Organisms as Complex Systems

By John Guckenheimer

Adaptability and "emergent" properties are two characteristics of complex systems, whether naturally occurring or engineered. Structurally, a complex system might be made up of a large number of simpler components, or it might be formed from hierarchies of smaller numbers of interacting subsystems. Organisms have all of these features. Animals are organisms that integrate different systems: the nervous system, the respiratory system, the immune system, the endocrine system, and the musculo-skeletal system, among others. Each of these systems has many components, often organized into subsystems. The human nervous system, for example, is estimated to have on the order of 10^{11} neurons; mediating their interactions are thousands of synapses connecting each neuron to others. Moreover, the brain is organized into regions; some process sensory information of different kinds, some regulate breathing and movement, and others contain hormone-releasing cells. All of this makes the whole organism a complex system. This essay discusses a few insights that result from viewing organisms from a systems perspective.

Two remarkable features of living creatures are (1) their reproduction and growth from a single cell into elaborate shapes characteristic of each species and (2) their ability to repair injury, recover from illness, and regulate their vital parameters within viable limits. Additionally, most animals are mobile, moving through their environment to find mates, capture food, and avoid predators. Despite spectacular advances in modern biology over the past sixty years, the organizing principles of these capabilities remain a mystery. Though some biologists maintain that genomes are the secret of life, the difference between dead and live animals is not a matter of genes: The important distinction is that a dead animal no longer interacts with its internal or external environment. Moreover, knowledge of genomes and libraries of protein structure is not enough to make us understand how organisms work, just as the parts list of an automobile cannot be substituted for assembly or driving instructions.

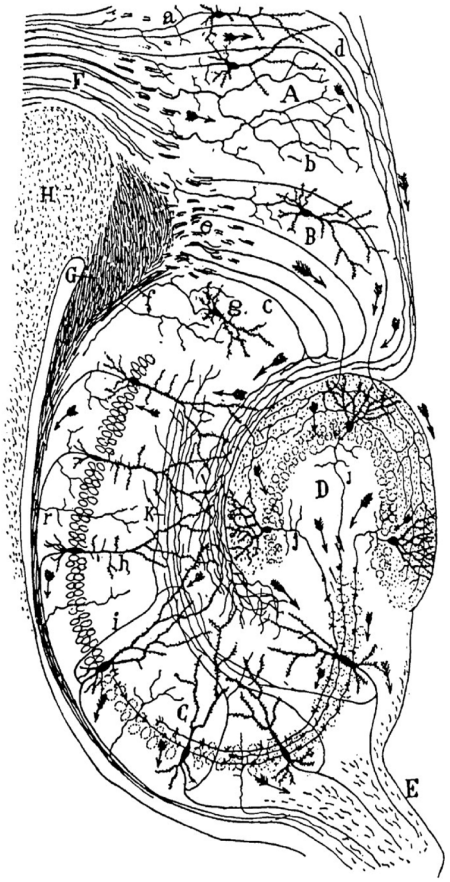
Here is a brief story that illustrates the last point. Many years ago, I attended a workshop organized by a federal agency to help plan future programs involving genomics. A group from a company with a large agricultural business described their efforts to produce potatoes with higher starch content. They said that they had no difficulty in identifying the genes and proteins central to starch production, or in producing mutations that enhanced the expression of these genes and led to more of the key proteins. Nonetheless, the starch content of the resulting potatoes was essentially unchanged. The group concluded that additional processes are involved in the regulation of starch content, and that understanding enough about these processes to effect the desired changes in starch content remained a formidable and elusive challenge.

Traditional breeding programs, by contrast, speed natural selection by mating individuals with different genotypes and selecting offspring with desired characteristics. Agricultural breeding sometimes has to settle for "top-down" approaches based on observations of what works best, rather than "bottom-up" approaches that target changes in specific molecules. This difference between genetic engineering and selective breeding mirrors the distinction between evolution and natural selection.

