# Simulations in Systems Biology

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| **Simulation 1** | **Grade:** |
|---|---|
| Construct a phase plane for mutually inhibiting circuit (X inhibits Y and Y inhibits X). Show that it is bistable. | ***Faculty Comments*** |

Mutually inhibiting circuit, in our example we take X inhibits Y and Y inhibits X simultaneously.

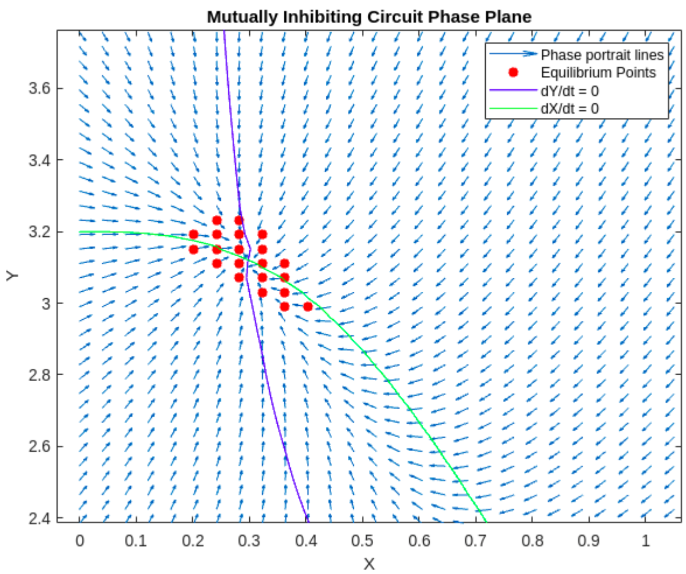
$$A \dashv B \text{ and } B \dashv A$$

Assuming there is some remnants of X and Y in the cell already, giving rate as $\gamma_1$ and $\gamma_2$ initially.
Then we add the repression term $\beta_1 * ((K^n)/(Y^n + K^n))$ and $\beta_2 * ((K^n)/(X^n + K^n))$. As Y represses X, Y's repression term is included in the rate law for X and vice versa.
Finally we add the standard degradation term, $\alpha_1 * X$ and $\alpha_2 * Y$. As the degradation of X and Y only depends on their own concentration the above terms are used to compress the degradation and dissolution effect.

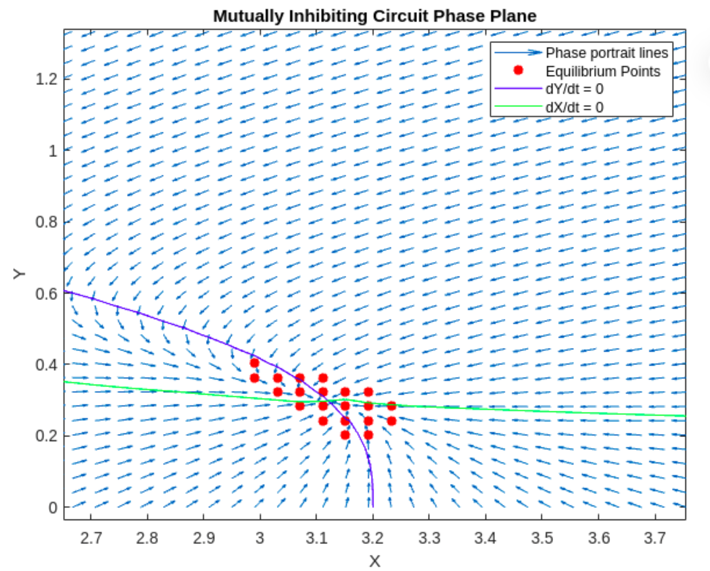
$$dX/dt = \gamma_1 + \beta_1((K^n)/(Y^n + K^n)) + \alpha_1 X$$

$$dY/dt = \gamma_2 + \beta_2((K^n)/(X^n + K^n)) + \alpha_2 Y$$

The nullclines can be obtained by equating, $dX/dt = 0$ and $dY/dt = 0$.
The graph obtained for the interaction:




