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Two classes of ODE models with switch-like behavior

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Abstract

In cases where the same real-world system can be modeled both by an ODE system $\mathcal{D}$ and a Boolean system $\mathcal{B}$ it is of interest to identify conditions under which the two systems will be consistent, that is, will make qualitatively equivalent predictions. In this note we introduce two broad classes of relatively simple models that provide a convenient framework for studying such questions. In contrast to the widely known class of Glass networks, the right-hand sides of our ODEs are Lipschitz-continuous. We prove that if $\mathcal{B}$ has certain structures, consistency between $\mathcal{D}$ and $\mathcal{B}$ is implied by sufficient separation of time scales in one class of our models. Namely, if the trajectories of $\mathcal{B}$ are “one-stepping” then we prove a strong form of consistency and if $\mathcal{B}$ has a certain monotonicity property then there is a weaker consistency between $\mathcal{D}$ and $\mathcal{B}$. These results appear to point to more general structure properties that favor consistency between ODE and Boolean models.

Keywords

Boolean system; Boolean approximation of flow; comparing dynamical systems models; consistency between models

1. Introduction

The dynamics of many real-world, in particular biological, systems exhibit switchlike behavior. Examples include gene regulatory networks, where at any given time a gene may be expressed (switched on) or not expressed (switched off) and neuronal networks, where at any given time a neuron may or may not fire. Mathematical models of such systems can often take the form of a differentiable flow $\mathcal{D}$ or a Boolean dynamical system $\mathcal{B}$. The former type of model usually incorporates more relevant details and appears biologically more realistic, while the latter type may be easier to analyze, at least by simulations. The literature describes a vast number of cases where Boolean and other discrete models have been successfully used to make realistic predictions about real-world systems; for example, several chapters of [1] review such success stories in biology.

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If the same real-world system can be modeled both as a differentiable flow $\mathcal{D}$ and a Boolean system $\mathcal{B}$ the question naturally arises how the two models are related. This question has several distinct aspects, two of which will be discussed in this note: translation between the two types of systems and consistency.

1.1. Translation between flows and Boolean systems

A system of ODEs

$$\dot{\vec{x}} = g(\vec{x}) \quad (1)$$

induces a differentiable flow $\mathcal{D}$ if the function g is locally Lipschitz, and may induce a continuous flow $\mathcal{D}$ under even milder assumptions. We will assume throughout this paper that (1) induces at least a continuous flow and use the redundant adjective “continuous” when we want to emphasize that no assumption about differentiable trajectories is made. While formally different mathematical objects, for convenience we will sometimes refer to the flow $\mathcal{D}$ and the ODE (1) as if they were synonymous. The state space of a differentiable flow is a subset M of some $\mathbb{R}^N$, typically a compact manifold.

The state space of an n -dimensional Boolean system is the set $\{0, 1\}^n$ of n -dimensional Boolean vectors s . The dynamics are given by a Boolean function $f: \{0, 1\}^n \rightarrow \{0, 1\}^n$ so that

$$s(\tau+1) = f(s(\tau)). \quad (2)$$

While a Boolean system is formally a pair $\mathcal{B} = (\{0, 1\}^n, f)$, the state space is already implied by the updating function f as its domain. Hence, we will sometimes use f itself as shorthand for specifying $\mathcal{B}$.

Translating a flow $\mathcal{D}$ on a subset of $\mathbb{R}^N$ into an n -dimensional Boolean system $\mathcal{B}$ where n may be different from N but typically satisfies $n \leq N$, requires at the minimum the construction of a map $S: M \rightarrow \{0, 1\}^n$ that we will call the *discretization* of M . Typically, this map is constructed by discretizing the values x_i for n of the variables in M and assigning to them the Boolean value $s_i = 0$ if x_i is below a threshold θ_i and $s_i = 1$ if x_i is above this threshold. In practical applications it may be far from obvious how to choose the thresholds θ_i (see [2]), but this issue is beyond the scope of this note. We want to point out that not all variables in M need to be discretized. For example, in models of gene regulation one may choose to incorporate only discretized values of mRNA concentrations but not of their translated proteins into the Boolean model. Similarly, the Boolean models constructed in [3] have only one Boolean variable per neuron, while the state of each neuron in the ODE model is characterized both by the cross-membrane voltage and a second, so-called gating variable.

Translating the ODEs (1) into a Boolean updating function f is less straightforward than discretizing some variables, except in special cases in which we have *strong consistency* (see Section 3) or when f itself is inherent in the construction of $\mathcal{D}$. In practice, the updating functions of Boolean models are usually based directly on the available empirical knowledge of the real-world system. Fortunately, for the results reported here, it does not matter how f is constructed. Therefore we somewhat informally assume that a given flow $\mathcal{D}$ has been translated into a Boolean system $\mathcal{B}$ by means of a discretization S and some unspecified “natural” choice of f and call the resulting $\mathcal{B}$ a *(natural) Boolean approximation of $\mathcal{D}$* . We need to emphasize that our usage of these phrases does not imply any consistency whatsoever between a given flow and its natural Boolean approximation.

While at least some ODE systems $\mathcal{D}$ have unique natural Boolean approximations, translation from Boolean into ODE systems cannot be a one-to-one procedure. However, for some types of real-world systems we may have a fairly good idea about a general class of ODE models that give a reasonably good description of the underlying mechanisms. Being able to identify a subset or a single representative of this class that will have a given Boolean system as its approximation can be a powerful tool for model selection in cases where the available data allow for construction of Boolean models. The caveats about the lack of uniqueness notwithstanding, we like to think about this process as translating Boolean into ODE models.

For example, *Glass networks* are an extensively studied class of simple ODE models for gene regulatory networks [4]-[8]. In these networks, the concentration x_i of the i^{th} mRNA (or gene product, if one prefers to think about them this way) is modeled by a DE

$$\dot{x}_i = F_i(\vec{x}) - \lambda_i x_i, \quad (3)$$

where F_i is a piecewise constant (usually discontinuous) production term and $-\lambda_i x_i$ is the decay term. Under certain technical assumptions a Glass network generates a continuous flow and has a natural Boolean approximation.

Similarly, Terman *et al.* [3] constructed a class of excitatory-inhibitory neuronal networks whose ODE models have natural Boolean approximations and showed that every Boolean system can be translated into a model in this class. Together with the theorem about consistency that was proved in [3], this makes both the continuous and discrete dynamical systems promising candidates for modeling actual neuronal networks that exhibit a phenomenon called *dynamic clustering*. As in Glass networks, some ODEs of [3] have right-hand sides with discontinuities.

Here we introduce two other classes of differentiable flows with natural Boolean approximations so that every Boolean system can be translated into a set of flows in each class. These classes are very broad and relatively easy to study, and the ODEs in our classes have Lipschitz-continuous right-hand sides. While these classes are not directly related to any applications of which we are aware, we believe they provide a convenient set of toy models for exploring the relationship between differentiable flows and their Boolean approximations. In particular, the study of these classes may allow us to identify which type of results about Glass networks or from [3] require discontinuities in the right-hand sides of the ODEs, such as in (3), and which ones do not.

1.2. Consistency

If an ODE system $\mathcal{D}$ and a Boolean system $\mathcal{B}$ are to function as useful models of the same real-world system, they should be *consistent* in the sense that they make equivalent predictions. In particular, we would like to assure that for all trajectories of $\mathcal{D}$ that start in a sufficiently large subset U of $\mathcal{M}$, the next Boolean state of the system will be what f_i or at least one of the coordinates of f predicts for the current Boolean state $\mathcal{S}(\vec{x}(t))$. While quite intuitive, this notion is not easy to formalize; in fact, it admits a number of nonequivalent formal definitions that seem plausible. The choice of the most appropriate one may depend on the context (see Section 7 for a brief discussion of one example). The problem is that while each state s of $\mathcal{B}$ has a well-defined successor state $s(+1) = f(s)$, time in the flow $\mathcal{D}$ increases continuously, and one has to pick a time $t^+ > t$ for which $\mathcal{S}(\vec{x}(t^+))$ will be considered the “next” Boolean state after time t . Here we study two such formal and quite natural notions; we call them *strong consistency* and *consistency*.

1.3. Outline of the paper and main results

In Section 2 we will describe methods for translating, in the sense of Subsection 1.1, a Boolean system $\mathbb{B} = (\{0, 1\}^n, f)$ into differentiable flows $\mathcal{D}_1(f, \overrightarrow{\gamma})$ and $\mathcal{D}_2(f, \overrightarrow{\gamma})$ with state spaces $\mathbb{R}^n$ and $\mathbb{R}^n$ respectively, where I will be a certain compact interval. Each real variable in the systems of type $\mathcal{D}_1(f, \overrightarrow{\gamma})$ will correspond to a separate Boolean variable; while for systems of the type $\mathcal{D}_2(f, \overrightarrow{\gamma})$ only the variables, x_i for $i \in \{1, \dots, n\}$ will have Boolean discretizations. We call these variables the *signature variables*, as they determine the Boolean state of the flow. Each signature variable x_i receives input only from x_{i+n} whereas x_{i+n} receives input only from the signature variables $x_1, \dots, x_n$.

One can think about the $\mathcal{D}_2(f, \overrightarrow{\gamma})$ systems as describing the dynamics of *agents* $X_i = \{x_i, x_{i+n}\}$ whose internal states are represented by the x_i s and who receive signals about the state of the system as a whole through x_{i+n} . Thus we will refer to the variables x_{i+n} as the *signaling variables*. The parameter $\overrightarrow{\gamma}$ will allow us to control the degree of separation of time scales between variables of the flows; in particular, between the dynamics of the signature variables and the signaling variables. Let us mention that $\mathcal{D}_1(f, \overrightarrow{\gamma})$ and $\mathcal{D}_2(f, \overrightarrow{\gamma})$ also depend on another parameter $\mathcal{Q}$ that can be thought of as the particular translation method or *conversion scheme*. Most of our results allow a lot of flexibility in the choice of $\mathcal{Q}$ but assume $\mathcal{Q}$ fixed; therefore, we will often suppress this parameter in our notation.

In Section 3, we formally define the notions of strong consistency and consistency. Next, in Section 4 we define the two important classes of one-stepping and monotone-stepping Boolean systems and show that strong consistency is possible only for one-stepping Boolean systems. We give some examples of (strong) consistency or lack thereof for very simple Boolean systems in Section 5. In Section 6 we prove the two main results of this paper, namely that sufficient separation of time scales guarantees strong consistency of $\mathcal{D}_2(f, \overrightarrow{\gamma})$ with f for one-stepping f and consistency of $\mathcal{D}_2(f, \overrightarrow{\gamma})$ with f for monotone-stepping f . In the final section, we discuss the relation of our results to similar work in the literature and we outline some directions of future research.

