Representing Model Ensembles as Boolean Functions

Robert Schwieger, Heike Siebert
Department of Mathematics, Freie Universität Berlin, Germany
August 3, 2018

Abstract
Families of ODE models $\dot{x} = f(x)$ characterized by a common sign structure $\Sigma$ of their Jacobi matrix $J(f)$ are investigated within the formalism of qualitative differential equations [4]. In the context of regulatory networks the sign structure of the Jacobi matrix carries the information about which components of the network inhibit or activate each other. Information about constraints on the behavior of models in this family is stored in a so called qualitative state transition graph $G_{QDE}(\Sigma)$ [4]. We showed previously that a similar approach can be used to analyze a model pool of Boolean functions characterized by a common interaction graph [13]. Here we show that the opposite approach is fruitful as well. We show that the qualitative state transition graph $G_{QDE}(\Sigma)$ can be reduced to a “skeleton” represented by a Boolean function $f^\Sigma$ conserving the reachability properties. This reduction has the advantage that approaches such as model checking and network inference methods can be applied to $G_{async}(f^\Sigma)$ within the framework of Boolean networks. Furthermore, our work constitutes an alternative to approaches like [14] and [15] to link Boolean networks and differential equations.

1 Introduction
Mathematical modeling in systems biology is often hampered by lack of information on mechanistic detail and parameters. Several approaches deal with this problem. Here we focus on the theory of qualitative differential equations (QDE). A qualitative differential equation model is an abstraction of a system of ordinary differential equation, consisting of a set of real-valued variables and functional, algebraic and differential constraints among them [11]. In the simplest case the objects of interest are systems of ordinary differential equations (ODEs) consistent with a given signed interaction graph $\Sigma \in \{-1,0,1\}^{n \times n}$, $n \in \mathbb{N}$ capturing dependencies between system components and the type of influence exerted, activating or inhibiting [4]. These ODEs are collected in a so called model ensemble. For this ensemble, a qualitative state transition graph
(QSTG) $G_{QDE}(\Sigma)$ can be constructed whose nodes represent derivative signs of the system components and edges indicate possible changes in the derivative over time. It can then be used to describe the behavior of the ensemble. This will be explained in Section 1.2. This constitutes a scenario of particular interest in application, where interaction information is usually more readily available than details on the processing logic of multiple influences on a target component.

In this paper we show that the graph $G_{QDE}(\Sigma)$ can be reduced to an asynchronous state transition graph of a Boolean function $f^{\Sigma}$. This allows us to study the graph $G_{QDE}(\Sigma)$ with existing tools for Boolean regulatory networks and to use theoretical results about Boolean regulatory networks to analyze it.

Our paper is structured in the following way: In the first section we state definitions and notions about Boolean regulatory networks. Afterwards, we review existing results for monotonic ensembles in the continuous setting and define a Boolean version of the qualitative state transition graph of such an ensemble denoted by $G_{QDE}(\Sigma)$. In Section 2 we introduce the skeleton of the graph $G_{QDE}(\Sigma)$ and prove that no information about reachability is lost during this reduction. Subsequently, we exploit the results by using model checking and outline how the result could be used for network inference.

### 1.1 Boolean networks

We denote with $f$ a Boolean function $\{0,1\}^n \rightarrow \{0,1\}^n$ and with $n \in \mathbb{N}$ the dimension of its state space. With $[n]$ we denote the set $\{1, \ldots, n\}$. For $v \in \{0,1\}^n$, $i \in [n]$ the value $v_i$ refers to the $i$-th component of the network.