(a) Stable Equilibria: Y is high, X is low




(b) Stable Equilibria: X is high, Y is low

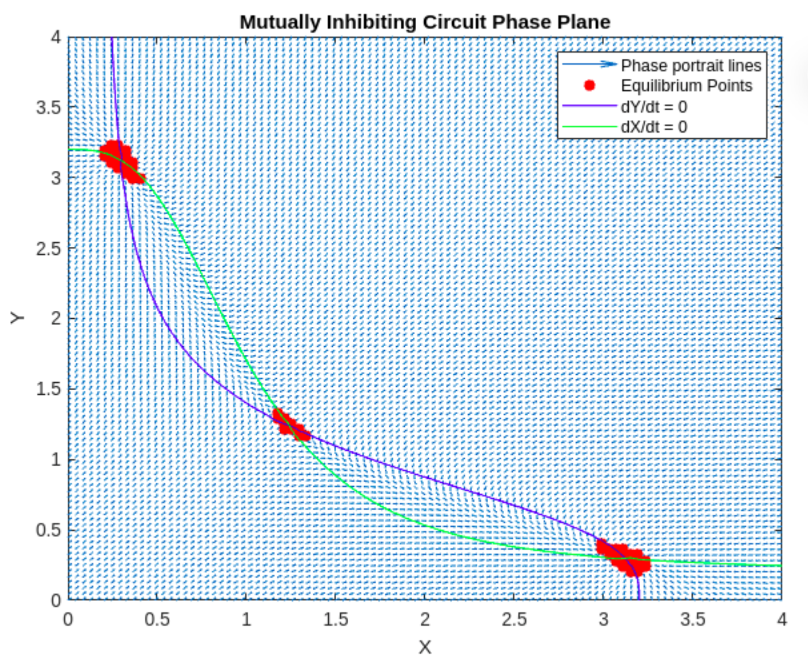



Figure 1: Double feedback loop phase plane for n = 3

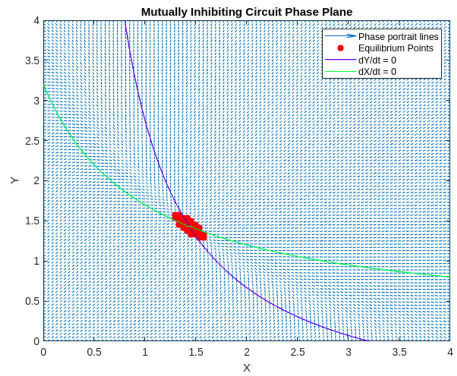
To obtain the above phase portrait, we have taken up a few constants for $\alpha_1 = \alpha_2 = 1$ and $\beta_1 = \beta_2 = 3$ and $\gamma_1 = \gamma_2 = 0.2$ and $n = 3$ and $K = 1$

The red spots show the equilibrium points. For this regulation, there are 2 stable equilibria and 1 unstable equilibria.

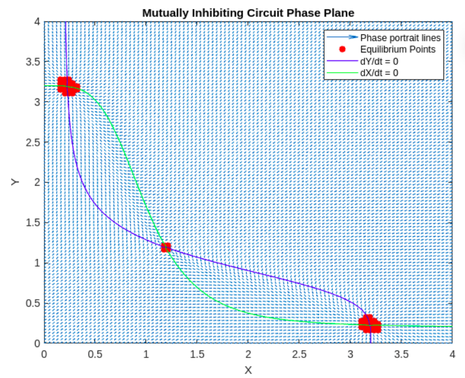
The 2 stable ones, when X is high in conc, Y is low and vice versa. We therefore get the stable points at the top left and bottom right of the graph.

The stable ones are: As shown, the direction of the lines point towards the equilibria showing stability.

