Cell Systems

CellPress

Voices

How can systems approaches help us understand and treat infectious disease?

Anna Kuchina
Institute for Systems Biology and University of Washington.

Unraveling persistence

Infectious disease is a broad term that describes the interactions of a host organism with many classes of pathogens. However, the rising issue for all of them is the emergence and rapid spread of antimicrobial resistance (AMR) contributing to an ongoing global health crisis. This problem is very complex and well-suited to be tackled with systems approaches, which include collecting, integrating, and analyzing large-scale, high-resolution, longitudinal datasets for both the host and the evolving pathogen. There are multiple ways in which such approaches could be tremendously useful to design better treatments, which would block the opportunity for the pathogen to either evolve genetic resistance or assume a temporary drug-tolerant state such as drug persistence.

In particular, the advent of high-throughput, massive-scale, single-cell resolution omics technologies for both the host and the pathogenic bacteria now sets the stage for the interrogation of the elusive, rare state of phenotypic persistence, which temporarily permits a fraction of cells to tolerate the treatment in the absence of genetic change, causing the relapse of infection after ceasing the therapy. Identifying the gene regulatory network changes that lead to a subpopulation of pathogenic bacteria developing persistence under different conditions will provide new targets for combination therapies that would exploit the discovered vulnerabilities and block the phenotypic transition to persistence. In addition, systems approaches are needed to understand the fundamental design principles of structured bacterial communities, or biofilms, which underlie many cases of persistent infections, and to help render them susceptible to treatment.

Jason Yang
Rutgers New Jersey Medical School.

Enabling therapeutic innovation

Infectious disease clinical outcomes emerge at the intersection of pathogen biology, human physiology, and therapeutic agents. Although infectious disease researchers often focus on studying pathogens and their direct interactions with host cells or therapeutic molecules, clinical outcomes for infectious diseases frequently involve complex epistatic interactions that occur across cell types and spatial scales. Systems approaches are uniquely suited for handling this complexity and are needed to drive innovation for curing high-burden diseases such as COVID-19, tuberculosis, and antimicrobial-resistant infections.

Systems approaches are already revolutionizing our understanding of pathogen biology and disease pathogenesis. Advances in next-generation sequencing, mass spectrometry, and machine learning are providing genome-scale predictive models of gene expression, metabolism, and signaling for both pathogens and host cells using data from domesticated laboratory strains and cell lines characterized in laboratory settings. These models can be extended to clinical specimens from human subjects to study mechanisms underlying natural variation in infectious disease phenotypes via high-throughput experimentation and transfer learning. Such activities can reveal mechanistic understanding into processes poorly modeled by experimental systems such as aerosol transmission.

Systems approaches can and will lead to next-generation therapies for infectious disease that go beyond eliminating a pathogen to promoting human health. For example, host-directed agents such as dexamethasone and metformin have already demonstrated clinical efficacy in treating COVID-19 and tuberculosis in human patients as antiviral or antimicrobial adjuncts. Systems investigations into specimens from patients with diverse clinical outcomes will inspire new classes of therapeutic agents that will translate naturally occurring immune mechanisms into innovative personalized medicines.

Bree Aldridge
Tufts University.

Heterogeneity and plasticity in infection

Infectious diseases are characterized by heterogeneity and flexibility in the pathogen and immune response. This complexity requires systems-level approaches to understand emergent behaviors, map how different subpopulations of cells respond to treatment, and devise practical strategies to improve treatment.

Pathogens exploit heterogeneity to establish infection and evade killing by the host immune response and drug treatment. They do this by occupying different microenvironmental niches so that each spatially segmented subpopulation of cells adapts to distinct environments. Heterogeneity is also generated at a single-cell level in processes that control growth, metabolic flexibility, and virulence. Together, heterogeneity is layered across multiple processes. We therefore need systematic measurement paired with intuitive modeling tools to characterize different subpopulations. The development of improved therapies requires that we understand how drug-tolerant cells are created and how they can be targeted with drug treatment rather than focusing on the behaviors of the bulk population.

To counter a wide variety of virulence strategies from different pathogens, the host must be plastic and precise in its defenses to be broadly protective. For example, macrophages choose the manner of cell death (e.g., apoptosis versus necrosis) based on which specific pathogen it is sparring with. Cellular behaviors must be responsive to subtle changes that are integrated into many signals, which are best understood using quantitative measurement and mathematical modeling.

Kevin A. Janes
University of Virginia.

Systems virology at every scale

Viruses are compelling systems-level perturbations. With a dozen to a few hundred encoded genes, one infectious virion can completely rewire a host cell and generate an emergent property—replication. The steps of infection operate on length scales that range from molecules to human populations. Instead of moving down from the top or up from the bottom, there is a great opportunity to start with the infected host cell and pursue systems virology from the "middle out."

