PARABOLIC - HYPERBOLIC SYSTEM: TRANSPORT ALONG MOLECULAR MOTORS

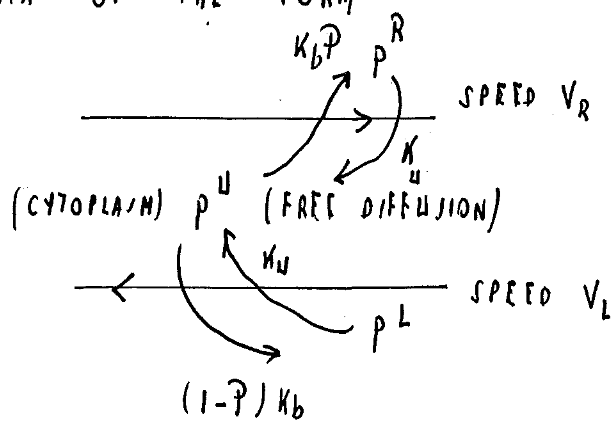
IN CELL BIOLOGY, PROTEINS ARE TRANSPORTED IN A BIDIRECTIONAL WAY ALONG MOLECULAR MOTORS. IN A 1-D MODEL THE DENSITY OF MOTORS ARE MODELED BY A REACTION - ADVECTION SYSTEM OF THE FORM

$$(1) \qquad \underline{p}_t = M \underline{p} + \frac{1}{\varepsilon} A \underline{p} \quad \text{ON} \quad 0<x<1,\ t>0$$

WHERE
$$M = \begin{pmatrix} -V_R \partial_x & 0 & 0 \\ 0 & V_L \partial_x & 0 \\ 0 & 0 & D_0 \partial_{xx} \end{pmatrix}, \qquad \underline{p} = \begin{pmatrix} \rho^R \\ \rho^L \\ \rho^u \end{pmatrix}$$

AND A IS A 3×3 TRANSITION MATRIX OF THE FORM

$$A \equiv \begin{pmatrix} -K_u & 0 & \theta K_b \\ 0 & -K_u & (1-\theta) K_b \\ K_u & K_u & -K_b \end{pmatrix}$$



REMARKS

(i) IN DIMENSIONLESS MODEL $\varepsilon = \dfrac{\bar{V}}{L\Gamma}$

WHERE $\bar{V}$ IS TYPICAL SPEED OF MOTORS, L IS DOMAIN LENGTH AND Γ IS A TYPICAL BINDING RATE (DIMENSIONAL VERSION OF K_b, OR K_u).

TYPICALLY, $L = 100\,\mu m$, $\bar{V} \sim 1\text{-}2\ \mu m/\text{SEC}$, $\Gamma \sim 0.1 - 0.5/\text{SEC}$

SO WE HAVE $\varepsilon \ll 1$. "STRONG BINDING" APPROXIMATION.

(ii) HERE V_L, V_R ARE NON-DIMENSIONAL MOTOR SPEEDS AND D_0 IS A NON-DIMENSIONAL DIFFUSIVITY.

(iii) K_u IS TRANSITION RATE FROM EITHER OF THE TWO MOTORS (LEFT AND RIGHT) TO CYTOPLASM. $K_b \theta$ WITH $0<\theta<1$ IS BINDING RATE TO RIGHT - MOVING STATE WHILE $(1-\theta) K_b$ IS BINDING RATE TO LEFT MOVING STATE.

NOW DERIVE CONSERVATION PRINCIPLE. WE OBSERVE THAT THE COLUMN SUM OF A VANISHES, AND SO IF WE ADD THE THREE EQUATIONS WE GET

$$\partial_t \left(p^R + p^L + p^U\right) = -V_R\, p^R_x + V_L\, p^L_x + D_0\, p^U_{xx}.$$

NOW INTEGRATING OVER THE DOMAIN,

$$\frac{d}{dt}\int_0^1 \left(p^R + p^L + p^U\right) dx = \left(-V_R\, p^R + V_L\, p^L + D_0\, p^U_x\right)\Big|_0^1$$

TO IMPOSE MASS CONSERVATION AND FIX THE DENSITIES AT $X = 0, 1$ WE SET

$$-V_R\, p^R + V_L\, p^L + D_0\, p^U_x = 0 \ \text{ AT } X = 0, 1 \ ; \qquad p^R = 0 \ \text{ AT } X = 0\ ; \ p^L = 0 \ \text{ AT } X = 1.$$

IN THIS WAY, THE SUM $p^R + p^L + p^U$ IS PRESERVED IN TIME.