1.4. Notation

Our mathematical notation is mostly standard. The set $\{1, \dots, n\}$ will be denoted by $[n]$. The cardinality of a set X will be denoted by $|X|$. Time in flows will be denoted by t . Since most Boolean systems are not time-reversible, we will only be interested in forward trajectories of the corresponding flows and, except in the proof of a technical lemma, will always assume that $t \in [0, \infty)$. States in flows will be denoted by $\overrightarrow{x}$, with $\overrightarrow{x}(t)$ denoting the state at time t of the trajectory with initial state $\overrightarrow{x}(0)$. Time in Boolean systems will be denoted by τ and will be assumed to be a non-negative integer. The components of a real-valued vector $\overrightarrow{x}$ will be denoted by x_i ; similarly, the components of a Boolean vector s will be denoted by s_i . Trajectories in a Boolean system $\mathbb{B} = (\{0, 1\}^n, f)$ are sequences $\{s(\tau)\}_{\tau=0}^{\infty}$ such that $s(\tau) = f(s(\tau-1))$ for all $\tau \geq 1$. The *Hamming distance* $H(s, s^*)$ between two Boolean vectors, s and s^* , is the number of indices i such that $s_i \neq s_i^*$.

2. The flows $\mathcal{D}_1(f, \overrightarrow{\gamma})$ and $\mathcal{D}_2(f, \overrightarrow{\gamma})$

2.1. General definitions

Fix n and let $s \in \{0, 1\}^n$. Let $N \in \mathbb{N}$ and define sets $W_i^s \subset \mathbb{R}^N$ for $i \in [n]$ as follows:

$$W_i^s = \begin{cases} \{\vec{x} : x_i < -1\} & \text{if } s_i = 0, \\ \{\vec{x} : x_i > 1\} & \text{if } s_i = 1. \end{cases} \quad (4)$$

We then define $W^s = \bigcap_{i \in [n]} W_i^s$

A *continuous conversion*, Q^f of a Boolean updating function $f: \{0, 1\}^n \rightarrow \{0, 1\}^n$ is a continuous function

$$Q^f = (Q_1, \dots, Q_n) : \mathbb{R}^n \rightarrow [0, 1]^n$$

such that

$$\forall s \in \{0, 1\}^n \forall \vec{x} \in W^s \forall i \in [n] \quad Q_i(\vec{x}) = f_i(s), \quad (5)$$

where f_i is the i^{th} component of $f = (f_1, \dots, f_n)$. For example, the piecewise linear function

$$L(x) = \begin{cases} 0 & \text{if } x \leq -1, \\ .5(x+1) & \text{if } -1 < x < 1, \\ 1 & \text{if } x \geq 1, \end{cases} \quad (6)$$

allows us to construct continuous conversions $L(x_i)$ for the projections $f_i(s) = s_i$ and $L^n := (L(x_1), \dots, L(x_n))$ of the identity function $f_{id}(s) = s$.

A *conversion scheme* is a map $\mathcal{Q}$ that assigns to each Boolean function a continuous conversion Q^f .

Now let $\mathcal{Q}$ be a conversion scheme, let $f: \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a function, and let $\vec{\gamma}$ be an n -dimensional vector of positive reals. Define an ODE system $\mathbb{D}_1(f, \vec{\gamma}, \mathcal{Q})$ (or simply $\mathbb{D}_1(f, \vec{\gamma})$ if $\mathcal{Q}$ is assumed fixed or implied by the context) by

$$\dot{x}_i = \gamma_i (g(x_i) + 6Q_i(\vec{x})), \quad (7)$$

where

$$g(x) = 3x - x^3 - 3, \quad (8)$$

and Q_i is the i^{th} coordinate of $Q = Q^f$.

While we assume here for simplicity that the parameters γ_i are constants, we want to remark that the arguments in this paper can be generalized to the case when these values are allowed to depend on the state or even change over time in a nonautonomous way, as long as they are all bounded and bounded away from zero, that is, if there are constants $C > c > 0$ such that $c < \gamma_i(\vec{x}, t) < C$ for all $i \in [n]$, $\vec{x}$, and t .

In order to see how the system $\mathbb{D}_1(f, \vec{\gamma})$ behaves, consider the family of flows generated by the one-dimensional ODEs

$$\dot{x} = \gamma (g(x) + h), \quad (9)$$

where we consider both γ and h as potential bifurcation parameters.

The only bifurcation with respect to γ occurs at the bifurcation value $\gamma^* = 0$. This one will be of no interest, since we will assume that $\gamma > 0$. Under this assumption, γ does not alter the qualitative behavior of Equation (9) but controls the speed at which trajectories are traversed, with small γ corresponding to slow change. Thus suitable choices of $\vec{\gamma}$ allow us to study the effect of separation of time scales.

Now observe that g has two local extrema, a local minimum $g(-1) = -5$ and a local maximum $g(1) = -1$. Thus for $\gamma > 0$ the family of flows defined by Equation (9) undergoes two saddle-node bifurcations with respect to h : For $h < h^* = 1$, there will be exactly one globally stable equilibrium $x^* < -1$; for $1 = h^* < h < h^{**} = 5$ there will be two locally stable equilibria $x^* < -1$ and $x^{**} > 1$ as well as one unstable equilibrium $x^o = (0, 1)$; and for $h > h^{**} = 5$, there will be exactly one globally stable equilibrium $x^{**} > 1$. This translates into the context of Equation (7) as follows.

Proposition 1. Assume Q_i is a constant. If $Q_i < 1/6$, then (7) will have exactly one globally asymptotically stable equilibrium $x^* < -1$; if $1/6 < Q_i < 5/6$ there will be two locally stable equilibria $x^* < -1$ and $x^{**} > 1$ as well as one unstable equilibrium $x^o = (0, 1)$; and if $Q_i > 5/6$, there will be exactly one globally asymptotically stable equilibrium $x^{**} > 1$.

Of course in our actual systems $\mathbb{D}_1(f, \vec{\gamma})$, as well as in the systems $\mathbb{D}_2(f, \vec{\gamma})$ that will be defined shortly, the values of Q_i will change along trajectories; much of our work in this note will be concerned with studying the consequences of such changes.

For $\mathcal{Q}$ and f as above and a $2n$ -dimensional vector $\vec{\gamma}$ of positive reals, we define an ODE system $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$ (or simply $\mathbb{D}_2(f, \vec{\gamma})$) if $\mathcal{Q}$ is assumed fixed or implied by the context) with variables x_i, x_{i+n} for $i = [n]$ by

$$\begin{aligned}\dot{x}_i &= -\gamma_i (g(x_i) + 6L(x_{i+n})), \\ \dot{x}_{i+n} &= -\gamma_{i+n} (g(x_{i+n}) + 6Q_i(x_1, \dots, x_n)),\end{aligned}\quad (10)$$

where Q_i is the i^{th} coordinate of Q^f and L, g are as in Equations (6) and (8).

In a sense, equations (10) are special cases of Equations (7). To see this, let $f = (f_1, f_2, \dots, f_n) : \{0, 1\}^n \rightarrow \{0, 1\}^n$ be given. For each $i = [n]$ we define an auxiliary function $c_i(\vec{s}) = s_{n+i}$ that copies the value of variable number $n + i$ to variable number i . Extend f to a Boolean function $f^+ : \{0, 1\}^{2n} \rightarrow \{0, 1\}^{2n}$ given by

$$f^+ = (c, f) = (c_1, \dots, c_n, f_1, \dots, f_n). \quad (11)$$

Then assuming a conversion scheme $\mathcal{Q}$ with $Q_i^{f^+} = L(x_{i+n})$ the system (10) becomes an instance the equations in (7) and defines $\mathbb{D}_1(f^+, \vec{\gamma}, \mathcal{Q})$.

Proposition 2. Let f be an n -dimensional Boolean function and let $\vec{\gamma}$ denote any vector of positive reals of suitable dimension. Let $x^- \approx -2.1038$ be the unique root of the polynomial $g(x) = 3x - x^3 - 3$ and let $x^+ \approx 2.1038$ be the unique root of the polynomial $g(x) + 6 = 3x - x^3 + 3$. Then $[x^-, x^+]^n$ is a forward-invariant set in $\mathbb{D}_1(f, \vec{\gamma})$ and $[x^-, x^+]^{2n}$ is a forward-invariant set in $\mathbb{D}_2(f, \vec{\gamma})$.

Proof. Let $\vec{x}(0) = [x^-, x^+]^n$. If the trajectory of $\vec{x}(0)$ were to escape the region $[x^-, x^+]^n$, then there would need to exist a time $t = 0$ and some variable x_i such that $x_i(t) = x^-$ with a negative derivative or such that $x_i(t) = x^+$ with a positive derivative. Consider the case $x_i(t) = x^-$; the argument in the other case is symmetric. Then equation (7) becomes

$$\dot{x}_i(t) = \gamma_i (g(x^-) + 6Q_i(\vec{x})), \quad (12)$$

which is always nonnegative by the choice of g , x^- , and the assumption that Q_i is a coordinate of a continuous conversion. It follows that trajectories cannot escape the specified region.

Thus, for our purposes, we will consider $M = [x^-, x^+]^n$ as the state space of the flow $\mathbb{D}_1(f, \vec{\gamma})$ and $M = [x^-, x^+]^{2n}$ as the state space of the flow $\mathbb{D}_2(f, \vec{\gamma})$. We define discretizations of individual variables in these flows by

$$S_i(\vec{x}) = \begin{cases} 0 & \text{if } x_i \leq 0, \\ 1 & \text{if } x_i > 0, \end{cases} \quad (13)$$

and define $S: M \rightarrow \{0, 1\}^n$ as

$$S(\vec{x}) = (S_1(\vec{x}), S_2(\vec{x}), \dots, S_n(\vec{x})). \quad (14)$$

In particular, S maps each of the sets W^s to s .

Note that even though the systems $\mathbb{D}_2(f, \vec{\gamma})$ have dimension $2n$, both in the case of $\mathbb{D}_1(f, \vec{\gamma})$ and of $\mathbb{D}_2(f, \vec{\gamma})$ the Boolean state $S(\vec{x})$ depends only on the signature variables $x_1, \dots, x_n$. According to Equations (10), in the systems $\mathbb{D}_2(f, \vec{\gamma})$ none of these signature variables is directly influenced by signature variables; all interactions are mediated by the signaling variables $x_{n+1}, \dots, x_{2n}$.

2.2. Examples of conversion schemes

Here we give examples of several specific conversion schemes $\mathcal{Q}$. All of them represent the functions Q_i as compositions

$$Q_i(\vec{x}) = P_i(L(x_1), \dots, L(x_n)), \quad (15)$$

where $P_i: [0, 1]^n \rightarrow [0, 1]$ is a continuous function. Such a $P = (P_1, \dots, P_n)$ will result in a continuous conversion $\mathcal{Q}$ of a Boolean function $f: \{0, 1\}^n \rightarrow \{0, 1\}$ that satisfies (5) as long as

$$\forall s \in \{0, 1\}^n \forall i \in [n] P_i(s) = f_i(s). \quad (16)$$

Wittmann *et al.* [10] give an algorithm for constructing polynomial functions of minimal possible degree that satisfy Equation (16) and prove their uniqueness. Together with Equation (15) these minimal-degree polynomials define a conversion scheme $\mathcal{Q}_W$.

While polynomial functions of minimal degree have desirable properties from our point of view (see Subsection 5.1) and may be optimal in some ways, we want to also allow for other possible conversion procedures.

A drawback of $\mathcal{Q}_W$ is that the algorithm of [10] requires evaluation of $f_i(s)$ at 2^n data points, even if f_i is given by a very simple Boolean formula. But for simple f_i it may be much easier to construct a suitable polynomial P_i . For example, the following choices of P_i satisfy Equation (16):

- If $f_i = s_j \wedge s_k$, let $P_i = x_j x_k$.

