

Appreciation of the Machinations of the Blind Watchmaker

ONE DANGER in using the language of engineering to describe the patterns and operations of the evident products of natural selection is that invoking principles of design runs the risk of invoking a designer. But as we analyze the increasing amount of data on the genome and its organization across a wide array of organisms, we are discovering there are patterns and dynamics reminiscent of designs that we, as imperfect human designers, recognize as serving an engineering purpose, including the purpose to be designable and evolvable.

There is no doubt that biological artifacts are the product of Dawkins' Blind Watchmaker, natural selection. But natural selection has at its heart one of engineering's most prized principles, optimization. Survival of the fittest, while not directly specifying an objective function that an organism must meet, nonetheless provides a clear figure of merit for long term biological success, persistence of lineages through reproduction of organisms, and is a well-formed if ever-changing specification. The mechanisms which provide the optimization algorithm for an organism to meet the demands of this changeable requirement, composed of a program subject to operations of mutation and interorganismal transfer and inheritance, are themselves under selection. Repeated rounds of this process leads, some argue, to architectures that facilitate evolution itself, the evolving of evolvability.

The survival-of-the-fittest objective function has many features that we might naturally expect would lead to recognizable engineering solutions. Organisms must sense the environment and transfer these signals through controllers which operate actuators that make the organism behave: forage for food, choose the best food sources, deploy predations, defend themselves, hide, mate and more in order to survive. There are physical constraints on how solutions can be implemented given the environment and the physico-chemical composition of the available components. The interplay of these goals suggests that part of the optimization must involve classical engineering problems like signal tracking and guidance, optimal filtering, and optimal estimation.

In the seventies, Howard Berg (who continues to produce beautiful work at the Rowland Institute in Cambridge, MA), and collaborators initiated an elegant set of papers on how a tiny bacterium, *Escherichia coli*, could sense a chemical gradient and somehow move up that gradient, chemotax, in the highly viscous world in which they live. He combined quantitative measurements in the form of, for example, three-dimensional tracking of bacterial movements in controlled environments and reasoned carefully about how the size of the bacterium, the Brownian forces upon it, the size of the chemical gradients it was able to track, the diffusion constants of the chemi-

cals and the probable density of receptors on the cell surface and their ability to absorb the signal molecules might affect the way cell could possibly move in the medium, the ability of the cell to optimally estimate a chemical concentration and temporally differentiate the gradient to determine if it is swimming towards a source. It was only in the nineties, when the molecular biologists had truly obtained a handle on the molecular mechanisms underlying the transduction of chemical sensing into actuation of motion by the flagella, that the basis of the engineering optimality for the observed chemotactic behavior could be traced to the molecular implementation of integral feedback loops and amplifiers necessary for the bacterium to solve the tracking problem became clear.

There are still deep questions surrounding how the functional geometry of and cross-talk among the multiple receptor systems leads to the dynamic range and amplification of which this system is capable. There are also questions of why different bacteria with nearly identical physical constraints upon them and homologous pathways to *E. coli*, nonetheless use significantly different circuitry and elaborated feedback systems to achieve the same goals. Thus, this system continues to provide challenges in measurement, physical theory, control theory, and molecular evolution that set the gold standard for the application of engineering methods and principles to the understanding of cellular systems.

The good news from this and the study of a number of other (relatively small scale) biological subsystems is that biological organization does look like engineering, and that much of the complexity of biology appears to be due to complex control requirements. Thus, engineering control methods apply directly to biology, even though the physical substrate is very different than in most engineering. This along with the increasing ease of quantitative and large scale measurement of cells has lowered the barrier for engineers and physical scientists to apply their trades and develop their questions in the profound substrate of biology. New categories of question, not traditionally of interest to the biologist are now entering that field. Answering questions of control, stability, coding capacity and information transfer, as well as more focused principles of optimality that survival of the fittest imply are now both feasible and interesting. This is a sea-change. A true biological engineering is emerging, cloaked in the names Systems and Synthetic Biology, that is dedicated to discovering and exploiting these results for predict, control and design cellular behavior.

The papers represented in this volume are a demonstration of the effect of these developments. This issue contains papers from some of the top names and brightest young stars in the many allied field of engineering including control and dynamical systems, optimization, signal processing, and statistics. The best engineering minds are finding intellectual stimulation in the problems presented biology that can now be dissected with ad-

vanced measurement and genetic tools. As might be expected at the beginning of the true merger of a two fields, biology and engineering, most applications reported here use existing methods modestly (and often very cleverly) extended for the new data types and systems.

It is telling that most analyses here are at the level of small circuitry. This is one of the many indicators that there are new challenges to engineering opened by biological systems which are, at best, only tangentially touched on by classical engineering theory practice. The biggest issue seems to be scalability in that none of our current techniques for treating these nonlinear, stochastic (and most often partially observed) systems scales to bigger networks. Engineering theory is just starting to look at large, distributed, asynchronous control systems, such as the internet, and even these systems pale, in many ways, against the heterogeneous complexity of the biological networks even in single cells. When one considers the largely structured networks of communication that arise among cells in a metazoan organisms and the less structured ad hoc networks of communication among populations of organisms then biological networks *seem* staggeringly complex compared to those systems that engineering is used to operating on.

Further, while biology does seem to make sense from this engineering perspective—evolution seems to yield designs with the same principles as engineering design—we need to develop better analysis and theory for some of the key differences in biological engineering. Biological systems constantly evolve, they self-replicate and transfer parts of their genetic programs around at, in some cases, alarming rates. How this can be as effective as it is in promoting the fitness and evolution of populations and eco-systems is a central engineering question. Does the Blind Watchmaker press towards modularity of its systems? Are the principles and selection for “evolvable” designs and architectures robust in the function over the lifetime of an organism but flexible in their function under mutation and evolutionary

time? Is there optimal coordination of mechanisms for evolution across a population such as induction of competence or hypermutation in subpopulations of bacteria? Are there ways of examining cellular networks and using the internal model principle to infer the key aspects of the environment canalizing the observed designs of these networks? For forward engineering synthetic biological systems, what are the principles of containment of populations and their genetic materials and of prevention and detection of function drift? It is these unique challenges and others that drawing engineers away from the more mature and traditional applications.

The engineering methods (and their applications) presented in this issue represent a large diversity of approaches. In many ways the varied assortment of papers represents also the pedagogical state of the field its application to biology. There has yet to emerge a coherent best practice in engineering application to biology. Engineers and biologists will have to meet each other half way so that an effective field can be coherently created. Though there is, and will be for a while, an uncomfortable partiality of knowledge of biology for the engineer and of engineering for the biologist we are lead to paraphrase Desiderius Erasmus: “In the country of the blind watchmaker, the one eyed man is king.”

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