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CONTENTS

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Editorial

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The Hallmarks of Failures in Cancer Research

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Shortly after the influential book *On the Origins of Species* (Darwin 1859) proposed a paradigmatic change on our understanding the way living beings evolve, the Scottish philosopher John Stuart Mill enunciated principles of what eventually would become a standard in evaluating scientific hypotheses. In 1869, he wrote,

> "If an instance in which the phenomenon under investigation occurs, and an instance in which it does not occur, have every circumstance save one in common, that one occurring only in the former; the circumstance in which alone the two instances differ, is the effect, or cause, or an indispensable part of the cause, of the phenomenon." (Mill 1869).

Most scientists, in particular those embracing empiricism, adopted this formula to conduct their own research and for assessing the research of others. For example, the American physicist Richard Feynman exposed his *modus operandi* and that of his peers as follows:

> "First, we guess it. (...) Then we compute the consequences of the guess, to see what, if this is right, if this law that we guessed is right, we see what it would imply. And then we compare those computation results to nature. Or we say, compare to experiment or experience. Compare it directly with observation, to see if it works. If it disagrees with experiment, it's wrong." (Feynman 2022 [1964]).

In other words, the empirical evidence favored invalidating the guessing and suggested dropping the hypothesis. Most physicists did and still do so—even those who are not empiricists. Probably, this type of intellectual detachment lays behind the much discussed "physics envy" attributed to reductionist biologists regarding physics' success as an "exact science".

In recent decades, cancer research has gone through embarrassing episodes. Despite the generous and rather extravagant amount of taxpayers' funding that it received in the last half a century, "thought leaders" and managers of those funds have little to show for it when guessing, explaining, and "curing" the disease. The constant moving of the explanatory goalposts and/or the addition of *ad hoc* alternatives have become a frustrating routine. More specifically, during the last century, cancer was considered: a genetic disease (remember Boveri, a stance still dominant today?); a parasitic disease (remember Fibiger?); a metabolic disease (remember Warburg?); an infectious disease (remember viral carcinogenesis, oncogenes?); a disease due to radiation (remember Hiroshima and Nagasaki?); an immune disease (remember McFarlane Burnet and followers?), and a combination of the above—and what not? In addition, when explanations failed, slightly modified updates of the original version were "resold" to the research community and to the public as novelties that would disentangle the cancer puzzle (most likely in the renewable next ten years). Consistently, however, these explanations were based on views claiming that cancer was a cell-based, genetic disease, caused by DNA mutations that would make the mutated cells proliferate autonomously. Such is the tenet of the Somatic Mutation Theory (SMT) and its *ad hoc* variants (see above). In fact, these are the hallmarks of the failures in cancer research. Alternative theories that explain carcinogenesis as organogenesis gone awry are seldom invoked.

Despite a lack of empirical evidence in its favor, the SMT and its successive and overlapping variants have been successfully "sold" to funding agencies as the necessary and sufficient condition for cancer to develop. As a result, research and academic institutes greatly

expanded in size and personnel. To the surprise of many molecular biologists turned cancer researchers, the enormously powerful technological advances generated by the Molecular Biology Revolution empirically documented that the single uncommon circumstance that Stuart Mill was referring to over 150 years ago did not lead to finding the somatic mutation component as the actual cause of cancers. In fact, somatic mutations in alleged cancer driver genes were found to be present both in normal and cancer cells. How this unexpected (from the SMT perspective) outcome could have been successfully managed before a critical public opinion? Thought leaders and managers who were on the record favoring the currently hegemonic SMT could have either a) reinterpreted the evidence or b) dropped the old paradigm and adopted instead alternative theories that were not at odds with the voluminous existent data. Clearly, this alternative represents a paradigmatic change of the magnitude described by (Kuhn 1962). Instead, if the first option was to be followed, then the repeated failure to validate the SMT could no longer be ignored. Dropping the failed theory, as Feynman naively advised, would generate a monumental sociological upheaval in scientific and academic circles.

Theoretical and empirical compromises as those described above tried to explain cancer for over a century. This has encouraged thought leaders to propose a new compromise, *i.e.* an *ad hoc* hybrid between the original, cell-based, and technologically driven SMT and a partner of convenience represented by the already discredited, 70-year-old, two-step initiation and promotion cancer model (Berenblum & Shubik 1947). This old-new epicycle considers driver genes' mutations as "necessary" but not sufficient, while inflammation triggered by air and other sources of pollution would act as "promoter" (Gallagher 2022). This will preserve the legitimacy of the search for more elusive driver genes and the survival of the status quo.

Who will be asked to decide what to do next? Basic and clinical cancer researchers increasingly compromised the good faith commitment of the public at large (*i.e.* taxpayers) and of young researchers (graduate students, postdocs) to foresee a bright future for science and for the lot of cancer patients. It is finally time to acknowledge that cosmetic changes will not do the job. The alternative of switching paradigms from reductionism to organicism in cancer research has become compelling. It would be sad and dangerous to our society and to science at large to admit that John Stuart Mill teaching on how to test an hypothesis has been ignored for no good reason, and that Max Planck might have been right when he concluded that,

> "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." (Planck 1950, pp. 33–34).

Let us all hope that a new generation of researchers is ready to acknowledge past conceptual failures and re-start cancer research based on reliable and evolutionarily relevant premises.

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Methods and Techniques

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On the Meaning of Averages in Genome-wide Association Studies: What Should Come Next?

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Abstract

Identifying the association between phenotypes and genotypes is the fundamental basis of genetic analyses. Although genomic technologies used to generate data have rapidly advanced within the last 20 years, the statistical models used in genome-wide associations studies (GWAS) to analyze these data are still predominantly based on the model developed by Fisher more than 100 years ago. The question is, does Fisher's theory need to be replaced or improved, and if so, what should come next? The theory developed by Fisher was inspired by the field of probability. To make use of probability not only did Fisher have to assume valid a number of questionable hypotheses, but he also had to conceptually frame genotype-phenotype associations in a specific way giving primordial importance to the notion of average. However, the "average" in probability results from the notions of "imprecision" or "ignorance". After reviewing the historical emergence and societal impact of probability as a method, it is clear what is needed now is a new method acknowledging precision in measurements. That is, a method that does not rely on categorizing or binning data.

Keywords: phenotype-genotype mapping, method of averages, GWAS, infinite population, normal distribution

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Introduction

Genome-wide association studies (GWAS) based on statistics have had a huge impact on the field of genetics by providing a method to map genotypes (DNA variants) and continuous phenotypes, namely the observable characteristics of an organism varying in a continuous way. GWAS has in turn facilitated the understanding of biology, the development of new therapeutics in medicine and the improvement of agricultural species (Visscher *et al.* 2017). Statistical models describing the relationship between genotype and phenotype were first developed by R.A. Fisher more than 100 years ago and remain a cornerstone of genotype-phenotype mapping today (Fisher 1919; 1923). However, ongoing debates exist in this field related to the validity of Fisher's theory (Nelson, Pettersson, & Carlborg 2013; Visscher & Goddard 2019), in turn, raising questions regarding the current paradigm in quantitative genetics.

Controversies exist in sciences because a given theory is not supported by a subset of observations or is limited in its ability to provide information.

Controversy can act as an engine of progress; resulting in the generation of new developments that better describe or enable better description of reality. Such new ideas are not necessarily radical, *i.e.* do not negate the seminal idea, but come as a generalization of seminal concepts. In this context, the best and probably most notable example is the transition that occurred in physics between Newton and Einstein regarding the notions of space and time.

However, because "scientists" are also immersed in a social culture, new ideas rarely come out the blue, but result from a specific construction of knowledge that is, to some extent, biased by the society in which they exist. That is to say, to understand the true meaning of seminal ideas, it is also strongly advised to be cognizant that they are in part a product of their time.

Scientifically speaking, GWAS are situated at a junction between genetics, statistics, and probability. Genetics is a field of knowledge that has been studied in depth both scientifically, epistemologically and sociologically by many renowned authors (Boichard *et al.* 2016; Gayon 2016; Prunet & Meyerowitz 2016; Quintana-Murci 2016; Schacherer 2016; Weissenbach 2016), and there would be very little gain to add more to these works. Likewise, the history of statistics is a field that has been covered by many authors and in particular by S.M. Stigler in his remarkable book (Stigler 1990). On the contrary, the field of probability and its repercussion on GWAS and statistics, both scientifically, epistemologically, and sociologically is less well known. In fact, most graduate students in quantitative genetics who tend to be remarkably good at using statistics, would find very difficult to dissociate statistics from probability. Indeed, they will know and use the normal distribution or similar probability density functions to substantiate their inference(s) but only a few, if any, will wonder what the limits regarding the use of such distributions are and where they come from. Students are not to blame for this since the blending of statistics and probability virtually exists in all books dealing with population biology or quantitative genetics. For example, if one were to ask oneself "what is a phenotype?" and then look into books to get an answer, one will rapidly find that the notion of phenotype is represented exclusively as a probability density function. Why this is the case is linked to the rise of probability in the field of biology.

The bond between statistics and probability has permeated virtually all fields of biology to the point where the coupling of "statistics and probability" is now a biological reality, *i.e.* not a thought construction or a method anymore. An example of such widespread and subconscious use of probability concerns the notion "significance". From cell biology to population genetics, any result is deemed scientifically adequate, *i.e.* significant, provided that its p-value falls within agreed limits. Whilst this approach is mathematically sound, it also includes a number of assumptions without consideration of the restrictions they impose. In this context, it is important to recall that probability density functions originate through the notion of "imprecision" or "error". The normal distribution was known originally as the "error function" or "law of errors". The error function states that if an experiment can be repeated *identically to itself an infinite number of times in identical circumstances*, then, provided that the outcome of experiments are numerical data, the distribution of those data should follow the error function (the normal distribution). In essence, the error function: (i) justifies why experimental results are not identical, even though they arise from repeated and identical experiments, and (ii) tells us that the average is the numerical value of the thing that was meant to be measured.

Whilst one is free to use the field of probability to extract any result from measurements, the use of a probability density function such as the normal distribution imposes that the object studied must be conceptualized in a certain way. Perhaps one of the most important aspect as far as genotype-phenotype mapping and biology are concerned, involves the fact that all individuals are considered "identical" entities. To what extent two individuals in a population are identical is open to question. A nonetheless important aspect is the notion of "infinity". Interpolating a histogram representing the frequency of occurrence of categories of phenotype values using the formula of the normal distribution requires this notion of the continuum limit to be valid. However, to what extent the notion of "infinity" is granted in any field of sciences is rarely discussed. It is worth recalling that to justify his theory Fisher had to use the "infinite population" hypothesis, which we know, is unrealistic, if not impossible.

This opinion paper is not about questioning the entire field of probability, but to indicate the shortcomings when using probability as a tool to conceptualize the relationship between genotype and phenotype. This will show that the rise and societal importance of the notion of "average" in genotype-phenotype mapping came, historically, from the field of "biometry" in a dark period of our civilization marked by the predominance of eugenics theory; and that using probability as a mathematical field to substantiate any such premise was, simply, based on wrong assumptions. Although eugenics thoughts have been relegated to history, the predominance of the notion of "average" resulting from our initial belief in the normal distribution is still very present in our society. In fact, the rise of the normal distribution as well as its impact on our society has been defined as "biopolitics" and is now an entirely dedicated research field in sociology or philosophy (Rose 2001). Whilst conceptualizing the average is, in itself, not the real issue, it is its connection with something that ought to be normal, *i.e.* the normal distribution, that poses problem; as the tendency is to think that any value that is not average is linked to some randomness or error, *i.e.* is a nuisance.

We shall see that this reflection opens the way to different concepts to provide accurate information on genotype-phenotype mapping that are not based on the notion of "error".

1. Statistics

At this point, it is important to recall what statistics is, at least for the sake of students. Statistics comes from the Latin *statisticium*, which refers to "the state of things" and is borne out from the need to order observations and represent those in the form of tables and graphs involving specific parameters summarizing the information contained in the data. Historically, collecting data outdates, by millennia, the field of probability and the reason is simple. Estimating the power of any chief of state, or similar, relies on good knowledge of characteristics related to population, military potential, wealth and so on. That is, governance and authority rely on data. Whilst Mesopotamians left traces of such activity in the form of tables of data made in clay dating back more than 6000 years (Droesbeke & Tassi 1990), the field of statistics as we know it today was reinvented through the rise of probability when scientists were trying to make sense of disparate data accumulated from scientific measurements. The need to determine as exactly as possible the "true" outcome or result of a set of scientific observations relied on understanding the notion of measurement errors, and it is the estimation of such errors that led to the collision between, and fusion of, the fields of statistics and probability.

To summarize, one can say that to draw inferences from the comparison of data, a method is needed that requires some understanding about its accuracy, including ways of measuring the uncertainty in data values. In this context, statistics is the science of collecting, analyzing, and interpreting data; whilst probability, defined through relative frequencies, is central to determining the validity of statistical inferences.

2. Probability

In early 20th century, the intertwined fields of statistics and probability had grown up to reach almost full maturity. Both fields arose through one of the greatest journeys of the human mind, trying to decipher the notion of evidence, *i.e.* what is provable, and provide this evidence in an interpretation to determine reality. Renowned authors in the field of probability agree that this field started with Jacob Bernoulli's (1654–1705) definition. Namely, that the probability of an event is the ratio of one outcome compared to all possible outcomes; defined by Bernoulli as,

> "that a particular thing will occur or not occur in the future as many times as it has been observed, in similar circumstances, to have occurred or not occurred in the past" (Stigler 1990, p. 65).

In Bernoulli's definition, the probability represents a degree of certainty that can only be described a posteriori using the frequency of occurrence of the "thing". Beyond characterizing a degree of certainty, this definition also encompasses indirectly a certain notion of "immanence" as the "thing" can be characterized by its reappearance. Indeed, the ratio of a specific outcome to all possible outcomes is "expected" to reoccur provided similar contexts are possible.

"Immanence" and "expectation" are interesting concepts when applied to sciences as they imply a certain

degree of stability or invariance that may result from the presence of laws. However, a line should be drawn here between the notions of probability and scientific law, as a degree of certainty is by no way a proof or a demonstration. "Proof" or "demonstration" involve an articulation, *i.e.* a causality, between elements leading to the "particular thing" to be observed. Consequently, the "thing" is only secondary to this articulation, as it is this articulation that provides a conceptual understanding of its occurrence and notably its reason of being. Therefore, with such an articulation or causality leading to the "thing", the "thing" is necessarily defined as an evident *a priori* resulting from the scientific law.

A different way to phrase this is to say that averages and variances can always be defined in any population of data. The point, though, concerns their scientific meanings or pertinences. Pierre-Simon Laplace (1749–1827) gave the example of the Sun rising every morning and the time at which this occurs. Whilst regularity would be found in the data it would not inherently inform one of gravitational laws (Laplace 1995). That is to say that whilst a scientific law fits Jacob Bernoulli's definition of the probability, the converse is not necessarily true. Consequently, there is a vast conceptual difference between "empirical" and "mechanistic" sciences.

In his unfinished work *Ars Conjectandi* published eight years after his death, Jacob Bernoulli provided, thanks to his measure of probability, the weak law of large numbers (Todhunter 2014, pp. 56–77; Stigler 1990, pp. 63–98). This law was refined by Abraham de Moivre (1667–1754) (de Moivre 2013; Stigler 1990, pp. 63–98) providing a proof that if an observable is "expected" to occur with a defined degree of certainty, it must follow what we call today the Bernoulli distribution.

To avoid confusion a precision is required concerning the works by de Moivre and Gauss. De Moivre was interested in the probability of winning a game. When playing with cards for example, the entire set of outcomes can be determined as the set of cards is known and given from the start. This is different than trying to determine the "true" outcome from a set of data since the entire set of possible outcomes is unknown and given only as observational measurements. This point has led to some controversies as to who discovered the "normal distribution" first between C.F. Gauss (1777–1853) and Moivre as Gauss was interested in observational measurements (not games). The point however is that both manage to deduce the mathematical form of the Normal distribution in different ways.

In short, what Moivre demonstrated is a version of what, today, we call the central limit theorem. Moivre's theorem stipulates that if it is possible to make a very large number of independent measurements of the same "thing" in similar contexts, then a specific distribution of that "thing" would ensue. This was the first mathematical description of what would become the normal distribution with the "thing" being the expectation, *i.e.* average, with a variance inversely proportional to the number of measurements made. In essence, by doing a very large (infinite) number of measurements one would amplify and make visible the "thing" to be observed.

To Abraham de Moivre, this distribution demonstrated the intervention of God in which the "thing" was just awaiting to be discovered and measured, namely the "thing" had to have a fundamental meaning. His work was supposed

> "to cure a kind of superstition, which has been of long standing in the world, that there is … such a thing as Luck, good or bad" (Moivre 2013, p. 4 of the 1718 preface, 1st edition).

