An improved method for finding attractors of large-scale asynchronous Boolean networks

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Boolean networks

- Boolean Networks (BNs) are simple but efficient mathematical formalism for modeling and analyzing complex biological systems [Schwab et al., 2020].
- BNs are interesting mathematical objects that have recently attracted various work in theory [Schwab et al., 2020].
- Furthermore, they have widely been applied to various areas from science to engineering [Valverde et al., 2020].

Synchronous vs. Asynchronous

- Synchronous BNs (SBNs) [Garg et al., 2008]:
  - The updating scheme of SBNs is synchronous and deterministic, i.e., all the nodes are updated simultaneously at each time step.
- Asynchronous BNs (ABNs) [Garg et al., 2008]:
  - The updating scheme of ABNs is asynchronous and non-deterministic, i.e., only one node is non-deterministically selected to be updated at each time step.
- ABNs are considered more suitable than SBNs in modeling biological systems [Thomas, 1991, Saadatpour et al., 2010].
  - In biology, the updating process of each component may spend various time from fractions of a second to hours.
  - Moreover, the information on time scales of components is usually lacking.

Attractor detection in BNs

- Analysis of attractors could provide new insights into systems biology [Albert and Thakar, 2014] (e.g., the origins of cancers [Béal et al., 2021], SARS-CoV-2 [Ibrahim et al., 2021], HIV [Oyeyemi et al., 2014]).
- Attractors also play an important role in the development of new drugs [Putnins and Androulakis, 2019].
- Attractors of BNs have been also used to study various other systems, such as, multivariate systems [Yang et al., 2021], complex systems [Gates et al., 2021].
- Note that attractor detection also gives a starting point for many control approaches for biological systems [Biane and Delaplace, 2018].

Motivations

- Whereas many efficient algorithms and tools have been developed for attractor detection in SBNs, few methods [Garg et al., 2008, Skodawessely and Klemm, 2011, Mizera et al., 2018] have been proposed for attractor detection in ABNs.
- Moreover, the efficiency of these few methods is strictly prevented when the ABN becomes large, e.g., the number of nodes is over 100.
- Recently, an efficient method (called **FVS-ABN**) has been proposed for exactly finding all attractors of an ABN [Trinh et al., 2020]. This method outperforms the state-of-the-art methods and can handle large-scale networks.
- In the biological context, comprehensive analysis of biological networks often requires formal models that possess hundreds or even thousands of elements [Mizera et al., 2018]. This fact motivates improving **FVS-ABN** to handle larger networks.

Contributions

- In theory:
  - We state and prove a new theorem on the relation between the dynamics of an ABN and a negative feedback vertex set of this ABN.
- In practice:
  - We propose an improved method (called **iFVS-ABN**) that includes two substantial improvements to **FVS-ABN**.

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Boolean networks

Boolean Network (BN)

A Boolean Network (BN) is defined as a 2-tuple (V, F), where $V = \{x_1, \dots, x_n\}$ $(n \geq 1)$ is the set of nodes and $F = \{f_1, \dots, f_n\}$ is the set of Boolean functions. Each node x_i is identified as a Boolean variable, and is associated with a Boolean function $f_i : \mathbb{B}^{|IN(f_i)|} \to \mathbb{B}$, where $IN(f_i)$ is the set of input nodes of f_i. $x_i(t) \in \mathbb{B}$ and $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))^T$ denote the state of node x_i and the state of the BN at time t, respectively.

In this research, BNs are implicitly considered as general BNs (i.e., there is no restriction on Boolean functions).

Dynamics of Boolean networks

- At each time step, node x_i can update its state by

$$x_i(t+1) = f_i(\mathbf{x}(t)).$$

- Then, a BN can transit from a state to another state (possibly identical). This is the *state transition*.
- The dynamics of a BN is captured by a *State Transition Graph* (STG) that shows states (nodes) and state transitions (arcs).

Asynchronous Boolean Networks

- ABNs were first studied in [Harvey and Bossomaier, 1997].
- At each time step, only one node is nondeterministically selected to be updated.
- The STG of an ABN of size n has 2^n nodes and $n \times 2^n$ arcs.

