Concept

Robustness: A Key to Evolutionary Design

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Why bother about robustness? Engineers wish to create systems that are both functional and robust. *Robustness* is the ability of a system to maintain its functionality across a wide range of operational conditions. Different conditions arise, for example, from environmental variation, input perturbation, sloppiness of system components, and subversion (e.g., computer viruses). In the life sciences, robustness has been an implicit theme for more than a century. For instance, biologists have long understood mechanisms of thermoregulation that enable homeothermic organisms to operate throughout an impressive range of ambient temperatures. It would thus seem like selling old wine in new bottles if one claimed robustness to be a new theme of the life sciences. New, however, is the recognition that robustness is a key to understanding the evolutionary design of virtually all living systems (see Kitano 2004 for an excellent review). This is why it is now worthwhile to further develop the biological concept of robustness and to reflect on its role in the life sciences.

The clockwork metaphor Unlike an engineer who designs his own system, a biologist studies a system that has been designed by the process of evolution. Understanding the functionality of living systems is therefore a matter of understanding the selective forces that have shaped these systems. The circadian clock, for example, is thought to have evolved as a means to regulate the phase relationships of different physiological processes during a daily cycle. This requires an oscillator with a period close enough to 24 hours so that it can be entrained. Circadian clocks produce their oscillation predominantly via a negative feedback loop (Rensing et al. 2001), a simple mechanism that would seem to explain the clock. Yet, the clock has to operate well under different temperatures, and the chemical reactions involved in the feedback loop are temperature-dependent. To understand the robustness of the clock, the mechanisms that compensate for the effect of temperature must be investigated (Bell-Pedersen et al. 2005). In other words, to understand the biological "clockwork" one has to study not only how its chemical "springs and wheels" produce an oscillation with a period of about 24 hours, but also how they maintain this period when environmental conditions change. Without asking about robustness, many "parts" of the clock would be incomprehensible. Important features of most evolved mechanisms will be difficult or impossible to understand without recognizing their role in creating or enhancing robustness.

Strategy versus stability The autopilot is designed to keep an airplane close to a preset course in the presence of perturbations. In a similar spirit, the entrainment mechanism of the circadian clock keeps it synchronized with the external diurnal rhythm—the preset cycle of the clock. It would be very misleading, however, to generalize from these examples that robustness typically means keeping the system near a preset point or path. The strategic view of robustness captures the idea that different environmental conditions often call for quantitatively and qualitatively different ways of maintaining functionality (for a review see Hagen and Hammerstein 2005). In the game-theoretic sense, a *strategy* is a list of instructions that specify how to acquire and use information to make decisions. Water fleas (*Daphnia*) provide a simple example. They have an evolved capability to grow a large helmet-like structure that defends them against predation. The helmet is expensive, however, so water fleas first probe the water for chemical traces of predators and grow the helmet only if predators seem to be present (Agrawal et al. 1999). Another example for conditional adaptive responses to circumstances is the diauxic shift found in yeast, where different metabolic pathways are chosen according to the availability of glucose and ethanol (DeRisi et al. 1997). Although robustness will often entail maintaining the system within a narrow range of parameters, it will also

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often entail strategically shifting the system into a dramatically different mode of operation.

Learning as a strategy to achieve robustness The case of the water flea shows that learning even a simple fact about the environment can play an important role in creating robustness. How much learning can contribute to robustness depends strongly on the *time scale* on which environmental variation occurs relative to the time scale of the potential responses; if the predator density of a water flea population changed unpredictably on an hourly basis, water fleas would have little to gain from probing the water for their long-term developmental decisions.

The vertebrate adaptive immune system is a prime example of a system that provides robustness via learning. It has to deal with an extremely wide range of different pathogens that all cause different operational conditions and may evolve rapidly, often within the host itself. Natural selection cannot generate specific responses against all pathogens. Instead it has "discovered" a powerful *abstraction* that applies to most pathogens: their proteins differ from host proteins. Thus, the process of natural selection itself "learned" about abstract properties of the environment that are stable on an evolutionary time scale, and it generated specialized cellular systems that learn on an ontogenetic time scale to identify pathogens by detecting their foreign protein. Leimar et al. (in press) discuss more subtle aspects of the interaction between natural selection and learning, showing that an organism can query its own genome for information about local environmental conditions on an intermediate time scale.

