Morphogen Profiles Can be Optimized to Buffer Against Noise

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Morphogen profiles play a vital role in biology by specifying position in embryonic development. However, the factors that influence the shape of a morphogen profile remain poorly understood. Since morphogens should provide precise positional information, one significant factor is the robustness of the profile to noise. We compare three classes of morphogen profiles (linear, exponential, algebraic) to see which is most precise when subject to both external embryo-to-embryo fluctuations and internal fluctuations due to intrinsically random processes such as diffusion. We find that both the kinetic parameters and the overall gradient shape (e.g. exponential versus algebraic) can be optimized to generate maximally precise positional information.

Keywords **— morphogen | precision | optimization | noise | bicoid**

I. Introduction

Morphogens play a vital role in biological development by inducing responses in a concentration-dependent manner [1]. In the standard model of morphogen gradients, morphogen proteins originate from a localized source, diffuse and are degraded, setting up a concentration gradient across the system. Developmental systems need to be robust to sources of noise – from external source fluctuations and internal stochastic noise - in order to generate precise patterns of gene expression using morphogen gradients. Here, we address a simple question: in the presence of noise, which morphogen profile is most precise in specifying the positions of gene expression boundaries? In principle, any spatially non-uniform profile could be used to position gene expression boundaries; our goal is to understand which profiles might be preferred.

This work is motivated by recent experiments in *Drosophila melanogaster* that have quantitatively studied the morphogen proteins Bicoid, Decapentaplegic and Wingless [2,3,4]. Interestingly, the observed profiles are all exponentially decaying.

II. Results

We focus on three classes of experimentally relevant morphogen profiles (linear, exponential, algebraic) to see which is most precise when subjected to the combined effects of both external and internal fluctuations. To calculate the positional imprecision due to internal fluctuations we have shown that, even for non-linear degradation processes, the morphogen number distribution is Poisson; in three-dimensions diffusion (which is a Poisson process) is able to prevent the build-up of non-Poisson correlations [5]. Our work reveals two important properties of morphogen gradients [5]:

A. Kinetic parameters can be optimized to buffer noise

Using a simple reaction-diffusion model, we find that the kinetic parameters describing morphogen profiles can be optimized to buffer against noise. For example, there exists an optimal decay length for exponential profiles that minimizes the effects of internal and external fluctuations.

B. Profile shape can be optimized to buffer noise

By comparing optimized profiles, we see that the overall shape of the profile (e.g. exponential versus algebraic) can also be optimized. Exponential profiles frequently emerge as the best compromise: such profiles are not particularly robust to either external or internal fluctuations taken singly, but when both types of fluctuation are taken together, exponential profiles can be most precise. These results are consistent with observed experimental morphogen gradients.

III. Conclusion

We propose a simple design principle for morphogen profiles, namely that evolution has selected gradients with optimal robustness to the combined effects of embryo-to-embryo and internal noise. Given that very high positional precision can be achieved by morphogens it seems plausible that optimization may well be exploited by evolution. Attaining maximal robustness to the combined effects of internal and external noise may be a powerful unifying principle in understanding the fundamental design of morphogen systems.

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References

[1] Lander AD (2007) Morpheus Unbound: Reimagining the Morphogen Gradient. *Cell* **128,** 245-256.

[2] Houchmandzedah et. al. (2002) Establishment of developmental precision and proportions in the early *Drosophila* embryo. *Nature* **415,** 798-802.

[3] Gregor T et. al. (2007) Stability and Nuclear Dynamics of the Bicoid Morphogen Gradient. *Cell* **130,** 141-152.

[4] Kicheva A et. al. (2007) Kinetics of Morphogen Gradient Formation. *Science* **315,** 521-525.

[5] Saunders T and Howard M, 10 April 2009, Morphogen Profiles Can be Optimised to Buffer Against Noise. q-bio.MN/ 09041637.