**GOAL:** Explore the phenomenology of asymmetric linear multiplicative noise in a bistable switch motif, motivated by application to dev bio; conclude that asymmetric noise can encode a state occupancy bias, even in the absence of deterministic bias.

**INTRODUCTION**

* 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).
* Sometimes, however, it is clear that additive noise is qualitatively not the right choice. For example, Holmes et al studied the Cdx2-Oct4 toggle switch in early mammalian development, and found that the TE and ICM attractors had an ‘ellipsoidal’ shape in Cdx2-Oct4 phase space. Additive noise yields circular/Gaussian attractors; meanwhile, some state-dependence easily creates the ellipsoidal effect.
* Asymmetric additive noise has been studied somewhat (citations?) However, asymmetric multiplicative noise has not been studied for gene regulatory networks. It is our goal to study it here in this toy model of a bistable switch, and see mathematically how the situation differs from additive/symmetric noise.

**CHOICE OF MODEL + BIOLOGICAL RELEVANCE**

* 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?

**METHODS**

**Brute force numerical simulations**

* SDEs simulated directly with Euler-Maruyama time step.

**Non-equilibrium dynamics path integral**

* 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 User’s 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!

**RESULTS**

**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)

**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.

**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)

**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.