

Spring 2020 - CHEME 5440

HW#5

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1.

Species balances:

$$\frac{\partial R_s}{\partial t} = -k_f R_s L + k_r (R_s^*) - (k_e^*) R_s + k_{rec} R_i + v_s$$

$$\frac{\partial R_s^*}{\partial t} = k_f R_s L - k_r (R_s^*) - (k_e^*) (R_s^*) + k_{rec} (R_i^*)$$

$$\frac{\partial R_i}{\partial t} = k_e R_s - k_{deg} R_i - k_{rec} R_i$$

$$\frac{\partial R_i^*}{\partial t} = (k_e^*) (R_s^*) - k_{deg} (R_i^*) - k_{rec} (R_i^*)$$

Solve for $\frac{\partial R_s}{\partial t} = 0$, $\frac{\partial R_s^*}{\partial t} = 0$, $\frac{\partial R_i}{\partial t} = 0$ and $\frac{\partial R_i^*}{\partial t} = 0$,

$$R_s = \frac{(k_{rec} + k_{deg}) v_s (k_{deg} k_e^* + k_{deg} k_r + k_{rec} k_r)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})}$$

$$R_i = \frac{k_e v_s (k_{deg} k_e^* + k_{deg} k_r + k_{rec} k_r)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})}$$

$$R_s^* = \frac{v_s (k_{deg}^2 k_f L + 2 k_{deg} k_f L k_{rec} + k_f L k_{rec}^2)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})}$$

$$R_i^* = \frac{v_s (k_{deg} k_e^* k_f L + k_{rec} k_e^* k_f L)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})}$$

Total concentration of active receptors = $R_s^* + R_i^* = R_a$

$$\begin{aligned} R_a &= \frac{v_s (k_{deg}^2 k_f L + 2 k_{deg} k_f L k_{rec} + k_f L k_{rec}^2)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})} + \\ &= \frac{v_s (k_{deg} k_e^* k_f L + k_{rec} k_e^* k_f L)}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})} \\ &= \frac{v_s L k_f (k_{deg} + k_e^* + k_{rec}) (k_{deg} + k_{rec})}{k_{deg} (k_{deg} k_e^* k_e + k_{deg} k_r k_e + k_{rec} k_r k_e + k_{deg} k_e^* k_f L + k_e^* k_f L k_{rec})} \end{aligned}$$

Without the recycling step ($k_{rec} = 0$)

solve for $\frac{\partial R_s}{\partial t} = 0$, $\frac{\partial R_s^*}{\partial t} = 0$, $\frac{\partial R_i}{\partial t} = 0$ and $\frac{\partial R_i^*}{\partial t} = 0$ with $k_{rec} = 0$

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

$$R_i = \frac{k_e v_s (k_e^* + k_r)}{k_{deg} (k_e^* k_e + k_r k_e + k_e^* k_f L)}$$

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

$$R_i^* = \frac{v_s k_e^* k_f L}{k_{deg} (k_e^* k_e + k_r k_e + k_e^* k_f L)}$$

Total concentration of active receptors *without recycling step* = $R_s^* + R_i^* = R_b$

$$R_b = \frac{v_s k_f L}{(k_e^* k_e + k_r k_e + k_e^* k_f L)} + \frac{v_s k_e^* k_f L}{k_{deg} (k_e^* k_e + k_r k_e + k_e^* k_f L)} = \frac{v_s k_f L (k_{deg} + k_e^*)}{k_{deg} (k_e^* k_e + k_r k_e + k_e^* k_f L)}$$

Taking L to infinity, the maximum concentrations of active receptors could be obtained:

$$\lim_{L \rightarrow \infty} R_a = \frac{v_s (k_{deg} + k_e^* + k_{rec})}{k_{deg} k_e^*}$$

$$\lim_{L \rightarrow \infty} R_b = \frac{v_s (k_{deg} + k_e^*)}{k_{deg} k_e^*}$$

$$\text{Since } \lim_{L \rightarrow \infty} R_a = \frac{v_s (k_{deg} + k_e^* + k_{rec})}{k_{deg} k_e^*} > \frac{v_s (k_{deg} + k_e^*)}{k_{deg} k_e^*} = \lim_{L \rightarrow \infty} R_b,$$

thus, adding a recycling step increases the maximum concentration of active receptors.

