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The Claude Bernard and Conrad Waddington Legacy: Homeostasis, When Observed for a Very Long Time, is Homeoresis

Alessandro Giuliani[a]*

[a] *Istituto Superiore di Sanità, Rome, Italy*

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

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Takens theorem states a very important issue: the dynamics of any complex system, living in an *n*-dimensional phase space spanned by *n* unknown variables can be reconstructed by considering the temporal evolution of only one of these variables. This temporal evolution (in the form of series of subsequent values registered at equally spaced discrete time points) allows the reconstruction of system attractor dynamics by the method of 'embedding', i.e transforming the series into a multivariate matrix having as rows the subsequent epochs and as columns *n* time lagged copies of the original series at a fixed delay (Broomhead, D. S., & King, G. P. (1986). Extracting qualitative dynamics from experimental data. Physica D: *Nonlinear Phenomena*, 20(2-3), 217-236).

Takens theorem is strictly related to the basic notion of what an organism is: an organized system emerging from the mutual relations among n factors whose 'trajectories in time' keep track of the latent organization of the system itself. The sad news are that time, is both the most relevant and the most neglected dimension in biology. A clear symptom of this paradoxical state of affairs is the existence of a specialist journal, serving a very tiny scientific community, named *Chronobiology International* mainly focused on biological rhythms observed at population (not individual) scale. The simple fact that a *Chronophysics International* journal could not exist (time is deeply embedded in any physical approach to reality and not confined to a small specialist field) tells us of the intrinsic difficulties to face time dimension in biology. The reasons for this lack of consideration are many and go from the difficulty to make regular observations in time in a natural setting for long duration to the extreme fragmentation of biological sciences that considers time at very separated non-communicating scales going from the nano-seconds of molecular dynamics to the millions of years of evolution passing by minutes/hour of physiologic signals and the (often sporadic) observations on development. In this paper, the authors surmount this gap and were able to build a regular embedding matrix at individual organism scale (the only physiologically relevant one) for a period going from birth to 10 years of age regularly sampled on a weekly base. The authors rely on the fact teeth grow in a way similar to the trees with a very regular pattern of deposition of dentine: laser ablation of subsequent layers of dentine and the measurement of elemental composition (zinc, copper, manganese…) on these layers allows to generate long series (around 500 equally spaced points on a weekly basis) of concentration fluctuations for each element. According to Takens theorem, the time series relative to these elements are the image in light of the 'entire metabolic dynamics' of organism (elements are tightly coupled with general metabolism intervening in many crucial reactions as such and as cofactors of essential enzymes) and their dynamics offers a unique way to study 'homeostasis in action' during development.

The authors wisely make use of non linear dynamics tools like Recurrence Quantification analysis (RQA) (Marwan, N., Romano, M. C., Thiel, M., & Kurths, J. (2007). Recurrence plots for the analysis of complex systems. *Physics reports, 438*(5-6), 237-329 and empirical phase space reconstruction (Broomhead and King, 1986) so not to impose any specific physical model to the time evolution. In this way they clearly recognize a development trajectory made of alternation of stasis (quasi-attractors) and transition to other attractors shared by all the healthy individuals analysed. This kind of dynamics was present in both development and post-adolescent (permanent teeth) phases,

When shifting to ALS (Amyotrophic Lateral Sclerosis) the authors demonstrate the patients dynamics get stuck into a single attractor and does not show the homeoresis behaviour of healthy individuals.

The predictive power of their model was very high (AUROC = 0.86) pointing to important clinical application in facing ALS before its clinical onset. Beside the specific result, the relevance of this work resides in the possibility to develop 'dynamics biomarkers' for both research and application so making temporal dimension to enter mainstream biology and filling a dramatic epistemic gap of biological sciences.

References

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