This way of thinking had to have a profound repercussion in different fields from biology to sociology. Indeed, this vision propelled the method of relative frequency, and therefore the normal distribution including its ontological parameters that are average and variance, as a reliable estimation of the *a priori* unknown probability. In short, the normal distribution had to happen since it provided the degree of certainty of the phenomenon observed. This, in turn, may explain why the notion of "infinite population" was used by Fisher as an attempt to promulgate scientific laws.

Whilst Thomas Bayes (1702–1761) and Pierre-Simon Laplace later demonstrated the weakness of the *a priori* argument as developed by de Moivre (see Appendix), the idea that the normal distribution was a fundamental trait of life was nonetheless accepted. The general acknowledgement of such trait of life was emphasized, for example, by Adolphe Jacques Quetelet (1796–1874) and his belief in the "average man" or the "social physics" (Porter 1985); or by Francis Galton's (1822–1911) narrative describing the "human ability" as a heritable trait (Galton 1886). As much as we know today that those sort of beliefs are strongly limited (wrong)

since they exclude the socialization of individuals; it is important to recall that Quetelet and Galton were, during their times, trying to "improve" society and can be regarded as some sort of "sociologists"— missing an adequate term that could allude the notion of "past or outdated sociology"—that were the product of their times (Wright 2009).

To justify this statement, it is important here to recast the sociological impact that the field of probability has had on our society. Indeed, with the normal distribution being a fundamental trait of life, thinking or solving problems in term of probability by using the method of relative frequency was essential. In fact, with this method, it was, at least in theory, possible to forecast any event (*e.g.* being killed in the street; dying of a disease; being wrongly judged by a barrister, etc.) (Laplace 1995; Samueli & Boudenot 2009). The point to be emphasized here is that the field of probability has been used as a "scientific justification" of a "general biometry" whereby a set of people/individuals were, and still are, modelled as a "population". As an example, Quetelet believed that one ought to investigate the "social body" and not the "peculiarities distinguishing the individuals composing it" (Faerstein & Winkelstein 2012). This way of framing individuals at the end of the 18th century allowed a shift in judicial and social policies in which the "social body", that is the distribution density function of any population of measurements and its properties (averages and variances), formed the core of what needed to be understood and controlled (Rose 2001). Thus, the singular identity of individuals disappeared into the "social body", and the "social body" became then a tool to process the identification of individuals. It is therefore not surprising that during the same period the "judicial anthropometry" emerged, whereby arrested individuals were measured to construct database aiming at identifying potential criminals in the society (García Ferrari & Galeano 2016). Likewise, it is not surprising that how different phenotypes can be, they are represented by distribution density functions today.

Given that the field of probability and its consequences, *i.e.* mean and variance, were "in the air" at that time, Fisher's theory, in which the notion of "average" is central was sociologically accepted by its contemporary society. Thus, the "infinite population" hypothesis that Fisher had to put forward to explain why genotype-phenotype can associate did not carry much doubt, how questionable it was.

More than 100 years later one can now try to think about those shortcomings.

3. Shortcomings of Genotype-Phenotype Mappings Using the Error Function

Whilst the notion of distribution opened the way to data analysis, the validity of the central limit theorem, *i.e.* the normal distribution, comes with some ties.

The first of which relates to the notions linked to the "thing" and "similar contexts", that is, the "thing" being measured as well as the context in which the "thing" is measured must be identical. The second tie resides in the utilization of "infinity", or the notion that a large number of experiments needs to be made for "God's will to be visible".

Those two ties are clear constraints concerning the use probabilities and as such are worth developing in the context of genotype-phenotype mapping since they will allow one to understand how the human mind has conceptually framed this field.

3.1. Identity and Probability

The first tie is a fundamental constraint as it reposes on a clear understanding of what identity is. One may say that one individual, say Paul, is identical to himself and that he defines his own context; but saying that Paul and Jacques can be considered as identical is a step that goes beyond any assumption defining a probability when biology is considered. Let us be precise. One can decide to measure Paul's height a large number of times and define a probability since the "thing" to measure and its "context" are always Paul's height and Paul, respectively. Accordingly, one would deduce Paul's average height and some standard deviation linked to some measurement errors. So, as much as a phenotype like height may be universally defined for human beings the identities between the individuals forming the population are different if two different individuals are measured, *i.e.* Paul is not Jacques. Naturally, nothing forbids us from determining the distribution of the phenotype height for each individual separately to reform the distribution of heights in a population. If so, one would then define the distribution of heights

but not the distribution of individual heights since the identities of Paul and Jacques would be dissolved into the former distribution. This remark underlines that using the distribution of phenotypes in a population is equivalent to dissolving contexts, in this case, identities. Accordingly, with the distribution of heights one is left with the few moments of the distribution, *i.e.* average, variance, skewness and so on, providing a very short summary of the diversity and identity of individuals. Deciding to consider a phenotype distribution, despite the definition of probability, is then equivalent to consider Paul and Jacques as meaningless envelops of something more important that would spread across the population. Clearly, that "thing" awaiting to be observed or measured are genes (or Mendelian factors) and their effects, and the distribution of any phenotype would result from a condensate of independent genes without envelop/identity limiting them. The notion of "condensate" is historically important as R.A. Fisher was influenced by physics and most particularly in how statistical physics managed to relate the microscopic and macroscopic properties of ideal gases (Fisher 1923; Morrison 1997). One can then understand R.A. Fisher's method as a way to define each gene microstate across the population distribution as being a particular gas molecule with given property. The sum of genes including their properties would then define the moments of the phenotype distribution, *i.e.* average value and variance for example.

However, if GWAS is used to determine genotype-phenotype relationships, then there is an apparent problem when the "method of averages" as advocated by R.A. Fisher does not recover the average and variance of the phenotype. In this case, the notion of "environment" is added to complete the phenotype distribution. Despite the fact that the environment is in general ill-defined, it is added with the implicit intention to recover the phenotype distribution, *i.e.* to complete the faith in the normal distribution. What is puzzling with such intention is that one knows that for each phenotype measured, namely each individual, corresponds to genes in specific states and one may wonder whether dissolving individuals into a phenotype distribution, and assuming its universal relevance, does not lead to more complications.

Let us frame this in the context of frequentist probability as used in GWAS. We said earlier that the normal distribution was known as the "error" function. In practice, the use of frequentist probability, and the resulting binning or categorization of data, is justified when inaccuracy exists in experimental measurement. For example, measuring a continuous phenotype such as the height of individuals with a ruler with centimeter graduations, *i.e.*, to the nearest centimeter, warrants the use of frequentist probability. In this case, a frequency table of phenotype values can be defined through 1 cm-width bins or categories, from which the probability density functions can be deduced to address the statistical inferences.

However, this method becomes problematic when the measurement of phenotype values can be carried out with very high precision, for example using highly advanced imaging techniques or biosensing technologies (Macdonald, Hawkes, & Corrigan 2021). In this case, each individual measured could return a unique phenotype value. The phenotype values being unique, how can "randomness in the data" be defined, and frequentist probability used, to determine any inferences?

In general, the solution to this problem is to increase the population size to sample, such as to recreate bins or categories matching the available precision. How strange that, whilst precision is fully available in the first place, the method advocating phenotype categories, *i.e.* creating a sort of wilful ignorance regarding phenotype values, is still suggested. Again, this is linked the hundredth-plus years old faith in the normal distribution, *i.e.* the error function and the importance we ought to give to the notions of average and variance.

3.2. Infinity and Probability

Let us now explore the second tie, namely the "infinite population" hypothesis. This hypothesis is fascinating as its attempt is to reconcile genotype-phenotype mapping, *i.e.* GWAS, with the field of probability. It is mathematically true that if one were able to repeat the same experiment an infinite number of times one would be entitled to use the normal distribution in the continuum limit as an *a priori*, and use its full mathematical expression. One may then question to what extent is the notion of "infinity" granted in any field of knowledge. As an example, the normal distribution is inherent to some branches of physics and no one with a background in physics would question its usage and validity.

One may then argue that if physics is allowed to use the normal distribution and deduces average(s), then why would this be an issue for quantitative genetics?

The answer to this question lies in the very definition of what physics and biology try to address as sciences. If physics defines average(s), *i.e.* can conceptually consider the normal distribution a.k.a. error function leading to the Dirac distribution as an asymptotic limit when no other parameter (such as the thermal energy or the Planck constant) constrain this limit, it is because physics aims to uncover the intemporal Laws of Nature. It is this notion of intemporal Laws that underscores the notion of infinity or immanence or potential repeatability of experiments in physics. This warrants the use of the central limit theorem.

On the contrary, life is driven by evolution, *i.e.* changes in average(s). Thus, life's average(s) are not absolute but function of time and their history, *i.e.* are not immanent(s) but contingent(s). Time and history are fundamental conceptual parameters for understanding life.

To conclude, whilst the normal distribution can be a useful representation of data, the conclusions drawn, need to be mindful of the underlying conceptualization of the system studied as well as the scientific interpretations underscored. As a result, the normal distribution and its ontological parameters, *i.e.* average and variance need to be handled very carefully. Indeed, distribution density functions can always be derived for any process when data points, *i.e.* numbers, form the outcome of this process. That is to say that because distribution density functions in biology can always be derived, average and variance are not necessarily scientifically pertinent parameters.

3.3. What is the Option, What Comes Next Beyond the Binning or Categorization of Phenotype Values?

Controversy exists in the field of genotype-phenotype associations (Nelson, Pettersson, & Carlborg 2013). Attempts are being made to ameliorate inferences drawn by GWAS. For example, Bayesian models have been used to enhance any potential evidence of genotype-phenotype relationships (Beaumont & Rannala 2004). Whilst Bayesian and Fisher models are conceptually different since they envision the notion of probability and therefore, evidence, differently, they both rely on the concept of an *a priori* in different ways. For Fisher's model it is the importance of moments and in particular the notion of average and variance, namely the normal distribution; and for Bayes, the need to use *a priori* "information" whose exact formulation is either difficult to obtain (or unattainable in most cases). Whilst those two models are conceptually different, they both use the notion of probability in a specific way by defining probability density functions. However, using probability density functions is the central issue at hand.

Indeed, the notion of "imprecision" or "error" defines the concept of density that in turn, form the core of distribution density functions that lead to the definition of average and variance (other moments can be included if needed). However, binning or categorizing data to create density is equivalent to loosing information (wilful ignorance). At the dawn of the 21st century, we are getting more precise in our measurements, and one may wonder what sort of scientific/mathematical tool we should be using if one were able to attain any level of precision wanted. Whilst this sounds a bit idealistic and, perhaps, unattainable, it is worth recalling that not long ago physicists were able to measure remarkably small gravitational waves (Abbott *et al.* 2016) that were deemed out of reach a century ago.

The questions are then: how can genotype-phenotype mapping be possible without losing information? What method should we employ when there is no randomness in the data? Or said differently, how can we re-integrate the identity and diversity of individuals within genotype phenotype mapping such as to re-transform a population into a set of individuals?

Such an enterprise means that the notion of average and variance must disappear from any association study, since it is the grouping of data into categories that generate those.

4. From the Method of Averages to a Method Based on Curves: Genomic Informational Field Theory (GIFT)

As stated, current genome-wide association studies rely on the consequences of using probability density functions in the continuum limit. That is, on the belief that the average and variance (and all the other moments of higher order if needed) are meaningful. However, other models can be suggested that do not require the grouping of data.

4.1. GIFT as a Method to Determine Genotype-Phenotype Mappings

GIFT is a method whose aim is to extract information from datasets without requiring the binning or categorization of data from which the notions of average and variance are ontological parameters when the method of relative frequencies is used. One way to position the problem is, therefore, to address how information can be extracted when phenotype and genotype are measured precisely enough such as to rule out the need of categories.

To answer this question, the best is to look at the impact of the notion of precision on data representations when one moves from imprecisions to precise measurements. Figure 1 demonstrates in the context of genome-wide association studies the impact of increasing the precision in phenotype measurements when a population has a finite size. The total number of individuals is 1000 in this case.

The conclusion is obvious: distribution density functions such as the normal distributions representing genotype and phenotype disappear. Instead, a set of code bars emerges. Those code bars are the individuals, *i.e.* people, forming the population. As a result, it is the structure of these code bars, namely their arrangement, that needs to be understood. Whilst, both color and spacing between the bars/individuals are important information since they are reminiscent from the use of the normal distributions to model genotype and phenotype initially, they are now two variables that were combined, or convolved, when the method of relative frequencies, *i.e.* normal distributions, were used.

To extract information from the code bars, let us now wonder what it means to have information on the phenotype as opposed to have none.

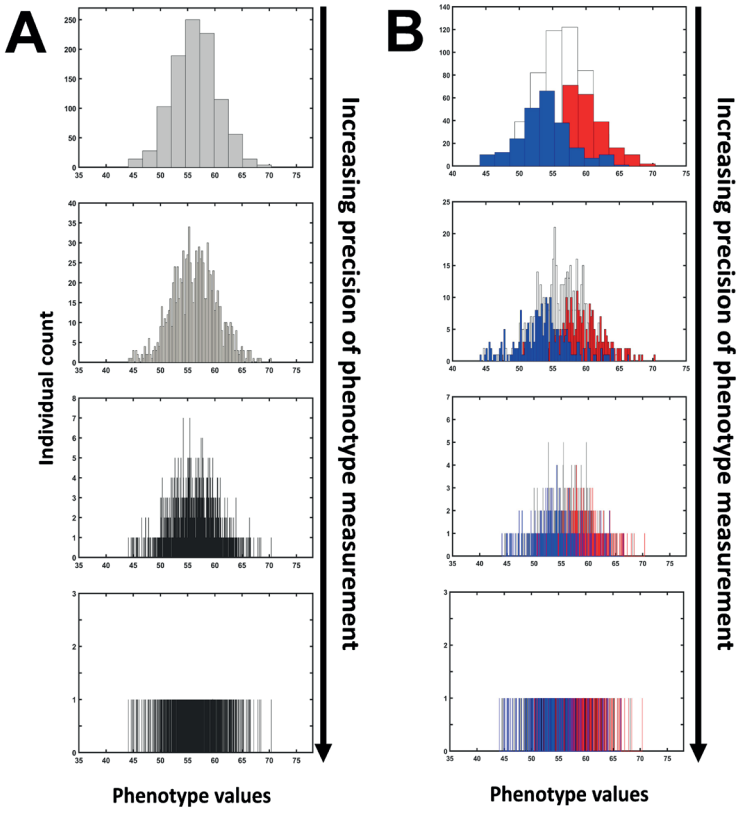

Figure 1: When applied to real data sets, current genome-wide association studies rely on probability distribution density functions (PDFs), namely the creation of frequency plots (method of relative frequencies) via the grouping of phenotype values into categories representing range of phenotype values (A, top-chart). The same method (PDFs) is then applied to genotypes (B, top-chart). For diploid organisms, such as humans, and for a binary (bi-allelic, A or a) genetic marker, any microstate (genotype) can only take three values that we shall write as "+1", "0" and "-1" corresponding to genotypes aa (blue), Aa (white) and AA (red), respectively. The comparison of the two top charts in (A) and (B) demonstrates how genotype are associated with the phenotype, as in this case any phenotype category can be decomposed using the underlying microstate categories. However, grouping data into categories is legitimate so long that the width of the category is justified. The width of categories is justified provided that imprecision exists in phenotype measurements. For example, if height in human was the phenotype of interest measured with a ruler with inch graduations, namely measured to the nearest inch (scale of imprecision), then the width of categories would be 1 inch. However, a method based on the notion of imprecision has limited value when precision is available, and new methods are required. Indeed, by increasing the precision in phenotype measurements it is possible to envision, in a near future, the possibility to deal with genotype and phenotype under the form of "code bars" (A & B, bottom-charts) as opposed to PDFs . The question is then, how can information be extracted from those "code bars"?

To answer this question the best thing is to further simplify the problem by considering the colored bars only and not their spacing. Imagine, therefore, that a set of individuals has been genotyped and that those individuals are picked at random. That is, there is no information on any phenotype. Imagine also that one decides to concentrate, for example, on the genome position 1000000 on chromosome 4 for all the individuals since this genome position happens to display a biallelic single nucleotide polymorphisms (SNPs) across the set of individuals.

Thus, upon calling randomly but sequentially individuals, the genotypic information obtained in due course can therefore be represented as a random string of genotypes including "+1", "0" and "-1" microstates (representing homozyte-AA, heterozygote-Aa and homozygote-aa). An example of such random configuration is:

[0, +1, 0, -1, -1, +1,0, ..., -1, +1, +1, 0, -1, 0, +1, ...,0, 0, -1, +1, 0, +1, -1]

Note that the order in which the individuals were called is linked to the position in the string. Let us now repeat the same experiment using the same individuals in a context where accurate information on a chosen phenotype is available. That is, we call the individuals as a function of the magnitude of their phenotype we consider. For example, if the phenotype is height, one starts by calling the smallest individual and all subsequent individuals through successive increments in their phenotype height. Note again that because each individual has a unique phenotype value there is no possibility for two individuals to be called at once.