Furthermore, we define for $v, w \in \{0,1\}^n$ the following sets:

**Definition 1.** For $v, w \in \{0,1\}^n$ the set $\text{diff}(v, w)$ contains all indices where $v$ and $w$ are different and the set $\text{comm}(v, w)$ the set of indices where $v$ equals $w$:

$$\text{diff}(v, w) := \{i \in [n] | v_i \neq w_i\},$$  
$$\text{comm}(v, w) := \{i \in [n] | v_i = w_i\}.$$

For a vector $v \in \{0,1\}^n$ the vector $v^A$ denotes its negation on the set of components $A \subset [n]$. More precisely:

**Definition 2.** Let $A \subset [n]$ and $v \in \{0,1\}^n$. Define $v^A \in \{0,1\}^n$ component wise like this:

$$v^A_i = \begin{cases} v_i & \text{if } i \notin A \\ \neg v_i & \text{if } i \in A \end{cases}.$$

We attribute to a Boolean function $f : \{0,1\}^n \rightarrow \{0,1\}^n$ a relation on $\{0,1\}^n$ in the following way:

**Definition 3.** We attribute to $f : \{0,1\}^n \rightarrow \{0,1\}^n$ an asynchronous state transition graph (ASTG) $G_{\text{async}}(f) = (V_{\text{async}}(f), E_{\text{async}}(f))$ with

$$V_{\text{async}}(f) := \{0,1\}^n$$
and
\[
E_{\text{async}}(f) = \{(s, t) \in V_{\text{async}}(f) \times V_{\text{async}}(f) \mid \{i\} = \text{diff}(s, t) \\
\text{and } f_i(s) = t_i \text{ or } s = t = f(s)\}.
\]

The ASTG captures a relation on the the set \(\{0, 1\}^n\). We can describe this relation also with a function \(\mu : \{0, 1\}^n \to \{0, 1\}^n\) such that for \(i \in [n]\)
\[
(v, v^{(i)}) \in E_{\text{async}}(f) \iff \mu_i(v)
\]
holds. To keep our notation simple and since we can identify a function \(\{0, 1\}^n \to \{0, 1\}^n\) with a logical formula, we write \(\mu_i(v)\) instead of \(\mu_i(v) = 1\).

**Lemma 4.** Assume \(f : \{0, 1\}^n \to \{0, 1\}^n\). Then for \(v, v^{(i)} \in \{0, 1\}^n\) and \(i \in [n]\) it holds
\[
(v, v^{(i)}) \in E_{\text{async}}(f) \iff \mu_i(v)
\]
and
\[
(v, v) \in E_{\text{async}}(f) \iff \forall i \in [n] : \mu_i(v)
\]
with \(\mu_i(v) := v_i \oplus f_i(v)\).

**Proof.** Consider
\[
(v, v^{(i)}) \in E_{\text{async}}(f) \iff i \in \text{diff}(v, f(v))
\]
\[
\iff v_i \oplus f_i(v)
\]
and
\[
(v, v) \in E_{\text{async}}(f) \iff \forall i \in [n] : v_i = f_i(v)
\]
\[
\iff \forall i \in [n] : \neg(v_i \oplus f_i(v))
\]

Expressing the relation represented by the graph \(G_{\text{async}}(f)\) via a Boolean function \(\mu\) will turn out useful in the sequel. Similar to Lemma 4 we can represent a graph constructed from a function \(\mu : \{0, 1\}^n \to \{0, 1\}^n\) as an ASTG of a Boolean function:

**Remark 5.** Lemma 4 implies that for a graph \(G = (V, E)\) defined by \(V = \{0, 1\}^n\) and
\[
(v, v^{(i)}) \in E :\iff \mu_i(v),
\]
\[
(v, v) \in E :\iff \forall i \in [n] : \neg \mu_i(v)
\]
for \(i \in [n]\) and \(\mu : \{0, 1\}^n \to \{0, 1\}^n\) it holds \(G_{\text{async}}(\mu \oplus \text{id}) = G\).

