

TrendsTalk

What Can Immunologists Learn from Systems Approaches?

The field of systems immunology has grown extensively over the past few years, spurred by the generation of large data sets, and new analytical tools and modeling approaches. In this piece and its counterpart in *Cell Systems* (<http://www.cell.com/cell-systems/home>), eight authors discuss what immunologists can learn from systems biology and, conversely, how systems biologists can use immune cells as a model, and outline the many directions in which this interdisciplinary field can expand.



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One reason that 'systems biology' approaches are not more widely appreciated by immunologists comes from a misunderstanding of just what the term means. Some think that probing large 'omic' data sets to find a key gene or pathway is a true systems analysis. I would argue instead that the real value of a systems approach is in the use of quantitative methods that provide insight into how the many 'parts' discovered by multiplex methods cooperate to give emergent behavior; that is, outcomes not obvious from the functions or properties of any single component. Informatic analyses of large data sets do not typically yield direct insight into the operation of host responses or how pieces of the system can be intentionally manipulated to give a predictable outcome. Computational modeling is an approach that can yield such insights. For example, if we are interested in more-rational vaccine design, then quantifying behavior at the key control points that regulate Tfh generation, germinal center development, affinity maturation, the choice between memory B cells and plasma cell fate, or the long-term survival of plasma cells, and computing just how much a change in any of these parameters would affect humoral responses in terms of quality, quantity, and durability would be major steps forward. Basically, I am arguing that systems biology is valuable because it represents a return in modern guise to the older concept of understanding the 'physiology' of a system; for example, gas exchange, renal clearance, cardiac output, based on considering the integrated operation of the various components of the lung, kidney, or heart in a quantitative manner. (These points come from an expanded discussion in [1].)



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While systems biology can mean many things to many people, the immune system clearly relies on several features where systems approaches apply. Quantifying the action of the immune system requires looking at how the whole system interacts with its parts and integrates those components to act in some collective manner. In vertebrates, groups of cells discriminate self from nonself over evolutionary timescales in innate immunity and over the course of a lifetime in adaptive immunity, inviting methods from areas such as the biophysics of molecular interactions and evolutionary dynamics. Immune cells are regulated from positive and negative signals, coming from both within and without the immune system, and this regulation is open to approaches such as information theory, network analysis, and modeling feedback processes. Moreover, molecular features used to recognize pathogens (and avoid self-recognition) can be stored in memory on both evolutionary timescales and over the course of the lifetime of an organism.

One wants to understand these features and integrate them into a framework that makes concrete predictions or discovers new immunology. For instance, class I antigen presentation is maintained by signaling and communication between cell types, involves biophysical mechanisms to process antigens, and is under substantial regulation. Given that this system underlies breakthroughs in cancer immunotherapy, advancing our understanding of its basic function is of great therapeutic consequence.

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For immunologists, this is the golden era of systems approaches, but it is important to clarify that there are two distinct strands that are complementary. In fact, I would argue that one without the other does not reflect the standards of contemporary immunology. Both strands were described in Lee Hood's original vision for Systems Biology in 2001: that systematic measurements of the biological system will enable an understanding of its systems-level properties.

One strand, system-wide or systematic measurements, such as single-cell RNAseq or CyTOF, enables one to characterize all immune cells and quantify their numbers in a given tissue sample in a single-shot experiment; in addition, a variety of imaging modalities are available that provide critical information about cellular spatial and temporal organization and ordering. These pose Big Data challenges of data processing and statistical analytics, which are adding new branches to bioinformatics to develop appropriate software tools, and require immunologists to undergo substantial training in using these software tools just to be able to meaningfully look at the data they generate.

The second strand pertains to the systems level properties; that is, how the immune system is in fact regulated, whether at the intracellular, organ, or organismal scale. Integrating diverse and complex data sets with mechanistic understanding (verified or hypothesized) requires mathematical modeling. There is in fact quite a bit of classic and recent literature on modeling hematopoiesis and development, immune surveillance and responses, inter- and intracellular signaling and epigenetic control, but this is clearly an area that will explode in coming years. Preparing immunology graduate students for the research of the coming decades must include training in dynamical systems modeling as an integral component of articulating hypotheses, interpreting data, and deriving conclusions.

As such, there is everything for immunologists to learn from systems approaches; the key then for immunologists is to embrace the quantitative training of both data analysis and mechanistic dynamical modeling.

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Systems biology complements quantitative experiments with computational models. These models can be used to both explain experimental observations and predict the outcome of experiments not yet tried, the latter of which aids in the generation of new hypotheses. Efforts to use systems approaches to model the immune system are steadily increasing in number. The immune system is an intricate ensemble of specialized cell populations interacting with each other and their environment to tune tissue-level responses, so at first glance it may appear impossible to accurately fit a computational model that captures this complexity. However, the systems biologist views the same complexity and has a different conclusion: the immune system, characterized by many feedback connections and nonlinear responses, is so complex that understanding it is impossible without computational and mathematical modeling complementing experiments. Indeed, as access to large-scale quantitative data sets increases, our ability to understand data through reason and intuition alone becomes limited, while our ability to create more-informative models improves. In addition, when experiments fail to directly prove or disprove a hypothesis, models can increase the value of even these less-informative experiments, because accumulated results can be used to alter and improve the model, generating new insights into how the immune system functions.



