Regulatory Matters

Editorial

In recent years, systems biology is not only being applied in fundamental science but also in drug development and healthcare. The application of real-world data in clinical research generates a large volume of data and information that is difficult to handle without a proper tool to process, decode, and interpret the data. That is where systems biology comes into play. In this article, Arunon Sivananthan introduces the idea of applying systems biology in clinical research and how it may play an important role in facilitating the process of drug development.

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Systems biology and real-world data as drivers of change in drug research and development

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Introduction

Research and development of drugs for polygenic diseases is complex, time-consuming, and has a high attrition rate.[1] Drug attrition is in part related to genetic heterogeneity, multifaceted pathophysiology, and complex environmental conditions that are difficult to reproduce within the context of randomised controlled trials (RCTs). Whilst RCTs have been instrumental in establishing the efficacy and safety of drugs since the 1960s.[2,3] RCTs are time-consuming, costly, and have limited applicability in clinical practice.

Studies into human physiology over the past several decades have developed qualitative understanding of the intracellular molecular interactions to whole-body phenotypic responses. Earlier reductionist approaches usually took the form of the "single path transduction model", which described the interactions of single drugs with a single receptor, thereby facilitating the discovery of ground-breaking drugs like propranolol or cimetidine.[4] Recently, advances in genetics, molecular, and systems biology techniques is fuelling the latest paradigm shift in drug development towards the use of "biological network transduction models" to analyse the effect that drugs have on biological networks through multiple interactions.

Systems biology uses a collection of quantitative experimental and computational methods to reveal the information flow between the genes, proteins, and metabolites essential in the functional pathways that exist among cells, tissues, organs, and organismal-level phenotypes. Systems biology helps to develop an understanding of the functional units contributing to disease phenotypes, ultimately leading to the identification of molecular mechanisms of drug action, and the design of therapeutic strategies that modify disease processes instead of simply controlling symptoms.[5]