WE NOW SEEK TO DERIVE AN EQUATION FOR $y(x,t)$ DEFINED BY

$$y(x,t) = p^R + p^L + p^U.$$

WE OBSERVE THAT $\underline{\psi}^T A = 0$ WHERE $\underline{\psi} = \begin{pmatrix}1\\1\\1\end{pmatrix}$. THUS ψ IS IN NULLSPACE OF A^T, SO THAT $A^T \underline{\psi} = 0. \quad (1)$

NOW LET $\underline{\Phi}$ BE EIGENVECTOR OF A CORRESPONDING TO A ZERO EIGENVALUE

$$A\underline{\Phi} = \underline{0}. \qquad (2)$$

WE ASSUME THAT $\dim \mathcal{N}(A) = 1$ AND WE NORMALIZE EIGENFUNCTIONS SO THAT

$$\underline{\psi}^T \underline{\Phi} = 1. \qquad (3)$$

WE THEN WRITE OUR SYSTEM AS

$$\underline{p}_t = \frac{1}{\varepsilon} A\underline{p} + M\underline{p} \qquad (*)$$

AND WE LOOK FOR A SOLUTION TO $(*)$ IN THE FORM

$$\underline{p} = y\,\underline{\Phi} + \underline{w} \qquad (4)$$

NOW MULTIPLYING BY $\underline{\psi}^T$ AND USING $y = \underline{\psi}^T \underline{p}$ AND $\underline{\psi}^T \underline{\Phi} = 1$ WE OBTAIN

$$\underline{\psi}^T \underline{p} = y\,\underline{\psi}^T \underline{\Phi} + \underline{\psi}^T \underline{w} \;\longrightarrow\; y = y + \underline{\psi}^T \underline{w} \;\longrightarrow\; \underline{\psi}^T \underline{w} = 0. \qquad (5)$$

THUS $\underline{w} \perp \underline{\psi}$. RECALL THAT $\mathcal{N}(A^T)$ AND $\mathcal{R}(A)$ ARE ORTHOGONAL COMPLEMENTS.
"NULL-SPACE" "RANGE"

THIS YIELDS THAT $w \in \mathcal{R}(A)$.

WE WOULD LIKE NOW TO DERIVE A PDE FOR $y(x,t)$ AND $\underline{w}(x,t)$.

WE FIRST MULTIPLY (*) BY $\underline{\psi}^T$ TO OBTAIN

$$\underline{\psi}^T \underline{p}_t = \frac{1}{\varepsilon}\,\underline{\psi}^T A\,\underline{p} + \underline{\psi}^T M \underline{p}$$

BUT $\underline{p}_t = y_t\,\underline{\Phi} + \underline{w}_t$ SO THAT

$$\underline{\psi}^T \left[y_t\,\underline{\Phi} + \underline{w}_t \right] = \frac{1}{\varepsilon}\,\underline{\psi}^T A \left[y\,\underline{\Phi} + \underline{w} \right] + \underline{\psi}^T M \left[y\,\underline{\Phi} + \underline{w} \right].$$ BUT $A\,\underline{\Phi} = 0$,

SO THAT $y_t\,\underline{\psi}^T \underline{\Phi} + \partial_t \left[\underline{\psi}^T w \right] = \frac{1}{\varepsilon}\,\underline{\psi}^T A\,\underline{w} + \underline{\psi}^T M \left[y\,\underline{\Phi} + \underline{w} \right]$

USING $\underline{\psi}^T \underline{w} = 0$ AND $\underline{\psi}^T \underline{\Phi} = 1$ WE GET WITH $\underline{\psi}^T A = (A^T \underline{\psi})^T = \underline{0}$ THAT

$$\underline{y}_t = \underline{\psi}^T M \left[y\,\underline{\Phi} + \underline{w} \right] \qquad (6)$$

NOW WE DERIVE A PDE FOR W: WE PUT (4) INTO (*) TO GET

$$\underline{\Phi}\, y_t + \underline{w}_t = \frac{1}{\varepsilon} A \left[y\,\underline{\Phi} + \underline{w} \right] + M \left[y\,\underline{\Phi} + \underline{w} \right]$$

WITH $A\,\underline{\Phi} = 0$ WE GET

$$\underline{w}_t = \frac{1}{\varepsilon} A\,\underline{w} - \underline{\Phi}\,\underline{y}_t + M \left[y\,\underline{\Phi} + \underline{w} \right]$$

COMBINING THIS WITH (6) YIELDS

$$\left.\begin{aligned} \underline{w}_t &= \frac{1}{\varepsilon} A\,\underline{w} + (I - \underline{\Phi}\,\underline{\psi}^T)\, M \left[y\,\underline{\Phi} + \underline{w} \right] \\ \text{WITH} \qquad y_t &= \underline{\psi}^T M \left[y\,\underline{\Phi} + \underline{w} \right] \end{aligned}\right\} \qquad (7).$$

REMARK THE SYSTEM (7) IS AN EXACT REFORMULATION OF (*) AND COUPLES THE SLOW MANIFOLD y TO THE DYNAMICS OF W.

