What is Aging? Why study aging?

* Aging is a fundamental question in biology yet, its mechanism remains elusive.
* It most likely occurred during the evolution in unicellular organisms because aging is observed in bacteria.
* It has been speculated that bona fide aging genes do not exist because there are no conserved causes of aging.
* Experimental data suggests that complex gene networks are involved in yeast aging.
* The complex nature of aging suggests that network is the key to understanding aging.
* There exists a universal characteristic of aging at the demographic level, known as the Strehler-Mildvan correlation, which suggests a common principle in the stochastic processes of aging.
* The dynamics of biological aging can be defined as a two-parameter Gompertz model:



where, m is the mortality rate, s is the survival fraction of a population and t is the time. The initial mortality rate, m0 is the innate susceptibility to dying. The Gompertz coefficient, G, determines acceleration rate of mortality rate over time and is therefore a parameter for rate of aging.

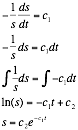
* The exponential increase of mortality rate is a universal characteristic of biological aging and has been observed in many organisms. It has been found that there is a negative linear correlation between G and ln(m0) in yeast. This negative linear correlation, which was first reported in humans, is called the Strehler-Mildan correlation.
* Given the Gompertz definition of biological aging, when G=0, mortality rate m becomes constant in which case we call an organism to be non-aging. Individuals from these populations will then be as good as new at any time point. Example: Bacterial phages. But they are not immortal, they just die with constant mortality rates.

Thus, for this equation:



When  

Using differential equations



We have our initial conditions: 

So we get



Also,

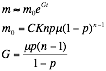


Thus, c1 can be anything. Therefore our final equation is ****

Which is an equation of exponential decay.

* NRMCA: Network Reliability model of cellular aging is the first mathematical model to demonstrate the network emergent aspect of cellular aging providing a conceptual framework to explain the seemingly inconsistent experimental data, individual plasticity, and universal demographic characteristics of cellular aging in yeast.
* Emergent Property: In order for cellular aging to be an emergent property of gene networks, the components of our model network should be non-aging (or having constant mortality rates).
* Basic Version of NRMCA: The network in basic NRMCA consists of ‘k’ essential modules where each module contains 1 essential and ‘n’ non essential genes. The biological function of each interaction is assumed to be non-aging and decays exponentially with a constant rate of μ. Death of a cell occurs when an essential gene loses all of its interactions, equivalent to deletion of an essential gene. Interactions are assumed to be stochastic, and the initial probability of an interaction being active is ‘p.’ When failures of models are independent, the analytic approximation for the system mortality rate is:

when t << 1/μ



where G is the rate of aging, C is a normalization constant.

So, the exponential increase of mortality rate over time, which is the defining characteristics of biological aging, can arise from a network model with non-aging components. We have shown that cellular aging is an emergent property of this model network.

The number of active interactions per gene, , can be viewed as a measure of network robustness. So there is a positive correlation between the Gompertz coefficient G and network robustness- more robust cells have higher rates of aging.

The Strehler-Mildvan correlation is the trade-off between G and m0. The property in which , where B and Intercept are constants based on K, μ, and p denotes the Streler-Mildvan correlation. It can be attributed to the common interacting patterns of gene/protein networks shared among most species.

According to NRMCA, the heterogeneity of gene interactions is an important factor between biological and non-biological aging. If intrinsic stochastic noises are removed from our model, increase of mortality rate would follow the Weibull model, the failure model of complex machinery.

NRMCA suggests a mechanistic link among robustness, gene networks and aging. It argues that G is a measure of robustness.

Based on predicted connection between network robustness and cellular aging, we focus on 3 important roles in robustness: power-law configuration, cooperativity and renewals/ repairs.

**POWER LAW** and error tolerant network configurations on cellular aging

NRMCA predicts that heterogeneity plays a key role during emergence of biological aging. A key source of heterogeneity in gene networks is its power-law feature: the degree distribution of genes follows , where k is the number of connections per gene, Z is the Ziemman function, and y is a coefficient. When y3, the variance of P(k) is infinite. In most biological networks, y is between 2 and 3, which indicates tremendous amount of heterogeneity in biological networks. Networks with power law features such as the Internet are robust to random failures but are fragile to deliberate attacks.

In yeast protein networks, highly connected genes (hub-genes) are less likely to directly interact with other hub genes in the protein interaction networks, which contributes to the error tolerance of protein networks.

We use simulation to study how power-law degree distribution and error tolerance features of gene networks influence aging dynamics, especially G. We generate the degree distribution based on , and then pair interacting nodes. The parameter y will be ranged from 1 to 3. Control studies will be conducted in networks with fixed numbers of interactions per gene, a Poisson distribution of degrees, and a log-normal distribution of degrees.

**MATLAB insert here**

To simulate the lifespan of an individual cell using NRMCA, we will first simulate the ages of all gene interactions based on exponential distributions (non-aging). The age of each essential module is the **maximum** age of its gene interactions. (Fig. 1), whereas, the age of this whole cell is the **minimum** age of all of its essential modules.

We expect that power-law and error-tolerant feature would render networks more robust to random failures and therefore lead to larger G values.

**Develop a comprehensive set of robustness proxies for yeast genes**:

Biological robustness means persistence of phenotype in the presence of genetic, environmental, or stochastic perturbations. Variations in morphology and expression levels have been used as proxies of robustness. Coefficient of Variation (CV) = Standard Deviation/Time is a normalized robustness proxy to compare phenotypic measures at different levels.

Aging

Study aging

Definition of scale free network

Random Graph: Erdos Renyi model

Influence of random change on aging effect

Why do we study power law on aging effect

Power law generation of noise

What is Biological Aging versus machine aging

Simulations: Math Lab

Evolutionary theory is more appropriate to explain early successes of biological species (eg. Reproductive success), rather than later failures (aging and death). This general theory of system failures is known as the theory of reliability which allows researchers to understand many puzzling features of mortality and lifespan not readily explainable otherwise (Gompertz law, mortality plateaus, compensation law of mortality).

Reliability theory is a body of ideas, mathematical models and methods directed to predict, estimate, understand and optimize the lifespan distribution of systems and their components. Reliability of the system refers to the ability to operate properly according to a specified standard. Reliability is described by the reliability function S(x), which is the probability that a system will carry out its mission through time x. The reliability function (survival function) at time x is the probability P that the failure time X is beyond time x. Thus, S(x) = P(X>x) = 1-P(Xx) = 1 – F(x), where F(x) is a cumulative distribution function in the probability theory.

Failure rate, 

When failure rate is constant, we have non-aging system that does not deteriorate with age. The reliability function of non-aging systems is described by the exponential distribution:



This failure law describes lifespan distribution of atoms of radioactive elements and it is also observed in many wild populations with high extrinsic mortality.

GOMPERTZ function defn: It is a type of [mathematical model](http://en.wikipedia.org/wiki/Mathematical_model) for a [time series](http://en.wikipedia.org/wiki/Time_series), where growth is slowest at the start and end of a time period.