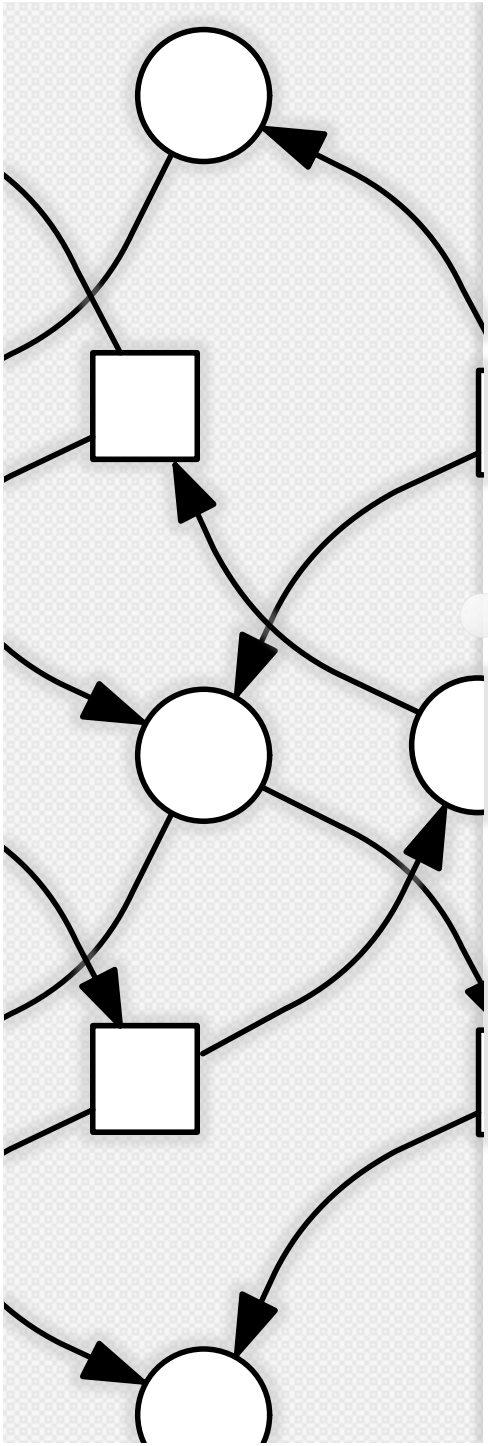
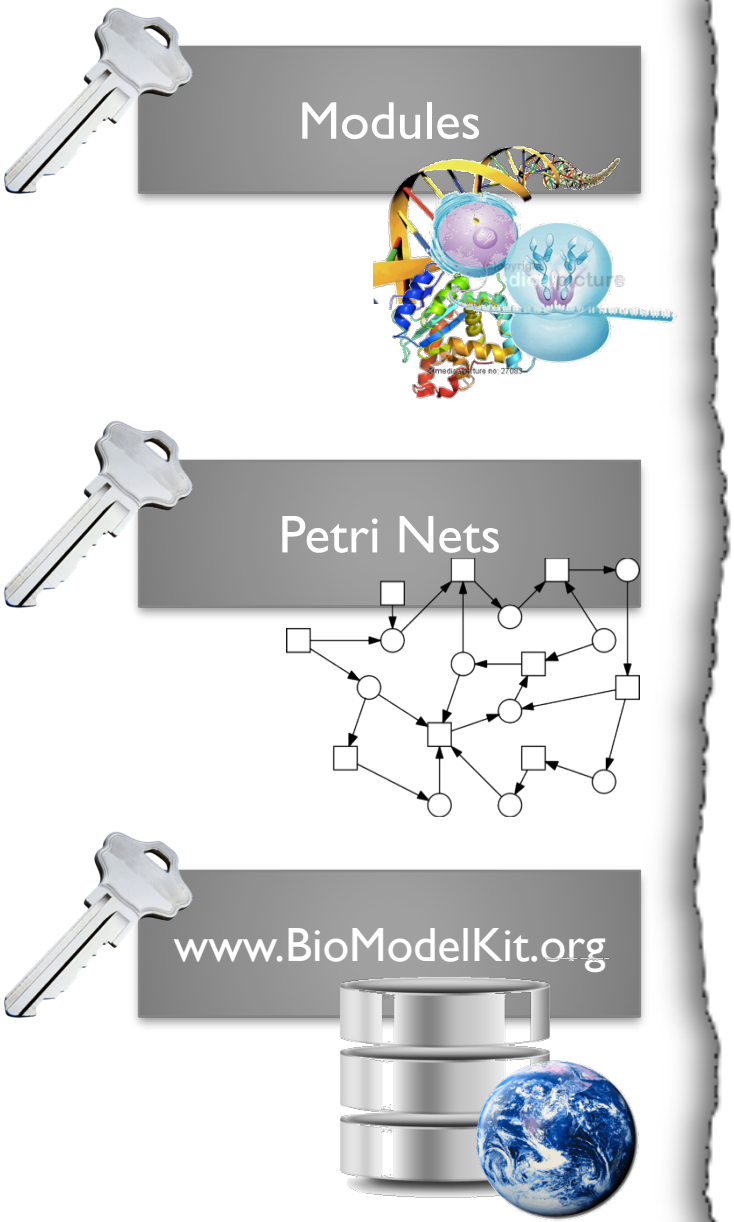


OTTO VON GUERICKE
UNIVERSITÄT
MAGDEBURG

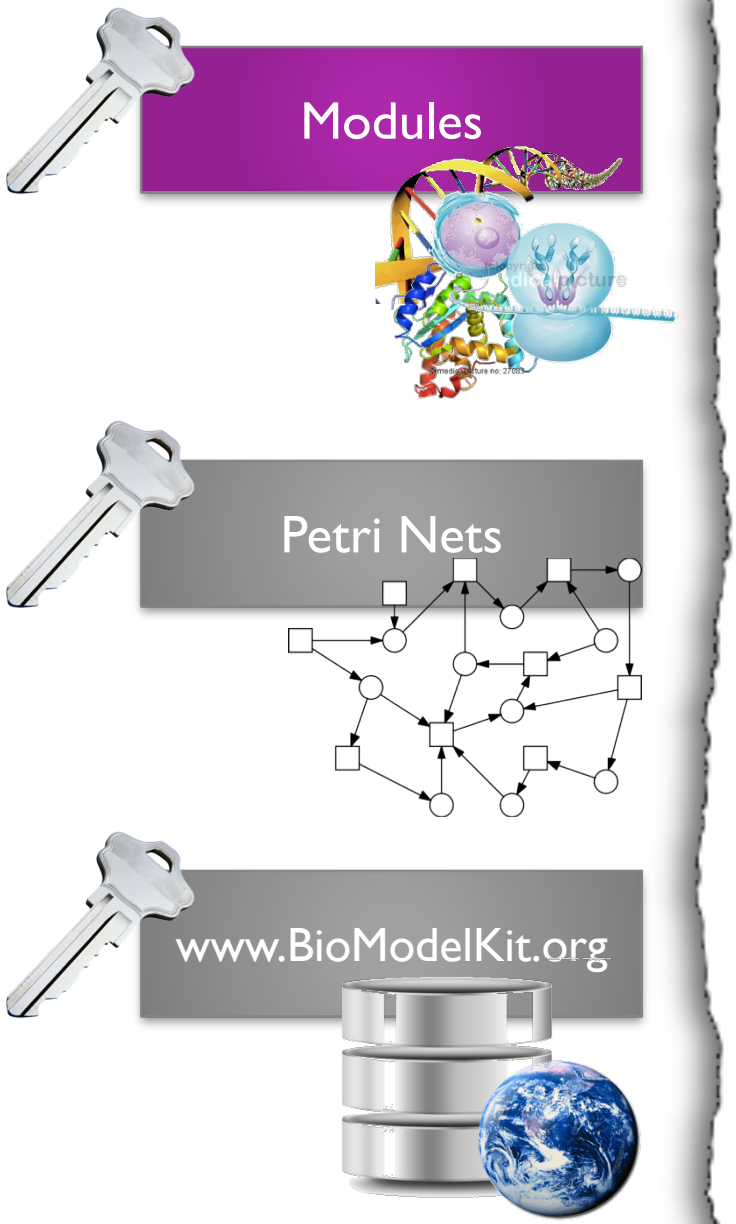
Petri nets for multiscale systems biology, 25TH June 2013, Milano

MODULES & MODEL COMPOSITION & ALGORITHMIC MUTATION

Modular Modelling Framework



Modular Modelling Framework



- Module design according to natural building blocks (gene, mRNA, protein)
- Description of how a biomolecule operates and executes its function

Module Types

Molecular Interaction

Protein Module

- Binding and Unbinding Reactions
- Formation and Cleavage of Covalent Bonds
- Conformational Changes

