Using Quasi Steady-State Approximation Methods to Analyze a Non-linear Biological Motor Transport System

Timothy Small. Supervisors: Leah Keshet, Michael Ward

In the cell, two families of motors transport materials between the nucleus and periphery in either direction. These kinesins and dyneins move in a similar fashion and can thus both be modelled mathematically in the same way. The analysis being performed will allow for simplification of the non-linear model proposed, such that the resulting PDE be solved numerically for varying parameters. The movement to be captured by this system is at its essence the binding, unbinding, left and right moving behaviours of these motors. The proposed model is the following:

$$\frac{\partial \hat{p}}{\partial t} = \mathcal{L}(\hat{p}) + \frac{1}{\epsilon}\begin{bmatrix} Qk_b p_3 g(p_3) - k_u p_1 \\ (1-Q)k_b p_3 g(p_3) - k_u p_2 \\ k_u p_1 + k_u p_2 - k_b p_3 g(p_3) \end{bmatrix} \tag{1}$$

for $\hat{p} = \begin{bmatrix} p_1 \\ p_2 \\ p_3 \end{bmatrix}$, $\mathcal{L}(\hat{p}) = \begin{bmatrix} -V\partial_x p_1 \\ V\partial_x p_2 \\ D\partial_{xx} p_3 \end{bmatrix}$, and $g(x) = \frac{1}{1+cx}$. The p vector represents the proportion of right moving, left moving, or cytosolic motors respectively, Q is the fraction of microtubules polarized to the right, meaning that $(1-Q)$ is the fraction polarized to the left, and k_b and k_u are respectively the affinities of motors to bind or unbind from the microtubules. The non-linear function g was picked in this case to emulate saturated binding. Other non-linear functions can be chosen to yield varying results in the end. This model includes conservation of mass, as illustrated by the three rows of the $1/\epsilon$ coefficient matrix adding to zero. Epsilon is a small parameter used to allow for long-term analysis of the model. The Quasi Steady-State line of attack was deemed most appropriate because solving the full system without reduction is not feasible, even numerically.

First, an asymptotic expansion in order epsilon is performed: $\hat{p} = \hat{p}^o(\alpha) + \epsilon\hat{r}(\alpha) + ...$ for a long-term solution $\hat{p}^o(\alpha) = \begin{bmatrix} p_1^o(\alpha) \\ p_2^o(\alpha) \\ p_3^o(\alpha) \end{bmatrix}$. The alpha variable that has just been introduced is a parameterizing feature made possible due to the implication of obtaining long-term dynamics: $f_1 = f_2 = 0 \implies f_3 = 0$, where each f is the given row of the matrix from equation 1. So, it can be made true that $\alpha = p_3^o$, reducing the problem by a dimension. Then, substitution into equation 1 and a linear approximation about the long-term solution vector yields the following:

$$\mathbb{J}\hat{r} = \frac{\partial \alpha}{\partial t}\left(\frac{d\hat{p}^o}{d\alpha}\right) - \mathcal{L}(\hat{p}^o). \tag{2}$$

Now, if a left eigenvector ψ^T can be found for the Jacobian, equation 2 simplifies to just

$$\frac{\partial \alpha}{\partial t}(\psi^T \left(\frac{d\hat{p}^o}{d\alpha}\right)) = \psi^T \mathcal{L}(\hat{p}^o). \tag{3}$$

Upon further inspection of the explicit Jacobian, ψ is simply the vector $\begin{bmatrix}1 & 1 & 1\end{bmatrix}^T$. So, the PDE

$$\frac{\partial \alpha}{\partial t}\left(\frac{dp_1^o}{d\alpha} + \frac{dp_2^o}{d\alpha} + \frac{dp_3^o}{d\alpha}\right) = -V\partial_x p_1^o + V\partial_x p_2^o + D\partial_{xx} p_3^o \tag{4}$$

results.

The penultimate step to getting the final form PDE is computing the values of each of the p_j^o by using the prior stated condition that $f_j(p_1^o(\alpha), p_2^o(\alpha), p_3^o(\alpha)) = 0 \ \forall j \in \{1, 2, 3\}$ for a long time scale. The final step will be reducing the algebra. Solving in terms of α, where we have mandated $p_3^o = \alpha$ yields that

$$\hat{p}^o = \begin{bmatrix} \gamma_1 \alpha (1 + c\alpha)^{-1} \\ \gamma_2 \alpha (1 + c\alpha)^{-1} \\ \alpha \end{bmatrix}, \tag{5}$$

where parameters $\gamma_1 = \frac{Qk_b}{k_u}$ and $\gamma_2 = \frac{(1-Q)k_b}{k_u}$ are created for ease of notation. Plugging this back into equation 5 and simplifying all of the algebra leaves the following PDE:

$$\frac{\partial \alpha}{\partial t} = Vk_1(\alpha)\frac{\partial \alpha}{\partial x} + k_2(\alpha)\frac{\partial^2 \alpha}{\partial x^2}, \tag{6}$$

for parameters $k_1(\alpha) = \frac{B-A}{A+B+1}$, $k_2(\alpha) = \frac{D}{A+B+1}$, $A = \frac{\gamma_1}{(1+c\alpha)^2}$ and $B = \frac{\gamma_2}{(1+c\alpha)^2}$.

Solutions to this PDE will result in a definition for the parameter α and thus an expression for the overall probability vector at long term steady-state. At this point, several tweaks can be made to study more interesting aspects of this model, including changing the non-linear function or making the Q parameter a function of space. These were explored in more detail in the project but will not be written here due to spatial restraint. Suffice it to say that after the fact, when the PDE from above was analyzed numerically with Matlab, some very interesting and intuitively sensical graphs resulted. These graphs give a good idea of the behaviour of the system after a long time has elapsed based on the parameters chosen, and therefore give insight into certain aspects of the full evolution of the system.

The purpose of this project was not only to analyze long term solutions of one or two non-linear models, but rather to demonstrate the capability of the Quasi Steady-State approximation method to be applied to all sorts of interesting biological cases, as long as the conservation of mass property is held. By reducing the initial problem, many interesting corollaries pop up during the process, each of which leads to exploring side-problems that later rejoin in relevance to the main analysis. Therefore, this project as a whole was structured to not only look at the narrow base case of the model, but to also lead to other interesting observations that support the claim that mathematical models work both robustly and flexibly in explaining biological phenomena.