Emergence of cellular aging from gene networks

Hong Qin[1]

Why would a genotypically homozygous population of cells live to different ages? I propose a mathematical model of cellular aging based on gene interaction network. This model network is made of only non-aging components, and gene interactions are inherently stochastic. Death of a cell occurs when an essential gene loses all of its interactions. The key characteristic of aging, the exponential increase of mortality rate over time, can arise from this model, demonstrating that cellular aging is an emergent property of gene networks. The model predicts that rate of aging is proportional to the average number of interactions per gene.

Keywords **— Cellular aging, gene networks, Gompertz model, emergence.**

I. Background

AGING is a fundamental question in biology, yet its mechanism remains elusive. Aging can be quantified by the normalized decline of viability (s) over time (t),

$$m = -\frac{1}{s}\frac{ds}{dt} = f(t), \qquad \text{Eq. 1}$$

where, m is called the mortality rate, and $f(t)$ is a function of time. It can be shown that change of mortality rate over time follows the Weibull model for homogenous systems like machinery (Eq. 2a) and Gompertz model for heterogenous systems like organisms (Eq. 2b), using a model with serial connected-blocks with redundant components [1].

$$m = c_1 t^{c_2} \quad \text{for machine aging} \qquad \text{Eq. 2a}$$

$$m = m_0 e^{Gt} \quad \text{for biological aging} \qquad \text{Eq. 2b}$$

Cellular aging is the basis of physiological aging. The unicellular eukaryotic organism, budding yeast *Saccharomyces cerevisiae*, is a model organism for cellular aging. Replicative lifespan of the budding yeast has been shown to follow the Gompertz model of aging [2].

Cellular aging is clearly has a complex mechanism. Yeast aging is shown to be a largely stochastic process [2]. The negative correlation between $\ln(m_0) \sim G$, the so-called Mildvan-Strehler correlation, is observed in yeast aging [2]. Although over 4000 genes have been deleted in yeast, none of 4000 deletion mutants suggests a direct mechanistic link to cellular aging. Experiments on yeast aging in different conditions and strain backgrounds can yield conflicting results.

Acknowledgements: This work was funded by NSF grant 1022294.

[1] Department of Biology, Spelman College, Atlanta, Georgia 30314, U.S.A. E-mail: hqin@spelman.edu

To provide a unifying theoretic framework on cellular aging, we proposed a mathematical model for cellular aging based on gene networks.

II. The Model

In our network reliability model for cellular aging (NRMCA), there are essential genes and non-essential genes (Figure 1). Genes are nodes, and gene interactions are edges. We assume the biological function of each gene interaction is non-aging and that its functionality declines with a constant mortality rate λ. Each gene interaction is active within cells with a probability of p. Each essential gene interacts with n number of non-essential genes. There are E number of essential genes in the network. It can be shown that the mortality rate of the entire network, i.e. a cell, grows exponentially with time (age),

$$m \approx m_0 e^{Gt} \qquad Eq.3a$$

$$m_0 = cEn\lambda p(1-p)^{n-1} \qquad Eq.3b$$

$$G = \frac{\lambda p(n-1)}{1-p} \qquad Eq.3c$$

Hence, we demonstrate that the key characteristic of biological aging, the exponential growth of mortality rate, can emerges from a gene network with non-aging components. By definition, we have shown that cellular aging is an emergent property of this model gene network.

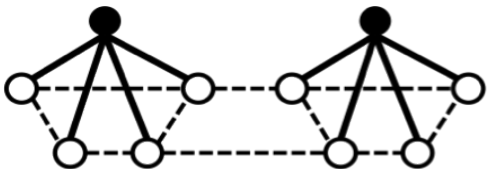

Figure 1. Network reliability model for cellular aging.

III. Summary

Our model demonstrates the emergent aspect of cellular aging and argues that the rate of aging is informative on network robustness.

References

[1] Gavrilov, L.A. and N.S. Gavrilova, *The reliability theory of aging and longevity.* J Theor Biol, 2001. **213**(4): p. 527-45.

[2] Qin, H. and M. Lu, *Natural variation in replicative and chronological life spans of Saccharomyces cerevisiae.* Exp Gerontol, 2006. **41**(4): p. 448-56.