Model Revision of Boolean Logical Models of Biological Regulatory Networks

Doctoral Program in Computer Science and Engineering

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Regulatory Networks

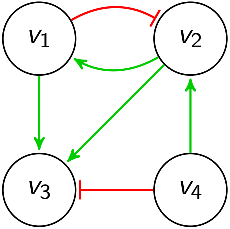
- Biological processes arise at the cellular level, governed by complex regulatory networks

- Regulatory network:
  - Collection of molecular compounds (e.g. proteins, genes)
  - Compounds interact with each other

- Computational modelling allows:
  - Functional understanding of the network
  - Test hypotheses
  - Identify predictions *in silico*
  - ...

Boolean Logical Model

- Different formalisms can be used [KS08]
  - We consider the Boolean logical formalism [Tho73]
- Compounds represented by a Boolean variable:
  - active/inactive
- Interactions defined as positive (activation) or negative (inhibition)
- Regulations defined as Boolean functions



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$$f_{v_2} = \neg v_1 \wedge v_4$$

$$f_{v_3} = v_1 \vee (v_2 \wedge \neg v_4)$$

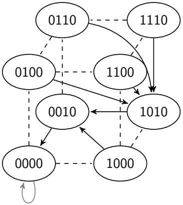
Dynamics

- The value of each node can change through time
  - Defining the state of the network

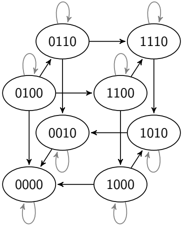
- The regulatory functions update the value of the corresponding node

- Different update schemes:

Synchronous

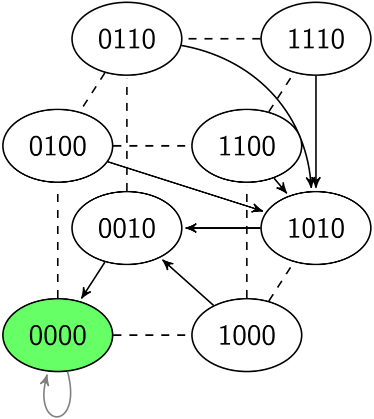


Asynchronous

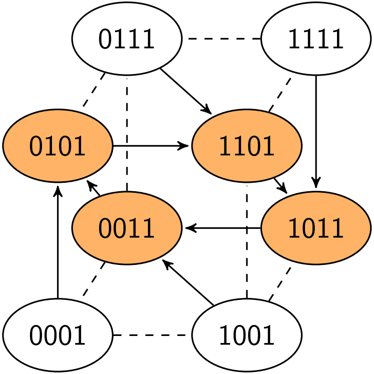


Dynamics

- State Transition Graph (STG) - synchronous update scheme



Stable State (Point Attractor)



Cycle Attractor

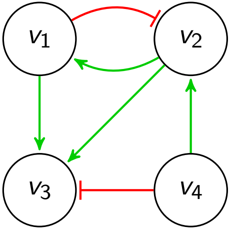
Motivation

- As new experimental data becomes available,
  models may become inconsistent
  - Models may not be able to reproduce the new information
  - Models need to be revised

- Model Revision is mainly a manual task
  - Performed by a modeller
  - Prone to error

Motivation

- How can we repair an inconsistent model?
  - Change a regulatory function?
    - ★ 2^{2^k} possibilities for each node!
  - Change the type of interaction?
  - Add or remove interactions?



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There are $\approx 10^{24}$ possible combinations!
(65536 Boolean functions with 4 regulators)

Contributions

- Model revision approach for Boolean logical models of biological regulatory networks
  - Confronting a model with:
    - ⋆ Stable state observations
    - ⋆ Time-series observations
  - Consider different dynamics:
    - ⋆ Synchronous update scheme
    - ⋆ Asynchronous update scheme

- ModRev tool
  - Implements the model revision procedure
  - Produces all optimum repair sets to repair an inconsistent model
  - ModRev available at https://filipegouveia.github.io/ModelRevisionASP/

