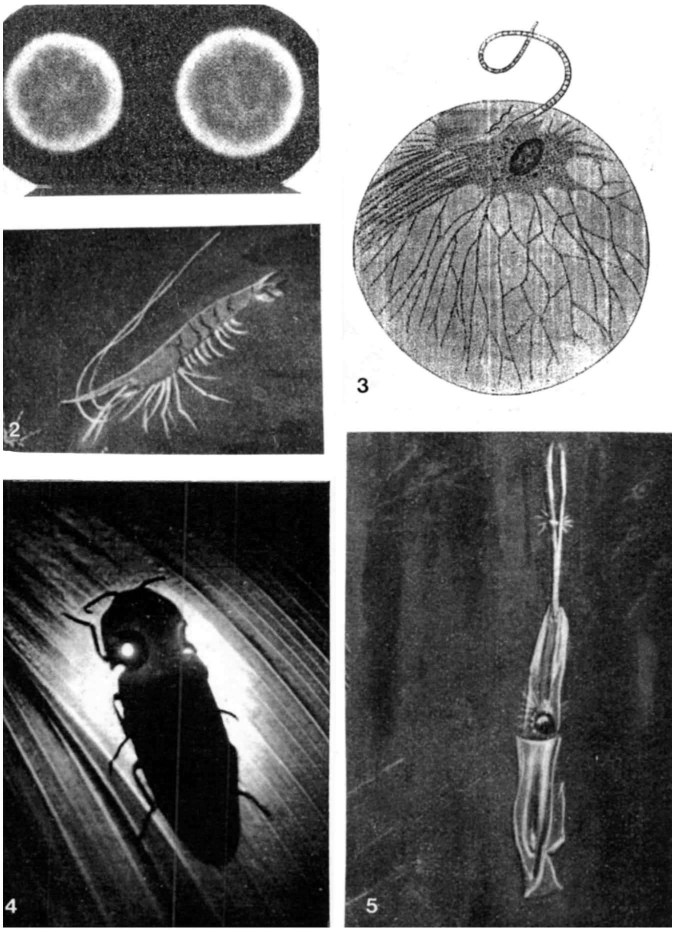


Figure 13: Bioluminescence. (1) Photobacteria, two colonies of *Photobacterium* photographed in obscurity. (2) Shrimp, a luminous crustacean species. (3) Noctiluca, adult stage of *Noctiluca* sp. (4) Insect, the strong light emitted by Pyrophorus. (5) Squid, mollusc, a luminous species.

Increasing grade of complexity	ABSENCE OF LUMINESCENCE	PRESENCE OF LUMINESCENCE	ORGANIZATION OF PHOTOEMITTERS
1	MINERALS Most non-luminous	MINERALS Over 20 are luminescent	CRYSTALS Fluorite Calcite
2	CYANOBACTERIA ALGAE Most non-luminous	EUBACTERIA *Photobacterium* *Vibrio* DINOFLAGELLATES Luminous	PHOTOCYTES Bacteria Hydrozoa Ctenophores
3	FUNGI (MYXOMYCOTA) Not luminous	FUNGI *Mycena* Luminous	LIGHT SECRETION Bivalvia Annelids Crustaceans
4	INVERTEBRATES Of 31 phyla 20 have no luminous species	INVERTEBRATES POLYCHAETA STARFISH JELLYFISH Weak luminosity	PHOTOPHORES Molluscs Insects Polychaeta
5	FLOWERING PLANTS Non-luminous FISH Most non-luminous AMPHIBIA Non-luminous	INVERTEBRATES MOLLUSCS INSECTS Extreme luminosity	GLANDS Cephalopods Fishes
6	REPTILES Non-luminous BIRDS Non-luminous MAMMALS Non-luminous	FISH Near-shore and abyssal Highly luminous	ELABORATE REFLECTORS LENSES SHUTTERS AND MIRRORS Molluscs Fishes

Table 6: PERIODIC TABLE OF LUMINESCENCE. Luminescence appeared with light intensity in simple organisms such as bacteria, insects and molluscs. It became maximal in fishes but was totally precluded in later evolution. Luminescence occurs in minerals, before the arrival of DNA and the cell, showing that this phenomenon is due to atomic and electronic processes. High light intensity emerges irrespective of the animal's phylogenetic location and it arose independently at least 40 times.

depths exceeding those of luminous fish. Non-luminous molluscs occur also at depths from 200 to 7,000 meters and the bats, which regularly live in darkness, did not become luminous.

The luciferase gene produces the sole enzyme responsible for luminescence. The complete DNA sequencing of luciferase genes demonstrates that they have been highly conserved (Choi *et al.* 2003). Following genetic manipulation flowering plants and rabbits have become luminous

The periodicity of luminescence is evidenced by the fact that "Bioluminescence is estimated to have evolved independently at least 40 times" (Hastings 2011) and all authors agree that luminescence has had independent origins throughout its evolution (Table 6).

3.7. Carnivory in Plants — Their Trapping Organs Contain: Doors, that Open and Close, Sensorial Hairs that Recognize Prey and Digestive Glands, but Have no Nervous System

Plants have no brains and no nervous system, yet they perform activities comparable to the brain functions of animals as shown by the analysis of their carnivorous behavior.

Carnivory in plants is not a "Paradoxical Event" but is due to the expression of specific genes and chemical modifications of DNA.

Mammals have not inhabited the planet for a long time, the animals of the order carnivores arose 10 million years ago (Wilson & Mittermeier 2009–2019). Equally, the carnivorous plants are not old. Flowering plants had their major radiation 125 million years ago, but all extant carnivorous plants are found in recently derived groups. McPherson (2010) states that carnivory is a "relatively young evolutionary invention" among flowering plants.

Its periodicity is evident. The 20 extant genera of carnivorous plants have turned out not to be closely related. Carnivory evolved at least on ten separate occasions and may have evolved independently 12 times (Williams *et al.* 1994, McPherson 2010).

The fusion of leaves is a primary event in the building of traps. This is determined by a battery of genes that have been isolated, cloned and sequenced (Glover 2007, Eilenberg *et al.* 2006).

Movements of tendrils, which are also part of carnivory, are decided by touch-inducible genes. Carnivory is also an epigenetic phenomenon; within the same individual plant, the leaf morphology changes during development resulting in the production, side by side, of non-carnivorous and carnivorous leaves.

DNA evolution has not allowed flowers to become carnivorous, which is a phenomenon limited to leaves. These have been successively modified resulting in highly advanced trapping organs such as: spiral branches, funnels, pitchers and bladders.

The origin of periodicity in carnivorous plants is elucidated by the finding that the basic structures and functions participating in carnivory, existed separately in multiple plant families, without having anything to do with flesh digestion. It is only when they were suddenly combined coherently that carnivory emerged (Table 7).

Traps take various forms from rosettes to trumpet-like tubes covered with hoods and in some species are closed by lids and in others by doors that open and close.

Hairs and bristles have sensorial functions. The trapping mechanism is so specialized that it can distinguish between living prey, and pebbles or sticks, that touch the leaf.

The inner part of the trap is covered by more than 6,000/cm^2 microscopic glands in Nepenthes. The glands not only secrete the digestive fluid but also absorb the products of the digestion (Figure 14).

The digestive enzymes in plants are the same that participate in animal digestion and also have the same active sites — another example of plant — animal similarity.

Carnivorous plants may use traps without or with active movements. In *Dionaea* the trap closes within 0.5 seconds, in *Aldrovanda* within 0.01 seconds and in *Utricularia* the door opens within 30 milliseconds following prey detection. This is a speed of reaction comparable to that found in the nervous system of higher mammals.

3.8. High Mental Ability — is Evident from Ants to Humans Reappearing Suddenly

The concepts of instinct, intelligence and selection were terms that belong to the 1800s when research on animal behavior and evolution were based mainly on an ignorance of genetics, biochemistry and biophysics. These were scientific disciplines that did not yet exist.

Increasing grade of complexity	LEAF TRANS-FORMATIONS	GLAND SECRETION	SENSITIVE HAIRS	DIGESTIVE ENZYMES	DIRECTED MOVEMENTS
1	*Drosophyllum* *Pinguicula* *Drosera* Leaves slightly curved	*Dionaea* *Genlisia* Microscopic and small glands	*Drosophyllum* *Drosera* No hairs	*Darlingtonia* No enzymes	*Drosophyllum* *Heliamphora* *Sarracenia* No movements
2	*Heliamphora* *Sarracenia* *Darlingtonia* *Cephalotus* Leaves forming tube with a lid	*Cephalotus* *Nepenthes* Nectar and digestive sessile glands	*Nepenthes* *Cephalotus* Hairs outside pitcher	*Utricularia* Some proteases plus phosphatases	*Darlingtonia* *Nepenthes* *Cephalotous* *Genlisia* No movements
3	*Nepenthes* Leaves forming two types of pitchers	*Pinguicula* *Drosophyllum* Mucous and sessile digestive glands	*Polypompholyx* *Utricularia* Hairs at entrance of bladder	*Aldrovanda* Proteases	*Pinguicula* Leaf rolls over prey *Drosera* Tentacles move
4	*Aldrovanda* *Dionaea* Leaves bilobed building trap	*Drosera* Mucous tentacles and digestive glands	*Dionaea* *Aldrovanda* Spines and trigger hairs	*Drosera* *Drosophyllum* *Dionaea* Proteases plus phosphatases	*Polypompholyx* Trap door opens and closes
5	*Genlisia* Leaves as spiralled branches	*Polypompholyx* Two-armed and four-armed glands	*Darlingtonia* *Sarracenia* Downward pointing hairs	*Sarracenia* Proteases nucleases and phosphatases	*Dionaea* Trap closes within 0.5 seconds *Aldrovanda* Trap closes within 0.01 seconds
6	*Polypompholyx* *Utricularia* Leaves building traps as a bladder	*Utricularia* Three types of large glands	*Genlisia* Complex system of hairs forming valves	*Pinguicula* *Nepenthes* Proteases lipases chitinases and others	*Utricularia* Trap door closes in 30 milliseconds

Table 7: PERIODIC TABLE OF PLANT CARNIVORY. Carnivory occurs solely in flowering plants. These arrived late in evolution and most species have about the same degree of organization. The periodicity is evidenced, among other features, by the same trait re-emerging in unrelated families. Besides each trait starts with a simple structure or function that becomes successively more complex in species with similar body complexity (since all are flowering plants). This property is divided into 5 main traits that result in the ability that plants have to trap and digest animal prey. Most traits start with simple structures and successively the complexity increases leading to extreme refinements, which due to their efficiency and speed, are comparable to the nervous system of animals. These traits are decided by specific genes. Carnivory re-emerges at least 10 times.

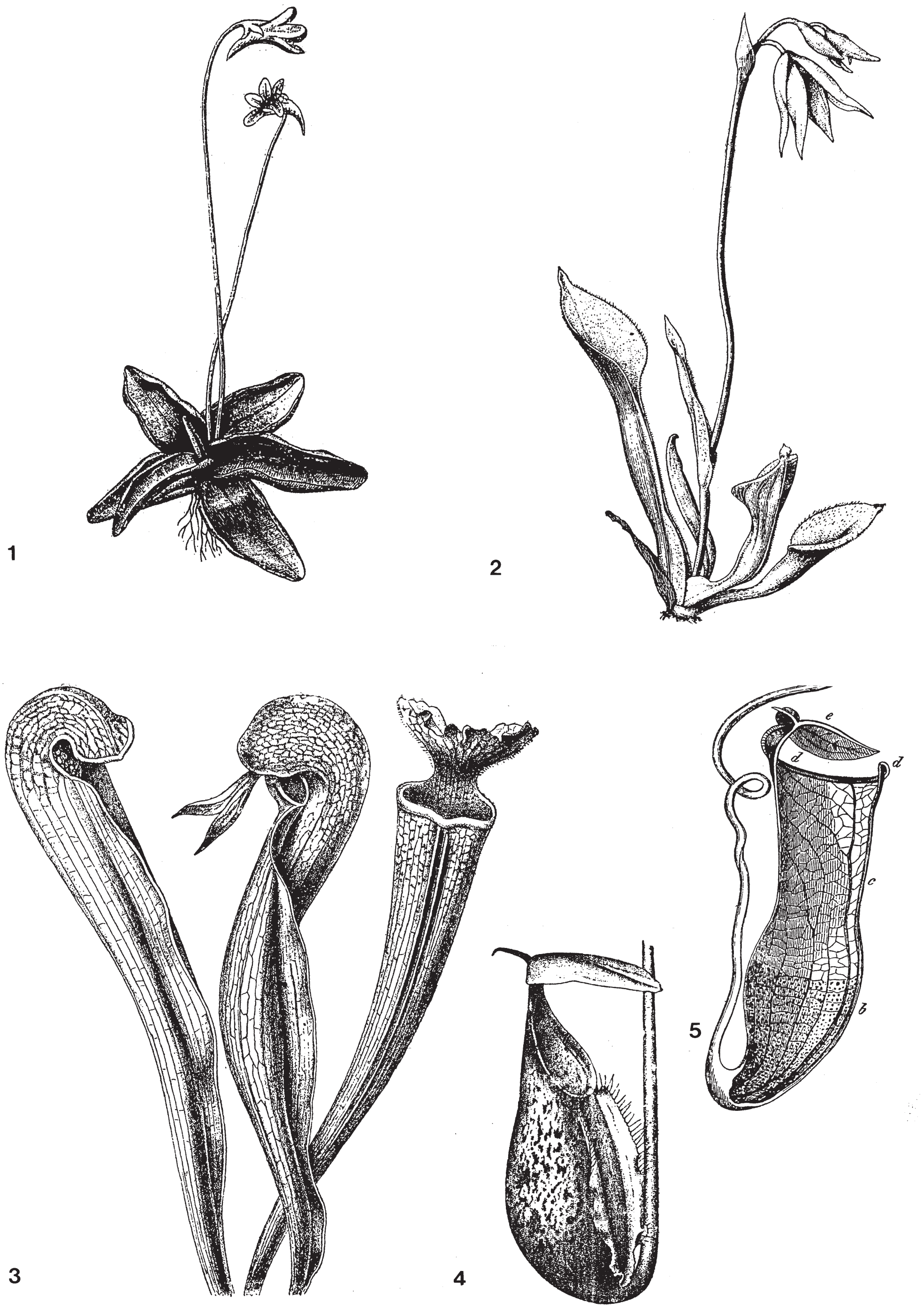


Figure 14: Plant carnivory. Evolution from simple to complex leaves. (1) *Pinguicula vulgaris*, flowering plant with a rosette of leaves slightly curved at the borders. (2) *Heliamphora nutans* with leaves building an amphora. (3) Leaves of *Sarracenia variolaris* (left), *Darlingtonia californica* (middle) and *Sarracenia liciniata* (right) building an open tube curved at the end. (4) *Nepenthes Dominii*, modified leaf as a pitcher with large lock. (5) *Nepenthes laevis*, transformed leaf (partly sectioned) showing numerous glands (as black specks) in the lower part (b) and accompanied by a spiralized tendril and a lid (e) at the top.

At present these concepts are being superseded. Instinct and intelligence were coupled to the assumption of human biological supremacy that now is shown to be less pre-eminent. Selection has turned out to be of little significance as molecular processes explain the pathways.

Periodicity at the mental level seems unexpected but mental processes are equally directed by the evolution of DNA sequences. The brain develops under the control of well defined Hox genes which decide the formation of part of the brain in vertebrates.

High mental ability has resurged without previous announcement. The formation of societies occurs in bees, ants, termites and humans. In insects it is accompanied by agriculture (raising of fungi in termites), animal husbandry (use of sugary products of other insects in ants), language (with dialects in bees), weaving (of leaves in ants) and other activities

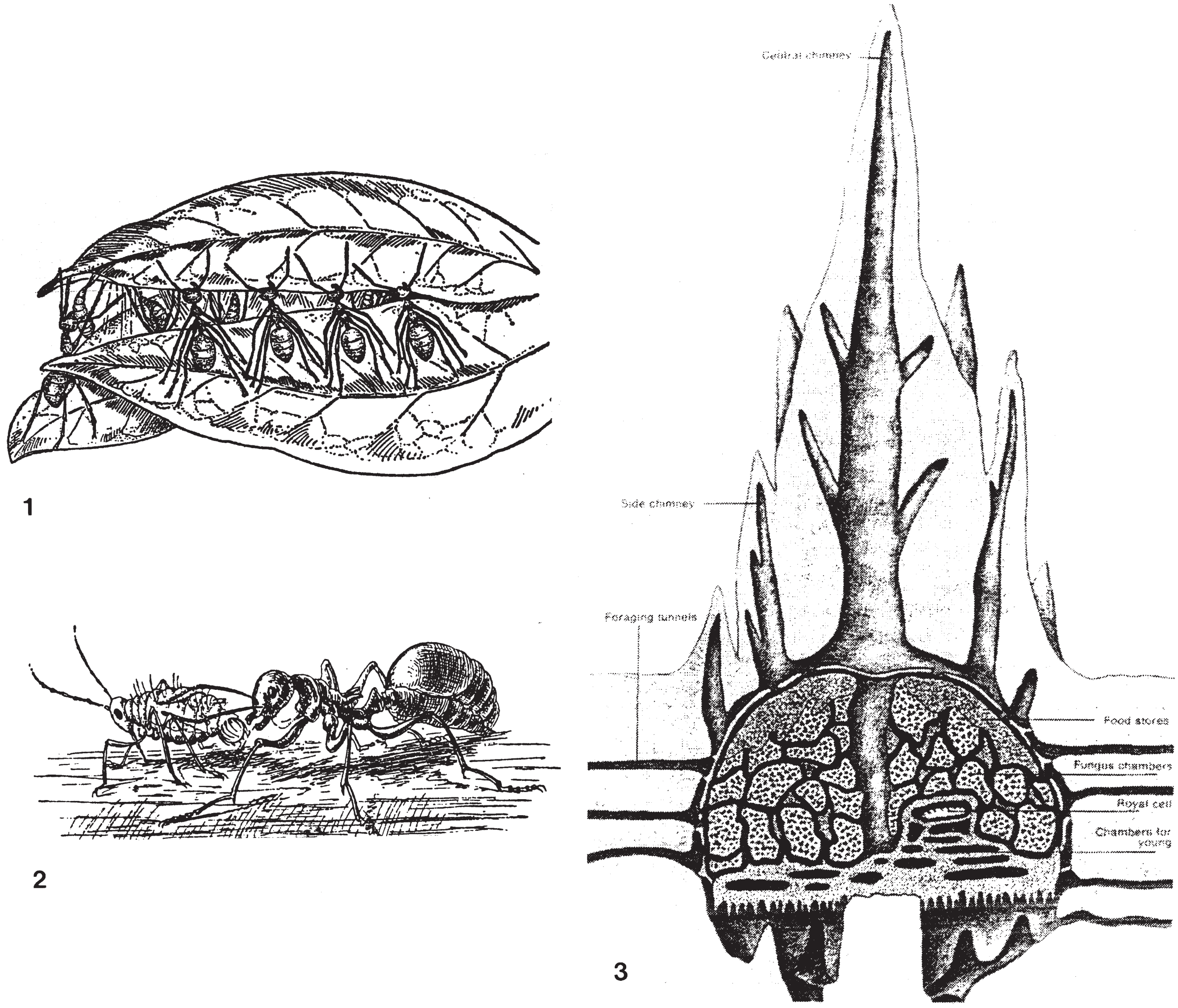


Figure 15: Mental ability in insects. (1) African weaver ant *Oecophylla longinoda*. Ant weavers use their feet and mandibles to combine the borders of leaves. Simultaneously, other ants carry larvae, which have in their mouth a liquid, that seals the leaves together. (2) Ant farming. *Formica* sp. Ants use aphids (insects), which excrete a sugary substance, as a source of nutrition. They even move them to appropriate sites where the aphids can better feed on the sap of plants. (3) Nest architecture in termites, *Hodotermes meriodinalis*. The central chimney keeps the temperature constant. Different compartments function as: foraging tunnels, food stores, the royal cell, and chambers for the young termites. There are also chambers where fungi are cultivated as a source of food.

previously considered to be limited to humans. Octopuses display the highest mental ability, among invertebrates, which is linked to the recruitment of novel genes (Figure 15).

The periodicity of mental ability is based on the following evidence (Table 8).

Insects are distributed into 29 orders. In only two of them: Hymenoptera (ants, bees and wasps) and Isoptera (termites) did social behavior lead to the formation of highly complex and dynamic societies. Hence, 27 orders did not acquire this behavior although they had millions of years of evolution at their disposal. Biologists were led to the conclusion that in insects: "social organization has evolved independently eleven times in the Hymenoptera, but only once in the Isoptera" (McFarland 1981).

Insects, birds and primates came to different solutions depending on the species. This diverse mental ability is dependent on genes. The gene *Fox P2* is responsible for singing in both birds and hu-

Increasing grade of complexity	PROBLEM SOLVING	NEST BUILDING	MIGRATION	TOOL MAKING
1	INSECTS ANTS Farming ARACHNIDS SPIDERS Web-repair MOLLUSCS OCTOPUSES 29 shapes	INSECTS AFRICAN ANT *Dorylus* INSECTS TERMITES *Macrotermes*	INSECTS MONARCH BUTTERFLIES LOCUSTS North-South CRUSTACEANS SPINY LOBSTERS Winter and summer residences	INSECTS WEAVER ANTS Leaves sealed ARACHNIDS SPIDERS Webs as traps MOLLUSCS OCTOPUSES Shelters
2	FISH ARCHERFISH Captures insects by projecting water	FISH SEA HORSES Nest building by male	FISH SALMONS EELS Migration from sea to fresh water	FISH No detailed information
3	AMPHIBIANS Maze learning	AMPHIBIANS Nest building by leaf folding	AMPHIBIANS FROGS TOADS Short distance (1 mile) between feeding and breeding sites	AMPHIBIANS No detailed information
4	REPTILES Parental care Counting-like skills	REPTILES PYTHON *Antaresia* Nest building	REPTILES MARINE TURTLES Long distance migration	REPTILES MONITOR LIZARDS Use forelimbs to extract prey
5	BIRDS HERONS Compensation for refraction	BIRDS MOST SPECIES WEAVERS BOWER BIRDS Complex nests with decorations	BIRDS MOST SPECIES From North to South and back	BIRDS RAVENS Insertion of twigs in crevasses
6	MAMMALS CHIMPANZEES Choose different squares	MAMMALS DORMICE CHIMPANZEES Build nests to overnight	MAMMALS ZEBRAS From forests to plains WHALES Between tropical and polar waters	MAMMALS CHIMPANZEES Putting sticks together

Table 8: PERIODIC TABLE OF MENTAL ABILITY. Problem solving, nest building, migration and tool making, attain remarkable development in simple invertebrates as well as in complex mammals. The genes involved in some of these processes are known: singing in birds and humans (*FoxP2* gene) and web building in spiders (proteins *MiSp*, Flag and *MaSp2*). Only two of the 29 orders of insects formed high complex and dynamic societies. Social organization evolved independently 11 times in one of these orders but only once in the other. Another feature of periodicity is that closely related species do not exhibit the same specific trait.

mans, and the silk of the spirals built by spiders, is the product of genes that have been isolated. Spirals are also drawn by humans and drugs lead in both cases to the drawing of irregular geometric figures. Moreover, the same brain chemicals are present in spiders and humans.

There is among animals a common form of abstract thinking: bees, birds and chimpanzees can count (Dacke & Srinivasan 2008).

The similarity between plants, invertebrates and vertebrates (including humans) is becoming more comprehensive as molecular biology expands.

Increasing grade
of complexity →

MARSUPIAL SERIES

POUCHED MOLE *Notoryctes*	MULGARA MOUSE *Darcycercus*	PHASCOG-ALE *Phascogale*	OPOSSUM *Caluromysiops*	ANTEATER NUMBAT *Myrmecobius*	GREATER GLIDER *Petauroides*	SUGAR GLIDER *Petaurus*	WATER OPOSSUM *Chironectes*	POUCHED HYENA *Borhyaena* Fossil	TASMANIAN WOLF *Thylacinus*	MARSUPIAL LION *Thylacoleo* Fossil	SABRE-TOOTH TIGER *Thylacosmylus* Fossil

PLACENTAL SERIES

MOLE *Talpa*	MOUSE *Mus*	SHREW *Sorex*	TARSIER *Tarsius*	ANTEATER *Tamandua*	SQUIRREL *Anomalurus*	COLUGO *Cynocephalus*	OTTER *Lutra*	SPOTTED HYENA *Crocuta*	WOLF *Canis*	LION *Panthera*	SABRE-TOOTH TIGER *Smilodon* Fossil

Table 9: PERIODIC TABLE OF EQUIVALENCE BETWEEN MARSUPIALS AND PLACENTALS. The similarity between these two series of animal species has been repeatedly described as an "intriguing case of convergence" and as a "curiosity". Their similarities were considered the product of random events and these animals, arising on distant continents, could hardly have the same genes. Again, molecular evidence revealed another scenario. There has been an extreme permanence. The protein coding genes of the monotremes (the early ancestors of these two groups) were compared with those of marsupials and placentals. The number of these genes in the monotreme platypus is 18,527, in humans 18,600 (placental) and 20,800 for opossum (marsupial). Besides 82% of the monotreme genes have homologues in these other species (Warren et al. 2008). The animals that emerged are members of the most different families: moles, mice, anteaters, gliders, wolves, lions and sabre-tooth tigers. There are impressive similarities species by species, this is why they have been called, by different authors, as "carbon copies".

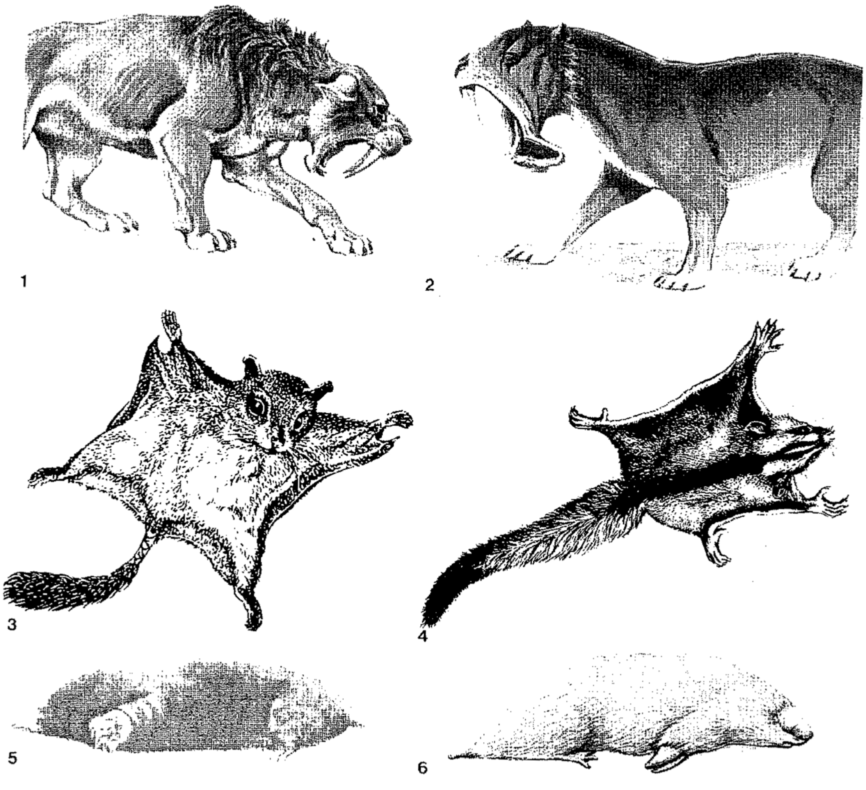


Figure 16: Some of the species that are "carbon copies" of one another in placental and marsupial mammals. (1) The sabretooth tiger *Smilodon* (placental) and (2) the sabretooth tiger *Thylacosmylus* (marsupial). Both are fossils. (3) Gliding squirrel *Anomalurus peli* (placental) and (4) the greater glider *Petauroides volans* (marsupial). (5) The common mole *Talpa europaea* (placental) and (6) the pouched mole *Notoryctes typhlops* (marsupial).

3.9. The Placental Mammals are "Carbon Copies" of the Marsupials

It has been repeatedly pointed out, by many authors, that the two groups are very much alike. However, this finding has not been examined in terms of periodicity. It was considered of marginal significance since it could not be explained by selection.

The first marsupials (that carry their young in pouches) arose 75 million years ago. The placentals (that retain the young inside the mother's body) appeared later 50 million years ago (Macdonald 1984). The "carbon copy" versions that emerged include species, genera, families and orders. Equivalents are found for members of carnivora, primates, rodentia, dermoptera, insectivora, edentata, perissodactyla and artiodactyla (Table 9). For instance, the fossil sabretooth tiger *Smilodon* (a placental) had a most similar species in the marsupial fossil *Thylacosmylus*. The European otter (placental) and the water opossum (marsupial) have the same body features and behavior. The same is the case of the common mole and the pouched mole (Figure 16). The genes in these two groups were also found to be most similar (Warren *et al.* 2008).

Periodicity is stressed by the finding that gliding species were produced, again and again, in marsupials and placentals.

3.10. Biological Periodicity is Characterized by the Following Features

The following text is a description of the main characteristics of biological periodicity and the enunciation of the Law of Periodicity. After four years, since they were written, it does not seem necessary to add or subtract any material to the statements made, which supports their validity (Lima-de-Faria 2017):

1. Biological periodicity is an event anchored in the mineral world where only simple atomic interactions decide the properties. These do not start at the biological level, as previously assumed, but existed before DNA and the cell arrived in evolution. Regeneration is evident in crystals of ammonium oleate, luminescence is pronounced in the minerals fluorite and scheelite as well as in 19 others. Also in vision the ability to deviate light rays (present in lens proteins) was already exhibited by calcite crystals with their double refraction.

2. The main feature of biological periodicity is its punctuated emergence. It seems to arise from nowhere coming and going without previous announcement. The organisms that exhibit flight, vision, plant carnivory, or any other of the described properties, do not show a relationship to their immediate predecessors. The pterosaurs were not directly related to the flying insects that preceded them, and carnivorous plants appear in plant families that are not closely related.

3. Periodicity emerges with few intermediate forms or abruptly in most cases. High mental ability is present in the building of elaborated societies by ants whereas many other insect species are solitary.

4. It is independent of organism complexity. Vision is present in bacteria in a way that it already resembles that of humans. The placenta emerges independently in plants, invertebrates and mammals.

5. It appears in a well defined organ or on a restricted species group. Plant carnivory is confined only to leaves and only to flowering plants. Luminescence became localized to specific organs and could not extend beyond the fishes.

6. The types of structures and functions that are an obligatory component of a given property (e.g. flight, mental ability, placenta formation) are essentially the same in all the different taxonomic groups that exhibit it. Flight in bats, birds and insects uses a wing whereas a quite different structural solution could have been created (such as jet propulsion in squids).

7. Periodicity occurs at regular intervals but of variable length. This is to be expected since we are dealing with living organisms which are more complex than simple atoms. High mental ability has re-emerged after millions of years but in plant carnivory the interval may have extended to only thousands of years.

8. It is independent of the organism's taxonomic location. The penis is as developed in invertebrates as it is in higher mammals.

9. It is also independent of the environment. Gliding has arisen in animal species living in the tropics as well as in Nordic climates. The marsupials that evolved in Australia (in a different en-

CHARTS OF CHEMICAL AND

PERIODIC TABLE OF CHEMICAL ELEMENTS

Increasing grade of complexity	ALKALI METALS	ALKALINE EARTHS	NONMETALS				HALOGENS	NOBLE GASES
								HELIUM 2 4.0
1	LITHIUM 3 6.9	BERYLLIUM 4 9.0	BORON 5 10.8	CARBON 6 12.0	NITROGEN 7 14.0	OXYGEN 8 15.9	FLUORINE 9 18.9	NEON 10 20.1
2	SODIUM 11 22.9	MAGNESIUM 12 24,3	ALUMINUM 13 26.9	SILICON 14 28.0	PHOSPHORUS 15 30.9	SULFUR 16 32.0	CHLORINE 17 35.4	ARGON 18 39.9
3	POTASSIUM 19 39.1	CALCIUM 20 40.0	GALLIUM 31 69.7	GERMANIUM 32 72.5	ARSENIC 33 74.9	SELENIUM 34 78.9	BROMINE 35 79.9	KRYPTON 36 83.8
4	RUBIDIUM 37 85.4	STRONTIUM 38 87.6	INDIUM 49 114.8	TIN 50 118.6	ANTIMONY 51 121.7	TELLURIUM 52 127.6	IODINE 53 126.9	XENON 54 131.3
5	CESIUM 55 132.9	BARIUM 56 137.3	THALLIUM 81 204.3	LEAD 82 207.1	BISMUTH 83 208.2	POLONIUM 84 (210)	ASTATINE 85 210	RADON 86 (222)
6	FRANCIUM 87 (223)	RADIUM 88 226.0	113	114	115	116	117	118

Increasing grade of complexity →

LANTHANIDE SERIES

LANTHANUM	CERIUM	PRAESEODYMIUM	NEODYMIUM	PROMETHIUM	SAMARIUM	EUROPIUM	GADOLINIUM	TERBIUM	DYSPROSIUM	HOLMIUM	ERBIUM	THULIUM	YTTERBIUM
57	58	59	60	61	62	63	64	65	66	67	68	69	70
138.9	140.1	140.9	144.2	(145)	150.4	151.9	157.2	158.9	162.5	164.9	167.2	168.9	173.0

ACTINIDE SERIES

ACTINIUM	THORIUM	PROTACTINIUM	URANIUM	NEPTUNIUM	PLUTONIUM	AMERICIUM	CURIUM	BERKELIUM	CALIFORNIUM	EINSTEINIUM	FERMIUM	MENDELEVIUM	NOBELIUM
89	90	91	92	93	94	95	96	97	98	99	100	101	102
(227)	232.0	231.0	238.0	237.0	(244)	(243)	(247)	(247)	(251)	(254)	(257)	(256)	(254)

Lima-de-Faria, A. 2017. Periodic Tables Unifying Living Organisms at the Molecular Level. The Predictive Power of the Law of Periodicity. World Scientific.

BIOLOGICAL PERIODICITY

PERIODIC TABLE OF LIVING ORGANISMS

Increasing grade of complexity	LUMINESCENCE	VISION	REGENERATION (WHOLE BODY)	PLACENTA	PENIS (SINGLE)	FLIGHT (IN AIR)	PLANT CARNIVORY (TRAP)	MENTAL ABILITY
1	MINERALS EUBACTERIA	MINERAL REFRACTION CYANOBACTERIA	CRYSTALS PROTOZOA	ONYCHOPHORANS BRYOZOANS	FLUKES	INSECTS	*Drosophyllum* Leaves slightly curved at top	ANTS TERMITES BEES
2	DINOFLAGELLATES	PLANT CELLS CNIDARIANS	ALGAE SPONGES	SPONGES WORMS FLIES	GNATHOSTOMULIDS GASTROTRICHA	SQUIDS	*Sarracenia* Tube with a lid	SPIDERS OCTOPUSES
3	FUNGI	CRUSTACEANS MOLLUSCS INSECTS	CNIDARIANS	ASCIDIANS FERNS	MOLLUSCS INSECTS	FISH	*Nepenthes* Pitchers of two types	ARCHERFISH
4	STARFISH JELLYFISH	FISHES AMPHIBIANS	FLATWORMS	SHARKS TOADS LIZARDS	CAECILIANS LIZARDS	PTEROSAURS	*Dionaea* Leaves bilobed and movable	MONITOR LIZARDS
5	MOLLUSCS INSECTS	REPTILES BIRDS	ECHINODERMS	FLOWERING PLANTS BANDICOOTS	OSTRICHES DUCKS	BIRDS	*Genlisia* Spirally twisted branches with claws	WEAVERBIRDS
6	NEARSHORE AND ABYSSAL FISH	MARSUPIALS PLACENTALS	FLOWERING PLANTS	EARLY PLACENTALS LATE PLACENTALS	MARSUPIALS PLACENTALS	BATS	*Utricularia* Bladder with movable door	CHIMPANZEES

Increasing grade of complexity →

MARSUPIAL SERIES

POUCHED MOLE	MULGARA MOUSE	PHASCOGALE	OPOSSUM	ANTEATER NUMBAT	GREATER GLIDER	SUGAR GLIDER	WATER OPOSSUM	POUCHED HYENA FOSSIL	TASMANIAN WOLF	MARSUPIAL LION FOSSIL	SABRE-TOOTH TIGER FOSSIL

PLACENTAL SERIES

MOLE	MOUSE	SHREW	TARSIER	ANTEATER	SQUIRREL	COLUGO	OTTER	SPOTTED HYENA	WOLF	LION	SABRE-TOOTH TIGER FOSSIL

Table 10 (previous pages): CHARTS OF CHEMICAL AND BIOLOGICAL PERIODICITY — PERIODIC TABLE OF CHEMICAL ELEMENTS COMPARED WITH PERIODIC TABLE OF LIVING ORGANISMS.

