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Attraction basins in a *lac* operon model under different update schedules

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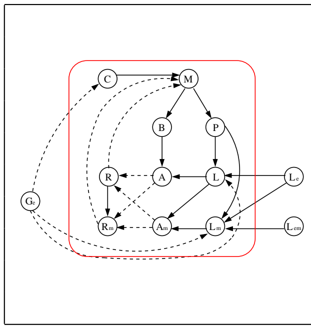
Abstract

In (Veliz-Cuba and Stigler, 2011) the authors proposed a Boolean model for the *lac* operon in *Escherichia coli* that is capable of predicting the operon being ON, OFF and bistable when the update schedule is the parallel one. We complement this work by using theoretical and algorithmic tools that allow us to know which are the configurations that converge to a fixed point or limit cycle (set namely *attractor basin*) for each deterministic update schedule. We show that, when bistability appears, about 70% of the dynamics have only the steady states ON and OFF. This latest having an attractor basin of an average size about 8 times bigger than that of ON. In the other 30%, the proportion is balanced between ON/OFF basins but the basins of limit cycles sum up, in average, about 5 times more than that of ON and OFF respectively. The techniques presented in this work are general and can be used to analyze other Boolean models.



$F_M = C \wedge \neg R \wedge \neg R_m$

$F_P = M$

$F_B = M$

$F_C = \neg G_e$

$F_R = \neg A \wedge \neg A_m$

$F_{R_m} = (\neg A \wedge \neg A_m) \vee R$

$F_A = L \wedge B$

$F_{A_m} = L \vee L_m$

$F_L = P \wedge L_e \wedge \neg G_e$

$F_{L_m} = ((L_{em} \wedge P) \vee L_e) \wedge \neg G_e$

Figure 1: The *lac* operon network (left) and its local functions (right) proposed in (Veliz-Cuba and Stigler, 2011). Dashed/solid edges represent inhibitions/activations.

Introduction

The *lac* operon in *Escherichia coli* is one of the earliest examples of an inducible system of genes being under both positive and negative control. This system is responsible for the metabolism of lactose in the absence of glucose and is known to exhibit bistability, in the sense that the operon is either induced (ON) or uninduced (OFF). In (Veliz-Cuba and Stigler, 2011) the authors proposed a Boolean model for it, showed in Fig. 1, where G_e and (L_e, L_{em}) are parameters (representing different concentration levels of extracellular glucose and lactose respectively) so that when certain values are assigned (L_e and L_{em} assigned stochastically) and considering that the order in which the nodes are updated (concept namely *update schedule*) is always the parallel one, the model is capable to predict the operon being ON, OFF and bistable depending of the fixed points (steady states) obtained, results that matches very well with the experimental data.

However, this model does not answer other dynamical question that can provide a more refined qualitative description of the *lac* operon; given a dynamic obtained with a specific update schedule, how are its attraction basins?

In this work, we address the previous question focussing on all the deterministic update schedules (an exponential number). The idea is to make an exhaustive analysis of all these dynamics but not by a brute force process (i.e., list all them, each composed of 2^{10} configurations and then calculate each attraction basin) but through the algorithm of (Aracena et al., 2013) specially adapted for the *lac* operon network that efficiently enumerates the set of all update schedules s with the property of being representatives of an equivalence class whose elements (other update schedules s') have exactly the same dynamics that s. Thus, the number of dynamics to analyze decreases dramatically. These tools have shown to be effective in other models such as the Yeast and Mammalian cell cycle networks studied in (Goles et al., 2013) and (Ruz et al., 2014).

