List of important papers in the mathematical modeling of biological pattern formation during early development

L S Shashidhara (IISER Pune)

1: PLoS Comput Biol. 2009 Aug;5(8):e1000486. Epub 2009 Aug 28.
Related Articles, Links

Stable, precise, and reproducible patterning of bicoid and hunchback molecules in the early Drosophila embryo.

Okabe-Oho Y, **Murakami H**, **Oho S**, **Sasai M**.

Department of Computational Science and Engineering, Nagoya University, Nagoya, Japan.

Precise patterning of morphogen molecules and their accurate reading out are of key importance in embryonic development. Recent experiments have visualized distributions of proteins in developing embryos and shown that the gradient of concentration of Bicoid morphogen in Drosophila embryos is established rapidly after fertilization and remains stable through syncytial mitoses. This stable Bicoid gradient is read out in a precise way to distribute Hunchback with small fluctuations in each embryo and in a reproducible way, with small embryo-to-embryo fluctuation. The mechanisms of such stable, precise, and reproducible patterning through noisy cellular processes, however, still remain mysterious. To address these issues, here we develop the one- and three-dimensional stochastic models of the early Drosophila embryo. The simulated results show that the fluctuation in expression of the hunchback gene is dominated by the random arrival of Bicoid at the hunchback enhancer. Slow diffusion of Hunchback protein, however, averages out this intense fluctuation, leading to the precise patterning of distribution of Hunchback without loss of sharpness of the boundary of its distribution. The coordinated rates of diffusion and transport of input Bicoid and output Hunchback play decisive roles in suppressing fluctuations arising from the dynamical structure change in embryos and those arising from the random diffusion of molecules, and give rise to the stable, precise, and reproducible patterning of Bicoid and Hunchback distributions.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19714200 [PubMed - in process]

PMCID: PMC2720536

2: Proc Natl Acad Sci U S A. 2009 Feb 10;106(6):1710-5. Epub 2009 Feb 3.
Related Articles, Links

Determining the scale of the Bicoid morphogen gradient.

Hecht I, **Rappel WJ**, **Levine H**.

Center for Theoretical Biological Physics and Department of Physics, University of California at San Diego, La Jolla, CA 92093, USA. inbal.hecht@gmail.com

Bicoid is a morphogen that sets up the anterior-posterior axis in early Drosophila embryos. Although the form of the Bicoid profile is consistent with a simple diffusion/degradation model, the observed length scale is much larger than should be expected based on the measured diffusion rate. Here, we study two possible mechanisms that could, in principle, affect this gradient and, hence, address this disagreement. First, we show that including trapping and release of Bicoid by the nuclei during cleavage cycles does not alter the morphogen length scale. More crucially, the inclusion of advective transport due to cytoplasmic streaming can have a large effect. Specifically, we build a simple model based on the (limited) experimental data and show that such a flow can lead to a Bicoid profile that is consistent with various experimental features. Specifically, the observed length scale is obtained, a steady profile is established, and improved scaling between embryos of different lengths is demonstrated.

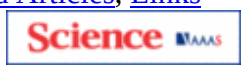
Publication Types:

- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 19190186 [PubMed - indexed for MEDLINE]

PMCID: PMC2644102

3: Science. 2008 Oct 17;322(5900):399-403.
Related Articles, Links



From signals to patterns: space, time, and mathematics in developmental biology.

Lewis J.

Vertebrate Development Laboratory, Cancer Research UK London Research Institute, London WC2A 3PX, UK.

We now have a wealth of information about the molecular signals that act on cells in embryos, but how do the control systems based on these signals generate pattern and govern the timing of developmental events? Here, I discuss four examples to show how mathematical modeling and quantitative experimentation can give some useful answers. The examples concern the Bicoid gradient in the early Drosophila embryo, the dorsoventral patterning of a frog embryo by bone morphogenetic protein signals, the auxin-mediated patterning of plant meristems, and the Notch-dependent somite segmentation clock.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 18927385 [PubMed - indexed for MEDLINE]

4: Dev Cell. 2008 Oct;15(4):558-67.
Related Articles, Links

Probing intrinsic properties of a robust morphogen gradient in Drosophila.

He F, **Wen Y**, **Deng J**, **Lin X**, **Lu LJ**, **Jiao R**, **Ma J**.