Contributions

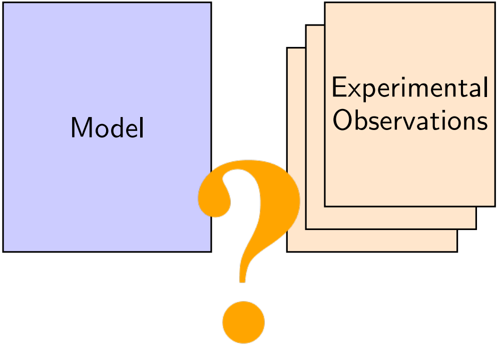
- “*ModRev - Model Revision Tool for Boolean Logical Models of Biological Regulatory Networks*”, CMSB 2020 [GLM20a]

- “*Revision of Boolean Models of Regulatory Networks Using Stable State Observations*”, Journal of Computational Biology [GLM20b]

- “*Model Revision of Boolean Regulatory Networks at Stable State*”, ISBRA 2019 [GLM19]

- “*Model Revision of Logical Regulatory Networks Using Logic-Based Tools*”, ICLP Doctoral Consortium 2018 [GLM18]

Model Revision



- A model is *consistent* if all of its nodes are consistent
  - Value of each node given by its regulatory function is equal to the observed value
- A model is *inconsistent* otherwise
  - Needs to be revised

Model Revision

Possible causes of inconsistency and repair operations:

Cause	**Repair Operation**
Wrong Regulatory Function	Function change
Wrong Interaction Type	Edge sign flip
Wrong Regulator	Edge removal
Missing Regulator	Edge addition

Model Revision

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Cause	Repair Operation
Wrong Regulatory Function	Function change
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Missing Regulator	Edge addition

Optimization Criteria:

1. Minimize interaction addition/removal
2. Minimize interaction type changes
3. Minimize Boolean function changes

Model Revision Approach

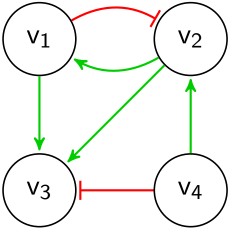
Iterate over each inconsistent node:

- Try to change the function
- Try to flip the sign of 1 edge
    - Consider changing the function again
    - Repeat this step for 2 edges, and so on
- Try to add or remove 1 edge
    - Consider changing the function and/or flip the sign of edges as previously
    - Repeat this step for adding or removing 2 edges and so on

Boolean Functions

Assumption: consider monotone non-degenerate Boolean functions

- **Monotone**: each regulator only has one role: positive/activation or negative/inhibition
  - each variable appears with the same sign in the function in Blake Canonical Form (BCF)



$f_{v_3} = v_1 \vee (v_2 \wedge \neg v_4)$ Monotone

$f_{v_3} = (v_1 \wedge \neg v_2) \vee (v_2 \wedge \neg v_4)$ Non-monotone

Boolean Functions

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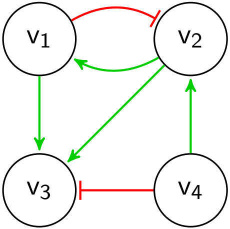
- **Non-degenerate**: each regulator is essential in the regulatory function
  - each variable has an impact on the truth table



$f_{v_3} = v_1 \vee (v_2 \wedge \neg v_4)$ Non-degenerate

$f_{v_3} = (v_2 \wedge \neg v_4)$ (missing v_1) Degenerate

Boolean Functions

- Relation $\preceq$ between monotone non-degenerate Boolean functions [CMC19]

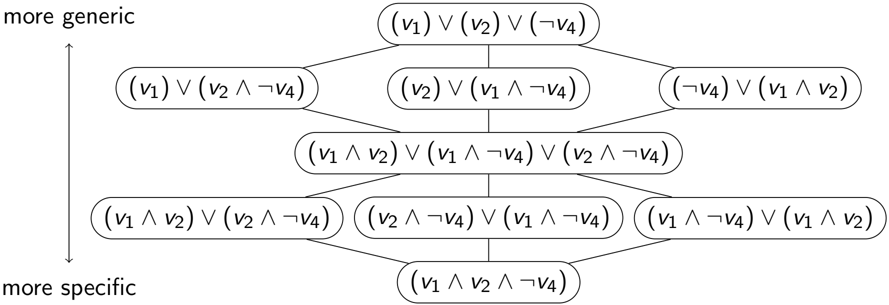
$$f \preceq f' \iff f(X) \Rightarrow f'(X).$$

where $f(X)$ denotes the entries where the function is **true** (or 1)