At the cellular scale, we have a relatively good handle on the core viral life cycle for most genera, although systems biologists would be well served to think creatively about rigorous ways to abstract thornier parts like the interferon response. Going downward in scale, the fate of one virus particle becomes hazier and probabilistic because of the small numbers involved. However, new live-cell single-virion approaches will soon enable us to build stochastic models that identify early bottlenecks useful for prevention. Moving upward in scale, it is fascinating how we all get sick differently. Viruses infect exponentially, meaning that small differences (e.g., polymorphisms, prior history) could have a profound effect when just the right individual encounters just the wrong infectious agent.

The data are out there; they require integration, analysis, and (oft-overlooked) systems models that put the raw information in context. Most importantly, we need to keep an open mind about how systems biology might intersect with infectious disease. Viruses are constantly exploring new ways to infect us—why shouldn't we do the same to study them?

Naeha Subramanian
Institute for Systems Biology and University of Washington.

Getting ahead in the arms race

Hosts and pathogens engage in an evolutionary arms race, co-evolving, adapting, and changing over time. Pathogens evolve much faster than their hosts, resulting in emergence of new strains, as evidenced by the SARS-CoV-2 pandemic, or antibiotic-resistant bacteria. Successful pathogens don't want to kill all their hosts, so many conceal themselves by entering latent or persister states. Despite this competitive edge to pathogens, the human species has endured several infectious bottlenecks throughout history and survived—so we too are adapting. Our multilayered immune system affords a robust and tailored response to pathogens. Further, immune genes are under positive selection, and evolution has introduced profound genetic variation into modern humans.

Understanding the contribution of these multitude forces in controlling the balance between protection and susceptibility to infections requires a deep dive into the pathogen and its host. Longitudinal monitoring of infected individuals from the time of diagnosis onwards using multi-omic technologies to collect data across scales from both the host and pathogen—including human genomes, transcriptomes, microbiomes, metabolomes, microbial genomes, single-cell RNA-seq of microbes and host cells, etc.—from the blood or stool, and from the site of infection when feasible, can enable this goal. When integrated with clinical data from electronic health records, such datasets can be informatically mined to (1) identify early warning signs or biomarkers to predict individuals who are at high risk for acquiring certain infections; (2) stratify individuals based on disease outcomes to identify *a priori* the likelihood of severe illness or long-term sequelae (when present) so that medical resources can be deployed to disadvantaged populations; (3) identify signatures of pathogens for early and accurate detection, especially of viable but non-culturable microbes that fail current tests, and avoid antimicrobial resistance; and (4) inform rational treatment strategies like novel drugs, host-directed therapies, or even repurposing of existing drugs. Such studies can unleash the full potential of systems biology, enabling personalized medicine as a path forward for not only chronic but also infectious disease.

Nevan J. Krogan and Mehdi Bouhaddou
University of California, San Francisco and University of California, Los Angeles.

Bridging scientific silos and connecting scientists

Given the evolving social, political, and ecological landscape of the 21st century, pathogens are an increasing threat to human health. Traditional scientific approaches often rely on reductionist thinking, which often fail to model the scale, scope, and complexity of host-pathogen interactions. Systems biology seeks to remedy this by merging systematic, large-scale, quantitative datasets with computational approaches to understand how systems of components drive emergent properties and phenotypic outcomes.

In our work, we often combine proteomics and genetics—integrating global proteomics, protein-protein interaction profiling, and genetic perturbation screens—to pinpoint mechanisms of pathogenesis. For example, direct and comprehensive measures of host responses to infection, host-pathogen protein interactions, and genetic perturbations of identified host factors can offer substantial insights into how pathogens work. We then use structural and chemical biology approaches, as they are uniquely poised to resolve the revealed mechanisms at an atomic scale as well as ultimately facilitate the design of novel therapeutics.

Importantly, systematic comparison of pathogens should be prioritized, with the potential to reveal common host targets and usher in a new era of host-targeting, pan-pathogen therapeutics. Critically, a multifaceted, collaborative team will maximize systems biology research, aiming to unite scientists from diverse backgrounds by removing silos between traditionally isolated disciplines, inspiring innovation and impact as new infectious diseases emerge.

Shirit Einav
Stanford University School of Medicine.

Virus-host interplays at high resolution

Viral infections are complex processes characterized by a large heterogeneity of both cellular and viral dynamics. Yet, until recently this heterogeneity was not captured, in part due to the lack of high-resolution systems approaches. Single-cell omics technologies have revolutionized our ability to capture and describe tissue heterogeneity (cell types, activation states, etc.) in viral infections in organoid models and human samples with an unprecedented degree of resolution. Coupling such technologies with simultaneous detection of viral elements, for example via dual or virus-inclusive single-cell RNA-seq (viscRNA-seq), has facilitated capturing viral heterogeneity (abundance, genetic diversity, etc.), identifying candidate target cells in complex tissues, and distinguishing infected from bystander cell responses. These approaches have provided insight into the pathogenesis of viral infections and have uncovered molecular and cellular determinants associated with disease outcome. Integrating these approaches with machine learning can facilitate the discovery of clinically usable biomarkers to predict disease outcome.

