October 24, 2017

Dear SIAM Scientific Computing Editor(s),

On behalf of all authors, we would like to submit the manuscript, “Stability-Optimized Runge-Kutta Methods for Pathwise Stiffness in Stochastic Differential Equations”, for consideration. This work

This work utilizes analytical calculations along with computational simulations of stochastic models to identify a novel mechanism for controlling the level of noise in gene regulatory signals without changing the mean signal. Using this mechanism, we show how noise control is required for downstream segmental sharpening in the zebrafish hindbrain, linking a spatial phenotype directly to a noise level and its control.

In many biological systems, concentrations of signaling molecules control cell fates. However, these biochemical interactions are intrinsically noisy, giving rise to the question of how robust fate decisions can occur. Changes to the signaling pathway are likely to change not only the amount of noise in the concentrations but also the mean concentrations, meaning that the ability to control the signaling noise in a general regulatory network while maintaining the correct fate decisions can be difficult if not impossible. Here we identify a mechanism through the intermediate states act naturally as a noise control mechanism. We show that this result extends to multiple different models, both with and without extra feedbacks, and does not require specific parameters, demonstrating that this is a general mechanism which can allow noise control in biological and synthetic networks.

During our analysis of the mean-independent noise control property, we develop a measure which relates changes between the mean and variance. We use this to show that our models accurately recapitulate the mean/variance relationship from our previously obtained high-precision concentration observations in the developing zebrafish hindbrain (Sosnik et al. Elife, 5, 2016). In addition, we show that this measurement can distinguish between different methods for modeling the stochasticity in biochemical networks. Significantly, this method is also able to identify differences between models which have the same mean qualitative behavior, giving an insight into how more detailed information about signaling networks can be uncovered through analyzing the noise in knockdown experiments.

Additionally, we apply this new noise-control principle to a spatial developmental system in which sharp segmental boundaries form despite that the inherently noisy spatial gradient patterns the gene expression domains. Previous results described a noise-induced switching mechanism for sharpening in downstream signaling in the specific case of the Zebrafish hindbrain (e.g. Zhang et al. MSB, 8:613, 2012). Here we show the mean-independent noise control mechanism regulates the noise to the proper level in the downstream response that enables effective noise-induced switching in order to successfully sharpen the segmental boundaries. In particular, we show that changes in the protein crabp2a directly change the spatial noise without moving the boundary location, and a knockdown of this protein disrupts downstream patterning. To our knowledge, this is the first direct connection between a stochastic spatial phenotype and the levels of noise, demonstrating how developmental processes have evolved to overcome the inherent biochemical stochasticity and achieve complex spatial phenotypes.

**Suggested Reviewers**

Alex Hoffman ([ahoffmann@ucla.edu](mailto:ahoffmann@ucla.edu)), UCLA, an expert on signal transduction and gene regulatory network experiments and modeling.

Michael Stumpf ([m.stumpf@imperial.ac.uk](mailto:m.stumpf@imperial.ac.uk)), Imperial College, an expert in systems biology and modeling gene regulatory network

Mustafa Khammash ([mustafa.khammash@bsse.ethz.ch](mailto:mustafa.khammash@bsse.ethz.ch)) ETH-Zürich, an expert on modeling and analysis of stochastic systems

Philip Maini ([maini@maths.ox.ac.uk](mailto:maini@maths.ox.ac.uk)) Oxford, an expert on developmental modeling and simulations

Tim Elston ([telston@ad.unc.edu](mailto:telston@ad.unc.edu)) University of North Carolina, an expert on gene regulatory network and signal transduction

We look forward to hearing from you!

Sincerely Yours



Qing Nie

Professor of Mathematics, Biomedical Engineering, Developmental and Cell Biology