

Chapter 2

Systems Biology: Unravelling Molecular Complexity in Health and Disease

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2.1 Introduction

Complexity in a biological system arises from a constant and dynamic interaction between different components of a living system which leads to non-linear perturbations [1]. As such, efforts to improve quality and efficacy of medical care are inextricably linked to complexity science and monitoring variability at both the level of the population and the individual [2]. Systems thinking, therefore, encompasses a holistic understanding of how things influence one another systemically [3]. In nature, examples of systems thinking include ecosystems in which various elements such as air, water, plants, and animals work together to survive or perish.

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In organizations, systems consist not only of people, but also the structures, and processes that combine to make the enterprise healthy, or unhealthy. To date, traditional healthcare relies on treatment methods that are typically focused on speciality care, or one organ system at a time (e.g. cardiology or urology). This classic approach, however, does not always yield optimal results since it does not account for the complex and often subtle interactions between organ systems, arising from the micro-environment within and surrounding a diseased organ, and the influence of more general environmental modulators. These interactions are especially evident in the complex physiologies associated with cancer and Alzheimer's disease, that take decades to develop [4, 5]. Thus, focusing research efforts, drug development strategies, and treatment modalities on one component of the system rather than the sum of the interacting parts is likely to blind us to the operating disease mechanisms. Complexity science is based on the premise that health and disease result from non-linear interactions between the somatic, psychological, social and cognitive dimensions of life. In the example of Alzheimer's disease, while preferentially displaying anatomical localization, its inherent systemic characteristics are evident in the pre-clinical stages and recognized using comprehensive molecular phenotyping approaches [6]. Such a complex system has multiple parts, with a variety of combinations between the entities: One part may interact with multiple adjacent or remote parts; one part may provide multiple functional capabilities; and/or, many parts providing singular overlapping functions. In such a complex biological system, each component part may respond differently to a variety of environmental stimuli. Such a differential response is based on either a set of intrinsic phenotypic operating rules that help shape how extrinsic influences affect the specific component part, or the direct alteration of phenotype by the extrinsic effects. In a biochemical system, for example, such an extrinsic effect could lead to modulation of metabolic pathways that would ultimately result in an altered phenotype for a component of or the entire organism. Several studies have shown that the ageing process not only leads to structural and functional modifications of individual components of the central nervous system, as well as the musculoskeletal system, but also in a system-wide re-wiring of interactions within and between the different levels and functional domains [7, 8]. Examining and treating different biological components in isolation, therefore, leads to loss of important context and information about the relationships that exist between the specific component and the entire system. Complexity science encourages researchers, medical educators and clinicians to incorporate a more holistic view of the human biological system for more accurate diagnostic and efficacious therapeutic purposes [9].

2.2 Holism: An Imperative for the Twenty-First Century

The concept of holism is based on the premise that the whole is more than the sum of its parts. To understand the entire system, therefore, you must also appreciate the intricate inter-relationships between components, in addition to understanding each

individual component. Understanding a complex system, therefore, is best directed to the level of governing principles influencing the behavior of the whole system, and not at the level of the structure and function of its component parts [10]. Thus, a holistic concept involves the study of the structure and dynamics of interacting components, forming networks at multiple levels, including molecular, cellular, organ, person, family, community and society. For the complex biological system existing in humans, the systemic interactions observed provide evidence for nearly constant change and increased uncertainty. Health and disease states, therefore, result from variations within physiological pathways resulting from a complex series of gene/environment interactions [11].

