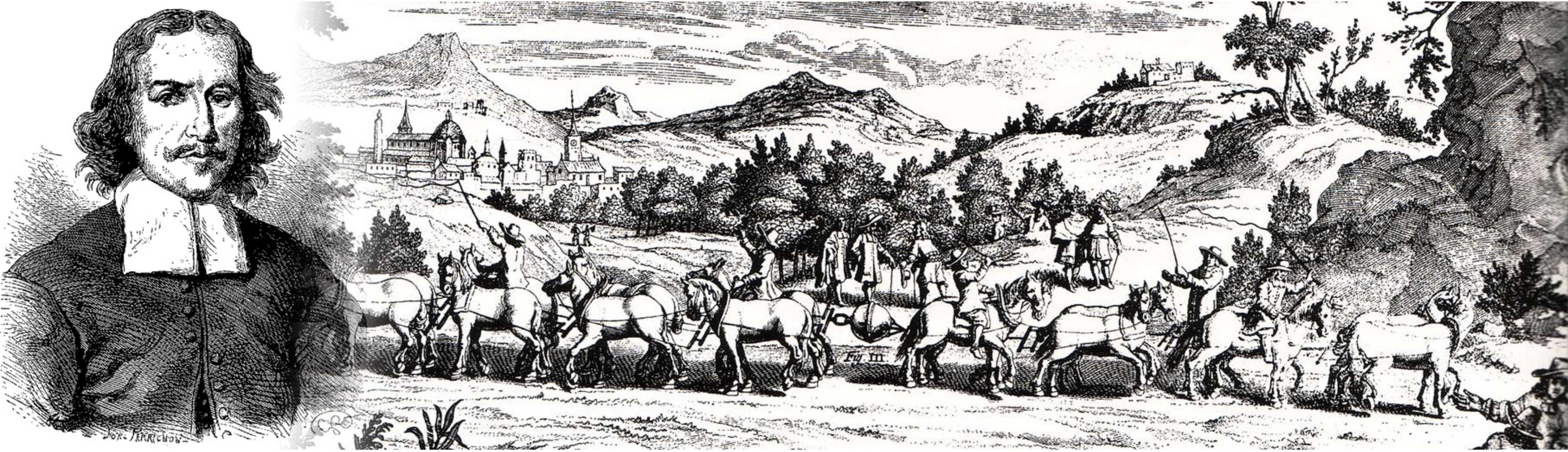

Sino-German Workshop "Multiscale Spatial Computational Systems Biology”, Beijing/China, 9th October 2015

Spatial Modelling based on the BMK-Framework

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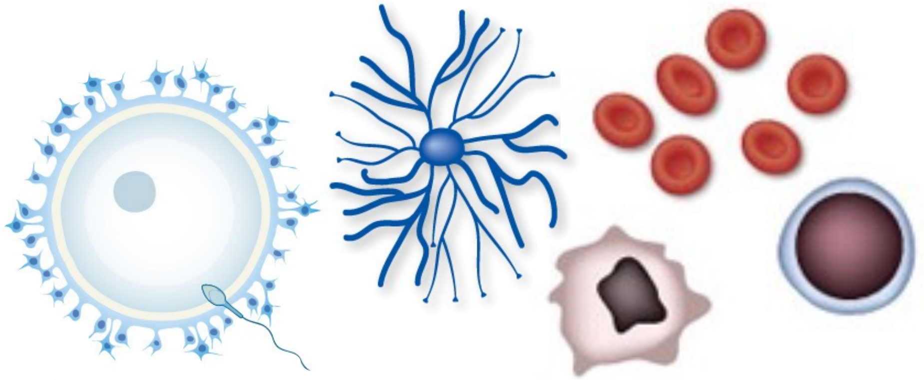
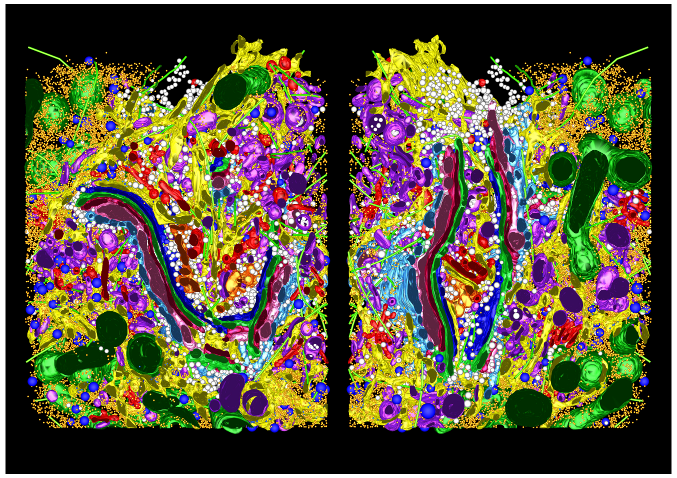
Background

- Systems Biology encouraged the modelling of bio-systems
  - detailed mechanistic & kinetic descriptions
  - ignore spatial aspects
- But space matters:



http://learn.genetics.utah.edu

cell size & shape



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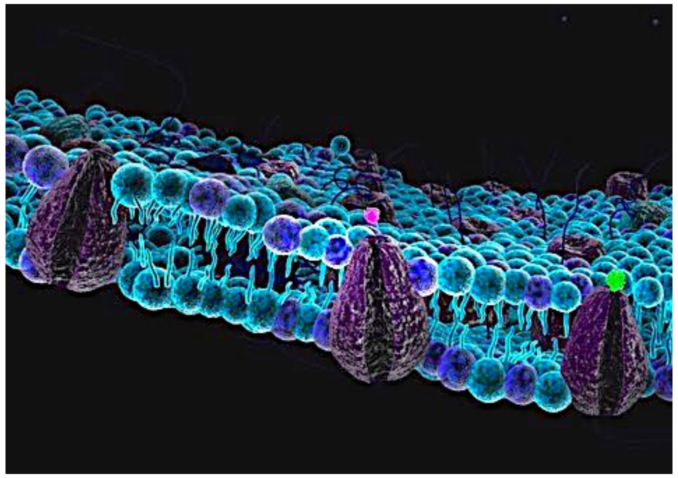
compartmentalisation, pools & organisation



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membrane composition

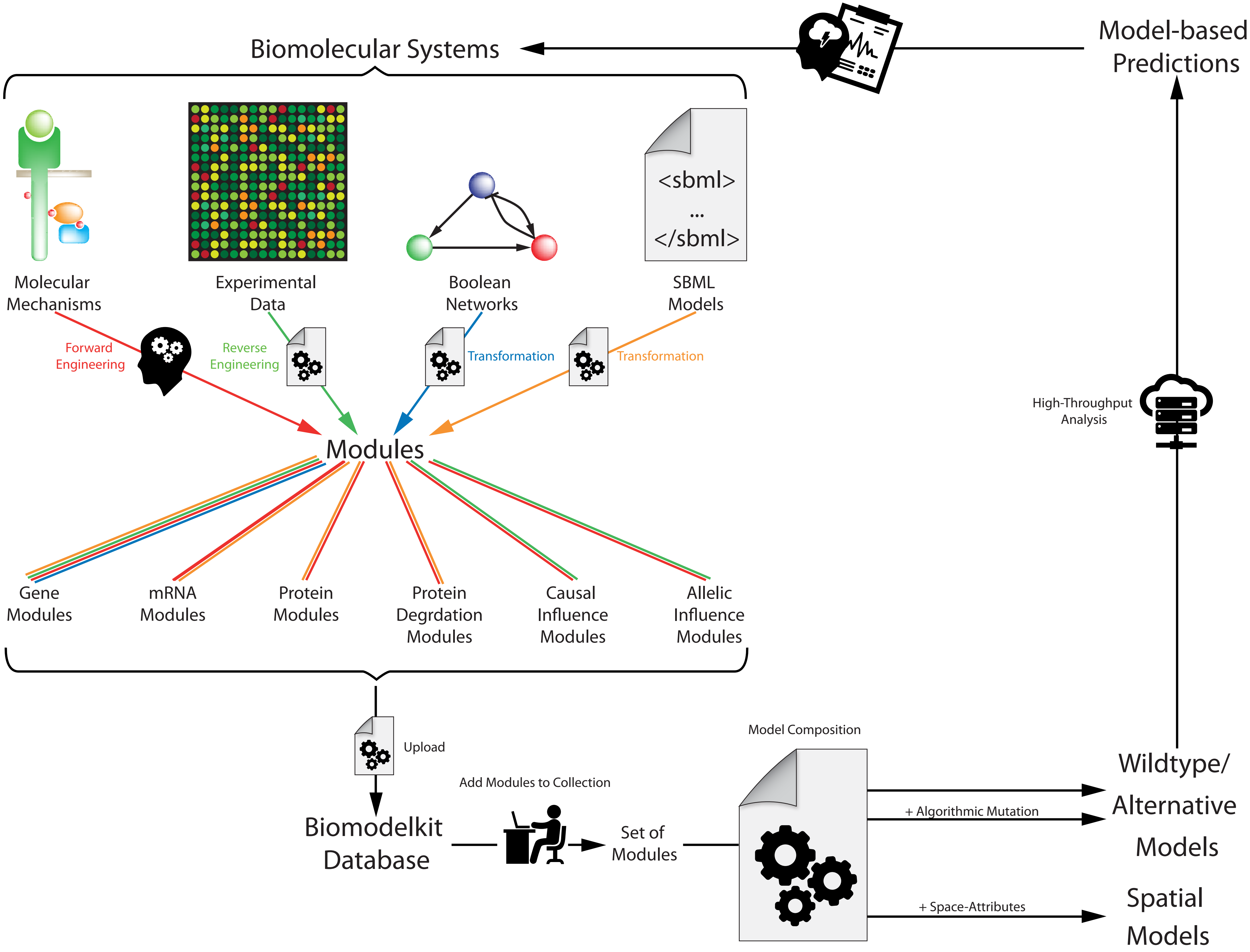
- Integration of spatial aspects in existing models is not straightforward
  - ➡ models have to be rebuild

Our Idea

- Extend models with spatial information to keep track of position and movement
- Biomolecule-centred modularisation of models