Single-cell omics technologies can also advance the discovery of candidate antiviral targets. Indeed, single-cell CRISPR and viscRNA-seq approaches have shown promise in the discovery of cellular factors that support or restrict viral infection. Expanding such studies to multiple viral infections has begun to reveal host pathways that are required across viral families as potential targets for broad-spectrum antivirals. Lastly, these approaches can contribute to understanding mechanisms of antiviral and tissue-protective effects of pharmacological compounds. With their growing applications and continuous development of new protocols, single-cell omics approaches are becoming a critical tool not only for understanding fundamental concepts in viral infections and disease pathogenesis at a whole-organism level and across viral families, but also for discovering prognostic biomarkers and targets for prevention or treatment.

Jason Papin
University of Virginia.

Computational models will lead us to future understanding

Even the smallest of infectious agents has incredibly complex biochemical processes that enable it to survive and thrive in physiological niches of a host, and once exposed to the agent, the host will often marshal a complex, multifaceted response. The complexity in both these processes necessitates a systems perspective to understand the mechanisms underlying disease and to develop effective therapeutic strategies. To characterize these complex systems, we often perform rapid and comprehensive profiling experiments to generate systems-level data that characterize how the infectious agent is infecting, growing, and adapting as well as how the host is sensing and responding. But we've all learned that more data doesn't necessarily mean greater understanding. These massive datasets have little use without context and without a framework to quantify relationships. As in many other areas of science and engineering, computational models are becoming a requirement to make use of these data.

In my research and teaching, I emphasize that the process of constructing a computational model can itself be incredibly valuable. As these models are built, we are forced to reconcile conflicting information in the literature and consequently begin to see relationships between components that we would otherwise not have noticed. Once constructed, computational models can provide context for interpreting data, be used to generate testable predictions about the biological system of interest, and enable testing of hypotheses. With challenges as complex as understanding mechanisms of the evolution of antimicrobial resistance, biochemical processes that a microbe uses over the course of a chronic infection, why a host's immune system goes awry, or how hosts with different genetics can have such varied responses to exposure to an infectious agent, it is imperative that we all embrace not just the power of the generation of large data profiling a biological system, but the creation and use of computational models to help provide understanding.

Ronald N. Germain
LISB, NIAID, and NIH.

Balancing input-output equations

Infections can disrupt physiological function in locally invaded as well as distant tissues. Despite use of systems methods to understand why infection is so hard to treat, we still lack a satisfactory explanation for why, for example, many people with COVID-19 wind up with irreversible acute respiratory distress syndrome (ARDS). When considering the physiological toll of infection, one must consider not only damage, but also repair. If the rate at which essential components of the body are rendered unusable exceeds the rate of repair, critical failure ensues. In many infectious diseases, including COVID-19, nearly all effort goes to measuring and preventing damage, and much less attention is paid to remedying inadequate repair. Single-cell RNA-seq analyses of postmortem COVID-19 patient samples revealed stress on the pneumocyte repair pathway, suggesting that some inflammatory cytokines can limit proliferation of pneumocyte stem cells, and past findings in influenza infection showed high levels of repair activity early in the infectious process, implicating inadequate repair as an issue.

Systems methods are only valuable if we place the data that emerge in a complete set of equations that properly balances input (repair) and output (damage). When this is done correctly, we should be able to identify and hopefully perturb the nodes on both sides of the equation in the right manner to rebalance the system—that is, to limit further damage while promoting repair that restores homeostasis. Just interfering with more tissue destruction, if this process has already reduced the "carrying capacity" of the system below a minimal effective level, will not save the patient on its own—that is presumably why so many COVID-19 patients never come off ventilators. But facilitating repair in such individuals while the physiological deficit is handled by a machine may provide much better outcomes. In short, systems methods can help in understanding and treating infections when we truly approach the host and pathogen as a system in which we need balanced equations for loss and gain.

DECLARATION OF INTERESTS

The Krogan Laboratory has received research support from Vir Biotechnology, F. Hoffmann-La Roche, and Rezo Therapeutics. N.K. has financially compensated consulting agreements with the Icahn School of Medicine at Mount Sinai, New York; Maze Therapeutics; Interline Therapeutics; Rezo Therapeutics; GEn1E Lifesciences, Inc.; and Twist Bioscience Corp. N.K. is on the Board of Directors of Rezo Therapeutics and is a shareholder in Tenaya Therapeutics, Maze Therapeutics, Rezo Therapeutics, and Interline Therapeutics.

M.B. is a financially compensated scientific advisor for GEn1E Lifesciences.

J.P. is on the editorial board for *Cell Systems*. J.P. also works (unpaid) with a company, Cerillo, Inc., that was built from work from his lab. However, there are no conflicts of interest between J.P.'s work with Cerillo and this manuscript.

K.A.J. is a member of the Advisory Board of *Cell Systems*.

All other authors declare no competing interests.