An Abstraction Theory for Qualitative Models of Biological Systems

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Multi-valued network models are an important qualitative modelling approach used widely by the biological community. In this paper we consider developing an abstraction theory for multi-valued network models that allows the state space of a model to be reduced while preserving key properties of the model. This is important as it aids the analysis and comparison of multi-valued networks and in particular, helps address the well–known problem of state space explosion associated with such analysis. We also consider developing techniques for efficiently identifying abstractions and so provide a basis for the automation of this task. We illustrate the theory and techniques developed by investigating the identification of abstractions for two published MVN models of the lysis–lysogeny switch in the bacteriophage λ.

1 Introduction

In order to understand and analyse the complex control mechanisms inherent in biological systems a range of formal modelling techniques have been applied by biologists (for an overview see for example [4, 7]). In particular, qualitative modelling techniques have emerged as an important modelling approach due to the lack of quantitative data on reaction rates and the noise associated with such data. Multi-valued networks (MVNs) [15, 18, 19] are a promising qualitative modelling approach for biological systems. They extend the well–known Boolean network approach [1, 4] by allowing the state of each regulatory entity to be within a range of discrete values instead of just on/off. In this way they are able to provide a compromise between the simplicity of Boolean networks and the more detailed differential equational models.

However, the analysis of MVNs is not without problems. They suffer from the well–known state space explosion problem, a problem which is exacerbated in MVNs by the possibly large set of states associated with each individual entity. Another important shortcoming is the lack of any techniques for relating MVN models at different levels of abstraction. This hinders the comparison of MVN models and means there is no basis for the incremental development of MVNs.

In this paper we begin to address these problems by developing an abstraction theory for MVNs. Abstraction techniques are a well established approach in the area of formal verification (see for example [6, 3]) which allow a simpler model to be identified which can then be used to provide insight into the more complex original model. The abstraction theory we present is based on using an abstraction mapping to relate the reduced state space of an abstraction to the original MVN model. We develop a notion of what it means for one MVN to correctly abstract another and investigate the scope and limits of the analysis properties that can be inferred from an abstraction model. We show that abstractions allow sound analysis inferences about reachability properties in the sense that any reachability result shown on the abstraction must hold on the original model. Importantly, we show that all attractors of an abstraction correspond to attractors in the original model.
We illustrate the theory and techniques developed by investigating the existence of abstractions for two published MVN models for the genetic regulatory network controlling the lysis–lysogeny switch in the bacteriophage λ [17, 5]. Bacteriophage λ [18, 14] is a virus which after infecting the bacteria Escherichia coli makes a decision to switch to one of two possible reproductive phases. It can enter the lytic cycle where the virus generates as many new viral particles as the infected cell’s resources allow and then lyse the cell wall to release the new phage. Alternatively, it can enter the lysogenic cycle where the λ DNA integrates into the host DNA providing it with immunity from other phages and allowing it to be replicated with each cell division. We consider a two and four entity MVN model [17] of the lysis–lysogeny switching mechanism and using the techniques we have developed identify corresponding abstractions for these models.

This paper is organized as follows. In Section 2 we provide a brief overview of the MVN modelling approach and present a simple illustrative example. In Section 3 we develop an abstraction theory for multi-valued networks and present a range of results concerning this theory. In Section 4 we consider the identification of abstractions and develop a basis for automating the abstraction process. In Section 5 we illustrate the theory and techniques developed by presenting two abstraction examples for published models of the lysis–lysogeny switch in bacteriophage λ. Finally, in Section 6 we present some concluding remarks and consider directions for future work.

2 Multi-valued Network Models

In this section, we introduce multi-valued networks (MVNs) [15, 18, 19], a qualitative modelling approach which extends the well-known Boolean network [1] approach by allowing the state of each regulatory entity to be within a range of discrete values. MVNs have been extensively studied in circuit design (for example, see [15, 12]) and successfully applied to modelling biological systems (for example, see [19, 5, 16]).

An MVN consists of a set of logically linked entities \( G = \{g_1, \ldots, g_k\} \) which regulate each other in a positive or negative way. Each entity \( g_i \) in an MVN has an associated set of discrete states \( Y(g_i) = \{0, \ldots, m_i\} \), for some \( m_i \geq 1 \), from which its current state is taken. Note that a Boolean network is therefore simply an MVN in which each entity \( g_i \) has a Boolean set of states \( Y(g_i) = \{0, 1\} \). Each entity \( g_i \) also has a neighbourhood \( N(g_i) = \{g_{i1}, \ldots, g_{il(i)}\} \) which is the set of all entities that can directly affect its state. (Note that \( g_i \) may or may not be a member of \( N(g_i) \).) Furthermore, interactions between one entity and another only become functional if the state of the source entity has reached some threshold state level (this threshold state level is always at least one). MVNs can therefore discriminate between the strengths of different interactions, something which Boolean networks are unable to capture. The behaviour of each entity \( g_i \) based on these neighbourhood interactions is formally defined by a logical next-state function \( f_{gi} \) which calculates the next-state of \( g_i \) given the current states of the entities in its neighbourhood.

We can now define an MVN more formally as follows.

**Definition 1.** An MVN \( MV \) is a four-tuple \( MV = (G, Y, N, F) \) where:

i) \( G = \{g_1, \ldots, g_k\} \) is a non-empty, finite set of entities;
ii) \( Y = (Y(g_1), \ldots, Y(g_k)) \) is a tuple of state sets, where each \( Y(g_i) = \{0, \ldots, m_i\} \), for some \( m_i \geq 1 \), is the state space for entity \( g_i \);
iii) \( N = (N(g_1), \ldots, N(g_k)) \) is a tuple of neighbourhoods, such that \( N(g_i) \subseteq G \) is the neighbourhood of \( g_i \); and
iv) $F = (f_{g_1}, \ldots, f_{g_k})$ is a tuple of next-state multi-valued functions, such that if $N(g_i) = \{g_{i_1}, \ldots, g_{i_n}\}$ then the function $f_{g_i} : Y(g_{i_1}) \times \cdots \times Y(g_{i_n}) \to Y(g_i)$ defines the next state of $g_i$. $\square$

In the sequel, let $MV = (G, Y, N, F)$ be an arbitrary MVN. In a slight abuse of notation we let $g_i \in MV$ represent that $g_i \in G$ is an entity in $MV$.

