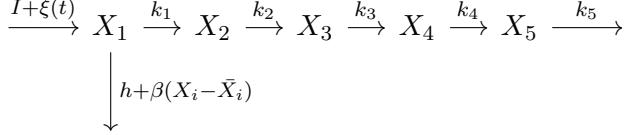


## Feedback Inhibition in a Chain

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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  $x_1$  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  $\beta$ . 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  $\beta$ . 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  $\beta$  increases. This holds true for all  $\beta$ . 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

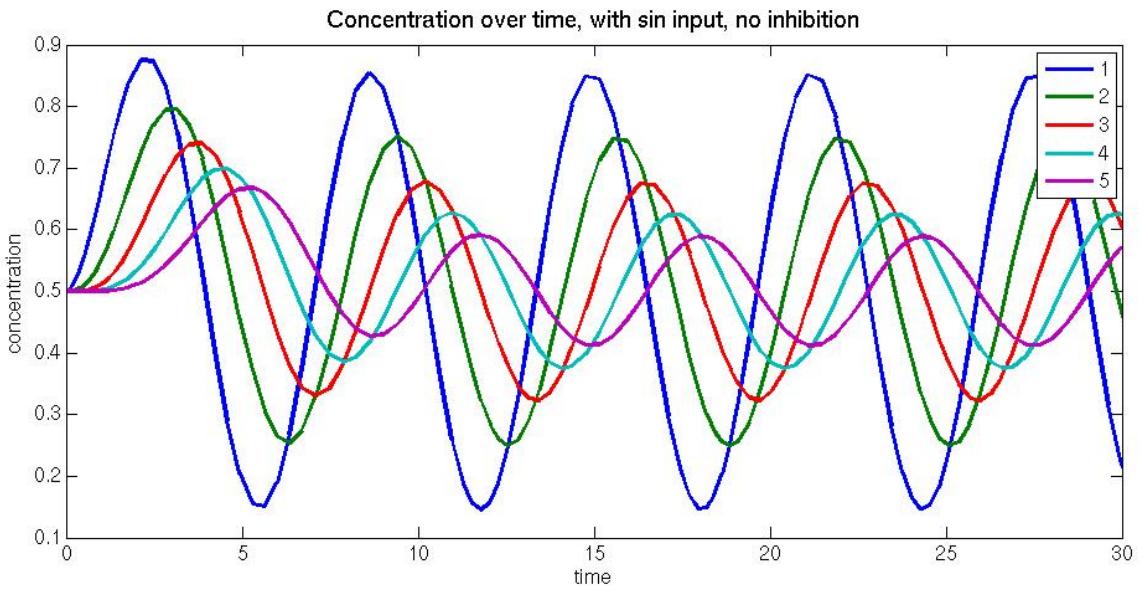


Figure 1: Concentration over Time

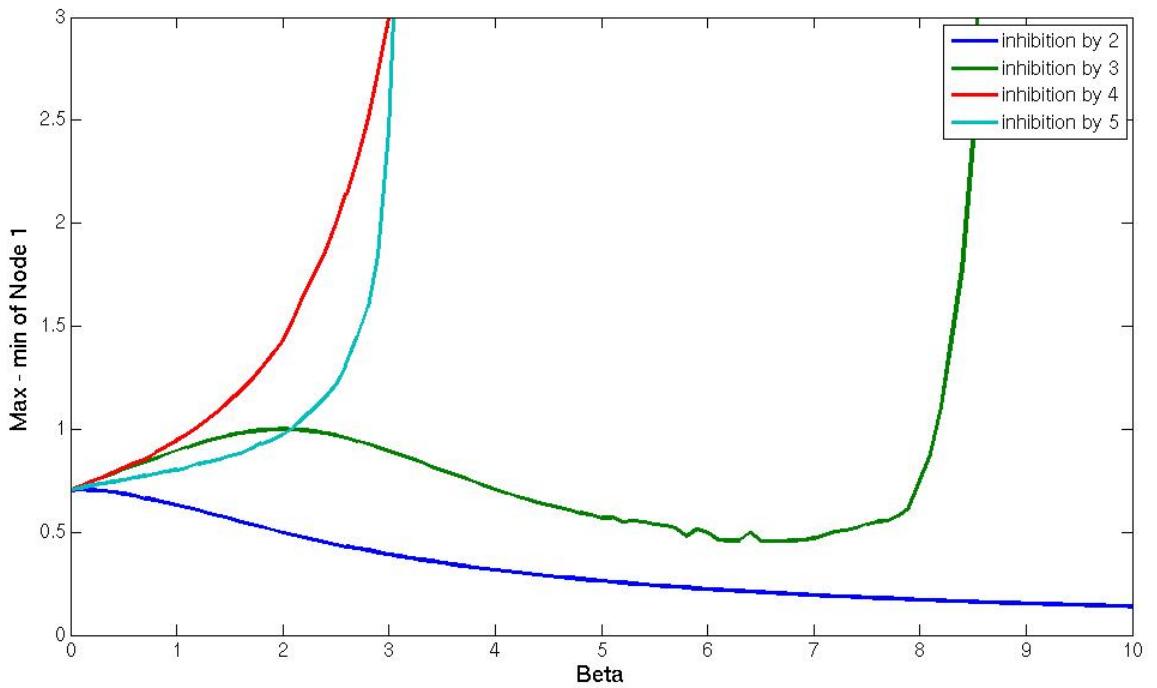


Figure 2: Difference between Max and Min  $X_1$  Values as  $\beta$  Varies

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  $\beta$  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  $2\pi$ . 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

