Efficient enumeration of fixed points in complex Boolean networks using answer set programming

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Boolean modeling

Boolean network modeling of **gene regulation** but also of other biological systems has had great successes over the last ∼20 years.

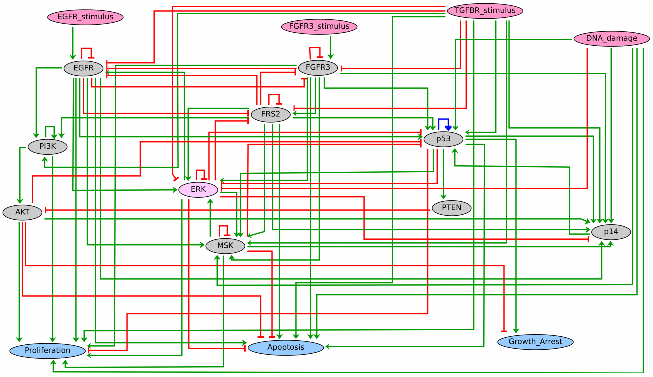


Figure: Boolean model of the MAPK regulatory network, whose involvement in bladder cancer is well established [Grieco et al., 2013].

Boolean networks

Boolean network

A Boolean Network (BN) $\mathcal{N}$ is defined as a 2-tuple (V, F), where $V = \{v_1, ..., v_n\}$ $(n \geq 1)$ is a set of nodes and $F = \{f_1, ..., f_n\}$ is a set of Boolean functions. Each node v_i is identified as a Boolean variable, and is associated with a Boolean update function $f_i : \{0,1\}^{|IN(f_i)|} \mapsto \{0,1\}$, where $IN(f_i)$ is the set of input nodes of f_i.

A state s is a mapping $s\colon V \mapsto \{0,1\}$ that assigns either 0 (inactive) or 1 (active) to each node.

The state space of $\mathcal{N}$ is $\{0,1\}^n$.

Dynamics of Boolean networks

At each time step t, node v_i can update its state by

$$s_{t+1}(v_i) = f_i(s_t).$$

An update scheme specifies the way the nodes will be updated.

Based on the update scheme, the Boolean network can transit from a state to another state (possibly identical). This is the *state transition* (denoted by $\longrightarrow$).

The dynamics of a Boolean network is captured by a *State Transition Graph* that is a directed graph whose nodes represent states and whose arcs represent the state transitions.

Example Boolean network

$$\begin{tikzcd}
v_1 \arrow[loop left] \arrow[r, bend left] & v_2 \arrow[loop right] \arrow[l, bend left]
\end{tikzcd}$$

$$\begin{cases} f_1 = (v_1 \land v_2) \lor (\neg v_1 \land \neg v_2) \\ f_2 = (v_1 \land v_2) \lor (\neg v_1 \land \neg v_2) \end{cases}$$

Boolean network

$$\begin{tikzcd}
01 \arrow[loop right] \arrow[d, bend left] & 11 \arrow[loop right] \\
00 \arrow[u, bend left] \arrow[r, bend right] & 10 \arrow[loop right] \arrow[l, bend right]
\end{tikzcd}$$

State transition graph

Fully asynchronous update scheme: only one node is non-deterministically selected in order to be updated at each time step.

Attractors

An *attractor* is a minimal non-empty set S of states s.t. $\forall x \longrightarrow y, x \in S \Rightarrow y \in S$.

$$\begin{cases} f_1 = (v_1 \wedge v_2) \vee (\neg v_1 \wedge \neg v_2) \\ f_2 = (v_1 \wedge v_2) \vee (\neg v_1 \wedge \neg v_2) \end{cases}$$

$$\begin{tikzcd}
01 \arrow[loop right] \arrow[d, bend left] & 11 \arrow[loop right] \\
00 \arrow[u, bend left] \arrow[r, bend right] & 10 \arrow[loop right] \arrow[l, bend right]
\end{tikzcd}$$

State set	Attractor	Type
$\{11\}$	yes	fixed point
$\{00, 01\}$	no	-
$\{00, 01, 10\}$	yes	cyclic
$\{00, 01, 10, 11\}$	no	-

Application

Attractor analysis has many applications in systems biology, since attractors correspond to biological *phenotypes*.

- new insights into the origins of diseases: cancers, SARS-CoV-2, HIV
- aid the development of new drugs
- starting point for many control approaches for biological systems, which play an important role in systems medicine

Applications in many other fields:

- computer science
- mathematics
- theoretical physics
- complex systems
- ...

Fixed points vs. cyclic attractors

To date, the analysis of fixed points remains a very useful/standard tool in understanding the behavior of complex biological models.

- in some cases the full computation of cyclic attractors remains intractable
- for many biological systems, the expected long-term behavior is not cyclic (as in the Cell Cycle, or Circadian rhythms for instance) but rather a stabilization to an observable *phenotype*
- fixed points are independent of the update scheme, but cyclic attractors are not
- crucial starting point for the state-of-the-art for computing cyclic attractors of BNs [Trinh et al., 2022]

More applications: coding theory, control theory, neural networks.

