Question 1 – Biological Robustness and Fragility

Robustness is a fundamental feature of many biological systems. It is not only observed across many species, but also at different organizational levels/biological contexts, for example from level of gene transcription to the level of the immune response network. Robustness has been described as a property that allows the system to maintain its functions despite the presence of perturbations. (Kitano, 2004)

Specifically, robustness deals with the preservation of a set of functions (specific functionality), and not all functions (state of the system). The concept of robustness is therefore distinct from that of homeostasis. In the case of homeostasis, a system when face with perturbations would remain completely unchanged in all properties. In this sense, there is an element of flexibility in robustness – a system is allowed to change its state or properties so long as it maintains functionality. When discussing robustness, it is thus important to specify the characteristic function that will be robust, the perturbation for which it is against and the biological context. Robustness can appear in two forms: 1) the function in question is return to the original state following perturbation, and 2) a transition to a new steady state that allows the system to still maintain functionality under different conditions.

A well-studied example of biological robustness is the case of adaptation in bacterial chemotaxis, which is a property that enables bacteria to sense and move along gradients of chemical attractants (e.g. nutrients) and repellents. Chemotaxis is achieved by controlling the frequency of abrupt direction changes in the bacteria's swimming motion, i.e. tumbling frequency. A change in the concentration of a chemical stimulant rapidly induces a change in the bacteria's tumbling frequency, which then gradually adapts back to precisely its prior original value. This response is known as exact adaptation and is robust over a wide range of concentration gradients and biochemical factors in the bacteria's chemotaxis response network. (Yi et al., 2000) This exact adaptation is made possible due to the presence of a feedback loop via receptor methylation. (Barkai and Leibler, 1997)

Biological robustness is a key feature for the fitness of living systems and their ability to adaptively cope with variation, be it genetic or environmental. Complex biological systems need to be robust against such perturbations to survive in unfavourable conditions. In fact, robustness is a vital part of the evolutionary process by facilitating evolvability in the long-term. Furthermore, evolution often selects for robust traits, which becomes a source of evolutionary change.

Though robustness is a fundamental aspect, there are limitations as to how robust the systems can be. These biological systems are usually robust against general uncertainities that the system was designed for and evolved to handle. Yet they are potentially fragile to certain types of unanticipated or rare perturbations. This trade-off is also known as the 'robust yet fragile' nature of highly optimized systems which views robustness as a conserved quantity. (Csete and Doyle, 2002).

Biological examples of such trade-offs are abundant. In the earlier example of bacterial chemotaxis, the tumbling control frequency is a property robust to changes in biochemical parameters, but yet it has been shown to be hypersensitive or fragile to changes in its network

structure. (Kitano, 2004) Adaptive immune system in vertebrates is another illustration of the 'robust yet fragile' concept. (Kitano and Oda, 2006) To defend against pathogen threats, the system must be able to detect different molecular signatures of pathogens and invoke effective response measures. Such molecular interactions take place in a characteristic bow-tie network which consists of highly conserved and efficient core processes along with multiple input and output processes. On one hand, the bow-tie structure enhances the robustness of the immune system by enabling it to cope efficiently with a broader range of pathogens with limited resources. On the other hand, the structure becomes fragile to attacks on non-redundant elements within its core as any breach will disrupt many processes. In TLR-mediated signalling in innate immunity, the dysfunction of MyD88 which is a non-redundant core element can cause devastating effects on the system. (Kitano, 2004) Diseases are also often manifestations of fragility in the system. In some cases, the mechanisms that confers robustness can be exploited by a disease or pathogen to its advantage. HIV for example hijacks the robust adaptive immune response mechanisms by infecting CD4+ helper T cells which are the central mediators and hence a core element of the network. This eventually causes the immune system to collapse, resulting the body to vulnerable to other infections.

From this perspective, we can see that there is coexistence of biological robustness and fragility, where fragility is in fact a by-product of robustness. In this regard, it is important to identify what the system has been adapted or optimized for and its sources of robustnesses. In doing so, we can then determine the fragile points associated with those mechanisms and develop necessary countermeasures. Some possible ideas include re-establishing control or even introducing artificial decoys as targets for attacks.

References

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