Bipartite graphs for computational modeling in systems biology: from KEGG to Petri nets

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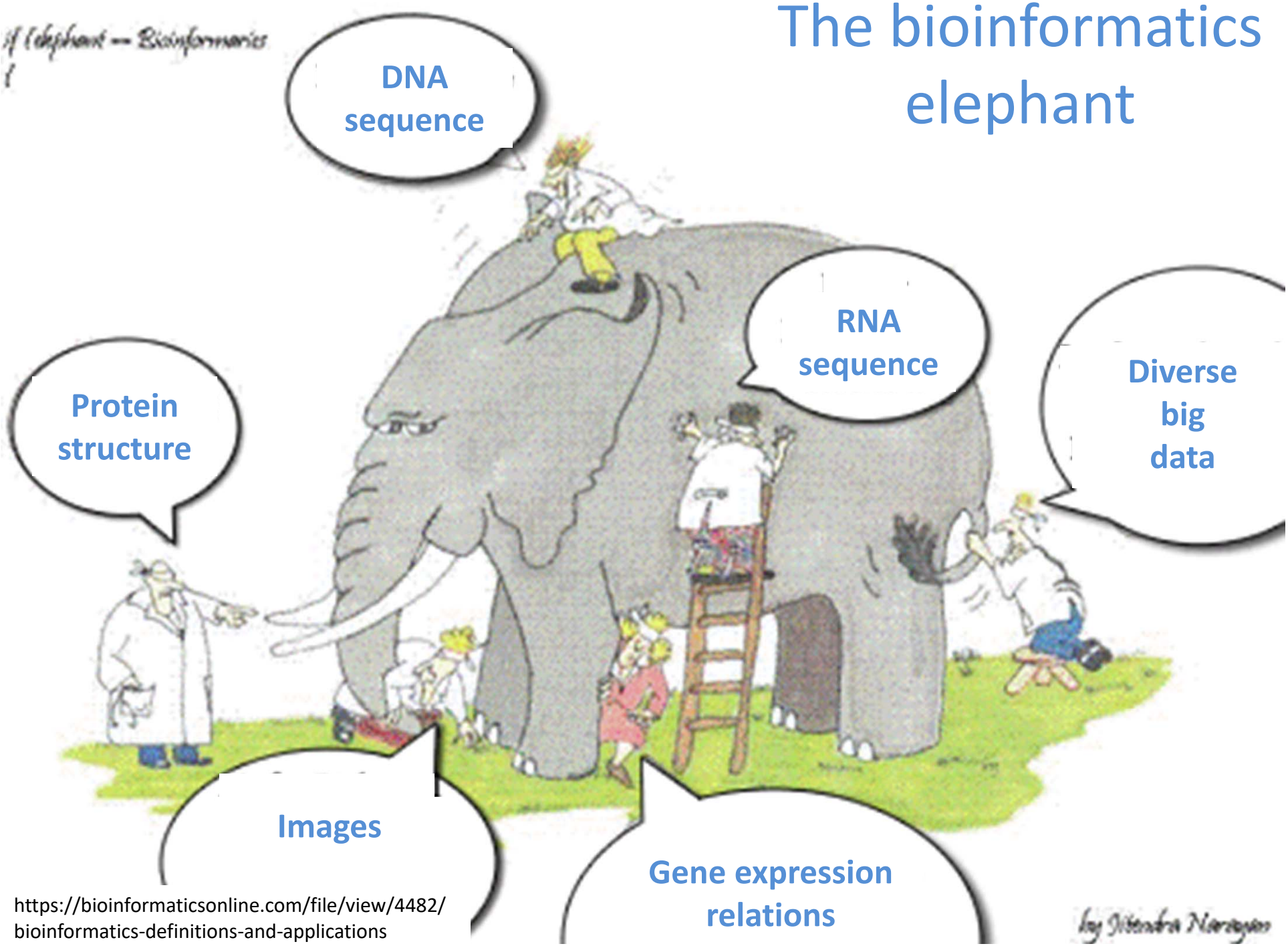
3rd Edition of the Workshop "Metabolism and mathematical models: Two for a tango"

The bioinformatics elephant



https://bioinformaticsonline.com/file/view/4482/bioinformatics-definitions-and-applications

Challenges of data integration

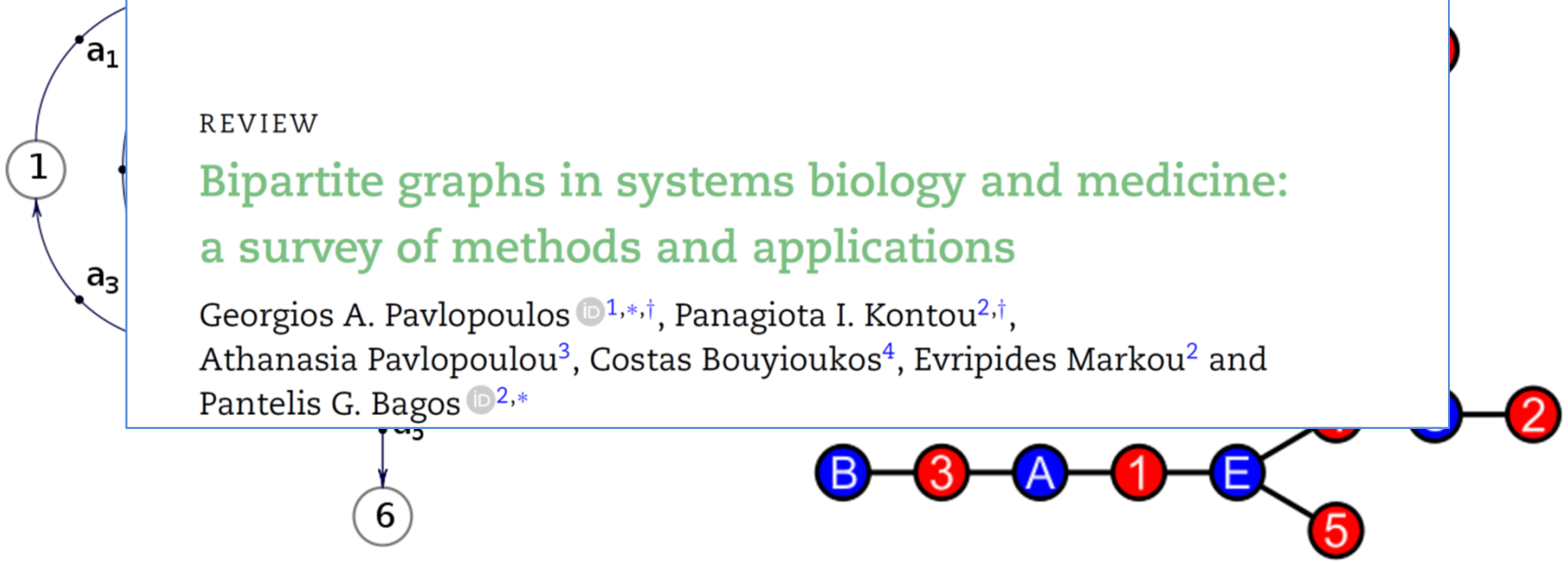
- Incomplete data
- Different time points and different locations in the cell
- Inc
- Different experiments under varying experimental conditions
- Different scales: genomics, transcriptomics, proteomics, metabolomics, interactomics, imaging, …

The quality and quantity of the data determine the modeling approach

Hypergraphs and bipartite graphs

A **hypergraph** is a generalization of a gr… join ar…

A **bipartite graph** (or **bigraph**) is a graph …to two



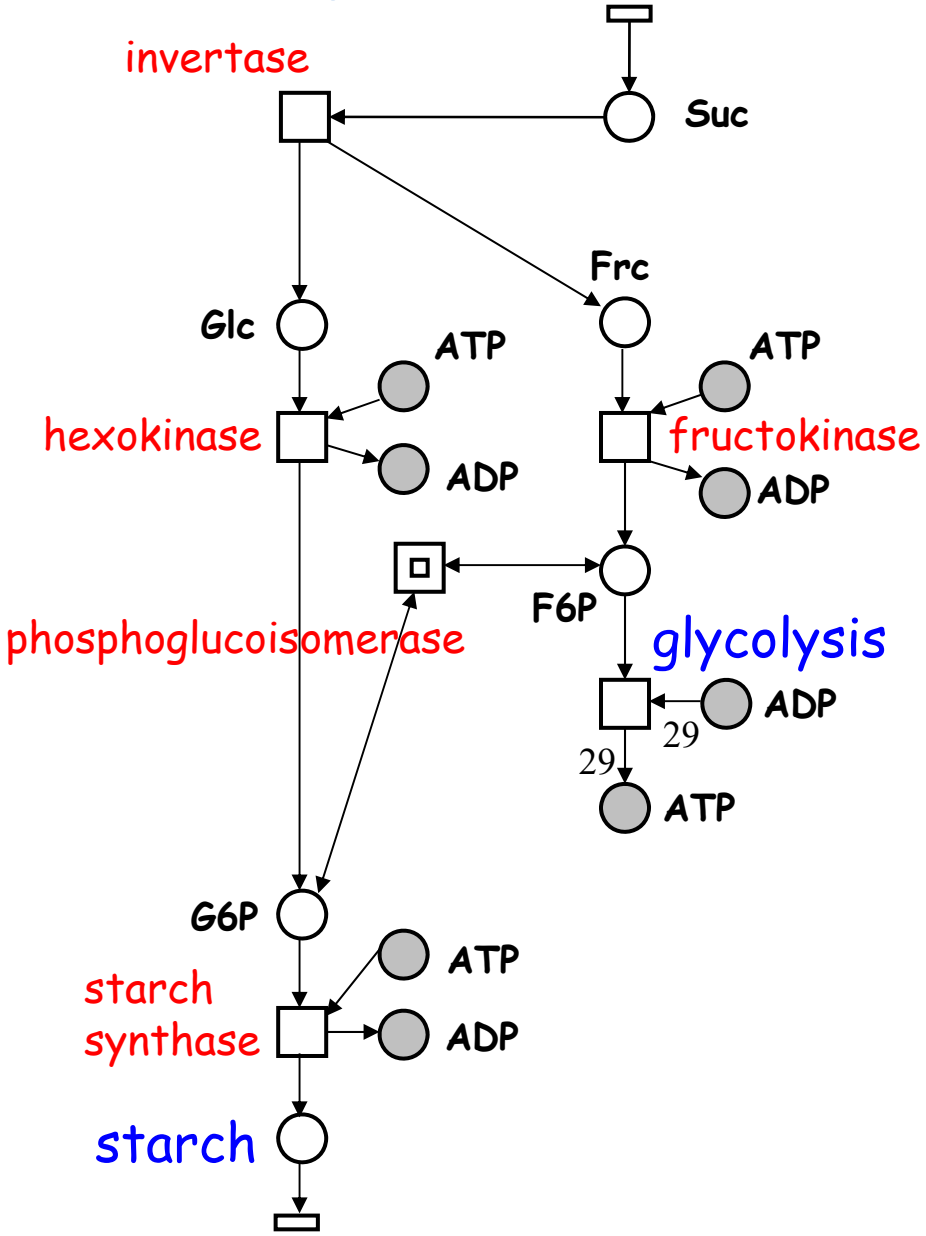
OXFORD
(GIGA)n SCIENCE
GigaScience, 7, 2018, 1–31
doi: 10.1093/gigascience/giy014
Advance Access Publication Date: 19 February 2018
Review