Protein Degradation

- Inactivation
- Internalisation
- Degradation

mRNA Module

- Transcription/Translation
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Gene Module

- Transcriptional Activity
- Binding and Unbinding Reactions
- Covalent Modification

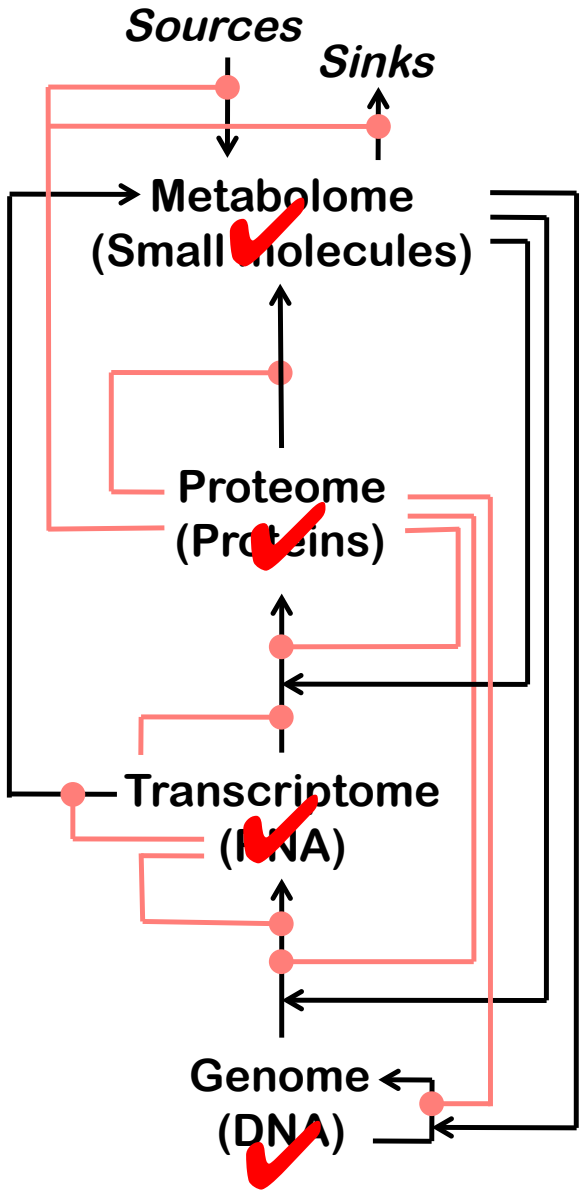
Causal Dependencies

Causal Interaction Modules

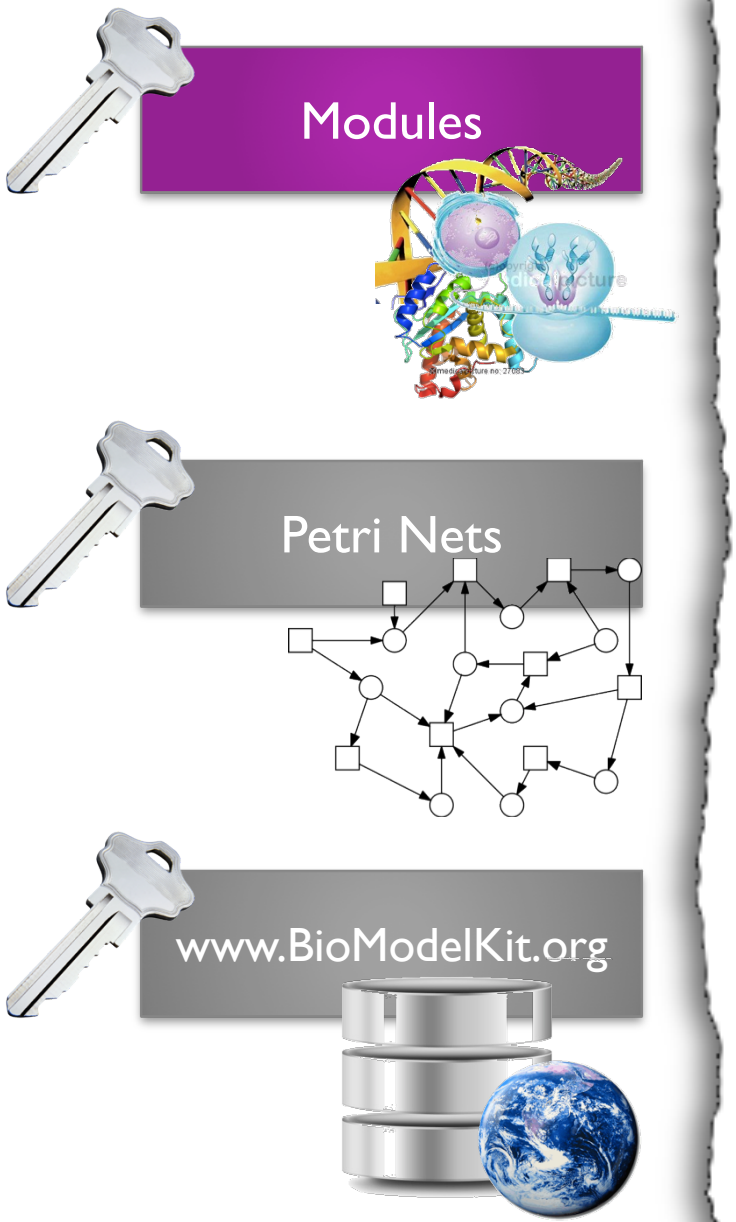
- Causal Influences on Molecular and Cellular Processes

