

# Understanding Alzheimer's disease with Network Biology

C.R. Kyrtsov & J.S. Baras  
University of Maryland  
2247 AV Williams Building  
College Park, MD 20742

**Abstract**—Alzheimer's disease (AD) is a complex disease showing dysregulation of several key pathways and an abnormal increase in levels of beta amyloid ( $A\beta$ ) and hyperphosphorylated tau. Although AD is the most common type of memory loss among the elderly, its pathogenesis is not well understood. Mathematical modeling offers a unique opportunity to gain a better understanding of the AD disease process by combining the current knowledge within a quantitative framework. Using a network model for AD, we discuss how the transition from a normal, healthy brain to an AD brain network can be modeled using a Markov model.

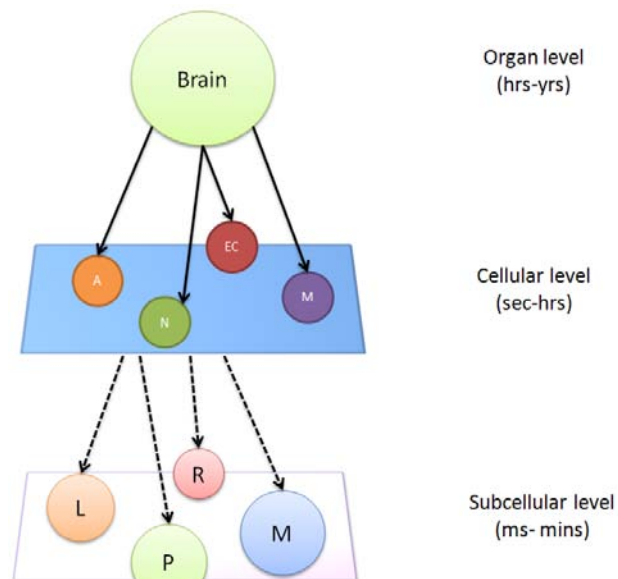
## I. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting nearly one out of six elderly individuals over the age of 65. Aside from memory loss, a variety of symptoms are observed, including depression, disruptions in circadian rhythm and loss of voluntary muscle control. Histological markers of AD include diffuse beta amyloid ( $A\beta$ ) plaques and oligomers in brain parenchyma and hyperphosphorylated tau in axons [1]. Neuroinflammation, as well as dysregulation of lipid metabolism and mitochondrial dysfunction, are also observed.

Given the significant complexity of the disease, using network biology to study the interactions between different molecules and various pathways opens new avenues of understanding the pathogenesis and key regulators of AD. Here, we present a network model that studies AD at both the intercellular and intracellular levels. Generalizing to an organ and systems level, we conclude with a discussion on the ability of hidden Markov models to study the transition from a 'healthy brain' state to a 'diseased brain' state in the context of networks describing other hierarchal levels.

## II. HIERARCHIES OF NETWORKS IN BIOLOGICAL SYSTEMS

One way of quantitatively thinking about diseases is to view them as aberrant networks. A given organism can be represented as a hierarchy of interacting networks, with nano- or picoscale interactions on one end of the spectrum (protein-protein, gene-protein and other biomolecular interactions) to systems-level interactions between various organs and the organism and its environment. Networks can interact within their respective hierarchal level, as well as with other levels. For example, energy available to a cell is dependent on mitochondrial function, ability of the cell to uptake nutrients from the local microenvironment, local blood flow rate, nutritional intake of the organism, and organismal response to the environment (stress, exercise, resting).



**Figure 1: Hierarchical network for AD.** A, astrocytes; N, neurons; EC, brain endothelial cells; M, microglia; L, lipid metabolism; P, proteomic network; R, regulatory pathways; M, energy metabolism

The natural hierarchy in biological networks is apparent not just from their structure, but also from the fact that interactions that occur between molecules, cells or organs on the same level tend to have time constants on the same order. Thus, modeling interactions between different levels of a systems biological network poses the problem of which time scale is most important to the overall behavior of the network.

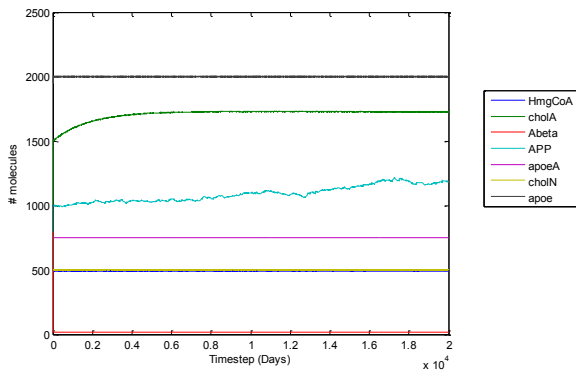
The quasi steady state approximation (QSSA), instead of standard Michaelis-Menten kinetics, is often used to overcome this issue in cases where there are variable time scales between coupled reaction networks, or where enzyme and substrate (or protein and protein) are of equivalent concentrations. In the case of a hierarchal model for AD, where the disease develops over the course of years, the QSSA can be used to simplify coupled reaction networks to approximate reactions with both fast and intermediate kinetics as nearly constant, aside from perturbations to the input values,

## III. A NETWORK MODEL FOR AD

The brain has been modeled as a system of several key cell types as seen in Figure 1: neurons, astrocytes, microglia, and brain endothelial cells (ECs). The brain has a finite volume, thus, there exists a limit, or carrying capacity or concentration threshold, for the number of cells, proteins, signaling

molecules, lipids and other biomolecules that can be contained in this volume. Above these concentration thresholds, regulatory systems are triggered in an effort to return the system back to a state of homeostasis. Independent of these regulatory mechanisms, cellular damage can occur due to activation of inflammatory pathways, mechanical loading, activation of apoptosis or necrosis, or changes in local osmolarity. In this model, the blood is considered to be a relatively infinite sink (as in previous models that we have developed) since the rate of blood flow is considered to be sufficient enough to transport any molecule that is transported across the BBB and out of the brain.

