



A circuit-preserving mapping from multilevel to Boolean dynamics

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ARTICLE INFO

Article history:

Received 1 June 2017

Accepted 14 December 2017

Available online 24 December 2017

MSC:

Primary 68R05

Secondary 92D99

Keywords:

Discrete dynamical system

Automata network

Boolean network

Regulatory network

Genetic regulation

Thomas' conjecture

ABSTRACT

Many discrete models of biological networks rely exclusively on Boolean variables and many tools and theorems are available for analysis of strictly Boolean models. However, multilevel variables are often required to account for threshold effects, in which knowledge of the Boolean case does not generalise straightforwardly. This motivated the development of conversion methods for multilevel to Boolean models. In particular, Van Ham's method has been shown to yield a one-to-one, neighbour and regulation preserving dynamics, making it the de facto standard approach to the problem. However, Van Ham's method has several drawbacks: most notably, it introduces vast regions of "non-admissible" states that have no counterpart in the multilevel, original model. This raises special difficulties for the analysis of interaction between variables and circuit functionality, which is believed to be central to the understanding of dynamic properties of logical models. Here, we propose a new multilevel to Boolean conversion method, with software implementation. Contrary to Van Ham's, our method doesn't yield a one-to-one transposition of multilevel trajectories; however, it maps each and every Boolean state to a specific multilevel state, thus getting rid of the non-admissible regions and, at the expense of (apparently) more complicated, "parallel" trajectories. One of the prominent features of our method is that it preserves dynamics and interaction of variables in a certain manner. As a demonstration of the usability of our method, we apply it to construct a new Boolean counter-example to the well-known conjecture that a local negative circuit is necessary to generate sustained oscillations. This result illustrates the general relevance of our method for the study of multilevel logical models.

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1. Background

Boolean models have proved very useful in the analysis of various networks in biology. However, it is often convenient to introduce multilevel variables to account for multiple threshold effects. We are often faced with choices between using Boolean variables or multilevel variables. This can be crucial since theoretical results are sometimes proved only for Boolean or multilevel networks. A particular example of this situation is in René Thomas' conjecture that a local negative circuit is necessary to produce sustained (asynchronous) oscillations. This paper stems from the simple idea that a Boolean counter-example to that conjecture could be found by transposing a multilevel counter-example found earlier by Richard and Comet. However, we believe the method developed in this paper, together with a handy script which implements it, is widely applicable to other theoretical studies which involves

discrete networks. We also find the notion of asymptotic evolution function defined in this paper sheds light on the understanding of relation between the state transition graph and the interaction graph.

1.1. Introduction

Introduced in the 1960s–70s to model *biological regulatory networks*, the logical (discrete) formalism has gained increasing popularity, with recent applications as diverse as *drosophila* development, cell cycle control, or immunology (see [Abou-Jaoudé et al. \(2016\)](#) for a survey). While many of these models rely exclusively on Boolean variables, it is often useful to introduce multilevel variables to account for more refined behaviour. However, many tools and theoretical results are restricted to the Boolean case (see e.g. [Stoll et al. \(2012\)](#), [MacNamara et al. \(2012\)](#) and [Helikar et al. \(2012\)](#)) This situation motivated the development of methods to convert multilevel models to Boolean ones ([Remy et al., 2006](#); [Van Ham, 1979](#)). A simple idea for such a conversion was introduced by [Van Ham \(1979\)](#), and this method has been shown to be essentially the only one that could provide a "one-to-one,

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neighbour and regulation preserving map” (Didier et al., 2011). One problem with the conversion is that the resulting Boolean model is defined only on a sub-region of the whole Boolean state space, called the *admissible region*, and how to extend the model outside that region is not trivial. This leads to potential problems with analytical tools designed to deal with the whole state space, as a property that is true in the restricted domain may be false on the whole state space, and vice versa. The primary goal of the present paper is to address this issue by introducing an extension of Van Ham’s method. More precisely, we introduce a new method for multilevel to Boolean model conversion which extends the domain of Van Ham’s model to the whole state space while preserving edge functionality and, therefore, local circuits. Our mapping yields a state transition graph with “parallel” trajectories that contains the one obtained by Van Ham’s mapping as a sub-graph in such a way that attractors of the dynamics are preserved.

We apply our method to investigate a particular class of theoretical results that connect the asynchronous behaviour of a model to the presence of *regulatory circuits* in the interaction graph. In the early 1980s, R. Thomas conjectured that the presence of a positive circuit (i.e. a circuit where each component directly or indirectly has a positive effect upon itself) in the interaction graph is a necessary condition for multi-stability, and a negative circuit (where each component has a negative effect upon itself) is necessary for sustained oscillations (Thomas, 1981). One particular formulation of the conjecture focuses on local or “type-1” circuits (Comet et al., 2013), i.e. circuits whose arcs are all functional in the same single point of the system’s state transition graph – as opposed to global circuits whose arcs may be functional anywhere. While the conjecture holds for positive circuits both at the global and local levels, and for multilevel as well as Boolean models (Remy et al., 2008; Richard and Comet, 2007), in the negative case the conjecture could only be proved true at the global level (Remy et al., 2008). At the local level, a counter-example has first been published for multilevel models (Richard, 2010), while the Boolean case remained open (Comet et al., 2013) until a Boolean counter-example was eventually discovered (Ruet, 2017), showing that contrary to expectations, a local negative circuit was not necessary to generate sustained oscillations. Interestingly, the approaches taken by P. Ruet and A. Richard are rather different, and their counter-examples have little in common. Applying our method to the Richard-Comet multilevel counter-example, we obtain a new Boolean counter-example to the conjecture that a local negative circuit is necessary to produce sustained oscillations.

