Question1:

Biological robustness is a ubiquitous and fundamental feature of complex and evolvable biological systems. It is defined as a property of a biological system to maintain systematic functions despite the perturbation raised from internal and external sources such as environmental and genetic[1]. However, a robust system often has its "Achilles' heel" where unexpected or rare perturbation compromise systematic function and causes system failure, and this phenomenon is defined as system fragility. Interestingly, a more robust system can be more fragile to certain perturbation, therefore, system fragility was often considered as a trade-off for system robustness[2]. Understanding biological robustness, fragility, and their interconnection is a critical path to deciphering numerous biological phenomena at the systems level[1].

Biological robustness exists in various cellular biological processes such as protein synthesis, cell cycle-controlled cell dividing, and intracellular signal transduction[3,4]. One example of robustness I found particularly interesting was the cell cycle robustness of yeast cells[5]. Li et al. discovered that within the yeast cell cycle, the initial states of proteins that control the cell cycle flow into the biological stationary states: either the state of cells or the state of checkpoints. In detail, the cell cycle of yeast cells is initiated by cell size and controlled by 11 proteins that form a network shown in Figure 1. Therefore, there are 2^{11}=2048 (activated or inactivated for each node) initial states within this 11-nodes network. Using a dynamic model, it shows that all initial states eventually fall into seven stationary states. Interestingly, 86% (1764 initial states) of the initial states fall into one super stationary state that represents the G1 phase of the cell cycle where the cell grows and commits to division. Furthermore, 1764 initial states are investigated to figure out their dynamic trajectory under different starting points. It is revealed that despite different starting points, the dynamic flow of the protein states is convergent onto the biological pathway, where the cell cycle follows the sequence of G1/S/G2/M phases. These two critical findings ensure the yeast cell cycle will not deviate from the biological cell cycle sequence and is robust against perturbations in protein states/starting points.

Biological robustness not only plays a crucial role in regulating biological processes but is also an integral part of survival. First, biological system components such as proteins, cells, organisms, and natural populations are frequently facing changing or even novel conditions. The biological functions must be robust to maintain satisfactory performance so an organism can survive when subject to sudden internal/external changes. For example, our body temperature needs to be in a range so that biological processes such as enzymatic reactions can function properly, which promote survival when we are facing body temperature perturbation. Second, robustness is a prerequisite for a biological system to be evolvable. Evolution requires a long period of time, and the integrity of a biological system needs to be maintained to support evolution. Therefore, biological robustness is essential for a system to resist enormous perturbations that could occur during a long period of time. In addition, evolution will also select the trait that enhances the robustness of biological systems/organisms to enhance their survival. For example, evolutions such as bipedalism and encephalization can only occur when our biological system is robust, and such evolution enhanced human survivability under harsh environments.

However, fragility is a by-product of robustness, the cell cycle can be extremely fragile to certain genetic perturbations where the cell becomes cancerous. For example, growth-promoting genes such as signal protein Ras can be upregulated, and tumor-suppression genes such as p53 can be

downregulated due to certain gene mutation. Therefore, after gene mutations, the cell cycle no longer follows a defined biological sequence: the mutation enables continuous cell division by compromising the ability of cells to exit the cell cycle[6]. Ironically, since the cell division process is intrinsically robust, it is difficult to revert the mutation once it occurred.

Biological fragility can lead to various serious consequences that compromise the life quality of human beings. This fragility often exists in elderly people and is proposed to be the cause of disability and chronic diseases. For example, age-related molecular and genetic perturbation lead to increased expression of inflammatory cytokines such as IL-6 that is associated with diseases such as cardiovascular diseases, rheumatoid arthritis, diabetes mellitus but also with obesity[7]. There are several ways to prevent or postpone fragility for human beings, such as increasing physical exercises such as daily movement to improve mineral bone density and increase overall health. Adequate nutrition supplementary such as vitamin D, calcium, and proteins can also prevent biological fragility within the human body. But nutrition supplementary needs to be determined and adjusted individually[8].

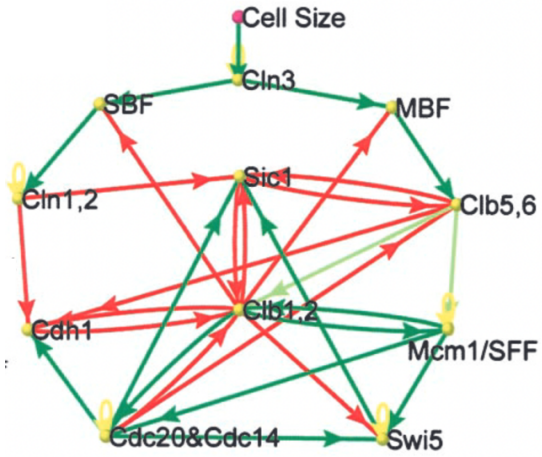

Figure 1 Cell size and 11 proteins form a network that controls yeast cell cycle. Green arrows indicate activation while red arrows indicate deactivation.

Reference:

1. Kitano, H. Biological robustness. *Nature Reviews Genetics* vol. 5 826–837 Preprint at https://doi.org/10.1038/nrg1471 (2004).
2. Whitacre, J. M. Biological robustness: Paradigms, mechanisms, systems principles. *Frontiers in Genetics* vol. 3 Preprint at https://doi.org/10.3389/fgene.2012.00067 (2012).
3. Zhu, H. & Mao, Y. Robustness of cell cycle control and flexible orders of signaling events. *Sci Rep* **5**, (2015).
4. Blüthgen, N. & Legewie, S. Robustness of signal transduction pathways. *Cellular and Molecular Life Sciences* **70**, 2259–2269 (2013).
5. Li, F., Long, T., Lu, Y., Ouyang, Q. & Tang, C. *The yeast cell-cycle network is robustly designed*. www.pnas.orgcgidoi10.1073pnas.0305937101 (2004).

6. Matthews, H. K., Bertoli, C. & de Bruin, R. A. M. Cell cycle control in cancer. *Nature Reviews Molecular Cell Biology* vol. 23 74–88 Preprint at https://doi.org/10.1038/s41580-021-00404-3 (2022).
7. Puts, M. T. E. *Frailty: biological risk factors, negative consequences and quality of life*. (Febodruk, 2006).
8. Brunilda, E., ErjonaAbazaj, Marsida, K. & Skender, T. Prevention of Frailty in the Elderly through Physical Activity and Nutrition. *J Geriatr Med Gerontol* **6**, (2020).