



Original articles

The future of computational biomedicine: Complex systems thinking

Marcel Joly*, Patrícia H.C. Rondó

Nutrition Department, Public Health School, University of São Paulo, São Paulo SP 01246-904, Brazil

Received 23 December 2014; received in revised form 26 May 2015; accepted 24 June 2015
Available online 17 July 2015

Highlights

- We are confronted to problems that would have been unthinkable just a few years ago.
- The study of the biomedical problems has become difficult and “complex”.
- What is new is the power of the whole, not the components.
- Systems thinking emerges as a foundational underpinning of modern bioinformatics.

Abstract

“More is different” (Philip W. Anderson). Complex systems thinking become instrumental for the modern understanding basis of life sciences in general and, hence, medicine and public health. In this perspective paper, we discuss recent literature and invite readers to explore the utility of complex thinking to properly addressing the constrained-based analysis of high-profile open questions in biomedicine with straightforward implications on public health. Recommendations are then proposed to encourage new multidisciplinary teams to come together in a timely manner in response to novel challenges in the theoretical physiology arena. We conclude that there is the need for far greater attention to the issue of complexity to aptly cope with a new array of problems that would have been unthinkable just a few years ago.

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Keywords: Complexity; Emergentism; Health; Systems biology; Systems theory

1. From *industriepalast* to systems biology

Philosophy¹ underlies all scientific endeavors. As early as 1920’s, in an insightful work that mirrored the technical and cultural state of development of Germany during the Weimar Republic, Fritz Kahn envisioned the human being in the form of an *industriepalast* (*industrial palace*) [63]. At that time, the novel idea of realizing a complex physiological system as an industrial chemical plant conveyed a simple, nevertheless paradigm-breaking message: *the human body is a collection of connected processes* [1] (Fig. 1, panels A and B).

* Correspondence to: Process Control and Simulation Laboratory, Chemical Engineering Department, University of São Paulo, São Paulo SP 05508-900, Brazil. Tel.: +55 11 3523 9819; fax: +55 11 3061 7867.

E-mail addresses: mjoly@usp.br (M. Joly), phcrondo@usp.br (P.H.C. Rondó).

¹ Abbreviations: AIDS, acquired immunodeficiency syndrome; DOHaD, developmental origins of health and disease; DNA, deoxyribonucleic acid, FFE, far-from equilibrium; HAART, highly active antiretroviral therapy, HIV, human immunodeficiency virus; NCD, non-communicable diseases; RNA, ribonucleic acid; V_A, vitamin A.