If the genome position 1000000 on chromosome 4 is involved in the formation of the phenotype, then one would expect a change in the configuration of the string of microstates based on the fact that homozygotes would be found at the extremities of the string and heterozygotes towards the middle (see Figure 1). An example of such a string would be:

[+1, +1, +1, +1,0, +1, +1, ..., +1, 0, 0, 0, -1, 0, -1, ..., -1, 0, -1, -1, -1, -1, -1]

Thus, the only thing that changes between the random and the phenotype-ordered configurations is the way the genetic microstates are allocated to positions in the string. However, as the genome position 1000000 on chromosome 4 is the only one that has been considered, the two configurations contain the same number of "+1", "0" and "-1", since the same individuals were considered between the two configurations.

The *ansatz* is then to consider the cumulative sum of microstates as a function of the position in the string. Indeed, it is clear from the examples given above that if one starts by adding the microstates together, then differences will be seen in the resulting cumulative sums. To give an example, let us consider the two strings above and note "$\theta_0(j)$" and "$\theta(j)$" the cumulative sums of microstates in the random and ordered configurations where "j" is the position in the string. Then adding the microstates starting from the left side of the strings one finds:

$\theta_0(j = 1) = 0 = 0$
$\theta_0(j = 2) = 0+1 = +1$
$\theta_0(j = 3) = 0+1+0 = +1$
.....

$\theta(j = 1) = +1 = +1$
$\theta(j = 2) = +1+1 = +2$
$\theta(j = 3) = +1+1+1 = +3$
....

As a result, the difference "$\theta(j)$-$\theta_0(j)$" is expected to be indicative of the importance of the phenotypic information. The fact that the same individuals were considered in both configurations also impose a conservation relation under the form: $\theta(N)$-$\theta_0(N) = 0$.

4.2. The notion of phenotypic fields

It is then possible to interpret the information on the phenotype as a field acting differently on microstates (Rauch *et al.* 2022; Wattis *et al.* 2022). The notion of phenotypic field is a natural concept since it is the information on the phenotype that promotes a migration of microstates, and as a result imposes a change between the two aforementioned configurations. To some extent, the different microstates "respond" differently to the phenotypic information and physics fields theory can be applied on this closed system. Closed system means that the individuals are the same between the two configurations.

Consider that there are "N_+", "N_0" and "N_-" genetic microstates "+1", "0" and "-1", respectively, it follows that when the random configuration is considered, at any position in the string the probability of finding either "+1", "0" or "-1", is simply: $\omega_+^0 = N_+/N$, $\omega_+^0 = N_0/N$ and $\omega_0^0 = N_-/N$. That is to say that when no information on the phenotype is available the presence probability of microstates can be derived relatively simply. Accordingly, the cumulative sum of microstates in the random configuration, θ_0, is simply

$$\theta_0(j) = \sum_{x=1}^{j}(+1)\cdot\omega_+^0 + (0)\cdot\omega_0^0 + (-1)\cdot\omega_-^0 = \sum_{x=1}^{j}(\omega_+^0 - \omega_-^0)$$

One notes here that the difference "$\omega_+^0 - \omega_-^0$" can also be rewritten as

$$\omega_+^0 - \omega_-^0 = \frac{N_+ - N_-}{N} = \frac{N_+ - N_-}{N_+ + N_0 + N_-} = \frac{\frac{(N_+ - N_-)}{N}}{\frac{(N_+ + N_0 + N_-)}{N}} = \frac{\omega_+^0 - \omega_-^0}{\omega_+^0 + \omega_0^0 + \omega_-^0}$$

For the second configuration, one can then deploy physics' arsenal and it is then possible to write (Rauch *et al.* 2022; Wattis *et al.* 2022) the presence probabilities of microstates "+1", "0" and "-1" at any position $j = 1,\ldots,N$ in the string as a function of the fields under the form

$$\omega_+(j) = \frac{\omega_+^0 e^{u_+(j)}}{\omega_+^0 e^{u_+(j)} + \omega_0^0 e^{u_0(j)} + \omega_-^0 e^{u_-(j)}}$$
$$\omega_0(j) = \frac{\omega_0^0 e^{u_0(j)}}{\omega_+^0 e^{u_+(j)} + \omega_0^0 e^{u_0(j)} + \omega_-^0 e^{u_-(j)}}$$
$$\omega_-(j) = \frac{\omega_-^0 e^{u_-(j)}}{\omega_+^0 e^{u_+(j)} + \omega_0^0 e^{u_0(j)} + \omega_-^0 e^{u_-(j)}}$$

Where "$u_+(j)$", "$u_0(j)$" and "$u_-(j)$" are field functions to be defined representing the impact of the information on the phenotype on microstates "+1", "0" and "-1", respectively. The latter formulae are similar to "Laplace's formula" (Box 1). When non-null, those fields guarantee a change in configurations. The second cumulative sum is then

$$\theta(j) = \sum_{x=1}^{j}(+1)\cdot\omega_+(x) + (0)\cdot\omega_0(x) + (-1)\cdot\omega_-(x) = \sum_{x=1}^{j}(\omega_+(x) - \omega_-(x))$$

As a result, the difference in the cumulative sums can be expressed as

$$\theta(j) - \theta_0(j) = \sum_{x=1}^{j}\left[\frac{\omega_+^0 e^{u_+(x)} - \omega_-^0 e^{u_-(x)}}{\omega_+^0 e^{u_+(x)} + \omega_0^0 e^{u_0(x)} + \omega_-^0 e^{u_-(x)}} - \frac{\omega_+^0 - \omega_-^0}{\omega_+^0 + \omega_0^0 + \omega_-^0}\right]$$

One deduces with this development that if the genome position 1000000 on chromosome 4 does not participate to the formation of the phenotype, *i.e.* when the fields are null, then one can set: $\theta(j)$-$\theta_0(j)$~0. That is, having no information on the phenotype is similar to an absence of genotype-phenotype association.

Finally, the conservation relation that is, $\theta(N)$-$\theta_0(N)$ = 0, is written as

$$\sum_{x=1}^{N}\left[\frac{\omega_+^0 e^{u_+(x)} - \omega_-^0 e^{u_-(x)}}{\omega_+^0 e^{u_+(x)} + \omega_0^0 e^{u_0(x)} + \omega_-^0 e^{u_-(x)}}\right] = N\frac{\omega_+^0 - \omega_-^0}{\omega_+^0 + \omega_0^0 + \omega_-^0}$$

4.3. Conceptual Consequences of GIFT: Genotype-Phenotype "Loop"

At the conceptual level, what has been done is intuitive and relatively simple. However, in term of genetics what has been achieved so far is rather at odds with traditional ways of thinking about the notion of gene. Indeed, by defining the difference "$\theta(j)$-$\theta_0(j)$" one can say that it is the phenotype, *i.e.* phenotypic field or information, that organizes the configuration of genotypes and not the converse.

In genetics, the tradition is to think of genes as causing phenotypes. Here, a different way of thinking is suggested since it is the variation in phenotype values, resulting in our ability to generate a ranking process, which interacts with the microstates. Therefore, the phenotype is able to "select" a set of genetic microstates. Recall that microstates "respond" to, or interact with, the phenotypic field only if they are associated with the phenotype.

Consequently, this model suggests considering a genotype-phenotype "loop", a.k.a. self-consistency. That is to say that if genes cause phenotypes (traditional view) and that phenotype selects gene microstates (present view), then an equivalence exists between phenotype and genotype.

Stepping further in that direction one can also say that the difference "$\theta(j)$-$\theta_o(j)$" resulting from a change in microstates configuration is a decomposition of the phenotype in the genetic space.

Let us call "$\theta(j)$-$\theta_o(j)$" as the "genetic paths difference" of genome position 1000000 on chromosome 4, one way to capture the conceptual importance of this "loop" is to say that whilst a gene is "Darwinian", the genetic paths difference is "Lamarckian" since the phenotype selects the set of microstates it needs to subsist. With GIFT those two visions (Darwin vs. Lamarck) are not mutually exclusive and as it turns out, Fisher's theory does not disagree with this viewpoint either since GIFT can be transformed to "classic" GWAS provided categories are considered.

5. From GIFT to Fisher's Theory by a Coarse-graining Process

GIFT is a method advocated when phenotype values are unique while traditional GWAS consider categories for the phenotype values. The correspondence between GWAS and GIFT can be determined provided artificial categories are created such as to lose information on the phenotype.

Let us consider the presence probability of the microstate "q" at the position "j" in the string, where "q" replaces the signs "+", "o" or "-" to allow for succinct notations. This probability is formally written as

$\omega_q(j) = \omega_q^o e^{u_q(j)}$

Note that the denominator given by,

$\omega_+^o e^{u_+(j)} + \omega_o^o e^{u_o(j)} + \omega_-^o e^{u_-(j)}$,

is equal to one as by definition any position can either be a "+", "o" or "-" microstate.

Consider now an interval of individual positions of width "Δj" centred around "j" and define by "ΔN_q" the number of microstates of type "q" in this interval. One can then determine the average number of microstates of type "q" in this interval under the form "$\Delta N_q/\Delta j$". As it turns out, "$\Delta N_q/\Delta j$" is also the presence probability of microstate of type "q" in this interval.

Consequently, "$\Delta N_q/\Delta j$" can also be written as

$$\frac{\Delta N_q}{\Delta j} = \sum_{x=j-\Delta j/2}^{j+\Delta j/2} \omega_q(x) = \omega_q^0 e^{u_q(j)} \sum_{x=j-\Delta j/2}^{j+\Delta j/2} e^{u_q(x)-u_q(j)}$$

The discreet sum can be transformed into a continuous sum under the form:

$$\sum_{x=j-\Delta j/2}^{j+\Delta j/2} e^{u_q(x)-u_q(j)} \rightarrow \int_{j-\Delta j/2}^{j+\Delta j/2} e^{u_q(x)-u_q(j)}\, dx$$

Where "dx", is defined as being the difference between two consecutive positions, that is the difference between the positions "x" and "x-1".

As GWAS involves the phenotype values, the previous relation must be amended to provide the correspondence between GWAS and GIFT.

Noting "Ω_x" the phenotype value at the position "x", one defines then the difference between two consecutive phenotype values as: $d\Omega_x = \Omega_x - \Omega_{x-1} \sim \lambda(\Omega_x)\, dx$. In this context "$\lambda(\Omega_x)$" is the rate of changes in phenotype values between two positions. Therefore, the difference between two positions "x" and "x-1", that is "dx", can be related to the difference of the two consecutive phenotype values at those positions under the form, $d\Omega_x/\lambda(\Omega_x) \sim dx$. Accordingly, the expression involving the integral can be transformed as follows

$$\omega_q^0 e^{u_q(j)} \int_{j-\Delta j/2}^{j+\Delta j/2} e^{u_q(x)-u_q(j)}\, dx$$
$$\rightarrow \omega_q^0 e^{\hat{u}_q(\Omega_j)} \int_{\Omega_j+\Omega_{\Delta j/2}}^{\Omega_j+\Omega_{\Delta j/2}} e^{\hat{u}_q(\Omega_x)-\hat{u}_q(\Omega_j)} \frac{d\Omega_x}{\lambda(\Omega_x)}$$

Where the hat on the field is added to inform that the field is now expressed in the space of phenotype values. Additionally, one can also drop the subscripts involving the position by re-writing "Ω_j" and "$\Omega_{\Delta j/2}$" as "Ω" and "$\Delta\Omega/2$", respectively.

The two terms "ΔN_q" and "Δj" need also to be expressed in the space of phenotype values.

By definition, "ΔN_q" is the number of microstates of type "q" in the interval of phenotype values "$\Delta\Omega$". Using probability density functions one can then rewrite, $\Delta Nq = N_q^o \cdot P_q(\Omega)\Delta\Omega$, where "$N_q^o$" is the total number of microstates of type "q" in the population for the genome position considered, and "$Pq(\Omega)$" is the probability density function of the microstate. Similarly, "Δj" is the number of individuals in the interval of phenotype values "$\Delta\Omega$". Likewise, one can then rewrite, $\Delta j = N \cdot P(\Omega)\Delta\Omega$, where "$N$" is the total number of individuals in the population, and "$P(\Omega)$" is the probability density function of the phenotype.

Consequently,

$$\frac{\Delta N_q}{\Delta j} = \frac{N_q^0 \cdot P_q(\Omega)\Delta\Omega}{N \cdot P(\Omega)\Delta\Omega} = \omega_q^0 \frac{P_q(\Omega)}{P(\Omega)}$$

And one deduces finally

$$\frac{P_q(\Omega)}{P(\Omega)} = e^{\hat{u}_q(\Omega)} \int_{\Omega-\Delta\Omega/2}^{\Omega+\Delta\Omega/2} e^{\hat{u}_q(y)-\hat{u}_q(\Omega)} \frac{dy}{\lambda(y)}$$

As a result, the field is a function of probability density functions taken as a whole, and not only a function of the average values. That is to say that the field contains information on all the moments of the probability density functions. With this formalism, the variance of microstate distribution density functions can be involved in "$\theta(j)$-θ_0 (j)", namely in genotype-phenotype associations.

To recover Fisher's theory let us assume an infinitely dense population (infinite population). In this case the interval "$\Delta\Omega$" can tend toward zero and as a result, the field can be expected to be almost constant over the very small interval of phenotype values "$\Delta\Omega$". One can then neglect the exponential in the integral since in this case $\hat{u}_q(y)$-$\hat{u}(\Omega)$~0. Furthermore, as by definition,

$$\int_{\Omega+\Delta\Omega/2}^{\Omega+\Delta\Omega/2} \frac{dy}{\lambda(y)} \sim 1$$

one obtains simply

$$\frac{P_q(\Omega)}{P(\Omega)} = e^{\hat{u}_q(\Omega)}$$

To express the field in Fisher context, consider now that the probability density functions of the microstate "q" and of the phenotype value are normally distributed, respectively written as,

$$P_q(\Omega) = \frac{K_q}{\sigma_q} exp\left(-\frac{1}{2}\left(\frac{\Omega-\langle\Omega\rangle_q}{\sigma_q}\right)^2\right)$$

$$\text{and } P(\Omega) = \frac{K}{\sigma} exp\left(-\frac{1}{2}\left(\frac{\Omega-\langle\Omega\rangle}{\sigma}\right)^2\right),$$

where Kq and K are normalization constants, "$\langle\text{-}\rangle$" denotes averages and "σ_q" and "σ" the variances.

In his seminal paper, (Fisher 1919), Fisher assumed also that the variance of microstates are similar to that of the phenotype, that is σ_q~σ. In this context one can defines Fisher's field for the microstate of type "q" as

$$\hat{u}_q(\Omega) = \left(\frac{\langle\Omega\rangle - \langle\Omega\rangle_q}{\sigma}\right)\left(\frac{\Omega}{\sigma} - \frac{1}{2}\frac{\langle\Omega\rangle + \langle\Omega\rangle_q}{\sigma}\right) + ln\left(\frac{K_q}{K}\right)$$

That is to say that based on Fisher's seminal idea the fields should be linear.

With this assumption, the gene effect, a = 1/2 [$\langle\Omega\rangle_+$-$\langle\Omega\rangle_-$], and the dominance, d = $\langle\Omega\rangle_0$-1/2 [$\langle\Omega\rangle_+$+$\langle\Omega\rangle_-$], correspond to derivative of the fields under the form

$$a = \frac{\sigma^2}{2}\frac{d}{d\Omega}[\hat{u}_-(\Omega) - \hat{u}_+(\Omega)]$$
$$d = \frac{\sigma^2}{2}\frac{d}{d\Omega}[\hat{u}_-(\Omega) + \hat{u}_+(\Omega) - 2\hat{u}_0(\Omega)]$$

6. Beyond Fisher

Assume now that σ_q≠σ, one deduces a more generic form for the field when normal distributions are employed,

$$\hat{u}_q(\Omega) = -\frac{1}{2}\left(\frac{\Omega - \langle\Omega\rangle_q}{\sigma_q}\right)^2 + \frac{1}{2}\left(\frac{\Omega - \langle\Omega\rangle}{\sigma}\right)^2 + ln\left(\frac{K_q}{K}\frac{\sigma}{\sigma_q}\right)$$

Thus, in the general case the fields are expected to be non-linear due to unequal variances. What the latter relation confirms also is that the variances as well as the averages are involved in genotype-phenotype associations.

Assume now that $\langle\Omega\rangle$~$\langle\Omega\rangle_q$. Traditional GWAS would conclude that the gene effect is null. However, in our case, provided that $\sigma_q \neq \sigma$, the fields would be non-null still suggesting potential genotype-phenotype association. This suggests that considering averages only resulting in the notion of gene effect linked to averages difference is too restrictive.