Fixed point enumeration

Characterization and complexity

A state s is a *fixed point* of $\mathcal{N}$ if and only if $s(v_i) = f_i(s)$ for every $v_i \in V$.

The problems of detecting a fixed point and enumerating all fixed points of a general BN have been shown to be respectively NP-hard and #P-hard [Akutsu et al., 1998].

In fact, for general BNs, there is no existing method that works faster than $k \times 2^n$ for any $k \geq 1$ [Mori and Akutsu, 2022].

Limit/knowledge gap

The fixed point enumeration problem has attracted researchers from various communities and many methods have been proposed [Mori and Akutsu, 2022].

With the increase in model size and complexity of Boolean update functions, the existing methods show their limitations.

State-of-the-art	**Bottleneck**	**Remark**
[Klarner et al., 2017]	prime implicants	hard to obtain + large number
[Paulevé et al., 2020]	DNF + locally-monotonic	sometimes hard to obtain + not handle general models
[Abdallah et al., 2017]	transition-based representation	# transitions may be exponential in the number of input nodes

Answer set programming and systems biology

Answer Set Programming (ASP) [Gelfond and Lifschitz, 1988] has been widely applied to the field of computational systems biology [Videla et al., 2015] because of its declarative characteristics as well as strong tools' support [Gebser et al., 2011].

Since BNs have become a popular in systems biology, naturally ASP has been quickly applied to modeling and analysis of BNs.

- enumerating fixed points [Klarner et al., 2017, Abdallah et al., 2017, Paulevé et al., 2020]
- enumerating or approximating attractors [Mushthofa et al., 2014, Klarner et al., 2017, Abdallah et al., 2017, Paulevé et al., 2020]
- inferring BNs from biological data [Rocca et al., 2014, Videla et al., 2015, Videla et al., 2017, Chevalier et al., 2020]
- controlling BNs [Kaminski et al., 2013, Videla et al., 2017]

Answer set programming and systems biology

The most recent and most efficient fixed point enumeration methods all rely on answer set programing [Klarner et al., 2017, Abdallah et al., 2017, Paulevé et al., 2020].

$\Longrightarrow$ We propose two new ASP-based methods for efficiently enumerating fixed points in a BN.

ASP-based methods for enumerating fixed points

Core ASP encoding

We intend to build an ASP encoding (say $\mathcal{L}$) for $\mathcal{N}$ such that its set of stable models one-to-one corresponds to the set of fixed points of $\mathcal{N}$.

For each node v_i, we introduce two atoms p_i and n_i.

The below ASP rules ensure that a stable model of $\mathcal{L}$ corresponds to a state of $\mathcal{N}$:

$$\leftarrow p_i, n_i \tag{1}$$

and

$$p_i, n_i \leftarrow \tag{2}$$

The translation from a stable model A of $\mathcal{L}$ to a state x of $\mathcal{N}$ is that for every $v_i \in V$,

$$\begin{cases} x(v_i) = 1 \text{ iff } p_i \in A, \\ x(v_i) = 0 \text{ iff } n_i \in A. \end{cases}$$

Core ASP encoding

Fixed points can be characterized by the conjunction of $v_i \leftarrow f_i$ and $\neg v_i \leftarrow \neg f_i$. We encode the two parts for every $v_i \in V$ as ASP rules.

To avoid the presence of negation, we use the Negative Normal Form (NNF) of a Boolean function.

The NNF is obtained by recursively applying De Morgan laws until all negations that remain are on only literals.

$$\neg(v_3 \vee \neg(v_1 \wedge v_2)) \Rightarrow \neg(v_3 \vee \neg v_1 \vee \neg v_2) \Rightarrow \neg v_3 \wedge v_1 \wedge v_2$$

NNF is much more efficient to obtain than DNF/CNF.

Core ASP encoding

$$v_i \leftarrow f_i$$
$$\Rightarrow$$
$$\gamma(v_i) \leftarrow \gamma(NNF(f_i))$$

where we define function γ as

$$\gamma(v_i) = p_i$$
$$\gamma(\neg v_i) = n_i$$
$$\gamma(\bigwedge_{1 \leq j \leq J} \alpha_j) = \gamma(\alpha_1), \ldots, \gamma(\alpha_J)$$
$$\gamma(\bigvee_{1 \leq j \leq J} \alpha_j) = aux_k$$

where aux_k is a new auxiliary atom and for each j add the rule $aux_k \leftarrow \gamma(\alpha_j)$.

Core ASP encoding

$$\neg v_i \leftarrow \neg f_i$$

$$\Rightarrow$$

$$\gamma(\neg v_i) \leftarrow \gamma(NNF(\neg f_i))$$

Theorem

The set of stable models of $\mathcal{L}$ one-to-one corresponds to the set of fixed points of $\mathcal{N}$.

