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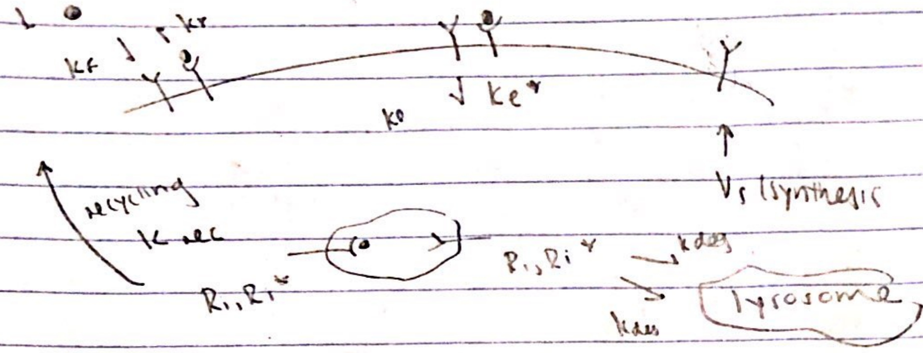
HW # 5

1) a)



mass balances

free surface receptor: $\frac{dR_s}{dt} = -k_f L R_s + k_r R_s^* - k_e R_s + V_s + k_{rec} R_s$ (1)

bound surface receptor: $\frac{dR_s^*}{dt} = k_f L R_s - k_r R_s^* - k_e^* R_s^* + k_{rec} R_s^*$ (2)

total internal receptor: $\frac{dR_i^T}{dt} = k_e R_s + k_e^* R_s^* - k_{deg} R_i^T - k_{rec} R_i^T$ (3)

where $R_i^T = R_i^S + R_i^*$

internal active receptor: $\frac{dR_i^*}{dt} = k_e^* R_s^* - k_{deg} R_i^* - k_{rec} R_i^*$ (4)

at SS: $k_{rec} R_s + k_{rec} R_s^* = k_{rec} R_i^T$

$\frac{dR_s}{dt} = 0 = -k_f L R_s + k_r R_s^* - k_e R_s + V_s + k_{rec} R_s$

$\frac{dR_s^*}{dt} = 0 = k_f L R_s - k_r R_s^* - k_e^* R_s^* + k_{rec} R_s^*$

Following the same steps to derive the solution as done in class

@ss $k_{deg} R_i^T = V_s$
from eqn (3)

$0 = k_e R_s + k_e^* R_s^* - V_s - k_{rec} R_i^T$

$0 = k_e R_s + k_e^* R_s^* - V_s - k_{rec} R_s - k_{rec} R_s^*$

solve for R_s

$$k_e R_s - k_{rec} R_s = V_s + k_{rec} R_s^* - k_e^* R_s^*$$

$$R_s = \frac{V_s + k_{rec} R_s^* - k_e^* R_s^*}{k_e - k_{rec}}$$

plug into eqn (2)

$$0 = k_f L \left(\frac{V_s + k_{rec} R_s^* - k_e^* R_s^*}{k_e - k_{rec}} \right) - k_r R_s^* - k_e^* R_s^* + k_{rec} R_s^*$$

solve for R_s

$$0 = \frac{k_f L V_s}{k_e - k_{rec}} + \frac{k_f L k_{rec} R_s^*}{k_e - k_{rec}} - \frac{k_f L k_e^* R_s^*}{k_e - k_{rec}} - k_r R_s^* - k_e^* R_s^* + k_{rec} R_s^*$$

$$\frac{k_f L V_s}{\cancel{k_e - k_{rec}}} = R_s^* \left[\frac{k_f L k_e^*}{k_e - k_{rec}} - \frac{k_f L k_{rec}}{\cancel{k_e - k_{rec}}} + \frac{(k_r + k_e^* - k_{rec})(k_e - k_{rec})}{\cancel{k_e - k_{rec}}} \right]$$

$$R_s^* = \frac{k_f L V_s}{k_f L k_e^* - k_f L k_{rec} + \underbrace{(k_e - k_{rec})(k_r + k_e^*}_{\text{divide every thing by this term}} - k_{rec})}$$

$$R_s^* = \frac{\dfrac{k_f L V_s}{(k_e - k_{rec})(k_r + k_e^* - k_{rec})}}{\dfrac{k_f L (k_e^* - k_{rec})}{(k_e - k_{rec})(k_r + k_e^* - k_{rec})} + 1}$$

use $K_{ss} = \dfrac{k_f (k_e^* - k_{rec})}{(k_e - k_{rec})(k_r + k_e^* - k_{rec})}$

