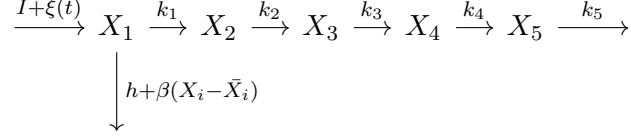


Feedback Inhibition in a Chain

Rachel Thomas

July 3, 2008

We are interested in the question of how feedback inhibition in a chain varies depending on which node is responsible for the inhibition. We'll consider systems of the general form:



Here, $\bar{x}_i = \mathbf{E}[x_i]$, and we are interested in $i = 2, 3, 4, 5$. The reactions $k_i x_i$ in the chain are linear. The concentration of x_1 is mediated by the concentration of a later node x_i in the chain. The $h + \beta(x_i - \bar{x}_i)$ term acts as a drain on x_1 . When the concentration of x_i is above average, more of x_1 is drained away from the chain. When the concentration of x_i dips below average, less of x_i is drained away.

Dave Anderson proved that the variance of the flow decreases down a chain, that is $\text{Var}(k_{i+1}x_{i+1}) < \text{Var}(k_i x_i)$. With all k_i equal, a change in the concentration of x_1 leads to a smaller change in the concentration of x_2 , an even smaller change in x_3 , and so on. This suggests that nodes closer to x_1 , such as x_2 , would be better able to moderate fluctuations in x_1 than a node further away, such as x_5 .

All code and figures were generated in Matlab. In general, we let $\xi(t)$ be the sin function. We considered four separate systems: the chain with x_1 inhibited by x_i , for $i = 2, 3, 4, 5$. We chose $k_i = 1$ for all i , and $h = 0.5$.

We first look at the base model with no inhibition and with sin input (see figure 1). Notice that the fluctuations decrease down the chain, and that there is a time delay for the fluctuations to reach each subsequent node.

We will now add the inhibition term and vary the values of β . In figure 2, the y-axis represents the difference between the maximum and minimum values of the concentration of x_1 , and the x-axis records the value of β . Notice that inhibition by x_2 produces the smallest variation in x_1 , and in general, the closer the inhibiting node is to x_1 , the lower the variation. For inhibition by x_2 , the variation of x_1 decreases as β increases. This holds true for all β . Consider the matrix of rate constants of the system:

$$A_2 = \begin{bmatrix} -1 & -\beta & & & \\ 1 & -1 & & & \\ & & 1 & -1 & \\ & & & 1 & -1 \\ & & & & 1 & -1 \end{bmatrix}$$

So $\dot{x} = Ax + J$, where J is the vector with $I + \xi - h + \beta\bar{x}_2$ in the first place and zeros elsewhere. The eigenvalues of A are -1 (with multiplicity 3) and $-1 \pm \sqrt{-\beta}$. The real parts of the eigenvalues

