Biological Robustness and Fragility

Biological robustness is a property that allows a system to maintain its function in the face of external and internal perturbations, not in absolute terms by keeping all properties intact, but relatively maintaining specific functions. This property allows organisms to change their mode of operation in a flexible manner - returning to the original state after a perturbation or entering a new state that maintains function under new conditions.

As one of the fundamental organising principles of biological systems, robustness mediates short- and long-term survival, reproduction and evolution, helps organisms generate flexible phenotypes to adapt to environment and contributes to the evolution of complex dynamic systems. Evolution always selects for a robust trait that can tolerate environmental perturbations, like the sub-optimal metabolic properties present in microorganisms such as *Bacillus subtilis* and *Escherichia coli*, investing valuable resources to predict changing environmental conditions at the expense of optimal growth, while complex biological systems must be robust to environmental and genetic perturbations in order to evolve. For any organism, systems must be robust in order to operate in unpredictable environments due to the unstable components.

There are many mechanisms to ensure system robustness, including system control, alternative (or fail-safe) mechanisms, modularity and decoupling. Where system control consists of negative and positive feedback, negative feedback is the main mode of control and allows for a robust response to perturbations. Bacterial tropism is its classic case, with *Bacillus subtilis* using negative feedback - particularly overall feedback - to obtain perfect adaptation. In the chemotactic movement of *B. subtilis*, the interaction between phosphorylated CheY and the receptor forms a negative feedback loop that inhibits CheA kinase in addition to the effects of methylation. These two mechanisms form a regulatory feedback loop - when there is an excess of

phosphorylated CheY, CheA is inhibited and inhibiting residue is preferentially methylated, whereas when the majority of CheY is unphosphorylated, CheA is not inhibited and activating residue is preferentially methylated. This feedback loop provides a regulatory mechanism for adaptation to *B. subtilis* deficiency.

Instead, biological fragility refers to the inability of an organism to maintain its original functions and properties in the face of a perturbation such as a change in the environment or loss of a functional component. Biological robustness and fragility are balanced to some extent, so often a increase in robustness at a particular frequency is compensated for by an equal fragility at other frequencies.

Examples of biological fragility are also common, for example, *E. coli* and *B. subtilis* share five immediate homologous proteins with apparently identical biochemistry to perform tumbling and running. In *B. subtilis*, cells still ran and tumbled when CheR methyltransferase or CheB methyl esterase was deleted, but in *E. coli* when CheB or CheR was deleted, cells could only perform one of the tumbling and running actions, representing the fragility of *E. coli* to the absence of both enzymes.

In biology, the main functions of systems are usually robust to various perturbations, but these systems may exhibit extreme fragility to other perturbations, and when this fragility is attacked, the system will be hard to maintain its original function and easily switch to other forms of expression. In the case of organisms, the consequences of fragility may be changes in metabolites, altered forms of locomotion or deficiencies in energy supply. One typical consequence is disease, for example, where the organism has acquired robustness against starvation, and diabetes can be considered a consequence of the organism's fragility to exposure to abnormal disturbances in a lifestyle of excess nutrition and low energy requirements. Because of the two regulatory feedback systems of glucose homeostasis are not symmetrical in direction, the feedback can tightly control glucose insufficiency, but loosely control excesses. One conjecture for this evolution is that historically erratic food availability

was an adapted and powerful perturbation for biological systems, but that overnutrition was an unusual external perturbation.

Theoretically, it is fundamentally difficult to avoid the emergence of fragility due to the fact that fragility is a by-product of robustness. Enhancing robustness often comes at the cost of complexity and another dimension of fragility, so perhaps upholding a middle ground, avoiding excessive demands for significant enhancements, and maintaining normal body functions are effective ways to avoid the emergence of extreme fragility.