As an example, consider the MVN $Ex1$ defined in Figure 1 which consists of two entities $g_1$ and $g_2$, such that $Y(g_1) = \{0, 1\}$ and $Y(g_2) = \{0, 1, 2\}$. The update functions for each entity are defined using state transition tables (see Figure 1(b)) where $[g_i]$ is used to denote the next state of an entity $g_i$. It can be seen that entity $g_1$ inhibits $g_2$ and that entity $g_2$ inhibits $g_1$ but only when it reaches state 2 (this is represented in Figure 1(a) by labelling the corresponding edge with a 2). Note that although $g_2 \in N(g_2)$ we have not drawn an edge for this in Figure 1(a) since $g_2$ has no regulatory affect on itself and is needed simply to allow the affect of $g_1$ to be precisely defined.

![Figure 1: An example MVN Ex1 which consists of two entities $g_1$ and $g_2$, including: (a) network structure; and (b) the state transition tables representing the corresponding next-state functions.](image)

A global state of an MVN $MV$ with $k$ entities is represented by a tuple of states $(s_1, \ldots, s_k)$, where $s_i \in Y(g_i)$ represents the state of entity $g_i \in MV$. Note as a notational convenience we often use $s_1 \ldots s_k$ to represent a global state $(s_1, \ldots, s_k)$. When the current state of an MVN is clear from the context we allow $g_i$ to denote both the name of an entity and its corresponding current state. The state space of an MVN $MV$, denoted $S_{MV}$, is therefore the set of all possible global states $S_{MV} = Y(g_1) \times \cdots \times Y(g_k)$. The state of an MVN can be updated either synchronously, where the state of all entities is updated simultaneously in a single update step, or asynchronously, where entities update their state independently (see [19]). In the following we focus on the synchronous update semantics since this has received considerable attention from the biological community. Given two states $S_1, S_2 \in S_{MV}$, let $S_1 \rightarrow S_2$ represent a synchronous update step such that $S_2$ is the state that results from simultaneously updating the state of each entity $g_i$ using its associated update function $f_{g_i}$ and the appropriate neighbourhood of states from $S_1$.

As an example, consider the global state 01 for $Ex1$ (see Figure 1) in which $g_1$ has state 0 and $g_2$ has state 1. Then 01 $\rightarrow$ 12 is a single synchronous update step on this state resulting in the new state 12. The sequence of global states through $S_{MV}$ from some initial state is called a trace. Note that in the case of a synchronous update semantics such traces are infinite. However, given that the global state space is finite, this implies that a trace must eventually enter a cycle, known formally as an attractor cycle [11] [19]. We make use of this fact to define a finite canonical representation for traces which specifies a trace up to the first repeated state.

**Definition 2.** Let $S_0 \in S_{MV}$ be a global state for $MV$. A trace is a list of global states $\sigma(S_0) = \langle S_0, S_1, \ldots, S_n \rangle$ such that:
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i) $S_i \rightarrow S_{i+1}$, for $0 \leq i < n$;
ii) $S_0, \ldots, S_{n-1}$ are unique states; and
iii) $S_n = S_i$ for some $i \in \{0, \ldots, n-1\}$.

The set of all traces $Tr(MV) = \{ \sigma(S) \mid S \in S_{MV} \}$ therefore completely characterizes the behaviour of an MVN model under the synchronous semantics and is referred to as the trace semantics of $MV$.

In our running example, $Ex1$ has a state space of size $|S_{Ex1}| = 6$ and so (under a synchronous update semantics) $Tr(Ex1)$ consists of the six traces presented in Figure 2(a) below.

$$\sigma(00) = \langle 00, 11, 10, 10 \rangle \quad \sigma(10) = \langle 10, 10 \rangle$$
$$\sigma(01) = \langle 01, 12, 01 \rangle \quad \sigma(11) = \langle 11, 10, 10 \rangle$$
$$\sigma(02) = \langle 02, 02 \rangle \quad \sigma(12) = \langle 12, 01, 12 \rangle$$

(a) (b)

Figure 2: The trace semantics for $Ex1$: (a) the set of formal traces; and (b) a graphical representation of the traces.

As mentioned above, each trace leads to a cyclic sequence of states known as an attractor cycle [11, 19]. For example, in Figure 2(b) we can see that $Ex1$ has three attractors: $10 \rightarrow 10$ and $02 \rightarrow 02$ known as point attractors; and $01 \rightarrow 02 \rightarrow 01$ which is an attractor cycle of period 2 [11].

Given a trace $\sigma = \langle S_1, \ldots, S_n \rangle \in Tr(MV)$ for an MVN $MV$ we let $att(\sigma)$ denote the attractor cycle that must occur in trace $\sigma$, i.e. $att(\sigma) = \langle S_k, S_{k+1}, \ldots, S_n \rangle$, for some $1 \leq k < n$ and $S_k = S_n$. We let $ATT(MV)$ denote the set of all attractors for $MV$, i.e.

$ATT(MV) = \{ att(\sigma) \mid \sigma \in Tr(MV) \}$.

Attractor cycles are very important biologically where they are seen as representing different biological states or functions (e.g. different cellular types such as proliferation, apoptosis and differentiation [10]). Thus, the identification and analysis of attractor cycles for MVNs is an important subject which has warranted much attention in the literature (for example, see [11, 19, 8]).