Division of Biomedical Informatics, Cincinnati Children's Hospital Research Foundation, 3333 Burnet Avenue, Cincinnati, OH 45229, USA.

A remarkable feature of development is its reproducibility, the ability to correct embryo-to-embryo variations and instruct precise patterning. In Drosophila, embryonic patterning along the anterior-posterior axis is controlled by the morphogen gradient Bicoid (Bcd). In this article, we describe quantitative studies of the native Bcd gradient and its target Hunchback (Hb). We show that the native Bcd gradient is highly reproducible and is itself scaled with embryo length. While a precise Bcd gradient is necessary for precise Hb expression, it still has positional errors greater than Hb expression. We describe analyses further probing mechanisms for Bcd gradient scaling and correction of its residual positional errors. Our results suggest a simple model of a robust Bcd gradient sufficient to achieve scaled and precise activation of its targets. The robustness of this gradient is conferred by its intrinsic properties of "self-correcting" the inevitable input variations to achieve a precise and reproducible output.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 18854140 [PubMed - indexed for MEDLINE]

PMCID: PMC2629455

5: J Theor Biol. 2008 Sep 21;254(2):390-9. Epub 2008 May 24.
Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Modeling the precision and robustness of Hunchback border during Drosophila embryonic development.

Hardway H, **Mukhopadhyay B**, **Burke T**, **James Hitchman T**, **Forman R**.

Department of Mathematics, Rice University, 6100 S. Main, Houston, TX 77005, USA. hardway@rice.edu

During anterior-posterior axis specification in the Drosophila embryo, the Hunchback (Hb) protein forms a sharp boundary at the mid-point of the embryo with great positional precision. While Bicoid (Bcd) is a known upstream regulator for hb expression, there is evidence to suggest that Hb effectively filters out "noisy" data received from varied Bcd gradients. We use mathematical models to explore simple regulatory networks which filter out such noise to produce a precise Hb boundary. We find that in addition to Bcd and Hb, at least one freely evolving protein is necessary. An automated search yields a number of examples of three-protein networks exhibiting the desired precision. In all such networks, Hb diffuses much slower than the third protein. In addition, the action of Hb on the third protein is the opposite of the action of the third protein on hb (i.e. if Hb activates the third protein, then the third protein inhibits hb expression, and vice versa). Most of the discovered systems satisfy the known biological properties, that Bcd activates hb, and that Hb activates its own expression. We find that all network topologies satisfying these constraints arise among the networks exhibiting the desired precision. Investigating the dynamics of these networks, we find that under a general class of non-uniform initial conditions, Bcd can be eliminated from the system and the spatiotemporal evolution of these two proteins alone is sufficient to recapture the dynamics. We hypothesize that Bcd is needed only to spatially disturb the gradient of the third protein, and then becomes unnecessary in the further evolution of the Hb border. This provides a possible

explanation as to why the Hb dynamics are robust under perturbations of the Bcd gradient. Under this hypothesis, other proteins would be able to assume the role of Bcd in our simulations (possibly in the case of evolutionary divergences or a redundancy in the process), with the only constraint that they act to positively regulate hb.

Publication Types:

- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 18621403 [PubMed - indexed for MEDLINE]

6: Phys Rev E Stat Nonlin Soft Matter Phys. 2008 Apr;77(4 Pt 1):041903. Epub 2008 Apr 8.
Related Articles, Links

Go to Publisher Site

Optimizing the readout of morphogen gradients.

Emberly E.

Physics Department, Simon Fraser University, Burnaby, British Columbia, Canada.

In multicellular organisms, the initial patterns of gene expression are regulated by spatial gradients of biochemical factors, known as morphogen gradients. Because of biochemical noise in the morphogen gradients there are associated spatial errors in the positions of target gene patterns. Using a simple single morphogen and/or single target gene model, we use propagation of error analysis to derive a condition on the amount of morphogen that needs to be produced in order to have precise spatial patterning of the target. We find that there is an optimal morphogen gradient profile that requires the least amount of morphogen to be produced. Experimental results for the Bicoid-Hunchback system in early Drosophila development are consistent with the predictions of this analysis. We also discuss our results in the context of recent work that analyzed this system using mutual information as an organizing principle, and show that minimizing the amount of morphogen produced also leads to a near optimal flow of information between input and target.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18517652 [PubMed - indexed for MEDLINE]

7: Curr Opin Cell Biol. 2008 Apr;20(2):137-43. Epub 2008 Mar 10.
Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

The Decapentaplegic morphogen gradient: a precise definition.