Example (written in Clingo's syntax)

$$\begin{tikzcd}
01 \arrow[loop right] \arrow[d, bend left] & 11 \arrow[loop right] \\
00 \arrow[u, bend left] \arrow[r, bend right] & 10 \arrow[loop right] \arrow[l, bend right]
\end{tikzcd}$$

$$\begin{cases} f_1 = (v_1 \land v_2) \lor (\neg v_1 \land \neg v_2) \\ f_2 = (v_1 \land v_2) \lor (\neg v_1 \land \neg v_2) \end{cases}$$

```
:- p1, n1.
p1, n1.

p1 :- aux1.
aux1 :- p1, p2.
n1 :- aux2, aux3.
aux2 :- n1.
aux3 :- p1.

p2 :- aux4.
aux4 :- p1, p2.
```

```
:- p2, n2.
p2, n2.


aux1 :- n1, n2.

aux2 :- n2.
aux3 :- p2.


aux4 :- n1, n2.
```

Example (written in Clingo's syntax)

```
:- p1, n1.
p1, n1.

p1 :- aux1.
aux1 :- p1, p2.
n1 :- aux2, aux3.
aux2 :- n1.
aux3 :- p1.

p2 :- aux4.
aux4 :- p1, p2.
n2 :- aux5, aux6.
aux5 :- n1.
aux6 :- p1.

#show p1/0.  #show n1/0.
```

```
:- p2, n2.
p2, n2.


aux1 :- n1, n2.

aux2 :- n2.
aux3 :- p2.


aux4 :- n1, n2.

aux5 :- n2.
aux6 :- p2.

#show p2/0.  #show n2/0.
```

Example (written in Clingo's syntax)

```
:- p1, n1.                          :- p2, n2.
p1, n1.                             p2, n2.

p1 :- aux1.
aux1 :- p1, p2.                     aux1 :- n1, n2.
n1 :- aux2, aux3.
aux2 :- n1.                         aux2 :- n2.
aux3 :- p1.                         aux3 :- p2.

p2 :- aux4.
aux4 :- p1, p2.                     aux4 :- n1, n2.
n2 :- aux5, aux6.
aux5 :- n1.                         aux5 :- n2.
aux6 :- p1.                         aux6 :- p2.

#show p1/0.  #show n1/0.            #show p2/0.  #show n2/0.
```

Example (written in Clingo's syntax)

```
:- p1, n1.                          :- p2, n2.
p1, n1.                             p2, n2.

p1 :- aux1.
aux1 :- p1, p2.                     aux1 :- n1, n2.
n1 :- aux2, aux3.
aux2 :- n1.                         aux2 :- n2.
aux3
```

$v_1 \leftarrow f_1$ with $f_1 = (v_1 \land v_2) \lor (\neg v_1 \land \neg v_2)$

```
p2 :- aux4.
aux4 :- p1, p2.                     aux4 :- n1, n2.
n2 :- aux5, aux6.
aux5 :- n1.                         aux5 :- n2.
aux6 :- p1.                         aux6 :- p2.

#show p1/0.  #show n1/0.            #show p2/0.  #show n2/0.
```

Example (written in Clingo's syntax)

```
:- p1, n1.                          :- p2, n2.
p1, n1.                             p2, n2.

p1 :- aux1.
aux1 :- p1, p2.                     aux1 :- n1, n2.
n1 :- aux2, aux3.
aux2 :- n1.                         aux2 :- n2.
aux3 :- p1.                         aux3 :- p2.

p2 :- aux4
aux4
n2 :- aux5, aux6.
aux5 :- n1.                         aux5 :- n2.
aux6 :- p1.                         aux6 :- p2.

#show p1/0.  #show n1/0.            #show p2/0.  #show n2/0.
```

$\neg v_1 \leftarrow \neg f_1$ with $\neg f_1 = (\neg v_1 \vee \neg v_2) \wedge (v_1 \vee v_2)$

Example (written in Clingo's syntax)

```
:- p1, n1.                         :- p2, n2.
p1, n1.                            p2, n2.

p1 :- aux1.
aux1
n1 :- aux2, aux3.
aux2 :- n1.                        aux2 :- n2.
aux3 :- p1.                        aux3 :- p2.

p2 :- aux4.
aux4 :- p1, p2.                    aux4 :- n1, n2.
n2 :- aux5, aux6.
aux5 :- n1.                        aux5 :- n2.
aux6 :- p1.                        aux6 :- p2.

#show p1/0.  #show n1/0.           #show p2/0.  #show n2/0.
```

$f_2 = f_1 = (v_1 \wedge v_2) \vee (\neg v_1 \wedge \neg v_2) \Rightarrow$ similar ASP rules for node v_2