REVIEW

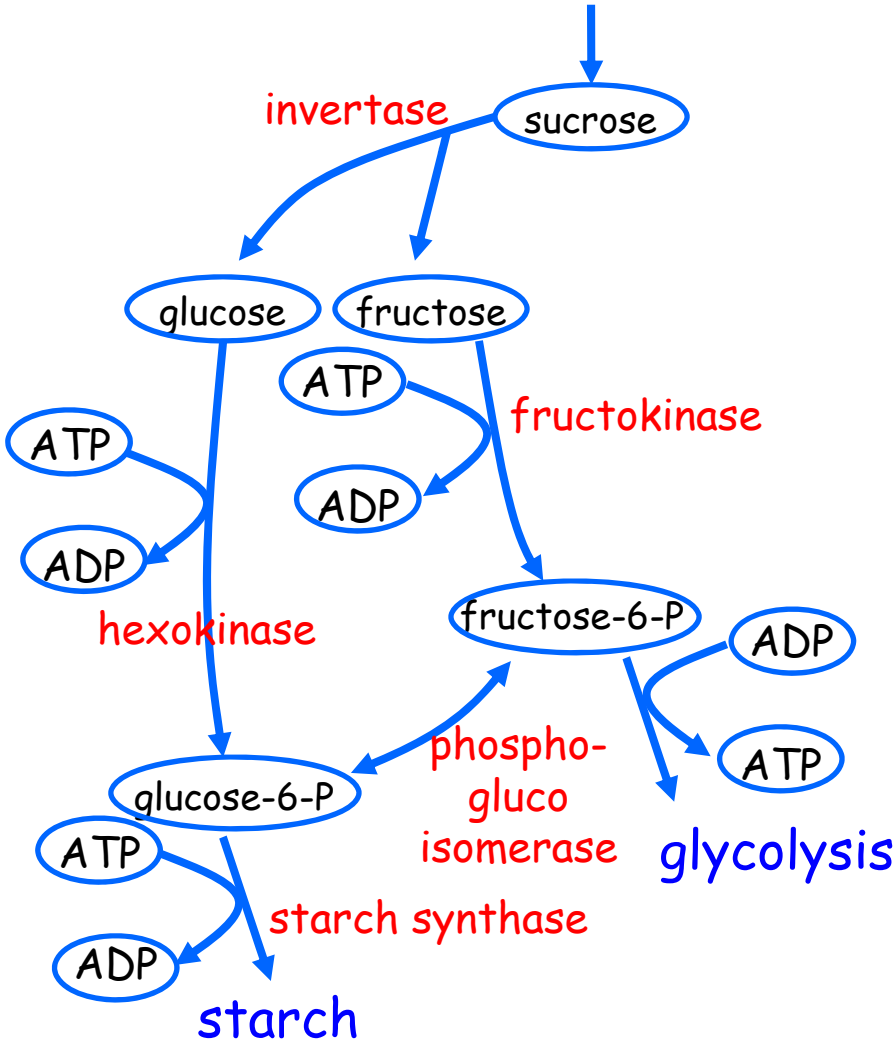
Bipartite graphs in systems biology and medicine: a survey of methods and applications

Georgios A. Pavlopoulos [1,*,†], Panagiota I. Kontou [2,†], Athanasia Pavlopoulou [3], Costas Bouyioukos [4], Evripides Markou [2] and Pantelis G. Bagos [2,*]

Bipartite graph (Petri net) representation

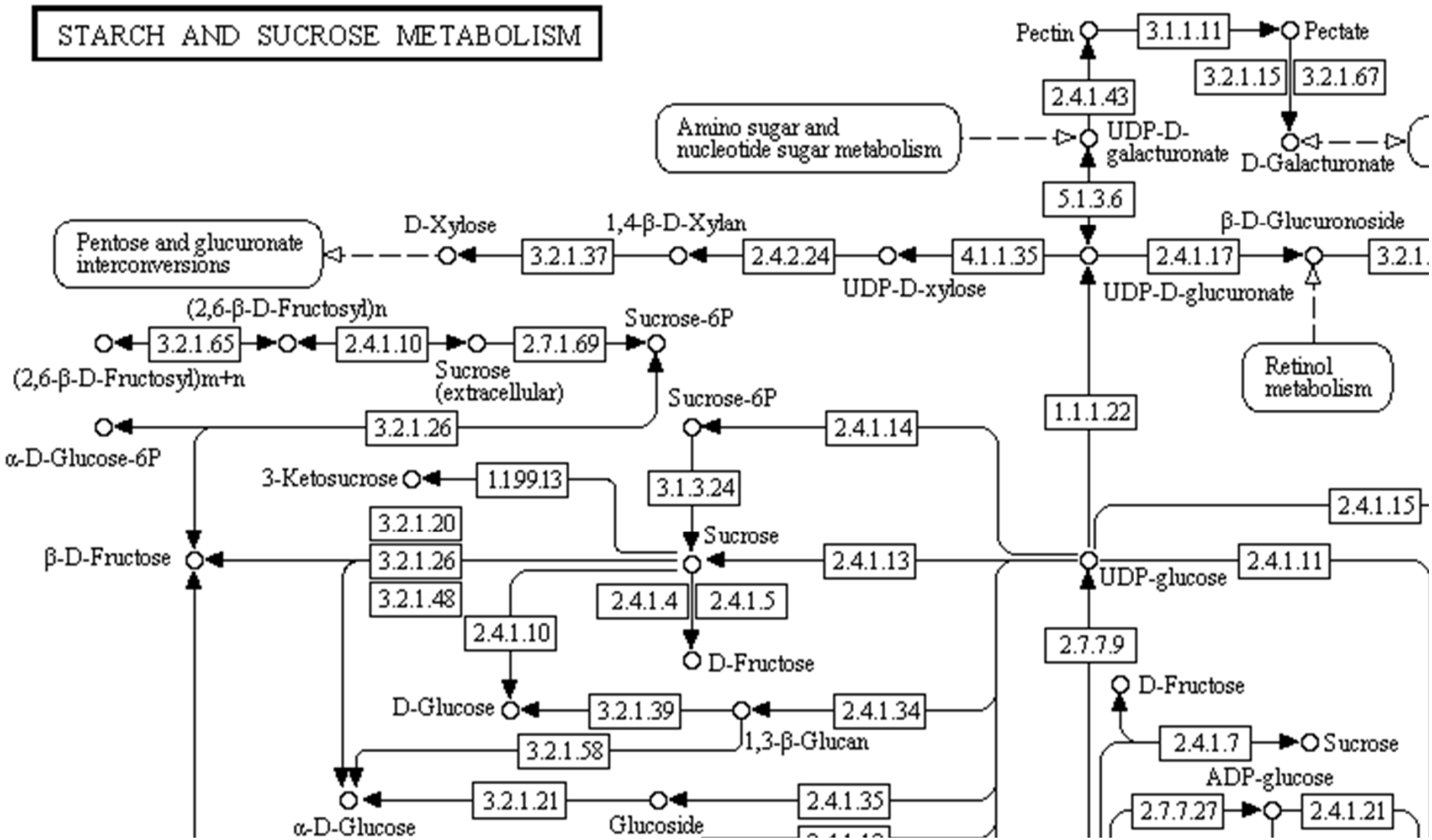


Hypergraph representation



Bipartite graph (KEGG) representation

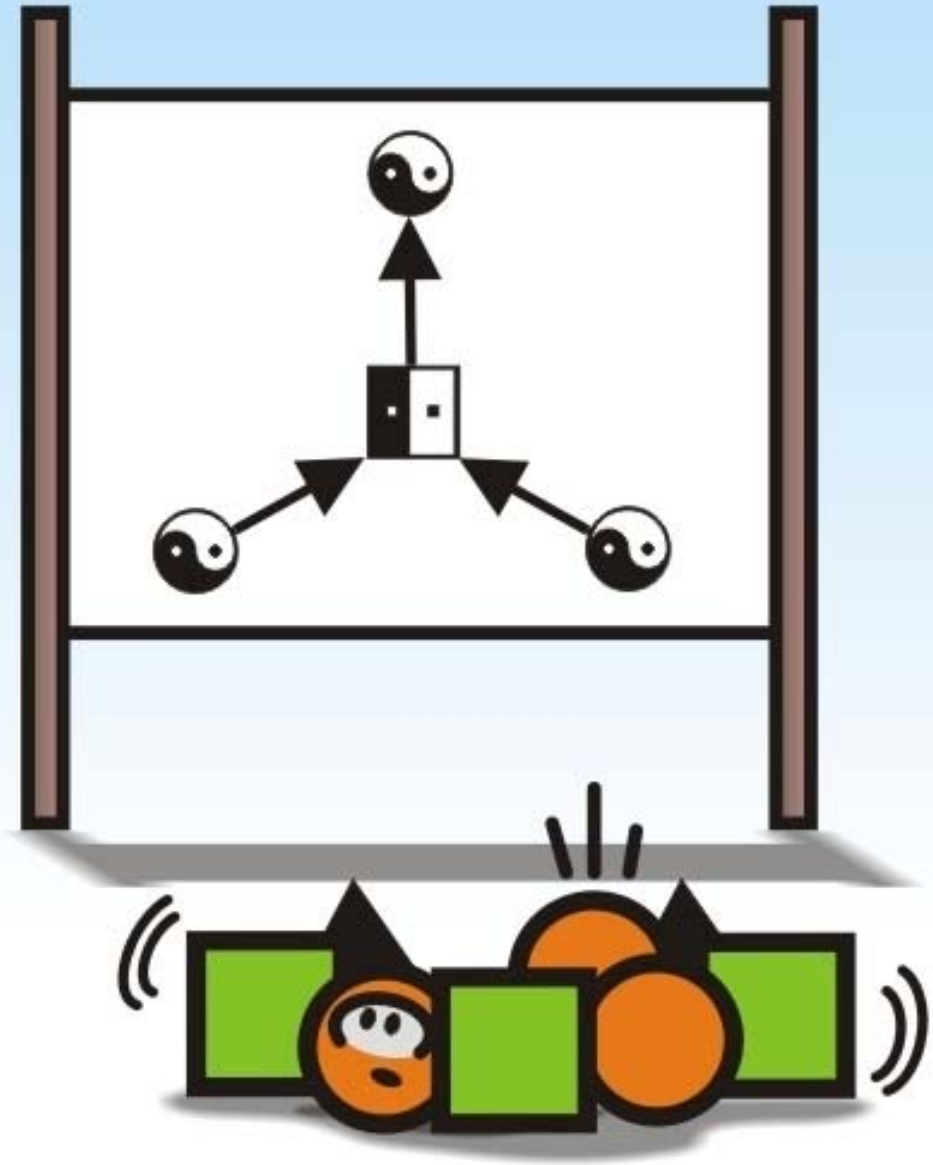
http://www.genome.jp/kegg/pathway/map/map00500.html



How and to what extent
can we analyze and predict
the system's behavior
without
knowing kinetic parameters?

Petri nets

Petri nets have nothing to do with Petri dishes



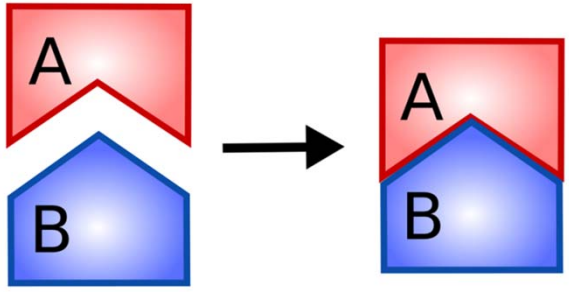
Carl Adam Petri
(1926 – 2010)

http://www.gridworkflow.org

Petri net definitions

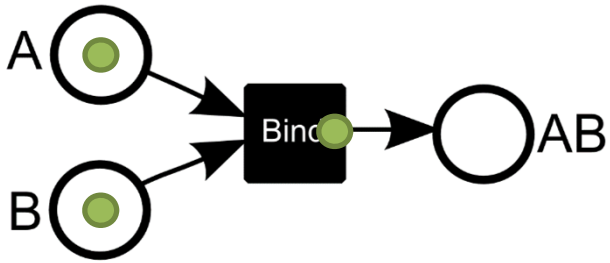
Elements	Symbols	Interpretation
Transitions		Active elements: processes, e.g., reactions
Places		Passive elements: biological species, e.g., compounds, define pre-/post-conditions
Tokens		Movable objects: molecules, proteins, enzymes, cofactors, bacteria, or cells, marking as system state
Edges or arcs		Relations, weighted to quantify pre-/post-conditions

Binding process

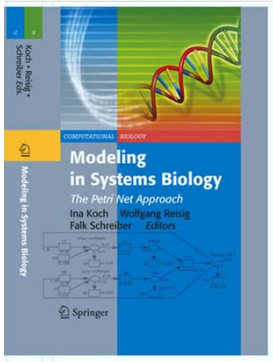


A+B ⟶ AB

Petri net



Firing rule: untimed (P/T net), timed-discrete, stochastic, continuous



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

Outline

Part I - Metabolism

- Modeling of the central carbon metabolism in potato tubers

Stéphanie Boue

Part II – Signal transduction

- Modeling of TNFR1-induced signaling pathway as Petri net, including the NF-κB pathway