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7. Environment and Heredity

The difference given by "$\theta(j)$-$\theta_0(j)$" provides a way to determine genotype-phenotype association that depends only on a difference between two

configurations involving microstates. That is there is no role given to the environment. In fact, the traditional notion of environment as defined in GWAS can be rederived considering the variance of microstates when the phenotypic field is considered.

In Fisher theory, the associations between genotype and phenotype are determined exclusively through the use of averages. In his seminal paper (Fisher 1919) and by considering one particular gene (Mendelian factor) involved in the formation of the phenotype, Fisher starts by defining two relations that relate the average value of microstate distribution density functions, $\langle\Omega\rangle_q$, to the average value of the phenotype, $\langle\Omega\rangle$, and to a new parameter called today the genetic variance, α^2, both expressed under the form

$$\langle\Omega\rangle = \sum_{q=+,0,-} \omega_q^0 \langle\Omega\rangle_q$$

$$\alpha^2 = \sum_{q=+,0,-} \omega_q^0 \left(\langle\Omega\rangle - \langle\Omega\rangle_q\right)^2$$

Accordingly, the environment is added to complete the phenotype distribution density function. More specifically, the effect of the environment is defined through a variance, σ_e^2, such that

$$\sigma^2 = \sigma_e^2 + \alpha^2$$

The variance linked to the environment can be derived explicitly. Let us recall the relation, $P_q(\Omega)/P(\Omega) = e^{\hat{u}_q(\Omega)}$, and rewrite it as, $\omega_q^0 P_q(\Omega) = \omega_q^0 e^{\hat{u}_q(\Omega)} P(\Omega)$. Summing the latter relation for each microstate, one deduces then

$$\sum_{q=+,0,-} \omega_q^0 P_q(\Omega) = P(\Omega) \sum_{q=+,0,-} \omega_q^0 e^{\hat{u}_q(\Omega)}$$

As $\sum_{q=+,0,-} \omega_q^0 e^{\hat{u}_q(\Omega)} = 1$, it follows that the two first moments can be determined by

$$\sum_{q=+,0,-} \omega_q^0 \int (\Omega - \langle\Omega\rangle) P_q(\Omega) d\Omega = \int (\Omega - \langle\Omega\rangle) P(\Omega) d\Omega$$

$$\sum_{q=+,0,-} \omega_q^0 \int (\Omega - \langle\Omega\rangle)^2 P_q(\Omega) d\Omega = \int (\Omega - \langle\Omega\rangle)^2 P(\Omega) d\Omega$$

Where the integrals involve all possible phenotypic values. Those integrals can be rewritten also as

$$\sum_{q=+,0,-} \omega_q^0 \int \left(\Omega - \langle\Omega\rangle_q + \langle\Omega\rangle_q - \langle\Omega\rangle\right) P_q(\Omega) d\Omega = \int (\Omega - \langle\Omega\rangle) P(\Omega) d\Omega$$

$$\sum_{q=+,0,-} \omega_q^0 \int \left(\Omega - \langle\Omega\rangle_q + \langle\Omega\rangle_q - \langle\Omega\rangle\right)^2 P_q(\Omega) d\Omega = \int (\Omega - \langle\Omega\rangle)^2 P(\Omega) d\Omega$$

Owing to the fact that $\int(\Omega - \langle\Omega\rangle_q) P_q(\Omega) d\Omega = 0$, the first integral gives

$$\sum_{q=+,0,-} \omega_q^0 \left(\langle\Omega\rangle_q - \langle\Omega\rangle\right) = 0$$

As $\sum_{q=+,0,-} \omega_q^0 = 1$, one deduces that the first integral provides indeed the first relation linking the averages as given by Fisher.

By developing the quadratic term in the second integral and owing to the fact that, $\int(\Omega - \langle\Omega\rangle_q)^2 P_q(\Omega) d\Omega = \sigma_q^2$, one deduces

$$\sum_{q=+,0,-} \omega_q^0 \sigma_q^2 + \sum_{q=+,0,-} \omega_q^0 \left(\langle\Omega\rangle_q - \langle\Omega\rangle\right)^2 = \sigma^2$$

As by definition $\alpha^2 = \sum_{q=+,0,-} \omega_q^0 (\langle\Omega\rangle_q - \langle\Omega\rangle)^2$, the environment is therefore linked to the variance of microstates under the form

$$\sum_{q=+,0,-} \omega_q^0 \sigma_q^2 = \sigma^2 - \alpha^2 = \sigma_e^2$$

To conclude, with GIFT the definition of the environment in genotype-phenotype associations results from the variance of microstates. However, a theory entirely focused on averages to determine associations and considering the variances as mere fluctuations would have missed the importance of the variance of microstates in the associations themselves. This is why the environment is often considered as an “intruder” in GWAS but always present, and why heredity linked to the variances and defined as the ratio between the genetic variance and the phenotypic variance is often used to determine genotype-phenotype associations.

Conclusion

The field of probability is borne out from our desire to provide a foundation to the notion of “evidence”. The method of relative frequencies is fundamentally based

on the notions of "imprecision", "uncertainty", "error" or "ignorance". Whilst there are some advantages to using frequentist probabilities to work with derived parameters such as, for example, the average or the variance when the conditions underlying the existence of probability are met; it is paramount to realize that the "average" and the "variance" result from the acknowledgement that a void exist in our knowledge. Because those two parameters have had a life on their own sociologically, mostly through diverse analogies such as for example the definition of the "social body", they appear legitimate to us. However, there are no good reasons to think always in term of "average" or "variance" or both. One can still feel ripples of such analogies in the 21st century. For example, the Body Mass Index (BMI) was invented by Quetelet (Faerstein & Winkelstein 2012) and is used to underscore health/obesity based on a distribution density function. One may then wonder about the universality of considering this distribution density function when rugby or American football players who won the six-nation tournament or the super bowl are considered, who would probably offset any BMI limits. The problem is that deciding to consider those players separately would split the "social body" demonstrating the overall futility of considering probability density functions as universal identifying of population. Again, it is the individuals/people that form a population, not the opposite way around.

Aside from considering "population", the problem culminates when, in addition, one tries to force a population into the field of probability as a number of assumptions need to be made that are not always realistic.

The method suggested (GIFT) tries to remove our reliance on the notion of average by considering the shortcoming of frequentist probability and creating a new mathematical object. This new mathematical object, called the genetic paths difference, takes for granted that no obvious void is present in our knowledge because precision (in phenotypic measurements) can exist. The advantage of using this model is that it does not contradict Fisher but, instead, generalizes it by giving a role also to the variance of microstates. Indeed, specific fields can be derived using Fisher's assumptions. The potential role of the variance of microstates in genotype-phenotype associations is, currently, a highly debated matter (Nelson, Pettersson, & Carlborg 2013). The model exposed herein will probably help in this matter.

Perhaps the most important point with this model (GIFT) is that, as opposed to using a population to determine genotype-phenotype associations, the reintegration of individuals into genome-wide association studies permits us to think about the self-consistency of genetics that is the "loop" that exists (and must exist) between phenotype and genotype. This can provide a basis to comprehend the notion of epigenetics and in particular the notion of phenotype plasticity in evolution and in genome-wide association studies, whereby phenotype alterations can happen without affecting the DNA composition (Fusco & Minelli 2010; Sommer 2020).

Data accessibility. The code used to generate the figure 1 can be found in the supplementary materials of Rauch, C *et al.* 2022, *bioRxiv*, p. 2022.02.25.479563. doi: 10.1101/2022.02.25.479563.

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Appendix: "Probability" (Abraham de Moivre) vs. "Conditional Probability" (Thomas Bayes) vs. "Generalized Probability" (Pierre-Simon Laplace)

The theory of probability is to define a mathematical framework to model random events. There are different ways to define, as well as interpret, a probability epistemologically. Defined by Bernoulli and developed by de Moivre the most common definition is when the frequency of events can be defined, also known as frequentist probability. In this case, the probability of a particular event can be defined objectively. However, the use of the normal distribution formula defined in the continuum limit implies the possibility to repeat independently an infinite number of times the same experiment. There is thus an empirical problem since it is not possible to clearly define "infinite number of

times". This in turn means that the probability can only be defined subjectively when dataset is limited. This subjective approach was developed by T. Bayes and is known as "conditional probability". Bayes managed to provide an expression for the resulting probability of a hypothesis upon the addition of some evidence to the antecedent body of knowledge. In this case, Bayes showed that the posterior probability varies directly as the prior or antecedent probability. That is to say that if the evidence is what is expected, it casts little credit upon any particular hypothesis. Consequently, trying to promulgate Bayes' method as an objective one is, practically speaking, impossible since there is nothing trivial in determining a meaningful antecedent probability out of the blue. In Bayes case, the only solution to generate an objective probability is by knowing all antecedent probabilities. This viewpoint was developed by Laplace. Laplace understood that the field of probability can be used as a measure of our "ignorance" concerning a process only in two different cases. Assume an event determined by different causes. One can then determine the probability of the event knowing the causes or, the probability of the causes knowing the event. To demonstrate this point, assume that three possible causes, noted "+1", "0" and "-1", generate an event and note by $P(+1)$, $P(0)$ and $P(-1)$ the probability of these causes. Then $P(+1)$, $P(0)$ and $P(-1)$ can be rewritten, respectively, as $P(+1) = N_{+1}/N$, $P(0) = N_0/N$ and $P(-1) = N_{-1}/N$, where "N_{+1}", "N_0", "N_{-1}" are the number of times the causes "+1", "0" or "-1" were observed/measured, and "N" is the total number of observations or measurements made. If among those "N" observations or measurements made the number of times the event "E" was observed/measured is "N_E", then the probability of the event "E" occurring is, $P(E) = N_E/N$. One can also determine the probability that the event "E" occurs as a result of the cause "+1", noted $P(E/+1)$. In this case, $P(E/+1) = (N_E)_{+1}/N_{+1}$, where "$(N_E)_{+1}$" and "$N_{+1}$" are, respectively, the number of times the event "E" and the cause "+1" were simultaneously observed or measured. Note that $(N_E)_{+1}$ is a subset of the total number of events "N_E" since they are only determined by "+1". Consequently, since only three causes can determine the event "E" one can write, $(N_E)_{+1}+(N_E)_0+(N_E)_{-1} = N_E$, and as a result, $N_E = P(E/+1)N_{+1}+P(E/0)N_0+P(E/-1)N_{-1}$. Dividing the latter relation by "N" one finds, $P(E) = P(E/+1)P(+1)+P(E/0)P(0)+P(E/-1)P(-1)$. One can then determine the probability that the event observed is caused by "+1" by using the ratio $(N_E)_{+1}/N_E = P(E/+1)N_{+1}/N_E$. By multiplying and dividing the right-hand side by "N" one deduces finally, $(N_E)_{+1}/N_E = P(E/+1)P(+1)/[P(E/+1)P(+1)+P(E/0)P(0)+P(E/-1)P(-1)]$. The ratio $(N_E)_{+1}/N_E$ is the probability that "+1" caused the event and as a result this ratio can be re-noted $P(+1/E)$. One deduces then the formula wrongly attributed to Bayes since Laplace derived it in 1776:

$$P(+1/E) = P(E/+1)P(+1)/[P(E/+1)P(+1)+P(E/0)P(0)+P(E/-1)P(-1)]$$

This type of formula is the one used in this manuscript and derived in (Rauch *et al.* 2022; Wattis *et al.* 2022). The important property of this relation is that the notion of "density" disappears since the right-hand side is a ratio of probabilities. Note also that if an event is always observed/measured then $N_E = N$ and the denominator is equal to one leading to: $P(+1/E) = P(E/+1)P(+1)$. The later relation is the true Bayes' formula.

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Feature

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The Pandemic and the 'Techno-fix'

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Abstract

The current pandemic was an announced possibility. Its potential causes were known: destroyed ecosystem niches, declining biological diversity, intensive farming, abuse of genetics, and biological manipulations. This paper deals with some aspects of the biological (and social) history of the ongoing COVID-19 pandemic but also with the history of previous epidemics, including the AIDS epidemics, which all have in common to be highly linked, enhanced or even the result of human activities. But now, the myth is setting in that an innovative technique for fast production of vaccines is the only *and sufficient* response to the crisis in the ecosystem and in health structures, of which this pandemic is a symptom. The reductionist and mechanistic approaches to the ecosystem and human biology are feeding the idea that the natural world may be fully manipulated and controlled ("the power to control Evolution" as in a recent book by a Nobel Award winner). This article calls for a critical thinking about the interfaces between the technosphere and the biosphere, their limits as well as for new frameworks for biology and medicine.

Keywords: pandemics, vaccine "techno-fix", technocracy, DNA-centric vision, human and ecosystems

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Introduction

The world and our lives have been turned upside down by an expected pandemic. In fact, experts have been denouncing an "epidemic of epidemics" since 1993. A well-documented 2015 book (Morand, Figuié & Coord 2018) and numerous articles have subsequently updated the data on this phenomenon, which is summarized in Figure 1: about 70% are zoonoses.

Surveillance of epidemics, epizootic and zoonoses has increased since the 2000s when the One Health's approach started to be promoted (Stephen & Karesh 2014). Governments are aware of the threat posed by this increase in epidemics, some of which have the potential to turn into a pandemic nightmare at lightning speed due to the huge, rapid and now very hard to control human travel and flows. They have taken seriously previous WHO warnings about the risk of an influenza pandemic.

First, in 2005, an epizootic of H5N1 avian influenza in intensive poultry farms in Asia caused a zoonosis that infected 114 people, 59 of whom died. Fearing that this zoonosis could lead to the emergence of a human-to-human transmission influenza virus, 120 million birds died in three months, most of them suffering from flu or having been sacrificed as a precaution (Ligon, 2005). States have adopted prevention plans and stockpiled antivirals, in particular tamiflu®, and masks. They were also prepared in 2009, when the WHO announced a risk of a human flu pandemic due to the H1N1 influenza virus, by prioritizing the production of new vaccines on an emergency basis (Mereckiene *et al.* 2012).

The dreaded pandemic finally arrived in 2020. It took the whole world by surprise because it did not

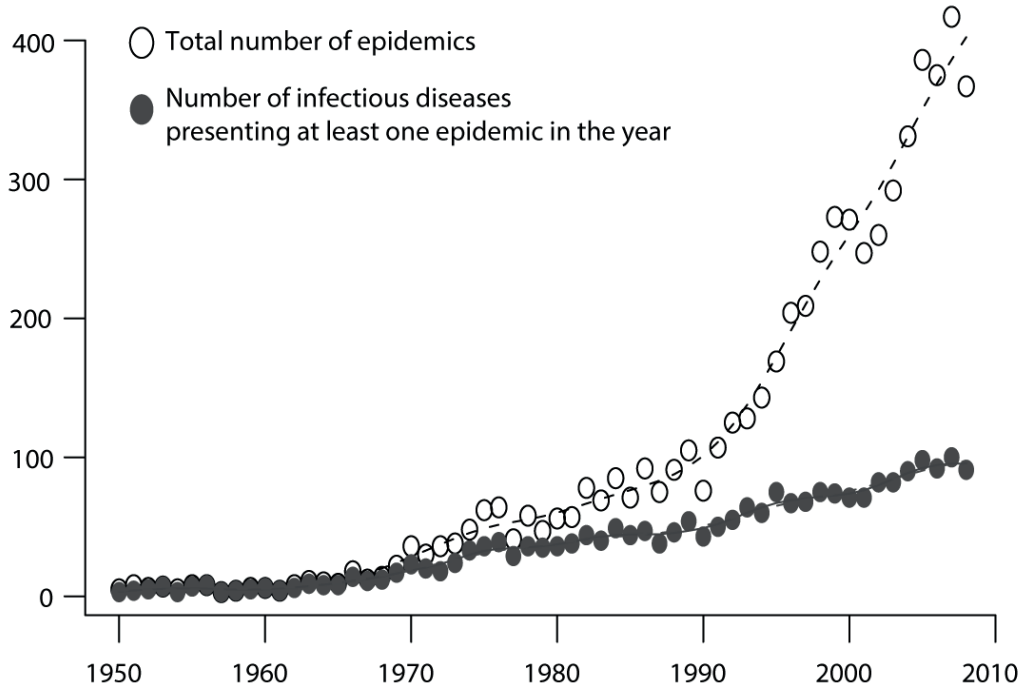

Figure 1: Evolution of the number of epidemics of infectious diseases in the world from 1950 to 2010: total number of epidemics in the year (upper curve in gray) and number of infectious diseases presenting at least one epidemic in the year—thus iterating (lower curve in black). Adapted from (Morand, 2015), upon kind permission by the Author.

come from the flu virus as expected, but from a new Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) that emerged at the end of 2019 in China. The states were not prepared for this pandemic (not enough masks, issues with PCR reagents, etc.). They accelerated the pace of research and focused essentially on vaccines, in particular on mRNA vaccines. This challenging technology, which consists in having the body produce a therapeutic protein of interest, was little studied after the early research in the 1990s but has undergone new developments recently, in particular as an alternative to conventional vaccine approaches (Pardi *et al.* 2018). The production of COVID-19 mRNA vaccines has been compressed in time thanks to a fast-track development in a public health emergency and a conditional marketing authorization allowing their large-scale use without the need to wait for full scientific knowledge in accordance with evidence-based medicine (Guyatt *et al.* 1992).