2.

a)

From the equations:

$$\frac{dc_a}{dt} = -d_a c_a + \frac{r_{oa} + r_a c_a^2}{1 + c_a^2 + c_r^2} \quad (1)$$

$$\frac{dc_r}{dt} = -c_r + \frac{r_{or} + r_r c_a^2}{1 + c_a^2} \quad (2)$$

For A:

From equation (1), c_a is in a form of $\frac{\alpha + c_a^2}{\beta + c_a^2}$, which means A is an activator on the production of A. From equation (2), c_a is also in this form, thus, A is also an activator on the production of R. d_a appears in the degradation term of equation (1) and should be the rate constant.

For R:

From equation (1), c_r appears in the denominator of the production term, which is positive. Thus, by increasing c_r , the production will decrease, meaning R is an inhibitor on the production of A. From equation (2), c_r does not appear in the production term, but only in the degradation term, thus, R itself has no effect on the production of R.

To find the basal rates of A production, the concentration of the activator (c_a) must be minimal. Therefore, for the production of A, the basal rate should be $\frac{r_{oa}}{1 + c_r^2}$. For the production of R, the basal rate is then r_{or} . As for the maximal rate, taking c_a to be much larger than c_r , r_{oa} and r_{or} , the maximal rates are r_a for the production of A and r_r for the production of R.

2.

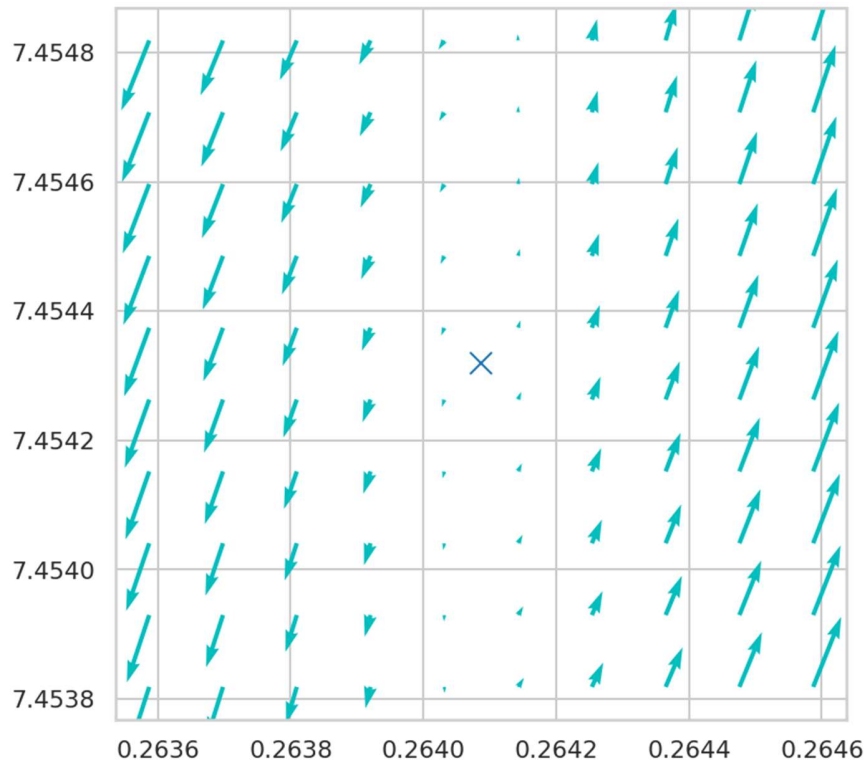
b)

To find the fixed points, equation (1) and equation (2) should be equal to 0:

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

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

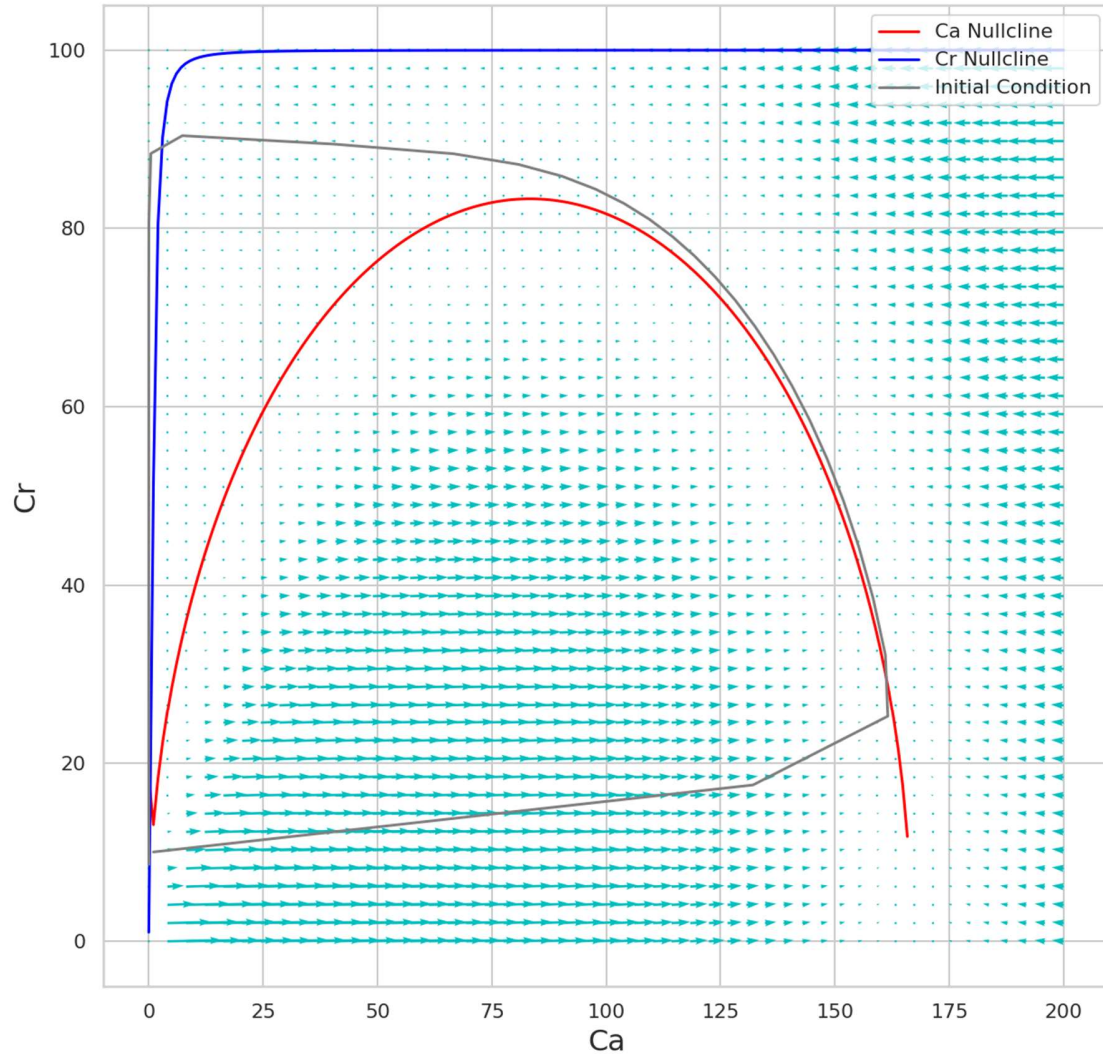
Solving the above equations above, the two nullclines intersect at $(c_a, c_r) = (0.264, 7.454)$



The steady state (fixed point, marked as “x” in figure above) is unstable because all vectors do not point towards it.

2.

c)