- If $f_i = \neg s_j$, let $P_i = 1 - x_j$.
- If $f_i = s_j \vee s_k$, let $P_i = x_j + x_k - x_j x_k$.
- If $f_i = s_j \oplus s_k$, where $\oplus$ denotes exclusive or, let $P_i = x_j + x_k - 2x_j x_k$.

If f_i is given in conjunctive or disjunctive normal form, then one can use the first three observations above to recursively construct P_i , which in conjunction with Equation (15) defines recursive conversion schemes $\mathcal{Q}_{Re}$ and $\mathcal{Q}_{Rd}$ respectively. Similarly, since the operation $\oplus$ is the same as addition in the field $\mathbb{F}_2$, the first and fourth of the above observations can be used to define a recursive conversion schemes $\mathcal{Q}_{RF}$ for Boolean functions that are given as polynomials over the field $\mathbb{F}_2$ in the form

$$f_i(s) = \prod_{j \in J_1} s_j \oplus \prod_{j \in J_2} s_j \oplus \dots \oplus \prod_{j \in J_k} s_j, \quad (17)$$

where $J_1, J_2, \dots, J_k$ are subsets of $[n]$.

In all three cases, if the relevant expressions for f_i contain few terms, then these recursive conversion schemes allow for faster computation of polynomials P_i than the algorithm of [10] for $\mathcal{Q}_W$ but are not guaranteed to return polynomials of minimal degree.

Suppose f_i is given as a polynomial over $\mathbb{F}_2$ as in (17). If k is relatively large, then using the recursive conversion method $\mathcal{Q}_{RF}$ becomes unwieldy. However, one can find a quick and easy conversion as follows. First replace (17) with a polynomial function $u: \mathbb{R}^n \rightarrow \mathbb{R}$ defined by

$$u(\vec{x}) = \prod_{j \in J_1} x_j + \prod_{j \in J_2} x_j + \dots + \prod_{j \in J_k} x_j. \quad (18)$$

Then define

$$P_i(\vec{x}) = 0.5 - 0.5 \cos(\pi u(\vec{x})). \quad (19)$$

The resulting function P_i is no longer a polynomial, but it is continuous, even analytic, and maps $[0, 1]^n$ into $[0, 1]$. According to (17), for $s \in \{0, 1\}^n$ the value $f_i(s)$ is 0 if an even number of the products $\prod_{j \in J} s_j$ evaluates to 1 and is 1 if an odd number of the products $\prod_{j \in J} s_j$ evaluates to 1. In other words, $f_i(S(\vec{x})) = 0$ if $u(\vec{x})$ is an even integer and $f_i(S(\vec{x})) = 1$ if $u(\vec{x})$ is an odd integer. Now (16) follows from (19).

This defines yet another conversion scheme $\mathcal{Q}_a$; we call it *arithmetic conversion*. It has the advantage of allowing very fast computation of the conversion for Boolean functions that are represented as polynomials over $\mathbb{F}_2$. A potential disadvantage is that P_i will in general take the values 0 and 1 at many points in the interior of $[0, 1]^n$, which may introduce additional equilibria of $\mathcal{D}_1(f, \vec{\gamma}, \mathcal{Q}_a)$ or $\mathcal{D}_2(f, \vec{\gamma}, \mathcal{Q}_a)$ that have no counterparts in terms of f . This may have a substantial negative impact on consistency in some cases; an example is given at the end of Subsection 5.1. However, Theorem 6 still applies, and we still get consistency in $\mathcal{D}_2(f, \vec{\gamma}, \mathcal{Q}_a)$ on a large region of the state space under the assumptions of the theorem.

Finally, we remark that for all conversion schemes described here, the right-hand sides of the ODEs (7) and (10) are Lipschitz-continuous.

2.3. Software for conversion and exploration

We wrote a software package *Boolean-Continuous GUI* that runs under Matlab and is capable of constructing, for user-specified f and $\vec{\gamma}$, ODE systems $\mathbb{D}_1(f, \vec{\gamma}, \mathcal{Q})$ and $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$, where $\mathcal{Q} = \{\mathcal{Q}_{RF}, \mathcal{Q}_a\}$. The software also allows for simulating trajectories in these flows, tracking the corresponding Boolean states, and detecting certain additional features. Both the software and its user-manual are available from the authors upon request.

3. Consistency and Strong Consistency: Definitions

Suppose $\mathbb{D}$ is a flow on a forward-invariant set $M \subseteq \mathbb{R}^N$, let $\mathbb{B} = (\{0, 1\}^n, f)$ be an n -dimensional Boolean system, and let $S: M \rightarrow \{0, 1\}^n$ be a fixed discretization. Let S_i denote the i^{th} component of S and let

$$B = \bigcup \left\{ bd \left(S_i^{-1} \{0\} \right) \right\}.$$

We will say that the trajectory of $\vec{x} = \vec{x}(0)$ has the *transversality property* if there exists an increasing sequence $\{t_k\}$, where $t_k \in [0, \infty]$ and $0 < k < K$, such that

- a. $t_0 = 0$ and $t_k < \infty$ for all $k < K$.
- b. For all $t \in [t_0, t_1)$ we have $\vec{x}(t) \notin B$. In particular, $S(\vec{x}(t))$ is constant for $t \in [t_0, t_1)$.
- c. For all $k+1 \leq K$ and all $t \in (t_k, t_{k+1})$ we have $\vec{x}(t) \notin B$. In particular, the function $S(\vec{x}(t))$ is constant for $t \in (t_k, t_{k+1})$.
- d. For all $0 < k < K$ we have $\lim_{t \rightarrow t_k^-} S(\vec{x}(t)) = \lim_{t \rightarrow t_k^+} S(\vec{x}(t))$.
- e. If $K = \infty$, then $\lim_{k \rightarrow \infty} t_k = \infty$.
- f. $t_K = \infty$.

If $\vec{x}$ does have the transversality property, then the sequence $\{t_k\} = \{t_k(\vec{x})\}$ that satisfies (a)–(e) above is uniquely defined. We call it *the sequence of switching times for $\vec{x}$* as it marks the times when the Boolean state of the system changes according to the given discretization. In particular, the case when K is finite signals that the Boolean state remains eventually constant. Given the sequence of switching times we can associate with $\vec{x}$ a sequence of Boolean states by recording these either at the midpoints of intervals (t_k, t_{k+1}) , or at a conveniently chosen time after the last switch has occurred.

$$s_{\vec{x}}(\tau) = \begin{cases} S\left(\vec{x}\left(\frac{t_{\tau+1} + t_{\tau}}{2}\right)\right) & \text{if } \tau+1 < K, \\ S\left(\vec{x}(t_{K-1} + 1)\right) & \text{if } \tau+1 \geq K. \end{cases} \quad (20)$$

Recall the definition of Boolean dynamics (2). This can be written in the form of n updating functions for the components f_i of $f = (f_1, \dots, f_n)$ as follows:

$$s_i(\tau+1) = f_i(s_1(\tau), \dots, s_n(\tau)). \quad (21)$$

A *fixed point* of a Boolean system $\mathbb{B}$ (or of f) is a state $s = (s_1, \dots, s_n)$ such that $f_i(s) = s_i$ for all $i \in [n]$.

Definition 1. Let $\mathbb{D}$, M , f be as above.

- i. We say that the trajectory of $\vec{s}$ in M is strongly consistent with $\mathbb{B}$ if it has the transversality property and for all τ :

$$s^{\vec{x}}(\tau+1) = f\left(s^{\vec{x}}(\tau)\right). \quad (22)$$

- ii. We say that the trajectory of $\vec{s}$ in M is consistent with $\mathbb{B}$ if it has the transversality property and for all τ :

$$\begin{aligned} \left(s_i^{\vec{x}}(\tau+1) = f_i\left(s^{\vec{x}}(\tau)\right) \vee s_i^{\vec{x}}(\tau+1) = s_i^{\vec{x}}(\tau) \text{ for all } i, \text{ and, } s^{\vec{x}}(\tau+1) = s^{\vec{x}}(\tau) \text{ if and only if } s^{\vec{x}}(\tau) \text{ is a fixed point of } \mathbb{B}.\right. \end{aligned} \quad (23)$$

- iii. We say that the flow $\mathbb{D}$ is (strongly) consistent with $\mathbb{B}$ on $U \subseteq M$ if every trajectory that starts in U is (strongly) consistent with $\mathbb{B}$.
- iv. We say that the flow is (strongly) consistent with $\mathbb{B}$ if it is (strongly) consistent with $\mathbb{B}$ on an open set $U \subseteq M$ that is universal in the sense that S maps U onto $\{0, 1\}^n$.

These above notions are defined relative to some subset U of all possible initial states. In most cases, we cannot have $U = M$; in other words, we cannot expect to achieve consistency along all solutions of the ODE system. For example, if the Boolean system $\mathbb{B}$ does not have any steady states, then we cannot get consistency along trajectories that start at fixed points of $\mathbb{D}$. Thus if the geometry of M implies the existence of a fixed point for every continuous flow on M , as will be the case for all systems that we consider in this of this paper, then we must always have $U \subsetneq M$.

Instead of the phrase “consistent with $\mathbb{B}$ ” we will often write “consistent with $\mathcal{F}$ ” for convenience.

4. One-Stepping and Monotone-Stepping Boolean Systems

Definition 2. Let $\mathbb{B} = (\{0, 1\}^n, f)$ be a Boolean system, and let $s \in \{0, 1\}^n$.

- i. We say that the trajectory $\{s(\tau)\}_{\tau=0}^{\infty}$ of $s = s(0)$ is one-stepping if

$$\forall \tau \quad H(s(\tau), s(\tau+1)) \leq 1. \quad (24)$$

- ii. We say that $\mathbb{B}$ is one-stepping if all its trajectories are one-stepping.

Example 1.

- i. Every Boolean trajectory that starts at a fixed point is one-stepping.
- ii. Let $f: \{0, 1\}^3 \rightarrow \{0, 1\}^3$ be defined by:

$$f_1(s) = \neg s_3 \quad f_2(s) = s_1 \quad f_3(s) = s_2. \quad (25)$$

Then the trajectory of this system given by

$$000 \mapsto 100 \mapsto 110 \mapsto 111 \mapsto 011 \mapsto 001 \mapsto 000$$

is one-stepping, while the trajectory

$$010 \mapsto 101 \mapsto 010$$

is not.

- iii. Let $\mathbb{B} = (\{0, 1\}^n, f)$ be any Boolean system. Define a Boolean system $\mathbb{B} = (\{0, 1\}^n, f^\circ)$ by letting $f_i^\circ = f_j(s)$ if $f_j(s) = s_j$ for all j with $1 \leq j < i$ and $f_i^\circ = s_i$ otherwise. Then $\mathbb{B}$ is one-stepping.

We remark that Example 1(ii) can be generalized as follows: Let $I \subseteq [n]$ and define $f: \{0, 1\}^n \rightarrow \{0, 1\}^n$ by $f_i(s) = s_{i-1}$ if $i \notin I$ and $f_i(s) = \neg s_{i-1}$ if $i \in I$, where the subscript $i-1 = 0$ gets treated as $i-1 = n$. If $|I|$ is odd, then f defines a Boolean system $\mathbb{B}$ with exactly one one-stepping orbit that has length $2n$. This result was derived in [11] based on a technique that is presented at pages 79–81 of [12].

