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Towards a systems level analysis of health and nutrition

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Although theoretical systems analysis has been available for over half a century, the recent advent of omic high-throughput analytical platforms along with the integration of individual tools and technologies has given rise to the field of modern systems biology. Coupled with information technology, bioinformatics, knowledge management and powerful mathematical models, systems biology has opened up new vistas in our understanding of complex biological systems. Currently there are two distinct approaches that include the inductively driven computational systems biology (bottom-up approach) and the deductive data-driven top-down analysis. Such approaches offer enormous potential in the elucidation of disease as well as defining key pathways and networks involved in optimal human health and nutrition. The tools and technologies now available in systems biology analyses offer exciting opportunities to develop the emerging areas of personalized medicine and individual nutritional profiling.

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Introduction

Biological scientists have historically suffered from a paucity of information. The technical difficulties associated with obtaining meaningful quantitative measurements on biological organisms, organs, tissue, cells or organelles under investigation have resulted in limited data output and information content. Furthermore, this reductionist-driven approach has led only to the development of simple biological models, as well as a rudimentary and incomplete understanding of complex biological systems. In order to overcome this shortage of biological information, scientists in the early 1990s forged the 'decade of measurements'. The advent of genomics was the harbinger of a crescendo of 'Omic Waves'. Genomics and transcriptomics were followed by proteomics, glycoproteomics, metabolomics and metal ionomics. Today, over 400 new omic fields of enquiry exist, ranging from antibodyomics to xenobiomics (see URL: http://omics.org/index.php/ for a complete list). Aside from the neologistic implications, the consequence of this 'Omics Revolution' has been the development of numerous high throughput analytical tools, technologies and platforms that now routinely produce copious and substantial datasets. The development and use of such omic platforms, particularly transcriptomics, proteomics and metabolomics is discussed in much more detail by Kussmann *et al.* [1] in this special section.

Each omic wave has crashed ashore promising new insight and affording unique datasets concerning the complexities of human biology, health, nutrition, physiology and cell biology. As these datasets have been acquired and analyzed, our perspective on biological processes such as homeostasis, disease onset and optimal nutrition appears to have been overly simplistic. For instance, even at the cellular level, simple pathways are highly interconnected, modulated, regulated with built-in redundancy [2,3]. It would appear that in the biological and life sciences, 'as we have learned more, we appear to understand less!' This has led to a radical rethinking about how we go about gathering biological data, and how we process and utilize the resulting information content in order to produce new understanding and knowledge about complex biological processes and systems. The emergence of systems biology, also referred to as pathway, network, or integrative biology, has been one attempt to address such pressing issues [2–6]. While this nascent field has attracted considerable attention and effort, a question remains as to whether such an approach can offer new insight into the complexities of human health, disease and nutrition.

Systems biology

Brief history

Recently, systems biology has been referred to as '*en vogue*' [7] and a 'burgeoning field' [8]. These comments were published in the journals *Nature Reviews-Molecular Cell Biology* plus *Nature Cell Biology* (joint supplement) and *Current Opinions in Biotechnology*, respectively. Both editorials captured the intense excitement and activity that is occurring in systems biology today. However, it should be noted that this field is still very much in its infancy. In its first generational incarnation, a systems approach to biology was predicated on theoretical considerations of complex systems analyses. Weiner introduced mathematical models of complex systems control and communication in the 1940s [9]. However, von Bertalanffys wrote in 1928 that "... a [system consists of] a

dynamic order of parts and processes standing in mutual interaction... the fundamental task of biology is the discovery of the laws of biochemical systems'', and he ultimately went onto develop General Systems Theory [10]. In the 1960s and 1970s, Biochemical Systems Theory and Metabolic Control Theory (also now known as Metabolic Control Analysis) attempted to create simple mathematical models of biological systems [11,12]. Such a systems level approach was not able to connect to the then experimental molecular sciences until the availability of quantitative molecular data provided by omic platforms developed in the 1990s [13].