(1) PERIODIC TABLE OF CHEMICAL ELEMENTS. Mendeleev's original Table contained only 61 chemical elements but at present the Table extends to 118. Over 700 different representations of the Periodic System have been published putting in evidence particular properties of the atoms (Mazurs 1974). In the present table are included the groups of atoms that exhibit the highest degree of regularity. Hydrogen (with its variable location) and the transition metals were not included. The eight vertical columns consist of elements which have the same basic property. This property resurfaces independently of whether the atoms are simple or most complex. The intervals are not all of the same length. The Periodic System contains many irregularities, which are usually not mentioned, since the Table is one of the icons of science. The two horizontal series comprise the Lanthanide Series and the Actinide Series which are compared with each other due to the following common atomic features: (1) The lanthanides are especially notorious for being chemically similar to each other. (2) The actinides are also similar to each other by being all radioactive. (3) The properties found in the elements of lanthanides parallel those of the actinides (Gray 2009) The comparison, of the marsupial series and the placental series, with that of the lanthanide series and the actinide series, may seem farfetched, but this is because it is still difficult to think of DNA's gene sequences in simple atomic and electronic terms.

(2) PERIODIC TABLE OF LIVING ORGANISMS. Like in the Table of the chemical elements there are eight columns in which the properties were grouped according to basic common features: (1) Luminescence, vision and regeneration start all three at the mineral and crystal level. (2) Placenta, penis and wings (flight) are organs that appear from nowhere. (3) Plant carnivory and mental ability are processes that lead primarily to the acquisition of nutrients followed by digestion and assimilation.

Periodicity is characterized by: (1) The same property re-emerging as much as 10 times (plant carnivory), and 40 times (luminescence). Simple eyespots have evolved also independently at least 40 times and probably as many as 65 times (Land & Fernald 1992). In sharks the placenta emerged independently on over 11 occasions and the placenta of reptiles "has evolved on more than 100 separate occasions". (2) A property suddenly appears in the simplest as well as the most complex organisms. This sudden recurrence takes place in organisms that are not phylogenetically closely related. (3) The properties arise without previous announcement. (4) The novel structures appear "ready made" being functional and coherent from the start. (5) Some properties arise at the mineral level, before DNA arrived in evolution, supporting the notion that biological periodicity has an atomic ancestry. The emergence of two independent series, in the lower part of the two charts, reinforces the connection between the two types of periodicity the chemical and the biological. Only future investigation, at the atomic level will elucidate properly this surprising similarity, that at present, may appear fortuitous.

vironment and having a different plant diet) became carbon copies of their European placentals. Flight occurs in air but also in water and in the water-air interface.

10. The degree of complexity of a given structure or function does not necessarily follow the general increase in complexity taking place during evolution. Flight in birds is not more complex than that of flies. Four wings occur in fishes and butterflies but birds have only two. The eye of a fish is not more advanced than that of an invertebrate cephalopod (Table 10).

3.11. The Molecular Mechanism Responsible for the Emergence of Biological Periodicity

1. Biological periodicity could not occur if the genes of most living organisms were not essentially similar. The sequenced genomes of algae (Chlamydomonas), flowering plants (Arabidopsis) and humans were compared revealing that their gene numbers are 15,143, 26,341 and circa 23,000 respectively. Besides many gene families can be easily recognized in these 3 types of organisms (Merchant *et al.* 2007).

2. Before the sudden re-emergence of a given property was considered a "paradoxical event". Biological periodicity could not even be contemplated because the genes directly responsible for a given structure and function were not known. Now a single gene, isolated in the test tube, such as Pax6, decides vision in nearly all animals (Gehring & Ikeo 1999).

3. Plants were considered to be genetically far away from animals and as a consequence could not be included in the same periodicity. The placenta which is a general feature of a whole group of mammals, could not be compared to that of

plants, but its emergence in these totally unrelated groups is now known to be decided by common genes (Spielman *et al.* 2001).

4. The ordered evolution of an organ, such as the eye, has been guided by self-assembly, a pure atomic event, independent of external intervention.

5. Coherence of structures and functions building a harmonious organ with high efficiency are most evident in plant carnivory, flight, mental ability and vision.

6. The novel organs appear as "ready made". Extra pairs of wings in flies, and extra pairs of wings in birds, obtained in the laboratory, are formed, from the onset, with the correct skeleton, articulations, muscles and blood vessels. The extra legs of insects, produced in the same way, are also organized consisting of the identical segments and articulations (Bender *et al.* 1983, Lawrence 1992, Gehring 1998).

7. The sudden absence of a property, as well as its equally sudden reappearance, is due to the repression and the expression of a gene or gene cluster. Gene repression and expression are decided by changes within the DNA of chromosomes but also by the intervention of small RNAs.

8. The same genetic constitution which is present within the same animal or within the same plant, allows or blocks the occurrence of a given property. The same individual plant produces side by side carnivorous and non-carnivorous leaves. Among annelids, brachiopods and bryozoans the adults have no eyes whereas the larvae have eyes.

9. The resurfacing of the same property may occur again and again. Bioluminescence is estimated to have evolved independently at least 40 times and plant carnivory also independently on 10 occasions. The placenta in reptiles has evolved on more than 100 separate occasions.

3.12. The Law of Biological Periodicity

Scerri (2007) who treated extensively the periodicity of the chemical elements in his work *The Periodic Table — Its Story and Its Significance* formulated the Law of Periodicity at the chemical level as follows: "The periodic law states that after certain regular and varying intervals the chemical elements show an approximate repetition in their properties". To be noted is that the intervals are regular but "varying" and that the repetition is "approximate". And he adds "periodicity among the elements is neither constant nor exact". However, he emphasizes that there is a fundamental relationship among the elements.

The evidence gathered at the molecular level that unifies living organisms independent of their complexity or phylogenetic location, exposes a periodicity that can also be concretized in the form of a law.

The law of biological periodicity states that after certain regular and varying intervals the living organisms show an approximate repetition in their properties.

The similarity between the periodicity at the atom level and that of living organisms is so striking that the law of biological periodicity is a paraphrase of the law of the chemical elements. This is astonishing and could hardly be expected since we tend to think about biological phenomena following antiquated ways of reasoning far removed from the laws of physics and chemistry.

Now, when the evidence is so compelling, one thinks that it could not be otherwise.

3.13. Predictions

Predictions can now be better formulated, and treated more extensively, because in the last four years more data have become available. A comparison with these results allows a clearer overview.

1. **Chemical ignorance limited prediction**

When Mendeleev produced his Table it contained only 61 elements, and as a consequence there were empty spaces in the columns. He realized that these were not faults, but were a sign that there existed chemical elements that had not yet been discovered, which occupied the empty squares. These elements were later found corroborating his predictions. But since then many others were discovered (total 118) that could not be predicted.

2.**Biological ignorance limits prediction**

The same situation is faced at present. The Biological Tables contain empty spaces. This is not surprising. The number of species in eukaryotes (organisms with a cell nucleus) is 8.7 million + - 1.3 million and comprise mainly: protozoa, fungi, plants and animals. Microbial species (without a cell nucleus) are 1 trillion (Mora *et al.* 2011, Locey & Lennon 2016). Most of them have never been studied in detail as regards structure, function or behavior. The ignorance is monumental. Treatises describing in detail each species were published only recently. *The Handbook of the Birds of the World* (del Hoyo *et al.* 1992–2011), comprises 16 volumes covering 9,600 species and the *Handbook of the Mammals of the World* (Wilson & Mittermeier 2009–2019) has just been published covering 9 volumes (5,339 species). No comparable works exist for fishes (24,500 species), amphibians (5,000 species) and reptiles (7,984 species). Novel properties are being added continuously allowing animals and plants to be located with precision in the empty squares. An example is the number of animals that can count, or recognize signs, which will successively fill the table of mental ability. Also, the number of fish and invertebrate species, that display luminosity, will increase in the boxes of this table. Regeneration is being actively investigated and new organs are being added. Besides, new properties, which so far have not been studied from the point of view of periodicity, will create new columns or Tables. The nearest candidate is dentition.

3. The inclusion of novel properties in the main Table

Teeth are eliminated and replaced at specific intervals, but it has not been realized before that this is a programmed event, decided by internal genetic processes, which are independent of the environment. In humans the upper and lower teeth (central incisors) erupt by 6 to 12 months of age and are shed when children are 6 to 7 years old. Other teeth follow exact programs such as wisdom teeth (eruption at 17-21 years). Fossil birds had teeth, but they were eliminated in living species and turtles also lack teeth. However in many fishes, amphibians and reptiles tooth replacement continues throughout life. As Romer and Parsons (1978) point out the replacement is in waves, and what at first sight "seemed madness" and a "jumble" is the result of "an underlying principle of order" It is this order that now makes dentition a perfect example of periodicity.

4. The length of the periods

The length of periods is already highly variable in the Periodic Table of Chemical Elements. This is recognized as "the really crucial property of the periodic Table", yet the lengths of the periods are still not explained at present. At the biological level this phenomenon will be still more difficult to unravel, but should not be out of reach. In flight the interval is of the order of millions of years (e.g. insects to pterosaurs and birds to bats) but it may be of the order of hundreds of years between the plant carnivory exhibited by different families, or by days in the formation of the placenta in reptiles.

5. The creation of novel organisms

Using genetic engineering it will become possible to obtain the resurgence of a given property and consequently to create organisms with a specific structure and function that did not exist before. These will occupy empty spaces at most unexpected sites.

6. The acceleration of evolution

It will become possible to accelerate or to retard evolution by interfering with the own evolution of the macromolecules that direct the cell processes.

7. The present interpretation of evolution is antiquated. Novel structures and functions arise as coherent combinations

Contrary to the present dominating view of evolution, genetic engineering and biotechnology are disclosing that novel structures and functions arise, from the start as coherent combinations of parts and organs. They are the product of new rearrangements of DNA sequences that lead to molecular cascades which determine a new development and establish a novel final pattern.

8. Novel organs appear "ready made"

Equally, the emergence of novel traits is not considered to be the result of numerous random mutations accompanied by long periods of selection. Instead novel organs (which have been obtained experimentally) appear "ready made". They arise again and again, irrespective of whether they have a positive or negative effect on the organism. The own evolution of DNA, RNA and the proteins follows only the laws of physics and chemistry.

9. **Canalization of events**

The electron is a prisoner of its energy states. It can jump from one orbital to another but cannot fall between orbitals. The energy alternatives are, from the beginning not of all kinds. The canalization of evolution, is present at the very dawn of matter and life, since elementary particles and atoms have not changed their properties when the cell emerged.

10. **Biological Periodicity a key to novel alleys in physics**

Just as the law of periodicity, resulting from Mendeleev's work, became the key to modern chemistry, the law of biological periodicity is expected to lead physics into new alleys of research, obliging molecular biology to become Atomic biology.

11. **Prediction is always a difficult process**

As Scerri emphasized "Almost nobody, including Mendeleev, had predicted or even suspected the existence of an entire family of new elements", the inert or noble gases.

12. **A mathematical equation defining the law of periodicity**

As knowledge enlarges, and mathematicians will start collaborating with atomic biologists, it is expected that, in a distant future, the law of periodicity will become crystallized into a simple mathematical equation.

Source of Tables and Figures

All Tables are from Lima-de-Faria (2017) and are Original Plates protected by copyright. They cannot be reproduced without permission from the Author and World Scientific, Singapore, New Jersey, London.

All Figures are from Lima-de-Faria (2017) except Figures 4 and 16 which are from Lima-de-Faria (1995).

Lima-de-Faria A 2017, *Periodic Tables Unifying Living Organisms at the Molecular Level. The Predictive Power of the Law of Periodicity*, Singapore: World Scientific.

Lima-de-Faria A 1995, *Biological Periodicity. Its Molecular Mechanism and Evolutionary Implications*, Greenwich: JAI Press Inc.

References

Affolter M *et al.* 1990, "Homeodomain proteins and the regulation of gene expression" *Current Opinion in Cell Biology*, vol. 2, pp. 485–495.

Andersson J 2020, *Allt du skäms för att du inte visste om Max IV och ESS, Lunds Universitet*, viewed 21 June 2020, <https://www.lu.se/artikel/allt-du-skams-att-du-inte-visste-om-max-iv-och-ess>.

Bender W *et al.* 1983, "Molecular genetics of the bithorax complex in Drosophila melanogaster", *Science*, vol. 221, pp. 23–29.

Björn L O 2015, "The diversity of eye optics", in: Björn L O (ed.), *Photobiology: The Science of Light and Life* (3rd edition), pp. 189–204, New York: Springer.

Bonner J T 1952, *Morphogenesis: An Essay on Development*. Princeton: Princeton University Press.

Branden C & Tooze J 1991, *Introduction to Protein Structure*, New York: Garland Publishing.

Brown T A 1999, *Genomes*, Oxford: BIOS Scientific Publishers.

Burnie D (ed.) 2004, *Animal: The Definitive Visual Guide to the World's Wildlife*, London: Dorling Kindersley.

Choi Y S *et al.* 2003, "Genomic structure of the luciferase gene and phylogenetic analysis in the Hotaria-group fireflies", *Comparative Biochemistry and Physiology, Part B*, vol. 134, pp. 199–214.

Cohn M J *et al.* 1997, "*Hox9* genes and vertebrate limb specification", *Nature*, vol. 387, pp. 97–101.

Dacke M & Srinivasan M V 2008, "Evidence for counting in insects", *Animal Cognition*, vol. 11, pp. 683–689, DOI: 10.1007/s10071-008-0159-y

del Hoyo J *et al.* (eds.) 1992–2011, *Handbook of the Birds of the World,* 16 volumes, Barcelona: Lynx Edicions.

Dunlap P V *et al.* 2007, "Phylogenetic analysis of host-symbiont specificity and codivergence in bioluminescent symbioses", *Cladistics*, vol. 23, pp. 507–532.

Eilenberg H *et al.* 2006, "Isolation and characterization of chitinase genes from pitchers of the carnivorous plant Nepenthes khasiana", *Journal of Experimental Botany*, vol. 57, no. 11, pp. 2775–2784.

Eriksson R 2015, *What do neutrons tell us?* /ESS. https://european_spallation_source.se/what-do-neutrons-tell-us2015-08-27.

Flemming A F & Blackburn D G 2003, "Evolution of placental specializations in viviparous African and South American lizards", *Journal of Experimental Zoology Part A, Comparative experimental biology*, vol. 299, no. 1, pp. 33–47.

Gehring W J 1998, *Master Control Genes in Development and Evolution: The Homeobox Story*, New Haven: Yale University Press.

Gehring W J 2014, "The evolution of vision", *WIREs Developmental Biology*, vol. 3, no. 1, pp. 1–40, DOI: 10.1002/wdev.96.

Gehring W J & Ikeo K 1999, "*Pax 6*: Mastering eye morphogenesis and eye evolution", *Trends in Genetics*, vol. 15, no. 9, pp. 371–377.

Glover B J 2007, *Understanding Flowers and Flowering*, Oxford: Oxford University Press.

Gray T 2009, *The Elements: A Visual Exploration of Every Known Atom in the Universe*, New York: Black Dog and Leventhal Publishers.

Haberlandt G 1902, "Culturversuche mit isolierten Pflanzenzellen", *Sitzungsberichte der Akademie der Wissenschaften mathematisch-naturwissenschaftliche Klasse*, vol. 111, pp. 69–92.

Hastings J W 2011, "Progress and perspectives on bioluminescence: From luminous organisms to molecular mechanisms", in: Roda A (ed.), *Chemiluminescence and Bioluminescence: Past, Present and Future*, RSC Publishing.

Jaffe H W 1988, *Introduction to Crystal Chemistry: Student Edition*, Cambridge: Cambridge University Press.

Land M F & Fernald R D 1992, "The evolution of eyes", *Annual Review of Neuroscience*, vol. 15, pp. 1–29.

Lawrence P A 1992, *The Making of a Fly: The Genetics of Animal Design*, Oxford: Blackwell Scientific Publications.

Lima-de-Faria A 1995, *Biological Periodicity. Its Molecular Mechanism and Evolutionary Implications*, Greenwich: JAI Press Inc..

Lima-de-Faria A 2017, *Periodic Tables Unifying Living Organisms at the Molecular Level. The Predictive Power of the Law of Periodicity*, Singapore: World Scientific Publishing.

Locey K J & Lennon T 2016, "Scaling laws predict global microbial diversity", *PNAS*, vol. 113, no. 21, pp. 5970–5975.

Macdonald D (ed.) 1984, *The Encyclopedia of Mammals: Vol. 1*, London: George Allen and Unwin.

Mazurs E G 1974, *Graphic Representations of the Periodic System During One Hundred Years*, Tuscaloosa: The University of Alabama Press.

McFarland D 1981, *The Oxford Companion to Animal Behaviour*, Oxford: Oxford University Press.

McGinnis W & Kuziora M 1994, "The molecular architects of body design", *Scientific American*, vol. 270, pp. 36–42.

McPherson S 2010, *Carnivorous Plants and their Habitats*, Dorset: Redfern Natural History Productions.

Merchant S S *et al.* 2007, "The *Chlamydomonas* genome reveals the evolution of key animal and plant functions", *Science*, vol. 318, pp. 245–251.

Mora C *et al.* 2011, "How many species are there on earth and in the oceans?", *PLoS Biology*, vol. 9, no. 8 e1001127, pp. 1–8.

Ohno S 1988, "On periodicities governing the construction of genes and proteins", *Animal Genetics*, vol. 19, pp. 305–316.

Ohno S & Ohno M 1986, "The all pervasive principle of repetitious recurrence governs not only coding sequence construction but also human endeavour in musical composition", *Immunogenetics*, vol. 24, pp. 71–78.

Padamsee H S 2003, *Unifying the Universe*, Bristol: Institute of Physics Publishing.

Perutz M 2003, *I Wish I'd Made You Angry Earlier: Essays on Science, Scientists, and Humanity*, Woodbury: Cold Spring Harbor Laboratory Press.

Purushothaman S *et al.* 2015, "Transcriptomic and proteomic analyses of *Amphiura filiformis* arm tissue-undergoing regeneration", *Journal of Proteomics*, vol. 112, pp. 113–124.

Romer A S & Parsons T S 1978, *The Vertebrate Body*, Philadelphia: W.B. Saunders Co.

Scerri E R 2007, *The Periodic Table*, New York: Oxford University Press.

Schuergers N *et al.* 2016, "Cyanobacteria use micro-optics to sense light direction", *eLife* 2016;5:e12620 DOI: 10.7554/eLife.12620.

Spielman M *et al.* 2001, "The epigenetic basis of gender in flowering plants and mammals", *Trends in Genetics*, vol. 17, no. 12, pp. 705–711.

Warren W C *et al.* 2008, "Genome analysis of the platypus reveals unique signatures of evolution", *Nature*, vol. 453, no. 7192, pp. 175–183. DOI: 10.1038/nature06936.

Weinberg S 2015, *To Explain the World*, London: Penguin Random House.

Wenk H R & Bulakh A 2004, *Minerals: Their Constitution and Origin*, Cambridge: Cambridge University Press.

Williams, SE et al. 1994, "Relationships of Droseraceae: A cladistic analysis of rbcL sequence and morphological data", *American Journal of Botany*, vol. 81, no. 8, pp. 1027–1037.

Wilson D E, & Mittermeier R A (eds.) 2009–2019, *Handbook of the Mammals of the World,* 9 volumes, Barcelona: Lynx Edicions.

Organisms

SAPIENZA
UNIVERSITÀ DI ROMA

History and Science

Vol. 4, No. 2 (2020)
ISSN: 2532-5876

DOI: 10.13133/2532-5876/17021

The Construction of the Genetic Order: A Short Critical History

Daniel Papillon [a]*

[a] *PhD, independent scientist*

***Corresponding author:** Daniel Papillon, Email: shrese@riseup.net

Abstract

Genetics, as all human activities, is a situated practice. Given its enormous cultural and epistemological influence, the young age of the discipline may be surprising—not even 150 years old. The creation of the science of transmission and production of traits in organisms responded to 19th century's epistemological needs in biology, as well as political and social developments: the transmission of characters and their variations throughout generations needed a new theory, the embryological development of organisms had to be explained, the unrest and disastrous living conditions provoked by the industrial capitalism and the colonial project in the West called for a reaction from the elites. The trajectory of genetics is one of permanent co-production between the different ontologies and practices it is situated in. As a science, it draws its legitimacy from the stories it tells (about the world or about itself), the interests it serves and the existing power relations it is part of. Given this background, the present work tries to shed some light on several aspects of the history of genetics that may help clarify its role and impact on our societies. The set of ontological and material transformations it underpins is referred to as the Genetic Order, and this is explored particularly in the context of the irremediable past and present association of genetics with eugenics, the construction of key notions such as heritability and the dichotomy Nature/Nurture, the enormous influence of cybernetics over biology and genetics after the second world war and the alliance between biotechnologies, genetics and neoliberalism in more recent years. One central notion that wanders throughout this text is that of control over bodies and life in general. This is illustrated by the recent explosion of the genomic prediction industry and its impact on contemporary subjectivities. In the end, it is a world of statistics, algorithms, predestination, risk management and control that the Genetic Order offers, echoing the hegemonic influence of the neoliberal cybernetic project where all that lives must be engineered, modelled, monitored, predictable and transparent.

Keywords: genetics, eugenics, history, genomic prediction, capitalism, neoliberalism, control, heritability, nature/nurture, cybernetics

Citation: Papillon D 2020, "The construction of the genetic order: A short critical history", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 69-97. DOI: 10.13133/2532-5876/17021.

Introduction

“We are painfully aware that genetic science has, for more than a century, played a central role in producing the ideology that supports systemic racism. [...] We understand that we cannot simply disavow this history, because many of our field’s fundamental concepts and approaches were established for the purpose of advancing eugenics, under the assumption of extensive racial differences within a social hierarchy.”

Department of Human Genetics, University of Chicago, *Statement on Police Violence, Racism, and Genetics* (2020)

Few modern sciences have had such an impact on our ontologies (the ways we define what the world is made of) and on the materiality of our lives (e.g., the food we produce and eat, how we heal ourselves, our relationships with each other and with other organisms, how we conceive ourselves as humans) than genetics.

The trajectory of the science of transmission (heredity) and production (development) of traits in organisms is one of permanent co-production between these ontologies, these practices and the science itself. New imaginaries and new sciences, here seen as context and content, do not generally come one after the other, but co-create each other, as Latour reminds us (Latour 1993). Born—alongside the eugenics project—during the industrial revolution and the colonial project in the West at the end of the 19th century, matured throughout the first half of the 20th century (through the first World War, the explosion of agribusinesses, the rise of fascism in Europe, the horrors of the second World War…) and literally taking over the whole of biology in the second half of the 20th century (through molecular biology, genetic engineering and the influence of cybernetics), genetics has reached a point where its original shortcomings are biting back. Pichot is one of the historian of science who has shown with most clarity the epistemological failure of genetics in helping us interpret and understand life phenomena in a coherent way: “The theory is that heredity is the transmission of an ordered substance (DNA) that controls the organization of an organism. But as experimental results accumulated, the order of this substance became increasingly uncertain and its correspondence with the organization of the organism more and more vague. So much so that today there is practically nothing left, neither of this order nor of this correspondence.” (Pichot 2003, transl. by the author). He therefore affirms that “genetics has no object, it only has a function.” (Pichot 2001, transl. by the author). The interpretation of the world that genetics promotes has lead to changes that need to be looked at critically and challenged. The set of ontological and material transformations underpinned by genetics will be referred to here as the Genetic Order (GO). This GO presents several well known characteristics that will be further discussed throughout this article. One is Geneticization, understood as the “the ongoing process by which priority is given to differences between individuals based on their DNA code” (Lippman 1993) but it also refers here to the fabrication of DNA and the gene as cultural icons and god-like entities (Kupiec & Sonigo 2000; Nelkin & Lindee 2004). Another feature of the GO is its reductionist and mechanistic aspect, described by many authors, for example Lewontin (1991), Morange (2003) or Nicholson (2014a). Geneticization is therefore a cultural process that produces genetic essentialism (the DNA molecule perceived as our essence, our “truth within” that defines our identity) and genetic determinism (our DNA dictates our morphology, our health, our personality, our behaviors).

The main specificity of an ontology is that it is extremely difficult, usually impossible, to think outside of it. However, the past months constitute an example where events have taken place that were unthinkable only few weeks before that. I am referring here to the shift of consciousness and to the possibilities opened by the recent wave of unrest against police violence and systemic racism, particularly in the USA. An element of this shift occurred in university departments, for example, departments of genetics and human genetics, which were forced to react to the massive uprisings taking place in their cities (see the opening quote from the Department of Human Genetics in Chicago). One of the most interesting aspect of this reaction was the acknowledgement of the contribution of genetics to systemic racism and its epistemological connection to the eugenics project. This shift has to be understood also in the context of the global Covid-19 pandemic, which had already raised similar issues. Not only, and unfortunately unsurprisingly, poor and racialized sections of the population are hit much harder by the virus, but dominant classes’ engrained eugenic beliefs (and readiness to mass sacrifice vulnerable populations) were suddenly brought to light notably through the push for "herd immunity" or the discussions of "hospital resources allocation". Therefore, a perhaps not-so-expected consequence of the Black Lives Matter movement is the emergence of a decisive counterstory against the official narrative that genetics' link with racism and eugenics is a thing of the past, solved after the second world war, and was the deed of some "bad apples" in the field. As an illustration, and mirroring the removal of slave owners and colonial figures' statues in many countries, genetics departments and other institutes are slowly changing their names or the names of their buildings that were related to famous eugenicists, in some cases after many years of dismissed and ignored local activism to achieve the very same thing (for example in University College London, UK).

Given this background, what I hope my contribution to be is to bring some light on several aspects of the history of genetics that may help clarify its role and impact on our societies. Drawing from the work—published in English—of critical biologists (Lewontin, Kupiec, and Noble) and social scientists (Nelkin, Lindee, Keller, Bliss, Cooper, and Rouvroy) as well as from untranslated French literature (Pichot, Bonneuil, Sonigo, and Lafontaine), this paper originates from the established understanding that genetics, as any other science, has been influenced by the epoch, the political context and the world views it has been practiced in, and has influenced them in return. In other words, genetics is a *situated* practice. One central notion that will run throughout this text is that of *control*: genetics as a recurrent project of control over (human) bodies, (human) evolution, the living world and the planet in general. This is explored particularly in the context of the irremediable past and present link between genetics and eugenics, the enormous influence of cybernetics over biology after the second world war and the alliance between biotechnologies, genetics and neoliberalism in more recent years.

1. Origins and structuring

1.1. Origins

There is no need to describe at length the main scientific theories about the natural world of the 19th century, other authors have described the birth of biology as an independent science and the paradigms shifts accompanying it (Kupiec & Sonigo 2000; Mayr 1982; Morange 2017; Pichot 1999). The 19th century biology inherited a predominantly fixist, essentialist, mechanistic (to be more exact, machinistic) and reductionist view of the living world. Species would reproduce their form, or essence, to the identical throughout generations, and the organism itself, perceived as a Cartesian machine, could be entirely understood through the study of its independent and separate parts. The strength of this mechanistic view of life is that it provided a good description and understanding of how an organism works and its "internal" causality mechanisms. Its weakness is that it could not explain developmental (under preformationism, the mode of generation associated with mechanistic biology, development does not need to be explained as organisms are always-already entirely present) nor evolutionary processes (Pichot 1999).

In the terminology of Pichot (2001), the reproduction of the same exemplified by preformationism is called the reproduction-generation mode. He points out that the identical reproduction of organisms is an ahistorical conception of life: if nothing changes, there is no history. When the living world is seen as ordered and fixed, then what biology needs to explain is the variation between individuals. A way to solve the dilemma about observed differences between beings was to establish a distinction between specific differences (the ones between the different forms/essences/species; the "real" differences that have a significance) and accidental differences (they do exist between individuals but they do not really matter for the understanding of the organisms). In this system of thoughts, the oppositions essence/existence and species/individuals are associated with these specific/accidental differences. Pichot partly explains the longevity of the preformationist ideas for theological reasons, as it complements perfectly the finalist and deterministic way of understanding organisms and the world: the organism's plan (its form or essence) pre-exists to its existence, and the unfolding of its life is determined by an external cause (Pichot 1999).

During the century, transformism (or evolutionism, the idea that species have evolved throughout history) will be more and more widely accepted. Fixism and essentialism will be slowly replaced by a historical, processual understanding of life (Kupiec & Sonigo 2000; Mayr 1982). One of Darwin's contribution was to put forward variation as a fundamental property of organisms, and he asserted that these variations were transmitted from one generation to the next. According to Kupiec (2019) and Rosanvallon (2012), this is a paradigmatic change. First, this is a blow to the idea of a well "ordered" living world. Second, if variation is a characteristic of organisms and can be transmitted, therefore, what needs to be explained from then on are the similarities between beings (and not their differences). One of the main question of biology emerges then, the one about the "reproduction of the similar", or in other words: what are the biological mechanisms that explain the similarities between parents and offspring?

This new historical and processual vision of life provoked epistemological issues in biology: one was the need to articulate the physico-chemical explication of the organism with a historical explanation and another was the questioning of the notion of species. Because of the latter, the concept of species could not refer any longer to eternal and separate entities. Indeed, as Kupiec and Sonigo (2000) propose, a "species" is more of an instant (like a photograph), whereas life is actually a historical process, the genealogy of lineages over time (a sequence like a video). Mayr (1982) insists on the importance, for the future establishment of genetics as a discipline, of what he calls "population thinking" (focusing on the diversity and variations between individuals within a population, rather than the essentialist thinking that focuses on the differences between species) and, from there, the necessity to compartmentalize and separate all the visible characteristics of organisms into individual traits. Therefore, the notion of the *specific form* was gradually replaced by the notion of an organism as a sum of individual characters, of which only a part are transmitted (even though it was still not known how). These characters will be called hereditary characters for two reasons: the previous observation of a kind of vertical transmission of exceptional characters such as hereditary diseases, and the construction of an equivalence to the legal/economical notion of heredity (transmission of wealth and properties, accumulation of possessions throughout generations…). Heredity, as a substantive, is imported to biology at this moment (Pichot 2001). This importation of concepts from the legal/economic field in biology is a reminder of the famous influence of Townsend and Malthus on Darwin for the formulation of the natural selection theory (which itself will influence back social sciences through social Darwinism) (Pichot 2000), illustrating this constant back and forth movement between natural sciences and politics.

Heredity, therefore, is the answer to the first epistemological issue mentioned above: the necessity of a historical component in the explanation of the organism. To have continuity between the generations, there needs to be a transmission of characters (and their variations). This is, in Pichot's terminology, the transmission-generation mode (Pichot 2001). Mayr (1982) describes the trajectory of ideas at the turn of the 19th/20th centuries that lead to the establishment of genetics, and especially the influence of mechanistic and reductionist thinking as well as physics methodologies. It is fascinating to follow this gradual narrowing down of the scientific focus from the cell (the Cell theory), to the nucleus then to the chromosomes (the Chromosome theory) and finally to the DNA and the gene, revealing the obsession for the search of "the" corpuscular unit of genetics (which was thought as the unit of heredity or the unit of development depending on the context and the specialty of the scientists involved). As the physiology of reproduction is better described, another central question of biology emerges: how can complex organisms made of so many different organs and types of cells can be produced from a single cell?

Prior to preformationist ideas, heredity was mostly understood as the transmission of entities (humors or materials) "collecting" the different parts of the body, or, as Pichot puts it, a kind of "representative sample" transmitted through the generations (Pichot 1999). In early 1890s Weismann, a German biologist drawing from the "representative sample" notion, will establish the bases of genetics as a science with his germ plasm theory and the germ/soma opposition. The germ plasm is a substance representing the germinal line, it is the structure that bears the heredity and is responsible for the transmission of characters. The soma is the rest of the body, it does not transmit anything. The birth of genetics relies therefore on a fundamental and irreducible new separation: between the organ of heredity and the rest of the body. This is reflected, in Weismann's theory, in the opposition between hereditary (the characters contained in the germ plasm and that can be transmitted) and acquired characters (that are related to the soma and that cannot be transmitted). Genetics becomes the science that studies the transmission of these hereditary characters. Keller, reflecting on these shifts, writes about internalization and substantiation (Keller 2010). The substantiation is the notion that what is transmitted is a substance, a material entity made of particles that resides in the body. This particulate form of heredity will be discussed further in the next part. The notion of internalization is summarized by Moore commenting on Keller (2010): "the word 'innate' came to be associated with heredity and the word 'acquired' came to be associated with the environment (i.e., that which is external to the body). This internal/external dichotomy allowed nurture to be disjoined from nature" (Moore 2012). The emergence of the new ontological alignments internal-innate-hereditary and external-acquired-environment will define genetics. Pichot (1996) clarifies the importance of this transition. Before Weismann, the fundamental opposition was between the acquired and the inherited characters – but all were inheritable, or hereditary. The fundamental opposition of the nascent genetics is different, it is the one between the in-principle-hereditary characters (be they inherited or not) and the in-principle-non-hereditary characters (acquired). This may seem very subtle as a difference but the implications are significant. It is indeed very difficult to clearly define what is a purely in-principle-hereditary character (this is further discussed in section 3.1).

With his theory, Weismann manages, according to Pichot (1996), to bring together the ideas of preformation as well as epigenesis (the ancestor of modern embryogenesis and the mode of generation associated to vitalism, the main rival theory to mechanistic biology at the time). Indeed, although it does not contain a pre-formed being, Weismann's germ plasm is supposed to contain the instructions of its formation. A digitalization before its time. Moreover, in this theory, the construction of the organism, while pre-written, is effectuated by epigenesis. The germ plasm acts as the material form of a "memory", a vision that will lend itself particularly well to the cybernetic framework 50 years later. Thus, by reconciling the two dominant theories of biology Weismann provides a framework that will satisfy the majority of biologists, a kind of neo-preformationism (Mayr 1982; Pichot 1996). The germ line would therefore be the only part of the organism that shows continuity in time; it is immortal, therefore timeless. Drawing from Weismann, geneticists will slowly deny any influence of the environment on the germ, making heredity a purely structural and a-historical phenomenon (Bonneuil 2015a). According to Kupiec, Weismann (together with De Vries) is responsible for a major leap in the foundation of genetics: introducing dualism into the theory of heredity by postulating that macroscopic traits are determined by the structure of microscopic elements, thereby giving the theory an Aristotelian structure (Kupiec 2019). Despite the upheavals of evolutionism in the 19th century, the organism is once again detached from its history and its environment – it is back to "order". In *Le siècle du gène* (2015a) Bonneuil argues that the emergence of this vision echoes the appearance of the mass production of objects during the industrial revolution. Previously, the value of an object was strongly linked to its history, its origin, who made it, by what technique, where, under what conditions... With mass production, the link between an object and its origin disappears, as does the link between an organism and its history.

Another explanation for the success of Weismann's theory, and its perpetuation in current genetic essentialism, lies in the idea of immortality. What could be the reasons explaining the powerful resonance of this idea of immortality with this particular era? The first that comes to mind is again the link with industrial capitalism. What is a business, a corporation? It is an entity whose existence can last a much longer time than that of the human scale, an entity whose hosts (owners, shareholders) are just passing through, although they must act in the "interest" of the company (Waters J, personal communication). The similarity becomes even more striking when one considers the familial character of certain companies, inherited from generation to generation within "entrepreneurial" dynasties. This echoes Lewontin's work on the adequacy between the mechanistic and reductionist ontology with the individualist view of the world (Lewontin 1991). With the development of industrial capitalism, and the concomitant change in social organization, a completely new vision of society emerged: the individuals as the primary and independent entities (in a permanent competition between themselves); society as a consequence, not a cause, of individual properties; organisms determined by internal factors, the genes ("the modem form of grace"). Just as genes determine individuals, individuals determine communities—thus, genes make cultures and determine societies: "We have become so used to the atomistic machine view of the world that originated with Descartes that we have forgotten that it is a metaphor. We no longer think, as Descartes did, that the world is like a clock. We think it is a clock." (Lewontin 1991)

Genetics, the actual name of the discipline, was then coined by Bateson in 1906 and Weismann's theory was quickly formalized with the creation of the terms gene, phenotype (first the average apparent type of a population but now defined as the set of the apparent traits of an organism) and genotype by Johannsen in 1909 (Mayr 1982).

1.2. End of the 19th century, genetics under the influence: eugenics

During this pivotal period between the 19th and 20th centuries, several core concepts in genetics emerged. One of the scientist most representative of these changes is Galton and the main thrust of this early bubbling is the creation of, and the articulation between, the notion of heritability and the Nature/Nurture dichotomy. Both ideas were associated to the political project of eugenics, a project aimed at controlling human populations and their evolution. One of the priorities of genetics became then the "improvement" of the human population. At the root of all this, as narrated by Keller (2010) was Galton's concern about how to stop the ongoing "degeneration" of his nation and ensure that more "geniuses" are produced. Old ideas that will flourish in the context of the emerging genetics and Darwinism. Of course, this "concern" must be understood in the light of the particular historical conditions of the late 19th century: the explosion of industrial capitalism and the massive urbanization (i.e., the expulsion of thousands of humans from the countryside to the cities) leading to horrendous living and sanitary conditions (the "degeneration" that provoked anxieties in Galton and many others), the enormous workers' movements and revolts, the formulation of the communist and anarchist theories, the beginning of feminist struggles, the colonization project and the conflicts it provoked, etc. The elites were worried about so much upheaval and resistance. Here Royer's intervention about the essence of capitalism as a "project against life" offers a striking perspective (Royer 2017). He argues that the immeasurable anthropological transformations of the 19th century in the West were marked by the triple alliance between the new mode of scientific production, the thermo-industrial capitalism (coal then oil) and the formation of the modern nation-state as we know it. According to him, this alliance is at the origin of what is going to become eugenics, which will constitute the ideological basis of a new mode of social engineering characterized by the transgression of the (mass) murder taboo. All of this being legitimized by the discourse of the new mode of scientific production built throughout the 19th century, the "Science with a capital S" as Carnino calls it (Carnino 2015). Eugenics is a true mass movement. At the time, most geneticists were eugenicists, including progressives, and the importance of promoting and creating a new human was widely accepted (Pichot 2000). From Royer's perspective, the eugenics project accompanies the West and capitalism towards the realization of their essence, a project of total death, embodied by the two major and concomitant events of the atomic bombs launched on Japan and the Holocaust (Royer 2017).