Proposition 3. Suppose $\mathbb{D}$ is a flow on M and the trajectory of $\vec{x} \in M$ under $\mathbb{D}$ is consistent with a Boolean function f for a given discretization. If the trajectory of $S(\vec{x})$ under iterations of f is one-stepping, then the trajectory of $\vec{x}$ is strongly consistent with f .

Proof: By the assumption of consistency, the trajectory of $\vec{x}$ has the transversality property

and the corresponding sequence of Boolean states $\{s(\tau)\}_{\tau=0}^\infty = \{s^{\vec{x}}(\tau)\}_{\tau=0}^\infty$ satisfies

Equation (23). By assumption, the Boolean trajectory $\{s^{\vec{x}}(\tau)\}_{\tau=0}^\infty$ has the property that $f(s(0))$ differs from $f^{+1}(s(0))$ in at most one coordinate, and it follows from Equation (23) by induction over τ that $f(s(0)) = s(1)$, which in turn implies (22).

While Proposition 3 indicates that one-stepping trajectories in Boolean approximations of differentiable flows are promising candidates for strong consistency, the next result shows that these are in a sense the *only* candidates for seeing strong consistency in a neighborhood. This is a well-known result, but not in this terminology, so we include a proof for completeness. First we need some terminology and a lemma.

Definition 3. Let M be a compact m -dimensional topological manifold with boundary and let $S: M \rightarrow \{0, 1\}^n$ be a discretization for some n . For $i \in [n]$ let Z_i be the set of all $\vec{x} \in M$ such that the i^{th} coordinate S_i of S takes the value 0. We call S weakly topologically degenerate if it satisfies conditions (a)–(c) below and topologically nondegenerate if in addition condition (d) holds.

- For all $i \in [n]$ both Z_i and $M \setminus Z_i$ are m -dimensional topological manifolds.
- For all $i \in [n]$ the boundary $\text{bd}(Z_i)$ in M is a union of finitely many $(m-1)$ -dimensional topological manifolds.
- For all $i, j \in [n]$ with $i \neq j$ the intersection $\text{bd}(Z_i) \cap \text{bd}(Z_j)$ is a union of finitely many compact topological manifolds of dimensions $\leq m-2$.
- If $\vec{x} \in \text{bd}(Z_i) \cap \text{bd}(Z_j) \cap \text{int}(M)$ and U is a neighborhood of $\vec{x}$, then for every $\vec{y} \in U$ with $\{i, j\} \subseteq \text{supp}(\vec{y})$ there exists a nonempty $V \subseteq U$ such that $S_i(\vec{y}) = 0$ and $S_j(\vec{y}) = 1$ for all $\vec{y} \in V$.

For example, the discretizations for our flows $\mathbb{D}_1(f, \vec{\gamma})$ and $\mathbb{D}_2(f, \vec{\gamma})$ are topologically nondegenerate. In fact, whenever M is a product of N compact nondegenerate intervals with $\vec{x} = (x_1, \dots, x_N)$ and S_i takes the value 0 or 1 depending on whether x_i is below or above some threshold $\bar{x}_i$, the resulting discretization S will be topologically nondegenerate.

Lemma 4. Let $\mathbb{D}$ be a continuous flow and let M be a compact m -dimensional manifold that is forward-invariant for $\mathbb{D}$. Let $S: M \rightarrow \{0, 1\}^n$ be a weakly topologically nondegenerate discretization of M , and let the sets Z_i be as in Definition 3. Let $i \neq j$ and suppose that $\vec{x}(0)$ is an initial condition and $0 < t_1 < t_3$ are times with $\{\vec{x}(t) : t \in [0, t_3]\}$ contained in the interior of M such that

- i. $\vec{x}(t_1) \in \text{bd}(Z_i) \cap \text{bd}(Z_j)$.
- ii. For all $\vec{y}(0)$ in some neighborhood U of $\vec{x}(0)$ we have

$$|\{t \in [0, t_3] : \vec{y}(t) \in \text{bd}(Z_i) \cap \text{bd}(Z_j)\}| \leq 1.$$

Then there exist a neighborhood W of $\vec{x}(0)$ and times t_0, t_2 with $0 < t_0 < t_1 < t_2 < t_3$ such that the set

$$NS(i, j) = \{\vec{y}(0) : \forall t \in [t_0, t_2] \vec{y}(t) \notin \text{bd}(Z_i) \cap \text{bd}(Z_j)\} \quad (26)$$

contains a dense open subset V of W .

Proof: Let $W \subset U$ be a sufficiently small closed neighborhood of $\vec{x}(t_0)$ such that for some times $t_0 < t_1 < t_2$, trajectories that start in W don't leave M during the time interval $[-t_2 + t_1, 0]$. This is the one place where we consider negative times; the assumption that $\vec{x}(t_0)$ is in the interior of M allows us to do so.

Define a map $F: W \times [t_0, t_2] \rightarrow M \times [t_0, t_2]$ by $F(\vec{z}(0), t) = (\vec{z}(t - t_0), t)$. Let J be the range of F . The function F is injective by uniqueness of trajectories and continuous in both variables. Since $W \times [t_0, t_2]$ is compact, F is a homeomorphism between $W \times [t_0, t_2]$ and J . Thus J is a topological manifold of dimension $m + 1$. By condition (c) of Definition 3, the set $B^* = (\text{bd}(Z_i) \cap \text{bd}(Z_j)) \times [t_0, t_2]$ is a union of finitely many compact submanifolds of dimension at most $m - 1$ of J . Consider the map $G: B^* \rightarrow W$ that assigns to each $(\vec{z}, t) \in B^*$ the unique $\vec{y}(0) \in W$ with $\vec{y}(t) = \vec{z}$. This map is continuous by continuity of the flow, and is injective by condition (ii). Thus, G is a homeomorphism, and it follows that its range,

$$R = \{\vec{y}(0) \in W : \exists t \in [t_0, t_2] \vec{y}(t) \in \text{bd}(Z_i) \cap \text{bd}(Z_j)\},$$

has dimension at most $m - 1$. In particular, $V = W \setminus R$ is dense and open in W , and the lemma follows.

Corollary 5. Suppose $\mathbb{D}$ is a continuous flow on a compact m -dimensional manifold M and $\mathbb{B} = (\{0, 1\}^n, f)$ is a Boolean approximation for a given topologically nondegenerate discretization $S: M \rightarrow \{0, 1\}^n$. Then strong consistency between $\mathbb{D}$ and $\mathbb{B}$ on any open $U \subset \text{int}(M)$ implies that for each $\vec{x} \in U$ the trajectory of $S(\vec{x})$ in $\mathbb{B}$ is one-stepping.

Proof: Suppose we have strong consistency on U . Since strong consistency implies strong consistency on each subset of U , we may without loss of generality assume that U is disjoint from the boundary of $S_i^{-1}(\{0\})$ for all $i \in [n]$. Assume towards a contradiction that $\vec{x} \in U$ is such that $f_{S(\vec{x})}(s_i, f_{S(\vec{x})}(s_j, \vec{x})) = s_j$ for some $i \neq j$. Assume without loss of generality $i = 0$. By the assumption about strong consistency we can find $t_1 > 0$ so that condition (i) of Lemma 4 holds. Moreover, by continuity and the transversality property, we can choose t_3 in such a way that condition (ii) of the lemma holds in some neighborhood of $\vec{x}$; for simplicity assume that U itself has this property. But then for all $\vec{y} \in NS(i, j) \cap U$ we must have either

$f_i(\vec{y}(0)) = s_i^*$ or $f_j(\vec{y}(0)) = s_j^*$; otherwise strong consistency along the trajectory of $\vec{y}$ would be violated. Thus for all $\vec{y} \in NS(i, j) \cap U$ we must have $\mathcal{S}(\vec{y}) \subseteq \mathcal{S}(\vec{x})$. But since $NS(i, j)$ contains a dense open subset of some neighborhood W of $\vec{x}$ by Lemma 4, we contradict condition (d) of Definition 3.

Definition 4. Let $\mathbb{B} = (\{0, 1\}^n, f)$ and let $s, s^* \in \{0, 1\}^n$.

- i. We say that s^* is strictly between s and $f(s)$ and write $s \preceq s^* \prec f(s)$ if $s_i = s_i^*$ for all i with $s_i \neq f_i(s)$ and $s^* \neq f(s)$.
- ii. We say that the trajectory $\{s(\tau)\}_{\tau=0}^\infty$ of $s = s(0)$ is monotone-stepping if the following holds:

$$\forall \tau \forall s^* (s(\tau) \preceq s^* \prec s(\tau+1) \Rightarrow f(s^*) = s(\tau+1)). \quad (27)$$

- iii. We say that $\mathbb{B}$ is monotone-stepping if all its trajectories are monotone-stepping.

Clearly, if $H(s, f(s)) = 1$, then the only s^* with $s \preceq s^* \prec f(s)$ is s itself. Thus, all one-stepping Boolean trajectories and Boolean systems are monotone-stepping, but not *vice versa*.

Example 2. The function $f: \{0, 1\}^3 \rightarrow \{0, 1\}^3$ given by

$$\begin{aligned} f(000) &= 110 = f(010) = f(100); f(110) = 111; \\ f(111) &= 101; f(101) = 001; f(001) = 011; f(011) = 111 \end{aligned} \quad (28)$$

defines a monotone-stepping Boolean system that is not one-stepping.

5. Consistency and Strong Consistency: Some Basic Examples

In this section we include some examples that will illustrate the constructions and definitions given in previous sections and will put our main results into context. More details and additional examples can be found in [9].

5.1. $\mathcal{D}_1(f, \gamma)$ for Boolean constants

Let $f: \{0, 1\} \rightarrow \{0, 1\}$ be a Boolean constant, that is, $f(s) = 0$ or $f(s) = 1$. Since we are working in one dimension here, the ODE that defines $\mathcal{D}_1(f, \gamma)$ becomes

$$\dot{x} = \gamma(g(x) + 6Q(\vec{x})). \quad (29)$$

If Q takes only values in the interval $[0, 1/6)$ (for $f(s) = 0$) or $(5/6, 1]$ (for $f(s) = 1$), then Equation (29) has only one globally asymptotically stable equilibrium that all trajectories will approach monotonically, and strong consistency on the whole state space follows. This will clearly be the case for the conversion scheme $\mathcal{Q}_w$, which returns a constant Q .

Other conversion schemes may not be so well-behaved. For example, the Boolean expression $(s \wedge \neg s)$ also represents the constant function $f(s) = 0$, but gets translated by $\mathcal{Q}_{Re}$ and $\mathcal{Q}_{Rd}$ into Q that takes on all values in the interval $[0, 1/4]$. These conversion methods return the following instance of Equation (29):

$$\dot{x} = \gamma(g(x) + 6L(x)(1 - L(x))). \quad (30)$$

Figure 1(a) shows the right-hand side for $\gamma = 1$, and it can be seen that strong consistency still holds.