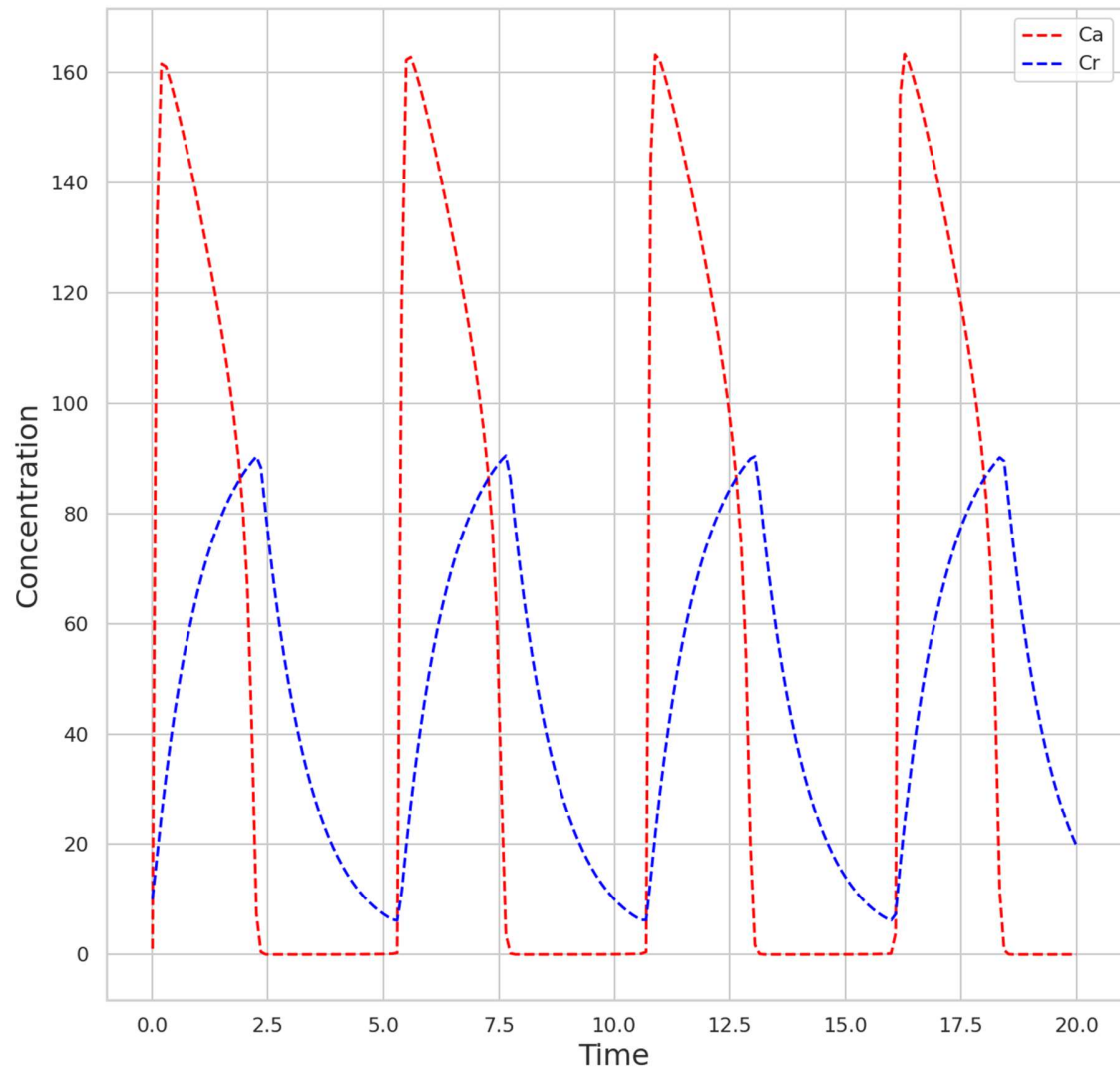


2.

d)

From the above figure, one can see that when both concentrations are low, c_a increases sharply while c_r increases slowly, and then c_a decreases. The relationship between c_a and c_r is kind of like they continue travelling along the gray line (the initial condition) in a counterclockwise manner, which could be observed from the arrows. From the magnitude of the arrows, one can observe that the increase of c_a is more rapid than c_r . This concept could also be demonstrated in the below figure.

2.
e)



3.

a)

