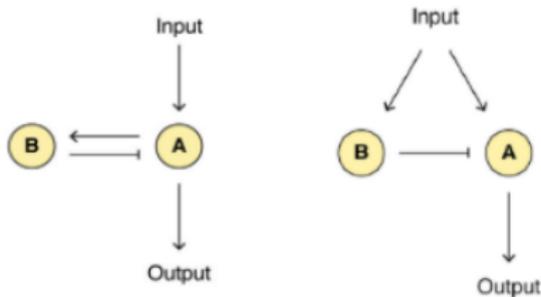


Dynamics of Cellular Signal Adaptation Mechanisms: A Comparative Study

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Abstract: Cells respond to external stimuli and adapt to prolonged exposure to persistent signals to maintain cellular homeostasis. There are a number of regulatory mechanisms to achieve signal adaptation, among them are negative feedback (**NFB**) and incoherent feed-forward (**FFS**) mechanisms. We have deterministically and stochastically studied these two mechanisms in terms of their capacity for producing complex dynamics such as oscillation and multiple steady states as well as how they process intrinsic noise and noisy input signals.

Background Information: Two of the cellular adaptation mechanisms involve negative feedback and incoherent feed-forward interactions which are depicted in the following figure. Left cartoon displays two-protein NFB model and right cartoon displays two-protein FFS model.



In the NFB mechanism, the input signal activates protein A, which activates protein B, then the activated form of protein B inhibits protein A by promoting its inactivation rate. In the FFS mechanism, the input signal interacts positively with both A and B but activated form of protein B inhibits protein A by promoting its inactivation rate. The model equations for NFB mechanism proposed in [1],[2] are

$$\frac{dA}{dt} = k_1 Input \cdot (1 - A) - k_2 A \cdot B \quad \text{and} \quad \frac{dB}{dt} = k_3 A \frac{1 - B}{K_3 + 1 - B} - k_4 \frac{B}{K_4 + B} \quad (1)$$

The model for FFS proposed in [1],[3] have the following equations

$$\frac{dA}{dt} = k_1 Input \cdot (1 - A) - k_2 A \cdot B \quad \text{and} \quad \frac{dB}{dt} = k_3 Input \frac{1 - B}{K_3 + 1 - B} - k_4 B \quad (2)$$

The NFB system is capable of initially responding to a constant input stimulus and later returning to near basal level for the parameters listed in the table.

Model	k_1	k_2	k_3	K_3	k_4	K_4
NFB	2	2	10	0.01	4	0.01
FFS	10	100	0.1	0.001	1	N/A

On the other hand, the FFS mechanism will initially respond to an input stimulus similarly but is later able to return to precisely where it started regardless of the parameter values. These phenomena are called near-perfect and perfect adaptation, respectively.

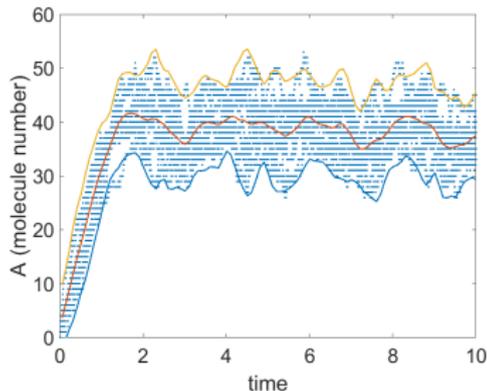
Steady State Analysis: The steady state analysis was performed on both models to determine if multiple steady states is possible. The concentrations of both A and B satisfy $0 \leq A, B \leq 1$ and parameters are assumed to be all positive. Solving both system (1) and (2) when $\frac{dA}{dt} = \frac{dB}{dt} = 0$ yield a pair of functions to be equal in which one function is monotonically increasing while the other is monotonically decreasing in the positive quadrant. From this, we conclude that there is only one intersection point regardless of the selection of parameter values.

Linear stability analysis: The model equations are linearized around a steady state (A^*, B^*) to see if oscillation is possible. The jacobian matrix simplifies to the following sign matrices for the models regardless of the selection of parameters.

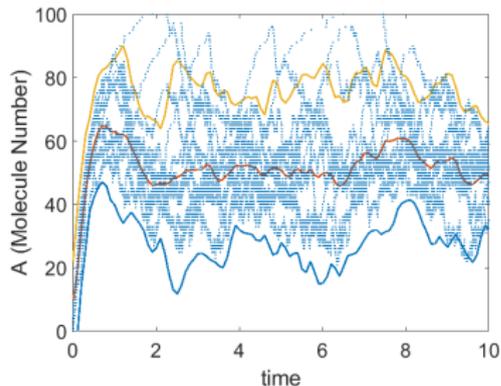
$$J_{NFB} = \begin{pmatrix} - & - \\ + & - \end{pmatrix} \text{ and } J_{FFS} = \begin{pmatrix} - & - \\ 0 & - \end{pmatrix}$$

Notice, the trace of both J_{NFB} and J_{FFS} are negative, eliminating the possibility that the steady state (A^*, B^*) is an unstable node or unstable spiral. Additionally, the determinants of both matrices are positive. This eliminates any possibility of saddle points, leaving the steady state to be either a **stable** node or stable spiral regardless of the parameter values. For some values of the parameters, the NFB system can oscillate around a steady state. On the other hand, for the FFS system, the steady state is always a stable node.

Stochastic simulation: Stochastic simulations on both models were performed using Gillespie algorithm [4] and the coefficient of variation (**CV**) are calculated over time for 100 runs to assess variability in A. Below are graphs depicting protein A molecule counts for NFB (left) and FFS (right) mechanisms. Solid lines are mean $\pm 2\sigma$ of A. CV values at steady state are $CV_{NFB} = 0.14$ and $CV_{FFS} = 0.27$, which indicates that FFS is two times noisier than NFB, on average.



(a) NFB



(b) FFS

Furthermore, CV values are also calculated for noisy input signals at different amplitudes using $L_{\text{noise}} = L_0 (1 + p \times z)$ where $z \sim N(0, 1)$ and p is the parameter measuring the amplitude of the noise in the signal, which are chosen so that the noisy input remained positive. For $p = 0.1$ and $p = 0.2$, which means 20 – 40 percent variation around L_0 , we have seen no significant difference in variability in the output A for both mechanisms.

References



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