

### **Question 1:**

#### **Biological Robustness and Fragility**

In biology, robustness and fragility refer to the resistance and vulnerability of biological networks to various environmental changes and mutations. Robustness in biology refers to the ability of an organism to maintain its function and structure in the face of external and internal perturbations, such as genetic mutations, temperature fluctuations and altered species interactions [1,2]. In contrast, fragility refers to the sensitivity and vulnerability of a system to a particular perturbation that may lead to impairment of its function or structure [3]. Previous research has shown that there is a correlation between the robustness and fragility of biological networks [3]. For example, a biological system may be optimised to become robust against some perturbations, but it may be highly fragile against other unexpected perturbations [3]. Therefore, achieving a balance between robustness and fragility is essential, as they are both crucial to the survival and adaptation of the biological system under different environments.

An example of biological robustness is the chemotaxis system of *Escherichia coli*. It can adapt accurately to changes in the chemical stimuli over a wide range of chemo-attractant concentrations [2,4]. The bacteria can move towards chemical attractants or away from chemical repellents by sensing and adapting to changes in chemical stimuli. This is achieved by precise adaptation, whereby the system responds quickly to changes and returns to its pre-stimulus state [4]. This robustness of the system ensures the effective function of the system even when the concentration of proteins in the network changes, making it a useful model for understanding how network-level processes arise from interactions between individual components.

An example of biological fragility is the immune system. Even though it is robust against pathogen threats, it is fragile against unexpected dysfunction of non-redundant core elements [3,5]. The bow-tie structure of the immune system is sensitive to attacks on non-redundant elements within its core [5], resulting in immunodeficiency and confusion in molecular pattern recognition, specifically in the MHC-peptide–TCR interaction, leading to autoimmunity. This fragility results from the need for the immune system to detect a broad range of molecular signatures for pathogens under resource-limited conditions, which has shaped its global architectural structure [5]. This also highlights the balance the immune system must maintain between providing robustness against pathogens and remaining functional.

Biological robustness is an integral part of survival as it allows biological systems to maintain their functions and adapt to changes in their environment, which means that they can better withstand different perturbations, increasing chances of survival. Studies have shown that robustness is present in various biological contexts [1]. For example, the ability of cells to adapt to modified regulatory regions in genes is essential for the survival of the cells, and the ability of animals to adapt to changes in temperature, pressure and hydration levels is critical for the survival of the animals [1]. The more robust an organism is, the higher its chances of survival. Furthermore, robustness against environmental and genetic perturbations is also critical for

evolvability as it allows organisms to adapt to changing conditions over time and improves species' survival chances [6].

When a fragile system is unable to maintain its functions or adapt to changes in the environment, the consequences can be severe, such as system failure or death. Particularly in biological systems, fragility can lead to reduced survival rates. As discussed earlier, robustness and fragility are often correlated, and an optimal balance between robustness and fragility is desirable. Therefore, the trade-off between robustness and fragility must be considered when designing an engineered biological network. In order to avoid fragility and maximise robustness, Shi et al. developed an algorithm to derive the Maximal-Robustness-Minimal-Fragility controller (MRMFC), based on the perfect Bayesian-Nash equilibrium [7], which enables biological network to achieve a good balance between robust stability and dynamical performance. Other methods of avoiding fragility could be designing the system with higher adaptability or including multiple systems that can take over in case of failure. Additionally, regular maintenance of the system can also help to detect and fix any issues before they lead to fragility.

In conclusion, robustness and fragility are essential characteristics to consider when designing a system. In order to develop an optimal system, the robustness should be maximised, and the fragility should be minimised.

## References

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