Leonie Amstein

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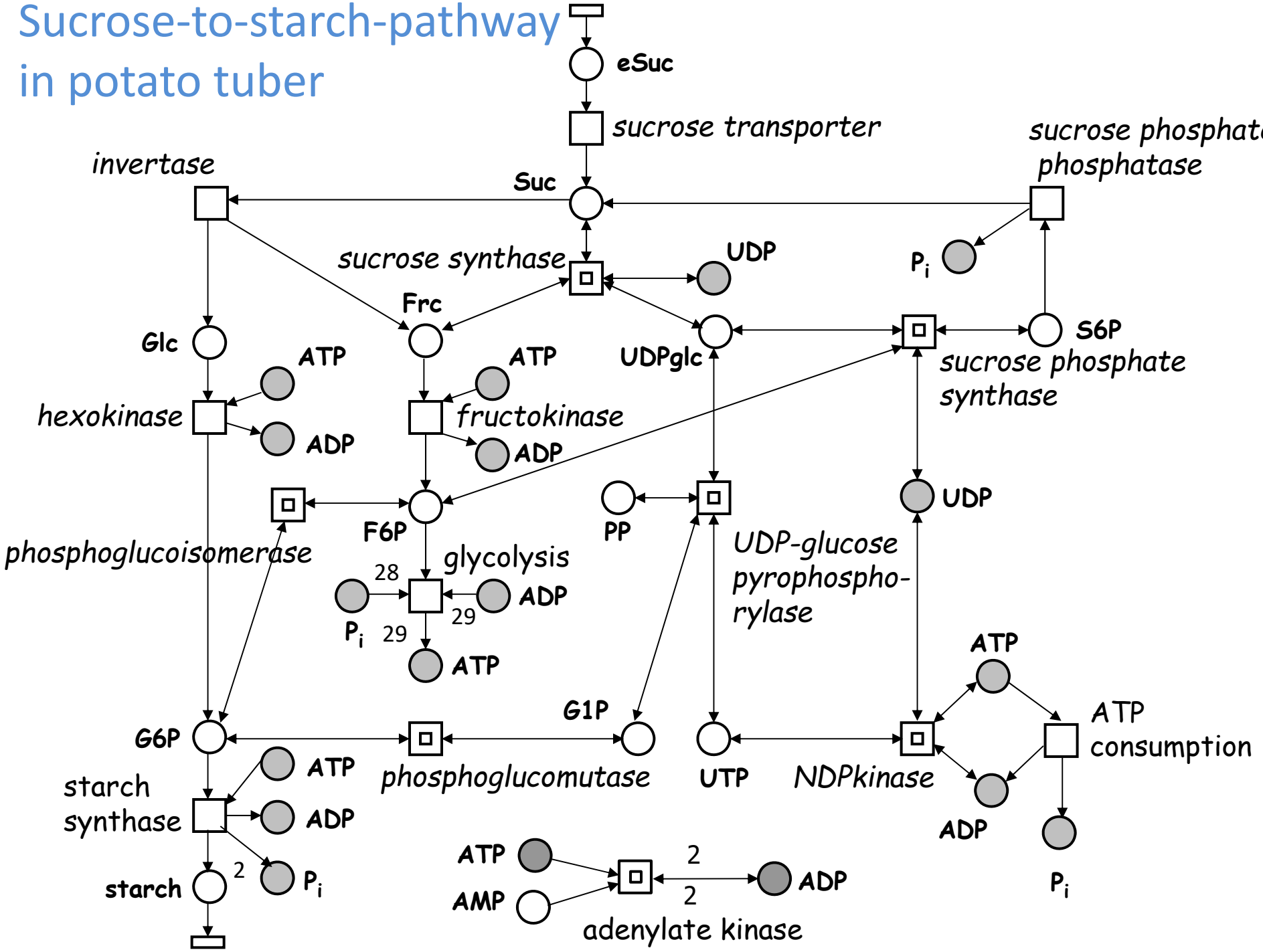
Sucrose-to-starch-pathway in potato tuber

Björn Junker

sucrose synthase:	Suc + UDP ↔ UDPglc + Frc
UDP-glucose pyrophosphorylase:	UDPglc + PP ↔ G1P + UTP
phosphoglucomutase:	G6P ↔ G1P
fructokinase:	Frc + ATP → F6P + ADP
phosophoglucoisomerase:	G6P ↔ F6P
hexokinase:	Glc + ATP → G6P + ADP
invertase:	Suc → Glc + Frc
sucrose phosphate synthase:	F6P + UDPglc ↔ S6P + UDP
sucrose phosphate phosphatase:	S6P → Suc + P_i
glycolysis (b):	F6P + **29** ADP + **28** P_i → **29** ATP
NDPkinase:	UDP + ATP ↔ UTP + ADP
sucrose transporter:	eSuc → Suc
ATP consumption (b):	ATP → ADP + P_i
starch synthesis:	G6P + ATP → 2P_i + ADP + starch
adenylate kinase:	ATP + AMP ↔ 2ADP
pyrophosphatase:	PP → 2 P_i
adenylate kinase:	AdK ↔ AMP + ADP

Sucrose-to-starch-pathway in potato tuber

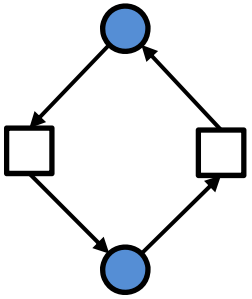


Invariant analysis at steady state

Substance conservations

Place invariants

- Sets of places whose weighted sum of tokens remains constant
- Substance conservations



Place invariant: $C^T x = 0$

Transition invariant: $C y = 0$

Solutions: **minimal, nonnegative, nontrivial, integer**

Minimal: $\exists z$: supp (z) $\subset$ supp (u) and the largest common divisor of all non-zero entries of u is 1

Functional modules

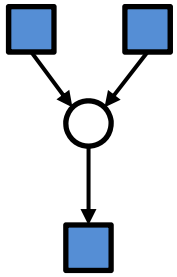
Transition invariants

- Multi-sets of transitions whose firing reproduces an arbitrary initial marking

  Lautenbach (1973) *GMD Report* No. 82

- Basic functional modules (elementary modes)

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



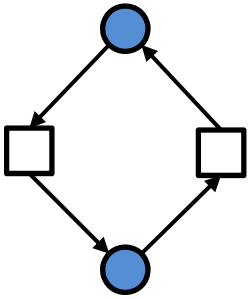
Invariant analysis for the sucrose-to-starch-pathway

Substance conservations

Place invariants

The net is not **covered by P-invariants**.

1. UDPglc, UTP, UDP
2. ATP, AMP, ADP
3. G6P, F6P, G1P, UTP, ATP(2), ADP, S6P, P_i, PP(2)



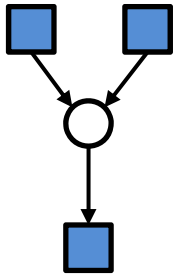
Functional modules

Transition invariants

The net is not **covered by transition invariants**!

Trivial:
1. SPS, SPS_rev
2. UGPase, UGPASE_rev
3. SuSy_SuSy_rev
4. PGM, PGM_rev
5. NDPkin, NDPkin_rev
6. AdK, AdK_rev
7. PGI, PGI_rev

Removing SPS_rev, AdK, and AdK_rev, the Petri net becomes **covered by transition invariants**



Transition invariant analysis

Invariant number	sucrose cleavage SuSy	sucrose cleavage Inv	hexoses go into Glyc	hexoses go into StaSy	ATP cons	ATP used for cycling Inv SuSy_rev	ATP used for cycling Inv SPS, SPP	ATP used for cycling SuSy SPS, SPP
8	x		x	x				x
9	x		x	x	x			
10	x		x	x				
11		x	x	x	x			
12		x	x	x			x	
13		x	x	x				x
14		x	x	x	x			
15		x	x	x				
16		x	x		x			
17		x	x				x	
18		x	x					x
19		x	x		x			

