

Semi-quantitative modeling in systems biology: the Petri net formalism

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e:Med Project Group
Modeling of Disease Processes
Online Seminar Series
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Semi-quantitative modeling in systems biology: the Petri net formalism

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December 7th 2022

E:Med Online Seminar : Modeling approaches for disease processes

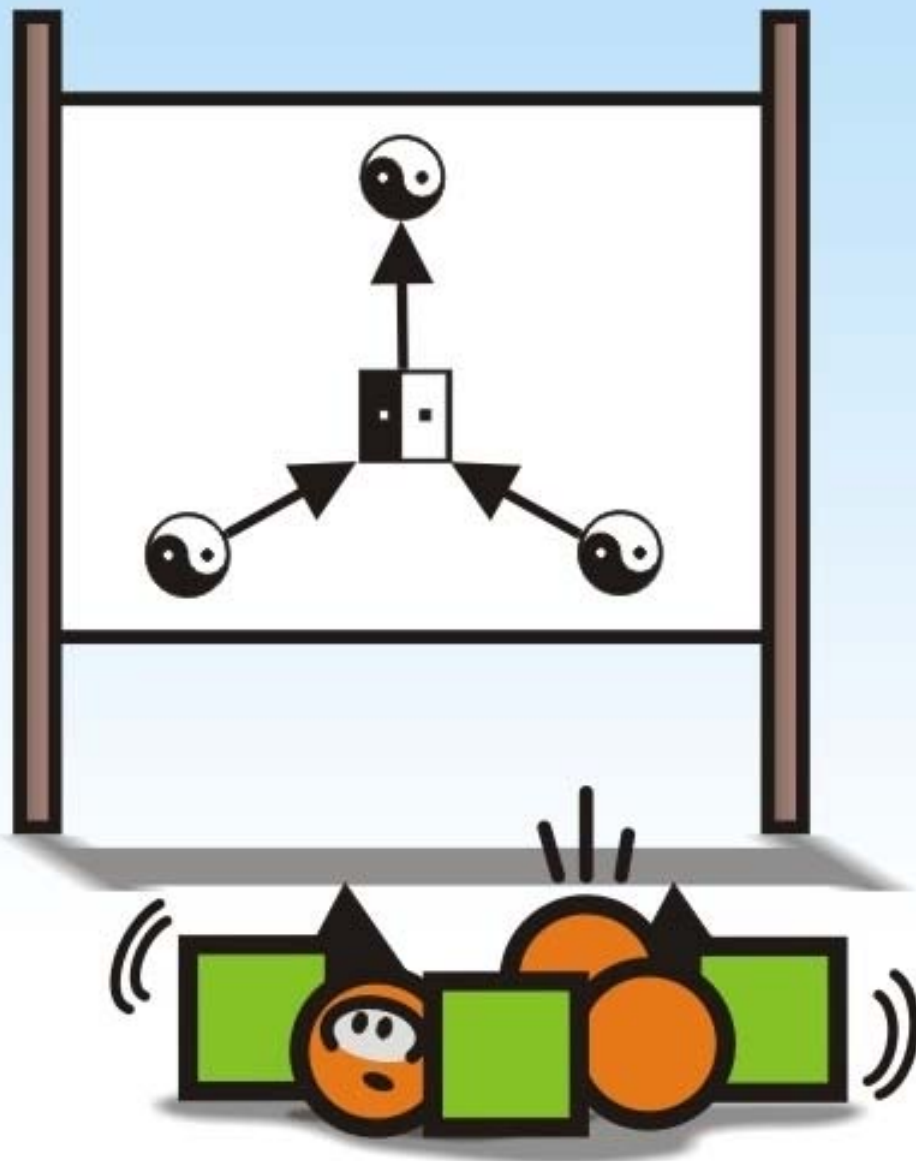
Outline

- ❖ Systems biology and data
- ❖ Introduction to Petri nets
- ❖ Signal transduction pathways
- ❖ Other Petri net projects
- ❖ Take-home messages

To model disease processes,
we have to understand
the function of proteins and
their interplay
in the biological system

Challenges in systems biology

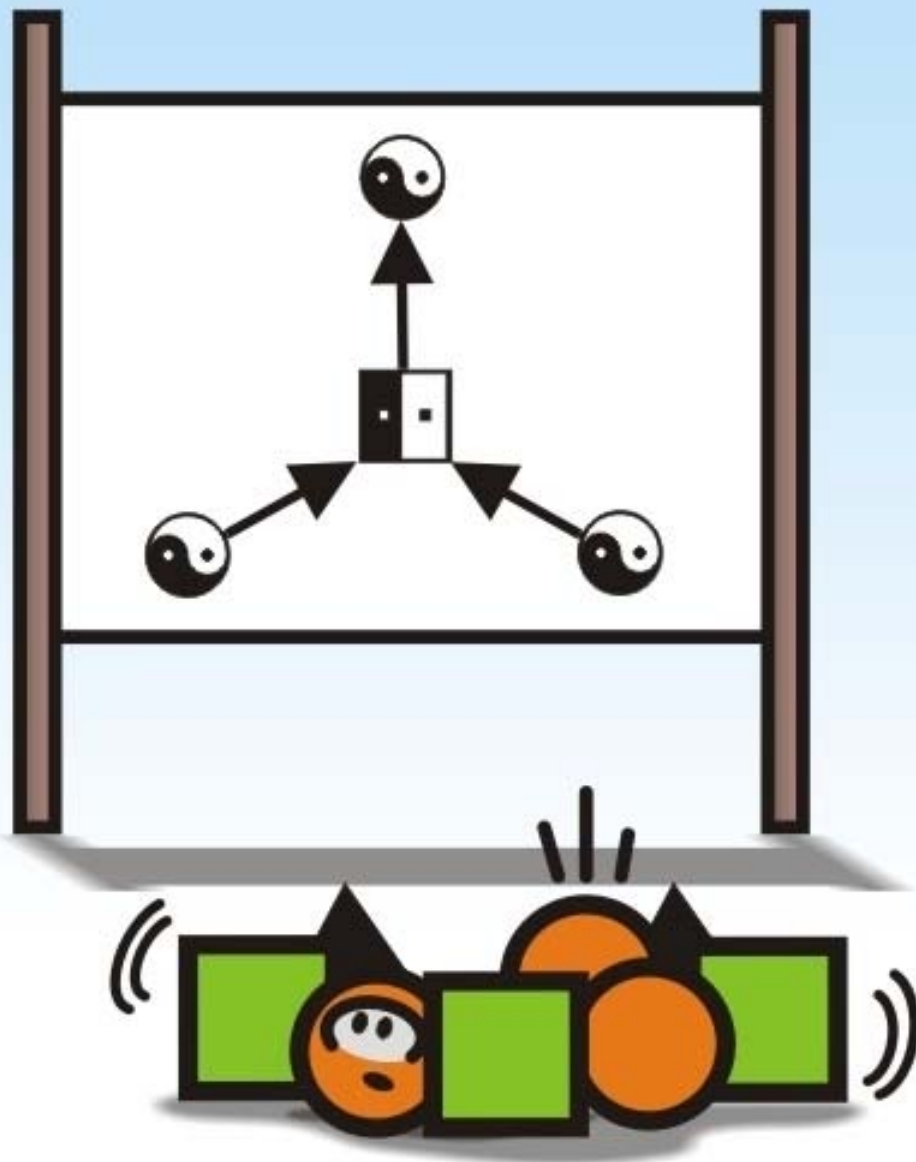
- ❖ Incomplete data
- ❖ Different time points and different locations in the cell
- ❖ Different **Data determine the choice of the modeling approach**
- ❖ Different experiments under varying experimental conditions
- ❖ Different scales: genomics, transcriptomics, proteomics, metabolomics, interactomics, imaging, ...



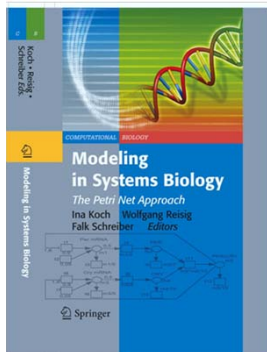
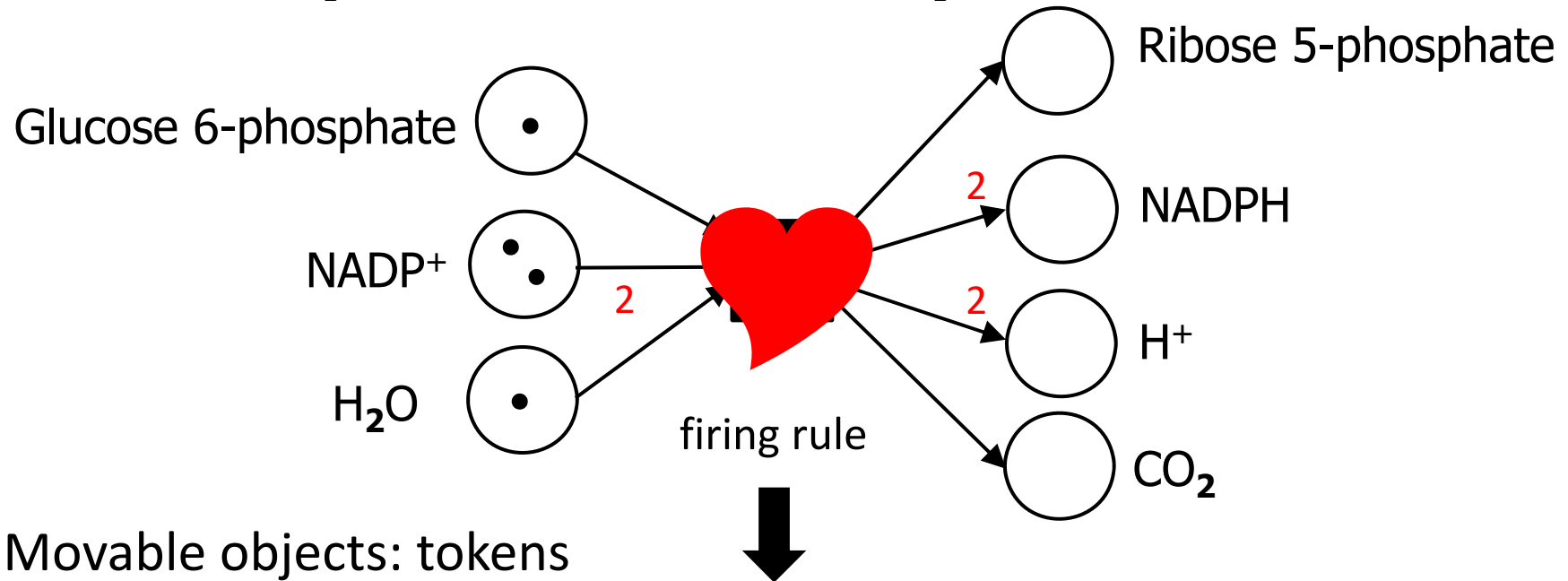
Petri nets

- ❖ Mathematical theory that describes systems with **concurrent** processes
- ❖ Developed by **Carl Adam Petri** (1926 – 2010)
- ❖ Basic definitions in his **PhD thesis** at University of Technology Darmstadt in **1962**
- ❖ **Many applications** in computer communication, operating systems, software dependencies, manufacturing systems, business processes
- ❖ Carl Adam Petri mentioned application to **chemical networks** already in **1976**
- ❖ First paper on biochemical application by **Venkatramana Reddy *et al.*** in **1993**
- ❖ Applications to **metabolic networks, signal transduction pathways, gene regulatory networks** using discrete, stochastic and continuous methods





Molecular Petri nets



Koch, Reisig, Schreiber (2011) Modeling in Systems Biology – The Petri Net Approach, Springer

Why Petri nets?

