Modeling a *Hox* Gene Network

Stochastic Simulation with Experimental Perturbation

Abstract

The *Hox* genes show a striking segment specific pattern of expression in a variety of vertebrate embryos, and have been the topic of many experimental analyses. There are now sufficient data to construct a higher-level model for the interaction and regulation of the *Hox* genes. This thesis presents the results of an investigation into a regulatory network for the early *Hox* genes. Instead of using conventional differential equation approaches for analyzing the system, a stochastic simulation algorithm has been employed to model the network. The model can track the behavior of each component of a biochemical pathway and produce computerized movies of the time evolution of the system that is a result of the dynamic interplay of these various components. The simulation is able to reproduce key features of the wild-type pattern of gene expression, and *in silico* experiments yield results similar to their corresponding *in vivo* experiments. This work shows the utility of using stochastic methods to model biochemical networks and expands the stochastic simulation algorithm methodology to work in multi-cellular systems. In addition, the model has suggested several predictions that can be tested i*n vivo*.

A tight connection was also created between the modeling and laboratory experiments. To investigate a connection between two components of the network, retinoic acid (RA) and *Hoxa1*, a novel laboratory experiment was performed to perturb

the system. An RA soaked bead was implanted into the neural tube of a developing chick embryo and the effect of the exogenous RA was assayed with an *in situ* hybridization for the gene *Hoxa1*. The resulting expression patterns suggested that one aspect of the model design was not accurate, and based on these results the model was modified to encompass the new data, without losing the fit to the original data sets. The thesis work was therefore brought full circle, thus showing the utility of an interconnected effort: the act of constructing and using the model identified interesting biology questions, and the answer to one of those questions was used to enhance the model.