



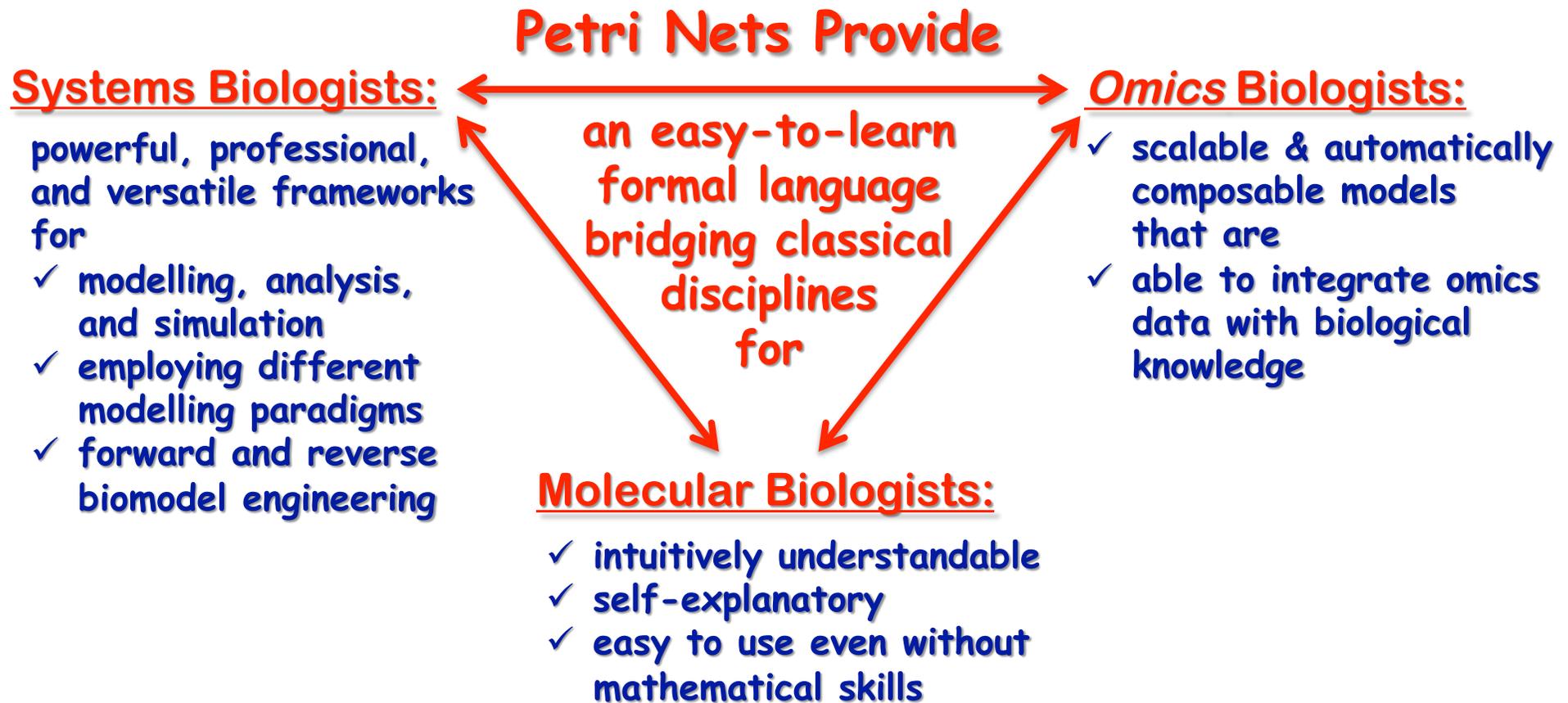
BioPPN 2012, Hamburg

**PETRI NETS, AN INTEGRATIVE FRAMEWORK FOR
ADVANCED BIOMODEL ENGINEERING OF
SIGNAL TRANSDUCTION AND OF
GENE REGULATORY NETWORKS**

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PETRI NETS OFFER A UNIFYING MODELLING LANGUAGE TO BIOLOGISTS AND TO SYSTEMS BIOLOGISTS



WHY ARE PETRI NETS POWERFUL MODELLING FRAMEWORKS SELF-EXPLANATORY TO BIOLOGISTS?

Petri nets

- ✓ are a **formal** modelling **language**
- ✓ are **mathematical structures**
- ✓ have a strictly defined, **simple syntax**
- ✓ provide powerful tools for **analysis** and **simulation**
- ✓ provide graphical **WYSIWYG** representation of **executable models**

The graphical representation of Petri nets

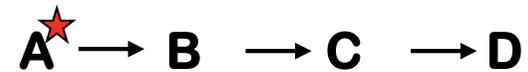
- ✓ provides a **simple formalism**
- ✓ is **intuitively understandable** even without mathematical skills
- ✓ is **like** biologists draw **biochemical reactions** or molecular interactions
- ✓ enforces users to be **consistent** in the **description** in modelling a biological process

Petri nets can

- ✓ model **qualitative** and **quantitative** processes concurrently
- ✓ be executed as qualitative, **continuous**, **stochastic**, or **hybrid** models
- ✓ cover multiple levels of abstraction by linking processes with **arbitrary resolution of details**
- ✓ may be **structured hierarchically**
- ✓ gain the **expressive power** of a programming language in the form of coloured Petri nets

THIS TALK REFERS TO SIGNAL TRANSDUCTION AND TO GENE REGULATORY NETWORKS NOT TO METABOLIC NETWORKS

Metabolic Networks: Flux of chemical compounds



Mass flow may be analysed e.g. by isotope labelling

Signaling Networks: Flux of information

It may occur through different types of molecular interactions

THIS TALK REFERS TO SIGNAL TRANSDUCTION AND TO GENE REGULATORY NETWORKS NOT TO METABOLIC NETWORKS

Signaling Networks:

The flux of information may occur through

- Protein-protein interactions
- Protein-nucleic acid interactions
- Small molecules as cofactors and mediators
- Ion flow or changes in membrane potential
- Translocation between different compartments
- Changes in the concentration of compounds, or through stochastic molecular events, or both

=> Stochastic or hybrid simulation may be necessary in order to make the model behave realistically

THIS TALK REFERS TO SIGNAL TRANSDUCTION AND TO GENE REGULATORY NETWORKS NOT TO METABOLIC NETWORKS

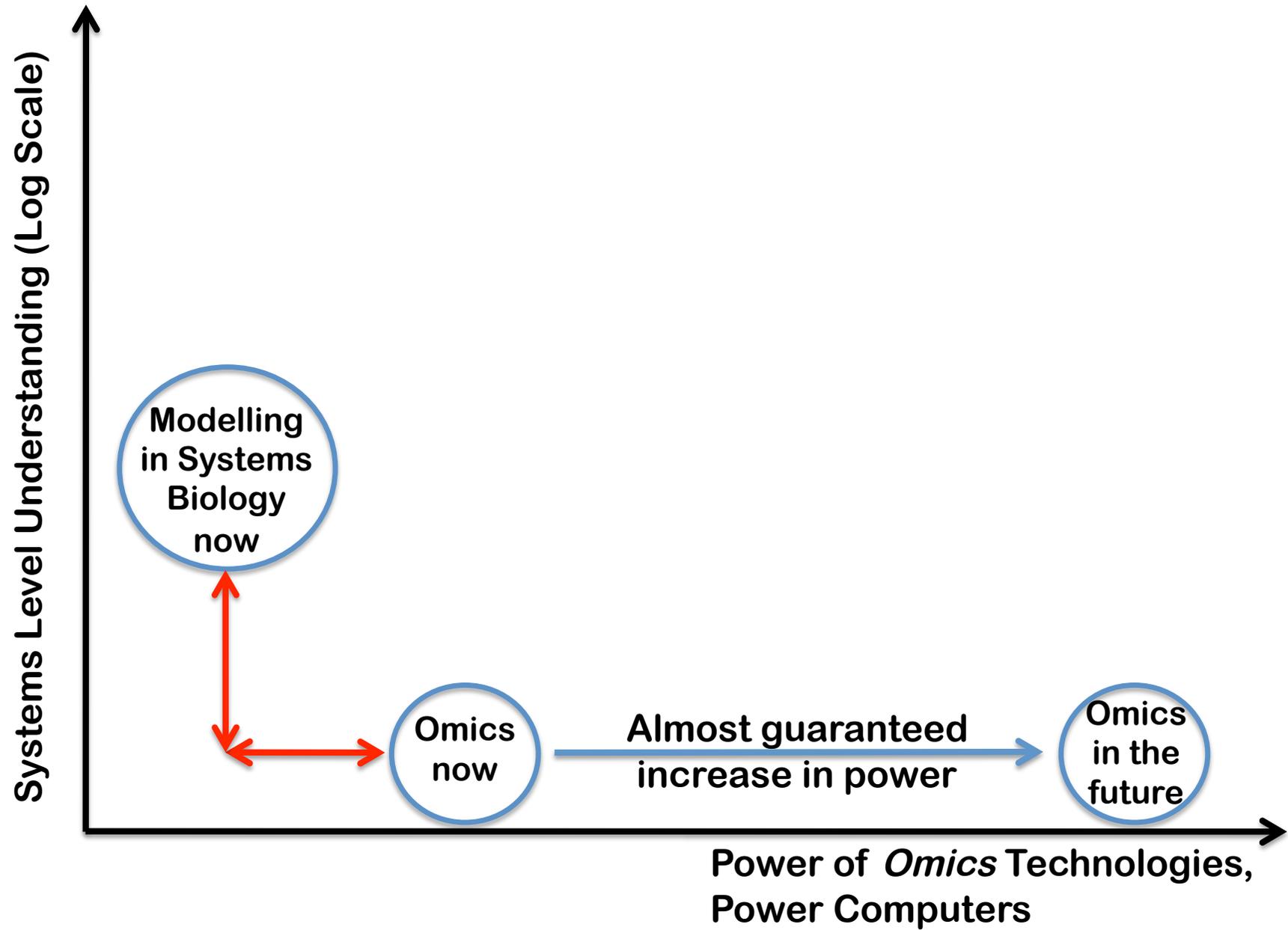
Signaling Networks:

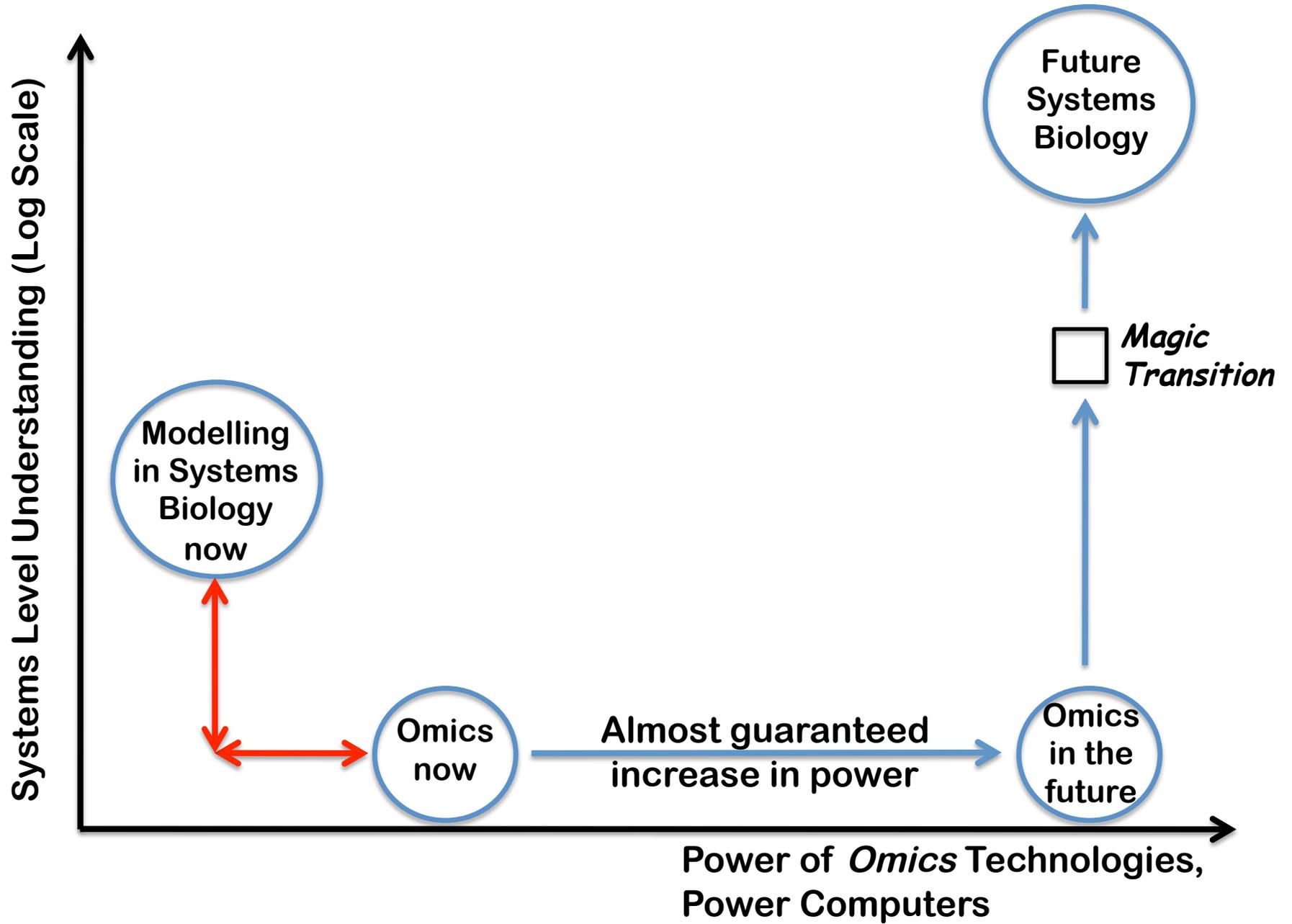
The flux of information may not be easily traceable because

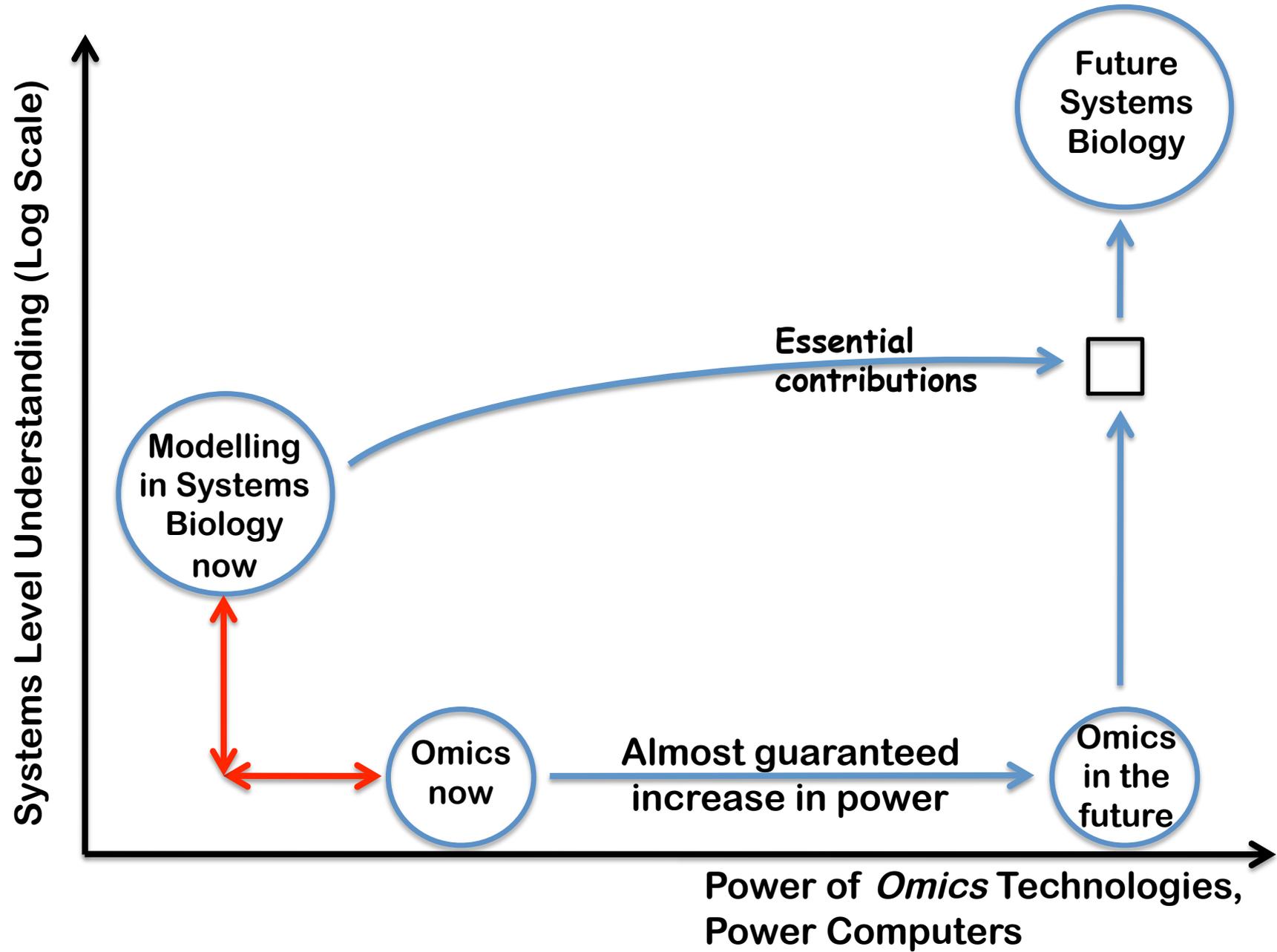
- Different types of molecular interactions are involved
- Not all physical interactions are functional
- Not all functional interactions are necessarily detectable as physical interactions
- Not all functional interactions are relevant to the phenomenon of interest
- Network elements may be redundant
- Networks may be robust to perturbations

