



## Systems biology approach: Panacea for unravelling host-virus interactions and dynamics of vaccine induced immune response



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### ABSTRACT

Systems biology is an interdisciplinary research field in life sciences, which involves a comprehensive and quantitative analysis of the interactions between all of the components of biological systems over time. For the past 50 years the discipline of virology has overly focused on the pathogen itself. However, we now know that the host response is equally or more important in defining the eventual pathological outcome of infection. Systems biology has in recent years been increasingly recognised for its importance to infectious disease research. Host-virus interactions can be better understood by taking into account the dynamical molecular networks that constitute a biological system. To decipher the pathobiological mechanisms of any disease requires a deep knowledge of how multiple and concurrent signal-transduction pathways operate and are deregulated. Hence the intricacies of signalling pathways can be dissected only by system level approaches.

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*Abbreviation:* DNA, deoxyribonucleic acid; RNA, ribonucleic acid; RNA-seq, ribonucleic acid sequencing; SNP, single nucleotide polymorphism; HPI, host pathogen interactions; miRNA, microRNA; PBMC, peripheral blood mononuclear cells.

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## 1. Introduction

*“The whole is more than the sum of its parts.”*

[Aristotle.]

Systems biology is a newly advancing field that uses an interdisciplinary approach aimed at understanding and predicting the properties of a living system through systematic quantification of all its components with intensive mathematical and computational modelling. In systems biology each component of the system is measured using high-throughput ‘omic’ techniques and in theory examined from the cellular level to the whole organism and is thus a holistic rather than reductionist approach. This approach requires the capture and integration of measurements from as many hierarchical levels of information as possible. These can include DNA sequences, RNA and protein measurements, protein–protein and protein–DNA interactions, bio modules, signaling, gene regulatory networks, cells, organs, individuals, populations, and ecologies (Tan et al., 2007). Organisms function in an integrated manner, but biologists have historically studied organisms part by part and celebrated the modern ability to study them molecule by molecule, gene by gene. Biological systems have “emergent properties”: that is, their sum is greater than their individual parts, and the biological outcomes of a system cannot be predicted by traditional reductionist methods that study only the individual components (Zak and Aderem, 2009). Regrettably, ‘systems biology’ is often used as a blanket term, mistakenly referenced in studies utilizing only high-throughput technologies or incorporated into titles to give extra weight or novelty. Integration of multiple high-throughput data types represents just a single dimension of the field necessary to elucidate host responses to infection (Xue and Miller-Jensen, 2012). In the case of systems virology, biological systems may range from virus-infected cells to tissues to whole organisms. Systems biology necessitates a global perspective when investigating infection and this approach to infectious disease research will furnish a greater understanding of the interplay between host and pathogen. Besides, mathematical modelling of interaction networks is essential for researchers to better relate changes at the molecular level to the global properties observed within a biological system during infection. Molecular studies of individual pathways have uncovered many viral host-protein targets; however, it is difficult to predict how viral perturbations will affect the signalling network as a whole (Xue and Miller-Jensen, 2012). Systems biology has the potential to discover novel pro-host therapeutic targets. By providing a more robust overview of the host cellular machinery and its response and interaction with a virus, these kinds of analyses offer inroads toward the development of innovative therapeutics that can act in concert with the host defence mechanism. Mathematical modelling together with documented virus-host interaction data can be used to predict key network components and/or connections (e.g. ‘bottlenecks’) that can then be assessed by introducing targeted perturbations and monitoring the effects of these changes on the network as a whole. Subsequent analysis of model-based predictions using siRNA knockdown studies or knock-out animal models relate model findings to infection phenotypes and disease outcome in these experimental systems, refining models and driving further predictions (Tisoncik and Katze, 2010). More recently, systems biology is being applied to vaccinology, with the goal of understanding the mechanisms by which vaccines stimulate protective immunity, and predicting the immunogenicity or efficacy of vaccines (Morrison and Katze, 2015; Law et al., 2013; Josset et al., 2013; Chakrabarti et al., 2010; De Backer et al., 2010). Several recent studies have attempted to model the dynamic host immune responses to different viruses (Hancioglu et al., 2007; Tchitchek et al., 2013; Morrison and Katze, 2015; Storey et al., 2005; Liquet et al., 2012; Wang et al., 2009; Law et al., 2013; Josset et al., 2013; Bonneau, 2008). Systems biology in a nutshell can be useful in understanding differences in resistance/susceptibility to a particular disease in different species, identifying disease markers, identifying early markers

of infection, prediction of the vaccine efficacy, identifying potential antiviral targets and understanding molecular mechanisms of the host-virus interactions (Chakrabarti et al., 2010; Josset et al., 2013).

### 1.1. Cybernetics and systems biology modeling

Systems biology finds its genesis in the quantitative modeling of enzyme kinetics, the mathematical modeling of population dynamics, the simulations developed to study neurophysiology, control theory and cybernetics. Norbert Wiener in his book “Cybernetics: or Control and Communication in the Animal and the Machine” defined cybernetics in 1948 as the scientific study of control and communication in the animal and the machine. Cybernetics is the study of human/machine interaction guided by the principle that numerous different types of systems can be studied according to principles of feedback, control, and communications. Mechanical analogies and cybernetic systems dominated the principles guiding systems biology modeling and simulation. Gene regulatory networks, metabolic networks, and signal transduction networks are also part of systems biology discourse and work with mechanical systems analogies. This mechanistic analogy is further combined with control theory in this form of systems biology. Control theory is the mathematical study of how to manipulate the parameters affecting the behavior of a system to produce the desired or optimal outcome. Heinz von Foerster, the founder of Biological Computer laboratory in 1958, is attributed as the originator of second order cybernetics. He is involved in studying similarities in cybernetic systems in biology and electronics and is widely known for his doomsday equitation, which predicted future population growth.

### 1.2. Reductionism and Holism

*Organisms function in an integrated manner. But biologists have historically studied organisms part by part and celebrated the modern ability to study them molecule by molecule, gene by gene. Systems biology is “a new science, a critical science of the future that seeks to understand the integration of the pieces to form biological systems”.*

[David Baltimore, Nobel Laureate.]

A fundamental tenet of systems biology is that cellular and organismal constituents are interconnected, so that their structure and dynamics must be examined in intact cells and organisms rather than as isolated parts. The last decade has witnessed a backlash against the reductionism of molecular biology. The philosophical antecedents of holism can be traced back to Aristotle, who is said to have pithily observed, “the whole is more than the sum of its parts.” The holistic host-directed approach stands in contrast to the more traditional reductionist approaches that focus on a pre-determined small set of molecules (genes, proteins or metabolites). Although often criticized for not being hypothesis-driven, systems-level (or discovery-based) analyses are instead increasingly being acknowledged as potent hypothesis generators. Moreover, for dynamical systems such as those involved in the host response to viral infection, systems-level analyses are considered the only way to understand emergent properties; that is, properties or biological outcomes that cannot be predicted by an understanding of the individual parts of a system alone, but rather only become apparent with knowledge of the specific organization and interactions between components. Because of this, systems virology is an essential and synergistic complement to traditional virology approaches (Law et al., 2013). Methodological reductionism and holism are not truly opposed to each other (De Backer et al., 2010). Each approach has its limitations. Reductionism may prevent scientists from recognizing important relationships between components or organisms in their natural settings, appreciating the evolutionary origins of processes and organisms, grasping probabilistic relationships underlying complicated and seemingly chaotic events, or perceiving heterogeneity

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