➡BioModelKit Framework

BMK-Framework



Biomolecular Systems

Model-based Predictions

Molecular Mechanisms

Experimental Data

Boolean Networks

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SBML Models

Forward Engineering

Reverse Engineering

Transformation

Transformation

High-Throughput Analysis

Modules

Gene Modules

mRNA Modules

Protein Modules

Protein Degrdation Modules

Causal Influence Modules

Allelic Influence Modules

Upload

Biomodelkit Database

Add Modules to Collection

Set of Modules

Model Composition

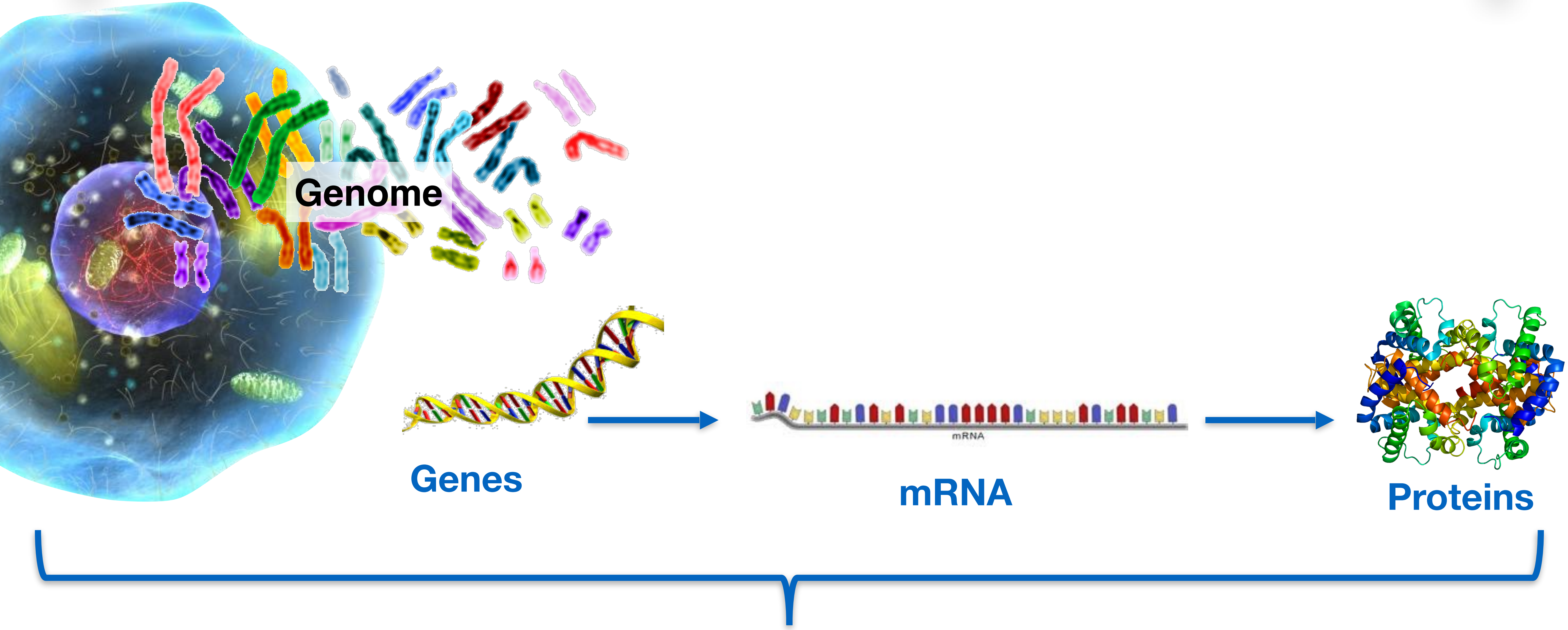
+ Algorithmic Mutation

+ Space-Attributes

Wildtype/ Alternative Models

Spatial Models

BMK-Framework - Modules



Genome

Genes

mRNA

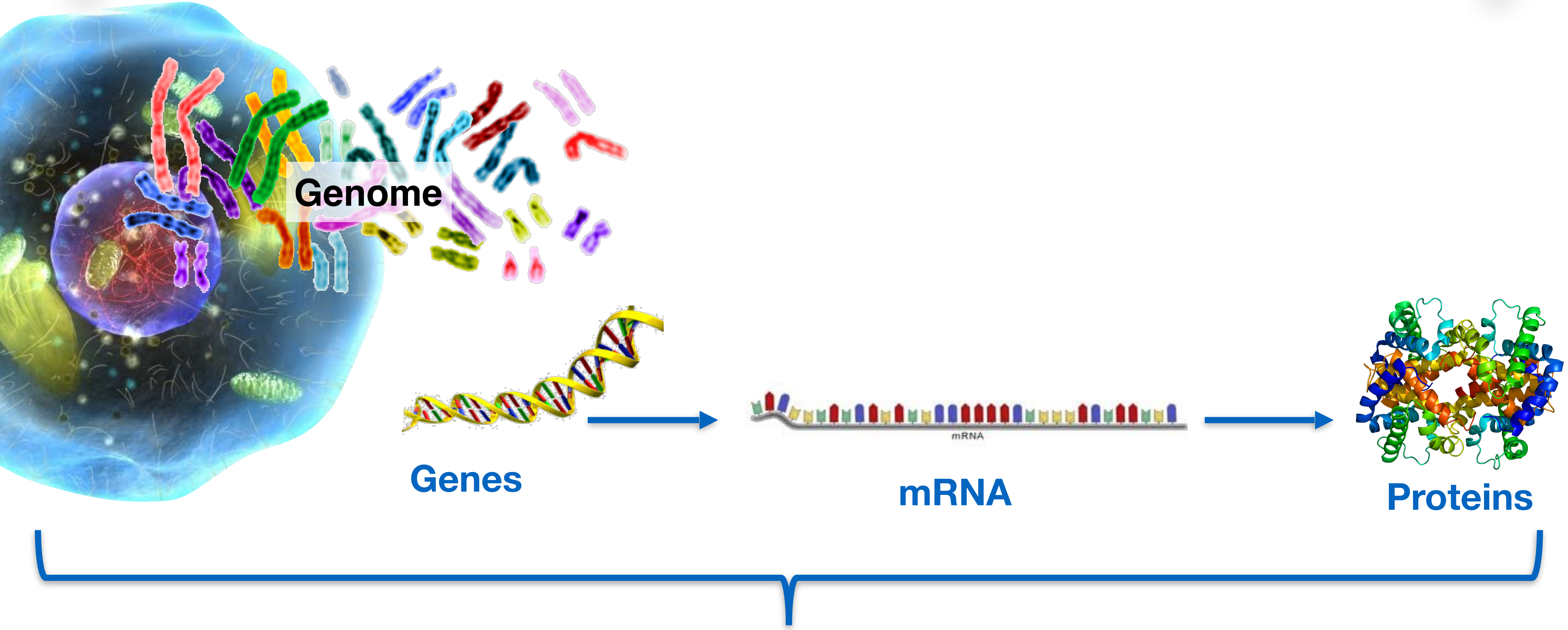
Proteins

Modules

- Modules are designed for the purpose of modular model composition
- Modules represent the functionality and interactions of individual biomolecules

Mary-Ann Blätke, Christian Rohr

BioModelKit - Modules



Genome

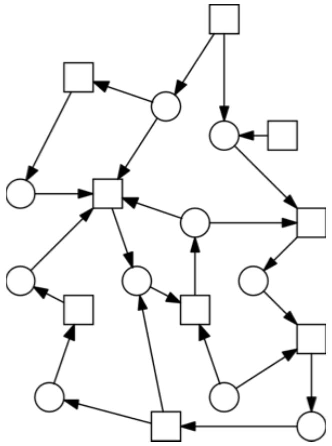
Genes

mRNA

Proteins

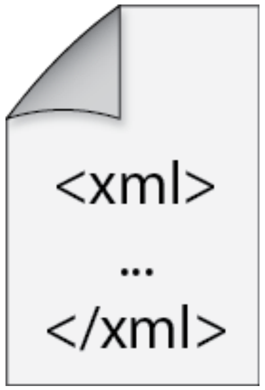
Modules

- description of functionality
- description interactions



Petri Net

+



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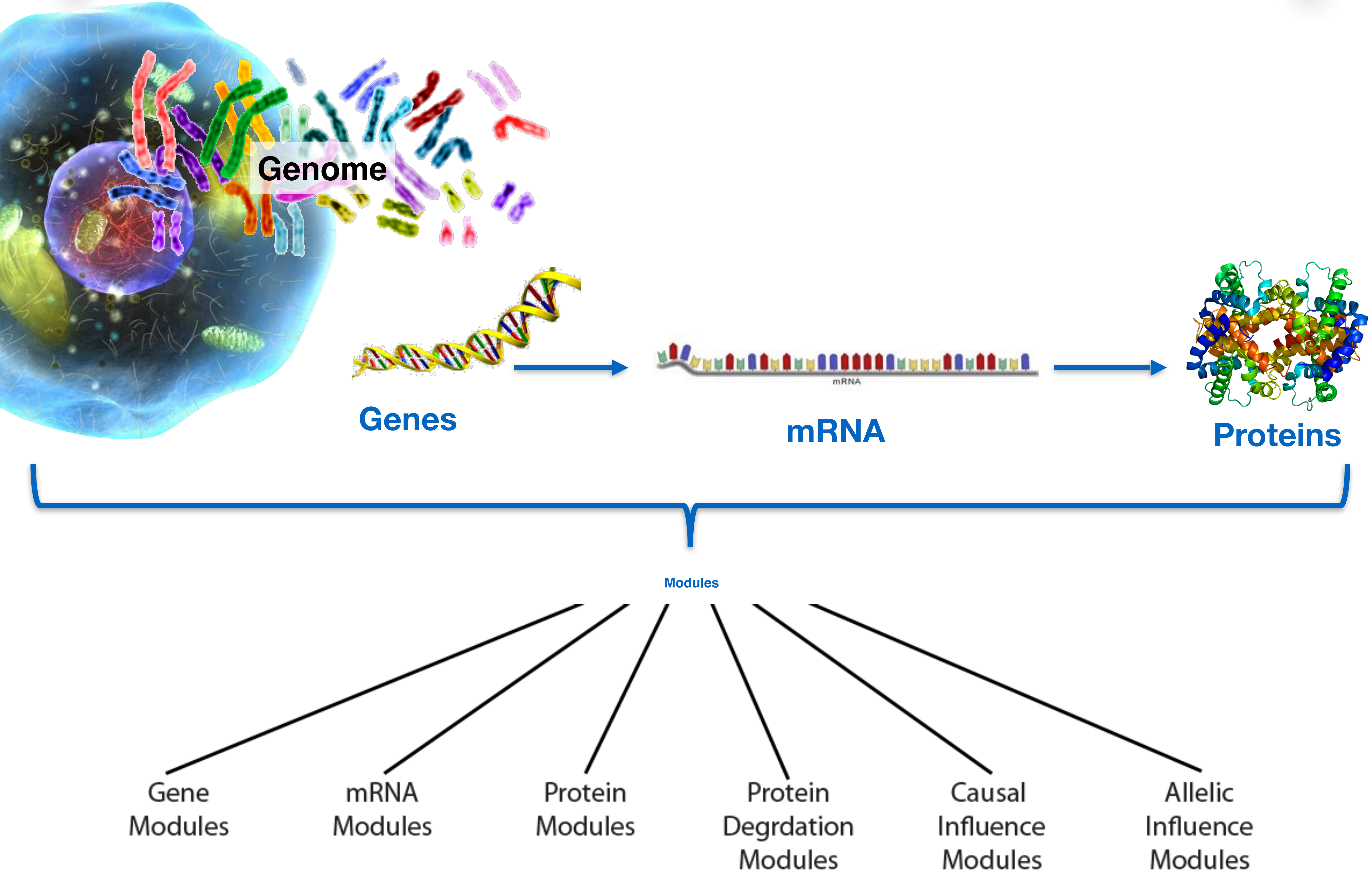
BMK-ML Annoations

- general information
- description of transitions
- description of places
- publication references
- bioDB references

BMK-Framework - Module Types



Genome

Genes

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Proteins

Modules

Gene Modules

mRNA Modules

Protein Modules

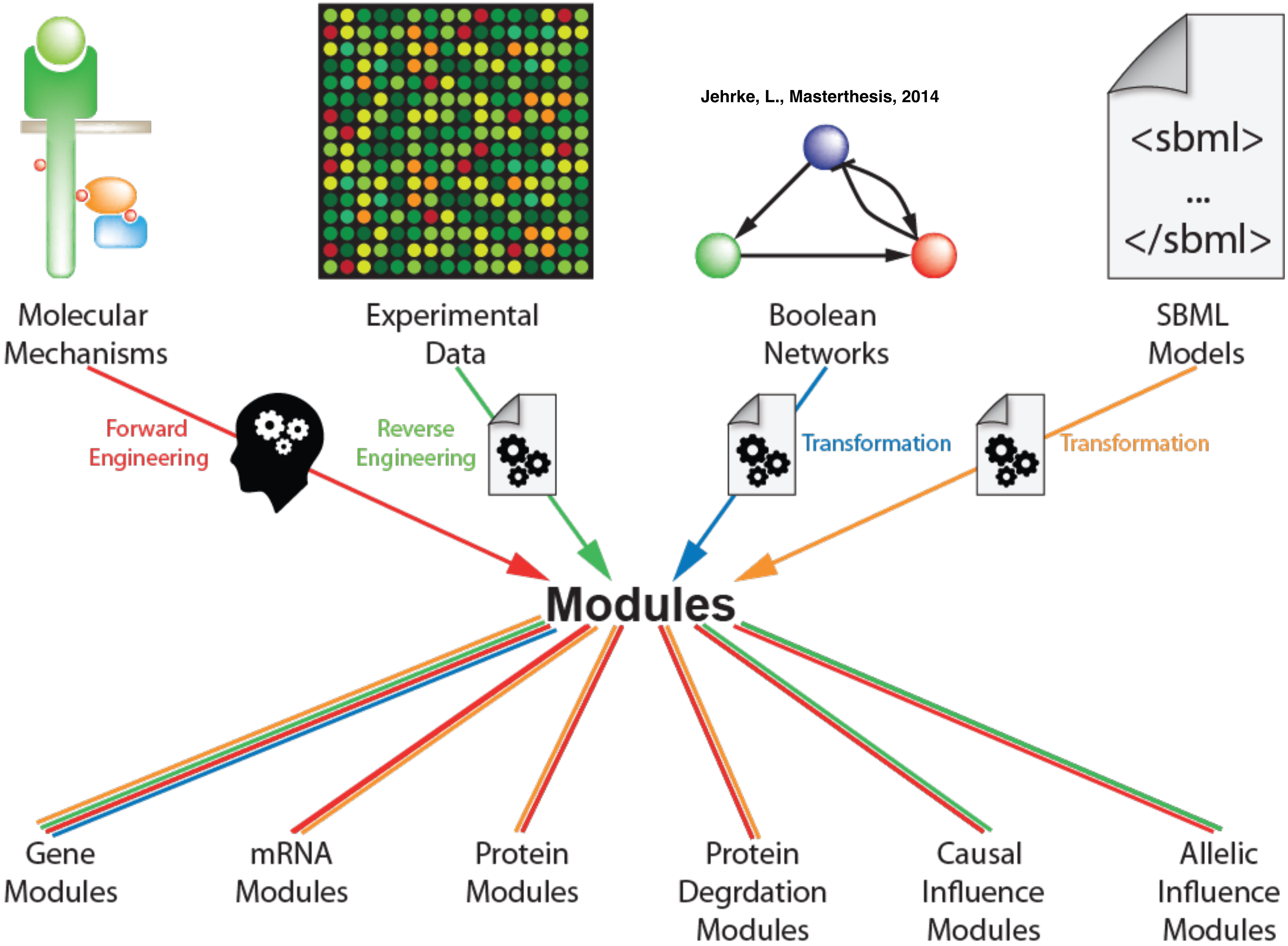
Protein Degrdation Modules

Causal Influence Modules

Allelic Influence Modules

Blätke, M.A. et al., CMSB 2012, Springer, LNCS/LNBI 7605, (2012)