3 An Abstraction Theory for MVNs

In this section we develop a notion of abstraction for MVNs by considering what it means for one MVN to abstractly implement the behaviour of another. This is based around the idea of showing that the trace semantics of one MVN is consistent with the trace semantics of a more complex MVN under an appropriate mapping of states.

We begin by defining how an entity’s state space can be simplified using a mapping to merge states.

**Definition 3.** Let $MV$ be an MVN and let $g_i \in MV$ be an entity such that $Y(g_i) = \{0, \ldots, m\}$ for some $m > 1$. Then a state mapping $\phi(g_i)$ for entity $g_i$ is a surjective mapping $\phi(g_i) : \{0, \ldots, m\} \rightarrow \{0, \ldots, n\}$, where $0 < n < m$.

The idea is that a state mapping reduces the set of states an entity can be in by merging appropriate states. The state mapping must be surjective to ensure that all states in the new reduced state space are
used. Note we only consider state mappings with a codomain larger than one, since a singular state entity does not appear to be of biological interest.

As an example, consider entity $g_2 \in E \times 1$ (see Figure 1) which has the state space $Y(g_2) = \{0, 1, 2\}$. It is only meaningful to simplify $g_2 \in E \times 1$ to a Boolean entity and so one possible state mapping to achieve this would be:

$$\phi(g_2) = \{0 \mapsto 0, 1 \mapsto 0, 2 \mapsto 1\},$$

which merges states 0 and 1 into a single state 0, and translates state 2 into 1.

Clearly, there are a number of different possible state mappings which can be applied to reduce a node’s state space from $m$ to $n$ states, for $1 < n < m$. The complete set of all such state mappings is denoted $MS(m, n) = \{ \phi \mid \phi : \{0, \ldots , m-1\} \rightarrow \{0, \ldots , n-1\} \text{ and } \phi \text{ is surjective} \}$. For example, the mapping set $MS(3, 2)$ consists of the following six mappings:

- (1) $\{0 \mapsto 0, 1 \mapsto 0, 2 \mapsto 1\}$
- (2) $\{0 \mapsto 0, 1 \mapsto 1, 2 \mapsto 1\}$
- (3) $\{0 \mapsto 0, 1 \mapsto 1, 2 \mapsto 0\}$
- (4) $\{0 \mapsto 1, 1 \mapsto 1, 2 \mapsto 0\}$
- (5) $\{0 \mapsto 1, 1 \mapsto 0, 2 \mapsto 0\}$
- (6) $\{0 \mapsto 1, 1 \mapsto 0, 2 \mapsto 1\}$

In order to be able to consider simplifying several entities at the same time during the abstraction process we introduce the notion of a family of state mappings as follows.

**Definition 4.** Let $MV = (G, Y, N, F)$ be an MN with entities $G = \{g_1, \ldots , g_k\}$. Then an abstraction mapping $\phi$ for $MV$ is a family of mappings $\phi = \langle \phi(g_1), \ldots , \phi(g_k) \rangle$ such that for each $1 \leq i \leq k$ we have $\phi(g_i)$ is either a state mapping for entity $g_i$ or is the identity mapping $I_{g_i} : Y(g_i) \rightarrow Y(g_i)$ where $I_{g_i}(s) = s$, for all $s \in Y(g_i)$. Furthermore, for $\phi$ to be well–defined we insist that at least one of the mappings $\phi(g_i)$ is a state mapping.

Note in the sequel given a state mapping $\phi(g_i)$ we let it denote both itself and the corresponding abstraction mapping containing only the single state mapping $\phi(g_i)$.

An abstraction mapping can be lifted and applied to the trace semantics of a model $MV$ as follows.

**Definition 5.** An abstraction mapping $\phi = \langle \phi(g_1) \ldots \phi(g_k) \rangle$ for $MV$ can be used to abstract a global state $s_1 \ldots s_k \in S_{MV}$ by applying it pointwise, i.e. $\phi(s_1 \ldots s_k) = \phi(g_1)(s_1) \ldots \phi(g_k)(s_k)$. We can lift an abstraction mapping $\phi$ to a trace $\sigma(S_0) = (S_0, \ldots , S_n) \in Tr(MV)$ by applying $\phi$ to each global state in the trace as follows

$$\phi(\sigma(S_0)) = \langle \phi(S_0), \ldots , \phi(S_n) \rangle.$$
Continuing with our running example, \( \phi(g_2) \) can be applied as an abstraction mapping to the trace semantics \( Tr(Ex1) \) (see Figure 2) resulting in the abstracted trace semantics \( \phi(g_2)(Tr(Ex1)) \), shown below in Figure 3 in which the states of \( g_2 \) have been reduced accordingly.

\[
\begin{align*}
\phi(g_2)(\sigma(00)) &= (00, 10, 10) \\
\phi(g_2)(\sigma(01)) &= (00, 11, 00) \\
\phi(g_2)(\sigma(02)) &= (01, 01) \\
\phi(g_2)(\sigma(11)) &= (10, 10) \\
\phi(g_2)(\sigma(12)) &= (11, 00, 11)
\end{align*}
\]

Figure 3: The trace semantics \( \phi(g_2)(Tr(Ex1)) \) resulting from abstracting \( Tr(Ex1) \) using \( \phi(g_2) \).

Note that \( \phi(g_2)(Tr(Ex1)) \) is non–deterministic in the sense that we have two different traces beginning with the same state 00 (i.e. starting in state 00 we have a non-deterministic choice between two abstracted traces, \( (00, 10, 10) \) and \( (00, 11, 00) \)). This occurs as we are viewing the more complex set of behaviours captured by \( Tr(Ex1) \) from a simpler perspective.