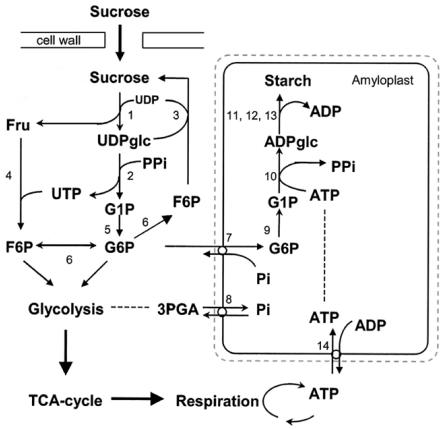
Evolution and natural selection are central to biology. Their combined effects lead to the survival of the fittest: organisms that perform optimally. We don't know exactly what is optimized, but we find creatures that have evolved remarkable adaptations. Nonetheless, evolution and natural selection are not the same thing. Evolution acts by mutation; changes in DNA produce changes in proteins that in turn change the characteristics (phenotype) of the organism. An evolutionary perspective emphasizes the parts of an organism, rather than its processes. Natural selection among mutations, on the other hand, depends on process and is insensitive to nucleotide sequences and protein structures. What matters is that organisms can eat and avoid being eaten while they grow, mature, and reproduce. Given the variability of the environment in which the organism lives, it needs to be adaptable and resilient. How do we connect the evolution of biological molecules to the fitness of the organism as an integrated whole? That is a question whose solution prompts the search for general principles about complex systems.

Morphogenesis

Consider the principles that govern morphogenesis, the growth and development of organisms. We are fascinated by the beauty and diversity of life forms. D'Arcy Thompson's marvelous book *On Growth and Form* [2], first published in 1917, is a classic investigation of the rules governing the shape and size of organisms. Research on this topic continues today. One of the current themes is that simple rules and/or physical laws can produce complex patterns. Mathematics, aided by computer models and simulations, is a means of exploring how geometry arises from simple rules.



Drawing of a rat hippocampus. Santiago Ramón y Cajal, Histologie du Système Nerveux de l'Homme et des Vertébrés, *Vols. 1 and 2, A. Maloine, Paris, 1911.*



Pathway for the conversion of sucrose to starch in potato tubers. From Peter Geigenberger, Regulation of sucrose to starch conversion in growing potato tubers, *J. Exp. Bot., 54:382 (2003), 457–465. Reprinted with permission.*

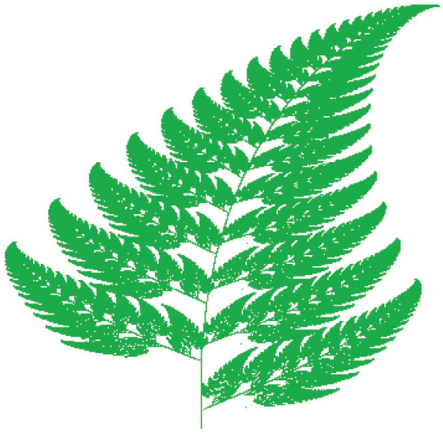
The "Barnsley fern" is a striking example: a mathematically constructed object, it looks just like a fern leaf. This fern is a "fractal," consisting of the limits of a small number of geometric transformations of the plane iterated in random orders. Each sequence of transformations has a limit in which a square is squeezed into a single point, but the limit point depends on the order in which the transformations are applied. Though there is no biology inherent in this construction, it prompts us to look for biological mechanisms that implement rules of pattern formation.

The shapes of the virtual and real ferns are strikingly similar, but we want still more from models of morphogenesis: We want to predict how developing organisms determine the location and size of their parts. How big should our brains, lungs, heart, bones, and other organs be? Individuals of a species vary in size, and the size of their parts must fit the size of their bodies. Cells do not have a map of the body, but they must decide when and how to differentiate. We want models that explain the geometry of differentiation.

We also want models that incorporate the "physics" of development. Morphogenesis results from physical processes that can be investigated experimentally. More than half a century ago, Alan Turing proposed that interactions of reaction and diffusion are such a process. Although diffusion acts to smooth spatial concentrations of a chemical, Turing observed that diffusion of reacting substances at different rates can lead to spatial patterns in their concentrations. Faster computers and better algorithms have enabled us to make detailed comparisons of patterns arising from simulated reaction–diffusion mechanisms: zebra stripes, eye spots on the wings of butterflies, and the color markings of sea shells, among others. These computations illustrate vividly how physical principles can help explain the complex geometric forms we find in the natural world.