Example (written in Clingo's syntax)

```
:- p1, n1.
p1, n1.

p1 :- aux1.
aux1 :- p1, p2.
n1 :- aux2, aux3.
aux2 :- n1.
aux3 :- p1.

p2 :-
aux4 :- p1, p2.
n2 :- aux5, aux6.
aux5 :- n1.
aux6 :- p1.
```

```
:- p2, n2.
p2, n2.


aux1 :- n1, n2.

aux2 :- n2.
aux3 :- p2.


aux4 :- n1, n2.

aux5 :- n2.
aux6 :- p2.
```

Exclude auxiliary atoms from stable models.

```
#show p1/0.  #show n1/0.        #show p2/0.  #show n2/0.
```

Example (written in Clingo's syntax)

```
:- p1, n1.                           :- p2, n2.
p1, n1.                              p2, n2.

p1 :- aux1.
aux1 :- p1, p2.                      aux1 :- n1, n2.
n1 :- aux2, aux3.
aux2 :- n1.                          aux2 :- n2.
aux3 :- p1.                          aux3 :- p2.

p2 :-
```

One stable model $\{p_1, p_2\} \sim$ fixed point 11

```
aux4 :- p1, p2.                      aux4 :- n1, n2.
n2 :- aux5, aux6.
aux5 :- n1.                          aux5 :- n2.
aux6 :- p1.                          aux6 :- p2.

#show p1/0.  #show n1/0.             #show p2/0.  #show n2/0.
```

Problem with source nodes

A node $v_i \in V$ is called a *source* node if and only if $f_i = v_i$.

The number of fixed points of a BN may be extremely large if it has many source nodes. Might be exponential in the number of source nodes.

In the core encoding as well as those of the state-of-the-art methods, a resulting stable model always corresponds to a single fixed point.

A bottleneck in number of source nodes $\Longrightarrow$ new method to overcome this

New method

$$\begin{cases} f_1 = v_1 \\ f_2 = v_1 \vee v_2 \end{cases}$$

$$\begin{tikzcd}
01 \arrow[loop right] & 11 \arrow[loop right] \\
00 \arrow[loop right] & 10 \arrow[u] \arrow[loop right]
\end{tikzcd}$$

Fixed point	**Stable model**
00	$\{n_1, n_2\}$
01	$\{n_1, p_2\}$
11	$\{p_1, p_2\}$

New method

Fixed point	Stable model
00	$\{n_1, n_2\}$
01	$A_1 = \{n_1, p_2\}$
11	$A_2 = \{p_1, p_2\}$
$\Rightarrow$ 01, 11	$A = \{p_1, n_1, p_2\}$

Our main idea is to group two stable models A_1 and A_2 of $\mathcal{L}$ into a Herbrand model A if they only differ in the atoms corresponding to a source node.

We add A to the set of stable models of $\mathcal{L}$, and then repeat the grouping process until there is no new stable model.

Note that this process introduces more stable models than before: A, A_1, and A_2. However, A covers all the fixed points represented by the two stable models constituting it. $\Rightarrow$ maximal set-inclusion stable models.

New method

We adjust the core encoding to make the above approach fully automated in the ASP solver.

- removing the condition $\leftarrow p_i, n_i$
- adding choice rules for only atoms corresponding to source nodes (i.e., $p_i \leftarrow$ not not p_i and $n_i \leftarrow$ not not n_i) $\Rightarrow$ making A to be a stable model

Theorem

The set of maximal set-inclusion stable models of $\mathcal{L}$ fully covers all fixed points of the BN.

Post-processing

A stable model can be group-able with multiple ones, thus one fixed point can belong to multiple maximal set-inclusion stable models.

A binary decision diagram to symbolically represent the set of maximal set-inclusion stable models.

Meta result for further analysis based on symbolic operators:

- list all fixed points if needed
- count the number of fixed points
- return the set of fixed points of the BN restricted by a given combination of values on source nodes
- ...

Experiments

Python tool `fASP`[1]. ASP solver = Clingo[2]

Our methods:

- `fASP-conj`: the core encoding
- `fASP-src`: modification to handle the case of many source nodes, cannot control the maximum number of resulting fixed points

State-of-the-art methods:

- `PyBoolNet` [Klarner et al., 2017]
- `mpbn` [Paulevé et al., 2020]
- `AN-ASP` [Abdallah et al., 2017]
- `FPCollector` [Aracena et al., 2021]: cannot control the maximum number of resulting fixed points

[1] `https://github.com/giang-trinh/fASP`

[2] `https://github.com/potassco/clingo`

Data sets

BBM repository[3]:

- a collection of real-world Boolean models from various sources used in systems biology
- 211 models, peaking at 321 variables, 1100 regulations, and 133 source nodes