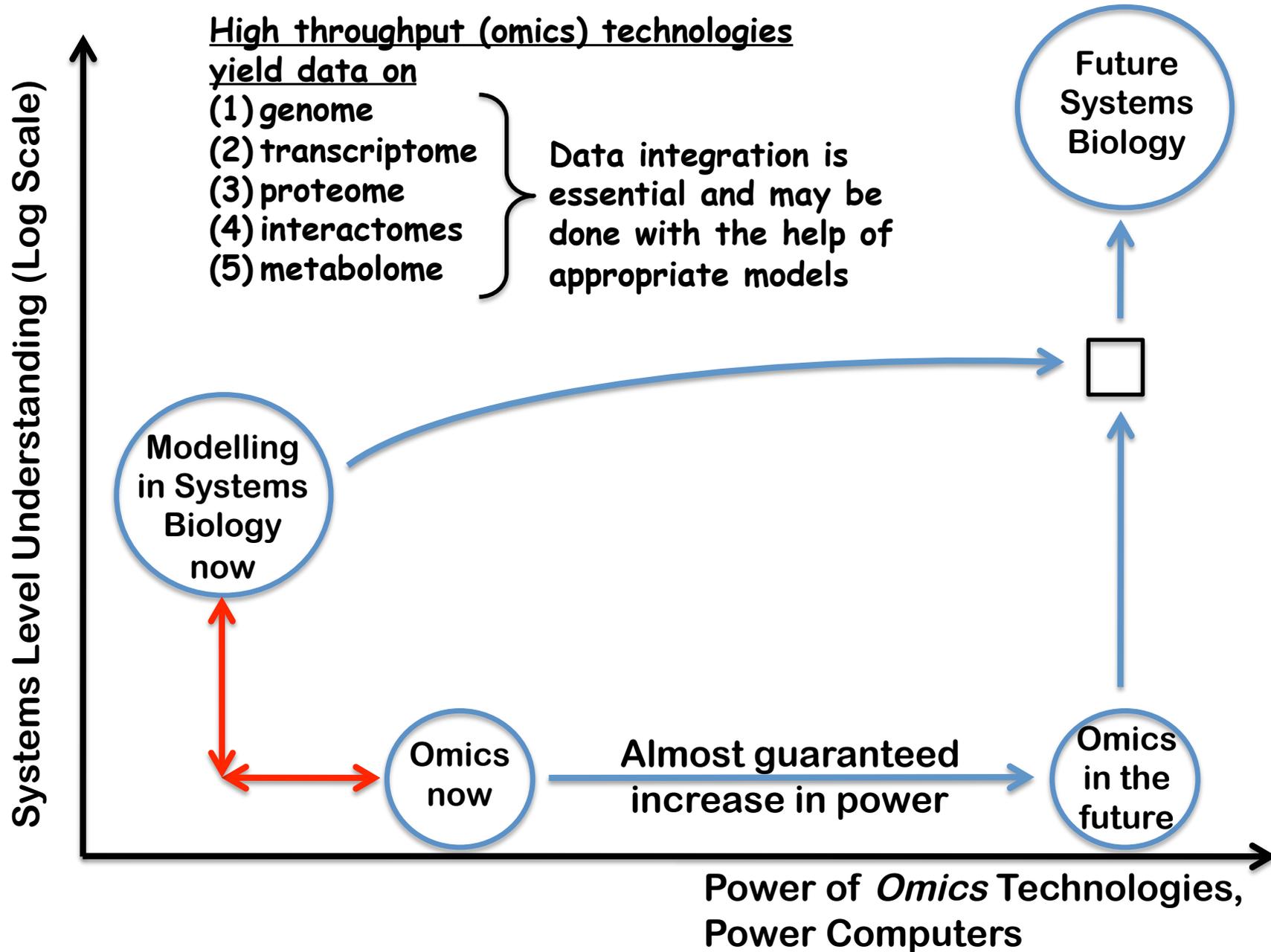
=> Reverse engineering approaches may be essential

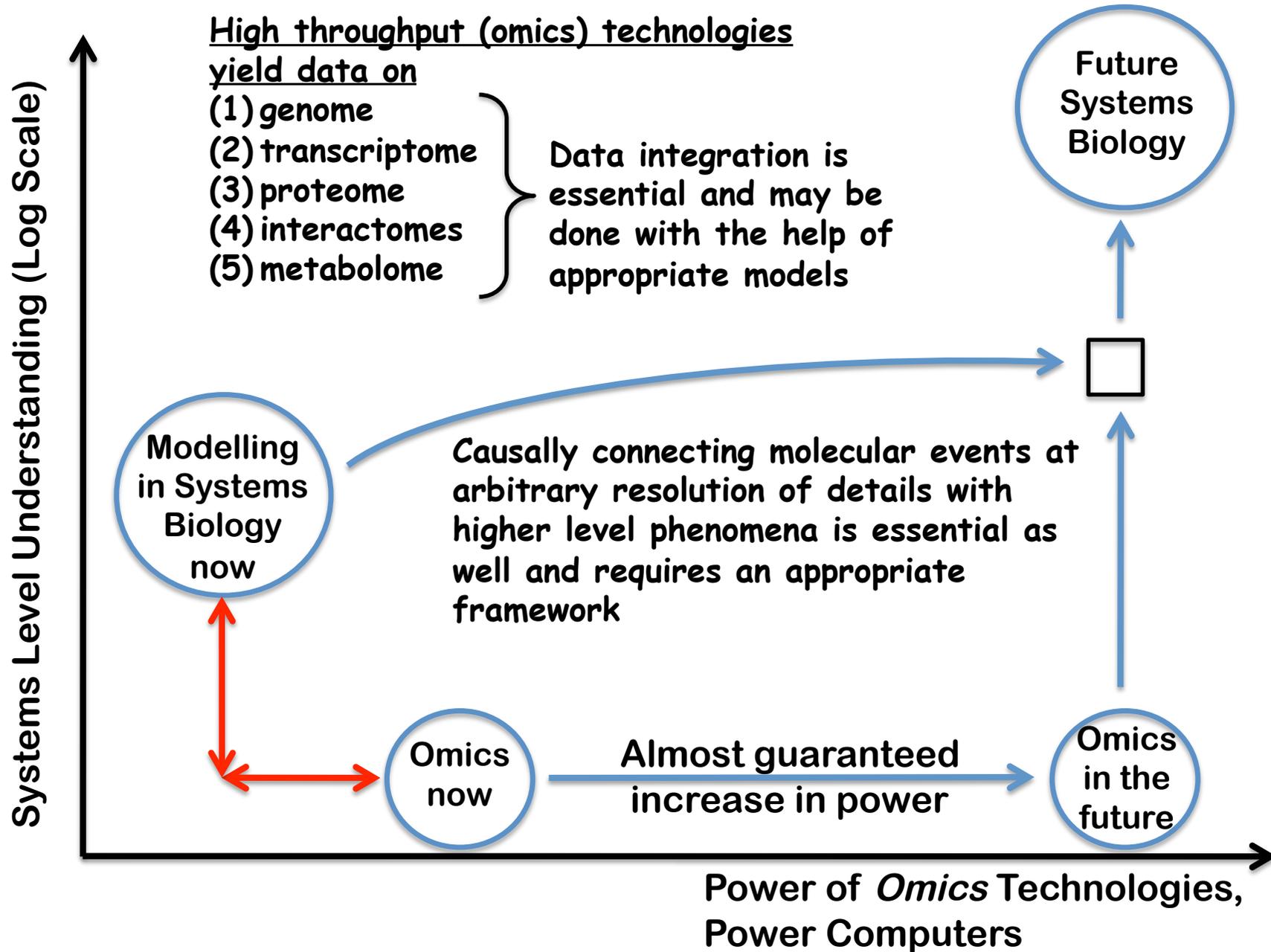
=> Biological knowledge may be integrated by forward engineering of the model

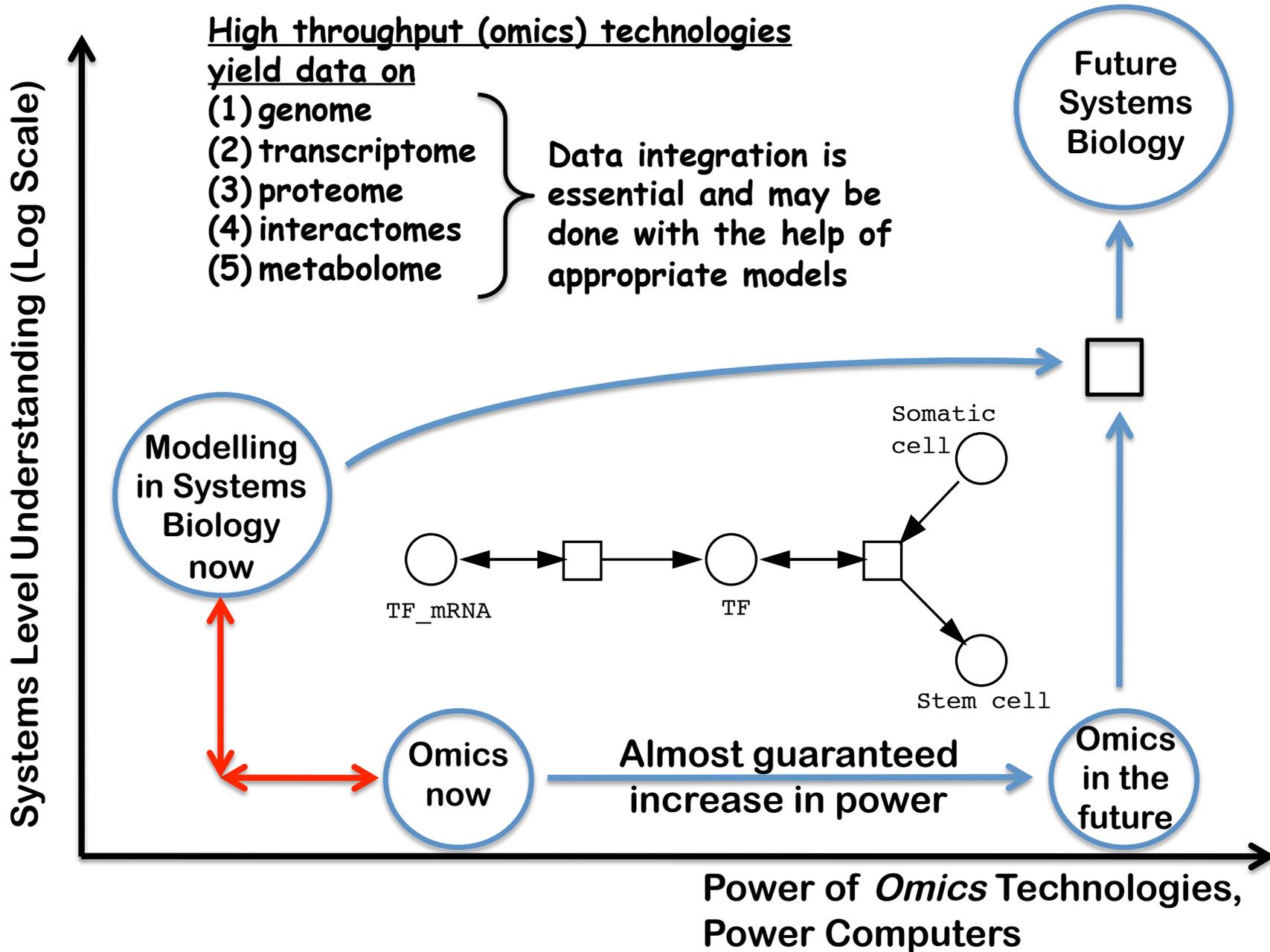


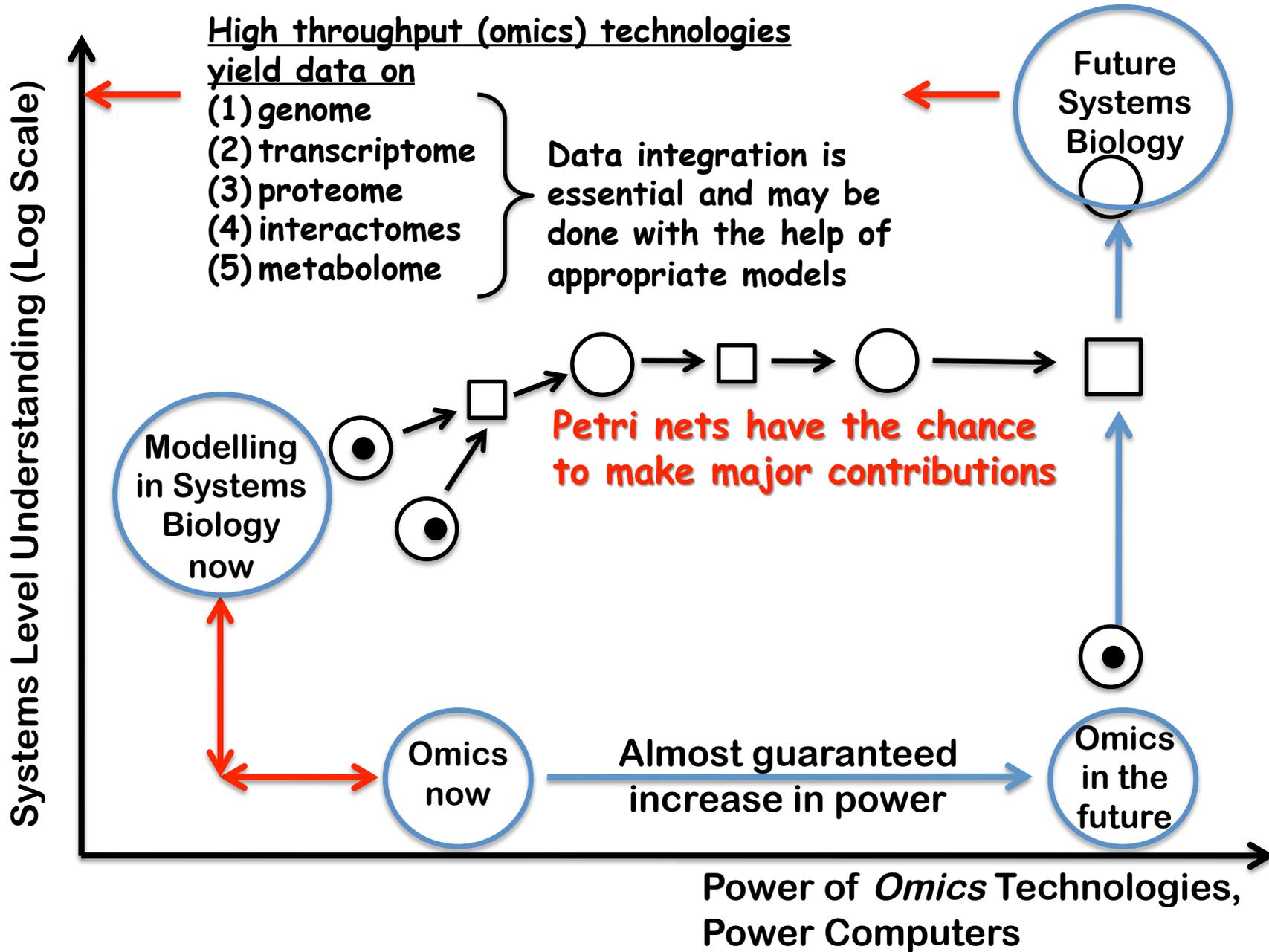












SYSTEMS BIOLOGY APPROACHES WITH PETRI NETS FOLLOWED IN MAGDEBURG

MODULAR PETRI NET MODELLING

AUTOMATIC NETWORK RECONSTRUCTION

A MODULAR APPROACH TO PETRI NET MODELLING

WE ADVERTISE A DATABASE OF PETRI NET MODULES RATHER THAN A COLLECTION OF MONOLITHIC MODELS



Current Systems Biology Models:

represent a bioprocess with a

- ☹ fixed resolution in detail, employing a
- ☹ fixed mathematical modelling paradigm (e.g. ODE or stochastic).

However, monolithic models are

- ☹ not easily assessed
- ☹ not easily updated
- ☹ not easily extended
- ☹ not easily combined with other models



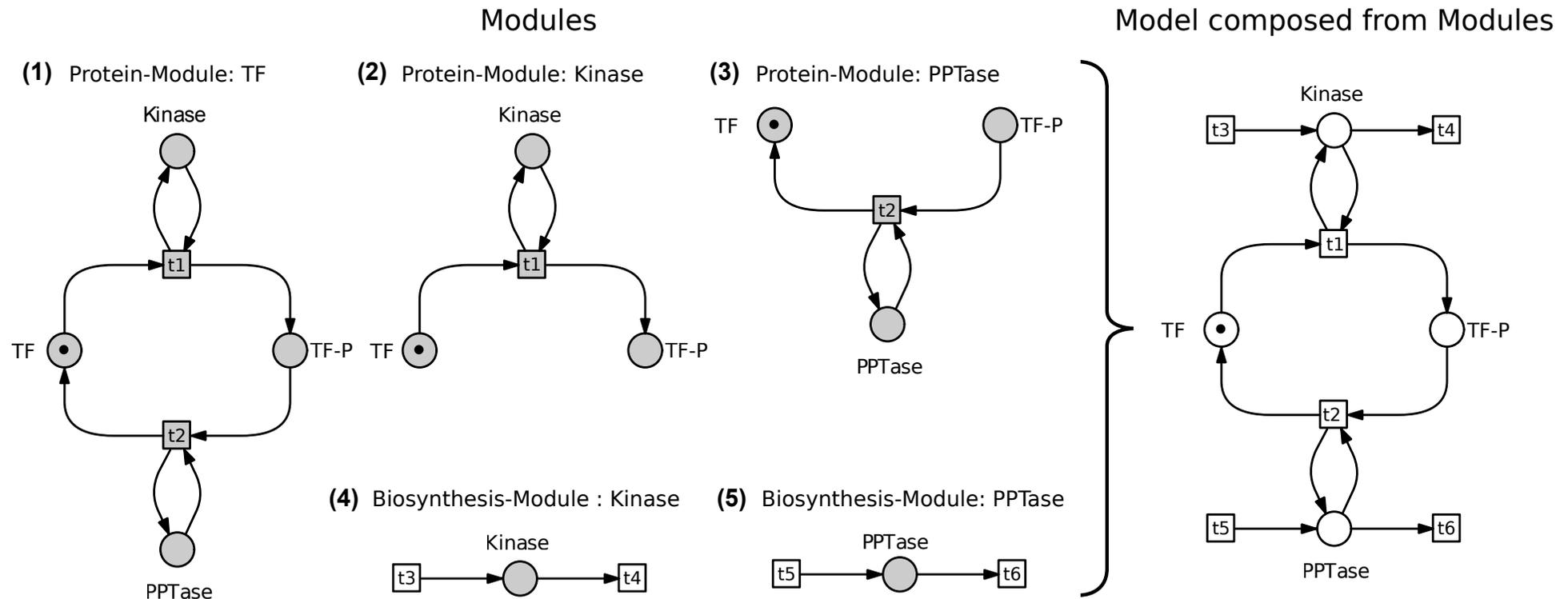
Modules can be easily

- ☺ composed
- ☺ reused
- ☺ curated
- ☺ updated
- ☺ modified
- ☺ exchanged

Modules

- ☺ are organised in a database
- ☺ contain searchable metadata
- ☺ may be a wiki-like minireview
- ☺ can be provided in multiple versions

A MODULE IS CENTRED AROUND A MOLECULE



A transcription factor, phosphorylated by a kinase and dephosphorylated by a phosphatase:

Protein Modules:

- ✓ Transcription factor (TF)
- ✓ Kinase
- ✓ Phosphatase (PPTase)

Biosynthesis Modules:

- ✓ Kinase
- ✓ Phosphatase (PPTase)

Protein Module

Petri Net

Binding and Unbinding
Reactions

Formation and Cleavage
of Covalent Bonds

Conformational Changes

Documentation &
Searchable Metadata

Protein Module:

- ✓ The Petri net is well-structured
- ✓ It displays the different reactions of a protein clearly arranged according to the types of reactions

Metadata are Essential for:

- ✓ Documentation
- ✓ Automatic model composition
- ✓ Version management
- ✓ Database searches
- ✓ *In silico* mutation

(a)

All Modules

ID	Gene Symbol	Protein Name	Accession	Approved	Release Date	
1	IL6	Interleukin-6	P05231	★	2011-11-08	■
2	IL6R	Interleukin-6 receptor subunit alpha	P08887	★	2011-11-08	■
3	IL6ST	Interleukin-6 receptor subunit beta	P40189	★	2011-11-08	■
4	JAK1	Tyrosine-protein kinase	P23458	★	2011-11-08	■
8	JAK1	Tyrosine-protein kinase	P23458	★	2011-11-10	■
5	STAT3	Signal transducer and activator of transcription 3	P40763	★	2011-11-08	■
6	PTPN11	Tyrosine-protein phosphatase non-receptor type 11	Q06124	★	2011-11-08	■
9	PTPN11	Tyrosine-protein phosphatase non-receptor type 11	Q06124	★	2011-11-10	■
7	SOCS3	Suppressor of cytokine signaling 3	O14543	★	2011-11-08	■

+ Add To Collection —Select Collection ▾

(b)

MODULE: IL6★ (ID:1 , Release Date: 2011-11-08)

General Information

Submitter(s): Blaetke, Mary Ann
Curator(s): Dittrich, Anna
Schaper, Fred

Protein: Interleukin-6 (Gene Symbol: IL6, Accession Number: P05231)
Connectable IL6R
Module(s): IL6ST
JAK1
JAK1_HYP1

