A network model of cellular aging and its applications.

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Why would a genotypically homogeneous population of cells live to different ages? We propose a mathematical model of cellular aging based on gene interaction network. This model network is made of only non-aging components, and interactions among genes are inherently stochastic. Death of a cell occurs in the model 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 network with non-aging components. Hence, cellular aging is an emergent property of this model network. The model predicts that the rate of aging, defined by the Gompertz coefficient, is proportional to the number of active interactions per gene and that stochastic heterogeneity is an important factor in shaping the dynamics of the aging process. Hence, the Gompertz parameter is a proxy of network robustness. Preliminary studies on how aging is influenced by power-law configuration, synthetic lethal interaction, and allelic interactions can be modeled. A general framework to study network aging as a quantitative trait has also been found, and the results has implication on missing heritability. Preprint for the basic model is available at http://arxiv.org/abs/1305.5784.

***Keywords* — Cellular aging, gene networks.**

I. Background of our model

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 machiner and Gompertz model for heterogenous systems like organisms, using a model with serial connected-blocks with redundant components [1].

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].

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

In our probabilistic gene network model for cellular aging, there are essential genes and non-essential genes (Figure 1). Genes are nodes, and gene interactions are edges. We assume the efficacy of each gene interaction is non-aging and that it 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. It can be shown that the mortality rate of the entire network, i.e. a cell, grows exponentially with time (age),

II. Applications of our model

One important application of our model is to evaluate a hypothesis that the conserved mechanism of lifespan extension is through improving reliability of gene interactions. With the availability of replication lifespan measures of thousands of yeast single gene deletion mutants, we can fit our network model with these mutants, and compared the fitted network parameters.

Another application is to use mixture distributions to model gene interactions with limiting effect on yeast lifespan.

Our model also provides a mechanistic explanation for aging as a quantitative trait. By comparing our network model with linear models in quantitative genetics, we may answer the question of missing heritability.

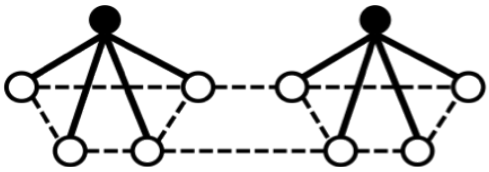

Figure 1. Network reliability model for cellular aging.

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