i. u and v

ii. α

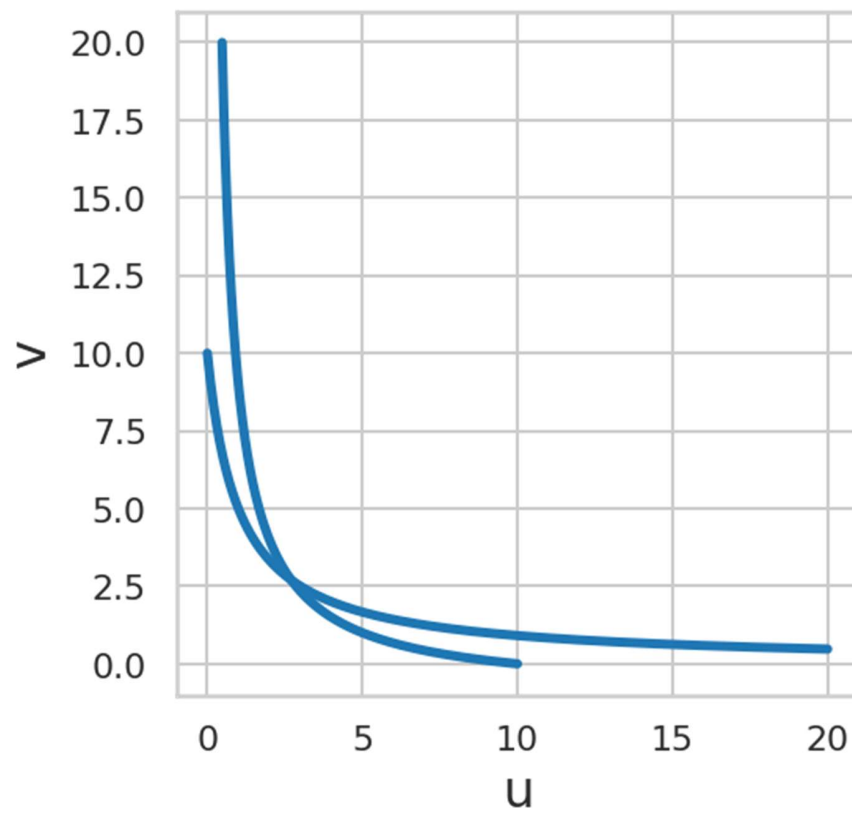
iii. n

iv. l

3.

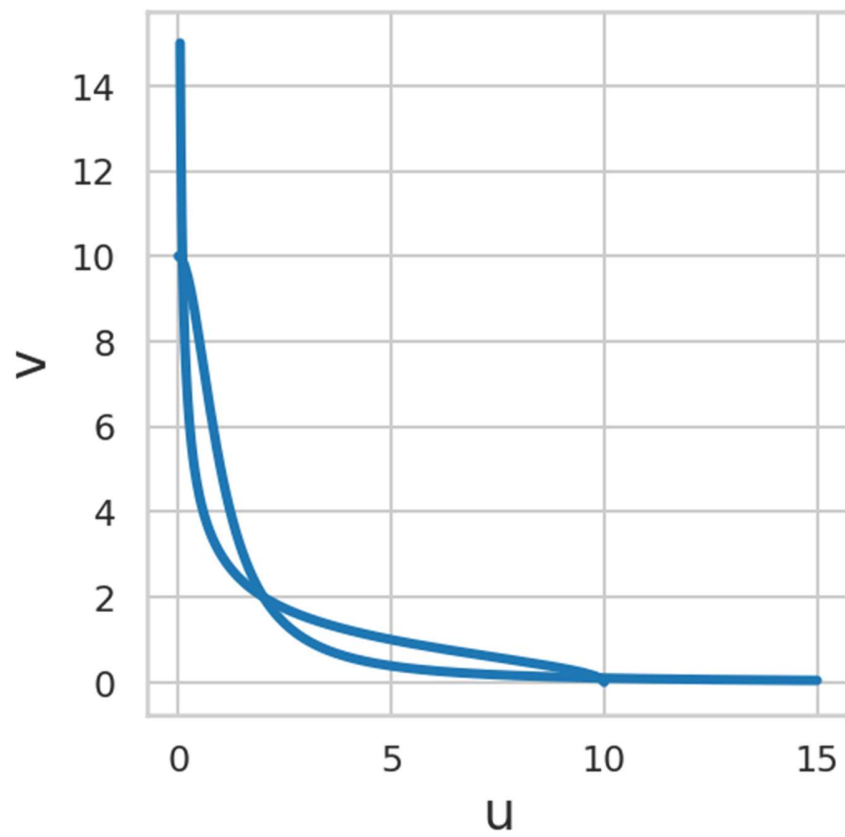
b)

For $n = 1$:



One steady state solution exists. (One fixed point)

For $n=2$:



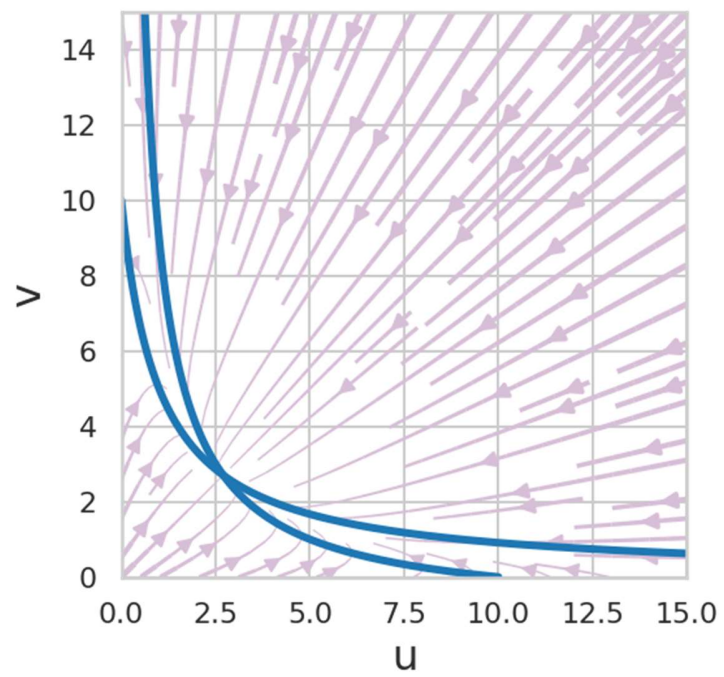
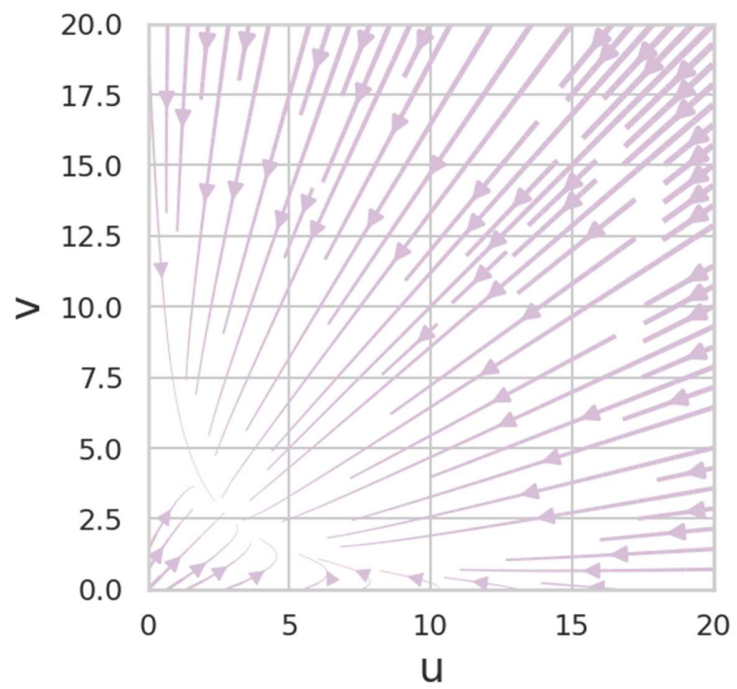
Three steady states exist. (Three fixed points)

n increases the number of steady states as it increases.

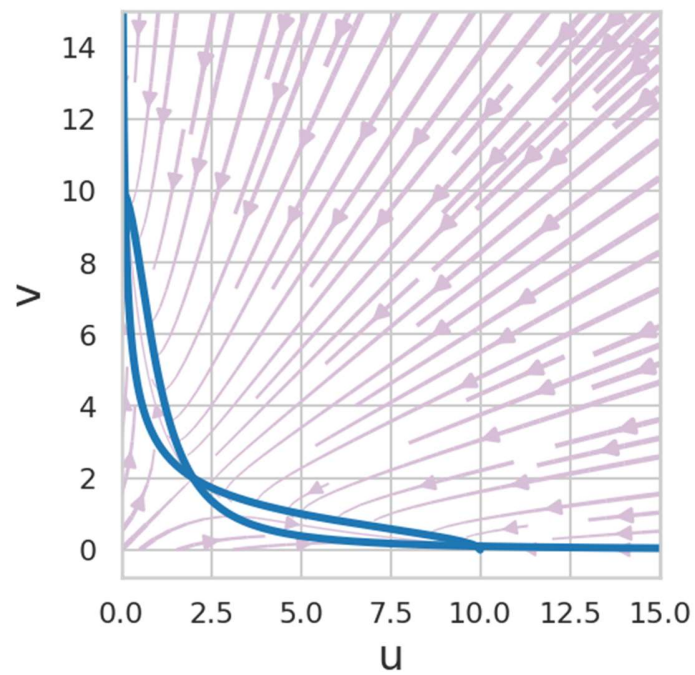
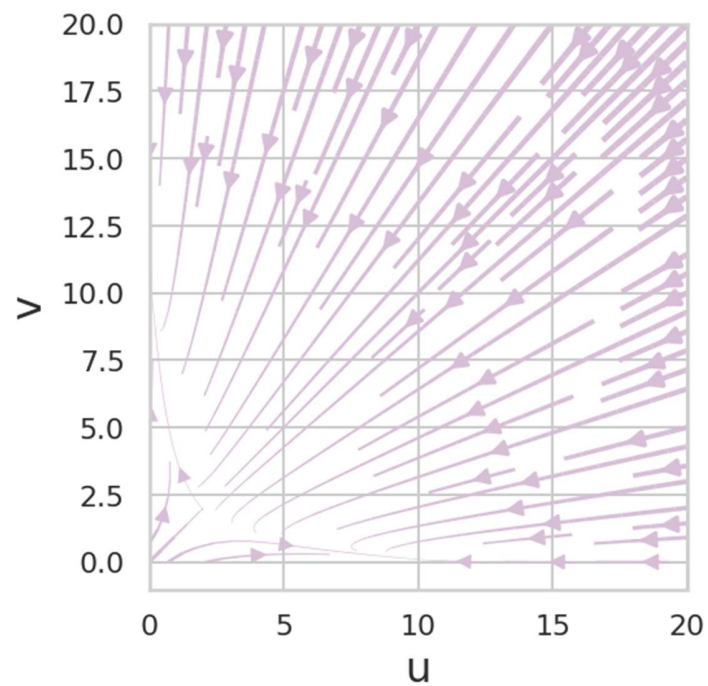
3.