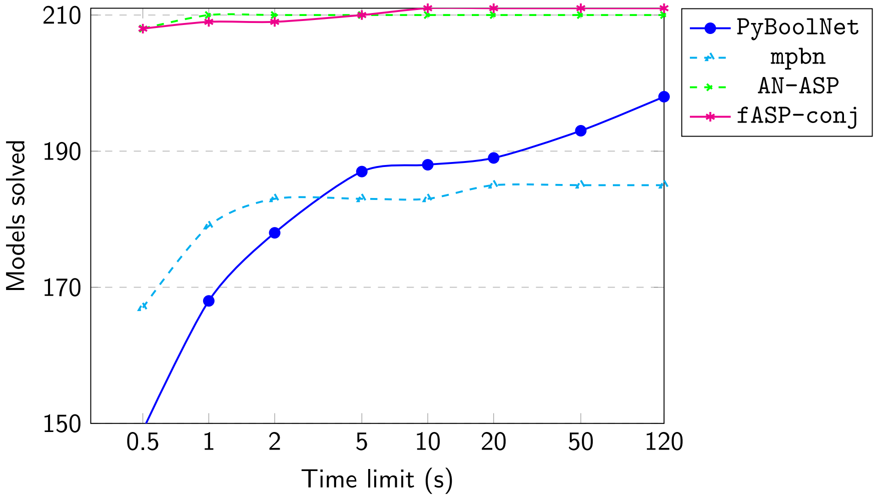
Pseudo-random models:

- structurally similar to the real-world models in the BBM repository
- 400 pseudo-random models ranging from 1000 to 5000 variables, 4145 to 63507 regulations, and 127 to 1171 source nodes

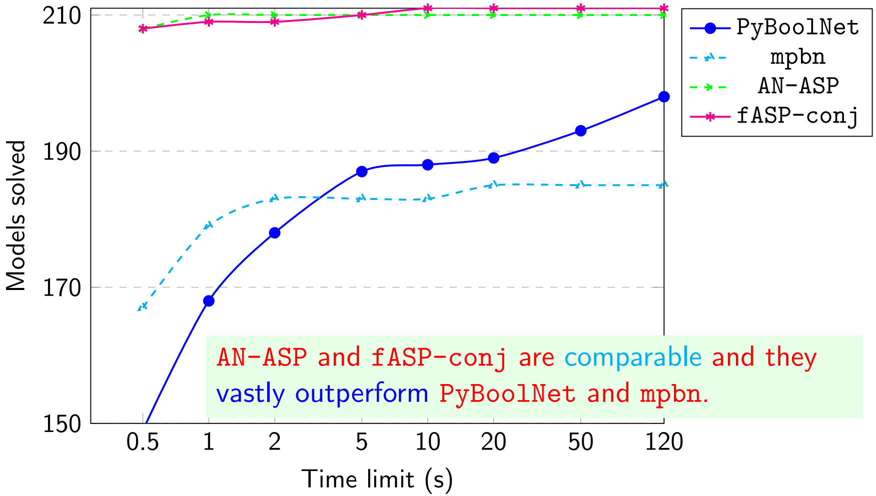
[3] `https://github.com/sybila/biodivine-boolean-models`

