# Spatially Uniform Binding Rate Down-regulation

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## Background

Various mechanisms exist which down-regulate ectopic activities in Drosophila. Experimental data detailed in [3] showed that an increase in $6^{\circ}$C in the environment of a developing fly embryo leads to a doubled synthesis rate of Dpp, or Decapentaplegic, which in turn binds with Tkv, or Thickvein to form complexes which govern the development of fly wings. Despite this ectopic activity, a down-regulating mechanism must exist which enables the fly's development to remain relatively constant. The possibility that a regulatory mechanism for reacting to ectopic activities is robustness-based and spatially uniform was presented in a proof-of-concept paper, [1].

## Problem

Biological mechanisms exist which allow us to exert control over the concentration of signaling morphogen gradients. A program has been initiated at UCI to model some of them mathematically and examine their implications [1, 2]. Work has been done in [2] analytically for the case of low receptor occupancy. Using *Mathematica*, we study the behavior of a spatially uniform robust signaling negative feedback mechanism on the ligand-receptor binding rate in *Drosophila*, paying particular attention to the concentration of *Dpp-Tkv* complexes.

## Standardizing Parameters

The following set of parameters is used in predecessor work

$$X_{\text{max}} = 0.01 \text{ cm}, X_{\text{min}} = 0.001 \text{ cm},$$

$$k_{\text{deg}} = 2 \times 10^{-4}, k_{\text{on}} R_0 = 0.01 \text{ sec}/\mu\text{m},$$

$$k_R = 0.001/\text{sec.}, k_{\text{off}} = 10^{-6}/\text{sec.}, k_L = 0$$

$$D = 10^{-7} \text{ cm}^2/\text{sec},$$

$$\overline{V}_L = 0.002\mu\text{M/sec.}, \overline{V}_R = 0.04\mu\text{M/sec.}$$

These are still present in the model, implicitly through non-dimensionalizations which made the equations easier to study and (by consequence) code.

## Results

Given the standardizing parameters:

| c | $\overline{R}_k$ | $\overline{R}_{k+1}$ | $\overline{b}(0)$ |
|---|---|---|---|
| 1 | 0.01364 | 0.01364 | 0.05801 |
| 2 | 0.01486 | 0.01487 | 0.05801 |
| 4 | 0.01835 | 0.01831 | 0.05801 |

| c | $\overline{b}(0;\overline{R}_k)$ | $\overline{b}(0;\overline{R}_{k+1})$ |
|---|---|---|
| 1 | 0.05517 | 0.05517 |
| 2 | 0.05486 | 0.05486 |
| 4 | 0.05405 | 0.05406 |

This quick convergence was attained in less than 10 iterations. The biological implication is also quite satisfying, as this is far below the acceptable threshold of robustness, 0.2, used in [2].

## The Model

The most generic version of the model is detailed in [1]. Here we discuss a non-dimensionalized steady state version of the model, given by

$$a'' - \frac{\overline{h_0} a}{\overline{\alpha}_0(1 + c\overline{R}_b^n) + \zeta_h a} - g_L a + \overline{v}_L H(-x) = 0,$$

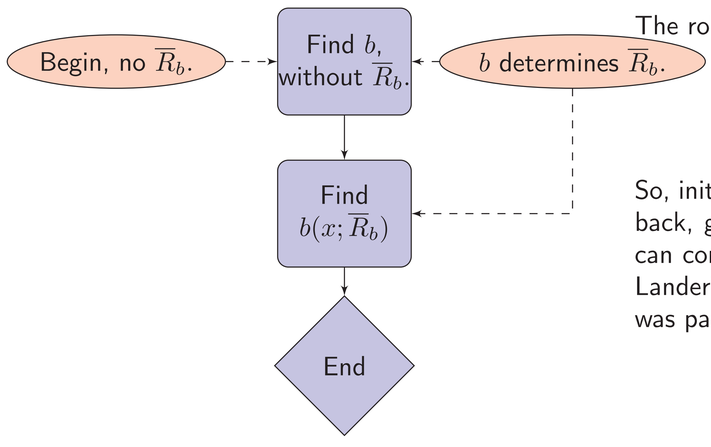
$$b(x;\overline{R}_b) = \frac{\overline{h_0} a}{g_0(\overline{\alpha}_0(1 + c\overline{R}_b^n) + \zeta_h a)} \qquad r(x;\overline{R}_b) = \frac{\overline{\alpha_0}(1 + c\overline{R}_b^n)}{\overline{\alpha_0}(1 + c\overline{R}_b^n) + \zeta_h a}$$

where

$$\overline{\alpha}_0 = 1 + \frac{f_0}{g_0}, \qquad \zeta_h = \frac{\overline{h}_0}{g_R}.$$

Here $a, b$, and $r$ denote, respectively, the concentrations of free morphogens, bound morphogens, and unoccupied receptors. **The behavior of the binding rate coefficient is encapsulated by** $h_0$.

## Iterative Scheme




The robustness index is given by

$$\overline{R}_b = \frac{1}{\overline{b}(0)} \sqrt{\int_0^1 [b(x;\overline{R}_b) - b(x)]^2 \, \mathrm{d}x}.$$

So, initial data was used from a system without feedback, given some fixed level of ectopicity (which we can control thanks to work done by S. Zhou in A.D. Lander's lab at UCI) and then a value of robustness was passed into the system described on this poster.

## References

[1] Simonyan A. Wan F.Y.M. Kushner, T. A new approach to feedback for robust signaling gradients. Studies in Appl. Math., 133:18-51, 2014.
[2] F.Y.M. Wan. Spatially uniform and nonuniform feedback for robust signaling gradients. 2016.
[3] S. Zhou. Diffusion creates the dpp morphogen gradient of the drosophila wing disc. Department of Development and Cell Biology, UC Irvine, 2011.

## Future Research

Biological mechanisms exist which allow us to exert control over the concentration of signaling morphogen gradients. A program has been initiated at UCI to model some of them mathematically and examine their implications [1, 2].
Through experimentation, we can control these mechanisms with the hopes that similar studies to this one can be tackled using adaptable iterative schemes, as the beginning of this project was to replicate previous work for general cases (for which results were done analytically but under some strong constraints which we removed in this analysis.) Understanding the ways in which developing organisms maintain morphogenesis given environmental factors will ultimately be insightful to the field of developmental biology as a whole.

## Contact Information

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