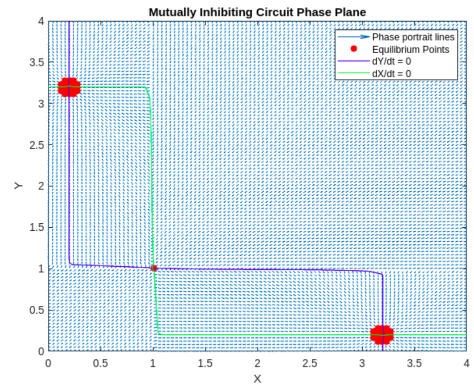
The unstable one, point in the middle, where X and Y are considerably high. It will move either to states




(a) n = 1




(b) n = 4




(c) n = 100

where X is high and Y is low and vice versa. The arrows move away from equilibria showing unstability,

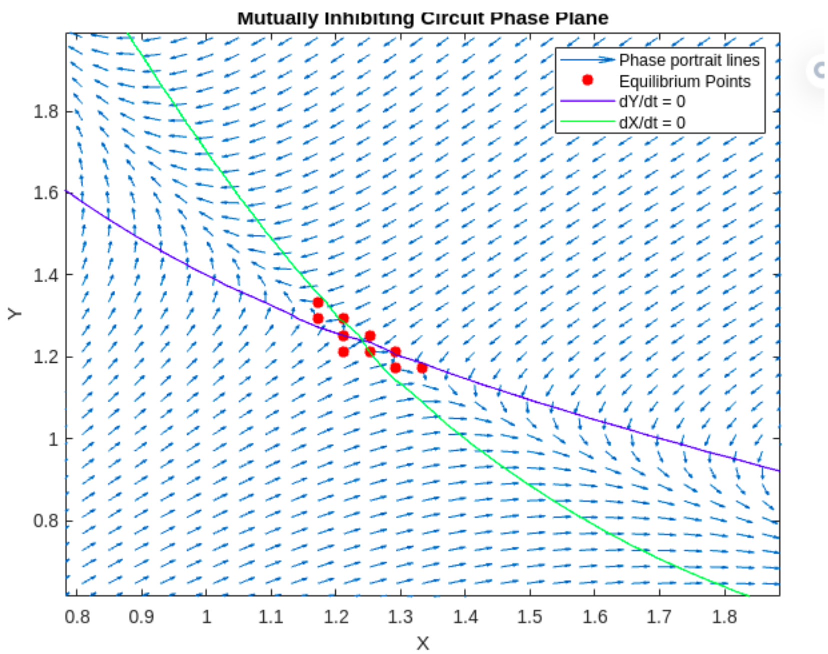



Figure 3: Unstable equilibria: X and Y are comparable

For different values of n: For $n = 1$ there is an intersection with X and Y positive. For $n > 1$, the system may admit multiple, typically three, positive equilibria For large values of n, The nullclines are very sharp, replicating a toggle-switch operation.

| **Simulation 2** | **Grade:** |
|---|---|
| Simulate fold change detection by incoherent feedforward loop. | ***Faculty Comments*** |

Sensory and cellular systems feature exact adaptation and the perception of relative changes. Weber's law characterizes this perception by relating the just-noticeable difference ($\Delta\ x_{min}$) to the background

signal ($x_0$), represented as $\Delta\ x_{min} = kx_0$. Such relative change perception is critical in distinguishing true input signals from noise.
Fold-change detection (FCD) is a key concept, with the I1-FFL circuit as a prime example. The I1-FFL achieves FCD through weak input binding (X) and strong repressor binding (Y).
The system follows these equations:

$$dY/dt = \beta_1 X - \alpha_1 Y$$

$$dZ/dt = \beta_2(X/Y) - \alpha_2 Z$$

When $dY/dt = 0$, $Y_{st} = (\beta_1 X_0)/alpha_1$, while when $dZ/dt = 0$, $Z_{st} = (\beta_2\alpha_1)/(\beta_1\alpha_2)$. This shows that when X signal changes by n-fold, we can expect no change in the final steady state value of Z.
Exact adaptation is observed, where Y is proportional to the background input $X_0$, while Z adapts exactly. This adaptability and sensitivity to relative changes are vital for robust signal discrimination in both biological and psychological contexts.