Overfitting Systems that achieve robustness via learning face a dilemma. Improved decision making requires the collection of increasing amounts of information, but more data can lead to worse decisions. Decision-making machinery must avoid tailoring decisions to the noise in the signal instead of the signal itself, a task that becomes increasingly difficult as the degrees of freedom in the decision machinery increase relative to the number of data points available. When information in the environment is structured in certain ways, the decision-making machinery can exploit that structure to make better, more robust decisions with *less* data. If, for example, environmental cues are *noncompensatory*, that is, if combinations of lower ranked cues cannot outperform higher ranked cues, simply relying on the highest ranked cue available and ignoring the rest can result in more robust decisions (Gigerenzer and Todd 1999).

Avoiding the cost of learning In the example of the water fleas, we saw that learning helped them to avoid building a costly helmet when there were no predators. While learning decreases certain costs of robustness, it may itself cost a lot. Imagine a person trying to explore the nutritional value of wild mushrooms by trial and error. The result would be fatal and the same person would be better off by imitating others who tried first and remained in good physical condition. Learning by imitation can thus be a particularly cheap way of achieving robustness (e.g., Boyd and Richerson 1985). This seems to be the key to understanding the evolutionary origin of mental design for cultural transmission, a Lamarckian process that makes it possible for humans to survive under a variety of severe environmental conditions.

Robustness tradeoffs Robustness of a system against certain challenges typically creates vulnerabilities to others. The "openness" of the human mind for cultural influence helps us avoid poisonous mushrooms but it also creates a risk of adopting dysfunctional behavior, such as sacrificing children to the gods. Kitano (2004) points to another well-known example of fragility that goes along with robustness. Human physiology evolved to support a lifestyle with high-energy demands in an environment with limited resources, but when challenged by overnutrition and a low-energy lifestyle it can lead to the modern plague of *Diabetes mellitus*.

Specifying robustness The tradeoffs between different robustness requirements and the cost of robustness imply that no system can be robust against all variations that might occur under real operational circumstances. Therefore, it is pointless to simply call a system robust or nonrobust. Two specifications are needed, namely, what the system is robust against and what functions are maintained. In studies of robustness and organismic design, the only functions that matter are those that have evolved by natural selection. One reason is that it is extremely unlikely that specialized robustness features would accompany any unevolved (e.g., by-product, or random) functionality. A deeper reason is that the very concept of design makes little sense in the absence of a design process, such as natural selection or engineering.

Signaling and subversion Signals play a particularly important role within organisms and among individuals of highly cooperative species. Because in both these cases there is little or no conflict of interest, signals should be as cheap as possible while still maintaining reliability. Cheap signaling systems enhance the efficiency of the organism or cooperative system but they are also more easily subverted by exploitative agents (Markl 1985), such as pathogens or politicians. Plants, for example, deter insect and mammalian herbivores by producing a number of alkaloids that closely mimic neurotransmitters (Wink 1998). For another example, there is a species of beetle that obtains food from ants by mimicking their feeding signals (Hölldobler 1977). Because the immune system relies on a variety of cheap chemical signals, it too is vulnerable to

subversion via its signaling network. Viral chemokines, for example, can mimic host chemokine function or act as receptor antagonists and thus help evade the immune response (Liston and McColl 2003). These examples show that signaling systems are usually vulnerable to some degree of subversion. Organism robustness then is not only to prevent subversion but also to maintain key functionality despite subversion.

Molecular systems As we just saw for immune system signaling, questions about robustness arise naturally in systems biology. Let us address another example. In cancer research, signaling cascades triggered by the RAS molecule have been investigated intensively. RAS is known to act as a switch in the context of cell division. A detailed look at RAS-activated MAP-kinase cascades shows that there are (a) many steps before the signal reaches the promoting areas of genes involved in cell division, (b) several links to other pathways along the path, (c) parallel paths, and (d) positive and negative feedback loops. Analyzing the pathway architecture raises the following questions relevant to robustness (Blüthgen and Herzel 2001). Are multiple steps needed to amplify the signal and thus make it more reliable, or are the steps nodes at which information is processed? Can the feedback loops be understood as design features that contribute to the stability of the switch? What prevents fatal cross-talk from occurring among somewhat connected signaling paths? Similar questions about the link between system design and robustness occur for many other molecular systems.