- f' is a **parent** of f iff $f \preceq f'$ and $\nexists f''$ such that $f \preceq f''$ and $f'' \preceq f'$
    - f is a **child** of f'

Boolean Functions

Hasse Diagram



more generic

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$(v_1 \wedge v_2 \wedge \neg v_4)$

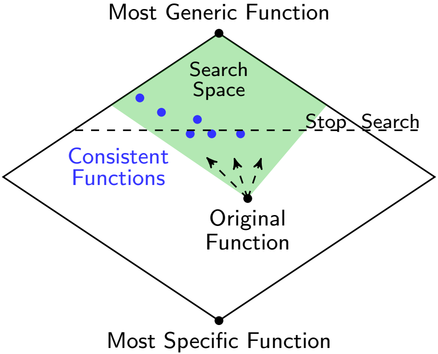
more specific

Function Repair

If a function is inconsistent:

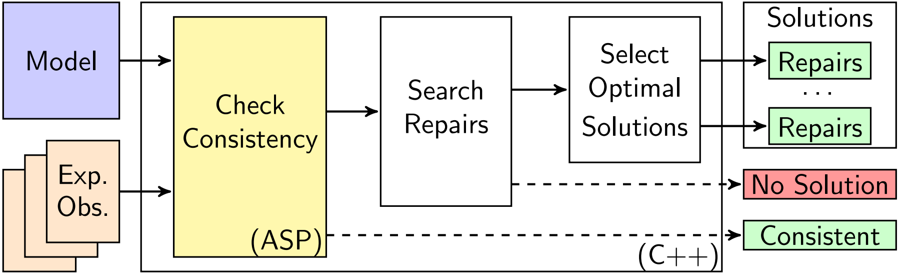
- Determine if is necessary to generalize or specify the function
- Compute set of parents (children) to go up (down) the diagram
- Continue to do so until a consistent function is found
    - or no function is found

If a function is found, is closest to the original function



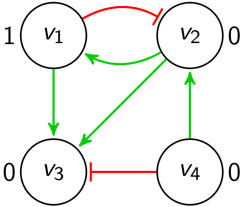
Model Revision

Architecture



Model Revision

Stable State Example



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- Inconsistent Model
- Node v_1 is inconsistent
- Change the interaction between v_2 and v_1
- Node v_3 is inconsistent
- Consistent Model

Model Revision

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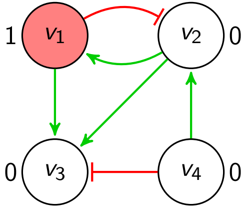

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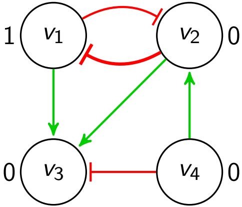

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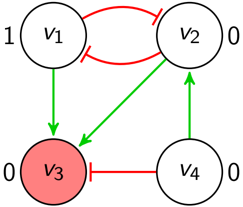

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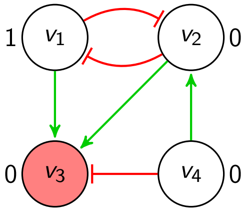

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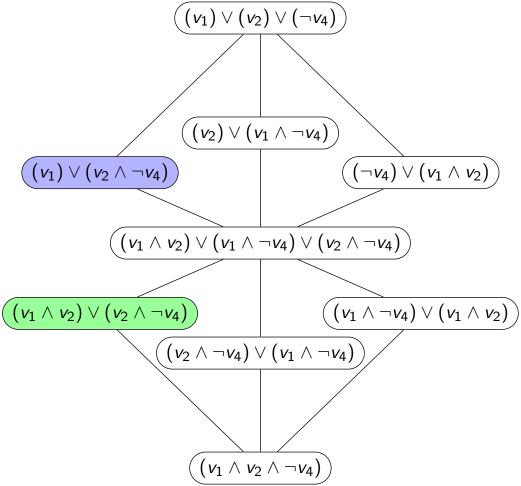

