Question 1:

Biological robustness is the ability of a biological system to maintain its function in the face of internal or external perturbations. On the other hand, fragility is the loss of this robustness in the face of unexpected or rare perturbations.[1,2]

An example of biological robustness can be seen in the human immune system. When we are threatened by one of the many foreign pathogens present in our environment (external perturbation), our immune system is able to counter and mitigate this infection through both the innate and adaptive immune responses. This eliminates the threat and ensures our continued survival (maintained function). Our immune system is very robust as it has the ability to recognize and eliminate a wide variety of pathogens, using both the innate immune system to non-specifically eliminate pathogens based on common characteristics, and the adaptive immune system to 'learn' and develop specific cell-mediated (T cell) and humoral (B cell) immunity to the pathogen. Adaptive immunity allows us to quickly mount a stronger immune response in case of reinfection by the same pathogen, essentially increasing our robustness against that pathogen. As there is often a trade-off between robustness and fragility, an example of fragility can also be found in the immune system. As CD4+ T cells are an important component of the adaptive immune system, infections like HIV which can selectively infect these cells can cause the immune system to collapse and render us vulnerable against opportunistic infections. In cases where the antigen presented by the pathogen is similar to native structures present in our own system, or mutations occur that causes our immune system to malfunction, autoimmune diseases can also develop where our adept immune system turns against our own body.[3]

As illustrated above, biological robustness plays an important role in survival as it allows us to cope with the multitudes of perturbations that we face every day in a dynamic environment. Perturbations can be external (eg. pathogens) or internal (eg. gene mutations). Being able to cope with genetic mutations – which happen spontaneously – also helps to ensure the evolvability of the species as a whole. By being robust against genetic perturbations, a variety of non-lethal or neutral genotypes can accumulate, which allows for diversity in the gene pool. In the face of extreme pressures that cause robustness mechanisms to breakdown, this diversity is exposed and it allows for selection and evolutionary change.[4–6] Hence, biological robustness is essential to both the survival of the individual and of the species.

On the other hand, fragility often leads to disease or death as shown above as well. Though fragility is unavoidable, there are mechanisms to increase robustness and reduce fragility. Kitano proposes four essential mechanisms for robustness in his review[7]. The first is by having extensive systems control, namely negative and positive feedback loops, which can help to maintain the system at a certain state or function despite perturbations. For example, negative feedback helps to maintain blood glucose levels within a normal range regardless of acute or small changes in caloric intake by adjusting insulin and glucagon levels based on blood glucose levels. Secondly, redundancy or phenotypic plasticity is a good way to maintain robustness. Redundancy involves having multiple copies or alternatives of a component/pathway, allowing for function to be maintained when only one copy fails. For example, in autosomal recessive diseases like cystic fibrosis or spinal muscular atrophy, if only one copy of the defective gene is inherited, the disease does not manifest because function can still be maintained with the other copy. Phenotypic plasticity on the other hand allows the organism to change its phenotype to adapt to perturbation. For example, the tardigrade can enter a dormant state under extreme dehydration, allowing it to survive for years.[1] Thirdly, having modularity in a system helps to prevent total system failure. This is because any fragility in one module will not affect others. If the module is not essential, the system can still function. Lastly, decoupling, the isolation of low-level noise from high-level functionality, is another way to ensure robustness. An example of this is the ability of heat shock proteins (HSPs) to fix misfolded proteins, providing a genetic buffer and preventing changes at the genotypic level from affecting phenotype and causing disease. Having all these features in a system can help to increase robustness and reduce fragility.

All in all, robustness is a ubiquitous and essential part of biological systems. Understanding robustness, its trade off with fragility and its control measures will help us to develop a better understanding of systems biology.

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