However, more complicated Boolean expressions for a contradiction may cause problems. For example, consider f that is given by the Boolean expression $f(x) = s \wedge \neg s$, where $s = s \wedge s \wedge s$. This may be recursively converted into the following instance of Equation (29):

$$\dot{x} = \gamma \left(g(x) + 6L(x)^4 (1 - L(x)^4) \right). \quad (31)$$

Figure 1(b) shows the graph for $\gamma = 1$. The system has three fixed points $r_1 = x^-$, $r_2 = 0.58875$, $r_3 = 0.87703$. We get strong consistency on $[x^-, r_2]$ (which is a universal set), but not on the whole state space.

For a second example along these lines, consider the representation of the constant Boolean function $f(s) = 0$ given by $s = s$. The arithmetic conversion scheme $\mathcal{Q}_a$ translates this representation into the following ODE:

$$\dot{x} = \gamma (g(x) + 3 - 3\cos(2\pi L(x))). \quad (32)$$

Figure 1(c) shows the graph for $\gamma = 1$. The system $\mathcal{D}_1(f, \mathcal{Q}_a)$ has three fixed points $r_1 = x^-$, $r_2 = -0.3817$, $r_3 = 0.6990$. We get strong consistency only on the set $[x^-, r_2]$, which is not even a universal set.

In view of these potential problems one may wonder why we consider conversion methods other than $\mathcal{Q}_w$ at all. There are at least four reasons for this. As we already mentioned in Subsection 2.2, speed of computing the conversion is one of them. Second, it seems to be a good idea to allow for more generality at a little extra cost of the exposition, especially since some of our recursive conversion schemes are quite natural for simple updating functions. Third, suppose for example that $f_i = s_1 \wedge s_3$. Even $\mathcal{Q}_w$ will translate this into a composition of a quadratic polynomial with L . However, if we investigate the behavior along a trajectory for which $s_3 = 0$, then f_i will behave along this trajectory as a Boolean constant in exactly the same way as any contradiction, while Q_i is not a constant. We want to build up a set of general tools that can be applied in such situations. Finally, recall that our goal is to use systems of the type $\mathcal{D}_1(f, \vec{\gamma}, \mathcal{Q})$ or $\mathcal{D}_2(f, \vec{\gamma}, \mathcal{Q})$ as a means for discovering phenomena that may influence consistency between ODE models of actual natural systems and their Boolean approximations. There is no guarantee that the implied conversions in such pairs of models are in any way optimal, and it is useful to study examples that illustrate, in a simple setting, what kind of problems may arise.

5.2. Conversions of copy-negation

There are two nonconstant Boolean functions $f: \{0, 1\} \rightarrow \{0, 1\}$ of one variable: $f(s) = s$ (the “copy” function), and $f(s) = \neg s$ (“copy-negation”). For the latter function, all Boolean trajectories satisfy

$$\dots \mapsto 0 \mapsto 1 \mapsto 0 \mapsto 1 \mapsto \dots$$

In order to have consistency with this function, we need some type of oscillation which is not possible in a one-dimensional flow, at least if the discretization is based on a single threshold. In particular, we cannot have consistency along any trajectory of $\mathcal{D}_1(f, \vec{\gamma}, \mathcal{Q})$, for any choice of $\vec{\gamma}$ and $\mathcal{Q}$.

Notice that the problem here is caused because f copies the negation of its variable to the variable *itself*, which is similar to the problem caused by *self-regulation* in Glass networks (see Subsection 7.1). Let us try to sidestep the problem by considering a two-dimensional system where the copying and negating steps are separated.

Let $f = (f_1, f_2) : \{0, 1\}^2 \rightarrow \{0, 1\}^2$ be defined by:

$$f_1(s) = \neg s_2 \quad f_2(s) = s_1. \quad (33)$$

This system has a single orbit given by

$$00 \mapsto 10 \mapsto 11 \mapsto 01 \mapsto 00. \quad (34)$$

Define $\mathbb{D} = \mathbb{D}_1(f, (\gamma_1, \gamma_2))$ by any of the conversion schemes $\mathcal{D}_W$, $\mathcal{D}_{Re}$, $\mathcal{D}_{Rd}$, or $\mathcal{D}_{RF}$. This gives:

$$\begin{aligned} \dot{x}_1 &= \gamma_1(g(x_1) + 6(1 - L(x_2))), \\ \dot{x}_2 &= \gamma_2(g(x_2) + 6L(x_1)). \end{aligned} \quad (35)$$

Since $n = 2$, we have the luxury of being able to perform an easy phase-plane analysis of $\mathbb{D}$. Figure 2 gives the phase portraits for two choices of (γ_1, γ_2) .

The two nullclines intersect at $(0, 0)$, which is the only steady state. The eigenvalues of the Jacobian at the steady state have positive real parts, and the system has a unique limit cycle that will be approached by all trajectories except the one that starts at the origin. It can easily be seen by inspection of Figure 2 that the flow $\mathbb{D}$ is strongly consistent with f on the set $U = [x^-, x^+]^2 \setminus \{0, 0\}$. This remains true for arbitrary vectors $\vec{\gamma}$; as Figure 2 suggests, only the shape of the trajectories and, in particular, the limit cycle will be affected by the choice of (γ_1, γ_2) , but not the qualitative behavior of the system.

Recall that for one-dimensional flows, we cannot get any consistency with copy-negation whatsoever. In a sense, we added just one dummy variable, and we obtained as much consistency with the Boolean dynamics as one possibly could hope. Note that $\mathbb{D}_1(f, (\gamma_1, \gamma_2))$ is really nothing else but $\mathbb{D}_2(\neg s, (\gamma_2, \gamma_1))$ with the roles of variables reversed, and the consistency result obtained here carries over to $\mathbb{D}_2(\neg s, (\gamma_2, \gamma_1))$. This may exemplify a more general tendency of intermediate variables to favor consistency. Our main result in Section 6 also points in the same direction.

5.3. An example that is not monotone-stepping

Define a Boolean updating function $f : \{0, 1\}^4 \rightarrow \{0, 1\}^4$ by

$$\begin{aligned} f_1(s) &= \neg s_2 & f_2(s) &= s_1, \\ f_3(s) &= \neg s_4 & f_4(s) &= s_3. \end{aligned} \quad (36)$$

This system is the direct product of the Boolean system defined by Equation (33) in Subsection 5.2 with itself. There are four pairwise disjoint orbits of length four each in this system:

$$\begin{aligned}
0000 &\mapsto 1010 \mapsto 1111 \mapsto 0101 \mapsto 0000, \\
0010 &\mapsto 1011 \mapsto 1101 \mapsto 0100 \mapsto 0010, \\
0011 &\mapsto 1001 \mapsto 1100 \mapsto 0110 \mapsto 0011, \\
0001 &\mapsto 1000 \mapsto 1110 \mapsto 0111 \mapsto 0001,
\end{aligned} \quad (37)$$

and it can be seen that the system is not monotone-stepping. Under several of our conversion schemes the flow $\mathbb{D}_1(f, \overrightarrow{\gamma})$ will be generated by the DEs

$$\begin{aligned}
\dot{x}_1 &= \gamma_1 (g(x_1) + 6(1 - L(x_2))), \\
\dot{x}_2 &= \gamma_2 (g(x_2) + 6L(x_1)), \\
\dot{x}_3 &= \gamma_3 (g(x_3) + 6(1 - L(x_4))), \\
\dot{x}_4 &= \gamma_4 (g(x_4) + 6L(x_3)),
\end{aligned} \quad (38)$$

with no interaction between the pairs of variables (x_1, x_2) and (x_3, x_4) . Thus, system (38) can be treated as a direct product of two flows to which the results of Subsection 5.2 apply.

It is not hard to infer that all trajectories of system (38) that start in the set

$$U = [x^-, x^+]^4 \setminus \{\vec{x} : x_1 = x_2 = 0 \vee x_3 = x_4\}$$

are consistent with f , regardless of the choice of γ . Strong consistency on open sets in this example is precluded by Corollary 5. For generic choices of $\overrightarrow{\gamma}$, the ODE dynamics on the attractor will become aperiodic (but not chaotic, only quasiperiodic), which precludes strong consistency with f for even a single trajectory of system (38).

After changing the order of variables, system (38) becomes $\mathbb{D}_2(f, \overrightarrow{\gamma})$ for $f: \{0, 1\}^2 \rightarrow \{0, 1\}^2$ defined by

$$f_1(s) = \neg s_1 \quad f_2(s) = \neg s_2, \quad (39)$$

and analogous observations about consistency and strong consistency apply. The choice of the word “analogous” rather than “the same” in the preceding sentence was deliberate, since when treating the same flow as $\mathbb{D}_2(\cdot, \overrightarrow{\gamma})$ rather than $\mathbb{D}_1(\cdot, \overrightarrow{\gamma})$, we are comparing its dynamics with a different Boolean system!

Note that the function f defined by (39) has two disjoint periodic orbits

$$00 \mapsto 11 \mapsto 00, \quad 01 \mapsto 10 \mapsto 01, \quad (40)$$

and, similar to the function (36), is not monotone-stepping.

6. Consistency for Monotone-Stepping Boolean Systems

In this section we will prove the following result.

Theorem 6. *Let $f: \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a Boolean function, let $\mathcal{Q}$ be conversion scheme, and let $\overrightarrow{\gamma}^- = (\gamma_1^-, \dots, \gamma_n^-)$ be a fixed vector of positive reals. Then there exist $\mu > 0$ and nonempty open set $U^s \subseteq W^s$ for $s \in \{0, 1\}^n$ such that for every extension of $\overrightarrow{\gamma}^-$ to a $2n$ -dimensional vector $\overrightarrow{\gamma}$ of positive reals with $\gamma_{i+n} < \mu$ for all $i \in [n]$, the following hold in $\mathbb{D}_2(f, \overrightarrow{\gamma}, \mathcal{Q})$:*

- i. For every $s \in \{0, 1\}^n$ whose trajectory in $\mathbb{B} = (\{0, 1\}^n, f)$ is monotone-stepping, the flow $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$ is consistent with $\mathbb{B}$ on U^s .
- ii. For every $s \in \{0, 1\}^n$ whose trajectory in $\mathbb{B} = (\{0, 1\}^n, f)$ is one-stepping, the flow $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$ is strongly consistent with $\mathbb{B}$ on U^s .
- iii. If $\mathbb{B} = (\{0, 1\}^n, f)$ is monotone-stepping, then the flow $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$ is consistent with $\mathbb{B}$.
- iv. If $\mathbb{B} = (\{0, 1\}^n, f)$ is one-stepping, then the flow $\mathbb{D}_2(f, \vec{\gamma}, \mathcal{Q})$ is strongly consistent with $\mathbb{B}$.

Before proving the theorem, let us make some comments. By choosing μ sufficiently small relative to $\min \vec{\gamma}^-$, the smallest coordinate of the vector $\vec{\gamma}^-$, we can assure that the values of the signaling variables x_{i+n} change at a slower timescale than the values of the signature variables x_i . Thus Theorem 6 tells us that the relevant consistency results hold, with fixed witnesses U^s or $U = \bigcup \{U^s : s \in \{0, 1\}^n\}$, under sufficient separation of time scales.

By our definitions, conclusion (iii) of the theorem follows from conclusion (i), and conclusion (iv) follows from conclusion (ii). Moreover, (ii) follows from (i) since by Proposition 3 for one-stepping trajectories strong consistency is the same as consistency.

