PhD Open Days

Model Revision of Boolean Regulatory Networks

PhD Program in Information Systems and Computer Engineering

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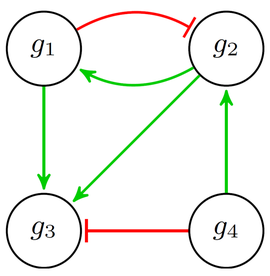
Biological Regulatory Networks

Regulatory network composed of:

- Nodes (eg genes/proteins)
- Interactions (activations or inhibitions)

Describe complex cellular processes.



Models of regulatory networks allow to:

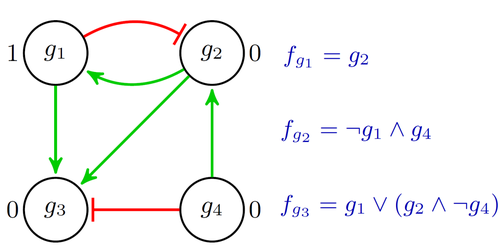
- Computationally reproduce existing observations
- Test hypotheses
- Identify predictions *in silico*

Different formalisms can be used [1]:

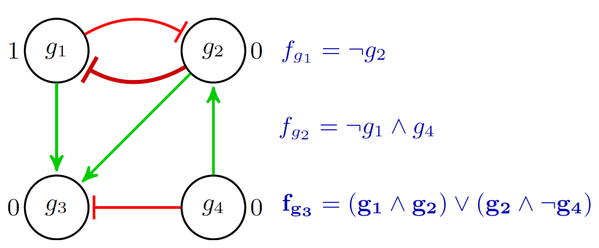
- We use *Boolean Logical Models* [2]

Motivation

- Construction of models is still mainly a manual error-prone task
- As the model is extended or new data is acquired the model may become inconsistent
  - $\Longrightarrow$ *Model Revision*



Inconsistent Model

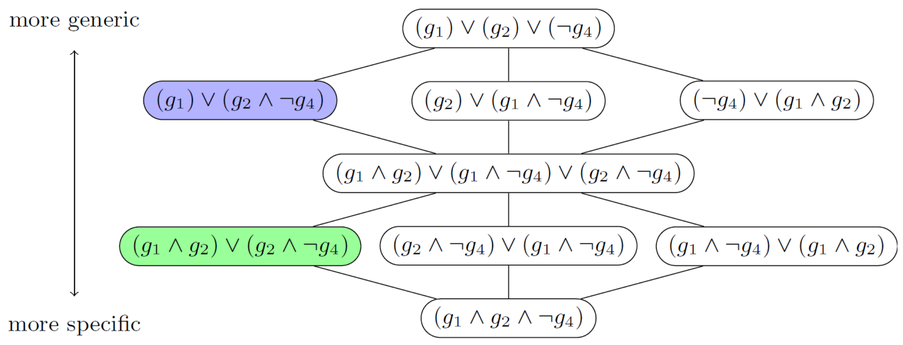


Revised Model

There are 2^{2^k} Boolean functions with *k* regulators

Monotone Non-degenerate Boolean Functions

- Partial order set can be defined over the set of all monotone non-degenerate Boolean functions [3]
- Can be represented by an Hasse diagram



Model Revision

Cause of Inconsistency	Repair Operation
Wrong Regulatory Function	Function Change
Wrong Interaction Type	Edge Sign Flip
Wrong Regulator	Edge Removal
Missing Regulator	Edge Addition

Assumptions

- Monotone Non-degenerate Boolean regulatory functions
- Consider only Stable State observations
- Higher level of confidence in the correctness of the network topology than in the regulatory functions of the model

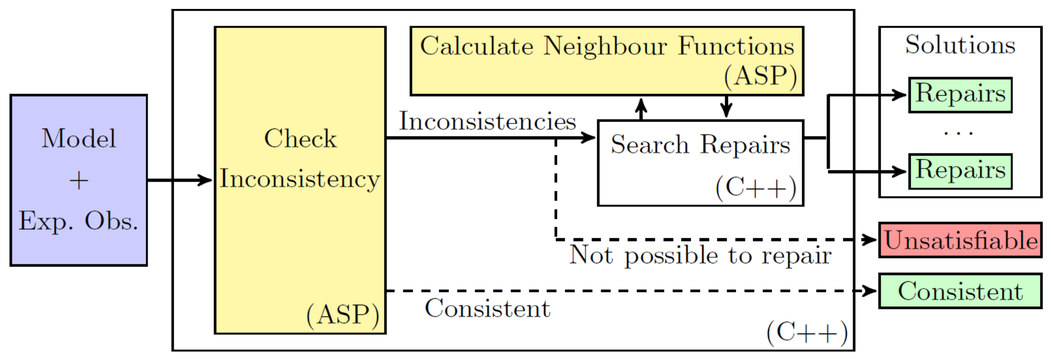
Optimization

1. Minimize number of add/remove edge operations
2. Minimize number of flip sign of an edge operations
3. Minimize number of change regulatory function operations

Approach

Use of Answer Set Programming (ASP) to

- Check model consistency and determine possible reasons of inconsistency [4]
- Calculate neighbour monotone non-degenerate Boolean functions



This tool determines if a model is consistent or gives a set of reasons of inconsistency if possible.
Given an inconsistent model and a set of reasons for inconsistency, the tool computes all the optimum set of repair operations in order to render the model consistent.

Conclusion

- Tool successfully tested using several well-known biological models
- Most instances repaired under 60 seconds
- Dimension of regulatory functions has the biggest impact on the tool performance

Future Work

- Consider model dynamics in the model revision procedure
- Use heuristics to reduce the set of repairs to be produced

References

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[3] Cury, J.E., Monteiro, P.T., Chaouiya, C.: Partial Order on the set of Boolean Regulatory Functions. arXiv preprint arXiv:1901.07623 (2019)
[4] Gouveia, F., Lynce, I., Monteiro, P.T.: Model revision of logical regulatory networks using logic-based tools. In: ICLP 2018 (Technical Communications). Schloss Dagstuhl-Leibniz-Zentrum fuer Informatik (2018)

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