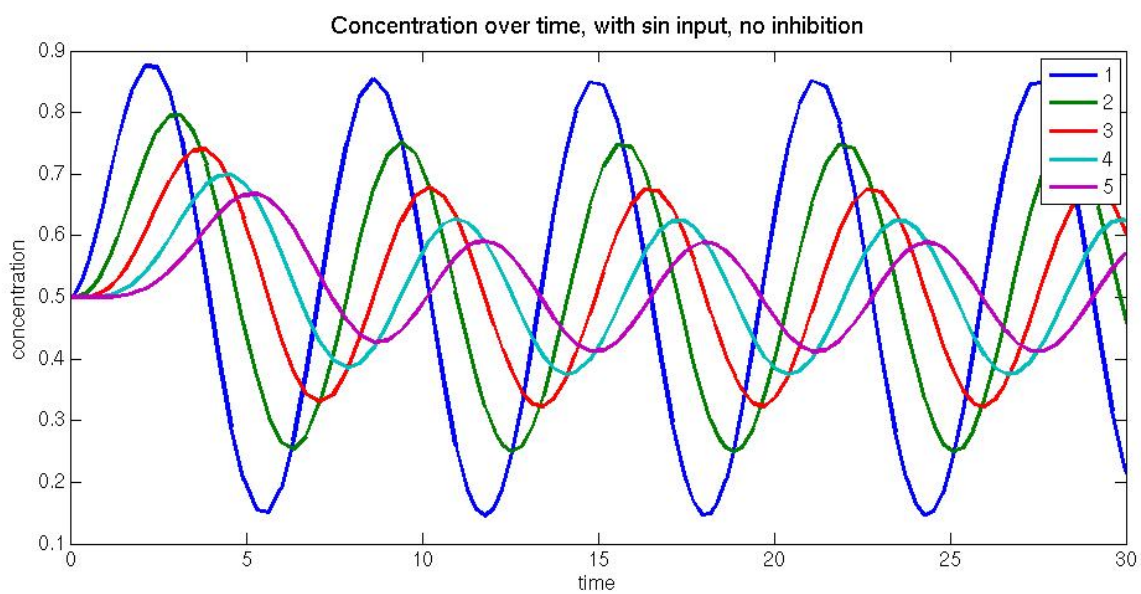


Figure 1: Concentration over Time

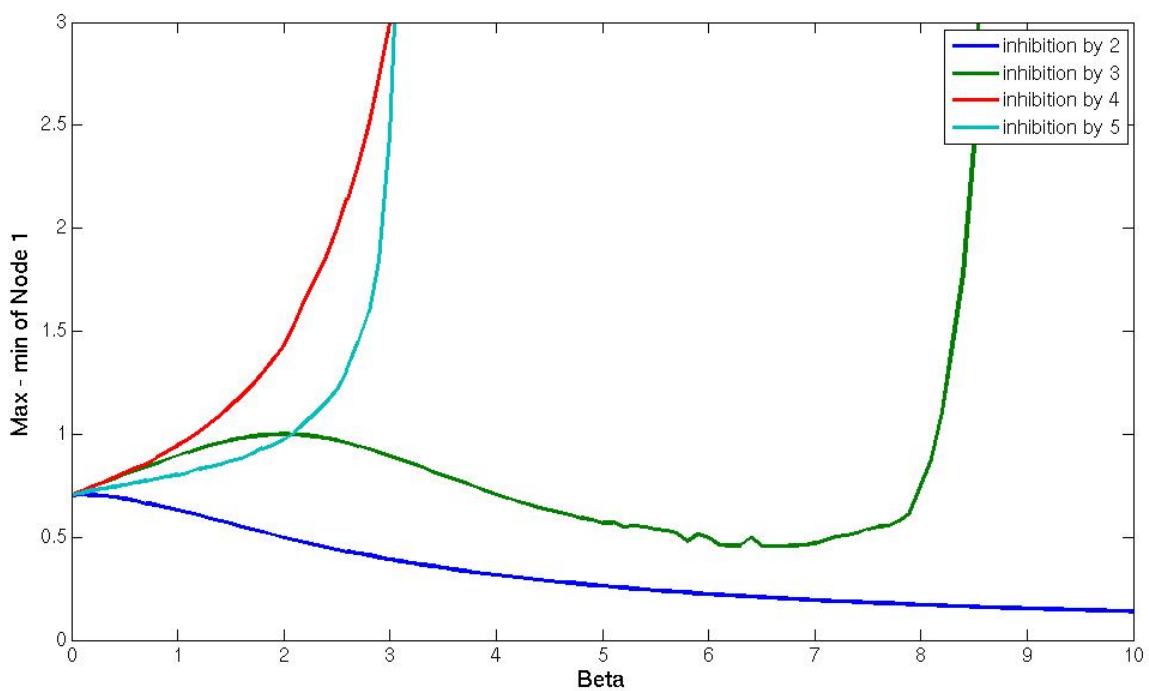


Figure 2: Difference between Max and Min X_1 Values as β Varies

are negative for all $\beta \geq 0$, so the equilibrium is stable.

