# Modelling signal transduction pathways of yeast with Petri nets

**Andrea Sackmann[1,2], Monika Heiner[3], Ina Koch[1]**

[1] Technical University of Applied Sciences Berlin, Bioinformatics group, Seestrasse 64, 13347 Berlin, Germany
[2]University Greifswald, Dept. of Mathematics and Computer Science, Fr.-L.-Jahn-Str. 15a, 17487 Greifswald, Germany
[3]Brandenburg University of Technology at Cottbus, Dept. of Computer Science, PO 10 13 44, 03013 Cottbus, Germany

andrea.sackmann@nexgo.de; monika.heiner@informatik.tu-cottbus.de; ina.koch@tfh-berlin.de

## Motivation

There are signalling modules, e.g., the heterotrimeric G-Protein and the mitogen-activated protein-kinase (MAPK) cascade, in eukaryotic organisms from yeast to human. *Saccharomyces cerevisiae* has proven indispensable in understanding the mechanisms, interrelationships and regulation of these components. Three essential signalling pathways of yeast and the known cross talks in between have been modelled as a Petri net. This mathematical structure of bipartite digraphs facilitates a step-wise model development and a trustworthy way of model validation.

## The Petri Net Model

- Modelling was performed according to [1][2][3][5][8] using the Petri net editor PED [7].
- The model contains the mating-pheromone response, the HOG and the filamentation pathway as well as the known cross talks in between, see Fig. 1.
- The net is a discrete and qualitative (purely causal) one.
- Proteins are modelled as places; signalling processes and other active system elements are represented by transitions.
- All moving objects - as molecules or above all signals - are modelled by tokens residing in places. Therefore, the flow of tokens represent fluxes of information (signals).
- Most of the used read arcs (excluding those, which are connected with P-invariants) are replaced by directed arcs for the analysis in accordance with [4].

## Qualitative Analysis using INA [6]

- The Integrated Net Analyzer (INA) [6] provides analysis techniques for analysing and accordingly validating the Petri net model [4].
- The net is connected via the logical nodes.
- There are five minimal P-Invariants and twenty minimal T-invariants.
- The net is covered by minimal T-invariants.

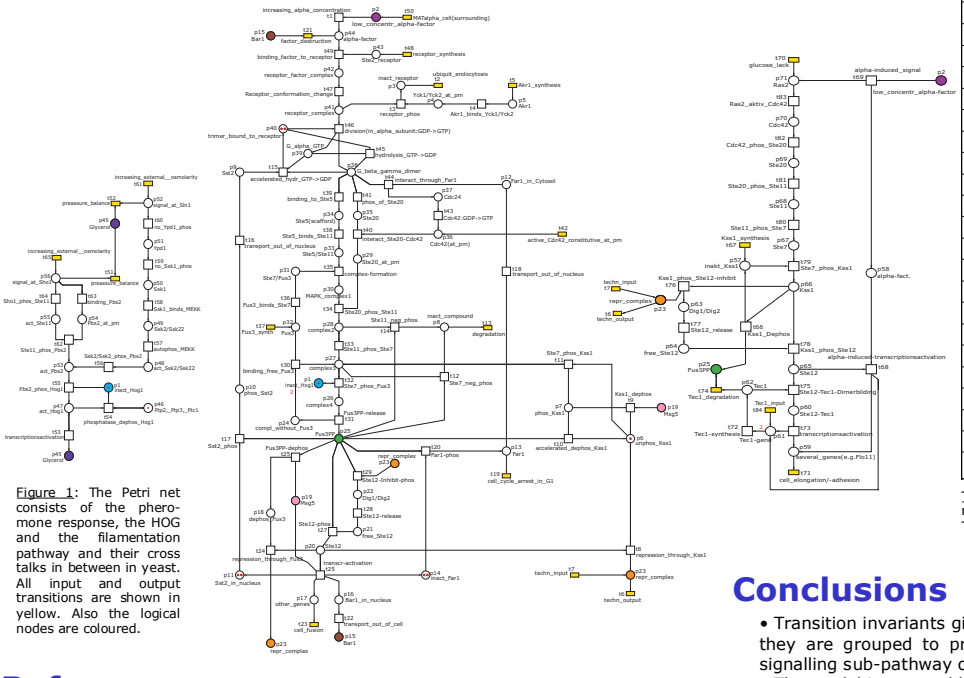

Figure 1: The Petri net consists of the phero-mone response, the HOG and the filamentation pathway and their cross talks in between in yeast. All input and output transitions are shown in yellow. Also the logical nodes are coloured.

