Towards a coherent theory of stochastic gene dynamics: from landscapes to green field theory

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***Short Abstract* — Introducing stochasticity into previously deterministic models of gene regulatory dynamics leads to a rich phenomenology that is qualitatively different, and has greater predictive power. But how should one study the effects of stochasticity on the Waddington landscape and cell state transitions? We assess the validity of stochastic differential equations models and associated Fokker-Planck, path integral, and Lagrangian descriptions for analyzing stochasticity in gene regulation, and discuss our results on noise in simple networks and preexisting data. We also discuss a fascinating analogy with physics that may lead to a 'green' quantum field theory.**

***Keywords* — stochastic models, noise, Fokker-Planck, path integral, Lagrangian, quantum field theory**

I. Introduction

Gene expression dynamics is often treated as *deterministic*, and modeled using systems of coupled ordinary differential equations. But gene expression is actually *stochastic*, and so-called *gene expression noise* has interesting biological consequences—beyond just being something that must be buffered against. For example, noise facilitates error correction in early mammalian development by allowing wrongly differentiated cells to fix their identity via a noise-induced transition [1].

In stochastic differential equation (SDE) models, extrinsic noise seems to be well-treated by an additive stochastic term, while some experiments have suggested that intrinsic noise should be modeled by a linear multiplicative stochastic term, which can lead to very different qualitative behavior. Even if we did have the data to parameterize these models, an important theoretical question is: what tools can one use to understand the influence of additive and linear multiplicative noise, and how does each kind of noise affect the Waddington landscape and cell state transitions?

II. Results

One theoretical tool associated with stochastic dynamics is the Fokker-Planck equation: a partial differential equation that describes the time evolution of the probability distribution associated with an ensemble of cells exploring the Waddington landscape. We have found approximate solutions for fairly general dynamics which describe how steady state gene expression distributions should qualitatively depend on both intrinsic and extrinsic noise; in particular, high intrinsic noise leads to *non-Gaussian* behavior. We suspect that probing this non-Gaussianity in experimental data will allow experimentalists to determine the relative importance of extrinsic and intrinsic noise.

The Fokker-Planck equation is equivalent to a path integral [2], a tool often used in nonequilibrium statistical mechanics to describe the probability of transitions between two states in a stochastic system. We use path integral methods to calculate the probability of transitions between different states, and the relative occupancies of those states, in simple models of gene regulatory network motifs like the bistable switch. The results agree with the results obtained via brute-force simulations and the Fokker-Planck equation.

Those tools lead one to consider the idea of a Lagrangian describing average stochastic gene expression dynamics. We have identified several candidate Lagrangians, which are more or less equivalent, and will discuss some of the physical and biological principles that may be behind them. With them, one can begin to discuss approximately conserved quantities analogous to energy and momentum. We speculate that one can draw an analogy between the Lagrangian/average cell description and classical mechanics; the Fokker-Planck/single cell description and quantum mechanics; and the complicated stochastic dynamics of many interacting cells and quantum field theory. Perhaps something like a quantum field theory will allow one to describe many cells interacting, being created, and being destroyed in a developmental process.

III. Conclusion

We believe that SDEs with linear multiplicative noise terms well describe intrinsic noise, and that the phenomenology associated with these equations can be systematically studied using Fokker-Planck, path integral, and Lagrangian descriptions. These tools all suggest provocative analogies with physics, which may lead to a quantum field theory analogue for interacting cells.

References

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