Pichot's perspective is that, in short, eugenics can be considered as the natural continuation of Darwinism—although not necessarily of Darwin himself (Pichot 2000). As mentioned, the industrialization associated to the massive urbanization lead to the multiplication of diseases and ill-health in big cities. For many established scientists of the time, this was interpreted as a sign of the degeneration of the occidental civilization. From 1859 and the publication of *On the Origin of Species*, Darwinism provided a "scientific" explanation to this phenomenon: this multiplication of diseases and social problems were not due to social conditions, but to the absence of natural selection in human societies. The solutions proposed were twofold: social Darwinism (the liberal *laissez-faire* promoting the survival of the fittest, or rather the elimination of the inferior, without any state intervention aiming at supporting the most vulnerable) and eugenics (a social selection driven by state intervention to replace natural selection) (Pichot 2000). This process went hand in hand with the construction of Science as the only institution able to help improve humanity (to advance it in the direction of betterment and happiness and progress; Carnino 2015) leading to mass sterilization policies targeting "criminals" (in practice, those considered mentally ill, the poor, the racialized people and other non-citizens) in several countries (for example in the United States or Sweden, where they will last until the 60s and 70s) and, eventually, to the Nazi exterminations (Pichot 2000; Royer 2017).

1.2.1 The construction of the Nature/Nurture dichotomy, part I

A first step in the establishment of eugenics as a discipline is the construction of the dichotomy Nature/Nurture. It is Galton who, in 1874, will inaugurate the conjunction "Nature and Nurture" as fundamental in genetics (Keller 2010). Previously, according to Keller, the ideas of Nature and Nurture were present but they were neither considered as fundamentally distinct categories nor in opposition. Keller uses the analogy of the seed (Nature) and its culture (Nurture) to describe the ontology of the time: one cannot go without the other in the production of an organism. The semantic operation of Galton's locution "Nature and Nurture" and then quickly "Nature versus Nurture" is not innocent. Indeed, two terms can only be brought together if they can first be considered disjointed and separate. Their coming together and their interaction imply their separation. Their separation implies that they can be studied and measured independently, compared and debated...

A central element of this new construction is the substantiation already mentioned: heredity is carried by a corpuscular substance (made of elementary, molecular and independent particles) that resides within the organism (although, in a way, it is separate from it) and is transmitted through the generations. The contributions of Mendel, Weismann and Galton were central to the double shift from blending (holistic) and *soft* inheritance to a particulate and *hard* inheritance (see Mayr 1982 and Bonneuil 2015a; this double shift is called "discretization of heredity" in Pichot 1999). This is exemplified by the comparison between Darwin's and Galton's view of heredity. Darwin, along many others at the time, accepted the particulate form of inheritance (he called these particles *gemmules*), that is to say he did not believe that heredity was a blending process of two complete organisms where the offspring was a mix of its parents (a holistic view). However, he considered that they were still influenced by the environment, still malleable (*soft*). With Galton, these particles will become fixed, discrete, independent and invariant entities (*hard*, see Keller 2010 and Mayr 1982). Nature and Nurture are then separated, among other things, by the elements of which they are composed of. Galton will establish for the following decades that : 1) the elements that make up Nature (the innate, or genetic forces) are the elements of heredity; 2) the elements that make up Nature are in competition with the elements that make up Nurture (the acquired, or environmental forces), this is the shift from Nature and Nurture to Nature versus Nurture; 3) the elements that make up Nature are, in the last resort, always more powerful than the elements that make up Nurture (Nature-first approach) (Keller 2010).

How does this theorization serve the eugenics project? This "discretization of heredity" and the creation of the Nature-Nurture divide were, I would propose, a necessity for the eugenics project. Both were framed as such and were essential for the hegemonic role of genetics in shaping our ontologies. Below are preliminary ideas that would of course need further exploring.

First, Keller (2010) suggests that in order to understand the origin and persistence of the separation and opposition between Nature and Nurture, it would be possible (or even preferable) to set aside eugenics. I would however propose that the construction of the categories Nature and Nurture is not distinct from the eugenics project that produced them. Neither is their hierarchization. Let us for a moment step aside towards Delphy, who offers a framework for interpreting the processes of creation of categories and their hierarchization (from a feminist but also anti-racist point of view) (Delphy 2008, 1993). She assumes that categories (such as male/female, black/white) do not exist in the "natural world". Divisions are social conventions, always created by humans, which order the materiality of the world (this echoes the debate around the concept of species between essentialists and nominalists). In the case of the male/female categories in humans, Delphy suggests that, contrary to the usual view, sex (biological or natural) does not precede gender (social or cultural): gender precedes sex. In other words, gender hierarchization (the patriarchal system) is not a phenomenon resulting from categorization but precedes it (and then the two phenomena reinforce each other). Hierarchy is at the origin of categorization. It is because the justification of a system of domination is necessary that categorization criteria, usually sought in the body/nature (naturalization), are established as universal and timeless. For Delphy, a similar mechanism is at work in the scientific justification of racism. The creation of the categories Nature and Nurture by the eugenics project could be interpreted in the same way. It is because there was a eugenic project that required a framework of thought in which the differences between humans had to be biological and inherited that the dichotomy was constructed in this way: a hierarchization and separation of Nature and Nurture (with Nature as the primary force in the transmission and formation of characters).

Second, to assimilate the elements of heredity only to Nature is to give natural scientists full responsibility for the study, interpretation and manipulation of the transmission, the development and the distribution of heritable traits, since Nature is the domain reserved to hard experimental sciences and no other.

The third line of thought is related to the understanding of the emergence of eugenics as one of the consequences of the scientific revolution in biology in the 19th century. Indeed, modern science had fundamentally been based on an opposition between the object being studied (nature, animals, plants etc.) and the subject (the one who conducts the study, i.e., humans). With the emergence of evolutionism and the increasingly clear positioning of humans within animals (starting with Linnaeus up to Darwin), the object/subject boundary is less and less clear. If humans are part of the animals, they can therefore be the object of science itself and its experiments (Rey 2015). Can we interpret the emergence of the Nature/Nurture dichotomy as a response to the blurring of the object/subject boundary after the Darwinian paradigm shift? It is not clear, but the naturalization of the elements of heredity in humans has undoubtedly provided the justification for the use of breeding and selection techniques (applied in the past to plants and non-human animals) on humans. Moreover, the closer groups of humans are associated to Nature (women, lower classes, mentally ill, enslaved, colonized…), the more they are seen as "objects" and the target of the eugenics project.

Fourth, the historical process of discretization of heredity played a major role in the creation of imaginaries echoing the eugenics project. Indeed, to consider the organism as an arrangement of independent, particulate traits, recombinable at will, responds to the demiurgic promise of human control over evolution (Bonneuil, 2021). For De Vries, one of the founders of modern genetics (although not a supporter of eugenics, see Pichot 1999), only "[s]uch an hereditary character, isolated from the rest, can now become the object of an experimental treatment." (De Vries 1889, cited in Bonneuil 2021). Pichot suggests another argument: during the first decades of the 20th century, through the discretization of both the phenotype and the genotype, the particles of heredity lost their "physical substance": they became mostly defined through the traits (or rather, the mutations) they corresponded to. This was a complete inversion of the way to study heredity: from a physical explanation (starting from the genotype to explain the phenotype) to a "mutationist" explanation (starting from the phenotype to explain the genotype). Pichot qualifies this second approach as "phenomenist" and statistic, a kind of "semiology" (an "interpretation of signs"), and argues that because of its practicality, all sorts of characters ended up being interpreted in this way, including psychological and social ones. Moreover, because these traits were usually identified through mutations associated to "monsters" or pathologies, this created an obsession of the "good" and "bad" genes (Pichot 1999). Using Darwinism, as mentioned above, the "proliferation" of these bad genes was interpreted as the consequence of the disappearance of the process of natural selection in human societies, leading to eugenics.

Finally, in this vision centered on genetic material, the body of the organism is excluded (see Nicholson 2014b). Organic complexity, the interactions between different biological elements, or between the biological and the social/environment… all are gradually being left aside in the analysis of heredity phenomena or the formation of phenotypic traits. The ontological scale, the one in which the explanation of the living is found, becomes that of the genetic factor, the molecule. In other words, since the traits of humans are mostly genetically inherited, society and culture have only a very limited role in the unequal distribution of these characteristics (in short, inequalities are "natural"). Politics and social or collective action are then of little use, since what counts in explaining who we are is the individual lineage, i.e., the traits directly transmitted by our parents. What would therefore allow us to "improve" our situation is the positive selection of "superior" natural characteristics or, and this has been the main methodology of eugenics, the negative selection of "inferior" characteristics (i.e., the elimination or sterilization of people with these traits). This exclusion of the body, associated with reductionism and eugenics, echoes and contributes to a deep, ancient and general affect characteristic of the West: the fear of the body (see section 3.3.1).

1.2.2 The construction of the notion of heritability, part I

Under the influence of the eugenics project, and following the ontological alignments identified by Keller (2010), the central question of genetics will then become the study and measure of the respective effects of Nature (innate) and Nurture (acquired) in the formation of traits. This question is still central today. These traits, in humans, will include the different parts of the body as well as personality traits and behaviors (like intelligence, a very early obsession of geneticists and eugenicists) and they are all conceived to be produced, entirely or at least partially, by the elements that make up natural forces. It should be reminded that there is nothing neutral about the choice of this research methodology. It can be partly explained because of the influence of physics and its methods on biology. Louart (2018) reminds us how much the direct transfer of these methods from one discipline to the other is inadequate (because of the necessity of simple and isolated objects from their environment, of the total control of parameters etc.). On another hand, underneath the differential measures of Nature and Nurture effects on traits development is a desire to develop ways to intervene on human reproduction and the necessity to define scientific criteria to justify and determine who will be able to reproduce or not. To measure the relative importance of genetic, the notion of heritability is created. Galton and others will use twin studies for this purpose (see Keller 2010). This era also marks the development and standardization of intelligence quotient (IQ) tests by the eugenics movement (for the control of reproduction of the feeble-minded and others considered "deviant"). The link between the measure and the studies of IQ's heritability and the science of eugenics is therefore historical, structural and fundamental. In 1918, Fisher, one of the founders of population genetics (also a eugenicist), proposed, according to Keller (2010), the most significant reformulation of the issues raised by Galton: 1) the question of causality between genetic elements and traits should be formulated in terms of differences in traits, and not on the basis of the traits themselves; and 2) there is a need to shift the analysis of heredity from individuals to populations. Until today, genetics is still struggling with this reformulation and has not yet escaped the political and linguistic traps that surround it. Since that founding moment, there has been a perpetual confusion between causality and correlation, causality and perturbation, individual and population, transmissibility and heritability, character and character variation etc. All of this will be discussed in more details in section 1.3 and 3.

But let us stay a moment longer on the hold of the eugenic ideology on genetics and biology at the beginning of the 20th century. It is worth mentioning the new obsession of the time: the genetic purity of beings. Genetic purity, i.e., the establishment of a lineage coming only from an individual and presenting no variations of the studied trait throughout generations, becomes both a quest and a standard of knowledge on heredity (Bonneuil 2015a). "Pure" genetic lines are established for flies (the fruit fly, a model animal for the study of the transmission of traits), cereals, yeasts (for beer), vaccines, etc. Bonneuil (2015a) recounts very clearly the ways genetics followed, supported and encouraged the entry and rationalization of living organisms in industry and agriculture (most of the main geneticists of the time were deeply associated to the agribusiness). Genetically stable, predictable, reproducible and calibrated life forms are produced in connection with the industrialization of the western world. At this time, the gene (as an abstract unit for the transmission of hereditary traits) is thought of as an inert, selectable and storable brick. As it is carried by chromosomes, it is therefore present only in the nucleus of the cell, which is then perceived as the control center of the organism, echoing the division of labor of the major industries of the time. Bonneuil (2019a) is also exploring another interesting line of research. This set of properties attributed to the gene feeds a vision of organisms in terms of genetic resources (which will lead to the notion of biodiversity) where they are perceived as a catalogue of properties that can be classified, hierarchized, exploited and "conserved". With respect to the link between the agribusiness and eugenics, it is interesting to note that in the 1930s, the Nazis began by banning plant seeds deemed "unproductive or susceptible to disease" (Bonneuil 2015a).

1.3 Genetic structuring and development

One mythical figure of genetics that has not been mentioned yet is of course Mendel and his famous laws of heredity (formulated in the 1860s) which, because they were established from very carefully selected characters and organisms, served mostly as counterpoint to all the exceptions that were later observed. This sequence of the history of genetics has been extensively covered, for example by Mayr (Mayr 1982) or, more critically, by Kupiec (2019) or Pichot (1999). From the "re-discovery" of Mendel's work in 1900 and during the first half of the 20th century, genetics developed in different branches (population, physiological and formal genetic). Genetics, from its very foundations, is therefore very heterogeneous in its methods and in the epistemological status of its components—one of the causes of the inability of genetics to become a "proper" science (Pichot 2001).

The beginnings of formal genetics (around 1915) focused mainly on locating mutations on the Drosophila chromosomes. The American biologist Morgan and his team (the main actors of this branch of genetics) worked frantically to map hundreds of mutations. Their laboratory infrastructures testified to a very profound evolution and scaling up of scientific practices, mirroring the general industrialization of the time. For Bonneuil (2015a), this is part of the "revolution of control" and the *systematic management* that was taking place in the large organizations and industries at that time, which inaugurated new forms of information management and biopolitics. This obsession with mapping will manifest itself again later with the hysteria of DNA sequencing, genomics and post-genomics. Morgan inaugurated in genetics the confusion between modelization and theorization, where the repetition, auto-confirmation and accumulation of experimental data constitute the basis and the aim of all inquiries (Pichot 1999). One might think that mapping is a neutral endeavor. It is, after all, only a matter of measuring, deciphering, observing, indexing, and representing a phenomenon in a graphic form. And yet, as The invisible committee reminds us in a fulgurant way: "One never maps a territory that one doesn't contemplate appropriating" (The invisible committee 2015). This interpretation is shared by Nelkin and Lindee: "the apparent precision of a map may make invisible the priorities and interests that shaped it. As forms of knowledge, all maps ... are the product of cultural choices." (Nelkin & Lindee 2004). What is represented, and how it is represented on a map, is as much a choice of visual power as it is a choice of persuasion and appropriation. A map is not an objective representation, it is contextual: "Mapping is the process of claiming territory—that was its historical purpose and it remains so today in molecular genetics. The 'commons' of human heredity has been divided up among the mappers, and the human genome is essentially, entirely patented..." (Nelkin & Lindee 2004). This is one of the fundamental thrust of genetics, established at the earliest stage of the discipline: cataloguing and mapping genomes for the purpose of appropriation. If there is one example of obscene clarity about the role of mapping in the conquest of territories, it is the colonial situation in Palestine. Against the mapping of the colonial power, Said proposed a counter-mapping, a counter-cartography of resistance: "In the history of colonial invasion, maps are always first drawn by the victors, since maps are instruments of conquest. Geography is therefore the art of war but can also be the art of resistance if there is a counter-map and a counter-strategy." (Said 1995). Echoing concerns about contemporary genetic essentialism, could we imagine a counter-mapping of the human genome?

Another contribution of Morgan and his team is the consecration of the conflations already mentioned: between the study of a character and the study of the variation of a character, between the population and the individual scale and between statistical measurement (correlation) and causality. Pichot tells us that the methodology of Morgan's school is part of the legacy of the role of hereditary diseases on the development of genetics, when they were used to establish the notions of hereditary characters and heredity, introducing a conceptual mistake. Indeed, a disease is not a biological trait, it is the alteration of one or several biological traits. The conceptual error (that of confusion between character and variation in character) will be reproduced on an industrial scale with Morgan's studies of the mutations/deformations of Drosophila. For example, his team claimed to study the heredity of the "white-eye" character, but in reality they were studying the heredity of a mutation that would cause a disease in which one of the most obvious symptoms were white eyes. It is therefore the study of the heredity of an alteration (amongst other alterations) of a trait, not the heredity of that trait (Pichot 2001). Keller shows that this conflation occurs through a three-step process: 1) the cause of a phenotypic difference observed in a population is attributed to a putative gene mutation, 2) the presence of a putative gene mutation signals the presence of a gene, and 3) the responsibility for the formation of that trait in an individual is attributed to that putative gene (Keller 2010). The existence of the mutation and the associated gene are, at the start, only hypotheses of Morgan's method. There is a shift from what begins as comparative genetics (the comparison of different phenotypes) to individual genetics (the study of the role of a particular gene in the production of a particular trait). Similarly, Mayr notes that "Galton's worst mistake … was that he transferred what was statistically true for the genotype as a whole to the mode of inheritance of individual characters." (Mayr 1982). The operation is so inherent to genetics methodology that it is generally invisible. However, this is very significant. To consider the gene simply as a *difference maker* (producer of variations) is not enough for the hegemonic project of genetics, it must also be a *trait maker* (producer of phenotypical characteristics) in order to have the power to act and create life, justifying its mobilization to control (human) evolution (Keller 2010). In other words, at the early stages of genetics, the notion of direct and unequivocal causality between a gene and a trait is essential to the justification of the eugenics project. Through the methodology developed by Morgan, genetics is enshrined as a science of the differential: it will henceforth focus of studying alterations, mutations and differences (the mutant type) in relation to a predefined norm (called the "wild type"). This is the distinction between "differential heredity" (the heredity of a difference, of the modification of a trait by mutation) and "absolute heredity" (the heredity of the actual trait) drawn by Pichot (Pichot 1999). It is therefore not by accident, or because some geneticists are ill-intentioned, that genetics is often used to define norms (natural and at the same time, because of its political aspect, social). This is its very essence, its methodological necessity and its way of constructing the world.

Between the 1930s and 1950s, the main story of modern biology emerged: the synthetic theory of evolution (STE or Modern Synthesis, also sometimes called neo-Darwinism). It is presented as a reconciliation between the young genetics and Darwinism. It is a theory of evolution centered on the gene (and later on the Genetic Program), reductionist, deterministic and that deepens the direct link between genes and traits and the exclusion of the environment (both the outside of the organism, the inner environment and even the composition of the gametes) (Noble 2015). Newman also notes that the STE theorists consciously set aside certain aspects of Mendel's and Darwin's work that were embarrassing to neo-Darwinism, but that will re-emerge throughout the 20th and 21st centuries (Newman 2013). This is the case for example of saltationism, rejected in favor of gradualism (see Mayr 1982). Gradualism is the idea that evolution takes place through a slow and regular accumulation of mutations causing tiny variations, selected as they go along when they give a certain reproductive advantage to individuals in a certain context (a reminder of the idea of the progressive accumulation of capital and wealth). The other aspect is of course the already mentioned dismissal of *soft* inheritance for a *hard* conception of heredity that will be perfectly complemented by the notion of the DNA molecule as independent, isolated from the outside and with a "perfect" replication system.

2. The construction of a hegemony

2.1 Cybernetics and genetics, an all-encompassing imaginary

The 1940s saw the birth of cybernetics, a science created by a group of mathematicians, logisticians, biologists, anthropologists, engineers, etc. One of their main goals was to try to forge a "theory of the mind" to understand and model how the mind, and therefore the brain, works. The analogy between the brain and the computer took root, nourishing both our perception of the brain (and by extension of organisms) but also, in turn, the proto Information technologies (IT) industry. Generally speaking, cyberneticists were very invested in the development of technologies and a large proportion of them had links with various industries, IT but also the military complex (the early work of cyberneticists in the 1940s is directly related to the Second World War and the development of weapons, notably prediction tools, for the United States' army). Cyberneticists eventually worked towards the modelization of a large number of cognitive, biological and social processes through mathematics and computer science. Concepts such as information, signals, networks, interactions and feedback loops acquired new fame. Cybernetics is therefore an essentially mechanistic science that tends towards a complete modelling of all biological and social phenomena. A central political aspect of cybernetics was its emergence as a science of *government* in response to the existential crisis experienced in the West in the first half of the 20th century, an ontological crisis stemming from the two wars and their respective atrocities, added to the major upheavals in the mathematical and physical sciences—a veritable crisis of modernity (Lafontaine 2004; Tiqqun 2020). Cybernetics was constructed in relation to a new need for order and certainty in the natural and social sciences, to an active desire for a new totality. By responding to the necessity of the times, "the metaphysical problem of creating order out of disorder" (Tiqqun 2020), it became a science of prediction, control and management, terrified by all that is unpredictable, i.e., life itself. In other words, cybernetics went beyond the modelization and mapping of territories (be they bodies, societies or anything else) to a project of (re)building these territories according to the constructed map. Last aspect of this crude summary of the discipline: cybernetics gave a central role to the concept of information. Not only did it reduce any problem to an information problem (and its communication), but it also worked stubbornly towards the idea of a transmission process that would neither alter the information being transmitted nor cause "background noise" (Tiqqun 2020). Lafontaine refers to an epistemological reversal of the interiority-exteriority axis where the interiority and substance of studied objects are no longer relevant to science, only their exteriority (the patterns of their relations and communications with the outside). For her, cybernetics is at the origin of an Informational paradigm, in which information and its communication is constructed as a response against the world tendency towards entropy and disorder. She traces the genealogy of this paradigm and shows that it has influenced most sciences throughout the second half of the 20th century: structuralism, ecology, anthropology, psychology, post-structuralism and of course biology, molecular biology and genetics (Lafontaine 2004).

At the same period, a new theoretical framework for biology emerges. This is imagined in 1944 by the physicist Schrödinger, who, echoing the question of "creating order from disorder", conceived heredity as the transmission of a physically ordered substance (Schrödinger 1944). According to him, the order of this substance commands the order of the organism, so there must be a correspondence between them (what he called a "code"): a microscopic specific signal (a pre-established original order) produces the macroscopic order of living organisms. For Schrödinger, the chromosomes constitute this substance and are both a law/code and a power of execution; they are the architect's plan and its execution by the craftsman. Schrödinger pointed out that his thesis of such an order required special physical laws for living beings. Indeed, Schrödinger's fundamental idea was that biological systems are of a different nature than physical systems (see Pichot for a summary of Schrödinger's contribution to the ideas around heredity, Pichot 1999). As pointed out by Kupiec, this principle of the biological macroscopic order originating in a microscopic order is the opposite of physics, which is able to comprehend the macroscopic order of matter from a microscopic disorder (Kupiec 2009).

After Avery's work (1944) suggested experimentally that the DNA is the support of heredity, and especially after Franklin, Watson and Crick's discovery of the structure of the DNA molecule in 1953 (the work of the former was kept invisible for many years), Schrödinger's conception became, with some accommodations, the theory of the Genetic program in the early 1960s (see Mayr 1982 and Morange 2003 for more details on this period). Thus began, as Bonneuil (2015a) calls it, the period of the gene-program, or the gene as "chief planner and factory cell engineer". Again, an imaginary in sync with the global economic system of the time. The gene is then seen both as a DNA segment and an informational molecule, and heredity is its message. In the purest Fordist logic of the time emerges the Central Dogma (Crick 1958). Although the Dogma's formulation is a little more subtle than many critics seem to think, it is nevertheless an instructive model with a predominantly unidirectional flow of coding information from top to bottom: from DNA to RNA and then to proteins. The genotype/phenotype dualism finds here a new justification. During the 1960s, the famous "genetic code" was elucidated. In fact, biologists simply understood in more details how cells use DNA to make proteins. Here, the influence of cybernetics is obvious. The production of proteins is ultimately simply a chemical reaction (the interaction of DNA with proteins and other molecules resulting in the production of other proteins), but it is the only one that is specifically described in terms of a "code" or "transmission of information". As proteins are, at the time, seen as the fundamental element of organisms, if DNA is the "code" used to build these proteins, it can therefore be considered as the source of all the information necessary for life. The DNA becomes the matrix of life. The ordered substance theorized by Schrödinger is assimilated to DNA. However, for Pichot (2002), the Schrödingerian principle is "relaxed" in this case, in the sense that the global correspondence between the order of genetic material and the organization of organisms has been replaced by a local correspondence between the internal order of genes and the internal order of proteins (the "genetic code"). This period of gene-as-a-DNA-segment is a culmination of molecular biology. Not only it recapitulates all main previous theories of heredity (Weismann, Morgan, Schrödinger) but it is a direct legacy of the late 19th century all-encompassing biological theories and their attributes: imperialist theories based on a single substance that is at the origin of all truth, a total physical and chemical explanation of the organism bordering with religion (Pichot 1999). Another significant shift effectuated by molecular biology is the inclusion of proteins and enzymes within the phenotype. Previously, it was thought that the factor of heredity was of proteic/enzymatic nature: the "gene" was a protein. Therefore, the expression of heredity was understood as *protein/gene → trait*. However, with the gene now identified as a DNA segment responsible for the production of a protein/enzyme, the expression of heredity became *DNA/gene → protein/enzyme → trait*. The physiological mechanisms between the protein and the traits were evacuated from the domain of genetics and heredity, which focused thereafter mostly on the explanation of the relation between the DNA and the protein (Pichot 1999).

This vision of the organism is sanctioned by Jacob and Monod and their work on the functioning and regulation of a particular region of a bacterial DNA, the lactose operon. They proposed a model of gene regulation that will constitute one of the foundations of molecular biology and that directly imports concepts from cybernetics such as specific signals, information transmission, regulation and feedback loop. The regulation of a gene will depend on the activity of other proteins that bind specifically to a particular region outside of the gene to transmit an activation or repression signal. In this model, according to Kupiec and Sonigo (2000), the world of signals (regulation) is conceived as separate from that of metabolism (which would be the domain of chemistry). The "signal world" will gradually become a universal explanation of the natural world. If something happens in an organism, it is because it was triggered by a signal. The world we experience is only a reflection of the world of signals, echoing the essentialist Theory of ideas of Plato. The other two important features of Jacob and Monod's regulation model are its instructive nature and the necessity of the concept of stereo-specificity (Kupiec & Sonigo 2000). If an entity waits to receive a specific signal in order to perform an action, this implies that it already possesses the ability to interpret the information carried by this signal: the result of the process always precedes, in a virtual way, the real process. Fitting a lingering and powerful tradition of essentialism in the West, "[an instructive and] deterministic model might seem perfectly relevant at first sight for accounting for the precision in the way an organism functions" (Kupiec 2009). The idea of stereo-specificity not only gives a central role to the DNA sequence (responsible for the amino acid sequence and therefore the spatial configuration of the corresponding protein) but is paramount to the theory/metaphor of the Genetic program. This most cybernetic metaphor (that appeared in 1961 in two independent papers, one from Mayr and one from Jacob and Monod) could be defined as an instructive model (with cascades of interactions, signalling pathways, gene networks...) where differential gene expressions are responsible for the differentiation of cells during embryogenesis and the functioning of the organism until its death. In this theory, proteins interact in an unambiguous way, with each molecule having one or very few partners, excluding stochasticity (see Kupiec 2010 for a critique of this). Information is the cause of the ensuing order and, again, the final form pre-exists the biological material that is transformed, a faithful legacy to the neo-preformationist theory of Weismann, embodying the microscopic order theorized by Schrödinger. In the 1970s new methods of cutting and manipulating DNA are developed, giving rise to genetic engineering (e.g., the manufacture of genetically modified organisms by transgenesis). "Lego" techniques, instructive models of DNA regulation and cellular differentiation, cybernetic metaphors invading genetics, the Central dogma, general genetic essentialism... organisms are perceived as a rigidly functioning machine and the idea of the Genetic program takes hold. This set of ontological representations are part of the Genetic Order, built on the foundations laid by Schrödinger, and it is to be understood as the answer of biology to the metaphysical problem of order following the Second World War.

For Sonigo the success of modern genetics and the world view it offers is due not only to the influence of cybernetics (where everything is only an immaterial exchange of information) but also to the central notion of the individual as a separate and independent biological entity, associated to a vision of the natural world as compartmentalized and discontinue (Sonigo & Stengers 2003). In order to understand the reproduction of the similar, these two influences have pushed the explanation towards an emphasis on the concept of information and denied the idea of a material continuity between generations (which Sonigo claims should be seriously revisited, see Sonigo 2013). But in the same way that the historical vision of life emerging in the 19th century had been a challenge to the centrality of the notion of species (see above), it should also have been a blow to the centrality of the notion of individual. For Sonigo and Kupiec, the species and the individual are only arbitrary snapshots of ongoing oscillating processes, respectively the evolution and the ontogeny—both processes that are considered equivalent in their model of ontophylogenesis (on these questions see their respective works Kupiec 2019, 2012, 2009; Kupiec & Sonigo 2000; Sonigo & Stengers 2003).

As early as the 1970s, numerous studies showed that the genome is more malleable and the gene more complicated than previously thought (Morange 2003; Burian 2013). It is becoming increasingly clear that, in eukaryotes, not only is there no strict correspondence between the order of the genetic material and the order of the living being (the direct causal link between genes and traits is particularly difficult to demonstrate, due for example to polygeny and pleiotropy), but there is also no strict correspondence between the order of the gene and the order of the protein. As a consequence, the Schrödinger's principle of the macroscopic biological order originating from a microscopic order requires numerous adjustments, which, for Pichot, are equivalent to a generalised weakening (he uses the notion of "softening" in Pichot 2002). As to the concept of gene, due to these difficulties, it is slowly losing its structural definition to go back to a more abstract, functional and "semiological" one where it is defined after its product (Pichot 1999).

2.2 Genetics and neoliberalism

The world economic order entered a new period at the end of the 1970s, that of neoliberalism. As usual, genetics will be part of this upheaval, while providing it with a powerful imaginary, in this back and forth movement typical of modern science. This can be seen first of all with the boom of genetic engineering, i.e., the birth of an industrial sector of biotechnologies which supplies molecules to the pharmaceutical, agricultural and petrochemical industries. At the academic level, Aguiton (2018) characterizes this pivotal period and the decades that followed by three major transformations: 1) transformation of the figure of the scientist into an entrepreneurial researcher/start-up creator; 2) transformation of intellectual property regulations, with an increasingly massive appropriation of genetic discoveries and modifications; 3) an ever closer link between science and industry, in terms of research programs, funding, curricula, etc.

Perhaps it is not a coincidence that *The Selfish Gene* was published at this time, in 1976. Dawkins offers a vision entirely centered on DNA and the gene. An extreme reductionism where the DNA, as the ontogenetic starting point of all that concern organisms, is both the source and the goal of biological processes. According to Noble's interpretation, what is important in the SGT is the dichotomy between the replicator (DNA, gene) and the vehicle (organism). The replicator is the fundamental element of heredity, and therefore of life, and its evolution. It is the entity whose different variants can replicate identically and, potentially, for eternity—an immortal entity. The organism, the body, is merely the vehicle created by the replicator to pass from generation to generation (Noble 2011). What is at stake in this construction of DNA as an immortal text is that it can reveal the essence of the present, the events of the past and the possibilities of the future. DNA is history and destiny, echoing the centrality of the notion of immortality in the imaginary of genetics, already mentioned in connection with Weismann's theory. The irony of the metaphor must be emphasized. Dawkins, who, despite portraying himself as a perpetual crusader against religious obscurantism, does not seem to realize the extent to which his theory appeals to one of the most classical theological dichotomies (and hierarchies), that of body and soul. DNA—the replicator—is the immortal essence, the spirit, or soul. While the body and the cell—the vehicle—is existence, it is the world that degrades, ages, and ultimately has little significance. It is impossible not to notice similarities with transhumanism, which presents itself as a movement at the cutting edge of technological modernity with marvelous promises but is, ultimately, based on the fear/hatred of the body and of organic, and therefore mortal, existence (Benasayag 2016). A fear shared with institutional monotheist religions.

The SGT opens the period of the 1980s where the gene became more of a unit of intellectual appropriation associated to a more generalised patenting of DNA sequences (Bonneuil 2015a). The general aim of research being to control and command the gene, genetic engineering and molecular biology explode. The frenzy of DNA sequencing (first of genes and then whole genomes) and genomics (the study of these genomes) begins in the late 1980s. Once again under the influence of cybernetic and computer language, and when it is simply a matter of determining an aspect of the structure of a molecule, DNA sequencing becomes "genome decoding". The genome is the key to living beings, and "deciphering" it means opening the "book of life" and understanding its mysteries. With the sequencing of the human genome, starting in 1990, physical and mental illnesses, addictions and homelessness will be overcome (see the incredible editorial of Science in support of the human genome sequencing project, Koshland 1989).

Several parallels can be drawn between the vision proposed by modern genetics (the SGT in particular) and certain characteristics of the developing neoliberalism. One is that all aspects of life are directed and shaped either by the minuscule or the gigantic. On the one hand, organisms, their functioning, development, behavior and all aspects of their existence are influenced or even directed by genes. These genes can be modified on demand, rearranged, ranked, corrected, extracted and then reintroduced. On the other hand, Neoliberalism is the commodification of all aspects of life, the marketization and entry of technology into the intimacy of minds, behaviors and bodies. The embodiment of cybernetics in neoliberalism, as Tiqqun (2020) describes it, is this back and forth movement where beings are emptied of what makes them active, creative and autonomous (through constant capture or extraction, be it bureaucratic, digital or of any other nature) and are then "fed back" (recreated as subjects) by those data that have previously been processed, ordered, hierarchized and arranged. Secondly, this shaping (of who we are, as social individuals or organisms by neoliberalism or DNA) is effected beyond our perception or our reach. The genes, those little elements that direct us, are invisible to us. They are tiny command centers and our bodies, these robot/machines, obey their programs. Similarly, we have almost no control over the extreme financialization of the economy, the fact that a huge part of wealth creation is now dematerialized, invisible, computerized, algorithmic, the way important decisions about this wealth creation and many other aspects of our lives are made somehow, in unknown places (at least with which we generally have no connection to)... Finally, genetics and Neoliberalism both mobilise representations involving an extreme reductionism. DNA is the source and goal of all biological phenomena, while competition and the free market are the sources and goals of all social phenomena. An explanation for the power of this essentialist and reductionist vision could be its simplicity and its complementarity to capitalism. Indeed, the SGT and free market theory are disarmingly simple and all encompassing, egoism and competition being the two main characteristics (King D, personal communication). All phenomena, social and biological, could be explained by these two mechanisms. Nelkin and Lindee (2004) summarize the "advantages" of genetic essentialism: 1) it shifts the source of social problems to the individual (and not to society), 2) it provides a kind of equivalence to moral redemption and/or absolution ("it's not my fault, it's my genes!"), and 3) it also provides a scientific, "neutral" and rational justification for social categories.

What is at stake in this pivotal sequence of the 1970s and 1980s is a paradigmatic shift in the order inspired by computer science and cybernetics. Since the end of the 19th century, the predominant model of order had been roughly that of Fordism: a highly hierarchical structure, with a top-down management of politics and economics. The Fordist model, which had become too rigid, had to change. This marked the emergence of the network society. There is no longer a single source of control, the model becomes that of a network system, made up of more or less equal nodes, regulated by feedback loops. This is the idea of "liquid nature" put forward by Bonneuil (2015b). He describes the transition from the Fordist form of capitalism (one of resource and industrial production) linked to a perception of life as a resource (a stock and a collection of entities and species) to a neoliberal form of capitalism (financial, based on assets and income, services and investments) associated with a perception of life as a set of functionalities and "services", organized in networks and made up of relationships.