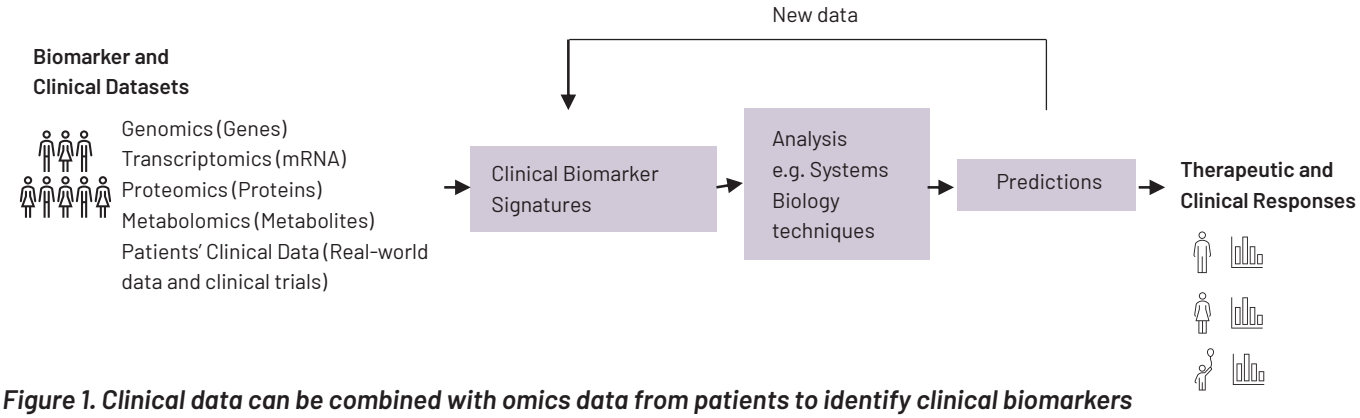
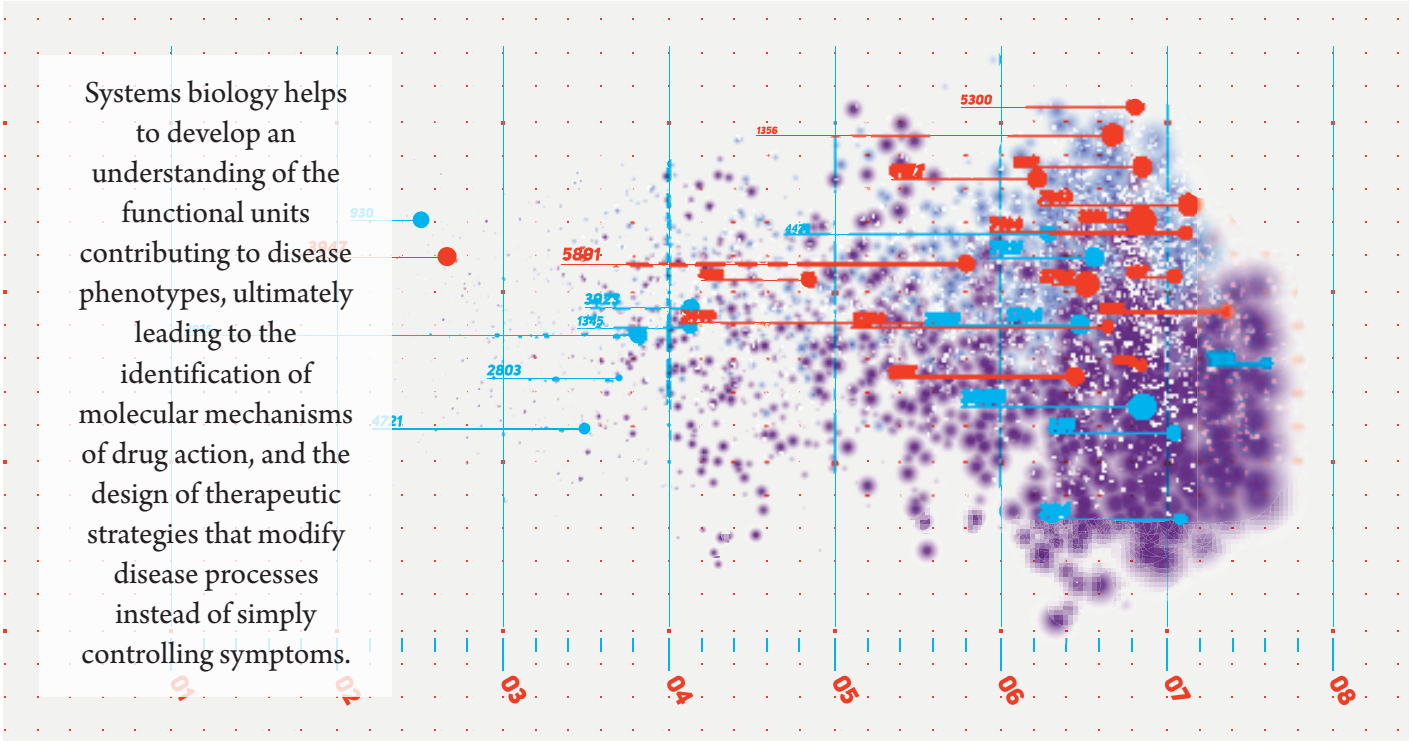


Figure 1. Clinical data can be combined with omics data from patients to identify clinical biomarkers
Using systems biology techniques in the analysis, these clinical biomarkers inform the construction of predictive models of disease course and patient response to therapy, thereby helping to form and update the biological model.



This article discusses the role of systems biology techniques in identifying and describing disease phenotypes, and the application of real-world data (RWD) and systems biology techniques to aid drug development.