Referring again to figure 2, the variation (as expressed by max - min) of x_1 with inhibition by x_3 spikes upward near $\beta = 8$. The concentration of x_1 swings through unstable oscillations of larger and larger magnitude as β increases past 8. The system is over-correcting for changes in x_1 . The reason behind this instability is apparent in the eigenvalues. The matrix of rate constants is:

$$A_3 = \begin{bmatrix} -1 & & & -\beta \\ 1 & -1 & & \\ & 1 & -1 & \\ & & 1 & -1 \\ & & & 1 & -1 \end{bmatrix}$$

The eigenvalues are: -1 (with multiplicity 2) and the roots of $(\lambda + 1)^3 + \beta = 0$. By considering the roots of -1 in the complex plane, we see that the critical value occurs when:

$$\begin{aligned} -1 + \frac{1}{2}\beta^{\frac{1}{3}} &= 0 \\ \beta &= 2^3 \end{aligned}$$

Similar analyses can be performed on the other cases. In these cases, it is more useful graphically to look at the concentrations of the node responsible for the inhibition (as opposed to x_1). These are graphed in figure 3.

Two reasons that inhibition of x_1 by x_5 is less effective than inhibition by x_2 are that the magnitude of perturbations decreases down the chain, and that there is a time delay as perturbations travel down the chain. With periodic input, the time delay may result in the feedback from x_5 being completely out of phase with the behavior of x_1 . This can be seen in figure 4.

Here, $\beta = .5$ and the period is 2π . Red is used to graph x_1 and x_2 in the system in which x_2 inhibits x_1 . Similarly, black is used to graph x_1 and x_3 in the system in which x_1 inhibits x_3 , and so on. In all cases, the solid line is used for the concentration of x_1 and the dashed line for the node responsible for the inhibition. Notice that in the system in which x_5 inhibits x_1 , the two nodes are completely out of phase. So when x_5 is high and x_1 is low, the feedback inhibition causes even more of x_1 to be drained away, thus inducing larger and larger oscillations.

This suggests that different input periods may be worse for different systems, depending on which node is responsible for the inhibition. Figures 5 and 6 illustrate how the variation of x_1 , as represented by the difference between the maximum and minimum concentrations, varies as the input period varies. In figure 5, $\beta = 1$, and in figure 6, $\beta = 2$. The x-axis is the period of the sin input, and the y-axis is the concentration of x_1 . The different colors represent which node is responsible for inhibiting x_1 .

In all cases, the variation of x_1 is low for very short periods and for very long periods, which fits with our intuition. When the period is very short, changes in concentration occur so frequently

