

Simplifying biological complexity

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There are huge and growing opportunities for fruitful interactions between physicists and biologists. Understanding how key components of a biological system interact across organizational levels is a major challenge, requiring an intimate link between theory and biological data.

Physics provides an understanding of the essential features underlying the phases of inanimate matter in terms of the principles of geometry and symmetry. Living matter is also governed by physical law, yet a unified, simple understanding has proved elusive. Biological systems are strongly interconnected and highly interdependent across an enormous range of spatial and temporal scales; it is often hard to distil their essential features. However, despite its underlying complexity, life manifests many common patterns, often arising from mechanisms that nature uses again and again. Physics and mathematics can help to explain these patterns — and themselves benefit from a range of new and important challenges¹.

Life is ultimately shaped by evolution and natural selection. The revolution in molecular biology sparked by the discovery of the structure of the DNA molecule has led to a breathtakingly beautiful picture of biological processes. The information encoded in nucleic acids is translated into proteins, which exhibit a multiplicity of structures and function. Nevertheless, a physics-based approach can provide a framework for understanding the common characteristics of globular proteins^{2,3}: their ability to fold rapidly and reproducibly to form a hydrophobic core; the fact that there are just a few thousand distinct modular folds (made up of helices and

almost planar sheets), and that these folds are flexible and versatile enough to accomplish a dizzying array of functionalities. Such a framework could then be used to explore why one protein behaves differently from another.

Moving from molecule to cell, we see a complex, orchestrated dance in which enzymes catalyse reactions (sometimes speeding them up by more than a factor of ten billion), interact with each other and with cell products, and feed back to regulate the synthesis of other proteins. Living cells are complex systems whose constituents interact selectively, nonlinearly and in a temporally orchestrated manner to yield coherent and robust behaviour⁴.

As we journey upwards from the cellular level, biology is replete with examples of emergent phenomena⁵ in which a system is more than the sum of its parts. It is potentially dangerous to presume that one can understand the behaviour of a biological system merely from knowing about the properties of its components. Often, one needs to deal with nonlinearities, stochasticity, feedback mechanisms and non-equilibrium dynamics; indeed these characteristics permeate all scales of biological dynamics, from protein folding through cell biology and neurobiology to population and ecosystem processes. Ultimately, alternative explanatory theories must be tested against empirical evidence.

COMPLEXITY AND SIMPLICITY ACROSS LEVELS

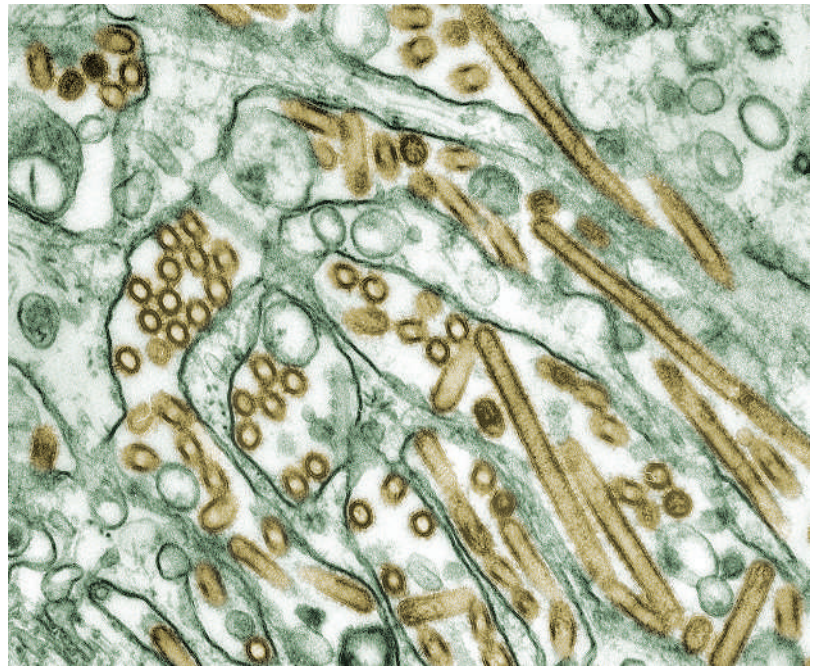
Biological systems are characteristically highly complex; the intricacies of the human brain and diversity of the vertebrate immune system are classic examples. If all of these complexities echoed upwards to larger scales of organization — for example, in ecology — developing a synoptic understanding of dynamics at these larger scales would be immensely challenging. However, simple dynamic patterns and scaling rules do sometimes emerge as we move from scale to scale.

We illustrate this by comparing two of the most basic actors in life's drama: the RNA viruses that cause the human diseases measles and influenza. Differences within hosts, in the way each virus interacts with the immune system, lead to differences at the level of the host population.

RNA viruses typically consist of a small amount of genetic material (RNA) enclosed in a protein capsule. To replicate themselves, they subvert the cellular machinery of more-complex organisms — often with catastrophic consequences for their hosts. Despite their simplicity, the interaction of these viruses with the defence mechanisms of human hosts can be extremely complex⁶. Initially, the viruses have to surmount physical barriers (such as mucus in the respiratory tract) and the first arm of the immune system: an array of non-specific, innate immune responses, which are based on complicated molecular signalling networks and involve the orchestration of dozens of host genes and many different cell types⁷. When a child is infected with a virus for the first time, it will eliminate the infection after several days. During this primary infection the second arm of the vertebrate immune system, the adaptive response, comes into play. This response is again the result of complex orchestration, involving, among other things, antibody production. The adaptive response enables infections to be eliminated more quickly the next time the host individual is challenged by a virus it recognizes, as the host retains a 'memory' of the virus.

