Optimizing positional information encoded by noisy gene regulatory networks

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***Short Abstract* — In early embryogenesis local cell fates are specified via spatial protein patterns. The robustness of this process is chiefly affected by the interplay between stochastic gene expression and spatial coupling. Any theory aiming at complete understanding of the underlying regulatory networks therefore must account for space. Motivated by the gap gene system in the fruit fly *Drosophila*, we develop a stochastic morphogenesis model that—for the first time—combines information theory with an explicit spatial description of the system. Optimizing information flow in this framework markedly improves predictions for optimal network parameters, opening up the way towards full quantitative agreement with experiments.**

***Keywords* — Embryo development, pattern formation, gene regulation, optimal information transmission, spatial-stochastic models, information theory, *Drosophila* patterning, gap genes.**

I. Introduction

TODAY it is well-known that the establishment of the body plan in early development is driven by spatial patterns of gene expression. Oftentimes, these patterns emerge from initially identical diffusively coupled cell nuclei upon reading out a spatially varying input signal, such as morphogen gradients. In spite of strong stochasticity in gene expression, these patterns typically display an astonishingly high precision and reproducibility [1, 2, 3, 4], suggesting that evolution has optimized these systems to convey positional information with maximal fidelity [3]. Yet, in a spatial-stochastic setting it is not a priori clear which architecture of the underlying gene regulatory network would be best to attain this goal. Here we address this question by an attempt to derive the regulatory wiring that maximizes transmission of positional information from basic biophysical constraints. To this end we combine information theory with an embryogenesis model that explicitly accounts for both spatial (diffusive) coupling and stochasticity. While our model is closely inspired by the gap gene network in the early embryo of the fruit fly *Drosophila* [1], the derived framework is analogously applicable to other developmental systems.

II. Methods

In the past years, information theory has been successful in predicting optimal signal distributions and input-output functions that maximize information flow in gene regulation [5, 6, 7, 8]. Strikingly, application of these methods to regulatory motifs present in the *Drosophila* gap gene system has yielded results which strongly suggest that this system operates close to the optimum set by its biophysical constraints [3]. Our framework is a natural continuation of this approach, which so far had neglected spatial coupling. Based on coupled stochastic equations, we calculated the means and covariances of gene expression levels on a cylindrical lattice representative of the spatial structure of the embryo. This allows us to perform information optimization in a realistic spatial setting, predicting system parameters and (spatial) input and output distributions that maximize positional information. These results are compared against experimental data from the *Drosophila* gap gene system.

III. Results

Our spatial information optimization framework predicts optimal parameters that show markedly better agreement with measured data. By systematically varying the strength of spatial coupling, we demonstrate that spatial averaging pushes the optimum towards lower activation thresholds and steeper input-output curves, allowing for a better partitioning of the available dynamic range. Our results show that a true quantitative agreement between predicted optima and experimental data is indeed feasible. Our next step is the extension of the spatial model towards multiple target genes, including regulatory cross-interactions. Optimization of the spatial multi-gene model will elucidate why nature has opted for the peculiar structure of gap gene interactions observed in *Drosophila* to optimally encode positional information.

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