**Proof.** Choose \(f = \mu \oplus \text{id}\) in Lemma 4.
1.2 The graph $G_{QDE}(\Sigma)$

Families of ODE models $\dot{x} = \vec{f}(x)$ characterized by a common sign structure $\Sigma = (\sigma_{i,j})_{i,j \in [n]} \in \{-1, 0, 1\}^{n \times n}$ in its Jacobi matrix $J(\vec{f})$ can be investigated using qualitative differential equations [4]. Such families of ODE models are called monotonic ensembles. Instead of the solutions $x(\cdot)$ of the ODE-systems, so-called “abstractions” are considered. Here, these abstractions are sequences of sign vectors of the derivatives of the solutions. A state transition graph $G_{QDE}(\Sigma)$ on the sign vectors can be constructed based on the sign matrix $\Sigma$, which captures restrictions on the behavior of the solutions. We give here a short review of the construction of $G_{QDE}(\Sigma)$. Since we are here only interested in the properties of the object $G_{QDE}(\Sigma)$, most definitions are skipped, but illustrated with an example. For details and exact definitions we refer instead to [13, Sec. 2.2.] and [4, Chapter 2.1-2.2]. For understanding the following sections nothing more than the definition of $G_{QDE}(\Sigma)$ is necessary which will be given in the end of this section.

We define an ensemble of ODE systems $\mathcal{M}(\Sigma)$ whose corresponding Jacobi matrices share a sign structure. The usual sign operator is denoted $[\cdot] := \text{sign}(\cdot)$. We abstract the solutions of the ODE-systems in the model ensemble to sequences of sign vectors that describe the slope of their derivatives.

**Example 1.** Let us assume our monotonic ensemble $\mathcal{M}(\Sigma)$ is characterized by the sign structure $\Sigma = \begin{pmatrix} -1 & 0 & 0 & -1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \\ 0 & 0 & -1 & -1 \end{pmatrix}$. As demonstrated in [13]

Example 2] an example of such a function would be $\vec{f}(x) - x$ with $\vec{f} : [0, 1]^4 \rightarrow [0, 1]^4$, $(x_1, x_2, x_3, x_4) \rightarrow (1 - \frac{x_4}{x_4+0.5}, \frac{x_1}{x_4+0.5}, 1 - \frac{x_4}{x_4+0.5}, 1 - \frac{x_3}{x_3+0.5})$. I.e. $J(\vec{f}(x) - x)$ is necessary which will be given in the end of this section.

This result motivates the following graph:

**Definition 6.** For a sign matrix $\Sigma = (\sigma_{i,j})_{i,j \in [n]} \in \{-1, 0, 1\}^{n \times n}$ we define the graph $G_{QDE}(\Sigma) = (V_{QDE}(\Sigma), E_{QDE}(\Sigma))$ by

$V_{QDE}(\Sigma) = \{-1, 1\}^n$
Figure 1.1: Trajectories of a solution of an ODE in the model ensemble. Its abstraction is given by $(-1, -1, -1, -1) \rightarrow (1, -1, -1, -1) \rightarrow (1, 1, -1, -1)$. The ODE system was parametrized with $x_0 = (0.6, 0.6, 0.6, 0.6)$.

and

$$
(v, w) = e \in E_{QDE}(\Sigma) \\
\iff \forall i \in \text{diff}(v, w) \exists j \in \text{comm}(v, w) : (v_i \cdot v_j \cdot (-1) \equiv \sigma_{i,j}) \quad (1.1)
$$

The graph $G_{QDE}(\Sigma)$ describes the dynamic restrictions on the solutions of the ODEs in the model ensemble imposed by the sign matrix $\Sigma$. Since we are here only interested in properties of the graph $G_{QDE}(\Sigma)$, we refer for details about the relation between the qualitative state transition graph and its model ensemble to [4]. Furthermore, we note that there is no one-to-one correspondence between the qualitative state transition graph and the corresponding sign matrix $\Sigma$. It is possible to change elements on the diagonal of $\Sigma$ without changing the graph $G_{QDE}(\Sigma)$. This is due to the fact that the sets $\text{diff}(v, w)$ and $\text{comm}(v, w)$ are disjoint and thus the diagonal elements do not play a role in (1.1). Consequently, the edge set does not change when changing the diagonal of $\Sigma$.

Since we are interested in the relation of the QSTG and Boolean networks, we redefine now the graph $G_{QDE}(\Sigma)$ on the node set $\{0, 1\}^n$.