To illustrate how invalid abstracted traces arise consider an MVN with two entities that has the following trace \( \sigma(00) = (00, 11, 01, 02, 02) \). When \( \sigma(00) \) is abstracted with the standard abstraction mapping \( \phi(g_2) = \{ 0 \mapsto 0, 1 \mapsto 0, 2 \mapsto 1 \} \) the result is the following

\[
\phi(g_2)(\sigma(00)) = (00, 10, 00, 01, 01)
\]

However, it can be observed that this is not a valid trace according to Definition 5 because global state 00 can lead to two different states and will therefore be omitted from the abstracted trace semantics.

We are now ready to define what it means for one MVN to be an abstraction of another.

**Definition 6.** Let \( MV_1 = (G_1, Y_1, N_1, F_1) \) and \( MV_2 = (G_2, Y_2, N_2, F_2) \) be two MVNs with the same structure, i.e. \( G_1 = G_2 \) and \( N_1(g_i) = N_2(g_i) \), for all \( g_i \in MV_1 \). Let \( \phi \) be an abstraction mapping from \( MV_2 \) to \( MV_1 \). Then we say that \( MV_1 \) **abstracts** \( MV_2 \) **under** \( \phi \), denoted \( MV_1 \triangleleft \phi MV_2 \), if, and only if, \( Tr(MV_1) \subseteq \phi(Tr(MV_2)) \).

An abstraction \( MV_1 \triangleleft \phi MV_2 \) indicates that the model \( MV_1 \) consistently abstracts the behaviour of a more complex model \( MV_2 \) by reducing the state space of those entities identified in the abstraction mapping \( \phi \). Note alternatively, we could consider \( MV_2 \) to be a **refinement of** \( MV_1 \) in the sense that \( MV_2 \) consistently extends \( MV_1 \) with the addition of further states. Such a notion of refinement is useful as it provides a framework for the incremental development of MVN models.

As an abstraction example, consider the MVN \( Ex2 \) defined in Figure 4 which has the same structure as \( Ex1 \) (see Figure 11) but is a Boolean model. Then clearly, given the abstraction mapping \( \phi(g_2) \) introduced earlier, we can see that \( Tr(Ex2) \subseteq \phi(g_2)(Tr(Ex1)) \) holds and so \( Ex2 \) is an abstraction of \( Ex1 \), i.e. \( Ex2 \triangleleft \phi(g_2) Ex1 \) holds.

\[
\begin{array}{ccc}
g_1 & g_2 & \phi(g_2) \\
0 & 0 & 1 \ \\
0 & 1 & 1 \ \\
1 & 0 & 0 \ \\
1 & 1 & 0
\end{array}
\]

\[
\begin{array}{c}
s(00) = (00, 11, 00) \\
s(01) = (01, 01) \\
s(10) = (10, 10) \\
s(11) = (11, 00, 11)
\end{array}
\]

Figure 4: State transition tables defining \( Ex2 \) and its associated trace semantics \( Tr(Ex2) \).
In special cases, an abstraction may exactly capture the behaviour of the original MVN model under the given abstraction mapping. We distinguish this stronger case with the notion of an exact abstraction.

**Definition 7.** Let $MV_1$ and $MV_2$ be two MVNs such that $MV_1 \prec^\phi MV_2$ for some abstraction mapping $\phi$. Then we say that $MV_1$ exactly abstracts $MV_2$ under $\phi$, denoted $MV_1 =^\phi MV_2$, if, and only if, $Tr(MV_1) = \phi(Tr(MV_2))$ and for every $\sigma \in Tr(MV_2)$, the abstracted trace $\phi(\sigma)$ is valid.

Exact abstractions are interesting as they indicate redundant states (normally corresponding to entity thresholds) which have no affect on the qualitative behaviour of an MVN. Subsequently, an exact abstraction provides a simpler representation of an MVN whilst preserving all its behaviour under the given abstraction mapping.

It is natural to consider whether every (non–Boolean) MVN has an abstraction. In other words, do there exist MVNs which contain regulatory interactions which are too subtle to be represented in a simpler state domain. This is an interesting question since it provides insight into the need for non-Boolean MVN models. Unsurprisingly, it turns out that abstractions do not always exist, as formalized in the following theorem.

**Theorem 8.** Not every non–Boolean MVN has an abstraction.

**Proof.** We simply construct a non–Boolean MVN which we show has no abstractions. Let $Ex_3$ be defined by extending $Ex_1$ (Figure 1) with a third Boolean entity $g_3$ which is inhibited whenever $g_2$ is in a state greater than or equal to 1. The complete definition for $Ex_3$ is given in Figure 5.

![State Transition Tables](image)

**Figure 5:** The state transition tables defining $Ex_3$ (used to prove Theorem 8).

We can see that $g_2 \in Ex_3$ now acts in two subtly different ways: on one hand $g_1$ is inhibited when $g_2 = 2$; and on the other hand, $g_3$ is inhibited when $g_2 \geq 1$. We can show that no abstraction exists for this model by exhaustively considering each possible abstraction mapping $\phi(g_2)$ and showing that for every possible candidate abstraction model $MV_A$ we have $Tr(MV_A) \not\subseteq \phi(g_2)(Tr(Ex_3))$. 

This is an important result which, although centered around the relationship assumption formalized by our abstraction theory, provides insight into the expressive power of MVNs and in particular, motivates the need for multi-valued modelling techniques.

One of the main motivations for defining an abstraction theory is to allow simplified models of an MVN to be identified to aid the analysis process. This therefore raises the question of what properties of an abstraction are preserved by the original MVN and we end this section by considering this question.

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1 An MVN is said to be non–Boolean if it contains at least one entity which has more than two possible states.
We begin by introducing a notion of corresponding states and traces.