Results on real-world models

1000 first fixed points

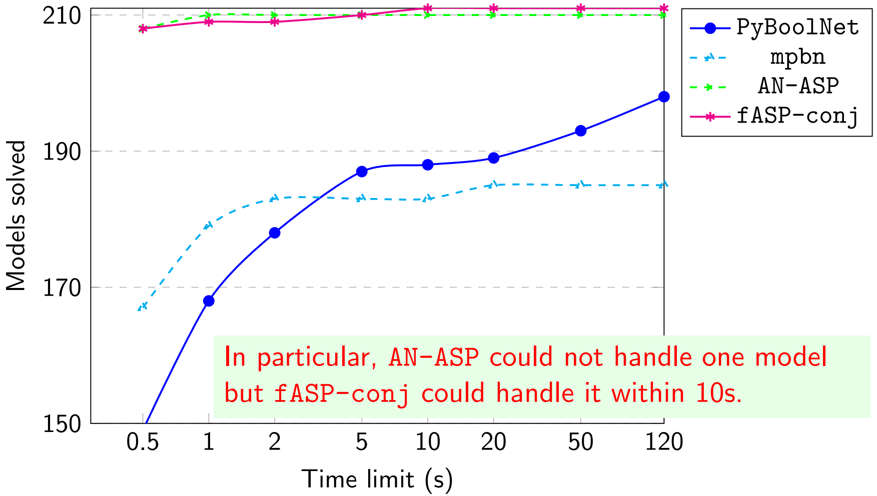


1000 first fixed points



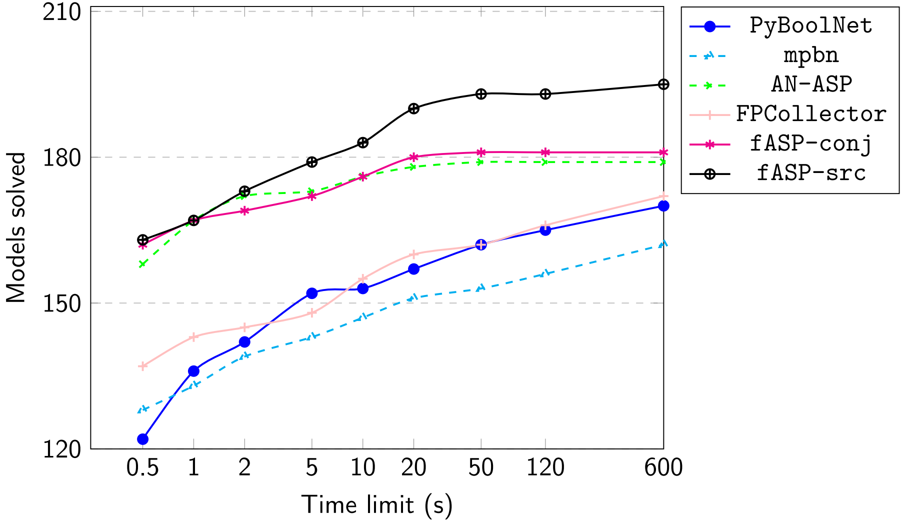
AN-ASP and fASP-conj are comparable and they vastly outperform PyBoolNet and mpbn.

1000 first fixed points

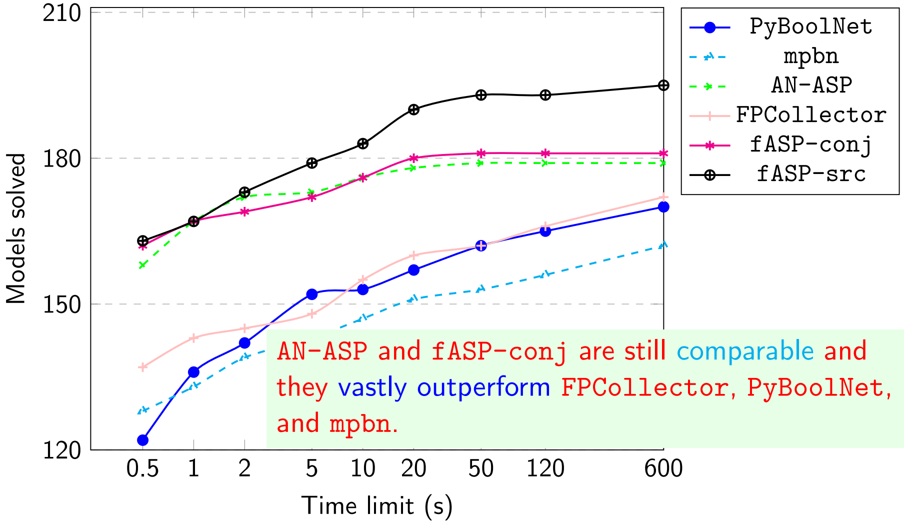


In particular, `AN-ASP` could not handle one model but `fASP-conj` could handle it within 10s.

All fixed points

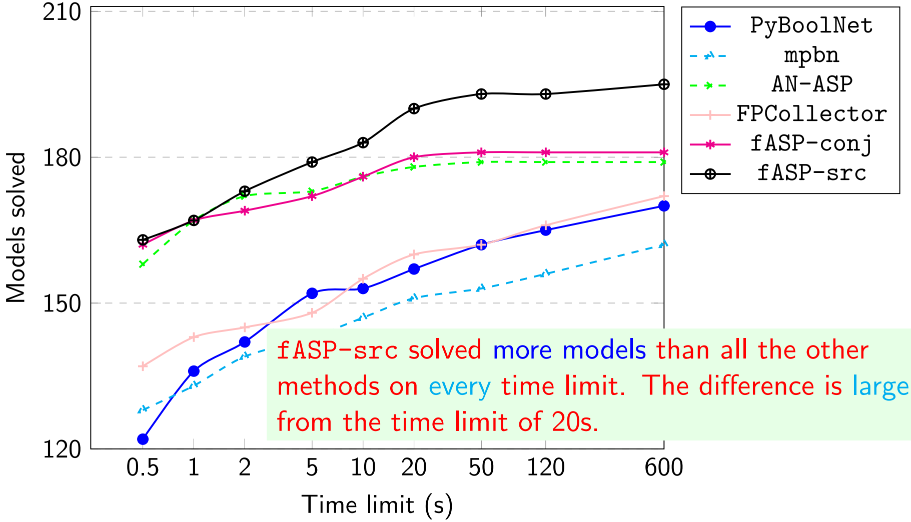


All fixed points



AN-ASP and fASP-conj are still comparable and they vastly outperform FPCollector, PyBoolNet, and mpbn.