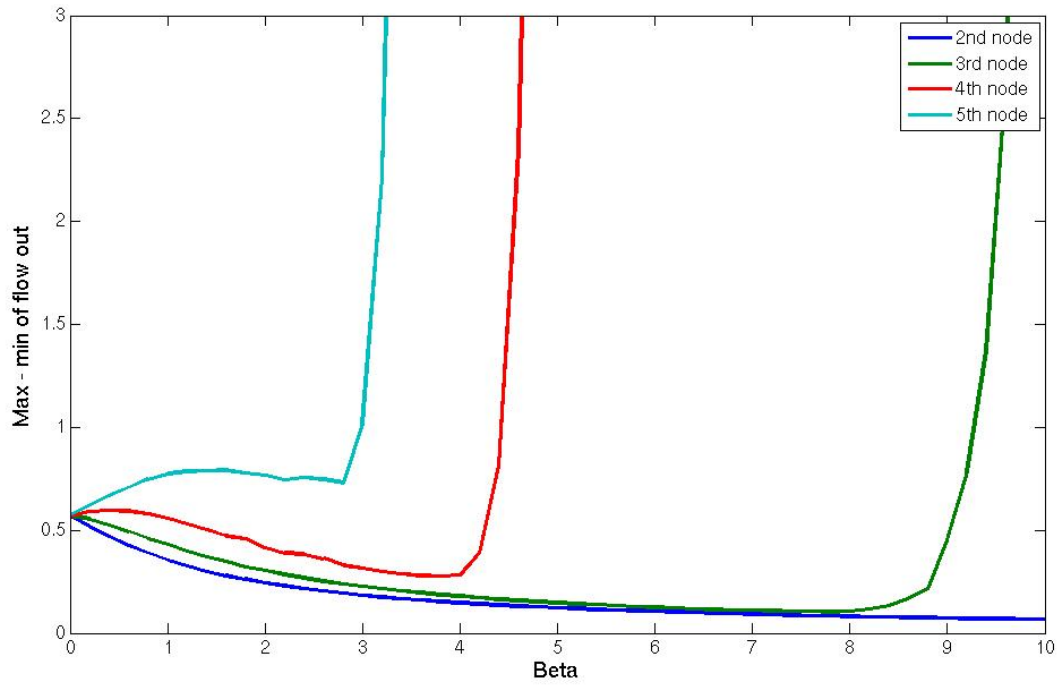


Figure 3: Difference between Max and Min of Node X_i responsible for Inhibition

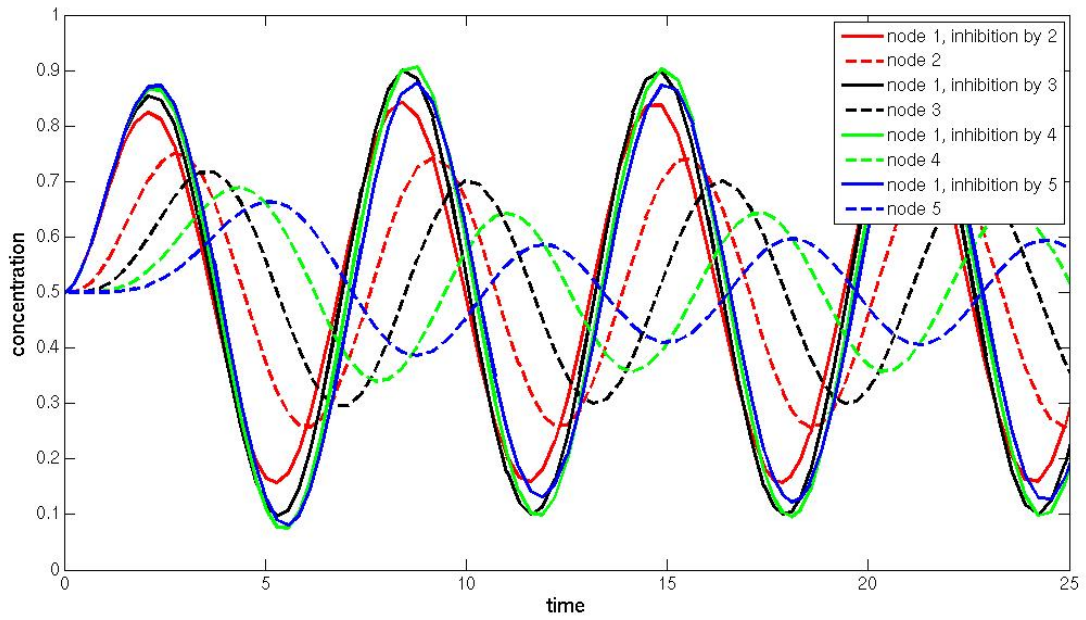


Figure 4: Concentration over Time

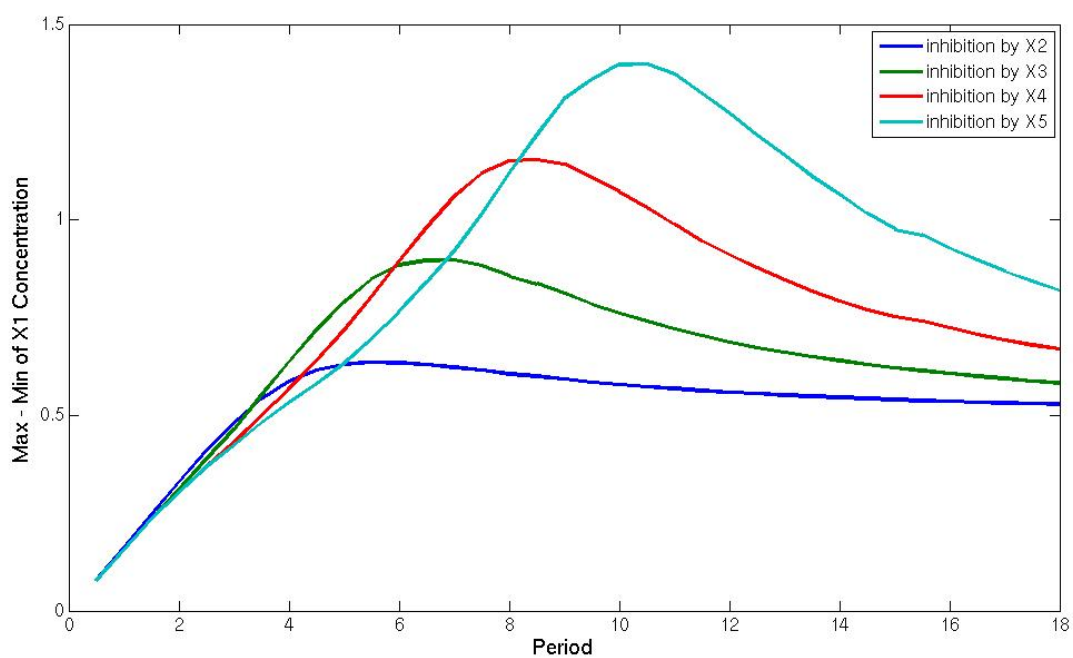


Figure 5: Concentration over Time

