Master equation simulation analysis of immunostained Bicoid morphogen gradient

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***Short Abstract* — Nucleus-to-nucleus variation (noise) in the gradient of the Bicoid morphogen were observed from fixed, immunostained *Drosophila* embryos. These observations were compared with a master equation model of Bicoid gradient formation which represents diffusion, decay and anterior synthesis. We show that the intrinsic noise of an autonomous reaction-diffusion gradient is Poisson distributed, but that the statistical signature of this process in the data is obscured by uncertainties of the staining procedure. Nevertheless, intrinsic noise and other sources of variation can be separated by their statistical signatures, and the noise observed in data can serve as a physical constraint for restricting the model's parameter space and predicting its dynamics.**

***Keywords* — stochastic model, intrinsic noise, MesoRD, reaction diffusion, gene expression, Drosophila segmentation.**

I. Purpose

THE concentration gradient of Bicoid protein which determines the developmental pathways in early *Drosophila* embryo is the best characterized morphogen gradient at the molecular level. Because different developmental fates can be elicited by different concentrations of Bicoid, it is important to probe the limits of this specification by analyzing intrinsic fluctuations of the Bicoid gradient arising from small molecular number. Stochastic simulations can be applied to further the understanding of the dynamics of Bicoid morphogen gradient formation at the molecular number level, and determine the source of the nucleus-to-nucleus expression variation (noise) observed in the Bicoid gradient.

II. Results

We compared quantitative observations of Bicoid levels in immunostained *Drosophila* embryos with a spatially extended Master Equation model which represents diffusion, decay, and anterior synthesis. We show that the intrinsic noise of an autonomous reaction-diffusion gradient is Poisson distributed. We demonstrate how experimental noise can be identified in the logarithm domain from single embryo analysis, and then separated from intrinsic noise in the normalized variance domain of an ensemble statistical analysis. We show how measurement sensitivity affects our observations, and how small amounts of rescaling noise can perturb the noise strength (Fano factor) observed. We demonstrate that the biological noise level in data can serve as a physical constraint for restricting the model's parameter space, and for predicting the Bicoid molecular number and variation range. An estimate based on a low variance ensemble of embryos suggests that the steady-state Bicoid molecular number in a nucleus should be larger than 300 in the middle of the embryo, and hence the gradient should extend to the posterior end of the embryo, beyond the previously assumed background limit. We exhibit the predicted molecular number gradient together with measurement effects, and make a comparison between conditions of higher and lower variance respectively.

III. Conclusion

Quantitative comparison of Master Equation simulations with immunostained data enabled us to determine narrow ranges for key biophysical parameters, which for this system can be independently validated. Intrinsic noise is clearly detectable as well, although the staining process introduces certain limits in resolution.

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