The *l*ac operon model background

In the model of Fig. 1, a configuration in its dynamics is represented by the vector $(M, P, B, C, R, R_m, A, A_m, L, L_m) \in \{0,1\}^{10}$. The G_e parameter can be in two states; low ($G_e = 0$) or high ($G_e = 1$) while that L_e and L_{em} can be in three states; low, medium or high which is represented by $(L_e, L_{em}) = (0,0)$, $(0,1)$ and $(1,1)$ respectively. The operon is OFF when the value of the triple (M, P, B) is $(0,0,0)$ and ON when $(M, P, B) = (1,1,1)$. Under the

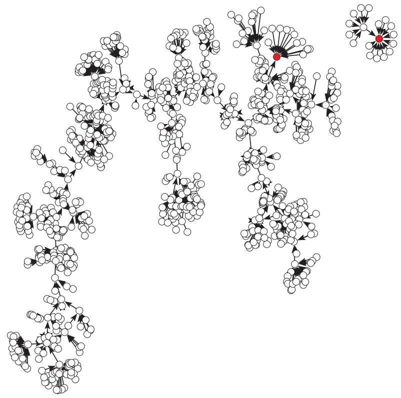


Figure 2: State transition graph of the *lac* operon model under the parallel update (bistability appears). The size of the attraction basins are 1006 and 18 for the steady states OFF and ON (in red), respectively.

parallel update schedule there are 4 possible cases:

Case 1: $\mathbf{G_e = 1}$. All configurations eventually reach the unique steady state $(0,0,0,0,1,1,0,0,0,0)$ (operon being OFF).

Case 2: $\mathbf{G_e = L_e = L_{em} = 0}$. All configurations eventually reach the unique steady state $(0,0,0,1,1,1,0,0,0,0)$ (operon being OFF).

Case 3: $\mathbf{G_e = L_e = 0 \wedge L_{em} = 1}$. All configurations eventually reach one of the two steady states; $(0,0,0,1,1,1,0,0,0,0)$ or $(1,1,1,1,0,0,0,1,0,1)$ (operon being OFF and ON, respectively). That is, the model is bistable (see Fig. 2).

Case 4: $\mathbf{G_e = 0 \wedge L_e = L_{em} = 1}$. All configurations eventually reach the unique steady state $(1,1,1,1,0,0,1,1,1,1)$ (operon being ON).

Analysis and discussion

For cases 1, 2 and 4 we proved the following Theorem:

Theorem 1. *Cases 1, 2 and 4 are valid for every deterministic update schedule.*

In case 3 we adapt the algorithm described in the introduction and the results are summarized in Table 1.

Theorem 1 guarantees that attraction basins of cases 1, 2 and 4 are the full state space (1024 configurations) whatever the update schedule. In Case 3 (bistability) about 70% of the dynamics have only the steady states ON and OFF. This latest having an attractor basin of average size about 8 times bigger than that of ON. In the other 30%, the proportion is balanced between ON/OFF basins but basins of limit cycles sum up, in average, about 5 times more than that of ON and OFF respectively. Fig. 3 is an example of a dynamic that has 3 limit cycles of length 4 plus one of length 2 (note that the update schedule is slightly different from the parallel one).

Case 3: $G_e = L_e = 0 \wedge L_{em} = 1$ (Bistability)			
Attractors	S	FP	LC
OFF	684.7	908.9	153.7
ON	124.4	115.1	146.5
Limit cycles	214.9	0	723.8

Table 1: Basin average size for case 3 calculated over S (the full set of deterministic updates schedules), $FP \subseteq S$ (those whose dynamic have only fixed points) and $LC \subseteq S$ (those whose dynamic have limit cycles), where $|S| = 102,247,563$ (100%), $|FP| = 71,891,966$ (70.3%) and $|LC| = 30,355,597$ (29.7%).

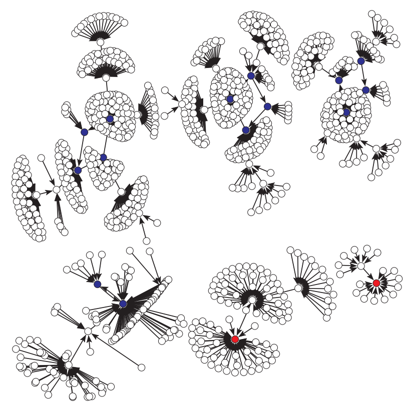


Figure 3: State transition graph of the *lac* operon model when the update schedule considered is such that $(M, P, B, C, R, A, L, L_m)$ are updated first simultaneously and then (R_m, A_m) simultaneously. The size of the attraction basins are 98 and 18 for the steady states OFF and ON (in red) respectively, and 908 for the limit cycles (in blue).

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