BERLIN WEEDS AND A PARADOX OF LIFE

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Berlin lets its weeds grow. The medians in the streets play out a lovely succession of flowers and seeds. The plants have diverse architectures, follow different schedules, and capture light and nutrients in various ways.

The aesthetic beauty arises from the haphazard order. Haphazard because no gardener planned, buzzed, and cleaned the beds – just whatever happens to grow. Ordered because those plants that do not follow a disciplined life course do not last; what does last must adhere to nature's harsh constraints.

What are nature's harsh constraints? The phrase "the economy of nature" captures the problem well. But somehow the easy smoothness of those words does not bite as hard as it should. Perhaps those words are too familiar to tell the story of the weeds.

One can, as always, find a nice quote from Darwin:

> *The elder Geoffroy and Goethe propounded, at about the same time, their law of compensation or balancement of growth; or, as Goethe expressed it, "In order to spend on one side, nature is forced to economise on the other side."*

The great statistician and biologist R. A. Fisher did even better in a note to Darwin's son, although Fisher's phrasing is rather technical:

> *An engineer finds among mammals and birds really marvelous achievements in his craft, but the vascular system of the higher plants [seems rather simple]. Is it like a First Law, not a great engineering achievement, but better than anything else for the price? Are the plants not perhaps the real adherents of the doctrine of marginal utility, which seems to be too subtle for man to live up to?*

Fisher's quote makes the same point as Darwin's, but evokes greater resonance between economic and biological thought. Fisher is simply saying that the disciplined side of nature does not create highly perfected organisms, but rather organisms that balance the benefits that may be gained by a certain improvement against the costs that must be paid to achieve that improvement. If the costs are too high, the cheaper strategy wins even if it seems to perform less well than it might.

In any case, the economy of nature produces haphazard order, which I find beautiful. Apparently, most people do not agree with my aesthetic judgment. Most cities, particularly in the wealthy neighborhoods, battle constantly against the weeds. Perhaps it says a bit too much about my life course that the little patches of weeds around Berlin evoke in me such strong feelings – both of relief and of joy.

I got to thinking about those lovely weeds, and about haphazard order, because I wondered what makes the Wissenschaftskolleg (Wiko) so successful as a place for scholars. One hears increasingly of how universities measure scholarly success by quantitative tabulations of citation rates, group sizes, or money acquired. The academic administrators have become aggressive gardeners, attempting to impose order along narrowly defined lines of success. Yet all the power of scholarly communities comes from natural diversity – the different plans of research, the various goals, the alternative methods.

By contrast, the Wiko adopts Berlin's benevolent attitude toward us scholarly weeds. A haphazard order does develop naturally here among the Fellows. We have, after all, already been long tested for our ability to survive and produce, just like the weeds that continue to thrive. Each year, I suppose, the Wiko academic community differs, depending on which seeds happen to arrive – never quite the same, but always following within a certain natural order imposed by the constraints of scholarship. The art is providing the right environment and yet letting the natural order grow of its own accord. It sounds simple, but the desire to intervene and arrange from above is so powerful that few weedy communities remain within the structured world of academies.

This year, I was part of the evolutionary immunology group. I developed two new collaborations, which never would have arisen outside of Wiko's opportunities for long, uninterrupted discussions. With Paul Schmid-Hempel, we started work on why some parasites make us very sick, whereas others do relatively little harm. With my wife of eighteen years, Robin Bush, we started our first formal scientific collaborations. In one project, we studied why individuals who are frequently exposed to dangerous infections, such as farmers or health care workers, seem to get sick relatively rarely. We suspect that, by frequent natural exposure to low levels of pathogens, such individuals may gain the same sort of benefit as a vaccination would provide.

Many other discussions among our immunology group proved very productive. But I want to return to the quote from Fisher that I gave above, particularly the line: "Is it like a First Law, not a great engineering achievement, but better than anything else for the price?" That simple idea, which must always be in effect, turned out to be the piece that I was missing in a problem regarding organismal design that had long bothered me.

The problem concerns an aspect of design that frequently arises in engineering. The problem is how to design a system to be more robust against inevitable failures in its components or against other sorts of perturbations to the system.