Feedback loops Chemotaxis (tracking chemical gradients) is a widespread method to find a target, but in order to work well, the chemotaxis mechanism has to be sensitive to differences in ligand concentrations that may vary by orders of magnitude. *Escherichia coli* has solved this robustness problem with the help of integral intracellular feedback (Barkai and Leibler 1997; Alon et al. 1999; Yi et al. 2000). In integral feedback control, a standard engineering technique, the difference between the actual output and the desired steady-state output is fed back into the system. The steady-state error will then be small despite fluctuations in the input or in the system parameters. This illustrates that at least in some cases there are close parallels between nature's approach to robustness and that of human engineers as seen in *control theory*. It also illustrates that the absence of a brain is not the absence of the sophisticated information processing machinery needed for robust adaptation.

Phage λ, a virus that infects bacteria, is one of the simplest living organisms. It can develop along one of two pathways. It either directs the bacterium to produce new phage particles (lysis) or it establishes dormant residency (lysogeny). The observed stability of this decision was originally thought to depend on fine-tuning of the binding affinity of promoters to the appropriate regulatory factors (Ptashne 1987). The decision then hinges on delicate chemical specificities. It is likely that such a design would lack robustness to, for example, mutations in the promoter region. Here, the worry about robustness immediately casts doubt on an otherwise plausible idea. Inspired by this doubt, researchers have shown that positive and negative feedbacks of the regulatory network are responsible for the stability of the decision (Santillan and Mackey 2004; Zhu et al. 2004). Differences in binding affinity are less important, and the decision mechanism is robust against point mutations in the promoter region. These results demonstrate impressively how well the concern about robustness of biological systems can guide our thoughts toward a better understanding of evolved design.

Modularity Modularity is an important design principle that helps reduce the damage caused by malfunctioning parts and the risk of unforeseen side effects of otherwise well-functioning processes. Modularity localizes damage and reduces unintended interactions, thus enhancing robustness against internal errors and dysfunctional interference. Not surprisingly, it has been found to be a characteristic of the design of both living and human-engineered systems (Hartwell et al. 1999; Schlosser and Wagner 2004; Callebaut and Rasskin-Gutman 2005).

Redundancy In order to be robust against failure of system components, it is useful to have more than one way of performing a task. A special version of redundancy is to possess two copies of the same system component, such as having two kidneys, or two identical alleles of a gene in a diploid genome, or duplicated genes in a haploid genome. Kitano (2004) expresses the view that nature rarely creates multiple identical alternatives. Analogously, if we look into a carpenter's toolbox, we would rarely find several functionally identical screwdrivers but rather an assortment of different ones. Yet, if one is lost, another screwdriver can often be found that replaces the missing one reasonably well. Redundancy may be particularly important for critical components that regenerate poorly or not at all. The liver regenerates well and this may relate to the fact that there is only one.

Development and robustness One of the miracles of life is that the developmental process and resulting phenotype vary remarkably little in response to genetic and environmental noise. This is why we can talk at all about species, sexes, developmental stages, organs, tissues, etc. The robustness can come from mechanisms that actively buffer against variation, such as thermoregulation, or it can come from mechanisms that are intrinsically insensitive to variation. von Dassow et al. (2000) have shown in their gene interaction model of the *Drosophila* segment-polarity network, for example, that the

network is intrinsically insensitive to significant variation in its parameters. An additional factor in robust development is the homogeneous environment created by the large number of very similar cells in growing tissues, which reduces robustness requirements. Of course, robustness problems had to first be solved at the cellular level in order to create this homogeneity. The concept of robustness in development is not new and seems to capture much of what is meant by *canalization* (Gibson and Wagner 2000).

Final remarks Our perspective on robustness differs from some others in that we emphasize strategies over stability per se. Strategies typically involve switches. The different states caused by the switch are often the means by which robustness is achieved in a world where operational conditions vary. The robustness of the switch itself is of secondary importance, yet systems biology sometimes emphasizes the latter over the former. A strategic perspective also enriches our understanding of robustness by, for example, incorporating various forms of learning as important elements of robustness. Furthermore, strategic analysis draws particular attention to tradeoffs among different robustness requirements and to the costs involved. Finally, since any strategic analysis is founded on the interests of agents, this approach highlights the importance of robustness to subversion.

Despite our emphasis on strategic analysis, we are not arguing that all such analyses adequately address robustness. Far from it. "Tit for tat" is perhaps the most famous strategy for cooperation in repeated games, and yet it is spectacularly nonrobust to errors of strategy execution (Selten and Hammerstein 1984). A single mistaken defection by one player prevents any future mutual cooperation.

Robustness is a broad theme that cannot be captured in any single definition. Nevertheless, it is essential to consider it when studying any organismic system. If such a system appears to be lacking important robustness features, one has probably misunderstood its evolved design.

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