## The Understanding of Biological Robustness and Fragility

Life is able to withstand internal and external fluctuations at various frequencies and timescales. These disturbances include genetic mutations, localized stochastic variations in molecular concentrations, infectious illnesses, and physical regime shifts. [1] Many biological systems have an inherent ability to sustain specific functions or qualities when subjected to specific disturbances, which is referred to as "biological robustness." [2] Biological robustness is one of the observed properties of biological systems. It is regarded as a fundamental property of complex, evolvable systems. Biological robustness is a characteristic shared by all biological systems. It ensures that specific system functions are maintained in the face of external and internal disruptions. The fundamental processes that provide resilience are system control, alternate (or fail-safe) procedures, modularity, and decoupling. [3] Numerous examples of biological robustness can be found in various biological systems. One of them is shown below. Because of integrated intracellular feedback that assures flawless adaptation and is independent of ligand concentration, Escherichia coli is capable of chemotaxis over a wide range of chemoattractant concentrations. [4-6]

Biological robustness allows changes in the structure and components of the system owing to perturbations, but specific functions are maintained. On the other hand, without robustness, the biological system is unable to change its model while maintaining essential functions for survival. Apart from that, in an evolutionary perspective, robustness is an intrinsic quality of complex evolving dynamic systems, and the various features that give rise to robustness enhance biological system evolution. The structural requirements of the system required for evolution, in particular, require resilience to be maintained such that disturbances from the external environment and internal perturbations from its own genetic mutations have no major detrimental impact on the biological system.

Biological fragility is a concept induced in the context of the trade-off problem of robustness in biological systems. In the context of biological robustness, biological systems that have good stability against general perturbations are extremely vulnerable in the face of rare perturbations. This is the problem of biological fragility and the robustness trade-off. [7-8] In response to fragility, consider the following: A forest buffer zone and tree planting patterns suited for specific types of fire can be very vulnerable to unanticipated types of fire that may ignite from unexpected directions. They also claimed that while a design with a high degree of freedom may be better for expected disturbances, it is extremely vulnerable to unexpected perturbations. Such trade-offs, of course, are not restricted to the basic design of buffer zone locations. If one decides to plant all the trees around a city in a circular pattern to be able to deal with fire from any direction, such a design may actually allow a fire to spread and encircle the city, causing significant damage. However, if all of the trees in the field are cut down, the city will be particularly vulnerable during the rainy season, as flooding will be more likely as a result of the trees' loss of water-absorbing ability. [9]

In HOT theory, biological fragility is an inevitable property of a biological system with good robustness, forming a trade-off with robustness. Therefore, we can start on robustness to avoid

vulnerability problems. Avoiding fragility could entail actively perturbing specific interactions or components to maintain or reduce robustness, identifying a point of fragility inherent in robust systems, and re-establishing control of the epidemic state by introducing a counter-acting decoy or new regulatory feedback.

## Reference

[1]Holling, C. S. (2001). Understanding the complexity of economic, ecological, and social systems. Ecosystems 4, 390–405.

[2] Visser, J., Hermisson, J., Wagner, G. P., Ancel Meyers, L., Bagheri Chaichian, H., Blanchard, J. L., Chao, L., Cheverud, J. M., Elena, S. F., Fontana, W., Gibson, G., Hansen, T. F., Krakauer, D., Lewontin, R.C., Ofria, C., Rice, S. H., von Das sow, G., Wagner, A., and Whitlock, M. C. (2003). Perspective: evolutionand detection of genetic robustness. Evolution 57, 1959–1972.

[3]Kitano, H. Biological robustness. Nat Rev Genet 5, 826-837 (2004). https://doi.org/10.1038/nrg1471.

[4]Alon, U., Surette, M. G., Barkai, N. & Leibler, S. Robustness in bacterial chemotaxis. Nature 397, 168–171 (1999). A seminal research paper on the robust adaptation observed in bacterial chemotaxis.

[5]Barkai, N. & Leibler, S. Robustness in simple biochemical networks. Nature 387, 913-917 (1997).

[6]Yi, T. M., Huang, Y., Simon, M. I. & Doyle, J. Robust perfect adaptation in bacterial chemotaxis through integral feedback control. Proc. Natl Acad. Sci. USA 97, 4649–4653 (2000).

[7]Carlson, J. M. & Doyle, J. Highly optimized tolerance: a mechanism for power laws in designed systems. Phys. Rev. E 60, 1412–1427 (1999).

[8]Carlson, J. M. & Doyle, J. Complexity and robustness. Proc. Natl Acad. Sci. USA 99 (Suppl 1), 2538–2545 (2002). An introductory article on the highly optimized tolerance (HOT) theory.

[9]Kitano, Hiroaki, (2007) Towards a theory of biological robustness. Molecular Systems Biology, 3. 137. doi: accession:10.1038/msb4100179.