Computer hard disks provide a good example. Making a superior disk that fails rarely is very expensive. In systems that store essential information, the current solution is to use an array of relatively cheap disks. Each disk may occasionally fail, but all data are spread over the array of disks such that a particular failure can be compensated without loss of information. As the overall arrays become more sophisticated and reliable, the reliability of the individual component disks becomes less of an issue for the overall performance of the system. In consequence, component disks are made cheaply and to modest standards of reliability, rather than expensively and to high standards.

I had, for many years, believed that a similar sort of design tradeoff must arise in the evolutionary history of organisms. But I could not quite frame the problem correctly, so I continued to circle and approach from different angles. This year at the Wiko, I read and reread numerous engineering textbooks on control theory – the design of regulators to control the heating of buildings, the tracking of missiles by anti-missile defense systems, the complex braking systems of modern automobiles, and just about every other designed system that acquires information in order to adjust performance.

After many months of study, I could see the great benefits of applying engineering control theory to analyze the design of particular biological systems. But I was no closer to the deeper question: How, in general, does increasing robustness affect the design of the individual components that together make up biological systems?

The hardest part of any study in theoretical biology is to figure out what does not matter. We seem to want to include everything we know, and so end up with a muddled list rather than insight. For example, feedback loops are essential in the design of robust control systems, and occur widely in biology. So, for a while, I focused on feedback loops as my point of attack. But, even though feedback loops do play a key role in many biological systems, that was not the right path. I had to put those loops aside: They hinder understanding of the general problem. I will need those loops later when, once at the most general statement of the problem, I then must build back up to explaining the particular structures of different systems.

In the end, as always, I had to go back to the economy of nature, and to figure out how nature would find designs that would be "better than anything else for the price". It does not matter whether I am thinking of the homeostatic systems that keep body temperature in a narrow range or the repair mechanisms that fix damage to the DNA of our cells. In every case, nature will adjust design to be better than anything for the price. But how does one turn that vague and generally true invariant into an insight about real organisms?

Let me restate the question: How do biological systems evolve to deal with perturbations from the environment, such as swings in temperature or chemicals that damage DNA? For now, I am not interested in the various control systems that deal with each individual sort of perturbation, but rather in the principles that tell us something very general about the evolutionary history of organismal design to protect against perturbation.

The answer turns out to create an interesting directionality in the history of life with regard to organismal design. The argument follows a series of simple steps.

Environmental perturbations favor organisms to become more robust. Enhanced robustness, as a shield designed to protect organisms from fluctuations caused by external challenges, also has the consequence that fluctuations in the organism's internal characters have less consequence.

If enhanced robustness protects the organism against fluctuations in its own internal traits, then greater robustness means that degradation of those internal traits has less consequence for organismal performance.

If a degraded trait does not reduce performance as much as it would have before protection by a robustness mechanism, then natural selection will often favor a less costly, lower performance trait. In other words, evolutionary design favors traits that are better than anything else for the price, not designs that are the best that nature could possibly make.

Over time, the dynamics play out as follows: robustness mechanisms reduce sensitivity to perturbation; those traits buffered by robustness degrade to lower performing and less costly states; new robustness mechanisms arise; further decay follows; the cycle continues. Robustness mechanisms that buffer against perturbations become layered on top of each other, while the underlying traits become replaced by cheaper, lower performance components.

This theory explains the evolutionary history of maladaptation – the evolution of traits that degrade and do not perform as well as they might. Again, the principle is: better than anything else for the price.

The paradox of robustness arises because each increase in robustness improves organisms by protecting them against perturbations, but evolutionary decay follows in the performance of the underlying characters that are shielded by enhanced robustness. Improvement and decay go together through evolutionary history, creating a directionality in the course of life.

One may feel a bit cheated to have worked all the way to the end here, to find that I just keep repeating "better than anything else for the price". What can I actually explain? What is the evolutionary history of mechanisms to regulate temperature against environmental perturbations? How have repair mechanisms actually evolved to protect against dangerous environmental chemicals?

Now that I have divested myself of all that does not matter, I understand the central paradox that tells me what to look for. So I can try to answer those questions. They set the stage for my next project.