A Heuristic for Reachability Problem in Asynchronous Binary Automata Networks

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Abstract On demand of efficient reachability analysis due to the inevitable complexity of large-scale biological models, this paper is dedicated to a novel approach: PermReach, for reachability problem of our new framework, Asynchronous Binary Automata Networks (ABAN). ABAN is an expressive modeling framework which contains all the dynamics behaviors performed by Asynchronous Boolean Networks. Compared to Boolean Networks (BN), ABAN has a finer description of state transitions (from a local state to another, instead of symmetric Boolean functions). To analyze the reachability properties on large-scale models (like the ones from systems biology), previous works exhibited an efficient abstraction technique called Local Causality Graph (LCG). However, this technique may be not conclusive. Our contribution here is to extend these results by tackling those complex intractable cases via a heuristic technique. To validate our method, tests were conducted in large biological networks, showing that our method is more conclusive than existing ones.

Keywords Asynchronous Binary Automata Networks · Local Causality Graph · heuristic

1 Introduction

Works on concurrent systems have been of interest for systems biology for a decade [6,7,28]. In this context, the challenges nowadays consist of not only model validation with regard to existing knowledge on systems but also behavior prediction of these systems. With quantities of available data provided by new technologies, e.g., DNA microarray [16], there is a growing need for high-performance analytic tools, especially for reachability problem, as many static and dynamical properties are transformable to the reachability of certain states. Reachability problem has been studied under many different modeling frameworks for decades [3,5,10,11,17,29] and takes an important part in Model Checking [9]. State Space Explosion problem arises in reachability analysis of concurrent systems as the state space is exponential to the number of components in the model, thus disables naïve approaches. More concretely, Peterson has shown that the reachability problem of Petri net is exponential time-hard and exponential space-hard [22], and this conclusion does not change even in some special situations [11]. We are prone to believe that the reachability of Boolean Network is also in this class, as there does not exist an efficient solution of polynomial complexity, although there does not exist such formal proof for the non-existence.

Related studies have been carried over various frameworks: Plateau et al. [23] propose a Stochastic Automata Network and study its steady-state behavior, while the reachability analysis is absent; Li et al. [14,15] investigate theoretically the stability, controllability and reachability of Switched Boolean Networks, but their method remains computationally expensive; Ben Abdallah et al. [1] designed an exhaustive algorithm for reachability using ASP (Answer Set Programming) [4]. Although ASP has a built-in optimization, the complexity is still exponential.

To tackle the persisting complexity issue, symbolic model checking [8] and SAT-solvers [2] have been considered over years, but the solution space of original problem remains huge. Paulevé et al. [12,19] have pro-
posed new discrete modeling frameworks for concurrent systems: Process Hitting and its updated Automata Network (AN) form. They provide an approach to address this issue by designing a static abstraction (with an over-approximation and an under-approximation of the real dynamics) inspired by abstract interpretation: Local Causality Graph (LCG). This static analysis drastically reduces the state-space and avoids costly global search.

In various circumstances, LCG is capable of giving a deterministic result of the reachability of desired states and corresponding realizing transition sequences (if reachable) in polynomial time to the number of automata, but its applicability is still limited. There are inconclusive cases which disable the reasoning of sufficient conditions, if there exists cycles or conflicts in the LCG. We will identify these cases later (in section 4).

Main Contributions

With the initiative of LCG, this paper is devoted to the study of general reachability problems in Asynchronous Binary Automata Networks (ABAN), then to gain a more profound understanding of the dynamics of biological systems. Many biological networks are encoded in Boolean style, because BN is a simple formalism but with strong expressiveness also due to the imprecision of raw data. Different from BN, ABAN is a finite state machine comprised by communicating automata. Each automaton has 2 states corresponding to the bit 0 and 1 in BN. One of the interests of studying ABANs is that BN may be not expressive enough in biological context. For example, to model the dynamic behavior “a ← 1 when b = 1”, we have a(t + 1) = b(t) in BN, a always follows the evolution of b, but with an unwanted behavior “a ← 0 when b = 0”. ABAN can model this dynamics as a = b1 → a0 without redundancy. More importantly, ABAN reduces the complexity of reachability analysis under some special conditions (e.g. LCG with cycles) and helps to embark on the most difficult inconclusive instances without globally traversing the state space, which is the main theme of this paper. Besides, BNs are transformable to Automata Networks, and this property makes our work more extensive (see Appendix C).