Kicheva A, **González-Gaitán M**.

Department of Biochemistry, University of Geneva, Sciences II, Quai E. Ansermet 30, 1211 Geneva, Switzerland.

Two key processes are in the basis of morphogenesis: the spatial allocation of cell types in fields of naïve cells and the regulation of growth. Both are controlled by morphogens, which activate target genes in the growing tissue in a concentration-dependent manner. Thus the morphogen model is an intrinsically quantitative concept. However, quantitative studies were performed only in recent years on two morphogens: Bicoid and Decapentaplegic. This review covers quantitative aspects of the formation and precision of the Decapentaplegic morphogen gradient. The morphogen gradient concept is transitioning from a soft definition to a precise idea of what the gradient could really do.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 18329870 [PubMed - indexed for MEDLINE]

8: Dev Biol. 2008 Apr 15;316(2):350-8. Epub 2008 Feb 13.
Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE FREE Author Manuscript in PubMed Central

Shape and function of the Bicoid morphogen gradient in dipteran species with different sized embryos.

Gregor T, **McGregor AP**, **Wieschaus EF**.

Howard Hughes Medical Institute, Princeton University, Princeton, NJ 08544, USA.

The Bicoid morphogen evolved approximately 150 MYA from a Hox3 duplication and is only found in higher dipterans. A major difference between dipteran species, however, is the size of the embryo, which varies up to 5-fold. Although the expression of developmental factors scale with egg length, it

remains unknown how this scaling is achieved. To test whether scaling is accounted for by the properties of Bicoid, we expressed eGFP fused to the coding region of bicoid from three dipteran species in transgenic Drosophila embryos using the Drosophila bicoid cis-regulatory and mRNA localization sequences. In such embryos, we find that Lucilia sericata and Calliphora vicina Bicoid produce gradients very similar to the endogenous Drosophila gradient and much shorter than what they would have produced in their own respective species. The common shape of the Drosophila, Lucilia and Calliphora Bicoid gradients appears to be a conserved feature of the Bicoid protein. Surprisingly, despite their similar distributions, we find that Bicoid from Lucilia and Calliphora do not rescue Drosophila bicoid mutants, suggesting that that Bicoid proteins have evolved species-specific functional amino acid differences. We also found that maternal expression and anteriorly localization of proteins other than Bcd does not necessarily give rise to a gradient; eGFP produced a uniform protein distribution. However, a shallow gradient was observed using eGFP-NLS, suggesting nuclear localization may be necessary but not sufficient for gradient formation.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 18328473 [PubMed - indexed for MEDLINE]

PMCID: PMC2441567

9: Development. 2008 Mar;135(6):1137-46.
Related Articles, Links

Precision of the Dpp gradient.

Bollenbach T, **Pantazis P**, **Kicheva A**, **Bökel C**, **González-Gaitán M**, **Jülicher F**.

Max-Planck-Institute for the Physics of Complex Systems, Dresden, Germany.

Morphogen concentration gradients provide positional information by activating target genes in a concentration-dependent manner. Recent reports show that the gradient of the syncytial morphogen Bicoid seems to provide precise positional information to determine target gene domains. For secreted morphogenetic ligands, the precision of the gradients, the signal transduction and the reliability of target gene expression domains have not been studied. Here we investigate these issues for the TGF-beta-type morphogen Dpp. We first studied theoretically how

cell-to-cell variability in the source, the target tissue, or both, contribute to the variations of the gradient. Fluctuations in the source and target generate a local maximum of precision at a finite distance to the source. We then determined experimentally in the wing epithelium: (1) the precision of the Dpp concentration gradient; (2) the precision of the Dpp signaling activity profile; and (3) the precision of activation of the Dpp target gene spalt. As captured by our theoretical description, the Dpp gradient provides positional information with a maximal precision a few cells away from the source. This maximal precision corresponds to a positional uncertainly of about a single cell diameter. The precision of the Dpp gradient accounts for the precision of the spalt expression range, implying that Dpp can act as a morphogen to coarsely determine the expression pattern of target genes.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18296653 [PubMed - indexed for MEDLINE]