Summary of summer research on network model of cellular aging

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1 Overview

Aging can be quantitatively defined by mortality rate $\mu(t)$,

$$\text{Mortality rate:} \quad \mu(t) = -\frac{1}{S(t)}\frac{dS(t)}{dt},$$

where t is time, and $S(t)$ is viability. Aging has been observed in bacteria, yeast cells, and many other organisms. An organism is non-aging when $\mu(t)$ is a constant, as is the case in bacterial phages. To explain how aging emerges from biological complexity, I proposed a network model for cellular aging. The key idea is that cellular aging is an emergent property of gene networks.

In the summer of 2013 at NIMBioS, I concentrated on further developing network models for cellular aging. My major efforts were to explore the effect of network configuration on network aging, develop a computational framework for limiting network modules on aging, and investigate the network impact on lifespan as a quantitative trait, detailed below.

My effort has led to following outcomes:

- Revised manuscript on network model for cellular aging.
- An NSF grant proposal on network model of cellular aging and its applications, submitted in July, 2013.

2 Network configuration and network aging

Biological networks tend to be power-law: the degree of nodes (k) follows $P(k) \sim k^{-\gamma}$. Here, we only need to focus on the essential genes for network aging. Let's assume that

$$P(k) = \frac{1}{C}k^{-\gamma} \quad \text{for } k \gg k_{low} \tag{1}$$

where k_{low} the lower bound of vertex degrees, and C is a normalizing factor. For m number of essential genes,

$$\text{Number essential genes with degree } k = mP(k) = \frac{1}{C} m k^{-\gamma} \tag{2}$$

For simplicity, let's assume no interaction between essential genes. Let's designate the chance of an essential gene's interaction to be active is p. The mortality rate of the entire network μ_{net} is the sum of mortality rate of all essential modules:

$$\mu_{net} = \sum_{j=k_{low}}^{m} \mu_j \quad \text{sum of all essential modules} \tag{3}$$

Therefore, we have

$$\mu_{net} \sim mc \sum_{k=k_{low}}^{k_{max}} P(k) \sum_{i=1}^{k} \binom{k}{i} p^i (1-p)^{k-i} i\lambda(\lambda t)^{i-1} \tag{4}$$

Because $i\binom{k}{i} = k\binom{k-1}{i-1}$, we have

$$\begin{aligned} \mu_{net} \sim & mc \sum_{k=k_{low}}^{k_{max}} P(k) \lambda k p \sum_{i=1}^{k} \binom{k-1}{i} (pt\lambda)^{i-1} (1-p)^{k-i} \\ = & m \sum_{k=k_{low}}^{k_{max}} P(k)\ R_k\ e^{G_k t} \end{aligned} \tag{5}$$

where

$$\begin{aligned} R_k =& ck(p\lambda)^k t_0^{k-1} \\ G_k =& \frac{k-1}{t_0} \\ & \text{for } k = k_{low}, k_{low}+1, \ldots k_{max} \end{aligned}$$

Parameter R_k and G_k are the initial mortality rate and Gompertz coefficient for a network module in which an essential gene interacts with k non-essential genes. Hence, Eq 5 suggests that the network mortality rate can be calculated from the weighted mean of modular network mortality rates.

3 Results on limiting modules and quantitative trait

I found a general framework to study the effect of limiting modules on network aging (Fig 1). We can partition the limiting module under study and the

remaining network into two super nodes, X and Y, each with its own viability function, $S(X)$ and $S(Y)$. Parallel and serial configurations of X and Y are the two special cases, and their viability functions can be found based on the reliability theory. The mixture of the two special cases can then describe the viability of the network as a system. I am developing numerical methods to apply this general framework to evaluate experimental lifespan data.

This network framework on limiting modules can be extended to study lifespan as a quantitative trait. In the simple case of a two-locus model, analytic solutions for the variance of network lifespan can be found. Comparison to the linear model used in the quantitative genetics can then shed lights on the missing heritability problem.

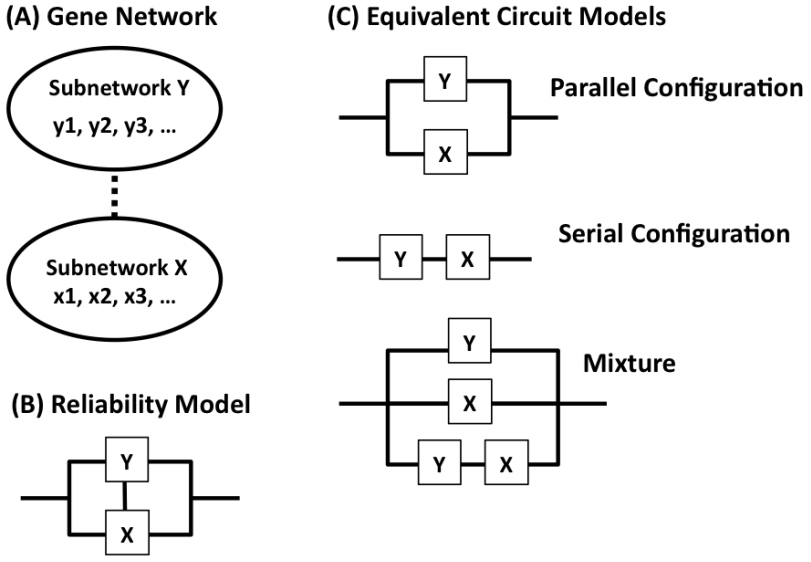

Figure 1: A general framework to study limiting modules for network aging