Dynamic feedback modeling to predict random infection outcomes

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Brian P. Lazzaro from Cornell University discusses the role of dynamic feedbacks in determining infection outcomes

Consider the widely used metric of LD50, which is the dose of a pathogen or toxicant that is lethal to 50% of the individuals to which it is administered. This is an intuitive measure for contrasting infections. More virulent pathogens have lower LD50; they cause death at lower doses. But what was the difference among the individual hosts within each population infected with the same pathogen? They all received the same infection, so why did half of them die while the other half survived?

In some cases, the difference between life and death can be a minor genetic difference or some small variation in the condition of the host at the time of infection. This concept lies at the heart of personalized medicine. Yet in experimental settings, some individuals will live while others die even when all of the hosts are genetically identical, reared in a common environment, and subjected to the same inoculation. Mortality then appears to be random. The same randomness observed in the lab must also contribute to variation in infection outcomes in less controlled settings.

Our research team studies this apparent randomness using bacterial infections of the fruit fly, Drosophila melanogaster. Using this system, we can give highly reproducible infections to thousands of genetically defined hosts under carefully controlled experimental conditions. We can measure attributes of host resistance to infection, as well as variations in pathogen behavior that may cryptically determine infection outcome. We combine empirical results and mathematical modeling with the goal of converting random into defined. Achieving this goal will implicate therapeutic interventions that can reduce or eliminate unexpected adverse infection outcomes in humans and other more complex systems.

Host condition can critically affect immune performance

At the moment of infection, the number of pathogen cells invading the host is small. The presence of the pathogen activates an immune response, but full immunity may take hours or days to manifest. That lag time provides a crucial window for the pathogen to establish in the host and begin to proliferate. Our modeling of bacterial infections in Drosophila indicates that if the pathogen can proliferate to a critical threshold before the immune response becomes sufficiently active, it will overwhelm and kill the host. However, if the immune response is activated strongly and quickly enough, the infection can be controlled before it reaches the

critical threshold. The initial hours of infection thus become a race between pathogen proliferation and immune activation, and the difference between living and dying can rest on a razor's edge.

What determines the relative speed of immune system activation? Individuals from natural populations of Drosophila, just as any other animal, are genetically diverse in their ability to fight infection. Some individuals have stronger immune systems, and some have weaker. The quality of the immune response is also shaped by non-genetic factors such as dietary nutrition and competing physiological demands.

Minute developmental differences may alter the immunological capacity of the host. Differences in the metabolic, endocrinological, or physiological condition of the host at the moment of infection can determine the intensity and rapidity of the immune reaction. Even seemingly inconsequential variables like the time since the most recent meal can have an impact. Any combination of these may result in among-individual variation in the speed of immune activation.

What happens at the critical pathogen density threshold?

Working with many diverse bacteria, we have shown that if the pathogen reaches the critical threshold before immune control, it continues to grow unabated and ultimately kills the host. However, death does not occur until hours or days after the critical threshold is reached. The critical threshold is not the lethal burden, but it is a point of no return, after which death is inevitable.

While we don't yet know exactly what is happening at this threshold with each distinct pathogen, our modeling gives us some insight.

The main defense Drosophila use against bacterial infection is the production of antimicrobial peptides (AMPs) that aggregate on bacteria and cause pathogen death, frequently by disrupting the bacterial cell membrane. Humans and other mammals use similar peptides to suppress infection in barrier tissues such as the lungs, gut, and mucosal surfaces. The killing efficacy of AMPs depends on their concentration relative to the number of bacteria, with hundreds or thousands of AMP molecules required to kill each bacterial cell. Our modeling indicates that high densities of growing bacteria effectively remove AMPs from circulation, sequestering them in sublethal numbers attached to each cell.

Surprisingly, we also find that bacteria that have been killed by the immune system act as a shield to protect living pathogens. Bacterial corpses and cell fragments act as sponges that continue to absorb AMPs, weakening the immune defense against living cells. The critical pathogen density threshold may therefore be the point at which there are a sufficient number of bacterial cells – living or dead – that they can detoxify the immunological environment and enable living pathogens to survive the host immune response.

Pathogenic bacteria also have more active mechanisms for withstanding the host immune response, some of which kick in only at high densities. At the individual cell level, bacteria can change their membrane structures to resist AMP attachment and killing. Pathogens also

secrete proteases that degrade host AMPs before they can exert their killing, but these are only effective when there are a large number of pathogen cells producing them in high concentrations. Cooperatives of bacteria can produce physical structures like biofilms that prevent AMPs from accessing the cell surface. Production of these structures is stimulated only when the bacteria reach high population densities.

Dynamic feedbacks determine chance outcomes

The race between host immune induction and bacterial proliferation to the critical threshold determines life versus death for the host, with outcome defined by a set of dynamic feedbacks between host and pathogen. Proliferating bacteria stimulate the host immune response, which in turn suppresses pathogen proliferation. Sufficient pathogen proliferation triggers mechanisms that reduce the efficacy of host immunity. Minor variability in host condition, physiological state, or genotype impacts the host immunological capacity, feeding back on the rate of proliferation, and in turn the probability that the pathogen will reach the threshold for overcoming host defenses. The feedbacks amplify minor differences in starting condition, which may be so small that they are initially unobservable, ultimately resulting in vastly different infection outcomes that have the appearance of being random.

We can capture these dynamics in mathematical models based on simplified experimental systems, such as bacterial infection in Drosophila.

We fully expect the same types of dynamics to play out in more complicated organisms and infection environments, such as human lungs and mammalian guts. Integrating these sets of feedbacks into an understood system of metabolic, physiological, and immunological interactions between host and pathogen is the first step toward predicting and managing infection outcomes. Our challenge now is to use the systems modeling to identify crucial points of intervention, where therapeutics can efficiently shift the trajectory and allow us to convert arbitrary outcomes into secure health.

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