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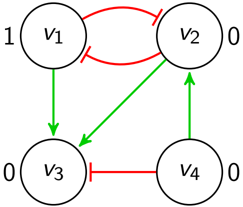

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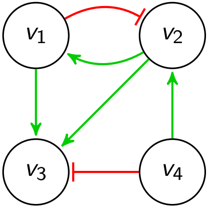
Model Revision

Time-series Example - Synchronous Update Scheme



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Model Revision

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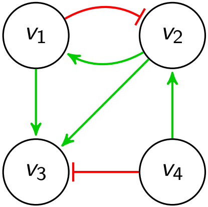

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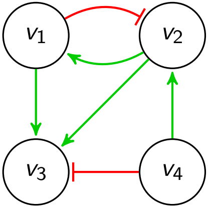

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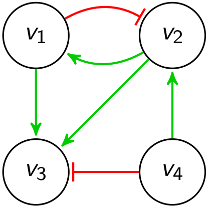

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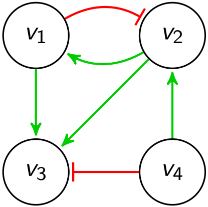

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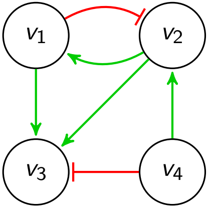

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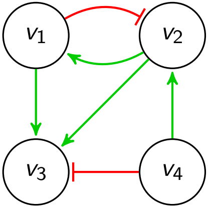

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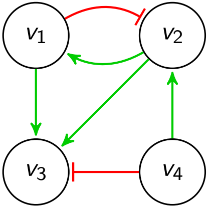

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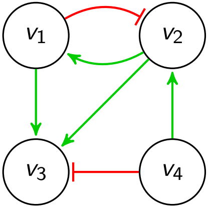

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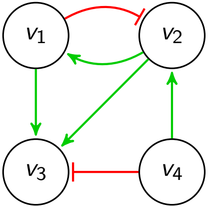

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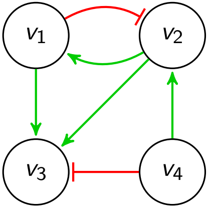

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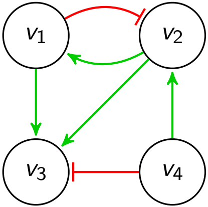

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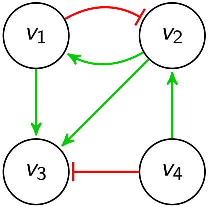
$\boldsymbol{v_2}$	1	0	1
$\boldsymbol{v_3}$	0	1	0
$\boldsymbol{v_4}$	1	1	1

Model Revision

Time-series Example - Synchronous Update Scheme



$f_{v_1} = v_2$

$f_{v_2} = \neg v_1 \land v_4$

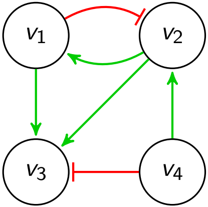
$f_{v_3} = v_1 \lor (v_2 \land \neg v_4)$

Time

Node	T_0	T_1	T_2
v_1	1	1	0
v_2	1	0	1
v_3	0	1	0
v_4	1	1	1

Model Revision

Time-series Example - Synchronous Update Scheme



$f_{v_1} = v_2$

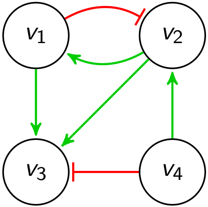
$f_{v_2} = \neg v_1 \wedge v_4$

$f_{v_3} = v_1 \vee (v_2 \wedge \neg v_4)$

	Time		
Node	$\boldsymbol{T_0}$	$\boldsymbol{T_1}$	$\boldsymbol{T_2}$
$\boldsymbol{v_1}$	1	1	0
$\boldsymbol{v_2}$	1	0	1
$\boldsymbol{v_3}$	0	1	0
$\boldsymbol{v_4}$	1	1	1

