1. Biological robustness and fragility definitions and examples

Biological robustness refers to that the biology maintains its regular functions against outside perturbations and uncertainty [1, 2], which can be divided into environmental and genetic robustness.

Environmental robustness has many common examples in system biologies, such as yeast [3] and glycolytic pathway changes in tumor metabolism [4], which can regularly sustain ATP production under environmental disturbances. In terms of genetic robustness, one of the famous studies is research on the protein Hsp90, which stabilizes the unstable signaling protein by buffering for the genetic mutation [5]. Rutherford and Lindquist validated that the offspring of drosophila maintain a stable abnormal phenotype proportion of individuals when Hsp90 is mutant or drug-treated (geldanamycin), making up approximately 5% and 8%. Specifically, the normal flies are similar in their normal state, while the mutant stocks are quite different, such as having deformed eyes and legs. Hence, Hsp90 buffering contributes to biological robustness as a mutation suppressor.

As a byproduct of robustness, biological fragility represents instability in biological systems caused by specific perturbations [1]. The 'Highly Optimized Tolerance' (HOT) proposed by Carlson and Doyle (2002) [6] believed that the relationship between robustness and fragility is conservation, which means the system tends to be extremely fragile to gain robustness. Kitano (2004) [7] elucidated that although the chemical agents are robust for tumors, some perturbations might cause tumors to become exceedingly frail. For example, the key regulator in cancer cells, hypoxia-inducible factor 1 (HIF1) refers to angiogenesis and metastasis, which is potential target that give rise to cancer fragility.

2. Biological robustness is integral part of survival

As Charles Darwin proposed in his theory of evolution, "survival of the fittest," all living organisms have to be robust to resist environmental and genetic perturbations in the evolution process. Lots of examples can prove the robustness involved in biological processes and mechanisms [8-13]. Evolution and robustness have similar requirements - evolutionary survival frequently selects traits that may promote robustness and vice versa; various mechanisms in organisms that cause robustness drive evolution [1]. Therefore, robustness is an inherent property of evolution and a necessary part of survival.

3. Fragility consequences and solutions

As a byproduct of robustness, biological fragility causes the trade-off, leading to catastrophic failures such as extinction and therapeutic countermeasure problems. When the fragility of the robustness systems is exposed, they are the most vulnerable. Furthermore, the point of fragility may exhibit robustness to natural and therapeutic countermeasures if they exploit the intrinsic mechanisms of robustness to develop their robustness, such as influenza [7].

According to the theory of biological trade-offs, introducing various robustness cannot make the system more stable and might scarify the resource demands and system performance [1]. Therefore, one of the most direct methods is proposed, which is to creatively respond to changes in the environment and fix the bugs in the system. For example, Danchin et al. (2011) illustrated that changing the side residues or backbone of flexible regions of proteins can effectively result in antifragility [14]. In addition, fragility is often overlooked because it is

difficult to be detected accurately. One of the solutions is developing more advanced diagnostic methods and tools, such as molecular prenatal diagnosis of SXF [15] and STORM super resolution imaging systems [16]. However, except merely against the fragility, it can also be against by adding additional resource demands moderately or reducing the performance because the features of biological trade-offs are not independent [17]. For diseases, fragility can also be avoided by identifying the point of fragility inherent in a robust system, thereby establishing a basis for new regulatory feedback, or introducing counteractive decoys, similar to Trojan horses, to control the course of the disease.

Essentially, to avoid fragility, it needs to understand the structural characteristics of whole systems' robustness and evolvability, as well as the inherent nature of robustness and fragility, and then formulate effective countermeasures according to the mode of system failure. Nevertheless, the theory of biological robustness is not mathematically well-founded. It is known that perturbations in all dimensions cannot be measured. Hence, the fundamental solution is building a mathematically solid, unified quantitative index of biological robustness and fragility.

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