Koch *et al.* (2005) *Bioinformatics*

Malik-Sheriff *et al*. (2020) *Nucl Acids Res*
BioModels ID: MODEL1308080002

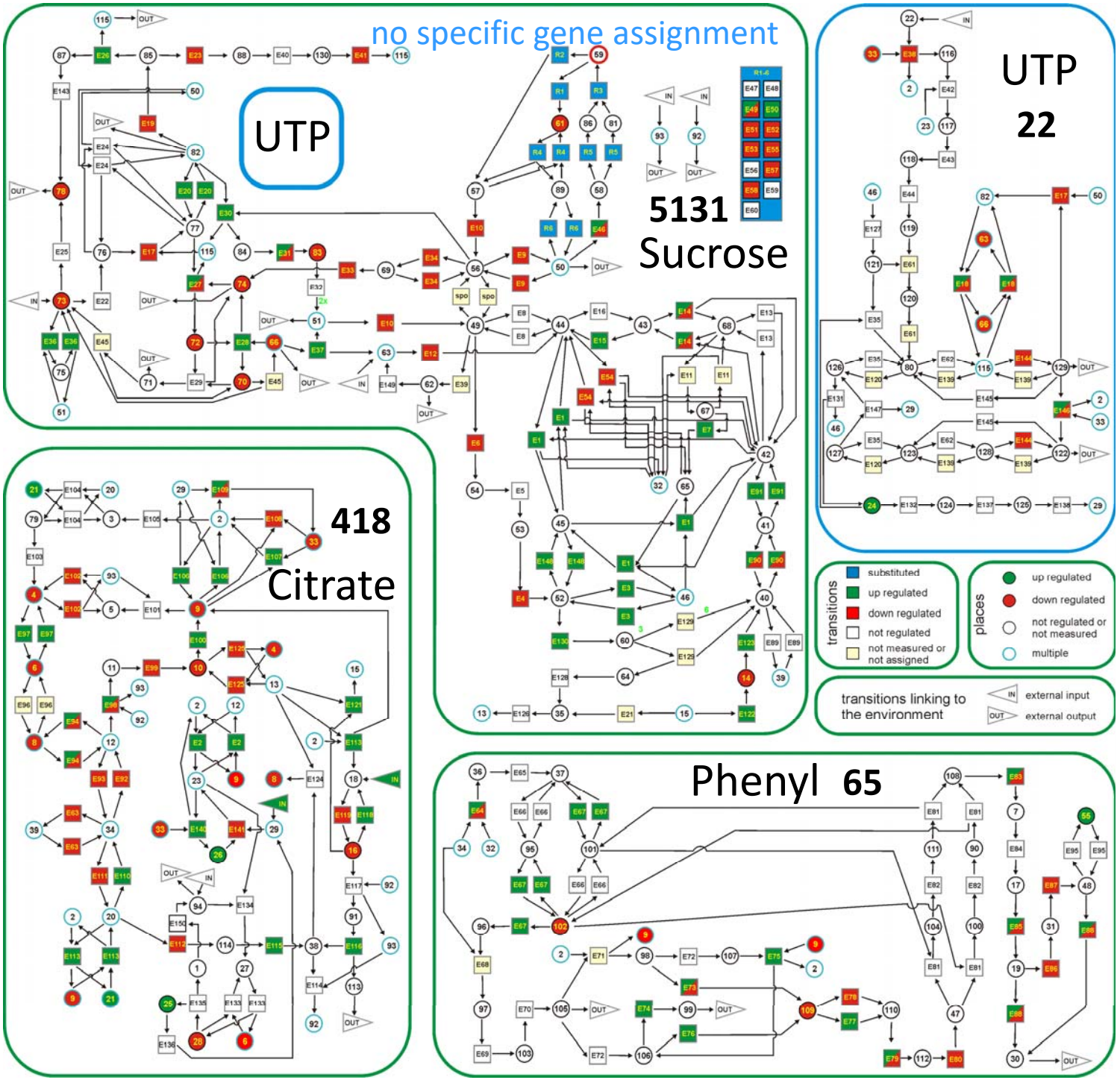
Arabidopsis thaliana

Complete network: Sucrose-, UTP-, Citrate-, and Phenyl-Pathway

transition invariants of each subnet

Koch et al. (2017)
Frontiers in genetics

MODEL1801090001



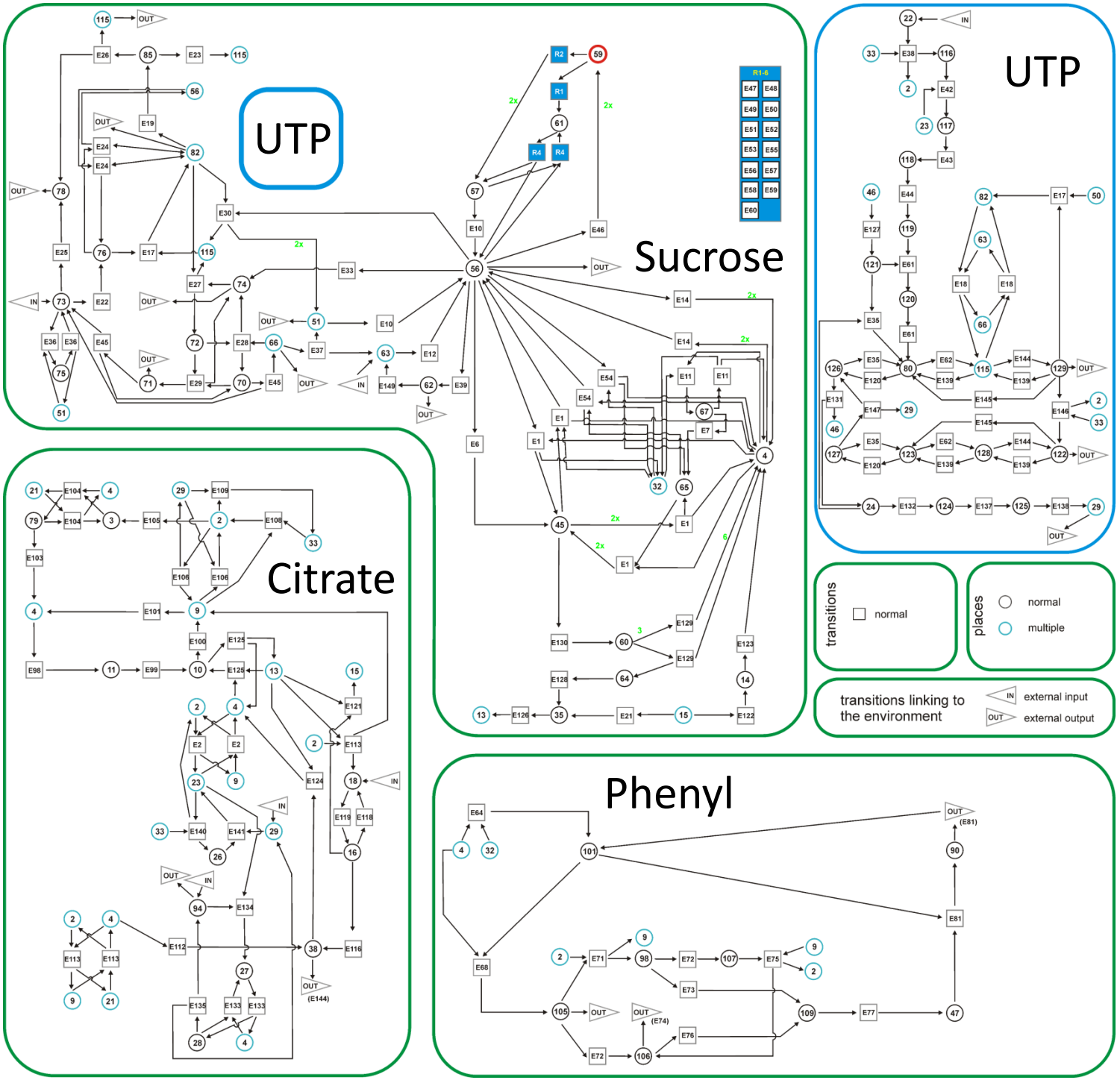
Reduced network

Net	Normal	Reduced
#pl.	130	61
#tr.	232	123
#ed.	539	309

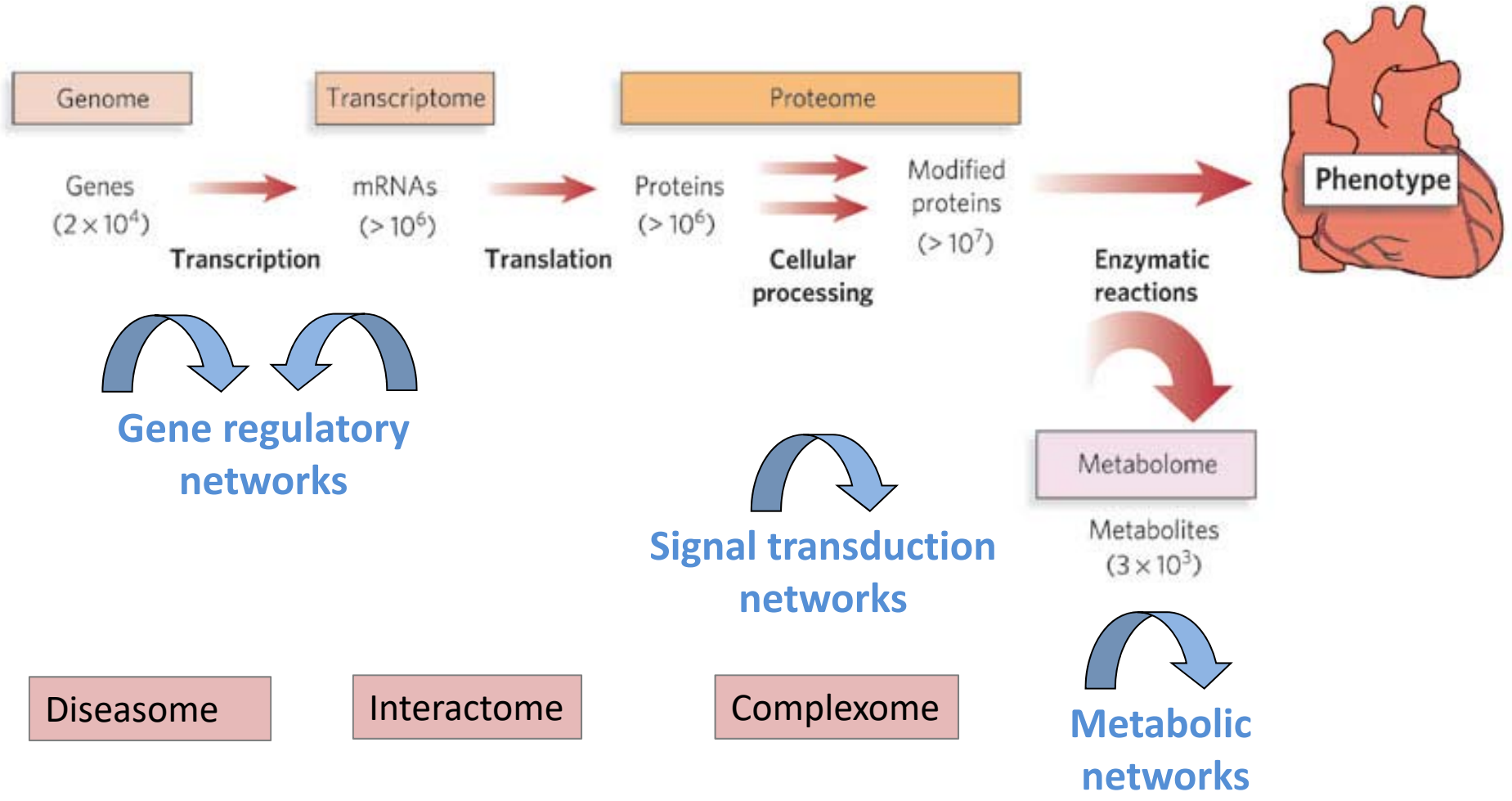
#transition invariants
9775

Koch et al. (2017)
Frontiers in genetics

MODEL1801090001



Data of different scales require different modeling methods



Gerszten & Wang (2008) *Nature* 451:949

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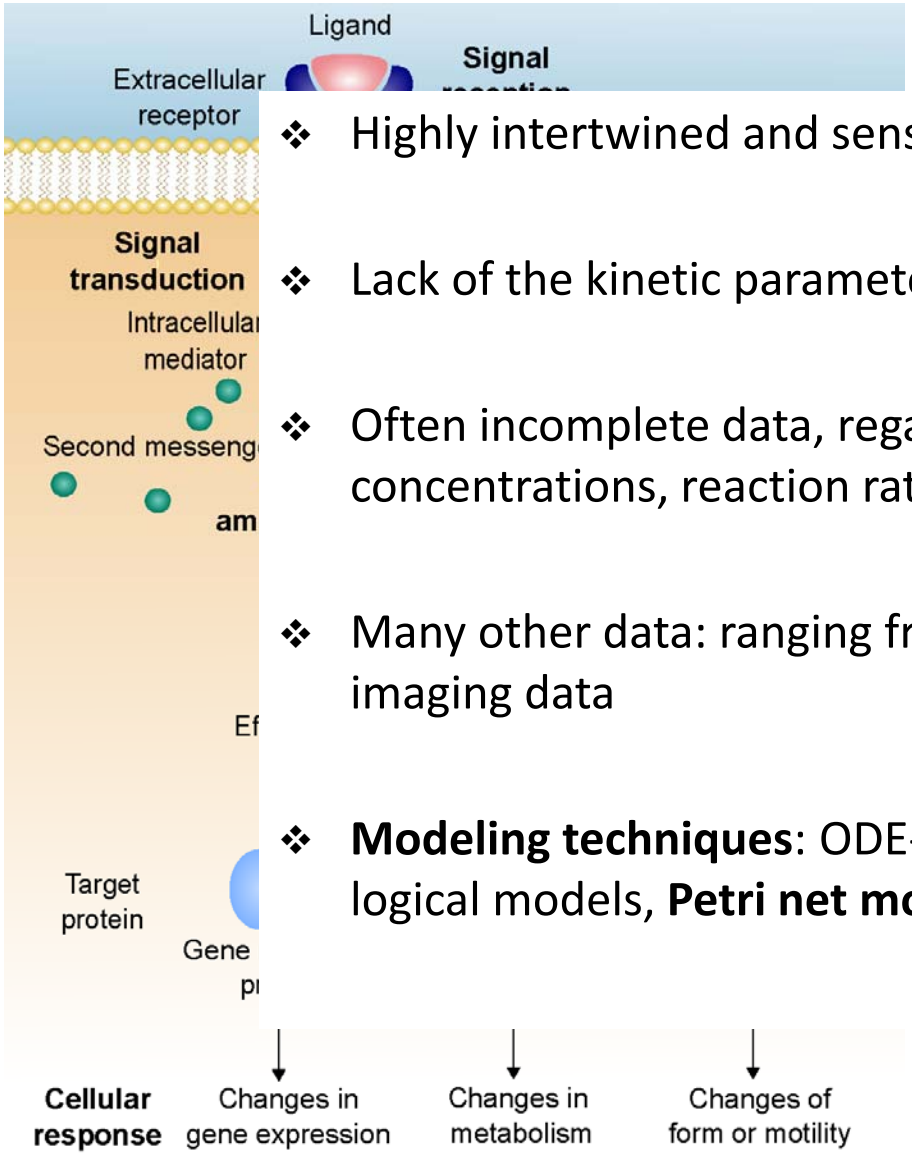
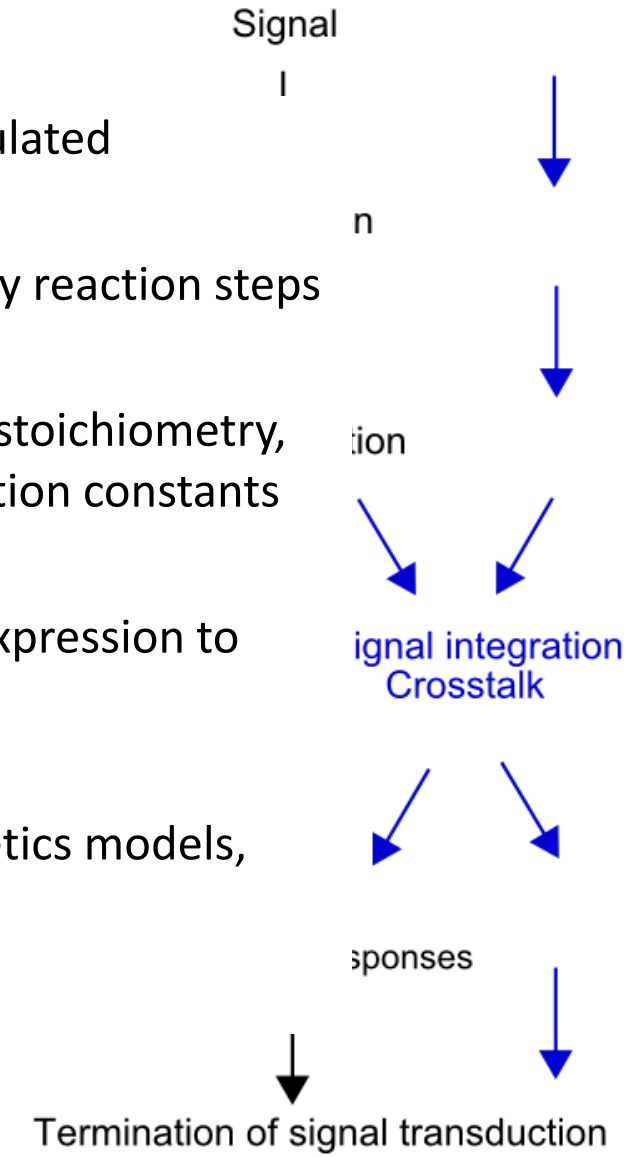
Leonie Amstein