1.2. Definitions

1.2.1. Evolution function and state transition graph

We work within the generalised logical framework introduced by René Thomas and collaborators (Thomas and D’Ari, 1990); see Abou-Jaoudé et al. (2016) for a recent review. Here, we introduce the notation we use throughout this paper. Fix positive integers n and $m_i (1 \leq i \leq n)$. Consider a system consisting of mutually interacting n genes, indexed by the set $I = \{1, 2, \dots, n\}$. Each gene a_i takes expression levels in the integer interval $\{0, 1, \dots, m_i\}$. The state of the system evolves depending on the current state. This leads to a discrete dynamical system represented by a *evolution function over M*

$$f = (f_1, f_2, \dots, f_n) : M \rightarrow M,$$

where $M = \{(x_1, \dots, x_n) \mid x_i \in \{0, 1, \dots, m_i\}\}$. As a special case when $m_i = 1$ for all $i \in I$, we denote $M = \mathbb{B}^n$ with $\mathbb{B} = \{0, 1\}$ and call the system *Boolean*. A basic question asks what we can tell about the asymptotic global behaviour of the dynamics, which is encoded in the *state transition graph*, from local data of f , which are encoded in the *partial derivatives of f* or the *interaction graph*.

The evolution of the whole system can be formally modelled by a certain kind of directed graph on M . We equip M with the usual metric $d(x, x') = \sum_{i=1}^n |x_i - x'_i|$ for $x, x' \in M$. Denote by $e_1 = (1, 0, 0, \dots)$, $e_2 = (0, 1, 0, 0, \dots)$, etc. the coordinate vectors of M . A *grid graph Γ over M* is a graph with the vertex set M satisfying that

- each directed edge connects a pair of vertices of distance one
- at each vertex x there are no two parallel outward edges; that is, $x - e_j \leftarrow x \rightarrow x + e_j$ is not allowed.

The state of the whole system is represented by the levels of genes, and corresponds to a vertex in Γ . At each time step, the state evolves to one of its neighbouring vertices connected by an arrow in the following way. To an evolution function over M , we associate a grid graph $\Gamma(f)$ over M called the (*asynchronous*) *state transition graph* with the edge set

$$\left\{ \begin{array}{l} (x_1, x_2, \dots, x_j, \dots, x_n) \rightarrow (x_1, x_2, \dots, x_j + \delta, \dots, x_n), \\ \delta = \begin{cases} -1 & (f_j(x) < x_j) \\ +1 & (f_j(x) > x_j) \end{cases} \end{array} \right\}. \quad (1)$$

Note that here we follow the standard convention that transition of states is *unitary* (see (Richard, 2010, §4)) so that the existence of an edge $x \rightarrow x'$ implies $d(x, x') = 1$; that is, at each step the level of a single gene changes at most by one.

Asymptotic behaviour of the evolution of a system can be captured in a graph theoretical entity of the state transition graph. An *attractor* is a terminal strongly connected sub-graph of Γ ; that is, any two elements of it are connected by a path and there is no edge from its elements to one in the complement. An attractor consisting of a single vertex is called a *stable state*, otherwise it is called a *cyclic attractor*. Intuitively, attractors are domains in Γ in which the system eventually resides; there is no way to escape once the system arrives in it, but each state in the domain can be visited after arbitrarily many steps.

1.2.2. Interaction graph and circuit functionality

A common practice in analysing interactions among genes in a network is to encode it in the form of a labelled directed graph called the *interaction graph*, where interaction is measured by the partial derivatives of the evolution function $f = (f_1, f_2, \dots, f_n) : M \rightarrow M$.

The *forward partial derivative* of f_i along the j th coordinate at $x = (x_1, \dots, x_n)$ with $x_j < m_j$ is defined by

$$\begin{aligned} \partial_j^+ f_i(x) &= f_i(x_1, \dots, x_j + 1, \dots, x_n) - f_i(x_1, \dots, x_j, \dots, x_n) \\ &= f_i(x + e_j) - f_i(x). \end{aligned}$$

The *backward partial derivative* along the j th coordinate at x with $x_j > 0$ is defined similarly by

$$\begin{aligned} \partial_j^- f_i(x) &= f_i(x_1, \dots, x_j - 1, \dots, x_n) - f_i(x_1, \dots, x_j, \dots, x_n) \\ &= f_i(x - e_j) - f_i(x). \end{aligned}$$

Partial derivatives $\partial_j^+ f_i(x)$ and $\partial_j^- f_i(x)$ are non-trivial when the i th gene’s target value changes along the change of the j th gene. They encode the dependence between genes locally at the state $x \in M$.

Remark 1. For a Boolean network, only one of the forward or the backward partial derivative exists at each x , so we just put them together to define the ordinary partial derivative denoted by ∂_j . On the other hand, in multilevel case, we have both the forward and the backward partial derivatives at some x . It is important to consider both of them (c.f. (Richard, 2010, Definition 8)).

Definition 1. The (local) *interaction graph* $Gf(x)$ of f at x is a graph over the vertex set I such that there exists an edge from j to i

- with label “+” if $\partial_j^+ f_i(x) > 0$ or $\partial_j^- f_i(x) > 0$
- with label “−” if $\partial_j^+ f_i(x) < 0$ or $\partial_j^- f_i(x) < 0$.

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