2.2.1 Disease Complexity: Malfunction of Molecular Networks

The P4 (Predictive, Preventive, Participatory, Personalized) medicine paradigm involves comprehensive understanding of regulation and dysregulation of complex molecular networks that dictate the phenotype of an individual [12]. Disease can be perceived as a consequence of aberrant reprogramming of cellular and molecular networks that lead to organ dysfunction. The interaction of the diseased organ with the entire being often leads to a cascade of multiple dysregulated networks, resulting in associated disease co-morbidities. Systems medicine aims to characterize specific perturbations resulting from alterations in genomic expression and metabolic networks that identify the inter-individual differences that augment or detract from monitoring responses to therapy. The information obtained from analyzing big data is likely to significantly decrease health care costs by personalizing care and treating the specific causes rather than the symptoms of disease [13]. Recent technological advances in genomic, proteomic and metabolomic technologies have provided researchers with unprecedented leverage in interrogating different levels of cellular expression. With the requisite bioinformatic integration of these data together with the individual clinical and social demographic strata of information, perturbations within the complex system can truly be developed on an individual basis, approaching the *cura personalis* goal.

2.2.2 Ethical Complexities in Systems Medicine

The systems biological approaches afforded by the technological advances seen in the twenty-first century have the potential to revolutionize healthcare and specifically the approach to patient care, in positive and negative ways. Both ramifications, together with an open and broad dialogue of specific issues raised by various technological advances, will minimize the risk to the “*primum non nocere*; first, do no harm” medical credo. The exploding knowledge base, mechanistic understanding,

and technological advances provided through investigations in network biology are impacting society's ability to interdict in various disease states and promote well-being. Unfortunately, such rapid advances in molecular methods are transforming the caring art of medicine, more and more, into an exact, often impersonal science. Caregivers must continue to pay attention to keeping the patient and their family foremost in consideration when novel diagnostic and therapeutic options are being proposed for development and implementation. As per the systems approach in general, it is important to remember that there are complex interactions within the entire person and to their surrounding environment (e.g. family and friends, co-workers, employer) related directly to options and actions we may offer as healthcare providers. In certain cases, having the capability of offering a diagnostic or treatment doesn't necessarily translate into a single right answer. An example could include an elderly individual with severe spinal pathology making it more difficult or impossible for them to walk, due to weakness or pain. Although surgical treatment options for their spinal pathology are present, should they be offered to that specific patient? Certain diagnostics and treatments need to be weighed as to their overall effects on the system (patient + environment), risks, best/worse case scenarios, and not just related to a specific disease or condition. The moral dilemmas and complex approaches required for achieving a determination of proper conduct in these situations are growing in parallel with the sophisticated innovations in science. Recent minimally invasive biomarkers for Alzheimer's disease are being developed and provide highly accurate measures of risk of developing the disease in asymptomatic subjects. What are the important issues to consider prior to offering such a test to a person, especially in the current environment where there are no viable therapeutic options to offer? Furthermore, how will the diagnosis affect the individual with regard to future planning, end of life decisions, and their concept of personhood? Approaches to ethics and ethical patterns of behavior will require expanded consideration and implementation in dealing with the growing complexities in healthcare arising from our scientific and technological advances. The holistic approach to systems biology demands it.

2.2.3 Improving Healthcare Through Complexity Science

Improving prevention and treatment of a given pathophysiology depends on increasing knowledge of the pathogenic basis with the promise of personalizing interventions based on an intimate knowledge of individual and their environment. It is broadly stated that the "omics" technologies will enable personalized medicine, and reverse the scourge of poor health care outcomes arising from inter-individual heterogeneity. Fundamental questions remain, however, as to how personalized medicine can be enabled, and how implementation of personalized medicine might augment the evolution to customized therapeutics. Significant questions remain unanswered pertaining to the correlation of complex disease onset, progression, and prognosis, and the underlying genetic and environmental influences, as well

