5440 Final

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1A. $\frac{dN_1}{dt} = F(D_2) - \gamma_N N_1$ $\qquad \frac{dN_2}{dt} = F(D_1) - \gamma_N N_2$

$\frac{dD_1}{dt} = G(N_1) - \gamma_D D_1$ $\qquad \frac{dD_2}{dt} = G(N_2) - \gamma_D D_2$

$\tau = \gamma_D t \qquad t = \frac{\tau}{\gamma_D}$

$\gamma_D \frac{dN_1}{d\tau} = F(D_2) - \gamma_N N_1 \rightarrow \frac{dN_1}{d\tau} = \frac{F(D_2)}{\gamma_D} - \frac{\gamma_N}{\gamma_D} N_1$

$\gamma_D \frac{dD_1}{d\tau} = G(N_1) - \gamma_D D_1 \rightarrow \frac{dD_1}{d\tau} = \frac{G(N_1)}{\gamma_D} - D_1$

$\gamma_D \frac{dN_2}{d\tau} = F(D_1) - \gamma_N N_2 \rightarrow \frac{dN_2}{d\tau} = \frac{F(D_1)}{\gamma_D} - \frac{\gamma_N}{\gamma_D} N_2$

$\gamma_D \frac{dD_2}{d\tau} = G(N_2) - \gamma_D D_2 \rightarrow \frac{dD_2}{d\tau} = \frac{G(N_2)}{\gamma_D} - D_2$

$\nu = \frac{\gamma_D}{\gamma_N} \qquad g(N_i) = \frac{G(N_i)}{\gamma_D} \qquad f(D_i) = \frac{F(D_i)}{\gamma_N}$

substitue $\nu$

$\rightarrow \frac{dN_1}{d\tau} = \frac{1}{\nu}\left(f(D_2) - N_1\right)$

$\rightarrow \frac{dD_1}{d\tau} = g(N_1) - D_1$

$\rightarrow \frac{dN_2}{d\tau} = \frac{1}{\nu}\left(f(D_1) - N_2\right)$

$\rightarrow \frac{dD_2}{d\tau} = g(N_2) - D_2$

when $\nu << 1$, $\frac{\gamma_N}{\gamma_D} >> 1$ which means Notch achieves SS quickly:

$\frac{dN_1}{d\tau} = 0 = \frac{1}{\nu}\left(f(D_2) - N_1\right)$

$f(D_2) = N_1$

$\frac{dN_2}{d\tau} = 0 = \frac{1}{\nu}\left(f(D_1) - N_2\right)$

$f(D_1) = N_2$

→ substitute into $\frac{dD_1}{d\tau}$ and $\frac{dD_2}{d\tau}$

$$\frac{dD_1}{d\tau} = g(f(D_2)) - D_1 = \frac{1}{1 + 10\left(\frac{D_2^2}{0.1 + D_2^2}\right)} - D_1$$

$$\frac{dD_2}{d\tau} = g(f(D_1)) - D_2 = \frac{1}{1 + 10\left(\frac{D_1^2}{0.1 + D_1^2}\right)} - D_2$$

from class notes:

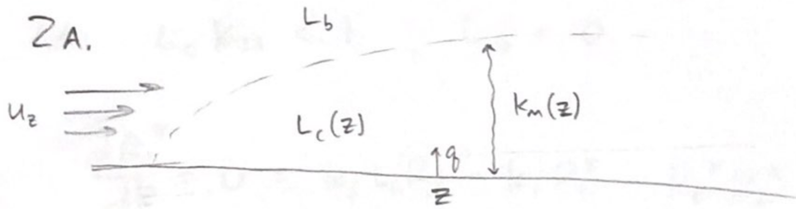
$$f(D_i) = \frac{D_i^2}{0.1 + D_i^2}$$

– see Julia code "prob1b.jl"

$$g(N_i) = \frac{1}{1 + 10N_i^2}$$

Using the phase portrait ("plot1b.png") it's evident that the middle steady-state is unstable while the two outer steady-states are stable. In this system, the cell with a greater initial Delta value assumes the primary fate (wins) and the other cell assumes the secondary fate. Therefore, lateral inhibition works here similarly as the case discussed in class where $\frac{\gamma_D}{\gamma_N} \gg 1$.