Allelic Influence Module

- Allelic Influences on Molecular and Cellular Processes

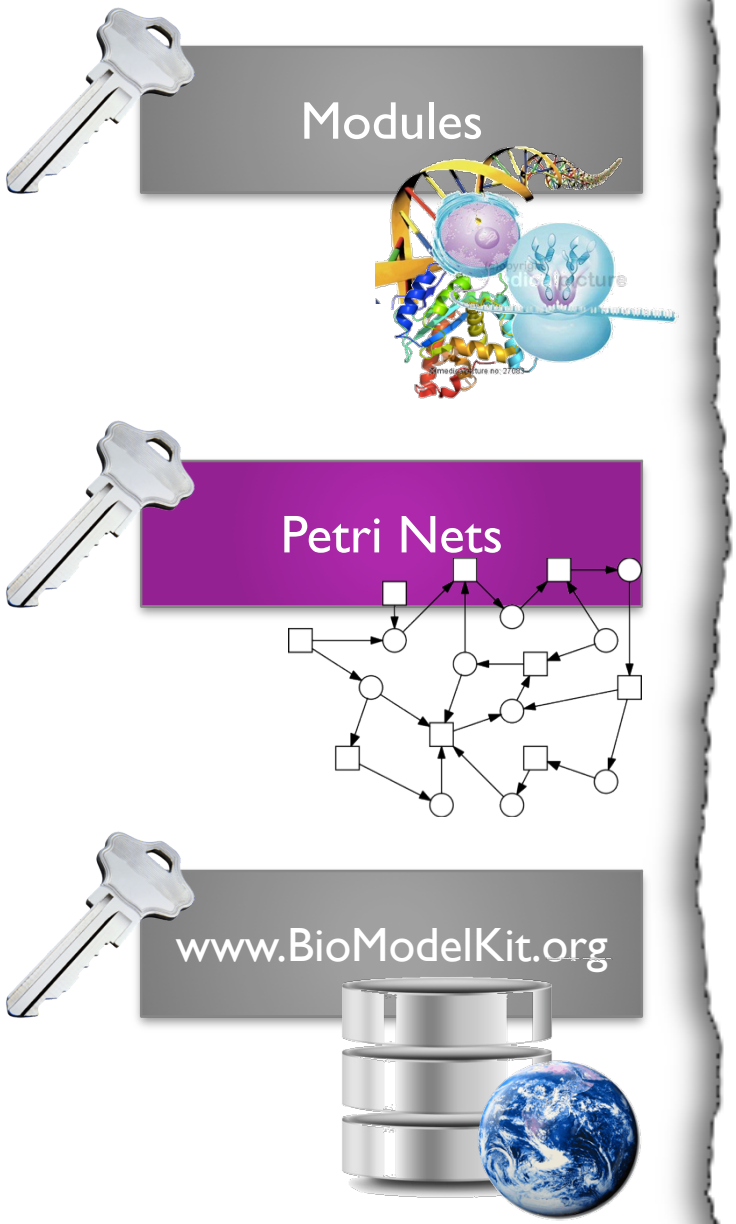


Modular Modelling Framework



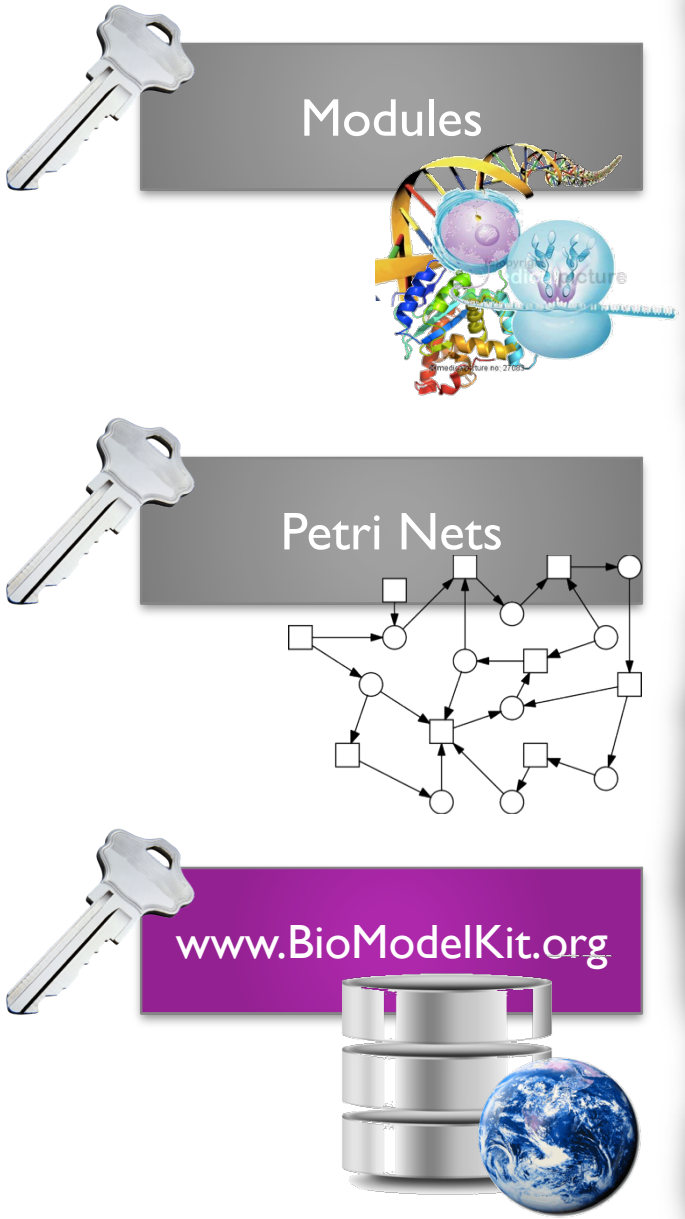
- Module design according to natural building blocks (gene, mRNA, protein)
- Description of how a biomolecule operates and executes its function
- Modules obey naturally implied structural criteria
- Composition through shared interface subnetwork of interactions

Modular Modelling Framework



- Formal language with operational semantics
- **W**hat-**Y**ou-**S**ee-**I**s-**W**hat-**Y**ou-**G**et Principle
- Switch between modelling paradigms
- Powerful simulation and analysis tools
- Compatible with SBML and other usual representation styles

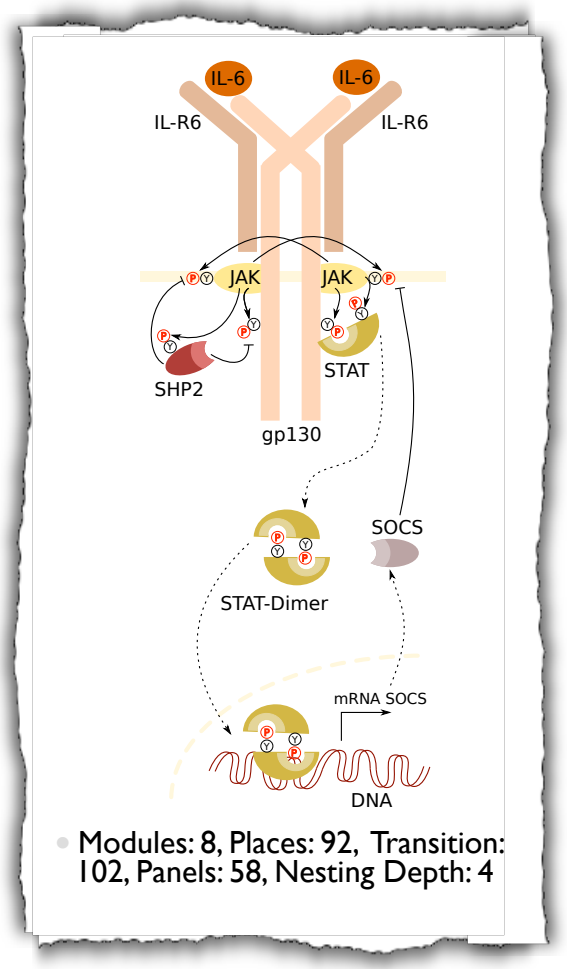
Modular Modelling Framework



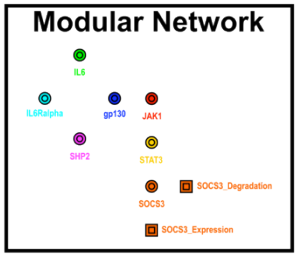
- Organisation of modules
- Explicit assessment of the network structure
- Extension of modules through metadata
- Support of:
  - Module versioning
  - Retrieve modules of interest
  - Automatic networks
  - Algorithmic mutation

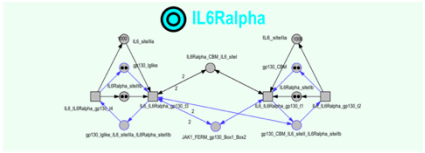
CASE STUDIES

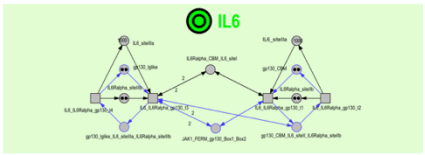
JAK-STAT Signalling

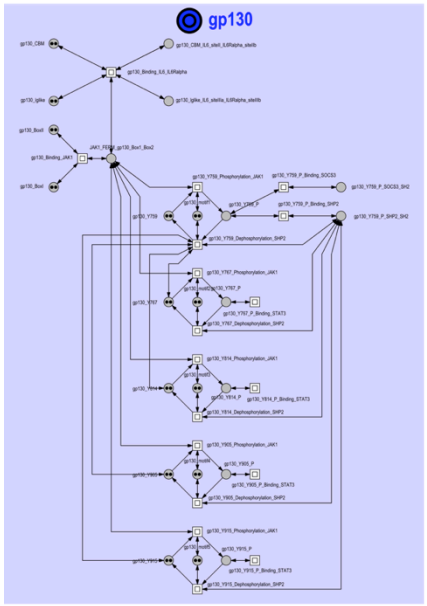


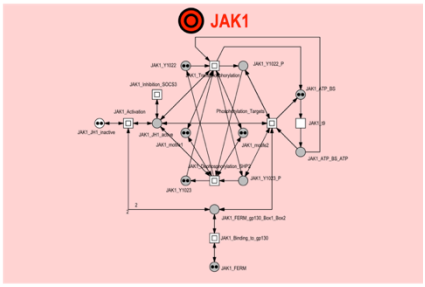
- Modules: 8, Places: 92, Transition: 102, Panels: 58, Nesting Depth: 4