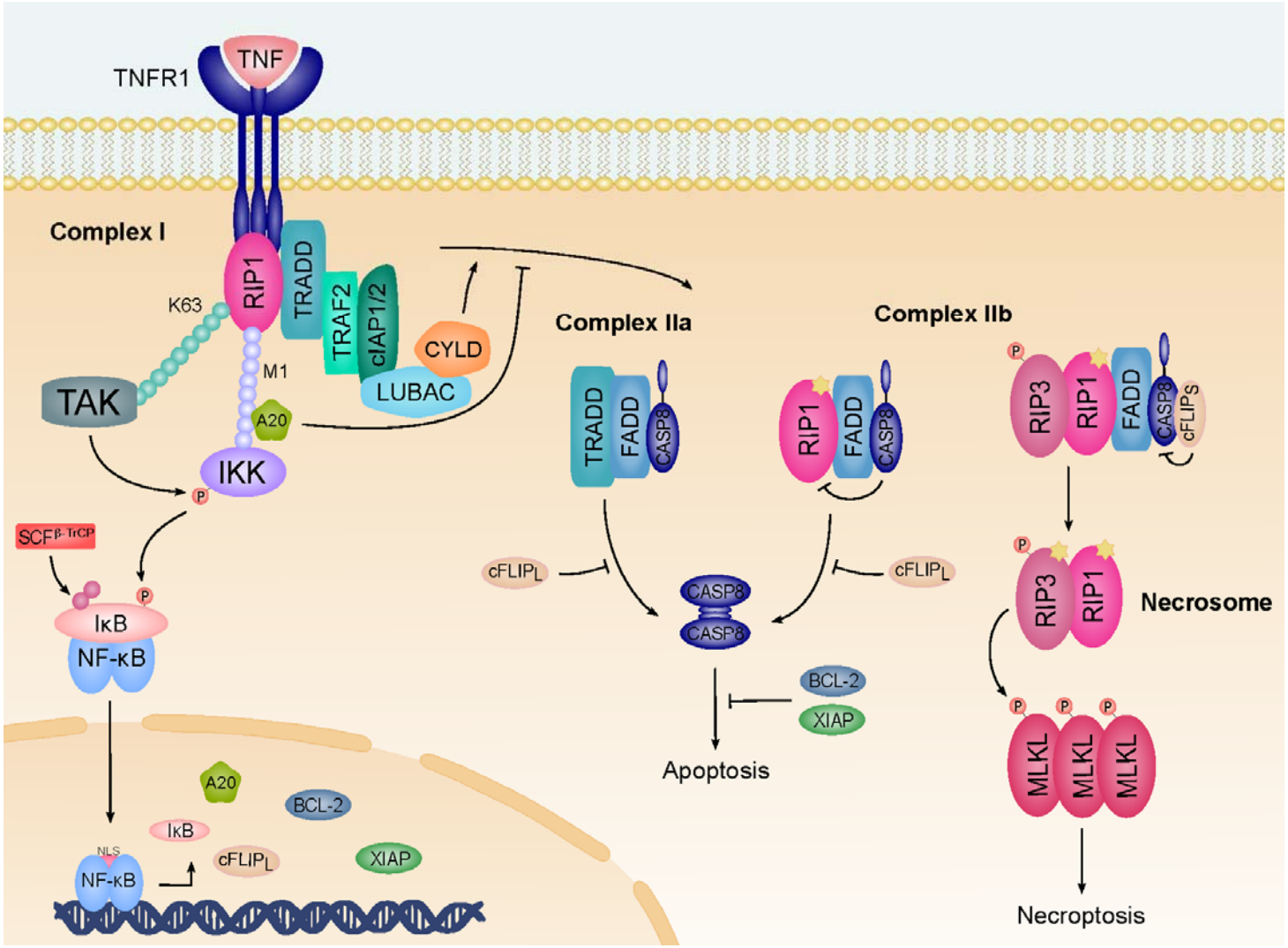
Functionality in signaling pathways



- Highly intertwined and sensitively regulated
- Lack of the kinetic parameters for many reaction steps
- Often incomplete data, regarding the stoichiometry, concentrations, reaction rates, or reaction constants
- Many other data: ranging from gene expression to imaging data
- **Modeling techniques**: ODE-based kinetics models, logical models, **Petri net models**

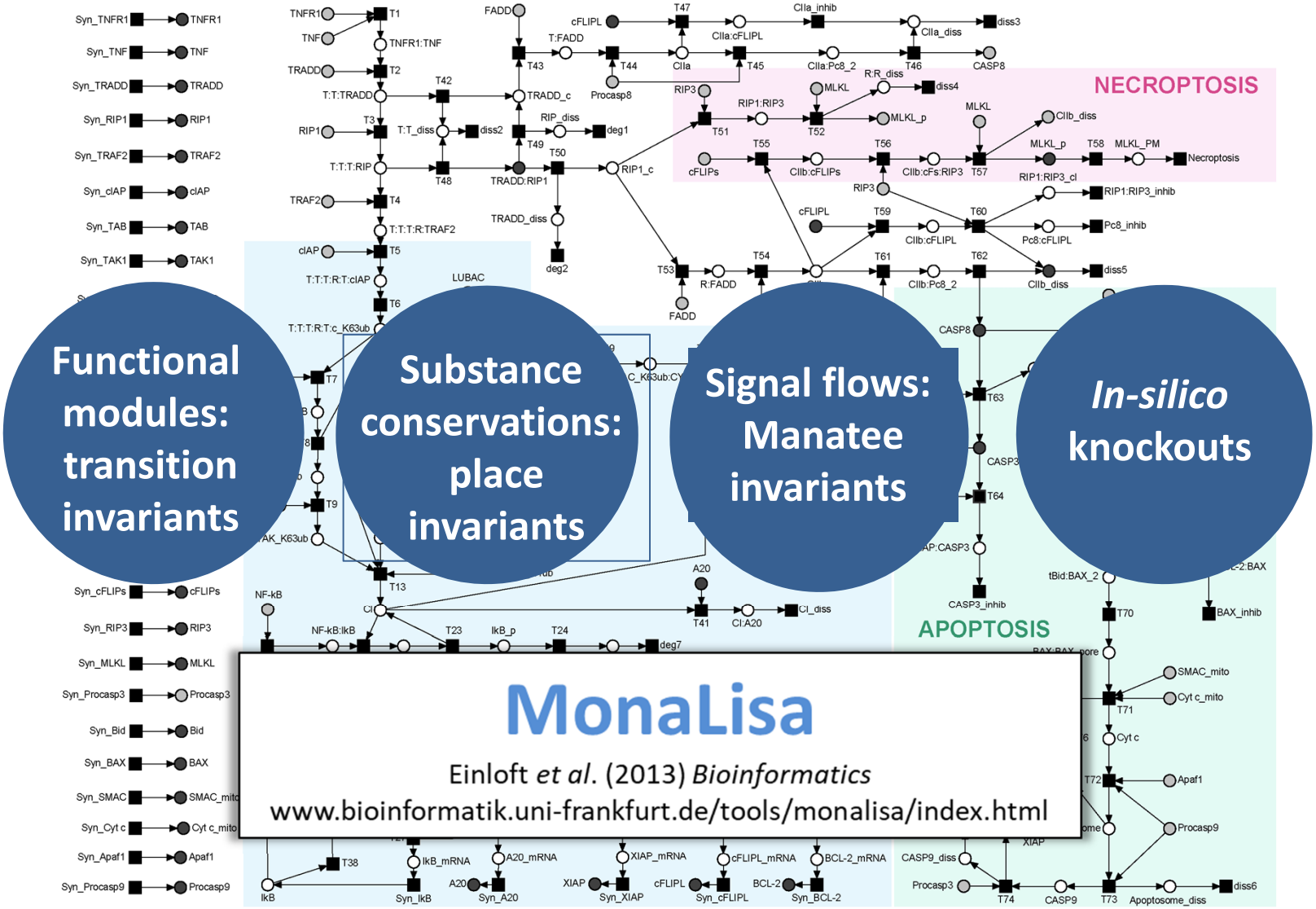


The TNFR1 signal transduction pathway



Amstein *et al*. (2017) *BMC Systems Biol* ; Amstein *et al.* (2022) *PLoS Comp Biol*

