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Editorial overview

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Life and living systems, in particular, are fascinating and complex. For example, it is not evident how to breathe life from fundamental laws such as Schrödinger's or Maxwell's equations. The quest for understanding the distinction(s) between living and dead systems has been with humanity since the dawn of civilization if not earlier. The developments in biology since Darwin to the discovery of DNA and the subsequent revolution in molecular biology, including the sequencing of the human genome, have provided us with a growing parts list subserving life. Hence, the emergence of systems biology can, in this perspective, be viewed as a response on how to handle and intellectually come to terms with this staggering complexity, while fundamentally still being driven by the quest for understanding living systems.

Pragmatically, the complexity and the sheer size of the data have driven mainstream biology to adopt new fields such as bioinformatics, computational biology and later systems biology. From a conceptual standpoint this is not novel, since fundamental biology has historically have had deep interactions across fields during certain time-windows, the discovery of the DNA helix and the elucidation of the action potential are two prominent examples. Yet, since systems biology has a good share of its intellectual roots in what could be referred to as difficult (and complementary) areas such as theoretical and mathematical biology, there is still a somewhat conservative stance to whether systems biology is useful or not. The current flurry of activity in systems biology across several core areas in biology such as understanding the cell cycle, cellular differentiation, stem cell biology, regulatory networks, and production of large data-sets in consortia style as in physics, are some examples in our time of such interactions between biology and techniques and quantitative approaches originating outside mainstream biology. These, what could be perceived as *unorthodox* activities, yet leading to insights, top-tier publications, and their related technological spinoffs, are sufficient in our view to support the notion that systems biology is indeed useful. However, one remaining barrier is *to what extent techniques and approaches derived from systems biology are useful for medicine and clinical practice*.

Here in this issue of *Current Opinion in Systems biology* we specifically assess the field using the lens of translational medicine. It is timely since, on the one hand systems biology has matured significantly and is used in numerous publications and on the other hand we have witnessed an increased number of studies targeting medical challenges, ranging from

deeper analysis of biomarkers for diagnosis, prognosis, response to therapy, to the elucidation of mechanisms of disease. This issue covers discussions and updates from leading investigators who here delineate current expectations and challenges as derived from their experiences using systems biology approaches in a clinical or translational context. Collectively, the suite of papers addresses the question of what is the real impact of systems biology in clinical applications and, most importantly, what would be useful modifications and advances to further propel systems biology toward becoming a translational reality.

The initial discussion targets the health of systems biology itself. First, systems biology research uses a holistic approach to investigate and elucidate how biological systems work. Secondly, systems biology was described in 2002 Kitano's view as a continuous cycle combining mathematical models generating predictions, experiments testing such predictions, and results from the experiments to be used for updating mathematical models. While systems biology was not such-a-well-known area prior Kitano's influential 2002 review, it has certainly matured over the past 15 years in its applications, methodologies, computational resources and design of synthetic systems. It is, therefore, timely to review the current state-of-the-art and challenges using Kitano's review as a reference point (Gomez-Cabrero and Tegner). Importantly, systems biology has expanded beyond understanding biological systems to its more recent applications in clinical research. For instance, systems biology methodologies are routinely used to characterize diseases when novel data-types are being used, such as deep profiling of long non-coding RNAs (lncRNA) (Bonetti et al.) or single-cell analysis of the immune system using, for example, single-cell transcriptomics and single-cell proteomics (Schultze et al.). Conceptually, every disease could be viewed through the lens of a new data-type, be it single cell transcriptomics or lncRNA, and a systems analysis of that (complex) data-type could therefore provide robust biomarkers for diagnostics, prognosis, drug response, and possibly shed some light on the mechanisms of disease.

But beyond using systems biology approaches to analyze disease-related data, the human body can be mathematically modeled as an integrated system considering several types of biochemical, physiological and environmental interactions [1,2]. Such approaches, having roots in physiology (mathematical and theoretical biology), have been further developed in the virtual physiological human framework [3]. Populating such models with richer molecular data targeting diseases specifically is one important hallmark of work often referred to as Systems Medicine. Using a model-based analysis paradigm has been very powerful in providing novel insights into disease mechanisms. Network medicine, for instance, applies tools and concepts from network theory to explain the relation between perturbations on the molecular level and phenotypic disease manifestations (Menche et al.). However, optimal use of network approaches requires a deeper understanding of the nature of the associations beyond a static graph to capture role(s) of disease-associated variants as eloquently argued by (Fuxman et al.). Other applications of systems medicine focus on modeling specific systems associated with the disease and then generating testable hypothesis from the models. Illustrative modeling examples discussed in the current issue are: modeling of post-translational modifications in cancer-related metabolic networks supporting the identification of novel therapeutic targets (Cascante et al.); modeling of the alterations and interactions within the immune system in the context of neurodegeneration as is the case of Multiple Sclerosis (Villoslada et al.); or the modeling the microbiome and microbiome interactions in disease to understand possible causal associations between disease and microbiome (Saeed et al.). Importantly, system approaches are unique tools in the context of, for instance, brain-diseases where access to the brain is possible only post-mortem, and hence investigators find such methodologies very useful for hypothesis generation (Dougherty et al.).

However, despite all recent exciting advances in systems biology and systems medicine, and the applications in clinical studies, a most important question remains: *what is the translational impact of such approaches*? Are these advances in essence only of academic interest or can they actually be useful for clinicians and patients in the end? Drug-repositioning constitutes one of the most important cases where all knowledge and data gathered on drugs and drugs-interactions over the recent years, allows the generation of novel possible uses for existing drugs in a cost-effective manner. The paper by (Aloy et al.) demonstrates the practical utility of these techniques where the uptake of this work by pharmaceutical companies serves as a proxy for real world validation. However, if systems biology has been a paradigm shift evolving over the time proving its value in research and pharmaceutical industry, the paper of (Maier) convincingly makes the argument that another shift of similar magnitude is required to occur in the organization of healthcare and public health to truly become able to deliver systems biology research outcomes in the clinic One first step towards such a change, would be unleashing the access and secondary uses of clinical registry and healthcare data, which is becoming a new Big Data challenge countered by several ethical challenges and constraints (Roca et al.). Here we can anticipate creation of new markets and innovations as large companies are already moving into this space.

In summary, we invite the reader to assess whether the papers presented in this issue provide sufficient evidence to demonstrate a realistic potential of Systems biology and Systems Medicine in clinical applications. However, as argued above, there are still major efforts, in part outside systems biology, in need to be orchestrated that requires a concerted effort involving both clinicians and researchers in an interdisciplinary setting [4], to make systems biology a "*game changer*" in the clinic. Given the current maturity of systems biology and the increasing inroads into the medical and clinical domains, we would not be surprised to observe an increased precision with which systems biology in a sense returns to its intellectual basis, investigating the fundamental dynamics of living systems thus providing fresh fuel to the ancient challenge of what is life [5]. This will undoubtedly further advance systems biology and provide new methods with strong repercussions into our understanding of diseases as perturbations of these very core processes of life.

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