INTERPRETATION AND SCALING OF POSITIONAL INFORMATION DURING DEVELOPMENT

Thesis by

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To Michelle,

for her love and support

Acknowledgments

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Abstract

Cells in a developing animal require information about their relative position in order to function and differentiate appropriately. In the classical view, cellular positional information is interpreted from the concentration of chemical signals known as morphogens. However, recent studies have questioned the ability of morphogens to establish gene expression patterns in a concentration-dependent manner. Here we combine theoretical tools and experimental work in *Drosophila melanogaster* to investigate the mechanisms by which positional information is interpreted from a morphogen gradient and the ability of patterns to scale with respect to the size of the system.

First, we study how a concentration gradient of the signaling molecule Hedgehog establishes multiple patterns of gene expression along the anterior-posterior axis of the *Drosophila* wing disc. Using mathematical modeling as a hypotheses-generating tool, we predicted that positional information cannot be explained by different concentration thresholds from a static Hedgehog gradient. Instead, we propose that cells take into account their history of Hedgehog signaling exposure to determine patterns of gene expression. We provide experimental evidence that supports our model and conclude that gradient dynamics, resulting from the gene network architecture of the Hedgehog signaling pathway, determine pattern formation in the wing disc.

Second, we introduce a theoretical formalism to study the role of morphogen gradient dynamics in developmental patterning. Given a mathematical model of pattern formation, we define and compute parameter perturbations that leave invariant the steady-state distribution of the relevant morphogen. We propose that this approach can be

used as a tool to design genetic experiments that assay the function of morphogen dynamics.

Lastly, we use dorsal-ventral patterning of the early *Drosophila* embryo as a model to study scaling of gene expression patterns with respect to natural variations in axis length, that is, the ability to establish positional information relative to the size of the system. We provide evidence that gene expression patterns that depend on the maternal factor Dorsal, scale along the dorsal-ventral axis. Our data suggest that scaling in this system is a gene-dependent rather than a position-dependent property. We propose that the mechanisms for scaling depend on feedback interactions downstream of Dorsal.

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