as the role of the microbiome. Conversely, the identification and characterization of therapeutic- or nutritional-responsive gene expression and metabolism that could lead to restoration of homeostasis requires a concerted research effort. Specifically, how does gene expression and metabolism differ qualitatively and quantitatively in health and disease? What can a systems approach reveal about the gene–environment interaction? What are the earliest anticipatory changes that can be detected to help predict the risk of disease development? What are the key intracellular and extracellular nutritionally dependent signals that trigger disease onset? The integration of data obtained from different “omics” technologies is likely to provide a roadmap for pathway-based responses that may be more effectively employed in the clinical management of a given disease phenotype. From a clinician’s point of view, by encountering the full spectrum of variability in response to specific treatment in patient population with similar disease presentation, a patient-centric systems medicine approach is likely to address why some individuals respond to therapy while others do not [14]. The goal of achieving an integrated data portal containing clinical, environmental, family history, pathology, and molecular data would provide greater depth of information, leading to more thoughtful and comprehensive treatment and care decisions under the “personalized medicine” paradigm [15, 16]. By integrating a variety of clinical and molecular data elements, and facilitating rapid analysis thereof, the practice of systems medicine will be enabled in future clinical settings, including personalized strategies for disease prevention and modification. The ultimate goal of such approaches would be advanced within a population health paradigm that incorporates such data acquisition and consideration for each individual, from cradle to grave, for the benefits provided to the individual and society as a whole.

2.3 Experimental Design for Systems Biology

In recent decades, several clinical cohort and studies using animal models have utilized various “omics” approaches for dissecting dysregulated molecular networks in health and disease. The results of these studies, however, are challenging to interpret and compare due to biological, analytical and pre-analytical variability [17]. Contributing factors to the intra- and inter-individual biological variability include environmental factors (e.g. diet, lifestyle), circadian rhythm, biological age, genetics, epigenetic factors and differences in the microbiome [18–22]. In recently reported blood and urine studies using human cohorts [23, 24], substantial intra-individual variability was found for several biomarkers, thereby diminishing the power to detect disease associations. While this variability may be less problematic when using inbred strains of animals for models, especially with controlled diet and environment, it is not absent [18, 25]. Results from mouse or other animal models [26], however, are not always predictable for human based applications and hence human clinical investigations are critical for developing biomarkers that can be validated in independent cohorts and ultimately be developed for clinical use.

Other confounds exist and need to be controlled even with clinically defined biological data, for proper interpretation. Pre-analytical variability is caused by inconsistency in sample collection and storage procedures. Analytical variability arises primarily within the diagnostic laboratory and from institutional differences in standard operating procedures. Both of these components of overall variability typically lead to a decrease in signal to noise ratio [17]. Thus the importance of study design that accounts and controls for these variables cannot be over-emphasized. Standard protocols have been proposed for different types of investigations and there have been calls for a central reporting database for investigators, that would detail various contamination parameters (e.g. the presence of blood in tissues), sample stability in storage, and possible changes in the properties of the analytical system accounting for batch to batch inconsistencies [27]. Furthermore, the challenge of comparing data from different batches affects many, if not all, high-throughput methods [28]. In addition data acquisition should include randomization of cases and controls [27, 28], and the use of pooled quality controls interspersed throughout the batch acquisition course of the run [27] so as to generate high quality data. In summary, experimental study design that minimizes pre- and post-analytic variables would ultimately lead to meaningful data with potential clinical relevance and utility [29].

2.4 Conclusions

It is evident that human physiology is remarkably flexible owing to evolutionarily selected, inherent compensatory mechanisms. It remains to be seen whether human behavioral biology can also respond positively to the changes required for a truly holistic approach to medicine. Such a transition from the conventional to the holistic, as described in this chapter is likely to result in marked improvements in healthcare delivery. Even when an individual is asymptomatic, the dysregulation of molecular networks or dysfunctional interactions between system components that eventually leads to organ malfunction or a diseased phenotype, may be accessible to our diagnostic queries. A full understanding of complex disorders such as cancer or neuro-degenerative diseases requires a comprehensive analysis of all of the factors that ultimately dictate the specific phenotype. It is increasingly evident that such an approach includes many factors beyond the genome. A systems medicine strategy to understanding human disease will requisitely analyze the combined impact of biological, environmental, ethical and socio-economic factors on disease progression. Identification of individual biomarkers, or more likely collections of orthogonal biomarkers, associated in certain cases with specific environmental factors, will allow diagnosis of disease stage, and prediction of therapeutic success or failure for certain interventions. If successful, such approaches will facilitate adoption of evidence-based clinical strategies that can be broadly applied to the healthcare of individuals as well as populations.

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