Efficient enumeration of minimal trap spaces in large-scale Boolean networks of gene networks

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Boolean models

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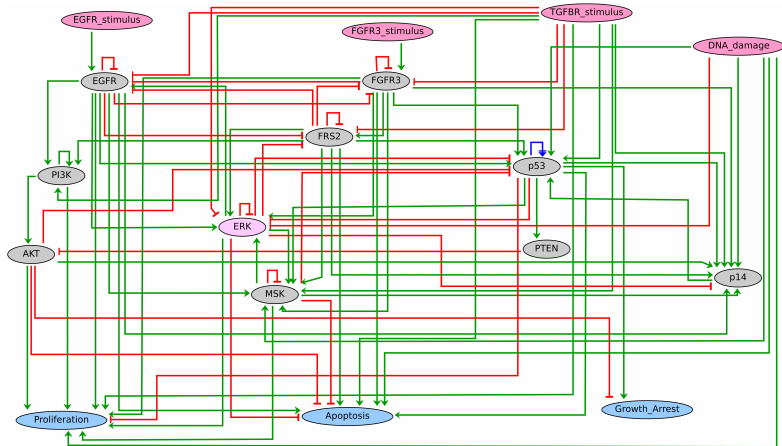

Figure: Boolean model of the MAPK regulatory network, whose involvement in bladder cancer is well established [Grieco et al., 2013].

Minimal trap spaces

Besides simulation, the analysis of such models is mostly based on *attractor* computation, since those correspond roughly to observable biological *phenotypes*.

The recent use of *trap spaces* as approximations of attractors made a real breakthrough in that field allowing to consider medium-sized models that used to be out of reach.

Minimal trap spaces

However, with the continuing increase in model-size as well as Boolean function complexity, the state-of-the-art methods for computing minimal trap spaces shows their limits on **running time** (PyBoolNet [Klarner et al., 2017], `trap-pn` [Trinh et al., 2022]) and **supporting types** of models (`mpbn` [Paulevé et al., 2020]).

`mpbn` can handle only locally-monotonic Boolean networks, whereas PyBoolNet and `trap-pn` can handle both locally-monotonic and non-locally-monotonic ones.

With this motivation, we propose a novel method to compute minimal trap spaces of a Boolean network via answer set programming.

Demonstration

We implemented our new method (called `ts-disj`) in the tool `trappist`[1], which also includes the implementation of our previous method (i.e., `trap-pn` [Trinh et al., 2022]).

We compared `ts-disj` with the three state-of-the-art methods: PyBoolNet [Klarner et al., 2017], `mpbn` [Paulevé et al., 2020], and `trap-pn` [Trinh et al., 2022].

The data set includes four real-world models obtained from the literature and one big random model obtained from the original paper of `mpbn` [Paulevé et al., 2020].

The time limit is three minutes and we only searched for the first 1000 solutions.

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[1] https://github.com/soli/trap-spaces-as-siphons

Running time in seconds

model	n	$|M|$	PyBoolNet	mpbn	trap-pn	ts-disj
Inflammatory Bowel Disease	47	1	DNF	NM	0.89	0.05
Erbb Receptor Signaling	247	1000^+	DNF	NM	0.49	0.64
Alzheimer	1169	1000^+	DNF	NM	0.77	0.77
Human Network	1953	1000^+	DNF	10.85	11.58	1.81
Random-10000	10000	1000^+	DNF	DNF	DNF	33.59

n: number of nodes

$|M|$: number of minimal trap spaces

NM: a non-locally-monotonic model that mpbn cannot handle

DNF: did not finish within three minutes

Conclusion

Computing minimal trap spaces is crucial.

We proposed a new method for the computation of minimal trap spaces of Boolean networks via answer set programming.

The evaluation on large models shows that our method can scale up much better than the state-of-the-art techniques.

We believe that this opens up the way to a much better analysis of large Boolean network models, hence **biological systems**.

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Ongoing work

Improving our method to deal with larger and more complex models.

Extending our method to that for multi-level logical models, which can model biological systems better.

Developing a Python toolbox that provides more features and a friendly graphical user interface.

Collaborating with our biology partners: aid them to construct Boolean network models from their data on **cancer cells**, then apply (adjust) our method to these models, finally try to get new biological insights together.

Thank you for your attention!

References I

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Minimal trap spaces

Boolean network $\mathcal{M} = (V, F)$

- Nodes $V = \{v_1, \ldots, v_n\}$
- Boolean functions $F = \{f_1, \ldots, f_n\}$

Defines a *State Transition Graph* (STG) where F and an update scheme (async., sync., etc.) link states in $\{0,1\}^n$ by transitions $\longrightarrow$

A *trap space* is

1. a *subspace* of the STG, denoted by e.g., $10\star \sim \{100, 101\}$
2. a *trap set*, i.e., $\forall x \longrightarrow y, x \in S \Rightarrow y \in S$

Trap spaces are independent of the update scheme [Klarner et al., 2017].

Minimal trap spaces $\implies$ *Good* approximations of attractors (i.e., inclusion-wise minimal trap sets)