The degree to which these within-host complexities are reflected in dynamics at the level of the host population depends crucially on the strength and duration of immunity following a primary infection, and how well immunity protects against different variants of a virus.

Changes to viral genetic material can change the protein molecules on the viral surface (known as antigens). Hence, mutation and reassortment of viral genes can result in the evolution of new viral strains and subtypes, some of which may be capable of evading the adaptive immune response (which responds much more rapidly to antigens it recognizes). Many RNA viruses can evolve particularly fast because the enzyme involved in replicating their genetic material generates many errors, and therefore a diversity of variant forms. If a variant takes longer to trigger the host's adaptive response, it has a higher chance of establishing and transmitting to new hosts. Consequently, there is strong selection pressure on the virus to evolve to evade the immune response.



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This is certainly the case in influenza: new variants can spread through host populations each year by infecting not only 'naïve' hosts but also hosts that have previously encountered a different version of the virus. Most spectacularly, the antigens of the influenza viral subtypes that infect humans occasionally undergo major change, probably as a result of genetic reassortment with other subtypes such as the H5N1 virus (Fig. 1) that is currently infecting birds, and some humans, in Europe and Asia. Thus evolution can lead to major pandemics, because almost everyone is susceptible to the resulting virus. Even in the absence of pandemic strains, the host-level dynamics we observe depend on a complex set of individual-level responses to infection⁸. Furthermore, vaccination is only effective for a relatively short time.

By contrast, in measles we do not need to know details of individual infection histories to understand the aggregate dynamics at the level of the host population. Once a person has been infected with measles, their adaptive immune system is able to recognize all known genetic variants of the virus⁹ (the reasons for this are still not well understood). Therefore, we can predict the resulting disease dynamics remarkably well, simply by dividing hosts into three categories: susceptible hosts, who have never seen the infection before; infected individuals; and hosts who have recovered from infection and are now immune. Epidemics occur when susceptibles become so abundant that, on average, an infected person passes the disease to one or more susceptibles. Epidemics extinguish themselves as the supply of susceptibles is depleted by immunity or death; there is then a period of low incidence until a build-up of susceptibles allows the next epidemic to take off. Children are susceptible from shortly after birth, so the period between epidemics (in the absence of vaccination) depends strongly

Figure 1 Avian influenza A H5N1 viruses (gold), grown in canine cells (seen in green in this coloured transmission electron micrograph). Evolution of the virus can make for complex immune dynamics at the population level.

on the birth rate. Seasonal and other variations in measles transmission, stochastic forces and spatial heterogeneity in mixing of hosts all complicate the details of disease occurrence¹⁰. Nevertheless, simple models can predict most of the observed variation in the system. Furthermore, the lifelong immunity to measles infection has enabled vaccination (effectively moving people from the 'susceptible' to the 'recovered' class) to virtually eradicate measles in industrialized countries⁹, although measles is still a major killer in developing countries, where vaccination coverage is much lower.

EMERGENCE OF SCALING

When one is unable to deal with the full dynamic complexity of a biological problem, scaling ideas from physics can be useful. This is especially so when the full details are not essential for the type of information that one is seeking. For example, biologists have described many relationships linking body size to rates of physiological processes and biological cycle times, over 21 orders of magnitude in body mass¹¹. These relationships usually take the form of power-law allometric scaling between the biological property of interest (for example, lifetime, rate of heart beat, or metabolic rate) and the body mass; scaling exponents, derivable from each other by dimensional analysis, suggest that the underlying explanation ought to be general and simple, and not dependent upon the specific metabolic machinery of particular types of organisms. A solution to this problem is likely to lie in the emergent scaling behaviour of directed transportation networks¹² (in this case, the circulatory networks), which has also been studied extensively in physics — for example, in understanding stress networks in granular materials¹³.

Another example of scaling arises when one wishes to understand the causes and the consequences of biodiversity. Species–abundance relationships (the number of species with a given population) and species–area relationships (the number of distinct species as a function of the area of real or virtual islands) can help inform ecological preservation efforts; these relationships follow interesting scaling

laws. Several basic questions are ripe for attack using the physics-based approach of distilling the essential ingredients of a system and incorporating them in tractable models whose predictions can then be compared with the observed data: What are the key factors that control the patterns of species abundance? What are the principal causes of extinctions and how may they be averted? What is the network of interactions between species and what impact does this network have on the fragility of the community and its ability to recover from a disturbance? A fruitful strategy to answering these questions, and others, could be to develop the analogue of an ideal-gas description^{14,15}, guided by data, and then the most important interactions, in the spirit of van der Waals.

CONCLUSION

The recent 'omic' revolutions (genomics, proteomics, metabolomics, and so on) are the most visible manifestation of a mass of information now becoming available to document complexity at different organizational levels of biology. A key challenge is to identify when underlying simplicity can be uncovered from seemingly bewildering complexity. Armed with an approach firmly rooted in biological data and knowledge, theoretical physics can provide powerful concepts and tools to understand biological processes across scales.

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