Algorithms for Finding Attractors of Generalized Asynchronous Random Boolean Networks

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Boolean networks and attractors

- Boolean networks (BNs) are popular models of gene regulatory networks. They are also interesting mathematical objects applied in many areas beyond systems biology.
- A central aim of Boolean network analysis is to find attractors which are important long-term behaviors of BNs.
  - In many research [Kauffman, 1992, Huang, 2006], attractors of a BN are linked to phenotypes.
  - Thus, analyses of attractors could provide new insights into the origins of cancer.

Classification of Boolean networks

- There are many different types of Boolean networks [Gershenson, 2002]:
  - Classical Random Boolean Networks (CRBNs)
  - Asynchronous Random Boolean Networks (ARBNs)
  - Generalized Asynchronous Random Boolean Networks (GARBNs)
  - Deterministic Asynchronous Random Boolean Networks (DARBNs)
  - Deterministic Generalized Asynchronous Random Boolean Networks (DGARBNs)
- CRBNs, ARBNs, and GARBNs have the same network structure. They differ in their updating schemes which specify the way the nodes will be updated.
- DARBNs and DGARBNs are added time parameters.

Motivations

- There are many theoretical studies on attractors in different types of BNs [Kauffman, 1992, Drossel et al., 2005, Gershenson, 2002, Saadatpour et al., 2010, Gershenson, 2004].
- In practical aspects, many methods have been proposed for attractor detection (i.e., finding all possible attractors) in CRBNs and ARBNs [Garg et al., 2007, Dubrova and Teslenko, 2011, Zheng et al., 2013, Garg et al., 2008, Zheng et al., 2013, Chatain et al., 2014].
- However, in our best knowledge, there is no study on attractor detection in GARBNs, DARBNs, or DGARBNs.
- In this paper, we focus on attractors of GARBNs.

Motivations (cont.)

The reasons for choosing GARBNs are:

- GARBNs are extensions of ARBNs. Thus, they can extend the modeling power of BNs.
- Attractors of GARBNs can be used to find attractors of ARBNs. This finding will be presented in our upcoming paper.
- GARBNs are also interesting mathematical objects themselves.

Contributions

- We present some properties of attractors in GARBNs.
- We then present relations between attractors in a GARBN and attractors in its CRBN counterpart.
- Based on these properties and relations, we propose three possible algorithms for attractor detection in GARBNs.
- All these algorithms use a data structure called binary decision diagram (BDD).
- The correctness of these algorithms are formally proved.
- Experiments are also conducted on real and artificial networks to compare the performance of the proposed algorithms.

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Outline

Boolean networks

- A BN contains many nodes (genes), each node takes either value 0 (inactive) or 1 (active).
- Interactions between the nodes are expressed by Boolean functions.
- In this paper, BNs are implicitly considered as random Boolean networks (i.e., there are no assumptions of any particular functionality or connectivity of the nodes).

Dynamics of Boolean networks

- At each time step, a BN can transit from a state to an other state. This is a state transition.
- Dynamics of a Boolean network are captured by a state transition graph (STG).
- A STG is a directed graph which shows states (nodes) and state transitions (arcs).

Classical Random Boolean Networks

- CRBNs were proposed by Stuart Kauffman [Kauffman, 1969] to model gene regulatory networks in cells.
- They have a synchronous and deterministic updating, i.e., all nodes are updated synchronously.
- The STG of a CRBN has 2^n nodes and 2^n arcs.

Generalized Asynchronous Random Boolean Networks

- GARBNs have semi-synchronous and non-deterministic updating.
- At each time step, they select randomly any number of nodes to update synchronously. This means that GARBNs can update synchronously no node, only one node, some nodes, or all the nodes.
- The STG of a GARBN has 2^n nodes and maximally 2^{2n} arcs.
- GARBNs are more much complex than CRBNs.

Classification of attractors

- We classify three types of attractors based on [Garg et al., 2008]:
  - self loops
  - simple loops
  - complex loops
- Simple loops can again divided into two subclasses:
  - simple loops (type1)
  - simple loops (type2)

Classification of attractors (cont.)

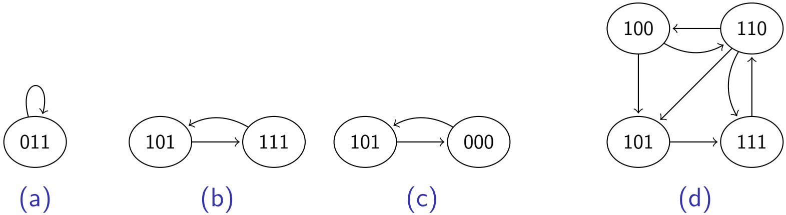

Figure: (a) A self loop. (b) A type1 loop. (c) A type2 loop. (d) A complex loop.