BMK-Framework - Module Construction

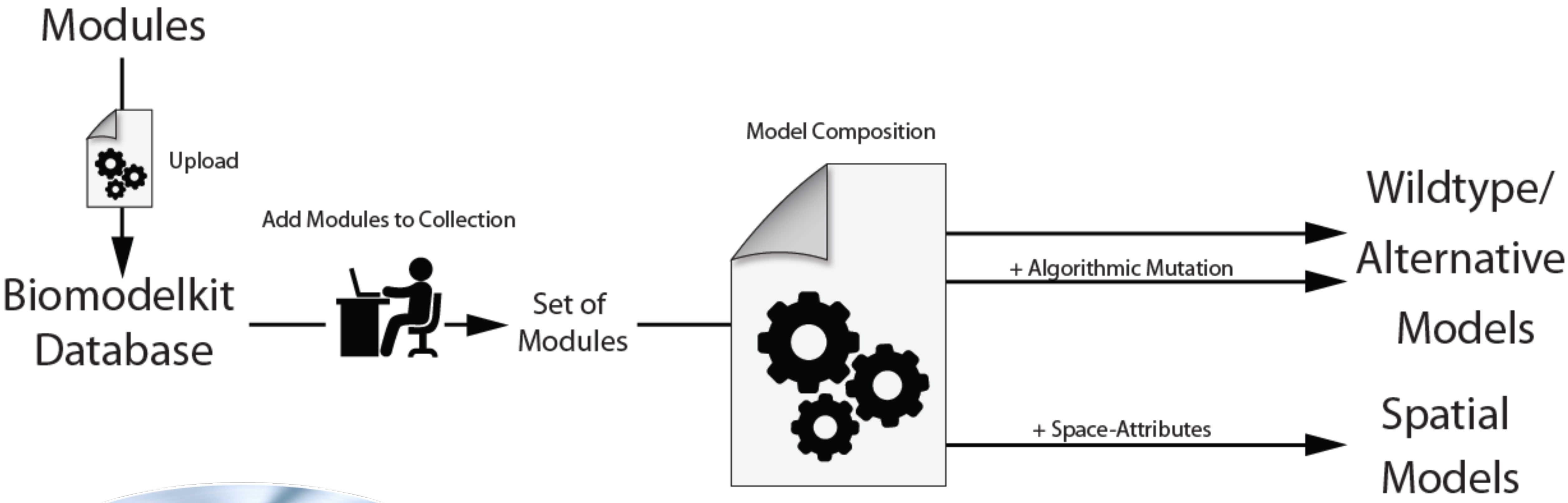


Soldmann, M., Masterthesis, 2015

Jehrke, L., Masterthesis, 2014

Blätke, M.A. et al., CMSB 2012, Springer, LNCS/LNBI 7605, (2012)

BMK-Framework - Database


Modules

Upload

Biomodelkit Database

Add Modules to Collection

Set of Modules

Model Composition

Wildtype/ Alternative Models

+ Algorithmic Mutation

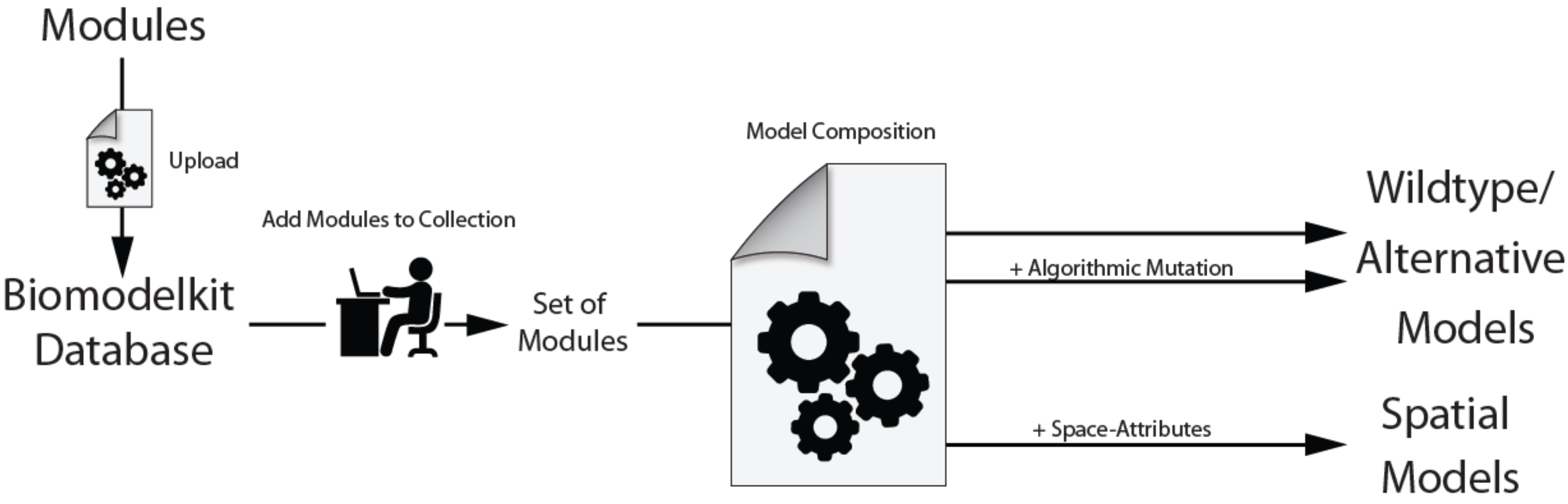
+ Space-Attributes

Spatial Models

MySQL:

- explicitly store graph structure
- explicitly store annotations
- link annotations and graph structure
- module versioning

BMK-Framework - Web-Interface



Modules

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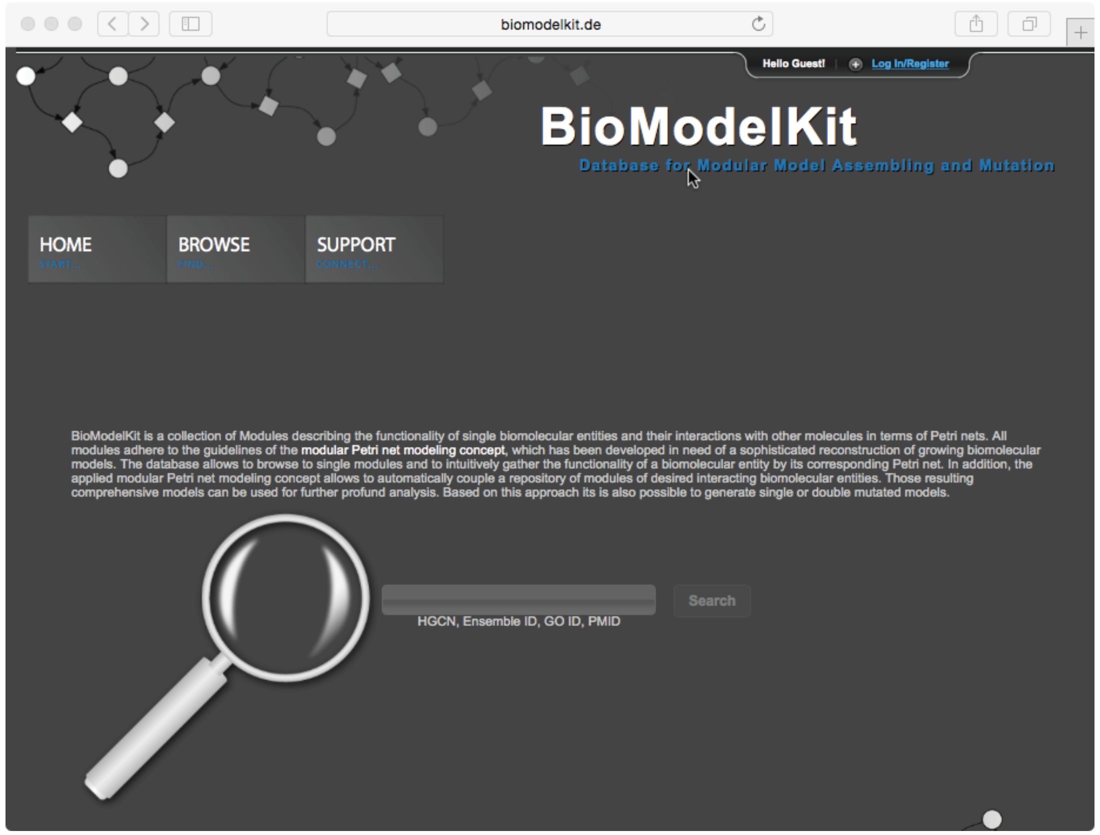


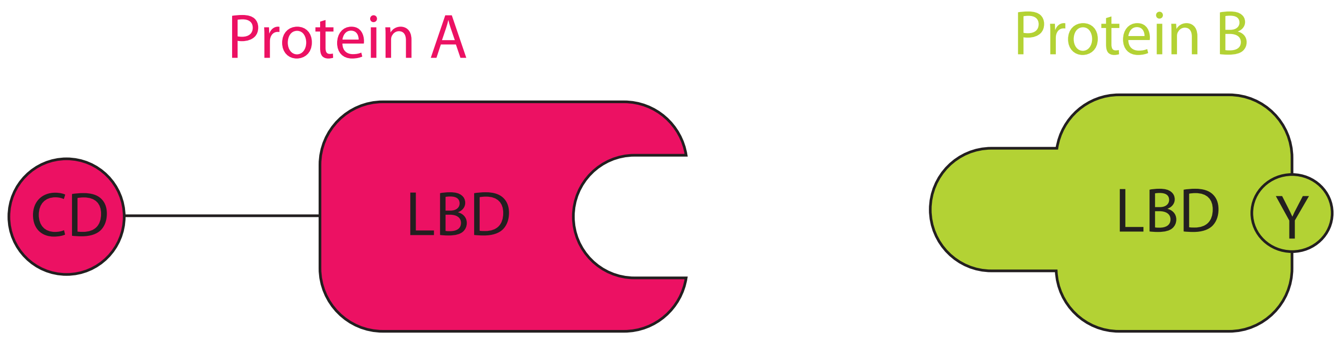
BioModelKit is a collection of Modules describing the functionality of single biomolecular entities and their interactions with other molecules in terms of Petri nets. All modules adhere to the guidelines of the **modular Petri net modeling concept**, which has been developed in need of a sophisticated reconstruction of growing biomolecular models. The database allows to browse to single modules and to intuitively gather the functionality of a biomolecular entity by its corresponding Petri net. In addition, the applied modular Petri net modeling concept allows to automatically couple a repository of modules of desired interacting biomolecular entities. Those resulting comprehensive models can be used for further profund analysis. Based on this approach its is also possible to generate single or double mutated models.