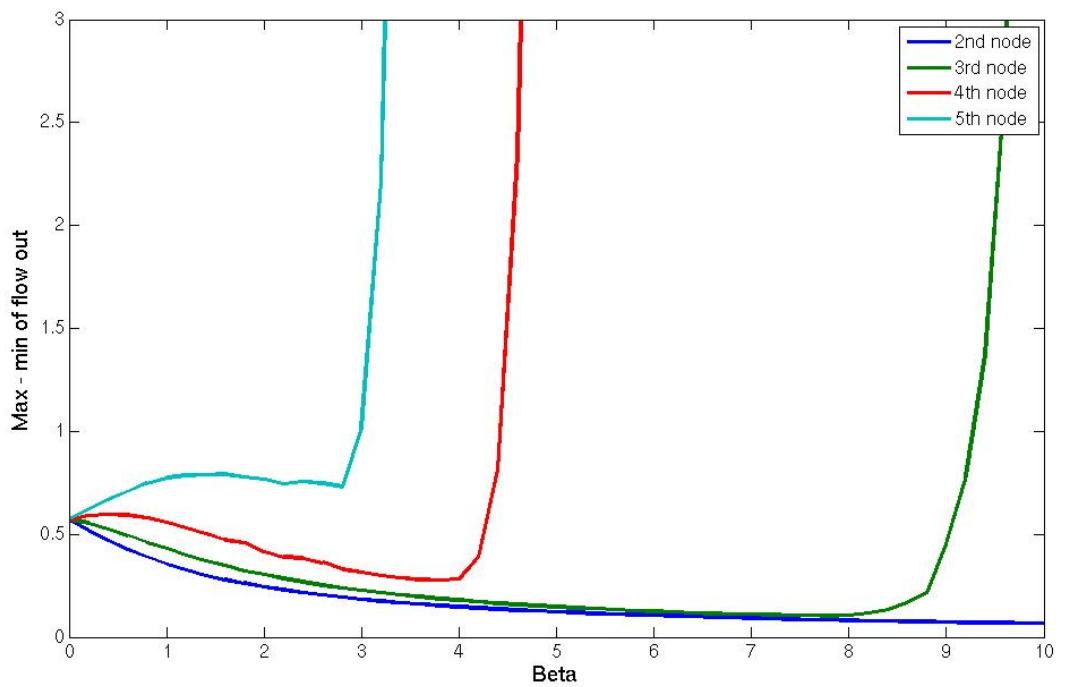


Figure 3: Difference between Max and Min of Node  $X_i$  responsible for Inhibition

