Phenomenology of linear multiplicative noise in a simple mutistable gene regulatory network via direct simulation and stochastic path integrals

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today

Abstract

Some genes are noisier than others; however, it is not clear how this asymmetry qualitatively affects gene regulatory network dynamics, and whether it can be ignored in network modeling. We claim that intrinsic gene expression noise asymmetries—particularly when intrinsic noise is assumed to be state-dependent (multiplicative) rather than state-independent (additive)—can encode state occupancy biases even when there is no deterministic asymmetry, and so lead to qualitatively new behavior. We use various models of a noisy multistable switch (consisting of two genes which inhibit each other and activate themselves), which can have up to four stable states, and study the phenomenology of noise-induced state transitions and the Waddington landscape using various tools from theoretical physics. In particular, we study transitions and the landscape using brute-force simulations of stochastic differential equations; the **Fokker-Planck equation** (KEEP THIS?); path integrals; and a Lagrangian description. We find that, regardless of the number of stable states present, noise asymmetries preferentially drive certain state transitions, and the path these transitions take through gene expression space is only weakly dependent upon noise.

1 Introduction

Noise in gene expression is expected to be different for different genes, because the physical processes that introduce randomness—for example, the bursting behavior of transcription and translation, diffusion-driven search and binding dynamics, and fluctuations due to low copy number—proceed at different rates for different genes. Indeed, in mice, the coefficient of variation (CV) of Oct4 is around 0.25 [CITATION], while the CV of Nanog is around 0.8 [CITATION]. [POSSIBLY INCLUDE ANOTHER REFERENCE HERE ABOUT BIOLOGICAL RANGES OF CV] What are the consequences of this reasonably wide range of noise levels? Does it matter that different genes have different amounts of noise, or can this be more or less ignored in the modeling of gene regulatory networks?

This question has previously been studied in the case of *additive* (i.e. independent of state/concentration) noise; RESEARCHERS ET AL found that FINDING [CITE]. However, it is known that noise (for example, the noise terms in the chemical Langevin equation [CITE GILLESPIE]) is generally state-*dependent*, and that state-dependent/multiplicative noise can lead to qualitative behavior not captured by additive noise. For example, Holmes et al [CITE] studied the Cdx2-Oct4 toggle switch in early mammalian development, and found that the system's two attractors had an ellipsoidal shape in Cdx2-Oct4 phase space; since additive noise yields circular/Gaussian attractors, they needed to incorporate noise with some state dependence in order for their model to reproduce this experimental observation.

In this paper, we will explore how *asymmetric multiplicative noise* (different amounts of multiplicative noise in different genes) affects cell state transitions and the topology of Waddington's epigenetic landscape in a simple model gene regulatory network. Using various techniques from physics to analyze our stochastic system—including brute-force numerical simulations, the Fokker-Planck equation describing the time evolution of the gene expression probability density, a Lagrangian description of the most likely stochastic behavior, and path integrals—we conclude that asymmetric noise *does* lead to qualitatively new behavior, and that it may be one way biological systems encode occupancy bias when noise-induced transitions are possible.

2 Choice of model and biological relevance

To study the effects of asymmetric noise on noise-induced cell state transitions and Waddington landscape topology, we must examine a noisy system with more than one attractor; a particularly choice with clear biological relevance is the bistable/multistable switch, consisting of two genes which inhibit each other and activate themselves. Depending on the system's parameters, it can have anywhere from one to four attractors. Furthermore, since there are only two species, the state space is not so large that the system becomes computationally intractable.

Protein X binds to gene Y to inhibit transcription, and protein Y binds to gene X to inhibit transcription.

2.1 Additive and linear multiplicative noise approximations

In principle, one can write down a chemical master equation (CME) corresponding to a biological system of interest, and study that equation to understand the stochastic dynamics of the system. More precisely, given a (appropriately parameterized) list of M reactions experienced by N molecular species, we can write

$$\frac{\partial P(\mathbf{x}, t|\mathbf{x}_0, t_0)}{\partial t} = \sum_{j=1}^{M} a_j(\mathbf{x}-\boldsymbol{\nu}_j)P(\mathbf{x}-\boldsymbol{\nu}_j, t|\mathbf{x}_0, t_0) - a_j(\mathbf{x})P(\mathbf{x}, t|\mathbf{x}_0, t_0) \ , \quad (1)$$

where $\mathbf{x} = (x_1, x_2, ..., x_N)$ is an arbitrary system state, $a_j(\mathbf{x})$ is the propensity function of the jth reaction, $\boldsymbol{\nu}_j$ is the stoichiometry vector of the jth reaction, and $P(\mathbf{x}, t|\mathbf{x}_0, t_0)$ is the probability that the system has state $\mathbf{x}$ at time t given that it had state $\mathbf{x}_0$ at time t_0.