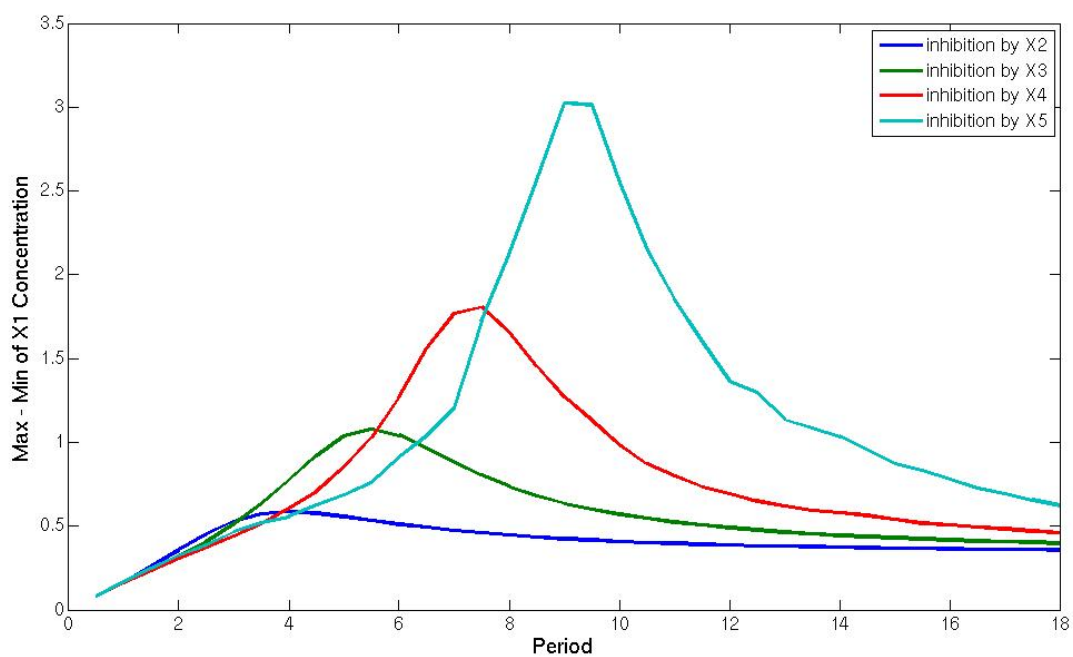


Figure 6: Concentration over Time

that the feedback can't be consistently off for any extended amount of time. When the period is very long, the feedback is not significantly out of phase, even with a long time delay.