To solve a problem which is costly for naive approaches, there are basically three methodologies:

1. abstract the original problem or find a simplified formalism
2. study polynomially solvable cases of the problem
3. apply heuristic

(1) guarantees a correct solution for the problem after abstraction which is not necessarily equivalent to the solution of the original problem; (2) guarantees a correct solution only for a part of instances; (3) keeps the original problem but does not guarantee a correct solution. We are going to walk on the pathway (3) of heuristic. After diving into the mechanics of LCG and the inconclusive cases, we figure out the reason why those cases are intractable by existing static reasoning. With a better understanding of the internal structure of LCGs, we develop a heuristic technique aiming at the application for general instances. This heuristic method has a better performance on conclusiveness than static reasoning, because it attempts to explore a part of the system dynamics via partial verification. In the end, we conduct tests on signaling networks of around 100 components (TCR and EGFR, see Section 5): the results of LCG contain inconclusive instances while our new method solves them.

This paper is organized as follows: in section 2, we will introduce the formal background, BN and Asynchronous Binary Automata Network (ABAN); section 3 presents the analysis of dynamics using only static reasoning; section 4 is the core content of this paper, concerning the solution of inconclusive cases; discussion about tests and conclusion are placed in section 5 and 6.

2 Preliminaries

Notations: :: sequential connector; ↑ state change; ∧ logic AND; ∨ logic OR; # cardinal; a.next the successor of a.

Asynchronous Binary Automata Network (ABAN) is a variant of traditional AN. Binary means that every automaton has exactly two possible states (0, 1) and asynchronous implies the update scheme with no more than one automaton can change its value at a time.

Definition 1 (ABAN) An ABAN is a triplet $AB = (\Sigma, L, T)$, where:

- $\Sigma \triangleq \{a, b, \ldots, z\}$ is the finite set of automata with every component having a Boolean state;
- $L_a \triangleq \{a_0, a_1\}$ is the set of binary states of automaton $a \in \Sigma$,
- $LS = \bigcup_{a \in \Sigma} L_a$ is the set of all local states,
- $L \triangleq \bigtimes_{a \in \Sigma} L_a$ is the set of global states, the state of automaton $a$ at state $s$ is denoted $s[a] = a_t$;
- $T \triangleq \{A \rightarrow b_j \mid b_j \in \Sigma \land A \in L\}$ is the set of transitions, where $A$ is the required state(s) for the transition, which allows to flip $b_j$ to the other Boolean state. In other words, transition $tr = A \rightarrow b_j$ is said firable iff $A \subseteq s$. 
Furthermore, to describe the evolution of an ABAN, we use the notion of trajectory:

**Definition 2 (Trajectory)** Given initial state \( s \in L \), a trajectory \( \delta \) from \( s \) to \( \Omega \) is a sequence of transitions in \( T \) that can be fired successively.

From a given initial state \( s \), the state after firing \( \delta \) is denoted \( s \cdot \delta \) and its local form of certain automaton \( a \) is noted \( (s \cdot \delta)[a] \). Fig. 1 shows an example of ABAN, with initial state \( s = \langle a_0, b_0, c_0, d_0, e_0 \rangle \) and a possible trajectory is \( \delta = d_0 \rightarrow b_1 \rightarrow b_1 \rightarrow d_0 \rightarrow d_1 \rightarrow e_0 \rightarrow \{b_1, c_1\} \rightarrow a_0 \). After firing \( \delta \), final state \( \Omega = s \cdot \delta = \langle a_1, b_1, c_1, d_1, e_0 \rangle \).

As to the reachability problem, given an ABAN, global reachability can be formalized as: global state \( \Omega \) is reachable iff there exists a trajectory \( \delta \) such that \( s \cdot \delta = \Omega \). Partial reachability is defined analogously: local state \( \omega = a_i \) is reachable iff there exists a trajectory \( \delta \) such that \( (s \cdot \delta)[a] = a_i \). Reachability is denoted \( reach(\Omega) \) or \( reach(\omega) \) and takes Boolean value 0 or 1.

In Fig. 1, we can see \( \Omega = \langle a_1, b_1, c_1, d_1, e_0 \rangle \) or \( \omega = a_1 \) is reachable from initial state \( s \) via trajectory \( \delta \), that is \( reach(a_1) = 1 \) and \( reach(\Omega) = 1 \).

To simplify the notations, all the initial states of ABAN are set to 0 by default.

### 3 Static analysis of reachability property

To approach various dynamical properties of such networks, Local Causality Graph (LCG) is an efficient static analytic tool for reachability put forward by Paulevé et al. [19]. LCG determines the existence of trajectory of the desired state without global verification.

