

Modeling a Hox Gene Network

The Interaction of Retinoic Acid, HoxA1, HoxB1, and HoxB2 in Rhombomeres 3-5.

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ABSTRACT

Shortly after the closure of the neural tube, the chick hind-brain develops a series of axial bulges called rhombomeres. The initial descriptions of the rhombomeres in the early part of the twentieth century resulted in some arguments about the importance of these structure but these arguments were finally quelled in the past decade when experiments showed that the segmentation of the hindbrain is a crucial process in hindbrain development[1].

In vertebrates, the Hox gene family is a set of transcription factors that play a pivotal role in regulating patterning and axial morphogenesis. Molecular expression studies have shown that members of the Hox family display rhombomere-restricted patterns of expression (reviewed in [5]) and recent studies have show the importance of Retinoic Acid (RA) in this process as it is able to directly regulate Hox family members (reviewed in [2]). But by virtue of the fact that these data have been gathered using molecular techniques, the data produced generally describes very localized events. The sheer amount of data that is now available allows us to take the next important step; that of integrating the results and constructing a higher level model for the interaction and regulation of members of the Hox family.

To accomplish this, we have adopted a stochastic simulation approach [3, 4] to modeling the biochemical reactions between RA, HoxA1, HoxB1 and HoxB2 in rhombomeres 3-5. This method is able to capture more of the actual biology (including the inevitable fluctuations and the low number of molecules) than the traditional continuous-valued kinetic equations, and allows for a direct connection between the the model parameters and the biologically meaningful parameters such as binding affinities and transcription rates. This model also allows us to track in detail the behavior of each component of a particular biochemical pathway and to produce computerized movies of the time evolution of the system that is a result of the dynamic interplay of these various components. The simulation has been able to reproduce several key observations seen in the laboratory. In addition, the simulation has suggested several new results from experiments (including perturbing endogenous RA levels and

introducing a dominant negative RA receptor) performed *in silico*. For validation and enhancement of the model, these experiments are currently being performed *in vivo*.

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