Better yet, as long as we consider time scales in which (i) the CME's propensity functions do not change appreciably and (ii) the average number of reactions per unit time is very high [CITE GILLESPIE], we can accurately approximate CME dynamics via a chemical Langevin equation (CLE)

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{M} \nu_{ji} a_j(\mathbf{x}) + \sqrt{\sum_{j=1}^{M} |\nu_{ji}| a_j(\mathbf{x})} \ \eta_i(t) \ , \ i = 1, 2, ..., N \qquad (2)$$

where $x_i(t)$ is the number of species i at time t, ν_{ji} is the change in the number of species i caused by reaction j, and the $\eta_i(t)$ are temporally uncorrelated and statistically independent Gaussian white noise terms.

It is clear from equation (2) that the noise term will generally be state/concentration-dependent. That is, the system may be *more* or *less* noisy depending on how many species there are at a given time.

But Langevin equations are often used as phenomenological tools to describe systems whose full list of reactions and parameters is generally not known; in these contexts, one often sees Langevin equations like

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{M} \nu_{ji} a_j(\mathbf{x}) + \sigma_i \eta_i(t) \tag{3}$$

or even

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{M} \nu_{ji} a_j(\mathbf{x}) + \sigma_i x_i \eta_i(t) \ . \tag{4}$$

While equations like (3) and (4) are generally not *correct* (even in an asymptotic sense), they are often thought to capture the effects of noise *well enough* in some regime a modeler is interested in.

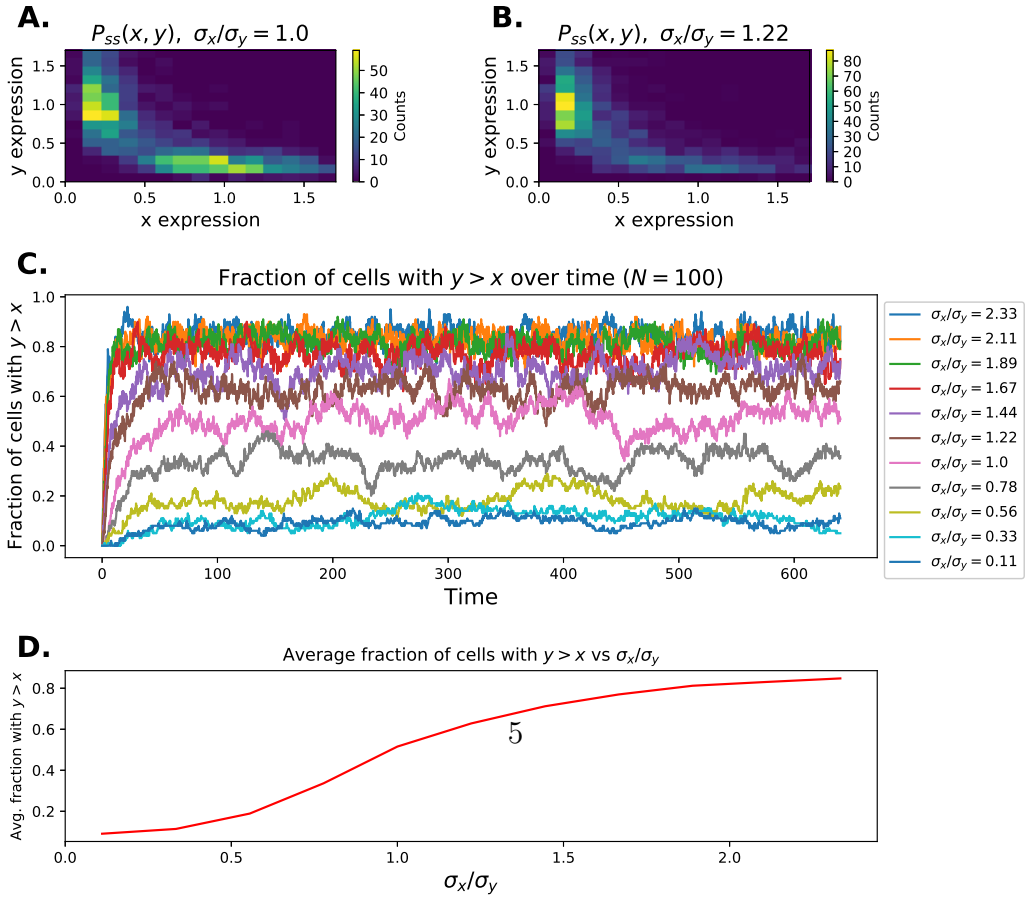
For most systems, stochastic fluctuations can appear somewhat complicated, and the corresponding steady state probability distributions are generally not Gaussian or unimodal. In other words,