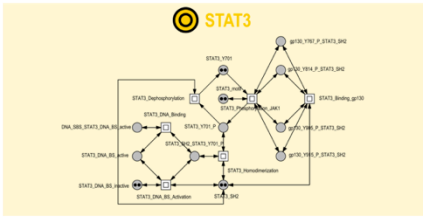


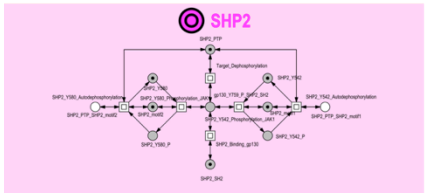


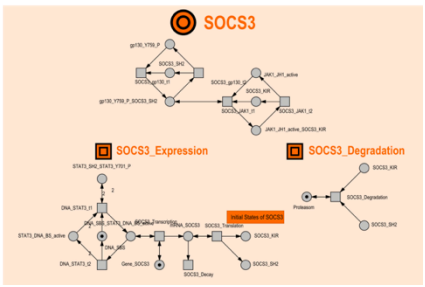






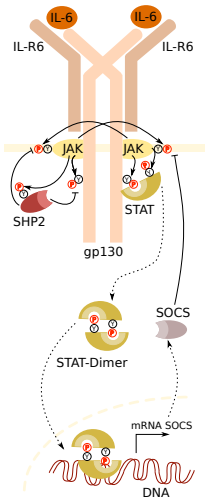






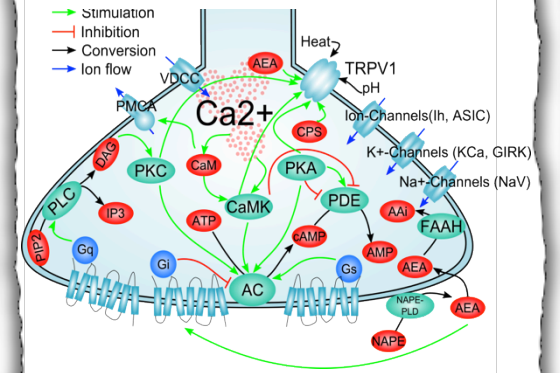
CASE STUDIES

JAK-STAT Signalling



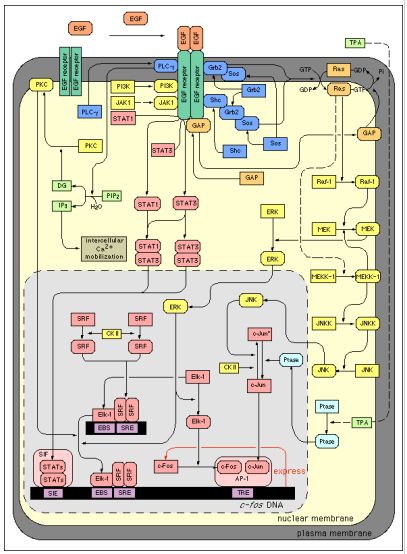
- Modules: 8, Places: 92, Transition: 102, Panels: 58, Nesting Depth: 4

Pain-Signalling



- Modules: 38, Places: 713, Transitions: 775, Panels: 325, Nesting Depth: 4

EGF-Signalling



- Modules: 15 + more (work in progress)

REUSE MODULES

Module Types

Molecular Interaction

Protein Module
- Binding and Unbinding Reactions
- Formation and Cleavage of Covalent Bonds
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Protein Degradation
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Causal Interaction Modules
- Causal Influences on Molecular and Cellular Processes

Allelic Influence Module
- Allelic Influences on Molecular and Cellular Processes

Module
- Petri Net
- Documentation
- Meta-Data

BioModelKit

Composed Models

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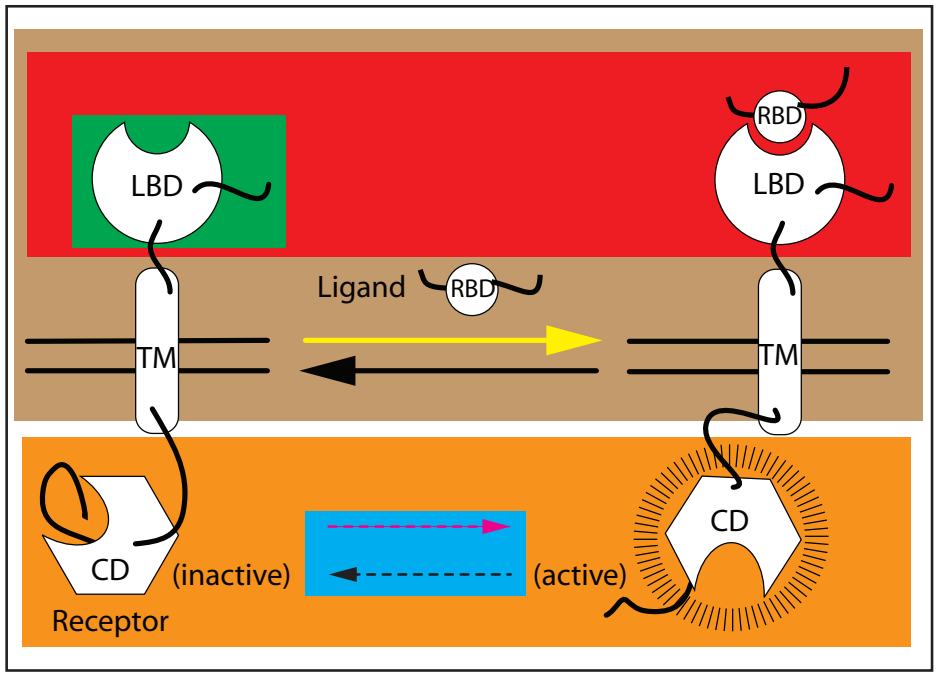
Algorithmic Model Mutation

Protein



Module

Structural Entity

Molecular State

Molecular Process

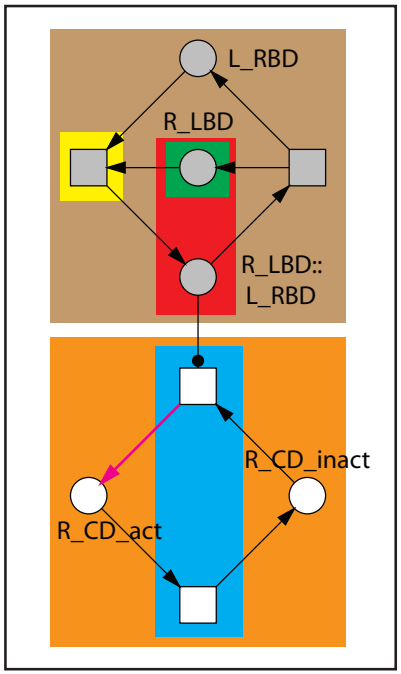
Molecular Event

Directed Connectors

Structural Enitity Subnetwork

Interface Subnetwork

Module

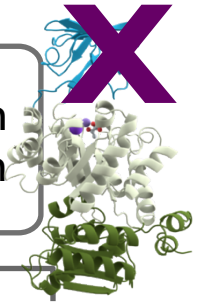


Algorithmic Model Mutation

Wild-Type Model

Gene Knockout

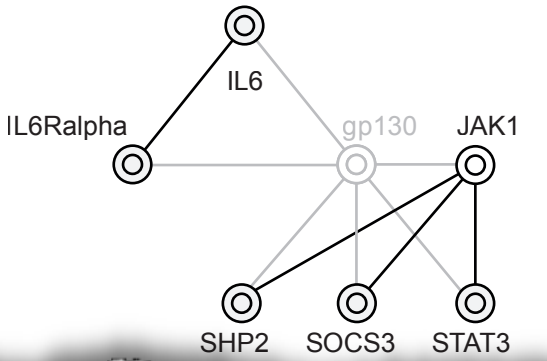
Modification of Protein Structure and Function



