CHEME 5440 - Final Exam
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Problem 1

a) Using the two cell model discussed in class, the Notch and Delta activity can be described by the following equations :-

$$\left.\begin{aligned}\frac{dN_1}{dt} &= F(D_2) - \gamma_N N_1\\ \frac{dD_1}{dt} &= G(N_1) - \gamma_D D_1\\ \frac{dN_2}{dt} &= F(D_1) - \gamma_N N_2\end{aligned}\right\} \text{①}$$

$$\frac{dD_2}{dt} = G(N_2) - \gamma_D D_2$$

N_x = Active notch in cell x
D_x = Active delta in cell x
F [=] Activation function
G [=] Inhibition function.
γ [=] degradation constant.

⇒ Assuming that N_x & D_x are already normalized by their maximum values, the system of equations can be normalized by substituting the following:-

$$\boxed{\tau_D = \gamma_D t} \quad \boxed{\upsilon = \frac{\gamma_D}{\gamma_N}} \quad \boxed{f(D) = \frac{F(D)}{\gamma_N}} \quad \boxed{g(N) = \frac{G(N)}{\gamma_D}}$$

Note
→ f & g are dimensionless rate
→ τ_D is dimensionless time
→ υ ⇒ ratio of degradation rates

→ Dividing by γ_D yields:-

$$\frac{1}{\gamma_D}\cdot\frac{dN_1}{dt} = \frac{F(D_2)}{\gamma_D} - \frac{\gamma_N}{\gamma_D}N_1 \xRightarrow{\text{sub. } f(D_2)} \frac{dN_1}{d\tau_D} = \frac{\gamma_N f(D_2)}{\gamma_D} - \frac{\gamma_N}{\gamma_D}N_1 \Longrightarrow \boxed{\frac{dN_1}{d\tau_D} = \frac{1}{\upsilon}\left(f(D_2) - N_1\right)} \text{ ②}$$

$$\frac{1}{\gamma_D}\cdot\frac{dD_1}{dt} = \frac{G(N_1)}{\gamma_D} - \frac{\cancel{\gamma_D}}{\cancel{\gamma_D}}D_1 \Rightarrow \boxed{\frac{dD_1}{d\tau_D} = g(N_1) - D_1} \text{ ③}$$

$$\frac{1}{\gamma_D}\cdot\frac{dN_2}{dt} = \frac{F(D_1)}{\gamma_D} - \frac{\gamma_N N_2}{\gamma_D} \xRightarrow{\text{sub } f(D_1)} \frac{dN_1}{d\tau_D} = \frac{\gamma_N f(D_1)}{\gamma_D} - \frac{\gamma_N}{\gamma_D}N_2 \Rightarrow \boxed{\frac{dN_2}{d\tau_D} = \frac{1}{\upsilon}\left(f(D_1) - N_2\right)} \text{ ④}$$

$$\frac{1}{\gamma_D}\cdot\frac{dD_2}{dt} = \frac{G(N_2)}{\gamma_D} - \frac{\cancel{\gamma_D}}{\cancel{\gamma_D}}D_2 \Rightarrow \boxed{\frac{dD_2}{d\tau_D} = g(N_2) - D_2} \text{ ⑤}$$

⇒ Considering the case when $\boxed{\upsilon = \frac{\gamma_D}{\gamma_N} \lll 1}$, we see that both N_1 and N_2 settle to steady state values for given delta activation. ∎

$$\therefore \quad \underbrace{\vartheta \frac{dN_1}{d\tau_D}}_{\approx 0 \text{ as } \vartheta \text{ is very small}} = f(D_2) - N_1 \quad \approx 0 \text{ for very small } \vartheta$$

$$\underbrace{\vartheta \frac{dN_2}{d\tau_D}}_{\approx 0, \text{ as } \vartheta \text{ is very small}} = f(D_1) - N_2 \quad \approx 0 \text{ for very small } \vartheta.$$

$\Rightarrow$ Thus;

$$\boxed{\begin{aligned} f(D_2) &\approx N_1 \\ f(D_1) &\approx N_2. \end{aligned}}$$