Proof of Theorem 6: It suffices to prove part (i). Let us first explain the basic idea. We extend the definition of the sets W_i^s given at the beginning of Section 2 for $i \in [n]$ in the obvious way to $i \in [2n]$, but retain the convention that $W^s = \bigcap_{i \in [n]} W_i^s$. Consider a Boolean state s . Think of $\vec{x}$ as a *clean state for s of Type I* if $\vec{x} \in \bigcap_{i \in [2n]} W_i^s$, and as a *clean state for s of Type II* if $\vec{x} \in W^s \cap \bigcap_{i \in [2n] \setminus [n]} W_i^{f(s)}$. Then $\mathcal{S}(\vec{x}) = s$ and $Q(\vec{x}) = s_i$ for all $i \in [n]$ in clean states of either type. This in turn implies that each of the equations in (10) has a unique, globally stable equilibrium x_j^* for $j \in [2n]$, with $\vec{x}^* = (x_1^*, \dots, x_{2n}^*)$ a clean state of Type II for s if $\vec{x}$ is a clean state of Type I, and $\vec{x}^* = (x_1^*, \dots, x_{2n}^*)$ a clean state of Type I for $f(s)$ if $\vec{x}$ is a clean state of Type II. Each variables x_j will travel towards the equilibrium x_j^* , at least initially. In other words, according to Equations (10), if all signature variables x_i were temporarily frozen, the system would move from a clean state of Type I for s to a clean state of Type II for s , and if all signaling variables were temporarily frozen, the system would move from a clean state of Type II for s to a clean state of Type I for $f(s)$. In reality of course, all variables change over time and additional equilibria may appear. The proof that we are giving here shows that despite these complications, under sufficient separation of time scales this idealized picture remains nearly true as long as the Boolean state s is *monotone for f* , that is, as long as $f(s) = f(s')$ for all $s \preceq s' \prec f(s)$.

The proof proceeds in three stages.

Stage 1: Choosing the sets U^s

We first enlarge the set of clean states for s to a set U^s of states that retains enough of the desirable properties of clean states. Let us introduce an additional parameter δ in the definition of the sets W_i^s of Equation (4):

$$W_i^s(\delta) = \begin{cases} \{\vec{x} : x_i < -1 + \delta\} & \text{if } s_i = 0, \\ \{\vec{x} : x_i > 1 - \delta\} & \text{if } s_i = 1. \end{cases} \quad (41)$$

Let $W^s(\vec{x}) = \bigcap_{i \in [n]} W_i^s(\vec{x})$. Since the functions Q_j are continuous, by Equation (5) there exists $\delta > 0$ such that for all s and $i \in [n]$ and all fixed $x_1, \dots, x_n \in W^s(\vec{x})$ the DE for x_{i+n} in (10) has a globally attracting equilibrium. We fix a sufficiently small δ throughout this proof.

Next we define, for $i \in [n]$ and sufficiently small $\delta > 0$, the set $F_i(\delta)$ of all states $\vec{x}$ that satisfy one of the following conditions:

$$x_i \in [-1+\delta, 1] \quad \text{and} \quad x_{i+n} \geq 2/3 - \alpha, \quad (42)$$

or,

$$x_i \in [-1, 1 - \delta] \quad \text{and} \quad x_{i+n} \leq -2/3 + \alpha. \quad (43)$$

Proposition 7. *There exist positive constants $\delta, \gamma > 0$ with $\delta < \min\{\delta, 2/15\}$ that depend only on $\vec{x}$ such that for all $\vec{x} \in F_i(\delta)$ we have*

$$|\dot{x}_i| > \gamma_i \beta. \quad (44)$$

Proof: First note that $x_{i+n} \geq 2/3 - \alpha$ if and only if $L(x_{i+n}) \geq 5/6 - \alpha/2$ and $x_{i+n} \leq -2/3 + \alpha$ if and only if $L(x_{i+n}) \leq 1/6 + \alpha/2$. Choose δ with $0 < \delta < \min\{\delta, 2/15\}$ such that the unstable equilibrium x^o of $\dot{x} = g(x) + 5 + 3$ satisfies $x^o < -1 + \delta$. For this choice of δ the unstable equilibrium x^o of $\dot{x} = g(x) + 5 - 3$ satisfies $x^o > 1 - \delta$. Hence, $\dot{x}_i \neq 0$ on the compact set $F_i(\delta)$. Now the existence of δ follows from the Extreme Value Theorem.

The inequality $\delta < 2/15$ is needed for technical reasons that will become apparent near the end of this proof. We will fix δ , as above for the remainder of this proof. Since δ is fixed, we will henceforth write F_i instead of $F_i(\delta)$. In view of Equation (44), in this region the variable x_i is guaranteed to move reasonably fast.

Now let us define analogues of the sets $W_i^s(\vec{x})$ for the variables x_{i+n} . For $i \in [n]$ and $\varepsilon > 0$ let

$$V_i^s(\varepsilon) = \begin{cases} \{\vec{x} : x_{i+n} < -2/3 + \varepsilon\} & \text{if } s_i = 0, \\ \{\vec{x} : x_{i+n} > 2/3 - \varepsilon\} & \text{if } s_i = 1. \end{cases} \quad (45)$$

As with W_i^s , we will write V_i^s instead of $V_i^s(0)$. The analogy between $W_i^s(\vec{x})$ and $V_i^s(\vec{x})$ is not perfect though. Note that $-2/3$ and $2/3$ are the bifurcation values with respect to x_{i+n} of the equations in the first line of system (10). While $\vec{x} \in W^s(\vec{x})$ implies that each of the equations for x_{i+n} in the system (10) has a unique, globally attracting equilibrium, $\vec{x} \in V_i^s(\vec{x})$ allows for the existence of multiple equilibria in the equation for x_i .

For each $s \in \{0, 1\}^n$ define the sets

$$\Delta(s) = \{i \in [n] : f_i(s) \neq s_i\} \quad \text{and} \quad \Gamma(s) = [n] \setminus \Delta(s).$$

Define

$$U^s = W^s \cap \prod_{i \in \Gamma(s)} V_i^s.$$

The set U^s is nonempty, open, and $S(\vec{x}) = s$ for every $\vec{x} \in U^s$.

Let

$$\alpha_s = \frac{|\Gamma(s)|}{n} \alpha = \frac{n - |\Delta(s)|}{n} \alpha.$$

Define $R^s \subseteq M$ as the open set of all states in the set

$$PR^s = \bigcap_{i \in \Delta(s)} W_i^s(\delta) \cap \bigcap_{i \in \Gamma(s)} W_i^s \cap \bigcap_{i \in \Gamma(s)} V_i^s(\alpha_s)$$

that satisfy the following condition for all $i \in [n]$:

$$\vec{x} \in W_i^s(\delta) \setminus W_i^s \text{ implies } \vec{x} \in V_i^{f(s)}(\alpha_s). \quad (46)$$

The role of the technical condition (46) will become apparent later in the proof. It is vacuously satisfied on the set U^s . Also note that $U^s \subseteq R^s$.

Stage 2: Episodes and reduction to Lemma 8

For a given state $\vec{x} \in M$, a given $s \in \{0, 1\}^n$, and $j \in [2n]$ consider the DE for x_j in (10). Let $x_j^*(\vec{x}, s)$ denote the locally stable equilibrium that is less than -1 if $s_j = 0$ or $s_{j-n} = 0$ and this equilibrium exists, or the locally stable equilibrium that is greater than 1 if $s_j = 1$ or $s_{j-n} = 1$ and this equilibrium exists. Similarly, let $x_j^+(\vec{x}, s) = x_j^*(\vec{x}, f(s))$. Moreover, let $x_j^\circ(\vec{x}, s)$ denote the unstable equilibrium in $(-1, 1)$ if it exists. In our arguments, we will omit the parameters $\vec{x}$ and s if they are implied by the context.

Equipped with this terminology, let us consider as a warm-up what happens to an ODE trajectory that starts in U^s when s is a fixed point of f . Then $f(s) = s$ and $s \in [n]$. In this case, the equilibria x_i° do not exist and $x_i^* = x_i^+$ will be globally attracting in the dynamics of x_j for all $i \in [n]$. Thus, the trajectory will never leave W^s . By the definition of U^s and the assumption that $f(s) = s$, all variables x_{1+n} are initially outside of $[-2/3, 2/3]$ and will keep moving away monotonically from this interval. It follows that U^s is forward invariant in this case; in particular, no change in the Boolean state will occur at any future time, and we get strong consistency on U^s with the Boolean trajectory of s .

If s is not a fixed point of f , things become more complicated. Consider a monotone Boolean state s that is not a fixed point of f and assume $\vec{x}(0) \in U^s$. We will show that the trajectory of $\vec{x}(0)$ over some time interval $[0, T]$ will proceed in *episodes* of three distinct types.

- For all times t in a *Type I episode*, we have $\vec{x}(t) \in R^s$; for some s with $s \preceq s \prec f(s)$.
- During a *Type II episode* for $i \in (s) \in [n]$, signature variable x_i moves monotonically either from $-1 +$ to 1 or from $1 -$ to -1 .
- For all times t in a *Type-III episode*, we have $\vec{x}(t) \in W^{f(s)}$. A Type III episode ends at a time $T > 0$ with $\vec{x}(T) \in U^{f(s)}$.

Figures 3–6 illustrate several prototypical scenarios for the three types of episodes for a situation when $s_1 = 0$ and $f_1(s) = f_1(f(s)) = 1$. The panels illustrate typical movements of variables x_1 and x_{1+n} as well as hypothetical right-hand sides of the equations (10) for x_1

and x_{1+n} as functions of only the corresponding variable for fixed values of the other variables that are possible in a given type of episode. One needs to keep in mind that the graphs of these functions may move up or down during an episode due to changes of the remaining variables.

Notice that since $R^s \neq P R^s \neq W^s(\cdot)$, Type I episodes cannot overlap with Type II episodes. Similarly, since $s \neq f(s)$ for all relevant s , Type III episodes cannot overlap with Type I or Type II episodes. However, Type II episodes for different i may overlap or even coincide. We will prove the following result.

Lemma 8. *Let s be Boolean state that is monotone for f but not a fixed point. Then there exists $\mu(s) > 0$ such that for every extension of $\vec{g}$ to a $2n$ -dimensional vector $\vec{\gamma}$ of positive reals with $\gamma_{i+n} < \mu(s)$ for all $i \in [n]$ and every $\vec{x}(0) \in U^s$ there exists a time $T > 0$ such that each time $t \in [0, T]$ belongs to an episode of Type I, II, or III and the following conditions hold:*

- A. *The last episode is of Type III.*
- B. *The only times $t \in [0, T]$ for which $x_i(t) \in [-1 + \gamma_i, 1 - \gamma_i]$, $i \in [n]$, belong to a Type II episode for $i \in [n]$.*
- C. *If $i \in [n]$, then the interval $[0, T]$ contains exactly one Type II episode for i .*

Let us first show how Theorem 6 follows from Lemma 8. Since a monotone-stepping trajectory visits only monotone states, these are the only Boolean states for which U^s is relevant in this proof. We have already dealt with the case of a fixed point, so assume s satisfies the assumption of the lemma. Moreover, assume that separation of time scales is sufficiently large in terms of $\mu(s)$ as in the lemma, let $\vec{x} = \vec{x}(0) \in U^s$, and consider $T > 0$ for which conditions (A)–(C) hold. Note that the Boolean state of a variable will change once during a Type II episode for this variable, but will not change during Type I or Type III episodes. Thus, according to (B), $s_i^{\vec{x}}$ will remain constant for $t \in (0, T)$ for all $i \in [n]$ with $f_i(s) = s_i$ and according to (C), exactly one switch of the Boolean value $s_i^{\vec{x}}$ will occur in the interval $(0, T)$ when $f_i(s) \neq s_i$. By the assumption on s we have $f(s) = f(s)$ for all s with $s \preceq s \prec f(s)$, which gives consistency between the Boolean and ODE systems on the interval $[0, T]$ in the sense of (23). Now by (A) and the definition of a Type III episode, $\vec{x}(T) \in U^{f(s)}$. If $f(s)$ is not a fixed point of f , the same argument applies to $\vec{x}(T)$ in place of $f(s)$ in a place of s and the theorem follows by induction.