Module Version(s): No other versions in this database.
Publication(s): Müller-Newen G, Heinrich PC, Behrmann I, Haan S, Hermanns HM, Schaper F: Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J.* 2003; 374 (Pt 1): 1-20 (PMID: 12773095)
Müller-Newen G: The cytokine receptor gp130: faithfully promiscuous. *Sci STKE.* 2003; 2003 (201): PE40 (PMID: 14506288)

Place Overview

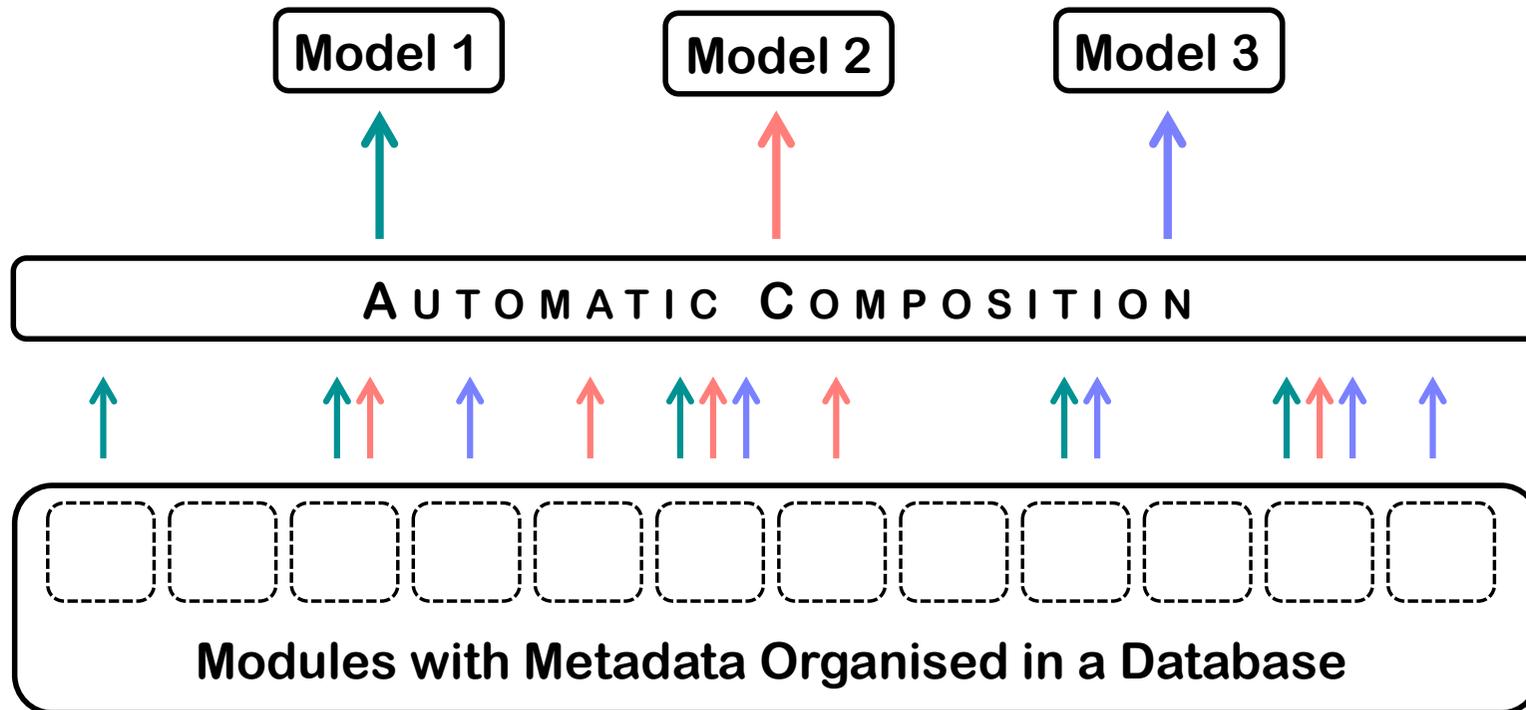
Place Name	Description
IL6R_CBM	cytokine binding module (CBM) of Interleukin-6 receptor subunit alpha (IL6R)
IL6R_CBM_IL6_siteI	cytokine binding module (CBM) of Interleukin-6 receptor subunit alpha (IL6R) bound to binding site I (siteI) of Interleukin-6 (IL6)
IL6R_siteIIIb	site IIIb (siteIIIb) of Interleukin-6 receptor subunit beta (IL6R)
IL6R_siteIIb	site IIb (siteIIb) of Interleukin-6 receptor subunit beta (IL6R)
IL6ST_CBM	cytokine binding module (CBM) of Interleukin-6 receptor subunit beta (IL6ST)
IL6ST_CBM_IL6_siteIIa_IL6R_siteIIb	cytokine binding module (CBM) of Interleukin-6 receptor subunit beta (IL6ST) bound to binding site IIa (siteIIa) of Interleukin-6 (IL6) and binding site IIb (siteIIb) of Interleukin-6 receptor subunit alpha (IL6R)
IL6ST_iglike	immunoglobulin-like domain (Iglike) of Interleukin-6 receptor subunit beta (IL6ST)
IL6ST_iglike_IL6_siteIIa_IL6R_siteIIb	immunoglobulin-like domain (Iglike) of Interleukin-6 receptor subunit beta (IL6ST) bound to binding site IIa of Interleukin-6 (IL6) and binding site IIIb (siteIIIb) of Interleukin-6 receptor subunit alpha (IL6R)
IL6_siteI	binding site I (siteI) of Interleukin-6 (IL6)
IL6_siteIIa	binding site IIa (siteIIa) of Interleukin-6 (IL6)
IL6_siteIIa	binding site IIa (siteIIa) of Interleukin-6 (IL6)
JAK1_FERM_IL6ST_Box1_Box2	4.1 ezrin radixin and moesin domain of Tyrosine-protein kinase JAK1 (JAK1) bound to Box1 and Box2 of Interleukin-6 receptor subunit beta (IL6ST)

Transition Overview

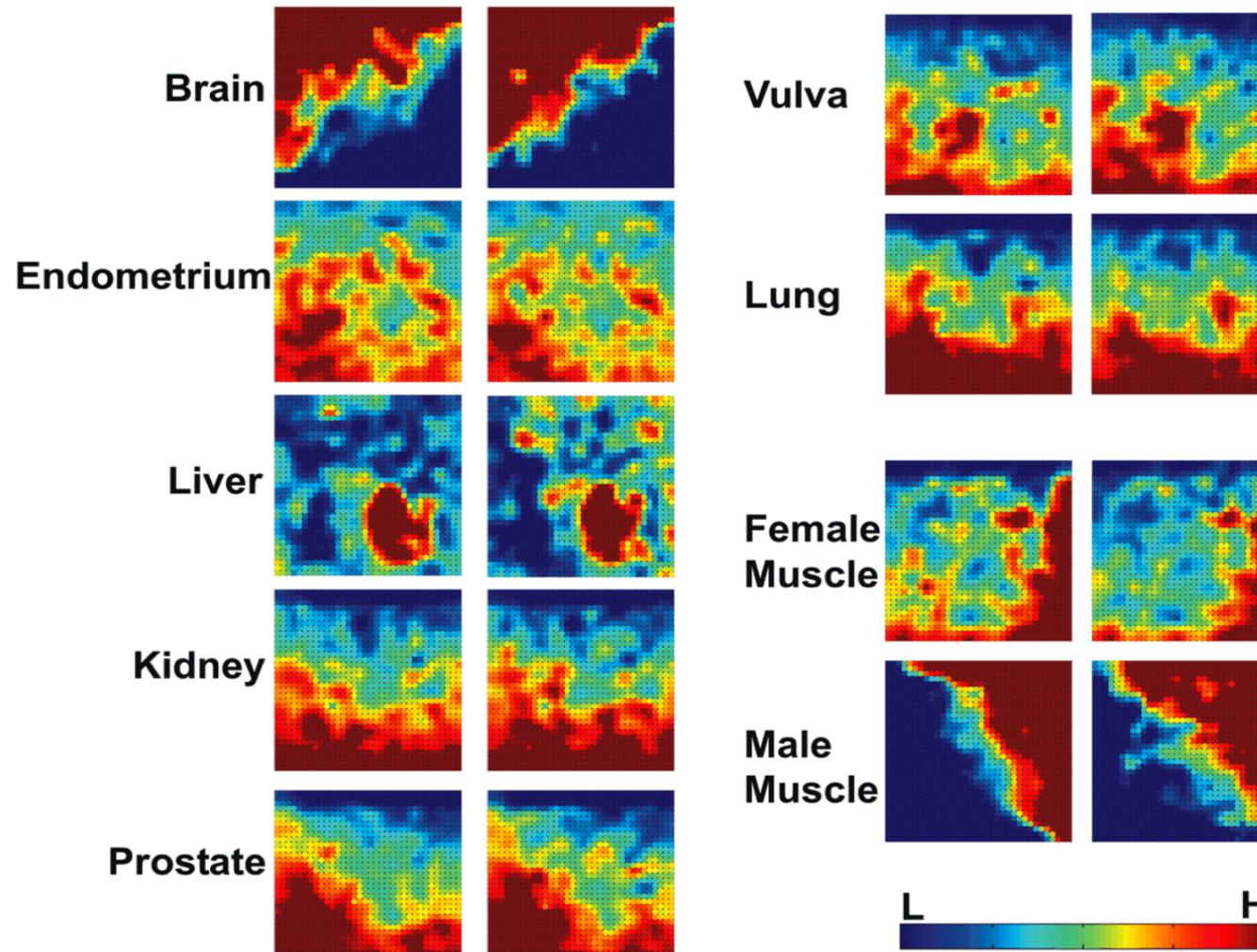
View/Download

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MODULES CAN BE COMPOSED INTO ALTERNATIVE MODELS



GENE EXPRESSION PATTERNS IN TISSUES OF 18 DIFFERENT PERSONS AS SELF-ORGANISING MAPS



This data was published in the paper:

Haverty, PM., Weng, Z., Best, N., Auerbach, K., Hsiao, L., Jensen, R., Gullans, SR. HugeIndex: a database with visualization tools for high-density oligonucleotide array data from normal human tissues. Nucleic Acids Research 30: 214-217, 2002.

Maps taken from: [GEDI-The gene dynamics inspector website](#)

THE GENE EXPRESSION PATTERN DETERMINES THE REACTION RATES IN A PROTEIN NETWORK

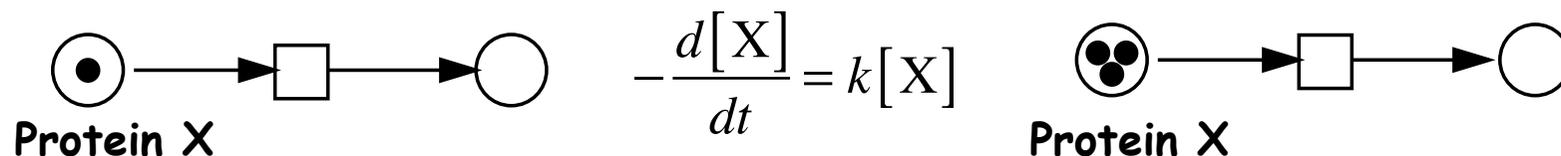
The pattern of genes expressed in a cell usually depends on:

- (1) cell type
- (2) physiological state
- (3) experimental condition
- (4) environmental condition
- (5) individual history of a cell



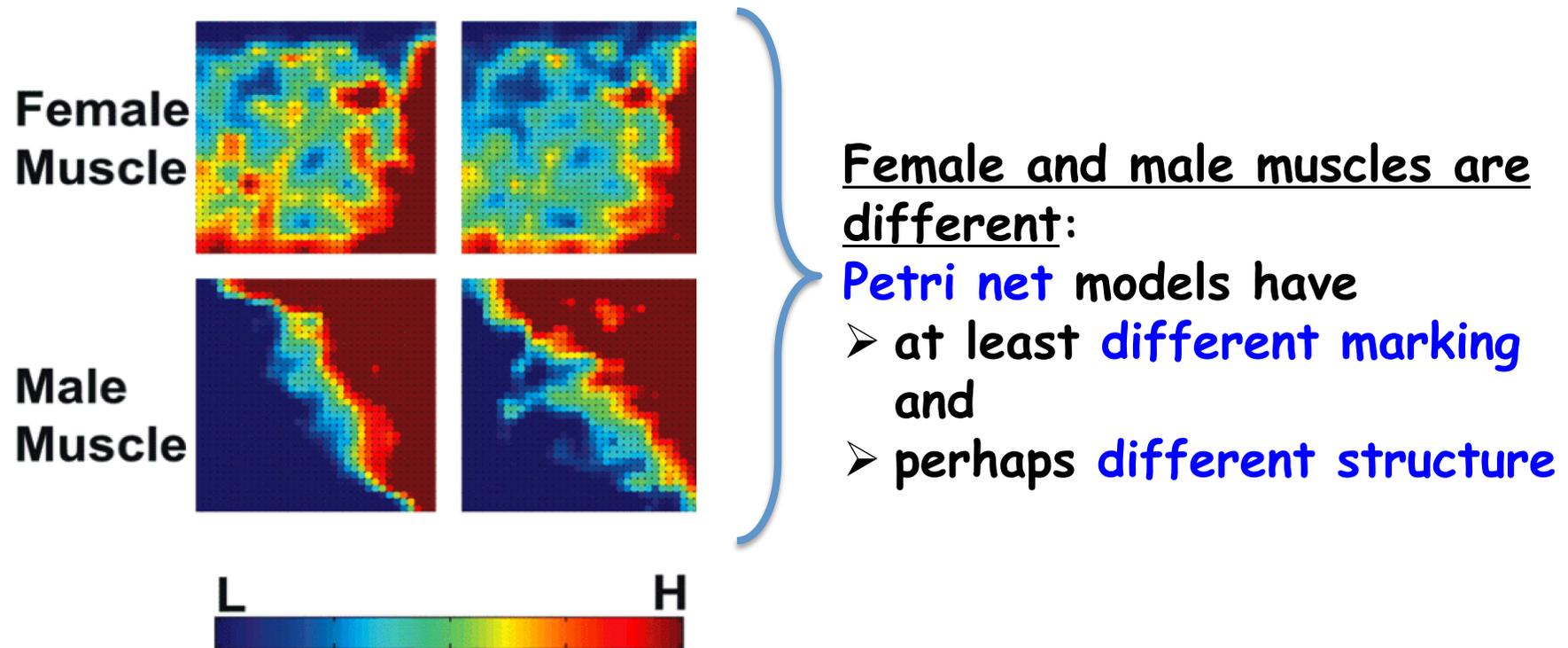
See for example: Schwanhäusser, B. et al. (2011): "Global quantification of mammalian gene expression control." *Nature* 473: 337-342.

The gene expression pattern influences the concentration of the encoded proteins and the reaction rates accordingly:



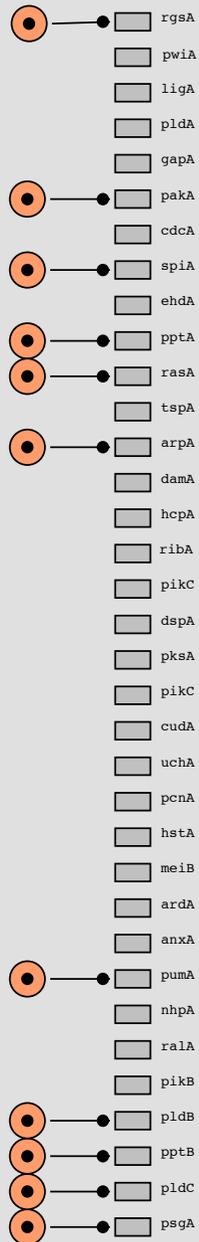
The marking of the PN must be updated when the gene expression pattern has changed.

GENE EXPRESSION PATTERNS IN TISSUES OF 18 DIFFERENT PERSONS AS SELF-ORGANISING MAPS

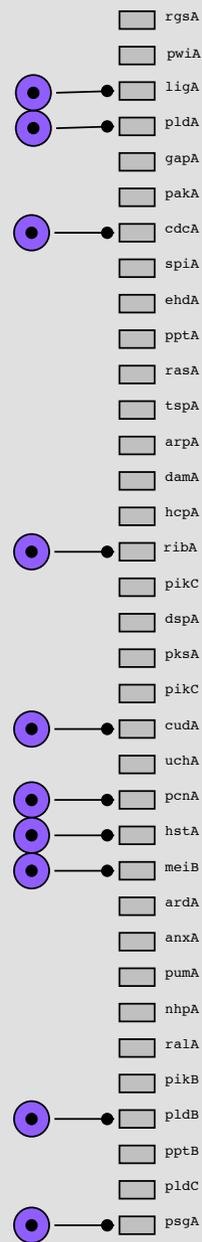


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Mutant 1



Mutant 2

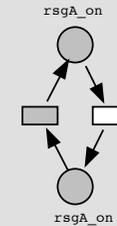


Mutant 3



Work in progress:

Gene expression patterns in cell differentiation mutants



The graphical display of the **gene expression patterns** in mutants gives a family of **executable genotype/phenotype models** based on a collection of modules

MOLECULAR INTERACTIONS

Protein Module

Petri Net

Binding and Unbinding
Reactions

Formation and Cleavage
of Covalent Bonds

Conformational Changes

Documentation &
Searchable Metadata

Protein Degradation Module

Petri Net

Inactivation
& Degradation

Documentation &
Searchable Metadata

CAUSAL DEPENDENCIES

Causal Interaction Module

Petri Net

Causal Influences on
Molecular and Cellular
Processes

Documentation &
Searchable Metadata

Gene Module

Petri Net

Transcriptional Activity

Binding and Unbinding
of Proteins

Covalent Modification

Documentation &
Searchable Metadata

RNA Module

Petri Net

Transcription

Processing of RNA
(Alternative Splicing)

Binding and Unbinding
Reactions

Translation

Degradation

Documentation &
Searchable Metadata

Allelic Influence Module

Petri Net

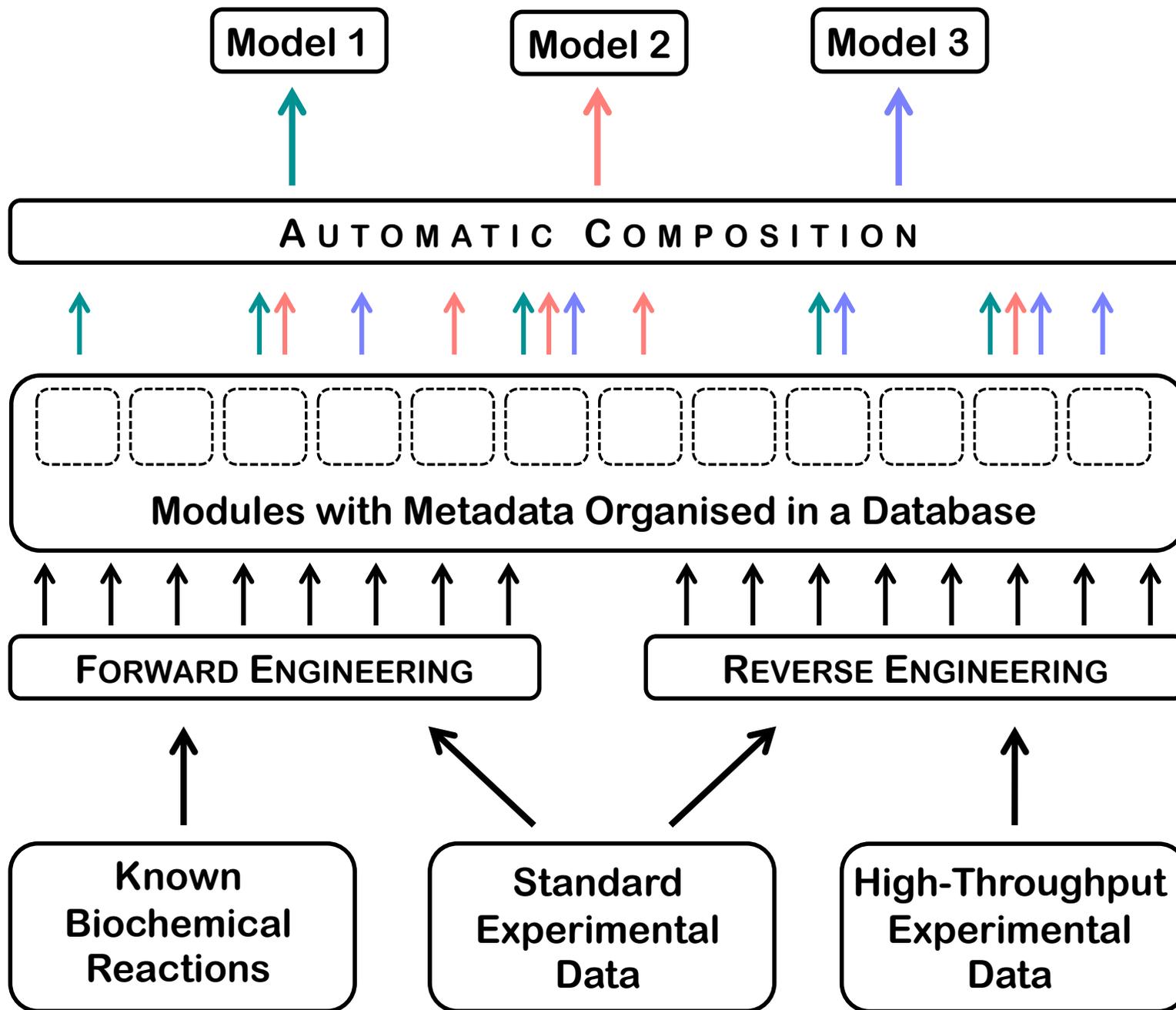
Allelic Influences on
Molecular and Cellular
Processes

Documentation &
Searchable Metadata

DEFINITION OF NEW MODULE PROTOTYPES PROVIDES A COMPREHENSIVE MODELLING FRAMEWORK FOR FORWARD AND REVERSE ENGINEERING

A minimal set of module prototypes supports:

- (1) linking **gene** expression to **protein** concentration
- (2) fully **automated** generation of **models** for **genome-wide** (omics) approaches
- (3) linking **genotype** to **phenotype** through non-obvious mechanisms
- (4) integration of **bottom-up** and **top-down** modules obtained by forward and reverse engineering



MODELLING WITH PETRI NET MODULES

Pain Signal Transduction

Blätke, M. A., Meyer, S., Stein, C. and Marwan, W.:

Petri net modeling via a modular and hierarchical approach applied to nociception.