Cooper offers a fascinating interpretation of the enormous shift of this era, taking the USA as an example, but that could be applied to the West in general (Cooper 2008). The difficulties of Fordist capitalism caused a transition in the North American economy (and therefore the world economy) towards an "economy of promise" that Cooper calls the Bioeconomy. Already pointed in the famous Club of Rome's report *Limits to Growth* in 1972, the realization of the natural limits of the planet will be all the more relevant in the context of the oil price increases due to the oil shocks of 1973 and 1979. Cooper describes how the American administration then decided to promote the development of both digital and biotechnologies. In fact, while appropriating certain concepts of ecology or theories of self-organization, the capital "realized" that although the planet's fossil energy resources were finite, life was constantly renewing itself. Lafontaine identifies here the cross-influence of cybernetics on certain concepts of the natural sciences (the ecology of systems, the planet and life as a large autonomous and self-regulated whole), on the development of the digital industry and on the birth of neoliberalism (Lafontaine 2004). The biotechnologies characteristic of these developments are GMOs, gene therapy, stem cells, reproductive technologies, synthetic biology, biofuels, etc. It is around these technologies that the Promise economy developed (Cooper 2008; Lafontaine 2014). They organized a speculative imagination, a faith in a future where the limits of life are constantly being pushed back, where the health of future generations is always-already prioritized over that of current generations. This is reflected in funding choices, where, for example, medical biotechnology research will be largely favoured over maintaining or improving public health systems (see also Duster 2003). Here lies an important node in Cooper's story. Neoliberalism and the transition to a Bioeconomy and a Promise economy are accompanied by an attack on the structures of the welfare state. Rouvroy, deciphering the relation between the sequence opened by the Human Genome Project (HGP) and neoliberalism, reaches a similar conclusion. She associates the process and the completion of the HGP to the emergence of a new "mode of governance by genetic risk". A central element to this new mode of governance is the major shift towards an individualized, self-responsible notion of health:

> "The narratives of genetics and the globally dominant messages of neoliberalism converge to make our post-genomic future visible and legible in advance through tales of a genetic mythology that promises a new transparency and precise calculability of individual health risks, behaviors and identities, and through a rhetorical insistence on the liberating virtues of privatising health insurance and dismantling welfare states." (Rouvroy 2008)

The transition to a Bioeconomy/Promise economy is also reflected in a fundamental shift in the economic relationship between the USA and the rest of the world: from creditor (since World War II) to debtor. The promise is therefore also in this debt-based relationship that is established in the following decades. A debt that, in reality, is so enormous and consubstantial to the global economy that it will never be repaid—an eternal promise: "Neoliberalism and the biotech industry share a common ambition to overcome the ecological and economic limits to growth associated with the end of industrial production, through a speculative reinvention of the future." (Cooper 2008). In short, the living, *life itself*, became a central resource for economic development, growth and added value. "Promising" life processes and molecules (giving perspectives of longer lives, miracle cures, stronger and healthier babies etc.) were, and still are, mobilized to leverage enormous amounts of preliminary investments, inflating an economy of bets and risks completely disconnected, for example, to actual public health and its social aspects. Combined with the explosion of information technologies, the neoliberal biotechnologies will have a huge impact. One must read or listen to Lafontaine for an overview of these major changes. She describes how the Bioeconomy is a process of marketization of the body, especially of women's bodies, through the development of reproductive technologies (artificial insemination, *In vitro* fertilization, ovules donation, surrogate pregnancies etc.) which are instrumental in the current trend towards forms of liberal eugenics (see below). This development of a form of bio-citizenship (a new form of citizenship centered on the optimization of the biological and bodily potentialities of individuals), accompanied with a molecularization of culture, has transformed our relations with our bodies and our health: ultra-individualization, redefinition of health in terms of risks, injunction to constant self-monitoring etc. (Lafontaine 2014).

2.3 Genomics and networks—a new ontology?

The genomic obsession starting at the end of the 1980s had the advantage of putting the theoretical difficulties of genetics already mentioned on hold, to give way to mainly technical problems (Pichot 2003). Relying on technology also provided a solution to these difficulties: "Faced with the apparent disorder of genetic material, geneticists have undertaken to 'draw up the text letter by letter' in order to entrust the analytical power of computers with the task of discovering a functional order (which, in the end, shows great loyalty to Schrödinger)." (Pichot 2002, transl. by the author). The mass production of data and the increasingly important role given to bioinformatics in the 2000s testify to a recomposition of methods and skills in biology (Aguiton 2018). However, even if this lead to "impressive" technical achievements, it is the same conceptual error that is repeated, one of the fundamental errors of biologists: thinking of the description of a phenomenon (even in its smallest molecular details) as an explanation of that phenomenon (the way formal genetics believed that "modelization was theorization" at the beginning of the 20th century). Indeed, once the human genome was sequenced, the scientific community realized that the knowledge of its 3 billion base pairs did not provide the fantasized answers to all its questions. But rather than questioning the conceptual errors that led to this research program, the industrial techno-scientific approach has simply moved up a level: it is now a matter of studying how the genome is used by the cell—the era of post-genomics. This is what Bonneuil calls the period of the network gene (2015a). This sequence is marked, amongst other things, by three developments described below.

The concept of the gene, already very vulnerable and subject to a chaotic history, is now crumbling. In a little over 100 years, the notion of gene has moved from an abstract nature to a protein nature, an undetermined physical location on chromosomes, an ordered physical structure, a discrete element of the DNA molecule that codes for a protein, a functional unit… only to be challenged by the results of molecular biology itself, reaching a climax in recent years with genomic and post-genomic studies. To exemplify the attitude of biologists towards these difficulties, François Jacob, when asked in 2000 "whether he and other molecular biologists were aware of how much the very notion of gene was threatened by his [late 1960s] findings?", answered: "Yes, we were aware of these theoretical difficulties, but we chose not to speak too much of them; the priority was to move forward." (cited in Gayon 2016). Nowadays, no one knows how to define a gene any more, which is somehow embarrassing for biology and genetics, of which the gene is the object (for a detailed history see Bonneuil 2015a; Burian 2013; Keller 2000; Mayr 1982; Pichot 1999; but also Gerstein *et al.* 2007 for the consequences of the HGP on the definition of the gene).

Epigenetics is a term created in the middle of the 20th century by Conrad Waddington (see Keller 2000), in reference to epigenesis, to refer to all the mechanisms involved in embryonic development including the influence of the environment. For example, the notion of gene regulation, that is part and parcel of the Genetic Program concept, is a form of epigenetics. Since the turn of the millennium, epigenetics has undergone a spectacular development (with the study of the chemical modifications of the chromatin, the non-coding RNAs, and their potential transmission). At first glance, the rapidly expanding discipline seems to call into question certain fundamental notions of genetics. One is the centrality of the gene as the unit of heredity. Since these epigenetic modifications can be caused by external stimuli (toxins, traumatic events, etc.) and be passed on from generations to generations, biology must now grapple with a concept that was rejected at the outset: the heritability of acquired traits (see Boskovic & Rando 2018 for a recent review on epigenetics and Noble 2015 for a discussion of the implications of epigenetics findings). However, other researchers, including biologists critical of the reductionist and deterministic mainstream approach of genetics, are not so enthusiastic about the results of epigenetics. For example, Kupiec understands the recent interest in epigenetic mechanisms mostly as a continuation of an old habit of geneticists' "double discourse" dating back to the notion of "reaction norm" created by Woltereck. In other words, when genetic determinism is being challenged experimentally geneticists invoke/accept some form of influence of the environment, without realizing that this is in contradiction with the theoretical foundations of their discipline. This is revealed, by the actual word itself where "epi-" means "above", so epigenetics would only be an additional layer added on top of genetics, and would not constitute a challenge to the determinism, to the centrality of the gene, nor to the idea of "order created from order" inherited from Schrödinger (Kupiec 2019).

In parallel with these developments, a systems biology is emerging. Systems biology is an ill-defined heterogeneous discipline, but Bizzarri *et al.* (2013) see two branches: theoretical and pragmatic. The pragmatic branch is the one that leads for example to synthetic biology, a techno-industrial approach that works towards the complete engineering of living beings. Starting in the 2000s, Synthetic biology built its promises on a critique of the genetic engineering of the 1970s, which was seen as too slow and approximate. Based mainly on the post-genomic techniques (transcriptomics, proteomics, metabolomics...), it is mostly a technical approach aiming at developing cheaper and more robust genetic modification techniques with better and faster transfer from laboratory to industry. A systematic engineering of life. Synthetic biology is still part of the reductionist paradigm in that it sees the organism as a collection of elements of unique, well-defined types that interact with each other, in the hope of maintaining a vision of life in which the causal relationships between specific entities and a biological function or trait are clearly defined, and therefore patentable. As such, it is a particularly telling example of the evolution of biology towards ever more engineering: the continuation and an acceleration of practices to turn organisms into "living factories" for industrial, pharmaceutical or other products. The story of the world we are telling ourselves, that of humans controlling and exploiting its environment, is exposed here with chilling clarity.

The theoretical branch of systems biology is built on a critique of the reductionist view of genetics and neo-Darwinism and the desire to re-inscribe the organism in the understanding of evolutionary, developmental and hereditary processes. It challenges the notion of Genetic program and the centrality of DNA in what constitutes the hereditary material, and proposes to take into account the non-DNA or cellular heredity (see for example Noble 2017). This new systems biology is both extremely complex and fascinating in its technical achievements and, at times, politically attractive for the imaginary it builds. Indeed, for this part of biology, it is now interactions, networks and systems (i.e., relations) that matter. The millions of interactions between proteins and between proteins and DNA are studied in an automated way, then modelled and represented. It is no longer the genes, or the proteins, but their patterns (configurations of relationships) that are the basis of the explanation. The fundamental entities change, or, as Bonneuil says: "From molecular biology to systems biology, we move from a substantial ontology to a relational ontology" (2015a, transl. by the author). This ontology is extended to the living world, seen as a network and a continuum, as a set of inter-relationships and inter-connected organisms. These ideas are appealing and correspond to a certain idea of relations that goes against the obsession of centrality, separation and compartmentalization, characteristic of biology and modernity in general. Yet, in these statements, as in their implications, there is a clear, if not determinism, at least an influence of cybernetics and its embodiment in neoliberalism. The gene, like life in general, is now seen as flexible, adaptive, connected, hybrid, innovative... echoing Bonneuil's critique of this relational ontology as "liquid nature" (Bonneuil 2015b). There is thus a major challenge here: (how) can biology contribute to (new) relational ontologies while escaping the terms of cybernetic capitalism?

3. The Genetic Order

3.1 The construction of the notion of heritability, part II

As told in section 1.2.2, the focus of the science of heredity shifted early on towards what is conceptualized as "the part of genetics" in the transmission (and formation) of traits in organisms. In other words, there has been a geneticization of the study of heritability. This next part is dedicated to the clarification of issues around heritability, the opposition hereditary/acquired and the notion of causality and its conflation with correlation.

Keller identifies two meanings given to the term heritability: ordinary and technical (Keller 2010). The ordinary meaning (often implied by scientists and the media) refers to a trait and its transmission/formation at the individual level (the transmissibility of this trait). Heritability studies tend therefore to be perceived as the determination of the share of the genetic component, as opposed to the social and cultural component, in the formation of traits. However, the (proper) technical meaning refers to the variation of that trait at the level of a population: a statistical measure related to the proportion of the influence of genetic variation on phenotypic variation in a specific population of organisms. These differences are extremely important. For Keller, geneticists and journalists are perpetually shifting between the ordinary and technical definitions of heritability. The latter definition is a statistical measure, not a measure of causality; it only makes sense in relation to a population, not at the individual level. Heritability studies therefore do not tell us anything about transmissibility, i.e. about the quality of a trait to be heritable. They are studies that are entirely context-dependent and have no implication on the mechanisms of transmission (of heredity) of traits between generations. To better understand the difference between the heritable quality (its transmissibility) of a trait and its (technical) heritability we can turn to a very simple example: the number of hands in humans. The number of hands (two) is an inheritable trait, it is transmitted from generation to generation with almost perfect regularity. Its heritability, the influence of genetic variation on the variation of this trait, is, however, close to 0. Indeed, the variation of the trait in human populations depends almost entirely on environmental causes (the loss of a hand by accident). An inheritable trait can therefore have almost zero heritability.

A similar argument can be drawn, based on one of the theoretical weaknesses of genetics already mentioned: the opposition between in-principle-hereditary (inherited or not) and in-principle-non-hereditary (acquired) traits (Pichot 1996). Pichot tries to unravel this confusion and explain that such defined hereditary and acquired characters are not comparable terms. In the case of acquired traits, one instantly thinks of phenotypic traits (an arm cut off in an accident, therefore an effect) but the acquired quality never applies to the cause (the external determinant that produced the cut arm, e.g. a machine). However, in the case of hereditary traits, are considered inheritable both the phenotypic traits (the effects) and their genetic determinants (the DNA sequences, the genotype, i.e., the causes). This is a fundamental imbalance, a hiatus in definition that has plagued genetics to the present day:

> "these notions [hereditary and acquired] have meaning only in cases where there is, if not a purely genetic (respectively external) determinism, at least an immediate linear relationship between the phenotype and the genotype (respectively the external environment). With the exception of the primary protein sequence (which is directly related to the corresponding genes—as a first approximation because in eukaryotes the structure of the genes is so complex that such a direct relationship could be disputed), however, such cases are very rare. They are almost non-existent at the macroscopic level. As a result, in practice, the concepts of hereditary and acquired are virtually inapplicable to phenotypic traits, even though they are supposed to apply to them." (Pichot 1996, transl. by the author)

Simply asking seriously the question "what is a hereditary trait?" leads to a critical deconstruction of the foundations of genetics. Taken further, the question of "what is a trait?" could also be explored. One can indeed wonder about the equivalence of traits such as the primary structure of a protein, eye color, the shape of the nose or behavior. Are they unique traits? Are they similar in nature? Are some not rather sets of characters? How can they be compared if they are not of the same nature? Genetics does not provide clear answers to these essential questions (Kupiec 2019; Pichot 1996). Moreover, if the amino acid sequence of proteins is an apparent trait of an organism (and therefore part of the phenotype), why not considering the nucleic acid sequence of DNA as an apparent trait of an organism? Is DNA part of the phenotype, and if yes, then what is left to make up the genotype?

Focusing on issues around heritability and the oppositions hereditary-acquired and genotype-phenotype also raises the question of causality in biology and how to establish it. Noble reminds us that, often, functional studies of genes repeat Morgan's conceptual error (studying the heritability of an alteration, among other alterations, of a trait, rather than the heritability of that trait) (Noble 2008). The problem with this method is that it cannot reveal the totality of the functions of a gene since it does not show the common effects between the mutant and the wild type. To illustrate this, let us take a hypothetical example of a gene A, which has five functions related to traits 1, 2, 3, 4 and 5 (the biologist does not know any of these functions a priori). Gene A is mutated and we will observe a major change in trait 5. We will have highlighted one possible function of gene A, but not all of them, since functions 1 to 4 have not been identified. However, the usual conclusion of molecular biologists is that the function 5 is the main function of gene A and the rest is generally dismissed as noise or pleiotropy. Noble also raises the issue of the Differential Genetic Effect. That is, most variations in DNA sequences, including changes in coding sequences, do not cause a change in phenotype. They are compensated for by the organisms, a property referred to as "robustness". The reason why this is rarely taken into account is that modern biology and its reductionism ignore the organism and is based on the idea of a sole upward causality, coming from the lower level (the molecular level) (Noble 2008).

Finally, the conflation between causality and correlation can be illustrated with the recent multiplication of Genome Wide Association Study (GWAS) papers and their Manhattan plots. Yet, in the end, what do these studies show? Only a statistical link, a correlation, between the presence of certain nucleotides and a trait, as the physiological link between the sequences containing (or close to) these bases and the trait has not been demonstrated. GWAS studies generally include comparisons of the genes identified to databases of annotated genes, therefore they can offer indirect leads regarding a link between the presence of DNA sequences and a trait. However, they main outcome is that biology is still confined to the accumulation of data and correlations, with very little theoretical or physiological progress. At this stage, it is useful to recall the study by Calude and Longo, which emphasized that "[t]oo much information tends to behave like very little information" (Calude & Longo 2017). Genetic essentialism finds a new robe and new justifications for the sequencing of even more human genome sequencing, while eugenics endeavors like the search for a genetic basis for intelligence ("educational attainment"), homosexuality or crime ("antisocial personality disorder") flourish (Davies *et al.* 2016; Rautiainen *et al.* 2016; Sanders *et al.* 2017).

3.2 The construction of the Nature/Nurture dichotomy, part II

Section 1.2.1 was dedicated to the historical construction of the opposition between Nature and Nurture, or genetic and acquired, in relation to the eugenics project. This dichotomy is so "banal" today that it does not even need to be thought of, argued or defended. It is self-evident, a stark example of a belief that can be considered ontological. Some people will lean towards the genetic and natural explanation, others towards the environmental and cultural explanation, but it is rare that the existence, history and role of this dichotomy are questioned.

Picking up the history of eugenics and the Nature/Nurture dichotomy where we left it, in the middle of the 20th century, the Nazi exterminations of the Second World War undermined the legitimacy of the eugenics project. While the term eugenics was not to be mentioned any more, official eugenics societies simply changed their names and certain ideas and practices went on (such as forced sterilization programs). With the emergence of medical genetics, the Nature/Nurture opposition was deployed even further. The search began for the "gene FOR" this or that disease, each of them considered a unique and singular trait, repeating again the conflations correlation-causality and gene-mutation. Lippman's definition of geneticization summarizes what is at stake here: "the process by which interventions employing genetic technologies are adopted to manage problems of health. Through this process, human biology is incorrectly equated with human genetics, implying that the latter acts alone to make us each the organism she or he is." (Lippman 1991). It is also worth pondering for a minute what could be the actual applications of medical genetics apart from eugenic preventative acts such as selective abortion and selection of embryos before implantation, or curative acts such as gene therapy (which has been an extremely expensive and, not surprisingly, mostly disappointing approach so far).

Another discipline emerging in those years was behavioral genetics (see Bliss 2018), which was to cause several scandals in the 1970s, particularly around the ever-present issue of the link between genes and intelligence (as measured by IQ). The discipline more or less metamorphosed into sociobiology, whose basic premise was that social behaviors, in a same way that physical traits, are based mainly on genetic foundations, are inheritable and are the results of evolution. Racism, for example, found here a new scientific rationalization (it would only be the result of the innate aggressiveness of humans and/or their propensity to protect those genetically close to them). The central idea of the emblematic work of the discipline (*The Bell Curve*, published in 1994), was that the class structure in the USA is based mainly on individual inequalities in terms of IQ, due to genetic differences. The authors accompanied their argument with "soft" eugenic recommendations, such as the prevention of immigration and the curb of welfare state provisions, which were seen as responsible for the decline and dilution of "cognitive elites" (Bliss 2018). Affected by the scandal provoked by this book, sociobiology morphed into evolutionary psychology. Much could be said about this discipline: its use of analogies, metaphors, circular logic and ad hoc explanations. All with the proclaimed goal of understanding what makes us specifically "human". Like its parent disciplines, evolutionary psychology will mostly lend itself to justify existing social hierarchies and the reactionary political projects that promote them (see also McKinnon 2005).

From the 2000s, the era of Big data in biology and medical imaging, especially of the brain, also witnessed an explosion of disciplines based on genetic and biological essentialism, such as cognitive genetics, neuroeconomics, neuropolitics, neurocriminology (heir to the old tradition of biocriminology) or sociogenomics. What they have in common is their focus on biology and genetics in the explanation of social phenomena. Bliss (2018) concludes that all these disciplines, which are intended to be transdisciplinary (including between the natural and social sciences), always end up reinforcing genetic/biological determinism as well as the opposition and separation between nature and nurture and favoring the "natural" explanation. Of course, these disciplines face many criticisms, coming from the human sciences or from critical biologists, but unfortunately the common point of these criticisms is that they do not try to question the framework of this opposition between Nature and Nurture, and therefore recognize it as valid and operative. The Nature/Nurture debate has therefore proven particularly difficult to escape. As Keller (2010) concluded, not only no one really knows how to define what we put behind the categories of Nature and Nurture, but it is also a haphazard mix of major issues (moral, political, philosophical, biological, sociological, religious, etc.) and the confusion surrounding it is exacerbated by the vagueness and ambiguities of language maintained by biology and genetics on heritability.

3.3 Eugenetics

The main problems with the Nature/Nurture dichotomy are the political vision of the world it carries and the fact that it is, ultimately, inoperative in the context of biological science. The world view conveyed by the Nature/Nurture opposition is complex (Table 1). For example, the "body" may be perceived on the side of Nurture or Nature depending on the context and the epoch. In the context of natural sciences, Nature is the world of essence, signals, DNA and genes, the replicator, the immortal lineage... Nature is understood as the ultimate, necessary and inescapable explanation of living beings. On the other hand, in power relations such as patriarchy, racism or capitalism, what is associated with Nature corresponds to what can be dominated, exploited or massacred (women, racialized people, certain social classes, the planet...). In both cases, to naturalize is to justify. To naturalize is to define Truth; and Truth is the prerogative of Science and scientists. Since God has lost his explanatory power about the world, it has been replaced by another entity: DNA. Genetics, like monotheisms, has its dogmas, its institutions and its "fundamentalists", and "like the Christian soul, DNA seems relevant to concerns about morality, personhood, and social place." (Nelkin & Lindee 2004). Of course, a whole discourse of justifications exists to mask this religiosity of genetics: from the necessity of a more productive agribusiness to the need for industrial innovation, progress and to always "move forward". But the ultimate and overwhelming argu-

Nature	Nurture
essence	existence
body	spirit, soul, mind
female	male
non-whites	whites
country side	cities
savages, the poor, criminals	civilized
non-humans	humans
biological	social, cultural
permanent	temporary
invariant	varying
immortal	ephemeral
germen	soma
germ line	body
hereditary	non-hereditary
genotype	phenotype
innate	acquired
gene	environment
signal	metabolism
DNA	organism
replicator	vehicle

Table 1: Dichotomies associated to the opposition Nature/Nurture.

ment is always the medical one. A reminder of how the fear of diseases and the imperfections of the body constantly gets mobilized to ensure our consent to new biotechnologies and potentially eugenic practices.

3.3.1 Fear of the body

It would have been possible to write this account of genetics not chronologically, but according to the different fears it has mobilized in the course of its history. If I had to choose one that seems to be the central point, it is indeed the fear of the body, characteristic of the West and its project, modernity. Rouvroy reminds us of Foucault's insight to whoever wishes to understand the exercise of bio-power (the governmental techniques for achieving the subjugations of bodies and the control of populations): "One needs to study what kind of body the current society needs…" (Foucault & Gordon 1980 cited in Rouvroy 2008). She also warns us, "the 'genetic information society'… socializes people through fears". In this society, the place we focus on to find commonalities between humans has shifted to "the 'invisible' but locatable and 'calculable' internal, molecular milieu" (Rouvroy 2008). Federici, reflecting on the neoliberal ontology of the body, draws poetically the same conclusion:

> "We internalize the most profound experience of self-alienation, as we confront not only a great beast that does not obey our orders, but a host of micro-enemies that are planted right into our own body, ready to attack us at any moment. Industries have been built on the fears that this conception of the body generates, putting us at the mercy of forces that we do not control. Inevitably, if we internalize this view, we do not taste good to ourselves. In fact, our body scares us, and we do not listen to it." (Federici 2016).

Bonneuil (2019b) situates this ontology of the fear of the body at least since Descartes and his "I think therefore I am". From this, humans can pretend that they do not have a body, nor any world. This is the specificity and the exceptionalism of humans: they have no place. Unlike Nature, they cannot be explained by a material process. Yet what does a body do? It breaks, it grows old, it changes and it dies. Here the fear of the body joins the fear of disease, decay and, in the last instance, death. A body is unpredictable, it is in relation with other bodies, with its environment, it creates its world and at the same time depends entirely on it. There is no body without a world and no world without bodies. Moreover, a body is difficult to define and its limits are not so clear. Modern science would like a body that is predictable, calibrated, perfect, "healthy" and independent of external fluctuations that are unpredictable and uncontrollable. Echoing the fears of the first eugenicists and dominant classes, a body lives and acts, has a power and a will. It organizes itself, revolts and rises, passively or actively, it is difficult to control. Eugenics, transhumanism or synthetic biology are therefore only the most visible symptoms of a morbid science. But are they really symptoms? The relation between genetics and eugenics is radical, in the sense of *root*. The founders of genetics, its methodologies, the ontology it co-creates (of essentialism, prediction, engineering and control) have everything to do with the eugenics project. Eugenics is not a corruption, an "extremist fundamentalism" or a "radicalization" of genetics—it is at the heart of it. *Eugenetics* (Eugenic genetics) lies at the intersection of three powers: fear of the body, capitalism and government (in the sense of the control of bodies, movements and attitudes). It is cybernetics that today embodies this project of total control of all life, an ontology terrified by the unpredictable, the recalcitrant, the chaotic, what escapes, slips or panics, while mobilizing in an almost contradictory manner the unstable, the resilient, the fluid, the connecting and the disruptive to justify a new mode of government. All of this obviously deserves to be explored further.

As a note, the term "Eugenics", coined by Galton, uses the prefix "Eu-", which means true, good or proper (therefore, it refers and promotes the "good and proper" genes, or the "well" born). The term "Eugenetics" is a hacking of this, and refers to what I suggest is the true and proper genetics, the eugenic one.

3.3.2 The genomic prediction industry

It is in this context of the ever present eugenics imaginary in the neoliberal era that we must understand the literal burst of the Direct-To-Consumer genomic testing (DTC) industry, as Rouvroy concluded: "A specificity of biotechnology as a new representational regime and of genetic risks as a new mode of governance is their proximity, the immediacy of their implementation in the body of individuals." (Rouvroy 2008). The rest of this section is dedicated to a closer look at the main components of the DTC industry, and how, in addition to deepening the hold of genetics on our understanding of the world, it vividly illustrates this position of eugenetics at the intersection of capitalism, fear of the body and the ideology of control. In the present work, the prediction industry together with association studies such as GWAS (from which the DTC companies build their scientific legitimacy) are understood as the foundation on which the contemporary eugenics projects deploys itself, notably through reproductive technologies.

The first component of the DTC industry analyzed here is the offer of ancestry tests. A smear from the inside of the cheeks is sent to a private company and results are received online: a table with a percentage of membership of each "ethnic group" among the hundreds included in the company's database, a map, all sorts of graphical representations... and one can self-narrate a new identity, a new existence. As a client of 23andMe, one of the main actors of the DTC market, shares with us: "You can't get any more knowing-about-yourself than processing you DNA" (23andMe, n.d,) strikingly echoing the assessment that Rouvroy made more than a decade ago on the genotype as "...the locus of authenticity and 'inner' truth, uncontaminated by political, social and economic circumstances. Genetic information is represented as particularly powerful and reliable: no other information about a person displays such a level of inalterability and stability" (Rouvroy 2008). And it is, of course, the return through the back door of the biological racial classification, necessary to the eugenics project (Duster 2003). One article from 2019 estimates that more than 26 million people in the United States have already undergone this type of test (Regalado 2019). As if a whole section of the population was obsessively longing for an identity, for stories to tell about their lives and origins. All these genomes are now available to private companies, some of which are openly collaborating with police forces (Hernandez 2019). Not having our own genome sequenced will not spare us. All that is needed is for someone in our family to do the genetic test, since parts of our genome is shared with our relatives. It should be stressed that this constitutes a profound change in contemporary subjectivation, as the genetic subject (the type of human being created by genetics) departs from the traditional autonomous, independent, liberal subject insofar as it extends beyond the limits of its own body to reach the body of its closest relatives (Rouvroy 2008). The ancestry test companies also offer an entirely new mode of socialization in relation to the test results: connecting with unknown family members or with people who share certain genetic characteristics, discussions on forums, organizing trips to our ancestors' countries... DNA is at the center of everything, it tells us who we are, where we come from and who to socialize with. Another consequence, explained by Bliss (2018), is that mass social actions and organizations around common experiences of social injustice (such as anti-racist political actions) are then replaced by these dematerialized and individualized sociogenomic predictions, by socialization on online chats based on the tests and by self-discovery via genomics and its personal development literature.

Another area of genomic prediction is the Inborn talent tests where parents may decide to test their children's DNA to determine their potential skills in many areas: music, mathematics, reading, running, languages, dancing or drawing, but also their propensity for depression, shyness, resilience, sociability, etc. (see Bliss 2018 for a chilling account). The advertising discourse of one of the company offering talents test (MapMyGene) is particularly telling. See http://seminar.mapmygene.com/ [18 December 2020] for a glimpse of the company marketing to advertise their talent tests and the associated "seminars" (the one referred to here is called "Set your child up for success"). It shows a comparison of the efficacy of "normal parenting" and "genetic parenting". The company, based in Jakarta, Indonesia, is not a major player of the DTC industry. Its marketing discourse is particularly shocking and uses quotes from R. Plomin and J. Watson. To my knowledge, no other DTC company dares mobilizing such a forceful genetic essentialism. As such, it merely reveals the inherent tendency of the DTC industry. The tests themselves are advertized here: https://mapmygene.com/services/talent-gene-test/ [18 December 2020]. The selling argument is essentially based on the guilt parents should feel when they do not give their children all the available chances. Parents who raise their children with the help of genetics (Genetic parenting) will make the right choices, save time and money, will know how to choose their children's activities according to their talents revealed by genetic analysis, and in the end, will be the happy creators of real prodigies. The bottom line is that if, as parents, we do not engage in genetic testing, we will spoil our child's potential and we are irresponsible. A glimpse of the world that genetic is offering is revealed in this quote from a client of MapMyGene who did the test with his daughter's DNA: "All in all, this has helped me understand my daughter better in a very scientific way and for that I'm very grateful" (https://mapmygene.com/reviews/ [18 December 2020]). A world where our relationships to others, including our children, have to be *scientific*.

Of course, the next step has already been taken: genetic testing of embryos prior to implantation during in vitro fertilization (IVF) procedures. These genetic tests are already routinely used to detect certain pathologies in the future embryos to implant (this is discussed below), however it is worth focusing on a specific case. A start-up (Genomic Prediction) made the headlines a while ago for proposing prospective parents to genetically test IVF embryos and select the "smartest" ones. According to the company's discourse, the idea is to test for embryos that present a risk for future "intellectual disability" and then to give parents the "choice" of which embryo to implant (https://genomicprediction.com/faqs/ [10 September 2020]. The company has now changed url (https://www.lifeview.net [18 December 2020]) and the FAQ does not mention "intellectual disability" anymore). This discourse of "free choice" needs to be clarified, insofar as choice has become the tool through which the "governance by genetic risk" is exercized (Rouvroy 2008). Justified by this discourse is a clear eugenic practice of selecting which kind of human deserve to be born, but without coercion, only "free choice". The same free choice we are, in theory, exercising when we are going shopping in a supermarket. This has been called "liberal eugenics", "flexible eugenics" or "neoliberal eugenics" and tends to overlook the fallacy of thinking about our choices and desires as completely separated or independent from the power relationships that exist at a given moment (Rouvroy 2008). The founder of Genomic Prediction, Stephen Hsu, made the headlines again more recently, but this time because of a campaign in his university asking for his resignation on the basis of his recent racist and eugenic comments (https://www.geneticsandsociety.org/biopolitical-times/firestephenhsu [18 December 2020]). This campaign sheds an interesting light on Hsu plan to, in the near future, rely on enough millions of human genomes to refine the algorithms that his company uses to predict complex characters (Schwartz 2019). I would however suggest that this only merely reflects the most common and normal scientific discourse. To illustrate this statement, let us take a detour outside genomic prediction to mention a major event of recent years, the creation of the first genetically modified humans: in November 2018, a Chinese scientist, He Jiankui, decided to modify the genome of two twin girls to allow their parents to reproduce biologically and to ensure the good health of the two little girls. The genetic manipulation (using CRISPR) concerns a particular gene that would allegedly prevent the girls from contracting AIDS knowing that one of their parents is HIV positive (there are, of course, already medical and/or social procedures addressing this risk). This type of genetic manipulation is sometimes referred to as Human germ line modification and is prohibited in most countries. The world of genetics and biology is still trying to recover from this earthquake, although it is almost certain that this manipulation has been attempted before, but not in an open, official and public way. There is a lot that could be said on this subject (I would refer to the very valuable work of the Center for Genetics and Society around these issues), but what is the most interesting here is the dominant reaction of the "scientific community". This has not so much focused on the eugenic principle of fabricating a new human being in a laboratory or the ethical and political aspects of such a project, but rather on the technical aspect: these experiments are not yet safe, we cannot guarantee the well-being of these babies, we do not yet control all the parameters of this kind of manipulation, etc. In a reaction to a recent interview of Jennifer Doudna (one of the "creator" of the CRISPR technique who was horrified by He's manipulation) (Doudna & Kearney 2020), Marcia Darnovsky, from the Center for Genetics and Society, highlighted that she "opens the door to using the CRISPR platform she helped develop in the service of a hugely controversial enterprise: altering the genomes and traits of future children and subsequent generations. She does so under the banner of responsible science and policy"(Stoffregen & Darnovsky 2020). Indeed, Doudna does not ask *whether* human germ line should be modified, but *how* it should be done and seems to mostly worry about potential stifling measures and the negative impact that He and other "bad apples" caused on the perception of the CRISPR technique. Another example is the reaction of the Nobel-prize winning geneticist David Baltimore: “[On a potential moratorium on human germ line alteration] With a science that’s moving forward as rapidly as this science is, you want to be able to adapt to new discoveries, new opportunities and new understandings. To make rules is probably not a good idea… [An international treaty binding on genetic manipulation] could hold back the science. Right now, there are many countries that have outlawed germ line editing and the way they have phrased it prevents certain kinds of experimental work from being done. That is unfortunate, because I think we want to move forward with experimentation… There’s nothing like actually moving ahead with research to teach us what the actual pitfalls are” (Hesman Saey 2019). In reality, none of the aspects of the Chinese scientist’s work are called into question here. He applied the ideology of scientism to the letter: there are no rules or limits, scientists must advance as quickly as possible without any restriction nor accountability (especially not from the outside, as they must decide for themselves) and it is only once the damage has been done that one can perhaps wonder whether it was worth doing it.

To conclude on the DTC industry, there are other areas that could be mentioned such as testing for athletic ability, genetically-adapted nutrition or medication etc. the industry is booming. However, the final type of tests discussed here are the medical genomic predictions, the most interesting aspect of the DTC industry as it raises the most delicate and difficult questions. In the public health sector, parents, embryos or fetuses would be tested for whichever list of pathologies the local region or country deems important to pre-empt (like the Down syndrome). In the private sector, adults send their DNA (or the one of their child) to a company and receive in return a table with a list of dozens of “hereditary” diseases and, next to it, a percentage or an estimate (low, medium, high) related to the possibility of contracting this disease in the future. Thus, medical genomic predictions propose an estimation of a risk for a future disease in order to either prepare for it, to eliminate fetuses or to select embryos prior to IVF. However, what does “preparing” for a disease after early detection actually mean? In reality, medicine cannot help us against most of the diseases that are part of these tests, apart from obvious lifestyle advice (diet, exercise) and medical monitoring. Preventive treatments are not numerous and gene therapies, already inherently problematic, are far from fulfilling their promises. Biotech-medicine pushes us to do predictive testing, but has little to offer to prepare ourselves for the fulfilment of its prophecies. What remains is the prospect of personalized genomic medicine, a fantasy that conveys the idea that supposed inequalities due to genetic differences could be erased individually. This narration speculates about a future access to specific individual drugs that will create some kind of total equality in front of diseases. In this way, the real social conditions that affect us are completely ignored. As Bliss comments: “Yes, being able to pop sociogenomically targeted drugs may liberate a person from stultifying depression or paralyzing rage, but it doesn’t liberate people from the real social conditions that affect them. In fact, popping a pill will likely lead to pacification, and potentially depoliticization” (Bliss 2018).

3.3.3 Control and Subjectivation

What is at stake here is a shaping of the ways of thinking about our own bodies and health: a new mode of subjectivation based on essentialism, guilt and an overwhelming individual responsibility associated with a cruel lack of control over the world and our own situation. The strength of this shaping, because it mobilizes the medical aspect, is that it plays with these deep fears already mentioned: fear of illness, fear of suffering, fear of not knowing the future, fear that our children will get sick, fear of not offering them the best possible life, etc. One classic example is the breast cancer risk testing: the presence of certain versions of a particular gene is tested because the risk of breast cancer increases significantly depending on which versions of the gene is present or not. It is delicate to criticize the use of this kind of test. Who does not want to know more about their own risk of developing cancer? How can anyone compare these tests with eugenics? These are questions not to be ignored, and challenging the hegemony of *eugenetics* on our ways of understanding our bodies must acknowledge all the fears that it instrumentalizes. The question that matters is not necessarily whether people are right or wrong to do genomic prediction tests, but what are the imaginaries conveyed by these sciences, approaches and technologies (taken individually but above all included in their context)? If one chooses to focus on one explanatory field (genetics), what are the fields that are being made invisible? For the benefit of what or who?

These issues are clarified by Rouvroy's suggestion of the emergence of the mode of governance based on genetic risk information, which is "used as a means of creating the ideal citizen of the post-Keynesian order, that is, the autonomous citizen who makes no legitimate claims on nationally organized collective solidarity but rather exercises his/her capacity for choice and manages his/her own self-care." This mode of governance therefore becomes "a privileged disciplinary tool of post-Keynesian governance: it functions as a 'technology of the self', urging individuals to get the most information they can about their genetic status, to act 'rationally and responsively' after having been so informed, and to take responsibility for the genetic health of their blood relatives"(Rouvroy 2008). A process of ultra-individualization through which the genetic subject reinforces and is reinforced by neoliberalism's subjectivity. In the end, it is a world of statistics, models, algorithms, predestination and control that the Genetic Order promotes, echoing the cybernetic neoliberal project of control and risk management where everything must be engineered, modelled, monitored, predictable and transparent. What will be the impact on our lives, our affects, our relationships with others when, in the near future, genomic prediction will not only be in common use but socially structuring?