The mathematical challenge of morphogenesis is to predict which shapes are inherent in a particular set of rules or principles. How does the shape of the fern depend on the parameters of its iterated transformations? We can explore this question with simulations, but we want something that is more efficient than simply trying many random possibilities. Ideally, a theory would predict the shape without performing the simulation at all. In the case of reaction–diffusion mechanisms, for example, theory tells us that reacting chemicals must diffuse at different rates if we are to obtain spatial patterns from reactions that do not oscillate.

A second physics-based approach to understanding morphogenesis is self-assembly. Given a collection of moving objects that can adhere to each other, what types of structures will form as large aggregates develop? The input for this problem includes the shape of the particles, the mechanism by which they stick to one another, and the physics of their motion. When we engineer components with particular shapes and adhesive properties, will they combine with each other under random thermal fluctuations to create coherent shapes? How are the remarkable shapes of radiolarian skeletons created by a single-cell protozoan? Experimental, computational, and theoretical studies of self-assembly are an especially active area of current research. Better theory that predicts emergent properties of self-assembled structures could bring substantial new insight to biology.



The Barnsley fern, described in Fractals Everywhere*, by Michael Barnsley, Academic Press, 1993. This image was produced by the author with the matlab script finitefern.m, www.mathworks.com/moler/ncm/finitefern.m.*

The butterfly Bicyclus anyana. *Image from http://lepdata.org/monteiro/. See A. Monteiro, V. French, H. Metz, G. Smith, and P.M. Brakefield,* Butterfly eyespot patterns: Evidence for an underlying morphogen gradient, *Acta Biotheoretica, 49 (2001), 77–88. Reprinted with permission.*

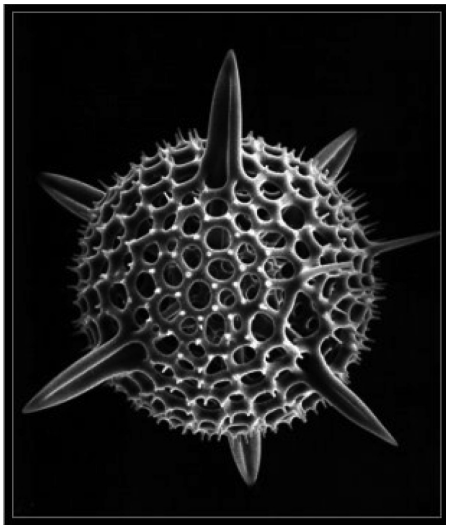
Bifurcation Theory

In his controversial 1972 book *Structural Stability and Morphogenesis* [1], René Thom theorized that mathematics can make far-reaching predictions about pattern formation. Inspired by the ideas of the biologist Christopher Waddington, Thom proposed that the mathematics of singularities, from his own pioneering work, produces shapes that serve as organizing centers for development. Thom's subtle reasoning offers one strategy for investigating complex systems.

Thom's key idea is to hypothesize a universe of plausible models for a phenomenon of interest and then to focus on generic behaviors within this universe. He describes at length two such universes: a "static" one that leads to his theory of elementary catastrophes and a "dynamic" one that leads to bifurcation theory of vector fields. The mathematics of singularities and catastrophes is more complete, but results of bifurcation theory have been astonishingly successful in predicting qualitative features of dynamical systems across the sciences. This theory of "simple" systems is usually regarded as a prototype for theories of complex systems. Because it also emphasizes dynamical processes rather than structure, a description of its basic concepts should be helpful.

The starting point for bifurcation theory is a system of differential equations (also called a vector field) that depends on parameters; an example can be found in the kinetics of a system of chemical reactions. In this example, the reaction rates are the parameters; if there is an exchange of chemicals with the environment, the exchange rates are additional parameters. The laws of thermodynamics imply that reactions isolated from the rest of the world tend to equilibrium. Organisms are not isolated: They eat and excrete, and their biological functions are always rhythmic.

Viewing organisms as systems of chemical reactions, we can ask some useful questions: For which parameters do all initial conditions lead to an equilibrium? For which parameters can the system continue to oscillate forever? Bifurcation theory addresses these questions by investigating qualitative changes that occur in a system as the parameters vary. The stability of an equilibrium state, for example, might change or even cease to exist as the parameters reach a threshold. Such thresholds,



A radiolarian. From http://www.popmath.org.uk/sculpture/pages/5life.html.

called bifurcations, form boundaries that partition the parameter space into regions in which the system has different types of long-term dynamics.