This gave the illusion of being able to control the circulation of a virus already dispersed throughout the world. Unfortunately, the mass vaccination failed to eradicate the virus but this does not seem to taint the logic of huge and repetitive vaccination by mRNA as a unique solution to face this health crisis in many countries and as recommended by WHO. This attitude ignores the causes of these repeated outbreaks, the limits of their unimodal solution, and their possible consequences for the future. In fact, it chooses to ignore fundamental knowledge in medical virology spanning from the history of coronaviruses, which we will recall, to the different severity of its various forms. Rather, the European Union as well as North America, Israel, Australia and many other countries focused on the quick and miracle technical solution of the mRNA vaccine. This technology is relatively easy to produce but its potential harmful effects are unknown, due to the lack of controlled clinical trials and sufficient follow-up time. In the urgency of the first waves of the epidemic, protecting the elderly or those vulnerable because of comorbidities *via* a vaccine with conditional marketing authorization was certainly justified. Unfortunately, the effectiveness of vaccines seems short-lived, with boosts mandated

every three months. Despite this, the main or only medical solution adopted for adult population remains the vaccine as a "techno-fix" (a technical shortcut with little scientific knowledge of its effects), which is proposed as a perfect technology that definitively solves the problem. This also contributed to disregarding the analysis of causes, which are rooted in a distorted relationship among the ecosystem and human beings, as well in the role of the health systems. In many cases, the failure in protecting lives was due to the unpreparedness of medical structures to face the largely predicted emergency.

We now need measured scientific and medical responses that do not rely on techno-science alone as many countries around the world have chosen to do. In this regard, see the review on the global turn towards mandatory COVID-19 vaccination policies by Bardosh and colleagues (Bardosh *et al.* 2022). It is typical of techno-science to deny its own limits, which are precisely based on a reductionist vision of the living world, including the reduced medical attention to the specificities of individuals ("one [vaccine] fits all") and the manipulation of DNA—seen as a context-free combinatorics of alphabetical signs—in order to "control evolution" (Doudna & Sternberg 2017). We also need to address urgently the actual causes of these repeated outbreaks and transform our relationship with nature, while embedding fantastic techniques to manipulate molecules into still missing scientific frames, as we will argue below. Governments must empower themselves to act according to the concept of One Health (WHO 2017) beyond the buzzword.

The direct contribution of humans to this inflation of epidemics is already a reality, as shown by examples mentioned in this article. We will first briefly survey some major epidemics or pandemics that affected humanity and their possible origins, including medical activities and laboratory experiments. Further, the health systems of many countries failed to provide adequate services in the expected emergency. Therefore, only extensive PCR tests and mass vaccination helped to maintain the impression of very active answers by governments, which avoided discussing the ecosystemic, technical, and healthcare failures. These shortcomings call for a critical thinking about the technosphere and its relation to the biosphere, while going beyond the dominant explanatory frameworks in biology and medicine.

1. Infectious Diseases and Epidemics: Brief Historical and Ecological Perspectives

Most major human infectious diseases are caused by pathogens transmitted by wild or domestic animals (Taylor, Latham & Woolhouse, 2001). The emergence of several of them is consecutive to the recent development—11,000 years ago—of agriculture accompanied by new cohabitations between human and animal populations, in particular domesticated ones. This is most likely the case for diphtheria, influenza A, measles, mumps, pertussis, rotavirus, smallpox, and tuberculosis (Diamond 1999). These new proximities between human and animal populations were unprecedented compared to the previous world of human hunters and gatherers. This multiplied the opportunities for transmitting pathogens as well as to ensuring their endemic persistence in human populations (Wolfe, Dunavan & Diamond 2007). The authors describe five steps necessary to transform an exclusively animal pathogen into a pathogen whose only host is human, as this is the case for measles, rubella, smallpox and syphilis for example. But the transition from one stage to the next one is not a fatality. In fact, some pathogens such as anthrax or West Nile virus do not cause secondary human infections while others, such as viral zoonoses like the Marburg virus disease or monkeypox only generate a few cycles of secondary human-to-human infections that lead to micro-epidemics (Wolfe, Dunavan & Diamond 2007).

Dobson and Carper focused on the settlement of infectious disease during human civilizations and identified three factors for understanding the impact, persistence, and spread of pathogens: the size and spatial distribution of the host population, the movement of infected and susceptible hosts and vectors, and the nutritional status of the human host population (Dobson & Carper 1996). The elements that may shed light on the epidemics of the past, which these authors studied based on numerous documented examples, are as diverse as malnutrition consecutive to a reduction in diet diversity associated with urbanization, diversity of herd immunities, number of siblings, human displacement, wars, access to health care, etc.

Thus, the causes of epidemics are multifactorial and span from natural history to human activities. Epidemics can be analyzed as resulting from interactions between

infectious agents and their hosts, whether they are single or multiple, and of ecological competition processes (Karesh *et al.* 2012). For example, the emergence of the Lyme disease, induced by the tick-borne *Borrelia burgdorferi* bacteria, in Northeastern United States during the 20th century, was largely facilitated by partial reforestation in fragmented forest landscapes, resulting in new prey-predator/host-pathogen balances (Allan, Keesing & Ostfeld 2003; Kilpatrick & Randolph 2012). Host-pathogen relationships can be affected locally, as in the example of Lyme, but also by a multitude of social, physical, chemical, and biological factors involving larger scales that require a holistic analysis.

In their review calling for a new paradigm of interdisciplinary biocomplexity, Wilcox and Colwell adopted such a framework. They integrated different scales and their reciprocal influence dynamics from regional ecosystems affected by environmental and anthropological variations (urbanization, agriculture, habitat) to the dynamics of host-pathogen interactions leading to emerging diseases (Wilcox & Colwell 2005).

In summary, epidemics have always existed and the emergence of infectious diseases is a complex phenomenon that only a societal and ecosystemic approach—including analyses of zoonoses—can clarify. Today, they are more frequent and more easily turn into pandemics.

2. Epi/Pandemics and their Zoonotic Origin in the Past 50 years: The Case of AIDS

What happened over the last 50 years after a century of very significant decline in the number of epidemics, particularly but not only in Europe? World population doubled and there was an eight or nine-fold increase in epidemics (Morand & Figuié 2018). As mentioned in Figure 1, about 70% of these recent epidemics have been the result of "zoonoses", *i.e.* they are due to microorganisms passing from animals to humans (more generally called "spill-overs"). Among the many causes of this astonishing "spill-over" growth, deforestation and human encroachment on natural habitats associated with an unprecedented loss of biodiversity in human history top the list. Often, this is worsened by the creation of huge intensive livestock farms near critical areas, which serve as perfect incubators for diseases or novel mutations thereof (Daszak, Cunningham & Hyatt 2000; Wilcox & Colwell 2005; Karesh *et al.* 2012)). Finally, laboratory accidents, medical procedures, and human genetic manipulations are also responsible for these outbreaks (Heymann, Aylward & Wolff 2004).

The last major pandemic, *i.e.* AIDS, is still raging around the world, since the early 1980s. AIDS is caused by two emerging viruses, HIV-1 and HIV-2, that are the product of several independent zoonotic transmissions of the simian immunodeficiency virus (SIV) occurred from monkeys to humans in the early 20th century (Hillis 2000; Korber *et al.* 2000). These zoonoses are not directly pathogenic for humans who have lived closed to several species of monkeys in the depths of the jungle for thousands of years (Poulsen *et al.* 2000; Lemey *et al.* 2003; Keele *et al.* 2006). However, the monkey's pathogens alone do not explain the origin of the AIDS pandemic, since emerging HIV viruses subsequently acquired human-to-human transmission properties (Marx, Apetrei & Drucker 2004). Several simian viruses transmitted separately and simultaneously to humans in African colonies at the beginning of the 20th century and led to the various groups of HIV-1 and HIV-2 (Hahn *et al.* 2000; Korber *et al.* 2000; Damond *et al.* 2004; Santiago *et al.* 2005). Large-scale colonial construction projects and crop development leading to deforestation, massive population displacements, urbanization and rapid socio-cultural changes have contributed to diffuse the virus also out of its natural forest habitat (Pepin 2011). Colonial medicine organized massive vaccination campaigns and antibiotic treatments by injection, or carried out blood transfusions with reusable syringes, including in SIV reservoir places (Schneider & Drucker 2006). This medicalization was most probably a determining factor in the cross-species transmission of simian viruses and their iatrogenic spread by blood contamination through syringes that were used for many consecutive people without intermediate sterilization (Lachenal *et al.* 2010). All these factors, which have contributed to the adaptation of the simian's SIV to humans over a short period of time are the result of human activities, including medical and altruistic ones (Chitnis, Rawls & Moore 2000; Drucker, Alcabes & Marx 2001; Marx, Alcabes & Drucker 2001; Apetrei *et al.* 2006; Schneider & Drucker 2006; Pépin 2021). In conclusion, the emerging AIDS disease is caused by the human immunodeficiency virus HIV, whose origin is the simian virus SIV transmitted by zoonosis to humans and which has evolved to acquire a strictly human tropism through the five intermediate stages mentioned above (Wolfe,

Dunavan & Diamond 2007). The example of the AIDS pandemic illustrates the complex origin of a pandemic combining natural, human, situational and historical factors, which cannot be reduced to a single cause.

Hepatitis C is a disease caused by a virus transmitted only by blood. Its epidemic in Central Africa is simpler case, since it has an essentially iatrogenic origin linked to the massive non-sterile injections practiced to fight trypanosomiasis and by colonial mass medicine between 1920 and 1960 (Njouom *et al.* 2007; Pépin *et al.* 2010).

Other epidemic episodes have become more and more frequent since these emergent diseases in the 20th century. Among them, the coronaviruses have been on alert for two decades with several appearances under close surveillance. First in 2002, a major epidemic of SARS-CoV caused great concern with the death of 800 people out of 8,000 cases recorded in about thirty countries (Drosten *et al.* 2003; Fouchier *et al.* 2003; Ksiazek *et al.* 2003; Zhong *et al.* 2003). This new epidemic came from an emerging coronavirus transmitted by small carnivores, civets, sold in southern China bushmeat markets (Guan *et al.* 2003; Song *et al.* 2005). However, the wild reservoirs of the virus were most likely bats (Hu *et al.* 2015).

A first human case of infection with a new coronavirus occurred in the Arabian Peninsula in 2012. This caused the Middle east respiratory syndrome (MERS) with cases of human-to-human transmission imported into Europe, in Asia and the United States (Zaki *et al.* 2012; Hemida *et al.* 2013). The virus was transmitted to humans by camels contaminated by bats, which are the reservoir of the virus (Alagaili *et al.* 2014; Sabir *et al.* 2016).

These examples highlight the role of many changes caused by humankind at unprecedented speed and scale over the last century, threatening biodiversity (Vitousek *et al.* 1997) and spreading by badly handled technologies. This set ideal situations for the emergence of new pathogens and enhanced the probability of their spreading, outpacing medicine (Keesing *et al.* 2010; Morand, Krasnov & Littlewood 2015).

3. Accidental Outbreaks of Pathogens Escaping from Laboratories

Numerous pathogens have accidentally escaped laboratories. This phenomenon is documented worldwide and has been regularly denounced (Furmanski 2014).

The Marburg virus, which belongs to the same family as the highly lethal Ebola virus, infected a few people in Germany during a micro-epidemic in 1967. Most of the infected people were working in research laboratories and handled tissue from grivet monkeys imported from Africa (Martini *et al.* 1968). Fortunately, only few nosocomial infections occurred in the hospitals where sick employees had been admitted. Retrospective studies have assessed the ratio of primary to secondary contaminations, outside the laboratories, at 21:3 in Marburg, 4:2 in Frankfurt and 1:1 in Belgrade (Slenczka & Klenk 2007; Ristanović *et al.* 2020). Many other accidental episodes involving a wide range of pathogens have been reported (Heymann, Aylward & Wolff 2004; Furmanski 2014). These laboratory leaks have killed hundreds of people in total, but none of them have gone beyond the geographically circumscribed outbreak, with the exception of the 1976–1977 flu.

This H1N1 pandemic originated from a virus strain that circulated in the 1950s and had disappeared (Kung *et al.* 1978). Since the 1950 and 1977 influenza viruses are genetically very similar, the hypothesis of an escape of the 1950 viral strain, preserved in a laboratory, is highly probable (Nakajima, Desselberger & Palese 1978; Scholtissek, von Hoyningen & Rott 1978; Furmanski 2015). The re-emergence of the H1N1 virus was first detected in Russia and China, but analysis of frozen biological samples and subsequent phylogeny methods showed that it was present some months earlier, making it impossible to trace back to the countries where the accidental re-introduction of the virus took place (Wertheim 2010). Fortunately, this pandemic, which mainly affected young people, was no more deadly than seasonal flu thanks to the collective immune memory of the epidemics of the 1950s (Kilbourne 2006).

This short history illustrates that human error can turn into a nightmare if more virulent pathogens escape and that science-fiction disaster scenarios could become reality (Klotz & Sylvester 2012). Among them, coronaviruses gained attention in 2002 with the emergence of SARS-CoV, which was placed under close surveillance with monitoring of highly pathogenic infections. Its zoonotic origin as well as the animal reservoirs that harbor it have been established (Cui, Li & Shi 2019). Most of the 8,000 cases identified are the result of a human-to-human transmission chain. However, at least four laboratory accidents resulting in human infections with the same virus were reported

in Asia in 2002 and 2003. One of these resulted in secondary infections, including one fatal (Heymann, Aylward & Wolff 2004). Following this SARS outbreak and the identification of the high pandemic risk of coronaviruses, the G20 countries reacted with a patchy and inconsistent investment in basic research, which turned to be relatively limited, considering the relevance of the SARS epidemics (Head *et al.* 2020).

In early 2020, governments around the world were helpless when faced with a devastating pandemic that rapidly became global. The pathogen, an emerging SARS-CoV, was quickly identified, related to SARS-CoV and named SARS-CoV-2. Its origin was soon officially declared to be a zoonotic virus. Its animal reservoir was the bat, with the pangolin as an intermediate host, in which it would have acquired its human-to-human transmission properties. On March 26, 2020, the WHO "dismissed" the non-natural origin of SARS-CoV-2: "However, all available evidence suggests that SARS-CoV-2 has a natural animal origin and is not a manipulated or constructed virus. SARS-CoV-2 virus most probably has its ecological reservoir in bats" (WHO 2020). A few days later, a scientific publication ruled out the hypothesis of an accidental origin of the virus by leak of a research laboratory and opened the track of the pangolin (Andersen *et al.* 2020).

However, many elements are missing from this explanatory puzzle and the examination of the artificial origin hypothesis involves geopolitical issues that complicate the work of experts on site (Harrison & Sachs 2022). In the case of COVID-19 pandemic, "accidental laboratory leakage" moved higher on the list of possible origins of SARS-CoV-2 (Decroly, Claverie & Canard 2021; Sallard *et al.* 2021). Some authors even consider since long time that the most imminent danger today comes more from the laboratory manipulation of this type of virus than from the new natural and recurrent zoonoses, which are most often dead-end infections (Klotz & Sylvester 2012; Lipsitch & Bloom 2012).

Finally, the origin of HIV AIDS viruses that are at the origin of the pandemic started in the 1970s has been established in the depths of Central Africa in the 1920s (Pépin 2013). However, the emergence of a new virus in China only two years ago has still not been elucidated despite the vastly improved technological sequencing capabilities available over the last decade.

4. Moratorium on "Gain-of-Function" Experiments and Scientific Precautionary Principle

If the hypothesis of an accidental escape of a laboratory virus were to be confirmed, then the question of whether the SARS-CoV-2 strain that caused the 2020 pandemic is natural or not is still open. In particular, the presence of a furin site, which is absent in other SARS-CoVs (Coutard *et al.* 2020), raises the question of whether this site could have been introduced by humans through genetic manipulation as part of gain-of-function genetic research (Sallard *et al.* 2020).

This type of experiment consists in increasing the virulence or the infectivity, or both, of a pathogen. It has divided scientists for a decade, after genetic manipulations involving H5N1 avian viruses were carried out to allow airborne transmission from mammal to mammal (ferret to ferret) in several laboratories (Imai *et al.* 2012; Russell *et al.* 2012). Opponents of these experiments consider that the benefit/risk ratio is very unfavorable and that by playing with fire, with the intention to be prepared for a pandemic, researchers risk producing precisely the pandemic they fear, like a "self-fulfilling prophecy" (Zimmer & Burke 2009; Klotz & Sylvester 2012; Lipsitch & Bloom 2012; Wain-Hobson 2013). In 2012, the US government listed 15 pathogens and toxins for which certain types of research are subject to new safety rules. The aim is to better control experiments on these pathogens for their dual-use research potential (United States Government 2012). Scientists' warnings about the danger of gain-of-function experiments reached the highest political levels, including in Europe (Enserink 2013).