The key cell types in the brain and their interactions with each other can be represented as a directed graph with both weak and strong connection strengths (Figure 1). Not all cell types interact with each other, and only the brain ECs have a direct connection with the blood for waste removal. Within this cellular network, each cell type possesses its own set of metabolic, lipidomic, proteomic and regulatory pathways that are expressed depending on what genes are currently active. This cellular sub-network can be considered cell-dependent topology. The following figure shows a sample simulation that was run for the equivalent of 60 years, demonstrating how most reactions quickly reach a steady state, while some vary slowly over timescales of years.



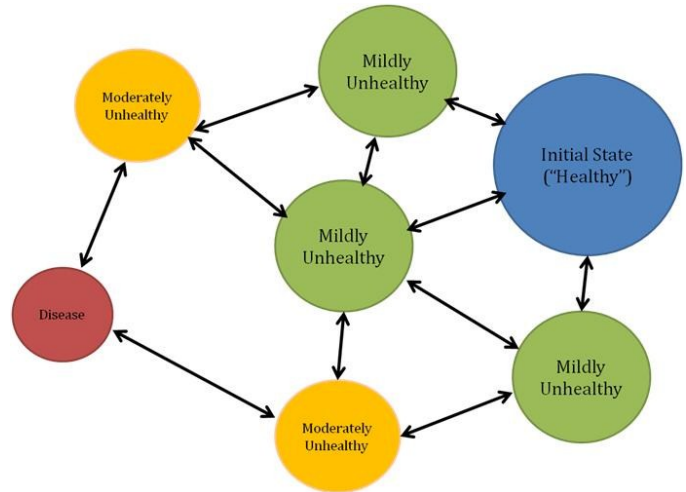
**Figure 2: Simulation Run.** The basic network for AD was simulated for approximately 20,000 days (about 60 years), demonstrating the relatively fast convergence of some pathways.

#### IV. MARKOV MODELS OF AD

Markov models have been used extensively in epidemiological studies, by insurance companies to determine the best course of treatment for AD and in certain diseases to model transitions from one state of the disease to another [2, 3]. The concept of using a Markov model to study the pathogenesis of networks in an AD model has not been discussed in the literature. By defining the overall output of the described network for AD as a state, a hidden Markov model can be developed to better describe whether the system is in a disease or healthy state, or whether it is in an intermediate state heading towards disease. Assume that initially, the brain starts in a healthy state  $i$ , where all pathways are interacting as expected and expression levels are also at the expected values. Over time, external influences, responses to the environment, oxidative stress and other

stimuli cause the system to shift from state  $i \rightarrow$  state  $j$ , which represents one of the many possible states of a perturbed network that is operating less efficiently.

There is a range of healthy states that are possible for a single organism to take one; that is, small deviations in the expression level or interaction between pathways lead to only minor changes in the system, which, as a whole, can adjust to such a perturbation. However, as enough of the networks become perturbed, expression and concentration levels slowly begin to deviate from the expected range, which leads to downstream consequences in other network topologies. This is the suggested beginning of many disease processes. The system may attempt to compensate initially, but if the external stimulus (environment, stressor, etc) is not removed or its effect ameliorated, the system converges to an alternative steady state, where pathways are running non-optimally, alternate pathways may be activated, and eventually networks must adapt and concentration levels change. Future work will continue to develop this hidden Markov model approach.



**Figure 3: AD as a Markovian State Space.** It is being proposed here that diseases, regardless of their underlying pathogenesis mechanisms, can be modeled as Markov state space. The highest probability is to find the system in the *healthy* state, which transitions to other states (*unhealthy states*) upon exposure to an environmental stimulus or other external factor. Over time, these transitions can tend towards a disease state. This may be a final, absorbing state, or there may be opportunities to escape this state.

#### V. CONCLUSION

In this paper, we have presented a network model for AD looking at both intercellular and intracellular interactions. A sample simulation representative of the various time scales that are present in this network was also given. The use of Markov models in studying the pathogenesis of AD was introduced as a future endeavor.

#### REFERENCES

- [1] Puglielli, L., R. E. Tanzi, et al. "Alzheimer's disease: the cholesterol connection." *Nat Neurosci.* vol. 6(4): 345-51, 2003.
- [2] Macdonald, A and D. Pritchard, "A mathematical model of Alzheimer's disease and the ApoE gene," *Astin Bulletin*, vol. 30, No. 1, pp. 69-110, 2000.
- [3] Seeting, M.J., V.T. Farewell and D. DeAngelis, "Multi-state Markov models for disease progression in the presence of informative examination times: an application to hepatitis C," *Stat. Med.*, vol. 29(11), pp. 1161-1174, May 2010.