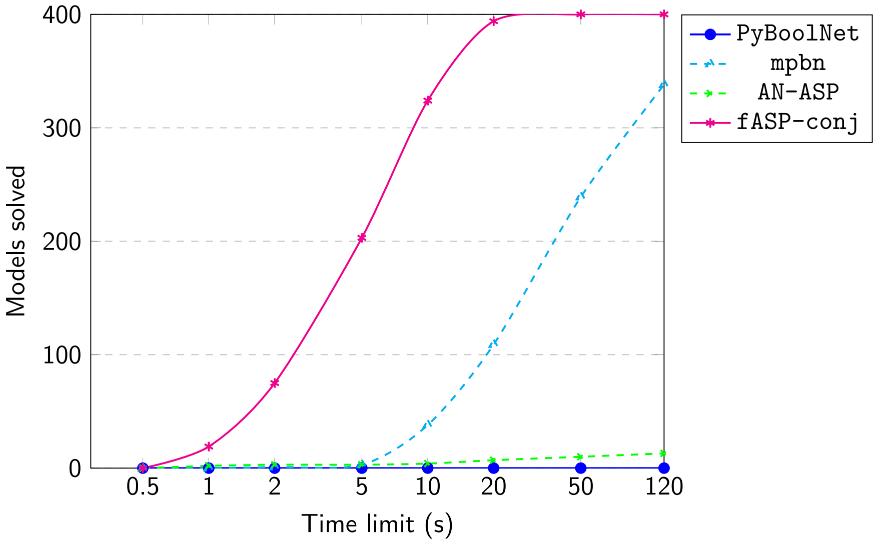
All fixed points



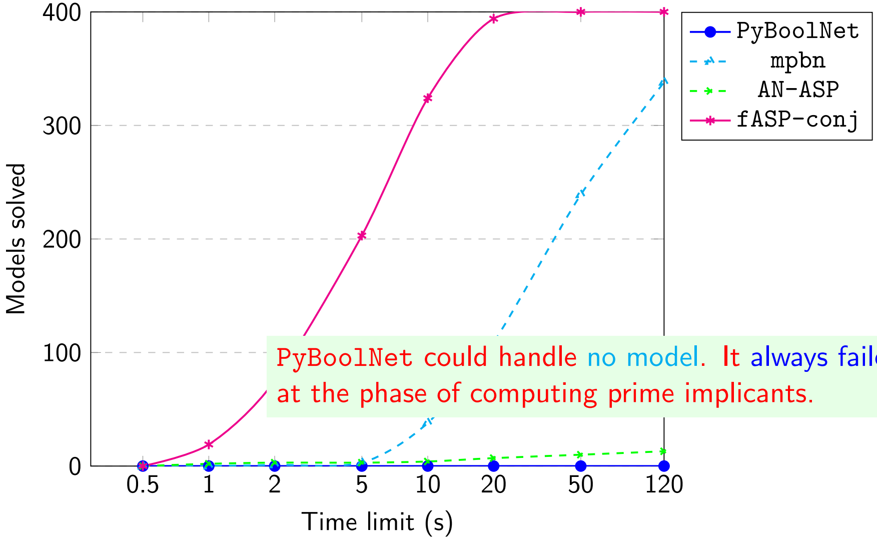
fASP-src solved more models than all the other methods on every time limit. The difference is large from the time limit of 20s.