**Definition 7.** For a sign matrix $\Sigma = (\sigma_{i,j})_{i,j \in [n]} \in \{-1, 0, 1\}^{n \times n}$ we define the graph $G_{QDE}(\Sigma) = (V_{QDE}(\Sigma), E_{QDE}(\Sigma))$ by

$$
V_{QDE}(\Sigma) = \{0, 1\}^n
$$
Figure 1.2: The graph $G_{\text{QDE}}(\Sigma)$ of the running example.

and

$$(v, w) = e \in E_{\text{QDE}}(\Sigma)$$

$$\iff \forall i \in \text{diff}(v, w) \exists j \in \text{comm}(v, w) : [\sigma_{i,j} \neq 0 \land (v_i \oplus^{\sigma_{i,j}} v_j)], \quad (1.2)$$

where $a \oplus^{-1} b := \neg(a \oplus b)$ and $a \oplus^{1} b := a \oplus b$ for $a, b \in \{0, 1\}$.

From the definition it is clear that the graph $G_{\text{QDE}}(\Sigma)$ and $\overline{G_{\text{QDE}}(\Sigma)}$ are the same after relabeling 0 to $-1$. It is easy to see that conditions (1.2) and (1.1) correspond to each other.

**Example 2.** In Fig. 1.2 the graph $G_{\text{QDE}}(\Sigma)$ from the previous example is depicted. We can see from this for example that no solution in the model ensemble has a direct transition from $(-1, 1, 1, -1)$ to $(-1, 1, 1, 1)$, since there is no edge $(0, 1, 1, 0) \rightarrow (0, 1, 1, 1)$ in the graph.
2 Skeleton of a Model Ensemble

In the previous section we defined the graphs $G_{QDE}(\Sigma)$ in such a way that for an edge $e = (v, w), v, w \in \{0, 1\}^n$ with $\text{diff}(v, w) = A$ the following conditions hold:

$$\forall i \in A \exists j \in A^c : \left( \sigma_{i,j} \neq 0 \land (v_i \oplus \sigma_{i,j} v_j) \right) \iff e \in E_{QDE}(\Sigma).$$

This implies that there are potentially edges $(v, w) \in E_{QDE}(\Sigma)$ where the set $\text{diff}(v, w)$ has cardinality bigger than one. However, we want to represent the graph $G_{QDE}(\Sigma)$ as an ASTG of a Boolean function. Therefore, we show now in the sequel that we can delete the edges $(v, w)$ with $|\text{diff}(v, w)| > 1$ without loosing information about reachability. $|\cdot|$ denotes the cardinality of a set.

For the sets $A \subseteq [n]$ with cardinality one ($|A| = 1$) these conditions are given by the following logical formula:

$$\mu_i^\Sigma(v) = \exists j \in [n] \setminus \{i\} : \left( \sigma_{i,j} \neq 0 \land (v_i \oplus \sigma_{i,j} v_j) \right)$$

$$= \bigvee_{j \in [n] \setminus \{i\}} \text{s.t. } \sigma_{i,j} \neq 0 \left( v_i \oplus \sigma_{i,j} v_j \right). \quad (2.1)$$

We prove now that we can restrict the graph $G_{QDE}(\Sigma)$ to its edges of the form $(v, v^A)$, $v \in \{0, 1\}^n$, $i \in [n]$ without loosing information about reachability.

**Proposition 8.** Assume there is an edge $(v, v^A) \in E_{QDE}(\Sigma)$ with $A \subseteq [n], A \neq \emptyset$. Then for each $B \subseteq A, A \neq B \neq \emptyset$:

$$(v, v^B) \in E_{QDE}(\Sigma),$$

$$(v^B, v^A) \in E_{QDE}(\Sigma).$$

**Proof.** We show first $(v, v^B) \in E_{QDE}(\Sigma)$: Since $B \subseteq A \iff A^c \subseteq B^c$

$$\Rightarrow \forall i \in A \exists j \in A^c : \left( \sigma_{i,j} \neq 0 \land (v_i \oplus \sigma_{i,j} v_j) \right)$$

$$\Rightarrow \forall i \in B \exists j \in B^c : \left( \sigma_{i,j} \neq 0 \land (v_i \oplus \sigma_{i,j} v_j) \right)$$

$$\Rightarrow (v, v^B) \in E_{QDE}(\Sigma)$$

For the second part we know due to $(v, v^A) \in E_{QDE}(\Sigma)$:

$$\forall i \in A \exists j \in A^c : \left( \sigma_{i,j} \neq 0 \land (v_i \oplus \sigma_{i,j} v_j) \right)$$

Let us call $C := \text{diff}(v^B, v^A) = A \setminus B$. We need to show

$$\forall i \in C \exists j \in C^c : \left( \sigma_{i,j} \neq 0 \land (v_i^B \oplus \sigma_{i,j} v_j^B) \right)$$

Before we start by noting two observations.

