Cell

Universal Rules of Regulation

The Serengeti Rules: The Quest to Discover How Life Works and Why It Matters

Author: Sean B. Carroll
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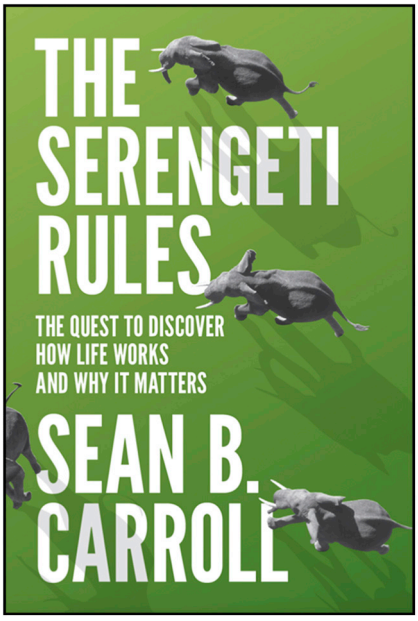
The latest book by the accomplished evolutionist and molecular biologist Sean B. Carroll was born during two trips to African natural reserves—Serengeti in Tanzania and the recovering Gorongosa National Park in Mozambique. Carroll is well known for his influential popular books on evolution and the science of evo-devo; however, writing in the background of Earth's most impressive ecosystems has turned his attention to ecology. *The Serengeti Rules* shows that the rules governing the behavior of ecosystems are no different from the molecular rules that regulate processes in our cells. This is a book about the universality of regulation in biological systems across scales and a powerful demonstration that biology indeed has simple unifying principles to lean on. The book manages to thoroughly explain the rules of regulation by telling exciting stories about discoveries of biological processes at the molecular level. These are discoveries carried out by famous scientists of the past and are followed by the discussion of less well known, but no less exciting, equivalent rules in natural ecosystems. The basic science stories are interspersed with accounts of how deregulation in biological systems impacts our daily lives not only in the form of disease, but also in the form of ecological disasters. Although science may offer solutions to these problems, the necessity to work out sensible public policies to implement them dominates the last part of Carroll's book.

The first two chapters of the book begin with episodes from his trips to the African savannah, leaving the impression that the structure of the book will follow this scheme. It turns out that Carroll merely uses the excitement of coming into close proximity of a charging elephant to introduce his first scientific hero, the Harvard physiologist Walter Cannon, who described the "fight-or-flight" response and used his war time experience of treating wounded soldiers in shock to establish the principle of homeostasis. Cannon's work revealed that physiological processes operate to maintain, or as Carroll likes to put it, regulate, body conditions within certain ranges. He points out that homeostasis is a unifying concept in physiology and biology, whose impact is comparable to Darwinian natural selection, and it is all about regulation. Interestingly, at about the same time, Charles Elton, from Oxford University, was discovering the basic rules that regulate animal numbers. By going on dangerous maritime trips to remote arctic islands or by using the historical records of lynx fur trappers of Hudson Bay Company, he set the foundations of the science of ecology. Although Cannon's and Elton's research goals and approaches couldn't have been more different, they converged on the same principle of homeostatic regulation and provided Carroll the opportunity to present the main point of his book in two short and fun-to-read chapters. These two scientific giants had no contact with each other, which underscores that neither the biological nor the ecological field holds the precedence in the discovery that regulation plays a major role in biological processes. While their work pointed to the importance of regulation in human health and in nature, it did not explain how such regulation works. The rules of regulation were worked out on yet another, molecular level of biological complexity, and it is the pioneering work of molecular biologists that Carroll turns his attention to next.



The following three chapters present the discoveries of Jacob and Monod in what was, in those times, considered as a rather boring subject of enzyme adaptation but turned out to be the second secret of life, Brown and Goldstein's discovery of cholesterol regulation that led to the establishment of the "penicillin for cholesterol" and prolonged countless lives, and finally, the story of the lone woman in the book (not Carroll's fault), Janet Davison Rowley, who worked on the role of chromosomal translocations in cancer. What emerged from these studies were the basic—as we would nowadays say—network motives of biological regulatory systems, namely the positive and negative regulation, double-negative regulatory logic, and feedback regulation. Carroll barely manages to contain his excitement over the science and the scientists. In those days, scientific careers were usually interrupted by a world war or involved a perilous sea voyage or some other form of adversity and ended with a Nobel Prize. All that makes for good storytelling, of which, Carroll is a master. Regarding the two medically oriented examples of biological regulation (cholesterol and cancer), Carroll discusses the challenges of transitioning from basic research insights into widely used and useful disease cures. It would have been an opportunity to point out that the roots of these therapies lie in the discovery of basic universal principles of regulation in systems quite remote from known medically relevant models (to name some extremes, bacteria and rabbit fox population dynamics). It is thanks to the universal nature of the rules of regulation that such seemingly abstract research is valuable. Instead, Carroll

