Boolean modelling of regulatory network data S28

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Summary

- quick qualitative simulation without need for parameterisation, rate laws or initial conditions
- regulatory network representation with a state oriented approach using the "rxncon" language
- update rules are automatically generated from reaction and contingency definitions
- unique mapping of a rxncon model to a boolean model with unique outcome --> allows network validation
- simulateable with R library "BoolNet"

Modelling steps

Example:
- two proteins A and B build a complex, if B is phosphorylated
- this reaction shall be reversible

I. rxncon language*:
A_[bsB]_ppi_B[bsA]; ! B_[(r)]-{p}
A_[bsB]_ppi-_B_[bsA]

Step 1 ↓

I. Rule based representation**:
A(bsB) + B(bsA, r~p) ⟶ A(bsB!1).B(bsA!1, r~p)
A(bsB!1).B(bsA!1) ⟶ A(bsB) + B(bsA)

Step 2 ↓

II. Boolean rules:
A_[bsB]_ppi_B_[bsA] = B_[(r)] -{p}
A_[bsB]_ppi-_B_[bsA] = 1
A_[bsB]--B_[bsB] = (A_[bsB]_ppi_B_[bsA] AND A_[bsB]--0 AND B_[bsA]--0)
OR (A_[bsB]--B_[bsbB] AND NOT(A_[bsB]_ppi-_B_[bsA]))

source state, **contingency state**, **product state**

Assumptions during the process:

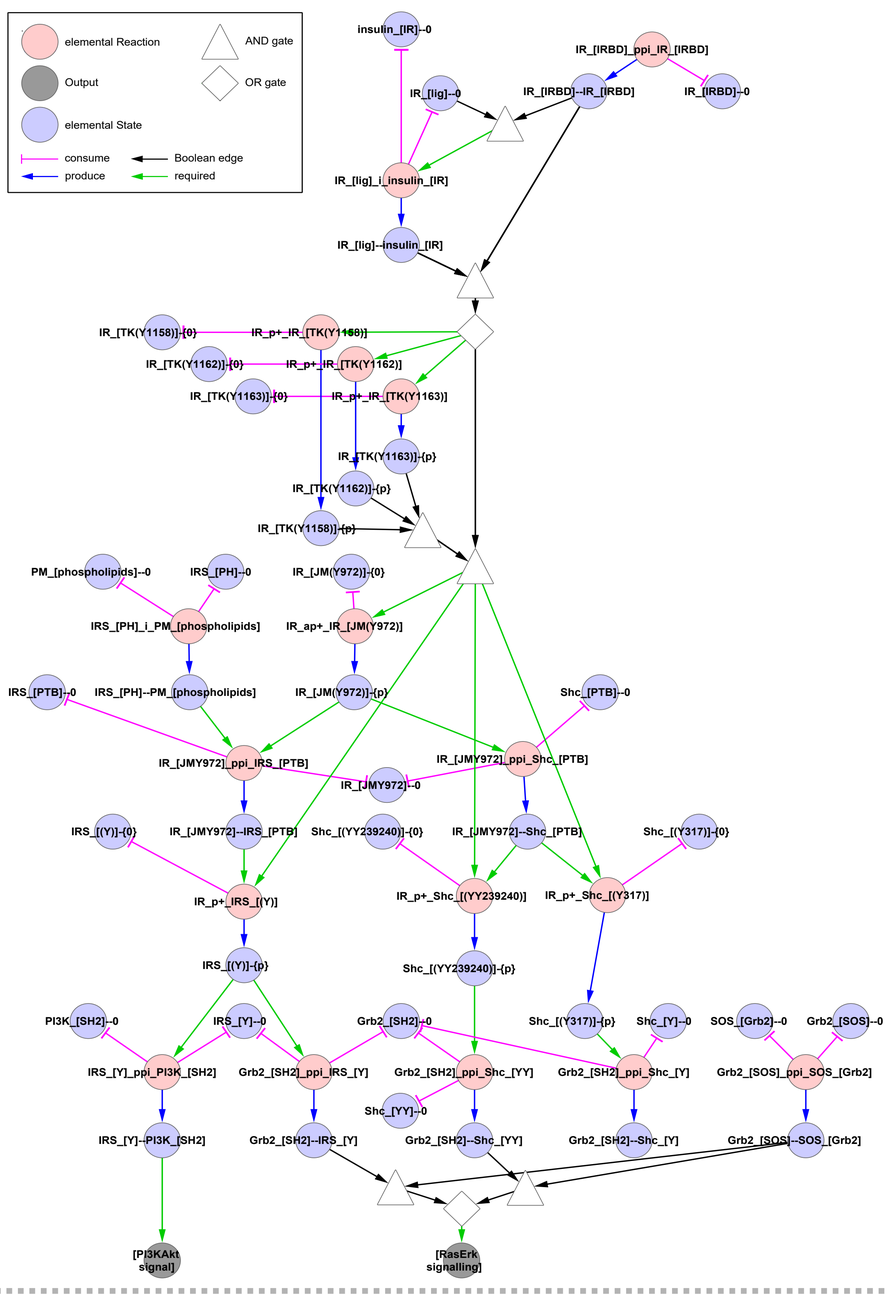
Step 1:
- single molecule level with mutually exclusive states
- here, the binding protein B must be phosphorylated and cannot have another modification on that residue
- source states are consumed, product state are produced, contingencies are constant

