# ASPIRE Student Research Proposal

# Investigation of the network configuration on its aging dynamics

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# 1. Specific aims

The aim of this proposal is to investigate how network configuration influences its aging dynamics

# 2. Introduction

Aging is a fundamental question in biology [[13-15](#_ENREF_13)]. Aging of an organism or a system can be described by the mortality rate *μ(t)*, which is the normalized declining rate of viability *S(t)* over time *t*:



Aging occurs when *μ(t)* is a positive increasing function that indicates increasing chance of dying over age. In general, *μ(t)* can be a power function for machine aging and an exponential function for biological aging [[19](#_ENREF_19), [20](#_ENREF_20)].



The exponential form of mortality rate (Eq. 3) is known as the Gompertz model of biological aging [[22](#_ENREF_22)]. The initial mortality rate, *R*, describes 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 bacteria, yeast, worms, fruit flies, mice, and humans [[4](#_ENREF_4), [13](#_ENREF_13), [23-26](#_ENREF_23)].

Our central hypothesis is that cellular aging is an emergent property of gene networks. Emergent property generally refers to a feature that can be found only at the system level but not at the component level. Classic examples include termite castles, schools of fishes, and flocking of birds.

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| (A) The basic network module.  Macintosh HD:Users:hongqin:Desktop:Screen Shot 2013-06-26 at 7.21.48 PM.png  **Figure. 1**. The basic version of network reliability model of cellular aging (NRMCA) and its equivalent classical reliability model as in Gavrilov & Gavrilova 2001[[19](#_ENREF_19)]. | (B) A stochastic modular network.  :figures:outputs:stochastic_modules:Slide1.tif |
| Dark circles are essential genes, and white ones non-essential genes. Biological functions of all gene interactions decay exponentially, i.e., *non-aging*. When an essential gene loses all of its interactions, it is equivalent to gene deletion and results in cell death. Consequently, only essential genes’ interactions influences aging and are represented by solid links. Dashed links are interactions that will not affect aging. Interactions are stochastic, and the chance of an interaction to be initially active is *p*. Independent failures are assumed for both essential modules and gene interactions. Graph and block presentations are mathematically equivalent and will be used interchangeably. Mathematical details are available in our preprint [[1](#_ENREF_1)]. | |

The basic version of NRMCA contains *m* number of essential modules, and each module contains 1 essential and *n* non-essential genes (Figure 1). Stochastic gene interactions follow a binomial

# 4. Research Plans.

Study structural reliability and aging process of the yeast protein interaction network, and compare them with permuted networks.

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| :::::Desktop:Screen shot 2013-07-02 at 2.14.09 PM.png  Evaluate network reliability and simulate aging process of the yeast protein interaction network. |

How reliable and robust is the yeast protein interaction network? This is the first question that we will address here (Figure 6). The structural reliability of a network can be evaluated by a reliability function of the system states [[17](#_ENREF_17)]. Each functional interaction is represented by 1, and failed one by 0. The combination of all the possible ‘1’s and ‘0’s in all interactions will then constitute the ‘state space’ for the entire network. How often a network fails in its state space is a measure of how reliable the network is.

Failures in NRMCA are caused by essential nodes, and failure of a single essential node leads to network failure. This indicates that we only need to check the active connectivity of essential nodes, and there is no need to search for traversal paths for the entire network connectivity. The computational complexity of identifying network failure in NRMCA is basically linear O(|V|), where |V| is the number of vertices or nodes. For comparison, the Dijkstra algorithm for a single source-node shortest path runs in O(|E|+|V|log|V|), where |E| is the number of edges. Therefore, it is much faster to calculate network reliability in our models than in other networks (for example, the internet and electric power grids). We will first implement the protein network in adjacency matrix to study basic principles, and then use linked lists to improve efficiency.

We will sample the state space by gradually introducing random interaction failures into networks with increasing failure frequency ε [[85](#_ENREF_85)]. Plot of chance of network failures ~ ε can then describe network reliability. This kind of curves is often sigmoidal, and the middle point of the transition can be found as a critical transition point. Both the yeast protein network and null network models will be evaluated and compared.

The role of error tolerance can be studied by using null networks with shuffled node labels (Figure 6). The role of network topology can be studied by using null networks with shuffled links (Figure 6).

How does network configuration of yeast protein interaction work influence its aging process? This is the second question that we will address. We plan to simulate the stochastic network aging using the exponential decay function, which is just another way of modeling random failures. The exponential distributed component ages can be conveniently generated using the exponential random number generator. The age of each essential node is the maximum of its interaction ages, and the minimal age of the essential nodes is the network age. Survivor curves of yeast network aging and random networks will be compared. In comparison to the state-space-approach, different failure rates can be assigned to different interactions.

We will start with the yeast mitochondrial protein interaction network, a subset of the yeast protein network. Mitochondrion can be considered as an endosymbiotic prokaryotic cell. The simulation will then be extended to the entire observed yeast protein interaction network [[81](#_ENREF_81)] (Figure 6).

It is probably expected that biological networks are more reliable than random networks. Alternatively, it is possible that biological networks have less ‘pure’ structural reliability when renewals/repairs are not considered. If this alternative scenario happened, it would offer us a golden opportunity to compare two different renewals/repair mechanisms: component renewals/repairs versus modular renewals (detailed in Aim 2.3).

Network evolutionary history may influence the reliability evaluation outcomes of the yeast protein interaction network. The PI’s postdoctoral research showed that evolution of the yeast protein interaction network mirrors the universal tree of life, and interactions tend to occur between genes with similar evolutionary histories [[5](#_ENREF_5)]. One option is to model interactions between genes with similar evolutionary histories as more reliable than others. Another option is to model reliability in proportion to their evolutionary history on the universal tree of life, based on our previous work [[5](#_ENREF_5)].

The PI will partition network simulations into small coding projects for students and integrate network research into courses, parlaying his past experiences (detailed in section 6).