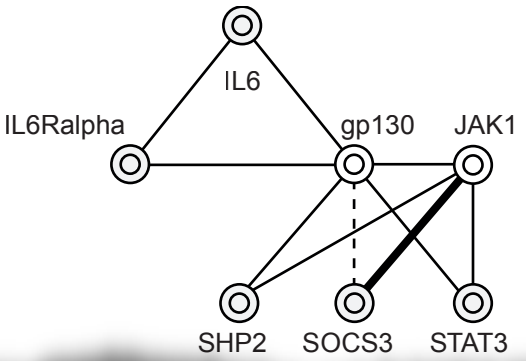
Delete Modules

Block Structural Entity Subnetworks

Block Tagged Molecular Actions



Interactions not available



Interactions increased, weakened, or unchanged

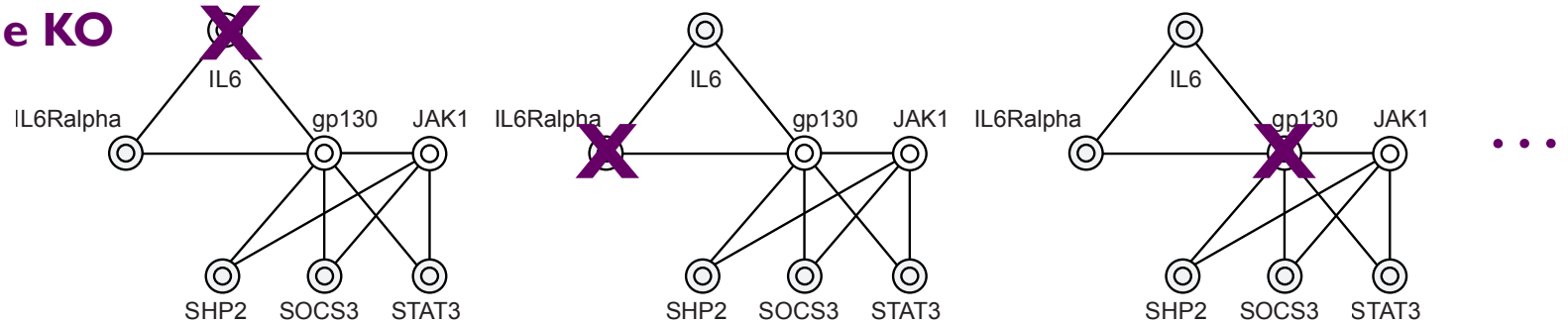
GENE KNOCKOUT

Algorithm 1 Module Knockout

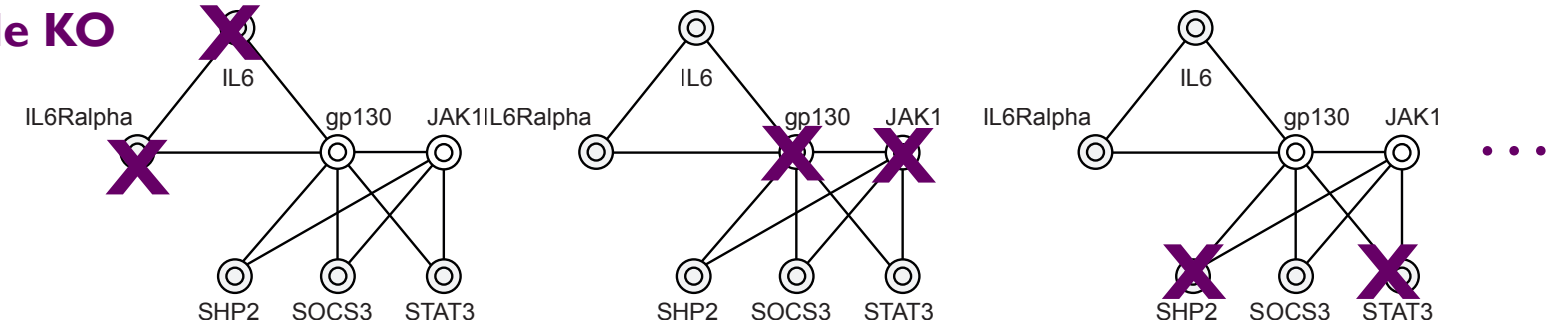
Require: Set of modules $\mathbf{M} = \{M_1, \ldots, M_n\}$ for the model composition.

1: *ComposeModel*(M); ▷ wild-type model
2: **for** $i := 1$ **to** n **do**
3: $\quad \mathbf{M}_{SKO} := M \setminus \{M_i\}$
4: $\quad$ *ComposeModel*($\mathbf{M}_{SKO}$) ▷ single knock-out of module M_i
5: $\quad$ **for** $j := i + 1$ **to** n **do**
6: $\quad\quad \mathbf{M}_{DKO} := \mathbf{M}_{SKO} \setminus \{M_j\}$
7: $\quad\quad$ *ComposeModel*($\mathbf{M}_{DKO}$) ▷ double knock-out of modules M_i and M_j
8: $\quad$ **end for**
9: **end for**

Single KO



Double KO



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8: $\quad$ **end for**
9: **end for**

Single KO

Double KO

Adaptable up to k-fold Knockout…

Number of mutated models:

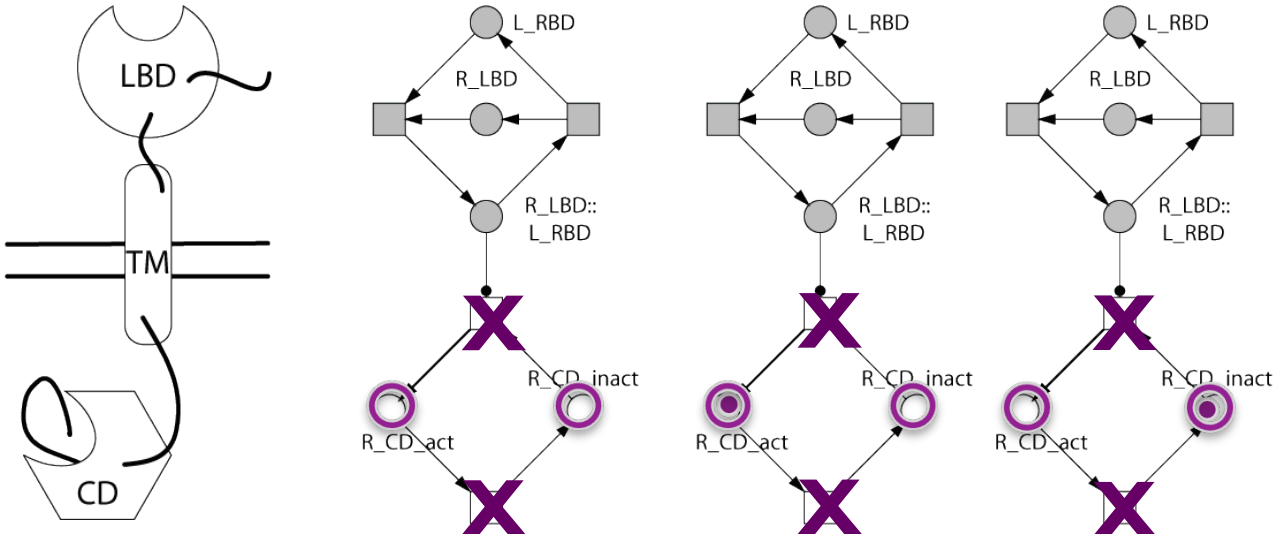
$$1 + \sum_{j=1}^{k} \binom{|M|}{j}, k < |M|$$

MUTATE STRUCTURAL ENTITY SUBNETWORKS

Algorithm 2 Deletion of Structural Entity Subnetwoks

Require: Set of modules $\mathbf{M} = \{M_1, \ldots, M_n\}$ with the total set of all structural entity subnetworks **SES** := $\{SES_1, \ldots, SES_s\}$ of **M**, where $SES_i = [P_i, T_i, F_i, m_0^{P_i}]$.

1: *ComposeModel*(**M**) ▷ wild-type model
2: **for** $i := 1$ **to** s **do** ▷ block molecular events of SES_i
3: $T_{backup} := T_i$
4: $T_i := \emptyset$
5: $m_0^{P_i} := 0$
6: *ComposeModel*(**M**) ▷ blocked and empty SES_i
7: $k := |P_i|$ ▷ number of elements in P_i
8: **for** $j := 1$ **to** k **do** ▷ Vary marking of the blocked SES_i
9: $m_0^{P_i}(j) := 1$
10: *ComposeModel*(**M**) ▷ blocked SES_i with place p_j^i marked
11: $m_0^{P_i} := 0$
12: **end for**
13: $T_i := T_{backup}$
14: **end for**



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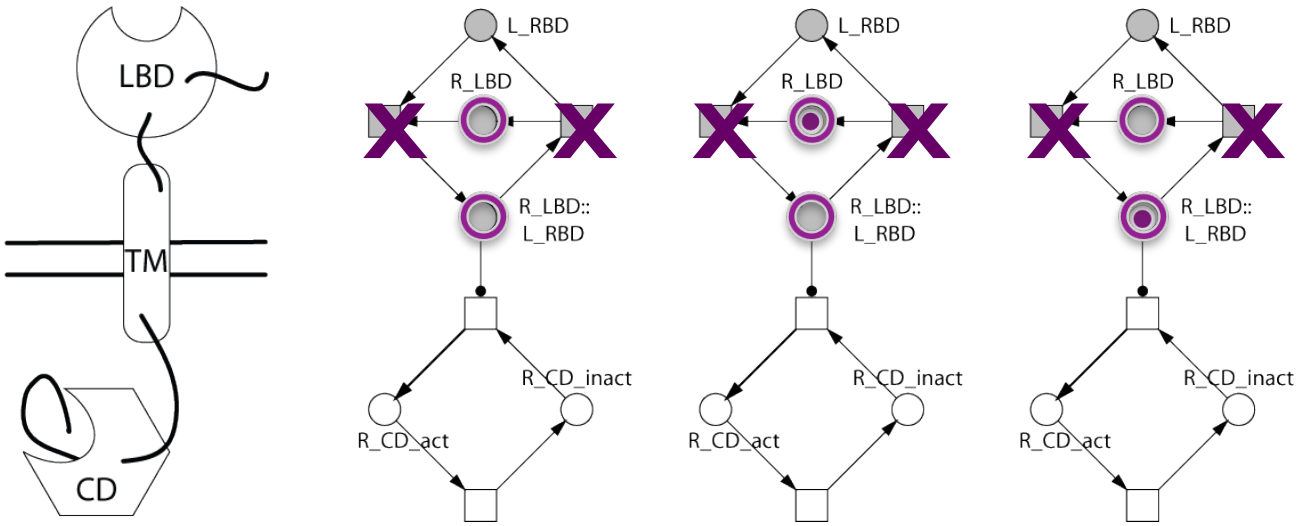