Insufficient kinetic data, but many qualitative data from “omics”

Dynamic's prediction becomes possible **without knowing** kinetic parameters

Analysis: model verification, reduction, decomposition,
invariant analysis, reachability analysis, liveness

Simulation: token game, synchronous, asynchronous, deadlocks,
token accumulation

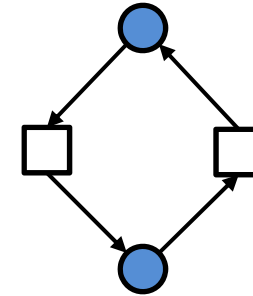
Strengths:

- ❖ Different models of abstraction (Boolean, discrete untimed & timed, stochastic, continuous) → hybrid models
- ❖ Flexibility in changing firing concepts (e.g., Fuzzy logics)
- ❖ Intuitive visualization and simulation combined with the analysis and simulation
- ❖ **Knockout analysis**

Petri net analysis at steady state

- ❖ **Minimal place invariants (PIs)**

substance conservations



- ❖ **Minimal transition invariants (TIs)**

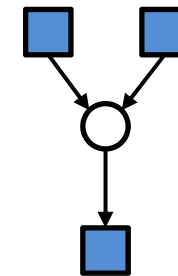
basic functional processes

cyclic firing sequences to the initial state

Lautenbach (1973) *GMD Report No. 82*

correspond to elementary modes

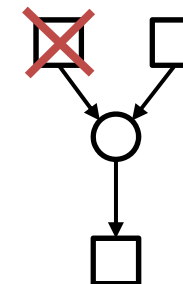
Schuster *et al.* (1993) *Second Gauss Symposium*



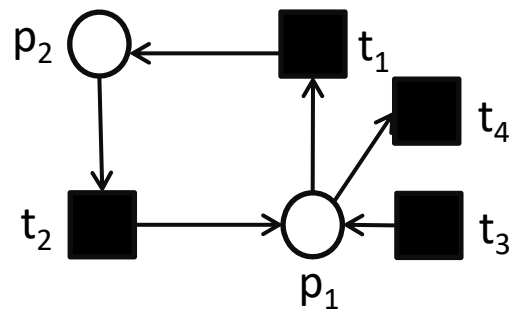
- ❖ ***In silico* knockout**

knockout matrix

Scheidel *et al.* (2016) *PLoS Computational Biology*

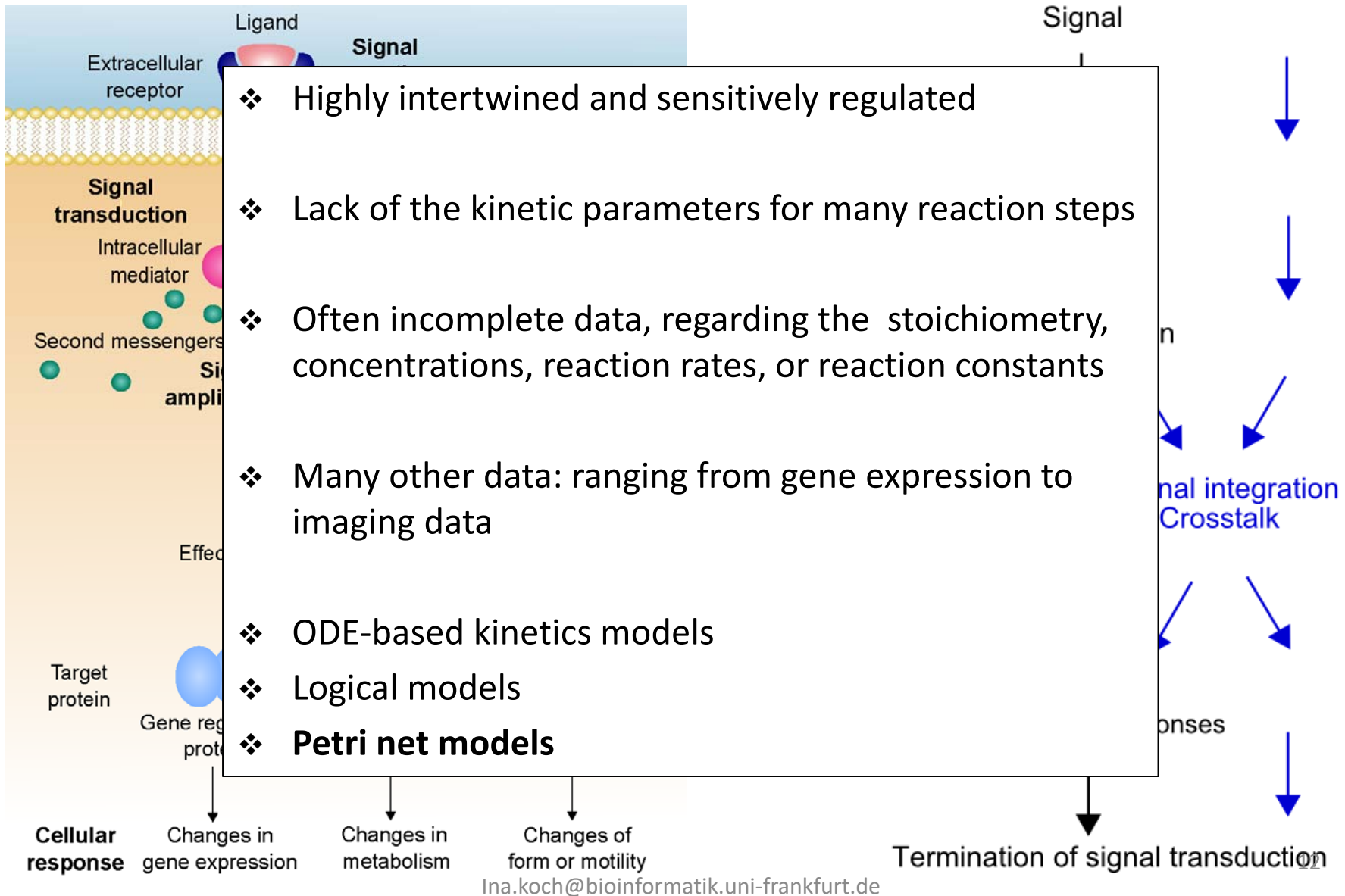


Example: transition invariants

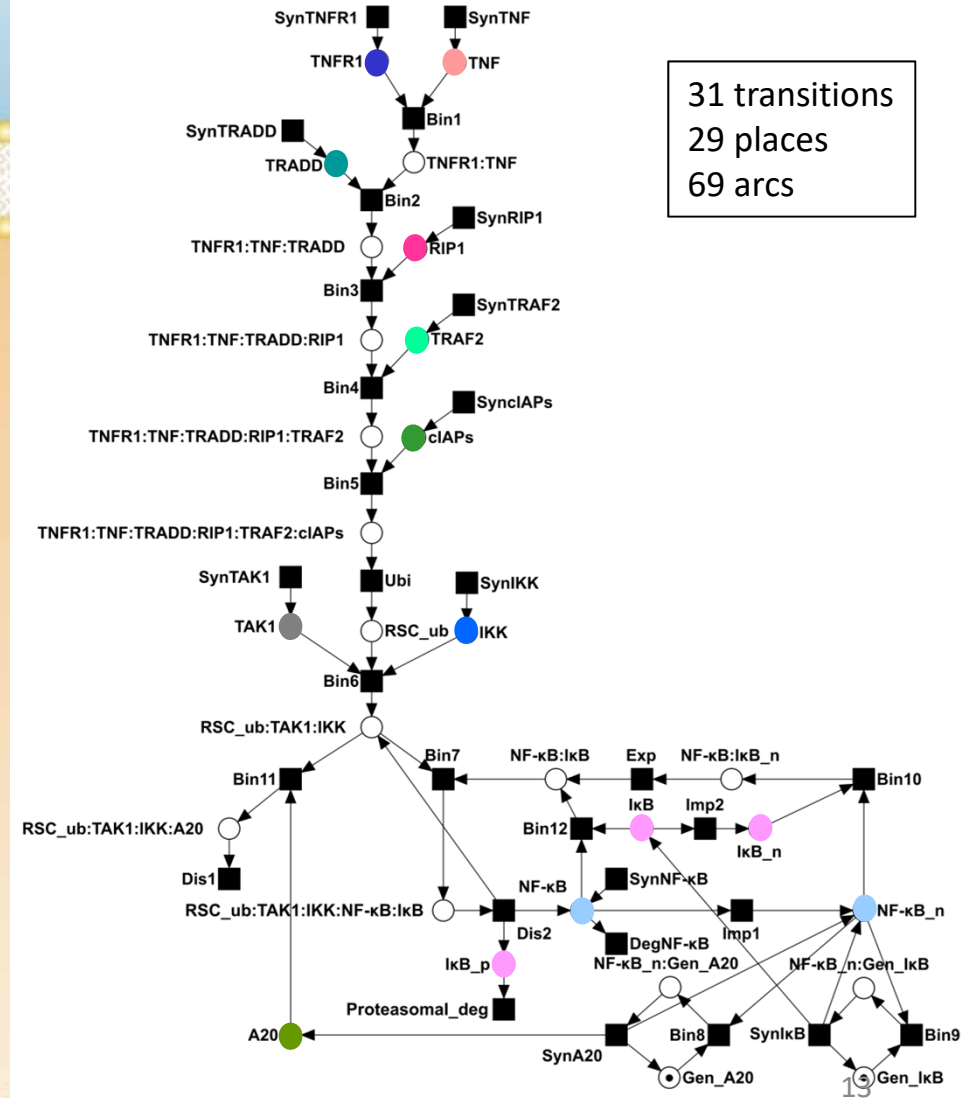
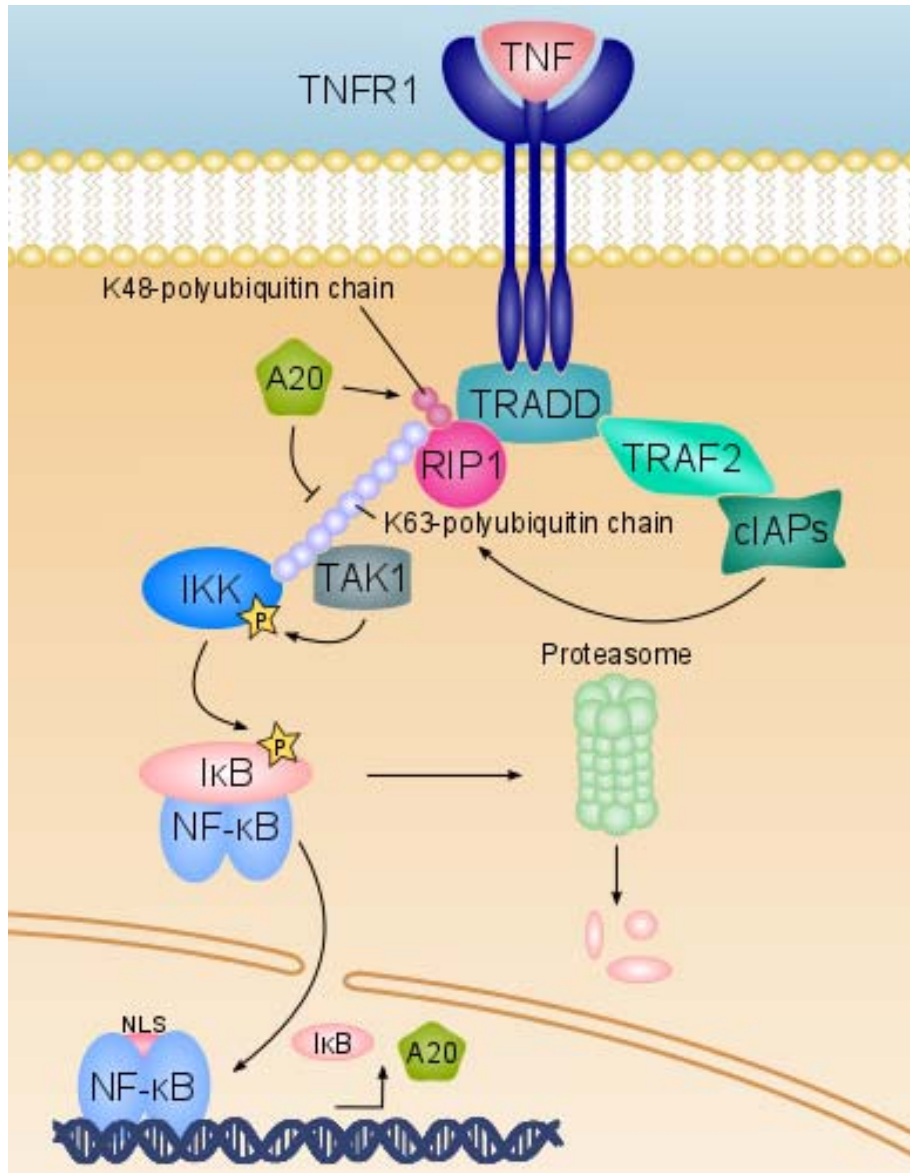