**Definition 9.** Let $MV$ be an MVN with an abstraction $MV_A$ under a given abstraction mapping $\phi$, i.e. $MV_A \prec^\phi MV$. Let $S^A \in S_{MV_A}$ be some global state of abstraction $MV_A$ and $S \in S_{MV}$ be a global state of the original model $MV$. Then we say that $S^A$ and $S$ correspond with respect to $\phi$, denoted $S^A \prec^\phi S$, if, and only if, $S^A = \phi(S)$. Furthermore, given traces $\sigma^A \in Tr(MV_A)$ and $\sigma \in Tr(MV)$ we say $\sigma^A$ and $\sigma$ correspond with respect to $\phi$, denoted $\sigma^A \prec^\phi \sigma$, if, and only if, $\phi(\sigma)$ is valid and $\sigma^A = \phi(\sigma)$. \hfill \Box

Let $S_1 \xrightarrow{\cdot} S_2$ denote the fact that global state $S_2 \in S_{MV}$ is reachable from global state $S_1 \in S_{MV}$ in the model $MV$. We now clarify the relationship between reachability properties in an abstraction and its corresponding original MVN model.

**Theorem 10.** Let $MV_A \prec^\phi MV$ for some mapping abstraction $\phi$ and let $S^A_1, S^A_2 \in S_{MV_A}$. If $S^A_1 \xrightarrow{\cdot} S^A_2$ in $MV_A$ then there must exist states $S_1, S_2 \in S_{MV}$ such that $S^A_1 \prec^\phi S_1, S^A_2 \prec^\phi S_2$, and $S_1 \xrightarrow{\cdot} S_2$ in $MV$.

**Proof.** Since $S^A_1 \xrightarrow{\cdot} S^A_2$ there must exist a trace $\sigma(S^A_1) \in Tr(MV_A)$ containing $S^A_2$. From Definition 6 we know that $Tr(MV_A) \subseteq \phi(Tr(MV))$ must hold. Therefore there must exist a state $S_1 \in S_{MV}$ such that $\sigma(S^A_1) \prec^\phi \sigma(S_1)$, i.e. $\phi(\sigma(S_1)) = \sigma(S^A_1)$. From this it is straightforward to see that there must exist the required state $S_2$ in trace $\sigma(S_1)$ such that $S^A_2 \prec^\phi S_2$ and $S_1 \xrightarrow{\cdot} S_2$. \hfill \Box

In other words, reachability properties of abstractions have corresponding reachability properties in the original MVN. However, since abstractions normally capture less behaviour than the original model, there are limitation on what can be deduced from an abstraction. It turns out that determining reachability in a model using an abstraction is a semi-decidable property: (i) By Theorem 10 we know that if one state is reachable from another in an abstraction then a corresponding reachability property must hold in the original model; (ii) However, if one state is not reachable from another in an abstraction then a corresponding reachability property in the original MVN may or may not hold and more analysis will be required.

The final result we present is important as it shows that the attractor cycles found in an abstraction are preserved by the original MVN.

**Theorem 11.** Let $MV_A \prec^\phi MV$ for some abstraction mapping $\phi$. Then $ATT(MV_A) \subseteq \phi(ATT(MV))$.

**Proof.** Let $\tau \in ATT(MV_A)$ then we need to show that $\tau \in \phi(ATT(MV))$. By definition we know there must exist a trace $\sigma_A \in Tr(MV_A)$ such that $\phi(\sigma_A) = \tau$. Since $MV_A \prec^\phi MV$ we know there must exist a trace $\sigma \in Tr(MV)$ such that $\phi(\sigma)$ is valid and $\sigma_A = \phi(\sigma)$. It follows that $\tau = \phi(\sigma)$ and so by definition we know that $\tau \in \phi(ATT(MV))$ as required. \hfill \Box

### 4 Identifying Model Abstractions

In the previous section we defined a formal notion of what it means for one MVN to be a correct abstraction of another. Given an MVN $MV$ and an abstraction mapping $\phi$ we can therefore define the set $AS(MV, \phi)$ of all abstractions of $MV$ under $\phi$, i.e.

$$AS(MV, \phi) = \{ MV_A \mid MV_A \prec^\phi MV \}.$$
Finding abstractions, i.e. members of \( \text{AS}(\text{MV}, \phi) \), is clearly an important task given that they provide a means of simplifying the analysis of a model and can help address the well-known problem of state space explosion. However, in practice, the brute force derivation of this refinement set becomes intractable for all but the smallest MVN. Specifically, if we have \( k \) entities each with \( n \) states, then we have a worst case upper bound of \( (n^k)^k \) possible candidate models to consider for any abstraction mapping. For instance, there are \( (2^3)^3 = 16777216 \) possible Boolean networks consisting of just three entities! The rest of this section considers techniques for efficiently identifying abstractions and provides a basis for automating this task. Initial ideas for implementing these techniques are presented in [2].

We begin by considering how an abstraction mapping can be applied to an MVN to produce a set of potential abstraction models.

**Definition 12.** Let \( \phi = (\phi(g_1), \ldots, \phi(g_i)) \) be an abstraction mapping for an MVN MV. For each entity \( g_i \in MV \) we can abstract the next-state function \( f_{g_i} : Y(g_{i1}) \times \cdots \times Y(g_k) \rightarrow Y(g_i) \) to a (possibly) non-deterministic next-state function

\[
\phi(f_{g_i}) : \phi(g_{i1})(Y(g_{i1})) \times \cdots \times \phi(g_k)(Y(g_k)) \rightarrow \phi(g_i)(Y(g_i))
\]

by applying \( \phi \) to its definition in the obvious way. We say that \( MV^A \) results from applying \( \phi \) to \( MV \) iff:

1. \( MV^A \) has the same entities and neighbourhood structure as \( MV \);
2. The state space of each entity \( g_i \in MV^A \) is the set \( \phi(g_i)(Y(g_i)) \);
3. For each \( g_i \in MV^A \) its next-state function \( f_{g_i}^A = f_{g_i} \) results from applying \( \phi(f_{g_i}) \).