MUTATE STRUCTURAL ENTITY SUBNETWORKS

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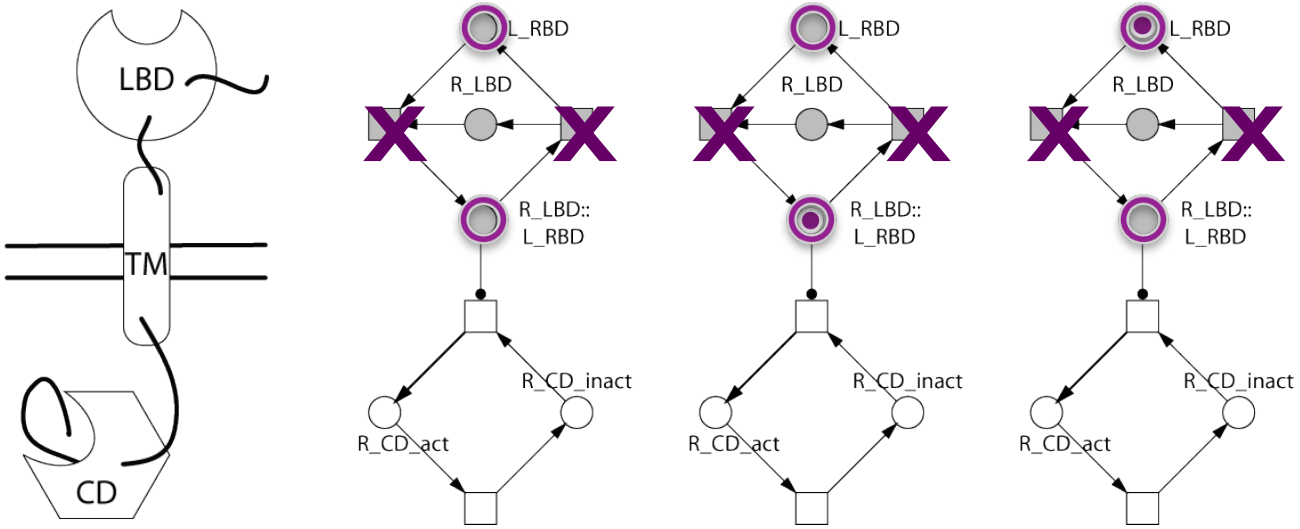
12: **end for**
13: $T_i := T_{backup}$
14: **end for**



MUTATE STRUCTURAL ENTITY SUBNETWORKS

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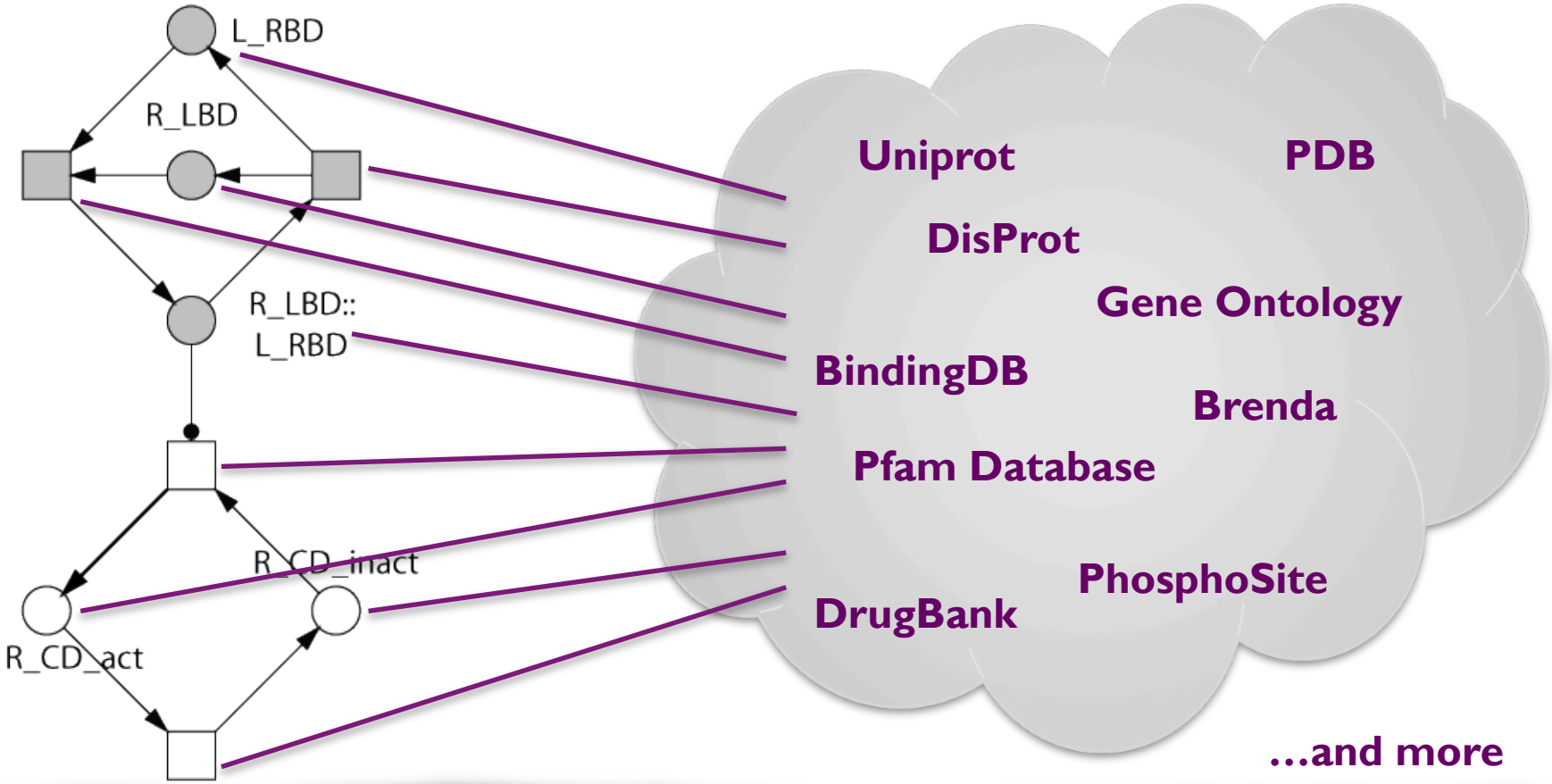
9: $m_0^{P_i}(j) := 1$
10: *ComposeModel*(**M**) ▷ blocked SES_i with place p_j^i marked
11: $m_0^{P_i} := 0$
12: **end for**
13: $T_i := T_{backup}$
14: **end for**

Number of mutated models:

$$1 + |SES| + \sum_{i=1}^{|SES|} |P_i|$$

SWITCH OF SPECIFIC MOLECULAR ACTIONS



Biomodelkit DB stores for each Node Cross-References to other Bio-DBs

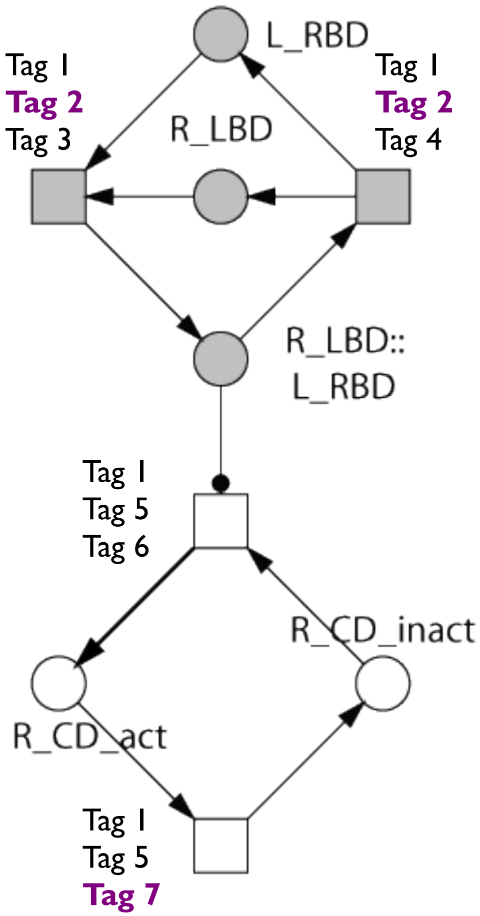
SWITCH OF SPECIFIC MOLECULAR ACTIONS

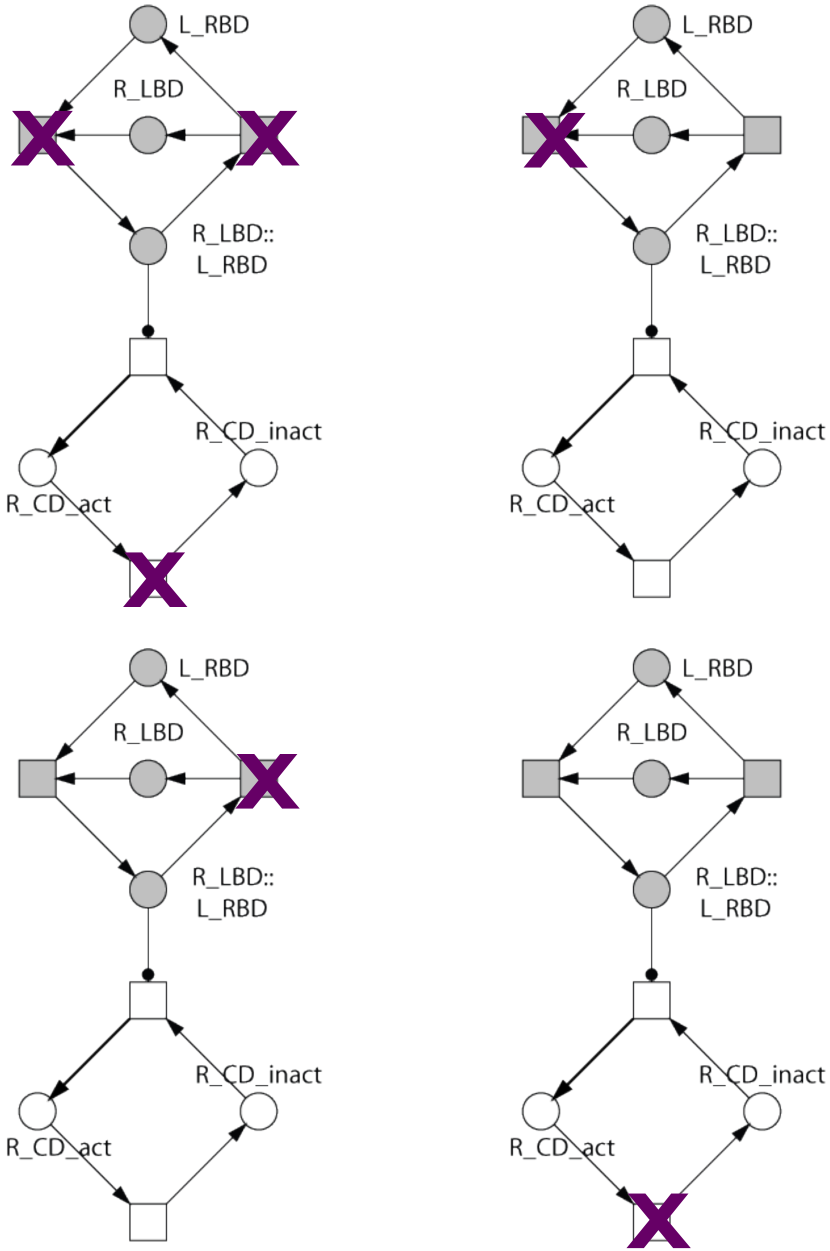
Algorithm 3 Deletion of Transitions based on Metadata-encoded Biological Knowledge

Require: Set of modules $\mathbf{M} = \{M_1, \ldots, M_n\}$ with transitions $\mathbf{T} = \{t_1, \ldots, t_m\}$,
set of tags to be used for the mutation $Tag_{mut} = \{tag_{mut,1}, \ldots, tag_{mut,l}\}$.

1: $Tag_{DB} := \emptyset$; ▷ set of tags from database
2: $\mathbf{T}_{block} := \emptyset$ ▷ set of transitions to mutate
3: *ComposeModel*(**M**) ▷ wild-type model
4: **for all** $t_i \in \mathbf{T}$ **do**
5: Select the set of tags $Tag_{DB} := \{tag_{DB,1}, \ldots, tag_{DB,k}\}$ of transition t_i from BMKdb
6: **if** $Tag_{DB} \cap Tag_{mut} \neq \emptyset$ **then**
7: $\mathbf{T}_{block} := \mathbf{T}_{block} \cup \{t_i\}$
8: **end if**
9: **end for**;
10: $k := |\mathbf{T}_{block}|$ ▷ number of elements in $\mathbf{T}_{block}$
11: $\mathbf{M}_{mut} := \mathbf{M}$
12: $\mathbf{T}_{mut} := \mathbf{T} \setminus \mathbf{T}_{block}$
13: *ComposeModel*($\mathbf{M}_{mut}$) ▷ all tagged transitions blocked at once
14: **for all** $t_i \in \mathbf{T}_{block}$ **do**
15: $\mathbf{M}_{mut} := \mathbf{M}$
16: $\mathbf{T}_{mut} := \mathbf{T} \setminus \{t_i\}$
17: *ComposeModel*($\mathbf{M}_{mut}$) ▷ only one tagged transition blocked at a time
18: **for** $j := i + 1$ **to** k **do**
19: $\mathbf{T}_{mut} := \mathbf{T}_{mut} \setminus \{t_j\}$
20: *ComposeModel*($\mathbf{M}_{mut}$) ▷ two tagged transition blocked at a time
21: **end for**
22: **end for**

Switch of Specific Molecular Actions





User: Tag 2, Tag7

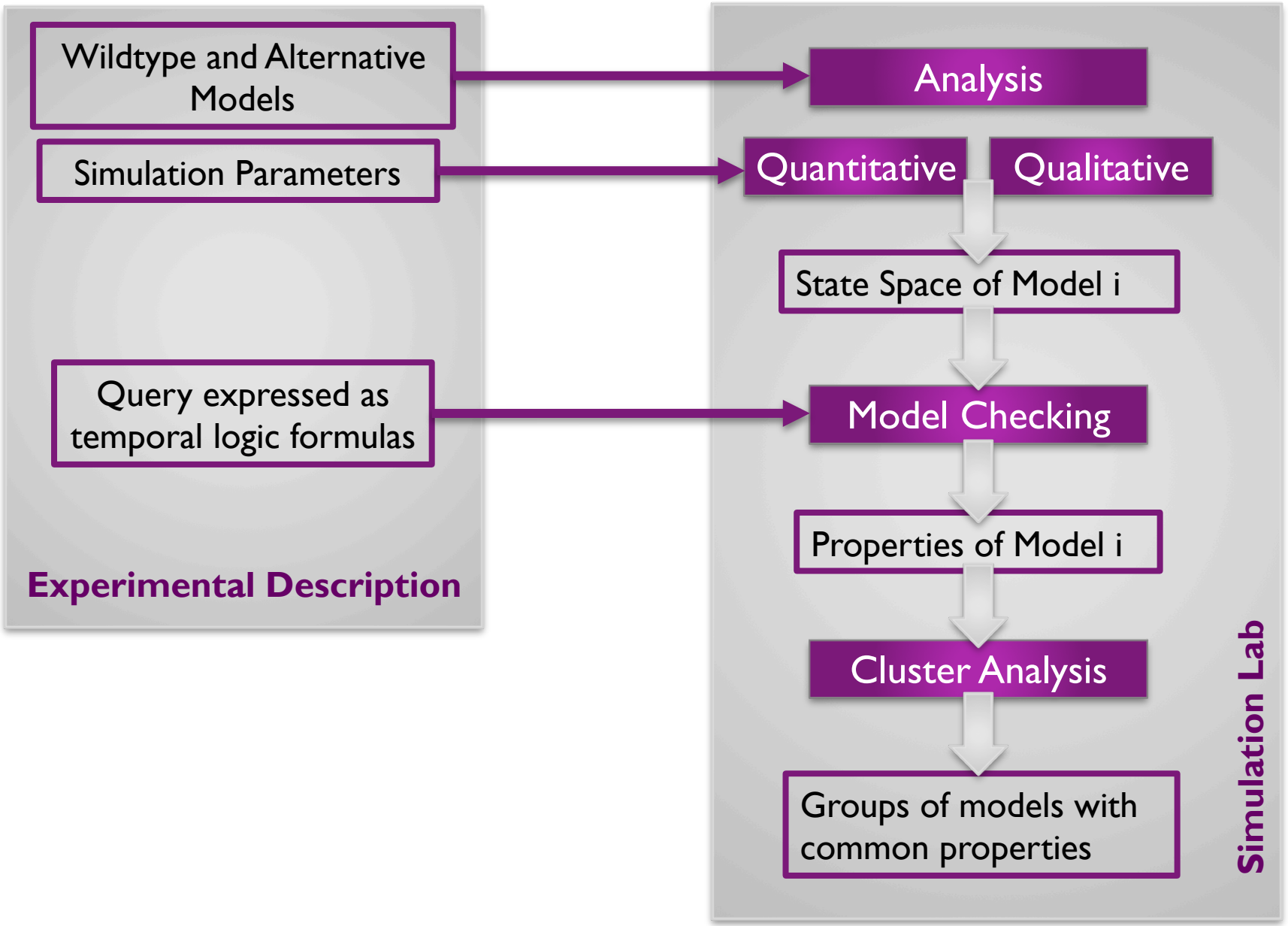
SWITCH OF SPECIFIC MOLECULAR ACTIONS

Number of mutated models:

$$2 + \sum_{j=1}^{k} \left(\begin{matrix} |T_{block}| \\ j \end{matrix} \right), k < |T_{block}|$$