THE SOLUTION FOR THE THREE COMPONENTS, APART FROM BOUNDARY LAYERS NEAR $X=0,1$, IS

$$\underline{P}(x,t) = y(x,t)\,\underline{\Phi} + \underline{w}(x,t). \qquad (8)$$

WE NOW CARRY OUT AN ASYMPTOTIC EXPANSION FOR W TO DECOUPLE (7). WE RECALL THAT

$$\underline{\psi}^T \underline{W} = 0 \quad \text{TO ALL ORDERS IN } \varepsilon.$$

WE EXPAND $\underline{W} = \underline{W}_0 + \varepsilon \underline{W}_1 + \cdots$

TO LEADING ORDER WE OBTAIN FROM FIRST EQUATION OF (7) THAT

$$A\,\underline{W}_0 = \underline{0} \qquad (9)$$

AND AT NEXT ORDER

$$A\,\underline{W}_1 = \underline{W}_{0t} - (I - \underline{\Phi}\,\underline{\psi}^T)\, M[y\,\underline{\Phi} + \underline{W}_0]. \qquad (10).$$

FROM (9), $\underline{W}_0 = \alpha\,\underline{\Phi}$ AND $\underline{\psi}^T \underline{W}_0 = 0 \rightarrow \alpha\,\underline{\psi}^T\underline{\Phi} = 0$ BUT $\underline{\psi}^T\underline{\Phi} = 1$ SO THAT $\alpha = 0$. THUS, $\underline{W}_0 = 0$.

AT NEXT ORDER

$$A\,\underline{W}_1 = -\,(I - \underline{\Phi}\,\underline{\psi}^T)\, M[y\,\underline{\Phi}]. \qquad (11)$$

WE NOW CLAIM THAT (11) HAS A UNIQUE SOLUTION. TO SHOW THAT $\exists$ A SOLUTION WE MUST SHOW THAT THE RIGHT HAND SIDE OF (11) IS IN THE RANGE OF A, OR EQUIVALENTLY HAS NO COMPONENT IN $\mathcal{N}(A^T)$. WE MULTIPLY (11) BY $\underline{\psi}^T$ AND GET

$$\underline{\psi}^T A\,\underline{W}_1 = -\underline{\psi}^T (I - \underline{\Phi}\,\underline{\psi}^T)\, M(y\,\underline{\Phi}) = -(\underline{\psi}^T - \underline{\psi}^T)\, M(y\,\underline{\Phi}) = 0$$

SINCE $\underline{\psi}^T\underline{\Phi} = 1$. THUS $(I - \underline{\Phi}\,\underline{\psi}^T)\, M(y\,\underline{\Phi}) \in \mathcal{R}(A)$.

THUS (11) HAS A SOLUTION, AND WE MAKE IT UNIQUE BY SETTING $\underline{\psi}^T \underline{w}_1 = 0$ AS REQUIRED BY EXPANDING (5) IN ε.

IN THIS WAY WE OBTAIN THAT, FROM (7),

$$Y_t = \underline{\psi}^T M \left[Y \underline{\Phi} + \varepsilon \underline{w}_1 + \cdots \right] \qquad (12).$$

LEADING-ORDER SOLUTION

IF WE NEGLECT THE $O(\varepsilon)$ TERM IN (12) WE HAVE

$$\left. Y_t \mathrel{\hat{=}} \underline{\psi}^T M (Y \underline{\Phi}) \right\} \qquad (13)$$

WE THEN SOLVE $\quad A \underline{\Phi} = 0 \longrightarrow \begin{pmatrix} -K_u & 0 & P K_b \\ 0 & -K_u & (1-P) K_b \\ K_u & K_u & -K_b \end{pmatrix} \begin{pmatrix} \Phi_1 \\ \Phi_2 \\ \Phi_3 \end{pmatrix} = \underline{0}$

WE OBTAIN IN TERMS OF A SCALING FACTOR $\frac{1}{\gamma}$ THAT

$$\underline{\Phi} = \frac{1}{\gamma} \begin{pmatrix} P K_b / K_u \\ (1-P) K_b / K_u \\ 1 \end{pmatrix} \qquad (14)$$

WITH γ CHOSEN SO THAT $\quad \underline{\psi}^T \underline{\Phi} = 1 \longrightarrow \frac{1}{\gamma} \left(\frac{P K_b}{K_u} + \frac{(1-P) K_b}{K_u} + 1 \right) = 1.$