HGCN, Ensemble ID, GO ID, PMID

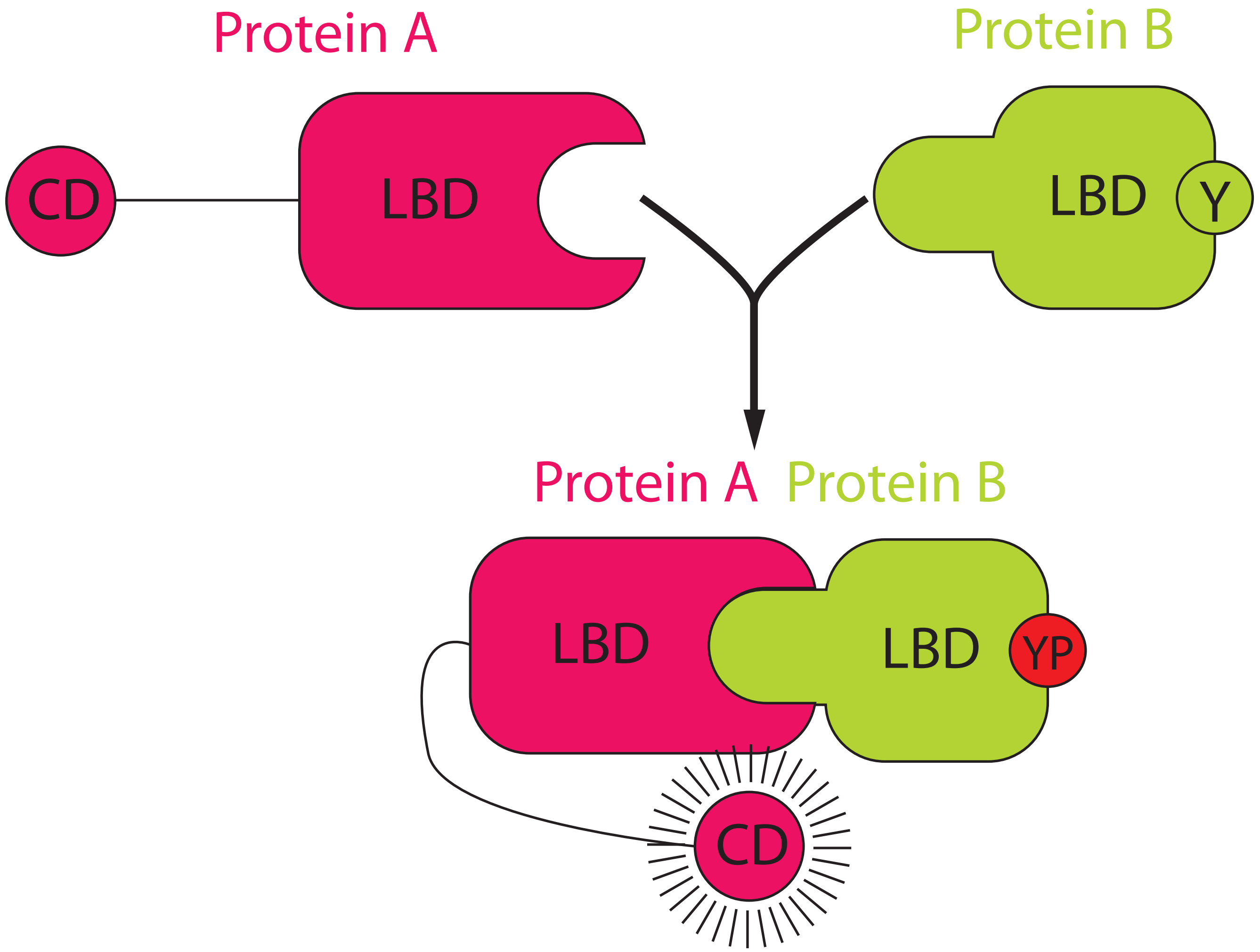
Web-Interface:

- upload modules
- module annotation
- browse/search for modules
- store modules collections
- automatic model composition
- algorithmic model mutation
- spatial extension