2A.




$$\frac{z}{n}\cdot\frac{dL_c}{dt} = -k_f R_s L_c + k_r R_s^* + q + \frac{k_m}{n_c}\left(L_b - L_c(z)\right)$$

steady-state:

$$0 = -k_f R_s L_c + k_r R_s^* + q + \frac{k_m}{n_c} L_b - \frac{k_m}{n_c} L_c$$

$$L_c\left(k_f R_s + \frac{k_m}{n_c}\right) = k_r R_s^* + q + \frac{k_m}{n_c} L_b$$

$$\boxed{L_c(z) = \frac{k_r R_s^* + q + \frac{k_m}{n_c} L_b}{k_f R_s + \frac{k_m}{n_c}}}$$

2B. transport-limited: $k_m$ is small

$$\boxed{L_c(z) = \frac{k_r R_s^* + q}{k_f R_s}}$$

When transport is limiting, the ligand concentration depends on the cell activity, i.e. binding and unbinding and production.

binding-limited: $k_m$ is big

$$L_c(z) = \frac{\frac{k_m}{n_c} L_b}{\frac{k_m}{n_c}}$$

$$\boxed{L_c(z) = L_b}$$

When binding is limiting, the ligand concentration ($L_c$) is only dependent on the bulk concentration. This makes sense because if binding is slow, then $L_c$ would approach the bulk value.

2c. $L_c K_{ss} < 1$, $L_b = 0$

$$\frac{dR_s^*}{dt} = 0 = k_f L_c R_s - k_r R_s^* - k_e^* R_s^*$$

$$k_f L_c R_s = R_s^* (k_r + k_e^*)$$

$$R_s = \frac{R_s^* (k_r + k_e^*)}{k_f L_c}$$

$$L(z)(L_b = 0) = \frac{k_r R_s^* + q}{\frac{k_m}{n_c} + \cancel{k_f}\left(\frac{R_s^*(k_r + k_e^*)}{\cancel{k_f} L_c}\right)}$$

$$L_c \frac{k_m}{n_c} + R_s^*(\cancel{k_r} + k_e^*) = \cancel{k_r R_s^*} + q$$

$$L_c = \frac{q - R_s^* k_e^*}{\frac{k_m}{n_c}}$$

$$R_i^* = \frac{k_e^*}{k_{deg}} R_s^*$$

$$R_s^* = \frac{K_{ss} L}{1 + K_{ss} L} \cdot \frac{V_s}{k_e^*} \rightarrow K_{ss} L \cdot \frac{V_s}{k_e^*}$$

$$R_T^* = R_s^* + R_i^*$$

$$\boxed{R_T^* = R_s^* \left(1 + \frac{k_e^*}{k_{deg}}\right)}$$

$$R_s^* = K_{ss}\left(\frac{q - R_s^* k_e^*}{\frac{k_m}{n_c}}\right) \cdot \frac{V_s}{k_e^*}$$

$$\frac{k_m}{n_c} \frac{k_e^*}{V_s} R_s^* = K_{ss} q - K_{ss} R_s^* k_e^*$$

$$R_s^* \left(\frac{k_m k_e^*}{n_c V_s} + K_{ss} k_e^*\right) = K_{ss} q$$

$$K_{ss} = \frac{k_e^* k_f}{k_e (k_r + k_e^*)}$$

$$R_{ss}^* = \frac{K_{ss} q}{k_e^* \left(\frac{k_m}{n_c V_s} + K_{ss}\right)}$$

2D. Mitotic activity

from notes: $\gamma =$

mitotic signal ($\gamma$) slope from Part II-2b notes

$$\gamma = \frac{100-0}{27-0} = \frac{100}{27}$$

Normalized rate: $\gamma \div R^{*}_{Total}$

$$\text{Norm rate} = \gamma \cdot \frac{K_{ss}\, q}{k_e^{*}\left(\frac{k_m}{n_c V_s} + K_{ss}\right)} \cdot \left(1 + \frac{k_e^{*}}{k_{deg}}\right)$$