We define \( \phi(MV) \) to be the set of all such MVNs, i.e.

\[
\phi(MV) = \{ MV^A \mid MV^A \text{ results from applying } \phi \text{ to } MV \}
\]

The trace semantics of \( \phi(MV) \) is then defined by \( \text{Tr}(\phi(MV)) = \bigcup_{MV^A \in \phi(MV)} \text{Tr}(MV^A) \)

To illustrate this idea, consider applying the abstraction mapping \( \phi(g_2) = \{ 0 \mapsto 0, 1 \mapsto 0, 2 \mapsto 1 \} \) to the example MVN Ex1 introduced in Section 2 (see Figure 1). The resulting abstracted next-state functions are presented in Figure 6. The set \( \phi(g_2)(Ex1) \) will contain two candidate abstractions in which the state space for \( g_2 \) is reduced to \( \{0, 1\} \) and whose next-state functions are given by the two possible interpretations (highlighted in bold) for the abstracted state transition table for \( g_2 \) given in Figure 6

\[
\begin{array}{c|cc}
  & g_1 & g_2 \\
\hline
 g_2 & 0 & 1 \\
   & 0 & 1 \\
   & 0 & 0 \\
\end{array}
\]

\[
\begin{array}{c|cc}
  & g_1 & g_2 \\
\hline
 g_2 & 0 & 1 \\
   & 1 & 0 \\
   & 1 & 0 \\
\end{array}
\]

\[
\begin{array}{c|cc}
  & g_1 & g_2 \\
\hline
 g_2 & 0 & 1 \\
   & 1 & 0 \\
   & 1 & 1 \\
\end{array}
\]

\[
\begin{array}{c|cc}
  & g_1 & g_2 \\
\hline
 g_2 & 0 & 0 \\
   & 0 & 0 \\
   & 0 & 1 \\
\end{array}
\]

\[
\begin{array}{c|cc}
  & g_1 & g_2 \\
\hline
 g_2 & 1 & 0 \\
   & 0 & 0 \\
   & 1 & 1 \\
\end{array}
\]

**Figure 6:** The (non–deterministic) state transition tables for \( \phi(g_2)(Ex1) \) which result from applying \( \phi(g_2) \) to the state transition tables of Ex1 (Figure 1).
An interesting observation arises by noting that for a given model \( MV \) and abstraction mapping \( \phi \), the trace semantics of the abstracted MVN \( Tr(\phi(MV)) \) is not in general the same as the abstracted trace semantics \( \phi(Tr(MV)) \). In fact, it turns out that an important relationship exists between the two, in that \( Tr(\phi(MV)) \) will always contain at least the traces of \( \phi(Tr(MV)) \), as shown by the following theorem.

**Theorem 13.** Let \( \phi = \langle \phi(g_1), \ldots, \phi(g_k) \rangle \) be an abstraction mapping for \( MV \). Then we have

\[
\phi(Tr(MV)) \subseteq Tr(\phi(MV)).
\]

**Proof.** Let \( \sigma = \langle S_0, \ldots, S_n \rangle \in Tr(MV) \) be an arbitrary trace, then we need to show that if \( \phi(\sigma) \) is a valid abstracted trace then \( \phi(\sigma) \in Tr(\phi(MV)) \). Let \( S_i \rightarrow S_{i+1} \) be an arbitrary state step in \( \sigma \). Assuming \( MV \) has \( k \) entities then this state step can be broken up into \( k \) components \( S_i \rightarrow S'_i \), for \( j = 1, \ldots, k \). Applying the abstraction mapping to each component gives \( \phi(S_i) \rightarrow \phi(g_j)(S'_i) \). Clearly, by Definition \( 12 \) there must exist \( MV'^a \in \phi(MV) \) whose next-state functions reproduce each of these abstracted component steps and so is able to reproduce the complete abstracted state step \( \phi(S_i) \rightarrow \phi(S_{i+1}) \). Since \( \phi(\sigma) \) is a valid abstracted trace it follows that we must be able to find \( MV'^a \in \phi(MV) \) which is able to reproduce all the abstracted state steps \( \phi(S_i) \rightarrow \phi(S_{i+1}) \), for \( i = 0, \ldots, n-1 \). Thus, we know \( \phi(\sigma) \in Tr(MV'^a) \) and so by Definition \( 12 \) we have \( \phi(\sigma) \in Tr(\phi(MV)) \) as required.

From this result, it follows that any abstraction of an MVN \( MV \) must be contained within the set of potential abstractions \( \phi(MV) \) as formalized in the corollary below.

**Corollary 14.** Given two MVNs \( MV_1 \) and \( MV_2 \) we have that

\[
MV_1 \prec^\phi MV_2 \implies MV_1 \in \phi(MV_2).
\]

**Proof.** By Definition \( 6 \) we know \( Tr(MV_1) \subseteq \phi(Tr(MV_2)) \) and so by Theorem \( 13 \) we have \( Tr(MV_1) \subseteq Tr(\phi(MV_2)) \). It therefore follows by Definition \( 12 \) that \( MV_1 \in \phi(MV_2) \).

Corollary \( 14 \) provides an important necessary condition for an MVN to be an abstraction of another for a given abstraction mapping. It gives us a way of restricting the models that need to be considered when iterating through possible candidate abstractions for an MVN; we simply apply the abstraction mapping to the MVN in question and then consider each possible deterministic model that results from this application. This observation results in an exponentially smaller search space and provides the basis for a more efficient abstraction finding algorithm.