Proceedings of the International Workshop on Biological Processes & Petri Nets (BioPPN 2010) Braga, Portugal. 131. 2010.

Blätke, M. A., Meyer, S. and Marwan, W.:

Pain Signaling - A Case Study of the Modular Petri Net Modeling Concept with Prospect to a Protein-Oriented Modeling Platform.

Proceedings of the 2nd International Workshop on Biological Processes & Petri Nets (BioPPN2011). Newcastle upon Tyne, United Kingdom, 1-19, 2011.

JAK/STAT Signal Transduction

Blätke, M. A., Dittrich, A., Rohr, C., Heiner, M., Schaper, F. and Marwan, W.:

JAK/STAT signalling - an executable model assembled from molecule-centred modules demonstrating a module-oriented database concept for systems- and synthetic biology.

Submitted 2012. [Preprint on arXiv.](#)

Generalisation through Module **Prototypes**

Blätke, M. A., Heiner, M. and Marwan, W.:

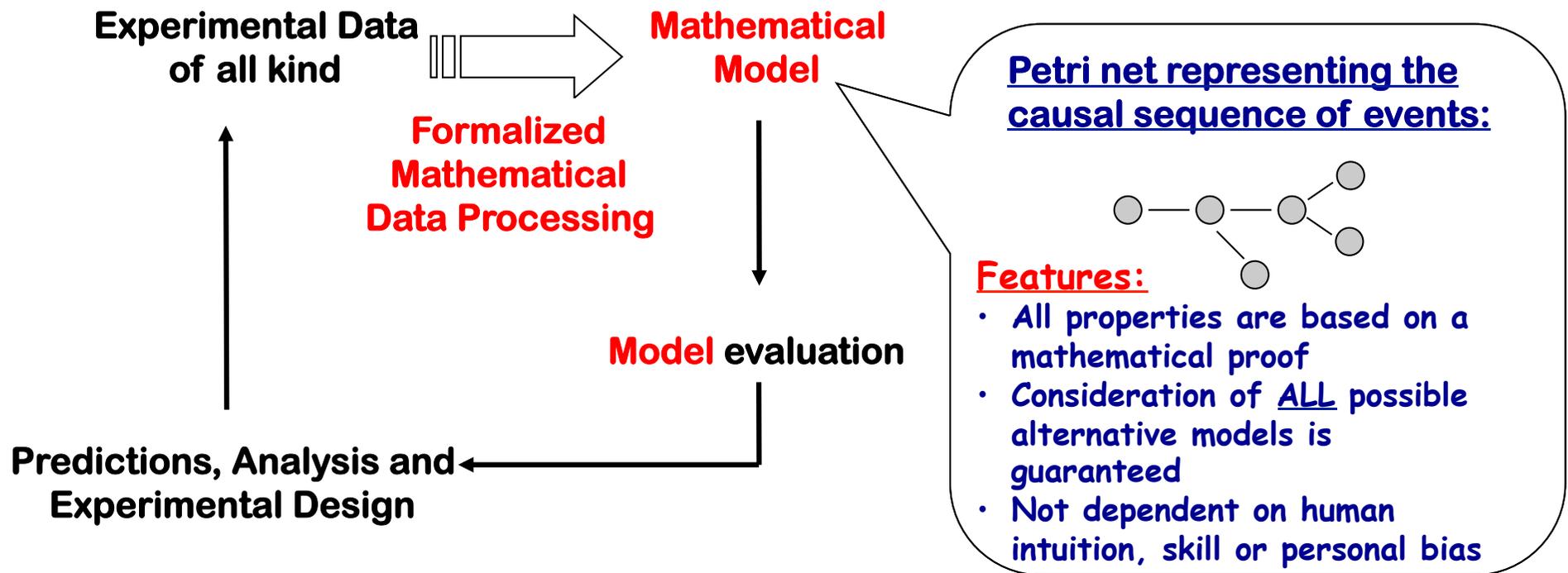
Predicting phenotype from genotype through automatically composed Petri nets.

Submitted 2012. [Preprint on arXiv.](#)

**AUTOMATIC RECONSTRUCTION OF NETWORKS
FROM TIME SERIES DATA SETS**

Molecular Networks:

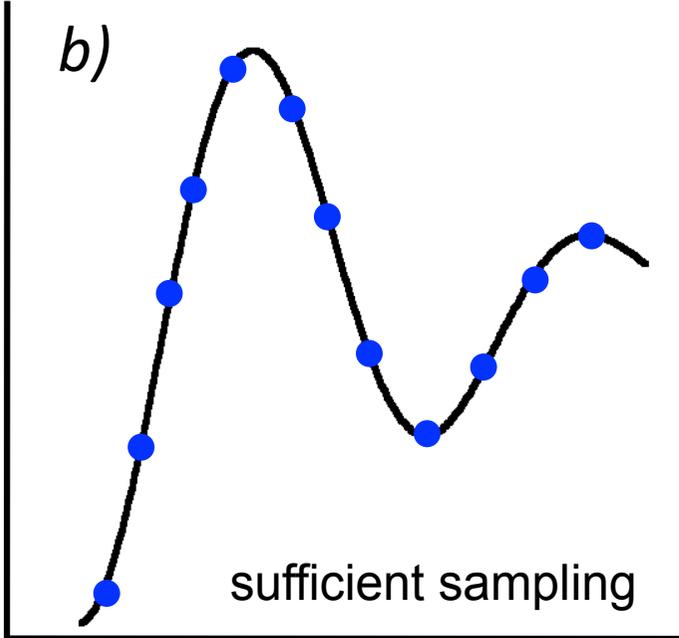
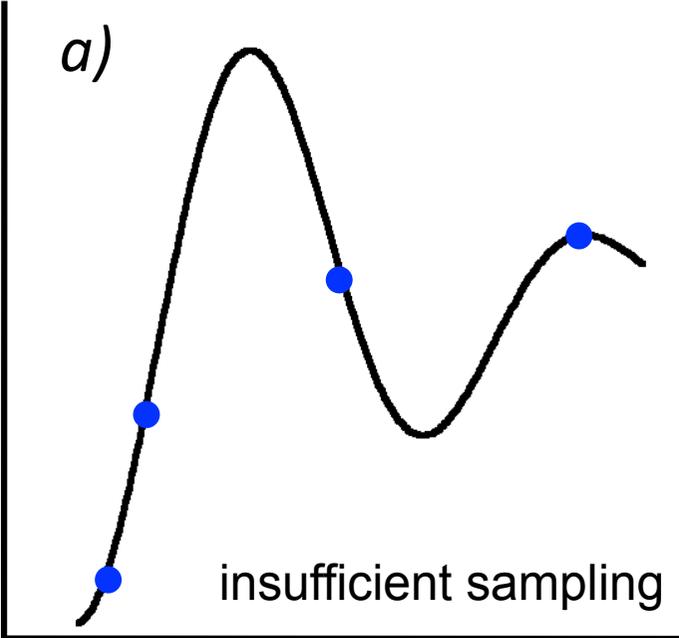
Modeling and Model Validation in the Biosciences **with Mathematics**



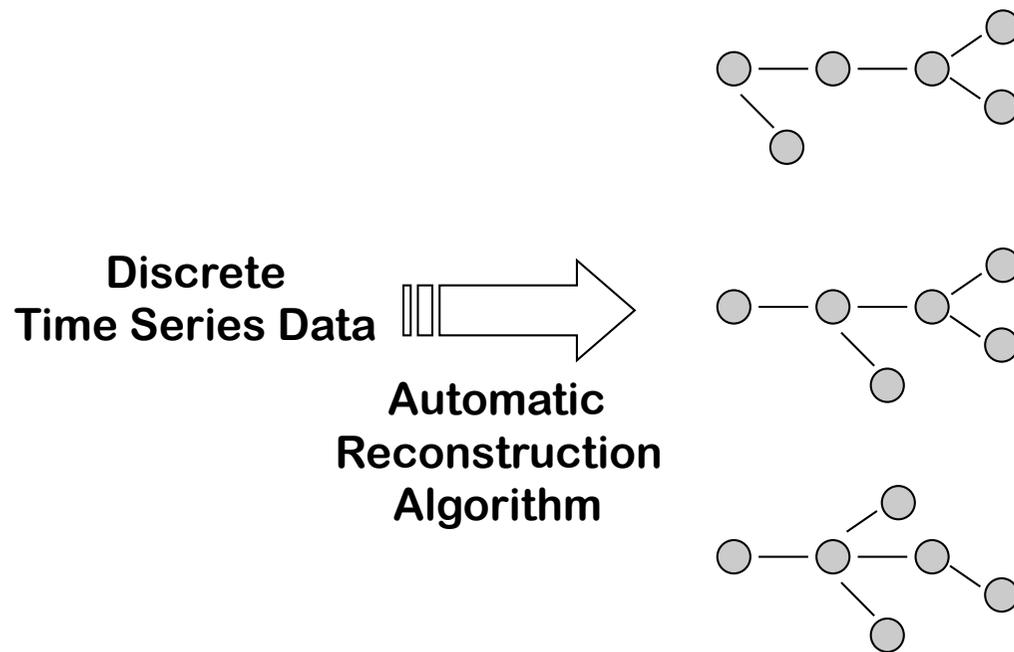
Repeat until the chosen level of resolution is obtained

The final model is based on a mathematical proof.

DATA MUST BE TAKEN WITH SUFFICIENT TIME RESOLUTION



AUTOMATIC NETWORK RECONSTRUCTION – THE PRINCIPLE



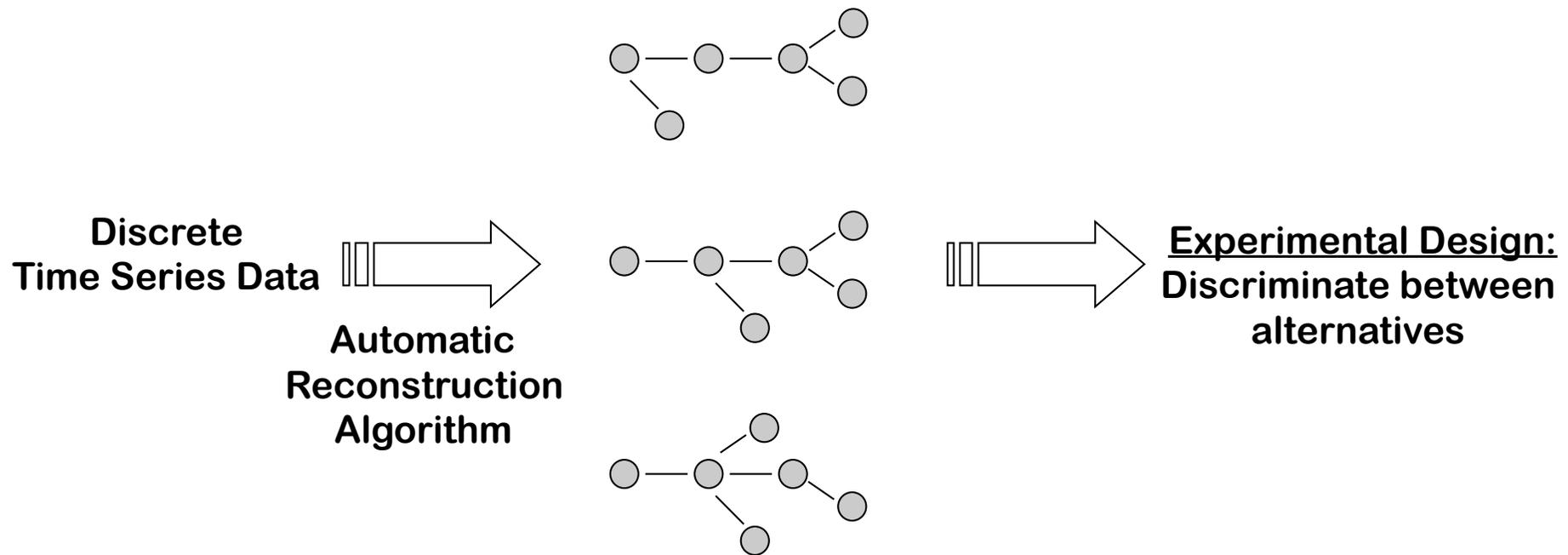
Incidence Matrices of Petri Nets:

- ✓ List of *all* alternative model structures
- ✓ Completeness guaranteed by mathematical proof
- ✓ No heuristics involved

Marwan, W., A. Wagler, and R. Weismantel (2008): *Math. Meth. Oper. Res.* 67, 117-132.

Durzinsky, M., A. Wagler, R. Weismantel, and W. Marwan (2008): *BioSystems* 93, 181-190.

AUTOMATIC NETWORK RECONSTRUCTION – THE PRINCIPLE



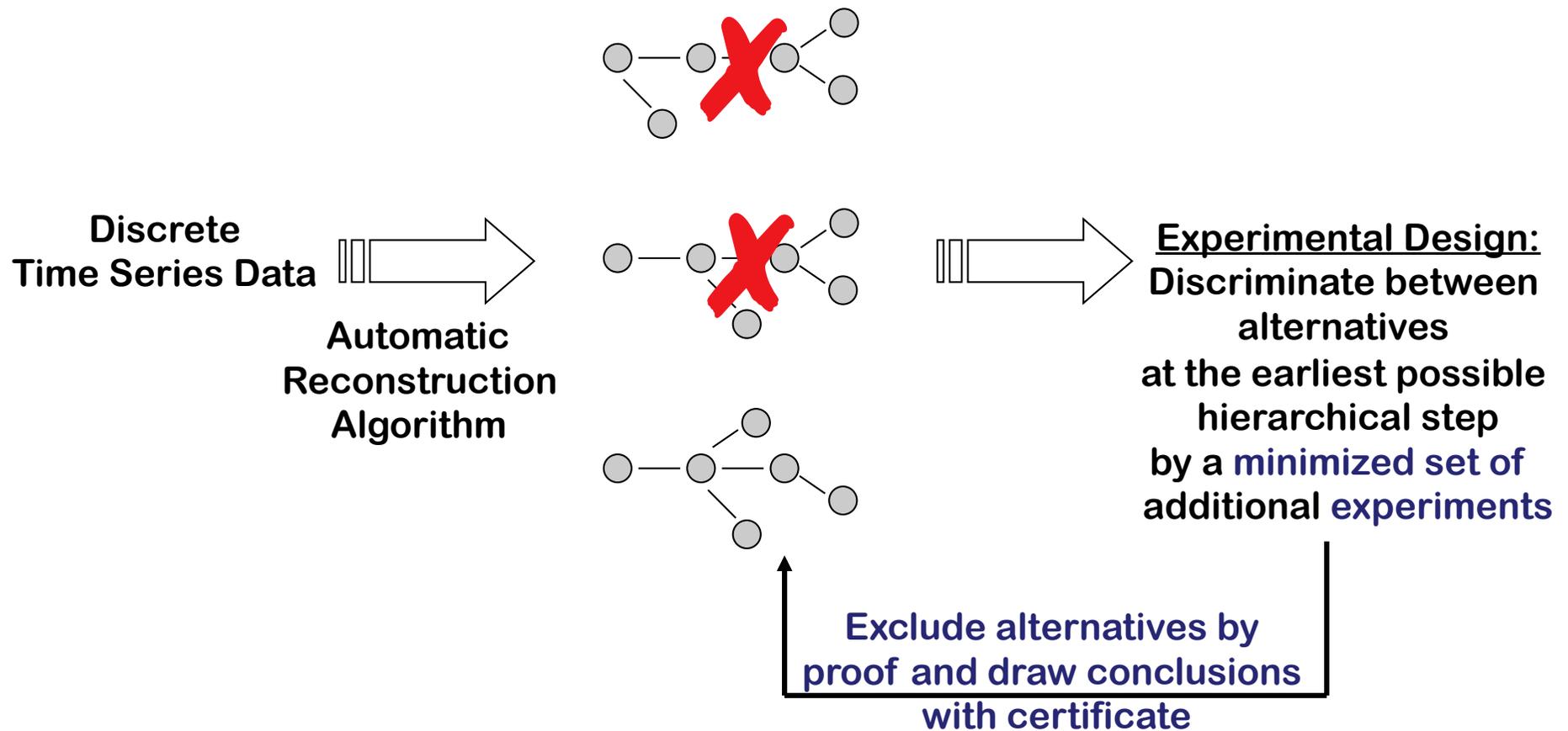
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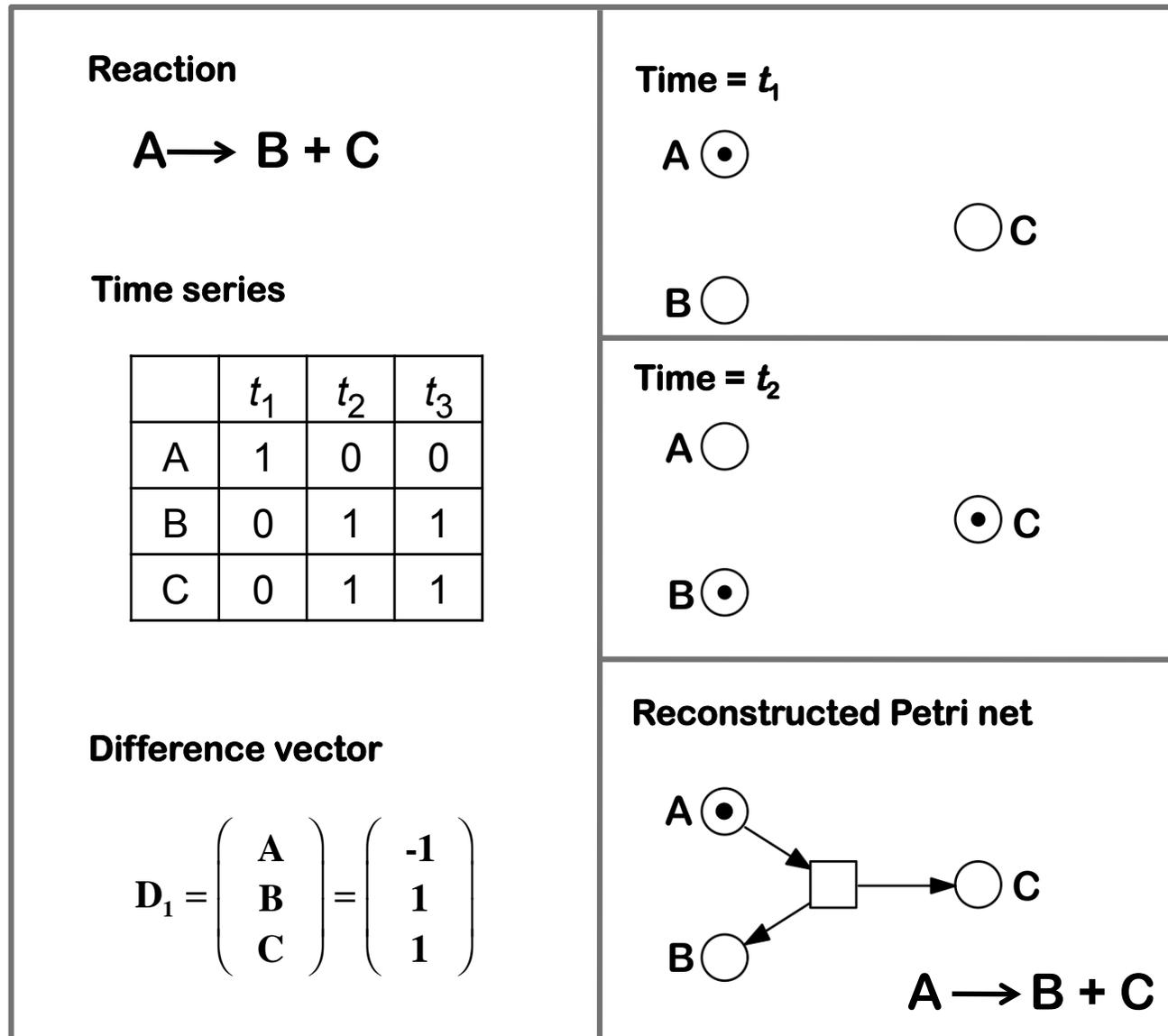
AUTOMATIC NETWORK RECONSTRUCTION – THE PRINCIPLE