LCG functions as follows: its over-approximation and under-approximation which give respectively a necessary condition and a sufficient condition of reachability. With these conditions, we can conclude in many cases.

| Over          | True | True | False | False |
|---------------|------|------|-------|-------|
| Under         | True | False|       |       |
| Reach         | True | Inconclusive | True | False |

**Table 1** Truth table of LCG

More importantly, LCG is also able to provide us with a trajectory if \( \omega \) is reachable suggested by under-approximation. We are not going to detail the original version of this trajectory finding technique, instead, we propose its adaptation for ABAN in order to approach the solution of inconclusive cases. In this paper, only binary networks are studied, so we propose a simplified form of LCG instead of two LCGs (over and under-approximation) which is well suited for the present need.

The drawback is also clear: there are inconclusive cases, which means LCG is neither able to solve in this situation, nor able to generate a trajectory (if reachable). To improve the conclusiveness (less inconclusive cases) of this method, we generalize the over- and under-approximation into one (SLCG) and add a more detailed reachability analysis.

Besides, LCG is a technique designed for Automata Networks [12]. To give it a wider applicability, in appendix \( \text{c} \) we can see that any BN is transformable to ANs and then SLCG is applicable to its analyses of dynamical properties.

#### 3.1 Simplified Local Causality Graph (SLCG)

**Definition 3 (SLCG)** Given ABAN \( AB = (\Sigma, L, T) \), initial state \( \zeta \) and a desired local state \( \omega \), SLCG \( \Lambda_\zeta = (V_\omega, E_\omega) \) is the smallest recursive structure with \( V_\omega \subseteq LS \cup Sol \) and \( E_\omega \subseteq V_\omega \times V_\omega \) which satisfies:

\[
\omega \subseteq V_\omega
\]

For some \( a_i \in V_\omega \cap LS \), \( \{(a_i, sol_{a_i}) | a_i \in \zeta \} \subseteq E_\omega \)

For some \( sol_{a_i} \in V_\omega \cap Sol \) \( \{(sol_{a_i}, \nu(a(sol_{a_i})) \} \subseteq E_\omega \)

Notations: \( Sol \) is the set of solutions and \( V \) is the set of required local states of \( sol_{a_i} \).

Intuitively, when the recursive construction is complete, SLCG is in fact a digraph with state nodes \( LS \) and solution nodes \( Sol \). \( E \) consists of the links between state nodes and solution nodes. To access certain local states, at least one of its successive solution (corresponding transitions form solution nodes) needs to be fired; similarly, to make one solution nodeirable, all of its local states need to be satisfied. A recursive reasoning of reachability begins with a state node representing desired local state, go through \( a_i \mapsto sol_{a_i} \mapsto b_j \cdots \) and end with initial state (reachable) or a local state without solution successor (unreachable).

In Fig. 2, the reachability of \( a_1 \) is computed locally. The left solution node of \( a_1 \) does not lead to the goal because its successor \( e_1 \) does not have any successive solution node, \( i.e. \ e_1 \) is unreachable; the right solution
node of $a_1$ requires $b_1$ and $c_1$, and they finally lead to $d_0$ then to $\emptyset$, which is to say, we need nothing to reach $d_0$ as $d_0$ is in initial state (trivial solution).

We can figure out state nodes act as an OR gates while solution nodes act as AND gates. The reachability suggested by SLCG $reach'$ (different from real reachability $reach$) is computed recursively as follows:

$\begin{align*}
reach'(a_1) &= reach'(c_1) \lor (reach'(b_1) \land reach'(c_1)) \\
&= reach'(b_1) \land reach'(d_1) = reach'(b_1) \\
&= reach'(d_0) = 1
\end{align*}$

The algorithm of SLCG construction is in Appendix B.

### 3.2 Limitation of SLCG

Although SLCG allows us to reason the reachability locally without traversing the whole state space, it is still providing us with a necessary condition (quasi-equivalent) of reachability because SLCG does not simulate the real evolution of the system.

The inequivalent condition does not suggest it is impossible to reveal the real dynamics of the system. We are going to show that an SLCG gives an equivalent condition of reachability iff it satisfies the following conditions:

1. No cycles in SLCG
2. No conflicts in SLCG

To be more formal, a cycle (1) is in the form of $a_i \rightarrow \cdots \rightarrow a_i$, i.e. to access $a_i$, we have to reach first $a_i$. This self-involvement makes the reachability inconclusive. A conflict (2) is that a solution node has multiple successors generating branches, and there are different states of the same automaton i.e. $a_i$ and $a_{-i}$. We can not decide the order of reaching these states, because reaching one state may disable the reachability of another one. Sometimes there exists a trajectory which accesses these states in certain order, sometimes there does not exist such.

