**GOAL:** To systematically study, in three few gene systems, the extent to which additive and linear multiplicative Langevin equation approximations are valid. Conclude that additive noise is good in some cases, while multiplicative noise is good in others.

**INTRODUCTION**

* CME too hard to work with directly, so Langevin equation approximations are often used.
* But since full list of reactions/parameter values for system of interest generally not available, noise term is often treated phenomenologically. More often than not modeled as additive (i.e. constant, and not state-dependent), but has occasionally been chosen to be linear multiplicative. Ex: Holmes et al used linear multiplicative noise because it yielded qualitatively correct steady state probability density behavior. (Attractors were ellipsoidal rather than spherical)
* When is either approximation (additive or linear multiplicative) justified? When is one preferred over the other? The answers to these questions are not clear, and it is our intent in this paper to explore them in a few simple to work with cases.

**TECHNICAL INTRO: CME TO LANGEVIN AND ADDITIVE/MULTIPLICATIVE APPROXIMATIONS**

* Mention CME, and Gillespie’s Langevin equation approximation to it.
* Reiterate that state-dependence of noise term is complicated in general; in real systems, likely too complicated to back-calculate, given that many reactions/rate parameters are unknown. Additive/linear multiplicative noise approximations are phenomenological, and mult noise can be justified as simplest choice of state-dependent noise. (Can be better justified as true for many systems close to equilibrium, as will see below for unregulated gene)
* Mention use of QSS approach: justify as simplest way to remove other species (although more accurate approaches, such as simulating some species via Gillespie algorithm, are available). Simplicity here is chosen over accuracy.
* Show explicitly how unregulated gene’s noise can be approximated as additive/multiplicative by Taylor expanding about equilibrium.

**SINGLE GENE RESULTS**

* For unregulated gene, prob dist is basically Gaussian, so additive noise works well. Multiplicative noise also works fine, although not quite as well.
* As feedback is increased, state-dependence becomes more important. See figure for a plot of this.

**BISTABLE SWITCH RESULTS**

* Uncoupled genes: Gaussian, of course, so additive works well. Genes coupled in first order fashion behave more multiplicative-like. Increasing amount of feedback increases state-dependence.

**DISCUSSION**

* In general, feedback (especially higher-order feedback) seems to make the state-dependence of noise more and more qualitatively apparent.
* Suggests that genes with low order feedback can be modeled safely with additive noise, while genes with higher order feedback require some kind of state-dependent noise terms (linear multiplicative being the simplest, but not the only, choice).
* Can possibly comment here on some implications for SDE models of development/cancer. Perhaps additive noise is used in some situations where it isn’t appropriate.

**CONCLUSION**

* We studied some simple few gene systems (a single gene with Nth order feedback, and two genes in a bistable switch motif with Nth order feedback), and found that linear multiplicative noise is a reasonable approximation for systems with N >= 2????? Feedback, and additive noise is a reasonable approximation for systems with less feedback.

**METHODS**

* Generating steady state probability distributions for Langevin dynamics.
* Calculating means/moments/peaks.
* Using Kullback-Leibler divergence/L1 norm to quantify difference between probability distributions.
* QSS assumption for mRNA/genes/binding.

**APPENDIX A: Derivation of protein SDE for single gene with Nth order feedback**

* Already wrote this up.

**APPENDIX B: Derivation of protein SDE for (Nth order?) bistable switch**

* Similar to above, but with messier notation.