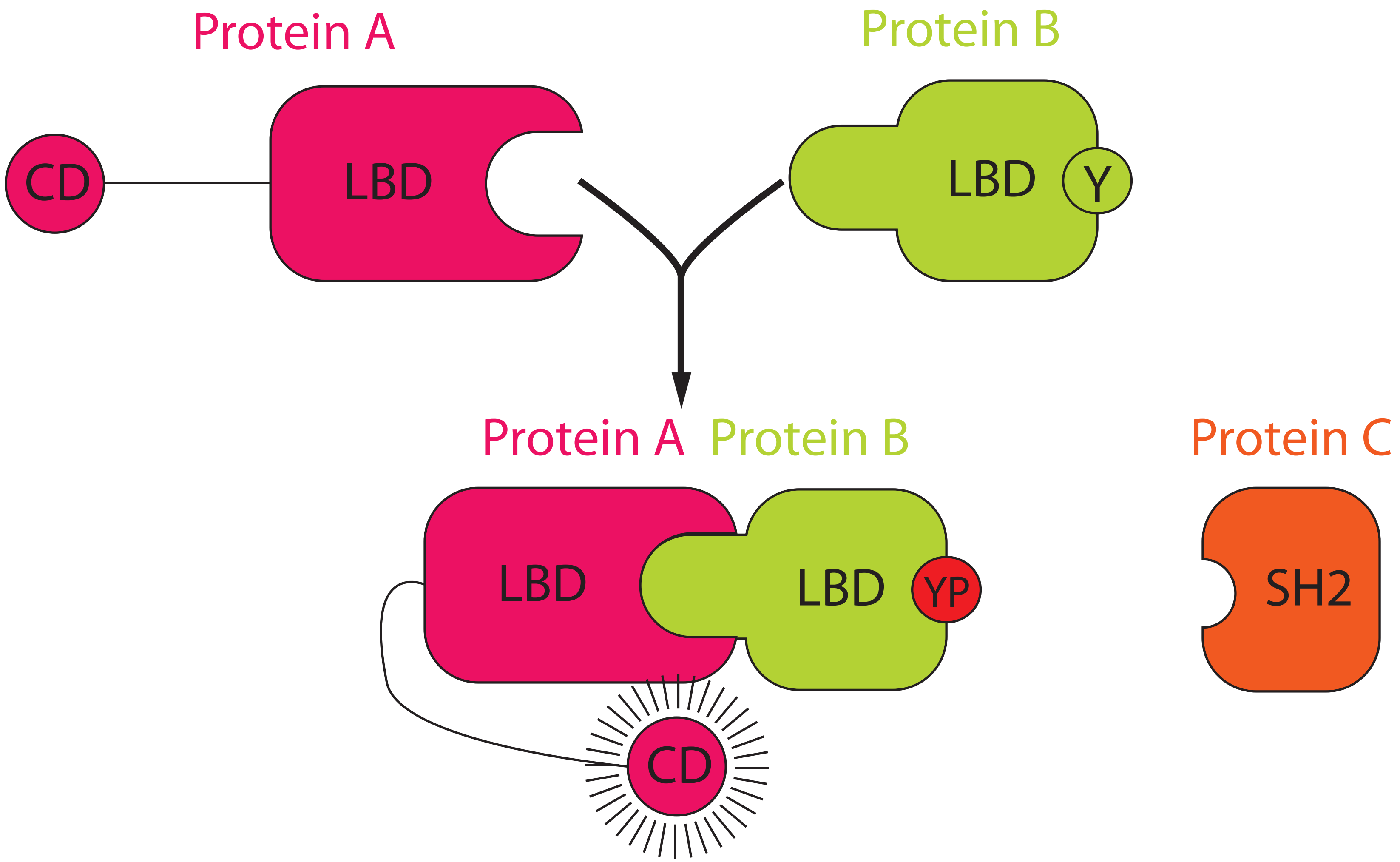
Running Example



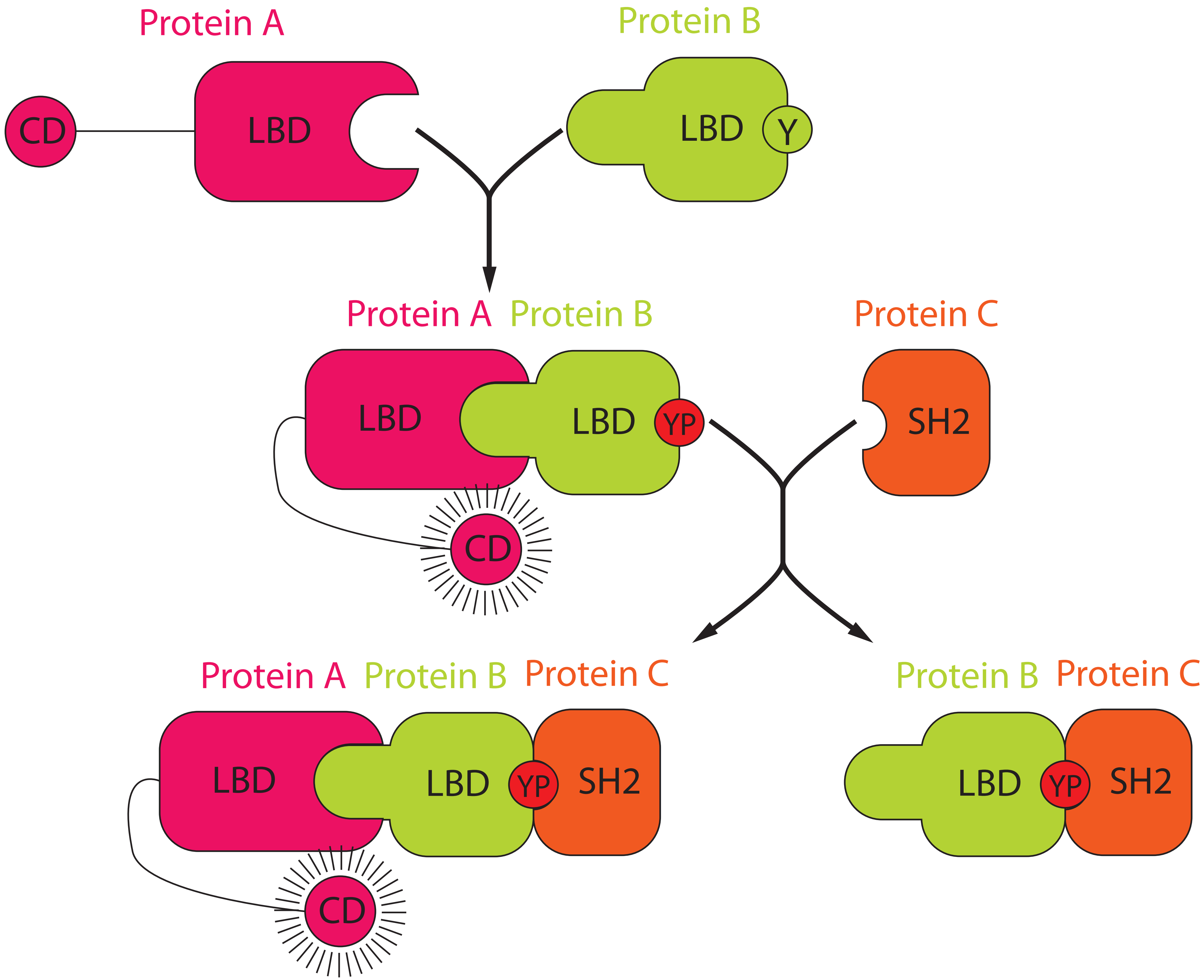
Running Example



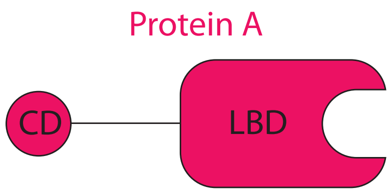
Running Example



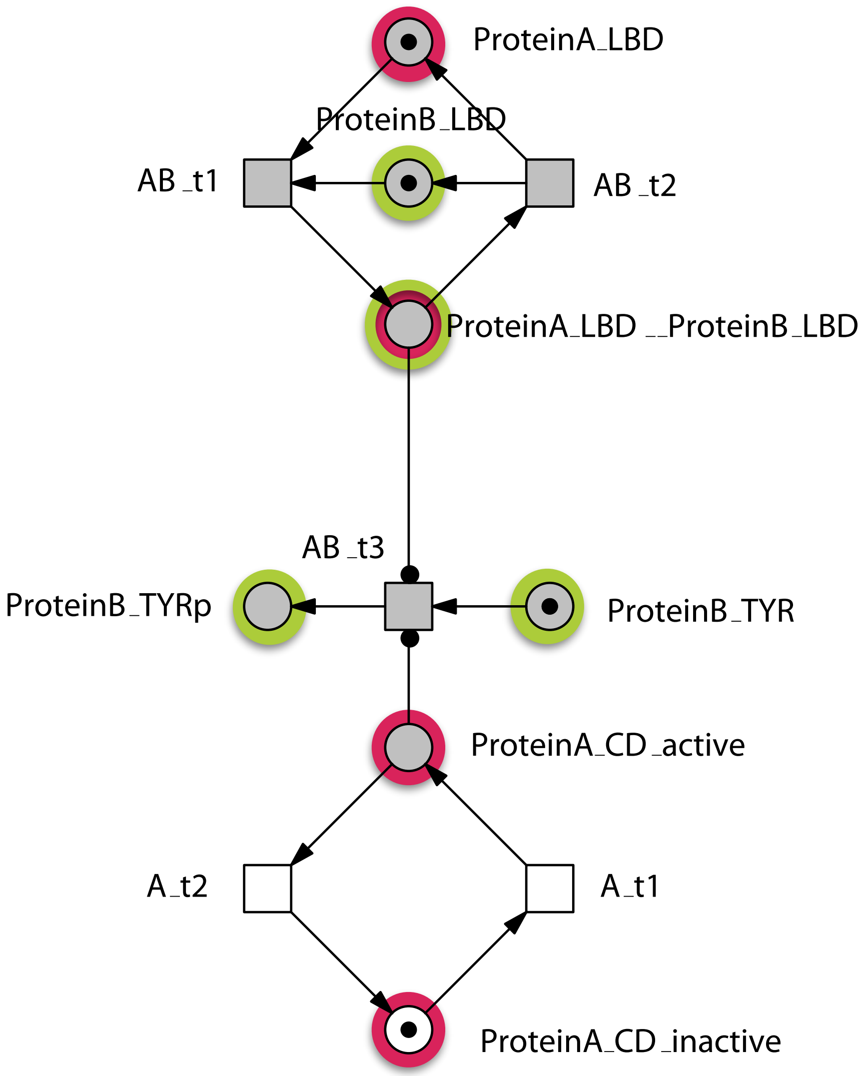
Running Example

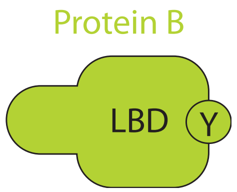


Modules of the Running Example

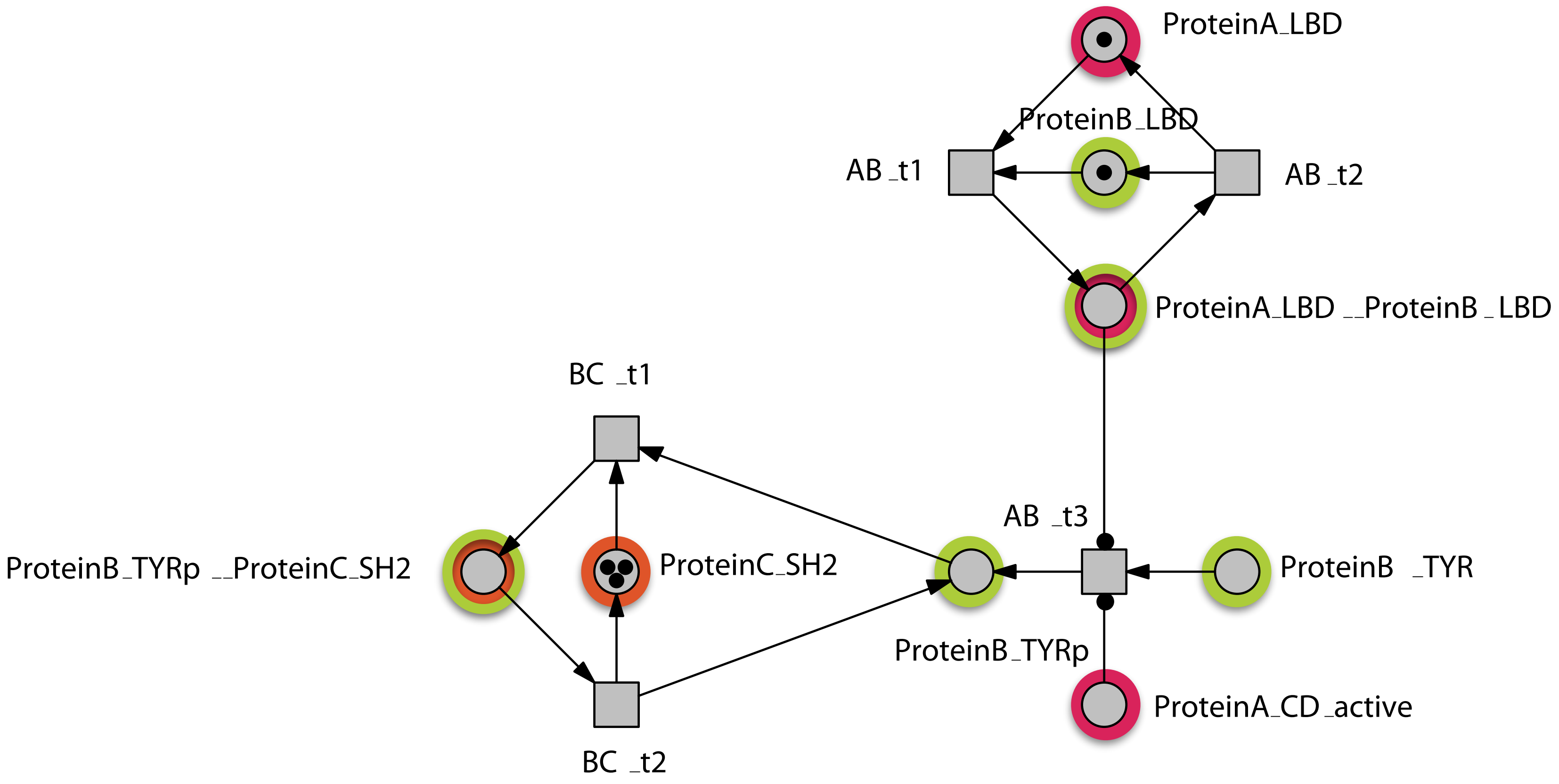


Module of Protein A





Module of Protein B

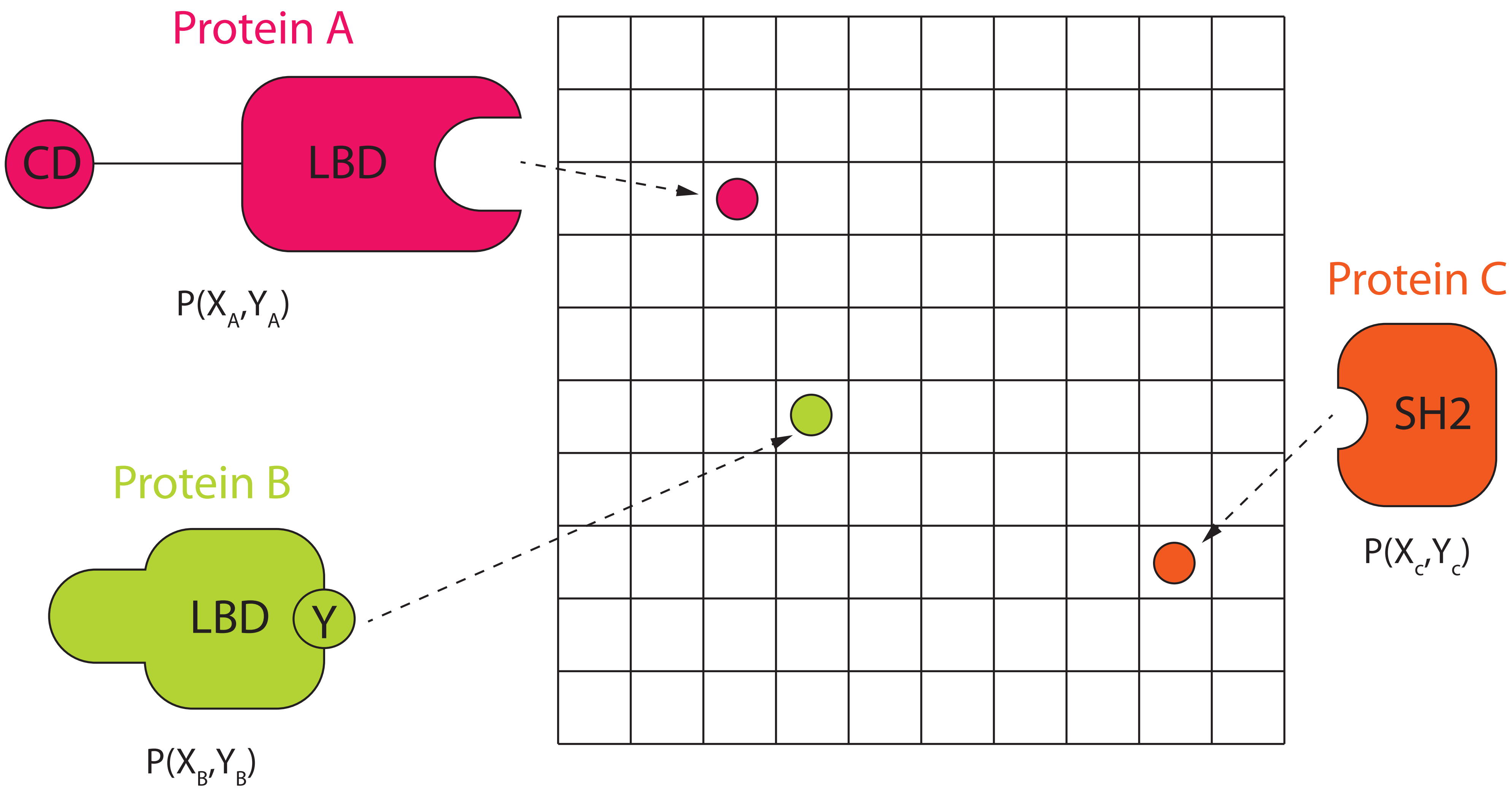


Spatial Transformation Algorithm

1. Explicit encoding of local positions
2. Local restriction of interactions
3. Explicit encoding of local position changes
4. Explicit encoding of component instances using coloured Petri nets

Step 1: Explicit Encoding of Local Positions

- Define a grid for each component (1D,2D or 3D)
    - e.g. 2D Grid: xDimA = 10, yDimA = 10
- Set a local position for each component
    - e.g. A(3,8), B(4,5), C(9,3)



Step 1: Explicit Encoding of Local Positions

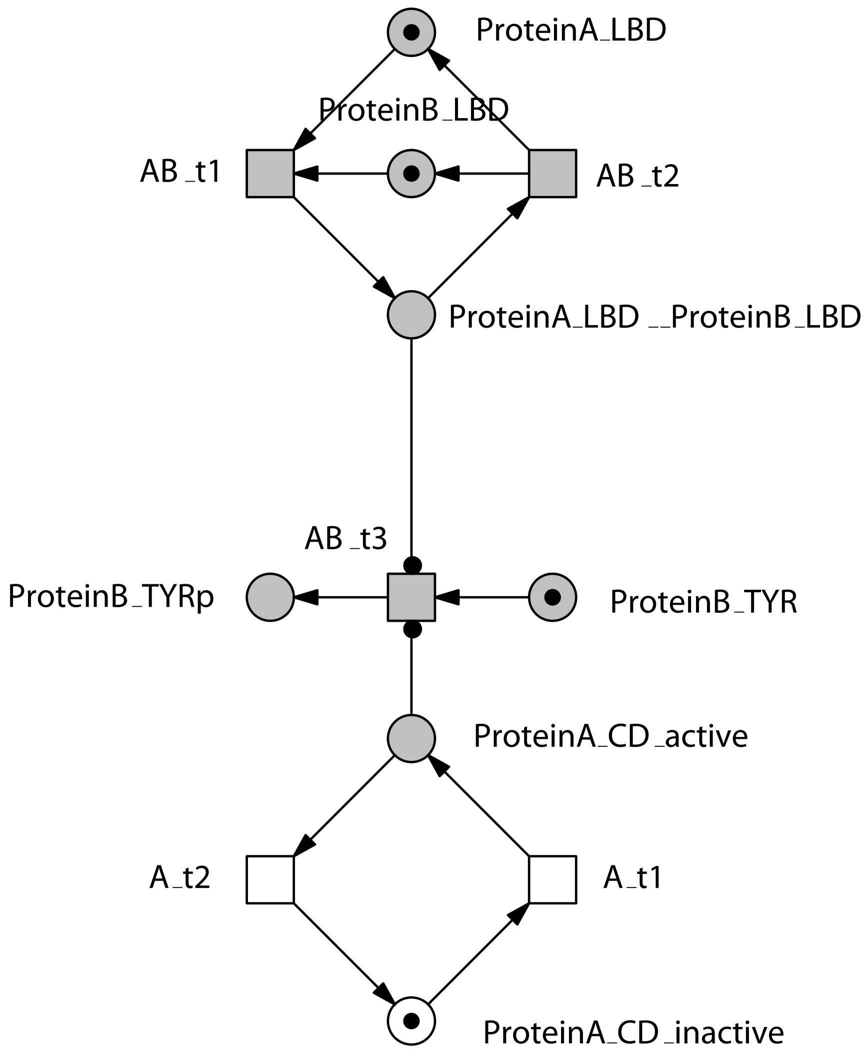
- Define a grid for each component (1D,2D or 3D)
  - e.g. 2D Grid: xDimA = 5, yDimA = 5
- Set a local position for each component
  - e.g. A(1,1), B(3,3), C(4,4)