c)

For $n = 1$:



For $n = 2$:



For $n = 1$, there exists a single stable steady state as all the vectors point towards the fixed point.

For $n = 2$, the fixed point at around $(2, 2)$ is at an unstable steady state as only

some of the vectors point toward it while others point away. For the fixed points at around (10, 0) and (0, 10), they are at a stable steady state since all vector points point towards them.

In conclusion, when the degree of cooperativity increases, stable steady states and unstable steady states increase.

3.

d) e)

No time to solve...

3.

f-1)

$$\frac{dR_i^*}{dt} = k_f R_i L - k_r (R_i^*) \quad (3)$$

$$\frac{dN_i^*}{dt} = k_f^{ND} N_i D_j - k_r^{ND} (N_i^*) \quad (4)$$

$$\frac{dD_i}{dt} = k_D (N_i^*) - \gamma_D D_i \quad (5)$$

$$\frac{dR_i}{dt} = \frac{\beta^n}{K^n + N_i^{*n}} - \gamma_R R_i \quad (6)$$

Solve for $\frac{\partial R_i^*}{\partial t} = 0$, $\frac{\partial N_i^*}{\partial t} = 0$ and $\frac{\partial D_i}{\partial t} = 0$

$$k_f R_i L = k_r (R_i^*)$$

$$k_f^{ND} N_i D_j = k_r^{ND} (N_i^*)$$

$$k_D (N_i^*) = \gamma_D D_i$$

Substitute N_i^* , D_j and R_i^* ,

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

$$\frac{dR_2}{dt} = \frac{\beta^n}{K^n + [R_1 \left(\frac{k_f^{ND} k_D k_f N_2 L}{k_r^{ND} k_r \gamma_D} \right)]^n} - \gamma_R R_2$$

f-2)

Substitute R_1 with uK , R_2 with vK , $\tau = \gamma_R t$,

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

$$K \frac{dv}{dr} \gamma_R = \frac{\beta^n}{K^n + u^n K^n \left(\frac{k_f^{ND} k_D k_f N_2 L}{k_r^{ND} k_r \gamma_D} \right)} - \gamma_R v K$$

Thus,

$$\frac{du}{dr} = \frac{\beta^n}{[1 + v^n \left(\frac{k_f^{ND} k_D k_f N_1 L}{k_r^{ND} k_r \gamma_D} \right)^n] (\gamma_R K^{n+1})} - u$$

$$\frac{dv}{dr} = \frac{\beta^n}{[1 + u^n \left(\frac{k_f^{ND} k_D k_f N_2 L}{k_r^{ND} k_r \gamma_D} \right)^n] (\gamma_R K^{n+1})} - v$$

Which could be simplified to

$$\frac{du}{dr} = \frac{\alpha}{[1 + v^n (\varepsilon)^n]} - u$$

$$\frac{dv}{dr} = \frac{\alpha}{[1 + u^n (\varepsilon)^n]} - v$$

Which is similar to equations (1) and (2) in problem 3 in the assignment.

When the concentration of ligand is high, then the production term both decreases and by increasing n , the system could be driven into instability.