User: Tag 2, Tag7

High-Throughput Model Screening

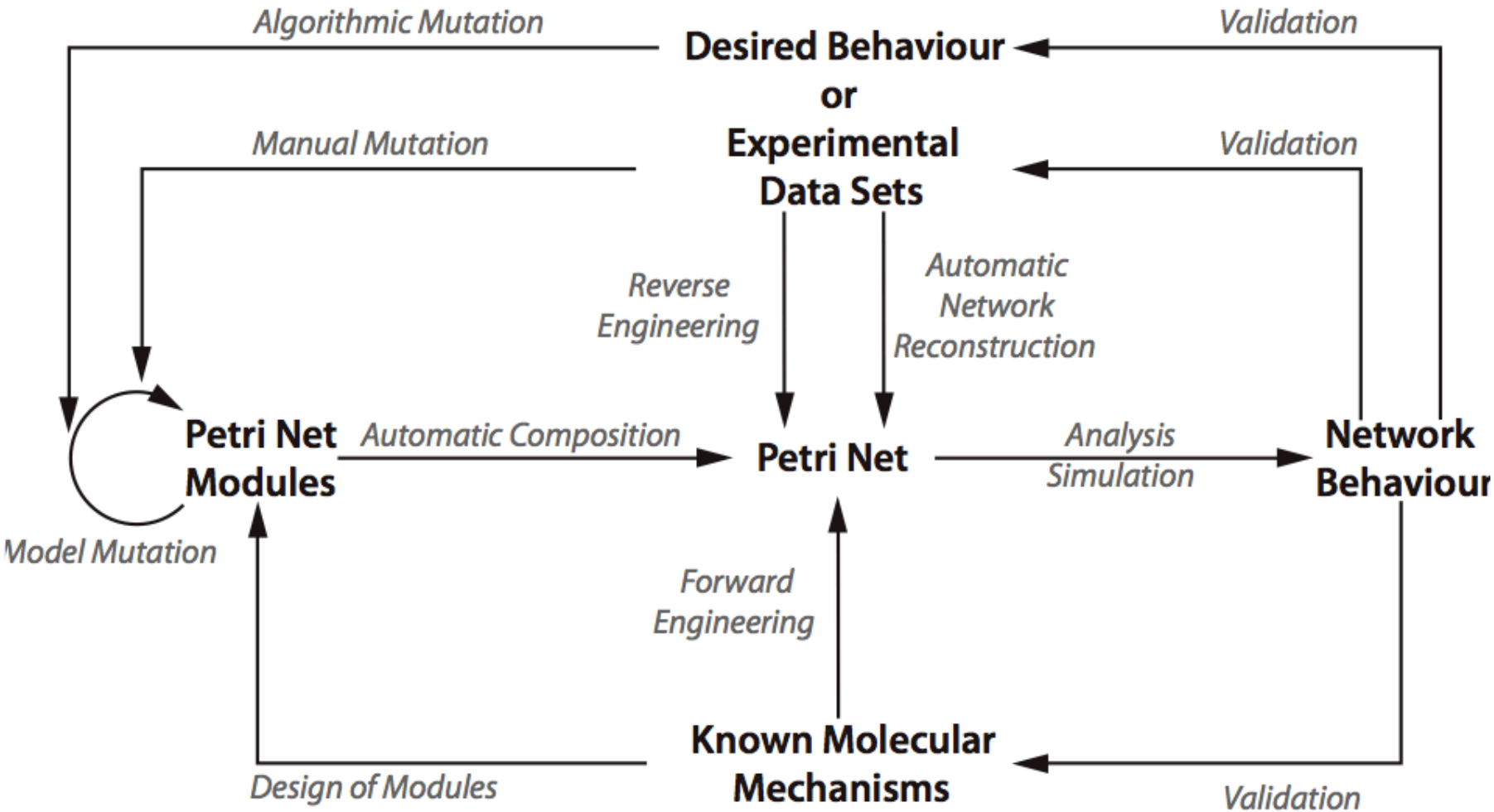


SUM UP…

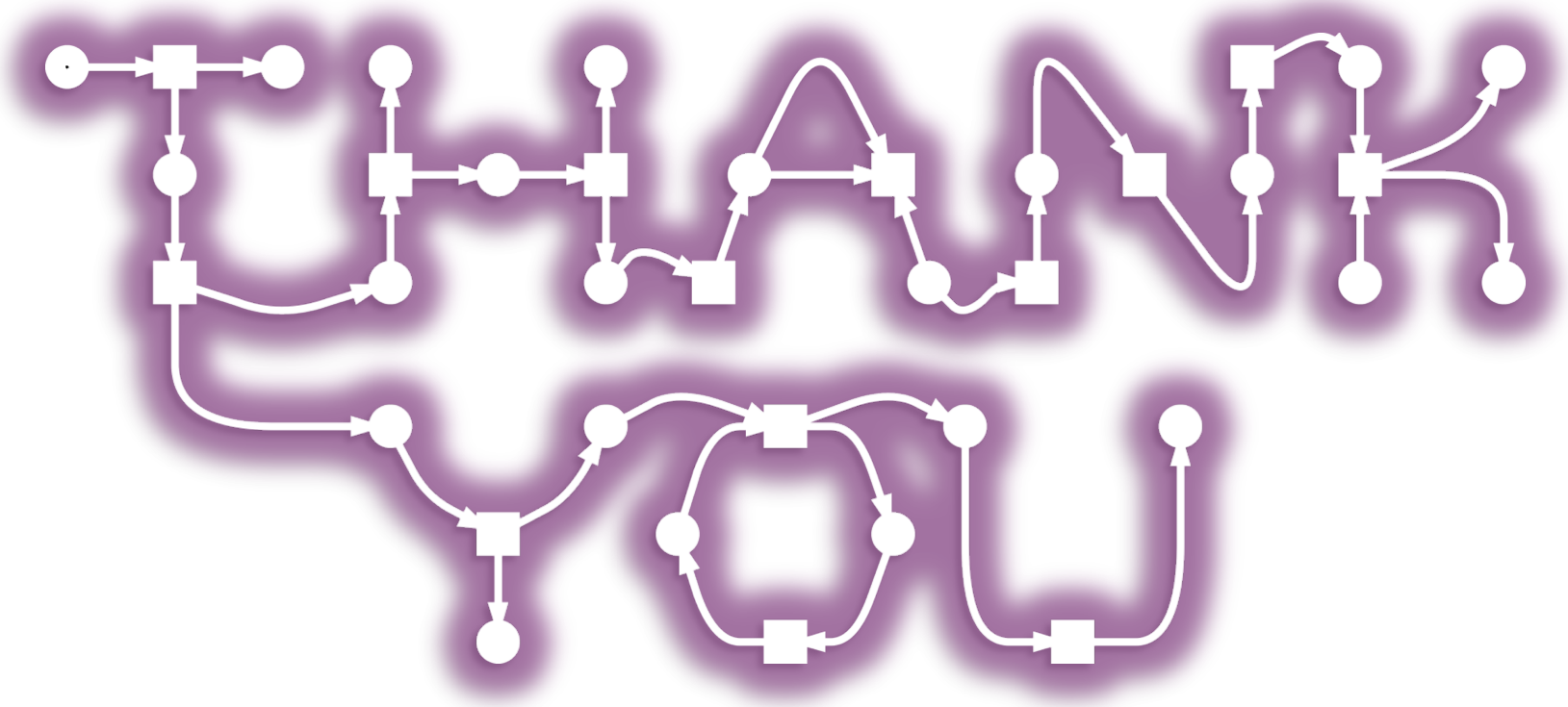
- Key features of the modular modeling concept
  - Purposefully designed modules
  - Petri net formalism
  - BioModelKit DB
  - Algorithmic model mutation
  - HT model screening

- Future Extension
  - Adding spatial information
  - Reengineering of modules
  - Reverse engineering of modules from OMIC data
  - Module reduction
  - …

SUM UP...



Powerful and Versatile Framework for Multiscale Biomodel Engineering



- **Cooperation Partners**
  - Monika Heiner and Co-Workers, BTU Cottbus
  - David Gilbert, Brunel University London
  - Fred Scharper and Co-Workers, OvGU Magdeburg
  - Tim Hucho, University of Cologne
- **Projects**
  - Consortium „Modelling of Pain Switches" 2009-2011
  - Consortium „NoPain" 2013-2015
- **Graduate School**
  - IMPRS Magdeburg

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