Attractors

Attractor [Mizera et al., 2018]

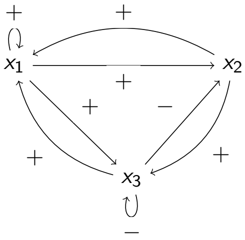
An *attractor* of a BN is a set of states satisfying any state in this set can reach any state in this set and cannot reach any other state that is not in this set.

An attractor can be either

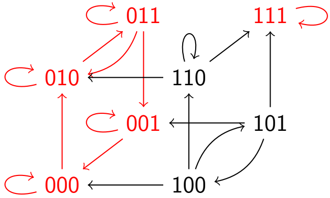
- a singleton attractor (or a fixed point) that has only one state;
- or a cyclic attractor that has at least two states and is formed by overlapping one or more cycles of states.

Example

$$f_1 = x_1 \wedge x_2 \wedge x_3,$$
$$f_2 = x_1 \vee \neg x_3,$$
$$f_3 = (x_2 \wedge \neg x_3) \vee (x_1 \wedge \neg x_2 \wedge \neg x_3) \vee (x_1 \wedge x_2 \wedge x_3).$$



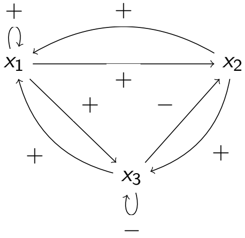
(a) Interaction graph of the ABN.



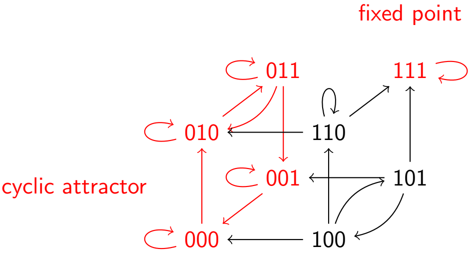
(b) STG of the ABN.

Example

$$
\begin{aligned}
f_1 &= x_1 \wedge x_2 \wedge x_3, \\
f_2 &= x_1 \vee \neg x_3, \\
f_3 &= (x_2 \wedge \neg x_3) \vee (x_1 \wedge \neg x_2 \wedge \neg x_3) \vee (x_1 \wedge x_2 \wedge x_3).
\end{aligned}
$$



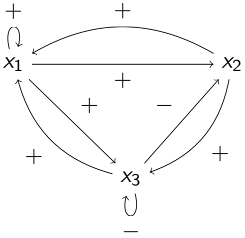
(a) Interaction graph of the ABN.



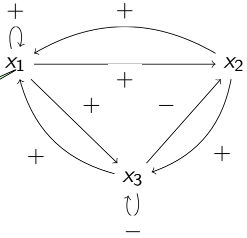
(b) STG of the ABN.

Feedback vertex set

A Feedback Vertex Set (FVS) of a signed directed graph G is a set of vertices U such that $G - U$ contains no cycle. This graph has two FVSs:
- $\{x_1, x_3\}$ (the minimum one),
- $\{x_1, x_2, x_3\}$.



Feedback vertex set



A Negative Feedback Vertex Set (NFVS) of a signed directed graph G is a set of vertices U such that $G - U$ contains no negative cycle (cycle with an odd number of negative arcs). This graph has four NFVSs:
- $\{x_3\}$ (the minimum one),
- $\{x_1, x_3\}$,
- $\{x_2, x_3\}$,
- $\{x_1, x_2, x_3\}$.