$$TI_1 = (t_1, t_2,)$$
$$TI_2 = (t_3, t_4)$$

Functionality in signaling pathways



TNFR-mediated NF- κ B activation



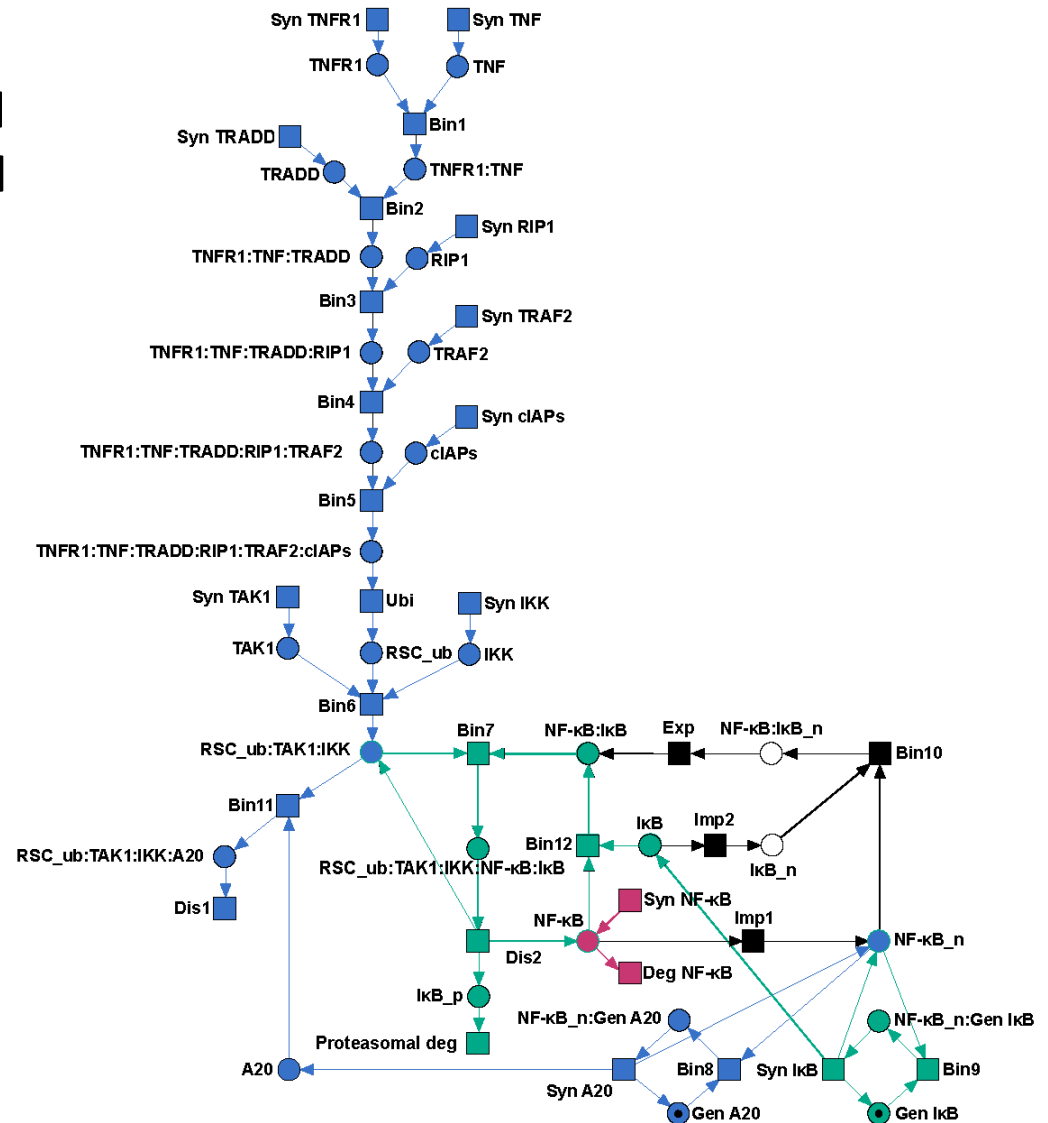
Motivation for Manatee invariants

❖ **Observation:** transition invariants (TIs) are unable to represent **signal flows from the receptor to the cell response** in networks with cycles

❖ **Aim:** mathematical concept to compute **all** signal flows from **receptor activation to the cell response**

❖ **Method:** linear combination of TIs to get **Manatee invariants (MIs)** based on **feasible TIs**

Sackmann *et al.* (2006) *BMC Bioinformatics*



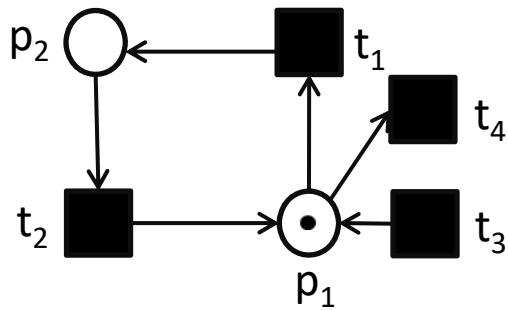
Manatee invariants

- ❖ **Aim: Prediction** and characterization of **complete** signal flows
→ from signal reception to cell response
- ❖ **Method:** Formation of **linear combinations** of feasible, minimal transition invariants, preserving the properties of feasibility and CTI.
- ❖ **Assumption: feasible** transition invariants represent complete signal flows in the Petri net



Amstein *et al.* (2017) *BMC Systems Biology*

Realizable TIs vs feasible TIs



$m_0 = (0, 0):$

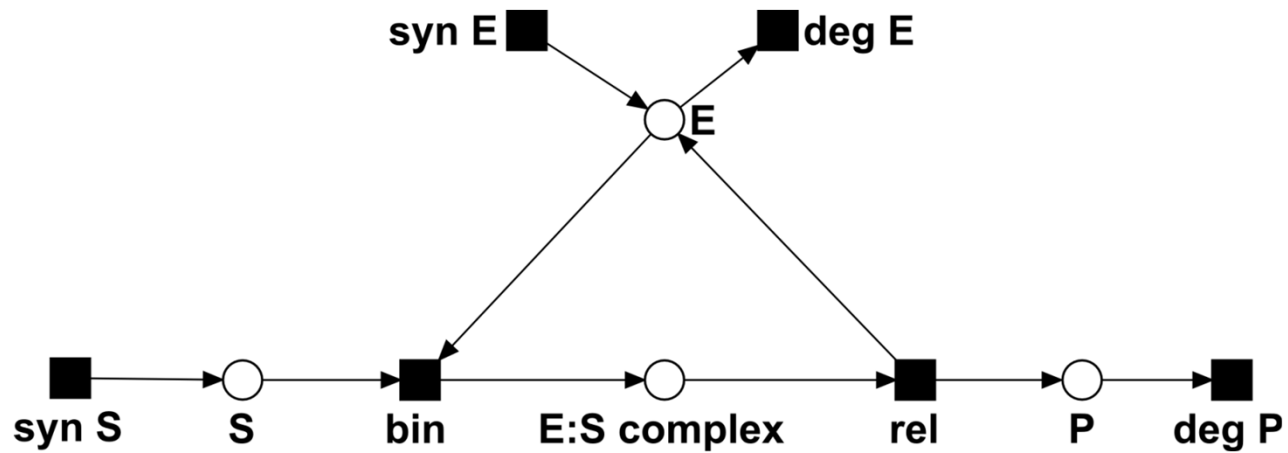
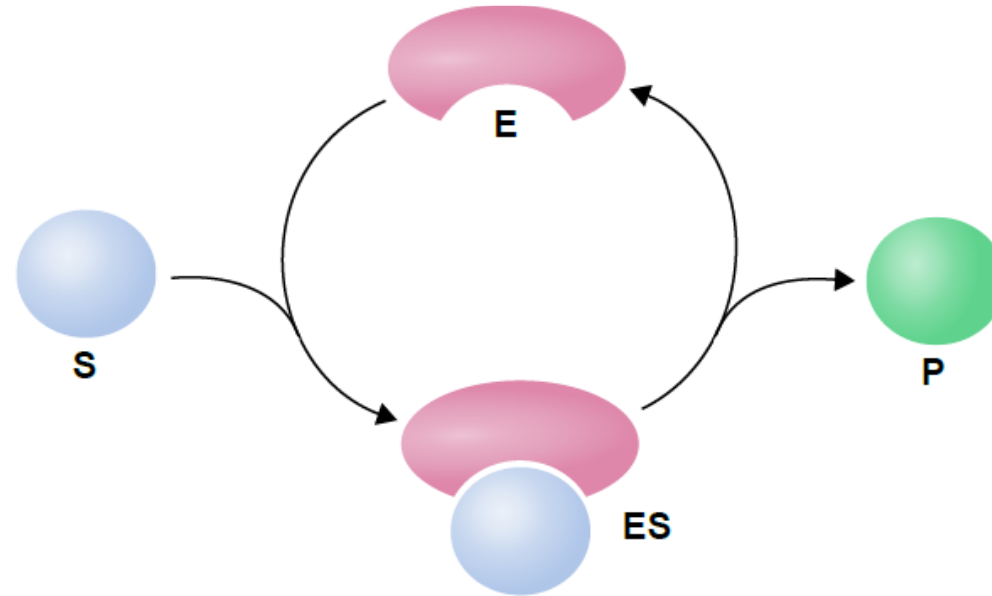
$Tl_1 = (t_1, t_2)$ realizable, not feasible

$Tl_2 = (t_3, t_4)$ realizable, feasible

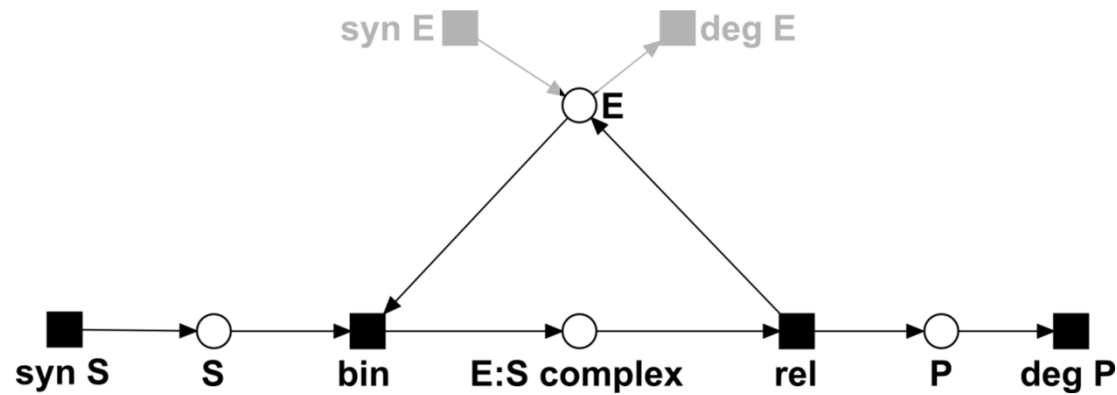
$m_0 = (1, 0):$

$Tl_1, Tl_2 \rightarrow$ realizable, feasible

Enzyme-catalyzed reaction



Enzyme-catalyzed reaction

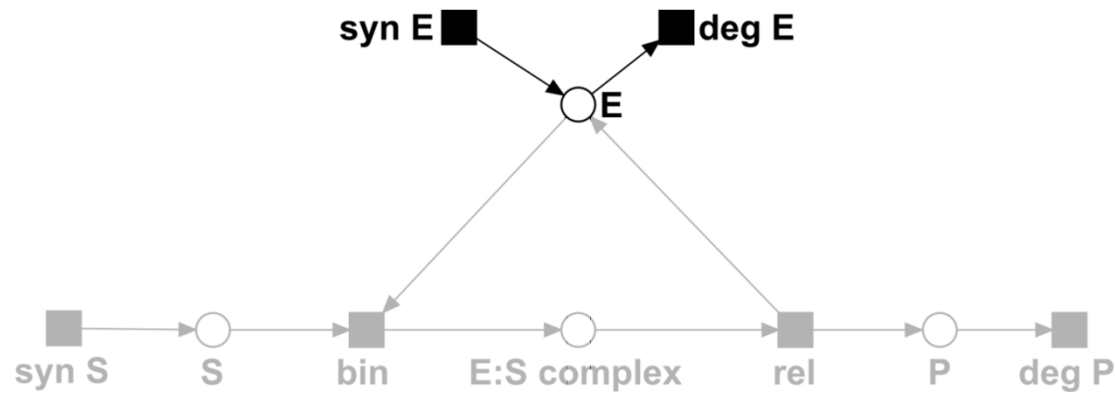


Transition invariants:

$$TI_1 = (\text{syn S}, \text{bin}, \text{rel}, \text{deg P})$$

The TI_1 -induced network

Enzyme-catalyzed reaction



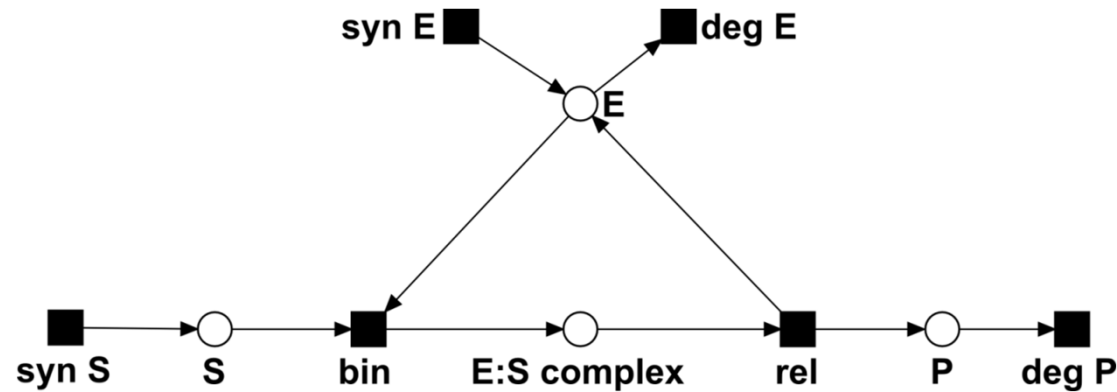
Transition invariants:

$$TI_1 = (\text{syn } S, \text{bin}, \text{rel}, \text{deg } P)$$

$$TI_2 = (\text{syn } E, \text{deg } E)$$

The TI_2 -induced network

Enzyme-catalyzed reaction



Transition invariants:

$$TI_1 = (\text{syn S}, \text{bin}, \text{rel}, \text{deg P})$$

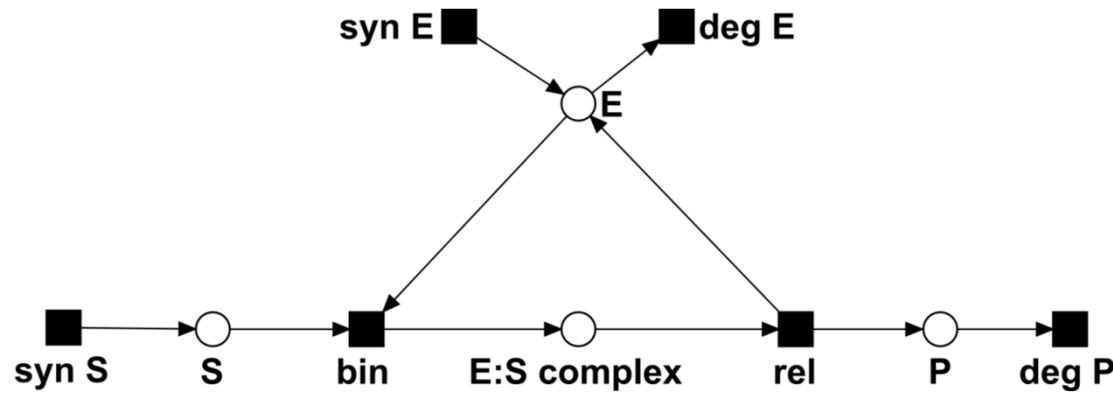
$$TI_2 = (\text{syn E}, \text{deg E})$$

- ❖ Both processes are biologically interrelated
- ❖ TI_1 is dependent on TI_2

For $m_0 = (0,0,0,0)$:

- ❖ TI_1 = realizable, not feasible
- ❖ TI_2 = realizable and feasible

Place invariant analysis

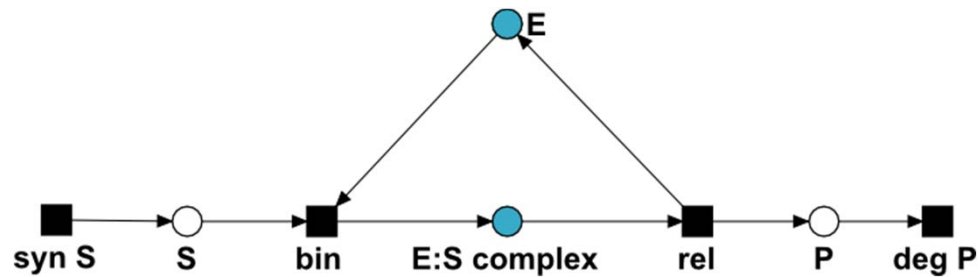


Transition invariants:

$$TI_1 = (\text{syn S}, \text{bin}, \text{rel}, \text{deg P})$$

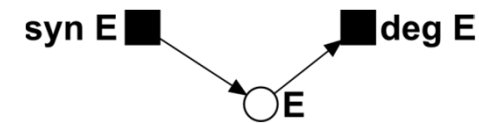
$$TI_2 = (\text{syn E}, \text{deg E})$$

TI_1 – induced network



$PI(TI_1) = (E, E:S \text{ complex}) \rightarrow$ **not feasible**

TI_2 – induced network

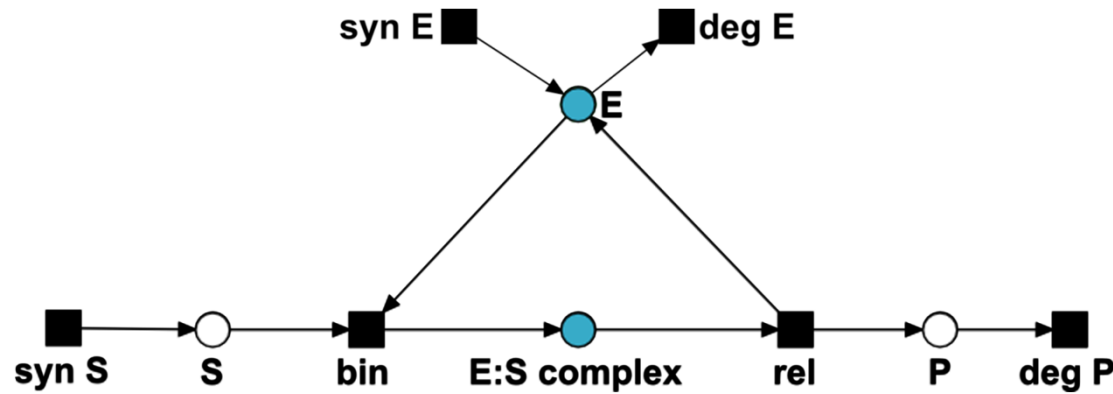


$PI\text{-free} \rightarrow$ **feasible**

Construction of Manatee invariants

- ❖ Determine cycles that cause disruptions in signal flows:
→ **PIs in TI-induced networks**
- ❖ Find processes that overlap with the cycles:
→ **TIs that serve places of the PIs in TI-induced networks**
- ❖ Combine interrelated processes:
→ **Construction of all possible linear combinations of TIs**
- ❖ **MI-induced networks are PI-free**
→ PI-free in contrast to the complete PN

Construction of Manatee invariants



Transition invariants:

$$TI_1 = (\text{syn S}, \text{bin}, \text{rel}, \text{deg P})$$

$$TI_2 = (\text{syn E}, \text{deg E})$$

Manatee invariants

$$MI_1 = TI_1 + TI_2$$

$$MI_2 = TI_2$$

PI-free MI-induced network

yes

yes

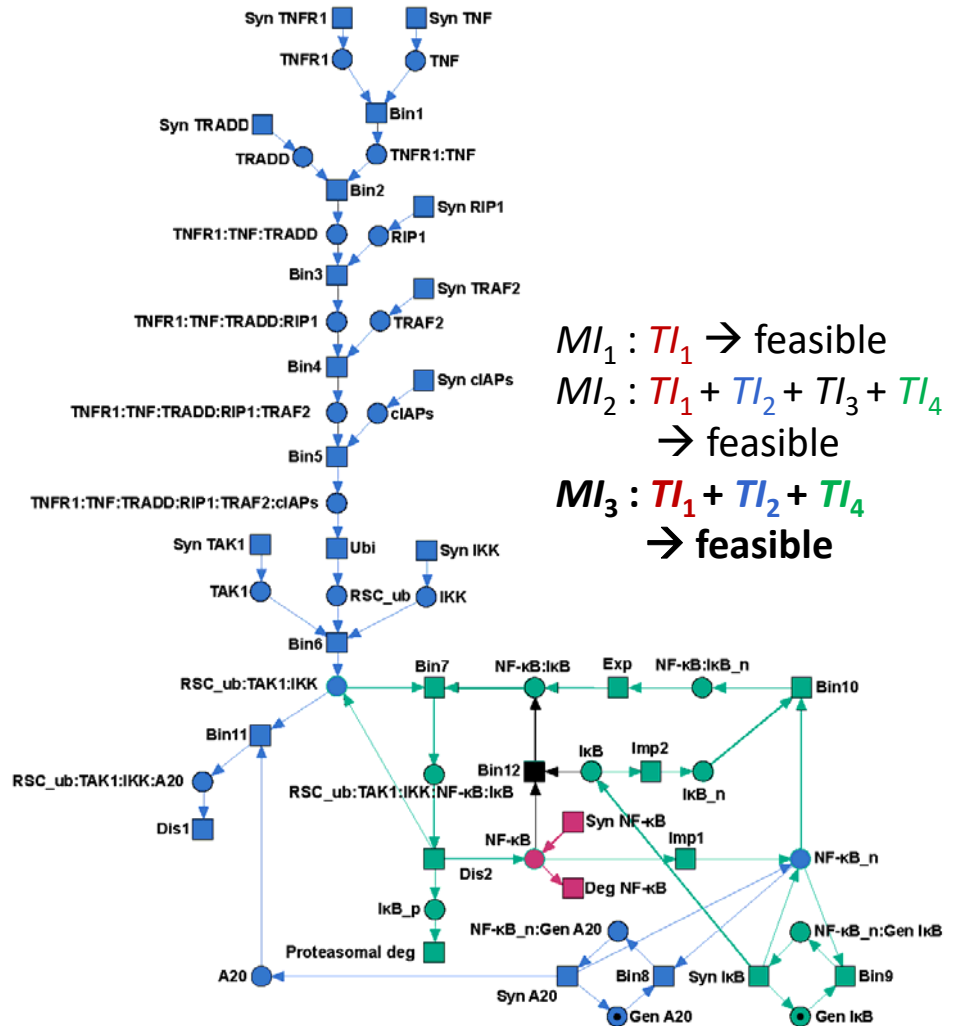
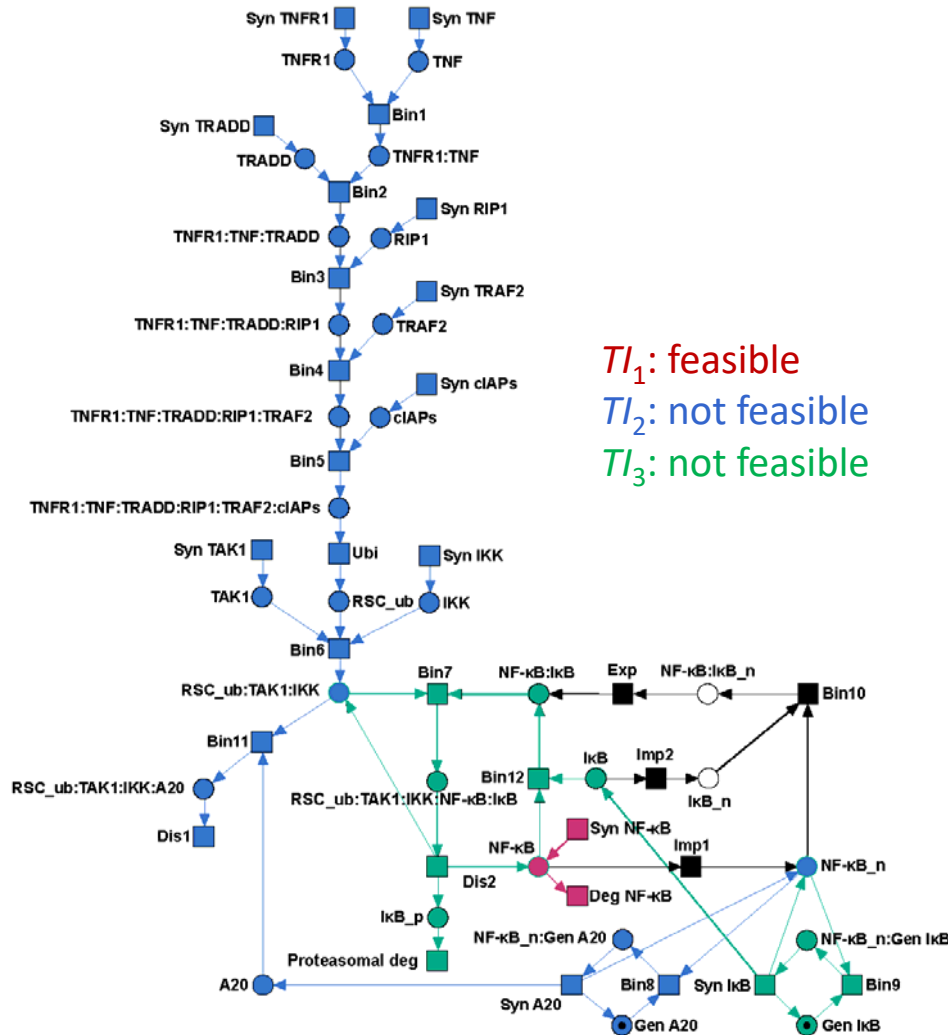
feasible