In the following examples, if we ignore those restrictions, SLCG does not imply real reachability, nor it is possible to extract a trajectory.

1. Example of Fig. 2 although there is a conflict, $a_1$ is reachable.
2. $\Sigma = \{a, b, c\}$, $T = \{b_0 \rightarrow a_0, a_0 \rightarrow b_0, \{a_1, b_1\} \rightarrow c_0\}$, desired final state $\omega = a_1$. Both $a_1$ and $b_1$ are reachable, but they can not be reached simultaneously. In the SLCG, there are two branches, $a_1 \rightarrow b_0$ and $b_1 \rightarrow a_0$, the automata $a$ and $b$ involve themselves in different branches, where a conflict appears.

3. $\Sigma = \{a, b, c\}$, $T = \{b_0 \rightarrow a_0, a_0 \rightarrow b_0, \emptyset \rightarrow a_1, \emptyset \rightarrow b_1, \{a_1, b_1\} \rightarrow c_0\}, \omega = a_1$. Similarly to example 2, both $a_0$ and $b_0$ are reachable, but they can not be reached simultaneously. In this example, we can see a cycle in the SLCG $a_1 \rightarrow b_0 \rightarrow b_1 \rightarrow a_0 \rightarrow a_1$.

In Example 1, $a_1$ is reachable, while in Example 2 and Example 3, $a_1$ is unreachable. This inconclusiveness is a limitation of SLCG.

As there are cycles in SLCG generated by feedback loops in biological regulatory networks, the existing approach does not allow a solution generally.

Even though we broadened the applicability of SLCG, this method is still not universally applicable for all ABANs or BNs due to the limitations. From the former examples, we realize that it is difficult to solve the reachability problem in general. In the rest of this paper, we are going to discuss how to improve the performance of existing approaches and our new methods.

### 3.3 Trajectory extraction for SLCG

In this section, we will first prove that if an AN is binary, reachability problem becomes equivalent to $reach'$ suggested by SLCG, with the restrictions in section B satisfied. With the equivalence, we propose a method.
Algorithm 1 Trajectory-extraction

Initialization: trajectory \( \delta \leftarrow \emptyset \), visited = \( \emptyset \)

Input: desired state \( a_i \)

function \( \text{EXTRACT}(a_i, \delta) \)

\( \text{sol} \leftarrow \text{random}(a_i, \text{next}) \)

\( \delta \leftarrow (\text{sol}.\text{next} \rightarrow a_i ; \delta) \)

if \( a_i \in \text{visited} \) then

return \( \delta \)

end if

if \( \text{sol}.\text{next} \neq \emptyset \) then

for \( b_j \in \text{sol}.\text{next} \) do

visited \( \leftarrow \) visited \( \cup \) \( b_j \)

\( \delta \leftarrow \delta : \text{EXTRACT}(b_j, \delta) \)

end for

end if

end function
solution nodes, i.e. no OR gate in the cycle), then all the local states in its cycles are unreachable and can then be deleted from the SLCG.

Proof Suppose an arbitrary cycle $C = a_1 \rightarrow \cdots \rightarrow b_j \rightarrow \cdots \rightarrow a_i$, with $\rightarrow$ an arrow in SLCG. Note that $reach(b_j) = reach(b_{j\text{next}}) = reach(b_{j\text{next}\text{next}}) \cdots$. As $C$ is a cycle, the reachability of all the local states are equivalent. Reaching any element $b_j$ in $C$ implies the reachability of all the elements in $C$. In SLCG, the reachability is deducted by reaching the initial state, i.e. if certain elements in $C$ are reachable, there exists at least one element $b_j$ belonging to the initial state. However $b_j$ should have no successor because it is reached already. This fact reveals that the fork containing $b_j$ can never form a cycle, contradiction. So none of the element in $C$ is reachable. □

With this theorem, we can also deal with cycles containing forks.

Lemma 1 The reachability of the elements in a cycle with forks equals to the disjunction of the reachability of the forks.

