A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets

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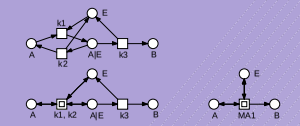
Some basic building blocks for biochemical pathways Enzymatic reactions (Mass Action)

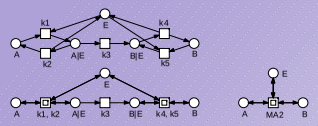
MA1, MA2, MA3: Patterns for enzyme reactions, with increasing degrees of complexity

$$A + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} A|E \xrightarrow{k_3} B + E$$



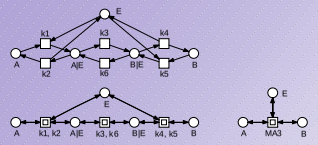
Model 1 (MA1)

$$A + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} A|E \xrightarrow{k_3} B|E \underset{k_5}{\overset{k_4}{\rightleftarrows}} B + E$$



Model 2 (MA2)

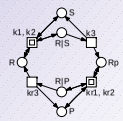
$$A + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} A|E \underset{k_6}{\overset{k_3}{\rightleftarrows}} B|E \underset{k_5}{\overset{k_4}{\rightleftarrows}} B + E$$



Model 3 (MA3)

Phosphorylation - dephosphorylation step Mass action Model 1

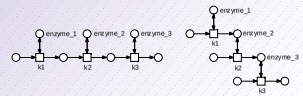
- R: unphosphorylated form
- R_p: phosphorylated form
- S: kinase
- P: phosphatase
- R|S unphosphorylated+kinase complex
- R|P unphosphorylated+phosphatase complex



$$R + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} R|S \xrightarrow{k_3} R_p + S$$

$$R + P \xleftarrow{kr_3} R_p|P \underset{k_2}{\overset{k_1}{\rightleftarrows}} R_p + P$$

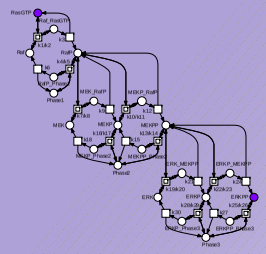
Metabolic pathway vs Signalling cascade



The essential structural difference between metabolic networks (left) and signal transduction networks (right) in terms of Petri net structures.

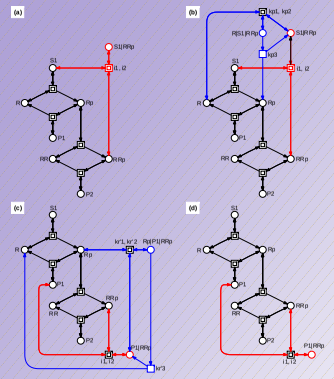
Signal transduction cascades

Composition of building blocks Levchenko model



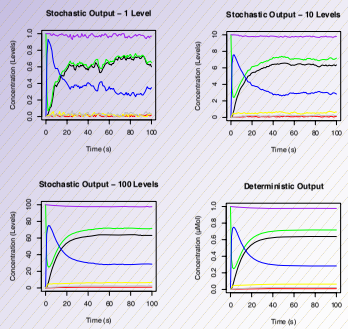
Phosphorylation cascade and feedback

Petri nets, for a two-stage cascade with (a) negative feedback, (b) positive feedback (the reaction sequence i1, kp1, kp3 contributes to the phosphorylation); alternative two-stage cascade with (c) negative feedback (the reaction sequence i1, kr'1, kr'3 contributes to the dephosphorylation), (d) positive feedback.

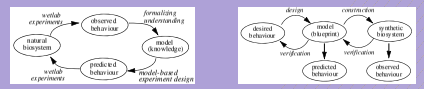


Stochastic vs continuous behaviour

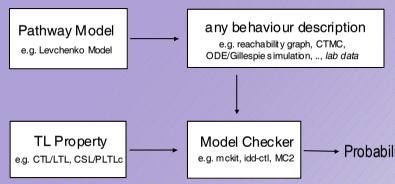
RKIP model (Cho et al)



Model checking



Systems biology:
Part of model design process, validate the model conforms to the observed data.
Synthetic biology:
Make sure the model and constructed bio system conform to the desired behaviour.



Stochastic Model Checking

Levchenko Model – (Gillespie algorithm)

S1: "What is the probability that RafP will increase when at a concentration X?"

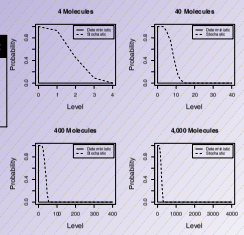
$P_{=?}[\ (RafP = X)\ U\ (RafP > X)\ \{RafP = X\}\ ]$

S2: "What is the probability that RafP will reach concentration X while MEKPP and ERKPP remain at 0?"

$P_{=?}[\ (MEKPP = 0 \wedge ERKPP = 0)\ U\ (RafP > \$X)\ ]$

Molecules	Property S1	Property S2
4	6s	10s
40	70s	78s
400	6 mins*	3 mins*
4,000	8 hrs*	20 mins*

Speedup in S2 due to constraint variables
* cluster processing

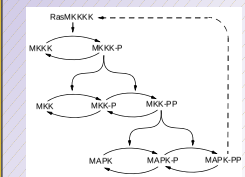


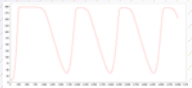
Continuous Model Checking

Phosphorylation cascade + negative feedback Kholodenko model – oscillations (ODE solver)

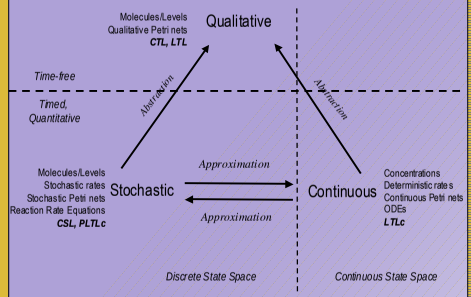
"MAPK_PP rises and falls, then rises and falls, ..."

$P_{=?}[\ F(d(MAPK_PP) > 0 \wedge F(d(MAPK_PP) < 0 \wedge F(d(MAPK_PP) > 0 \wedge F(d(MAPK_PP) < 0 \ldots))))]$





Conceptual Framework



We have used a framework which unifies the qualitative, stochastic and continuous worlds, as a basis for our overall approach to modelling and analysing the biochemical pathways.

Model checking in these worlds exploits a variety of *temporal logics*.

References

David Gilbert, Monika Heiner and Sebastian Lehrack (2007). A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets. In Proceedings CMSB 2007, LNCS/LNBI Volume 4695, pp. 200-216.

Rainer Breitling, David Gilbert, Monika Heiner, Richard Orton (2008). A structured approach for the engineering of biochemical network models, illustrated for signalling pathways. Briefings Bioinformatics, in print.

Monika Heiner, David Gilbert, and Robin Donaldson (2008). Petri Nets for Systems and Synthetic Biology. In M Bernardo, P Degano, and G Zavattaro (eds.): SFM 2008, LNCS Volume 5016, pp. 215–264.

Tools & Resources

- Snoopy and Charlie: www-dssz.informatik.tu-cottbus.de, in cooperation with Wolfgang Marwan/Magdeburg Centre for Systems Biology
- BioNessie (University of Glasgow): www.bionessie.org
- MC2: www.brc.dcs.gla.ac.uk/software/mc2
- gillespie2: www.basis.ncl.ac.uk/software.html