Marwan, W., A. Wagler, and R. Weismantel (2008): *Math. Meth. Oper. Res.* 67, 117-132.

Durzinsky, M., A. Wagler, R. Weismantel, and W. Marwan (2008): *BioSystems* 93, 181-190.

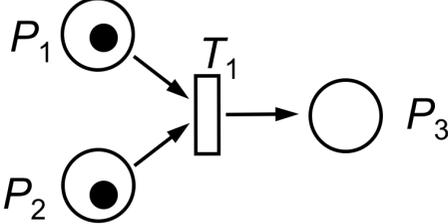
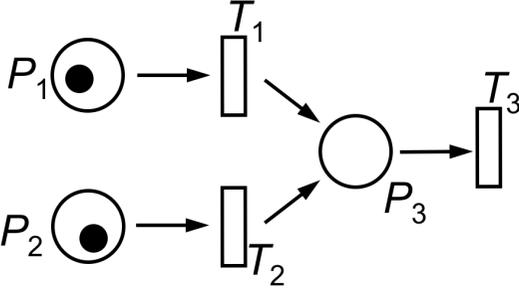
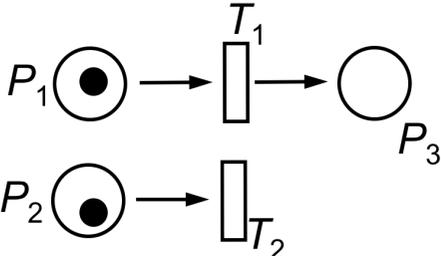
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AUTOMATIC NETWORK RECONSTRUCTION – THE PRINCIPLE

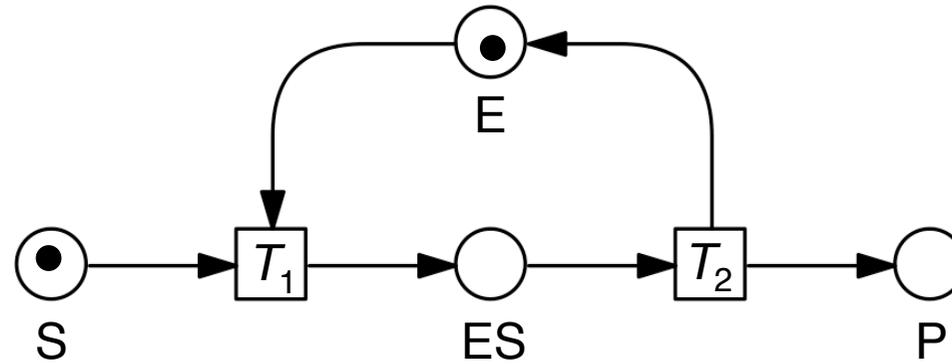
Difference Vector	Incidence Matrix	Petri Net																				
<p>a)</p> $D = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix}$ $D = R_{19}$	<table style="border-collapse: collapse; margin: auto;"> <tr> <td style="border-right: 1px solid black; border-bottom: 1px solid black;"></td> <td style="border-bottom: 1px solid black; text-align: center;">T_1</td> </tr> <tr> <td style="border-right: 1px solid black; text-align: center;">P_1</td> <td style="text-align: center;">-1</td> </tr> <tr> <td style="border-right: 1px solid black; text-align: center;">P_2</td> <td style="text-align: center;">-1</td> </tr> <tr> <td style="border-right: 1px solid black; text-align: center;">P_3</td> <td style="text-align: center;">1</td> </tr> <tr> <td style="border-right: 1px solid black; border-top: 1px solid black;"></td> <td style="border-top: 1px solid black; text-align: center;">R_{19}</td> </tr> </table>		T_1	P_1	-1	P_2	-1	P_3	1		R_{19}											
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P_1	-1	0	0																			
P_2	0	-1	0																			
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P_1	-1	0																				
P_2	0	-1																				
P_3	1	0																				
	R_{22}	R_{11}																				

EXPERIMENTS SUGGESTED BY THE RECONSTRUCTED NETWORKS

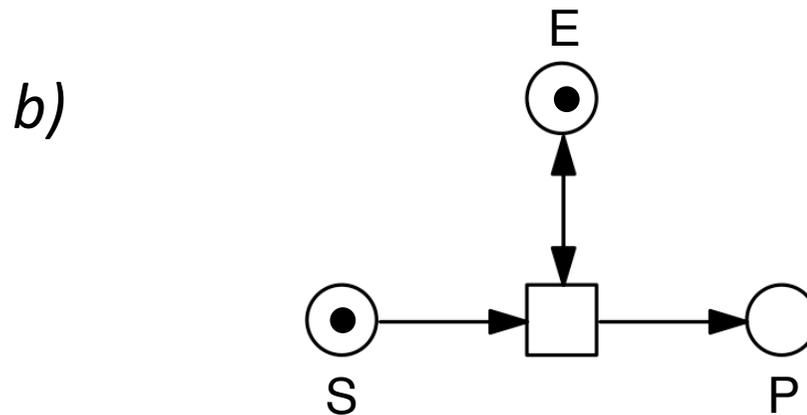
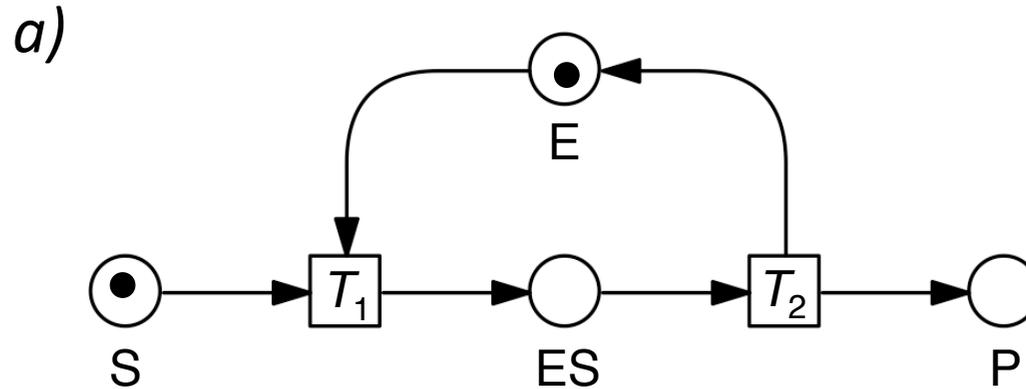
Experiments for Model Discrimination	Petri Net
Does the formation of P_3 need P_1 and P_2 ?	
Is P_3 formed from either P_1 or P_2 ?	
Is P_3 formed from P_1 only?	

CATALYTIC REACTIONS ARE REPRESENTED BY READ ARCS

a)



CATALYTIC REACTIONS ARE REPRESENTED BY READ ARCS



Enzymes and genes are considered as catalysts by the network reconstruction algorithm and modelled with test arcs

**RECONSTRUCTION OF EXTENDED PETRI NETS
AND ITS APPLICATION TO
SIGNAL TRANSDUCTION AND TO GENE
REGULATORY NETWORKS**

ESSENTIAL STEPS IN THE RECONSTRUCTION OF AN EXTENDED PETRI NET

b) States Matrix

	x_0	x_1	x_2	x_3	x_4
A	1	0	0	0	0
B	1	0	1	1	1
C	0	1	0	0	0
D	0	0	1	0	0
E	1	1	1	1	1
F	0	0	0	1	1

c) Difference Vector Matrix

	d_1	d_2	d_3	d_4
	$x_0 \rightarrow x_1$	$x_1 \rightarrow x_2$	$x_2 \rightarrow x_3$	$x_3 \rightarrow x_4$
A	-1	0	0	0
B	-1	1	0	0
C	1	-1	0	0
D	0	1	-1	0
E	0	0	0	0
F	0	0	1	0

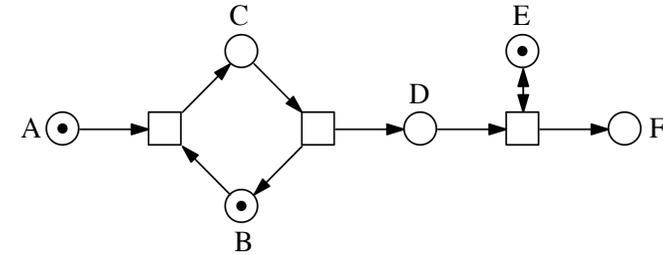
d) Reaction Vector Matrix of d_1

	r_1	r_2	r_3	r_4	r_5	r_6	r_7
A	-1	-1	-1	0	-1	0	0
B	-1	-1	0	-1	0	-1	0
C	1	0	1	1	0	0	1
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0

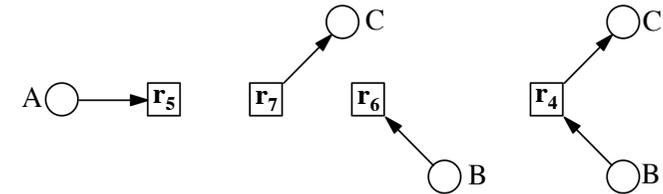
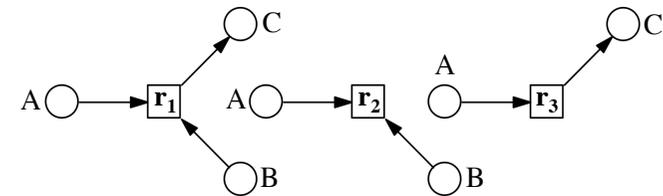
f) Complete Decomposition of d_1 .
Reactions may occur in arbitrary sequence:

- $d_1 = r_1$ (1 Permutation)
- $d_1 = r_2 + r_7$ (2 Permutations)
- $d_1 = r_3 + r_6$ (2 Permutations)
- $d_1 = r_4 + r_5$ (2 Permutations)
- $d_1 = r_5 + r_6 + r_7$ (6 Permutations)

a) Given Petri Net



e) Reaction Vector d_1 may be composed using the following reactions:



g) 1st Permutation (r_1, r_2):

$$\begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \quad \begin{pmatrix} 1 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \end{pmatrix} + \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \end{pmatrix}$$

Try all reactions with all terminal states:

r_i	x_0	x_4	
A	1	0	$f_i = A$
B	1	1	r_4 ← ● A
C	0	0	
D	0	0	
E	1	1	r_4 ← ○ F
F	0	1	$f_i = NOT F$
f_i	1	0	

2nd Permutation (r_3, r_4):

$$\begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} + \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \quad \begin{pmatrix} 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \end{pmatrix}$$

r_i	y_2	x_4	
A	0	0	
B	1	1	
C	0	0	
D	0	0	
E	1	1	r_4 ← ○ F
F	0	1	$f_i = NOT F$
f_i	1	0	

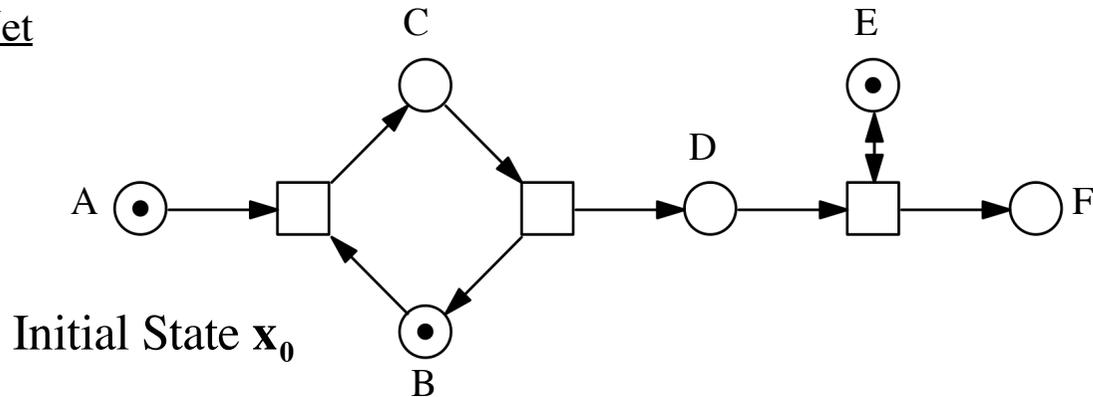
Exclude all reactions r suggested to be on and off with state vectors identical with a terminal state, i.e. at $(x_n \vee y_m) = x_r$, respectively.

Durzinsky, M., et al.:

[BMC Systems Biology 5, 113, 2011.](#)

TIME SERIES DATA OBTAINED FROM A TOY PETRI NET

a) Given Petri Net



b) States Matrix

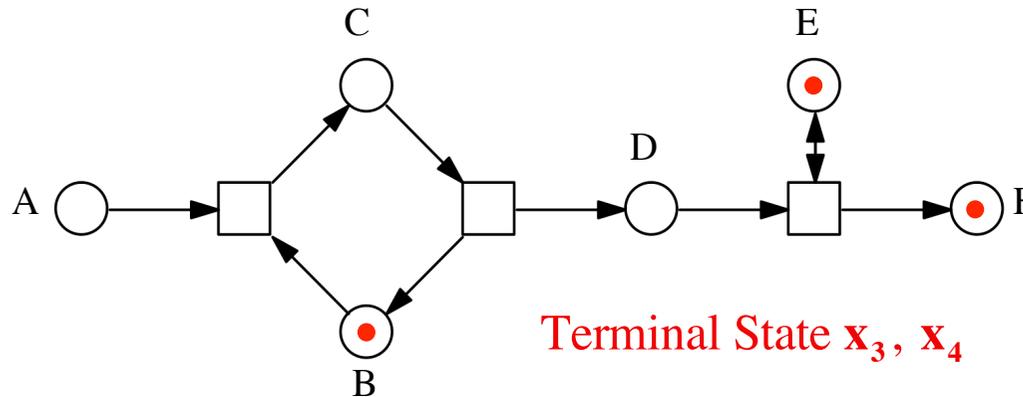
	x_0	x_1	x_2	x_3	x_4
A	1	0	0	0	0
B	1	0	1	1	1
C	0	1	0	0	0
D	0	0	1	0	0
E	1	1	1	1	1
F	0	0	0	1	1

c) Difference Vector Matrix

	d_1	d_2	d_3	d_4
	$x_0 \rightarrow x_1$	$x_1 \rightarrow x_2$	$x_2 \rightarrow x_3$	$x_3 \rightarrow x_4$
A	-1	0	0	0
B	-1	1	0	0
C	1	-1	0	0
D	0	1	-1	0
E	0	0	0	0
F	0	0	1	0

TIME SERIES DATA OBTAINED FROM A TOY PETRI NET

a) Given Petri Net



b) States Matrix

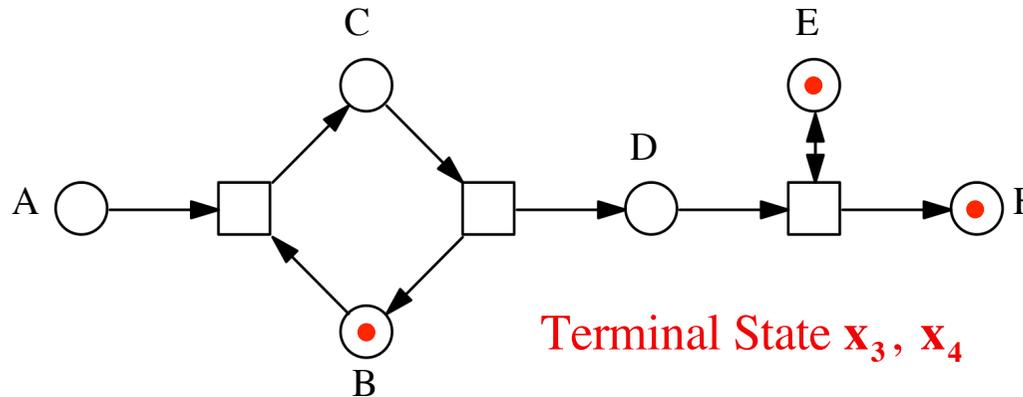
	x_0	x_1	x_2	x_3	x_4
A	1	0	0	0	0
B	1	0	1	1	1
C	0	1	0	0	0
D	0	0	1	0	0
E	1	1	1	1	1
F	0	0	0	1	1

c) Difference Vector Matrix

	d_1	d_2	d_3	d_4
	$x_0 \rightarrow x_1$	$x_1 \rightarrow x_2$	$x_2 \rightarrow x_3$	$x_3 \rightarrow x_4$
A	-1	0	0	0
B	-1	1	0	0
C	1	-1	0	0
D	0	1	-1	0
E	0	0	0	0
F	0	0	1	0

