

78g Computational, Genetic, and Biochemical Analysis of Egfr Control by Multiple Feedback Loops

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The epidermal growth factor receptor (EGFR) network is a key regulator of animal tissues and the most extensively modeled eukaryotic signaling system. Most of the current models have been formulated at the molecular and cellular levels. We will present the experimental and computational work on the formulation, analysis, and validation of a quantitative model of the EGFR system in tissues.

One of the main difficulties associated with the tissue-level modeling of EGFR system is its immense structural complexity. The mammalian EGFR is activated by multiple ligands that generate multiple homo- and heterodimers that signal through a number of intracellular pathways. The *Drosophila* EGFR system is considerably simpler: there is only one receptor that signals a single signal transduction pathway (the evolutionarily conserved Ras/MAPK cascade) [1]. Recently, ligand-receptor interactions in the *Drosophila* EGFR network have been quantitatively characterized using a combination of biochemical, biophysical, and cellular approaches [2]. Data from these experiments, in combination with the powerful techniques of *Drosophila* genetics, enable the formulation and systematic experimental validation of quantitative models of the EGFR network in tissues.

We have developed and begun to experimentally test a computational model of EGFR signaling in patterning of the *Drosophila* embryonic ventral ectoderm [3]. The model describes EGFR activation by two of its locally produced ligands (Spitz and Vein) as well as EGFR inhibition by Argos, a secreted protein that controls EGFR signaling by ligand sequestration. We constrain the model based on the experimental data on genetic and biochemical interactions of Spitz, Argos, and Vein. We then use the model to explore EGFR control by ligand sequestration and to make experimentally testable predictions about the robustness of ventral ectodermal patterning by EGFR. We implement these predictions using the standard techniques for tissue-specific gene expression in *Drosophila*. Finally, we discuss the quantitative constraints on the relative length scales of secreted EGFR ligands (Spitz and Vein) and secreted EGFR inhibitor (Argos).

[1] B. Z. Shilo. *Exp Cell Res.* 284 (1):140-9, 2003. [2] D. E. Klein, V. M. Nappi, G. T. Reeves, S. Y. Shvartsman, and M. A. Lemmon. *Nature*, 430: 1040-1044, 2004. [3] G. T. Reeves, R. Kalifa, D. E. Klein, M. A. Lemmon, and S. Y. Shvartsman. *Dev. Biol.* in press, 2005.