Summer 2016

NSERC USRA Report

Quasi Steady-State Reduction of Non-linear PDE Models of Cellular Systems
&
Turing Analysis on Steady-State Pattern Formation

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This summer I worked on several projects unrelated to each other. The first project was an extension of what I researched last summer with Dr. Keshet and Dr. Ward. Our group looked at several models of nonlinear motor dynamics in the cell, including kinesins along microtubules, as well as myosins along actin filaments. These models were essentially a collection of nonlinear coupled PDEs describing the advection, diffusion, and reaction components of the system states. The system itself represented the probability density of the motors as a vector with three states; right moving (or walking for myosins), left moving (or treadmilling for myosins), and freely diffusing. The boundary conditions of the system were no-flux, and there was ensured conservation in the system. The system of such equations for the kinesin model is shown below:

$$\begin{aligned}
\frac{\partial p^R}{\partial t} &= -v\frac{\partial p^R}{\partial x} + Pk_b g(p^U) - k_u p^R, \\
\frac{\partial p^L}{\partial t} &= v\frac{\partial p^L}{\partial x} + (1-P)k_b g(p^U) - k_u p^L, \\
\frac{\partial p^U}{\partial t} &= D_0\frac{\partial^2 p^U}{\partial x^2} - k_b g(p^U) + k_u p^R + k_u p^L.
\end{aligned}$$

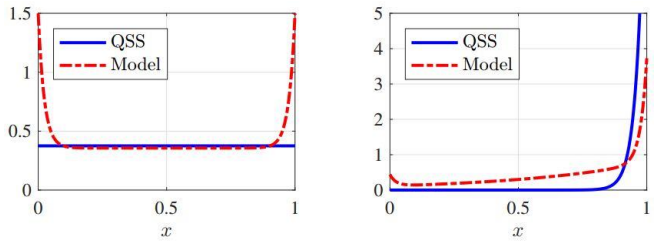
The various p components are the system states, and the other parameters each describe the dynamics of the system in a unique way.

The procedure we implemented involved changing the time-scale of the original system such that it could be scaled by a small parameter ε, a function of the model parameters. This allowed for an asymptotic expansion in order of ε, which could then be plugged back into the original system. When orders were collected, a main solvability condition surfaced. In the end, one of the original states from the three-vector could be parameterized by a scalar variable α, and expressions for the other states in terms of α were found. A one dimensional non-linear PDE for α resulted from satisfying the solvability condition:

$$\frac{\partial}{\partial t}\left(\frac{k_b}{k_u}g(\alpha)+\alpha\right) = \frac{\partial}{\partial x}\left(\frac{k_b}{k_u}(1-2P)g(\alpha) + D\frac{\partial \alpha}{\partial x}\right).$$

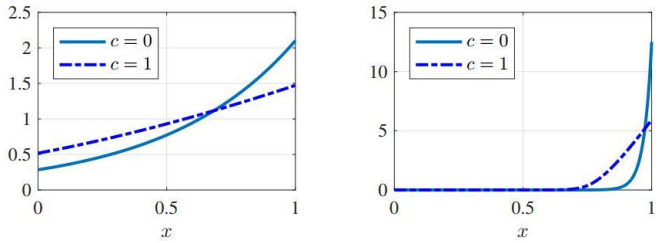
*Supervised by Dr. Leah Keshet, Dr. Michael Ward. With Cole Zmurchok.

The originally complex system of PDEs was thus reduced to a much simpler 1D PDE of one parameter at quasi steady-state, and this could then be solved numerically to determine parameter dependence of the solution curves. For example, the microtubule polarity bias parameter P directly influences the sign and magnitude of the effective velocity in the reduced PDE. Similarly, the binding affinity k_b is directly proportional to the effective velocity and inversely proportional to the effective diffusion. Therefore, it was expected that when affinity to bind exceeds affinity to unbind, advective behaviour should dominate over diffusive behaviour and vice versa. These predicted patterns were confirmed by numerically solving the reduced PDE and graphing its solution across space.



(a) $P = 0.5$ (b) $P = 0.6$

The above figures demonstrate how a P value of exactly half causes pure diffusion to occur, whereas a P skewed even slightly away from half yields evident bias in the solution caused by velocity effects.



(a) $k_b = 0.1 < k_u = 1$ (b) $k_u = 0.3 < k_b = 0.5$

The above figures show how dominance of binding affinity causes skewing of the solution due to favored advection over diffusion, and vice versa.

Many such graphs were plotted to show the collection of results that popped up in both the kinesin and myosin models when analyzing the effects of tweaking certain parameters to induce expected phenomena. In all cases, there was agreement between the theoretical and simulated, even to the point of near-complete convergence to the steady-state solution of the full model as ε limited to zero.

The quasi steady-state method as a way to reduce fully nonlinear systems of PDEs to a solvable and analyzable one dimensional PDE was successful and illustrative in the various model cases we tried out, and can most likely be applied to further difficult and/or intriguing examples in future work.