$$R_i^* = \frac{K_{ss} L}{1 + K_{ss} L} \left(\frac{V_s}{k_e^* - k_{rec}} \right)$$

use eqn (4) to get R_i^*

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$$0 = k_e^* R_s^* - k_{deg} R_i^* - k_{rec} R_i^*$$

$$k_{deg} R_i^* + k_{rec} R_i^* = k_e^* R_s^*$$

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

$$R^*_{total} = R_s^* + R_i^*$$

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

$$= \frac{K_{ss} L}{1 + K_{ss} L} \left(\frac{V_s}{k_e^* - k_{rec}}\right) \left(1 + \frac{k_e^*}{k_{deg} + k_{rec}}\right)$$

$$\boxed{R^*_{total} = \underbrace{\left(\frac{1}{k_e^* - k_{rec}} + \frac{k_e^*}{(k_e^* - k_{rec})(k_{deg} + k_{rec})}\right)}_{\text{resistance to activation}} \underbrace{\left(\frac{K_{ss} L}{1 + K_{ss} L}\right)}_{\text{bound fraction (ranges from 0 to 1)}} \underbrace{V_s}_{\text{synthesis}}}$$

max occurs when bound fraction = 1

$$\boxed{R^{*,max}_{total} = \left(\frac{1}{k_e^* - k_{rec}} + \frac{k_e^*}{(k_e^* - k_{rec})(k_{deg} + k_{rec})}\right) V_s}$$

compare this to process w/o recycling

$$R^{*,max}_{total} = \left(\frac{1}{k_e^*} + \frac{1}{k_{deg}}\right) V_s$$

looking at the first term, $\frac{1}{k_e^*}$ vs $\frac{1}{k_e^* - k_{rec}}$

Recycling increases the max concentration of active receptors by keeping them in circulation which can increase overall binding

2) $$\frac{dc_a}{dt} = -d_a c_a + \frac{r_{0a} + r_a c_a^2}{1 + c_a^2 + c_r^2}$$

$$\frac{dc_r}{dt} = -c_r + \frac{r_{0r} + r_r c_a^2}{1 + c_a^2}$$

at SS $\frac{dc_a}{dt} = \frac{dc_r}{dt} = 0$

(1) $d_a c_a = \dfrac{r_{0a} + r_a c_a^2}{1 + c_a^2 + c_r^2}$ (2) $c_r = \dfrac{r_{0r} + r_r c_a^2}{1 + c_a^2}$

a) from this, we can draw the following conclusions

(1) R has no effect on R (no c_r on right side of eqn 2)

(2) A is an activator of R (indicated by increasing sigmoidal shape eqn 2)

(3) R is an inhibitor of A (only appears in denominator of eqn 1)

(4) A is an activator of A (sigmoidal shape of eqn 1 right side)

Basal rates:

$c_A + c_r = 0$

$\frac{dc_a}{dt} = r_{0a}$ $\frac{dc_r}{dt} = r_{0r}$

d_a is a degradation constant for c_a

maximal rates

$\frac{dc_a}{dt} \rightarrow$ max occurs when $c_r = 0$

$$\frac{dc_a}{dt} = -d_a c_a + \frac{r_{0a} + r_a c_a^2}{1 + c_a^2}$$

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(b) used PS5 2 B .jl and PhasePortrait V2.jl to generate plot 1
The fixed point is where the two nullclines (red lines) intersect. Since the phase portrait shows that the vectors / trajectories do not all point towards this point, the fixed point is unstable

(c) see plot 1

d) In the plot there is no clear relationship between C_r and C_A. This is due to the oscillatory nature of the system. There is a peak value of both C_A + C_r. The loop-like structure of the trajectory plotted for $C_{A0} = 1$ and $C_{r0} = 10$ exemplifies the oscillatory pattern that the concentrations follow over time

e) see file "PS5N2e.m"
attempted to use this code to solve the ODE system and plot. For some reason, the MATLAB solver was unable to solve this ODE system, though I tried it with other differential equations and the code worked