TIME SERIES DATA OBTAINED FROM A TOY PETRI NET

a) Given Petri Net



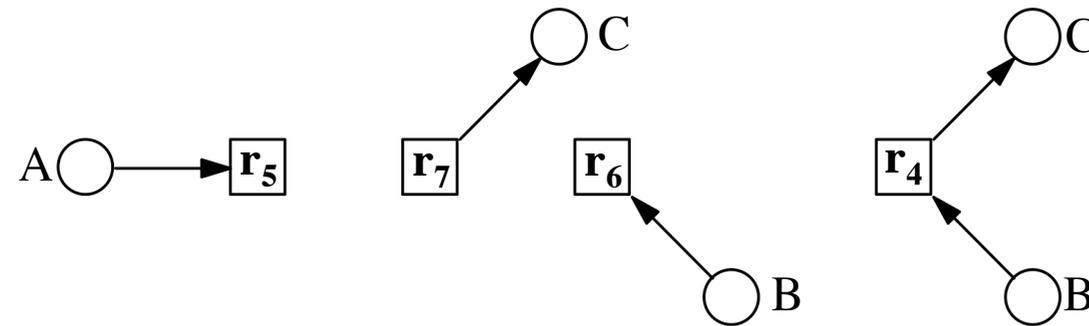
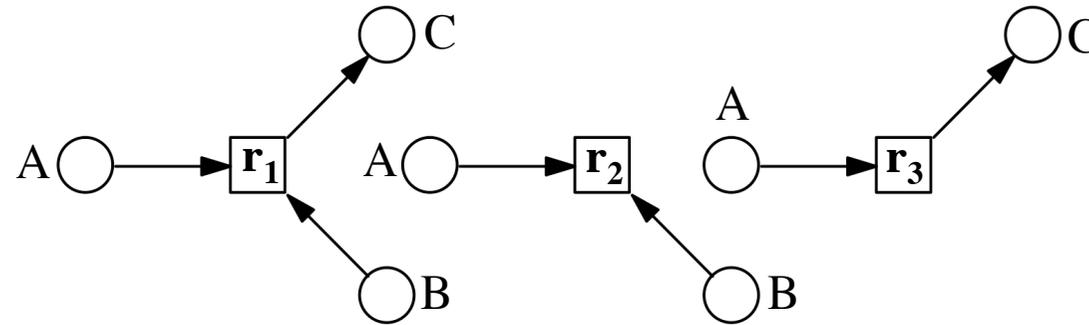
b) States Matrix

	x_0	x_1	x_2	x_3	x_4
A	1	0	0	0	0
B	1	0	1	1	1
C	0	1	0	0	0
D	0	0	1	0	0
E	1	1	1	1	1
F	0	0	0	1	1

c) Difference Vector Matrix

	d_1	d_2	d_3	d_4
	$x_0 \rightarrow x_1$	$x_1 \rightarrow x_2$	$x_2 \rightarrow x_3$	$x_3 \rightarrow x_4$
A	-1	0	0	0
B	-1	1	0	0
C	1	-1	0	0
D	0	1	-1	0
E	0	0	0	0
F	0	0	1	0

Difference Vector \mathbf{d}_1 may be composed using the following reactions:



Difference Vector \mathbf{d}_1

	\mathbf{d}_1
	$\mathbf{x}_0 \rightarrow \mathbf{x}_1$
A	-1
B	-1
C	1
D	0
E	0
F	0

Reaction Vector Matrix of \mathbf{d}_1

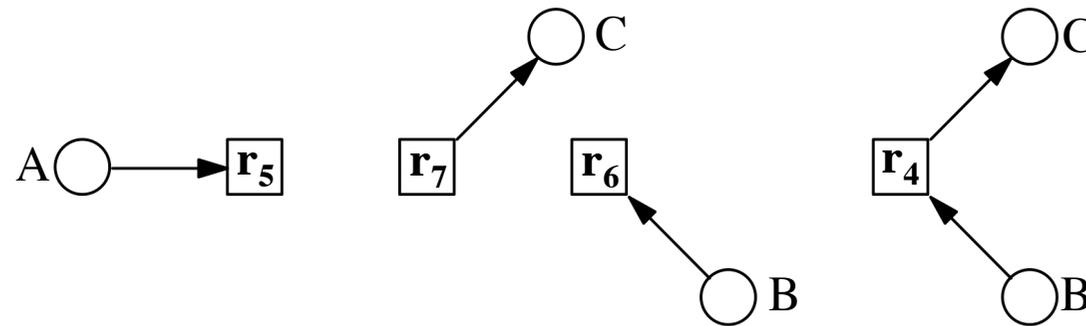
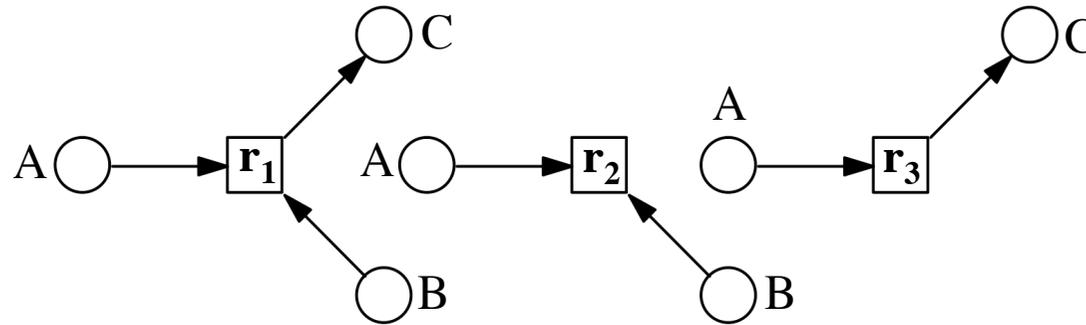
	\mathbf{r}_1	\mathbf{r}_2	\mathbf{r}_3	\mathbf{r}_4	\mathbf{r}_5	\mathbf{r}_6	\mathbf{r}_7
A	-1	-1	-1	0	-1	0	0
B	-1	-1	0	-1	0	-1	0
C	1	0	1	1	0	0	1
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0

Complete Decomposition of \mathbf{d}_1

Reactions may occur in arbitrary sequence:

- $\mathbf{d}_1 = \mathbf{r}_1$ (1 Permutation)
- $\mathbf{d}_1 = \mathbf{r}_2 + \mathbf{r}_7$ (2 Permutations)
- $\mathbf{d}_1 = \mathbf{r}_3 + \mathbf{r}_6$ (2 Permutations)
- $\mathbf{d}_1 = \mathbf{r}_4 + \mathbf{r}_5$ (2 Permutations)
- $\mathbf{d}_1 = \mathbf{r}_5 + \mathbf{r}_6 + \mathbf{r}_7$ (6 Permutations)

Difference Vector \mathbf{d}_1 may be composed using the following reactions:



Difference Vector \mathbf{d}_1

	\mathbf{d}_1
	$\mathbf{x}_0 \rightarrow \mathbf{x}_1$
A	-1
B	-1
C	1
D	0
E	0
F	0

Reaction Vector Matrix of \mathbf{d}_1

	\mathbf{r}_1	\mathbf{r}_2	\mathbf{r}_3	\mathbf{r}_4	\mathbf{r}_5	\mathbf{r}_6	\mathbf{r}_7
A	-1	-1	-1	0	-1	0	0
B	-1	-1	0	-1	0	-1	0
C	1	0	1	1	0	0	1
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0

Complete Decomposition of \mathbf{d}_1

Reactions may occur in arbitrary sequence:

$\mathbf{d}_1 = \mathbf{r}_1$ (1 Permutation)

$\mathbf{d}_1 = \mathbf{r}_2 + \mathbf{r}_7$ (2 Permutations)

$\mathbf{d}_1 = \mathbf{r}_3 + \mathbf{r}_6$ (2 Permutations)

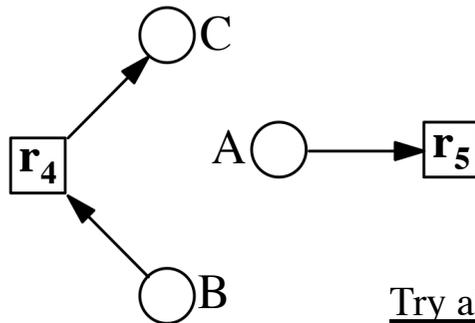
$\mathbf{d}_1 = \mathbf{r}_4 + \mathbf{r}_5$ (2 Permutations)

$\mathbf{d}_1 = \mathbf{r}_5 + \mathbf{r}_6 + \mathbf{r}_7$ (6 Permutations)

IDENTIFY REACTIONS POTENTIALLY CONTROLLED BY TEST ARCS

Decomposition of d_1

2 Permutations:
 $d_1 = r_4 + r_5$
 $d_1 = r_5 + r_4$



y_1 and y_2 are potential intermediate states
 not represented in the reaction vector matrix

1st Permutation (r_4, r_5):

$$\begin{matrix} x_0 & + & r_4 & = & y_1; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix}
 \quad ; \quad
 \begin{matrix} y_1 & + & r_5 & = & x_1 \\ \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}
 \end{matrix}$$

If (r_4, r_5) is chosen:

r_4 is applied at $x_0 \Rightarrow f_4(x_0) = 1$

r_5 is applied at $y_1 \Rightarrow f_5(y_1) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

\Rightarrow done by a token in A or no token in F

r_4	x_0	x_4	
A	1	0	$f_4 = A$
B	1	1	
C	0	0	
D	0	0	
E	1	1	
F	0	1	$f_4 = \text{NOT F}$
f_4	1	0	

2nd Permutation (r_5, r_4):

$$\begin{matrix} x_0 & + & r_5 & = & y_2; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix}
 \quad ; \quad
 \begin{matrix} y_2 & + & r_4 & = & x_1 \\ \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}
 \end{matrix}$$

If (r_5, r_4) is chosen:

r_4 is applied at $y_2 \Rightarrow f_4(y_2) = 1$

r_5 is applied at $x_0 \Rightarrow f_5(x_0) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

\Rightarrow done by no token in F

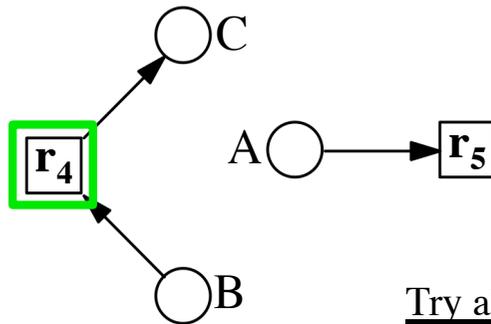
r_4	y_2	x_4	
A	0	0	
B	1	1	
C	0	0	
D	0	0	
E	1	1	
F	0	1	$f_4 = \text{NOT F}$
f_4	1	0	

Exclude all reactions r suggested to be on *and* off with state vectors identical with a terminal state, i.e. at $(x_n \vee y_m) = x_T$, respectively.

IDENTIFY REACTIONS POTENTIALLY CONTROLLED BY TEST ARCS

Decomposition of d_1

2 Permutations:
 $d_1 = r_4 + r_5$
 $d_1 = r_5 + r_4$



y_1 and y_2 are potential intermediate states
 not represented in the reaction vector matrix

1st Permutation (r_4, r_5):

$$\begin{matrix} x_0 & + & r_4 & = & y_1; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix} \quad ; \quad \begin{matrix} y_1 & + & r_5 & = & x_1 \\ \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} \end{matrix}$$

If (r_4, r_5) is chosen:

r_4 is applied at $x_0 \Rightarrow f_4(x_0) = 1$

r_5 is applied at $y_1 \Rightarrow f_5(y_1) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

\Rightarrow done by a token in A or no token in F

r_4	x_0	x_4	
A	1	0	$f_4 = A$
B	1	1	
C	0	0	
D	0	0	
E	1	1	
F	0	1	$f_4 = \text{NOT F}$
f_4	1	0	

2nd Permutation (r_5, r_4):

$$\begin{matrix} x_0 & + & r_5 & = & y_2; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix} \quad ; \quad \begin{matrix} y_2 & + & r_4 & = & x_1 \\ \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} \end{matrix}$$

If (r_5, r_4) is chosen:

r_4 is applied at $y_2 \Rightarrow f_4(y_2) = 1$

r_5 is applied at $x_0 \Rightarrow f_5(x_0) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

\Rightarrow done by no token in F

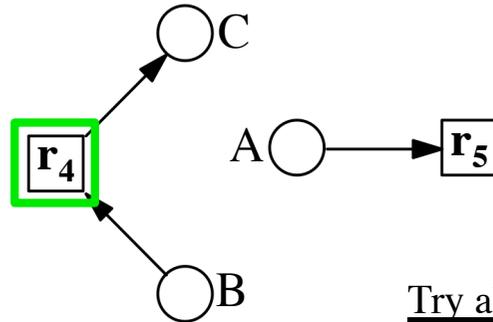
r_4	y_2	x_4	
A	0	0	
B	1	1	
C	0	0	$f_4 = \text{NOT F}$
D	0	0	
E	1	1	
F	0	1	
f_4	1	0	

Exclude all reactions r suggested to be on *and* off with state vectors identical with a terminal state, i.e. at $(x_n \vee y_m) = x_T$, respectively.

IDENTIFY REACTIONS POTENTIALLY CONTROLLED BY TEST ARCS

Decomposition of d_1

2 Permutations:
 $d_1 = r_4 + r_5$
 $d_1 = r_5 + r_4$



y_1 and y_2 are potential intermediate states
 not represented in the reaction vector matrix

1st Permutation (r_4, r_5):

$$\begin{matrix} x_0 & + & r_4 & = & y_1; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix}
 \quad ; \quad
 \begin{matrix} y_1 & + & r_5 & = & x_1 \\ \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}
 \end{matrix}$$

If (r_4, r_5) is chosen:

r_4 is applied at $x_0 \Rightarrow f_4(x_0) = 1$

r_5 is applied at $y_1 \Rightarrow f_5(y_1) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

\Rightarrow done by a token in A or no token in F

r_4	x_0	x_4	
A	1	0	$f_4 = A$
B	1	1	r_4 ↔ A
C	0	0	
D	0	0	
E	1	1	r_4 ↔ F
F	0	1	$f_4 = \text{NOT F}$
f_4	1	0	

2nd Permutation (r_5, r_4):

$$\begin{matrix} x_0 & + & r_5 & = & y_2; \\ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}; \\ \end{matrix}
 \quad ; \quad
 \begin{matrix} y_2 & + & r_4 & = & x_1 \\ \begin{pmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{pmatrix} & + & \begin{pmatrix} 0 \\ 0 \\ 1 \\ -1 \\ 0 \\ 0 \end{pmatrix} & = & \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}
 \end{matrix}$$

If (r_5, r_4) is chosen:

r_4 is applied at $y_2 \Rightarrow f_4(y_2) = 1$

r_5 is applied at $x_0 \Rightarrow f_5(x_0) = 1$

r_4 is applicable at terminal state x_4

$\Rightarrow r_4$ must be disabled $\Rightarrow f_4(x_4) = 0$

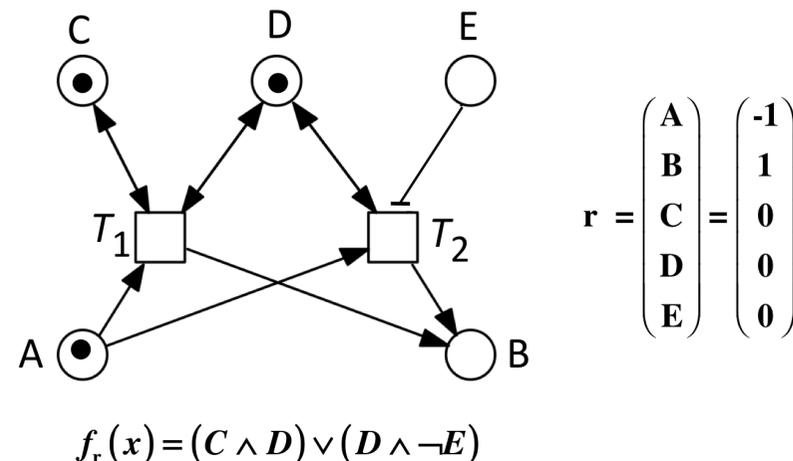
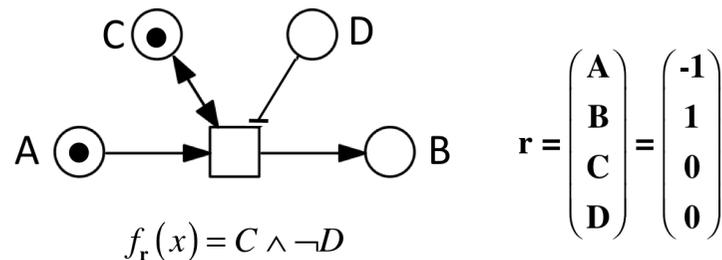
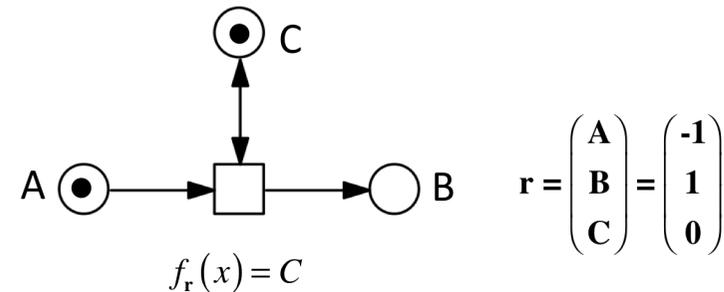
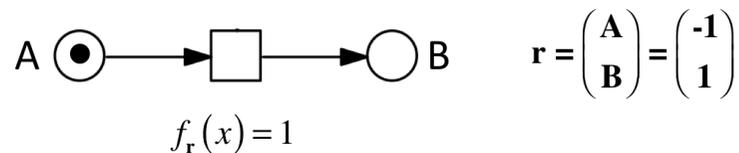
\Rightarrow done by no token in F

r_4	y_2	x_4	
A	0	0	
B	1	1	
C	0	0	
D	0	0	
E	1	1	r_4 ↔ F
F	0	1	$f_4 = \text{NOT F}$
f_4	1	0	

Exclude all reactions r suggested to be on *and* off with state vectors identical with a terminal state, i.e. at $(x_n \vee y_m) = x_T$, respectively.