ends this section of the book with a conservative, albeit rather optimistic outlook on the march toward cancer therapy, which departs from the main narrative thread of the book.

Nonetheless, all these intimately familiar molecular stories have just been a warm up. In the second part of the book, Carroll takes us on an excursion to the less known science of ecology, which, although not marked by a string of Nobel prizes, offers no less compelling tales of biological regulation and scientific serendipity. We meet Robert Paine, zoologist from Seattle who would travel for years to a Mukkaw Bay at the tip of the Olympic Peninsula and with his own hands would hurl starfish, the local predator, from the patch of intertidal zone out into the ocean. Soon, his ecology experiment was yielding results: the composition of species changed, mussels, one of the main food sources for starfish, grew numerous, and he witnessed the rise of a predator snail. Back on the African Serengeti, we follow Tony Sinclair's work on regulation of abundance of different animal species in this amazing place. Smaller preys—such as various species of antelopes—are regulated by predators, while larger mammals—such as hippos—are limited by food supply and population density. The effects spread through food chains or webs, concepts first introduced by Elton, and indirectly affect animals that do not even compete with each other for food or space. Carroll expresses these interesting animal relationships in the form of simple network diagrams, first introduced in the molecular chapters, indicating who eats whom in the food chain. In doing so, he drives home the major message of the book: both ecology and molecular biology follow the same set of general rules of regulation.

Just as deregulation of genes causes cancer, ecosystems can be thrown off balance with widespread and unpredictable consequences. Carroll documents sick ecosystems in diverse examples from around the world—from algae overgrowth in Lake Erie in Ohio, to devastation of rice fields by planthoppers in Cambodia, and to baboon invasion in Ghana. And just as cancer can sometimes be healed by targeting the regulatory mechanism gone awry, knowing the rules of regulation in particular ecosystems also offers opportunities for local intervention, including the gradual remedying of the often economically devastating problems. Carroll again presents several compelling examples, with the one closest to his heart being Lake Mendota in his own backyard in Wisconsin. To his credit, Carroll avoids being dogmatic, admitting that introduction of a predatory fish to the lake, based on scientific analysis of its dysfunctional food chain, was not the sole reason for turning its fortune. A major issue coming to the forefront in these chapters on ecological reverse engineering is the subject of public policy and support for these science-based initiatives, which, unlike in cancer treatment, not only affect an individual, but entire communities and nations. The slow recovery of Mozambique's Gorongosa National Park, once a paradise of biodiversity, and later reduced to ashes by years of war, serves as a backdrop for these discussions. Carroll highlights the crucial role of the American entrepreneur turned philanthropist, Greg Carr, in essentially rebuilding the Gorongosa ecosystem from scratch.

In the final chapter, Carroll argues that the way forward to solve the major ecological challenges lies in local initiatives driven by scientists, philanthropists, politicians, governmental agencies, nonprofit organizations, and the public. The final example of the book describing the eradication of smallpox with minimal resources but sound management based on scientific principles shows that targeted local approaches can be successful and add up to generate global impact. Carroll finds a surprising ally in Pope Francis and his encyclical letter "On Care for Our Common Home." Perhaps deliberately nowhere in the book Carroll mentions the politicised issue of global warming, although it is very much related to the subject of his book—de-regulation at the level of the ultimate, planetary scale.

For biologists, Carroll's book successfully conveys a powerful message: although biology is infinitely complex and diverse, simple sets of rules of regulation that apply across scales, from molecules to the entire planet's ecosystem, can and have been identified. They are also remarkably easy to explain, as shown by the many beautiful examples described in the book. So perhaps, next time a physicist or mathematician views biological research as lacking fundamental theoretical underpinning, a glimpse into Carroll's book, along with a primer on natural selection's theory, might help them reconsider their arguments. *The Serengeti Rules* is a great read, and it's not string theory.

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