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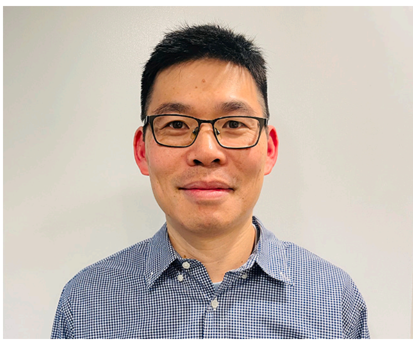
Cell Systems

Voices

What unique insights can modeling approaches capture about the immune system?



Hao Yuan Kueh
Washington University

Models uncover design principles

The immune system, optimized by evolution to maintain health and prevent disease, is remarkably good at what it does. It detects pathogens and monitors physiological stresses with a sensitivity and selectivity that far surpasses that of man-made biosensors. It then mounts potent yet precise responses, enabling the body to maintain homeostasis amid varying internal milieu and external threats.

Cutting-edge experimental approaches are allowing us to profile and perturb molecular and cellular components of the immune system with unprecedented depth, throughput, and precision; however, they cannot explain how these components work together to implement sensing and response capabilities. They also do not reveal design principles: why the immune system works in the way that it does, and why the system designs selected by evolution may be more effective than others.

Reductionist modeling approaches can provide penetrating insights into immune system function and design. By evaluating the performance of key immune components and interactions from the bottom up, these models can reveal system features and designs essential for effective function. By comparing alternate parameter regimes or topologies, modeling can further shed light into why particular designs may outperform others. Over the last few decades, reductionist models across scales have revealed biophysical rules for antigen recognition, signaling feedback topologies for selective antigen sensing, and cell fate decision-making strategies for robust immune memory. Moving forward, these bottom-up modeling approaches will be critical as we seek to make sense of the high-throughput data from modern experimental approaches. Tight modeling and experimental integration will ultimately allow us to uncover immune system design principles and leverage them to more reliably reprogram immunity for human health.

Andreas Handel
University of Georgia

Tools for careful thinking

The immune system is a complex, dynamic network of interacting components that constantly change in response to internal and external signals. This complexity poses a significant challenge when answering specific scientific questions. Experimental studies probe small parts of this system, but it is often unclear whether the data obtained fully capture the (sub)system of interest.

Combining data with models, especially mechanistic models, can help identify the strengths and limitations of both the data and our understanding of the system. Models require explicit assumptions and allow for direct comparison with data, which can strengthen or challenge support for specific mechanisms. This process encourages disciplined and careful analysis of immunological questions.

Well-designed and validated models can capture complex interactions that are often impractical to study experimentally. They allow researchers to study the immune system as an integrated whole rather than isolated parts. Models are also relatively quick and inexpensive to implement, enabling rapid exploration, hypothesis testing, and simulation of scenarios or interventions that may be difficult or impossible to test in the lab.

As data quantity and quality improve, modeling approaches will also continue to grow in sophistication. This will enable us to gain a more thorough and detailed understanding of the immune system.

Alexander Hoffmann
University of California Los Angeles

Big-data immunology—Do we need dynamical systems modeling?

Two fundamental hallmarks stand out for me about the immune response. First it is highly dynamic; when multiple components are needed, they are phased. Second, the immune response relies on a few outlier cells, e.g., the high affinity lymphocyte. And the flipside is true when things go wrong, such as autoimmunity: outliers, not the average, are responsible.

Experimental approaches struggle with both aspects. Advances in single-cell technology have the resolution we need, but when outliers are rare, it remains challenging to identify them.

Dynamics are even more challenging. Most experimental technologies are destructive and so they cannot be repeatedly applied to the same sample. Dynamics can be inferred (pseudotime) but then we lose true single-cell resolution.

Mathematical modeling that respects time and captures knowledge about regulatory mechanisms can address these gaps. Incomplete data can still be used to parameterize them and then simulations can extrapolate beyond training range to provide experimental testable predictions. Our own work on macrophage responses and B-cell fate decisions are examples.

People expressed concern that mechanistic biology may be pushed aside by the dominance of data rich/omic measurement approaches coupled to statistical/AI-powered approaches. I actually think that the current phase will enable the generation of much more ambitious mechanistic mathematical modeling of tissues, immune organs, and tumors at single cell resolution.