3 Choice of model and biological relevance (OLD)

One relatively straightforward way to model a system whose genes have different amounts of noise is to write down

- CME is often well approximated by Langevin-type dynamics (cite Gillespie). - Given that not all reactions are known, and that the approximation seems reasonably consistent with experiments (citation?), noise in these models is often chosen to be additive (i.e. constant, or state-independent).

Figure 1: **Panel A:** This panel depicts a numerical approximation to the steady state probability distribution of the system given that $\sigma_x = \sigma_y = 0.45$. It is meant to show that, given that the equations governing x and y are completely symmetric, the steady state distribution comes out completely symmetric, with two attractors. **Panel B:** This panel depicts a numerical approximation to the steady state probability distribution of the system given that $\sigma_x = 0.55$ and $\sigma_y = 0.45$. The asymmetric noise coefficients produce noticeable occupancy asymmetry, even though they do not seem that different. **Panel C:** This panel depicts the fraction of cells with their y coordinate *greater* than their x coordinate over time, given a population of $N = 100$ cells, for a variety of σ_x/σ_y choices. It is meant to show that, as noise asymmetry is introduced, the fraction of cells in each attractor changes dramatically. Of course, the fraction of cells with $y > x$ is not a *perfect* proxy for the relative fractions, but it is pretty good given the reasonably large cell population, and that cells do not generally spend much time in the intermediate region between the attractors. **Panel D:** This panel depicts the average fraction of cells with their y coordinate eventually *greater* than their x coordinate, as a function of σ_x/σ_y (where σ_y has been fixed). It is meant to show that, as noise asymmetry is introduced, there is initially a dramatic change in relative occupancy. Eventually, relative occupancy saturates.



One reasonable way to represent gene regulatory networks is as a system of coupled differential equations: ordinary differential equations (ODEs) if one only cares about capturing deterministic dynamics, and stochastic differential equations (SDEs) if one wants to include noise. By design, this modeling approach tends to be phenomenological, as gene-gene interactions may not be direct (partly to keep network size computationally manageable, and partly due to a lack of experimental knowledge), expression levels are treated as continuous variables, equation parameters are too numerous to fix via experiment, and the complicated interplay of physical processes that determine noise is reduced to a small set of mechanistically opaque parameters. Despite this, differential equations-based models still offer tremendous insight into the qualitative behavior of complex systems, and the quantitative scientist has a remarkable suite of tools at their disposal for analyzing them.

THIS IS IRRELEVANT, ONLY ITO IS CORRECT FOR CLE Lessons from non-equilibrium statistical mechanics suggest that different SDE interpretations correspond to different physical situations: for example, ARTICLE X says that anti-Ito interpretation is valid for BROWNIAN PARTICLE AGAINST WALL. We use the popular Ito interpretation out of convenience, rather for any belief that it may reflect particular principles underlying stochastic gene expression. We do not expect that using a different interpretation will qualitatively change the moral of our story.

Qualitatively, there are two different kinds of noise: intrinsic noise (randomness in gene expression due to randomness involved in the physical creation of that gene's protein), and extrinsic noise (population-level randomness due to cells not being synchronized, or having slightly different environments).
using the bistable switch as our model gene regulatory network (GRN). The bistable switch (or toggle switch [ref to sniffers buzzers]) is a common GRN motif involving two genes which inhibit each other and activate themselves. It is conceptually interesting because it seems to provide a mechanistic way to think about developmental bifurcations—'forks in the road' that a cell takes en route to its final cell fate.

The bistable switch is an important model gene regulatory network because recapitulates developmental 'forks in the road'. Examples: Cdx2-Oct4, Nanog-Gata6, Sox2-Oct4, ...

This work is in large part a follow-up to [Holmes work], and is intended to flesh out some of the phenomenology from that model more deeply.

