SYSTEMS BIOLOGY

The Origins of Stability

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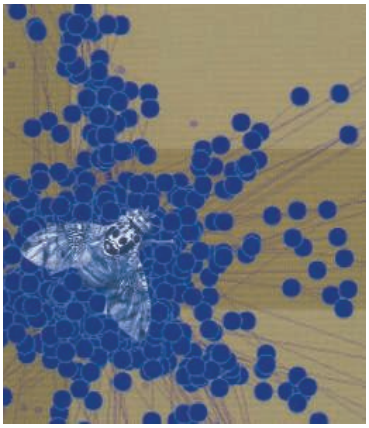
In the last few months, five airliners have crashed in various places around the world, apparently due to unrelated failures. On reflection, this is not so surprising—considering the amount of time that I spend sitting on tarmacs waiting for cockpit warning lights to be heeded. Manifold failures must be occurring frequently, so I assume that engineers have built in fail-safe mechanisms that allow planes to cope with them. So too must organisms be robust to genetic and environmental perturbations. Only instead of having been designed to be robust, they have evolved that way. In *Robustness and Evolvability in Living Systems*, Andreas Wagner synthesizes the mechanisms and consequences of such biological buffering. The book, a volume in the Princeton Studies in Complexity series, is sure to lay the foundation for growth of research in this underappreciated field of study.

Robustness and Evolvability in Living Systems
by Andreas Wagner
Princeton University Press, Princeton, NJ, 2005. 383 pp. $49.50, £32.50. ISBN 0-691-12240-7. Princeton Studies in Complexity.

In the first half of the book, Wagner (a computational and theoretical evolutionary biologist at the University of New Mexico) provides a masterful survey of the literature on robustness at all levels of biological organization, from the genetic code through RNA and protein structure to metabolic organization and pattern formation during development. Biologists and engineers alike will find snippets of interest in these chapters, and taken together they ought to convince even the most skeptical reader that robustness to perturbation is a pervasive aspect of biology. In the book's second half, Wagner reviews the theory of robustness. His readily comprehensible account uses only such mathematics as is essential to convey the key concepts. Wagner offers some new theory, but for the most part his treatment is synthetic. Nonetheless, it certainly provokes thought in new directions.

Perhaps the most crucial chapter of *Robustness* is the one that hinges the book's two main parts, in which Wagner introduces the concept of a neutral space. Rather than being defined in terms of adaptive value, the term neutral is used more loosely in reference to the observation that there are always multiple different ways to achieve any objective: all of the equivalent solutions occupy a neutral space. For example, the long neck of a giraffe could have evolved either by addition of extra cervical vertebrae or by lengthening of the existing ones. Or, considering changes at the molecular level, any given RNA or protein secondary structure can be achieved by hundreds of different sequences so long as substitutions don't disrupt the folding energy. Wagner makes three observations about neutral spaces: (i) They are ubiquitous at all levels of organization from molecule to organism. (ii) Different points in neutral space will generally vary in their robustness to perturbation. (iii) Natural selection will tend to favor the most robust solution.

It may seem intuitive to conclude from these observations that the evolution of robustness is inevitable, but Wagner recognizes and explores two reasons why this is not actually the case. First, the most robust solution may not be accessible from all places in the neutral space. (Adding and growing cervical vertebrae are completely different developmental mechanisms; once one has been settled on, it is almost impossible to explore the alternative.) Second, selection only leads to evolution if the variation is heritable. Unfortunately, quantitative genetics—which is central to understanding the capacity for genetic components of robustness to evolve under selection—is the one aspect of the theory of robustness that the author does not treat in much detail in the book.



Nevertheless, Wagner does a wonderful job of outlining the parameters of the debate. He recognizes two basic difficulties. One is a catch-22: the more robust a system becomes, the less variable it is (by definition), and the less raw material there is available for selection to act on. A possible—but as yet unsubstantiated—solution to this dilemma is that environmental variation is always present. Thus, so long as selection acts to reduce environmental noise, genetic robustness might be expected to evolve in parallel. A more basic conundrum is that robustness must involve non-additive genetic interactions, but quantitative geneticists have—for the better part of a century—generally accepted that it is only the additive component of genetic variation that responds to selection. Consequently, we are faced with the observation that biological systems are pervasively robust but find it hard to explain exactly how they evolve to be that way.

Wagner's provocative suggestion is that very often the robustness may be an intrinsic property of biological systems, an inevitable consequence of processes that make order out of chaos. He considers two basic buffering mechanisms, redundancy and distributed robustness, and he concludes that the latter is much more commonly responsible for robustness. That is, whereas gene duplication (for example) certainly provides fail-safe switches on occasion, it does not appear to be the general solution we might naïvely expect. Rather, we should look to the capacity of whole systems to absorb the effects of environmental noise and genetic mutation, whether through compensatory nucleic acid or amino acid interactions or by shunting metabolites through alternate components of the network. Perturbation is distributed, and robustness is built into the very structure of biochemical and physiological organization.

Several years ago, Stuart Kauffman prefaced *The Origins of Order* with the observation that "no body of thought incorporates self-organization into the weave of evolutionary theory" (*1*). *Robustness and Evolvability in Living Systems* adds an extra dimension to this endeavor. Wagner contributes significantly to the emerging view that natural selection is just one, and maybe not even the most fundamental, source of biological order. His two-page epilogue throws out seven open questions for systems biologists and neo-Darwinians to consider; hopefully they will do so.

Reference

1. S. A. Kauffman, *The Origins of Order: Self-Organization and Selection in Evolution* (Oxford Univ. Press, New York, 1993).

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