Results on pseudo-random models

1000 first fixed points

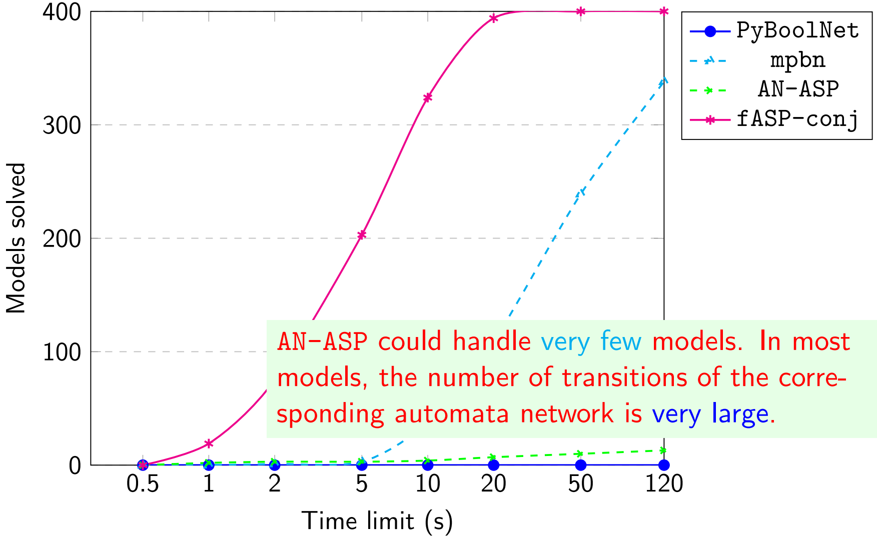


1000 first fixed points



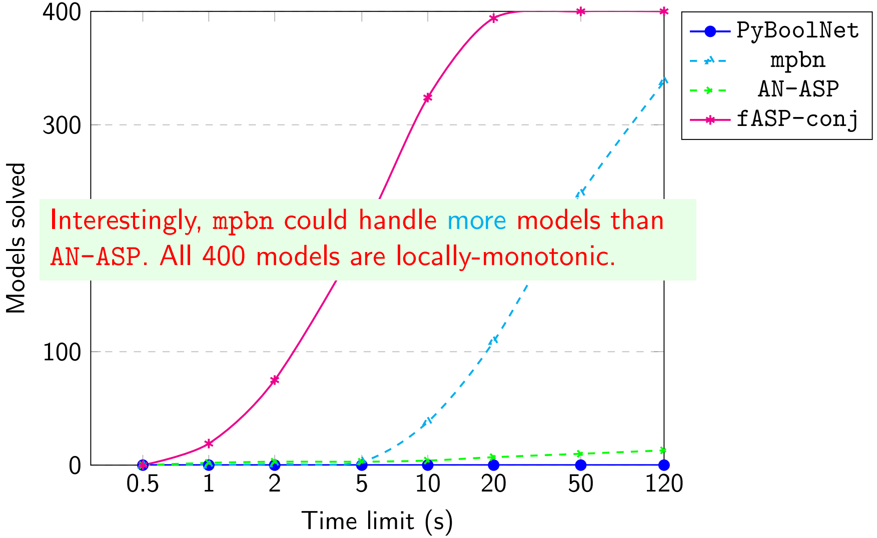
PyBoolNet could handle no model. It always failed at the phase of computing prime implicants.

1000 first fixed points



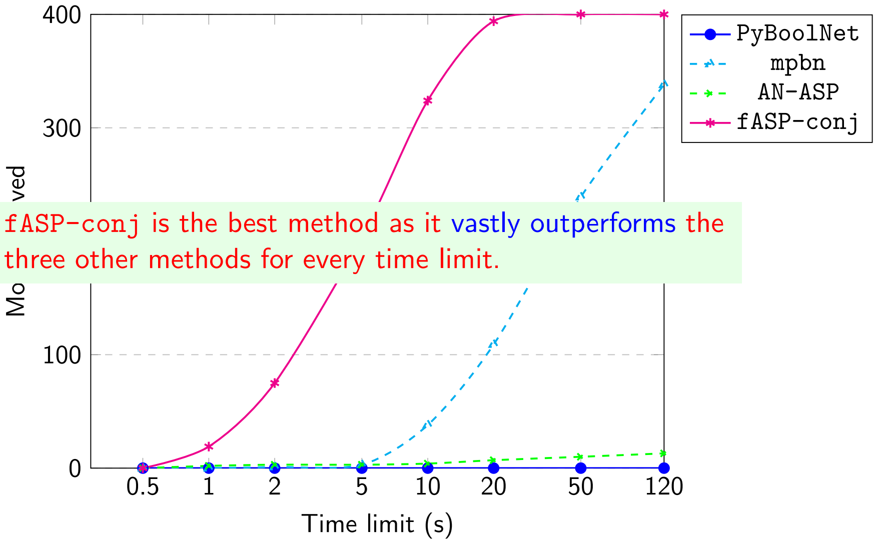
AN-ASP could handle very few models. In most models, the number of transitions of the corresponding automata network is very large.

1000 first fixed points



Interestingly, mpbn could handle more models than AN-ASP. All 400 models are locally-monotonic.

1000 first fixed points



fASP-conj is the best method as it vastly outperforms the three other methods for every time limit.

All fixed points

For every model, all the compared methods failed to obtain all the fixed points as they quickly met the OOM error.

The reason is that the number of all fixed points (even stable models for the `fASP-conj` method) is actually too large due to a lot of source nodes (> 100).

Room for improvement.

Conclusion

Fixed points are important and standard in Boolean network analysis.

Two new methods based on ASP for enumerating fixed points in Boolean networks: `fASP-conj` and `fASP-src`.

Main advantages:

- Both rely on NNFs of Boolean functions, which are much more efficient to obtain than other representations used by previous methods (e.g., prime implicants, DNFs, automata networks).
- `fASP-src` provides a more compact representation of the results based on BDDs, which can give both memory and run-time benefits.

Conclusion

`fASP-conj` and `fASP-src` vastly outperform all the state-of-the-art methods.

In particular, `fASP-src` shows its superiority to all the other methods in enumerating all the fixed points of models with many source nodes.

These results exhibit the great potential of ASP to tackle complex challenges in biology, which is in line with the direction of the LIRICA group.

Future work

Boolean network models of biological systems usually contain many source nodes, which might be hard to avoid in the modeling process [Aghamiri et al., 2020]. Hence, improving `fASP-src` is necessary.

Optimize the number of auxiliary atoms needed to use.

Extend the proposed methods to those for computing trap spaces of Boolean networks [Klarner et al., 2017], which are more general than fixed points and useful approximations for attractors in Boolean networks.

Thank you for your attention!

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