The Petri net analysis

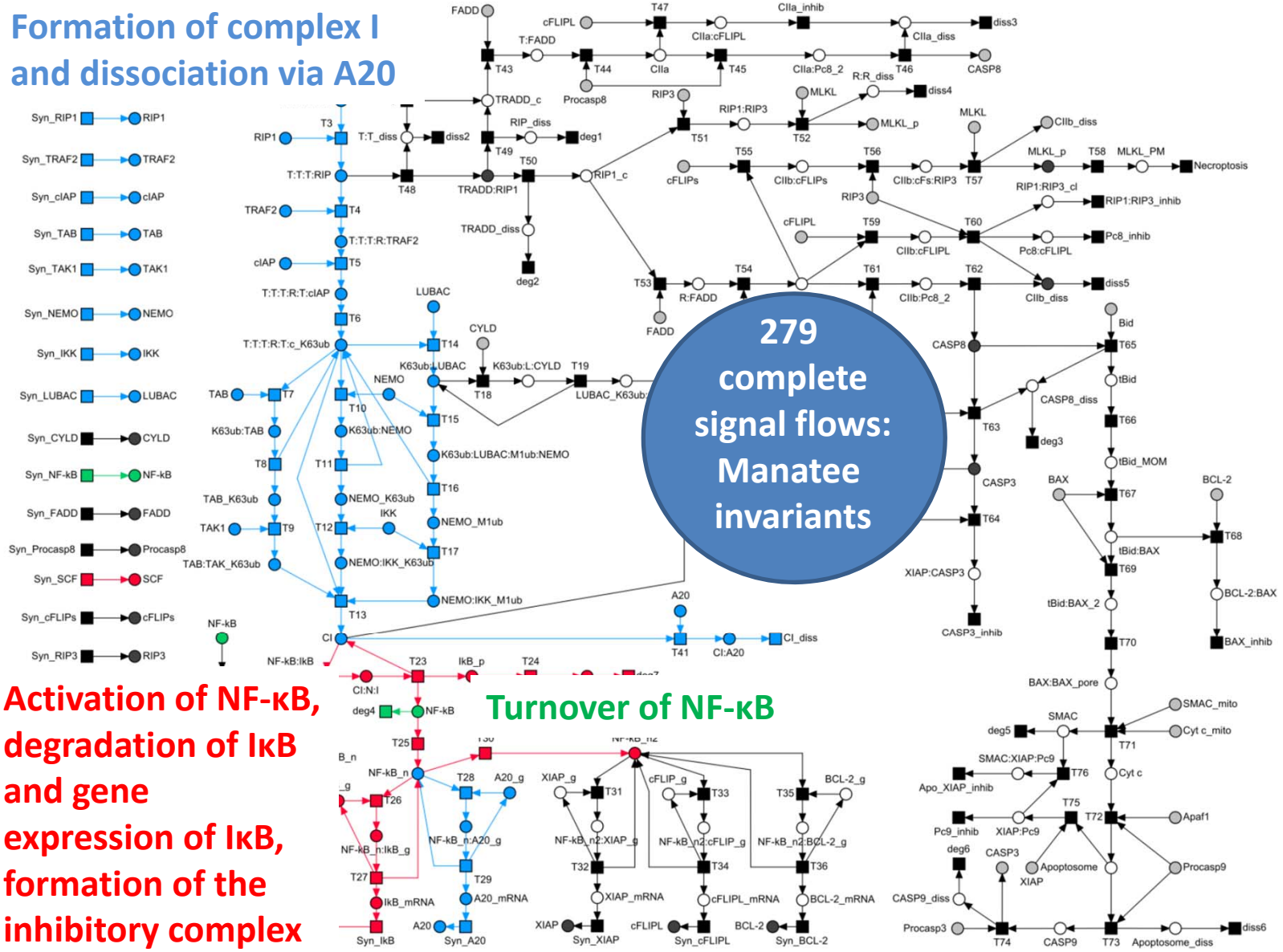


Malik-Sheriff *et al*. (2020) *Nucl Acids Res*

BioModels ID: MODEL2210170001

Manatee invariants predict signaling pathways

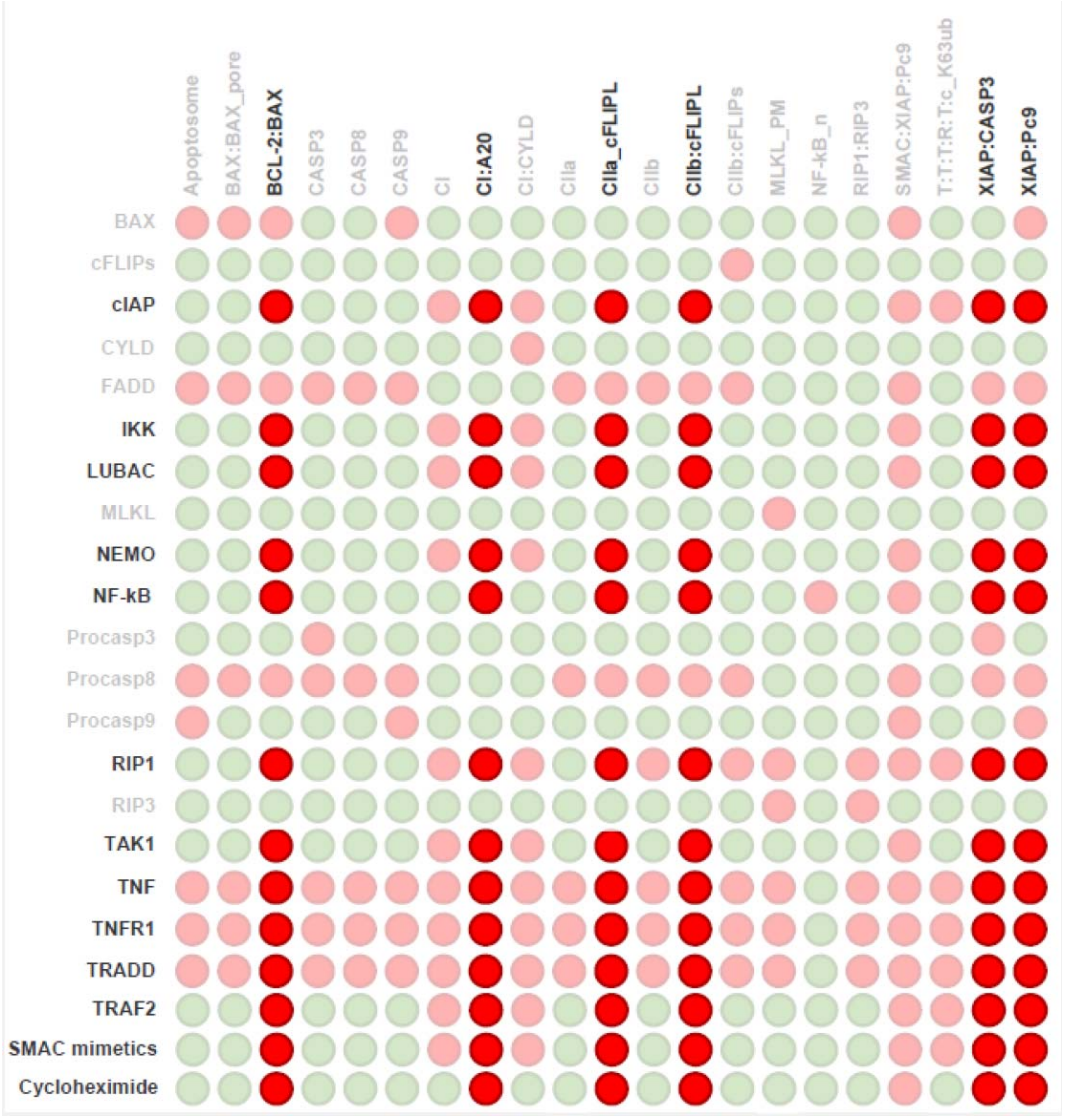
Formation of complex I and dissociation via A20



Activation of NF-κB, degradation of IκB and gene expression of IκB, formation of the inhibitory complex

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

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 functional patterns

isiKnock

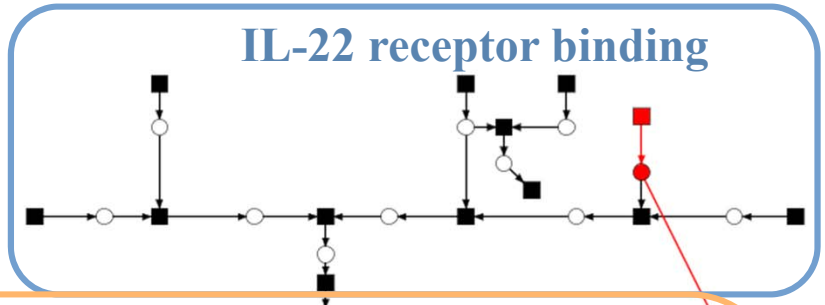
Jennifer Hannig (former Scheidel)

Hannig *et al*. (2018) *Bioinformatics*

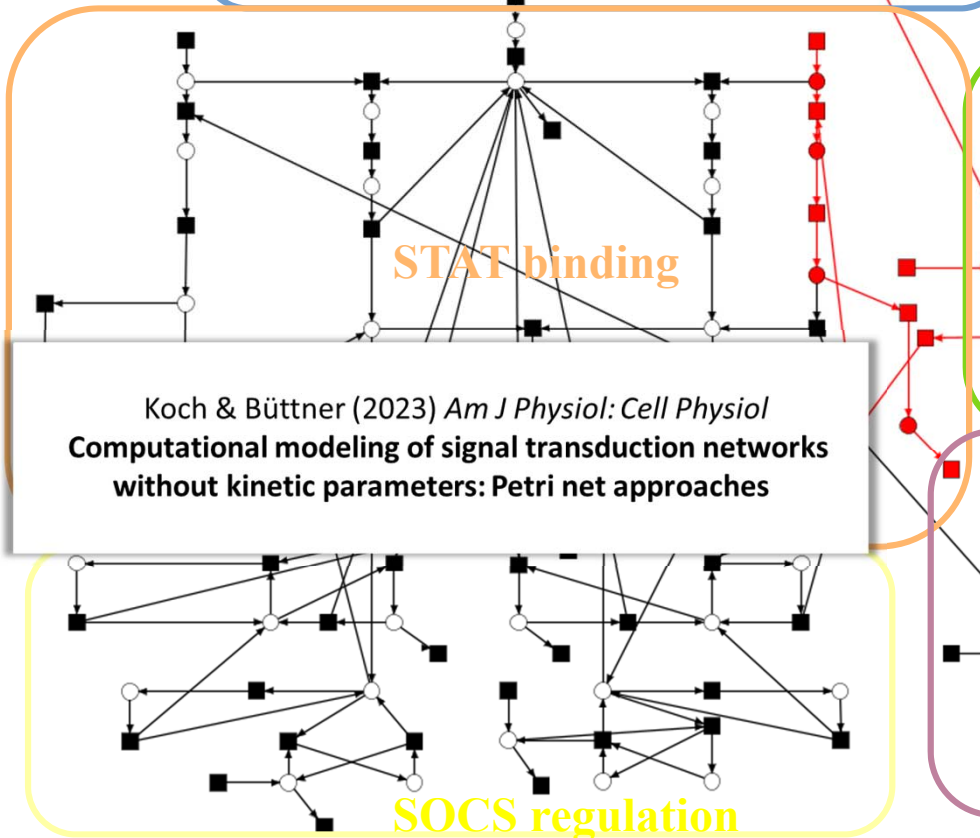
Christoph Welsch

Ongoing projects

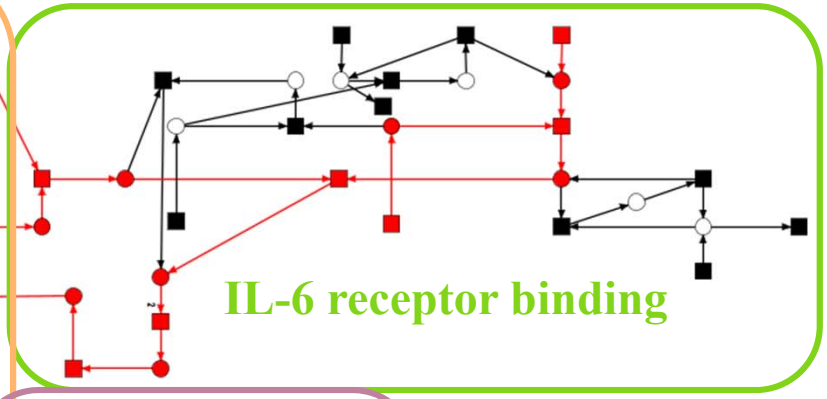
Heiko Mühl

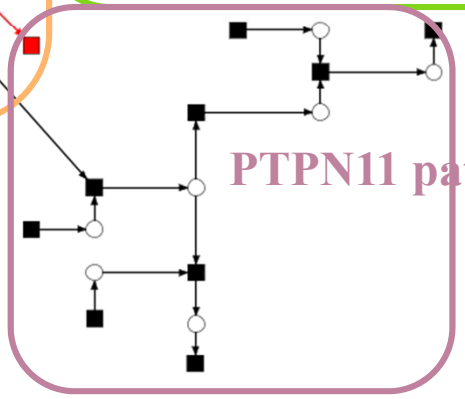


Classical Petri net and development of a mass-action reaction model showing the interactions between IL-6 and IL-22 pathways
unpublished



Koch & Büttner (2023) *Am J Physiol: Cell Physiol*
Computational modeling of signal transduction networks without kinetic parameters: Petri net approaches





Marcus Keßler

Ongoing projects

Influence of the gut microbiota on the translocation of bacteria and fungi in patients with ACLF

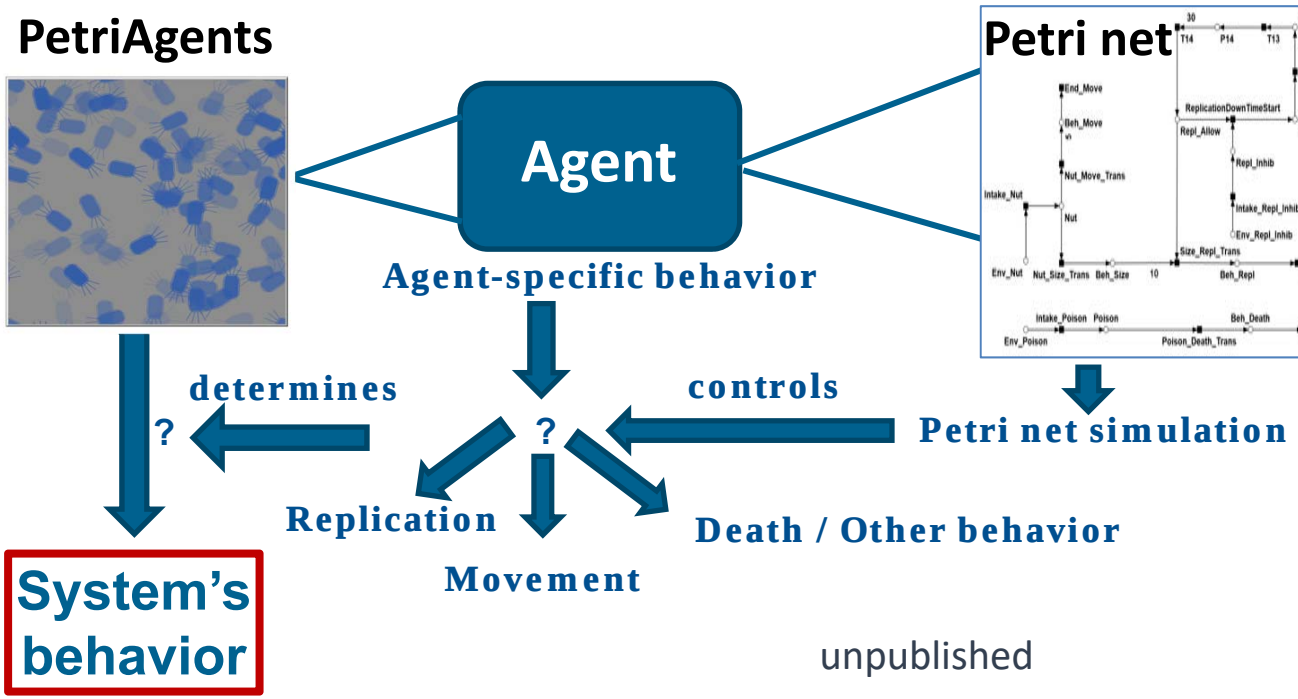
Agent-based model on the interaction between antibiotics and microbiota

- Bacterial movement through gut motility (peristalsis, laminar flow, water absorption
- **Bacterial metabolism** (production of SCFA)
- Bacterial growth in dependence on the pH value

Kristiyana Tsenova

Jörg Ackermann

Marius Kirchner

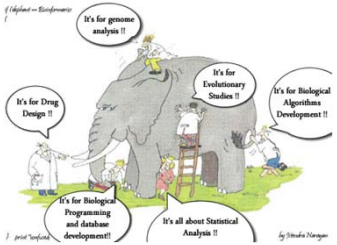


unpublished

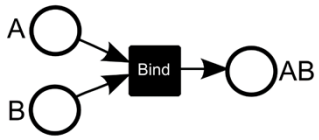
EnABLE
Ein Clusterprojekt des Landes Hessen