Proof Suppose a cycle $C = a_1 \rightarrow \cdots \rightarrow b_j \rightarrow \circ \rightarrow c_k \rightarrow \cdots \rightarrow a_i$, where $\circ$ represents a solution node. Suppose there is one fork located at $b_j$, $b_{j\text{next}} = \{c_k, \{d_i\}\}$, where $\{d_i\}$ are outsiders of the cycle. According to the reasoning of SLCG, $reach(b_j) = reach(c_k) \lor (\lor reach(d_i))$. As in the proofs above, all the local states in the cycle share the same reachability: $reach(b_j) = reach(c_k) \rightarrow reach(b_j) = reach(b_j) \lor (\lor reach(d_i))$. To keep this equation always valid, there must be $reach(b_j) = \lor reach(d_i)$. Similarly, we can obtain the reachability in a cycle with plural forks: $reach(C) = \lor reach(forks)$.

With Theorem 2 and Lemma 1 before stepping into the next part of dealing with AND gates, we can perform a recursive preprocessing by deleting the cycles in SLCG to ensure no cycle remaining.

4.2 AND Gates in SLCG

After preprocessing, we can get rid of cycles. The guideline is then to analyze an SLCG with only AND gates. To achieve this goal, we need to find a trajectory reaching all the components of given AND gates simultaneously. These components form a sub-state, and if the sub-state is reachable, the corresponding transition of AND gate can be fired.

Definition 4 (sub-state) The set of sub-states $S$ is the Cartesian product of the local states of several automata: $S \triangleq \times \subseteq L_\Sigma$, where $\Sigma' \subseteq \Sigma$.

Example: in Fig 4 sub $= \{b_1, c_1\}$ is a sub-state, when sub is reached, transition $\{b_1, c_1\} \rightarrow a_0$ is firable.

As the cycles do not persist, the order reaching the members in a sub-state is the only factor that affects the final reachability. The reachability of a sub-state can be then formulated as sequential reachability:

Definition 5 (Sequential reachability) Let $sub = \{l_{s_1}, \ldots, l_{s_n}\}$ and sequence $seq = l_{s_1} : \ldots : l_{s_n}$, the sequential reachability of sub is denoted $reach(seq) = reach(l_{s_1}) : \ldots : reach(l_{s_n})$, i.e. from initial state, the sub is reachable in the order seq by following the trajectories given by SLCG.

Example: Fig 5 shows the SLCG for reachability of $c_1$ in ABAN with transitions $T = \{a_1, b_1 \rightarrow c_0, b_0 \rightarrow a_0, c_0 \rightarrow b_0\}$.

Fig. 5 Reachability depends on firing order

$a_1$ and $b_1$ are reachable respectively but is not necessarily for $c_1$. If we begin with the fork $a_1$, $sub = \{a_1, b_1\}$ is reachable with trajectory $b_0 \rightarrow a_0 : c_0 \rightarrow b_0 : \{a_1, b_1\} \rightarrow c_0$. However if we begin with the fork $b_1$, after firing $c_0 \rightarrow b_0$, $b_0$ is no longer reachable, resulting the unreachability of $a_1$. We have $reach(a_1 : b_1 : c_1) = 0$ and $reach(b_1 : a_1 : c_1) = 0$.

As the firing order matters, we come to verify all the possible sequential reachabilities of certain sub-state to obtain its reachability.

Theorem 3 Given sub-state $sub = \{l_{s_1}, \ldots, l_{s_n}\}$, with all the local states in sub are reachable: $reach(l_{s_i}) = 1$, $\forall i \in [1, n]$, the set of permutations of sub is denoted $Perm(sub) = \{(l_{s_1} : l_{s_2} : \ldots : l_{s_n}), \ldots, (l_{s_1} :: l_{s_{n-1}} : \ldots, : l_{s_1})\}$. $\lor reach(Perm(sub)) = 1$ is a quasi-equivalent condition of $reach(sub) = 1$.

Proof Notation: $a_i \triangleright b_j$ means that $a_i$ must be present before $b_j$.

Necessity: if there exists a permutation $perm_i \in Perm$ s.t. $reach(perm_i) = 1$, then sub can be reached according to $perm_i$.