In 2014, following three separate laboratory incidents reported by the CDC, over 200 scientists signed the Cambridge Working Group declaration asking for a cessation of experiments on potential pandemic pathogens (Cambridge Working Group 2014). Indeed, President Obama administration imposed a moratorium on gain-of-function studies on influenza, SARS, and MERS (United States Government 2014; NIH 2015). This moratorium, which was relatively respected (Lentzos & Koblentz 2022), lasted only three years (NIH 2017) and new funds and funding procedures, framing the gain-of-function experiments (United States Department of Health and Human

Services 2017), were enacted in January 2017 (Burki 2018; Klotz & Koblentz 2018).

We know now that laboratory manipulation of this type of virus implies a high risk of spillover. Therefore, risky manipulations should be conceivable only under severe restrictions and in scientific frames. Instead, for example, CRISPR-Cas9 toolkits can be easily bought and handled by any biology laboratory to be then extensively used under the pressure of "publish or perish" and "patent" logics. Further, this happens within a reprehensible mechanistic conceptual frame that, in our views, misses the organismal and ecosystemic interactions of DNA and its functions. In view of the power of the existing technical tools, a "scientific precautionary principle"—*i.e.* no more actions without an open critical reflection on fundamental principles—should govern science, as we will further hint below. Fundamental research should be at the core of a scientific approach also when dealing with these emergent but expected phenomena.

Finally, two non-minor, yet neglected issues emerge. Correctness of programs or their possible manipulation under cyber-attacks are far from being remote challenges. Computer driven DNA manipulation is a widespread technology, often based on piling up of programs working in immense databases. This may easily lead to inconsistencies, hence to incorrect programs. Correctness is an undecidable property at the core of major research work and applications, e.g. in Flight Control Systems where it has been closely studied for decades (Henzinger & Sifakis 2006), while the authors of this paper could never see this issue mentioned in reference to genetic manipulations. As for the computer systems' vulnerability to attacks, "the risks of using gene sequencing technologies to corrupt databases by altering sequences or annotations" and the work of computer scientists who "designed a DNA sample that, when sequenced, resulted in a file that allowed the hacker to remotely control the sequencing computer and make changes to DNA sequences" have been described (Baumann *et al.* 2022; Mueller 2021). The myth of cell and computer as exact Cartesian Machine (Monod 1970) fails even more blatantly when the two interact in open networks. In short, techniques show their limits, and more science seems required, at least as much as it is applied in Flight Control Systems.

5. Technology as the Only Solution to Recurring Pandemic Threats?

The emergence of an acute infectious disease in human population is a transitory phenomenon leading to a new dynamic equilibrium between pathogens and their hosts in a prey-predator type relationship (Wilcox & Colwell 2005), also known as homeorhesis, as it continually changes (Waddington 1953). The endemization of the new pathogen is one of these possible evolutions as it is regularly the case with the variants of influenza virus—carriers of antigenic shifts that explain the particularly deadly nature of certain flu pandemics (Kilbourne 2006). Four known strains of coronaviruses are endemic in the human population (Kahn & McIntosh 2005). Nasopharyngeal swabs and sera from 466 patients with upper respiratory tract disease collected between 1962 and 1967 were analyzed in an epidemiological study. This showed that endemic coronavirus infections accounted for up to 35% of total respiratory viral activity during epidemics (Mcintosh *et al.* 1970).

The emergence of the OC43 coronavirus strain was most probably at the origin of the deadly "Russian" flu of 1889 and 1894, the symptomatology of influenza and coronavirus infection being similar (Vijgen *et al.* 2005; Korsia-Meffre 2020). After a few deadly waves and the acquisition of immunity in the human population, this strain is now circulating without any particular harm, except for some vulnerable persons (Kistler & Bedford 2021). The same process is occurring today with SARS-CoV-2, which after several highly lethal epidemic waves, continues to circulate in an endemic way, without unusual severity, thanks to a host-virus coevolution leading to a peaceful equilibrium (del Rio & Malani 2022). The notion that such a pathogen could be completely eradicated by any sort of intervention in such an integrated world as ours was simplistic or even an illusion (Wilcox & Colwell 2005).

How these iatrogenic and laboratory accidents are being addressed? And what about their various anthropic causes, which have a common origin in a techno-science that destroys both the ecosystem and science? The aggressive use of powerful combinatorial techniques with little scientific content—see below and (Longo 2021) for more—increases the chances of disaster. Yet, on these grounds, some have—once again—proposed a technical solution, a quick "techno-

fix" serving as a molecular "magic bullet", allegedly successful in the short term, but not viable in the long run. However, causes are rooted in a distorted, anti-scientific, and mechanistic relationship with the ecosystem, following in the footsteps of Francis Bacon and treating plants and animals as machines through the early bio-technologies (Hartley 1937). The consequences are zoonoses following unlimited deforestations and intensive animal breeding as well as abusive experiments with no theoretical frames, but the myth of "re-programming life" like a computer.

In itself, the invention of messenger RNA vaccines is an innovative and very interesting technical possibility (Zhang *et al.* 2019). However, the scientific understanding of RNA and its "independent" functions in the proteome has long been delayed by the dominant geno-centric vision, according to which everything is played out at the level of DNA. In particular, this narrow vision has prevented for too long the funding of heterodox research, coined by many as "epigenetics", which has been proposed since the 1990s, for example by the pioneer of RNA studies, Katalin Karikó in the USA (Sahin, Karikó & Türeci 2014) and by Bruno Canard in France (Canard 2020). Moreover, it did not promise anything profitable in the short term. However, in face of the pandemic and once corporate actors understood the potential financial gains of this technology, gigantic pharmaceutical companies such as Pfizer grasped the value of the possible role of RNA-based tools. Then they quickly repurposed the RNA intervention platforms towards a vaccine against COVID-19, whose technical basis had been developed by a few small start-up-style laboratories that were in fact, so far, unsuccessfully working on cancer mono-antigenic immunotherapies (BioNTech). This was only possible due to very substantial public funding that was never repaid to date despite corporate record profits. These technical interventions, *i.e.* vaccines, applied first and urgently on elderly or fragile individuals, may have saved hundreds of thousands of lives, according to many government and health authorities. But… now what? Will we reflect on the causes of this dramatic increase of epidemics, which are now easily becoming pandemics? Will we resume the commitments made to the public health infrastructure in the early months of its spreading?

Everyone should remember that many governments, for example, France and Italy, acknowledged the needs of hospitals that had been so long neglected and turned into business enterprises, where every "act of care" had to be evaluated first financially and in the short term, mask storage included. More than 1000 head of intensive or urgent care hospital services had resigned in France before COVID-19, as they considered impossible to handle safely the "normal" incoming flu epidemics (Zéau 2020). We also remember how health care workers took control of their core business by adapting to the situation during the first lock-down. This was done at great personal cost and against the financial priorities imposed on them. Some of them died from COVID-19, often for lack of a sufficient, standard protection. For a few months, hospitals prioritized medicine before financial optimization and governments recognized the needs of community medicine, which was unable to provide care on an outpatient basis or at home. Since long, this has been forgotten: only "the vaccine" is mentioned. Any critical discussion on the subject is conveniently condemned and labeled as "anti-vax" whereas the criticisms stressing the limits of COVID-19 mRNA vaccination is based more on rational arguments than on *a priori* irrational positions (Schwarzinger *et al.* 2021), acknowledging its effectiveness in the short term for elderly or fragile people.

6. Technoscience's Denial of its Own Limitations

The effectiveness of messenger RNA vaccines in protecting the elderly or the vulnerable has been soundly stressed and pointed out by many colleagues and institutions (Joshi *et al.* 2021; Bardosh *et al.* 2022; WHO 2022). Notwithstanding, techno-science is blind to its own limitations, as spelling them out requires a broader scientific understanding based on principles (Longo 2019).

In fact, since mid-2021, the dominant political trend pushed for vaccinating everyone, including children who are almost never at risk of becoming seriously ill from SARS-CoV-2 (French National Academy of Medicine, 2021). In spite of this, the whole world should receive these short-lived vaccines as the only way out. An absurd idea that billions of people could be vaccinated on a tri-annual basis or even more frequently. Moreover, in the absence of data consolidated by time and sufficient hindsight, only limited considerations of the benefit/risk balance seem reasonable. The potential benefit

for people who are vulnerable because of their age or comorbidities, even in the absence of such data, may justify the governments' incentives to vaccinate them before the final FDA or EMA approval of the vaccines. This approval is still awaited, as it is conditioned by a methodology established to provide a sufficient level of scientific evidence (Doshi, Godlee & Abbasi 2022). For other people, those for whom the chances of serious consequences of SARS-CoV-2 infection are very low—and we know this since May 2020 through confirmed observations (Ioannidis 2021)—the benefit of the vaccine is questionable, especially when its related risks are still unknown. This holds more true as, today, the Omicron variant of SARS-CoV-2 is in the process of becoming endemic (del Rio & Malani 2022): more contagious but less pathogenic, it tends to be similar to the four endemic coronaviruses that have already been in circulation for decades or centuries (Lavine, Bjornstad & Antia 2021; Sonigo, Petit & Arhel 2021; Murray 2022).

To develop and devise future sustainable strategies in light of the soon-to-be endemic nature of SARS-CoV-2, it is mandatory to consider the success of these vaccines in the context of their limitations. Some scientific articles have shed light in vain on the fact that even vaccinated people can efficiently transmit SARS-CoV-2 infection also to fully vaccinated people (Singanayagam *et al.* 2021). Thus, sanitary passes or "certifications" are barely, if at all, effective against the spread of the virus, whereas hygiene measures, including masks, are helpful in protecting against SARS-CoV-2. Prevention around food and beverage handling is very important too. Unfortunately, too often politicians and journalists have been confusing the speed of contagion with pathogenicity and the effectiveness of the vaccine with its lack of protection against infection (Nainu *et al.* 2020; Brouqui *et al.* 2021). Ireland reached the highest rate of adult vaccinations in Europe in September 2021 (BBC 2021). However, it presented the highest rate of infection (Worldometer 2022). Indeed, "The epidemiological relevance of the COVID-19-vaccinated population is increasing", as soon observed in The Lancet, November 2021 (Kampf 2021). Sanitary passes based on vaccination may favor risky behaviors, thus the spreading of the virus.

Our human collective is falling into the fallacy of deeming ourselves in control of viruses if only the whole world, regardless of their vulnerability, participates in the technical solution (a "techno-fix")—this time an experimental vaccine. So, many politicians, while insisting on the vague notion of "herd immunity" for months (at 70% of the population?), suddenly started to accuse the unvaccinated 10% for the continuing crisis. And this focus on vaccines only makes us forget the multiplication of zoonoses following deforestation and persistent encroachment of natural habitats as well as laboratories carrying out gain-of-function research with potential pandemic pathogens.

Similarly, the degradation of our health systems, for example in France, continues unabated, with decreasing human and financial resources. Instead of facing these problems, the answer is then based on new vaccines, or even on a "universal vaccine", whose aim is to make all diseases disappear, including those of the future triggered by unknown and non-existent pathogens. The international Coalition for epidemic preparedness innovations (CEPI) was launched in 2017 with the ambitious goal of creating "a world in which epidemics are no longer a threat to humanity". It called for "platform technologies to enable rapid vaccine development against unknown pathogens", and released major funding "to develop a transformative rapid-response technology to create vaccines", with a special interest in early 2019 for "the RNA Printer™—a mRNA vaccine platform that can rapidly combat multiple diseases" (CEPI 2019).

The advantages of mRNA vaccine technology, since it can be quickly manufactured, is that it can be easily implemented in large-scale emergencies, as was done massively in 2020 to stop the COVID-19 pandemic. Moreover, it can be adapted in near real time to protect against variants that follow each other in quick succession due to the rapid evolution of the virus during the period of its emergence (Zhang *et al.* 2019). In the meanwhile, we compensate for the ephemeral efficacy of the current vaccine by repeated injections, which is the reason for the multiple boosters recommended in many countries. This perfect business model is also an ideal solution in theory. However, it is difficult to be satisfied with it in the current state of our knowledge.

Never has a vaccine been developed so quickly or delivered so massively in the absence of any pharmacovigilance data on possible long-term adverse effects, due to the lack of hindsight. Even the efficacy of COVID-19 mRNA vaccines raises questions as it is unclear whether they prevent severe forms of

the COVID-19 or not, in the absence of the raw data underlying the clinical trials (Doshi, Godlee & Abbasi 2022). Before the start of the vaccination campaigns, Peter Doshi, associate editor of the British Medical Journal, explained how the methodology of the clinical trials did not allow to know the protective value of vaccines against serious and deadly forms of SARS-CoV-2 infection (Doshi 2020). The randomized controlled trials (RCT) are considered as the gold standard for decision making but post-hoc modifications of some key elements of the trial plan have been shown to be frequent and worrisome (Eichler & Rasi 2020; Shepshelovich *et al.* 2020). However, adherence to the original trial design is fundamental to ensuring its scientific validity intended to address a precise medical purpose. In the absence of robust epidemiological data and sufficient hindsight, it seems fundamental to us to remain aware of the limits of technology without being classified as "anti-vax" people for this. Enough health scandals have warned us about it (Nature 1992; Mullard 2011; Fénichel, Brucker-Davis & Chevalier 2015; Wise 2015; The Lancet 2021). In particular, the precautionary principle is not an irrational attitude. It is especially relevant for those subjects who are not at risk of severe forms of the disease, such as children and young people. This awareness is a scientific attitude.

As a matter of fact, the first precaution must be scientific, as we hinted above: strongly needed research on "epigenetic" activities of RNA have been delayed for more than twenty years by the geno-centric perspective. In turn, this denied, a priori, the possibility of any side effect of the mRNA vaccine during the pandemic, on the grounds that... the RNA does nothing, alone, in the proteome (except in the case of retroviruses, of course, as they act on DNA). This response is grounded on the same anti-scientific attitude, which, through its action on ecosystems or by molecular manipulations based on the flawed vision that organisms are Baconian mechanisms programmed by Lego-like DNA segments, is at the origin of almost all the epidemics of the last decades, sometimes transformed into pandemics. And the techno-scientific "solution" keeps making promises on the basis of the same lack of scientific knowledge.

Indeed, the engines that may generate pandemics continue at full speed and, undoubtedly, the next pandemic is already in the making. In fact, we will be lucky if it does not break out before this one has finally become endemic.

7. A Failed Conception of the Living World

As stressed above, from the scientific point of view, most of these manipulations (intensive destruction of ecosystems as well as laboratory experiments) are based on a techno-scientific vision of organisms. Let us now analyze this vision. It is based on an "alphabetical combinatorial" approach to DNA, which is seen as a "computer program" or "code" of life that can be manipulated at will—with little if any understanding about the organism, its ecosystem, and its history.

The book *A crack in creation: The new power to control evolution* by 2020 Nobel Award winner, J. Doudna (Doudna & Sternberg 2017) offers a good example of such an anti-scientific attitude. The book focuses on a very relevant technique that has allowed to transfer to the laboratory bench the "mechanism" used by bacteria to detect and destroy the DNA of invading bacteriophages. This remarkable invention *per se* certainly deserves a Nobel Award. Unfortunately, the technical advance is framed in a totally wrong or vague theoretical frame. As for the wrong part, the Central Dogma of molecular biology (CD) is advocated explicitly, a statement claiming that "the genetic/hereditary information is completely contained in the DNA", or that the DNA fully guides the embryogenesis and the ontogenesis. In spite of several rephrasing, this assumption is at the core of the CD, as long as the usual "information/programming" language is used: since "information goes from DNA to RNA to proteins" and proteins cannot reverse the information back to the DNA, no other source of "information/programming" has to be found. Some sort of essentialist-Thomist view frames this perspective, like in the reference, since 2001, to the "decoding of human DNA": once known the chemico-physical structure of DNA (a major advance) we know its *essence*. Now, the DNA matters also, or mostly, for what it does. And this depends on the context (Longo 2021)). As for the "vague" part of the assumptions, the wording of "information" and "program" are referred to in the usual sloppy way proper to molecular biology, where it is not clear if the first refers to discrete data types information, Shannon's or Turing's approaches, which significantly differ concerning entropy and complexity (Longo 2020). These precise but wrong assumptions plus vague notions, such as genetic information and genetic

program, make a vast and powerful community take strong stances: by editing, acting on, and modifying DNA we can drive, program, and control organisms, species... and even evolution.