1. **Observation:** $\forall j \in A^c : v_j^A = v_j^B$
2. Observation: \( \forall i \in C : v_i = v_i^B \)

Now we are ready to prove the statement of the Proposition.

Since \( B \cup C = A \) we have \( C \subseteq A \). It follows

\[
\forall i \in A \exists j \in A^c : (\sigma_{i,j} \neq 0 \land (v_i \oplus^{\sigma_{i,j}} v_j))
\]

\[
\Rightarrow \forall i \in C \exists j \in A^c : (\sigma_{i,j} \neq 0 \land (v_i^B \oplus^{\sigma_{i,j}} v_j))
\]

And due to Observation 1 and 2 we obtain:

\[
\Rightarrow \forall i \in C \exists j \in A^c : (\sigma_{i,j} \neq 0 \land (v_i^B \oplus^{\sigma_{i,j}} v_j))
\]

Since \( C \subseteq A \iff A^c \subseteq C^c \) finally

\[
\Rightarrow \forall i \in C \exists j \in C^c : (\sigma_{i,j} \neq 0 \land (v_i^B \oplus^{\sigma_{i,j}} v_j)) \Leftrightarrow (v_i^B, v_j^A) \in E_{QDE}(\Sigma)
\]

Proposition \( \S \) shows that we can restrict ourself to the edges induced by the sets \( \{1\}, \ldots, \{n\} \) without loosing information about reachability of nodes in \( G_{QDE}(\Sigma) \). This graph can have significantly less edges. Since each edge is of the form \( (v, v^{(i)}) \), it should be possible to represent this graph as the ASTG of a suitable Boolean function, which we will call \( f^\Sigma \). Indeed, due to Lemma \( \H \) we define \( f^\Sigma \) in the following way:

**Definition 9.** We define the function \( f^\Sigma : \{0,1\}^n \rightarrow \{0,1\}^n \) according to Lemma \( \H \) i.e. for \( i \in [n] \):

\[
f_{i}^\Sigma(v) = \mu^\Sigma_i(v) \oplus v_i,
\]

where \( \mu_i^\Sigma(v) := \exists j \in [n]\setminus \{i\} : (\sigma_{i,j} \neq 0 \land (v_i \oplus^{\sigma_{i,j}} v_j)) \). We call the graph \( G_{async}(f^\Sigma) \) the skeleton of \( G_{QDE}(\Sigma) \).

For two nodes \( v, w \in \{0,1\}^n \), \( v \neq w \) there is a directed path in \( G_{async}(f^\Sigma) \) if and only if there is a path in \( G_{QDE}(\Sigma) \). The reduction of \( G_{QDE}(\Sigma) \) to \( G_{async}(f^\Sigma) \) has not only the advantage that \( E_{async}(f^\Sigma) \) can be significantly smaller than \( G_{QDE}(\Sigma) \) but also that certain structural features of \( G_{async}(f^\Sigma) \) can be deduced directly from \( f^\Sigma \). This includes attractors \( \H \), \( \H \), trap spaces \( \S \) and no-return sets, i.e., sets of states that no trajectory enters.

