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TRANSIENT FEEDBACK AND ROBUST SIGNALING GRADIENTS

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Abstract. Robust development of biological organisms in the presence of genetic and epi-genetic perturbations is important for time spans short relative to evolutionary time. Gradients of receptor bound signaling morphogens are responsible for patterning formation and development. A variety of inhibitors for reducing ectopic signaling activities are known to exist and their specific role in down-regulating the undesirable ectopic activities reasonably well understood. However, how a developing organism manages to adjust inhibition/stimulation in response to genetic and/or environmental changes remains to be uncovered. The need to adjust for ectopic signaling activities requires the presence of one or more feedback mechanisms to stimulate the needed adjustment. As the ultimate effect of many inhibitors (including those of the nonreceptor type) is to reduce the availability of signaling morphogens for binding with signaling receptors, a negative feedback on signaling morphogen synthesis rate based on a root-mean-square measure of the spatial distribution of signaling concentration offers a simple approach to robusness and has been demonstrated to be effective in a proof-of-concept implementation. In this paper, we complement the previous investigation of feedback in steady state by examining the effect of one or more feedback adjustments during the transient phase of the biological development.

Key words. Morphogen gradients, robustness, feedback mechanism.

1. Introduction

Robust development in the presence of genetic mutation and/or epigenetic perturbations is important for biological organisms. Gradients of receptor bound signaling morphogens are known to be responsible for pattern formation and development. The morphogen (aka *ligands*) Decapentaplegic (*Dpp)* in a Drosophila wing imaginal disc, for example, is synthesized at a localized source and transported downstream by active or passive diffusion for binding with signaling receptors Thickvein (*Tkv*) to form a signaling spatial gradient. Graded differences in receptor occupancy at different locations underlie the signaling differences that ultimately lead cells down different paths of development [1, 2, 3, 4].

Genetic and epigenetic changes often alter the ligand synthesis rate resulting in abnormal signaling. Experimental results by S. Zhou in A.D. Lander's lab [4] show that *Dpp* synthesis rate doubles when the ambient temperature is increased by $6°C$. With such an increase in Dpp synthesis rate, the simple models developed in [5, 6, 7] would predict signaling gradients qualitatively different from that at the lower ambient temperature. Yet, little abnormality in the actual development of the wild-type wing imaginal disc is seen under such a change of ambient temperature (see also [8, 9]). In effect, patterning of the Drosophila wing is largely insensitive to a significant increase in synthesis rate. In general, an important requirement

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for normal biological development is for the relevant signaling morphogen gradients not easily altered by genetic or environmental fluctuations that cause significant changes in the constitution of the developing organism. The development is said to be *robust* when the output of the biological system is insensitive to variations in input or system parameters.

A variety of agents for regulating signaling activities are known to exist and their specific role in down– or up–regulating the abnormal activities reasonably well understood. These include molecular entities (such as heparan sulfate proteoglycans [10]) that bind with signaling ligands but the resulting complexes do not signal. Such non-signaling molecular entities are called *nonreceptors*; their presence has been observed to reduce the amount of morphogens available for binding with signaling receptors. That nonreceptors down-regulate cell signaling has also been confirmed theoretically in [11] and references therein. (For other possible mechanisms for down-regulating signaling gradients, see discussion in [12] and references cited there.) Just how a developing organism manages to up-regulate inhibition (such as nonreceptor concentration) or activation (such as raising the binding rate) in response to genetic and/or environmental changes remains to be uncovered.

Evidence exists that adjustments for abnormal signaling activities require one or more feedback mechanisms to stimulate the needed level of correction. Feedback has long been seen as a mechanism for responding to an enhanced signaling gradient and stimulating up-regulation of inhibitors of morphogen signaling to achieve robustness (see [13, 14, 15, 16] for examples). Specific feedback loops identified in the literature include:

- BMP-2 causes significant up-regulation of Sox9 and the BMP antagonist Noggin expression [14, 17].
- High levels of Wingless signaling induce Notum expression and Notum modifies the heparan sulfate proteoglycans Dally-like and Dally that contribute to shaping Wingless gradient [18].

Just how a specific feedback is induced by ectopic signaling morphogen concentration has been an area of current research (see also [19, 20, 21] and references cited there).

In [12], we initiated a different approach to the role of feedback in ensuring robust signaling gradients. The overall goal of the project is to investigate the effectiveness of feedback mechanisms other than a negative feedback of the Hill's function type on signaling receptor synthesis (which is known to be ineffective [19, 20, 21]). With the ultimate effect of many inhibitors (of the nonreceptor type) being a reduction of the availability for signaling morphogens for binding with signaling receptors, we embarked in [12] a proof-of-concept examination of a new spatially uniform nonlocal feedback process (distinctly different from the conventional (spatially nonuniform) Hill function feedback) on the morphogen synthesis rate. This negative feedback is based on a root-mean-square measure of the spatial distribution of signaling concentration offers a simple approach to robustness and has been demonstrated to be effective in [12] for a signaling gradient in steady state. In this paper, we examine the corresponding transient problem with repeated feedback adjustments taking effect during the transient phase of the development.

2. Signaling Gradients and Pattern Formation

2.1. The Initial-Boundary Value Problem for the Basic Model. The basic process of biological developments is reasonably well understood by biologists.