Quasi-sufficiency: in Definition 4 SLCG is the smallest structure which leads to desired local state. To reach sub, every local state in SLCG is mandatory to be reached. Then the question of sufficiency becomes:

Given $\lor reach(Perm(sub)) = 0$, does there exist a permutation $perm(Ls)$ s.t. $reach(sub) = 1$?
Although all the local states in sub are reachable, the existence of conflicts leads to potential unreachability of sub. Some conflicts are solvable, see Fig 5. There are also unsolvable ones. An unsolvable conflict can be formalized as: \(ls_1 \triangleright ls_2 \triangleright \cdots \triangleright ls_1\), where \(ls_1\) is before \(ls_2\) and \(ls_2\) is before \(ls_1\), which is impossible in asynchronous semantics. Example: in Fig 5 to reach \(\{a_1, b_1\}, a_1 \triangleright b_1 \triangleright a_1\), so the sub-state is unreachable. We can see the conflict is unsolvable no matter how we change the order of firing. For solvable conflicts, \(\text{perm}(\text{sub})\) probably covers one of the admissible order. One possible counterexample is shown in Fig. 6.

It is remarkable that the former approach is efficient in deciding reachability and finding reaching trajectory, but it has a drawback: if there exists a solvable conflict in different forks, traversing permutations may be not able to find the trajectory towards goal state. In Fig 6, if \(sol_{a_1}\) is resolved first, automaton \(d\) will be on state \(a_1\), which disables the reachability of \(b_1\). In other cases, the trajectory of \(a_1\) is findable.

\[\begin{array}{c}
\text{Fig. 6 Conflicts in different forks}\n\end{array}\]

For one sub-state, the number of permutations is \(A^I_j = I!\), as \(I = O(1)\), this number is adjustable by controlling \(I \approx 5040\), \(10! = 3.6 \times 10^6\).

However there is more than one AND gate in general biological networks and those AND gates could be chained e.g. \(25\), i.e. the successors of certain AND gate contain other AND gates. We analyze first the simple AND gates \(\text{simp}\) (without successive AND gates) by traversing its permutations. If all elements in \(\text{simp}\) are reachable, update initial state by firing all the transitions in extracted trajectory via (section 5.3), and delete the successors of \(\text{simp}\), then restart the process from finding simple AND gates. During the whole process, if an AND gate is not reachable after traversing its permutations, the final goal state is not reachable as the SLCG is linked by logical AND. Otherwise, when the process terminates, there is no AND gate, SLCG is conclusive as there is no cycle or conflict.

The statement above is the worst case: in reality, all AND gates are not necessarily composed of exact \(I\) components, and permutations are determined to be unreachable before verification as its subsets may have been confirmed unreachable in other tentatives.

For example: given an AND gate \(sol_0 = b \land c \land d\), where \(b, c, d\) are local states. Normally 6 realizing orders need checking: \(b::c::d, b::d::c, c::b::d, c::d::b, d::b::c\) and \(d::c::b\). If we find the order \(b::c::d\) is not realizable when verifying the first realizing order, then we do not have to verify the reachability of \(b::c::d\) and \(d::c::b\) where \(b\) occurs before \(c, d\). \(b::c::d\) is not included, because firing \(d\) changes its state before firing \(b::c\).

### 4.3 Heuristic on OR Gates

In the previous section, without OR gates (one state node has multiple solution successors), reachability problem is solvable in polynomial time even with AND gates if \(I = O(1)\) as the reasoning of SLCG is linear with the number of local states.

In general SLCGs, there exist both AND gates and OR gates. Every disjunction may generate a fork in global reasoning, except the cases where global state satisfies all local states in a fork simultaneously and reduce the possibilities of final states and simplifies the computation. If an OR gate is followed by an AND gate, there are multiple initial states for the reasoning of the AND gate, i.e. there are multiple sets of permutations to verify, the size of problem multiplies.

To deal with the concern brought by OR gates, if they are numerous to enumerate, general SLCG can be regarded as a decision tree, where we need to make a choice at each OR gate in order to make every involved AND gate take the value 1.

To simplify the computation, we suppose that all of the AND gates are already transformed to equivalent solution nodes. We are going to prove: under this hypothesis, the general reachability problem is at most as complex as random walks problem \(21\) (see appendix A) of the same size.

We associate every OR gate with its predecessor and successor, more precisely, every OR gate is responsible for the reachability of its predecessor and also for the choice of its successor.

In the worst case, there is only one configuration over all disjunctions that makes objective reachable. To obtain the exact reachability by brute force search, thanks to the limit of the in-degree of OR gates, \(2^D\) trials are needed with \(D\) being the number of disjunctions. \(2^D\) is still in exponential. To deal with such case, we transform the problem into the one with much less complexity but with a high probability of reaching the correct answer.
Theorem 4 The reachability problem of an SLCG with solely OR gates is equivalent to the Random Walks problem of size \#OR.