Model Revision

Time-series Example - Synchronous Update Scheme



$f_{v_1} = v_2$

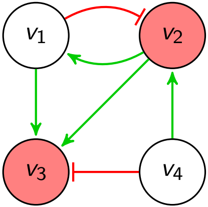
$f_{v_2} = \neg v_1 \wedge v_4$

$f_{v_3} = v_1 \vee (v_2 \wedge \neg v_4)$

		Time		
		$\boldsymbol{T}_0$	$\boldsymbol{T}_1$	$\boldsymbol{T}_2$
Node	$\boldsymbol{v}_1$	1	1	0
	$\boldsymbol{v}_2$	1	0	1
	$\boldsymbol{v}_3$	0	1	0
	$\boldsymbol{v}_4$	1	1	1

Model Revision

Time-series Example - Synchronous Update Scheme



$f_{v_1} = v_2$

$f_{v_2} = \neg v_1 \land v_4$

$f_{v_3} = v_1 \lor (v_2 \land \neg v_4)$

		Time		
		$\boldsymbol{T}_0$	$\boldsymbol{T}_1$	$\boldsymbol{T}_2$
Node	$\boldsymbol{v}_1$	1	1	0
	$\boldsymbol{v}_2$	1	0	1
	$\boldsymbol{v}_3$	0	1	0
	$\boldsymbol{v}_4$	1	1	1

Evaluation

- 5 well-known biological models considered

Abbr.	**Model**	**#N**	**#E**	**#SS**	**Reg.**	**Ref.**
FY	Fission Yeast	10	27	12	5	[DB08]
SP	Segment Polarity	19	57	7	8	[SCT02]
TCR	TCR Signalisation	40	57	7	5	[Kla+06]
MCC	Mammalian Cell Cycle	10	35	1	6	[Fau+06]
Th	Th Cell Differentiation	23	35	3	5	[MX06]

Evaluation

- Random changes were made according to probabilistic parameters:
    - F% : Change a **F**unction
    - E% : Flip the sign of an **E**dge
    - R% : **R**emove an existing edge
    - A% : **A**dd a missing edge

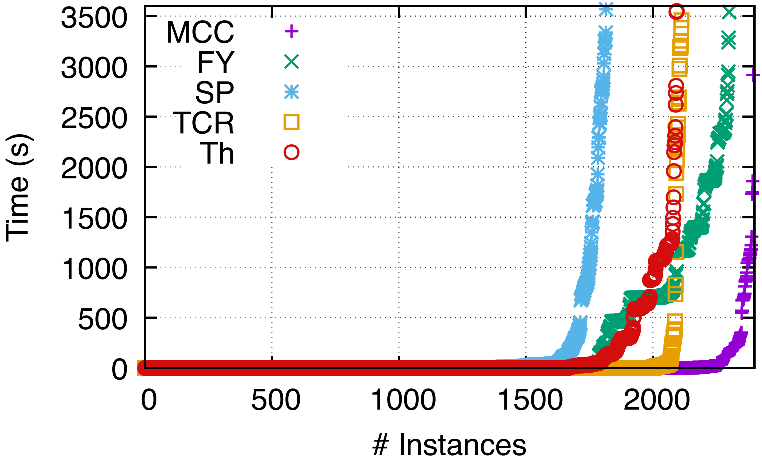
- Several configurations of these parameters were considered