A simple loop is a cycle of states such that each state have exactly one successor state.

- A type1 loop is simple loop and any two consecutive states of the loop differ in exactly one single gene expression.
- A type2 loop is simple loop and at least two consecutive states of the loop differ in more than one gene expression.

Example of Boolean networks

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

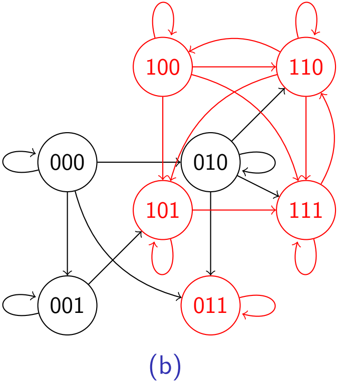

Figure: Example of BNs. (a) STG of the CRBN. (b) STG of the GARBN.

Outline

Encoding Generalized Asynchronous Random Boolean Networks in BDDs

- The STG of a GARBN can be easily modeled as a transition system, which then can be encoded into a Binary Decision Diagram (BDD) [Bryant, 1986] which is a useful data structure used for representing a Boolean function.
- The authors of [Garg et al., 2007] have proposed the method to encode the STG of an ARBN into a BDD. This encoding can be applied similarly for GARBNs.
- We can only replace the state transition formula of the ARBN by the state transition formula of the GARBN.

The state transition formula of the GARBN

Let x and x' be two consecutive states of the GARBN. The state transition from x to x' is expressed the following formula. This formula can be easily encoded into a BDD with the set of $2n$ BDD variables $V = \{x_1, ..., x_n, x'_1, ..., x'_n\}$.

$$T(x, x') = ((x'_1 \leftrightarrow x_1) \vee (x'_1 \leftrightarrow f_1(x))) \wedge ... \wedge ((x'_n \leftrightarrow x_n) \vee (x'_n \leftrightarrow f_n(x)))$$

Contents

Attractors in GARBNs

- We present some properties of attractors in GARBNs.
- We present some relations between attractors in a GARBN and attractors in its CRBN counterpart.
  - Self loops and type1 loops of the CRBN are also self loops and type1 loops of the GARBN, and otherwise.
  - In a GARBN, any complex loop always contains a type2 loop of the corresponding CRBN of the same BN.
- Attractors of a CRBN can be used to find attractors of its GARBN counterpart.

Algorithms for attractor detection of GARBNs

- From these properties and relations, we propose three possible algorithms to detect all attractors of a GARBN.
  - Algorithm 1
  - Algorithm 2
  - Algorithm 3
- All three algorithms use CRBN attractors to find GARBN attractors since:
  - GARBNs are more complex than CRBNs.
  - There are many efficient methods for finding attractors of CRBNs.
- We use the method in [Garg et al., 2008] for finding CRBN attractors.

Outline

Algorithm 1

- Algorithm 1 is inspired from the GenYsis tool [Garg et al., 2007] which builds the total transition system (for all states of the network) and then calculates backward reachable sets.

Intuitive idea

- Because the set of self loops and type1 loops of a CRBN is also the set of self loops and type1 loops of its GARBN counterpart, we only need to consider the set of type2 loops of the CRBN.
- For each type2 loop *att*, if $FR^{GARBN}(\{s\}) \subseteq BR^{GARBN}(\{s\})$ where s is an arbitrary state in *att*, then $FR^{GARBN}(\{s\})$ is a complex loop of the GARBN.

Outline

Algorithm 2

- In the case of too large backward reachable sets, the running time of Algorithm 1 may become extremely longer, even fails to obtain the result due to out of memory.
- The calculation of the total transition system also makes Algorithm 1 easily crashed.
- With the special properties of attractors of GARBNs, the calculation of total backward reachable sets is unnecessary.
- We propose here Algorithm 2 which improves Algorithm 1.

Intuitive idea

- Algorithm 2 calculates restricted backward reachable sets instead of total backward reachable sets.
- Hence, Algorithm 2 does not need to build the total transition system of the GARBN. It only builds partial transition systems.
- The condition $FR^{GARBN}(\{s\}) \subseteq BR^{GARBN}(\{s\})$ in Algorithm 1 is replaced by $FS = BR_{res}^{GARBN}(\{s\}, FS)$ where $FS = FR^{GARBN}(\{s\})$.