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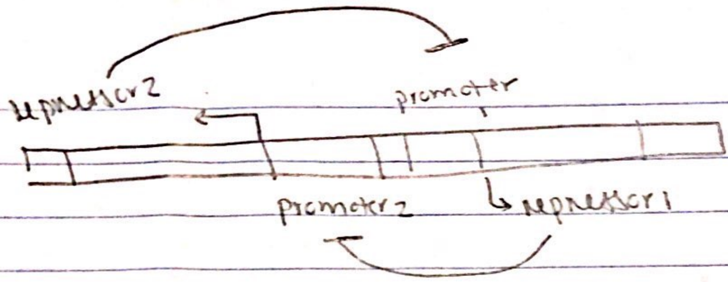
3)



$$\frac{du}{dt} = \frac{\alpha}{1+v^n} - u = f(u,v)$$

$$\frac{dv}{dt} = \frac{\alpha}{1+u^n} - v = g(u,v)$$

a)

u, v = (i) conc of a repressor of gene expression

$\frac{du}{dt}, \frac{dv}{dt}$ = (ii) effective rate of synthesis of repressor

n = (iii) cooperativity of repression

1 = (iv) degradation constant

α = effective rate of synthesis (according to Collins paper)

b+c) see "PS 5 Plots"

Linear stability analysis

d) (1) Find steady states: $f(u_s, v_s) = g(u_s, v_s) = 0$

(2) linearize system around steady state of interest for perturbations:

$U = u - u_s$

$V = v - v_s$

$$\frac{dU}{dt} = \overbrace{f(u_s, v_s)}^{0} + \left.\frac{df}{du}\right|_{u_s,v_s} U + \left.\frac{df}{dv}\right|_{v_s,v_s} V$$

$$\frac{dU}{dt} = -U - \left.\frac{\alpha n v^{n-1}}{(v^n+1)^2} V\right|_{v_s,v_s}$$

$$\frac{dU}{dt} = -U - \frac{\alpha n v_s^{n-1}}{(v_s^n+1)^2} V$$

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$$\frac{d\bar{V}}{dt} = g(\cancel{u_s}, v_s)^{0} + \frac{dg}{du}\Big|_{u_s, v_s} \bar{U} + \frac{dg}{dv}\Big|_{u_s, v_s} \bar{V}$$

$$\frac{d\bar{V}}{dt} = -\frac{\alpha n u^{n-1}}{(u^n+1)^2}\Big|_{v_s, v_s} \bar{U} - \bar{V}$$

$$\frac{d\bar{V}}{dt} = -\frac{\alpha n v_s^{n-1}}{(u_s^n+1)^2} \bar{U} - \bar{V}$$

in matrix form

$\dot{\vec{x}} = \overleftrightarrow{J}\, \vec{x}$

where $\vec{x} = \begin{pmatrix} \bar{U} \\ \bar{V} \end{pmatrix}$, $\boxed{\overleftrightarrow{J} = \begin{pmatrix} -1 & \dfrac{-\alpha n v_s^{n-1}}{(v_s^n+1)^2} \\ -\dfrac{\alpha n u_s^{n-1}}{(u_s^n+1)^2} & -1 \end{pmatrix}}$

* see next page for the rest of part d

jumping to (e)

$\alpha = 10$, $n = 1$ and 2

∴ find numerical value of unter steady state $(u = v)$

$\boxed{n=1}$

$$\frac{10}{1+u^1} - u = 0$$

$$u = \frac{1}{2}(\sqrt{41} - 1) \approx 2.7016$$

consistent w/ graph from part b

$\boxed{n=2}$

$$\frac{10}{1+u^2} - u = 0$$

$u = 2$ consistent w/ part b

Use MATLAB eig function to find λ's (see PS5N3E.m)

for $n = 1$ $\lambda = -1.7298$, -0.2702

both $\ominus$ ∴ stable

2 d) Finding eigenvalues

$$\overleftrightarrow{J}\vec{x} = \lambda\vec{x} \Rightarrow \left(\overleftrightarrow{J} - \lambda\overleftrightarrow{I}\right)\vec{x} = 0$$

non trivial soln if

$$\det\left(\overleftrightarrow{J} - \lambda\overleftrightarrow{I}\right) = \left|\overleftrightarrow{J} - \lambda\overleftrightarrow{I}\right| = 0 \rightarrow \text{stability eqn}$$

$$\begin{vmatrix} -1-\lambda & \dfrac{-\alpha n v_s^{n-1}}{(v_s^n+1)^2} \\ \dfrac{-\alpha n u_s^{n-1}}{(u_s^n+1)^2} & -1-\lambda \end{vmatrix} = 0$$

$$\Rightarrow (-1-\lambda)(-1-\lambda) - \left[\frac{-\alpha n v_s^{n-1}}{(v_s^n+1)^2}\right]\left[\frac{-\alpha n u_s^{n-1}}{(u_s^n+1)^2}\right] = 0$$

$$\lambda_\pm = \frac{tr(\overleftrightarrow{J}) \pm \sqrt{tr(\overleftrightarrow{J})^2 - 4\det(J)}}{2}$$

where $tr(\overleftrightarrow{J}) = -2$

$$\det(\overleftrightarrow{J}) = 1 - \left(\frac{\alpha n v_s^{n-1}}{(v_s^n+1)^2}\right)\left(\frac{\alpha n u_s^{n-1}}{(u_s^n+1)^2}\right)$$

$$\lambda = \frac{-2 \pm \sqrt{-2 - 4\left(1 - \left(\frac{\alpha n v_s^{n-1}}{(v_s^n+1)^2}\right)\left(\frac{\alpha n u_s^{n-1}}{(u_s^n+1)^2}\right)\right)}}{2}$$