yes

yes

Manatee invariants are linear combinations of TIs that induce PI-free networks!

Signal flows described by Manatee invariants



Motivation and aim of the work

- ❖ Joint project with physicians from Goethe-University Frankfurt am Main

Simone Fulda



Ivan Dikic

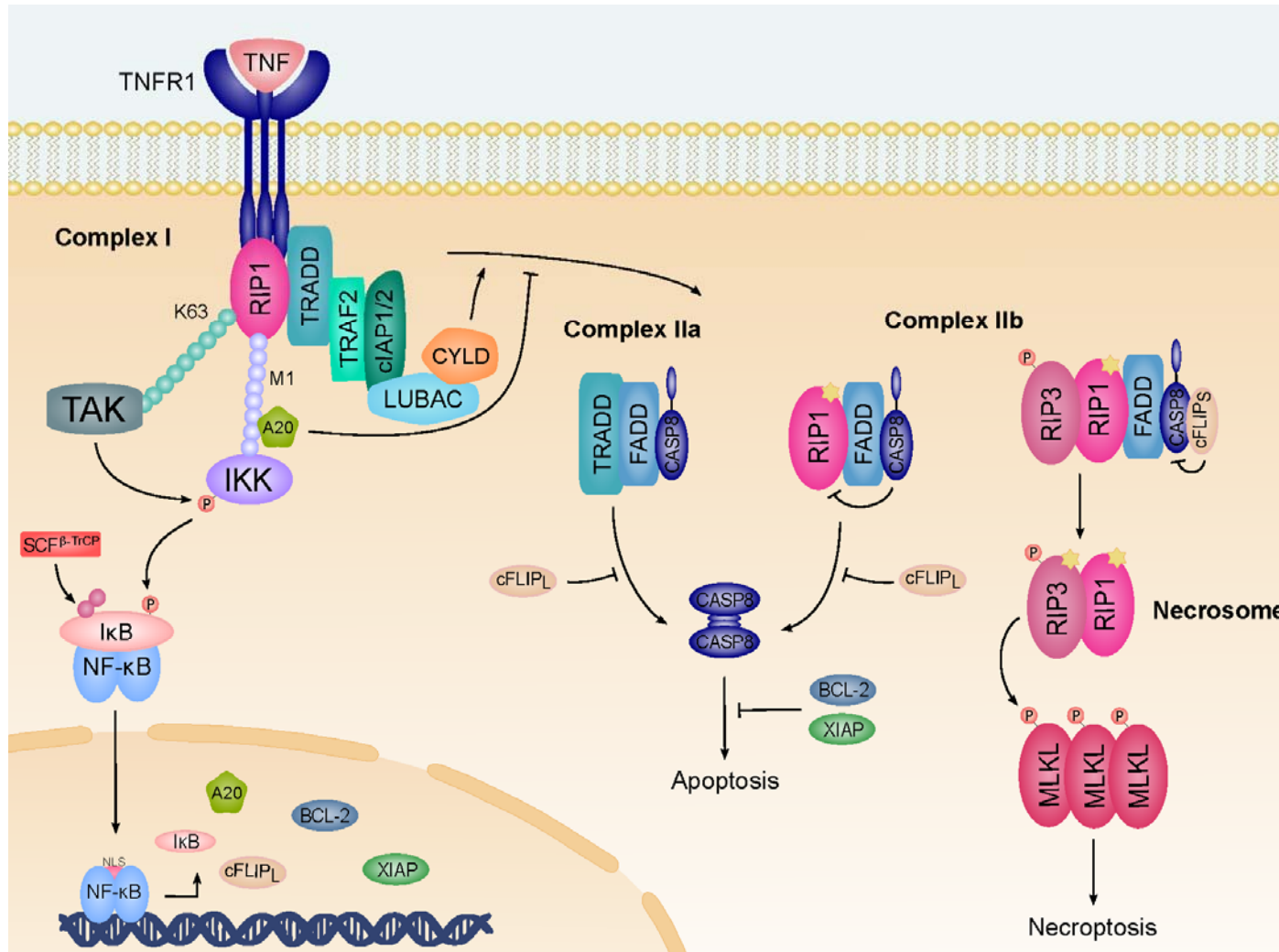


Leonie Amstein

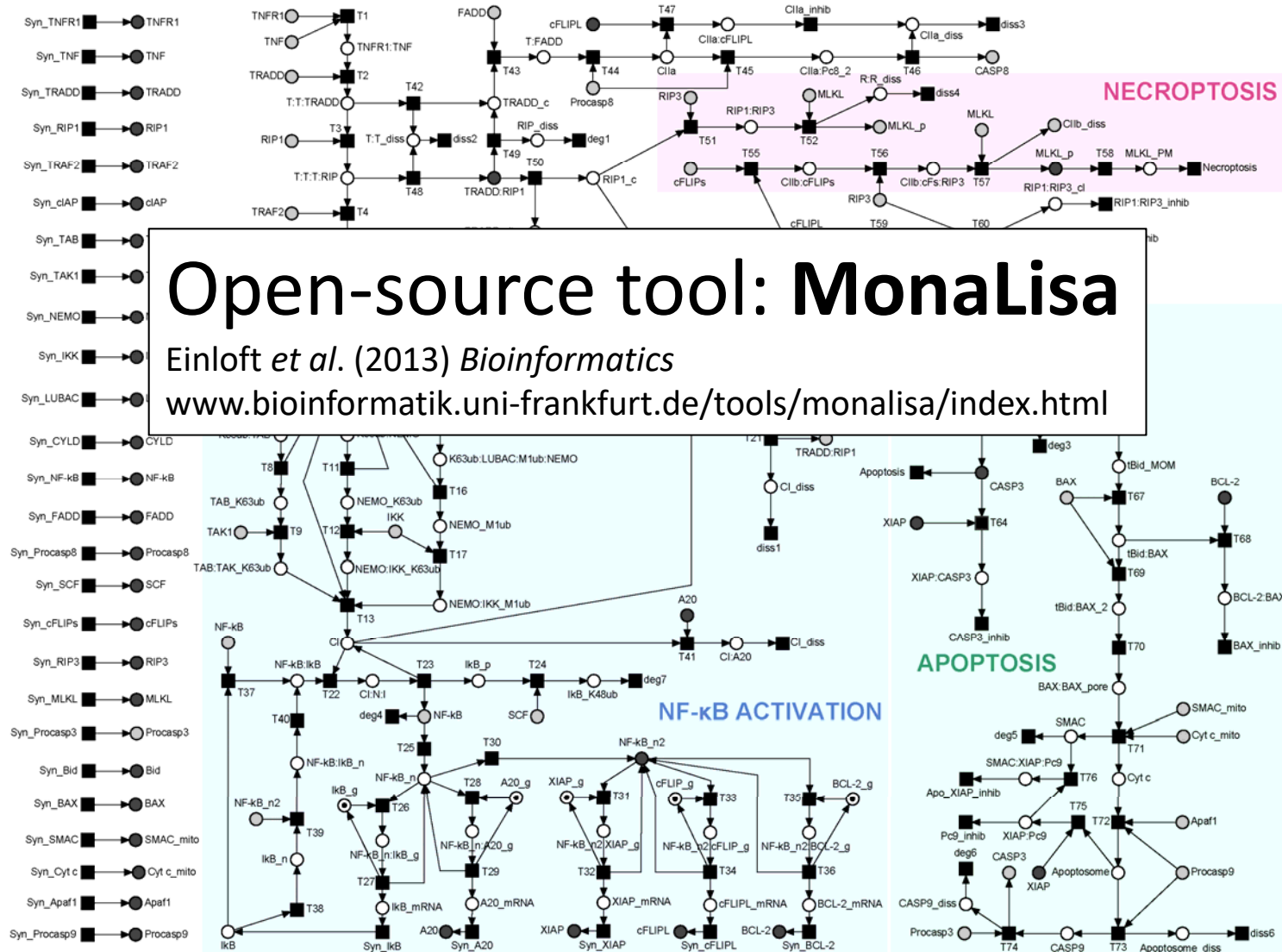
- ❖ Knowledge compilation into a mathematical model
- ❖ Computational verification of the model
- ❖ Role of RIP1 and other proteins as molecular switch between apoptosis and necroptosis