The simulation is demonstrated in 3 graphs:
The 3 graphs are placed one below each other, as shown, When the X signal changes $\gamma$ fold, the production of Y, or the $Y_{st}$, i.e. the standard state of Y, will also increase $\gamma$ fold. Z, however will only increase to a constant value, as mentioned in the above explanation.

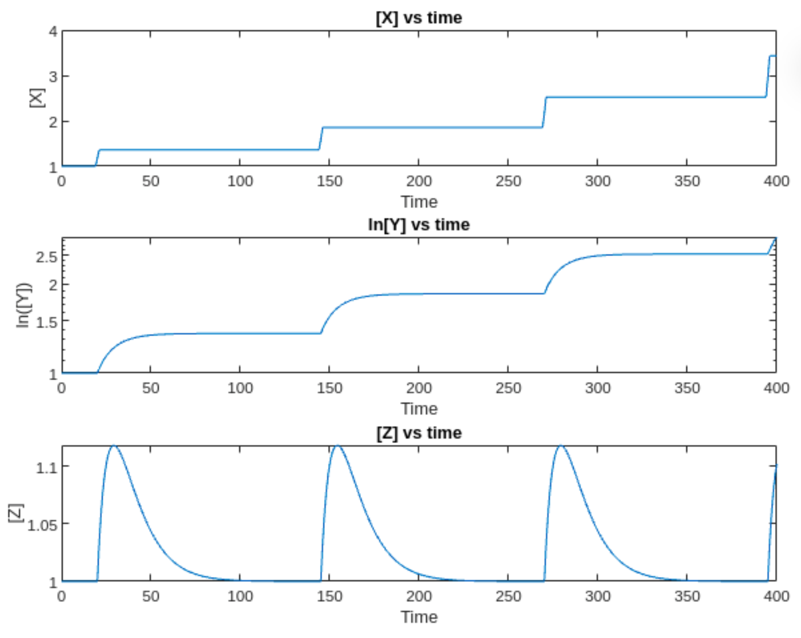



Figure 5: As shown, the Z value is constant and shows exact adaptation

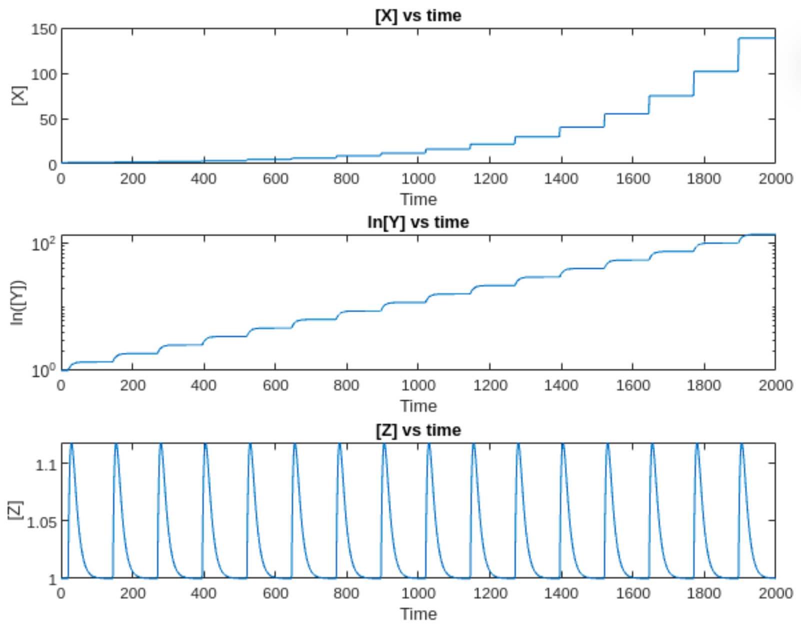



Figure 6: for time interval of upto t = 1500

| **Simulation 3** | **Grade:** |
|---|---|
| Simulate incoherent feedforward loop, with X changing linearly. | ***Faculty Comments*** |

When X changes linearly, Y increases rapidly. But Z shows a decrement slowly with time. As X production does not keep up with the repression of Y. It no longer shows exact adaptation.