where $k_m(z) = \left(\frac{\dot{\gamma} z^2}{D_L}\right) \cdot \frac{D_L}{z}$

manipulation of Sherwood number equation

see "prob2d.jl"

and "prob2db.png"

for predicted profile

"[illegible]" in DL1 folder

3A. $\dot{m}_i = r_{x,i}\,\bar{u}_i - (\mu + \theta_{m,i})\,m_i$

$$\dot{p}_i = r_{L,i}\,w_i - (\mu + \theta_{p,i})\,p_i$$

from prelim I,

@SS: $\dot{m}_i = 0 = r_{x,i}\,\bar{u}_i - (\mu + \theta_{m_i})\,m_i^*$

$$m_i^* = \underbrace{\left(\frac{r_{x,i}}{\mu + \theta_{m,i}}\right)}_{K_{x,i}} \bar{u}_i = K_{x,i}\,\bar{u}_i$$

where

$$r_{x,i} = k_{E,i}^{x}\,R_{x,T}\left(\frac{G_i}{\tau_{x,i}K_{x,i} + (\tau_{x,i}+1)G_i}\right)$$

$$\bar{u}_i = \frac{w_1 + w_2 f_I}{1 + w_1 + w_2 f_I} \qquad f_I = \frac{I^n}{K^n + I^n}$$

similar derivation for $p_i$:

@ SS: $\dot{p}_i = 0 = r_{L,i}\,w_i - (\mu + \theta_{p,i})\,p_i^*$

$$p_i^* = \underbrace{\left(\frac{r_{L,i}}{\mu + \theta_{p,i}}\right)}\,w_i \qquad \text{where}$$

$$r_{L,i} = k_{E,i}^{L}\,R_{L,T}\left(\frac{m_i}{\tau_{L,i}K_{L,i} + \cancel{(\tau_{L,i}+1)m_i}^{\,0}}\right)$$

$$\tau_{L,i}K_{L,i} >> (\tau_{L,i}+1)\,m_i$$

$$p_i = \frac{k_{E,i}^{L}\,R_{L,T}}{\mu + \theta_{p,i}} \cdot \frac{K_{x,i}\,\bar{u}_i}{\tau_{L,i}\,K_{L,i}}\,w_i$$

$$p_i = \underbrace{\frac{k_{E,i}^{L}\,R_{L,T}}{(\mu + \theta_{p,i})(\tau_{L,i}K_{L,i})}}_{K_{L,i}} K_{x,i}\,\bar{u}_i\,w_i$$

$$K_{x,i} = \frac{r_{x,i}}{\mu + \theta_{m,i}} \qquad \bar{u}_i = \frac{w_1 + w_2 f_I}{1 + w_1 + w_2 f_I}$$

$$\underline{p_i^* \approx K_{L,i}\,K_{x,i}\,\bar{u}_i\,w_i} \qquad K_{L,i} = \frac{k_{E,i}^{L}\,R_{L,T}}{(\mu + \theta_{p,i})(\tau_{L,i}K_{L,i})}$$

All parameters are in "Parameters.toml"

3b. see "prob3.ipynb" – Julia code, also "plot3b.png"

3c. As $K_p > 1$, the $\bar{p}_i$ curve goes up as a function of $\bar{u}_i$.
This trend is displayed in "plot3c.png" which shows trajectories for $K_p = 1, 10, 100$.

This happens because when more ribosomes are reading messages, i.e. when $K_p$ is increasing, more protein is able to be produced by the collective effort.

4. see "prob4.ipynb" in P4 folder.

Results:

A.

$W_1 = 0.045$

$W_2 = 98.95$

B. Tune $K_i$ and $n$ (Hill parameters) until model fits data

$K_i$ : $9 \times 10^{-2}$ mM

$n = 4.40$

C. see "plot4c.png"

Yes, this proposed model can fit the data well.

- All