

A discrete, multi-level framework to model gene regulatory networks

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Modeling framework

As before [1], a regulatory network with N nodes is described with an $N \times N$ connection matrix J such that $J_{ij} = +1$ if the edge $i \leftarrow j$ is activating and $J_{ij} = -1$ if the edge is inhibitory; $J_{ij} = 0$ if there is no edge from j to i . In contrast to each node taking one of two values ($s_i = \pm 1$) in previous work, each node i in a gene regulatory network can now take one of four possible values: $s_i \in \{-1, -\frac{1}{2}, +\frac{1}{2}, +1\}$. The network dynamics are then modeled in discrete time as follows:

$$s_i(t+1) = \begin{cases} -1 & \frac{1}{\sum_j |J_{ij}|} \sum_j J_{ij} s_j(t) < -0.5 \\ -\frac{1}{2} & -0.5 \leq \frac{1}{\sum_j |J_{ij}|} \sum_j J_{ij} s_j(t) < 0.0 \\ +\frac{1}{2} & \text{if } 0.0 < \frac{1}{\sum_j |J_{ij}|} \sum_j J_{ij} s_j(t) \leq 0.5 \\ +1 & \frac{1}{\sum_j |J_{ij}|} \sum_j J_{ij} s_j(t) > 0.5 \\ s_i(t) & \text{otherwise} \end{cases} \quad (1)$$

Note that the total input to node i at time t (given by $\sum_j J_{ij} s_j(t)$) is normalized by the total number of edges with their end points at node i (given by the sum $\sum_j |J_{ij}|$ in Eq. 1).

Definition of frustration

In the previous Boolean modeling framework, for a given network state we defined each network edge as either (fully) frustrated or not frustrated [1]. Now, we consider a third possibility: “half-frustrated” or “partially” frustrated edges. For a given network connection matrix J and a network state $\{s_i\}$, the edge $i \leftarrow j$ is defined as fully frustrated if $J_{ij} s_i s_j < 0$ and $|s_i| = |s_j|$. The edge is defined as “half-frustrated” if $J_{ij} s_i s_j < 0$ and $|s_i| \neq |s_j|$. If $J_{ij} s_i s_j > 0$, the edge is said to be not frustrated. The total frustration for a given state in the case of a network with E edges is then given by

$$\text{frustration}(\{s_i\}) = \frac{1}{E} (\# \text{fully frustrated edges} + \frac{1}{2} \# \text{half-frustrated edges}) \quad (2)$$

Previous work

Previous studies that have used multi-level discrete dynamic frameworks to model biological systems include [2], [3], and [4].

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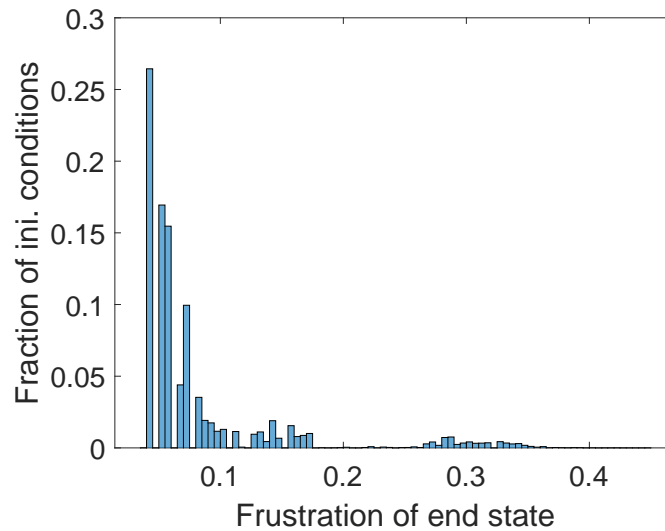


FIG. 1. We simulated the dynamics of the 26-node EMT network using the modeling framework described above starting from 50000 random initial conditions. In each case, the dynamics were simulated for 500 discrete time steps. The distribution of the frustration of the end states obtained is shown here. This distribution indicates that steady states with low frustration are far more likely to be encountered as compared to steady states with high frustration. Thus, low frustration is likely to correlate with large basins of attraction in the newly proposed modeling framework as well.

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