However, if we change perspective and see the DNA as the (amazingly important) physico-chemical trace of a history (evolution) and as a constraint to macromolecular, largely stochastic, flows, then we may aim at understanding its fundamental role both in phylogenesis and ontogenesis (Soto, Longo & Noble 2016). Further, we may get rid of the myth of driving/programming them by editing DNA-alphabetic sequences.

Coupled to the mechanistic insensitivity to the ecosystemic issues, *i.e.* unlimited extractivism and the use of plants and animals as machines, this "editing/programming" attitude prevails in too many laboratories, where powerful techniques are used with no scientific grounds. The "publish or perish" criteria further encourage all sorts of manipulations with no scientific knowledge, hoping for any output that may justify a publication.

In summary, in either case—zoonosis or loss of control over genetically manipulated pathogens—the root "cause" is our relationship with nature. Many of us (Association of Friends of the Thunberg Generation, the European Network of Scientists for Social and Environmental responsibility, and the Cardano Group), are calling for a radical change in order to prevent future pandemics, and more generally, to preserve a viable life on the planet. We need to understand biology in its evolutionary and historical context including all its diversity and singularities (Sonigo & Stengers, 2003). Instead, we treat plants, forests, animals, and humans as machines constructed by the gears of Descartes and Bacon's clocks, which still serve as the main reference for the founding fathers of mainstream molecular biology (Monod, 1970) and bio-technologies (Hartley, 1937). The pupils of the latter consider organisms as driven by a software written in the DNA, which can be programmed and reprogrammed at will. In a recent talk, Nobel Laureate Jennifer Doudna announced that the new CRISPR-based gene editing techniques will allow to "cure (all) diseases" (Doudna 2022). Jointly to the other speakers, Andrea Crisanti from Imperial College London, bioethicist Françoise Baylis from Dalhousie University, and WHO Chief Scientist Soumya Swaminathan, she conjectured that CRISPR will help facing the ongoing ecosystemic changes by driving animal and plants towards viable evolutionary paths.

Possibly the current pandemic and certainly many previous failures or unrealized promises illustrate that this is not only a scientifically flawed assumption but also a dangerous project (Longo 2018). Just consider the fifty-year old, iterated promises to cure or even eliminate cancer by acting on genes within... 2015 (von Eschenbach 2003). The financial support of this enterprise was opposed to the search for environmental causes of cancer, in spite of its doubling incidence in forty year. This increase, a paradigmatic case for our analysis, is largely due to human/ecosystem interactions (Soto & Sonnenschein 2010). We introduced 80,000 new molecules in the biosphere in less than a century. The current paradigm gets rid of this fact stating that most of these new molecules are small and not (stereo-) specific to organismal macromolecules (Zoeller *et al.* 2012), so they cannot act as "key-lock" in the cellular "cartesian mechanisms", thus it is impossible that they interfere with the genetic program. Instead, they do interfere with hormone cascades in varying probabilities and kill people. Corporate interests once more meet a view of nature that, in turn, is kept alive by those interests and their financial support.

Conclusions

We need to think better, and collectively, about the current and future possible debacles. There is an urgent need for more expertise than that currently showed in the debate about COVID-19. In particular, more knowledge is needed in the disciplines that understand the ecosystem or laboratory origins of epidemics to propose countermeasures and new research guidelines and directions. Rapid technical responses are only palliatives, which confirm a flawed logic. Unfortunately, they are financially hegemonic. Even in urgency, investments and research on medical care and multi-antigenic vaccines must proceed in parallel. Precautionary, broad measures taken ahead of time addressing the root causes of pandemics will allow us to avoid the hasty and risky emergency actions we have seen during this pandemic. Building on the theoretical and practical knowledge of a broad range of experts and actors, who aim to look after the biosphere while fostering critical thinking about the technosphere, seems to us the way forward to avoid a repetition of the current debacle.

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Georges Canguilhem, the Health-Disease Transition and the Return of Organicism

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Abstract

The Normal and the Pathological is a remarkable book by Georges Canguilhem, originally published almost 80 years ago. It should play a much more important role in medical education and in the study and praxis of biology because of its rich and relevant approach to the knowledge of organisms. Indeed, only organisms can go through sickness and health; these states are axiological categories as they represent values. However, when it was published, the molecular biology revolution introduced the idea of genetic program and that organisms would be a kind of computer. This concept combined the naive 19th-century physicalism with the metaphor of programs and signals borrowed from mathematical theories of information. As a consequence, the main concepts of biology, such as teleology, agency and normativity—the latter, a central concept in Canguilhem's thought—were abandoned by biologists and medical doctors.

Over the last 20 years, the failure of ideas guiding the molecular biology revolution allowed for the growth of organicism, a tradition committed to the autonomy of biology and its irreducibility to physics and chemistry. These developments encouraged theoretical biologists and philosophers to re-examine the aforementioned biological concepts rejected by reductionism. Their critical work produced versions of these concepts that are now compatible with notions of scientific causality, and therefore, an opportunity to present Canguilhem's work to new generations of biologists and physicians.

Canguilhem's work advances the understanding of biological entities by introducing the axiological notion of individuality, the concept of organismal "normativity" (i.e. the capacity of organisms to create their own norms) and, related to these two concepts, the organism's propensity to make mistakes—an exclusive property of biological systems.

Keywords: Georges Canguilhem, axiology, normativity, polarity, health and disease, organicism

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Introduction

About 50 years ago, as a follow up to Monod's dictum that what is good for *E. coli* is good for the elephant, molecular biologists proclaimed that biology could finally be reduced to chemistry and physics. In short, this analogy suggested that development was just a problem of gene expression. At that time, medical students were still learning about anatomy, embryology and physiology in their basic courses. For centuries, medical students were taught to examine patients by taking a medical history and performing a physical examination searching for signs related to the symptoms that brought the patient to the doctor. Indeed, plenty of talking, observing and touching took place before the physician asked for clinical chemistry measurements, x-rays or anything else that could not be accomplished using the doctor's five senses and intellect.

Today, we are concerned about physicians' ignorance of those classical clinical skills and their current dependence on both technology that they do not fully understand and machines driven by proprietary algorithms. Since the beginning of the current century, these trends have become accentuated due to the proletarianization of biological and medical thought (Soto & Sonnenschein 2021). In addition, the failure of molecular biology to provide a causal understanding of disease (in fact, most diseases are due to a constellation of "causal" factors) has led to the introduction of what was initially called "personalized medicine" and then "precision medicine", terms that imply that the "old" way of practicing medicine was neither personal nor precise. Those topics are based on the collection of "big data", namely, genome sequencing, transcriptomic analysis, epigenomics, and additional "omics".

Pragmatically, however, "big data" has not helped to improve medicine. To the contrary, technological tools have not replaced the knowledge that physicians usually gathered during a traditional clinical examination. For example, new tools such as a handheld ultrasound, which was proposed to supplant the 200-year-old stethoscope, have been shown to compromise the accuracy of diagnosis of certain heart conditions (Fuster 2016). This impoverishment of medical competence needs to be corrected. The situation goes hand in hand with the theoretical impoverishment that has been affecting biology in the last century. Canguilhem's contributions to the epistemology and history of biology are even more relevant today than they were at the time of their publication, because they could correct the harm caused by almost a century of dominant reductionist thinking in the biomedical sciences.

1. Canguilhem, Both a Philosopher and a Physician

Canguilhem's work has recently been introduced into the English-speaking world by translations and commentaries of his work. Michel Foucault succinctly described his place in French philosophy in the preface of Canguilhem's, *The Normal and the Pathological*, as follows:

> "... take away Canguilhem and you will no longer understand much about Althusser, Althusserism and a whole series of discussions which have taken place among French Marxists; you will no longer grasp what is specific to sociologists such as Bourdieu, Castel, Passerson and what marks them so strongly within sociology; you will miss an entire aspect of the theoretical work done by psychoanalysts, particularly by the followers of Lacan. Further, in the entire discussion of ideas which preceded or followed the movement of '68, it is easy to find the place of those who, from near or from afar, had been trained by Canguilhem" (Canguilhem 1991, p. 8).

In France, the recent publication of his *Oeuvres completes* is facilitating the work of those who, like us, want to know more about the genesis of the ideas developed in his books.

The Normal and the Pathological is based on Canguilhem's medical doctoral thesis. In the introduction to the first edition, he explains that on the one hand, "philosophy is a reflection for which any foreign matter is good", which implies that the author's interest in medicine was more speculative than professional. On the other hand, he also stated that:

> "Two problems that occupied us, that of the relationship between science and technology, and that of Norms and the Normal, seemed to us to benefit, for their precise position and clarification, from a direct medical culture" (Canguilhem, 2021).

Indeed, his interest in medicine was already evident in 1929, as illustrated by a commentary he wrote on Dr. René Allendy's book, who contrasted "analytical

medicine" (dealing with diseases) with "synthetic medicine" (dealing with the patients and their individuality). In that article, Canguilhem declared:

> "The human body is doubly individuated. It is so as a living being, like any animal; but it is so—and how much more so—as a human being, that is to say inseparable from a mind, from a personality. It is such a person that the doctor must save, and undoubtedly the Humanity in each one. But it is this humanity, in no way abstract, that makes his suffering, his ailment different from those of a dog, of a horse … since they are animals and they do not think" (Canguilhem, 1929).

This comment already showed a concern with the fact that medicine must deal with the sick rather than with diseases, and that the sick are individuals. From this perspective it follows that the sick go to the doctor when they feel ill, again stressing the fact that health and disease are values.

Canguilhem studied medicine amid the German occupation of France during World War II. The school of medicine of Strasbourg had moved to the *zone libre* and continued its activities in Clermont-Ferrand. Canguilhem recognized the influence its faculty had on him. His professors had a philosophical formation that permeated their medical teachings. His medical thesis, later published as *The Normal and the Pathological*, is not only about a medical problem, but also about the very foundations of biology and biological individuality. It addresses some of the fundamental problems in biology that make this discipline different from physics.

2. The Normal and the Pathological

About two centuries ago, Xavier Bichat bluntly stated that, unlike biological entities, planets do not get sick. This truism meant that biological sciences must approach their objects of study in a different way than the one that made Newtonian physics the pinnacle of science up until the end of the 19th century. Canguilhem's central contribution to the understanding of this difference was his conception of health and disease as axiological categories, *i.e.* vital values that cannot be reduced to mere scientific entities. From this, he proposed an axiological conceptualization of individuality.

Axiology and medicine

Axiology (from Greek *axios*, "worthy" and *logos*, "science"), also called Theory of value, is the philosophical study of goodness, or value, in the widest sense of these terms. Its significance lies (1) in the considerable expansion that it has given to the meaning of the term "value" and (2) in the unification that it has provided for the study of a variety of economic, moral and aesthetic questions (Encyclopaedia Britannica 2015). In the context of this article, "value" is positive or good when a person feels well and is negative when the person feels unwell or ill. The patient is not passive regarding these values, *i.e.* just feeling good or unwell. For example, the patient tries to find a position that mitigates a local pain. This action is normative and the norm is to find the hedonic feeling of relief.

Medicine is a good point to start with the normal and the pathological because the patient can communicate with the observer, a physician. Nevertheless, the health-disease transition is not exclusive to humans: it pertains to all living entities. Bacteria can be infected by plasmids, and this forced interaction can result in either death or survival. Moreover, a bacterium that has survived an infection may develop a memory of such an event and gain resistance to a second attack by the plasmid, a phenomenon known as "adaptive immunity" (García-Martínez, Maldonado, Guzmán, & Mojica 2018; Mojica & Rodriguez-Valera 2016).

Let us move back to medicine. In order to address this dynamic health-disease-health transition, it is useful to start with Leriche's idea, namely, "health is life in the silence of the organs" and "disease is what irritates men in the normal course of their lives and work, and above all, what makes them suffer" (Canguilhem 1991, p. 91). The state of health is a state of unawareness. From such a silence, how can one study something that does not seem to give any signs about what it does? Canguilhem states that the following text by Leriche is one of the most profound thoughts on the problem of the pathological:

> "At every moment there lie within us many more physiological possibilities than physiology would tell us about. But it takes disease to reveal them to us" (Canguilhem 1991, p. 100).

Then Canguilhem completes this thought with another equally profound one:

> "Physiology is the science of the functions and ways of life, but it is life which suggests to the physiologist the ways to explore, for which he codifies the laws. ... Health is organic innocence. It must be lost, like all innocence, for knowledge to be possible"(Canguilhem 1991, p. 101).

In the first part of his book, Canguilhem refutes the idea that this transition is a quantitative problem, as proposed by Claude Bernard and others. It should be understood that this is not a quantitative problem but a problem of values. It is the patient that declares that he/she feels unwell and seeks a physician. At this point, it is easy for us, physicians, to say that the reason the patient does not feel well has an underlying physio-pathological cause—and then reduce the disease to the anatomical-functional levels that range from tissues to molecules. As an example, Canguilhem presents the case of an autopsy revealing a cancer in a person that was feeling healthy until his sudden death. Was this man ill? This is a fact that requires interpretation. It is because there are patients that there is a medical discipline, and that physicians learn about disease; this knowledge was gathered in the distant past and is still being gathered today to construct medical knowledge. This medical knowledge is in turn applied to new patients. Thus, the physician can relate a given patient's feeling unwell with the presence of a tumor thanks to the patients that felt ill and were examined long ago. A person may have a cancer in an organ and not experience symptoms during his/her lifetime. In the same vein, a person may be SARS-CoV-2 positive but be completely asymptomatic. In both cases the person is not unhealthy because s/he is not experiencing being ill. Thus, where should one locate the disease? Canguilhem's answer is the following:

> "To look for disease at the level of cells is to confuse the plane of concrete life, where biological polarity distinguishes between health and disease, with the plane of abstract science, where the problem gets a solution. We do not mean that a cell cannot be sick if by cell we mean an entire living thing, as for example a protist [unicellular organism], but we do mean that the living being's disease does not lodge in parts of the organism"(Canguilhem 1991, pp. 223-224).

If a disease is located in the organism as a whole, where does the pathologist's diagnostic claims fit in? Canguilhem states that the problem of the pathologist is that s/he cannot eliminate the subjectivity of his/her object of study. But one

> "can practice objectively (impartially), a research whose object cannot be conceived and constructed without relation to a positive and negative qualification, whose object is therefore not so much a fact as a value"(Canguilhem 1991, p. 229).

This health-disease transition, this polarity, could be seen as opposing incompatibles. Canguilhem opted to consider illness as constitutive of health:

> "to be in good health is to be able to fall sick and to get up again ... The healthy man ... measures his health by his capacity to overcome the organic crises to establish a new order"(Canguilhem 1991 p. 200).

3. On Value, Polarity, and Normativity

The central theme of Canguilhem's conception of the normal and the pathological was the axiological notion of individuality that he extended beyond human medicine, and which led to the concept of biological normativity. While developing these ideas he became aware of the contribution to this subject by the German neurologist Kurt Goldstein which he acknowledged extensively in his book (Goldstein 1995). The argumentative part put forward by Canguilhem extends beyond medicine by bringing these three concepts (polarity, value, and normativity) to the very center of biology. Here we will transcribe paragraphs of *The Normal and the Pathological* dealing with these concepts.

> "We maintain that the life of the living being, were it that of an amoeba, recognizes the categories of health and disease only on the level of experience, which is primarily a test in the affective sense of the word, and not on the level of science. Science explains experience but it does not for all that annuls it" (Canguilhem 1991, p. 198).

The biological individual has preferences and thus positive and negative values, a polarity: referring to physical objects and the principle of inertia, Canguilhem states that "... inertia is precisely an indifference with respect to directions and variations in movement". In contrast:

> "Life is far removed from such an indifference to the conditions which are made for it; life is polarity. The simplest biological nutritive system of assimilation and excretion expresses a polarity. When the wastes of digestion are no longer excreted by the organism and congest or poison the internal environment, this is all indeed according to law (physical, chemical, etc.) but none of this follows the norm, which is the activity of the organism itself. This is the simple fact that we want to point out when we speak of biological normativity"(Canguilhem, 1991 p. 129).

> "We do not ascribe a human content to vital norms but we do ask ourselves how normativity essential to human consciousness would be explained if it did not in some way exist in embryo in life. We ask ourselves how a human need for therapeutics would have engendered a medicine, which is increasingly clairvoyant with regard to the conditions of disease if life's struggle against the innumerable dangers threatening it were not a permanent and essential vital need. From the sociological point of view it can be shown that therapeutics was first a religious, magical activity, but this does not negate the fact that therapeutic need is a vital need, which, even in lower living organisms (with respect to vertebrate structure) arouses reactions of hedonic value or self-healing or self-restoring behaviors. The dynamic polarity of life and the normativity it expresses account for an epistemological fact of whose important significance Bichat was fully aware. Biological pathology exists but there is no physical or chemical or mechanical pathology"(Canguilhem, 1991 p. 127).