Conclusion: Against genetics and its world

Here we are at the end of this story. Let us go back to one of its main characters, the gene, the central entity of genetics—the science of heredity. For Pichot, the succession of the different nature/definitions of the gene, gradually stacked one on top of the other, denotes a glaring theoretical weakness and the intellectual impoverishment of a scientific community that clings to its dogma for mainly sociological and ideological reasons. The gene is such a volatile concept that it is then possible to affirm that modern genetics is a science without an object (Pichot 2002). It has only a few functions left. In addition to its original function of unifying the historical and physical explanations of organisms through the notion of heredity, its "role" has also been to steer biology in a direction very much influenced by the dominant political, ideological and economic interests and imaginaries of the epoch. Louart, in his work on the perception of living beings as machines, reached a similar conclusion: "today more than ever, the conception of the organism as a machine is irremediably linked to the fact that we live in a capitalist and industrial society: it reflects what the authorities that dominate society would like the organism to be, in order to be able to do with it as they wish" (Louart 2018, transl. by the author). By nourishing a pseudo-rational and all-powerful essentialist and mechanistic imaginary, by promising ever more predictive power, personalized medical treatments and increased industrial productivity, genetics emulates strong affects and amasses a phenomenal amount of funding, masking its theoretical weaknesses and its deadly endeavors.

For Kupiec and Sonigo (2000), genetics is a theory of heredity that breaks the material link between ancestors and descendants by substituting it with a virtual link (an information, a program) carried by DNA. But this virtual link cannot constitute an explanation of the reproduction of the similar because it implies the pre-existence of the structures of the organism, and therefore suggests a deterministic vision of the organism, where it is the result of a pre-established objective of the mechanisms of development and evolution: "Biologists have dreamed of an accessible, readable demiurge in the world of molecules" (Kupiec & Sonigo 2000). They have to give up this fantasy.

The Genetic Order has never ceased to be inspired and to nourish the harmful imaginaries of essentialism, eugenics, capitalism and cybernetics. Following Rouvroy's intuition, "genetic knowledge, or 'genetic truth discourses', and the currently experienced shifts in the modes of governance, are in a relationship of co-production" (Rouvroy 2008). Genetics deserves a special attention and radical criticisms. It provides us with a nefarious worldview and a framework of thought utterly limited to help us understand organisms and life in general. Should we try to change it from the inside, decenter it from its obsession with the gene and the DNA molecule to make it a science that makes more sense to the world we are living in and to the direction it needs to go? Or, as the Invisible Committee (2017) invites us to do with institutions, should it be *destituted*?

Acknowledgments

I would like to thank Dr. D. Shaw for her regular support, inspiration and help, including for this paper.

References

Aguiton S A 2018, *La démocratie des chimères: gouverner la biologie synthétique*, Lormont: Le Bord de l'Eau.

Benasayag M 2016, *Cerveau augmenté, homme diminué*, Paris: La découverte.

Bizzarri M, Palombo A, & Cucina A 2013, "Theoretical aspects of Systems Biology", *Progress in Biophysics and Molecular Biology*, vol. 112, no. 1–2, pp. 33–43.

Bliss C 2018, *Social by Nature: The Promise and Peril of Sociogenomics*, Stanford: Stanford University Press.

Bonneuil C 2021, *Moderniser la vie*, Paris: Champvallon.

Bonneuil C 2019a, "Seeing nature as a 'universal store of genes': How biological diversity became 'genetic resources', 1890–1940", vol. 75, pp. 1–14.

Bonneuil C 2019b, "How not to govern the living?" *Vassivières*, http://radiovassiviere.com/2019/05/enregistrements-des-conferences-des-journee-detudes-habiter-etre-habite-e-quelles-relations-au-vivant/ [18 December 2020].

Bonneuil C 2015a, "Le siècle du gène" in: Bonneuil C & Pestre D (eds.), *Histoire des sciences et des savoirs. 3. Un siècle de technosciences (depuis 1914)*, Paris: Seuil, pp. 297-317.

Bonneuil C 2015b, "Une nature liquide ? Les discours de la biodiversité dans le nouvel esprit du capitalisme" in: Thomas F & Boisvert V (eds.), *Le pouvoir de la biodiversité. Néolibéralisation de la nature dans les pays émergents*, Paris: Quae, pp. 193–213.

Boskovic A, & Rando, O J 2018, "Transgenerational Epigenetic Inheritance", *Annual Review of Genetics*, vol. 52, no. 1, pp. 1–21.

Burian R M 2013, "Qu'est-ce qu'un gène : la fin d'une évidence?" in: Kupiec J-J (ed.), *La vie, et alors? Débats passionnés de l'Antiquité à nos jours*, Paris: Belin, pp. 115–130, 391.

Calude C S & Longo G 2017, "The deluge of spurious correlations in Big Data", *Foundations of Science*, vol. 22, no. 3, pp. 595–612.

Carnino G 2015, *L'invention de la science: la nouvelle religion de l'âge industriel*, Paris: Éditions du Seuil.

Club of Rome, 1972, "The Limits to Growth." http://www.donellameadows.org/wp-content/userfiles/Limits-to-Growth-digital-scan-version.pdf [18 December 2020]

Cooper M 2008, *Life as Surplus: Biotechnology and Capitalism in the Neoliberal Era*, Seattle: University of Washington Press.

Crick F 1958, "On protein synthesis", *Symposia of the Society for Experimental Biology*, vol. 12, pp. 138–163.

Davies G *et al.* 2016, "Genome-wide association study of cognitive functions and educational attainment in UK Biobank (N=112 151)", *Molecular Psychiatry*, vol. 21, no. 6, pp. 758–767.

Delphy C 2008, *Classer, dominer: qui sont les "autres"?*, Paris: La Fabrique.

Delphy C 1993, "Rethinking sex and gender", *Women's Studies International Forum*, vol. 16, no. 1, pp. 1–9.

Doudna J, & Kearney W 2020 "A Viable Path Toward Responsible Use", *Issues in Science and Technology*, vol. 36, no. 3, available from: https://issues.org/jennifer-doudna-interview/ [18 December 2020].

Duster T 2003, *Backdoor to Eugenics*, 2nd ed. New York: Routledge.

Federici S 2016, "In praice of dancing bodies", in: *A Beautiful Resistance: Everything We Already Are: Gods & Radicals Journal*, vol. 1.

Foucault M, & Gordon C 1980, *Power/Knowledge: Selected Interviews and Other Writings, 1972-1977*, 1st American edition, New York: Pantheon Books.

Gayon, J 2016, "From Mendel to epigenetics: History of genetics", *Comptes Rendus Biologies*, vol. 339, no. 7-8, pp. 225–230.

Gerstein M B *et al.* 2007, "What is a gene, post-ENCODE? History and updated definition", *Genome Research*, vol. 17, no. 6, pp. 669–681.

Hernandez S 2019, "One of the biggest at-home DNA testing companies is working with the FBI", *BuzzFeed News*, https://www.buzzfeednews.com/article/salvadorhernandez/family-tree-dna-fbi-investigative-genealogy-privacy [18 December 2020].

Hesman Saey T 2019, "A Nobel Prize winner argues banning CRISPR babies won't work", *Science News* (April 2), available from: https://mybiology.net/a-nobel-prize-winner-argues-banning-crispr-babies-wont-work/ [18 December 2020].

Keller E F 2010, *The Mirage of a Space Between Nature and Nurture*, Durham: Duke University Press.

Keller E F 2000, *The Century of the Gene*, Cambridge: Harvard University Press.

Koshland D 1989, "Sequences and consequences of the human genome", *Science*, vol. 246, no. 4927, pp. 189–189.

Kupiec J-J 2019, *Et si le vivant était anarchique: la génétique est-elle une gigantesque arnaque?*, Paris: Les Liens qui libèrent.

Kupiec J-J 2012, *L'ontophylogenèse: évolution des espèces et développement de l'individu*, Versailles: Éditions Quae.

Kupiec J-J 2010, "On the lack of specificity of proteins and its consequences for a theory of biological organization", *Progress in Biophysics and Molecular Biology*, vol. 102, no. 1, pp. 45–52.

Kupiec J-J 2009, *The Origin of Individuals*, New Jersey: World Scientific.

Kupiec J-J, & Sonigo P 2000, *Ni Dieu ni gène: pour une autre théorie de l'hérédité*, Paris: Seuil.

Lafontaine C 2014, *Le corps-marché: la marchandisation de la vie humaine à l'ère de la bioéconomie*, Paris: Seuil.

Lafontaine C 2004, *L'empire cybernétique. Des machines à penser à la pensée machine*, Paris: Le Seuil.

Latour B 1993, *We Have Never Been Modern*, Cambridge: Harvard University Press.

Lewontin R C 1991, *Biology as Ideology: The Doctrine of DNA*, Toronto: Anansi.

Lippman A 1993, "Prenatal genetic testing and geneticization: Mother matters for all", *Fetal Diagnosis and Therapy*, vol. 8, no. 1, pp. 175–188.

Lippman A 1991, "Prenatal genetic testing and screening: Constructing needs and reinforcing inequities", *American Journal of Law & Medicine*, vol. 17, no. 1–2, pp. 15–50.

Louart B 2018, *Les êtres vivants ne sont pas des machines*, Vaour: La Lenteur.

Mayr E 1982, *Histoire de la biologie: diversité, évolution et hérédité*, Paris: Fayard.

McKinnon S 2005, *Neo-liberal Genetics: The Myths and Moral Tales of Evolutionary Psychology*, Chicago: Prickly Paradigm Press.

Moore D S 2012, "Evelyn Fox Keller: The Mirage of a Space Between Nature and Nurture: Duke University Press, Durham, NC, 2010" [review], *Science & Education*, vol. 21, no. 4, pp. 583–590.

Morange M 2017, *Une histoire de la biologie*, Paris: Points.

Morange M 2003, *Histoire de la biologie moléculaire*, Paris: Découverte/Poche.

Nelkin D & Lindee M S 2004, *The DNA Mystique: The Gene as a Cultural Icon*, Ann Arbor: University of Michigan Press.

Newman S A 2013, "The demise of the gene", *Capitalism Nature Socialism*, vol. 24, no. 1, pp. 62–72.

Nicholson D J 2014a, "The machine conception of the organism in development and evolution: A critical analysis", *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, vol. 48, pp. 162–174.

Nicholson D J 2014b, "The return of the organism as a fundamental explanatory concept in biology", *Philosophy Compass*, vol. 9, no. 5, pp. 347–359.

Noble D 2017, *Dance to the Tune of Life: Biological Relativity*, Cambridge: Cambridge University Press.

Noble D 2015, "Evolution beyond neo-Darwinism: a new conceptual framework", *Journal of Experimental Biology*, vol. 218, no. 8, pp. 1273–1273.

Noble D 2011, "Neo-Darwinism, the Modern Synthesis and selfish genes: Are they of use in physiology?", *The Journal of Physiology*, vol. 589, no. 5, pp. 1007–1015.

Noble D 2008, "Genes and causation", *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, vol. 366, no. 1878, pp. 3001–3015.

Pichot A 2010, "Le racisme scientifique". Nantes, https://www.youtube.com/watch?v=UhXnLSH1O2s [18 December 2020]

Pichot A 2003, "Mémoire pour rectifier les jugements du public sur la révolution biologique", *Revue Esprit* (August-September), p. 104

Pichot A 2002, "Notion de programme génétique", *Philosophia Scientiae*, 6 (1), 2002, 163—172.

Pichot A 2001 "La génétique est une science sans objet", *Revue Esprit* (May), p. 102.

Pichot A 2000, *La société pure: de Darwin à Hitler*, Paris: Flammarion.

Pichot A 1999, *Histoire de la notion de gène*, Paris: Flammarion.

Pichot A 1996 "Hérédité et évolution (l'inné et l'acquis en biologie)", *Revue Esprit* (June), p. 7.

Rautiainen M-R *et al.* 2016, "Genome-wide association study of antisocial personality disorder", *Translational Psychiatry*, vol. 6, no. 9, pp. e883–e883.

Regalado A 2019, "More than 26 million people have taken an at-home ancestry test", *Technology Review* [online], https://www.technologyreview.com/s/612880/more-than-26-million-people-have-taken-an-at-home-ancestry-test/ [18 December 2020].

Rey O 2015, "Le Darwinisme en son contexte": https://archive.org/details/RMU041ReyDarwinisme [18 December 2020]

Rosanvallon J 2012, "Pure variation and organic stratification", *Progress in Biophysics and Molecular Biology*, vol. 110, no. 1, pp. 137–149.

Rouvroy A 2008, *Human Genes and Neoliberal Governance: A Foucauldian Critique*, New York: Routledge-Cavendish.

Royer J-M 2017, *Le monde comme projet Manhattan: des laboratoires du nucléaire à la guerre généralisée au vivant*, Lyon: Éditions le Passager Clandestin.

Said E W 1995, *Peace and its Discontents: Essays on Palestine in the Middle East Peace Process*, New York: Vintage Books.

Sanders A R *et al.* 2017, "Genome-Wide Association Study of Male Sexual Orientation", *Scientific Reports*, vol. 7, no. 1, p. 16950.

Schrödinger E 1944, *What Is Life?*, Cambridge: Cambridge University Press.

Schwartz O 2019, "What if an algorithm could predict your unborn child's intelligence?", *OneZero* (9 July), https://onezero.medium.com/what-if-an-algorithm-could-predict-your-unborn-childs-intelligence-a546153707de [18 December 2020]).

Sonigo P 2013, "Ondes et Particules de vie", https://www.canal-u.tv/video/iea/conference_de_pierre_sonigo_ondes_et_particules_de_vie.13281 [18 December 2020]

Sonigo P & Stengers I 2003, *L'évolution*, EDP Sciences.

Stoffregen R, & Darnovsky M 2020 "Risks and rewards of gene editing: A discussion of 'A Viable Path Toward Responsible Use' by Jennifer Doudna and William Kearney", *Issues in Science and Technology*, vol. 36, no. 4, available from: https://issues.org/risks-and-rewards-of-gene-editing-doudna-interview/ [18 December 2020].

The Invisible Committee 2017, *Now*, South Pasadena: Semiotext(e).

The Invisible Committee 2015, *To Our Friends*, South Pasadena: Semiotext(e).

Tiqqun 2020, *Cybernetic Hypothesis*, Los Angeles: Semiotext(e).

23andMe n.d., "Breaking down stereotypes barrier, Angelina's 23andMe story" [online] https://www.23andme.com/en-int/stories/#PLazxh2pBdQ [18 December 2020].

Organisms

History and Science

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/175353

The Stones of Madness and the City of Madness

Dalmazio Frau,[a]*

[a] *Illustrator, writer, and lecturer*

***Corresponding author:** Dalmazio Frau, dalmatiuspf@gmail.com

Abstract

The pre-modern existential metaphor of mental healthcare is analyzed through two relevant works of art, one by Hieronymus Bosch and another by Pieter Brueghel the Elder.

Keywords: madness, medicine, alchemy, spagira, Hieronymus Bosch, Pieter Brueghel the Elder

Citation: Frau D 2020, “The stones of madness and the city of madness”, *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 99-104. DOI: 10.13133/2532-5876/175353

The mystery of human madness is perhaps still far from being completely solved still in the twenty-first century, with the new drugs available and the current science, often that veil remains that cloaks the demons of the Id and the most hidden and profound states of psyche.

Perhaps never as in these days affected by the so-called Covid 19 pandemic, the theme of madness had been so present in the world, cohabiting with a virus, but always present with the same humanity, so much so as to be a frequent theme in the art of every era and culture. We have therefore chosen two examples, similar to each other in terms of place and period, but different enough to see the sides of that coin which is mental insanity in the long autumn of the Middle Ages and, if you like, in what for us was the golden Renaissance, but which in Northern Europe took on darker and more disturbing tones.

The first work we will see is *The Stone of Madness*, by Hieronymus Bosch.

The fascination exerted by Bosch’s mysteriously simple works and life has always led those who paid attention to his paintings to try to enter and interpret the fantastic worlds that are depicted in them. What probably turned out to be manifest or in any case intelligible at various levels to the Flemish painter’s contemporaries, has become increasingly obscure with the progress of the centuries and so we have come to see in these plates, from time to time, the action of a madman, of an erotomaniac, of a demonic cultist, of an *ante litteram* drug addict or of a heretic, and to finally interpret them, on the basis of the current psychoanalytic discipline.

Others, more wisely, have intuited the existence of various types of messages ranging from magical to alchemical, often hidden under the guise of the religious and moral imagery typical of the time. We wish to remember that Bosch is remembered above all as a “painter of devils” by his contemporary admirers who immediately recognize him as the initiate who is able to see with a “second sight” the supernatural creatures belonging to Heaven, the Underworld and those Intermediate Worlds. They recognized in this way, even within a hermetic Christian discourse, the existence of beings that do not belong either to the Kingdom of Light or to that of Darkness or even of the Elementals, of which Paracelsus will then treat. The alchemical aspect, on the other hand, is undoubtedly less evident to the profane eye, hidden in symbols and forms, in its crystalline or siliceous structures, tools or biomechanical buildings: one would say today that undoubtedly these images refer to ampoules, stills and flasks or to the Fulcanellian athanor. The alchemical process, *Opus*, in Bosch's paintings is to be found in the reading and deciphering of many tables as long as it is possible to understand the "code" hidden therein. In a certain sense he pictorially anticipates the "occult" method of Michel de Nostredame that will follow him years later, with his *Centuries*.

However, there is a painting in particular, a work considered youthful by some critics, which behind the veil of irony and moralizing allegory hides some messages of alchemical or spagyric origin. The painting in question is known as *The Extraction of the Stone of Madness* and was previously attributed to the private property of the Bishop of Utrecht. This fact once again demonstrates how almost all of Hieronymus's patronage was strictly religious and prelatic, albeit in the context of that particular Catholicism typical of Northern Europe which would later flow into the Lutheran Reformation. So from this we can already assume that the bishop was interested in a type of "hermetic" readings that were considered perfectly legitimate within an exoteric orthodoxy; a fact that leads us to exclude—as already claimed elsewhere and not only by me—that Bosch has never been in the "smell of heresy" and therefore close to suspicious groups such as the "Brothers of the Free Spirit" or the sect of the "Adamites".

The tondo that encloses the actual painting is not, however, a religious work, but depicts a moment in the action of three men and a woman, perhaps a nun. The central character is a monk, presumably an Augustinian judging by the habit. The black frame around the central circle is decorated with gothic letters and arabesques that refer to the illuminated manuscripts of international gothic, in a precious gold color that reads: "*Meester snynt die Keye ras / Myne name is lubbert das*", i.e., "Maestro, quarry out the stones, my name is Lubbert Das ". The vulgate sees in this "Lubbert Das" the equivalent of "fool", of "simpleton" who is deceived by the "surgeon-magician" who extracts the then well-known "stone of madness" from his forehead and which literally means "castrated dachshund". This is precisely the common and immediate explanation of the painting, based on the simple allegory of the sin of a fool who deceives another like him.

In fact, at the time when Hieronymus lived, in Flanders, it was common practice to witness this intervention carried out by wandering healers on some mentally-ill patients, who had an elusive "stone of madness" extracted from their foreheads. Probably this surgical operation was only simulated, little more than a clever sleight of hand, as is still the case in many aboriginal populations by shamans and medicine men.

Now, instead, let's try to see why it is possible to attempt a reading of the painting that leads back to the alchemical doctrine or, perhaps better in this case, to its spagyric declination. First of all, let's look at the table in detail (Figure 1).

Figure 1: *The extraction of the stone of madness*, Hieronymus Bosch, around 1494, Oil on wood, 48 × 35 cm, Museo del Prado, Madrid.

An autumnal landscape, between low slopes and woods of lime trees in a row, the gothic spiers of some churches and the ramparts of a fortress stand out against the blue distance of the background, in the foreground, on a clearing of grass main scene where four characters act. The first from the left for the observer is the mysterious healer dressed in a long old pink tunic; a simple clay pitcher hangs from his black leather belt. The surgeon wears a hood of the brown color of the earth, on whose right shoulder stands an enameled coat of arms depicting a black bird on a gold field. From the lapels of the tunic and from the hood, a tight scarlet red dress emerges. Finally, a funnel is placed on the doctor's head which is the object that is the most incomprehensible and has always directed critics towards an ironic reading of the whole image. The surgeon is intent on incising with a scalpel the receding hairline of what would appear to be an old drunkard with a red nose from too much drinking, dressed in a white shirt and tunic and with red stockings and black shoes. The patient, from whose head the "stone of madness" is extracted, is tied tightly to the high back of a chair with a white linen sash and his civilian belt, complete with pouch and kidney dagger, which hangs inert from an armrest. The bench then, on the bottom, shows a special cavity where a pair of shoes are contained, perhaps wooden clogs that could belong to the doctor himself. To give comfort to the patient, whose symbolic name we have seen to be Lubbert Das, a monk in a black habit is placed with an exhortative attitude. He holds in his left hand a pewter jug with a lever lid. The religious man leans his left elbow, almost indolently, on a round table with a decidedly curious shape. The top of the table would appear to be of polished gray stone and so is its base, both joined in a vertical by a single leg carved in wood with a motif of acanthus or perhaps vine leaves. The remains of a flower lie abandoned on the shelf, probably the rest of a previous operation. Finally, on the right, a female figure dressed in a white bonnet and the wimple of the nuns and a long brown habit that almost blends into the ground leans on the table, as if attending interested but not too much in what is happening. Almost bored, the nun carries the other object hovering over her head which, together with the funnel on the doctor's head, literally drove scholars crazy: a closed red book. A swollen pouch hangs from the nun's cord, also red like her petticoat.

The "surgeon" is therefore the myste, the trickster, the "doctor of the soul" who is called to intervene with his science in bringing back to normality, therefore to bring back the Order from the Chaos of madness, a madman. He is therefore the Spagira who acts in practice, highlighted in this by the color of his robe which brings together all the other three colors. Red and white, respectively symbolic colors of *Rubedo* and *Albedo*, have merged into the antique pink of her surcoat, while *Nigredo* has remained in the belt.

The Raw Material is the brown hood that hides the upper parts. It is there that the noble seal stands out, qualifying him as a doctor accredited to the ducal court. In fact, the coat of arms is crowned with silver, but depicts a raven—the alchemical symbol of one of the phases of the *Opus*—on a gold field that does not require further explanation. The symbolism of the crow, an animal sacred to Apollo, is also linked to the solitude necessary for the one who—like the healer—has chosen to live on a higher plane of being, but is also linked to the virtue of hope. Its black color is alchemically linked to the night of the *Opus* and the earth and therefore to all those operations of fertilization and germination of the alchemical procedure. Moreover, living in the airspace, the crow is also associated to all those demiurgic operations due to the celestial powers. Since he is a bird he is—like Odin's two ravens or Badb in Ireland—he is also a heavenly messenger and therefore possesses magical and divinatory abilities. The crow and the doctor are therefore the same entity in several respects.

The scarlet red, hidden by the overcoat with fur cuffs, recalls the royal nature of which the doctor is invested, his Ars regia is also so because it is recognized by his sovereign. We come now to the mysterious funnel. An ancient instrument, in the Middle Ages the upside down funnel is a symbol commonly used to identify madness; the fact that the surgeon wears it accredits him as a doctor specialized in this type of treatment, but the funnel is also an essential tool for the alchemical and spagyric operation, furthermore placed in this way recreates the typical pointy headdress of the Magician and like a spire it reconnect to the sky. We do not know if the doctor has bare feet in contact with the ground, but the shoes left under the chair would make us suppose, thus confirming his nature as a medium between the higher and the earthly states. Finally, earth and water are present in the symbol of the clay jug hanging from its belt.

The surgical procedure is applied to the other protagonist of the event: the "madman" known as Lubbert Das, a sort of Bertoldo or Zanni from the Netherlands. He is certainly the simpleton of the country, but he is also "The Fool" of the Tarot, a card that has no number. He is the one who sees other realities beyond human ones and is always wandering from place to place. We recall that the Fool, from the remotest antiquity up to the threshold of the Modern Age, before psychoanalysis intervened, was cloaked in a sacred aura and therefore of respect, being sometimes touched by a god, or else being a mystic or a hermit or a traveling musician.

Every initiate can therefore appear insane to ordinary men as even evangelically human wisdom is madness in the eyes of God and *vice versa*.

Lubbert Das, tied by his own sash to the chair, carries all three colors of the *Opus* on himself. The red breeches also symbolize—just like in the Tarot blade of the same name—not only the alchemical stage of *Rubedo* but also Strength and Action. They are the perennial fire that always pushes him to go and move. The body covered in white is the *Albedo* but it is also the "purity" due to its non-evil madness. Finally appears the *Nigredo*, abandoned on the chair, represented by the belt with dagger and pouch, in continuation with the same one worn by the doctor and shoes.

In this case the Fool, the one who makes fun of the rules, is stopped and forced in a place: his Chaos is brought back to Order by the sharp knife of the surgeon-spagira.

What the surgeon extracts from Lubbert's flesh and blood is that natural formation which was known—as we have already written—by the singular name of "stone of madness", but in this particular painting it appears as two small flowers.

The symbolism of the stone is well known, as well as the properties of many "stones" naturally produced by some organisms and to which magical or otherwise extraordinary properties have been attributed since the most remote antiquity and especially in the Middle Ages and the Renaissance. They are called *bezoars* in ancient lapidaries and grimoires and are found in animals or even humans. In this case, the stone is also the soul which, transmuted, healed, rises towards God, and this is why it has become a flower and is also the link between man and the Divine. In this case it becomes the seal that allows the madman to open the "doors of perception" and in fact it seems to be located in the same place occupied by the pineal gland or the so-called "third eye". Meister Eckhart teaches that "the stone is synonymous with knowledge" and while it not only becomes the Philosopher's Stone for alchemists, for Ramon Llull it is a symbol of the regeneration of the soul through the redemption of divine grace.

Thus, if on the one hand the healing operation carried out by the doctor restores the Cosmos by bringing the Fool back to "reason", at the same time it closes a passage between the worlds and returns the medium - which is represented by the Stone—to its kingdom of origin in the form of a flower. Lubber Das is thus cured and will no longer upset human rules with the irruption of an uncontrolled supernatural power.

However, he, who is happy to be crazy, is convinced to undergo this rebalancing operation, by a monk, or rather by the "reason" of religion which naturally cannot allow deviations. The Augustinian friar with his black habit is therefore easily identifiable with the dark and nocturnal aspect, with the *Nigredo* but also with the uniformity to the ecclesiastical teaching and scholastic doctrine that is the doctrinal backbone. He only wishes to bring Lubber Das back to the bosom of the mother Church so that he no longer disturbs the people by remembering that other realities exist. In his hand, the friar holds a metal flask with a lid, in contrast to the earthenware jug which, on the other hand, is without a stopper, tied to the waist of the surgeon. The metal here is opposed to the worked earth, and is sealed, thus preserving something that must not be left free to flow arbitrarily. Perhaps in this pewter jug they go to macerate the flowers that were stones; or perhaps also in it there is something that has an anesthetizing function for the patient, perhaps a product of alcoholic distillation—or "quintessence" if you prefer. The comfort expressed by the monk is therefore in support of the work of the Spagira.

The table is the apparently most alien element to all this *en plein air* action, but it is at the same time the most indicative for a hermetic reading of the painting. The table consists of two circular discs connected by a vertical element. The axial symbolism represented by the single leg of the table is easily understandable: a wooden beam carved in the form of Greek leaves reconverted to Gothic ones. Therefore, it reconnects not only to the myth of the tree of knowledge and that of life, but to the whole vegetable world from which Spagira takes part of its creations. This wooden axis is one with the landscape and joins together the two disks of cut and smoothed stone which are presumably Heaven and Earth or in any case two planes of being, two worlds. As we have already seen, what appear to be residual flowers abandoned on the tabletop could be what remains of previous surgeries or even flowers used for the preparation of other spagyric and colloidal solutions.

The nun, in her detached attitude, almost bored by an operation that she has probably seen many times and about which she seems not to care too much, was exploited by the surgeon or the friar as a piece of furniture on which to place a book. In fact, this is not placed on the table top as it would be logical, but it has been placed on the head of the nun, as if it did not exist or was nothing more than a non-indispensable, non-vital element. This female figure does not perform any function neither of aid to the doctor as a nurse, nor of religious aid to the monk with his prayers. The brown color of her habit also refers to the earth element and replaces the friar's black at a lower level. The nun, therefore, is the feminine, prosaic, material element that is not interested in understanding what is happening around and in front of her, and this is the reason for the scarlet-colored book placed on her head, where she cannot read and, being immobile, not even feel it. The knowledge contained in the book is precluded to this woman withdrawn exclusively on her own thoughts. The book, the pewter jug and the funnel are positioned on the same horizontal line and are therefore three symbolic elements, three of the tools necessary for the whole operation. Without the book, however, closed by a gold clasp, from which wisdom knowledge was learned, the metals of the funnel and jug could not be used. The closed book, alchemically, is also the Virgin Matter which keeps its secret as a mineral substance in its raw state is kept in the mine.

Finally, but not to be forgotten as secondary or irrelevant, the decorative scrolls of the words in Gothic letters placed on the black background are directly related to other similar ones designed in the same period by Leonardo da Vinci and then by Albrecht Dürer. Their symbolic geometric interweaving find their origin in the mystical decorations of the Sufis and in the fantastic ones of the Celtic populations. They offer a completely original synthesis between North, South, East and West merged in the decoration of the Gothic beyond the Alps and in its illuminated manuscripts.

The second work we wish to analyze is *The Healing of Madness*, by Pieter Brueghel the Elder.

This is not a paint. It is rather an engraving known as *The Witch of Malleghem* which—as can be read in the lower margin of the sheet—promises healing to the citizens of Malleghem:

"Ghy lieden van Malleghem wilt nu wel syn gesint / Ick VrouwHexe wil hier oock wel worden bemint / Om v te genesen ben ickgecomen hier / Tuwen dienste met myn onder meesten fier. / Compt vry den meesten met den minsten sonder verbeyen / Hebdyde wesp int hooft, oft loteren v de keyen", which translated would sound like "Oh people of Malleghem, be happy! / I, lady witch, want to be venerated by you too. / To cure you I

Figure 2: *The witch of Malleghem*, Pieter Brueghel the Elder, Engraving and etching, 1559 by Johann Theodor De Bry.

have come here / at your service, with my assistant. / Hurry up, all of you, / the nobles with the last ones, / since your head is full of wasps and sprouting stones."

Hence the theme of the "stones of madness" already seen in Bosch returns, while the city of Malleghem would be nothing more than an imaginary inhabited center that takes its name from the same madness, since in the Flemish language of the sixteenth century, the word *mal* precisely means crazy, while *ghem* would indicate a place. We could therefore translate Malleghem, (possibly today's Maldegem, located on the border between Belgium and Holland), as "The city of Madness".

The scene drawn by Brueghel therefore takes place outdoors, near the wheel of a water mill, a symbol of the eternal cycle of life, of the succession of births and deaths, of years and days. At a short distance from the mill, at the edge of a wood, stands a crazy conical construction that once again reminds us of the buildings in the woods, just as the monstrous creatures that creep into the crowd are similar to Hieronymus's crickets.

In the center, on the right, appears the witch with her disheveled hair, carrying a viola da gamba on her left shoulder and at the same time holding a box containing numerous unidentified ampoules under her right arm. Perhaps these are medicaments, potions or elixirs of spagyric origin.

The musical instrument, a viol, is carried upside down, as if to indicate a possible subversion of the *Armonia Mundi*. The witch is therefore perhaps the only wise man in a country of madmen who carry out the most absurd actions and who are also easy prey for the many charlatans who sell them the most improbable medicines. While a madman is transported to the place where the disturbing stone is removed from his skull, the same one robs his Cyrene, taking the money from his purse. He is followed by a man, certainly a soldier, who still wears parts of an armor.

Another sorceress spills the contents of a jug onto the head of a patient, from whom a stone has just been extracted by her sister hag who is showing to bystanders what she has just removed, in proof of her ability as a curator. In the meanwhile a person who could be her assistant lights the scene with a blind lantern. This character, however, might be not human: her familiar demon could hide under his guise.

All this happens when, half-hidden under the plank, an accomplice with his lips tightened by a heavy padlock, takes new stones from a basket to be passed as a result of the operations and on his right sleeve the emblem of the ancient can be clearly observed "Mother of the madmen of Dijon".

Finally, on the right of the engraving, a crowd of individuals suffering from the dark evil of madness, each with their own stone, throng, waiting for their turn to be cured.

On the left side of the table instead, some cheerful wives with strange cloaks, curious, examine some jars perhaps containing potions placed on a table, next to which there are strange jars and other tubes made from guts joined together. A sort of falcate halberd rests on the edge of the table together with a bone-handled knife. Meanwhile, a perched owl observes the viewer, seated on a corner of the building inside which are shelves, pottery and other madmen. On one of these jars we read "Honich", i.e., "honey" and on the other "Sever", which means "vinegar", as if to indicate once again the duplicity and the extremes of the world, which in fact turns out to be so "bittersweet".

Finally, on the lower right corner, contained within the Cosmic Egg, the patient and the surgeon once again perform their surgical ritual of extracting the stone of madness, this time multiplied in a cascade of spherules that they trickle out of the egg itself, disappearing into the street.

Therefore, the Mystery remains and persists also in this work by Brueghel, offering us innumerable ideas for multiple interpretations and keys for investigating and reading it on several levels. Perhaps, it is suggesting that the care for what rational men consider madness, could not be the best way to the Knowledge of the Universe, as the wise never have dreams as beautiful as the those of the fool.

Special Section: COVID-19 Pandemic

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17354

Where is Science Going?
An Interview with Professor Giorgio Agamben

Andrea Pensotti,[a]*

[a] *University Campus Bio-Medico of Rome, Italy*

***Corresponding author:** Andrea Pensotti, Email: andreapensotti@gmail.com

Abstract
The political management of the COVID-19 pandemic has showed worrysome biosecurity issues, which are linked to the very nature of science as a self-declared, undeniable 'truth'.

Keywords: pandemic, truth, science, biosecurity, naked life, delinguisticization of knowledge

Citation: Pensotti A. 2020, "An interview with Professor Giorgio Agamben", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 105-109. DOI: 10.13133/2532-5876/17354.

During the first months of the Covid-19 pandemic the philosopher Giorgio Agamben has published a series of thoughts, successively included into a book titled *Where Are We Now: The Epidemic as Politics* (Agamben 2020). The core of his thinking was the relationship between science and society, namely medicine and politics. Agamben highlighted the risks linked to the emergence of the concept of "biosecurity", i.e., the blocking of all social activities in order to preserve "biological life". How far can a society go to defend biological life? How far can politics stretch to control both society and the biological life of citizens?

Agamben's book has generated different and mainly negative reactions. However, it is undeniable that it addresses some unavoidable questions we are currently facing. We were surprised to see that most of the arguments made against him were flawed by (unmentionable) ideological prejudices.

To deepen those questions, we propose herewith an exclusive interview with Giorgio Agamben.

Naked Life

The concepts of personalization and prediction are gaining ground in medicine. Thanks to new diagnostic tools and big data, medicine claims to predict the individual risk of developing certain diseases in life. Once these risks are known, people can be directed towards appropriate lifestyles. Besides these screenings for genetic predisposition, new technological tools known as "wearables" enable the constant monitoring of certain vital parameters. Today, they are mainly meant for sportspersons who want to continually improve their performance. Soon, however, they could be extended to all citizens. Apparently such an approach to medicine is guiding us toward what you have defined as life reduced to mere biology—"naked life". Nonetheless, many scientists are questioning the ethical and technical feasibility of such a scenario. Would you share a reflection on this topic? Also, in your opinion, what should be done to reverse the trend?

In the perspective that you have outlined, the critical moment is crossing the threshold beyond which personalization, prediction, and screening are no more lifestyle advice and suggestions, but become legal obligations. This threshold has now been crossed. What used to be presented as a health right has become an obligation to be fulfilled at any price. Cardiovascular diseases represent the most frequent cause of mortality in our country. We know they could decrease if we practice a healthier way of life and adhere to a particular diet. However, no doctor had even thought of their own lifestyle and dietary advice for patients to become the subject of a legal regulation, which decrees *ex lege* how to live and what to eat, transforming the whole of existence into a health obligation. Moreover, the Italian doctor's professional oath prohibited this by mentioning, "respect for civil rights regarding the person's autonomy" (see also WMA Declaration of Geneva: "I will respect the autonomy and dignity of my patient" and "I will not use my medical knowledge to violate human rights and civil liberties, even under threat"—*translator's note*). This is what has happened for COVID-19. At least for now, people have accepted not only to give up their constitutional freedoms, social relations, and political and religious beliefs—they have even let their loved ones die in solitude and without a funeral. In this sense, it can be said that human existence has been reduced to a biological fact, to a naked life to be saved at any cost. This happened despite the IFR, i.e. the real mortality rate of the disease, is less than 1% according to studies reported in your journal. A process of increasing medicalization of life has occurred. The unity of the vital experience of each individual, which is always both corporeally and spiritually inseparable, has split into a purely biological entity on one side and a social, cultural, and emotional existence on the other. Such a fracture is by all evidence an abstraction. This abstraction, though, is so powerful that people have sacrificed their normal conditions of life to it. I said that the splitting of life is an abstraction. However, as you know, modern medicine realized this abstraction around the middle of the 20th century. It did it through intensive care devices, which can keep a human body in a state of pure vegetative life. The intensive care unit, with its mechanical ventilators, cardiopulmonary bypass, and equipment for maintaining body temperature can indefinitely suspend a human body between life and death. This is a dark area, which must not go beyond its strictly medical boundaries. Instead, what happened with the pandemic is that this purely vegetative life, this body artificially suspended between life and death, has become the new political paradigm for citizens to regulate their behavior. What is most impressive in what we are experiencing is that—at any price—a naked life is kept separate in an abstract way from an intellectual and spiritual life. Then, it is imposed not as a criterion of life, but of mere survival.