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General approach of **FVS-ABN**

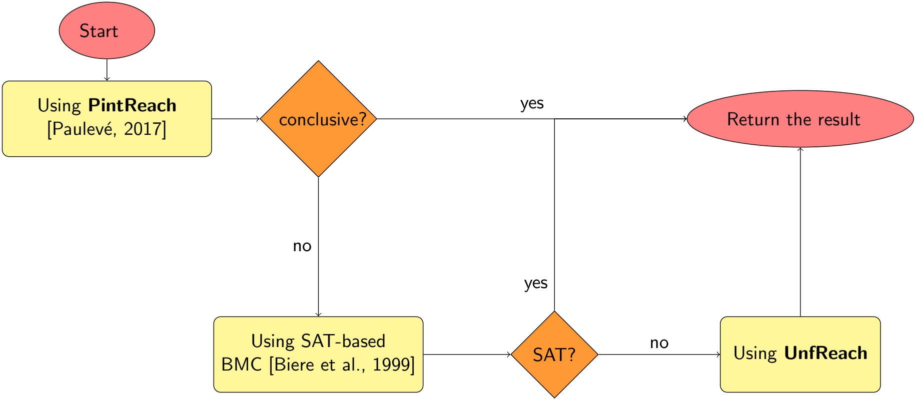
- **FVS-ABN** uses an FVS to systematically remove arcs in the STG of the ABN to get a candidate set of states that covers all attractors of the ABN.
- Then, **FVS-ABN** uses reachability analysis on the ABN to filter out this set. For checking the reachability in ABNs, **FVS-ABN** uses a method called **UnfReach** that relies on Petri net unfoldings [Schwoon and Romer, 2016].
- The obtained result is a set of states such that there exists a one-to-one correspondence between the set of states and the set of attractors. This set is sufficient because starting from a state in an attractor, we can enumerate all other states in the attractor by listing all states reachable from this state [Garg et al., 2008].
- We formally prove the correctness of **FVS-ABN**.

Improved method

- We propose an improved method (called **iFVS-ABN**) that includes two improvements to **FVS-ABN**.
- The first improvement is a new method (called **ABNReach**) for checking the reachability in ABNs.
- The second improvement is to use an NFVS instead of an FVS to get the candidate set of states.
- We also prove the correctness of **iFVS-ABN**.

First improvement

In general, **ABNReach** is a reasonable combination of multiple previous techniques for checking the reachability in ABNs. The result of **ABNReach** is correct.



Second improvement

Theorem

Let $\mathcal{A}$ be an ABN. Let U^- be an NFVS of $IG(\mathcal{A})$ and B^- be a set of retained values corresponding to the nodes of U^-. Let *att* be an attractor of $\mathcal{A}$. Then there exists a state s such that $s \in att$ and s is a fixed point of the reduced STG with respect to U^- and B^-.

We also show that this theorem does not hold for the case of positive feedback vertex sets.

Second improvement (cont.)

- By the new theorem, the candidate set obtained by using an NFVS still covers all attractors of the ABN, thus preserving the correctness.
- In an interaction graph, the size of its minimum NFVS is less than or equal to the size of its minimum FVS, since an FVS is also an NFVS [Montalva et al., 2008]. Hence, the use of NFVSs opens a chance to get a smaller candidate set.

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Evaluation

- We have implemented **iFVS-ABN** in a JAVA tool.
- We then conducted experiments on various types of networks to evaluate the efficiency of the two improvements.
- The experimental results show that
  - The two improvements are effective and **iFVS-ABN** outperforms **FVS-ABN**.
  - In particular, **iFVS-ABN** can handle large networks with up to 1000 nodes in terms of randomly generated networks and 321 nodes in terms of real biological networks.

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Conclusion

- We have formally stated and proved a new theorem on the relation between an NFVS of the interaction graph of an ABN and the dynamics of the ABN.
- We have proposed an improved method **iFVS-ABN** that includes the two substantial improvements to the previous method, **FVS-ABN** [Trinh et al., 2020].

Future work

- Having only two levels of activation is sometimes not always enough to fully understand the dynamics of real biological systems [Mushthofa et al., 2018]. Hence, we plan to extend **iFVS-ABN** to that for attractor detection in multi-valued networks [Gan and Albert, 2018], a generalization of Boolean networks.
- In **iFVS-ABN**, we use SAT (All-SAT) to compute a candidate set of states. For the case of multi-valued networks, we intend to use fuzzy answer set programming [Nieuwenborgh et al., 2007], which has been used to model multi-valued networks [Mushthofa et al., 2018], to compute the candidate set.

Thank you for your attention!

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