- 100 instances were generated for each configuration for each model

- Timeout of 3600 seconds was considered

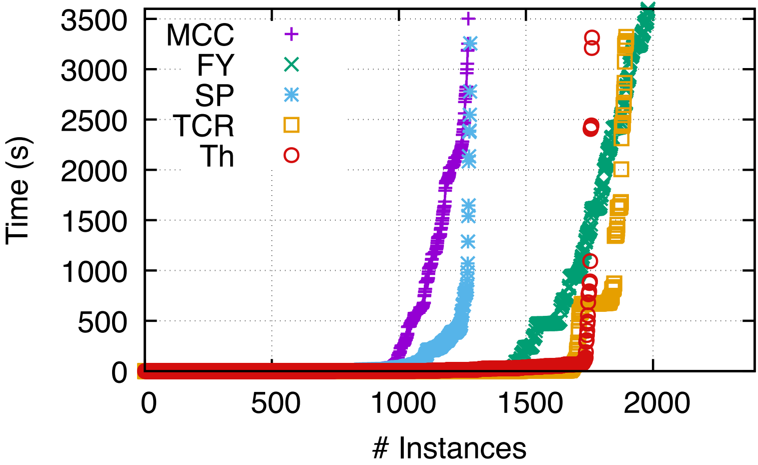
Results

Stable State Results



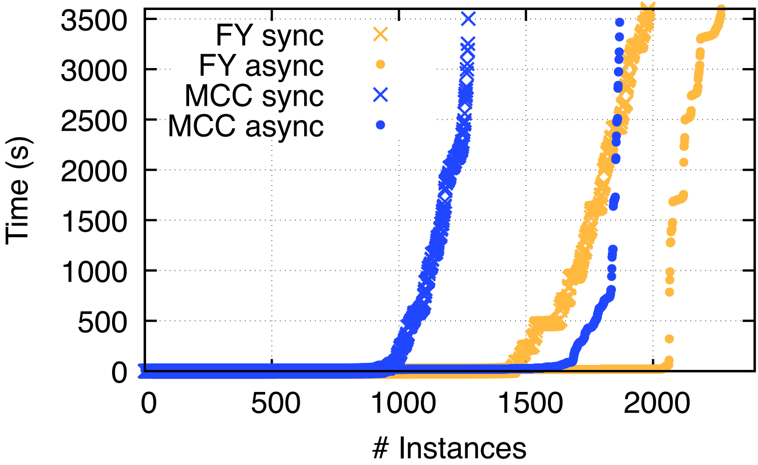
Results

Time-series Results - Synchronous (5 observations, 20 time steps)



Results

Time-series Results - Synchronous vs Asynchronous



Results

- More connected networks have higher solving times

- Topologically corrupted models lead to higher solving times
    - Change the sign of edges
    - Remove edges
    - Add edges

- Asynchronous update scheme performs better than the synchronous update scheme:
    - 91,82% of instances solved considering asynchronous update scheme
    - 76,84% of instances solved considering synchronous update scheme

Conclusion

- Proposed a model revision approach for Boolean logical models of biological regulatory networks

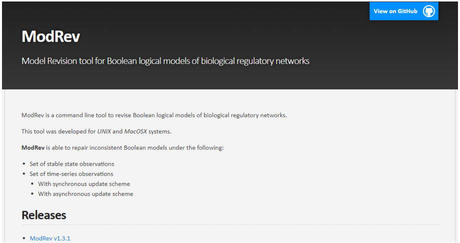
- Considering both:
  - Stable state observations
  - Time-series observations

- Considering different dynamics:
  - Synchronous update scheme
  - Asynchronous update scheme

Conclusion

- Model revision approach computes optimum sets of repair operations
  - Optimisation criterion defined

- Model revision approach implemented as a tool: ModRev
  - Assess whether a Boolean logical model is consistent with a set of observations
  - Produces all optimum repair sets to repair an inconsistent model
  - ModRev available at https://filipegouveia.github.io/ModelRevisionASP/



ModRev

Model Revision tool for Boolean logical models of biological regulatory networks

ModRev is a command line tool to revise Boolean logical models of biological regulatory networks.

This tool was developed for *UNIX* and *MacOSX* systems.

ModRev is able to repair inconsistent Boolean models under the following:

- Set of stable state observations
- Set of time-series observations
  - With synchronous update scheme
  - With asynchronous update scheme

Releases

- ModRev v1.3.1

Conclusion

- Approach successfully tested using five well-known biological models
- Able to solve 84,89% of the (108 000) instances
  - Most of the instances solved under 60 seconds
- Degree of connectivity plays a big role on the model revision procedure
- The dimension of the regulatory functions has the biggest impact on the performance
  - Number of monotone non-degenerate Boolean functions increases exponentially

Discussion and Future Work

- Heuristics could be used to reduce the number of solutions
- Study the solutions produced to determine common repair operations
- Consider different approaches:
  - Different ASP encodings
  - Use other logic-based approaches
- Facilitate the interoperability of ModRev with other tools
  - BioLQM toolkit

Thank you!

MODREV https://filipegouveia.github.io/ModelRevisionASP/

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