Truth and Falsification

In 2016, Nature *published the results of a survey revealing that over 1,500 scientists had failed to reproduce data obtained by colleagues. Dr. Glenn Bagley, the oncology director of the multinational corporation, Amgen, encountered the same problem in 2011. Before investing several million euros in a new drug research project, he had decided to replicate the 53 experiments on which their development strategy was based. He could only replicate 11% of them (Baker 2016; Begley 2012).*

Paradoxically, science is facing an unprecedented, deep crisis of credibility when it comes to the reliability of the data it produces and the truthfulness of its statements. Despite this, it seems almost impossible to bring out hypotheses and results other than those that are universally recognized as "scientific truths" at the level of both public and academic opinion. Further, political and economic decisions are often made on the basis of these truths. You recently published a post: "On True and False". Would you help us further investigate this issue?

Here, we see first hand that the problem of truth is not an abstract philosophical problem. Rather, it is something extremely concrete, which determines the life of human beings in a considerable way. As far as scientific truth is concerned, a famous book by Thomas Kuhn had already shown that the scientific community's dominating paradigm is not necessarily the truest, but simply the one that is able to conquer the largest share of followers. This is also real, now, beyond scientific truth. Humanity is entering a phase of its history in which truth is reduced to a moment in the movement of the false. In other, more precise words, this movement is the omnipervasive unfolding of a language that no longer contains any criteria for distinguishing what it is true from what is false. True is that speech which is declared as such and which must be kept true, even if its untruth is proven. In the end, it is essential for the system that any distinction between true and false fades. Hence, confusion grows among conflicting news that is even spread by official bodies. This means calling into question the language itself as the place where truth manifests itself.

Now, what happens in a society that has renounced the truth and in which human beings can only silently observe the multiform and contradictory movement of falsehood? In order to stop this movement, everyone must have the courage to ask the only question that matters without compromise: what is a true word? From the Gospel, everyone can recall Pilate's well-known question to Jesus, which Nietzsche considered "the subtlest joke of all time": "what is truth?" Actually, Pilate had responded to Jesus' immediately preceding statement, "for this I have come into the world: to testify of the truth". In fact, there is no experience of truth without testimony: true is that word for which we cannot but commit ourselves to bear personal witness. Here, the difference between a scientific and a philosophical truth emerges. In fact, while a scientific truth is (or at least should be) independent from the subject who enunciates it, the truth we are talking about is such only if the subject who pronounces it is wholly at stake in it. Indeed, it is a veridiction and not a theorem. Faced with a non-truth imposed by law, we can and must testify of the truth.

The Disappearance of the Hypotheses

In one post, you pointed out that the concept of "news" often substitutes that of "idea". Hence, the expression "fake news" was introduced as a weapon for silencing ideas or hypotheses. In your opinion, why do people—regardless of education—still believe the news whose falsehood has been well documented? What communication strategy should a scientist use if he or she has valid documentation proving the falsity of the official narratives?

In a society that is no longer able to distinguish true from false, news necessarily tends to replace reality. The media operate on this omnipervasive substitution of news for reality. Today's media are a key tool of politics precisely because they guarantee this replacement that is so essential to the functioning of the system. In a world where only news exists, only the dominant news is true and, at the limit, no news is more true than another. Hence the need to set up, as our government in fact did, a commission for deciding which news should be considered true and which news should be false. In notes taken during World War II, Heidegger defined the age in which he was living as "a machination of the nonsensical" where an absolute absence of meaning is algorithmically formulated and relentlessly calculated. What we have under our eyes today looks like that.

The Betrayed Oath

The first point from the modern Italian version of the Hippocratic Oath reads, "I swear to practice medicine in autonomy of judgment and responsibility of behavior, countering any undue conditioning that limits the freedom and independence of the profession." How much autonomy do doctors still have? Is the very figure of the physician being transformed into something new? What do you think the doctor-patient relationship of trust will be like in the future? How do you relate personally to your own doctor and the care for your health?

What you have mentioned is just one of the points of the professional oath that are systematically transgressed today. In addition to the aforementioned points 4 and 5 about respecting the patient's civil rights and autonomy, point 15 is also threatened. This requires the need "to respect professional secrecy and to protect the confidentiality of everything that was shared with me, that I am observing or have observed, understood, or intuited in my profession or by reason of my state or office." While this confidentiality was always observed in the past, anyone who is positive (even simply positive, not just sick) today is publicly denounced as such and isolated. Consequently, even point 6, which requires the need "to treat every patient with care and commitment, without any discrimination", is transgressed. We have reached the point where the doctor does not visit positive patients.

It is difficult to maintain a relationship of individual trust with a doctor who also acts as a representative of a governmental system. Medicine and therapy must remain separate from power and legislation.

Medicine as a Religion

In several contributions, you have presented the idea that medicine and science have become today's religion. However, many doctors and scientists would find it hard to perceive themselves as representatives *of this religion. Perhaps we are referring to different concepts while using a single name, such as medicine or science? Would you help us distinguish what kind of medicine and science have turned into a religion?*

The analogy I was suggesting is not merely metaphorical. If we call religion what people think they believe in, then science is certainly a religion today. However, a distinction must be made in every religion between the dogmatic apparatus (the truths in which one must believe) and the cult, that is, the behaviors and practices that derive from it. The common believer could ignore the dogmas and heresies that theologians had passionately debated. Likewise, the common person of today can completely ignore the scientific theories that scientists argue about. However, the cult, i.e. the practices and behaviors increasingly define him or her, and this is particularly true for medicine. Furthermore, just as the Christian religion proposed salvation through the cult, so does medicine target *health* through therapy. The first is about sin and the other is about illness, but the analogy is clear. Health in this sense is nothing other than a secularization of that "eternal life" that the Christians hoped to obtain through their cultural practices. The medicalization of life had already been growing beyond all measure in recent decades, but it has become permanent and all-pervasive in the situation we are experiencing today. It is no longer a question of taking medicine or having a medical examination or surgery, if necessary: the whole life of human beings must become the place of an uninterrupted worship at every moment. The enemy, the virus, is invisible and always present and must be fought with no truce in every moment of one's existence.

Transhumanism

More and more funding for science comes from the IT industry. This has launched numerous researches on the merge of man and machine which, on the one hand, represents a new market. On the other is a new promise: potential human faculties and prolonged life. What do you think of this progressive digitization and robotization of life?

I think it is appropriate to consider the phenomenon you are talking about in the perspective of the development of the human species. We owe the idea of pedomorphosis or constitutive immaturity of homo sapiens to a brilliant Dutch scientist, Ludwik Bolk. Almost a century has now passed since he had foreseen that the technical apparatuses humans increasingly rely on to survive as a species would have reached a point of extreme exasperation. There, these apparatuses would have reversed into their opposite and ended up causing the end of the species. Paul Alsberg discussed the external technological projection of body organ functions in the '20s of the 20th century. He showed that the result is the progressive deactivation of these organs in favor of the artificial instruments that replace them. While the animal adapts its bodily functions to natural conditions, man deactivates them, entrusting them to artificial instruments. Thus, every exosomatic technical progress corresponds to a regression of the endosomatic functions. But if this regression goes beyond a certain limit, then the very survival of the species is called into question.

I believe we are at this threshold today. However, experience shows that what seems inevitable does not always happen. In the words of Euripides: "The expected does not turn out; for the unexpected the gods find a way".

Language

You pointed out that the very terminology seems selected to support a paradigm of society. For example, the term "social distancing" could have been different, e.g. "personal" or "physical" distancing. Do you think the language is somehow spun, or rather, are we already so immersed in a new governance paradigm that such a language emerges spontaneously at all levels of society? I mean—like some sort of natural evolution? Many scientists have long struggled with misleading and inappropriate terms and yet, despite numerous strong arguments, we are unable to influence the universal language. What are the mechanisms that make certain terms acquired and consolidated?

The relationship between humans and language, and the experience that the speakers have of their language is not simple. Perhaps this is the first problem that thought must deal with. Language is something that human beings try to master and manipulate and, at the same time, it is what they have always been dominated and determined by—something that must necessarily be dealt with.

It goes without saying that the great transformation wrought by modern technology and science would not have been possible without a profound change in the experience of language.

The ancient world could not and did not want to have access to science and technology in the modern sense. The reason is that—despite the development of mathematics (significantly not in algebraic form)—its experience of language could not refer to the world in a way purportedly independent from how the world revealed itself through language. Language was not a neutral tool, replaceable by figures and algorithms. Rather, it was the place where things first reveal themselves and communicate in their truth. Only the reduction of language to a neutral instrument, which took place with Ockham and the late nominalism, allowed the delinguisticization of knowledge which culminated in modern science. Truth moved from the realm of words and language to that of numbers and mathematics. Language became a system of pure conventional signs and looked, at least in appearance, as dominable and manipulable. Since then, it was no longer the place of a possible truth. Now, precisely a language that is no longer related to truth can turn into a prison—a sort of machine that seems to work autonomously and from which it seems we cannot get out. Perhaps human beings have never been so helpless and passive in the face of a language that increasingly determines them.

Philosophy of Nature

In the past, science used to be identified as the "Philosophy of Nature". People like Goethe who were interested in science, philosophy, and literature were considered the most intelligent. Today, science has turned toward a constantly increasing specialization that has undoubtedly led to enormous technical-scientific advances. These are two radically divergent paths. What do you recommend to young students and researchers who are taking their first steps in the world of science today?

An important moment in the history of the West is when philosophy realizes that it can no longer control science, since science has enfranchised itself from it. This is perfectly clear in Kant. His philosophy represents the last attempt to maintain a relationship with science, aiming to be a doctrine of knowledge capable of setting limits to any experience. I do not think that anything similar fits the tasks of philosophy today. The relationship between thought and science is not played on the level of knowledge. Philosophy is not a science—nor can it be resolved into a doctrine of knowledge. In fact, science has shown that it does not need it at all. Philosophy is always about ethics. It always implies a form of life. Now, this is true for every single human being and, therefore, also for every scientist who does not want to give up being human. Of course, scientists have shown that they are ready to unscrupulously sacrifice ethics for the interests of science. Otherwise we would not have seen illustrious scientists experimenting on Nazi camp deportees. I would remind a young person taking his first steps in science to never sacrifice an ethical principle to his own will to know.

Resistance

You spoke of the need to develop new forms of resistance. What do you mean? Can you give us some examples?

I am a philosopher, not a strategist. Of course, the clear awareness of one's situation is the first condition for finding a way out. I can only add that I do not believe today's way out necessarily passes, as perhaps it has been long believed, through a struggle for the conquest of power. There can be no good power—and, therefore, no good state either. We can only, in an unjust and false society, attest to the presence of the right and the true. We can only, in the middle of hell, testify of heaven.

References

Agamben G 2020, *Where Are We Now: The Epidemic as Politics*, London: Eris (English translation of Agamben G 2020, *A che punto siamo? L'epidemia come politica*, Macerata: Quodlibet).

Baker M 2016, "1,500 scientists lift the lid on reproducibility, Survey sheds light on the 'crisis' rocking research", *Nature*, vol. 533, no. 7604, pp. 452–454, available from: https://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970.

Begley S 2012, "In cancer science, many "discoveries" don't hold up" [online], *Reuters*, https://www.reuters.com/article/us-science-cancer-idUSBRE82R12P20120328.

Special Section: COVID-19 Pandemic

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/16990

A Numerical Method to Estimate the Peak of New Infected and the SARS-CoV-2 Outbreak in Italy

Federico Zullo

[a]DICATAM, University of Brescia, Via Branze 38, Brescia, 25123, Italy

Corresponding author: Fedrico Zullo, Email: federico.zullo@unibs.it

Abstract

We give some numerical observations on the total number of infected by the SARS-CoV-2 in Italy. The analysis is based on a tanh formula involving two parameters. A polynomial correlation between the parameters gives an upper bound for the time of the peak of new infected. A numerical indicator of the temporal variability of the upper bound is introduced. The result and the possibility to extend the analysis to other countries are discussed in the conclusions.

Keywords: COVID-19, SARS-CoV-2, epidemiological models, peak estimation

Citation: Zullo F 2020, "A numerical method to estimate the peak of new infected and the SARS-CoV-2 outbreak in Italy", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 111-119. DOI: 10.13133/2532-5876/16990.

Introduction

In most epidemics it is hard to determine the true number of new infected individuals per day. This is the case for the new coronavirus disease, since asymptomatic people or with very mild symptoms may not seek medical assistance and cannot be identified (Baud *et al.* 2020). Realistic data are fundamental to understand the epidemic and to steer the efforts to inhibit the disease in the right direction. Also, the dynamical variables of epidemiological models usually are linked to, or describe directly, the evolution of the true number of infected: the comparison with the empirical data may be problematic if those numbers are not realistic. On this side, researches about the estimation of the real scale of the epidemic or of the proportion of the asymptomatic already appeared in the literature—see e.g. (Li *et al.* 2020) or (Kenji *et al.* 2020).

On the other hand, under very reasonable hypotheses, it is possible to assume that suitable measurable quantities are determined by the relative values of certain characteristics of the population only (in opposition to global absolute values): in this case the knowledge of only a fraction of new infected individuals per day may still be useful to estimate some of the measurable quantities. This property (we will refer to it as "scale invariance") must be reflected in a scale-independent property of the underlying epidemiological model. In this paper we assume that the time of the peak of new infected by the SARS-CoV-2 in Italy has the scale-invariance property. We are aware of the fact that this assumption can be considered at best a rather crude approximation to a very complex system of interactions. In our opinion however, when taken as a working hypothesis, it can provide a well-founded basis, or at least a starting point, to achieve reasonable estimates. This point of view will be justified further in section (1) on the basis of the SIR epidemiological model.

Since the start of the epidemic in China, a certain number of studies appeared in the mathematical community about this subject: the description of the spatial or temporal diffusion of the infected in given regions (Fanelli & Piazza 2020), (Gaeta 2020a; 2020b), (Giuliani *et al*. 2020), the transmission dynamics of the infection (Kucharski *et al*. 2020), the economic and financial consequences of the epidemic (Albulescu 2020), the effect of atmospheric indicators on the spread of the virus (Wang *et al*. 2020), are only a fraction of the topics under investigation in these days. A certain number of epidemiological studies are connected to the SIR model. The SIR model is one of the simplest non-linear deterministic continuous (in time) model of epidemiology: the overall population is divided in three disjoint classes: S, i.e. the number of susceptible individuals, I, the number of infectious individuals and R, the number of recovered individuals. Albeit its non-linearity, the dynamic of the model is fairly uncomplicated and manageable from an analytical point of view and displays very interesting and realistic properties such as the existence of an *epidemic threshold*—see e.g. (Braun 1993) and (Murray 2002).

We must underline that the assumption of the scale invariance is not specific of the SIR model: rather, the SIR model is seen here as an instance among the family of models possessing the scale invariance.

The paper is organized as follows: in section 1 the SIR model is introduced and briefly discussed. In section (2) we analyze the data of the cumulative number of infected in Italy on the base of two simple hypotheses. An upper bound for the time of the peak of new number of infected is obtained. This upper bound is dynamic: when more data are added to the model in the course of the epidemic it may changes in time. In section (3) we will discuss the predictive validity of the model on the basis of a numerical indicator measuring the temporal variability of the upper bound. In the conclusions, we will comment about the results and look for possible extensions.

1. The SIR Model and the Scale Invariance Property

The SIR model describes the evolution of the individuals in the susceptible *(S)*, infectious *(I)* and recovered *(R)* classes with the following differential equations:

$$\begin{cases} \dfrac{dS}{dt} = -r\dfrac{SI}{N}, \\ \dfrac{dI}{dt} = r\dfrac{SI}{N} - aI, \\ \dfrac{dR}{dt} = aI. \end{cases} \tag{1}$$

The total population $N = S + R + I$ is a conserved quantity from the dynamical point of view, meaning that there are only two independent variables in the set of equations (1). The characteristics of this model are well-known and the interested readers can look for example at the discussions in the classical books of (Braun 1993) and (Murray 2002). Here we will make only few observations, relevant for the next sections.

Some authors do not include the denominator N on the right hand side of (1), since it is a constant and can be absorbed by a re-definition of the parameter r. However, we will keep it: in this way it is indeed evident the scale invariance property of the model: if the initial conditions (S_o, I_o, R_o) are scaled by a common constant factor k, (and so the total population is scaled by a factor k), the solution is scaled by the same factor. Indeed it is enough to observe that, if $(S(t), I(t), R(t))$ are the solutions of equations (1) corresponding to the initial conditions (S_o, I_o, R_o), then $(kS(t), kI(t), kR(t))$ are the solutions corresponding to the initial conditions (kS_o, kI_o, kR_o).

Some temporal properties of this model, like the time corresponding to a maximum in I (the time of the peak of the infected), do not depend on the scaling factor k. This property is very useful, since the actual number of infected or susceptible (and then of recovered) is in general not known. The reasonable assumption that the *same fraction* (with respect to the total) of infected, susceptible and recovered individuals are known, gives the possibility, in this case, to compare the measured data with the properties that are scale-independent.

The solution of the system (1) cannot be given explicitly in terms of known functions. However, if the epidemic is not severe, i.e. the number $R(t)$ can be considered small compared to the overall population, an explicit

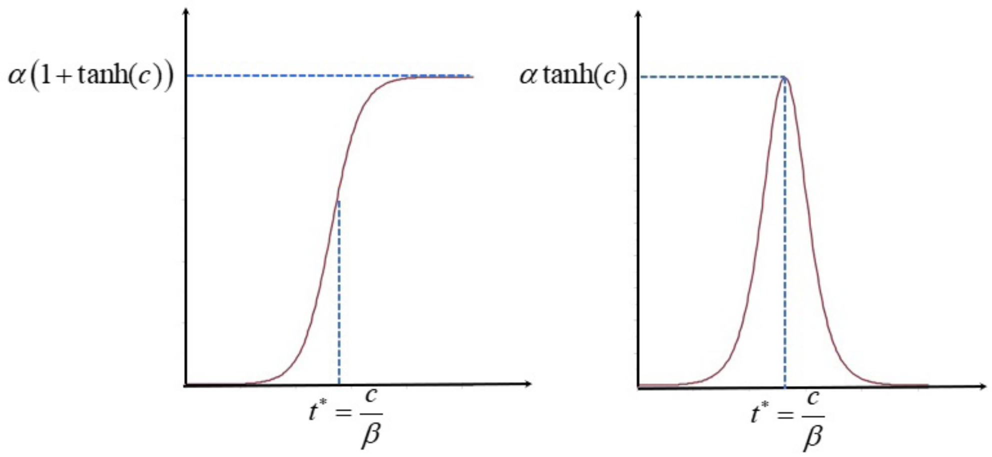


Figure 1: The plot of the function (2) (left) and of its derivative (right) as functions of time for generic values of the parameters (α, β, c). The epidemiological interpretation of the parameters is shown.

formula for the number of recovered can be obtained in terms of the hyperbolic tangent function. Here, we will not give the details: the interested reader can look for example in (Kermack & McKendrick 1927) and (Murray 2002). The function reads as

$$R(t) = \alpha\tanh(\beta t - c) + \alpha\tanh(c), \qquad (2)$$

where we used the initial value $R(0) = 0$. The important point for the rest of the paper is not the exact solution of the system of equations (1), neither the behavior of the solution. Rather, the possibility to represent an epidemiological curve with a simple and manageable formula like (2) will be crucial in this study. The parameters (α, β, c) possess an explicit representation in terms of the parameters a and r of the SIR model (1) and of the initial conditions (S_o, I_o, R_o). The formulas are quite cumbersome and the interested reader can look for example in (Murray 2002). Our aim here is not to analyze the data to fit the solutions of the system (1), but to make use of the explicit formula (2) in a way that will be clear in the next pages. In passing, we would like to underline that, if on the one hand the SIR model gives a mathematical basis to formula (2), on the other hand it would be possible to consider (2) as a postulate and to assess the soundness of this postulate from the truth value of the conclusions obtained. From this point of view, formula (2) can be considered as one of the examples of the so-called s-shaped epidemiological curve (with a peaked derivative, the function sech^2) that universally describes an infection disease (Braun 1993). As can be seen from the second formula in the set of equations (1), once the value of R is given, the value of the number of infected can be obtained by derivation, i.e. $aI(t) = \alpha\beta\text{sech}(\beta t - c)^2$. When considering the cumulative number of infected, $R + I$, the contribution of sech^2 is negligible on the tails, whereas it is more pronounced in correspondence of the maximum of sech^2, but it is however small if the value of the parameter β is less than one. In this case, the value of $R + I$ is well approximated by a tanh formula like (2), with a certain different value of c. For the sake of clearness, we report in Figure (1) a plot of the function (2) (left) and a plot of its derivative (right): as can be seen from the figures, an epidemiological interpretation of the parameters (α, β, c) can be the following: $t^* = c/\beta$ is the time of the peak of new number of infected, $\alpha(1 + \tanh(c))$ is the cumulative final number of people infected, whereas $\alpha\tanh(c)$ is the maximum of the new number of infected.

As a final remark we want to make two observations about the scale invariance and the usefulness of formula (2). The first observation is the following: the scale invariance property assumes that the same fraction of the true number of infected, susceptible and recovered is measured. However it is tacitly assumed that this fraction does not vary in time. If the epidemic persists in time, there is the possibility that the value of such fraction changes significantly. For this reason the number of data to be analyzed must span a limited interval of time. In the following section we will take the data of the outbreak in Italy from the 6th of March (15 days after the 21st of February, when the outbreak started, in order to have enough statistical data) to the 2nd of April, for a total of 28 days. The second observation is about the usefulness of formula (2). We are aware that this formula is a very crude approximation of the real curve, but, for limited intervals of time (like the interval that we are going to consider), it is able to incorporate, in a simple way, the main characteristics of the epidemic. For large time, the epidemic curve may be asymmetric and surely its differential will develop with different velocities. For the above reasons, in the next section we are going to use the above formula only for a limited amount of data. As we will see, this is enough to obtain some relevant information about the time of the peak of new infected.

2. Analysis of Data with a tanh Model

The discussion made at the end of the previous section, despite to be very basic, has the advantage to be manageable and to incorporate the main properties of the SIR model. It is not by chance that the first application of the SIR model (the Bombay plague of 1905) by Kermack and McKendrick (Kermack & McKendrick 1927) used precisely the tanh formula above.

In the following we will base our analysis on two hypothesis:

1. We assume that the cumulative number of infected is described by a tanh model, when the data analyzed span a limited interval of time (as explained in section (2)). Although this assumption is coherent with the founding of the SIR model, it does not depend on the particular dynamical model considered.
2. We assume that, whatever it is the underlying model describing the evolution of the number of infected, this model is scale invariant, in the sense specified in the previous section.

The second hypothesis is fundamental since we are going to look at scale-independent quantities: even in the case the measured number of infected and recovered individuals are different from the actual values, it is possible to estimate these quantities.

The cumulative total number of infected that will be considered in the next lines are those of the entire Italian territory. There are at least two reasons that suggested to not taking regional or local data: the first one is that the epidemic started to spread across three different regions (Lombardy, Veneto and Emilia-Romagna), and there could not be a correspondence between the locality where a certain fraction of inhabitants reside and the region where this fraction was infected. This is also true at a national level, but the fraction is assumed to be smaller. The second reason is that a non-negligible number of workers and students moved, just before the lockdown, from the northern regions to their regions of origin in the center and south of Italy.

The possibility that a non-negligible flow of infected people passed from the north to other regions should be taken into consideration. By taking the entire national set of data, we overpass the above issues.

The data can be taken for example from WHO (World Health Organization, 2020) or from Worldometer (Worldometer, 2020). The cumulative total number of infected will be indicated by F_n, with $F_1 = 21$ corresponding to the number of infected on 21st of February 2020. The subscript n stays for the number of days from the starting of epidemic. These data will be opposed to the continuous formula

$$f(t, \alpha, \beta, c) = \alpha \tanh(\beta t - c) + \alpha \tanh(c). \quad (3)$$

The value of β will be taken to be constrained by the equation

$$\alpha \tanh(\beta - c) + \alpha \tanh(c) = F_1. \quad (4)$$

The function f (3) then depends on two parameters, α and c. When necessary, to stress the dependence on these parameters, we will denote the function with $f_{\alpha,c}(t)$. The cumulative final number of infected expected from formula (3) is given by $f_\infty = \alpha(1 + \tanh(c))$. It is possible to estimate the parameters α and c by minimizing the difference between the actual and predicted number of cases, i.e. minimizing

$$S_n = \sum_{i=2}^{n} (F_n - f(n))^2 \quad (5)$$

In order to have a reasonable minimum number of data, we start the analysis by taking $n \geq 15$. The values of the parameters minimizing the sum S_n are reported in table (1). Please note that some values are slightly different from those of the preprint version of this paper since some data on the cumulative number of infected F_n have been corrected according to (Worldometer, 2020). These values have been obtained by equating the derivative of the expression (5) with respect to α and the derivative with respect to c both to zero. The solutions, for each given n, have been found numerically. Due to the strong non-linearity of equation (3) it is not easy to find estimates for the confidence intervals.

A plot of $df_{\alpha 42,c42}/dt$ and of $F_n+1 - F_n$ is reported in Figure (2). A fundamental observation is that the function S_n actually has a basin of depressed values, showed in detail in Figure (3) for a given value of n. This basin of

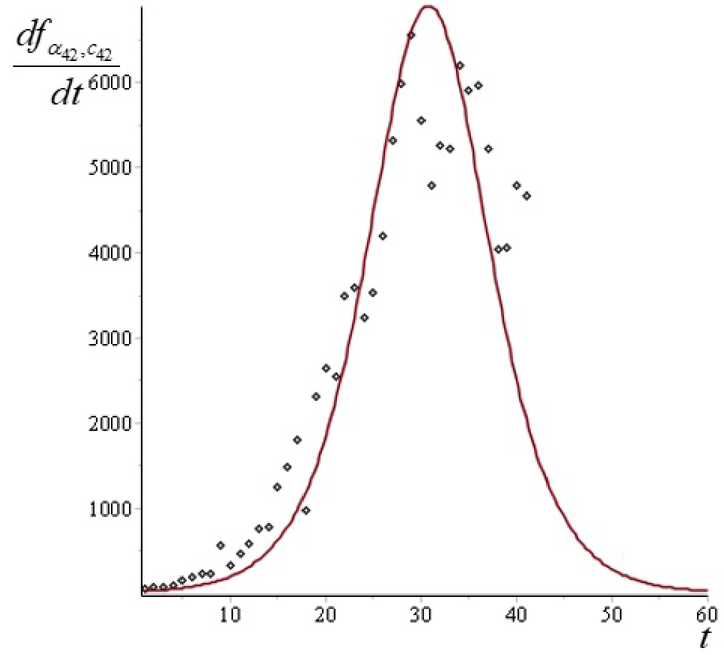


Figure 2: The number of new infected and the continuous curve given by $df_{\alpha42,c42}/dt$

n	α_n	c_n	n	α_n	c_n
15	3514.0	2.506	29	30995.0	3.403
16	4703.0	2.618	30	35166.7	3.455
17	6482.9	2.749	31	38541.2	3.492
18	8757.1	2.876	32	40737.4	3.515
19	8748.9	2.862	33	42602.6	3.533
20	9908.2	2.926	34	44297.6	3.548
21	12158.0	3.011	35	46317.8	3.566
22	14102.9	3.074	36	48397.7	3.582
23	16946.5	3.151	37	50527.0	3.599
24	19752.4	3.216	38	52472.3	3.613
25	21453.2	3.251	39	54030.3	3.624
26	22862.5	3.278	40	55380.4	3.633
27	24679.2	3.309	41	56736.1	3.642
28	27439.8	3.353	42	58161.2	3.650

Table 1: the estimated values of α_n and c_n

minimum seems to indicate that there is a given function $\alpha(c)$ giving a family of tanh curves with reduced values of S_n. The curve $\alpha(c)$ is quite stable by varying n (see section (4)) and suggests to look at the values of α_n as functions of c_n. In Figure (4) we report the plot of the values of α_n and c_n given in table (1) as a function of n, whereas in Figure (5) the plot of the values (c_n, α_n). The values of α_n vs c_n, as explained above, describe the basin of depressed values for S_n as a function of $\alpha(c)$. We make a cubic fit, with linear coefficients, in order to get a rough description of the curve $\alpha(c)$:

$$\alpha = \sum_{k=0}^{3} a_k c^k \qquad (6)$$

Clearly, by considering a number N of values of α_n and c_n to fit a_k, $k=0,\dots,3$, we will obtain a set of values $\{a_{k,N}\}$. By fitting all the data available (i.e. by taking $N = 28$), we get the following values for the coefficients a_k:

$$a_0 = -999707,\ a_1 = 1077192,\ a_2 = -389358,\ a_3 = 47555. \qquad (7)$$

It is possible to get more terms in the sum (6), but the cubic term is sufficient to get a formula accurate enough to what we are going to say.

The plot of the fit is given in Figure (6), together with the values of the residuals,

$$\alpha_n - \sum_{k=0}^{3} a_k c_n^k,$$

where the values ak are those given in equation (7).

A comparison between the curve $\alpha(c)$ and the basin of minima for S_n has been plotted in Figure (7): the red curve is the function (6) with the black dots giving the actual values of (c_n, α_n) in table (1).

The function $\alpha(c)$ denotes a trend in the data that may be useful. If in the next days the values of the infection continue to rise, it is reasonable to expect that the values of α and c will be constrained closely by the same curve. Clearly, the model used here is rough, but it can give at least an idea about the future trend of the data. We are tacitly assuming that there will be no other cluster of infection around Italy in the next days: the point will be discussed later.

Now we consider the function f in (3) as a function of t and c alone, since the value of α is constrained by the curve (6). The plot of the derivative of this function (with respect to t) gives the time of the peak of infections. The plot is reported in Figure (8): we notice that the maximum of the derivative of the cumulative number of infected increases with n up to $c \sim 4.3$ and then *decreases* by increasing c. This gives an upper bound for the peak of new number of infected (the point where the

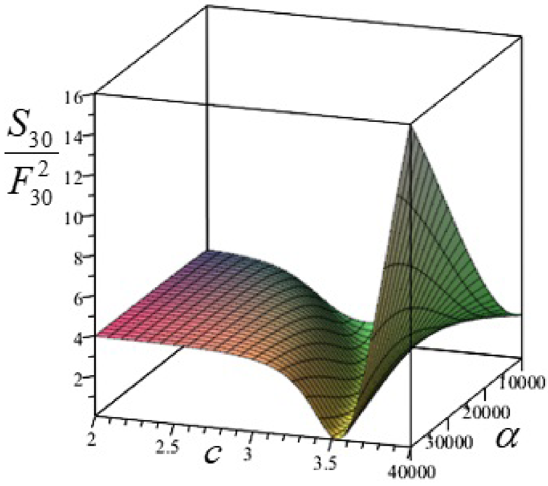
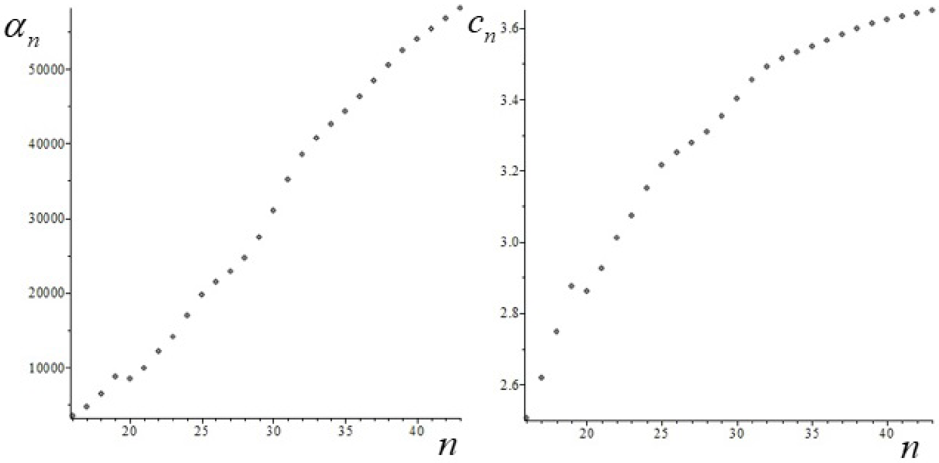


Figure 3 (left): The basin of depressed values of S_{30}: the values have been re-scaled to F_{30}^2 for easy of plotting.

Figure 4 (down): The values of α_n and c_n vs n as given in table (1)



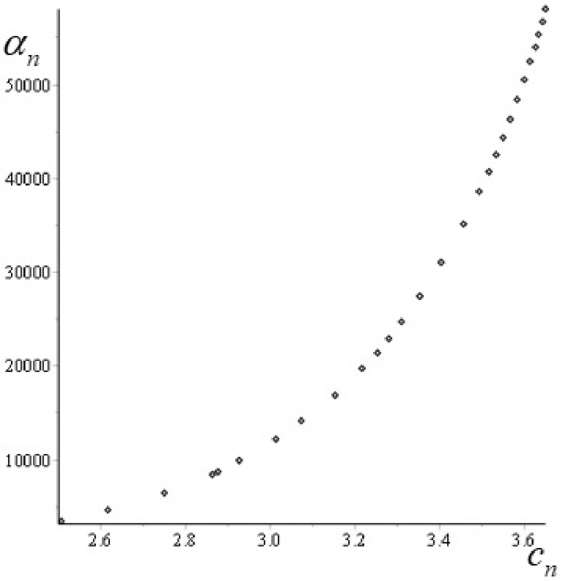


Figure 5: The values of α_n vs the values of c_n as given in table (1)

second derivative of $f(t)$ (3) is zero), given by 36 days after the data corresponding to F_1 (21st of February).

3. Temporal variability of the upper bound

The basin of minimum of S_n, for each fixed n, is described by a function $g_n = \alpha(c)$: this function gives a family of tanh curves with reduced values of S_n. The curve $\alpha(c)$ has been described in the previous section by fitting the values of α_n and c_n in table (1) with a cubic formula. We obtained just one curve by making use of all the data available, i.e. 28 couples (c_n, α_n). It is possible to ask how the curves $g_n(c)$ depend on the number of the data available: if the curves g_n have a temporal stability, then they can be used to make a reliable estimation of the time of the peak of new infected. To address this question we fit the data (c_i, α_i), with the index i from 15 to N, by varying the number of data taken (i.e. by varying N). The fit is again cubic, like in (6). In this way we follow the temporal variation of the curve $g_N(c)$. In plot (9) we report the curves $g_N(c)$ for N in the interval [30, 42]: they correspond to the last thirteen curves (in order of time). It is possible to see that indeed the convexity of the curves is slowly increasing, so that the differences are more pronounced for higher values of c. To have a measure of the variability of these curves we introduce a parameter giving the relative increase of $g_n(c)$ for c fixed and equal to the last available value (i.e. $c = c_{42}$ in table (1))

$$P_N = \left.\frac{\sum_{k=0}^{3} a_{N,k}c^k}{\sum_{k=0}^{3} a_{30,k}c^k}\right|_{c=c_{42}} \qquad (8)$$

The values of P_N, $N = 30 \ldots 42$, are also reported in Figure (10): the maximum value is obtained for $N = 42$ corresponding to $P_{42} = 1.058$.