To illustrate the above ideas let us consider finding all the abstractions for \( Ex1 \) under \( \phi(g_2) \), i.e. calculating the abstraction set \( AS(Ex1, \phi(g_2)) \). Using the results from Corollary \( 14 \) we begin by abstracting the state transition tables for \( Ex1 \) using the given abstraction mapping (shown previously in Figure \( 6 \)) and identifying the potential abstractions contained in \( \phi(g_2)(Ex1) \). We can see that the behaviour of \( g_2 \) is non-deterministic when \( g_1 = 0 \) and \( g_2 = 0 \). As such, we have just two possible candidate models \( AB_1 \) and \( AB_2 \) to consider, shown respectively by Figure \( 7 \)(a) and Figure \( 7 \)(b) (where the rules highlighted in bold are the only ones that differ).

In order to verify whether \( AB_1 \) and \( AB_2 \) are indeed abstractions according to our theory, we check if their trace semantics are contained within \( \phi(g_2)(Tr(Ex1)) \). By considering Figure \( 3 \) and Figure \( 4 \) we can observe that \( AB_1 \) is not an abstraction according to Definition \( 6 \) since \( Tr(AB_1) \not\subseteq \phi(g_2)(Tr(Ex1)) \); in other words, its behaviour is not regarded as being consistent with \( Ex1 \). On the other hand, we find that \( AB_2 \) is a correct abstraction as \( Tr(AB_2) \subseteq \phi(g_2)(Tr(Ex1)) \). (Indeed, we can see that \( AB_2 \) is precisely
the same MVN as Ex2 which was introduced as an abstraction in the previous section. Thus, we have shown that the refinement set \( AS(Ex1, \phi(g_i)) = \{ AB_2 \} \).

It can be observed that exact refinements occur precisely when the translated MVN has a singleton set of candidate abstraction models, as shown by the following theorem.

**Theorem 15.** Let \( \phi \) be an abstraction mapping for some MVN \( MV \). Then we know the following:

1. if \( \phi(MV) = \{ MV^A \} \) is a singleton set, then \( MV^A = \phi(MV) \);
2. if \( \phi(MV) \) is not a singleton set, then no exact abstraction for \( MV \) can exist under \( \phi \).

**Proof.** To prove (1), we observe that if \( \phi(MV) = \{ MV^A \} \) is a singleton set then for each \( g_i \in MV \) the abstracted next-state function \( \phi(f_{g_i}) \) must be deterministic. This implies that all abstracted traces \( \phi(\sigma) \), for \( \sigma \in \text{Tr}(MV) \) must be valid. Furthermore, by Definition 12 and Theorem 13 it follows that \( Tr(MV^A) = \phi(\text{Tr}(MV)) \) as required.

To prove (2), note that if \( \phi(MV) \) contains more than one potential abstraction model then there must exist at least one abstracted next-state function \( \phi(f_{g_i}) \) which is non–deterministic. This implies there must exist at least one abstracted global state which leads to two or more different traces. Clearly, either some of these abstracted traces are invalid or \( \phi(\text{Tr}(MV)) \) must contain more traces than any single abstraction model could capture. Therefore, there cannot exist an exact abstraction for \( MV \). \( \square \)

## 5 Illustrative Biological Examples

In this section we illustrate the theory and techniques developed in the previous sections by investigating the existence of abstractions for two published MVN models for the genetic regulatory network controlling the lysis–lysogeny switch in the bacteriophage \( \lambda \) [17, 5]. We begin with a brief introduction to the bacteriophage \( \lambda \) (see [14] for a more detailed introduction).

The temperate bacteriophage \( \lambda \) is a virus which infects the bacteria *Escherichia coli* [18, 14]. After infection of the host cell, a decision is made by \( \lambda \) based on environmental factors between two very different methods of reproduction, namely the *lytic* and *lysogenic* cycles [18]. In most cases, \( \lambda \) enters the *lytic cycle*, where it generates as many new viral particles as the host cell resources allow before producing an enzyme to lyse the cell wall, releasing the new phage into the environment. Alternatively, the \( \lambda \) DNA may integrate into the host DNA and enter the *lysogenic cycle*. Importantly, genes expressed
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in the λ DNA synthesize a repressor which blocks expression of other phage genes including those involved in its own excision. As such, the host cell establishes an immunity to external infection from other phages, and the phage λ is able to lie dormant, replicating with each subsequent cell division of the host.

5.1 The Two Entity Core Regulatory Model

A simple MVN model of the core regulatory mechanism for the lysis–lysogeny switch was proposed in [17]. This model, which we denote as PL2, is presented in Figure 8 and is based on the cross–regulation between two regulatory genes, CI (the repressor gene) and Cro. It can be seen that Cro inhibits the expression of CI and at higher levels of expression, also inhibits itself. The gene CI inhibits the expression of Cro while promoting its own expression. The full synchronous trace semantics Tr(PL2) for this MVN is presented in Figure 8(c). We can see from the state transition graph in Figure 8(d) that PL2 has three attractor cycles, where the attractor cycle 10 → 10 represents the lysogenic cycle since the repressor gene CI is fully expressed and 01 → 02 → 01 represents the lytic cycle.