CONTROL FUNCTIONS REPRESENT REGULATORY INTERACTIONS

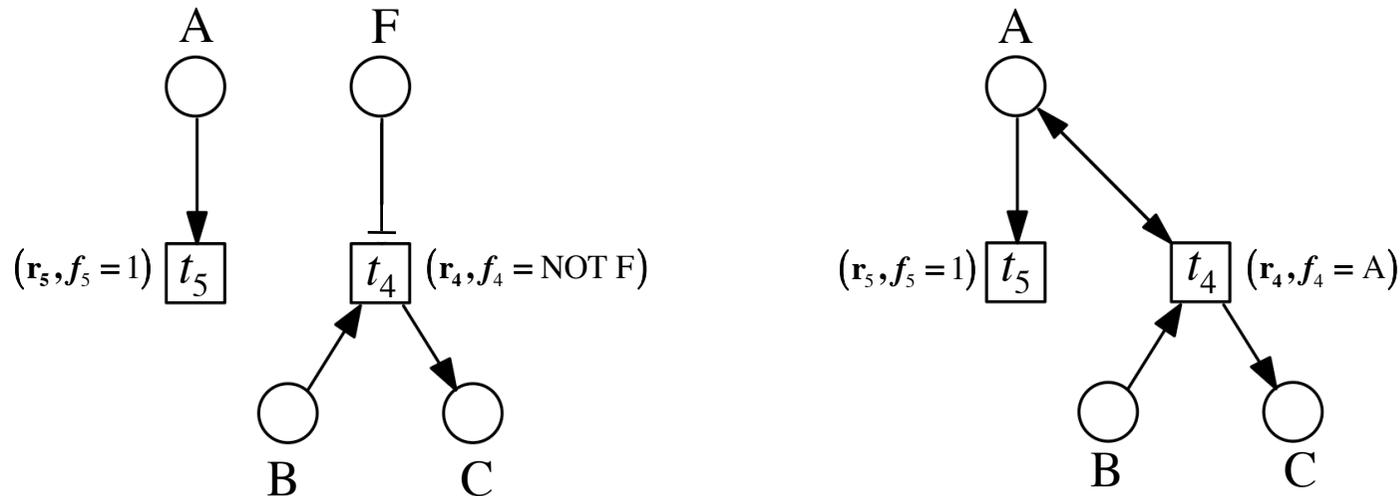
Introduction of control functions allows the reconstruction of sophisticated regulatory mechanisms



- Petri Nets with control arcs
- The transitions are encoded by controlled reactions (r, f_r)

SETS OF CONTROLLED REACTIONS DEFINE ALTERNATIVE PETRI NET STRUCTURES

Each Controlled Reaction (\mathbf{r}, f_r) Gives a Transition in the Reconstructed Petri Net:



Controlled Reactions (\mathbf{r}, f_r) :

1st Permutation $(\mathbf{r}_5, \mathbf{r}_4)$:
 $(\mathbf{r}_5, f_5 = 1), (\mathbf{r}_4, f_4 = \text{NOT } F)$

2nd Permutation $(\mathbf{r}_4, \mathbf{r}_5)$:
 $(\mathbf{r}_4, f_4 = \text{NOT } F), (\mathbf{r}_5, f_5 = 1)$

or

$(\mathbf{r}_4, f_4 = A), (\mathbf{r}_5, f_5 = 1)$
 without Permutations

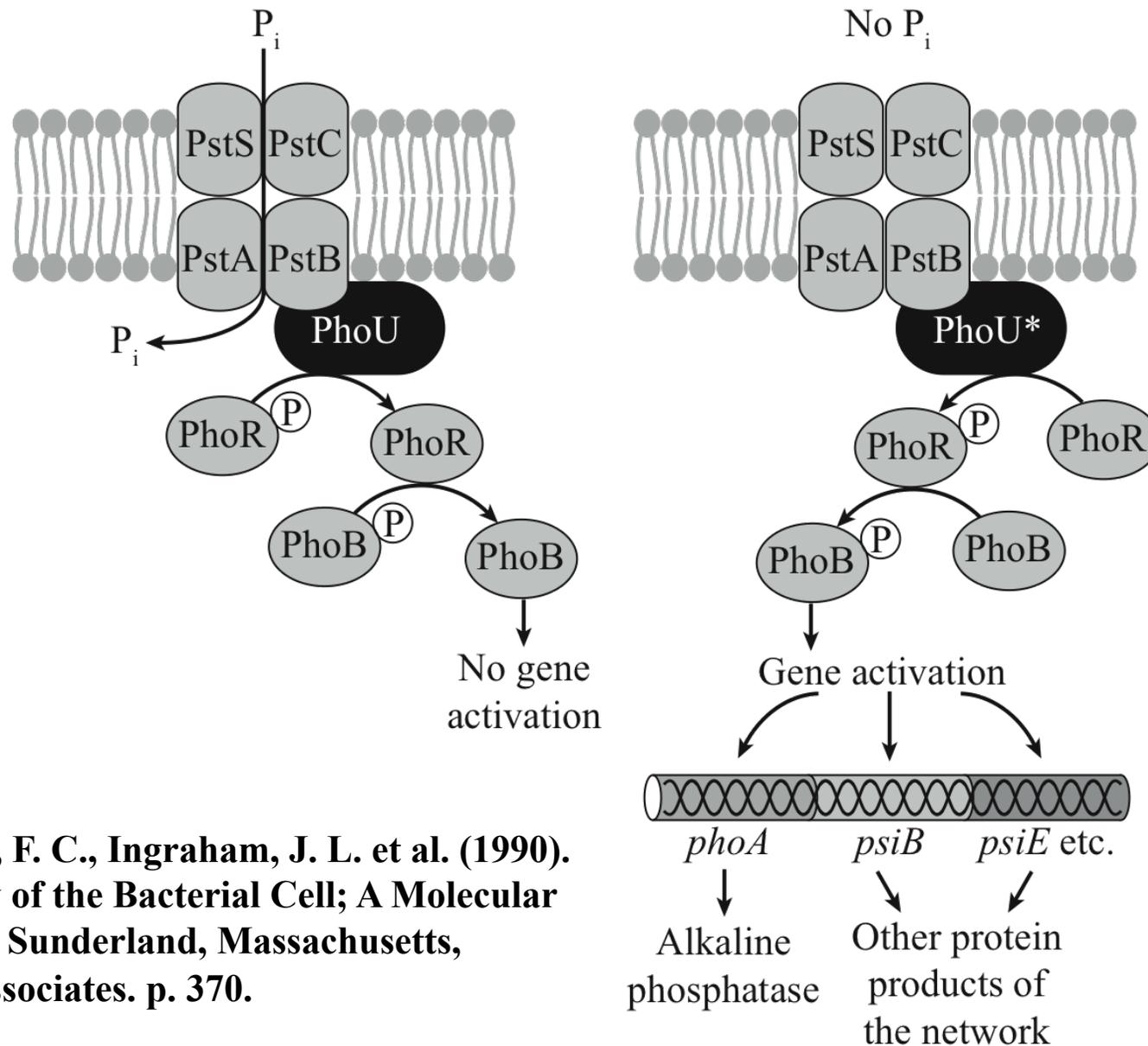
COMPOSING A FUNCTIONAL PETRI NET FROM THE COMPLETE LIST OF CONTROLLED REACTIONS

Complete list of possible controlled reactions (\mathbf{r}, f_r) for each of the subsequent difference vectors \mathbf{d}_i :

\mathbf{d}_1	\mathbf{d}_2	\mathbf{d}_3	\mathbf{d}_4
(\mathbf{r}_1, f_1)
$(\mathbf{r}_2, f_2), (\mathbf{r}_7, f_7)$
$(\mathbf{r}_7, f_7), (\mathbf{r}_2, f_2)$
$(\mathbf{r}_3, f_3), (\mathbf{r}_6, f_6)$
$(\mathbf{r}_6, f_6), (\mathbf{r}_3, f_3)$
$(\mathbf{r}_4, f_4), (\mathbf{r}_5, f_5)$
$(\mathbf{r}_5, f_5), (\mathbf{r}_4, f_4)$
.....
.....

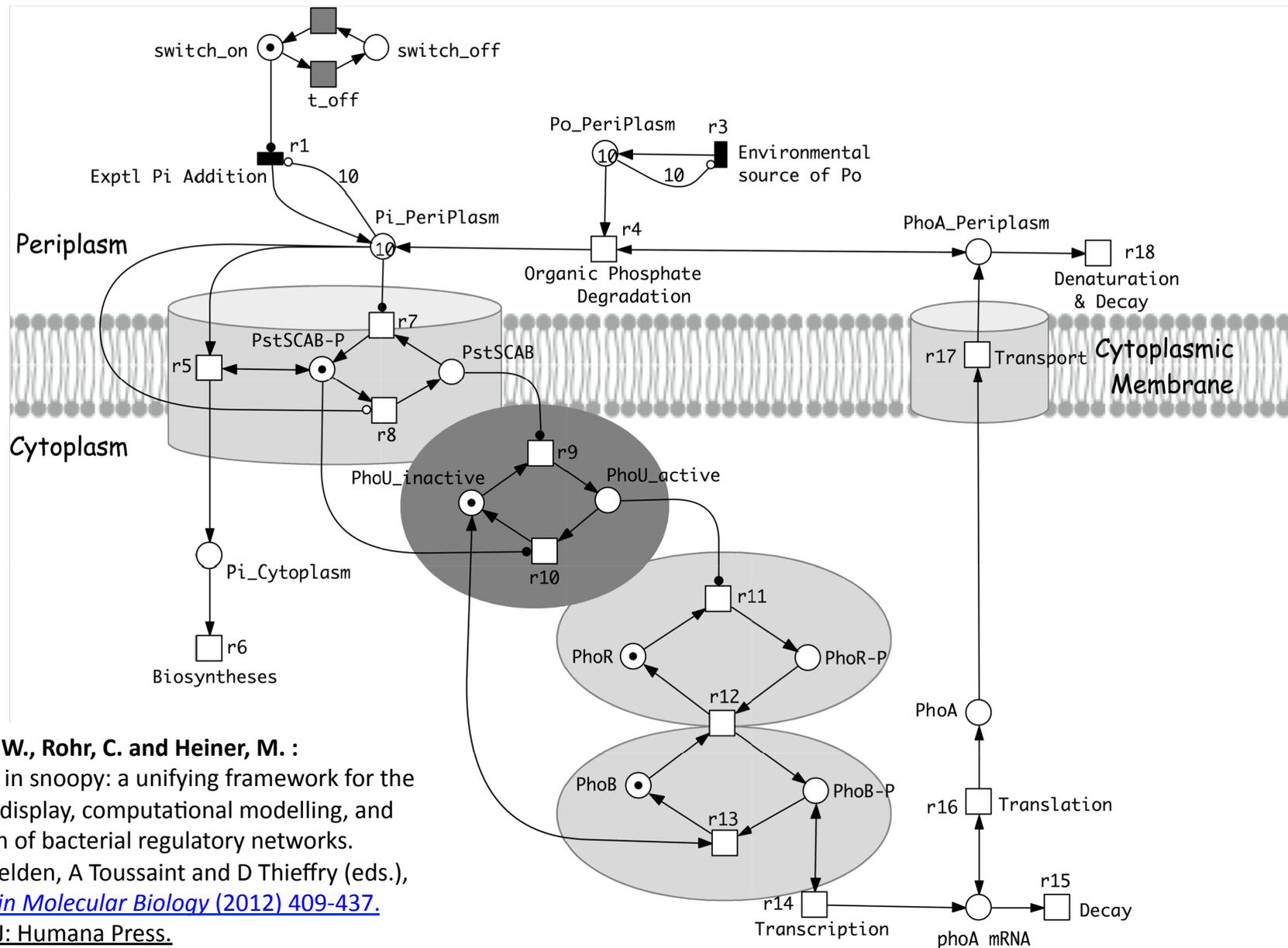
Any arbitrary sequence of controlled reactions obtained by taking one difference vector from each of the subsequent columns gives one functional extended Petri net which is compatible with the time series data set that originally served as input

Phosphate Regulation in Enteric Bacteria



Neidhardt, F. C., Ingraham, J. L. et al. (1990). **Physiology of the Bacterial Cell; A Molecular Approach.** Sunderland, Massachusetts, Sinauer Associates. p. 370.

Petri Net Model of Phosphate Regulation

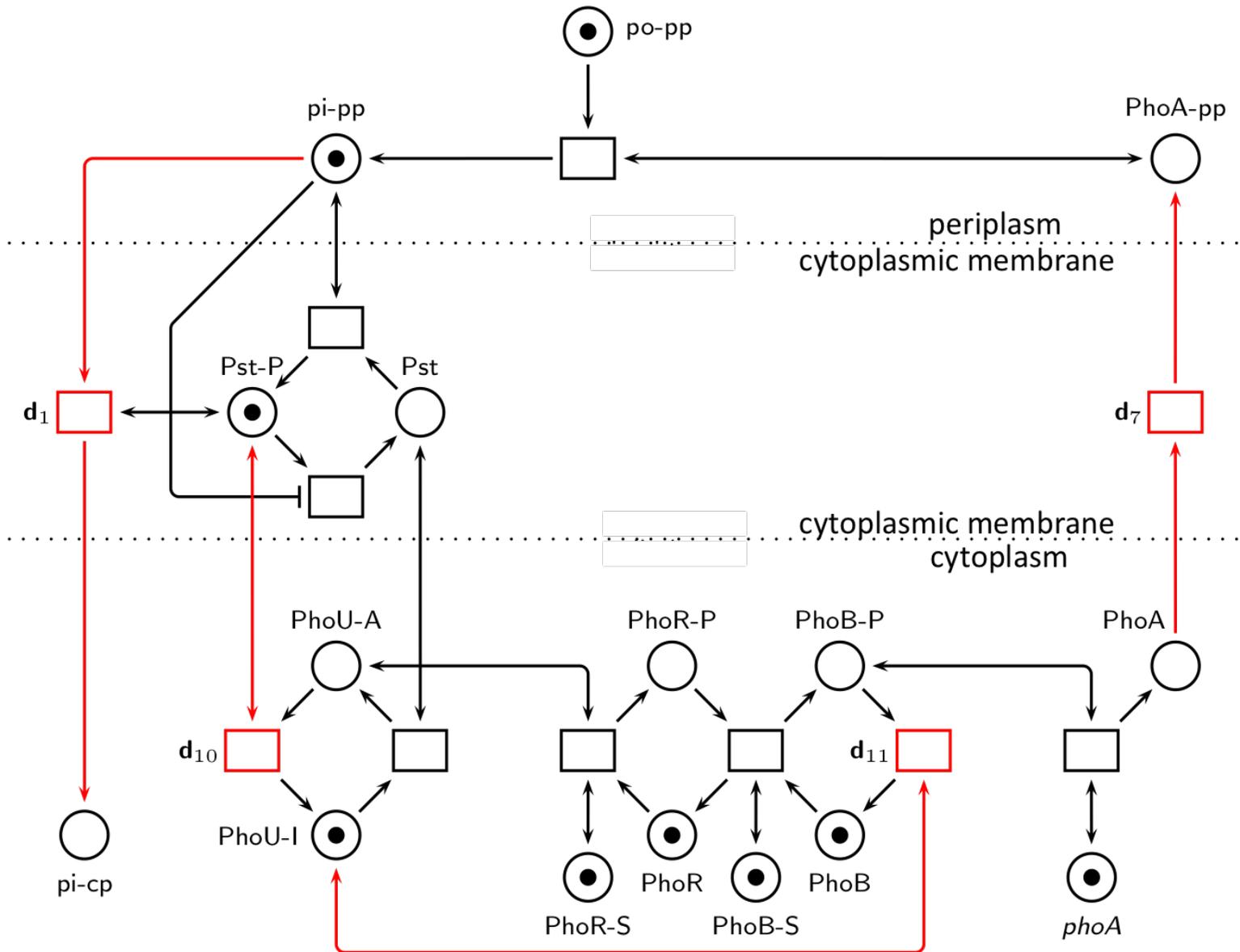


Marwan, W., Rohr, C. and Heiner, M. :
 Petri nets in snoopy: a unifying framework for the graphical display, computational modelling, and simulation of bacterial regulatory networks.
 In J van Helden, A Toussaint and D Thiéffry (eds.),
[Methods in Molecular Biology \(2012\) 409-437.](#)
 Clifton, NJ: Humana Press.

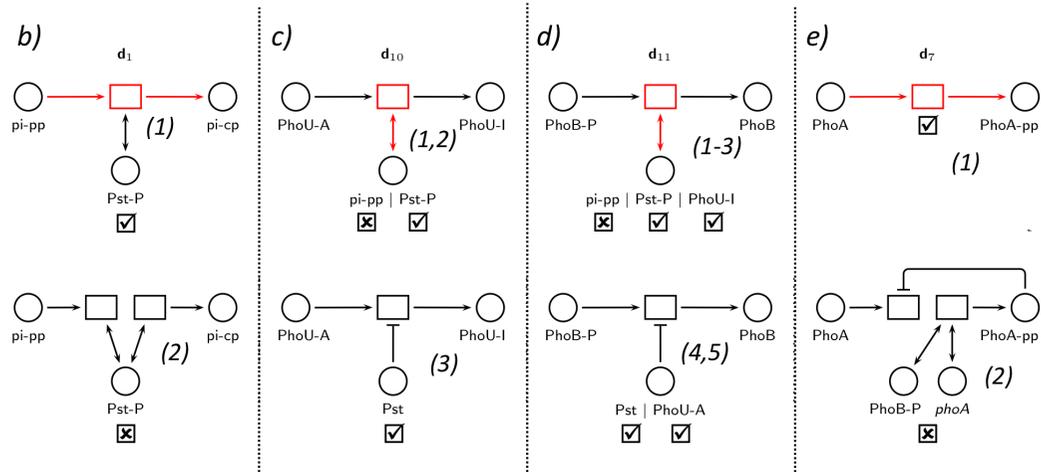
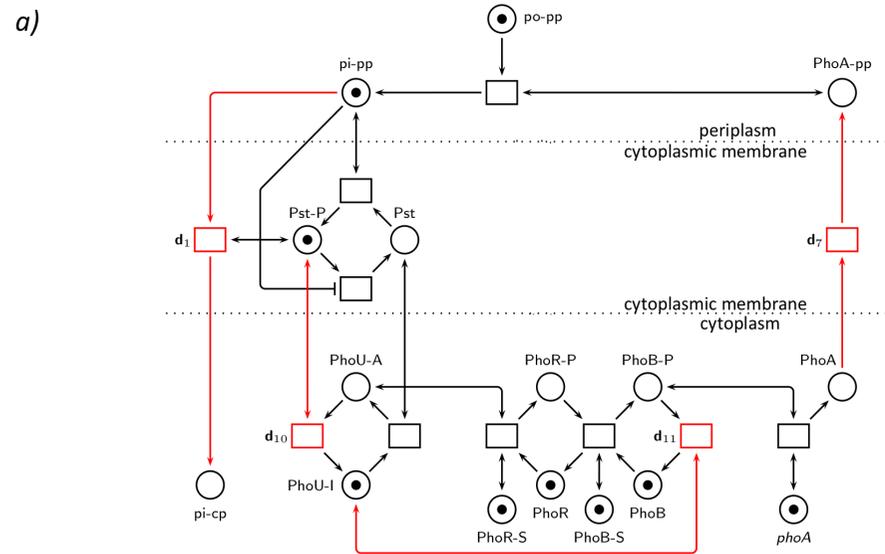
in silico Mutants and Phenotypes

Experiment	Genetic background	Experimental perturbation	Petri net implementation
Exp #1	Wild-type	Switch off inorganic phosphate	Petri net as shown in Figure 8
Exp #2	Wild-type	Switch off organic phosphate	Petri net as shown in Figure 8
Exp #3	Wild-type	Inhibition of transcription / translation	no token in Pool place
Exp #4	$\Delta pstSCAB$	Absence of inorganic phosphate	no tokens in places Pst-P, Pst, pi_pp
Exp #5	$\Delta pstSCAB$	Presence of inorganic phosphate	no token in places Pst-P, Pst
Exp #6	$\Delta phoU$	Switch off inorganic phosphate	no token in places PhoU-A, PhoU-I
Exp #7	$\Delta phoR$	Switch off inorganic phosphate	no token in places PhoR, PhoR-P
Exp #8	$\Delta phoB$	Switch off inorganic phosphate	no token in places PhoB, PhoB-P
Exp #9	<i>phoR</i> Δ Psite	Switch off inorganic phosphate	no token in place PhoR-S
Exp #10	<i>phoB</i> Δ Psite	Switch off inorganic phosphate	no token in place PhoB-S