4. Discussion

Optimal responses to public health emergencies must be tailored to the regional context and must take into account different aspects of the epidemic, like its severity and the type of risks, and different aspects of the local capacity to manage and mitigate the spreading. From this side the quantity and quality of healthcare infrastructures and the coordination across public and private sectors appear to be crucial for a successful implementation of the control strategy. On the other side, mathematical modeling tools can surely be decisive to properly assess the intensity, evolution and

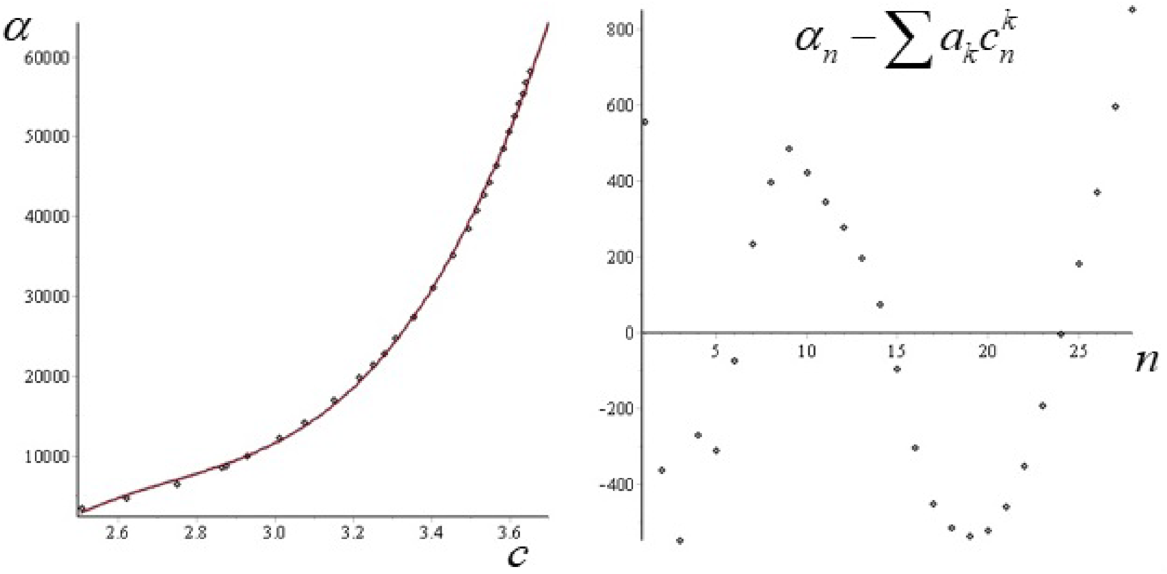
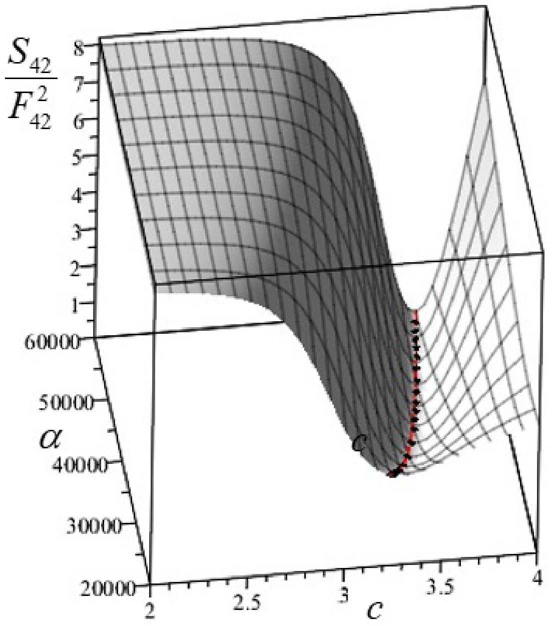


Figure 6: The plot of the fit (6) (left) and the values of the residuals $\alpha_n - \sum_{k=0}^{3} a_k c_n^k$



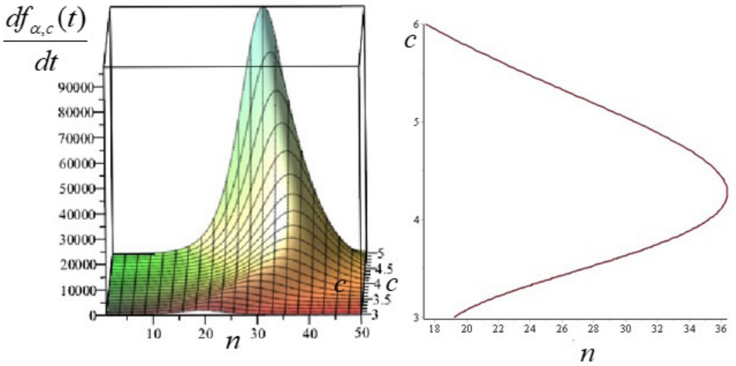


Figure 8 (top): The values of the derivative of the function f (t) vs n and c (left) and the corresponding values of maxima as a function of n and c (the points where the second derivative of f (t) vanishes) (right).

Figure 7 (left): The basin of minima together with the curve (6) (in red) and the actual values (c_n, α_n) (black dots).

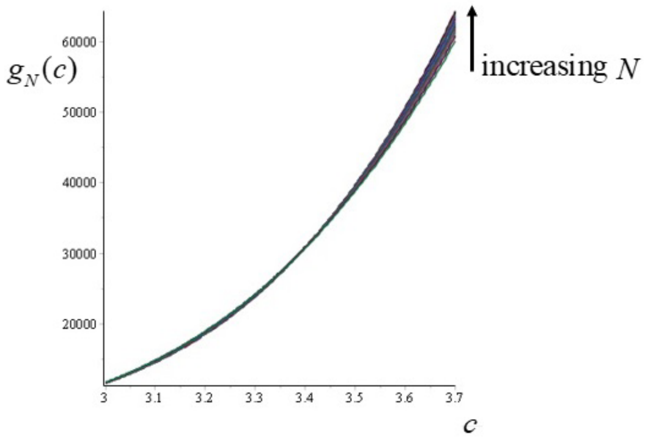


Figure 9: The functions gN (c), for N = 30...42: the curves overlap in a small region of the plane (α, c).

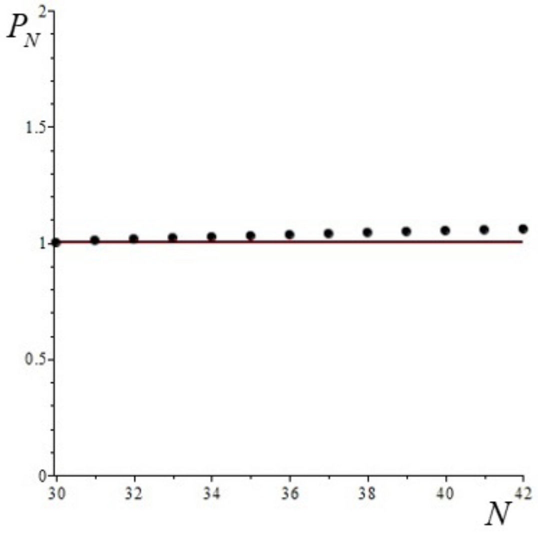


Figure 10: The values of the parameters P_N, N = 30...42, measuring the temporal variability of the curves g_N (c).

duration of the emergency. A reasonable estimate of the peak of new infected in epidemic outbreaks may be useful not only to rightly evaluate the dynamic of the infection, but also to give an (a posteriori) assessment of the effectiveness of the containment strategies: the perseverance of the infections may denote some degeneration of the control strategy or some change in the social situation. Clearly, the peak of new infected is just one of the multiple indicators that should be taken into account: deterministic or stochastic models, r_o and r_t indexes, risk parameters and spatio-temporal simulations are all fundamental to provide a quantification of the evolution of the infectious disease and develop a rapid decision making process.

Conclusions

The above analysis, despite using a rough function for the total number of infected, is able to give an upper bound for the time of the peak of new infected (27th of March) thanks to the observation that the values of αn are, in a certain sense, not independent on the values of cn and are well described by a polynomial interpolation with linear coefficient. The hypothesis about the scale invariance of the underlying model (that, we repeat, not necessarily is represented by the SIR model) and the low temporal variability of the upper bound are fundamental for the accuracy of the result. Another underlying assumption is that the restrictive measures will be kept and observed in the next days and there will be no other clusters in the south of Italy (in the SIR model language, the values of S_0 are below the epidemic threshold, see e.g. (Murray, 2002)). In the unfortunate case that there will be other clusters (the preprint version of the paper appeared before March 27, 2020 on arXiv, see: https://arxiv.org/abs/2003.11363v1), it is possible to think of a substitution of the tanh curve by a combination of such functions: if there are two clusters of comparable magnitude, then we will have

$$f(t) = \alpha_1 \tanh(\beta_1 t - c_1) + \alpha_1 \tanh(c_1) + \alpha_2 \tanh(\beta_2 t - c_2) + \alpha_2 \tanh(c_2) \qquad (9)$$

A statistical analysis of the data given in table (1) will surely help to improve the results here given and will be provided in a next paper, where other sets of data, from different countries, will be analyzed.

Acknowledgments

The author would like to acknowledge the support of the University of Brescia, GNFM-INdAM and INFN.

References

Albulescu C 2020, "Coronavirus and oil price crash", *Working Papers, HAL*, https://ideas.repec.org/p/hal/wpaper/hal-02507184.html.

Baud D *et al.* 2020, "Real estimates of mortality following covid-19 infection", *The Lancet Infectious Diseases*, vol. 20, no. 7, p. 773. DOI: https://doi.org/10.1016/S1473-3099(20)30195-X.

Braun M 1993, *Differential Equations and Their Applications: An Introduction to Applied Mathematics*. Berlin: Springer.

Fanelli D, & Piazza F 2020, "Analysis and forecast of COVID-19 spreading in China, Italy and France", *Chaos, Solitons and Fractals*, vol. 134, 109761. DOI: https://doi.org/10.1016/j.chaos.2020.109761.

Gaeta G 2020a, "Data analysis for the COVID-19 early dynamics in northern Italy", *eprint Arxiv*, https://arxiv.org/abs/2003.02062.

Gaeta G 2020b "Data analysis for the COVID-19 early dynamics in northern Italy. The effect of first restrictive measures", *eprint Arxiv*, https://arxiv.org/ abs/2003.03775.

Giuliani, D, Dickson M M, Espa G, & Santi F 2020, "Modelling and predicting the spatio-temporal spread of COVID-19 in Italy". *BMC Infectious Diseases*, vol. 20, art. no. 700, DOI: https://doi.org/10.1186/s12879-020-05415-7.

Kenji M, Katsushi K, Alexander Z, & Gerardo C 2020, "Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship", *Euro Surveillance*, vol. 25, no. 10, DOI: 10.2807/1560-7917.ES.2020.25.10.2000180.

Kermack W, & McKendrick A 1927, "A contribution to the mathematical theory of epidemics", *Proceedings of the Royal Society A*, vol 115, no. 772, pp. 700–721, DOI: http://doi. org/10.1098/rspa.1927.0118.

Kucharski A *et al.* 2020 "Early dynamics of transmission and control of COVID-19: A mathematical modelling study", *Lancet Infectious Diseases*, vol. 20, no. 5, pp. 553–558, DOI: 10.1016/S1473-3099(20)30144-4.

Li D *et al.* 2020, "Estimating the scale of COVID-19 epidemic in the United States: Simulations based on air traffic directly from Wuhan, China", *medRxiv* [preprint], DOI: 10.1101/2020.03.06.20031880.

Murray J 2002, *Mathematical Biology*, vol. 1, Berlin: Springer.

Wang J *et al.* 2020, "Impact of temperature and relative humidity on the transmission of COVID-19: A modeling study in China and the United States" *BMJ Open, Forthcoming*, Available at SSRN: https://ssrn.com/abstract=3551767 or http://dx.doi.org/10.2139/ssrn.3551767

World Health Organization 2020, *Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update*, [online] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

Worldometer 2020, *Coronavirus, 2020*, [online], https://www. worldometers.info/coronavirus/country/italy/.

Special Section: COVID-19 Pandemic

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17224

The Role of Airflow in Airborne Transmission of COVID-19

Rodolfo Guzzi[a]* & *Leopoldo Stefanutti*[b]*

[a] *Emeritus, Optical Society of America OSA*

[b] *Former director of the Geophysica-EEIG, Director of the Sundrone Project*

***Corresponding authors:** Rodolfo Guzzi, Email rodolfoguzzi2@gmail.com; Leopoldo Stefanutti, Email l.stefanutti@sundroneproject.com

Abstract

The spreading of virus via air pathway has been investigated with simple examples using the Navier–Stokes equations and their application with uncompressible flow and in presence of convection due to heat transfer. Given the results, we argue that the minimum spacing for safety between persons depends on the ratio between the height and length of an artifact, here shown as a cavity box. We found that the best spacing among people is obtained when the ratio is 1:5. This means that the safety consists in staying as far away as possible or using mask properly. In case of confluence between street and square, the Navier–Stokes equations exhibit turbulence at the edges of the system.

Keywords: aerosol, flow, COVID-19, droplets.

Citation: Guzzi R & Stefanutti L 2020, "The role of airflow in airborne transmission of COVID-19", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 121-131. DOI: 10.13133/2532-5876/17224.

Introduction

In a recent paper, Zhang *et al.* (2020) explain the contribution of airborne transmission on Covid-19. They consider dominant the role of aerial transmission and state that airborne transmission may have played a role in pathogenic avian influenza.

Their experimental and observational studies on interhuman transmission seem to indicate a significant role of aerosols in the transmission of many respiratory viruses, including influenza virus, SARS-CoV-1, and Middle East Respiratory Syndrome coronavirus (MERS-CoV). For example, airborne coronavirus MERS-CoV exhibited strong capability of surviving, with about 64% of microorganisms remaining infectious 60 min after atomization at 25 °C and 79% relative humidity (RH). On the other hand, rapid virus decay occurred, with only 5% survival over a 60-min procedure at 38 °C and 24% RH, indicative of inactivation. Recent experimental studies have examined the stability of SARS-CoV-2, showing that the virus remains infectious in aerosols for hours (see Van Dorelman, 2020) and on surfaces up to days (see Chin *et al.* 2020). They based their argument on the measurements done in Wuhan hospitals and outdoor in northern Italy. Of course, the concentration of virus is accumulated in close environment and diluted in open air. Removal of virus bearing particles by deposition is size dependent; residence time in air is closely associated to air mixing. The lifetime of droplets injected in air from infected persons is subjected to complex mechanisms. First of all, in absence of turbulence larger particles > 5 microns are settled out in short range and contaminate surface, object and persons while atomized particles < 5 microns are dispersed in air. The lifetime depends on various factors mainly the presence of high humidity and temperature. The wind velocity may dry the droplets. In principle the atomized droplets, arising from coughing and sneezing, interact with dry or wet aerosol present in air and can be dispersed in a longer range due to flow of air. Binbin Wang *et al.* (2020) made a model of the transport and fate of human expiratory droplets using different approaches and applying different particle models for the free fall of droplets. They explored continuous and impulse cough jet to turbulent fluctuations. Their results presented a model to understand the fundamental dynamics of exhaled droplets in human respiratory activities. The model solves the governing equations of droplets and uses a continuous random walk model to simulate turbulent fluctuations in violent expiratory events. The validation of the model shows the improvement in the prediction of dispersion of median-sized droplets. They show that these droplets are sensitive to environmental conditions, including temperature, humidity, and ambient flows. Applying the model to a set of idealized conditions such as free-fall and continuous jets, they demonstrate significantly different impacts of environmental parameters on different size droplets. The interesting point lays in a realistic droplet size distribution and cough duration, quantifying the transport and fate of droplets in the near field of source and the potential influences by ambient conditions. In veterinary medicine, Zhao at al. (2019) have recently confirmed the role of dust transport in viral epidemics spread among farms, such as foot-and-mouth syndrome in cattle and pigs and avian influenza.

Burgio *et al.* (2020) did not consider the hypothesis of airborne transmission to be of primary importance. They assume that at least in this initial phase of the epidemic in Italy, the areas characterized by the highest lethality rates are also the most polluted of the country. Their claim has long been known: atmospheric particulate matter (droplets) is an effective vector for the transport of viruses and for the spread of viral infections. During the avian flu outbreaks, it was even shown that the particulates had carried the fearsome H5N1 for long distances and that there was an exponential correlation between the quantities of cases of infection and the concentrations of PM10 and PM2.5. Even though correlation between the presence of viruses in the particulate matter and epidemic outbreaks has never yet been proved, there is increasingly evidence that most of the infections occur through human contact and in closed and crowded environments (families, public places, and unfortunately hospitals and healthcare residences). Minimal quantities of viruses transported by the particulates do not seem to play a significant role in this context.

As Zhang *et al.* (2020) observed, the pattern of contagiousness in Wuhan, Italy, New York City, and all the United States had different fate. According to their analysis, contagiousness in Italy and New York City started dropping not when the lockdown was issued, but only after a massive use of face masks was imposed (see Figure 1). From the same figure one may see that Italy's lockdown started on March 9th, but only on April 6th the use of face masks became compulsory. The interval between these two dates is of about 4 weeks, while the incubation time of SARS-COV-2 is of about two weeks. In Italy (Figure 1 in the middle), the lockdown was issued on April 6, but only after April 20 the number of new infections started to decrease. A similar pattern was observable in New York City. In Wuhan, after the strict lockdown the number of new cases remained constant (see Liu *et al.*, 2020).

The interval between the previous dates is of about 4 weeks, while the incubation time of SARS-COV-2 is of about two weeks. During these 4 weeks, no reduction in the number of new infected people was measured, and most of the new infected, often in critical conditions, were hospitalized in intensive care departments. Curve B and C indicate, relatively for Italy and New York City, the reduction of contagiousness after April 6 in Italy and April 20 in New York City, while in the rest of the United States the contagious continued to grow, as shown in Figures 2 and 3.

We have drawn in Figure 4 and Figure 5a,b, similar curves for Italy during the same period. It is evident that the policy of social distancing and face masks had a tremendous differentiating effect between Italy and the USA, where a policy of lockdown, social distancing, and face masks were adopted in a chaotic way and reopening was often decided while the infection was growing.

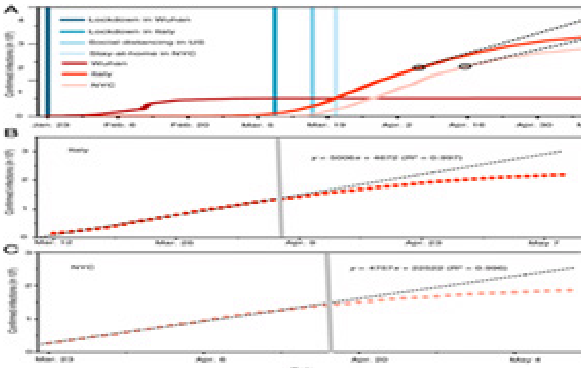


Figure 1: All three figures show the evolution of the infections in Wuhan, Italy, and New York City. Source: Zhang et al. (2020).

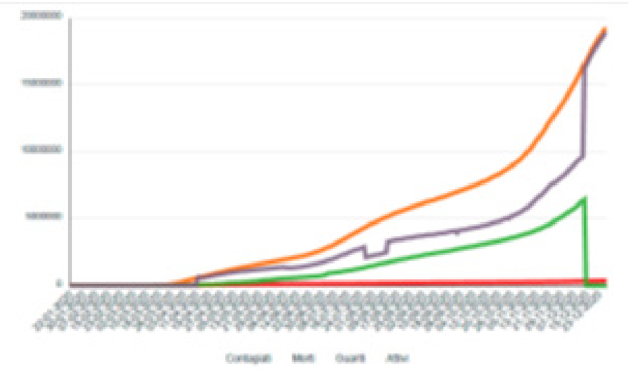


Figure 2: Coronavirus in USA from March 18, to December 23, 2020. Yellow: affected. Green: recovered. Black: active ill. Red: dead. Source: https://statistichecoronavirus.it/.

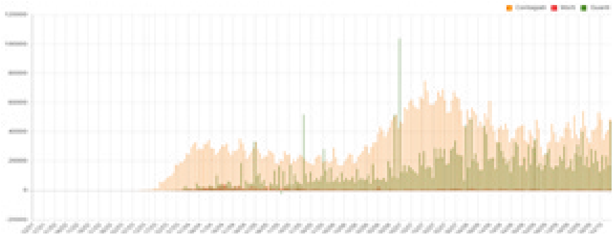


Figure 3: The U.S. new cases from March 2020 to today. Brown: contagious. Green: recovered. Dark brown: dead. Source: https://statistichecoronavirus.it/.

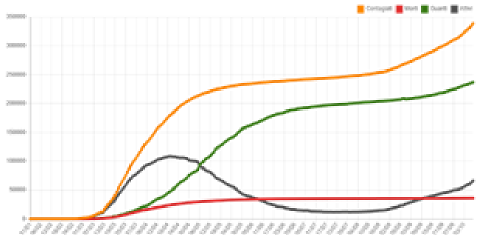


Figure 4: Covid 19 cases in Italy. Yellow: affected. Green: recovered. Black: active ill. Red: dead. Since April the curve grows very slowly up to the end of August, but the curve representing the dead remains flat. Source: https://statistichecoronavirus.it/.

In order to understand the virus spread dynamics, this paper analyzes the flow modes of air in selected case studies from which we can derive the dispersion of droplets. By our numerical experiment, based on a simulation, we explored the flow dispersion both inside a street canyon and in a close site where the combined effect of flow and temperature play an important role.

1. Modelling the flows

In order to improve the prediction of spreading of median-sized droplets, which are sensitive to the environment and critical to the decision of public health we need to model the flow in different situations.

Viruses are acellular organisms of sub-microscopic dimensions of the order of 60-120 nm. For lacking autonomous metabolism, they are parasites and replicate inside cells of other organisms. By coughing, but also by just breathing, we emit micro droplets of the order of the micron. The virus may travel on such droplets. In the absence of wind such droplets reach rapidly the floor or are dispersed in air, and their concentration per unit volume rapidly decreases. In the presence of strong droplets concentration, as in the case of fog or relevant atmospheric pollution, the high concentration of infected droplets could remain in air for a longer period. It is important to know the survival conditions of the virus (humidity, temperature, and pressure). Only this way it is possible to establish for how long and in which conditions the virus can remain dangerous in air. Probably the virus diffusion on the big cruise ships occurred via the air conditioning pipes, fresh air, and relatively high humidity. Such investigation is not simple and rapid. Aerosols can travel for thousands of kilometres, at different altitudes. As an example, we may recall that there are polluting clouds travelling at heights above 5000 m from South East Asia to Europe. We do not believe that such clouds can transport the virus, but to tackle such a complex problem it would be important

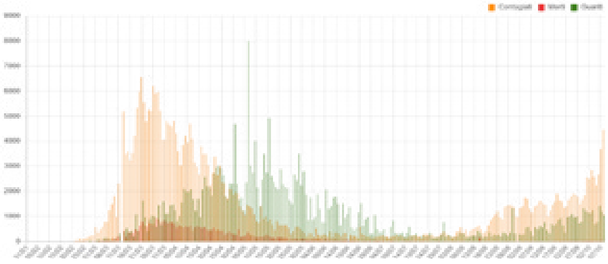


Figure 5a: Daily new cases in Italy since April 2020. Brown: contagious. Green: recovered. Dark brown: dead. Source: https://statistichecoronavirus.it/.

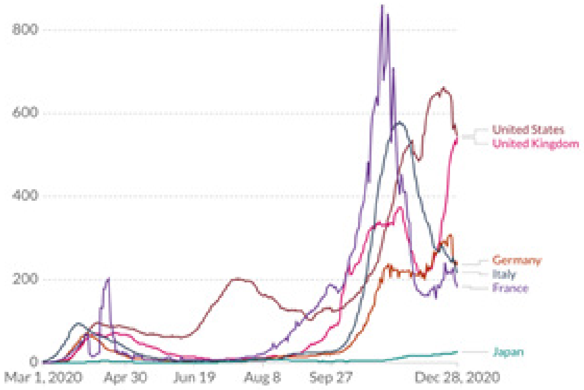


Figure 5b: Confirmed positive cases per million of inhabitants. Rolling 7-average. This picture shows the difference in health policies in several European countries, the U.K., U.S.A., and Japan. Source: https://ourworldindata.org/coronavirus/.

the study of the virus inside a climatic chamber, where temperature, pressure, humidity, aerosol concentration, etc. could be varied. It is also crucial to understand the difference between aerosol and droplets. Even though the droplets need a hygroscopic nucleus to grow, aerosol is the solid part embedded in air (air plus solid). Droplets are due to condensation of water vapor before the saturation in presence of condensation nuclei. We, hence, believe that it is fundamental to determine the time during which the concentration of virus remains high in air. This depends both from the survival time in air of the virus and by the possibility, when survival time is not negligible (order of seconds), that the concentration of the virus remains high, even in the presence of a mild wind and is transported in high concentration. We assume that this may occur when the airflow remains laminar. In a closed environment, the air does not move or moves slowly, and its movement may be due to air conditioning systems. In any way, we can assume, as it probably happened in the ducts transporting the air conditioned from one cabin to the other in the great cruising ships that the air speed is always below one msec^{-1}.

In a closed environment, if the air motion is laminar, as in figure 6a, it is possible that a high virus concentration remains in the environment.

The passage from laminar to turbulent flow is ruled by the Reynolds number:

$$\mathrm{Re} = \frac{uL}{\nu} = \frac{\rho u L}{\mu}$$

Where u, is the air velocity, v is the air density, equal to 1,23 Kgm^{-3}; μ is its viscosity equal to 0,0185, mPa at 25°C, and L indicates the width of a pipe or similar. The passage from laminar to turbulent flow occurs in region of Re of the order of 2000.

In a closed environment, all virus transmission systems may operate simultaneously (direct contact, deposition, and aerial transport). Outside, the situation may be different.

As first numerical experiment, we have simulated the condition occurring in one of the streets of our ancient cities: narrow and with not very high buildings. We have considered the simplest case: an open box, simulating a street, with different ratios between the height of the buildings and the width of the street, i.e. 1:2, 1:3, and 1:5.

Figure 7 presents the most general cavity open at the top where the top lid can slide horizontally. When the top lid is not moving, the internal air (or fluid) is stationary. However, when the lid starts moving it makes the fluid circulate inside the cavity. This can resemble a street canyon where the lateral walls of box are buildings, and the bottom of the box represents the surface of the street. The top lid movement simulates the windy condition. Appendix 1 shows the detail of the model and the CFD techniques we used.

As the computing time is very long and complex, we have carried out, more systematically, a 2D simulation of the airflow in a cross section of the street, as shown in the following figures.

The wind at the top of the building is assumed equal to 1 m sec^{-1}. At the ground and on the sides of the buildings the wind is equal to 0 msec^{-1}. The result for Re =100 is reported in figure 8. The ratio between height and length is 1:1. We use the 2D Navier–Stokes equations with constant temperature. The other parameters are shown in Figure 7.

The variation of the Reynolds number between 100 and 2500 did not change the figure but in squeezing the two lobes and producing a very small lobe at the bottom left with no influence on the middle-high flow.

Figure 8 allows us to observe two mega cells, a larger one in the upper side, and a smaller one in the lower part. Substantially, the air flux remains laminar in the two cells. This means that viruses emitted by a person standing on the left side of the street, near the wall, can reach the opposite side keeping the same concentration. Hence, if the concentration is high enough, a breathing person on the other side of the street will inhale a high concentration of viruses.

Further, by keeping Re=100 we changed the ratio between the height of the buildings and the width of the street to 1:2, 1:3, 1:4, and 1:5. We plotted the results respectively in Figure 9 (left and right) and Figure 10 (left and right).

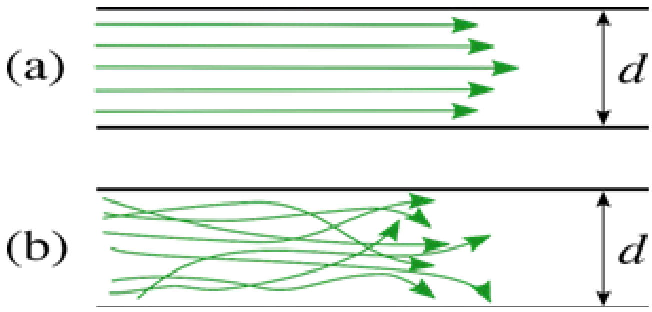


Figure 6: Laminar (a) and turbulent air flow (b).

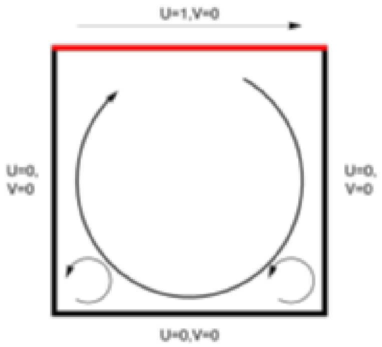


Figure 7: Cross section of the simulated street, u and v indicate the wind velocity in the horizontal and vertical direction.

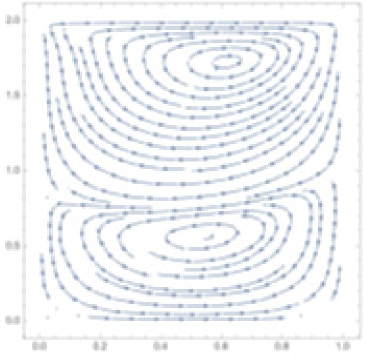


Figure 8: Air flow in the street cross section, computation for Re=100 and u at the top of the street equal 1 m/sec.

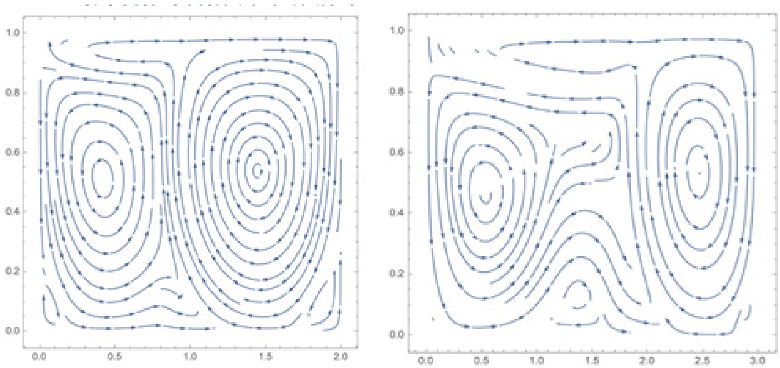


Figure 9: Flow for Re= 100 where the ratio between high and length is 1:2 (left); Re=100 with ratio between High and Length 1:3 (right).

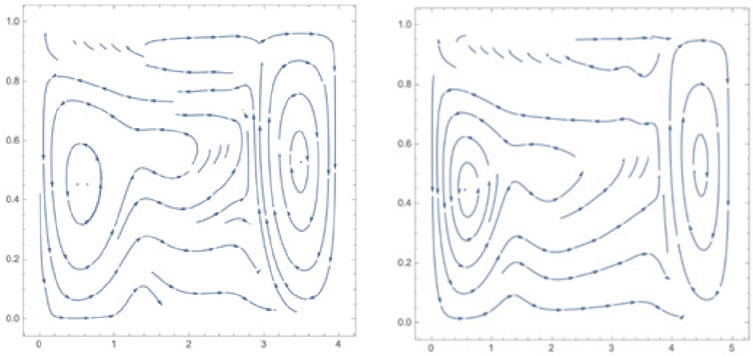


Figure 10: 1:4 height and length ratio (left) and 1:5 height and length ratio (right).

The system of flow shows two interacting lobes. This indicates that the ratio between height and width is a critical parameter. It is then apparent that the behaviour of the airflow depends strongly on the ratio between height of the buildings and the width of the street. As this ratio increases, i.e., as the street becomes larger than the height, the system of flow produces non-interacting lobes.

Since the virus lifetime strongly depends on temperature and humidity and may decay more rapidly in the case of high Relative Humidity, we introduce the effect of temperature along the walls (see Figure 11). Here, the system exhibits different patterns. The cavity is closed and he ratio between the height and the base is 1:1.

We have used the most general 2D Navier–Stokes with heat transfer incorporating the Boussinesq approximation (see Appendix 1) coupled with thermal convection diffusion equation. In this model, where the flow is governed by the continuity equation, the equation of motion and the energy equation under Boussinesq hypothesis is given in Appendix 1.

As result we obtain the figures 12a,b, where the ratio between height and the base is 1:2.

Figures 12a and 12b show the existence of one cell; the flow seems even more regular and horizontal for most of the area of the cross section, with a sharper ascent (warm side) and descent (cold side) along the walls.

In our simulation we use the Rayleigh Number equal to 100000. In Figure 12a we show the temperature pattern and in figure 12b the air flow in case of ratio 1:2.

The same experiment done with the ratio between height and base is 1:5 as shown in Figure 13.

In this case, the temperature difference has caused the air flux to become much more regular than in the case of Figure 9 (right), where the same ratio 1:5 has been assumed but no temperature difference between the two different walls had been assumed. In the previous case, two non-interacting lobes occurred. In this case, the circulation is extremely regular from one side to the other of the walls. It is interesting to note the effect of the temperature when the hottest and the coldest fluid mix, as can be seen in the sequence of Figure 14. In this case, the ratio between walls height and base length is 1:2, with the number of Prandtl Pr = 0.71 and the number of Rayleigh $Ra=10^5$.

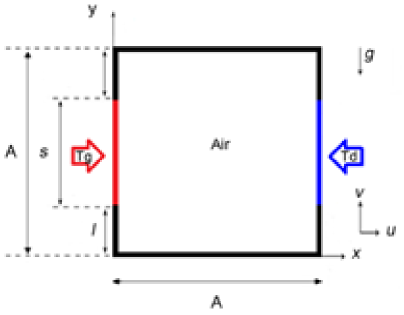


Figure 11: One side of the street is illuminated by the sun, the other side is in the shade. Source: Kane et al. (2017).

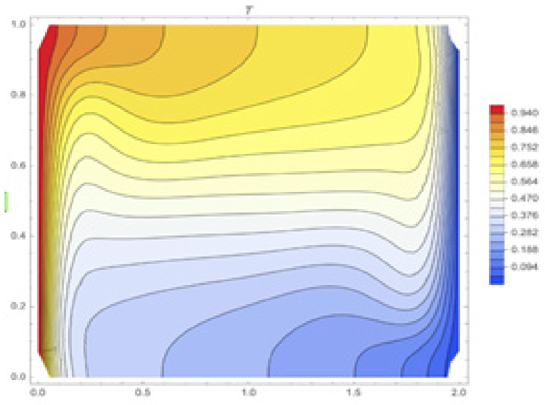


Figure 12a: Temperature pattern.

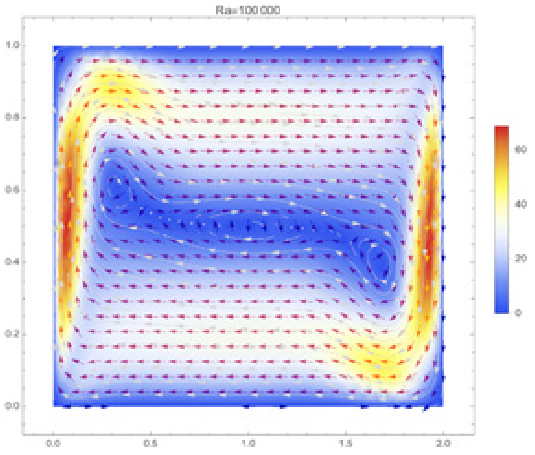


Figure 12b: Corresponding air flow.

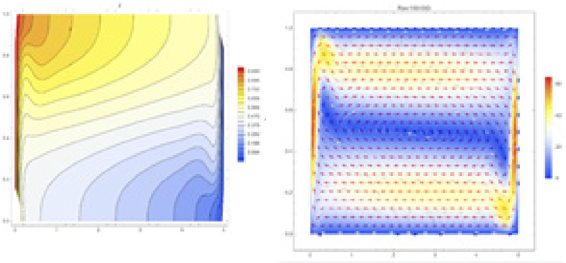


Figure 13: Same as figure 12a,b but with a ratio 1:5.

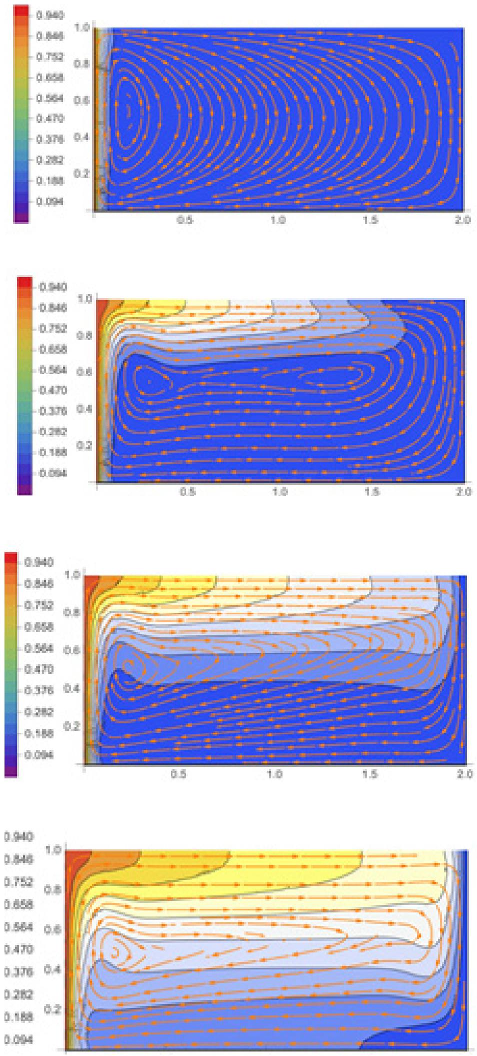


Figure 14: Sequence of mixing fluid in presence of a temperature gradient. From the first to the last picture the system shows the flow following the distribution of temperature. The computation has been performed at steps of 30 sec. The gradient between the "hot" and the "cold" walls is of some degree (the gradient is contained into Rayleigh number).

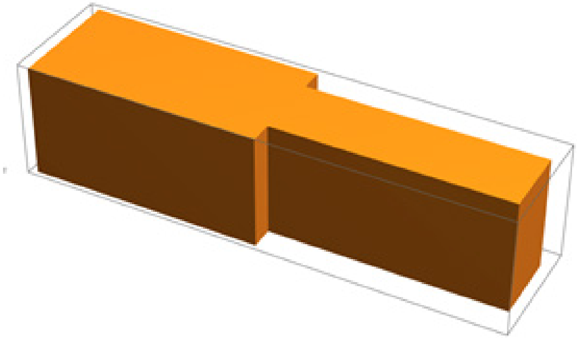


Figure 15: Example of 3D representation for simulating the confluence of a street in a square.

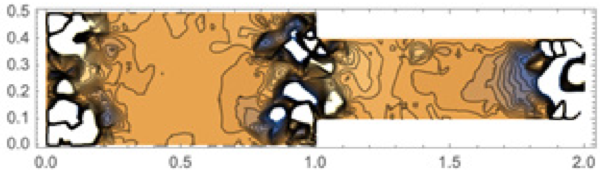


Figure 16: Half-height horizontal cross section of a square-street confluence. In case of edges, the Navier–Stokes exhibit turbulence.