(*) Plugging back the above expressions into (3) & (4) yields the following dynamical equations for the evolution of Delta:-

$$\boxed{\begin{aligned} \frac{dD_1}{d\tau_D} &= g(f(D_2)) - D_1 \\ \frac{dD_2}{d\tau_D} &= g(f(D_1)) - D_2 \end{aligned}} \Bigg\} \text{ dynamical equations in dimensionless form.}$$

b) The functional forms of the dimensionless Notch and Delta activation rates, results in the following set of equations:-

$\rightarrow$ Function forms of $f(D)$ and $g(N)$:-

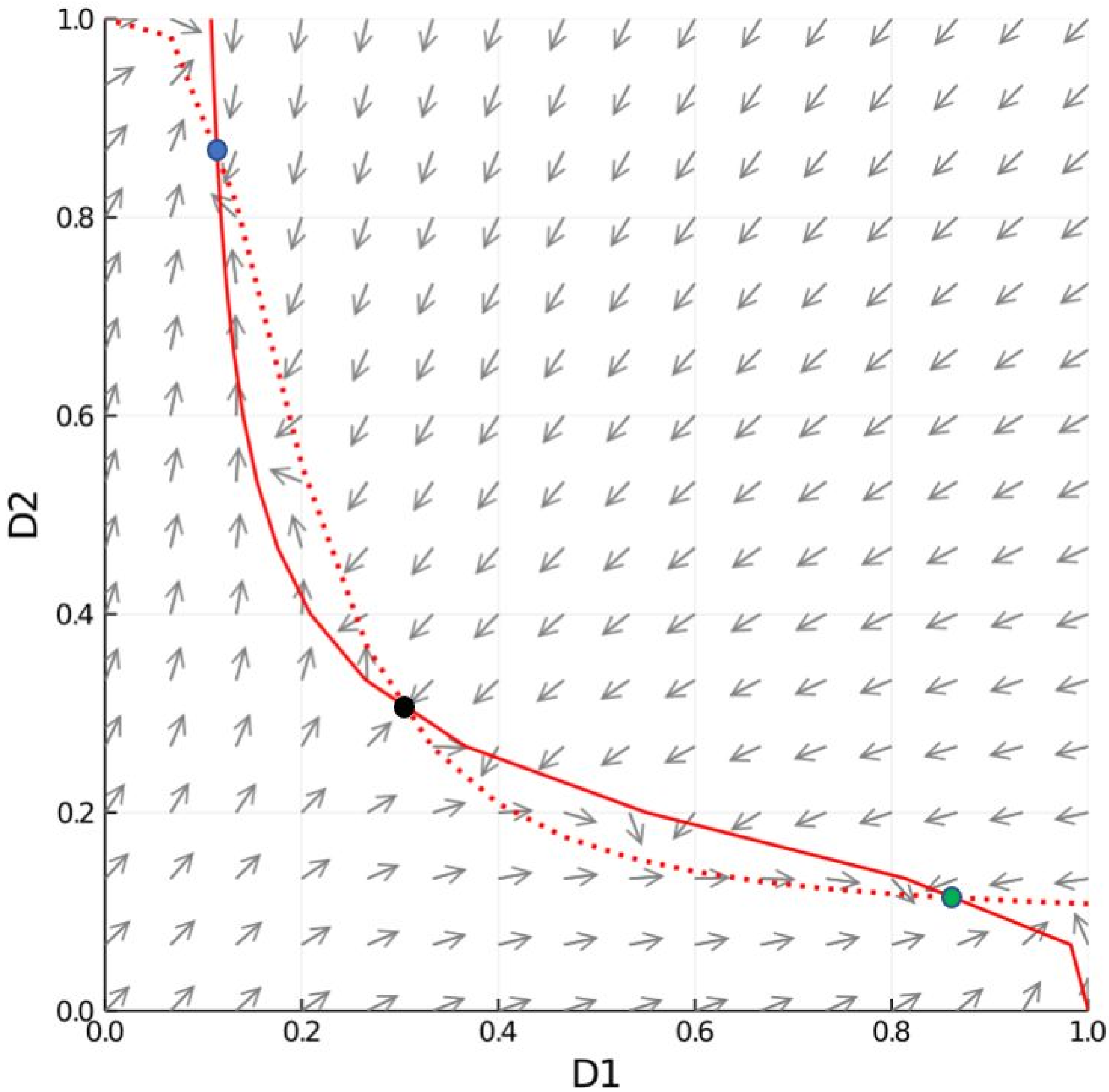
- $f(D) = \dfrac{D^2}{0.1 + D^2}$
- $g(N) = \dfrac{1}{1 + 10N^2}$

