Q1

Biological system is defined as the merging of mutual dependent biological element networks into a whole [1]. According to Kitano [2], biological robustness is the ability of a biological system to conserve its functionality from alternation by extremal or internal perturbations. He believes that robustness is the fundamental property of the evolvable complex biological system, yet these robust systems also possess fragile characteristics. Fragility is the by-product of system robustness. The bio-fragility makes the complex system more or less susceptible to random mutations leading to different levels of alteration for the system functionality, such as gain-of-function (GOF) or loss-of-function (LOF) [3].

Biological robustness is an integral part of survival for the evolutionary organisms, which can be observed ubiquitously. Being robust does not mean that everything remains absolutely static in the biological system, it is the specific functions that need to be maintained while the system's structure and components are flexible for variation as long as they are reproducible [2]. For instance, the essential genes of the organisms that encode for products necessary for cell or organism survival in context of cell division and regulation, such as the human *TP53* gene. These essential genes will need to be naturally insensitive to external or internal disturbance, as perturbation such as knockout mutation will result in the increased rate of fatality of the organism, such as cancer development. Since the essential product required is no longer being produced due to the LOF of the corresponding essential gene, which will lead to lethal defects. While the non-essential genes that experience alternation may lead to phenotypic gene variants, but will not cause lethality. Biological robustness can also be seen in the embryonic development of *Drosophila melanogaster* in context of the anterior-posterior (segment) polarity, in which the segments identity are established, is an example of robustness, which in normal circumstances lead to normal growth and function. The pair-rule genes in *Drosophila* is essential for the regulation and maintaining para-segment boundaries, if mutation occurs, deletions may lead to reduction in segmentation. However, if the pair-rule genes in human such as hCbfa is mutated, skeletal formation defects will happen where one will have more fragile bones and absent of certain bones such as the collarbones. These gene mutations may not be lethal in short term but will to some extent affect ones living.

Systems with more optimizing networks tend to experience lower biological fragility as they are more responsive and less susceptible from perturbations [4]. However, most existing networks are not as optimized and tend to have higher fragility and lower responsiveness towards unexpected perturbations. For example in cancer immunoediting, the human immune system experience fragility when tumor cells are unable to be successfully eliminated by the adaptive and innate immune system leading to exhaustion in immunosurveillance and escape of tumor cells leading to promotion of cancer development. The enhancement of the robustness in human immunity must be done in order to overcome and suppress the tumor development, for instance the use of combinational cancer therapies. While in another extreme where excessive immune tolerance will lead to increase risk and fragility consequences such as autoimmune disease. Therefore, there must be an equilibrium between high robustness and low fragility, where the system is regulated to be resistant to stress and perform in high efficiency while reduction of accumulation in unwanted factors [5]. Another example would be the *Diabetes mellitus*, which the human metabolic system is vulnerable from over-nutrition and low-energy utilization lifestyle leading to the chronic disorder [6]. In which the upregulation of the glucose system must be maintained in order for the normal performance and prevention of disorder development led by these susceptible stress factors.

Robust yet fragile characteristic is the principle property of complex dynamic biological systems, The dysregulation and total breakdown of biological system's robustness will lead to fatal consequences. The understanding of the architectural structure allows understanding of biological phenomena and disease pathogenesis allowing for enhanced therapeutical treatment development.

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