Diego Chowell
Icahn School of Medicine at Mount Sinai

Self or non-self? A question that requires mathematics

One of the most intriguing questions in immunology is how our immune system strikes a balance between defense and tolerance, enabling our survival. This delicate balance between immune defense and self-tolerance lies at the core of immunology. Mathematical and computational modeling are powerful tools to explore this question, distilling the intricate interactions of cells, receptors, and signals into testable rules underlying the mechanisms of immune recognition.

A demonstration of the power of modeling is Perelson's analysis of HIV-1 dynamics within the host. This work quantified viral clearance rates, infected cell life spans, and generation times, revealing the virus's rapid turnover—free virions have a half-life of just 6 h and infected cells survive only 1.6 days. These findings reshaped our understanding of HIV replication and underscored the importance of therapies targeting multiple stages of the viral life cycle, ultimately informing the development of combination antiretroviral treatments.

The immune system's ability to differentiate self from non-self relies on stochastic processes shaped by millions of molecular interactions. For example, T cell receptors (TCRs) must identify foreign antigens while avoiding self-antigens—a feat that is impossible to observe directly in experiments. Computational models can reveal the underlying dynamics, showing how small changes in antigen presentation or receptor specificity can lead to immune escape, autoimmunity, or tolerance.

Looking ahead, computational advances like language models hold transformative potential for immunology. Initially developed to interpret human language, these models can be adapted to study the complex dynamics between TCRs and antigens. By revealing new insights into immune recognition, they could drive innovations in next-generation immunotherapies and deepen our understanding of immune responses.

Rachel A. Gottschalk
University of Pittsburgh

Linking signaling to genes

Computational modeling can capture the complexity of biochemical signaling pathways to support a predictive understanding of dynamic events that orchestrate diverse and specific immune gene programs. In these signaling-to-gene networks, temporally and combinatorially complex signals are decoded in a gene-specific manner. While experimental approaches have been used to define an expansive repertoire of receptors, kinases, and transcription factors required for immune function, as well as to comprehensively characterize their influence on chromatin accessibility and gene expression, computational modeling is required to predict specific response genes from quantitative signaling features. Building on work modeling mechanisms that shape stimulus-specific kinase and transcription factor dynamics, machine learning approaches can be leveraged to link these dynamic features to transcriptional programs with gene-level resolution.

This type of integrative approach can provide unique insights into how context-dependent cell states impact signaling-to-gene networks. For example, while it is well appreciated that previous inflammatory challenge or tissue-specific cytokine microenvironment alters signal-response relationships, modeling can help untangle contributions of epigenetic states and reciprocally shaped state-dependent proteomes. With mechanistic modeling, we can explore how variation in signaling network proteins impacts the magnitude and duration of signaling responses to control the sensitivity and specificity of gene induction. We can couple these mechanistic models to machine learning approaches to identify genes that are well predicted by signaling variation. Thus, modeling can capture how variation in signaling networks can shift thresholds for immune activation and shape context-specific immune function.

Harinder Singh
University of Pittsburgh

Modeling immune cell fate dynamics and learning architecture

The value of formalized biological models lies in their ability to explicitly define processes and articulate assumptions about underlying agents and interaction rules. This is crucial given potential ambiguity in biological terminology and the complexity of the processes being analyzed. Models are particularly valuable when they generate precise, testable predictions or reveal unanticipated properties that, if validated, represent major conceptual advances. Consistent application and widespread dissemination of such modeling frameworks will yield transformative insights into the immune system. Immune cells exhibit diverse developmental and differentiation states driven by complex, dynamic signaling inputs. Modeling molecular circuits that integrate signal transduction with gene regulatory networks will provide deeper explanations of immune cell state transitions, stability, and context-dependent effector properties. These properties drive inflammation, pathogen clearance, oncogenic or stressed cell elimination, and tissue repair. Temporal and spatial modeling of immune cell dynamics is needed to illuminate the initiation, amplification, and resolution of immune responses. Developing the next generation of immune cells for therapy will rely heavily on modeling these control circuits. Finally, the immune system has extraordinary learning capabilities as it continuously generates and modifies its representation of "self" by using supervised *central* developmental processes to select complex repertoires of B and T cells that discriminate between "self" and "non-self" as well as beneficial and harmful agents. Memories of encounters in the *periphery* are retained and generate learning updates. Models of these bipartite immune learning architectures and their crosstalk could be transformative in our understanding of this distinctive sensory-effector system and revolutionize AI applications.

