Viewpoint on Biological Robustness and Fragility

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Robustness and fragility are two correlated features of biological systems at all organizational levels and time scales. As introduced by Kitano, biological robustness can be defined as a fundamental property that allows a complex system to maintain its functions against external and internal perturbation, which is a broader and more general concept than stability or homeostasis (Kitano, 2007). However, it is counterintuitive that systems evolved to have a high level of complexity and robustness often harbor devastating fragilities. Biological fragility is the side effect of mechanisms embedded in robustness that leads to the failure of a complex system under certain perturbations. The two inseparable features make up the "robust yet fragile" trade-offs in a complex biological system (Alderson & Doyle, 2010).

Take gene regulation as an example, the development and differentiation of genes controlled by the hierarchical GRNs (Gene Regulatory Networks) are highly robust (Macneil & Walhout, 2011). For instance, the specific expression of *Hox* genes is tightly controlled to be within particular levels which determine the body structure and segment plan of the developing *Drosophila* embryo. The protein product of each *Hox* gene is a TF (transcription factor), which acts together with each other to control the increase or decrease in the expression of their downstream targets. In some insects, *Hox* genes are regulated by gap genes and pair-rule genes, which are in turn regulated by mRNA. Also, RNA binding proteins interact with mRNAs and regulate translation, and microRNAs repress mRNA stability by hybridizing to sequences within their mRNA targets. Thus, a complete control chain and a feedback loop are formed to withstand changes in stimuli and noise. Further, gene regulation is not a linear process, but rather occurs in the complex hierarchical networks of interactions, robustness is then generated.

Here, using the same example to explain fragility. Fragility is often unrelated to the size or frequency of perturbations, but catastrophic responses to small variations. As stated above, gene regulation is highly robust, but as the system is evolving to be more complex, more fragile sites are shaped too. Most diseases, including cancer, are initially due to single mutations, single gene or protein alterations, and their corresponding effects on the biological phenotype, which cause a cascade reaction in the whole cell and individual (Bianconi et al., 2015). *Hox* genes are at the heart of gene regulation, but research showed that misexpression of these genes can result in the formation of an extra pair of wings or the generation of legs in the place of the antenna (Casares, Calleja M Fau - Sánchez-Herrero, & Sánchez-Herrero). Although the probability of such an event is small, when a fragile site is exposed, it can have serious consequences for the whole system.

Biological robustness is an integral part of survival. It arises from the constructed mechanisms including redundancy, modularity, hierarchy, etc., which facilitate the adaptation and evolvability of the system. Redundancy, like isozymes and various cofactors, can make compensations for the system's viability and functionality when an error occurs; modularity and insulation can contain perturbations and allow parts to damage locally while minimizing effects on the whole system; hierarchies and feedback loops facilitate layered regulation and originate efficient management between the modules. These mechanisms determine how robust a system can be, and allow it to become a dynamic complexity to tolerate external and internal changes. Hence, robustness is the key for a biological system to gain adaptation and evolvability, and maintain specific functions for survival.

The consequence of fragility is always a catastrophic response leading to failures that affect the entire system. Robustness and fragility are inseparable, so what we need to consider is not how to avoid fragility alone, but how to achieve a balance between robustness, complexity, and fragility while optimizing the system. One important method is that robustness should be distributed to avoid a topological "bow-tie" architecture which leads to high potential sources of fragility (Whitacre, 2012). Besides, a simultaneous increase in robustness and reduction of fragility may be achieved if system performance is sacrificed. Trade-offs between resilience to repeated exposure and sensitivity to new and rare exposure in a biological system should be considered in systems design.

References

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