Proof Numerate OR gates as \( OR = \{or_1, \ldots, or_n\} \), where \( or_i = \{0, 1\} \). Initializing \( OR \) with random configuration, every modification on an OR gate is equivalent to a “step” in random walks, in the worst case, after \( 2D^n \) trials, the probability of reaching the goal is greater than one-half, if we execute \( \log_2 n \) (number of loops is adjustable) sets of trials, the probability of reaching the “correct configuration” is greater than \( 1 - \frac{1}{2^n} \) (details in Appendix A). If we still do not find the desired trajectory, we consider the goal is unreachable. In this case, the possibility of false negative is at most \( \frac{1}{2^n} \) and that of false positive is 0. \( \square \)

The proof above shows the worst case of our heuristic method. In fact, if the desired state is reachable, it is probable that exact solution is found during the trial because:

1. Starting choice is probably not the farthest from correct choice
2. There are more than one choice that makes the desired state reachable

4.4 Overall Process

Combining all the parts in section 4 and trajectory extraction technique in section 1, the whole process of PermReach is shown as follows:

1. Precondition initial SLCG, cycles are deleted (Section 4.1)
2. Build decision trees for AND gates and OR gates
3. Launch the heuristic on OR gates, obtain an SLCG with pure AND gates (Section 4.3)
4. Compute the reachability on AND gates, if reachable, quit; if not, return to step 3 (Section 4.2)

5 Implementation and Benchmarks

The overall process in section 4.4 is implemented on Matlab1. To evaluate the performance in large in silico networks, we take T-cell Receptor model (TCR)2,3 and epidermal growth factor receptor model (EGFR)4 as examples, with the former one containing 95 components and 206 transitions and the latter one containing 104 components and 389 transitions respectively.

These models are originally Boolean networks. According to Appendix C, they are transformable to ABANs.

We then take several automata as input, varying exhaustively their initial states combinations (\( 2^{\text{init state}} \)), take the reachability of the states of another automata set as output. We first test the performance of traditional model checkers, Mole and NuSMV, in which Mole turns out to be timeout for 6 in 12 outputs, and all timeout for NuSMV in model EGFR. Due to the big state space, traditional model checkers are not effective.

To validate our approach, we first use a small model: phage-\( \lambda \) model2 to compare with an alternative reachability analyzer Pint3. In this model with 4 components and 12 transitions (without taking consideration of the self-regulations), our result shows complete decidability while Pint is not able to figure out the reachability of [cll = 1]. In big examples TCR and EGFR, although PermReach takes more time than Pint, it outputs the sequence from initial state towards final state. More importantly, it gives decidable reachability for any input. In the TCR tests, PermReach gives exactly the same result as Pint did. As for EGFR tests, PermReach takes the inconclusive cases of Pint as input, and returns decidable outputs.

As seen in the previous results, our heuristic technique is more conclusive than the reasoning of Pint. In the configuration of the heuristic approach, if there are less than 20 OR gates after preprocessing in Section 4.1, the computation will be shifted from heuristic to global search as the size of enumeration is acceptable. There are only 11 OR gates in EGFR model, therefore the results are firmly conclusive. Even though we do not shift to the global search, the conclusiveness is high enough according to Theorem 4.

To sum up, PermReach has a better time performance than traditional exhaustive model checkers (Mole and NuSMV); on the other hand, it is more conclusive than abstract analyzers (Pint) while keeping a reasonable time performance.

Table 2 Results of the tests on large-scale examples using Intel Core i7-3770 CPU, 3.4GHz, 8.00G RAM. Column Pint gives the related results on ANs, while column PermReach gives the results for ABANs. True, Inconclusive and False define respectively the number of different results of reachability, while Max time and Total time depict respectively the maximum time of the individual computations.

\[ \]
6 Conclusion and future work

This paper proposes an expressive formalism ABAN to study the reachability problem. The original approach SLCG has limited conclusiveness because static and local reasoning does not simulate all real system dynamics. Due to the complexity of global search, developing a heuristic technique based on sub-states becomes a feasible choice. The heuristic method reproduces the system dynamics by traversing possible orders of transitions. This “dynamic tentative” makes it closer to real dynamics than LCG is.

Future work: in the reasoning of AND gates, the computation on permutations is expensive but is still not conclusive enough, see Fig. To speed up the whole procedure and improve the conclusiveness, we plan to apply SAT (Satisfiability) solvers or Answer Set Programming (ASP) to refine the analysis of transition orders (>) in the same fork and those across forks. In addition, we may contemplate the extension of our heuristic technique to multivalued models.