We implemented the generation of the Boolean function \( f^\Sigma \) from \( \Sigma \) into Python. The source code is available in [https://github.com/RSchwieger/ASTG_from_IG](https://github.com/RSchwieger/ASTG_from_IG). We illustrate the construction of \( f^\Sigma \) with the following example:
Example 3. Let’s construct the functions $\mu^\Sigma$ and $f^\Sigma$ from the running example:

$$
\begin{align*}
\mu_1^\Sigma(v) & = \lor_{j \in \{4\}} (v_1 \oplus \sigma_{1,j} v_j) = \neg (v_1 \oplus v_4) \\
\mu_2^\Sigma(v) & = \lor_{j \in \{1\}} (v_2 \oplus \sigma_{2,j} v_j) = v_1 \oplus v_2 \\
\mu_3^\Sigma(v) & = \lor_{j \in \{2,4\}} (v_3 \oplus \sigma_{3,j} v_j) = (v_2 \oplus v_3) \lor \neg (v_3 \oplus v_4) \\
\mu_4^\Sigma(v) & = \lor_{j \in \{3\}} (v_4 \oplus \sigma_{4,j} v_j) = \neg (v_3 \oplus v_4)
\end{align*}
$$

And

$$
\begin{align*}
f_1^\Sigma(v) & = v_1 \oplus \mu_1^\Sigma(v) = \neg v_4 \\
f_2^\Sigma(v) & = v_2 \oplus \mu_2^\Sigma(v) = v_1 \\
f_3^\Sigma(v) & = v_3 \oplus \mu_3^\Sigma(v) = v_3 \oplus ((v_2 \oplus v_3) \lor \neg (v_3 \oplus v_4)) \\
f_4^\Sigma(v) & = v_4 \oplus \mu_4^\Sigma(v) = \neg v_4
\end{align*}
$$

In Fig. 2.1 the skeleton of the running example is depicted. The graph $G_{QDE}(\Sigma)$ has 50 edges and its skeleton $G_{async}(f^\Sigma)$ has 36 edges (without counting the two self-loops).

3 Applications

The reduction of graph $G_{QDE}(\Sigma)$ to its skeleton $G_{async}(f^\Sigma)$ allows us to use the asynchronous state transition graph to analyze the graph $G_{QDE}(\Sigma)$. In order to demonstrate the usefulness of the skeleton we select two possible applications.

3.1 Consistency with time series data

A common way to validate a model of a gene regulatory network is to test whether a given time series data is compatible with it. Such time series data can contain for example concentration levels of proteins or mRNA. In practice, often not all components of the regulatory network are measured and also the amount of measurements can be relatively low compared to the size of the system. Due to the lack of precise empirical data, qualitative models are used frequently. Here it often plays only a role which components of the system influence each other and what is the sign of their influences (activating or inhibiting). In the framework of QDEs testing for compatibility translates to the task of testing whether the graph $G_{QDE}(\Sigma)$ possesses a trajectory containing specific nodes representing our measurements. Thereby, the nodes of the graph $G_{QDE}(\Sigma)$ represent signs of activity trends of its components. The matrix $\Sigma$ contains the information about the influences in the gene regulatory network. If the modeler does not
Figure 2.1: Skeleton of the running example.
find such a trajectory in $G_{\text{QDE}}(\Sigma)$, the measurements are not compatible with
the sign matrix $\Sigma$.

We can formulate the question of compatibility as a model checking query. Model
checking is a formal method from computer science that solves the problem of deciding
whether a temporal logic specification is satisfied by a given transition system. In
the field of qualitative differential equations it has been used to analyze the QSTG [11].
Our result shows that we can solve the problem of compatibility also on the transition
system induced by $f^\Sigma$. However, we do not know if this offers any advantages
with respect to the running time. In any case it is interesting to elucidate in how far
analysis methods and tools from these fields are related.

For a systematic introduction into model checking we refer to [1] and [7, Chapter 3].
Definitions and definitions in this subsection follow roughly [7].