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

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

$\rightarrow$ A phase portrait for the dynamics of Delta can be plotted (refer to corresponding images and attached Julia code).

Phase portrait for Delta dynamics between two cells, where v = γ_D/γ_N << 1:



(***Note***:- The nullcline for $(dD1/dt)$ is represented as the bold red line, the nullclline for $(dD2/dt)$ is represented by the dotted red line, and the steady states are indicated by dots - steady-state 1 (blue), steady-state 2 (black) and steady-state 3 (green) (*The dots were added via Paint after the portrait was produced through Julia*))

As seen in the phase portrait, the system has 3 steady states (as there are 3 intersection points between the nullclines). From visual inspection of the phase portrait, we can estimate that steady-state 1 (blue) occurs at **(0.12 , 0.86)**, steady-state two (black) occurs at **(0.30 , 0.30)** (i.e. when D1 and D2 are equal), and steady-state 3 occurs at **(0.86 , 0.12)**. As indicated by the vector arrows, we can also conclude that the fixed points corresponding to steady-states 1 and 3 are both stable, while the fixed point at equal D1 and D2 (middle point) is unstable. In the long-time limit, the system is seen to settle into one of the stable states, where one cell assumes the primary fate (indicated by higher delta activity) and the other cell assumes the secondary fate (lower delta activity). This is highly dependant on which cell has a relatively higher Delta activity. For example, in *Figure 1*, when D1 = 0.95 and D2 = 0.9, we see the system transition to steady-state #3, where cell 1 assumes the primary fate. While in *Figure 2*, when D1 = 0.1 and D2 = 0.15, the system transitions to steady-state #1, where cell 2 has the advantage and assumes the primary fate.