The role of systems biology techniques in disease characterisation

The fundamental principle of systems biology is that any biological phenotype of interest to the study of human physiology is the outcome of a multitude of molecular interactions.[6] These molecular interactions can occur at any one time at and between the cellular-, tissue-, organ-, and organismal-levels.[6] Diseases are the result of disturbed molecular interactions, meaning it is essential to investigate numerous interacting partners and analyse the networks for accurate diagnoses and understanding of its mechanisms.[7,8]

Factors that can disrupt or perturb the network may be intrinsic, such as mutations in certain genes, or extrinsic, like environmental cues, to the human system.[9,10] The native network will respond differently to each disruption depending on unique robust characteristics, thereby producing distinct phenotypic responses that constitute a corresponding pathological state.[11] Studies into individual disruptions and development of "biological network transduction models" require investigations at the genomic, transcriptomic, miRNomic, proteomic, and metabolomic levels. Large-scale data collection is made possible with advanced wet-lab technologies such as quantitative polymerase chain reaction (qPCR), mass spectrometry, and next generation sequencing. Fitting the results together to analyse large-scale databases is aided by systems biology techniques.

Real-world data and therapeutic evaluations

Regulatory approval of drugs and medicinal products has shifted its focus to the evaluation of therapeutic interventions based on tailor-made precision treatments in stratified patient populations,[4] which is often supported using RWD. RWD provides long-term data generated from clinical practice that can aid the research and development of therapeutic interventions. A major value of RWD is that they fill knowledge gaps between controlled clinical trials with the information regarding patients' health in clinical practice.

RWD are data and stored information related to the patient's health status derived from a variety of sources such as patient registries, health institutions, social media, and patient-generated data from wearables.[12,13] The analysis of RWD includes the use of systems biology techniques and generates real-world evidence (RWE) for demonstrating drug effectiveness and safety for marketing authorisation and for advancing drug development.[14] Combining RWD with prediction models developed by systems biology can contribute significantly to support regulatory decision-making (Figure 1).[15]

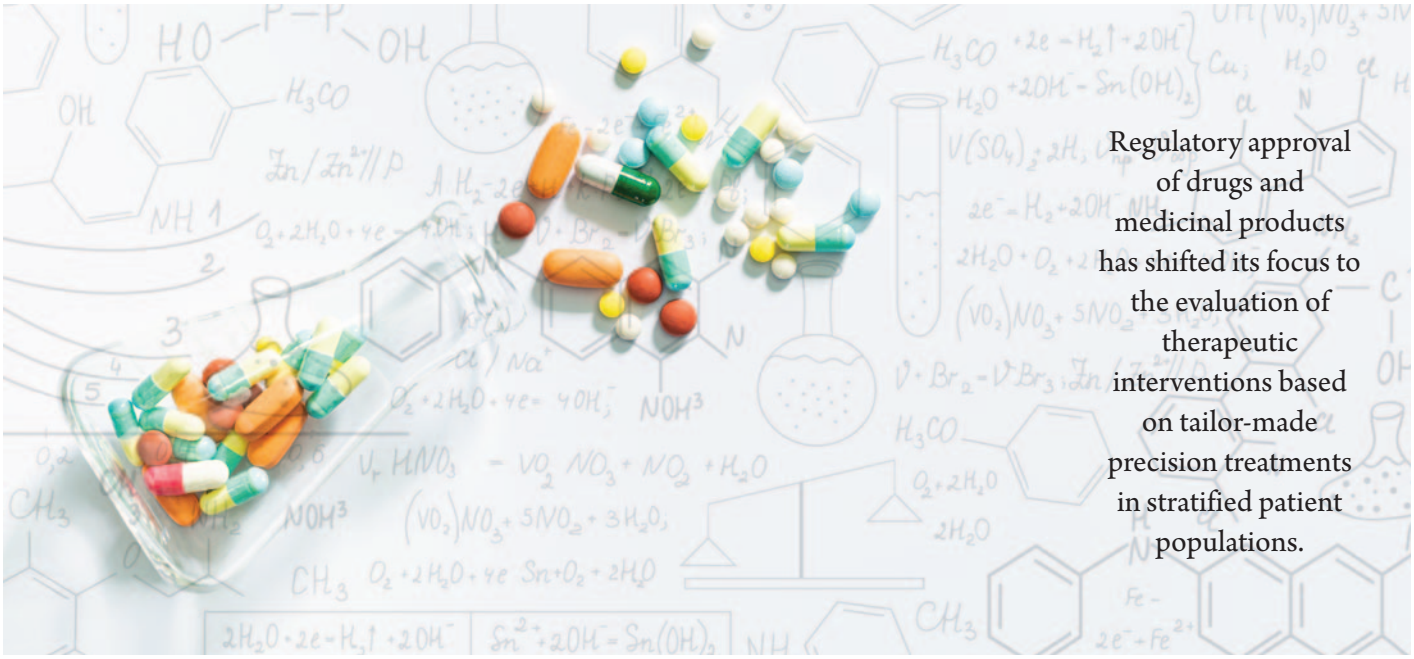
Hybrid study designs incorporating RWD or RWE have been applied in clinical trials for regulatory decision-making. The hybrid study designs were used:[16]