This certainly applies to the emerging discipline called "molecular" pathology. In fact, although Canguilhem stressed the "hedonic value" of some behaviors that lessen pain, for example, by "freezing" an articulation in a given position to lessen pressure on the articular surfaces, we would like to stress that "hedonic value" also includes playful behaviors. These have been described not only in mammals but in other vertebrates (Burghardt 2015) and also in invertebrates (Zylinski 2015).

4. The Ebb and Flow of Biological Stances: From Physicalism to Organicism

During the 18th and 19th centuries, biologists made explicit their stance regarding whether physical principles could explain biology entirely. While a group known as physicalists thought that biology should be entirely explained by physical principles, another group known as vitalists thought that to explain biological phenomena, in addition to physical principles, it was necessary to invoke a vital force. To these vitalists, this force was comparable to the force of universal gravitation; both forces were equally mysterious but neither contradicted the physical principles current in the 18th century. At the end of the 19th century, progress in organic chemistry tipped the balance between these two stances towards a reductionist physicalism. In other words, they ignored Bichat's insight (see above). In the 20th century, agency, a property of organisms that traditionally served as a quality to distinguish the alive from the inert, was transferred from the organism to other entities, including natural selection (Moss 2003; Walsh 2015), genes, and proteins (Soto & Sonnenschein 2020). This enormous change resulted in the almost complete disappearance of agency, normativity, and individuation from biological language. In addition, from the 1920s to 1950s, classical Darwinian selection theory was merged with Mendelian inheritance in the form of population genetics, resulting in the Modern Synthesis (Huxley 1943). This development led to the disappearance of the organism from the entities useful to this updated version of evolutionary theory. The new useful entities were Mendelian traits and natural selection. By extension, during the ascent of molecular biology (from the late 1950s to today), the organism became just a "readout". In short, while Canguilhem was developing his important work concerning individuality, normativity, health, and disease, the biological mainstream was becoming more physicalist and mechanicist. Meanwhile, an alternative view, namely organicism, was being proposed.

The organicist school emerged between the two World Wars in continental Europe, Great Britain and the United States. Their early proponents rejected the traditional opposite views of reductionism and vitalism and aimed to create a third way that circumvented the limitations of both. They considered organisms as organized systems, rather than an aggregate that can be reduced to physics or chemistry. Thus, they believed that biology was an autonomous discipline that needed its own theories. Accordingly, alternative ways to explore causality had to be constructed (Nicholson & Gawne 2015). Implicit in the organicist view is the idea that organisms are not just "things" but relentlessly

changing objects. However, the introduction of computer sciences and molecular biology "won the day" for a while during the heady times when the DNA structure and the processes of transcription and translation were being described. A few years later both philosophers and biologists started to realize the shortcomings of the "new biology".

5. Organicism: The Return of Canguilhem?

Advances in the understanding of dissipative non-equilibrium physical systems that self-organize gave impetus to those interested in the origin of life (Kauffman 1993; Nicolis & Prigogine 1977). Additionally, starting around 1970, a new wave of organicism inspired by the Kantian concept of biological organization ("a thing exists as a natural end if it is cause and effect of itself") emerged. This explanatory alternative recognized that Kantian organization is dissimilar from spontaneous self-organization, while arguing for a new regime of circular causation (Gánti 2003; Maturana & Varela 1980; Pattee 1972; Piaget 1967; Rosen 1991; Waddington 1968). In this circular organization regime, the parts depend on the whole and vice versa; this organizational regime not only produces and maintains the parts that contribute to the functioning of the whole integrated system, but the integrated system also interacts with its environment to promote the conditions of its own existence.

During the last 20 years, organicists have worked out the conceptualization of teleology, agency, and normativity in ways that are compatible with scientific notions of causality. For example, the cause should precede the effect (Moreno & Mossio 2015; Mossio & Bich 2017; Walsh 2015). These "naturalized" concepts are addressing "minimal" instances of these concepts, as in the case of minimal biological agency in bacteria. They are being re-introduced into biology by way of theoretical principles a century after having been removed by geneticists and molecular biologists (Soto, Longo, Montévil, & Sonnenschein 2016; Soto, Longo, & Noble 2016).

Organicists first addressed the problem of organization as a source of stability through interdependence. However, organisms are relentlessly changing during their life cycle, the novelties they produce are the substrate of evolution (descent with modification). To build a theory of organisms addressing the entire lifecycle, the concept of biological organization is necessary but additional concepts must deal with other features of the living. Thus, we have proposed three founding principles: 1) the default state of cells, whereby cellular agency manifests as constitutive proliferation with variation and motility (Soto *et al.* 2016); 2) a principle of variation generated at the cellular and supra-cellular level during the iteration of morphogenetic processes (Montévil, Mossio, Pocheville, & Longo 2016), and 3) a principle of organization having its roots in circular causation (Montévil & Mossio 2015).

This theory of ontogenesis would complement the theory of evolution that addresses phylogenesis. Additionally, the aforementioned foundational principles frame experimental research and define the proper organismal observables. From this theoretical perspective, morphogenesis would then be the result of the default state producing both the cells and the extracellular matter making the organism, the principle of variation creating novelty and plasticity, and the principle of organization making the organism and its parts interdependent while providing robustness and stability. Additionally, this perspective conceives the organism as an agent that can and does create its own norms rather than just preserve the initial ones. Thus, its organization regime is not just about maintaining the system alive, but to recompose itself as it undergoes morphogenesis or faces illness and/or environmental changes. We posit that this ability is to be found at the points of articulation among the three principles (Soto *et al.* 2016 , Miquel & Hwang 2022).

In conclusion, the time is ripe to progress from the initial successful attempts to further naturalize these main biological concepts by taking Canguilhem's contributions into consideration. Of particular significance is the axiological idea of individuality and normativity and the notion that biological entities are prone to making mistakes. Judging by the renewed interest in his oeuvre, we are confident that we are not alone in this quest.

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Commentaries

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Old Ideas Die Hard, Particularly in Cancer Biology

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Cells in a clonal population always display substantial phenotypic heterogeneity of non-genetic origin (Brock, Chang, & Huang 2009). Heterogeneity arises from the inherent stochasticity of molecular interactions, including gene expression that produces a large variety of cell phenotypes. It has been assumed that constraints and forces of selection shape this heterogeneity (Bizzarri 2018). These forces probably arise from interactions between the cells locally and at the level of tissues but may be intrinsic, depending on the individual life trajectories within the cell population. There are also extrinsic forces, such as physical parameters and nutrient availability. Together, they may act on the diversity of cell phenotypes and produce new populational structures and tissue organization. This is a typical Darwinian mechanism based on random variation and selective stabilization. It has been proposed that normal cell differentiation and embryonal development but also pathological processes such as cancer proceed through a Darwinian mechanism (Kupiec 1997; 2020; Paldi 2020). Both aspects have been discussed in *Organisms*.

The fact that the cells proliferate and generate a heterogenous population spontaneously without the need for external instructions or signals is now well known. However, the idea that this represents a fundamental feature (Montévil 2016) has some difficulty in being accepted. The typical way to frame the issue of heterogeneity is to implicitly assume that cell populations are homogeneous on their own and that diversity is generated by specific mechanisms. For example, in the case of normal development, it is typically assumed that cells differentiate or divide only when they receive an external inducing signal. This is a classical deterministic reasoning that has been challenged (Sonnenschein & Soto 2021). A corollary of this deterministic logic is that cellular diversity found in clonal populations of cancer cells must have specific cell intrinsic causes. Indeed, if the origin of cancer lays in genetic mutations that empower an individual cell to proliferate faster than others, as stipulated by the somatic mutation theory (SMT), then the emergence of more malignant subclones must also result in the accumulation of more genetic mutations. Although SMT faces a number of conceptual contradictions inherent to the theory itself and directly contradicts many essential observations (Sonnenschein & Soto 2020), it still remains hegemonic. Attempts are regularly made to update it, typically using *ad hoc* propositions to resolve some of these contradictions. They also usually reinforce SMT deterministic nature while pretending to introduce some Darwinian logic.

A recent example of such an *ad hoc* proposition was provided by Khatib and colleagues in a paper entitled

"Understanding the cause and consequence of tumor heterogeneity" (Khatib *et al.* 2020). The authors examine the origin of cancer heterogeneity, and ask a typically SMT-inspired question: "Does a common mechanism exist that drives cancer heterogeneity to achieve the fitness and survival of a given cell community?" The question itself—putting aside its anthropocentric flavor—is founded on several implicit assumptions. First, it postulates the existence of specific mechanisms shared by all cancer types that generate cell heterogeneity on purpose. Second, the cancer cell community is supposed to have its own fitness. Unfortunately, these assumptions are not made clear, hence no arguments support them. The authors favor a superficial analogy involving forest fires and cell death. Namely, since natural or manmade fires promote biodiversity in natural ecosystems, it is proposed that "selective cell death within each tumor ecosystem may be one mechanism that induces cancer cell heterogeneity thus confers a survival advantage on these cells". In support to their proposition, the authors claim that there is an association between the apoptotic index in a selection of tumor types and the cancer cell diversity estimated on the basis of transcriptome analysis and patients' survival.

Although the correlation between the increased cell turnover and the aggressiveness of a tumor could be interesting, the authors miss the opportunity to propose a more coherent systemic explanation based on such a solid theoretical foundation as the Darwinian Theory. The superficial analogy with the natural ecosystems may give the illusion that the authors incorporate a Darwinian logic in their explanatory scheme. This is clearly not the case. Their proposition that apoptotic cells purposefully "induce" heterogeneity in the cancer cell population to promote the survival of the fittest sub-clones in the tumor is at odd with any Darwinian logic. Rather, this appears as a simple deterministic reasoning seeking linear causality behind complex phenomena. Such an idea might be compelling but, unfortunately, is misleading. Indeed, this interpretation is regrettably common in biology and it represents a major hindrance for the development of a coherent theory of living organisms (Soto *et al.* 2016).

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Perspectives and Hypotheses

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What Happens with the Mind when the Brain Dies?

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Abstract

A neuroscientist reflects on his near-death experience to ponder the nature of the human mind and the survival of consciousness after death. Ancient traditions, manifold personal experiences, nuanced philosophical views, and recent scientific evidence, all point to the brain as a filter (or receiver) of consciousness rather than its fanciful producer. No doubt, good-old-fashioned materialists —nowadays rebranded as physicalists, crypto-dualists, or illusionists wearing virtual reality goggles— insist that minds are "nothing but" what brains do. Nevertheless, a trans-materialist science can expand the scope and depth of the answers (and the questions) that really matter not only to science but also to human flourishing.

Keywords: consciousness studies, near-death experiences, current neuroscience, dogmatic skepticism, trans-materialist science

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Please think of water. Visualize it for a moment. I bet you conceived it as a liquid, neglecting nearly by default that it can also be found in gas and solid forms. Something similar happens with the human mind.

Our culture gives priority to the waking state. The only alternative to caffeinated alertness seems to be alcoholic drowsiness or drugged-induced sleep, often interpreted as a mere mechanism to restore our productive capacities. We oscillate between functionality and recovery throughout most of our lives.

However, there is more mind within us. The beam of light of consciousness, when striking our brain as a prism, can refract (not just reflect) itself in a range of colors that goes beyond the scrawny binary of on and off. I am referring to the so-called "altered" states of consciousness, or "anomalous" experiences (although qualifiers like this often fail to do justice to the nature of these phenomena and their relative frequency of occurrence amongst laypeople).

The list is longer than what one could a priori presume: lucid dreams, hypnosis, regressions, trance, meditative states, psychedelic experiences, spiritual awakenings, out-of-body experiences, etc. Amongst them, we also find near-death experiences.

You may have probably heard of them. Indeed, we do not talk much about them; and yet, when a person does, people confess "me too" (Woollacott & Lorimer 2022). I had one in March of 2021. As Bosch masterfully depicted more than half a millennium ago in *The ascent of the blessed* (a painting that is part of a four-panel polyptych entitled *Visions of the Hereafter*), I found myself in the fabled tunnel of light (Figure 1). Three loving figures were waiting for me. I knew who they were. I was not afraid, but I knew that if I continued, then there would be no return. It felt like I decided to postpone that journey. Calmed and aware, I came back. A few days later, the surgeon and her team did the rest, together with the prayers of my family and friends.

Scientific studies show that one out of five people resuscitated after cardiac arrest declares having lived a similar experience (van Lommel *et al.* 2001), including out-of-body experiences, life review, or interacting with deceased people. Maybe it is all just a hallucination caused by the lack of proper brain blood supply. Or maybe not. Why the rush to settle the question? If it was only a matter of physiological malfunction, why did not the rest of the patients have an experience at all? And, for those who have it, why is it so universally consistent despite different backgrounds, cultural and otherwise? Moreover, how could such an intense (and transformative) experience take place during clinical death, with a flat electroencephalogram? There is so much more to learn (Vicente *et al.* 2022).

Those thoughts are a function of brains, there is no doubt. There is no need for fancy neuroscientific experiments to prove the point: one simply needs to knock somebody out. The really interesting question is whether, as the psychologist William James posed, such a function is "productive" or "permissive" (James 1898), namely, whether the brain secretes mind as the liver secretes bile or, on the contrary, whether it filters it as a radio does when receiving electromagnetic waves. The brain-computer metaphor is exhausted and rather exhausting (Gomez-Marin 2022). A truly new science of consciousness should challenge the dominant vision of a universe made of dull matter, transmuting it into a vibrant materiality whose matrix hosts the ability to know thyself.

In the meantime, scientistic skepticism and peremptory religion meet in "neuro-soteriology," also known as "promisomics" (Gomez-Marin 2021): promises of salvation whereby, disbelieving in heaven, eternal life is assured by means of an upload to the cloud (billionaires first). Such is the nightmarish dream of techno-transhumanism, conceptually cheap but big-budgeted. Elevating us to demigods, we strip our humanity from us. The prophecy is about immortalizing our soul as an algorithm in silicon chips. Not today, always tomorrow...

One does not need to be technically dead to live a near-death experience. The medical literature is crowded with reports of similar phenomena in traffic accidents, cases of asphyxia, or postpartum shock, amongst others. Not only the reality of such experiences is undeniable, but also their impact is personally indelible and phenomenologically invaluable (Bitbol 2014).

Similar cases defying orthodox explanations are also often described in palliative care units, when contravened curing gives way to compassionate caring for those patients labelled as terminal. Recently coined "terminal lucidity" (Nahm *et al.* 2012), and traditionally known as "*mejoría de la muerte*" in Spanish-speaking countries, the unexpected and sudden return of mental clarity and memory right before death in patients suffering from pronounced cognitive disorders, puzzles families, doctors, and scientists.

We are not talking about mere anecdotes that can be casually dismissed. The plural of anecdote is data. Thousands of accounts by people from different backgrounds consistently point in the same direction, as health professionals also attest.

But there is more. Eastern traditions such as Buddhism offer thorough descriptions of what happens not only close to death, but also during dying, and even after (Dalai Lama 2002). Think of the *bardo*, an intermediate state between death and reincarnation, or of *tukdam*, a meditative state in which the corpse does not breathe but neither decomposes even for weeks, which is being studied in laboratories (Lott *et al.* 2021). One only needs to look at the *Tibetan Book of the Dead* to realize what an exquisite investigation of the mind can be carried out with one's own mind. Western neuroscientists should take notice.

So, what happens to the mind when the brain dies? Nothing at all, for sure, dogmatic materialists would confidently claim. According to their doctrine (more philosophical than scientific, and too often professed with the zeal of a stubborn ideology), the mind is "nothing but" brain activity. A near-death experience must be the brain's last goodbye. The afterlife can only occur in the heads of those who stay. A true skeptic, however, would confess that she or he does not know the answer. Doubt is very different from denial. Inquiry is the mirror image of neglect. Our obligation as researchers is to investigate what we do not understand, especially when it challenges our deepest beliefs. Let us thus not offer premeditated nor improvised explanations, neither deploy conversation stoppers embroidered via self-refuting prefixes in adjectives such as "para-normal", "super-natural" or "pseudo-scientific". This only reveals a mulish prejudice disguised as scientific rationality. Great taboos can become fertile fields of exploration.

Whether one believes in the "thereafter" or not, something important ends "hereafter" (Tolstoy 1981).

Figure 1: Sketch of my near-death experience scene. I was not in a horizontal tunnel but in a vertical dwell, looking upwards. Three known figures (none of which was a family member) offered to help me climb. Without words, I kindly refused. I was not afraid, but calmly aware

.

Most likely, the ego vanishes. In the meantime, our ancestors live in our memory. Nevertheless, does any aspect of human consciousness survive after permanent bodily death? The possibility of a "life after life" should not distract us from the existential question of the meaning of death. Our thanato-phobic culture strives for a kind of orphan wisdom that would allow us to look at death in the face, loving what will not live forever. As the author and activist Stephen Jenkinson says, the solution to broken-heartedness is not less heart (Jenkinson 2015). Mortality is a burden and a blessing (Jonas 1992). Life is a miracle. Death remains a mystery.

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Organisms

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