The second project I explored was completely different in nature and was an offshoot of a larger project being worked on by Ajay Chitnis et al. That group had a system of five coupled PDEs to describe chemical processes such as signalling and positive/negative feedback occurring across a domain. I was instructed to examine a reduced version of that system consisting of two coupled PDEs, in order to see if certain parameter choices could cause Turing pattern formation at steady-state. This reduced model is shown below to demonstrate its interconnected complexity:

$$\frac{\partial W}{\partial t} = P_W W_A - d_W W + D_W W_{xx} \equiv f(W, D_{kk1}) + D_W W_{xx} \tag{13a}$$

$$\frac{\partial D_{kk1}}{\partial t} = P_{Dkk1} F_A^2 W_A - d_{Dkk1} D_{kk1} + D_D (D_{kk1})_{xx} \equiv g(W, D_{kk1}) + D_D (D_{kk1})_{xx} \tag{13b}$$

Supplemented with

$$F_A \approx \hat{P}_{FA} \frac{F^2}{1 + F^2 + K_a W_A^2} + b_{FA}, \quad \hat{P}_{FA} = \frac{P_{FA}}{d_{FA}}$$

and

$$W_A \approx \hat{P}_{WA} \frac{W^2}{1 + W^2 + K_c D_{kk1}^2 + K_b F_A^2} + b_{WA}, \quad \hat{P}_{WA} = \frac{P_{WA}}{d_{WA}}$$

As can be seen above, the system of PDEs isn't too daunting: it is merely a reaction diffusion type system. However, the reaction coefficients are very nasty, as they depend nonlinearly on the main variables and are also coupled to one another, making things like differentiation somewhat of a headache.

The algorithm to finding parameter conditions for Turing patterns is as follows. First, the Jacobian of the reaction terms must be found. These are the partial derivatives for f and g. Next, the steady-state values for the system have to be found numerically. This was done by writing a multivariable Newton's method scheme in Matlab. Then, the eigenvalues need to be found in order to yield the Hopf Bifurcation point where the real part of these eigenvalues is zero. Finally, several Turing conditions have to be met. These are as follows:

$$\frac{\partial f}{\partial a} + \frac{\partial g}{\partial b} < 0 \tag{1}$$

$$\frac{\partial f}{\partial a}\frac{\partial g}{\partial b} - \frac{\partial f}{\partial b}\frac{\partial g}{\partial a} > 0 \tag{2}$$

$$D_D \frac{\partial f}{\partial a} + D_w \frac{\partial g}{\partial b} > 2\sqrt{D_D D_w (\frac{\partial f}{\partial a} * \frac{\partial g}{\partial b} - \frac{\partial f}{\partial b} * \frac{\partial g}{\partial a})} \tag{3}$$

These conditions are just functions of the entries in the Jacobian as well as the diffusion parameters. The first two conditions imply stability at steady-state assuming no diffusion, and the last one implies diffusive instability. All three must work in conjunction in order to cause pattern formation at steady-state.

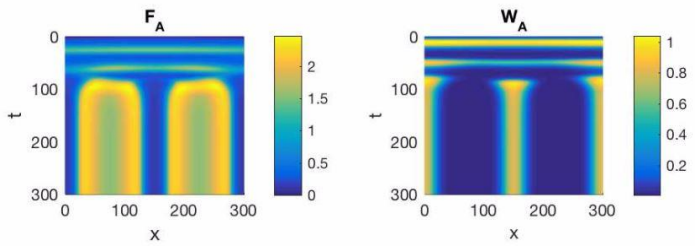
Due to the complexity of the problem, I first set the parameter k_b to be zero. This got rid of one coupling in the reaction coefficients and made the math easier. After doing the above steps on this simplified version, I couldn't manage to get the real part of the eigenvalues to be non-negative. This meant that the

system would always be stable at steady-state and no patterns were likely to be found. Though I tried changing the parameters several times, I couldn't get all of the Turing conditions to coincide.

Therefore, I reintroduced the k_b parameter to the system. Doing so made the Jacobian much harder to calculate, but it was doable through a series of implicit differentiation steps and substitutions. Therefore, the steady-states could also be found numerically as before. However, the complexity made finding the eigenvalues a nearly impossible task by hand.

I am currently working on finishing up this analysis to see if I can numerically tweak the parameters in order to satisfy the Turing conditions. If I can, I'll use these parameters in my code that runs the full simulation of the original coupled PDEs to steady state. Hopefully patterns will then emerge in the solutions.

From the work done on the original non-reduced PDE system, parameters can be selected to achieve pattern formation at steady-state. Such a situation is shown below, courtesy of Cole Zmurchok.



Waves can be seen to form in the above images, indicating patterns at steady-state. Minor adjustment of the system can cause the wave number of these patterns to change, meaning that many more than two waves can be observed at steady-state if desired.

My goal was to try to achieve similar results as above using the slightly simplified coupled model that I was given. I think there is a good chance that there exist parameters that induce pattern formation, but if this ends up not being the case, perhaps adjustments in the nonlinear aspects of the reaction coefficients can be made to "push" the system toward this anticipated behaviour.