Amstein *et al.* (2017) *BMC Systems Biol*

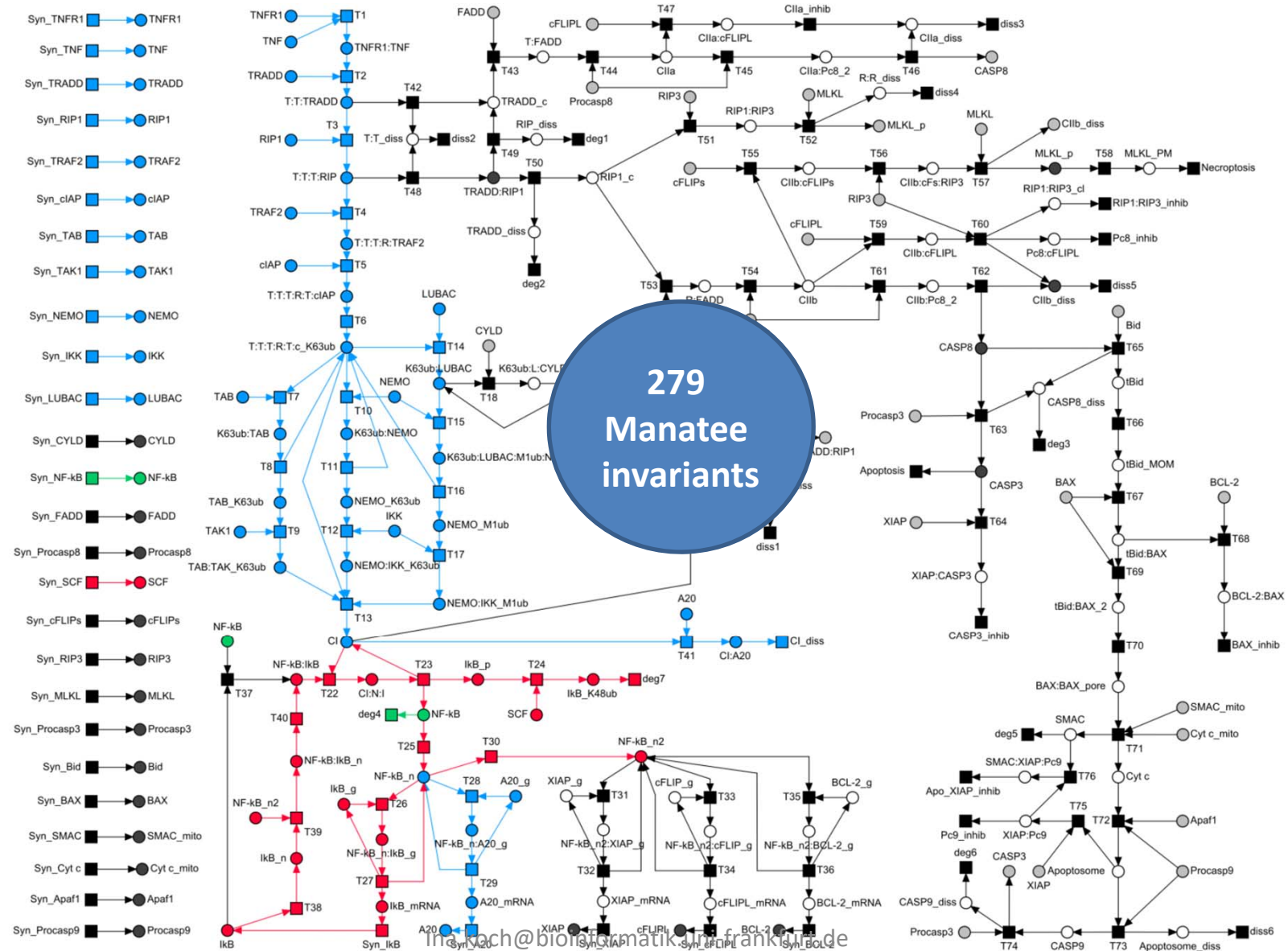
The TNFR1 signal transduction pathway



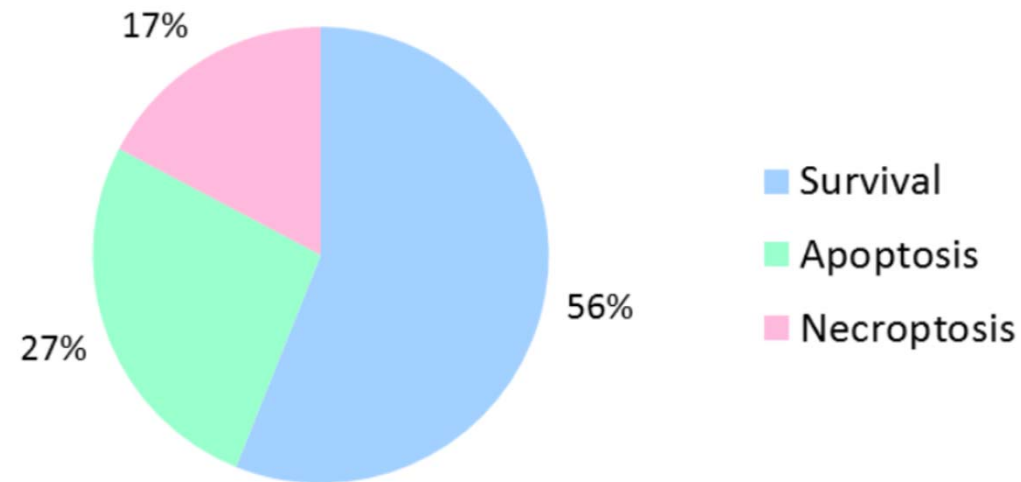
The Petri net of the TNFR1 signaling pathway



Manatee invariants predict signal transduction



Pathway classification based on MIs

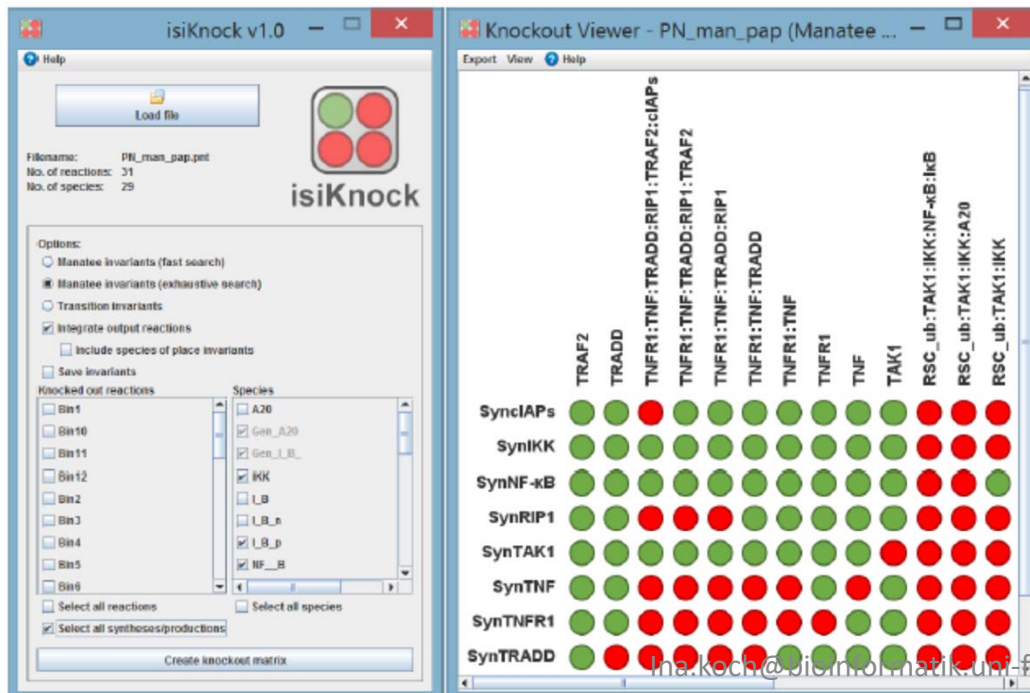


- ❖ Classification von 214 Manatee invariants according to their cellular outcome
- ❖ Robust *survival* response: in agreement with experimental observations

Ting & Bertrand (2016) *Trends in Immunology*

In silico knockouts

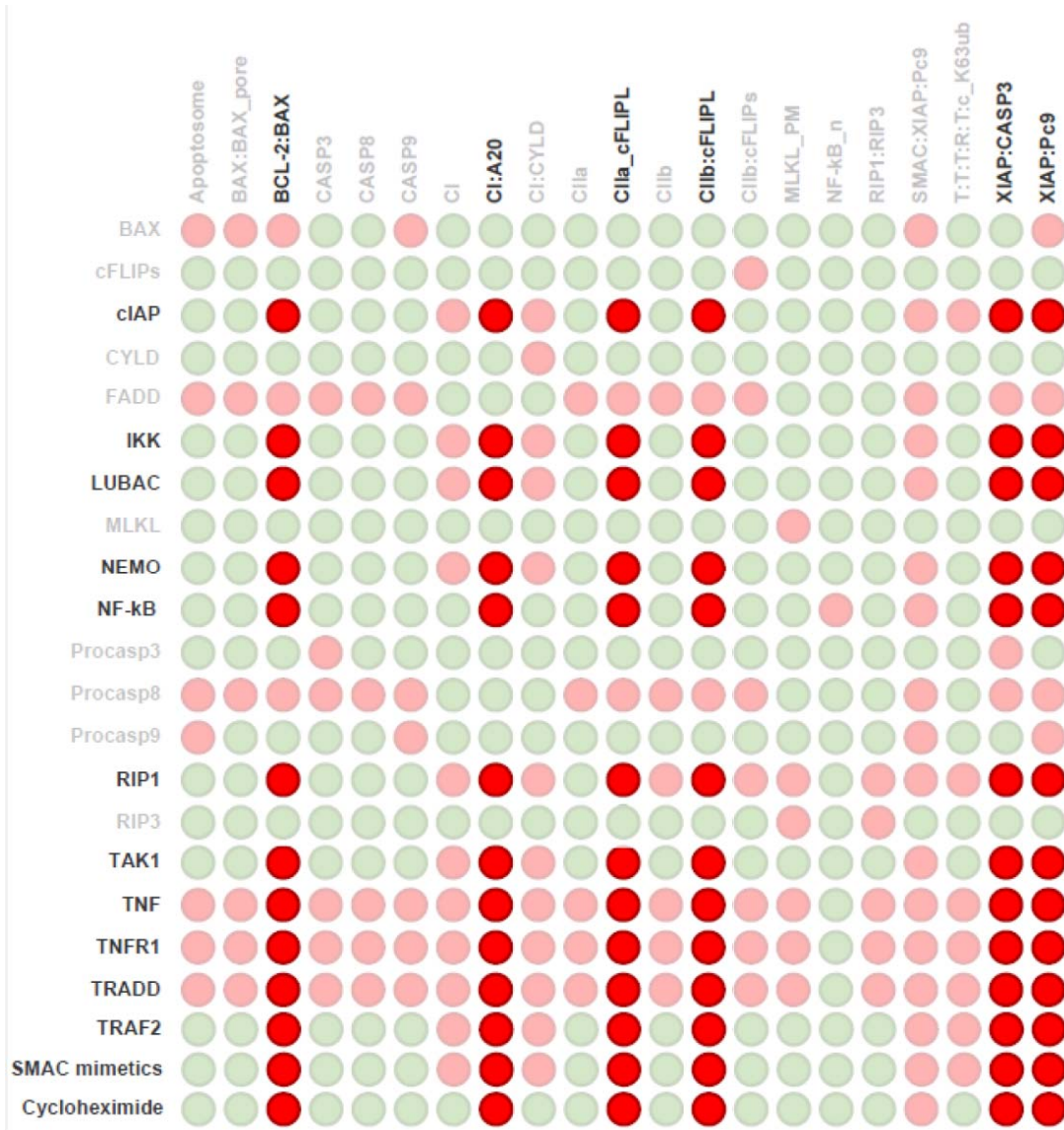
- ❖ Allow for perturbation analyses based on transition and place invariants
- ❖ Matrix representation: illustrates the effects of (single as well as multiple) knockouts of each network component
- ❖ The software **isiKnock** combines the concept of *in silico* knockouts with the computation of Manatee invariants





Scheidel *et al.* (2016) *PLoS Computational Biology*
 Amstein *et al.* (2017) *BMC Systems Biology*
 Hannig *et al.* (2018) *Bioinformatics*

 Unaffected places  Affected places

In silico knockouts of the TNFR1 Petri net



- ❖ Knockout matrix based on Manatee invariants
- ❖ 20 *in silico* knockouts, 2 therapies (SMAC mimetic, cycloheximide), 21 complexes
- ❖ Identification of knockouts that overcome the robust *survival* response
- ❖ Identification of the most important check points of the *molecular switch*

 Unaffected places
  Affected places

Take-home messages

- ❖ **Petri net formalism** is useful for many applications in biology and medicine at **different levels of abstraction**
- ❖ Critical points are **incomplete and diverse data**
- ❖ We have to **understand the experiments and biological processes**
- ❖ **Transition invariants** are useful for dynamic and functional pathway analysis
- ❖ **Manatee invariants** define **complete signaling pathways**, from receptor activation to the cell response
- ❖ The *in silico* **knockout analysis** can be used for **model verification** and generation of **new hypotheses**
- ❖ Try to **interpret** and **visualize** the results