Ronald N. Germain and Martin Meier-Schellersheim
Laboratory of Immune System Biology, NIAID, NIH

Mechanistic models: Pain and gain

Modeling has been a robust part of immunology for decades and has played an important role in the development of the field's current views of how the immune system operates. But mechanistic modeling is now increasingly being replaced by machine learning-based methods that avoid requiring the modeler to specify the components and the processes they are seeking to analyze. This renders model development far simpler and circumvents the need to measure or fit parameters that describe those components and processes quantitatively. However, will data-driven, agnostic machine learning models, although useful for predicting behavior of the immune system, enable us to advance the detailed understanding we need for targeted manipulation of immunity? It is the careful curation of molecules, cells, and other biological components and their arrangement into connected networks that connects a model to previously acquired experimental data, to the important but incomplete knowledge of experts in the field. The differences in quantitative and temporal behavior between a model's output and experiment can suggest the nature of a missing element or connection in the circuit, while continuously improving technology is making it easier to identify specific molecules and cells as candidates for the missing components. Developing and testing mechanistic models can be painful, but the gain from their quantitative rigor will be new knowledge of elements that control immunity and how they work together—exactly what we want.

Kathryn Miller-Jensen
Yale University

Robustness balances fragility

With modeling, we can start to capture how the immune system has evolved to balance robustness with fragility. Single-cell measurements in tissues reveal significant heterogeneity in immune cell states. We have observed that heterogeneous immune cells operate as communities to respond to attacks and enforce immune homeostasis through paracrine feedback. Computational models show that intercellular negative feedback can effectively control many variations from normal cell behavior to maintain homeostatic immune setpoints robustly. Regulatory T cells eliminating autoreactive T cells in the thymus and other tissues is a key example. On the other hand, modeling demonstrates how intercellular positive feedback enables rapid responses to assaults and sharp transitions between cell states. For example, a small fraction of "sentinel" innate immune cells respond strongly to pathogenic stimuli and signal neighboring cells to follow. Yet, suppose activation thresholds are too low or negative intercellular feedback is disrupted. In that case, these same circuits can amplify small deviations from normal behavior, leaving the immune system vulnerable to harmful unrestrained responses and exposing fragility. Going forward, modeling could enable us to quantify which deviations in immune cell circuits in tissues move the system out of homeostasis and connect these to the initiators of complex diseases, including autoimmunity, dysregulated responses to infection, and cancer.

Grégoire Altan-Bonnet
National Cancer Institute

A predictive and falsifiable model of immune functions, at last?

The explosion of -omics measurements since the turn of the millennium has fostered the accumulation of ever-more-granular datasets documenting how leukocytes respond to pathogenic challenges, cancer, and autoimmune disorders. Yet, a comprehensive framework to tackle such complexity is lagging. A two-pronged approach to quantitative modeling provides us with a falsifiable method of bridging this gap.

(1) Top-to-bottom: deploying tools from machine learning (e.g., autoencoders, or supervised neural networks) captures low-dimensional representations (so-called latent spaces) of the experimental datasets.
(2) Bottom-up: output from mechanistic models of the immune dynamics analyzed in the latent space generates insights about the key regulators of immune function and helps in the predictions of perturbations to drive novel immune functions.

The ability to create a falsifiable model of the immune system is not only critical to understand what leukocytes do in normal settings but also to help design novel immunotherapies relying on molecular perturbations, cellular engineering, and synthetic biology. In the same way that quantitative measurements and theoretical modeling upgraded the study of planetary motions from astrology to astrophysics in the XVIth–XVIIth century (CE) and enabled space exploration, one can hope that similar combinations will boost more predictive, falsifiable, and deployable understanding in immunology.

DECLARATION OF INTERESTS

D.C. is a co-inventor on two patents related to predicting cancer immunotherapy response. The first patent (US11230599/EP4226944A3), filed by MSKCC, covers the use of tumor mutational burden for this purpose and is licensed to Personal Genome Diagnostics (PGDx). The second patent (US20240282410A1), filed jointly by Cleveland Clinic and MSKCC, describes a multi-modal machine learning model for predicting immunotherapy response and is licensed to Tempus. K.M.-J. is affiliated with Yale University.