**Definition 10** ([7, Def. 16]). A discrete time series is a sequence $P = (p_0, \ldots, p_m)$
of $m \in \mathbb{N}$ vectors $p_i \in \{0, 1, ?\}^n$, where $p_i$ represents the $i$-th measurement
of the experiment. Components not measured are marked with the symbol $?$. For
a vector $p \in \{0, 1, ?\}^n$ we denote with $S[p]$ the set $S[p] = \{s \in \{0, 1\} | \forall i \in [n]:
(p_i \neq ?) \rightarrow (p_i = s_i)\}$. For a vector $p \in \{0, 1, ?\}^n$ we denote with $S[p]$ the set $S[p] = \{s \in \{0, 1\} | \forall i \in [n]:
(p_i \neq ?) \rightarrow (p_i = s_i)\}$. For a vector $p \in \{0, 1, ?\}^n$ we denote with $S[p]$ the set $S[p] = \{s \in \{0, 1\} | \forall i \in [n]:
(p_i \neq ?) \rightarrow (p_i = s_i)\}$.

**Definition 11.** For a given sign matrix $\Sigma$, the graph $G_{\text{QDE}}(\Sigma)$ or $G_{\text{async}}(f^\Sigma)$
is called compatible with a time series $P = (p_0, \ldots, p_m)$ iff there is a sequence
of states $(x_0, \ldots, x_m)$ with $x_i \in S[p_i]$ such that for every $0 \leq i < m$ there is a
directed path starting in $x_i$ and ending in $x_{i+1}$ in $G_{\text{QDE}}(\Sigma)$ or $G_{\text{async}}(f^\Sigma)$.

The compatibility statement for a given times series $P$ can be translated
into a computation tree logic formula (CTL formula). For example the CTL
formula that queries whether the time series $(p_0, p_1, p_2)$ is compatible with a
given a model is defined by nesting $EF$ operators in the following way:

$$\phi := p_0 \land EF(p_1 \land EF(p_2))$$

with initial state(s) defined by $p_0$. The letter $E$ stands for the existential “there
is a path” and the letter $F$ stands for the “finally” operators [7, p. 31].

**Definition 12.** The nested reachability query $R(P)$ for a time series $P =
(p_0, \ldots, p_m)$ is defined recursively by

$$\phi_m := p_m$$
$$\phi_{m-t} := p_{m-t} \land EF\phi_{m-t+1}, t = 1, \ldots, m$$

and $R(P) := \phi_0$.

Such queries can be implemented in PyBoolNet. In order to test compatibility
of a time series $P$ with a given model $\Sigma$ we need to test then if there exists
a path satisfying $R(P)$. We demonstrate this with our running example:
Example 4. Let us assume we are given a biological system with four species $v_0, v_1, v_2$ and $v_3$. We want to know if the matrix $\Sigma$ is a realistic interaction graph for our biological system. Experiments suggest that there is a trajectory from the subspace $11??$ to $0100$. We use here PyBoolNet [10], which uses the model checker NuSMV. We can check this property with the CTL query $\phi := EF((v_0 & v_1) & EF((\neg v_0 & v_1 & \neg v_2 & \neg v_3))$. Checking this query reveals that this is not the case and therefore $\Sigma$ is not an accurate model for the considered biological system.

3.2 Network inference

Instead of testing whether a given model is compatible with time series data, we could use the data to construct a model from scratch (network inference). In our context this means we want to find a function $f^{\Sigma}$, which agrees with the given data. Then we can read off from $f^{\Sigma}$ the matrix $\Sigma$. Due to the definition of $\mu^{\Sigma}$ in Eq. (2.1) and $f^{\Sigma}$ in Eq. (2.2), we can restrict the inference problem to the following set of Boolean functions:

$$I_i := \{ f : \{0, 1\}^n \to \{0, 1\}, x \mapsto x_i \oplus \bigvee_{j \in A}(x_i \oplus \sigma_j x_j) \mid A \subseteq [n]\backslash\{i\}, \forall j \in A : \sigma_j \in \{-1, 1\}, i \in [n], \}$$

$$I := \prod_{i=1}^{n} I_i, \quad \forall j \in A : \sigma_j \in \{-1, 1\}, i \in [n],$$

Different approaches for solving inference problems have been developed [6, 2, 3, 12], which can be adopted to the set of Boolean functions $I$.

