

Robustness can be studied through the lenses of network theory, control theory and natural selection. It refers to the intrinsic ability of biological networks to maintain their stable state of functionalities and traits while being insusceptible and invariant with respect to both internal and external perturbations and uncertainty. Robustness is not necessarily a binary yes or no question. It also has a quantitative measurement dimension to it which refers to the maximum size of perturbations such as mutations, recombinations and the environment that the network or system can tolerate [1]. Mathematically, it can be modelled as the following: Assume if there is a network composed of a set of nodes,  $V$ , then  $V^*$  can be constructed as a set of perturbed variables,  $V^* \subset V$ . If the majority of nodes in this network are sparsely connected, then a random single deletion of a node will still make the network robust while a targeted deletion, say of a hub, will however make it fragile.

Fragility as a characteristic of biological networks on the other hand, is often seen as a trade-off associated with robustness.[2] Fragility can mostly be expressed in two ways, by point mutation and knockout mutation.[3]. In biological networks, robustness and fragility share a symbiotic relationship and are often correlated with each other. There can never be perfect robustness as an increase in robustness often reveals a new side of fragility. For example, Carlson and Doyle (2002) [4] explained that biological systems that evolved to be robust against most general perturbations have in fact been fragile against some forms of rare perturbations.

One example to consider is genetic robustness of biological systems to expected mutations. If one makes a random change to the DNA sequence in organisms, there will not be a genetic change of genotypes from being neutral to being adaptive. Specifically, the brain cells maintain robustness and resist changes in the gene expression levels, that is, brain gene expression profiles [5]. There are coordinated activities of genes that operate in brain cells throughout the process of the organism's brain development. In gene regulatory networks where the context is cell nucleus and the perturbation is chromatin remodelling, the robustness property is exhibited through gene expression patterns. It continues to function despite noisy expression of its constituent genes. The former refers to the capacity to generate a reproducible trait in spite of changing conditions.

One example of fragility in skin biology is the manifestation of genetic skin disorders. It is also known as epidermolysis bullosa with the clinical features of the skin exhibiting blistering, erosions and painful wounds as a result of compromised skin structure and weakened skin resistance to external mechanical and environmental forces. There is empirical evidence to suggest that this condition is triggered by mutations in eighteen distinct genes that encode proteins which are responsible for epidermal integrity and dermal-epidermal adhesion [6].

Robustness is a crucial biological property and integral to survivability since when most mutations have no effect, then there is less phenotypic variation for selection to act on in response to genotypic variation. While on the one hand this is thought to impede evolutionary innovation, on the other hand, it can be viewed as a higher order control that modulates and regulates the quantity and quality of heritable phenotypic variation which is good. There is also empirical evidence on the correlation between quantity of variation and opportunity for fitness adaptation, thus promoting evolvability [7].

One consequence of fragility is that it can lead to a key negative outcome of genome and chromosomal instability as its inability to complete DNA replication drives cancers and neurological diseases. The fragile genomic regions are unable to conform and become susceptible to deletions and/or functional alterations [8]. Fragility cannot be completely avoided, rather it can be controlled for. Overcoming fragility involves exploring the process of antifragility. This notion implies a property where agents improve their ability to thrive and survive under different and extreme conditions such as shock. It can also be taken to understand that biological networks will retain their same performance both before and after mutations [9].

#### References :

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