Comparison and cross-talk of the canonical and non-canonical NF- κ B pathways

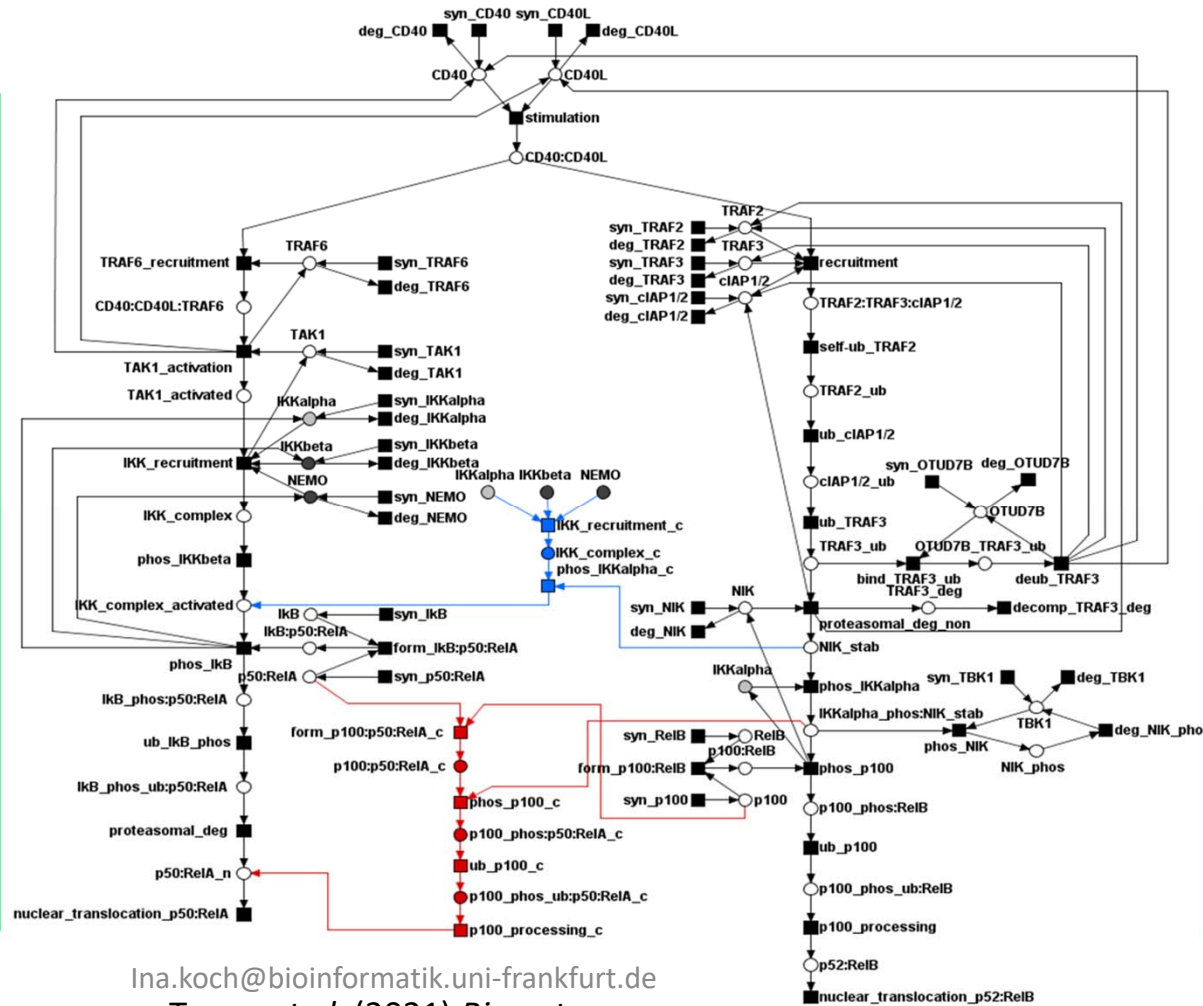


Kira Trares



Franziska Krämer

Canonical pathway



Non-canonical pathway

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Trares et al. (2021) *Biosystems*

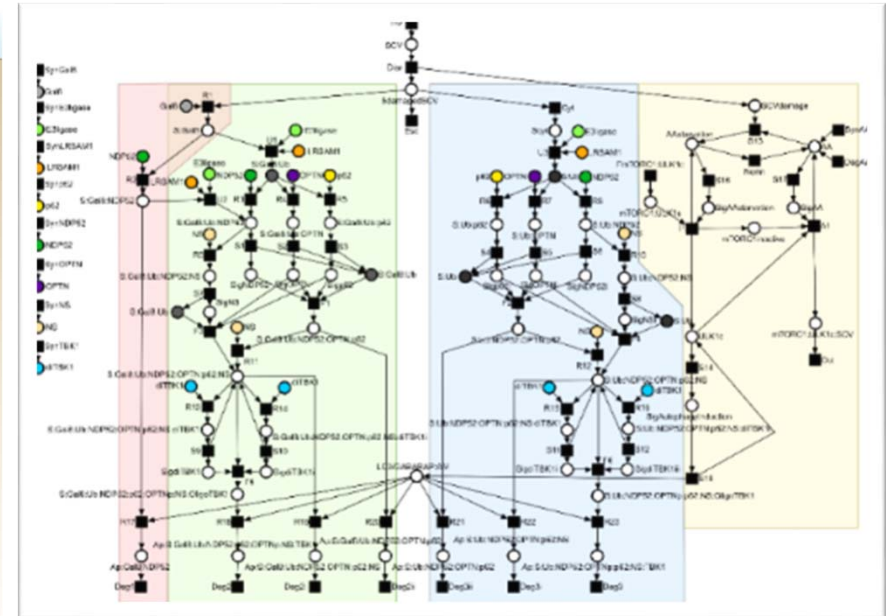
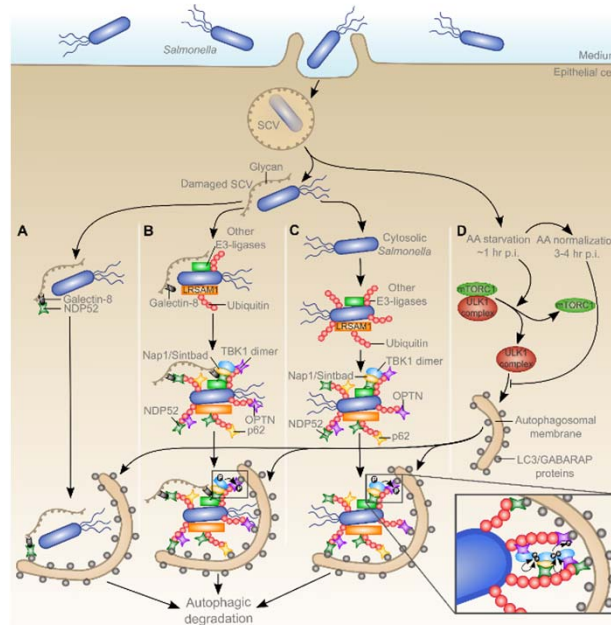
Xenophagy in epithelial HeLa cells after *Salmonella* Typhimurium infection



Jennifer Hannig



Ivan Dikic



- ❖ Classical Petri net
- ❖ Stochastic Petri net

Hannig *et al.* (2018) *Bioinformatics*
 Scheidel *et al.* (2016) *PLoS Computational Biology*

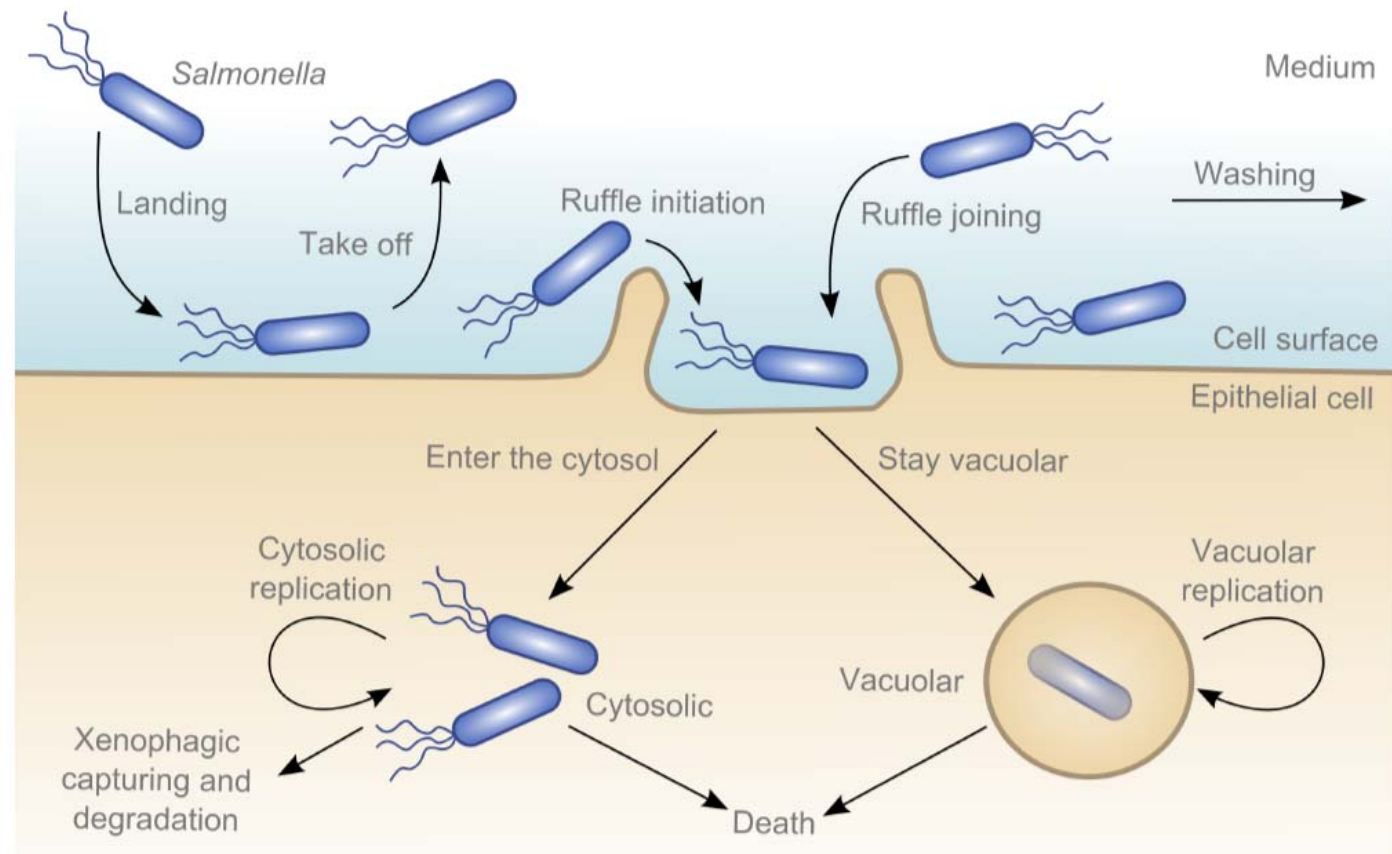
Agent-based model of *Salmonella* movement on the cell surface