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for $n = 2$ $\lambda = -2.6, 0.6$

not both $\ominus$ $\therefore$ unstable

change in cooperativity changes the stability of the steady state of interest

f1) $$\frac{dR_1^*}{dt} = k_f L R_1 - k_r R_1^* \qquad \frac{dR_2^*}{dt} = k_f L R_2 - k_r R_2^*$$

$$\frac{dN_1^*}{dt} = k_f^{ND} N_1 D_2 - k_r^{ND} N_1^* \qquad \frac{dN_2^*}{dt} = k_f^{ND} N_2 D_1 - k_r^{ND} N_2^*$$

$$\frac{dD_1}{dt} = k_D R_1^* - \gamma_D D_1 \qquad \frac{dD_2}{dt} = k_D R_2^* - \gamma_D D_2$$

$$\frac{dR_1}{dt} = \frac{\beta^n}{k^n + N_1^{*n}} - \gamma_R R_1 \qquad \frac{dR_2}{dt} = \frac{\beta^n}{k^n + N_2^{*n}} - \gamma_R R_2$$

since (3)–(5) assume fast equilibrium

$$\frac{dR_1^*}{dt}, \frac{dR_2^*}{dt}, \frac{dN_1^*}{dt}, \frac{dN_2^*}{dt}, \frac{dD_1}{dt}, \frac{dD_2}{dt} = 0$$

$$0 = k_f^{ND} N_1 D_2 - k_r^{ND} N_1^*$$

$$N_1^* = \frac{k_f^{ND} N_1 D_2}{k_r^{ND}} \qquad (N_1 = \text{const})$$

$$0 = k_D R_2^* - \gamma_D D_2$$

$$D_2 = \frac{k_D R_2^*}{\gamma_D}$$

$$0 = k_f L R_2 - k_r R_2^*$$

$$\therefore R_2^* = \frac{k_f L R_2}{k_r}$$

$$D_2 = \frac{k_D k_f L R_2}{\gamma_D k_r}$$

$$N_1^* = \frac{k_f^{ND} N_1 k_D k_f L R_2}{k_r^{ND}}$$

$$\frac{dR_1}{dt} = \frac{\beta^n}{k^n + \left(\frac{k_f^{ND} N_1 k_D k_f L R_2}{k_r^{ND}}\right)^n} - \gamma_R R_1$$

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similar expression for $\frac{dR_2}{dt}$

$$\boxed{\frac{dR_2}{dt} = \frac{\beta^n}{k^n + \left(\frac{k_f^{ND} N_2 k_D k_f R_1}{k_r^{ND}}\right)^n} - \gamma_R R_2}$$

f2) non dimensional variables

$$u = \frac{R_1}{K}, \quad v = \frac{R_2}{K}, \quad \tau = \gamma_R t$$

$$\frac{dR_1}{dt} = \left(\frac{\beta^n}{k^n + \left(\frac{k_f^{ND} N_1 k_D k_f L R_2}{k_r^{ND}}\right)^n} - \gamma_R R_1\right.$$

$$\frac{1}{k} \cdot \frac{dR_1}{dt} = \left(\frac{\beta^n}{k^n + \left(\frac{k_f^{ND} N_1 k_D k_f L}{k_r^{ND}}\right)^n R_2^n} - \gamma_R R_1\right)\frac{1}{k}$$

$$\frac{du}{dt} = \frac{\beta^n}{k^{n+1} + \left(\frac{k_f^{ND} N_1 k_D k_f L}{k_r^{ND}}\right)^n v^n} - \gamma_R u$$

β $\frac{conc^{n+1}}{time}$

k conc

N_I conc

$$\frac{du}{d\frac{\tau}{\gamma_R}} = \frac{\beta^n}{k^{n+1} + \left(\frac{k_f^{ND} N_1 k_D k_f L}{k_r^{ND}}\right)^n v^n} - \gamma_R v$$