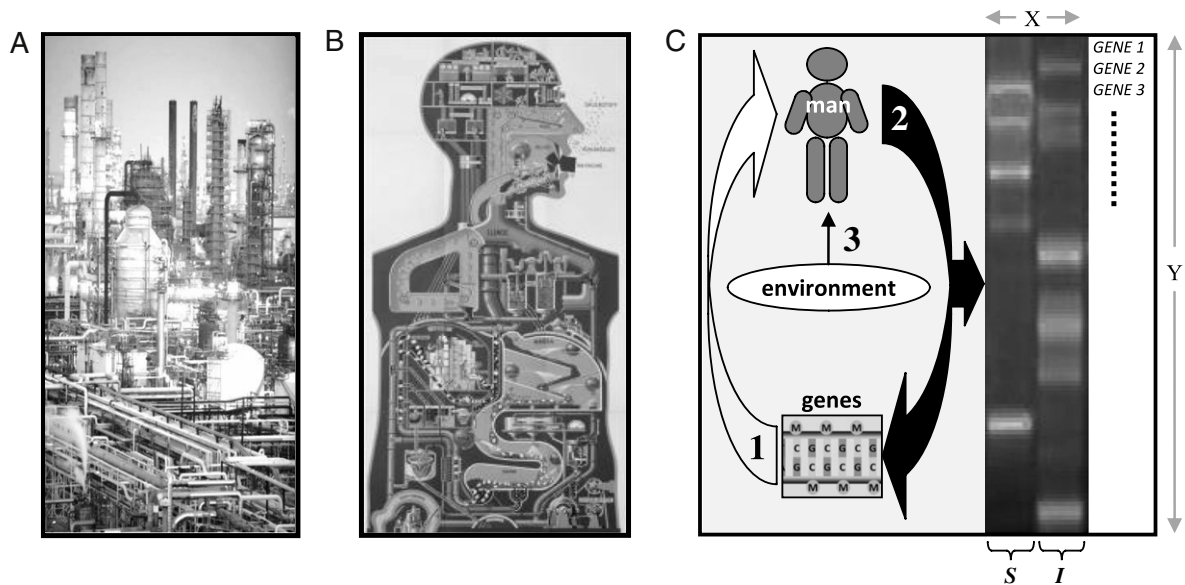


Fig. 1. What do chemical plants, the human body and metabolic pathways have in common? By sharing similar network structures (see [101]) – hub oligarchy – these systems are unusually organized, optimized and robust (see [40,103]). Panels A and B: in a period during which psychology was dominated by a conception which may be epitomized as the robot model of human behavior, the synthesis of the first two examples (panels A and B) induced the doctrinaire realization by Dr. Kahn of the man as an *industrial palace*: ‘the most competent machine in the world’ [63] (source: <http://www.nlm.nih.gov>). Panel C: philosophical underpinnings of systems biology involve antagonistic streams (see [95]). The preponderance of network models inspired by a reductionist, bottom-up view in which transmission of information is one way from DNA to the whole organism (the so called ‘*upward causation model*’; arrow 1) seems to neglect the importance of bidirectional interactions across spatial scales and domains, as proposed by organicist approaches (or ‘*downward causation models*’; arrows 1 and 2) [95]. In fact, higher levels in biological systems impose boundary conditions on the lower levels (arrow 2) [95]. Examples include triggering of cell signaling (e.g., hormonal regulation of cellular mechanisms by the endocrine system; see Fig. 15) and socioenvironmental controls of gene expression. This is conceptually illustrated in the most right panel where distinct socioenvironmental conditions (X axis) impose differentiated regulation of gene expression (Y axis) (see [30]). Abbreviations: S , solitary individual; I , socially integrated individual.

And much has happened since those charming, but disruptive years. Astonishing scientific progresses in biotechnology, molecular biology, information technology, and mathematical approaches and techniques (e.g., [65,132]) were conjugated to an avalanche of evolutionary and functional information from genome sequences. This has not only expanded – in an unprecedented way – the possibilities of mathematical modeling in applied research in life sciences in general, and biology in particular, but also has made initial philosophical forays [12] into novel systems approaches a reality. A prime example is *systems biology* (the systematic study of complex interactions in biological systems [37,67,68]), “a ‘reincarnation’ of *systems theory* (the study of organization and behavior *per se* [15]) applied in biology” [137].

Everything is connected to everything else, and it seems therefore that a basic problem posed to modern science – irrespective of its dominion – is a general theory of organization. Many natural (e.g., metabolic pathways) and artificial (e.g., the Internet) systems can be seen as networks [3], which provide the context in which components act, including their relationships and interactions [37,103,101]. Networks, in addition, are potentially characterized by a central property of complex systems – *emergence* – a notorious philosophical concept of art whose origins can be traced back to antiquity.

In his famous, yet controversial statement “the whole is more than the sum of its parts”, Aristotle (384–322 BC) was probably the first person to claim that “more is different”, as contemporarily proclaimed by the condenser-matter physicist and Nobel laureate Philip W. Anderson [47]. This understanding paved the way to define the ontological meaning of emergence, as implicitly stated in “... wholes are so related to their parts that not only does the existence of the whole depend on the orderly cooperation and interdependence of their parts, but the whole exercises a measure of determinative control over its parts” ([110] quoted by [118]). Typically, emergence appears only when the system passes a certain level of complexity. Roughly speaking, emergent entities are those properties that ‘arise’ out of more

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