Two technicalities still need to be mentioned here. First, the constant $\mu(s)$ in Lemma 8 depends on s , whereas the theorem postulates a universal constant μ for separation of time scales. Since there are only finitely many Boolean states, we can take μ as the minimum of all $\mu(s)$ for s as in the assumptions of the lemma. Second, condition (e) of the transversality property requires the sequence of switching times $\{t_k\}$ to approach infinity unless the Boolean trajectory reaches a fixed point. This will be satisfied if there exists $T_{\min} > 0$ such that $T > T_{\min}$ whenever T witnesses conditions (A)–(C) of Lemma 8. The existence of such $T_{\min}$ follows from (A) and the assumption that s is not a fixed point of f , which imply that at least one of the x_i 's has to traverse the entire interval $[-1, 1]$ between times 0 and T . Since

$|\dot{x}_i| \leq 5 \gamma_i$ (see Inequality (48) below), this will take at least $\frac{2}{5\gamma_i}$ time units. Taking γ as the largest component of the vector $\vec{\gamma}$ here gives a required $T_{\min}$.

Stage 3: Proof of Lemma 8

Fix a Boolean state s that satisfies the assumption of Lemma 8, and assume $\vec{x}(0) \in U^s$. In order to reduce clutter in our notation, we will write μ instead of $\mu(s)$. Notice that the definition of U^s implies that time 0 belongs to a Type I episode. Thus for the first part of the lemma it suffices to show that each episode of Type I–II is followed by an episode of one of the Types I–III until we reach the end of a Type III episode.

Now consider a time t in a Type I episode with $\vec{x}(t) \in R^s$ for some s with $s \preceq s' \prec f(s)$. Notice that such s must be monotone and must satisfy $f(s) = f(s)$, $(s) \models (s)$ and (s)

(s) . Thus during this episode, all x_i for $i \in (s)$ move towards the equilibrium $x_i^* = x_i^+$. Similarly, by the choice of s' , each variable x_{i+n} for $i \in (s)$ will move towards the unique globally stable equilibrium $x_{i+n}^* = x_{i+n}^+$. In particular, throughout a Type I episode, the system will stay within the set

$$\bigcap_{i \in \Gamma(s')} W_i^{s'} \cap \bigcap_{i \in \Gamma(s')} V_i^{s'}(\alpha_{s'}),$$

and, as long as no signature variable x_i for $i \in (s)$ reaches the boundary $1 \in \{-1 + \epsilon, 1 - \epsilon\}$ inside the set

$$\bigcap_{i \in \Delta(s')} W_i^{s'}(\delta) \cap \bigcap_{i \in \Gamma(s')} W_i^{s'} \cap \bigcap_{i \in \Gamma(s')} V_i^{s'}(\alpha_{s'}) \subseteq PR^{s'}.$$

In contrast, each variable x_{i+n} for $i \in (s)$ will move towards the unique globally stable equilibrium x_{i+n}^+ . Thus if $\vec{x}(t) \in W_i^s(\delta) \cap bsdW_i^s$ at some time during the episode and condition (46) holds at time t , it will remain satisfied. Moreover, $\vec{x}$ can enter the set

$W_i^s(\delta) \cap bsdW_i^s$ only at a time t with $\vec{x}(t) \in V_i^{f(s)} \cap V_i^{f(s)}(s)$. Thus the trajectory will remain inside R^s as long as $\vec{x}(t) \in W^s(\delta)$.

Eventually for some $i \in (s)$ either $\vec{x}(t)$ will enter $V_i^{f(s)}$, or some x_i will the interval $[-1 + \epsilon, 1 - \epsilon]$, that is, $\vec{x}$ leaves $W_i^s(\delta)$. In the former case, x_i^+ becomes the globally stable equilibrium of the DE (10) for x_i and x_i starts moving towards the boundary of $[-1 + \epsilon, 1 - \epsilon]$. This movement can be arrested only if x_{i+n} changes direction, which in turn requires some variable x_j to enter the interval $[-1 + \epsilon, 1 - \epsilon]$. The upshot is that a Type I episode must end at a time t_s such that $x_i(t_s) \in [-1 + \epsilon, 1 - \epsilon]$ for at least one variable x_j with $i \in (s)$.

This condition marks the onset of a Type II episode for i . We need to show that under sufficient separation of time scales, the condition for the onset of a Type II episode for i implies that the variable x_i will move monotonically from $-1 + \epsilon$ to 1 or from $1 - \epsilon$ to -1 , so that a genuine Type II episode ensues, while not much movement of all signaling variables x_{i+n} occurs during this episode. For ease of exposition, consider the onset of a Type II episode for i at time t_i with $x_i(t_i) = -1 + \epsilon$; the case $x_i(t_i) = 1 - \epsilon$ is symmetric. By Inequality (44), the variable x_i will keep monotonically increasing and will reach the value 1 at some time $T_i > t_i$ with

$$T_i - t_i < \frac{1}{\gamma_i \beta} \quad (47)$$

unless $x_{i+n} < 2/3 - \frac{1}{\gamma_i \beta}$ for some time $t > t_i$ with $t - t_i < \frac{1}{\gamma_i \beta}$. We need to show that the latter cannot happen. This is where condition (46) enters the picture. It implies that at time t_i we

have $x_{i+n}(t) > 2/3 - \frac{(n-1)\alpha}{n}$ for some s . Thus sufficient separation of time scales will guarantee that x_i can complete its journey from $-1 + \frac{1}{\gamma_i \beta}$ to 1 before x_{i+n} can possibly take a value less than $2/3 - \frac{(n-1)\alpha}{n}$.

Note that since Q_i is assumed to take values only in the interval $[0, 1]$, the shape of g implies that we have at all times t and for all $j \in [2n]$

$$|\dot{x}_j(t)| \leq 5\gamma_j. \quad (48)$$

Now consider t_{i0} that marks the onset of the first of k overlapping Type II episodes for $i \in I(s)$. Then we must have $k \leq |I(s)| \leq |I(s)|$, and the combined length of Type II episodes

is at most $\frac{k}{\beta \min \gamma^-}$. Let

$$0 < \mu < \frac{\alpha \beta \min \gamma^-}{5n}, \quad (49)$$

and assume $x_{j+n} < \mu$ for all $j \in [n]$.

Condition (46) applies to all $i \in I$ at time t_{i0} , and for each such i we must have $\vec{x}(t) \in V_i^{s'}$ (s) at some time t in these overlapping Type II episodes. But by Inequality (48), for each i

it will take x_{i+n} more than $\frac{k}{\beta \min \gamma^-}$ time units to travel a distance of more than $\frac{k\alpha}{n}$ units. This shows that all x_i for $i \in I$ will reach their destinations in $\{-1, 1\}$ before the

system has a chance to move out of $\bigcap_{i \in I} V_i^{s'}$ (s). Similar considerations apply to the variables x_{j+n} for $j \in (s)$; while we do not have much control over Q during a Type II episode and these variables may move briefly in the wrong direction, each of them will

move by less than $\frac{k\alpha}{n}$ units.

More precisely, for overlapping Type II episodes as above, let s' be such that $s''_i = s'_i$ for all i

$[n] \setminus I$ and $s''_i = 1 - s'_i$ for all $i \in I$. Then $s' \prec s \preceq f(s)$. If $s = f(s)$, then s is monotone, $(s) = (s \setminus I)$ and $(s) = (s) \cup I$. In this case, if $\vec{x}(t_{i0}) \in R^s$, after completion of these Type II episodes, the system will have entered a state in R^s , and the next Type I episode starts. This alternation of Type I and Type II episodes will continue until all variables x_i with $i \in (s)$ have crossed the interval $[-1, 1]$, exactly once, assuming the value 0 at exactly one time along the way, which implies condition (C). Moreover, all variables x_i with $i \in (s)$ will stay in $[x^-, -1) \cup (1, x^+]$, which implies condition (B).

Eventually, after completing the last Type II episode, the system will reach a state $\vec{x}(T^-) \in R^{f(s)} \cap W^s$ where $s = f(s)$. Such time T^- will mark the onset of a Type III episode. We only need to show that under sufficient separation of time scales during a Type III episode the trajectory will move from $R^{f(s)}$ into $U^{f(s)}$ while staying inside $W^{f(s)}$. This will imply (A) without violating (B) or (C) and complete the proof of the theorem.

We need not assume that $f(s)$ is monotone, but we still need to consider the set $(f(s))$ and show that at some time $T = T^-$ we have $\vec{x}(T) \in \bigcap_{i \in \Gamma(f(s))} V_i^{f(s)}$ while $\vec{x}(t) \in W^{f(s)}$ for all $t \in [T^-, T]$. Notice that at time T^- for each $i \in [n]$ the variables x_i and x_{i+n} will be on the same side of 0 and travel in the direction of the locally stable equilibria $x_i^*(f(s))$ and $x_{i+n}^+(f(s))$. Consider $i \in \Gamma(f(s))$ with $x_{i+n}(T^-) \in [-2/3, 2/3]$. The variable x_{i+n} must have entered this interval during a Type II episode (after leaving it and releasing x_i if $i \in \Gamma(f(s))$) and can have subsequently moved deeper into this interval only during some of the Type II episodes when we didn't have control over Q . Thus, by Inequality (48) the distance of x_{i+n} from the nearest endpoint of this interval can be at most $5 \sum_{j \in \Gamma(f(s))} T_j^*$, where T^* denotes the combined duration of all Type II episodes since time $t = 0$. By Inequality (47), we can estimate

$$T^* \leq \frac{n}{\beta \min \vec{\gamma}^-}. \quad (50)$$

On the other hand, while $\vec{x}(t) \in W^{f(s)}$ and $x_{i+n} \in [-2/3, 2/3]$, by Equation (5) and the shape of g we have

$$\gamma_{i+n} \leq |\dot{x}_{i+n}(t)|. \quad (51)$$

Let $T = T^- + \frac{5n}{\beta \min \vec{\gamma}^-}$. Now Inequalities (50) and (51) imply that the trajectory of $\vec{x}(T^-)$ will reach $V_i^{f(s)}$ at or before time T as long as it stays inside $W^{f(s)}$ during the time interval $[T^-, T]$. But the trajectory can leave $W^{f(s)}$ only after some x_{i+n} has crossed over to the other side of the interval $[-2/3, 2/3]$, which, in view of Inequality (48), takes at least $\frac{4/3 - 2\alpha}{5\gamma_{j+n}}$ time units. Since we assumed that $\alpha < 2/15$, we have $\frac{4/3 - 2\alpha}{5} < \frac{1}{5}$, and it follows from the choice of μ in Inequality (49) that $\vec{x}(t)$ will stay inside $W^{f(s)}$ during the time interval $[T^-, T]$ as long as $x_{i+n} < \mu$ for all $i \in [n]$.

