Ingenious Genes: How Gene Regulation Networks Evolve to Control Development

Author: Wray, Gregory A.

Source: BioScience, 62(12) : 1084-1085

Published By: American Institute of Biological Sciences

URL: https://doi.org/10.1525/bio.2012.62.12.10

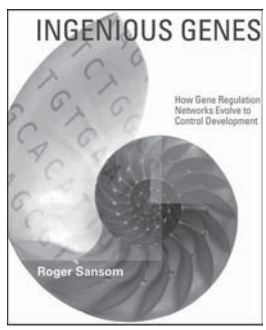
Adaptation and Gene Networks

Ingenious Genes: How Gene Regulation Networks Evolve to Control Development. Roger Sansom. MIT Press, 2011. 144 pp., illus. $30.00 (ISBN 9780262195812 cloth).

Systems biology is almost unique within the broad field of molecular and cellular biology in taking an explicitly antireductionist approach. Its basic premise is that analyzing networks of interacting molecules can provide insights that cannot be gleaned from focal studies of single components, no matter how thorough and detailed those studies might be. Systems biologists have devoted considerable attention over the past decade to identifying gene and protein networks in a variety of organisms—descriptive efforts that have, at times, dominated the discipline.

The goal, however, has always been more ambitious than merely mapping circuitry. One sign that systems biology is maturing as a discipline is its growing impact on other fields. In the book *Ingenious Genes: How Gene Regulation Networks Evolve to Control Development*, author and philosopher of science Roger Sansom examines the implications that the growing understanding of gene networks has for adaptation, one of the fundamental processes in evolution. The central question that Sansom tackles is deceptively simple: How is it possible for biological networks to evolve adaptive complexity?

One reason this question is important is that most of what we know about adaptation comes from theory and case studies involving single genes. Indeed, a basic assumption of population genetic theory is that most genetic variation affecting complex traits acts additively; that is, each gene's contribution to a particular trait is largely independent of every other gene. This assumption may have seemed reasonable when it was proposed more than 70 years ago during the Modern Synthesis, before the structure of DNA was elucidated and at a time when gene function was a complete mystery. Today, however, the notion that genes affecting complex traits typically act in isolation seems absurd. This matters, because gene interactions are likely to increase *pleiotropy* (mutations that affect multiple traits), which population genetic theory predicts will constrain adaptation.



A second and more specific reason to pay attention to Sansom's question comes from the theory of systems biology itself. In 1985, the mathematician Stuart Kauffman published a book chapter in which he argued that natural selection cannot alter gene regulatory networks to achieve optimal configurations (Kauffman 1985). Kauffman's basic argument, amplified in his subsequent books, was that the more complex a network becomes, the more unlikely it is that random mutations can improve its function. Kauffman suggested that most real gene regulatory networks are composed of a large proportion of suboptimal interactions and that their overall organization is largely determined by chance mutation rather than adaptation.

However, most biologists would argue that real gene regulatory networks are manifestly not randomly organized but structured in ways that meet distinct and specific functional demands. From the cell cycle to embryonic development, immune responses, and beyond, systems biologists have identified interactions between proteins and genes that seem exquisitely well suited to carrying out specific tasks. The strong impression—admittedly challenging to quantify—is that real gene regulatory networks are shaped by functional demands to a considerable extent. This implies that changes in gene networks are often altered through adaptation.

There exists a conflict, then, between the assumptions of population genetics and the theory of gene networks on one hand and what we observe in the natural world on the other. Sansom is certainly correct in his premise that understanding how gene networks evolve adaptively represents an important challenge to both systems biology and evolutionary biology. One possibility is that the theory of classic population genetics is correct in assuming that adaptive mutations are generally not pleiotropic, whereas chance mutations, which are much more numerous, are mostly deleterious. Even if this were known to be a true statement, it does not explain how adaptive mutations are able to avoid influencing interconnected genes.

Sansom is more concerned with the specific challenge posed by Kauffman's theory, however. He devotes most of the first half of *Ingenious Genes* to explaining Kauffman's model and exploring some of its assumptions. For instance, in Kauffman's model, only mutations that achieve optimal network connections in a single step can be detected by natural selection. Not surprisingly, adaptive mutations are vanishingly rare under this scenario. By constructing a variant model that allows for incremental fitness

doi:10.1525/bio.2012.62.12.10

differences, Sansom demonstrates that natural selection can operate more efficiently to increase overall network fitness. After examining several other assumptions of Kauffman's model, Sansom concludes that it is simply too unrealistic to be useful as a general framework for understanding how natural selection operates on gene regulatory networks. He finds Kauffman's model particularly far removed from the processes that take place during embryonic development, which have been a focus of systems biologists and which involve some of the most thoroughly investigated gene networks.