A Random Walks problem

Definition 6 (Random Walks) Start with an arbitrary natural number \( n \), at each time step, the number add or minus 1 with equal probability, how many expected steps \( Z \) does it take to reach certain goal \( n \)?

Starting from \( n \), there is no need to move, thus the expectation of steps \( E[Z_n] = 0 \); starting from 0, the only possibility is to move rightwards, \( E[Z_0] = 1 + E[Z_1] \). Similarly, starting from \( 0 < i < n \) we have

\[
E[Z_i] = \frac{1}{2}(E[Z_{i+1}] + 1) + \frac{1}{2}(E[Z_{i-1}] + 1)
\]

With these recurrence relations, we can obtain \( E[Z_0] = n^2 \) (worst case for \( 0 \leq i \leq n \)), i.e. it takes \( n^2 \) steps on average to start from 0 to reach \( n \) and less than \( n \) if \( i > 0 \). By applying Markov’s inequality \( P(Z \geq a) \leq \frac{E(Z)}{a} \), we have \( P[Z > 2n^2] \leq \frac{1}{2} \), the possibility of taking more than \( n^2 \) steps to reach \( n \) is less than a half. The proof of Markov’s inequality is shown as below:

\[
E[X] = \sum_{k=0}^{n} k \cdot P[X = k] + \sum_{k=n+1}^{\infty} k \cdot P[X = k] \\
\geq 0 + 2n^2P[X > a] \Rightarrow P[X > a] \leq \frac{E(X)}{a}
\]

For one tentative of \( 2n \) steps, it has at least \( \frac{1}{2} \) possibility to reach \( n \), we initiate \( \log_2 n \) tentatives, we have at least the possibility of \( 1 - (1 - \frac{1}{2})^{\log_2 n} = 1 - \frac{1}{n} \) to have at least one tentative reaching the goal \( n \). As long as we increase the number of tentatives, the possibility of success will get closer to 1.

B Algorithm

The construction of an SLCG is realized by iterative updates:

Algorithm 2 SLCG construction

Initialization: \( L_s \leftarrow \{\omega\}, L_S \leftarrow \{\omega\}, Sol \leftarrow \emptyset \)

while \( L_s \neq \emptyset \) do

for \( a_i \in L_s \) do

\( L_s \leftarrow L_s \setminus a_j \)

if \( a_i \in \text{init\_state} \) then

\( a_{i, \text{next}} \leftarrow \text{sol}_{a_i} \)

\( \text{sol}_{a_i, \text{next}} \leftarrow \emptyset \)

else

for \( \text{sol} = A \rightarrow a_i \rightarrow T \) do

\( a_i, \text{next} \leftarrow a_i, \text{next} \cup \text{sol} \)

for \( b_j \in A \) do

\( \text{sol}\_\text{next} \leftarrow b_j \)

end for

end if

end for

end while

return \( (L_S, \text{Sol}) \)

C Transformation from general BNs to ABANs

Given Boolean functions \( v_i(t+1) = f_i(V_i) \), with \( V_i \) the set of participating variables among \( v_1(t), \ldots, v_n(t) \). Boolean operators are transformable to the composition of \( \neg, \land, \lor \) (e.g. \( \text{XOR} b = (a \land \neg b) \lor (\neg a \land b) \)), and Boolean functions possess an equivalent CNF (clausal normal form) thanks to its distributivity. As ANs interpret transitions in the way of disjunctions of conjunctions, all BNs are transformable to ANs. We can see that it does not matter whether the dynamics is synchronous or asynchronous, because these transformations are only exerted on functions/transition.

Example:

Let \( G_B = (V, F) \) a BN with \( V = \{a, b, c, d, e\} \), and has only one Boolean function, \( F = \{f(a) = (b \lor c) \land (d \lor e)\} \), we have \( f(a) = (b \land d) \lor (b \land e) \lor (c \land d) \lor (c \land e) \), and \( \neg f(a) = (\neg b \land \neg c) \lor (\neg d \land \neg e) \). The equivalent AN is then constructed: 5 automata \( \Sigma = \{a, b, c, d, e\} \), with transitions: \( T = \{b_1, d_1\} \rightarrow a_0, \{b_1, e_1\} \rightarrow a_0, \{c_1, d_1\} \rightarrow a_0, \{c_1, e_1\} \rightarrow a_0, \{b_0, c_0\} \rightarrow a_1, \{d_0, e_0\} \rightarrow a_1 \}.

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