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Apart from characterizing the constitutive parts of the immune system, understanding an immune response requires a systems-level approach because we are studying a collective response that involves the interaction of many components at many different scales: receptor diversity, signaling pathways, differentiation dynamics, cell–cell communication, and even evolutionary lymphocyte dynamics. A systems approach has a long tradition in immunology, going back to the ideas of Jerne and Burnett's clonal selection theory, which relies on a pre-existing diverse set of different B and T cells that is constantly updated and modified as immune cells develop, expand, and contract. Despite this theory, an immune response was still largely seen as the expansion and contraction of a handful of specific clones.

Yet, from recent high-throughput repertoire experiments, we now know that the response of immune repertoires occurs at the level of the whole repertoire, and is a true systems-wide response. It is not characterized by the expansion of a single clone that binds the antigen the strongest, but instead the concentration of many different clones changes in ways that we currently do not quantitatively understand. This response is also probabilistic, and largely unique to each individual, even when exposed to the same challenge. The converse of the observed crossreactivity is that many clones can recognize the same pathogen, and each pathogen has many epitopes. It is also important to note that an increase in frequency is not necessarily indicative of a response. For all these reasons, a probabilistic systems approach that considers the repertoire as a whole, responding to a complex antigenic signal, is emerging as key to understanding how the immune system protects us from pathogens.



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Systems biology aims to integrate many aspects of a biological system into a unifying computational model. Large-scale data sets together with innovative analysis tools have brought new insights into the field of cell biology, where researchers analyze genomics, transcriptomics, proteomics, and metabolomics as layers of the same cellular system.

Similar to the 'omics' boom in systems biology, technological advances, such as single cell analysis or immune repertoire sequencing, have opened new avenues in the field of immunology. Large-scale studies have expanded beyond the single organism level and have investigated immune responses in cohorts of hundreds of individuals. Simultaneously, profound leaps have been made on other factors affecting human health, such as the microbiome, microbial metabolites, genetics, and personalized diets.

Despite this progress, our understanding of the interplay between the immune system and other factors is still in its infancy. Just as the overarching view of various 'omics' data sets has advanced our mechanistic knowledge on a cellular level, taking a holistic, multidimensional perspective on immunology alongside other fields will grow our knowledge of the interwoven processes governing human health. A multivariate analysis of immunological data, microbiota composition, genetics, and diet in large human cohorts will help to elucidate the complex orchestration of the human body as a whole and will pave the way for novel therapeutic approaches.

Remarkably diverse types of information can be obtained using systems approaches for the study of immune development, immune responses, and immunological diseases. Systems approaches that focus on gene expression and genomics data sets

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have been used most frequently to establish relationships between cell types. Moreover, by examining gene expression profiles and chromatin landscapes, signaling pathways and transcription factors that carry out diverse immunoregulatory functions can be identified. In addition to developing refined computational tools for characterizing immunological systems, it will be necessary to further advance our understanding of fundamental principles governing gene regulation and signal transduction to fully realize the potential of systems immunology.

Before the genomics revolution, studies were restricted to individual model genes and pathways, with the goal of using these focused studies to uncover mechanistic principles. Current systems approaches rely on principles established by these early studies (e.g., the properties of promoters and enhancers and the components of key signaling pathways), but they are limited by the fact that our knowledge of the principles and underlying logic of gene regulation and signal transduction remain incomplete. Importantly, the same data sets required for conventional systems approaches are central to efforts to uncover the broad mechanistic principles and logic that were beyond the reach of the focused studies of the past.

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Immune system behaviors result from interactions among many components, including cells, genes, and proteins. Thus, systems biology embraces discovering the unknown, from the components to the interactions among them, by using modern technologies, such as single cell transcriptomics to identify novel cell populations and states, and ChIP-seq to map intracellular transcriptional networks. To achieve a predictive, quantitative understanding, the mathematical parameters governing interactions among the components are also needed. Therefore, systems biology develops experimental and computational approaches for obtaining these parameters and for iteratively building quantitative models to assess emergent behaviors of the system against experimental observations. Immunologists need to embrace the notion that a good quantitative model does not need to be correct, but it has to be useful for highlighting knowledge gaps and guiding the next iterations of experiments and model building. Systems biology may ultimately reveal that a detailed reductionist, mechanistic understanding is unrealistic because an emergent phenotype may be governed by a complex web of molecular and cellular interactions, with each component or interaction contributing only minutely. Here, the call for systems biology to uncover higher-level design and operating principles, as exemplified by the identification and analysis of recurrent network motifs, may help satisfy our appetite for understanding. Indeed, systems biology may provide a solid quantitative foundation to revive rigorous pursuits of theories in immunology.

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Reference

1. Germain, R.N. (2017) What really constitutes the study of 'systems biology' and how might such an approach facilitate vaccine design? *Cold Spring Harb. Perspect. Biol.*

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