THIS YIELDS THAT $\quad \gamma = \frac{K_u + K_b}{K_u} \quad$ AND SO $\quad \underline{\Phi} = \frac{K_u}{K_u + K_b} \begin{pmatrix} P K_b / K_u \\ (1-P) K_b / K_u \\ 1 \end{pmatrix} \qquad (15)$

NOW TO LEADING ORDER FROM (13) WE HAVE

$$Y_t \mathrel{\hat{=}} (1 \;\; 1 \;\; 1) \begin{pmatrix} -V_R \partial_x & 0 & 0 \\ 0 & V_L \partial_x & 0 \\ 0 & 0 & D_0 \partial_{xx} \end{pmatrix} \begin{pmatrix} Y \Phi_1 \\ Y \Phi_2 \\ Y \Phi_3 \end{pmatrix}$$

$$Y_t \mathrel{\hat{=}} - V_R \frac{\partial}{\partial x} (Y \Phi_1) + V_L \frac{\partial}{\partial x} (Y \Phi_2) + D_0 \partial_{xx} (Y \Phi_3) \qquad (16)$$

NOW PUTTING (16) INTO (15) WE OBTAIN THAT

$$Y_t \mathrel{\hat{=}} - V_R \frac{(K_b / K_u) K_u}{K_u + K_b} (Y P)_x + \frac{V_L (K_b / K_u) K_u}{K_u + K_b} \left[(1-P) Y \right]_x + \frac{D_0 K_u}{K_u + K_b} Y_{xx}$$

THIS BECOMES

$$Y_t \simeq -\frac{K_b V_R}{K_u + K_b}\left(Y P\right)_x + \frac{K_b V_L}{K_u + K_b}\left[(1-P)Y\right]_x + \frac{D_0 K_u}{K_u + K_b} Y_{xx}. \qquad (17)$$

NOTICE THAT THIS IS A CONVECTION-DIFFUSION EQUATION FOR $Y(x)$. HERE WE HAVE ALLOWED FOR $P = P(x)$ IN $0 < P(x) < 1$, THAT CHANCE OF BINDING TO EITHER LEFT OR RIGHT MOTOR DEPENDS ON X.

NOW IN THE SPECIAL CASE WHERE P IS A CONSTANT, INDEPENDENT OF X, THEN (17) CAN BE WRITTEN AS

$$Y_t \simeq V_{EFF}\, Y_x + D_{EFF}\, Y_{xx}$$

WHERE

$$V_{EFF} \equiv \frac{K_b}{K_u + K_b}\left(-V_R P + V_L (1-P)\right)$$

$$D_{EFF} = \frac{D_0}{(1 + K_b/K_u)}$$

NOTICE THAT K_b/K_u MEASURES AMOUNT OF TIME (IN RELATIVE TERMS) THAT THE CARGO REMAINS IN FREE-STATE AS COMPARED TO BEING ATTACHED TO A MOTOR. IF $V_R = V_L = V^*$, THEN $V_{EFF} = \frac{K_b}{K_u + K_b} V^* (1 - 2P)$ WHICH VANISHES IF $P = 1/2$ AS EXPECTED.

<u>REMARK</u>: ONE CAN GO TO HIGHER ORDER TO CALCULATE W_1. FOR AN INTERPRETATION AND GENERALIZATION OF THE METHODOLOGY SEE:

[1] J.M. NEWBY, P. BRESSLOFF, BULL MATH BIOLOGY (2010): 72 1840-186

[2] D. Dauvergne, L. Edelstein-Keshet, J. Theor. Biol. 379: 47-58, (2015).

FOR AN EXTENSION OF THE ANALYSIS TO THE CASE OF NONLINEAR BINDING, WHERE THE MODEL HAS THE FORM

$$\underline{p}_t = \frac{1}{\varepsilon}\,\underline{F}(\underline{p}) + M\underline{p} \quad \text{WITH} \quad M \equiv \begin{pmatrix} -V_1 \partial_x & 0 & 0 \\ 0 & V_2 \partial_x & 0 \\ 0 & 0 & D_0 \partial_{xx} \end{pmatrix}$$

AND $\underline{p} = \begin{pmatrix} p_1 \\ p_2 \\ p_3 \end{pmatrix}$, $\underline{F} = \begin{pmatrix} F_1 \\ F_2 \\ F_3 \end{pmatrix}$ WITH $F_1 + F_2 + F_3 = 0$

SEE SECTION 3 OF THE PAPER

ZMURCHOK ET AL., BULL. MATH BIO. VOL. 79, NO. 9, (2017) pp. 1923 - 1978

ON MY webpage.