

Question 1

Biological robustness is defined as a property in biological systems where specific functions or traits of the system are maintained in the presence of internal and external disturbances. In response to such perturbations, robust systems can either return to its current attractor (termed robust adaptation) or transition to a new attractor that still maintains the system's functions (Kitano, 2004).

Separately, systems are described as fragile when they are affected by unexpected mutations. According to the Highly Optimized Tolerance (HOT) theory (Carlson & Doyle, 2004), there is an intrinsic trade-off between robustness and fragility, as robust systems are usually highly optimized for a given set of perturbations, which inevitably results in higher susceptibility towards rare and unexpected perturbations (Kitano, 2007).

An example of robustness is in bacterial chemotaxis, which utilizes a mechanism called integral feedback control to respond dynamically to various kinds of stimuli. Bacterial chemotaxis is defined as the directing of bacteria movement, such as that in *Escherichia coli*, towards more favorable environments (i.e., those with higher concentrations of beneficial chemicals) and away from less favorable ones (i.e., those with more toxic chemicals), by detecting changes in chemical gradients of ligands in their surroundings (Wadhams & Armitage, 2004). Movement in a new direction is determined by tumbling events. Modifying the tumbling frequency will consequently enable the bacterium to move to its desired location. The robustness of this process becomes evident when observing how these tumbling frequencies respond to ligand concentration. In a homogeneous ligand environment, the frequencies are insensitive to ligand concentrations, hence they are still able to detect chemical gradients irrespective of how much the ligand concentrations change. This adaptation property can be further explained by changes in methylation of chemoreceptors, which can appropriately compensate for the effects of ligand on tumbling frequency (Barkai & Leibler, 1997).

Meanwhile, an example of fragility would be during Myeloid Differentiation factor 88 (MyD88) deficiency in the immune system (Kwon & Cho, 2008). The immune system is generally robust against a wide range of pathogenic threats and can effectively mobilize an innate or adaptive immune response to combat these foreign bodies (Chaplin, 2010). However, when there is an unexpected mutation in the MyD88 gene and subsequent loss of the functional MyD88, important immune pathways where MyD88 plays crucial roles in are affected, such as the toll-like receptor pathway and NF- κ B pathway. The toll-like receptor pathway is involved in recognizing molecular patterns derived from various pathogens and activating transcription factors NF- κ B and IRFs, which then mounts the appropriate innate immune response (Kawasaki & Kawai, 2014). Breakdown of these pathways will thus result in an impaired immune response and higher susceptibility to pathogenic infections and cancer (Wang et al., 2016).

Robustness is essential for survival as it ensures that organisms maintain system functionality in the face of perturbations. These perturbations affect biological systems at various levels, frequencies, and timescales, through genetic mutations, fluctuations in molecular concentrations, loss of structural integrity, infectious diseases, cancer,

temperature changes, altered species interactions and regime shifts in physical environment (Whitacre, 2012). Without robustness, survivability of an organism will be reduced as core processes vital for survival may be negatively influenced by such disturbances and lose their overall functions. An organism's ability to adapt and survive in different environmental conditions will also be impaired as there is no mechanism to regulate fluctuations in temperature, pH, pressure etc. Hence, robustness is critical to ensure core functions are maintained and the organism is equipped to cope with internal/external perturbations.

In contrast, fragile systems would result in higher susceptibility to diseases, mutations, cancer, and other disturbances, and if core functions are impacted, it could decrease survivability as well. While it may be challenging to manage internal disturbances such as mutations, one could avoid other forms of external perturbations like environmental conditions by managing them appropriately. Vaccinations such as that of SARS-CoV-2 help to induce robust immune response against the virus and other emergent variants, by triggering T cell response against the viral epitopes (Skelly et al., 2021). Managing air quality can also help reduce cancer risk by decreasing the amount of carcinogenic air pollutants (Turner et al., 2020). Hence, proper management of some perturbations can help to avoid the consequences of fragility in systems.

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