- For each component and each axis add a place

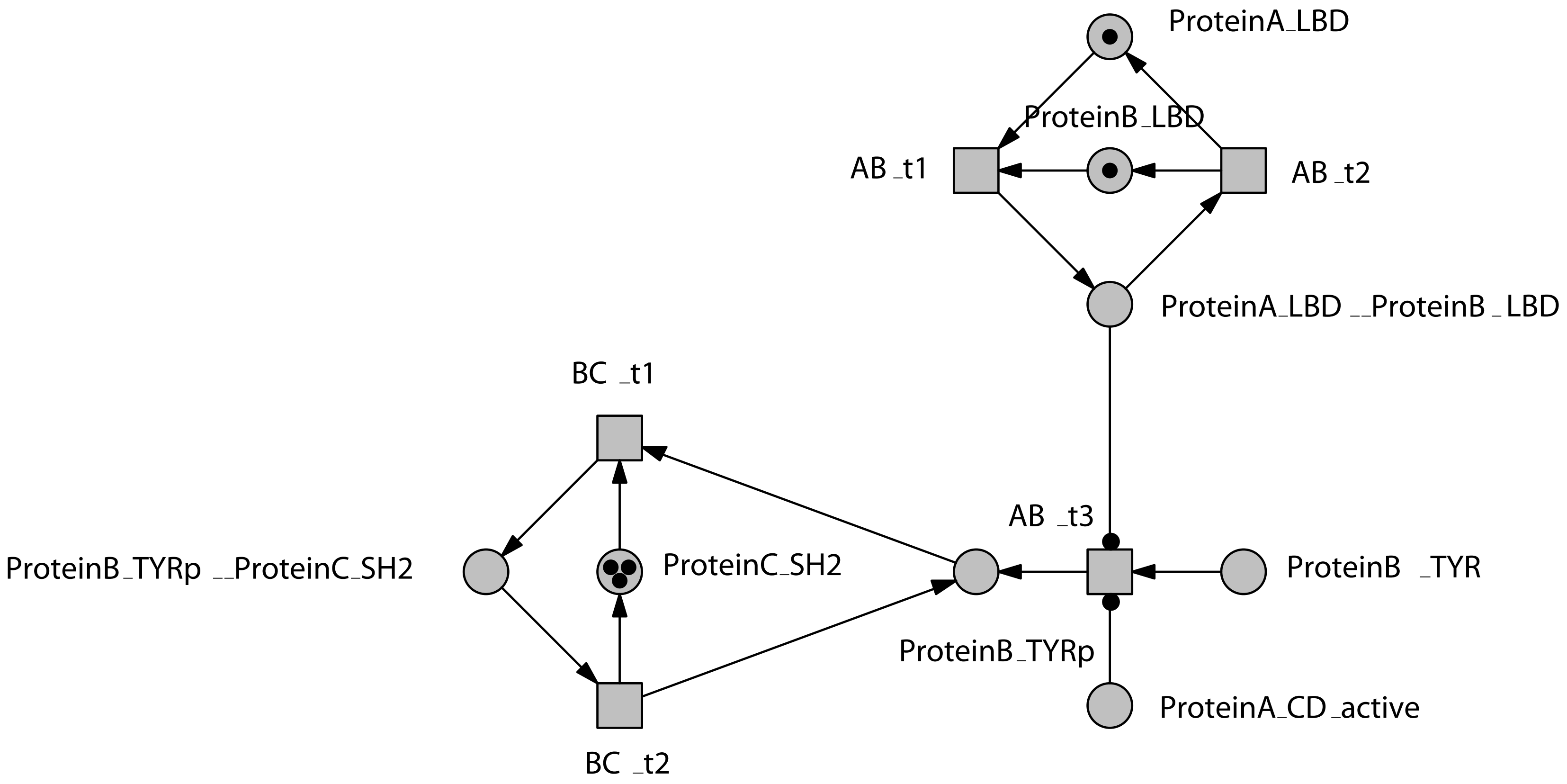
- Mark coordinate place according to initial local position

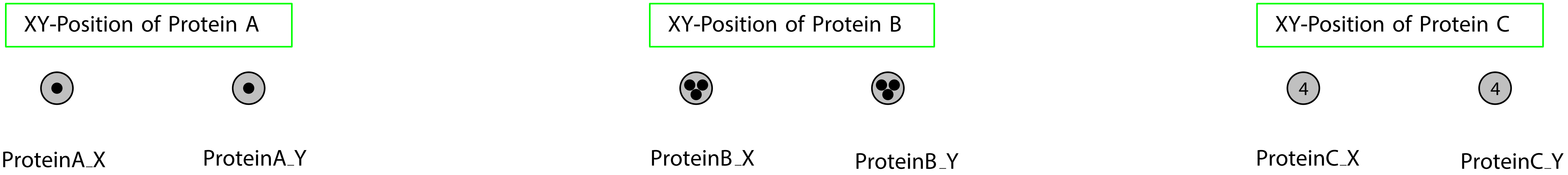
Step 1: Explicit Encoding of Local Positions

Module of Protein A



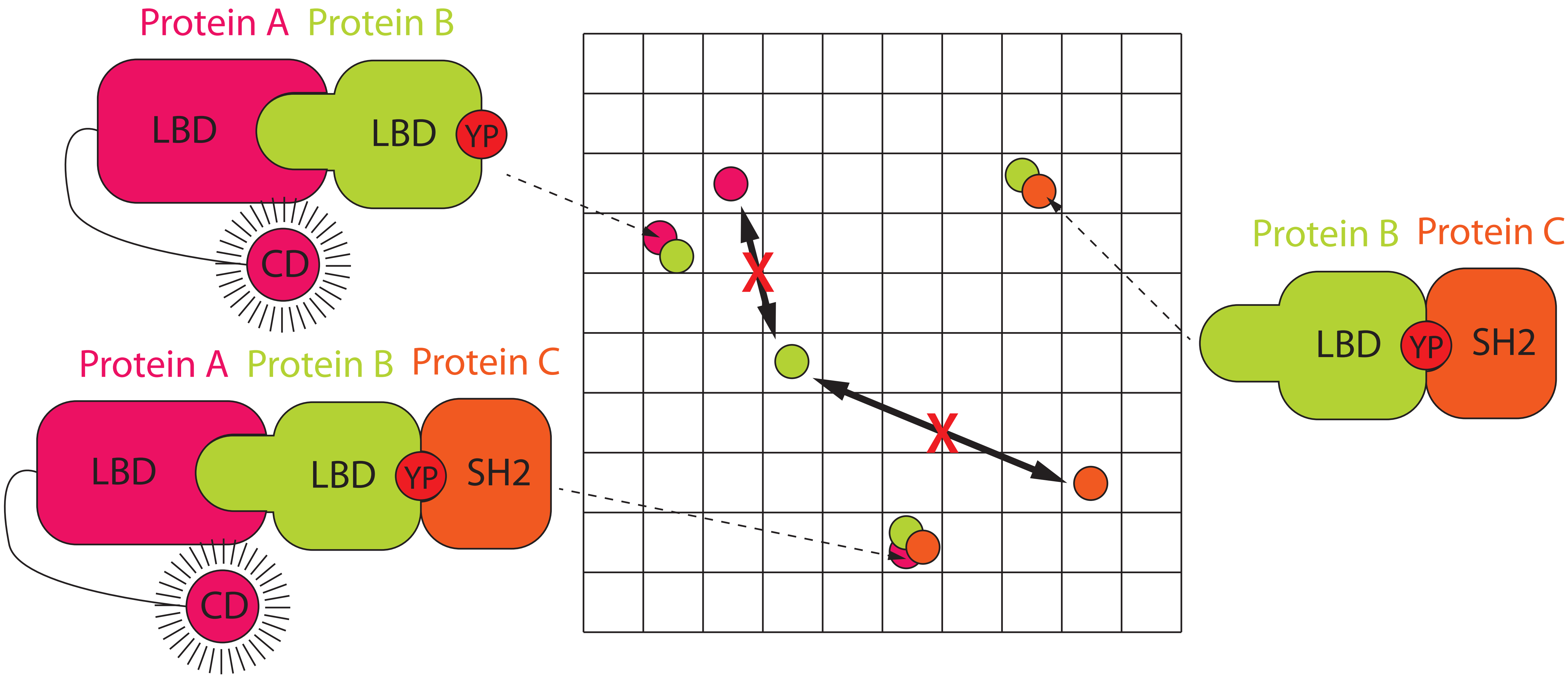
Module of Protein B





Step 2: Local Restriction of Interactions

- Components can <u>only</u> interact if they fulfil a defined neighbourhood relation
- Define a neighbourhood relation
  - e.g. local positions of components must be identical



Step 2: Local Restriction of Interactions

- Components can only interact if they fulfil a defined neighbourhood relation
- Define a neighbourhood relation
  - e.g. local positions of components must be identical

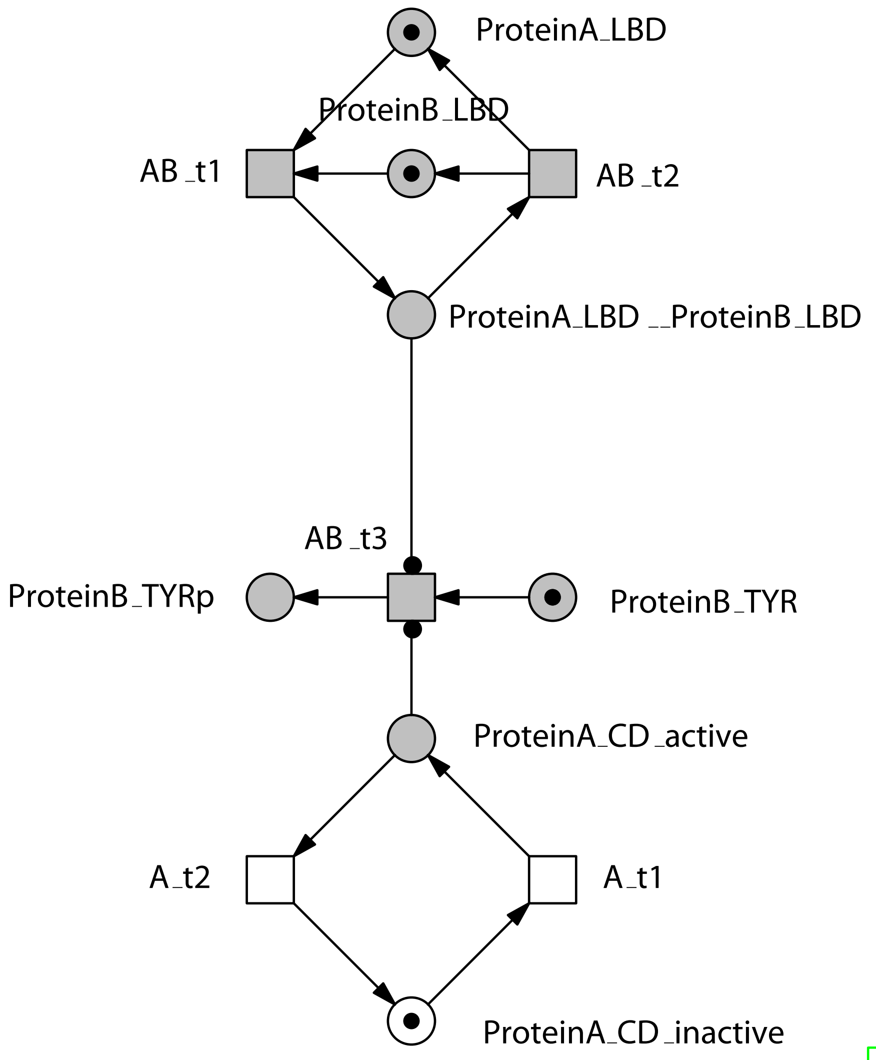
For each transition representing an interaction:

- add coordinate places of each interacting component

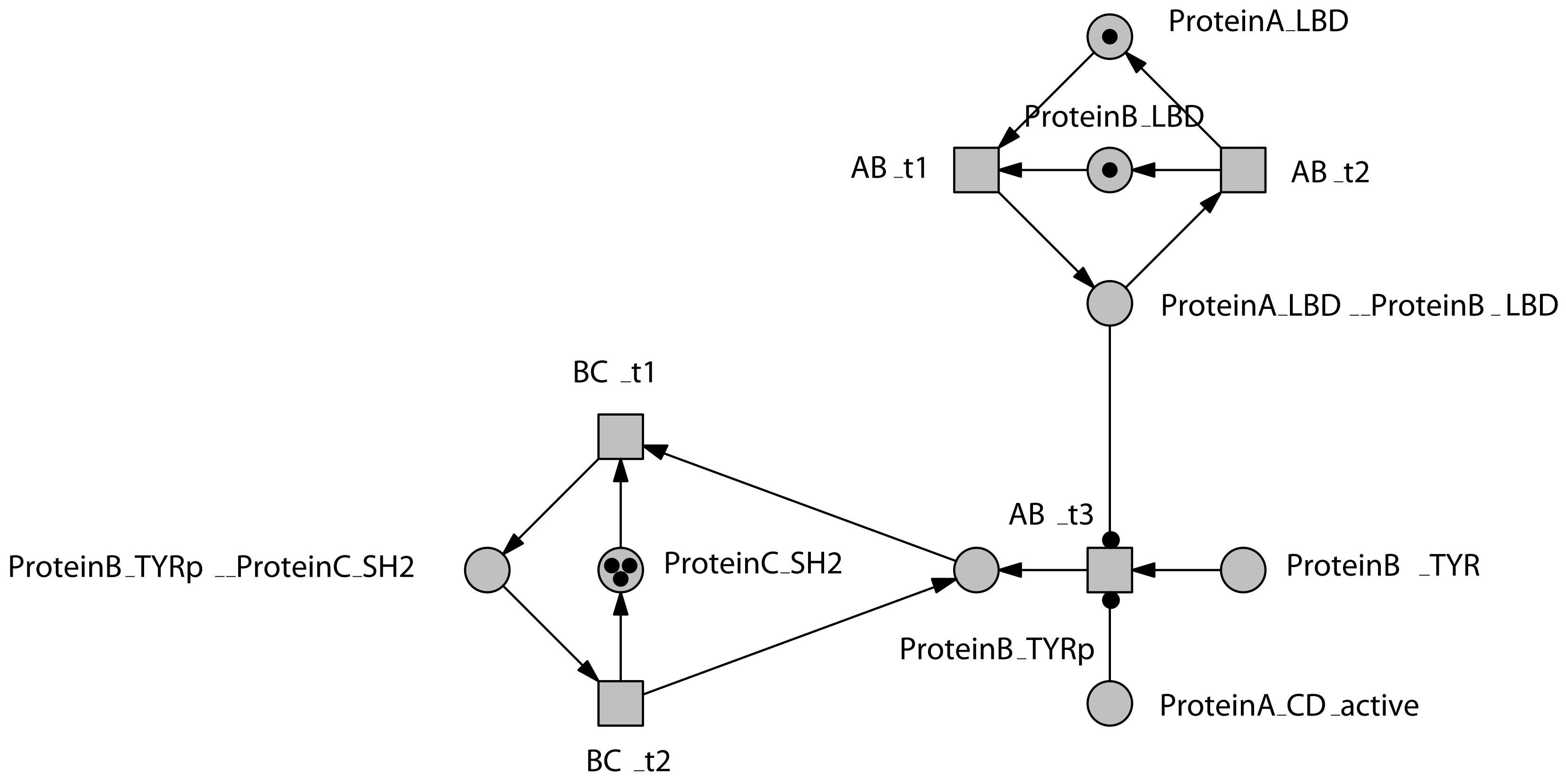
- multiply firing-rate with a boolean expression evaluating the distance between the interacting components

Step 2: Local Restriction of Interactions

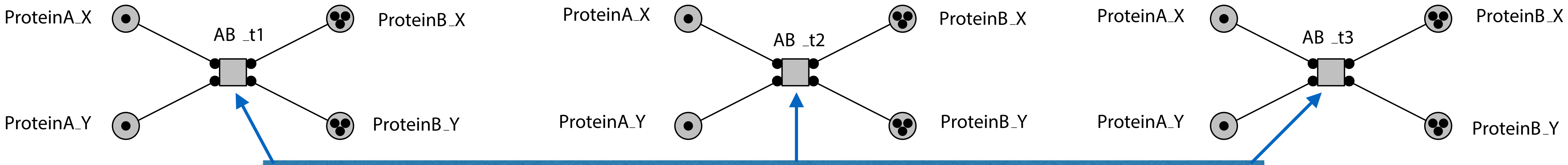
Module of Protein A



Module of Protein B



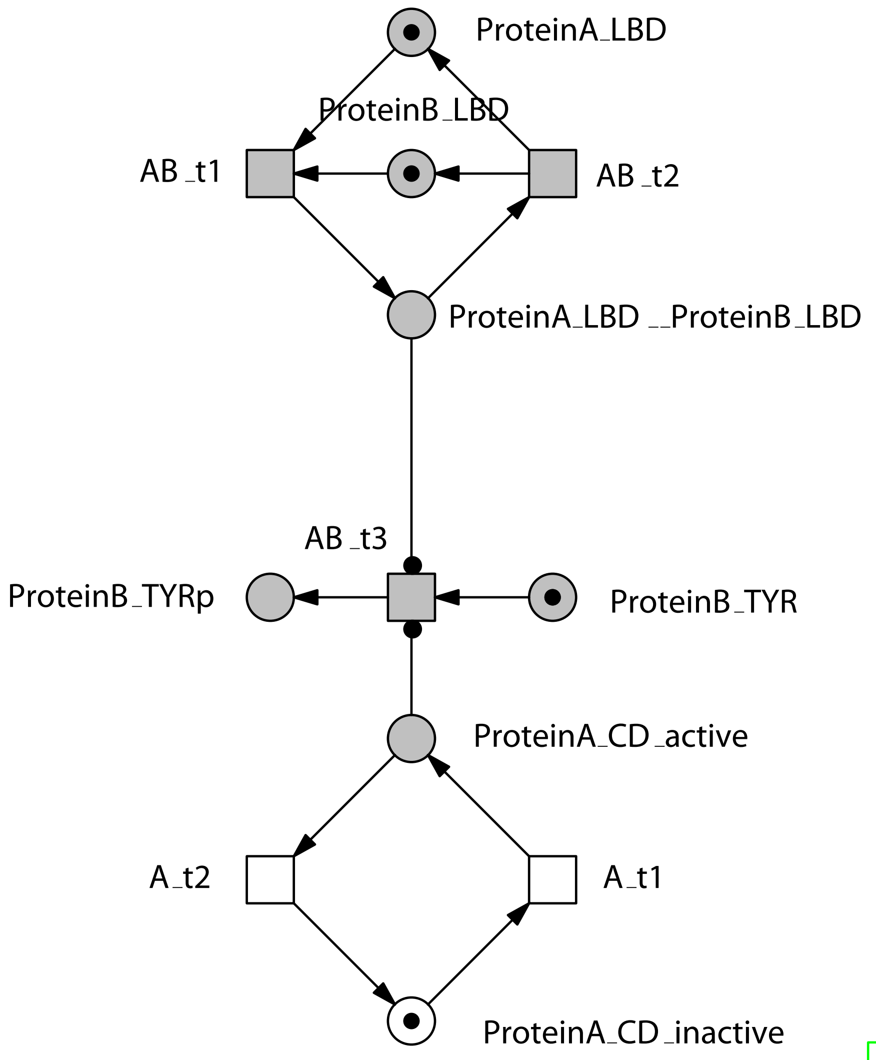
Restricted Interaction - Only if ProteinA (X,Y) = ProteinB (X,Y)



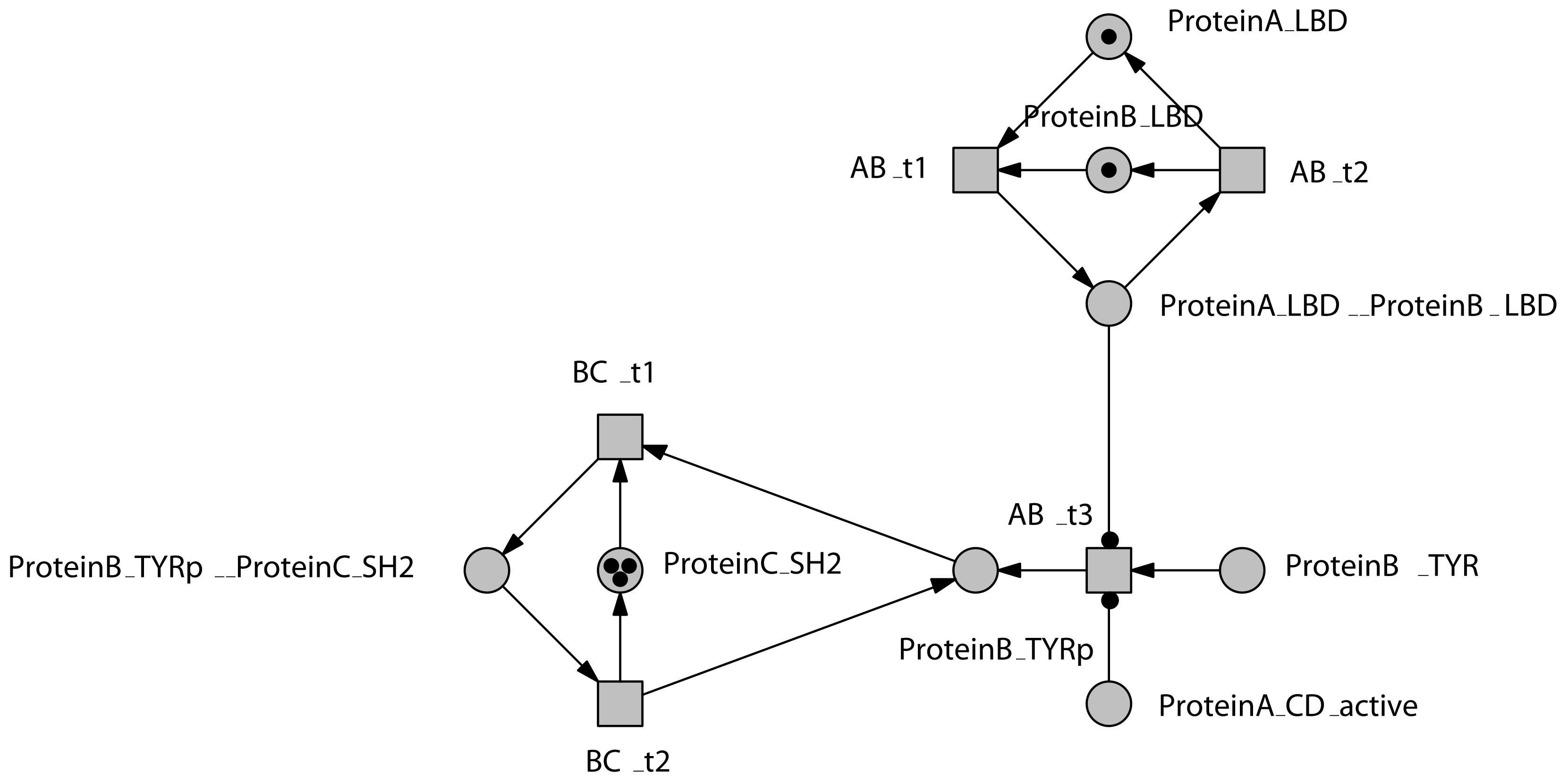
(ProteinA_X = ProteinB_X) & (ProteinA_Y = ProteinB_Y)*h(t)