4 Conclusion and outlook

The graph $G_{QDE}(\Sigma)$ is useful in applications to find restrictions on the behavior of solutions in the model ensemble induced by $\Sigma$. When analyzing the graph $G_{QDE}(\Sigma)$ one is typically interested in statements about the reachability between nodes in $G_{QDE}(\Sigma)$. We proved that for a reachability-analysis it is enough to consider a skeleton $G_{async}(f^{\Sigma})$, which is the ASTG of a Boolean function $f^{\Sigma}$. For this purpose we redefined the graph $G_{QDE}(\Sigma)$ stemming from [4] over the state space $\{0, 1\}^n$. The graph $G_{async}(f^{\Sigma})$ can have significantly less edges than $G_{QDE}(\Sigma)$.

This reduction allows us furthermore to use existing methods developed for Boolean networks for analyzing the graph $G_{QDE}(\Sigma)$. We selected two applications – consistency with time series data and network inference – to demonstrate how this link can be used. Such potential applications should be further researched. Especially it is interesting to investigate in how far Boolean inference algorithms restricted to the set $I$ perform in comparison to other Boolean inference algorithms.

---

1 NuSMV uses the symbol $\&$ to denote a logical “AND” and $!$ to denote a negation.
References

[1] Christel Baier and Joost-Pieter Katoen, *Principles of model checking*, MIT Press, 2008.

[2] Shohag Barman and Yung-Keun Kwon, *A novel mutual information-based Boolean network inference method from time-series gene expression data*, PloS one 12 (2017), no. 2, e0171097.

[3] Natalie Berestovsky and Luay Nakhleh, *An evaluation of methods for inferring Boolean networks from time-series data*, PloS one 8 (2013), no. 6, e66031.

[4] Klaus Eisenack, *Model ensembles for natural resource management*, Ph.D. thesis, Freie Universität Berlin, 2006.

[5] Abhishek Garg, Alessandro Di Cara, Ioannis Xenarios, Luis Mendoza, and Giovanni De Micheli, *Synchronous versus asynchronous modeling of gene regulatory networks*, Bioinformatics 24 (2008), no. 17, 1917–1925.

[6] Mahdi Imani and Ulisses Braga-Neto, *Optimal gene regulatory network inference using the Boolean Kalman filter and multiple model adaptive estimation*, 2015 49th Asilomar Conference on Signals, Systems and Computers, Nov 2015, pp. 423–427.

[7] Hannes Klarner, *Contributions to the analysis of qualitative models of regulatory networks*, Ph.D. thesis, Freie Universität Berlin, 2015.

[8] Hannes Klarner, Alexander Bockmayr, and Heike Siebert, *Computing maximal and minimal trap spaces of Boolean networks*, Natural Computing 14 (2015), no. 4, 535–544 (English).

[9] Hannes Klarner and Heike Siebert, *Approximating attractors of Boolean networks by iterative CTL model checking*, Frontiers in Bioengineering and Biotechnology 3 (2015), no. 130.

[10] Hannes Klarner, Adam Streck, and Heike Siebert, *PyBoolNet-a python package for the generation, analysis and visualisation of Boolean networks*, Bioinformatics (2016), btw682.

[11] Benjamin Kuipers, *Qualitative simulation*, Encyclopedia of Physical Science and Technology 3 (2001), 287–300.

[12] Shoudan Liang, Stefanie Fuhrman, and Roland Somogyi, *Reveal, a general reverse engineering algorithm for inference of genetic network architectures*, Pacific Symposium on Biocomputing 3 (1998), 18–29.

[13] Robert Schwieger and Heike Siebert, *Graph representations of monotonic Boolean model pools*, Computational Methods in Systems Biology. CMSB 2017. Lecture Notes in Computer Science 10545 (2017).
[14] El Houssine Snoussi, *Qualitative dynamics of piecewise-linear differential equations: A discrete mapping approach*, Dynamics and Stability of Systems 4 (1989), no. 3-4, 565–583.

[15] Dominik M Wittmann, Jan Krumsiek, Julio Saez-Rodriguez, Douglas A Lauffenburger, Steffen Klamt, and Fabian J Theis, *Transforming Boolean models to continuous models: Methodology and application to T-cell receptor signaling*, BMC Systems Biology 3 (2009), no. 1 (English).