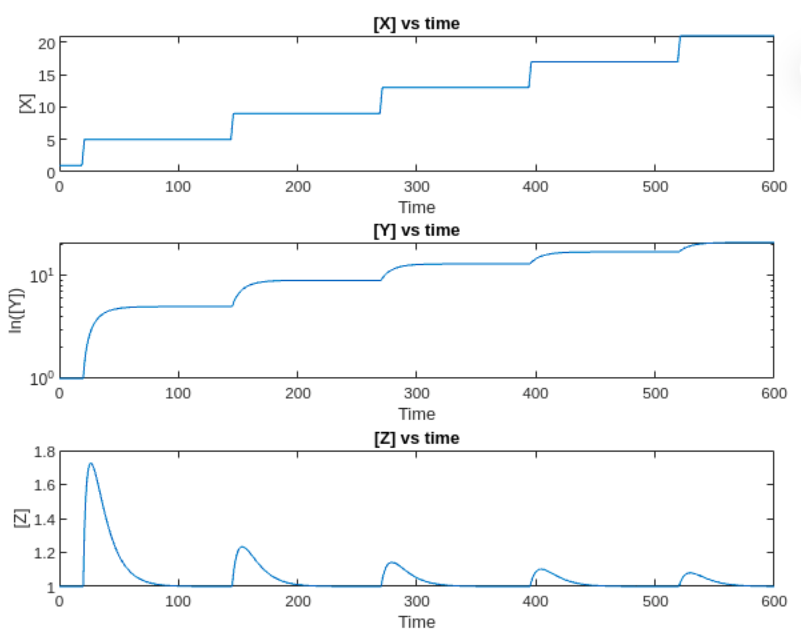



Figure 7: As shown, the Z value is decreasing and does not shows exact adaptation

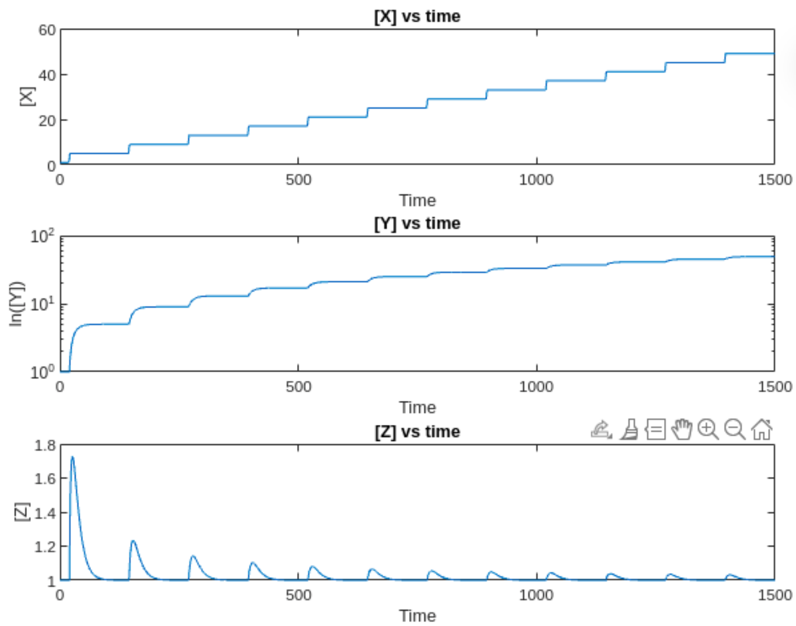



Figure 8: for time interval of upto t = 1500