Nasrin Alikhani
Chamgordani



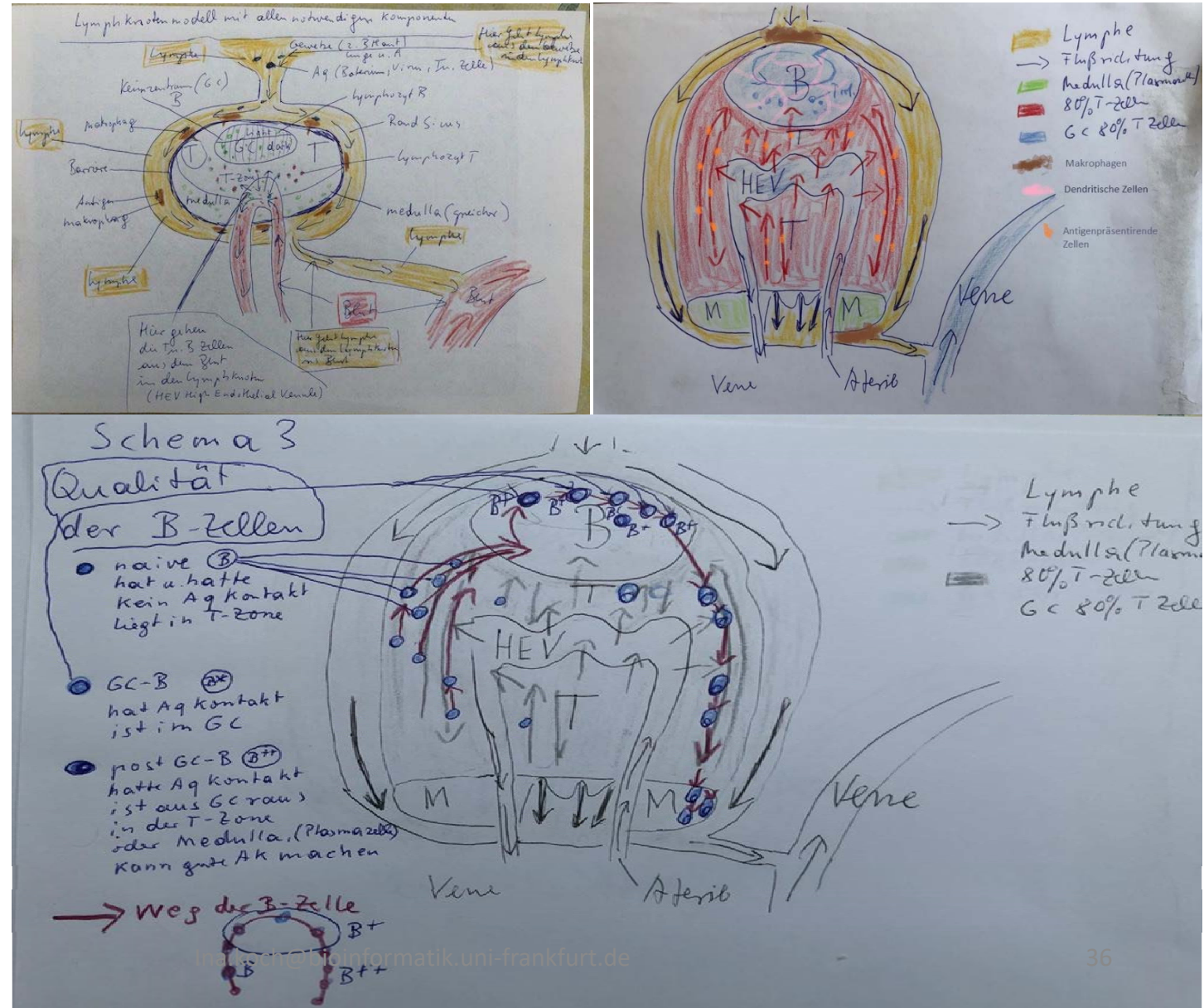
Jennifer Hannig



A Petri net model of the human lymph node



Martin-Leo Hansmann



unpublished

mailto:mhs@bioinformatik.uni-frankfurt.de

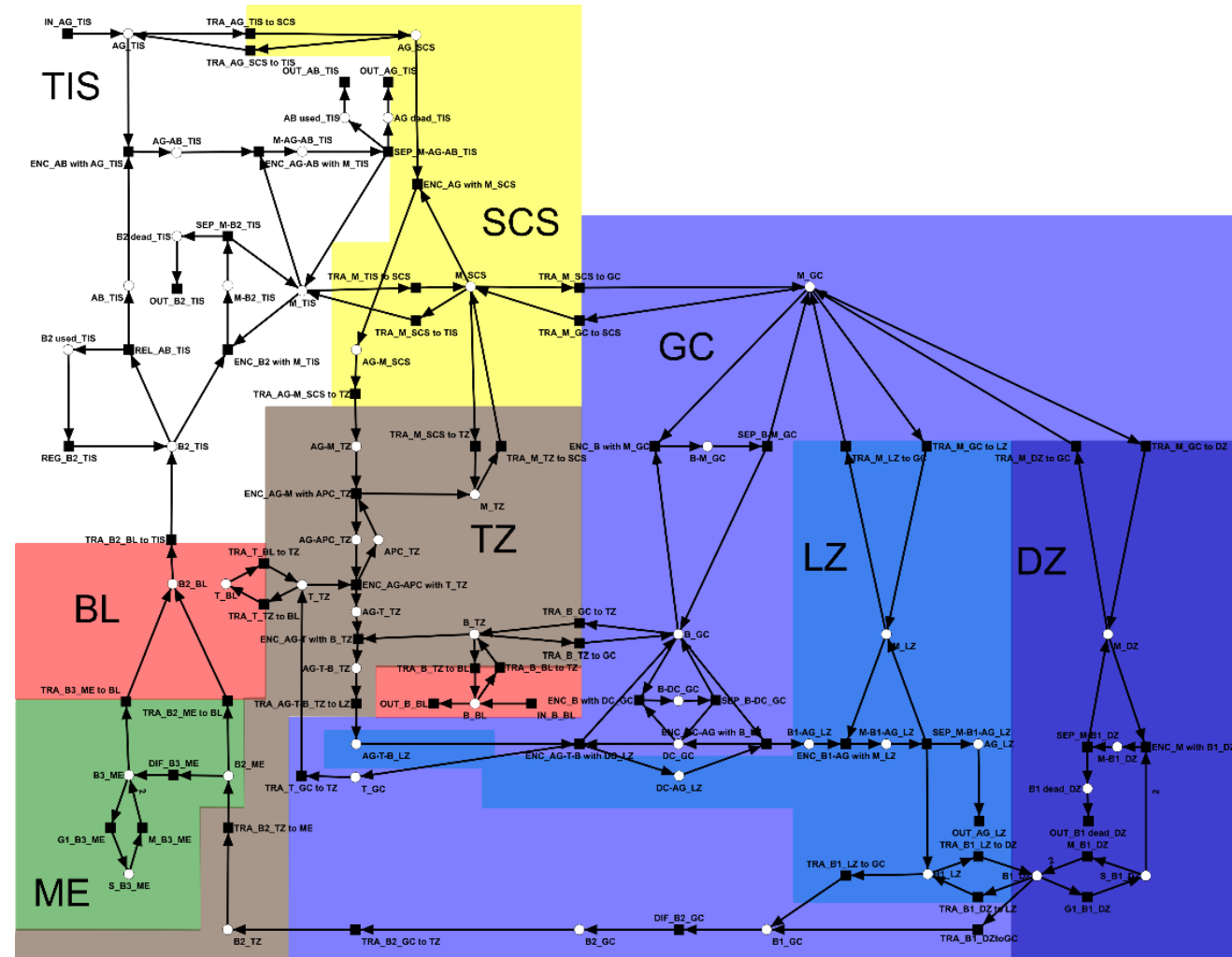
A Petri net model of the human lymph node



Martin-Leo
Hansmann



Sonja Scharf



- ❖ Based on the tremendous knowledge of pathologists and on own experimental 2D and 3D data

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unpublished

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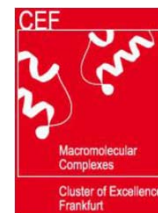
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Goethe University Frankfurt

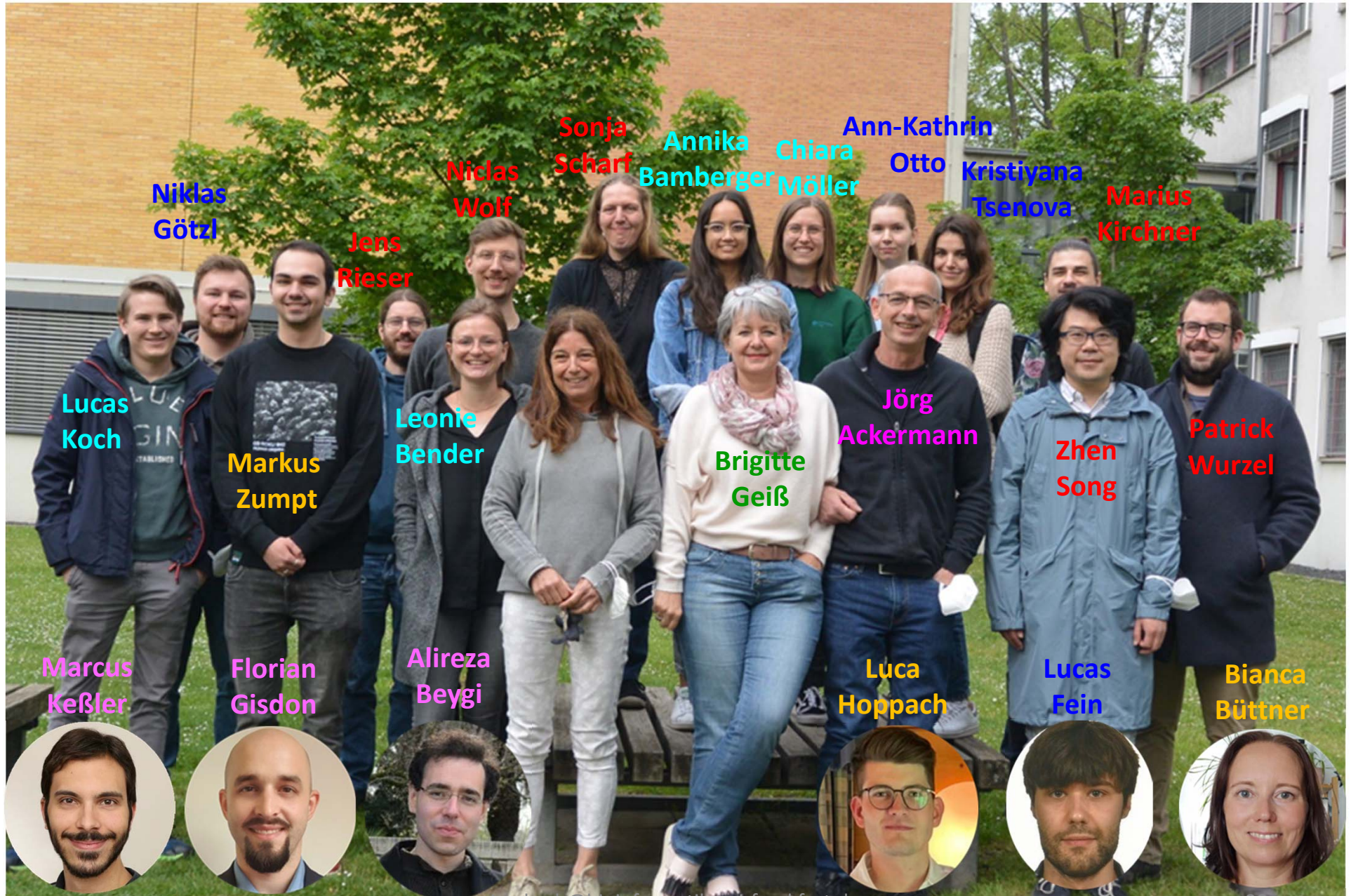
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Prof. Dr. Simone Fulda



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Master student

Bachelor student

PhD student

Postdoc

Administration

Alumni

Thank you!

System's invariants

Transition Place	r_1	r_2	r_{3f}	r_{3b}
C	-2	-1	-1	+1
O ₂	-1	-1	0	0
CO	+2	0	+2	-2
CO ₂	0	+1	-1	+1
init	0	0	0	0

place (P-) invariant: $C^T x = 0$

transition (T-) invariant: $C y = 0$

0: steady-state constraint

Search for **minimal nonnegative, nontrivial integer** solutions

Minimal: $\nexists z: \text{supp}(z) \subseteq \text{supp}(u)$ and the largest common divisor of all non-zero entries of u is 1

P-invariants

$$\begin{aligned}
 -2x_1 - 1x_2 + 2x_3 &= 0 \\
 -1x_1 - 1x_2 + 1x_4 &= 0 \\
 -1x_1 + 2x_3 - 1x_4 &= 0 \\
 +1x_1 - 2x_3 + 1x_4 &= 0 \\
 +3x_1 + 2x_2 - 1x_5 &= 0 \\
 -2x_3 - 1x_4 + 1x_5 &= 0
 \end{aligned}$$

T-invariants

$$\begin{aligned}
 -2y_1 - 1y_2 - 1y_3 + 1y_4 + 3y_5 &= 0 \\
 -1y_1 - 1y_2 + 2y_5 &= 0 \\
 +2y_1 + 2y_3 - 2y_4 - 2y_6 &= 0 \\
 +1y_2 - 1y_3 + 1y_4 - 1y_6 &= 0 \\
 -1y_5 + 1y_6 &= 0
 \end{aligned}$$

Parikh vector: vector of firing frequencies

Thank you for joining!

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