A New Framework for Modeling Biochemical Signaling Networks across Evolutionary Boundaries

Maya R. Said
MIT Department of Electrical Engineering and Computer Science
Room 36-613, 77 Mass. Ave.
Cambridge MA 02139
mayasaid@mit.edu

Alan V. Oppenheim
MIT Department of Electrical Engineering and Computer Science
Room 36-615, 77 Mass. Ave.
Cambridge MA 02139
avo@mit.edu

Douglas A. Lauffenburger
MIT Biological Engineering Division
Department of Chemical Engineering
Room 56-341, 77 Mass. Ave.
Cambridge MA 02139
lauffen@mit.edu

ABSTRACT

Signal transduction pathways have been extensively studied over the past decade. New molecular techniques as well as sequencing of genes involved in the signaling cascades have helped elucidate many of the elements involved and their mechanisms of actions. However, as more pathways are discovered, their complexities and the intricate interactions among signaling molecules are quickly becoming intractable. Models are therefore needed to define layers of abstractions in order to understand these complex responses.

Most current models for signaling pathways can be classified in one of two categories: biochemical models which define the system in terms of kinetic equations governed by the Law of Mass Action or Michaelis-Menten kinetics and biophysical models which are concerned with the mechanical forces and spatial distributions necessary to generate a response. In this work, we propose an alternative approach to representing and modeling biochemical signaling networks based on linear algebra and statistical control and signal processing theory. Specifically, we present a framework for studying signaling networks in an evolutionary context.

Our approach is used to study the dynamics and evolution of the formation of the apoptosome: one of the major programmed cell death pathways leading to apoptosis and present in many animals including worms, flies, and vertebrates. The apoptosome is an active complex required for the activation of caspase 9 in mammals (or one of its homologs in other species) and is formed by the association of this caspase with the protein cofactor Apaf-1 (or one of its homologs). Upstream signaling includes molecules from the Bcl-2 family. In our work, we study the dynamics of the network associated with this complex in three species covering three phylogenetic branches of metazoans: nematodes, insects, and mammals. Specifically, we model the apoptosome formation signaling network in *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Homo sapiens*.

Evidence suggests that, both in mammals and fruitfly, apoptosome formation requires release of mitochondrial cytochrome c induced by cellular stress of various sorts while cytochrome c release does not seem to be involved in apoptosis in the nematode [1] [2] [3]. Specifically, in *C. elegans*, caspase activation by Ced-4, the nematode Apaf-1 homolog, requires the inhibition of Ced-9, an apoptosis inhibitor and Bcl-2 family member, by another Bcl-2 family member Egl-1 while in mammals activation of Apaf-1 requires cytochrome c release which is activated by the inhibition by Bid of the apoptosis inhibitor Bcl-2. Similarly, in Drosophila the Apaf-1 homolog, ark (also known as dapaf-1, dark, or hac-1) requires cytochrome c for caspase activation. Our goal is to cast each of these signaling networks in terms of our new modeling framework and examine how the structure and dynamics of the network change as complexity increases with organismal evolution.

The modeling framework we develop builds from a set of recent models based on networks of interacting Markov chains. A class of such chains has been developed in [4] in the context of control systems engineering. Markov chains have also been proposed and studied in [5] in the context of the MAP kinase signaling cascade. In the present work, we combine these two approaches into a more general model in which each molecule and/or protein in the signaling network is represented by a Markov chain which represents a node in a graph. Chains at each node can differ in order and structure depending on the nature of the molecule and the number of states it can take (for example the number of phosphorylation states in one protein may not be the same as the number of cleaved forms of another molecule). In addition, the interactions between different molecules in the network is represented by the fact that the evolution of each chain can be influenced not only by its own present state but also by the state of the chains that influence it, i.e. that connect to it in the network graph. The set of evolution rules or the way neighboring nodes influence other nodes is formulated based on our current knowledge of the nature of the interactions between specific molecules in the network and as a result, are not constrained to be multilinear as is the case in [4]. Together, the set of evolution rules, the individual matrices associated with the Markov chains, and the network influence matrix associated with the connectivity of the graph represent a full characterization of the signaling network within our modeling framework and therefore, our model is compactly represented using linear algebra tools. These tools allow efficient computation of the network dynamics and time evolution.

In this work, we formulate a network model for apoptosome signaling network in *C.elegans*, *Drosophila*, and human, and validate it by showing that the computed time evolution and steady state protein values correlate with published measured protein data. A thorough analysis of the structure and dynamic differences among the three models is also presented and the

evolutionary advantage of integrating mitochondrial cytochrome c release to the apoptosome signaling network is discussed.

REFERENCES

[1] Brody, T. The Interactibe Fly. Cell Death Regulation in Drosophila: Conservation of Mechanisms and Unique Insights. http://sdb.bio.purdue.edu/fly/aignfam/apoptosis.htm.

[2] Ameisen, J.C. On the Origin, Evolution, and Nature of Programmed Cell Death: a Timeline of Four Billion Years. Cell Death and Differentiation (2002) 9, 367-393.

[3] Moreno, E., Minhong, Y., and Basler, K. Evolution of the TNF Signaling Mechanisms: JNK-Dependent Apoptosis Triggered by Eiger , The Drosophila Homolog of the TNF Superfamily. Current Biology. Published online July 8, 2002.

[4] Asavathiratham, C., Roy, S., Lesieutre, B., and Verghese, G. The Influence Model. IEEE Control Systems Magazine, (December 2001), 52-64.

[5] Said, M.R., Lauffenburger, D.A., and Oppenheim , A.V. ``A Markov Chain Model of the MAPK Signaling Cascade'' in Proc. Int. Conf. on Systems Biology (ICSB 2001), (Pasadena, CA), November 2001.