Summary

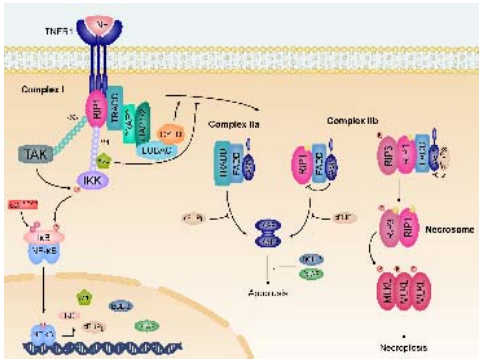
Challenges of data integration

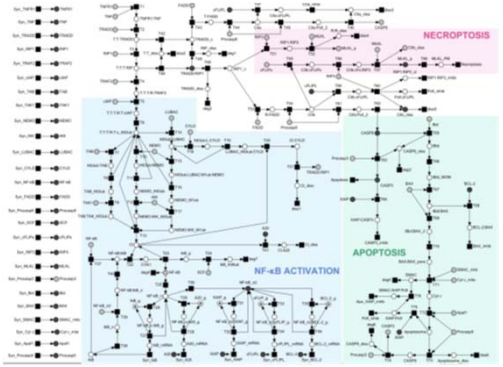


Petri nets

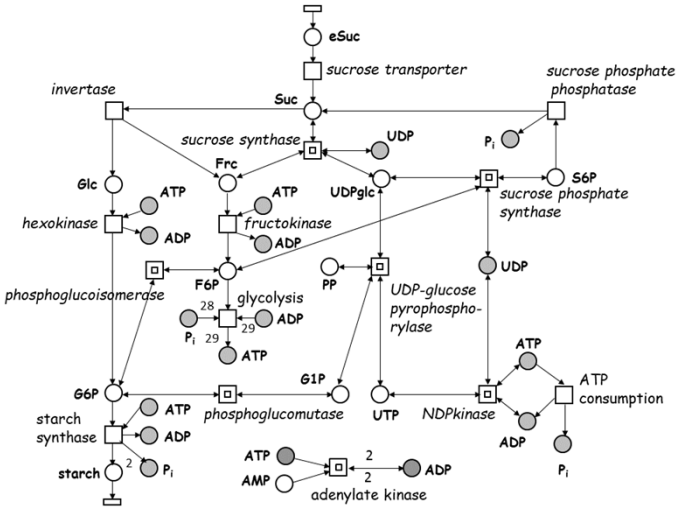


Petri net model of the TNFR1-mediated signaling pathways

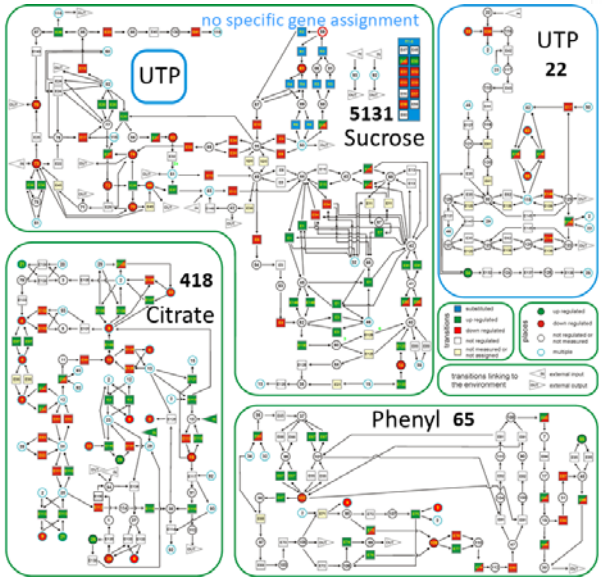




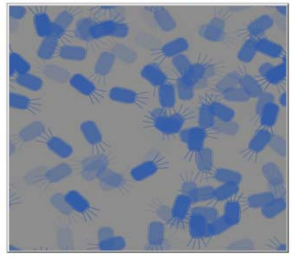
Petri net model of the carbon metabolism in potato tubers and in *Arabidopsis thaliana*



Knockout analyses



PetriAgents



Take-home messages

- The quality and quantity of the data determine the choice of the modeling method -> **Check your data** carefully
- The system's behavior can be predicted **without knowing the kinetic parameters,** using, e.g., Petri nets -> invariant and knockout analyses
- **Place invariants** describe **substance conservations**
- **Transition invariants** represent **functional modules**
- **Manatee invariants** are **linear combinations** of transition invariants **-> complete signaling pathways**
- **The bottleneck** is the availability of data of sufficient quality and quantity, especially for machine learning applications
- The exploration of **all possible system states** is still a challenge

There are many databases related to metabolism,
and there are for a given organism,
many metabolic networks that have been
reconstructed that provide different
and not always compatible information.
How the community could address these issues?

- Standardization
- Computational verification methods
- Database improvement by automatic curation, checking for contradictions
- **Validation, validation, validation!**

Acknowledgments

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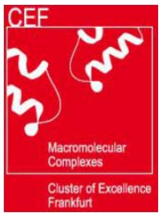
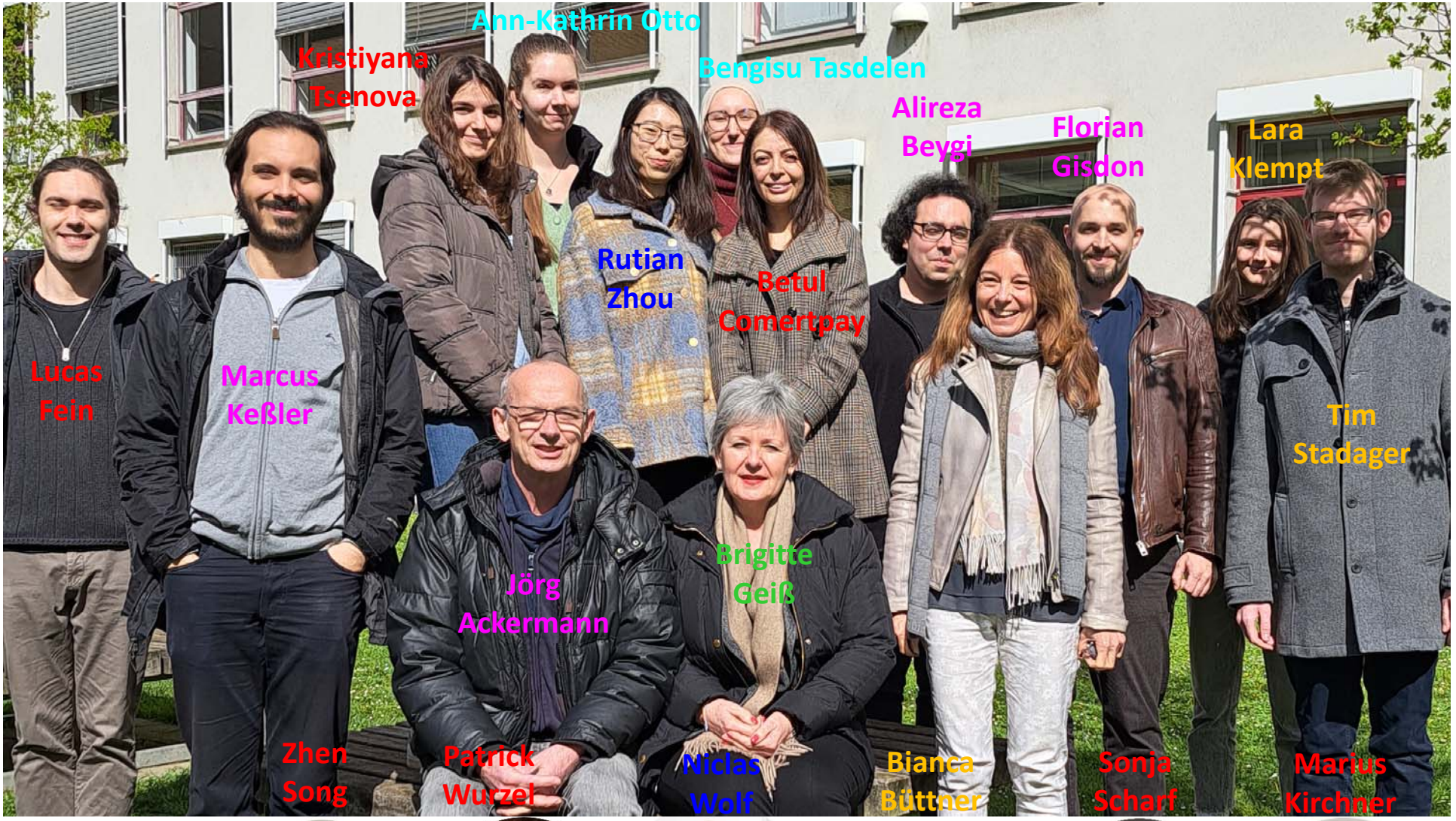
Prof. Dr. Maria Vehreschild

Ecole Normale Supérieure Paris
Prof. Dr. Denis Thieffry

University of Evry Val d'Essonne, Évry
Prof. Dr. Anna Niarakis



April 2023 MolBI



Administration
Bachelor student
Master student
Ph.D. student
Postdoc, Alumni






Thank you
for
your attention!

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: $\nexists z$: supp (z) $\subset$ 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

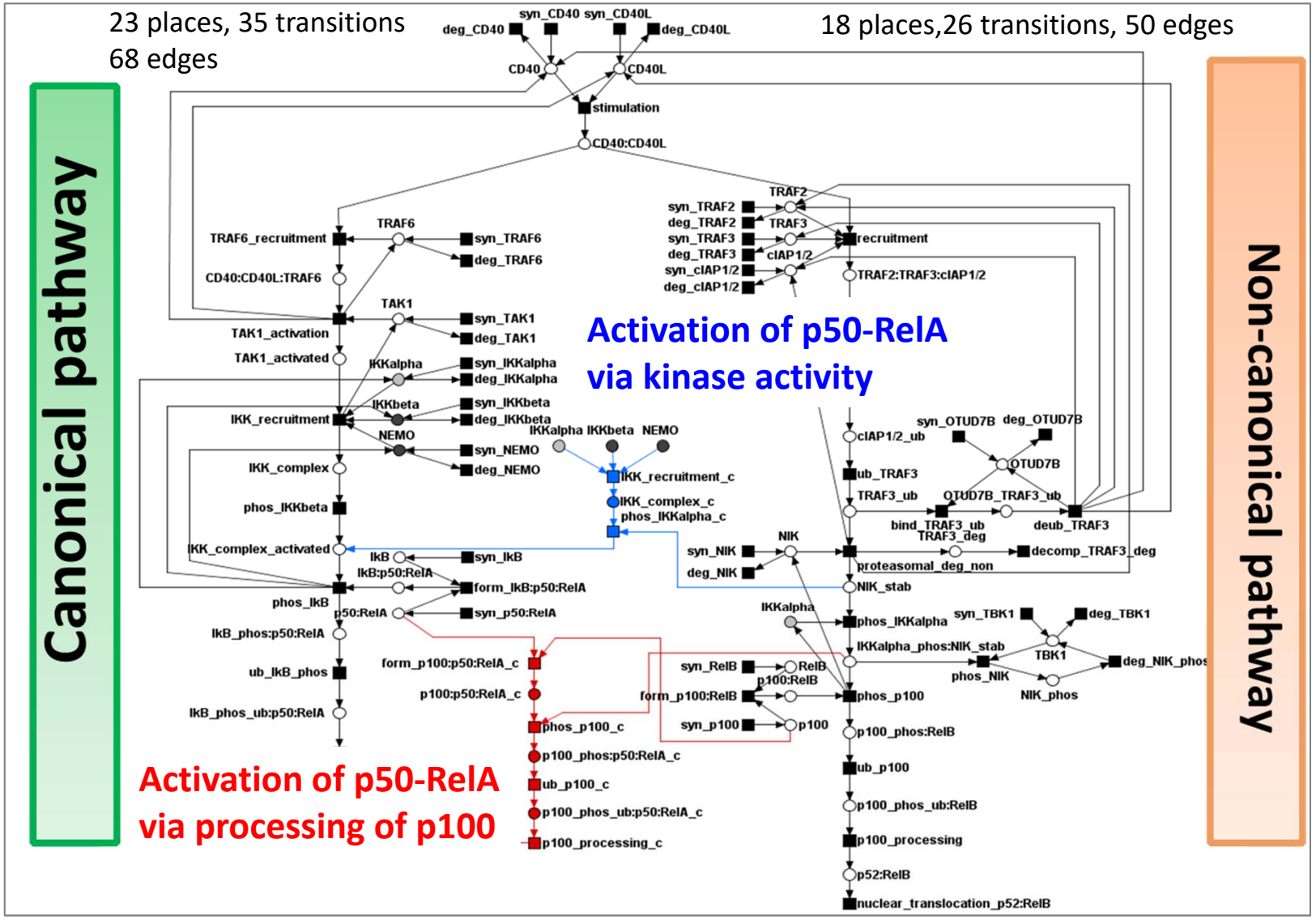
$$
\begin{aligned}
-2y_1 - 1y_2 - 1y_3 + 1y_4 + 3y_5 &= 0\\
-1y_1 - 1y_2 + 2y_5 &= 0\\
+2y_1 + 2y_3 - 2y_4 - 2y_6 &= 0\\
+1y_2 - 1y_3 + 1y_4 - 1y_6 &= 0\\
-1y_5 + 1y_6 &= 0
\end{aligned}
$$

Parikh vector: vector of firing frequencies

The canonical and non-canonical NF-κB pathways and their crosstalk: a comparative study based on Petri nets

