Systems Biology and Scale Relativity

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Background: Systems approaches in biology are as old as physiology founded by William Harvey (Auffray and Noble *Int. J. Mol. Sci.* 2009, *10*, 1658-1669).

Discussion: Two conjectures for systems biology on stochasticity and biological space-time (Auffray et al. *Phil. Trans. R. Soc. Lond.* A 2003, 361:1125-1139).

"We conjecture that biological systems self-organize because they operate as a conjunction between the relatively variable part of a stable organization and the relatively stable part of a *chaotic network of fluctuations*, and in a space with a changing number of dimensions: *biological space-time*."

Question 1: is it possible to complement the four Cartesian precepts of *objectivity, reductionism, causality and exhaustivity* with the four systemic precepts of *contextualisation, relatedness, conditionality and pertinence*? We will argue that this is a necessary condition for systems approaches to biological systems to succeed.

Question 2: what is the nature of the *chaotic network of fluctuations* in self-organizing systems? We will argue that it is an intrinsic and fundamental property that plays a key role in driving the behaviour of biological systems, not simply "noise".

Question 3: can *biological space-time* be formalized in the scale relativity framework? We will discuss the extension of the principle of relativity to scales, and how its associated mathematical tools can help modelling and understanding biological systems, and resolve theoretically and practically the problem of integration across multiple scales and levels of organisation in biological systems (Auffray and Nottale, *Progr Biophys Mol Biol* 2008, 97:79-114; Nottale and Auffray *Progr Biophys Mol Biol* 2008, 97:115-157).

Origins of systems biology in William Harvey's masterpiece on the movement of the heart and the blood in animals.

Charles Auffray and Denis Noble. *Int. J. Mol. Sci.* 2009, *10*, 1658-1669.

In this article we continue our exploration of the historical roots of systems biology by considering the work of William Harvey. Central arguments in his work on the movement of the heart and the circulation of the blood can be shown to presage the concepts and methods of integrative systems biology. These include: (a) the analysis of the level of biological organization at which a function (e.g. cardiac rhythm) can be said to occur; (b) the use of quantitative mathematical modelling to generate testable hypotheses and deduce a fundamental physiological principle (the circulation of the blood) and (c) the iterative submission of his predictions to an experimental test. This article is the result of a tri-lingual study: as Harvey's masterpiece was published in Latin in 1628, we have checked the original edition and compared it with and between the English and French translations, some of which are given as notes to inform the reader of differences in interpretation.

Self-organized living systems: conjunction of a stable organization with chaotic fluctuations in biological space-time

Charles Auffray, Sandrine Imbeaud, Magali Roux-Rouquie and Leroy Hood
Phil. Trans. R. Soc. Lond. A 2003, 361:1125-1139.

Living systems have paradoxical thermodynamic stability, the intrinsic property of self-organization, fluctuation and adaptation to their changing environment. Knowledge accumulated in the analytical reductionist framework has provided useful systematic descriptions of biological systems which appear to be insufficient to gain deep understanding of their behaviour in physiologic conditions and diseases. A state-of-the-art functional genomics study in yeast points to the current inability to appraise 'biological noise', leading to focus on few genes, transcripts and proteins subject to major detectable changes, while currently inaccessible small fluctuations may be major determinants of the behaviour of biological systems. We conjecture that biological systems self-organize because they operate as a conjunction between the relatively variable part of a stable organization and the relatively stable part of a chaotic network of fluctuations, and in a space with a changing number of dimensions: biological space-time. We propose to complement the precepts of the analytical reductionist framework with those of the biosystemic paradigm, in order to explore these conjectures for systems biology, combining in an iterative mode systemic modelling of biological systems, to generate hypotheses, with a high level of standardization of high-throughput experimental platforms, enabling detection of small changes of low-intensity signals, to test them.

Scale relativity theory and integrative systems biology:

1 Founding principles and scale laws.

Charles Auffray and Laurent Nottale
Progr Biophys Mol Biol 2008, 97:79-114.

In these two companion papers, we provide an overview and a brief history of the multiple roots, current developments and recent advances of integrative systems biology and identify multiscale integration as its grand challenge. Then we introduce the fundamental principles and the successive steps that have been followed in the construction of the scale relativity theory, and discuss how scale laws of increasing complexity can be used to model and understand the behaviour of complex biological systems. In scale relativity theory, the geometry of space is considered to be continuous but non-differentiable, therefore fractal (i.e., explicitly scale-dependent). One writes the equations of motion in such a space as geodesics equations, under the constraint of the principle of relativity of all scales in nature. To this purpose, covariant derivatives are constructed that implement the various effects of the non-differentiable and fractal geometry. In this first review paper, the scale laws that describe the new dependence on resolutions of physical quantities are obtained as solutions of differential equations acting in the scale space. This leads to several possible levels of description for these laws, from the simplest scale invariant laws to generalized laws with variable fractal dimensions. Initial applications of these laws to the study of species evolution, embryogenesis and cell confinement are discussed.

2 Macroscopic quantum-type mechanics

Laurent Nottale and Charles Auffray
Progr Biophys Mol Biol 2008, 97:115-157.

The first paper of this series was devoted, in this new framework, to the construction from first principles of scale laws of increasing complexity, and to the discussion of some tentative applications of these laws to biological systems. In this second review and perspective paper, we describe the effects induced by the internal fractal structures of trajectories on motion in standard space. Their main consequence is the transformation of classical dynamics into a generalized, quantum-like self-organized dynamics. A Schrödinger-type equation is derived as an integral of the geodesic equation in a fractal space. We then indicate how gauge fields can be constructed from a geometric re-interpretation of gauge transformations as scale transformations in fractal space–time. Finally, we introduce a new tentative development of the theory, in which quantum laws would hold also in scale space, introducing complexergy as a measure of organizational complexity. Initial possible applications of this extended framework to the processes of morphogenesis and the emergence of prokaryotic and eukaryotic cellular structures are discussed. Having founded elements of the evolutionary, developmental, biochemical and cellular theories on the first principles of scale relativity theory, we introduce proposals for the construction of an integrative theory of life and for the design and implementation of novel macroscopic quantum-type experiments and devices, and discuss their potential applications for the analysis, engineering and management of physical and biological systems and properties, and the consequences for the organization of transdisciplinary research and the scientific curriculum in the context of the Systemoscope Consortium research and development agenda.