In order to understand more about the effect of a 3D flow in absence of temperature effect, we have also simulated the case of a square and a street, assuming the square to be as in figure 15.

To better understand the effect of the edges we sliced the 3D object in different layers. The results of one of them is given in Figure 16.

At the edges, we note a strong concentration of air turbulence and an increase of airflow velocity due to Venturi effect. This might cause locally a strong additional concentration of viruses even if the flow is now turbulent.

Conclusions

Our simulations evidence that in order to avoid the transport of infected droplets, a several-meter distance, depending on the ratio between the boundaries, is required.

The Reynolds number shows that the circulation remains laminar in a street whose width is up to 10 meters when the wind velocity at the top of the buildings is equal to 4 msec^{-1}. Only when we consider locations larger than 100 m, then the circulation appears to be always turbulent. The distance to avoid completely the contagion is of the order of 50 meters.

In case of heat convection, in the presence of high Relative Humidity the droplets' lifetime could be of the order of 1 min, while in the case of low humidity it can reach values up to 8 minutes before settling. If we consider an air velocity of 1 m sec^{-1}, then the parcel may travel 60 meters in 1 minute and 480 meter in 8 minutes. The presence of heat flow influences the spreading of particles. The flow changes in a few minutes and its pattern mixes the warm and cold air that transports the particles to a further distance.

In this paper, the spreading of virus for air pathway has been investigated with simple examples using the Navier–Stokes equations and their application with uncompressible flow and in presence of heat transfer convection. Given the results, we argue that the minimum safe spacing between people depends on the ratio between the height and length of an artefact, here proposed as a cavity box. We found that the best spacing among people is achieved when the ratio is 1:5. This means that it is safe to stay as far away as possible or properly use mask. A 3D model applied to a more complex structure, such as a street-square confluence. The NS equations exhibit turbulence at the edges of the system.

Appendix 1

The main ruling differential equation of fluid flow and heat transfer is given through the Navier-Stokes (N-S) equations, which are are based on the conservation of mass, linear momentum (Newton second law), and energy (first law of thermodynamics). Due to different mathematical characters of governing equations for compressible and incompressible flow, the Computational Fluid Dynamics CFD codes are usually written for only one of them. For compressible flow simulation, it is usual to drop the viscous terms obtaining the Euler's equation. This is of common use for obtaining the pressure distribution around a flying body, where the viscous effects are squeezed inside e very thin boundary layer. On the other hand, uncompressible flows have a known constant value. In this paper we use an incompressible flow approach that is valid for any coordinate system.

In fluid dynamics, the Reynolds number, Re=$\rho UL/\mu$, corresponds to the ratio of inertial forces to viscous forces. It measures how turbulent the flow is, where low Reynolds number flows are laminar and high Reynolds number flows are turbulent.

The Mach number, M=U/c, corresponds to the ratio of the fluid velocity, U, to the speed of sound in that fluid, c and measures flow compressibility.

In Cartesian flows we have the following equations:

$$\frac{\partial u}{\partial x}+\frac{\partial v}{\partial y}+\frac{\partial w}{\partial z}=0$$

$$\frac{\partial u}{\partial t}+u\frac{\partial u}{\partial x}+v\frac{\partial u}{\partial y}+w\frac{\partial u}{\partial z}=-\frac{1}{\rho}\frac{\partial p}{\partial x}+v\left(\frac{\partial^2 u}{\partial x^2}+\frac{\partial^2 u}{\partial y^2}+\frac{\partial^2 u}{\partial z^2}\right)+f_x$$

$$\frac{\partial v}{\partial t}+u\frac{\partial v}{\partial x}+v\frac{\partial v}{\partial y}+w\frac{\partial v}{\partial z}=-\frac{1}{\rho}\frac{\partial p}{\partial y}+v\left(\frac{\partial^2 v}{\partial x^2}+\frac{\partial^2 v}{\partial y^2}+\frac{\partial^2 v}{\partial z^2}\right)+f_y$$

$$\frac{\partial w}{\partial t}+u\frac{\partial w}{\partial x}+v\frac{\partial w}{\partial y}+w\frac{\partial w}{\partial z}=-\frac{1}{\rho}\frac{\partial p}{\partial z}+v\left(\frac{\partial^2 w}{\partial x^2}+\frac{\partial^2 w}{\partial y^2}+\frac{\partial^2 w}{\partial z^2}\right)+f_z$$

$$\rho c_p\left(\frac{\partial T}{\partial t}+u\frac{\partial T}{\partial x}+v\frac{\partial T}{\partial y}+w\frac{\partial T}{\partial z}\right)=k\left(\frac{\partial^2 T}{\partial x^2}+\frac{\partial^2 T}{\partial y^2}+\frac{\partial^2 T}{\partial z^2}\right)+\phi$$

Where v is the viscosity, p is the pressure, T is the temperature, ρ is the density, c_p is the specific heat, u, v and w are the flow components related to the coordinates x, y, z. and k is the thermal conductivity.

$$\phi=\mu\left\{2\left[\left(\frac{\partial u}{\partial x}\right)^2+\left(\frac{\partial v}{\partial y}\right)^2+\left(\frac{\partial w}{\partial z}\right)^2\right]+\left(\frac{\partial v}{\partial x}+\frac{\partial u}{\partial y}\right)^2+\left(\frac{\partial w}{\partial y}+\frac{\partial v}{\partial z}\right)^2+\left(\frac{\partial u}{\partial z}+\frac{\partial w}{\partial x}\right)^2\right\}$$

The dissipation function is given by

The previous equations represent the conservation of mass (the first one), the conservation of linear momentum (the next three) and the conservation of energy for incompressible flows (the last).

In order to simplify the system for computation, it is preferable to write the governing equations in nondimensional form, selecting characteristic quantities that describe the flow problem. These are the characteristic length L of a flow, its velocity U_c, pressure p_c, and temperature T_c, f_x, f_y, f_z are the external forces applied to the fluid that in our case are zero.

Then the following nondimensional parameters can be defined:

$$t^* = \frac{t}{L/U_c}, x^* = \frac{x}{L}, y^* = \frac{y}{L}, z^* = \frac{z}{L}, u^* = \frac{u}{U_c}, c^* = \frac{v}{U_c}, w^* = \frac{w}{U_c}, \dots$$
$$\dots, p^* = \frac{p - p_c}{\rho U_c^2}, T^* = \frac{T - T_c}{\Delta T}$$

Where ΔT is a known reference temperature difference in the flow field between a constant wall temperature and T_c. Using the characteristic quantities, previous equations can be converted as:

$$\frac{\partial u^*}{\partial x^*} + \frac{\partial v^*}{\partial y^*} + \frac{\partial w^*}{\partial z} = 0$$
$$\frac{\partial u^*}{\partial t^*} + u^* \frac{\partial u^*}{\partial x^*} + v^* \frac{\partial u^*}{\partial y^*} + w^* \frac{\partial u^*}{\partial z^*} = \frac{\partial p^*}{\partial x^*} + \frac{1}{Re}\left(\frac{\partial^2 u^*}{\partial x^{*2}} + \frac{\partial^2 u^*}{\partial y^{*2}} + \frac{\partial^2 u^*}{\partial z^{*2}}\right)$$
$$\frac{\partial v^*}{\partial t^*} + u^* \frac{\partial v^*}{\partial x^*} + v^* \frac{\partial v^*}{\partial y^*} + w^* \frac{\partial v^*}{\partial z^*} = \frac{\partial p^*}{\partial y^*} + \frac{1}{Re}\left(\frac{\partial^2 v^*}{\partial x^{*2}} + \frac{\partial^2 v^*}{\partial y^{*2}} + \frac{\partial^2 v^*}{\partial z^{*2}}\right)$$
$$\frac{\partial w^*}{\partial t^*} + u^* \frac{\partial w^*}{\partial x^*} + v^* \frac{\partial w}{\partial y^*} + w^* \frac{\partial w^*}{\partial z^*} = \frac{\partial p^*}{\partial z^*} + \frac{1}{Re}\left(\frac{\partial^2 w^*}{\partial x^{*2}} + \frac{\partial^2 w^*}{\partial y^{*2}} + \frac{\partial^2 w^*}{\partial z^{*2}}\right)$$
$$\frac{\partial T^*}{\partial t^*} + u^* \frac{\partial T^*}{\partial x^*} + v^* \frac{\partial T^*}{\partial y^*} + w^* \frac{\partial T^*}{\partial z^*} = \frac{1}{\mathrm{RePr}}\left(\frac{\partial^2 T^*}{\partial x^{*2}} + \frac{\partial^2 T^*}{\partial y^{*2}} + \frac{\partial^2 T^*}{\partial z^{*2}}\right) + \frac{Ec}{Re}\phi^*$$

The following quantities have been introduced: the Reynolds number ($Re = U_c L / \upsilon$) in the momentum and energy equations, the Eckert number ($Ec = U_c^2/(c_p \Delta T)$) which is the ratio of flow's kinetic energy to a representative enthalpy difference, the Prandtl number ($Pr = \upsilon/\alpha = \upsilon/(k/\rho c_p)$) which is the ratio of momentum and thermal diffusivities. In case of incompressible viscous flow, it is usual to introduce the Reynolds number Re=100, 1000.

Solving the above system in general is difficult but a simple experiment can imitate some common environmental dynamics.

After selecting the geometry, it is necessary to define the dynamic boundary and thermal conditions. Since there are not known analytical solutions, the only choice is to obtain a solution using numerical methods by the treatment of the derivatives.

Here is the algorithm we have followed.

i) Take the domain and discretize it, that means the solution *u(x,y,z)*, v(x,y,z), w(x,y,z) are computed at discrete points x_i, y, z defining a set of grid.

ii) The derivatives are expressed as some linear combination of *u(x,y,z)*, v(x,y,z), w(x,y,z)

iii) The final system is changed from a system of differential equations to a system of algebraic equations for *u(x,y,z)*, v(x,y,z), w(x,y,z), solved using one of many root finding algorithms.

Following the algorithm outlined above, the first step is to define the domain. This means that we have to define the geometry, for instance a cavity, open or not, depending if we are making some numerical experiment in a room or in a canyon street. The second step is to find an approximation to the derivatives that are approximated as:

$$\frac{\partial u}{\partial x}(x_i, y_i, z_i) \approx \sum a_{ij} u(x_j, y_j, z_i)$$

This form of approximation is called finite difference approximation. The coefficients can be computed using the traditional Taylor series.

We use the Dirichlet boundary conditions that are the values that a solution needs to take along the boundary of the domain and take into account its shape. In order to simulate the flow we divided the area given from Figure 7 with 100 points (see figure A1). At each of these grid points, the velocities and pressure have to be computed.

In figure A1 we present the most general cavity open at the top where the top lid can slide horizontally. When the top lid does not move, the internal air (or fluid) is stationary. However, when the lid starts moving, the motion of the lid makes the fluid circulate inside the cavity. This can resemble a street canyon where the lateral box walls represent buildings and the box bottom

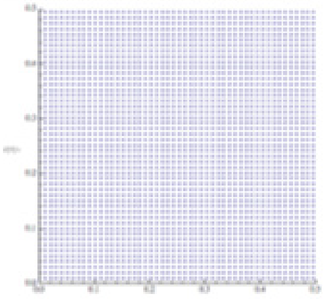


Figure A1: The area of figure 7 with 100 points.

represents the street surface. For the flow in this cavity, the Navier–Stokes equations can be simplified. Let us assume that the flow does not change in function of time, that it does not change in the z direction, and that the temperature remains constant. This simplifies our equations to:

Equation 1A

$$\frac{\partial u^*}{\partial x^*} + \frac{\partial v^*}{\partial y^*} = 0$$

$$u^* \frac{\partial u^*}{\partial x^*} + v^* \frac{\partial u^*}{\partial y^*} = \frac{\partial p^*}{\partial x^*} + \frac{1}{Re}\left(\frac{\partial^2 u^*}{\partial x^{*2}} + \frac{\partial^2 u^*}{\partial y^{*2}}\right)$$

$$u^* \frac{\partial v^*}{\partial x^*} + v^* \frac{\partial v^*}{\partial y^*} = \frac{\partial p^*}{\partial y^*} + \frac{1}{Re}\left(\frac{\partial^2 v^*}{\partial x^{*2}} + \frac{\partial^2 v^*}{\partial y^{*2}}\right)$$

The top lid drags the fluid below it, which generates a swirling motion. This initial swirling motion produces in turn its own swirling motion —a big gear turning smaller gears. A cross-section of the u, v indicates the wind velocity in the horizontal and vertical direction. The wind at the top of the building is assumed equal to 1 msec^{-1}. At the ground and on the sides of the buildings the wind is equal to 0 msec^{-1}.

The cavity can be made as larger or as smaller as we desire. In the second case top, the lid can be moved fast or slow simply by changing the Reynolds number. We varied the Reynolds number between 100 and 2000. This number can also be used to describe whether the fluid inside the box is water, air, or any other substance of choice. When the fluid of particles flows without intersecting the paths of each other and the velocity of the particles is always tangential to the path of the particle, the flow is said to be streamline. When the streamline flow occurs, the layers of fluid particles tend to slide over the adjacent particle without disturbing the motion of others, and this occurs in layers or laminas of fluid flow. Such a flow is known as a laminar flow. Laminar flow or streamline flow occurs when the fluid velocity is relatively low. In laminar flow, the layer in contact with a stationary surface has zero velocity and, in the direction perpendicular to the surface, the velocity of the layers tends to increase. Also, the velocity, pressure, density, and other fluid dynamic properties remain unchanged at every point in the space of the flow. Reynolds number indicates how well a fluid may undergo laminar flow. When the Reynolds number is low, the flow tends to be laminar, and the viscous forces are the dominant form of interaction between the layers. When the Reynolds number is high, the flow tends to be turbulent, and inertial forces are the dominant form of interaction between the layers.

When the fluid properties in a flow vary rapidly with time, i.e., when the changes in the velocity, pressure, density, and other flow properties show random and arbitrary changes, the flow is known as a turbulent flow. The fluid flow within a uniform cylindrical pipe with a finite length, also known as a Poiseuille flow, will have turbulence in the flow when the Reynolds number reaches the critical number, around 2040. However, generally, the flow may not explicitly be turbulent when the Reynolds number is more than 10000.

Eddies, cross currents and vortices are typical of any turbulent flow.

- Laminar flows feature low velocities and low Reynolds number, while turbulence flows show high velocities and high Reynolds number.
- Laminar flows feature a regular and streamline path of the fluid lines, no lateral disturbance, and layers. Turbulent flows have irregular and chaotic patterns.
- Laminar flows are constant at a point in space, where turbulent flows are stochastic.

In case of a room one can choose a cavity differentially heated, formed by two vertical walls as reported in figure 11. In this case of natural convection, we use a second model given by the equation 2A. The problem to be considered is that of the two-dimensional flow of a Boussinesq fluid of Prandtl number 0.71 in an upright square cavity of side L. Both velocity components are zero on the boundaries. The horizontal walls are insulated, and the vertical sides are at temperatures Tg and Td. The solution is given by DeVahl Davies (1983). Convection is the transfer of thermal energy due to the motion of fluids. Natural convection is defined as the fluid flow and heat transport arising due to density and temperature differences in the fluid. The chosen geometry is a square cavity differentially heated. It is formed by two vertical walls, each of which is heated at its center. The left active part has a higher temperature (Tr + ΔT/ 2) than that of the right active part (Tr − ΔT /2). The boundary conditions are Dirichlet type.

The flow is governed by the continuity equation, the equations of motion and the energy equation under convection in the Boussinesq hypothesis. U_r =

α/A for velocity, A for length, A/U_r = A2/α for time and θ= (T−Tr)/ΔT corresponds to the dimensionless temperature. Then:

Equation 2A

$$\frac{\partial U}{\partial X}+\frac{\partial V}{\partial Y}=0$$

$$\frac{\partial U}{\partial \tau}+U\frac{\partial U}{\partial X}+V\frac{\partial U}{\partial Y}=-\frac{\partial P}{\partial X}+Pr\left(\frac{\partial^2 U}{\partial X^2}+\frac{\partial^2 U}{\partial Y^2}\right)$$

$$\frac{\partial V}{\partial \tau}+U\frac{\partial V}{\partial X}+V\frac{\partial V}{\partial Y}=-\frac{\partial P}{\partial Y}+Pr\left(\frac{\partial^2 V}{\partial X^2}+\frac{\partial^2 V}{\partial Y^2}\right)+Ra\cdot Pr\cdot\theta$$

$$\frac{\partial \theta}{\partial \tau}+U\frac{\partial \theta}{\partial X}+V\frac{\partial \theta}{\partial Y}=\frac{\partial^2 \theta}{\partial X^2}+\frac{\partial^2 \theta}{\partial Y^2}$$

We have the following boundary conditions (hydrodynamic and thermal) at the walls:

X=0, (Heated part of the left wall), U=V=0, θ=1;

X=1, (Heated part of the right wall), U=V= 0, θ=0;

X=0 and X1, (Adiabatic parts of left and right walls), U=V=0; ∂θ/∂x = 0;

Y=0 and Y =1 (Lower and upper walls), U=V=0; ∂θ/∂y = 0.

The dimensionless numbers used is the Prandtl number Pr=v/α, that is physically defined as ratio of momentum diffusivity to thermal diffusivity. It provides a measure of the efficiency of diffusion transport through the velocity boundary layer and the thermal boundary layer. Rayleigh number, Ra, is physically the ratio of buoyancy and viscosity forces multiplied by the ratio of momentum and thermal diffusivities. Below the critical value of the Rayleigh number, heat transfer is primarily due to conduction. Above this critical value, heat transfer is due to convection: Ra =g βΔTA^3/vα. The numbers for Ra=10^3,10^4,10^5. For Pr=0.71 the relation between Ra number and Re is Re=0.085$Ra^{0.455}$ (see Grossmann & Lohse, 2002).

References

Wang B, Wu H, Wan X-F (2020), “Transport and fate of human expiratory droplets—A modeling approach, *Physics of Fluids*, vol. 32, 083307. Available from: https://doi.org/10.1063/5.0021280

Burgio E *et al.* (2020) COVID-19 (27 Aprile 2020) “Covid-19: The Italian drama”, *Epigenetwork* [online] https://www.epigenetwork.it/2020/04/25/covid-19-the-italian-drama/.

Chin A W H *et al.* (2020). “Stability of SARS- CoV-2 in different environmental conditions” *Lancet Microbe*, vol 1, no. 1, E10. Available from: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30003-3/fulltext.

De Vahl D G (1983), “Natural Convection of Air in a Square Cavity: A Benchmark Numerical Solution”, *International Journal for Numerical Methods in Fluids*, vol. 3, pp. 249–264.

Grossmann S & Lohse D (2002), “Prandtl and Rayleigh number dependence of the Reynolds number in turbulent thermal convection”, *Physical Review E*, vol. 66, no. 1, 016305.

Liu Y *et al.* (2020), “Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals”, Nature, vol. 582, pp. 557 –560. DOI: 10.1038/s41586-020-2271-3.

Kane M K *et al.* (2017), “A study of natural convection of air in a square cavity with partially thermally active side walls”, *Open Journal of Fluid Dynamics*, vol. 7, no. 4, pp. 623–641.

Zhang R *et al.* (2020) “Identifying airborne transmission as the dominant route for the spread of COVID-19” *PNAS*, vol. 117, no. 26, pp. 14857-14863. Available from: www.pnas.org/cgi/doi/10.1073/pnas.2009637117.

van Doremalen N, Bushmaker T, & Morris D H (2020), “Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1”, *The New England Journal of Medicine*, vol. 382, pp. 1564–1567. DOI: 10.1056/NEJMc2004973.

Zhao Y *et al.* (2019) “Airborne transmission may have played a role in the spread of 2015 highly pathogenic avian influenza outbreaks in the United States”, *Scientific Reports*, vol. 9, 11755. Available from: https://www.nature.com/articles/s41598-019-47788-z#citeas.

Organisms

SAPIENZA
UNIVERSITÀ DI ROMA

Special Section COVID-19 Pandemic

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17354

Science and the Narration of Science: The Shadow Line Between Explanation and Manipulation

Andrea Pensotti[a]*

[a] *University Campus Bio-Medico of Rome, Italy*

***Corresponding author:** Andrea Pensotti, Email andreapensotti@gmail.com

Abstract

The current use of science as a political argument reveals an old bias: the idea that science is about truth and therefore is potentially authoritarian. In reality, science is about doubt. The public management of the COVID pandemic should make us reflect about several aspects of our society.

Keywords: COVID-19, media, narration, science.

Citation: Pensotti A 2020, "Science and the narration of science: The shadow line between explanation and manipulation", *Organisms: Journal of Biological Sciences*, vol. 4, no. 2, pp. 132-136. DOI: 10.13133/2532-5876/17354.

Disputes on data and observation reliability is not what caused Copernicus' heliocentric model to be unaccepted in the short term. Rather, his model undermined the "main stream" narration of the time.

It is worth noting that the geocentric Ptolemaic model could explain and predict almost every celestial bodies' movements. Hence, the irregularities were seen as a needed update of the model instead of a need for a radical paradigm change (Kuhn 1957).

"*L'amor che move il sole e l'altre stelle*" (Love that moves the sun and other stars)—even a great poet like Dante Alighieri (Paradise, xxxiii v. 145) considered the Ptolemaic model as a truth rather than a model. This is no longer a matter of scientific method but of narration. The popular Indian "blind men and an elephant" paradox (Goldstein 2010, p. 492) (see Figure 1) clearly shows how the implicit premises that lie in our mind and the implicit accepted narratives may affect our personal representation of reality.

Depending on both the point of view and different conceptual premises, one can interpret the same phenomenon differently. When we begin to interpret it, we use words and metaphors. Here lies the "shadow line" between observation and explanation—between science and the narration of science.

A question arises: how can we handle a scientific model or metaphor once it has permeated the collective imagination, which is already full of other representations?

If this process develops inside the scientific community, then everything is fine. Almost all scientists know that they are making interpretations, hypotheses, and models. Scientists know the limit of the models and the circumstances under which a model is reliable or not.

On the other hand, if this process enters in the domain of popular communication and political decision making processes, then things change. This is even more so nowadays, where talk shows have given more emphasis to the emotional part of the talk instead of its reliability (Dahlstrom 2014).

By using emotions to tell facts, the media can obtain a more persuasive message over a scientific one (Jones & Anderson Crow 2017). This is one of the main causes of misinformation that has spread throughout social media (Cinelli *et al.* 2020).

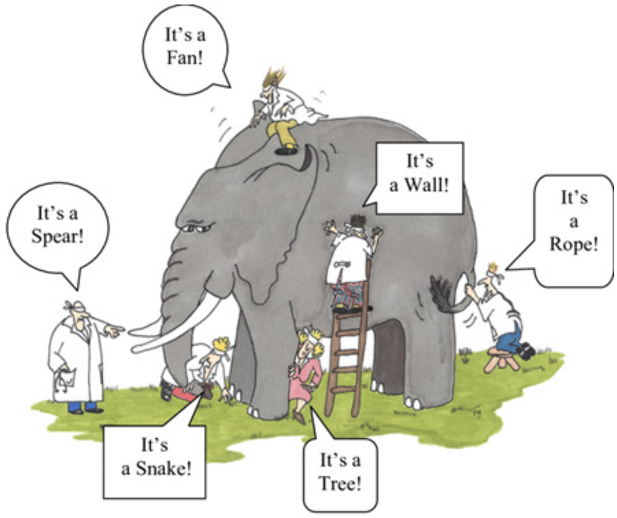


Figure 1: Original cartoon by Anon (CC BY-NC licence).

In fact, the World Health Organization (WHO) warned the public about the risk of *infodemia* during the COVID-19 pandemic.

The so-called "main stream media" launched a communication war against "fake news" to combat the spread of misinformation across social media platforms.

Media are using all their persuasive power in this battle against misinformation. It is worth remembering that, for media, the logic of the show is more important than science. Persuasion cannot be obtained through scientific evidence alone. What matters most is the trust that the narrator (journalist, anchorman, or editor) has from his public. The problem with the ongoing COVID-19 pandemic is that scientific knowledge on this virus has been continuously constructed. Scientists may change their opinion. This is normal under research processes but could be misinterpreted by the general public. Clearly, if this process happens under the spotlight every day, then the result can lead to a loss of trust from citizens who start paying more attention to misinformation on social media.

Another variable to consider is the strategy and the will of the governments that pave the way for the political interpretation of scientific data (Abbas 2020). With all these variables on the stage—data evolution, different scientific models, political interpretation, governmental strategies, and the need for an audience—a good storyteller has to manage the flow of information in order to tell the narrative that best fits the needs of the government/system without leaving space for other interpretation.

The "blind men and an elephant" paradox shows how many variables are available to a narrator who wants to tell his narrative and even politicize it.

For example, take Italy at the beginning of the pandemic where the narrative was: no need to panic. Politicians took pictures of aperitifs among young people just to show that normal life can and must go on.

However, fear among the population grew because media were using expressions like "case fatality rate", meaning the proportion of deaths from a certain disease compared to the total number of people diagnosed with that disease in a given period. It was as if they had meant mortality rate, which is the measure of the relative number of deaths (either in general or due to a specific cause) within the entire population per unit of time. Furthermore, previous news from China had scared the West.

Therefore, TV programs invited experts who tried to explain the difference between these two expressions. This presented the case fatality rate as something deeply connected to the number of cases diagnosed, so a number that is generally stabilized only after the occurrence of the epidemic or pandemic. The takeaway message, as understood by both journalists and the public, was that there was no need to panic—at least in the Italian case.

This narrative met the government's need to reassure the population.

A few weeks later, however, the government's need moved toward preventing a possible spread of the pandemic. They then preferred to put pressure on the population to ensure more compliance to the safety norms.

The narrative needed to shift from "do not panic" to "stay alert, we are under threat."

"*The flu is more harmful than the coronavirus in Italy: But fear raises awareness*" (D'Aria 2020) is a headline from one of Italy's main newspapers.

Those same experts then came back to TV following the same trick of the "blind men and an elephant" under new terms: the R_0, or the basic reproduction number. This indicates the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection. These experts, who had assured the population that the number of deaths were not as high as the "potential/supposed" number of infections, now told citizens that they had to be careful because R_0 must be lower than 1 and it is dangerously on the rise instead.

Most likely, journalists and audiences do not know that R_0, according to Wikipedia (entry: Basic reproduction number),

> “can be calculated from many different mathematical models. Each of these can give a different estimate of R_0, which needs to be interpreted in the context of that model. Therefore, the contagiousness of different infectious agents cannot be compared without recalculating R_0 with invariant assumptions (...) R depends on many factors, many of which need to be estimated. Each of these factors adds to uncertainty in estimates of R.”

But when you match such a delicate concept with adjectives like “dangerous” or “worrying”, then the real meaning of data shift toward a fictional narration of data. Headlines suddenly appeared: “Alarm in Germany, R0 Goes up Again” or “R0 on the Rise and so is Fear” or “R0 Leap to 1.13 and Now We Fear a New Diffusion”.

This communication could better frame another concept: social distancing. The cognitive process that has been introduced is clear. We need to reduce R0 in order to rescue our society from the virus. If people stay away from each other, then the R0 index will go down. Thus, it is important to respect social distancing and lockdowns.

Daily updates on the R0, hospitalizations, and deaths are meant to encourage like details on burning calories following physical activity do for a person who wants to slim down. It is a motivational process (Verstuyf *et al.* 2012), and it does not matter if the concept of calories still do not clearly and strictly correlate to slimming down (Del Gobbo *et al.* 2018). What does matter is that this concept should be coherently interpreted through a specific narrative that may be untrue but at least effective for a specific purpose.

Science, however, should try to grasp “the elephant” in its wholeness. Temporary disagreement among scientists due to different perspectives are usually solved once a global viewpoint/systemic model is established. Generally, time plays a crucial role in this process.

With COVID-19 still ongoing, it is difficult to establish clear data and general considerations. Nevertheless, scientists are starting to agree on numbers like the global fatality rate, assessed around 0.5–1% (Mallapaty 2020). A recent WHO bulletin outlined that “the infection fatality rates tended to be much lower than estimates made earlier in the pandemic,” explaining that “justification for various non-pharmacological public health interventions depends on the infection fatality rate. Some stringent interventions that potentially also result in more noticeable collateral harms may be considered appropriate, if the infection fatality rate is high. Conversely, the same measures may fall short of acceptable risk–benefit thresholds, if the infection fatality rate is low” (Ioannidis 2021).

Furthermore, the average age of death has been 80 years. Accordingly, Mitra and colleagues (2020) focused on the potential lifespan that has been lost.

From a global point of view, the consequences of the COVID-19 pandemic appear to be mild in terms of both general health and mortality if compared to all previous pandemics. Nevertheless, the current narrative diverges from the reality of data (Schwab 2020, p. 12).

Recently, one interesting narrative was proposed by the Director of the World Economic Forum, Professor Klaus Schwab:

> “The world as we knew it in the early months of 2020 is no more, dissolved in the context of the pandemic. Radical changes of such consequence are coming that some pundits have referred to a “before coronavirus” (BC) and “after coronavirus” (AC) era ... We should take advantage of this unprecedented opportunity to reimagine our world, in a bid to make it a better and more resilient one as it emerges on the other side of this crisis” (Schwab 2020, p. 19).

The author is probably right. However, is this change due to COVID-19 or the current narrative?

In looking for an answer to this question, it is worth remembering the end of Plato’s Republic allegory of the cave:

> “SOCRATES: And now, I responded, consider this: If this person who had gotten out of the cave were to go back down again and sit in the same place as before, would he not find in that case, coming suddenly out of the sunlight, that his eyes are filled with darkness?”
>
> GLAUCON: Yes, very much so.

SOCRATES: Now if once again, along with those who had remained shackled there, the freed person had to engage in the business of asserting and maintaining opinions about the shadows -- while his eyes are still weak and before they have readjusted, an adjustment that would require quite a bit of time -- would he not then be exposed to ridicule down there? And would they not let him know that he had gone up but only in order to come back down into the cave with his eyes ruined -- and thus it certainly does not pay to go up.

SOCRATES: And if they can get hold of this person who takes it in hand to free them from their chains and to lead them up, and if they could kill him, will they not actually kill him?

GLAUCON: They certainly will."

References

Abbas A H 2020, "Politicizing the pandemic: A schemata analysis of COVID-19 news in two selected newspapers", *International Journal for the Semiotic of Law,* July 3 [ahead of print]. Available from: https://doi.org/10.1007/s11196-020-09745-2

Bruce Goldstein E 2010, *Encyclopedia of Perception*, New York: SAGE Publications.

Cinelli M *et al.* 2020, "The COVID-19 social media infodemic", *Scientific Reports*, vol. 10, article no. 16598. Available from: https://doi.org/10.1038/s41598-020-73510-5

"Coronavirus, Zingaretti aperitivo pubblico a Milano: "Niente panico, isolare i focolai. Il governissimo? Non c'è la crisi" 2020 (27 February), *Repubblica* [online] https://www.repubblica.it/politica/2020/02/27/news/coronavirus_zingaretti_contro_il_panico-249718891/

"Coronavirus, Galli: "Fatti pochi tamponi, il numero dei contagiati è più alto di quello ufficiale" 2020 (13 March), *Repubblica* [online] https://video.repubblica.it/dossier/coronavirus-wuhan-2020/coronavirus-galli-fatti-pochi-tamponi-il-numero-dei-contagiati-e-piu-alto-di-quello-ufficiale/355754/356320)

Dahlstrom M 2014, "Using narratives and storytelling to communicate science with nonexpert audiences", *PNAS*, vol. 111, no. 4, pp. 13614-13620.

D'Aria I 2020 (12 February), "Coronavirus, in Italia fa più danni l'influenza. Ma il timore del virus ci rende più attenti", *Repubblica* [online] https://www.repubblica.it/salute/medicina-e-ricerca/2020/02/12/news/il_coronavirus_fa_paura_l_influenza_no_ma_si_rispettano_di_piu_le_regole_di_igiene-248416492/) .

Gardner *et al.* 2018, "Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The DIETFITS randomized clinical trial", *JAMA*, vol. 319, no. 7, pp. 667–679. DOI:10.1001/jama.2018.0245

Ioannidis J P A 2021, "Infection fatality rate of COVID-19 inferred from seroprevalence data", *Bulletin of the World Health Organization*, no. 99, pp. 19-33F. Available from: https://www.who.int/bulletin/online_first/BLT.20.265892.pdf.

Jones M D & Anderson Crow D 2017, "How can we use the 'science of stories' to produce persuasive scientific stories?", *Palgrave Communications*, vol. 3, article no. 53. Available from: https://doi.org/10.1057/s41599-017-0047-7.

Kuhn T 1957, *The Copernican Revolution: Planetary Astronomy in the Development of Western Thought*, Cambridge: Harvard University Press.

Mallapaty S 2020, "How deadly is the coronavirus? Scientists are close to an answer", *Nature*, vol. 582, pp. 467-468. DOI: https://doi.org/10.1038/d41586-020-01738-2

Mitra *et al.* 2020, "Potential years of life lost due to COVID-19 in the United States, Italy, and Germany: An old formula with newer ideas", *International Journal of Environmental Research and Public Health*, vol. 17, no. 12, p. 4392. DOI:10.3390/ijerph17124392.

Schwab K 2020, *COVID-19: The Great Reset*, Cologny/Geneva: Forum Publishing.

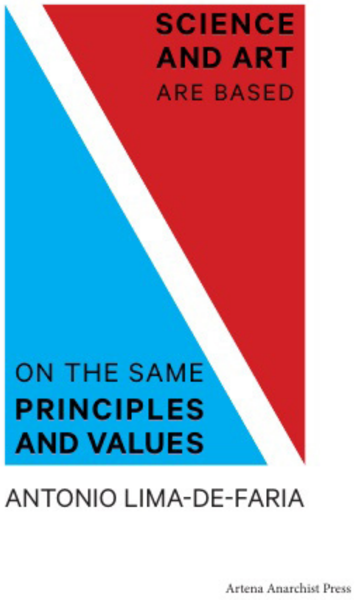
Tebano E 2020 (2 May), "Coronavirus, come si calcola l'indice di contagio R_0 da cui dipenderà quando potremo tornare a uscire", *Corriere della Sera* [online] https://www.corriere.it/cronache/20_maggio_02/coronavirus-come-si-calcola-l-indice-contagio-r0-cui-dipendera-quando-potremo-tornare-uscire-3dc473dc-8c3a-11ea-9e0f-452c0463a855_preview.shtml?reason=unauthenticated&cat=1&cid=556p_wkq&pids=FR&credits=1&origin=https%3A%2F%2Fwww.corriere.it%2Fcronache%2F20_maggio_02%2Fcoronavirus-come-si-calcola-l-indice-contagio-r0-cui-dipendera-quando-potremo-tornare-uscire-3dc473dc-8c3a-11ea-9e0f-452c0463a855.shtml.

Verstuyf J *et al.* 2012, "Motivational dynamics of eating regulation: a self-determination theory perspective", *International Journal of Behavioral Nutrition and Physical Activity* , vol. 9, article no. 21. Available from: https://doi.org/10.1186/1479-5868-9-21 .

Books

Vol. 4, No. 2 (2020)
ISSN: 2532-5876
Open access journal licensed under CC-BY
DOI: 10.13133/2532-5876/17356

Lima-de-Faria A 2020, *Science and Art Are Based on the Same Principles and Values*, Artena: AAP



A key, critical figure in contemporary biology and scientific thought, Antonio Lima-de-Faria (1921) is Professor Emeritus of Molecular Cytogenetics at Lund University, Lund, Sweden. After editing the *Handbook of Molecular Cytology* (1969), Antonio Lima-de-Faria wrote *Molecular Evolution and Organization of the Chromosome* (1983) and *Evolution without Selection. Form and Function by Autoevolution* (1988). This last book was translated into Russian, Japanese and Italian. Later he wrote *Biological Periodicity. Its Molecular Mechanism and Evolutionary Implications* (1995, translated into Japanese) and *One Hundred Years of Chromosome Research and what Remains to be Learned* (2003). Subsequently appeared *Praise of Chromosome "Folly." Confessions of an Untamed Molecular Structure* (2008, translated into Russian), *Molecular Geometry of Body Pattern in Birds* (2012) and *Molecular Origins of Brain and Body Geometry* (2014). Recently appeared *Periodic Tables Unifying Living Organisms at the Molecular Level. The Predictive Power of the Law of Periodicity* (2017), which was praised, by American and English colleagues, as a "wonderful and pioneering work." His work in molecular biology has won him, among other honors, the decorations Knight of the Order of the North Star by the Swedish King and Great Official of the Order of Santiago by Portugal's President. He is member of five scientific academies.

With this book, he leaves us his scientific testament while approaching his 100th year of life. As a "lonely wolf howling in the immensity of the night," he launches his straightforward warning: "At present a wave of obscurantism is spreading over Western countries affecting both science and art in a deadly way." "Modern technology has been most successful in transforming our daily lives and in allowing us to conquer outer space. These impressive achievements have, to a large extent, made us dumb, making it difficult to perceive the danger that lies ahead. Hence, there is a pressing need to bring forward the original sources in which, leading scientists and renowned artists, explained the principles that they followed in their discovery of novel phenomena and in the creation of unique works of art. It turns out that both types of minds speak the same language. There is a basic denominator that unites the human endeavor." (Publisher: artenarchist@gmail.com)

Organisms

ISSN: 2532-5876