In the second half of his book, Sansom develops an alternative model that he calls *connectionist networks*. He bases this model on concepts that were originally developed in the field of artificial intelligence, where they are known as *parallel distributed processors* or *neural networks*. A key feature of connectionist networks for Sansom is accuracy, which in this context, means that a gene's expression responds in appropriate and useful ways to changes in its microenvironment (in the broad sense, including, e.g., not just the physical environment, but hormones, disease, the developmental stage). This contrasts with Kauffman's view that gene expression occurs in fixed cycles and is largely independent of what is going on outside the cell.

The central thesis of *Ingenious Genes* is that connectionist networks provide a more biologically realistic model of gene network function than Kauffman's model does and that this model explains why gene networks can be highly adaptable. Perhaps not surprisingly for a philosopher of science, Sansom argues these points primarily from first principles rather than from a body of experimental evidence. (This is not a book for those brushing up on the latest empirical research in systems biology.) However, he does outline some general empirical predictions that can be tested. Many of these predictions are based on what happens to the expression of a gene when its regulators are expressed in different combinations and at different levels (e.g., Do multiple regulatory inputs act in a Boolean, additive, or nonlinear manner to influence the target gene? Do regulators consistently act as either activators or repressors?).

Interestingly, systems biology has barely begun to explore these questions of regulatory logic. *Ingenious Genes* provides a compelling reason to begin a serious empirical investigation of the logic of gene regulation, with a particular view to understanding how this logic evolves. Models serve a variety of functions in biological research. Precisely how well connectionist network models conform to real biological networks is, to my mind, less important than the fact that they provide an excellent framework for future research. By identifying an important, unresolved problem and laying out a clear proposed solution, *Ingenious Genes* makes a thought-provoking contribution to both systems biology and evolutionary biology.

Reference cited

Kauffman SA. 1985. Self-organization, selective adaptation and its limits: A new pattern of inference in evolution and development. Pages 169–207 in Depew DJ, Weber BH, eds. Evolution at a Crossroads: The New Biology and the New Philosophy of Science. MIT Press.

GREGORY A. WRAY

Gregory A. Wray (gwray@duke.edu) is a professor in the Department of Biology at Duke University in Durham, North Carolina.

DISSECTING THE INSECT SURVIVAL GUIDE

How Not To Be Eaten: The Insects Fight Back. Gilbert Waldbauer. University of California Press, 2012. 240 pp., illus. $27.95 (ISBN 9780520269125 cloth).

Metaphorical evolutionary arms races, such as those between prey and their predators, are well-studied and important examples of coevolution (see, e.g., Geerat J. Vermeij's book *Evolution and Escalation: An Ecological History of Life*). The participants in these races must compensate for newly evolved defenses and counterdefenses by evolving new capabilities. Critical examples often come from studies of insects, in part because the multitude of possibilities is extensive as befits such a diverse group. The natural history of insects always tantalizes, offering us unexpected glimpses into a world seldom recognized except by keen observers. Vintage writing about insect natural history—seen in *Life on a Little Known Planet* by Howard E. Evans, Niko Tinbergen's *Curious Naturalists*, and May R. Berenbaum's monthly columns in *The American Entomologist* (collected in her book *Buzzwords*)—represents some of the best examples of the genre. In *How Not To Be Eaten: The Insects Fight Back*, author Gilbert Waldbauer successfully frames the natural history of insect predator–prey interactions against the understanding that predation has an inordinate influence on insect adaptation. This is important, given that insects play significant and central roles in natural food webs and ecosystem function.

The book emphasizes the incredible diversity of solutions that insects have displayed through evolution to ward off the continual challenges that face them. To illustrate such a diverse array of predator–prey interactions, Waldbauer organizes his book according to the many ways that prey can thwart detection or reduce predators' capture efficiency—fleeing and hiding, mimicking or appearing to be something not considered edible, inducing startle responses, reducing risk through safety in numbers, maneuvering with defensive tactics, and warning predators by using chemical defense signals. To complete the continuously evolving cycle, Waldbauer also describes predator countermeasures that arise to combat these prey defenses.

How Not To Be Eaten is engaging in its descriptive and wide-ranging examples. Waldbauer's writing highlights an understanding of the detailed