Outline

Algorithm 3

- Both Algorithm 1 and Algorithm 2 reply on the calculation of backward reachable sets (total or restricted). The state transition systems used for this calculation are usually large. That can make the algorithms fail to obtain the result due to out of memory.
- We propose a new algorithm named Algorithm 3 to overcome this problem.

Intuitive idea

- Contrary to these algorithms 1 and 2, Algorithm 3 does not calculate backward reachable sets, but uses a filtering process.
- We use a filtering set called *o_filter* which is initialized with the set of type2 loops of the CRBN.
- For each type2 loop *att* in *o_filter*,
  - if *att* reaches to an other type2 loop or a self loop or a type1 loop of the CRBN in the STG of the GARBN, then it can be filtered out *o_filter*;
  - otherwise, $FR^{GARBN}(\{s\})$ (s is an arbitrary state in *att*) is a new attractor of the GARBN.

The correctness of these algorithms

Theorem

Algorithms 1, 2, and 3 are correct, i.e., they find correctly all attractors of a GARBN.

We have formally proved the correctness of these algorithms in our paper.

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Implementation

- We have implemented the proposed algorithms based on BDDs and logic operators on them.
- The implementation is in JAVA language and uses JDD library [Vahidi, 2015] for BDD manipulation.

Experiments

- All experiments are conducted in a computer whose environment is CPU: Intel Core i7 2.4 GHz, Memory: 16 GB, Windows 10 Home 64 bit.
- We use two sets of models:
  - Real networks which are get from literature include *budding yeast cell cycle regulation* [Li et al., 2004], *mammalian cell cycle regulation* [Fauré et al., 2006], *fission yeast cell cycle regulation* [Li et al., 2004], *T-helper cell differentiation* [Mendoza and Xenarios, 2006], *T-cell receptor signaling pathway analysis* [Klamt et al., 2006].
  - Artificial networks are randomly generated with *Bool Net R* package [Hopfensitz et al., 2013].
- The evaluation metric is here computational time.

Experimental results on real networks

Name	n	Number × length of attractors	Algorithm 1 (s)	Algorithm 2 (s)	Algorithm 3 (s)
Budding yeast	12	7 × 1	0.153	0.128	0.127
Mammalian cell	10	1 × 1, 1 × 128	0.130	0.121	0.119
Fission yeast	10	13 × 1	0.122	0.119	0.129
T-cell receptor	40	8 × 1	-	-	0.171
T-helper cell	23	3 × 1	214.361	0.190	0.197

n denotes the number of nodes.
"-" denotes the case in which the program fails to detect attractors due to out of memory.

Experimental results on artificial networks

Name	Number × length of attractors	Algorithm 1 (s)	Algorithm 2 (s)	Algorithm 3 (s)
20-node	2 × 6144, 2 × 12288	84.430	1.321	0.480
22-node	1 × 4194304	222.753	51.836	7.431
24-node	2 × 1	-	0.332	0.136
26-node	1 × 1048576	-	46.588	3.466
28-node	6 × 1	-	1.328	1.226
30-node	4 × 1	-	-	14.674
31-node	1 × 4096, 1 × 8192	-	-	6.083
32-node	4 × 128, 2 × 256	-	-	212.927
33-node		-	-	-
34-node	5 × 1	-	-	81.797
35-node	2 × 32	-	-	127.547
36-node		-	-	-
37-node		-	-	-
38-node	1 × 32	-	0.272	0.234
39-node		-	-	-
40-node	4 × 6	-	-	0.307

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Conclusion

- We have studied on some properties of attractors in GARBNs and relations between attractors of GARBNs and CRBNs.
- Based on these properties and relations, three algorithms are proposed to detect all attractors of a GARBN.
- Experiments are also conducted to compare the performance of these algorithms. Experimental results show that Algorithm 3 outperforms Algorithms 1 and 2.

Future work

- All three algorithms must firstly calculate the forward reachable set. If this forward reachable set is too large, that maybe leads to fail to obtain the result due to out of memory. A decomposition approach may be useful in this case.
- We will extend our approach for attractors in multi-valued GARBNs.
- Further studies on attractors in other types of BNs such as DARBNs, DGARBNs are also important.

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Thank you for your attention!