Current status

Second generation systems biology has its roots in omic measurement capability, bioinformatics, metabolic engineering, computational sciences and mathematics. It is an attempt to establish a more integrated and hierarchical paradigm that facilitates the creation of new biological pathways and networks at the cellular level [6]. This should provide a framework for understanding the holistic system of genetic, genomic, protein, metabolite and cellular events that are in flux and interdependent. In order to facilitate such efforts, two distinct approaches have evolved, namely computationally based systems biology [2,14,15] and data-derived systems biology [16,17,18•]. The former relies primarily on computational modelling and simulation tools. While there has been some confusion in the past about terminology it is also now referred to 'bottom-up' systems biology [19]. The latter approach predominantly utilizes datasets that are mined in a discovery manner for new knowledge using a variety of bioinformatics and knowledge assembly tools and is now categorized as 'top-down' systems biology [19].

Bottom-up systems biology initiates the analysis of the system from its constitutive elements. These parts are then integrated and formulated in order to predict systems behaviour. The ultimate goal of this approach is to combine pathway models into a global model for the entire system under consideration. This deductive approach was pioneered by Kitano [2,4]. He defined four essential elements needed for systems biology to be useful, and they include systems structure identification, systems behaviour analysis, systems control and systems design [2]. More recently he has extended this to include the importance of biological robustness in systems biology [20]. He defines biological robustness as ''... a property that allows a system to maintain its functions against internal and external perturbations''. As this approach has evolved, the basic biological model is augmented by incorporation of additional processes containing more mechanistic detail. This is exemplified in the combined modelling and experimental work of Lauffenburger and Sorger on cell signalling in general and signal transduction pathways in particular [21•], as well as Michels and co-workers modelling the central carbon metabolism of *Trypanosoma brucei* [22].

The development of top-down systems biology had to await the advent of the omic revolution and the availability of high throughput platform analysis. However, it has now ''emerged as [the] new and dominant method'' [23••]. This inductive approach attempts to define and determine new molecular mechanisms employing integrated data acquisition, analysis, combination and correlation [17]. Iteration of this process should result in the formulation of new hypotheses ''... concerning co-regulation and inter-regulation of groups of those molecules. These hypotheses then predict new correlations, which can be tested in new rounds of experiments or by further biochemical analyses'' [23••]. Data-driven systems biology has been championed by Hood [16] and Naylor and co-workers [17,24,25]. Both have attempted to develop a more applied methodology for systems biology analysis. They have used a variety of omic platforms in concert with sophisticated statistical, bioinformatics and knowledge assembly tools to transform the discovery process by studying, in parallel, complex relationships among genetic, genomic, proteomic and metabolic pathway and networks. This approach has been further refined and more recently has been used to investigate a number of complex biological problems involving clinical aspects of Alzheimer's disease, drug efficacy and animal toxicity [18•].

Definition and process

In 1964, US Supreme Court Justice Potter Stewart attempted to define hard-core pornography by saying ''I shall not today attempt further to define the kinds of material I understand to be embraced ... *but I know it when I see it*''. Partly this same conundrum of definition applies to systems biology today. A specific definition of systems biology appears to vary as a function of the expertise of the individual pontificating on the issue. Partly the lack of a clear definition for systems biology is due to a number of factors and includes the fact that the practitioners of systems biology come from a multitude of scientific disciplines with their own scientific-centric perspective. A consequence of this fact is that the language of systems biology, needs to cross numerous scientific disciplines and therefore be standardized. Historically, standards or common language formats have emerged as necessitated by demand. Examples of such established standards include a Hypertext Transport Protocol (HTTP) and an Extensible Markup Language (XML) for structuring data. In systems biology a number of data standards relevant to systems biology have emerged and include Gene Ontology (GO) for describing gene function1, Minimum Information About a Microarray Experiment for describing microarray experiments, Systems Biology Markup Language (SBML) and Cell Markup Language (CellML) for describing biomolecular