We may see consistency even in systems that are not monotone-stepping; one example is given in Subsection 5.3. In this example, the flow $\mathbb{D}_2(f, \vec{\gamma})$ is a direct product of two flows with one-stepping Boolean approximations whose variables don't interact. Theorem 6 clearly applies to each factor and thus generalizes to direct products of monotone-stepping systems. It remains an open problem to find the most general assumptions under which the conclusion of Theorem 6 holds.

7. Discussion

7.1. Related results

The literature contains a few results on consistency between differentiable flows and Boolean systems; here we discuss how these are related to our Theorem 6. The best-known examples are the results for Glass networks. These models were developed by Glass in [5]–[8] based on earlier work on similar models by Glass and Kauffman [13]. The paper [4] gives a review of the major results and a unifying approach to the extensive literature on these networks. As we already mentioned in Subsection 1.1, under suitable assumptions about the functions F_i and decay constants δ_i in Equation (3), these systems induce continuous flows that are consistent with their Boolean approximations. Consistency becomes problematic though in the presence of *self-regulation*, that is, if F_i depends on x_i . As our work in Subsection 5.2 shows, similar problems may occur in our systems $\mathbb{D}_1(f, \vec{\gamma})$.

While the results about consistency in Glass networks do not require an assumption of monotone-stepping trajectories, Corollary 5 applies and strong consistency does require one-stepping Boolean trajectories.

In contrast, Terman *et al.* [3] constructed a class of excitatory-inhibitory neuronal networks whose ODE models have natural Boolean approximations and showed that *every* Boolean system can be translated into a model in this class so that we have a form of strong consistency. Corollary 5 does not apply to these networks because the notion of consistency in [3] is different from the notion given in Definition 1 and seems more appropriate for the dynamics of these networks. Essentially, switches of the Boolean states of several variables are treated as simultaneous if they occur within small time-windows marking the boundaries between episodes of synchronous firing. This opens a promising avenue of future research on generalizations of this notion of consistency as well as possible generalizations of Theorem 6 in this direction.

Gehrmann and Drossel [14] obtained results about consistency between ODE models for two small gene regulatory networks and their Boolean approximations. In contrast to Glass networks and [3], the right-hand sides of the ODEs in these models are Lipschitz-continuous, as they are in the models studied here.

The systems of [3, 14] and our systems of type $\mathbb{D}_2(f, \vec{\gamma})$ all can be conceptualized as *networks of interacting agents*, where the ODE variables are grouped into pairwise disjoint sets X_i that constitute the i^{th} agent and only one Boolean variable is assigned to each agent. Roughly speaking, in [3], an agent corresponds to a neuron whose state is characterized by a cross-membrane voltage and a so-called gating variable, while in [14], an agent corresponds to a gene whose state is characterized by its mRNA concentration and the concentration of the corresponding gene product. Similarly, in $\mathbb{D}_2(f, \vec{\gamma})$, we have $X_i = \{x_i, x_{i+n}\}$. Such a partition into agents appears natural in many models of real-world systems and may favor consistency between an ODE system and its Boolean approximation. For example, self-regulation does not cause the kind of problems for consistency in our system $\mathbb{D}_2(f, \vec{\gamma})$ as it may cause in system $\mathbb{D}_1(f, \vec{\gamma})$ or Glass networks, where all variables are discretized. Identifying and perhaps classifying general mechanisms in such networks of interacting agents that favor or guarantee some form of consistency is another promising avenue for further research.

In particular, we are planning to generalize Theorem 6 to much larger classes of networks of interacting agents. The mechanism that gives Theorem 6 of course is sufficient separation of timescales in addition to suitable bifurcations in the internal dynamics of the signature variables, and the theorem should generalize in this form. The consistency result in [3] also relies on separation of time scales, with voltages changing much faster than gating variables, but an additional synchronization mechanism is built into the network architecture. In contrast to Theorem 6, very large separation of time scales destroys the consistency for the first system studied in [14], despite the fact that its Boolean approximation is one-stepping. Thus the mechanism for consistency at other time scales that is reported in [14] must be different.

There are some similarities between the proof of our Theorem 6 and the results in [15] about certain models of gene regulatory networks with steep sigmoid functions. In particular, recall that in our systems of type $\mathbb{D}_2(f, \vec{\gamma})$ each signaling variable regulates exactly one signature variable. This has a parallel in Assumption $\mathcal{A}$ of [15] that every transcription factor regulates exactly one gene at each of its thresholds. It appears, however, that proving analytical results about gene regulation with steep continuous sigmoid function is in general

more challenging than proving analogous results for the classes described here (see [15] and references therein for description of some difficulties in the former classes).

Many Boolean systems that have been studied in the literature are one-stepping. The one-input systems considered in [13] are a special case. We mentioned already [14], and the Boolean approximation of the models considered in [16] are another example. The latter paper compares various approximations, not only Boolean ones, to a complete nonlinear model of gene regulation and reports that substantial discrepancies can arise between the predictions of various models for even such a simple system. This is another piece of evidence that our models are better behaved than would be expected of models of gene regulation.

7.2. Chaos

Chaos in differentiable flows has been widely studied. A notion of chaos in classes of Boolean systems has been proposed by S. Kau man and has been fairly extensively studied (see [17, 18] for reviews). It is a natural question to ask whether there is any connection between these two notions of chaos in the sense that differentiable flows that can be translated into a chaotic Boolean system must be or will tend to be chaotic flows, or *vice versa*. In other words, it is natural to ask whether the two notions of chaos are saying something equivalent about the underlying natural system or whether they are just two different mathematical properties that happen to share a name.

Chaos in individual Boolean systems can be defined in terms of the *slope of the Derrida curve at the origin*, that is, the average Hamming distance after one updating step for randomly chosen initial states with Hamming distance 1. If this slope exceeds 1, the system can be considered chaotic. It is easy to see that there cannot be a straightforward correspondence between chaos in flows and chaos in this sense in their Boolean approximations. For example, the two-dimensional system with f given by

$$f(00)=00, \quad f(01)=11, \quad f(10)=01, \quad f(11)=10$$

is chaotic in this sense, but the corresponding two-dimensional flow $\mathcal{D}_1(f, \vec{\gamma})$ cannot exhibit chaos.

It seems quite likely though that there are some more subtle connections between the two notions of chaos or between chaos and consistency. Exploring such connections leads to interesting and quite challenging questions. For example, it would be interesting to know under what conditions the sets U^s of Theorem 6(ii) must intersect a unique (attracting) periodic orbit, which would preclude chaos in this region of the state space. This remains an open question even for the one-stepping trajectories of Example 1(ii) and the conversion schemes that we presented in Subsection 2.2. Our software has a module for estimating Lyapunov exponents and allows for numerical explorations of such problems.

7.3. Conclusions

We constructed, for every Boolean system with updating function f , two classes of ODE systems $\mathcal{D}_1(f, \vec{\gamma}, \mathcal{Q})$ and $\mathcal{D}_2(f, \vec{\gamma}, \mathcal{Q})$ for which the Boolean system $\mathbb{B} = (2^n, f)$ is a natural approximation. $\mathcal{Q}$ Theorem 6 shows that sufficiently large separation of time scales guarantees consistency between $\mathcal{D}_2(f, \vec{\gamma}, \mathcal{Q})$ and $\mathbb{B} = (2^n, f)$ on a large region of the state space of the former, as long as f is monotone-stepping. Classes of ODE systems that were previously investigated in the literature for consistency with their natural Boolean approximations either have discontinuities in their right-hand sides or tend to not satisfy the

counterpart of Theorem 6 in its most general form. In our opinion, this makes the models presented here a promising class of toy models for elucidating general mechanisms that favor or entail consistency between an ODE system and its Boolean approximation. It seems likely that the insights from studying such mechanisms in the context of our models would, at least to some extent, carry over to classes of realistic but analytically less tractable models of natural, in particular biological, phenomena.

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Highlights

- Two classes of ODE models with natural Boolean approximations are constructed.
- Every Boolean system has counterparts in each of the classes.
- A notion of consistency between Boolean and ODE models is studied.
- Separation of time scales implies consistency under certain assumptions.
- These ODE models constitute a convenient framework for studying consistency.

Figure 1.

Plots of the right hand side of the differential equation generated by $\mathbb{D}_1(f, 1)$ for different conversion schemes. (a) For the conversion $\mathcal{Q}_w$, we get $\dot{x} = g(x) + 6L(x)(1 - L(x))$.

(b) For $\mathcal{Q}_{Rc}$ and $\mathcal{Q}_{Rd}$, we get $\dot{x} = g(x) + 6L(x)^4(1 - L(x)^4)$.

(c) For the arithmetic conversion $\mathcal{Q}_a$, we get $\dot{x} = g(x) + 3 - 3 \cos(2 L(x))$

Figure 2. Nullclines and direction arrows for $\mathcal{D}_1(f, (1, 1))$ (left panel) and $\mathcal{D}_1(f, (10, 1))$ (right panel).

Figure 3.

Early stage of a Type I episode. (a) x_1 trails the locally stable equilibrium x_1^* . The graph of $\dot{x}_1(x_1)$ moves up. (b) Some movement of $\dot{x}_{1+n}(x_{1+n})$ may occur, but there will be a unique globally stable equilibrium > 1 . The variable x_{1+n} increases and moves towards $2/3$.

Figure 4.

Later stage of a Type I episode. (a) The graph of $\dot{x}_1(x_1)$ continues moving up and has undergone a bifurcation. x_1 increases past -1 and moves towards the positive globally stable equilibrium. (b) Some movement of $\dot{x}_{1+n}(x_{1+n})$ may occur, but there will be a unique globally stable equilibrium > 1 . The variable x_{1+n} has crossed the bifurcation value $2/3$ and keeps increasing.

Figure 5.

A Type II episode for 1. (a) The graph of $\dot{x}_1(x_1)$ may move up or down and there may be one, two, or three equilibria, but only one of them may be larger than x_1 , which rapidly increases throughout the episode from $-1+$ to 1. (b) The location of $\dot{x}_{1+n}(x_{1+n})$ may alter drastically during the episode, and we have no control over the direction of movement of the variable x_{1+n} . We only know that it will stay close to $2/3$ and move by no more than $1/n$ units during the episode.

Figure 6.

A Type III episode. (a) The graph of $\dot{x}_1(x_1)$ moves up. x_1 will keep trailing the positive equilibrium and will stay in the interval $(1, x^+)$ throughout the episode. (b) Since we assumed $f_1(f(s)) = 1$, Equation (5) implies that $\dot{x}_{1+n}(x_{1+n}) = {}_{1+n}g(x_{1+n}) + 6$. If x_{1+n} has entered the interval $[x^-, 2/3]$ during a recent Type II episode, it will leave this interval through $2/3$.