Reconstructed Petri Net

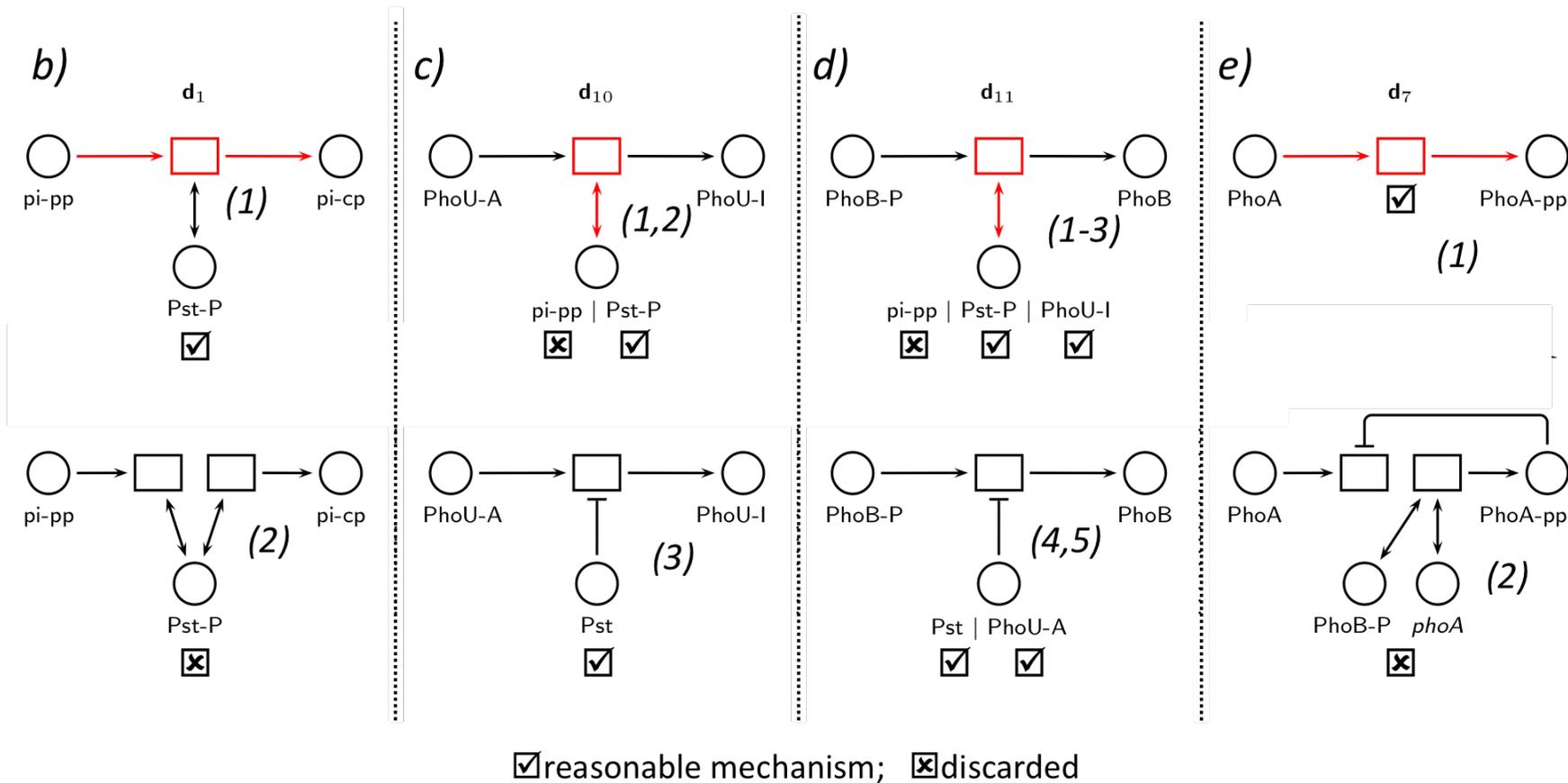


Reconstructed Petri Net



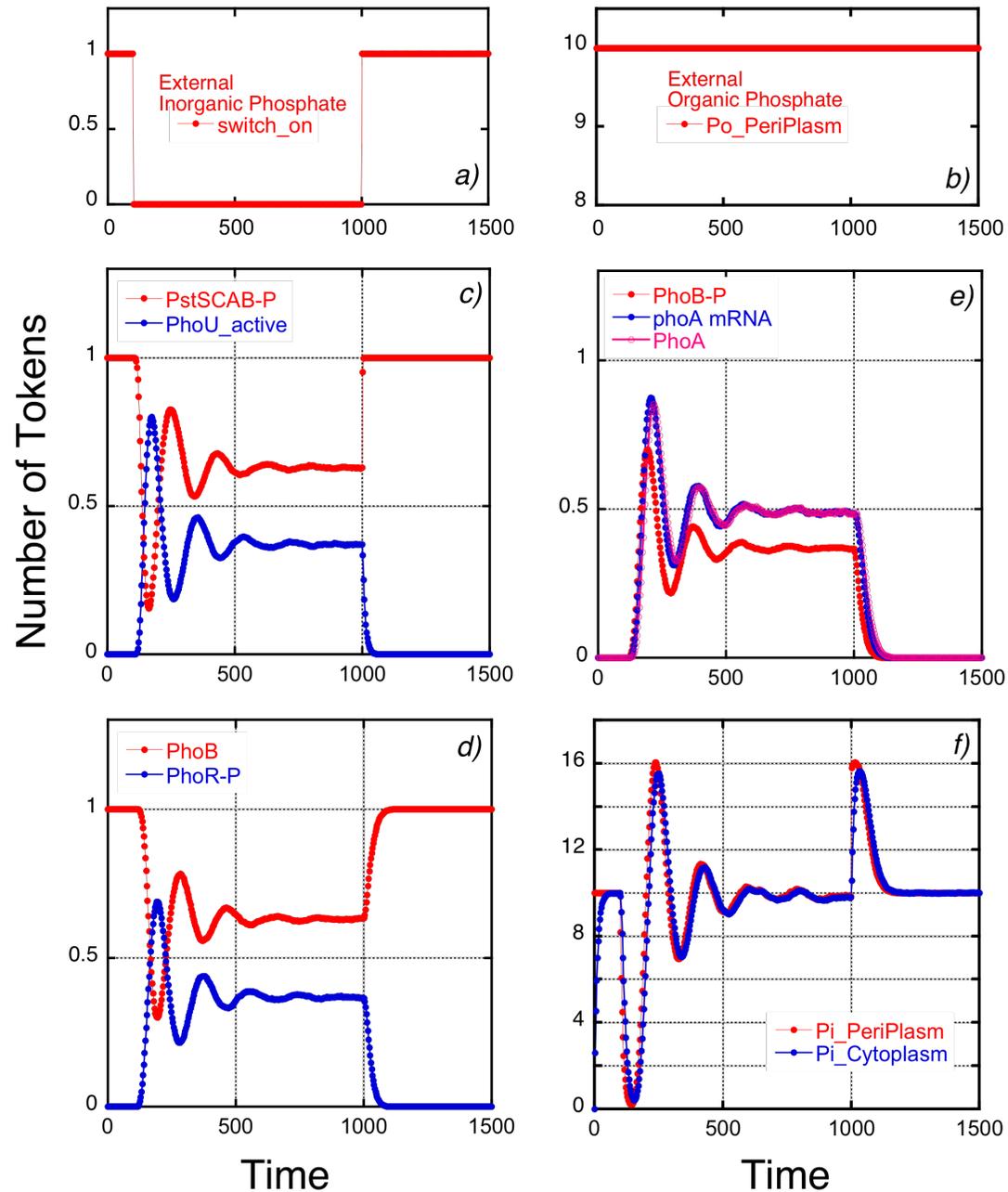
☑ reasonable mechanism; ☒ discarded

Reconstructed Petri Net: Alternative Reactions



- Alternatives:**
- may be redundant
 - may suggest biologically reasonable mechanisms

RECONSTRUCTED PETRI NET – KINETIC SIMULATION



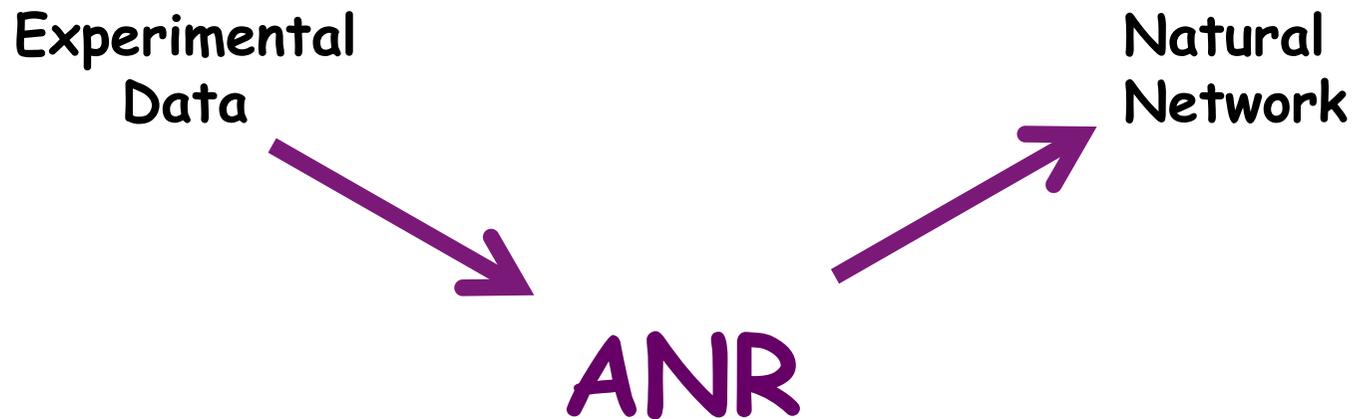
Marwan, W., Rohr, C. and Heiner, M. :

Petri nets in snoopy: a unifying framework for the graphical display, computational modelling, and simulation of bacterial regulatory networks.

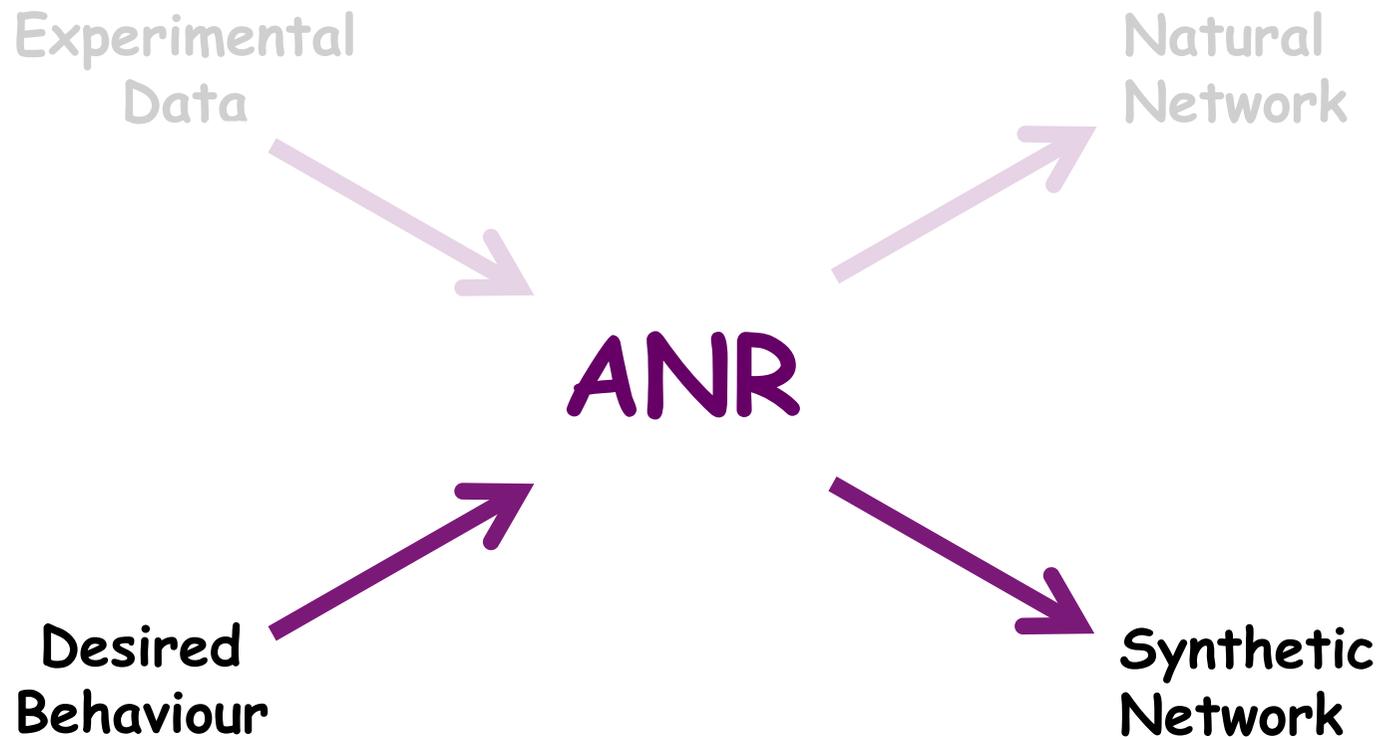
In J van Helden, A Toussaint and D Thieffry (eds.), [*Methods in Molecular Biology* \(2012\) 409-437.](#)

Clifton, NJ: Humana Press.

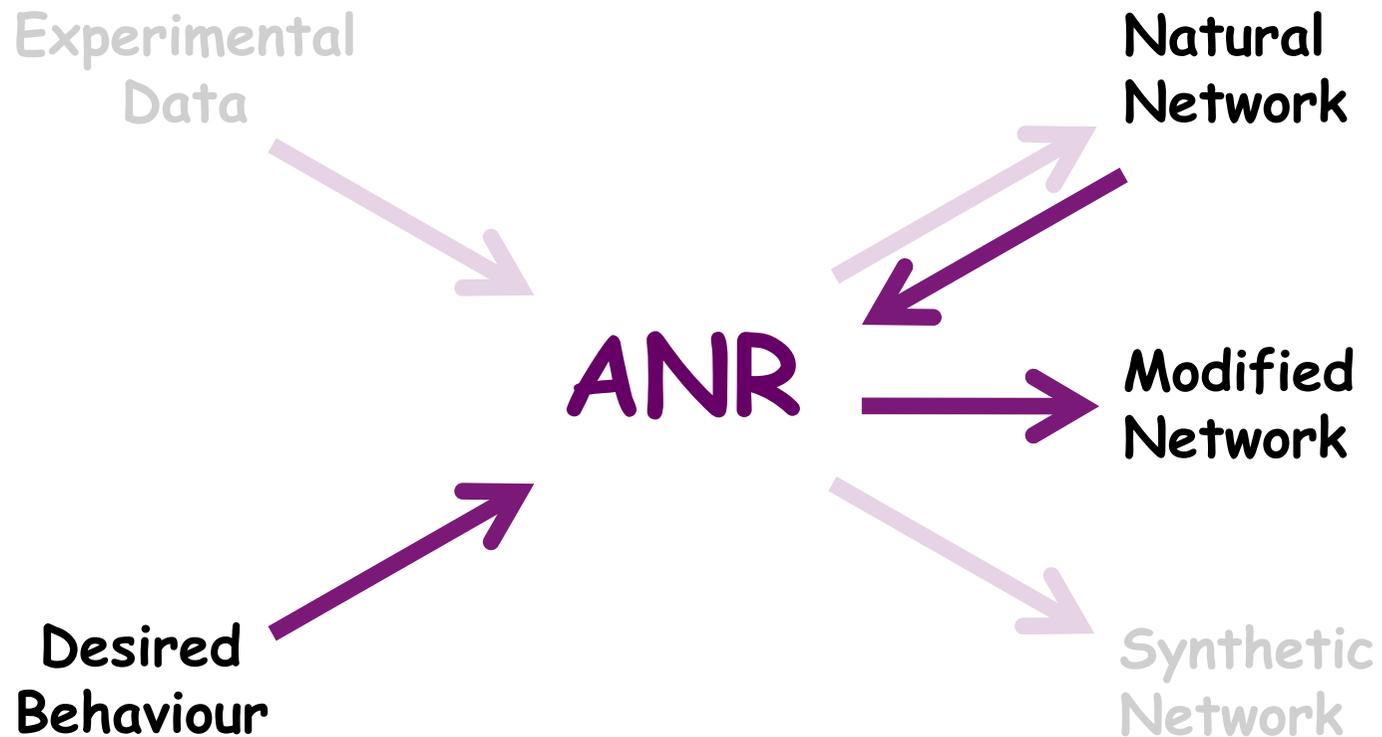
AUTOMATIC NETWORK RECONSTRUCTION (ANR) FOR SYSTEMS & SYNTHETIC BIOLOGY



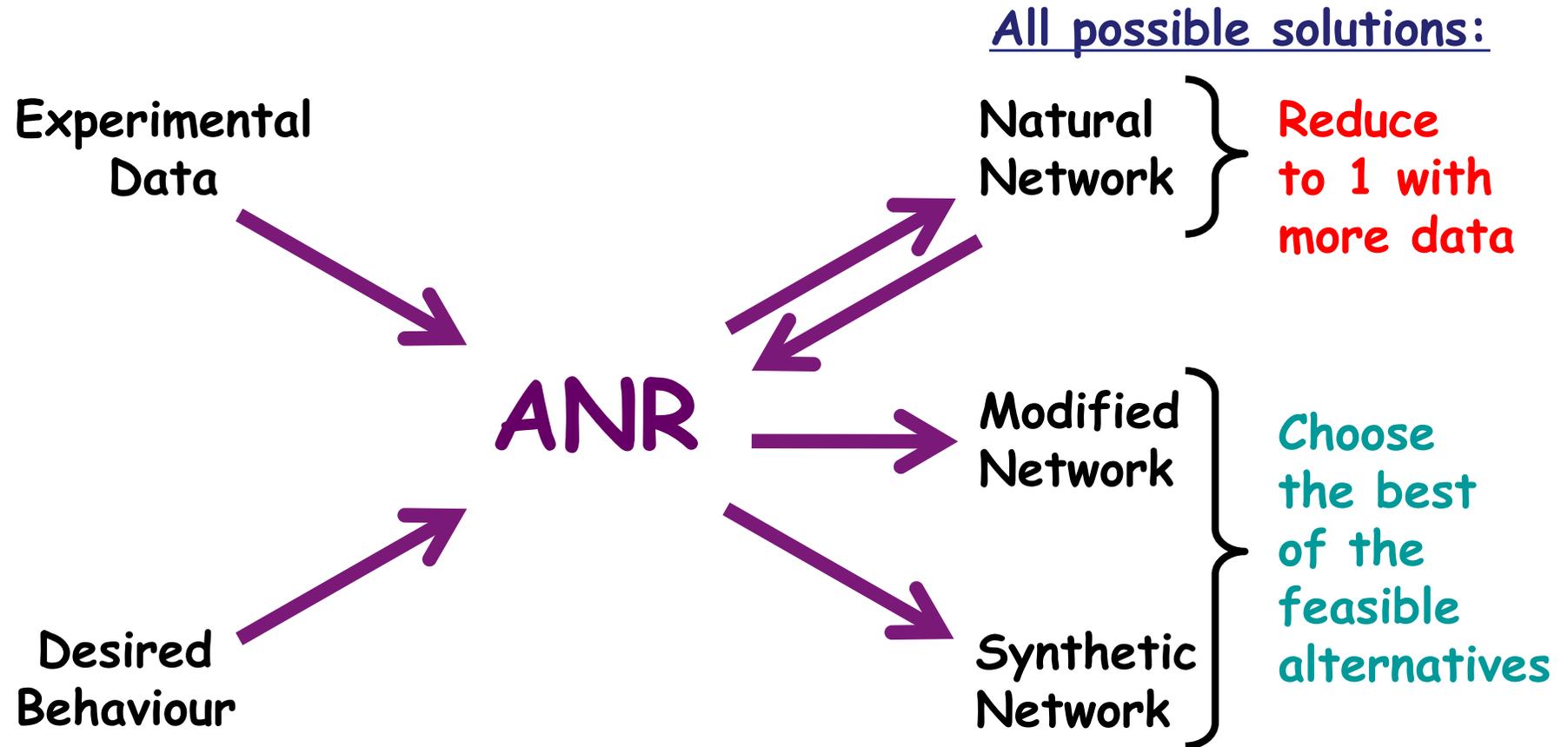
AUTOMATIC NETWORK RECONSTRUCTION (ANR) FOR SYSTEMS & SYNTHETIC BIOLOGY



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AUTOMATIC NETWORK RECONSTRUCTION (ANR) FOR SYSTEMS & SYNTHETIC BIOLOGY



AUTOMATIC NETWORK RECONSTRUCTION

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Thank you!



MAX-PLANCK-GESELLSCHAFT



GEFÖRDERT VOM

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und Forschung

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