

Rebirth of Environmental Epidemiology?

Alessandro Giuliani *

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

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

Citation: Giuliani, A, 2018, "Rebirth of Environmental Epidemiology?", *Organisms. Journal of Biological Sciences*, vol. 2, no. 1, pp.17-18. DOI: 10.13133/2532-5876_3.6.

Commentary on

Curtin, P et al., 2018, "Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder", *Sci. Adv.*, vol. 4, eaat 1293-

1. Epidemiology: a different approach

I immensely liked this paper for different reasons. A very personal one is the satisfaction to have had the occasion to be part of something potentially very useful for health when, many years ago, together with my friends Joe (Zbilut) and Chuck (Webber) I contributed to develop Recurrence Quantification Analysis (RQA), the non-linear signal analysis technique at the basis of the present paper (Zbilut *et al.* 1998). But this is a purely personal (and a little bit egoistic) issue, the by far more important point is that this work seems to me the re-birth of a crucially important science widely considered to be stuck in a dead end: environmental epidemiology.

The famed paper by Taubes and Mann (1995) was very elegant and straightforward to put in evidence that classical epidemiology turns into a fabric of chance correlations, and missed opportunities, when facing subtle and complex exposure patterns. Namely, when the exposure patterns are supported by an intermingled (and practically impossible to factorize) network of personal susceptibility, modulating factors, complex mixtures

of 'sub-threshold' toxicants, dietary habits and so forth. Methodological tools developed for the individuation of single causative agents (the name of the investigation field is borrowed from 'epidemics', in which pathogenesis is chiefly supported by a microbial single etiologic agent) are very powerful when applied to massive industrial work exposition to toxic agents (e.g. aromatic amines), or to substances with very specific clinical endpoints (e.g. Asbestos), but are totally out of scale when dealing with complex exposures.

Notwithstanding that, statistics on cancer, neurologic degenerative syndromes and other chronic diseases are telling us there are still important environmental health problems out there, but we do not have clear ideas on how to cope with. The most diffuse answer (with a style very typical of these times) is 'turning big', relying on huge data sets in which we measure a lot of exposure variables, whose global pattern could allow the 'answers' to emerge by a large scale correlation approach. This is the answer of the research efforts dealing with the so-called 'exposome' approach (Lioy and Rappaport, 2011).

I have nothing against the 'exposome' research avenue (by the way, a great part of my work deals with multidimensional statistics), but the proposal by Curtin et al. is much more elegant and innovative and consequently puts into play the fundamentals of scientific method.

2. Hallmarks for the environmental health

The three 'big ideas' that make this article a milestone of environmental health, in my opinion are:

1. The focus on time. The cyclical character of environmental exposure to toxicants has a quasi-periodic and highly non-stationary behavior. This fact, together with the lack of very long series, prevented to face the time dimension in epidemiological studies. This contingency undermined the detection power of epidemiological studies for the 'leveling off' due to averaging across time. The authors, by the introduction of a non-linear time series analysis technique like RQA, totally independent from stationary assumptions and suited for dealing with very short series, are able to get a quantitative estimation of the dynamics of exposure and (still more important) of the dynamics of response of the affected system.
2. The focus on individual temporal structure. The relevant scale at which temporal structures do appear is the individual level and focusing on individual temporal pattern implies the analysis locates at the right scale of definition. This in turn opens the way to a sort of 'biological statistical mechanics' in which general issues like 'the degree of order' or temporal determinism of the biological system are studied as such without referring to particular microscopic level mechanisms.
3. The choice of the correct viewpoint. The two above methodological points are empowered by the choice of the right biological material, i.e. the teeth, that, like growing plants, allow for a time resolution of the concentration changes of relevant agents (here metals) across many months, with a single day resolution.

The aforementioned three points allowed the scientists to discriminate almost perfectly (93% to 100% correct predictions) between healthy and autism affected subjects. Healthy individuals showed a very periodic oscillation of copper and zinc driven by the natural metabolic cycles of the organisms (both copper and zinc are necessary micronutrients being part of the

prosthetic group of enzymes), while pathological cases had a much less regular dynamics of the above metals. This happens in absence of any relevant changes in total amount of the two metals. It is the dynamics - not the dose - that makes the difference.

This crucially important result goes hand-in-hand with very elegant statistical treatment (analysis of twins, repeatability checked with independent data sets in different nations, etc.).

This is a precious paper I suggest to carefully read. A last remark: looking at the list of authors we note a 'collective entity' named 'Emergent Dynamical System Group'. This indicates that Mount Sinai Hospital created a stable team focused on biological systems dynamics: the philosophy that inspires 'Organisms' is here to stay.

References

- Zbilut, J. P., Giuliani, A., & Webber Jr, C. L. 1998 Detecting deterministic signals in exceptionally noisy environments using cross-recurrence quantification *Physics Letters A*, vol 246, no 1-2, pp. 122-128.
- Taubes, Gary, and Charles C. Mann. 1995 Epidemiology faces its limits *Science* vol 269, no. 5221, pp. 164.
- Lioy, Paul J., and Stephen M. Rappaport. 2011 Exposure science and the exposome: an opportunity for coherence in the environmental health sciences *Environmental health perspectives* vol 19, no. 11, a466.2008, *Physics*, Oxford University Press, Oxford, New York.
- 2006, *Metaphysics*, Oxford University Press, Oxford, New York.
- Bechtel, W, 2006, *Discovering cell mechanisms: The creation of modern cell biology*, Cambridge University Press, Cambridge.
- 2007 Biological mechanisms: Organized to maintain autonomy in: FC Boogerd, FJ Bruggerman JS Hofmeyr, HV Westerhoff et al., (eds), *Systems biology: Philosophical foundations*, pp. 269-302. Elsevier, New York.