1. for exploratory new drug submissions that use RWE to gain insights to clinical outcome or safety data;
2. as methods for single-arm trials that require external controls; and
3. in clinical trials that need RWE to satisfy post-marketing requirements for additional safety or effectiveness to support a regulatory decision.

Hybrid study designs that are better equipped to capture long-term outcomes should harness methodologies such as decentralisation (e.g. trained nurses), direct-to-patient approaches (e.g. wearables), and databases (e.g. registries, claims).[16]

Systems biology in action

Systems biology approaches have been used to investigate fundamental processes such as metabolic rewiring that determine T cell activation.[17] The value of combining metabolomic and computational approaches have enabled researchers to overcome complex cell regulatory networks that have hindered the discovery of the metabolic requirements of certain biological systems. For example, Puleston,



Regulatory approval of drugs and medicinal products has shifted its focus to the evaluation of therapeutic interventions based on tailor-made precision treatments in stratified patient populations.

et al. (2021)[18] and Wagner, et al. (2021)[19] applied metabolic, computational, and genetic approaches to demonstrate the important role of polyamine metabolism in determining the path of T helper cell fate commitment.

Recently Wimmers et al. (2021)[20] employed a multi-omic approach that used systems biology approaches to assess long-term immune responses to influenza vaccines. These researchers compared the human immune landscape in response to three types of vaccinations, i.e. the trivalent inactivated seasonal influenza vaccine and the avian H5N1 pre-pandemic influenza vaccine with and without an adjuvant. Their analysis involved a comparison of epigenomic imprinting, transcriptional profiles, and chromatin accessibility at single-cell level, as well as cytokine production that respond to viruses at different time points after vaccination. The two key outcomes were: i. epigenetic effects of vaccination lasted 6 months and were more pronounced in innate immune cells; ii. chromatin accessibility to loci mediated by AP-1 transcription factors were reduced over time and correlated with lower production of inflammatory cytokines.

Another example of how systems biology was used in clinical research is illustrated with the pivotal role that the monoclonal antibody daclizumab plays in multiple sclerosis (MS). Daclizumab prevents the formation of the high affinity IL-2 receptor[21,22] and obstructs FoxP3$^+$ T-regulatory cells activity.[23,24] Should this observation be interpreted in a linear, reductionist fashion, a conclusion may be that T-regulatory cells do not play an immunoregulatory role in MS, with negative consequences. In fact, daclizumab also activates the regulatory cell population, CD56^{bright} NK cells,[25] which are part of the same *in vivo* functional network as T-regulatory cells.[24] The steady state of T-regulatory cell activation and proliferation achieved by daclizumab treatment is clearly beneficial for MS patients.

Summary

Systems biology has a positive impact on clinical research by combining and examining data from various omics approaches. The ability to combine large volumes of data using experimental and computational sources enable the development of complex models of molecular interactions. These models can provide valuable insight to aid drug development such as drug/target interactions, drug repositioning, and the identification of novel disease networks.

With the aid of systems biology, the incorporation of RWE plays an important part in developing models that are robust enough to develop our understanding of disease states. Observing the consequences of changes to these models, like genetic mutations or differences in medicinal regimens or target group, may facilitate the process of drug development.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by his employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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