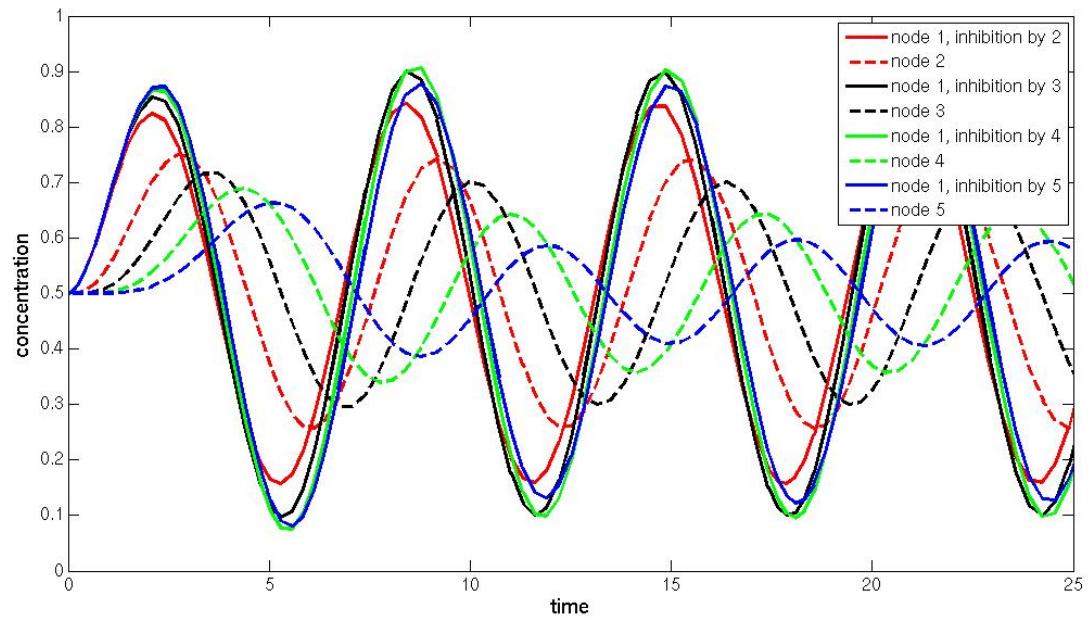


Figure 4: Concentration over Time

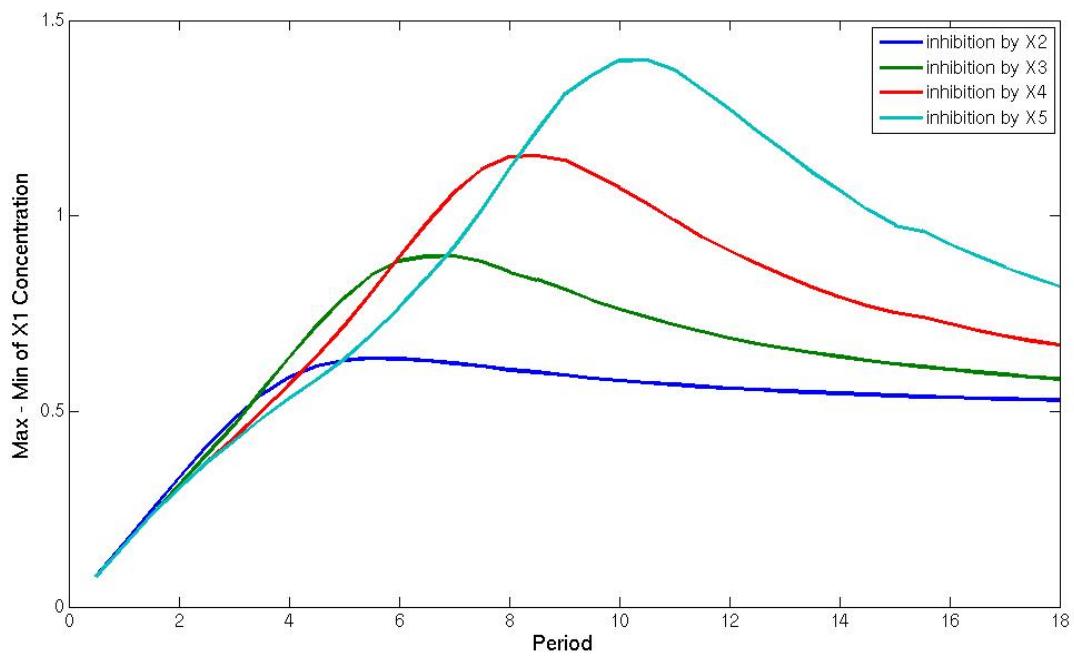


Figure 5: Concentration over Time

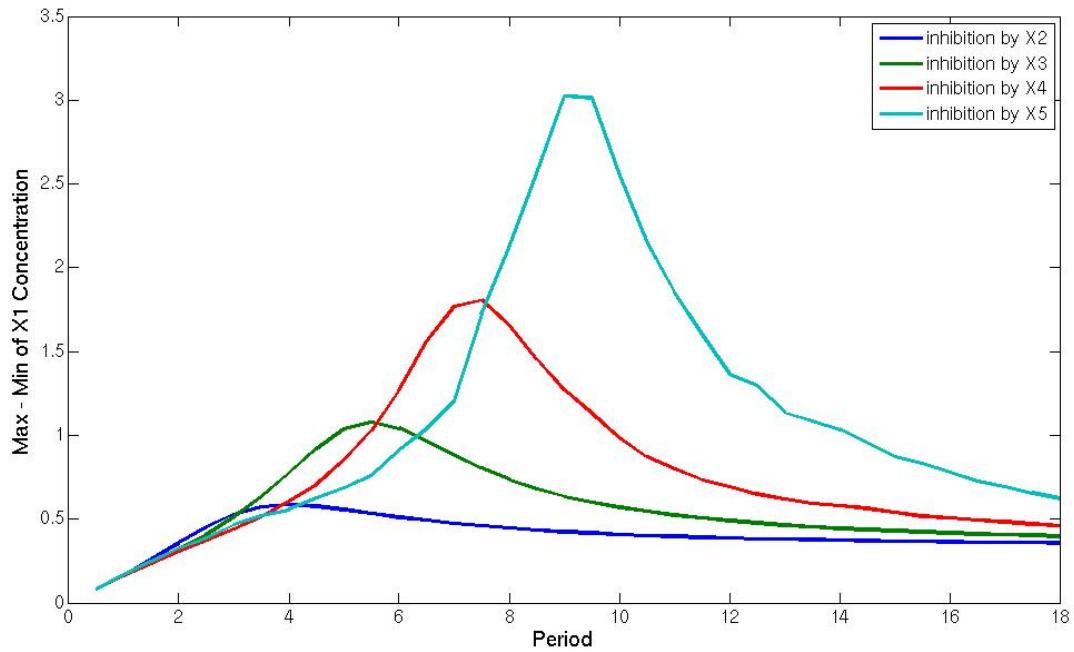


Figure 6: Concentration over Time

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.