Trares *et al.* (2022) *Biosystems;* **BioModels ID: MODEL2207210001/2/3**

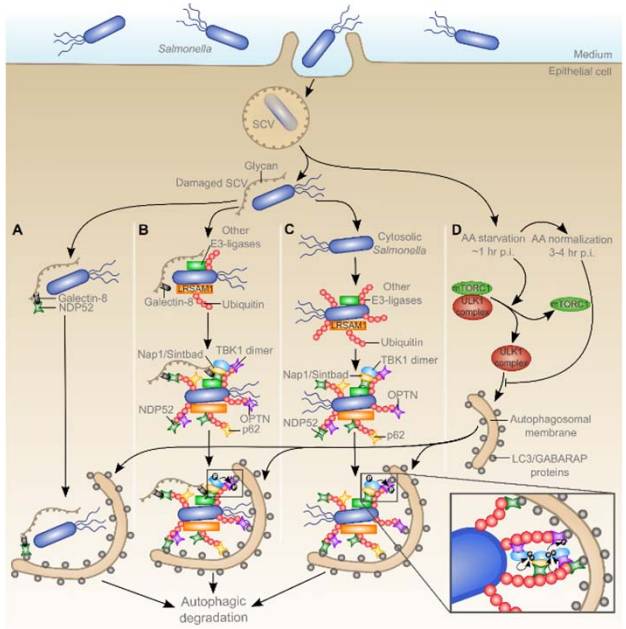
Kira Trares

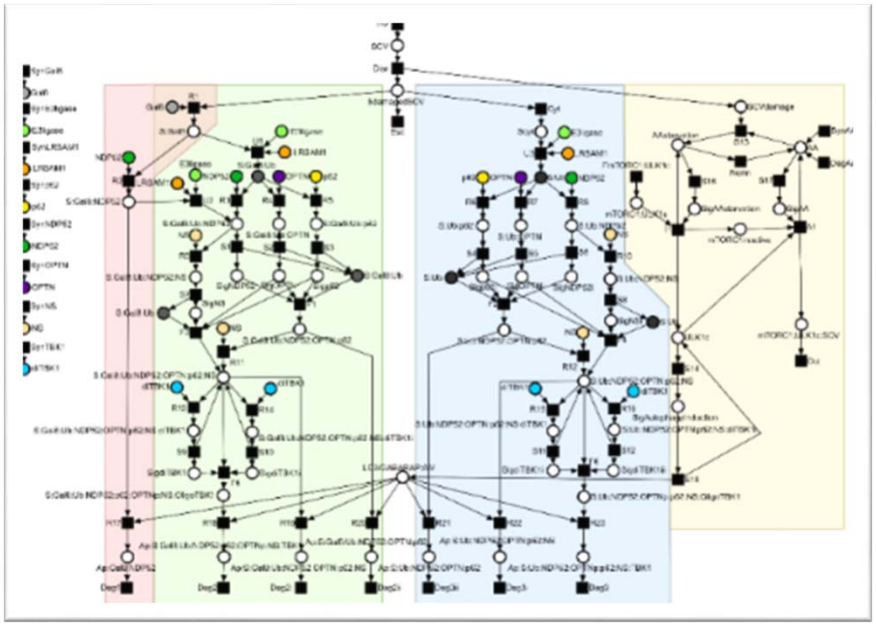


Xenophagy in epithelial HeLa cells after *Salmonella* Typhimurium infection

Jennifer Hannig

Ivan Dikic





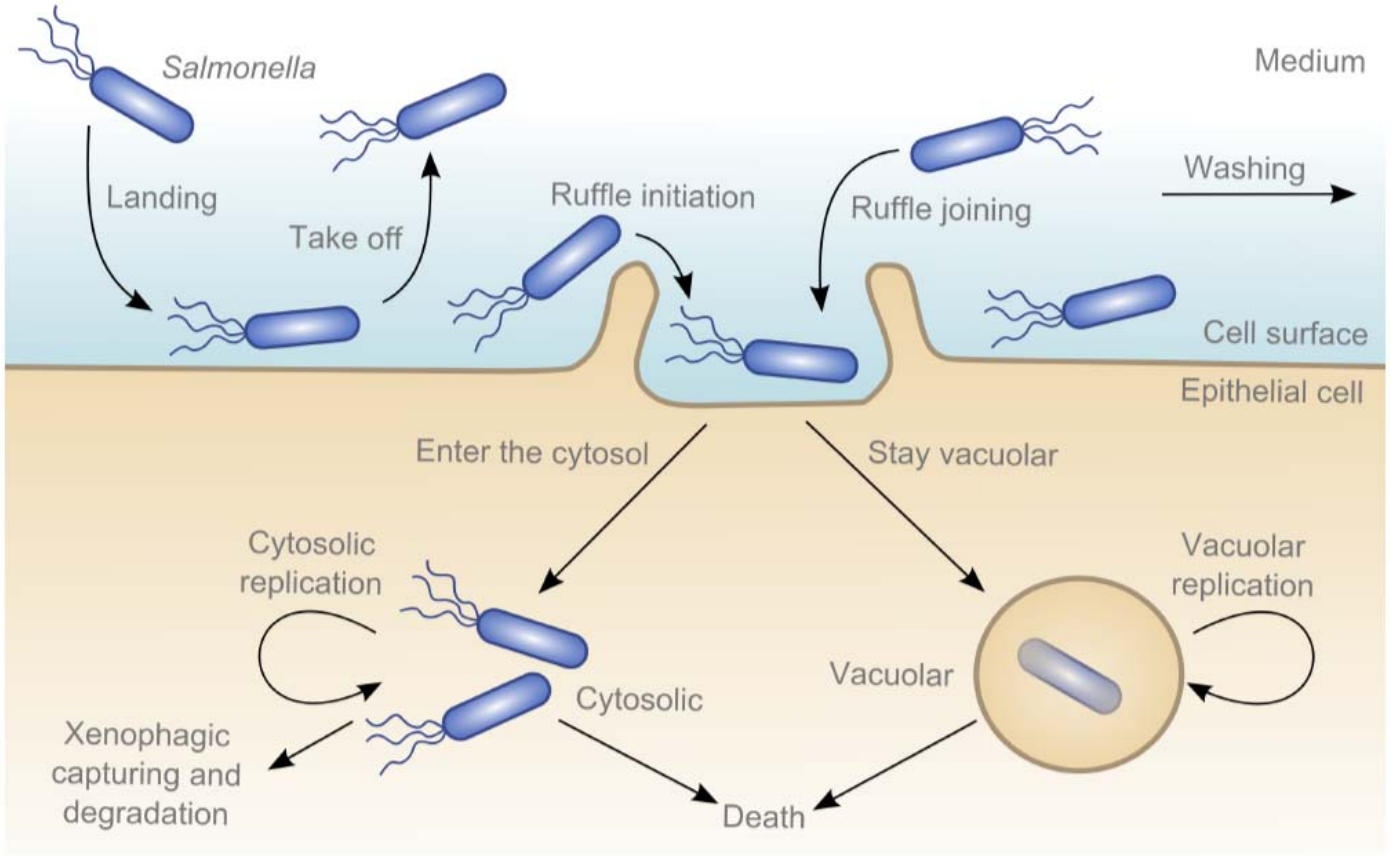
- Classical Petri net
- Stochastic Petri net

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

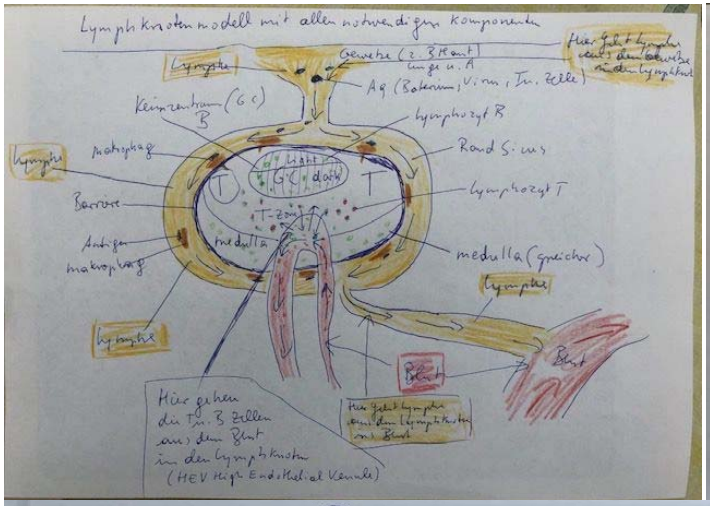
Jennifer Hannig

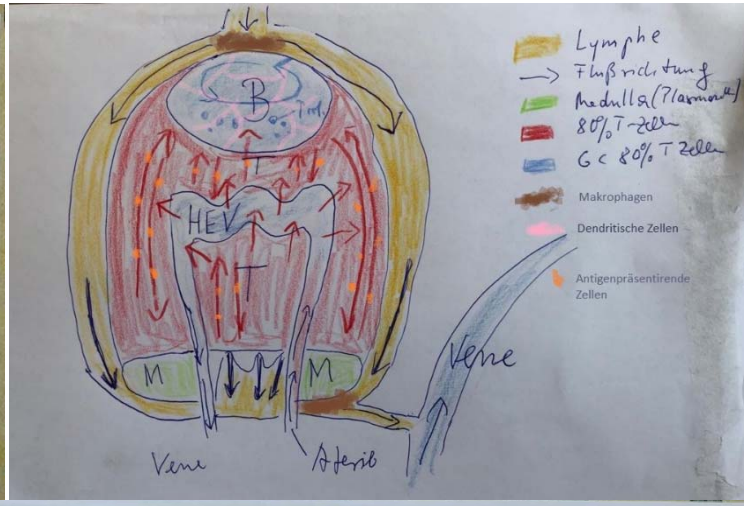


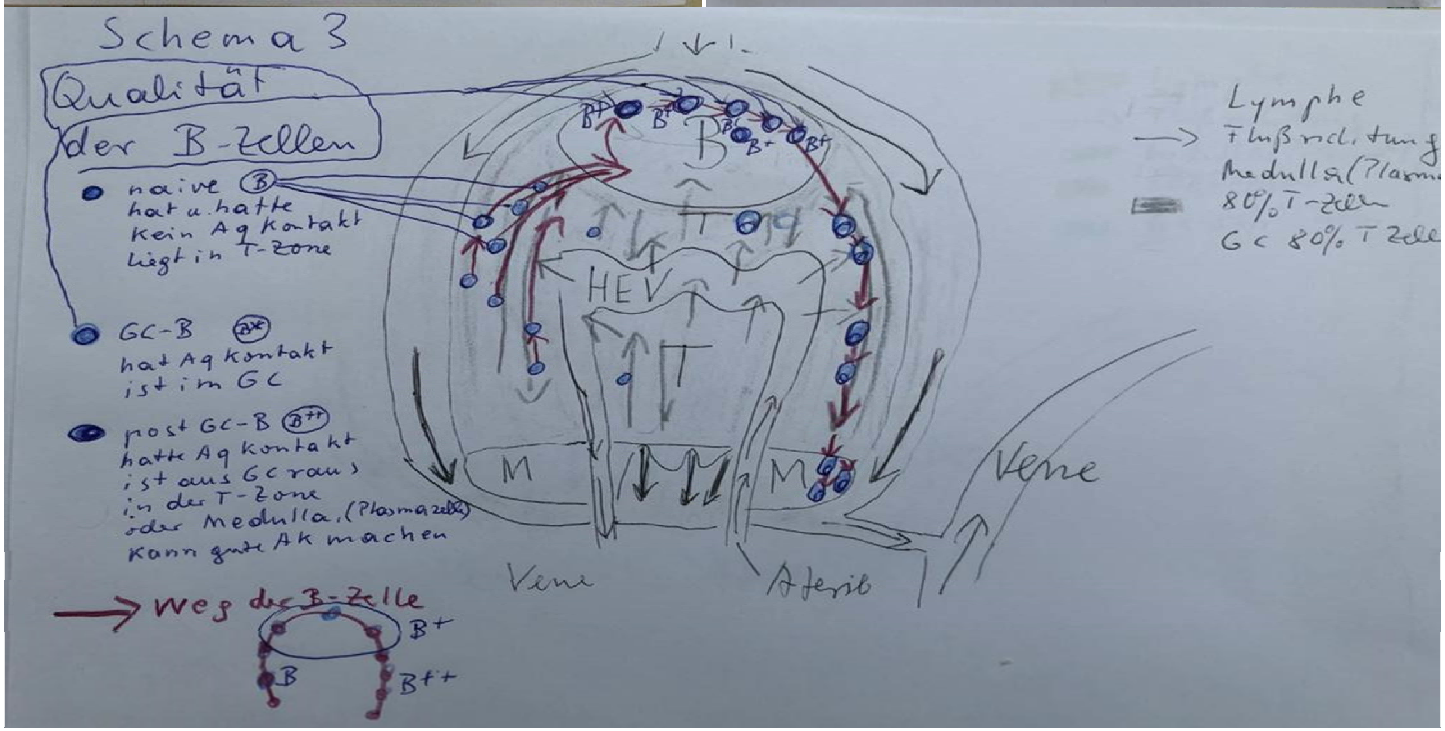
unpublished

A Petri net model of the human lymph node

Martin-Leo Hansmann







unpublished