- Mention bistable/toggle switch as an important motif for developmental biology (show figure of cartoon, and possibly schematic of TE-¿ICM) - Linear multiplicative noise is simplest choice of state-dependent noise; clear from some experimental data that additive is not always sufficient. - Known that Cdx2 has CV 35%, Oct4 has CV 25%. Clear from data that noise is not well approximated as additive. What are the phenomenological consequences of asymmetric multiplicative noise?

4 Methods

4.1 Brute force numerical simulations

- SDEs simulated directly with Euler-Maruyama time step.

4.2 Non-equilibrium dynamics path integral

$$L = \frac{(\dot{x} - \mu_x)^2}{2\sigma_x^2} + \frac{(\dot{y} - \mu_y)^2}{2\sigma_y^2} \tag{5}$$

$$P(x_f, y_f, T; x_i, y_i, 0) = \int\int \mathcal{D}x\mathcal{D}y \; e^{-S} \tag{6}$$

$$S = \int L \; dt \tag{7}$$

- Least action path obtained directly by trying many possible transition paths; path space was explored systematically using a Metropolis-Hastings-type algorithm. Go into some details regarding thermalization; discarded paths; sweeps; etc. Cite Users Guide paper. - Results from previous search used to calculate transition probabilities. - Note that others have used path integral (cite Jin Wang, quantifying transition paths, paper), but have not seen it used to study noisy GRNs without some sort of semiclassical approximation. In other words, use of method is NOVEL!

Our starting point is an SDE which describes the dynamics of two genes connected with a bistable switch circuit topology: they inhibit each other and activate themselves. We will choose our SDE to be a generic set of coupled Langevin equations, which read

$$dx = \mu_x(x, y)dt + \sigma_x(x, y)dW \tag{8}$$
$$dy = \mu_y(x, y)dt + \sigma_y(x, y)dW \ , \tag{9}$$

where

- $x(t)$ is the amount/concentration of gene X at time t.
- $y(t)$ is the amount/concentration of gene Y at time t.
- $W(t)$ is a Wiener process.
- $\mu_x(x, y)$ controls the deterministic time evolution of $x(t)$, and depends only upon $x(t)$ and $y(t)$.
- $\mu_y(x, y)$ controls the deterministic time evolution of $x(t)$, and depends only upon $x(t)$ and $y(t)$.
- $\sigma_x(x, y)$ controls the amount of noise in $x(t)$, and depends only upon $x(t)$ and $y(t)$.
- $\sigma_y(x, y)$ controls the amount of noise in $y(t)$, and depends only upon $x(t)$ and $y(t)$.

Once again, we use the Ito interpretation of SDEs for convenience.

Our objective is to compare cell state transitions and the Waddington landscape for various specific instantiations of the above set of equations. In particular, we will use

$$\mu_x(x, y) = k\left[b + S + \frac{x^n}{c^n + x^n}\right]\left[(1 - I) + I\frac{c^n}{c^n + y^n}\right] - x$$
$$\mu_y(x, y) = k\left[b + \frac{y^n}{c^n + y^n}\right]\left[(1 - I) + I\frac{c^n}{c^n + x^n}\right] - y$$

and

$$\sigma_x(x,y) = \begin{cases} \sigma_x \\ \text{ex} + \sigma_x x \end{cases}$$
$$\sigma_y(x,y) = \begin{cases} \sigma_y \\ \text{ex} + \sigma_y y \end{cases}$$

5 Results

5.1 Asymmetric noise causes steady state occupancy bias

- Not as extreme as for deterministic bias (see figure) - Looks kind of sigmoidal; saturates at both low and high asymmetry (see figure) - Only depends on multiplicative noise coefficient ratio, rather than both of them independently. - Effect less extreme for additive noise (see figure)

5.2 Asymmetric noise affects transition paths

- Least action path only sensitive to noise ratio rather than both individually (see figure). This can be justified via the Onsager-Machlup function/theory of stochastic path integrals.

6 Discussion

- Biologically, asymmetric noise can be a useful way to impose a preference for one attractor over another. Unlike deterministic asymmetry, the effect of noise asymmetry is not necessarily overwhelming (i.e. some deterministic asymmetry causes a huuuuge state bias, but noise asymmetry can cause something like 3:1) - Mention that chemical Langevin equation can be symmetric but have asymmetric noise when reactions are at QSS (so that they contribute to noise, but not mean time evolution)

7 Conclusion

- Asymmetric (multiplicative) noise creates a state occupancy bias, even in the absence of any deterministic asymmetry. This bias is qualitatively much more drastic than it is for additive noise asymmetry, and suggests the possibility that biology uses it to encode state biases.