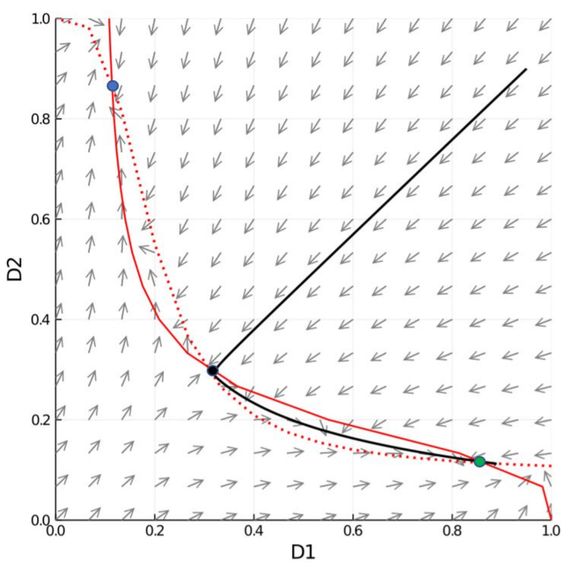


Figure 1: Initial point of (0.95,0.90) leading to S.S. #3

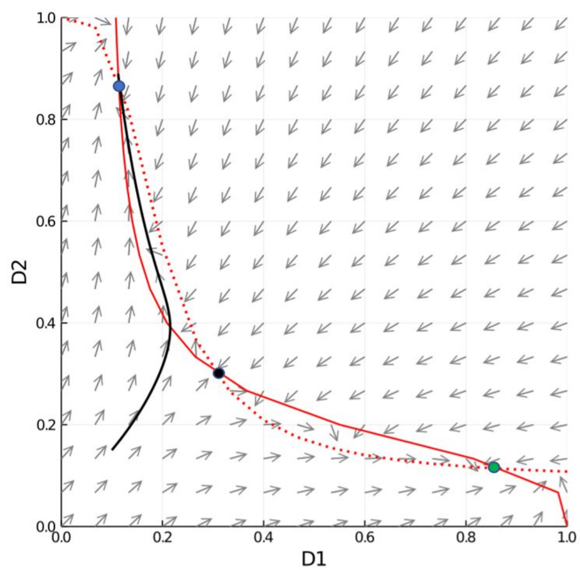


Figure 2: Initial point of (0.10,0.15) leading to S.S. #1

This is also the case for the unstable fixed point, as any small perturbation in one cell, results in the system moving to one of the stable steady states. For example, if **D1 increases to 0.31**(seen in *Figure 3*), while D2 remains at 0.3, we see the system move to steady-state 3, where **cell 1 assumes the primary fate**. Similarly, if **D1 decreases to 0.29** (seen in *Figure 4*), while D2 remains at 0.3, the system moves to steady-state 1, where **cell 2 now assumes the primary fate**.

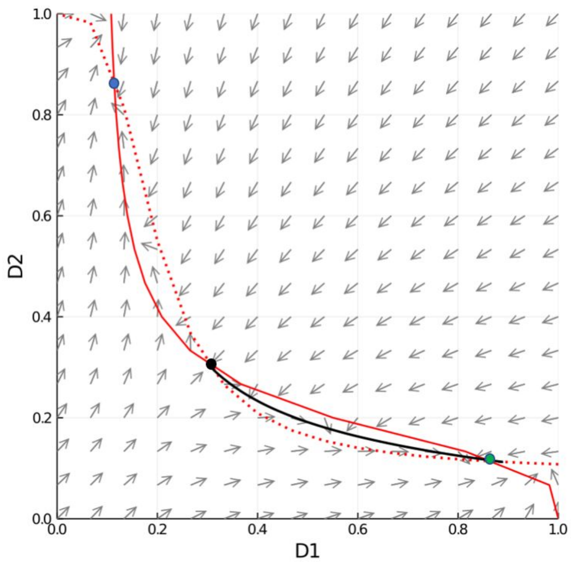


Figure 3: Perturbation to increase D1 from 0.30 to 0.31

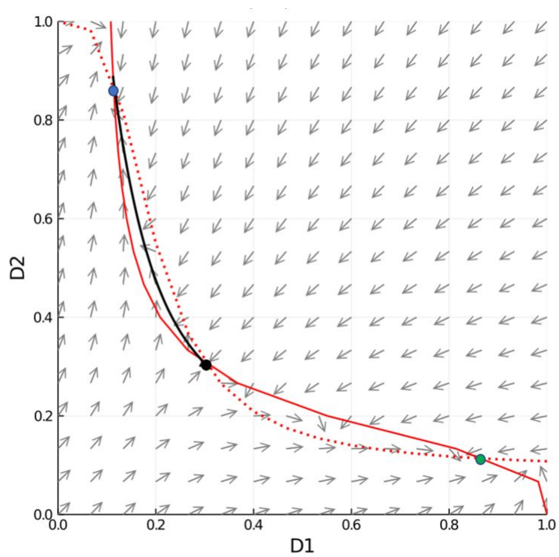


Figure 4: Perturbation to decrease D1 from 0.30 to 0.29

This is also the **<u>same conclusion</u>** that was reached for the case where $v = \gamma_D/\gamma_N >> 1$ - that is, in the long-time limit, the two cells will assume different fates, where one cell assumes the primary fate (higher Notch activity) and the other cell assumes the secondary fate (lower Notch activity). There are still 3 steady states, with the middle fixed point being unstable and the other two fixed points being stable. The only noticeable difference between the phase portrait for **$v = \gamma_D/\gamma_N << 1$ and $v = \gamma_D/\gamma_N >> 1$** is where the fixed points occur in the coordinate plane, and this could be attributed to the fact that each portrait represents either the Notch or Delta activity