In order to identify an abstraction for PL2 we begin by selecting an appropriate state mapping \( \phi(Cro) : \{0,1,2\} \rightarrow \{0,1\} \) for the only non-Boolean entity Cro. We use our understanding of the behaviour of Cro to define the following state mapping

\[
\phi(Cro) = \{0 \mapsto 0, 1 \mapsto 1, 2 \mapsto 1\}.
\]

We can then view \( \phi(Cro) \) as an abstraction mapping and following the approach in Section 4 we restrict the abstraction search space by applying the abstraction mapping \( \phi(Cro) \) to PL2. This results in a set \( \phi(Cro)(PL2) \) which contains two candidate abstraction models. It turns out that only one of these is a correct abstraction and we present this abstraction model APL2 in Figure 9. It is straightforward to check that the trace semantics of APL2 (see Figure 9) is indeed consistent with the abstracted trace semantics of PL2 (see Figure 10), i.e. \( Tr(APL2) \subseteq \phi(Cro)(Tr(PL2)) \). Thus, we know \( APL2 \triangleleft \phi(Cro) PL2 \) holds.
Figure 9: Abstraction model $APL_2$ for $PL_2$ and associated trace semantics $Tr(APL_2)$.

\[
\begin{align*}
\phi(Cro)(\sigma(00)) &= \langle 00, 11, 00 \rangle & \phi(Cro)(\sigma(01)) &= \langle 01, 01 \rangle \\
\phi(Cro)(\sigma(02)) &= \langle 01, 01 \rangle & \phi(Cro)(\sigma(10)) &= \langle 10, 10 \rangle \\
\phi(Cro)(\sigma(11)) &= \langle 11, 00, 11 \rangle
\end{align*}
\]

Figure 10: The traces $\phi(Cro)(Tr(PL_2))$ resulting from abstracting the traces of $PL_2$ using $\phi(Cro)$.

It can be seen that the abstraction $APL_2$ acts as a good approximation to the behaviour of the original MVN $PL_2$ and in particular, we can see that the abstraction has captured all three attractor cycles that were present in $PL_2$.

5.2 The Four Entity Regulatory Model

The core regulatory model presented above was extended in [17] to take account of the actions of two further regulatory genes, $CII$ and $N$. The resulting four entity MVN model $PL_4$ is presented in Figure 11 (note that the state transition tables presented use a shorthand notation where an entity is allowed to be in any of the states listed for it in a particular row). This MVN is more detailed than $PL_2$ and contains two entities with non-Boolean state spaces, namely $CI$ with states $\{0, \ldots, 2\}$ and $Cro$ with states $\{0, \ldots, 3\}$. The resulting state space for the model consists of 48 global states and for this reason we do
not reproduce its trace semantics here. Instead, we simply note that \( PL4 \) has the following three attractor cycles (where the first corresponds to the lytic cycle and the remaining two to the lysogenic cycle):

\[
0300 \rightarrow 0200 \rightarrow 0300, \quad 1000 \rightarrow 2100 \rightarrow 1000, \quad 2000 \rightarrow 2000
\]

We begin by looking to abstract the non-Boolean entities \( CI \) and \( Cro \) by defining appropriate state mappings. After considering the model, we define the following state mappings:

\[
\phi(CI) = \{0 \mapsto 0, 1 \mapsto 1, 2 \mapsto 1\}, \quad \phi(Cro) = \{0 \mapsto 0, 1 \mapsto 1, 2 \mapsto 1, 3 \mapsto 1\}
\]

which we use to define the abstraction mapping \( \Phi = \langle \phi(CI), \phi(Cro), I_{CI}, I_N \rangle \). Again, following the approach presented in Section 4 we first apply this abstraction mapping to \( PL4 \) resulting in the set \( \Phi(PL4) \) of candidate abstraction models. By analysing \( \Phi(PL4) \) we are able to establish that there are 256 possible candidate abstraction models (we have 4 choices for \( CI \), 4 choices for \( Cro \), 8 choices for \( CII \), and 2 choices for \( N \)). After investigating these candidate models we were able to identify two abstractions for \( PL4 \) under \( \Phi \), denoted \( APL4_1 \) and \( APL4_2 \), which are presented in Figure 12. Interestingly, both abstractions appear to capture the key behaviour of \( PL4 \) in the sense that both contain the attractor cycles 0100 \( \rightarrow \) 0100 and 1000 \( \rightarrow \) 1000 which correspond to those present in \( PL4 \).

![Figure 12: The transition tables for the two abstractions APL4\(_1\) and APL4\(_2\) identified for PL4 under \( \Phi \), where all the transition tables are the same except for \( CII \) where 011 \( \rightarrow \) 1 for abstraction APL4\(_1\) but 011 \( \rightarrow \) 0 for abstraction APL4\(_2\).](image)

### 6 Conclusions

In this paper we have developed an abstraction theory for MVN models based on the idea of using an abstraction mapping to relate the reduced state space of an abstraction to the original model. The problem of identifying suitable abstractions for an MVN was discussed and some initial ideas for restricting the number of candidate abstraction models that need to be considered were proposed. We showed that abstractions can be used to analyse an MVN since they preserve reachability properties and importantly, since all the attractor cycles of an abstraction will correspond to attractor cycles in the original model. This work was motivated by the need to be able to relate MVN models at different levels of abstraction and in particular, the idea of abstracting an MVN to a simpler model which is more amenable to analysis and visualization techniques. The abstraction theory presented can also be seen as providing a framework for an incremental refinement approach to constructing MVNs.
We illustrated the abstraction theory and techniques developed by considering two examples based on published MVN models of the genetic regulatory network for the lysis-lysogeny switch in phage λ [17, 5]. We considered a simple two entity model and then an extended model that contained four entities (two of which were non-Boolean). In both cases we were able to identify meaningful Boolean abstractions which captured the key attractor cycles contained in the original models.

Further work is now needed to build on the ideas presented in Section 4 to develop tool support for automatically checking and identifying abstractions. Initial ideas for such tool support have been presented in [2] and work is on going to develop efficient algorithmic solutions to support the abstraction process. Other researchers have considered abstracting MVNs by reducing the number of regulatory entities while preserving important model dynamics (see for example [13, 20]). It would be interesting to consider combining such an approach with the abstraction theory we have developed here. Finally, we note that extending the abstraction theory to asynchronous MVN models is an interesting but challenging area of future work. In particular, ways of coping with the non-deterministic choices inherent in the dynamic behaviour of asynchronous models will be needed.

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