Bifurcation theory classifies bifurcations that occur in generic families of vector fields. It provides archetypes, called normal forms, for the limited number of bifurcations that it identifies. Further analysis of the normal forms determines dynamical information that we can use as a guide for interpreting qualitative changes in a system, whether we are studying empirical data or computer simulations. In the case of equilibrium point bifurcation, transformation of a system to its normal form can be accomplished without solving the equations. This means that we can predict system behavior efficiently, without resorting to simulation.

Hopf bifurcation is an example. At a Hopf bifurcation, oscillations emerge from an equilibrium. Algebraic transformations of the vector field to its normal form determine the stability and magnitude of these oscillations close to the bifurcation. Calculations of this type have been used to determine the boundary between quiescent and spiking states in model neurons.

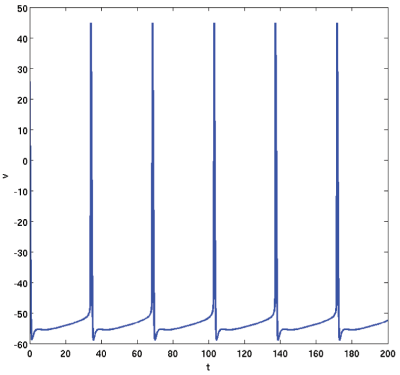
The language of bifurcation theory can be daunting, but those who persevere can gain an interesting perspective on natural selection. For processes described by differential equations, bifurcation theory predicts how the processes might change in response to mutations. If a mutation changes the parameters of the system, bifurcation analysis can reveal whether a qualitative change produced by that mutation will give new functionality to the system or make it stop working. The concept of structural stability is important here: A system is structurally stable if small changes in parameters cannot produce qualitative changes in the dynamics. Regulatory mechanisms may evolve to maintain the structural stability of an organism over broader ranges of environmental conditions, analogous to a feedback controller of an engineered system. To remain responsive to inputs, however, it seems that many biological systems sit pretty close to bifurcation boundaries, where they can switch behaviors in response to appropriate small stimuli. Also in contrast to engineered systems that are designed in a modular fashion, the coupling of biological systems within an organism seems more entangled, with each system affecting the entire organism. That makes holistic approaches to studying organisms attractive, but difficult.

Modeling and Model Reduction

By building dynamic models of complex systems and implementing them as computer simulations, we can test and deepen our understanding of how these systems work. But how can we get started, and how much detail should we put into the models? These questions don't have single answers. Too much detail makes models difficult to parameterize and compare with data, but biological systems are intricate and details often do matter. Developing a hierarchy of models that differ in complexity seems to be an appropriate strategy, often expressed in terms of "model reduction" when the move is from larger to smaller models.

Experimentally, bottom-up and top-down approaches are complementary. Taking human vision as an example, at the bottom we investigate neurons in the eye and brain and the ways in which they are connected. At the top we perform psychological studies of optical illusions and facial recognition. Experiments of both types produce information that can be used in developing models of the visual system. Complex systems theory is useful for creating models, motivating experiments, and placing the results into a coherent conceptual framework.

The maxim "form follows function" is commonplace in biology texts, but biologists sometimes say that function follows form. Pragmatically, the distinction is less important than the question of whether we can predict function from form. In functional genomics, the end goal of many investigations is to produce metabolic and regulatory networks that show which molecules interact with one another. Implicit in this goal is a belief that the function of the network will be evident when its structure is visible. That is seldom the case, however, as shown by the example of the disappointingly engineered potatoes presented earlier. Dynamic models that integrate fundamental processes into complex systems greatly facilitate predictions about network function. I predict that dynamic modeling of biological systems will continue to accelerate as the lack of good models increasingly becomes a bottleneck in understanding organisms as complex systems.



Time series of voltage (mv) vs. time (msec) for a model of a motor neuron, created by the author. Model from V. Booth, J. Rinzel, and O. Kiehn, Compartmental model of vertebrate neurons for Ca^{2+}-dependent spiking and plateau potentials under pharmacological treatment, *J. Neurophysiol., 78 (1997), 3371–3385.*

References

[1] R. Thom, *Structural Stability and Morphogenesis*, Addison-Wesley, Reading, Massachusetts, 1975.

[2] D'arcy Wentworth Thompson, *On Growth and Form*, Cambridge University Press, Cambridge, UK, 1917.

John Guckenheimer is a professor of mathematics at Cornell University.