## Processing of the T- invariants

- Transitions are grouped in a set of transitions iff they appear in the same T-invariants. Table 1 lists the sets of transitions with their biological meaning in the model.
- Because of the remaining read arcs some of the calculated minimal T-invariants have to be combined ensuring them to be realisable. Table 2 shows the processed T-invariants.

| Set | Transitions | Biological meaning |
|---|---|---|
| 1 | 1, 47, 48, 49 | Receptor activation |
| 2 | 2, 3, 4, 5 | Receptor endocytosis |
| 3 | 15, 16, 17, 20, 21, 22, 23, 26 | transcription of genes in response to pheromone |
| 4 | 18, 43, 44 | Far1 transmitted interaction Gβγ & Cdc24 |
| 5 | 24, 25 | Ste12 repression through inactive Fus3 |
| 6 | 26, 28, 29 | Ste12 activation in response to pheromone |
| 7 | 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 | MAP kinase cascade in the pathway of pheromone response |
| 8 | 54, 55 | De-/phosphorylation of Hog1 |
| 9 | 56, 57, 58, 59, 60 | HOG-signal over Sln1-branch |
| 10 | 62, 63, 64 | HOG-signal over Sho1-branch |
| 11 | 67, 71, 76, 77, 78 | Ste12-dependend transcription of filamentation-genes |
| 12 | 68, 69 | α-induced signal in the pathway of filamentation |
| 13 | 70, 79, 80, 81, 82, 83 | MAP kinase cascade in the pathway of filamentation |
| 14 | 73, 75 | Tec1-depandent transcription of filamentation-genes |

Table 1: The transitions grouped in sets over their occurrences in the same T-invariants. The right column contains the biological meaning of the resulting groups.

| № | T-Invariants consist of the transitions | | Min? |
|---|---|---|---|
| | set of trans. | single trans. | |
| 1. | - | 6, 7 | yes |
| 2. | 1, 2 | 50 | yes |
| 3. | 1 | 45, 46, 50 | yes |
| 4. | 8, 9 | 61 | yes |
| 5. | 8, 10 | 65 | yes |
| 6. | 1, 3, 6, 7 | 7, 9, 11, 19, 46, 50 | yes |
| 7. | 1, 3, 5, 6, 7 | 7, 19, 46, 50 | yes |
| 8. | 1, 3, 4, 6, 7 | 7, 9, 11, 46, 50 | yes |
| 9. | 1, 3, 4, 5, 6, 7 | 7, 46, 50 | yes |
| 10. | 11, 12, 13, 14 | 7, 50, 72 | yes |
| 11. | 11, 13, 14 | 7, 72, 84 | yes |
| 12. | 8, 9 | 52, 53, 61 | no |
| 13. | 8, 10 | 52, 53, 61, 65 | no |
| 14. | 8, 9 | 51, 53, 61, 65 | no |
| 15. | 8, 10 | 51, 53, 65 | no |
| 16. | 1, 6, 7 | 8, 45, 46, 50 | no |
| 17. | 1, 7 | 10, 11, 45, 46, 50 | no |
| 18. | 1, 7 | 12, 13, 45, 46, 50 | no |
| 19. | 1, 7 | 13, 14, 45, 46, 50 | no |
| 20. | 1, 7, 13 | 45, 46, 50, 66 | no |
| 21. | 1, 7, 11, 12, 13 | 7, 45, 46, 50, 72, 74 | no |
| 22. | 1, 7 | 45, 46, 50, 72, 74, 84 | no |

Table 2: The T-invariants of the net after processing them. They all are realisable and have biological plausibility. The right column shows if the T-invariant is still minimal, i.e. non-processed.

## Conclusions

- Transition invariants give biological signalling pathways through the net and they are grouped to provide sets of sub-processes representing a special signalling sub-pathway of the net.
- The model is covered by T-invariants, which all enjoy biological meaning.
- The place invariants can be interpreted as protein conservation properties.
- The model is validated by ensuring the structural consistency of the net and biological plausibility of the net analysis results.

## Outlook

- Extension of the validated model by known mutants behaviour
- Refinement to a continuous Petri net integrating known concentration-dependent reaction-rates

## References

[1] Bardwell L: Peptides, **25**, 1465-76 (2004)
[2] Dohlman HG, Thorner JW: Annu Rev Biochem, **70**, 703-54 (2001)
[3] Gustin MC, Albertyn J, Alexander M, Davenport K: Microb and Mol Bio Rev, **62**, 1264-1300 (1998)
[4] Heiner M, Koch I: Proc 25th ICATPN 04, Bologna, Italy, LNCS **3099**, 216-37 (2004)
[5] Pan X, Harashima T, Heitman T: Microbiol, **3**, 567-72 (2000)
[6] Starke PH, Roch S: http://www.informatik.hu-berlin.de/~starke/ina.html, HU Berlin (1999)
[7] Tiedemann R: Internal Technical Report, BTU Cottbus, Dept. of CS (1997)
[8] Westfall PJ, Ballon DR, Thorner J: Science, **306**, 1511-12 (2004)

SPONSORED BY THE
Federal Ministry of Education and Research

This work is partly supported by the Federal Ministry of Education and Research of Germany (BMBF) , BCB project 0312705D.

Projektträger Jülich
Nationales Genomforschungsnetz