Step 2:
- $x_i(t+1) = b_i(x(t)),\ 1 \leq i \leq n$ x := gene, b:= rule, t:=time
- system wide level, states not mutually exclusive
  - multiple instances and configurations of components
- here, we lose the information which B is the phosphorylated one. Considered is whether the reaction can take place in the current or the next time-step
  --> time smoothing
- reactions become active (true) when contingencies are fullfilled
- states become true when forward reactions and their source states are true
- states remain true when no reverse/degrative reactions are true

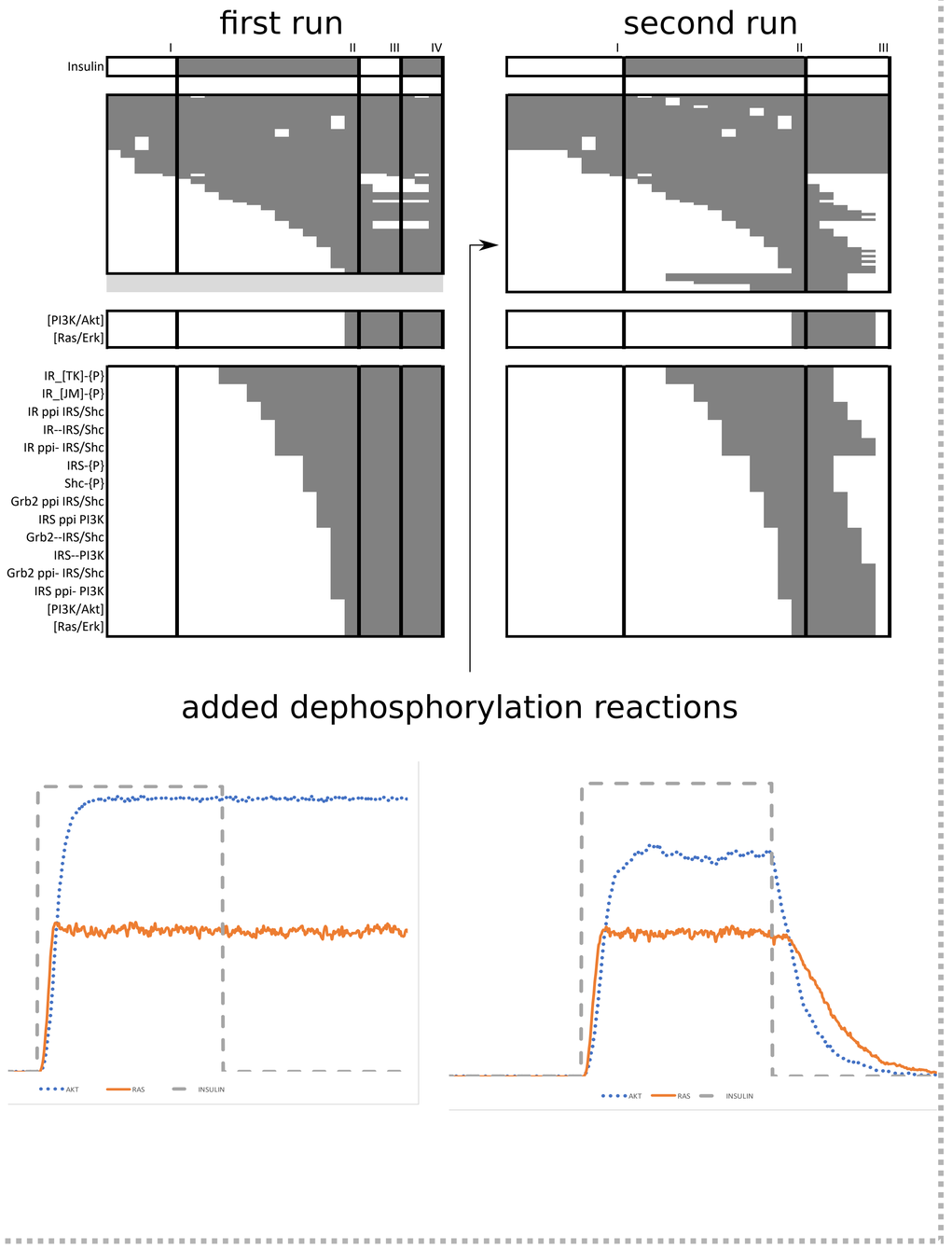
For more information on these steps see: * poster S24, Marcus Krantz
** poster S27, Jesper Romers

Simulation: human insulin pathway

Model graph



Simulation



Read more:
- C. Müssel, M. Hopfensitz and H. A. Kestler. BoolNet - an R package for generation, reconstruction and analysis of Boolean networks. Bioinformatics, 26(10):13781380, 2010
- Romers J., Thieme S., et al; Using rxncon to develop rule based models. Submitted

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