Step 2: Local Restriction of Interactions

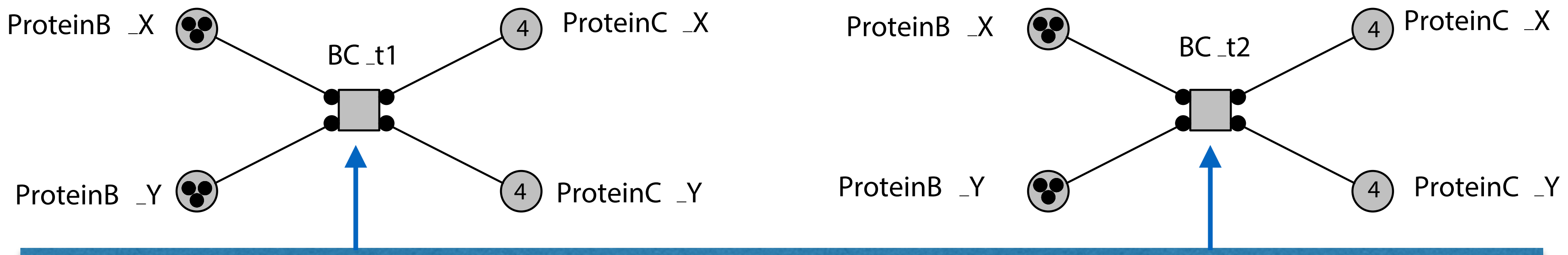
Module of Protein A



Module of Protein B



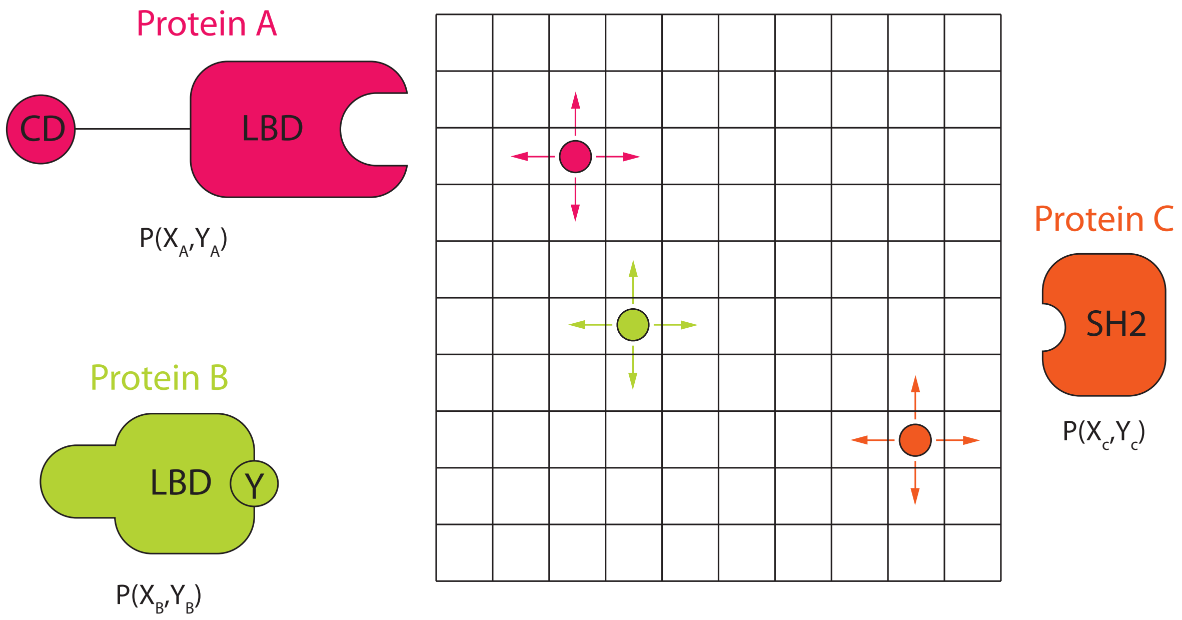
Restricted Interaction - Only if ProteinB (X,Y) = ProteinC (X,Y)



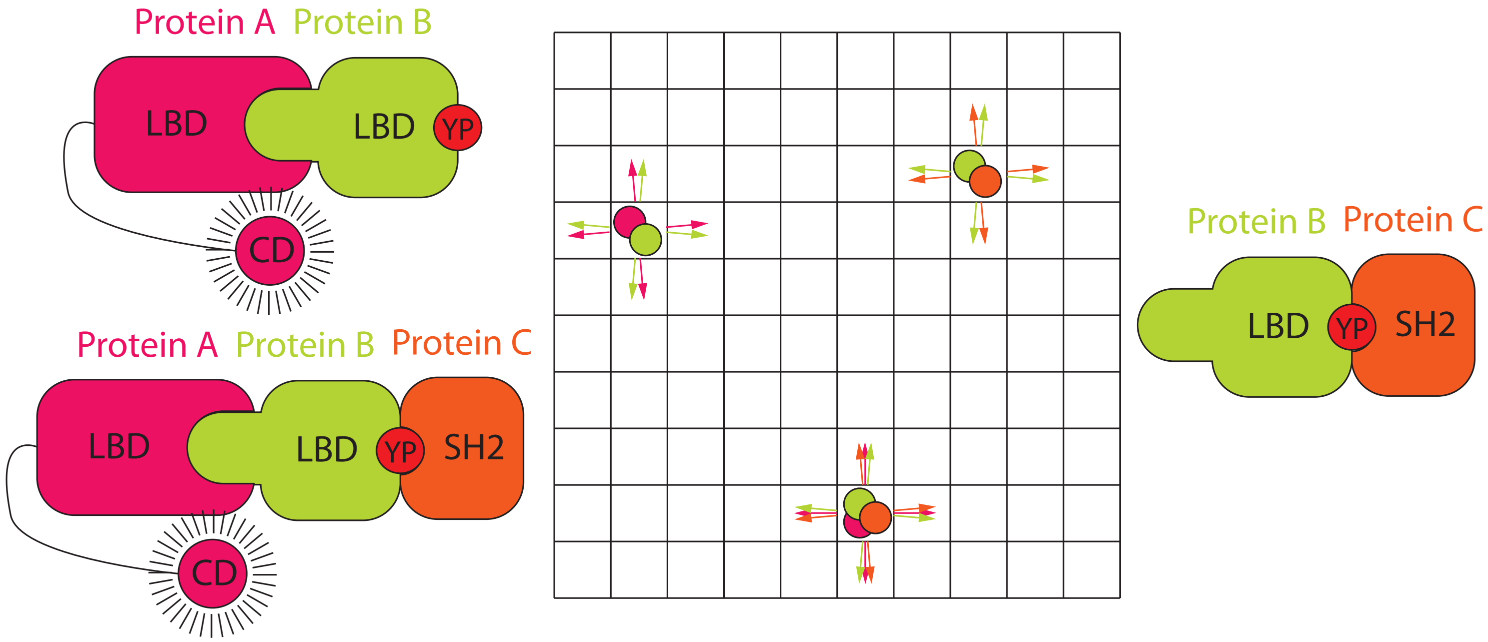
(ProteinB_X = ProteinC_X) & (ProteinB_Y = ProteinC_Y)*h(t)

Step 3: Explicit Encoding of Local Position Changes

Case 1: Movement of components as a single entity

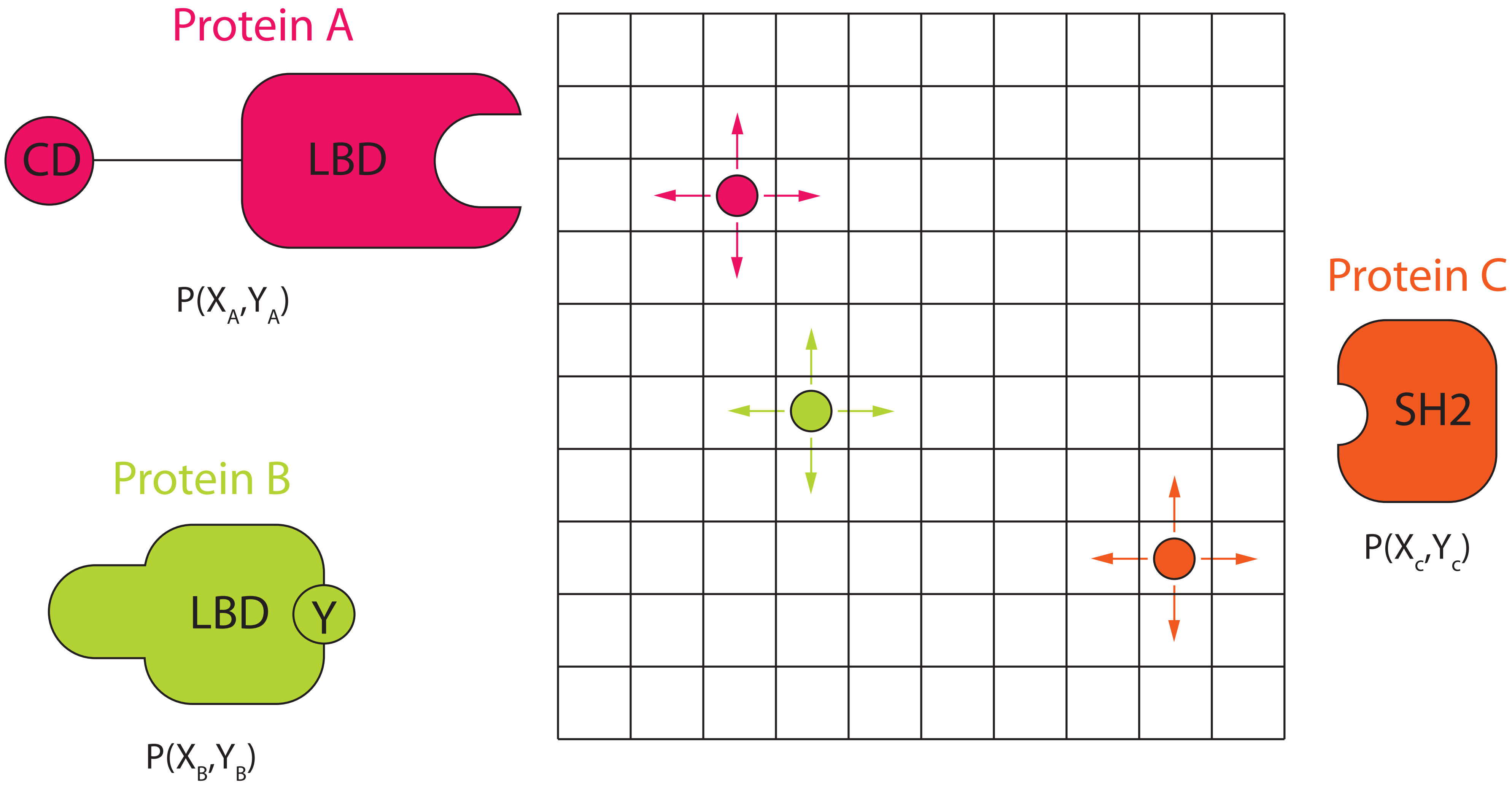


Case 2: Movement of components as complex



Case 1: Movement of components as a single entity

- Movement along the axes in respect to the defined grid size
  - e.g. 2D-Grid -> 2 direction of movement per axis
- Movement only if all interaction sites are unused
  - e.g. Protein B is not allowed to interact with Protein A or Protein C



Case 1: Movement of components as a single entity

- Movement along the axes in respect to the defined grid size
  - e.g. 2D-Grid -> 2 direction of movement per axis
- Movement only if all interaction sites are unused
  - e.g. Protein B is not allowed to interact with Protein A or Protein C

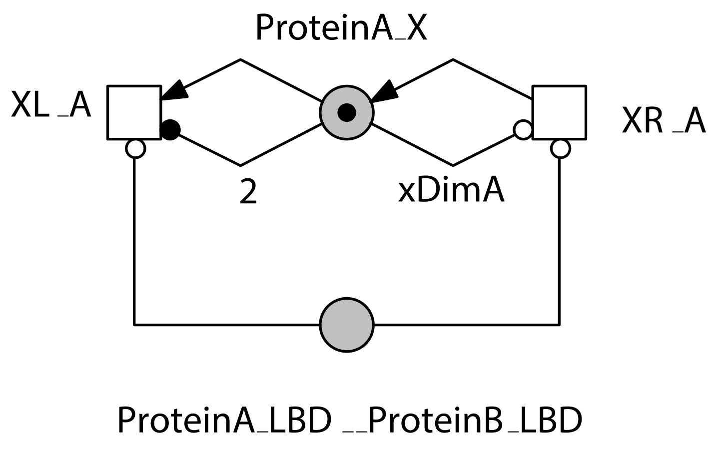
For each component and each axis

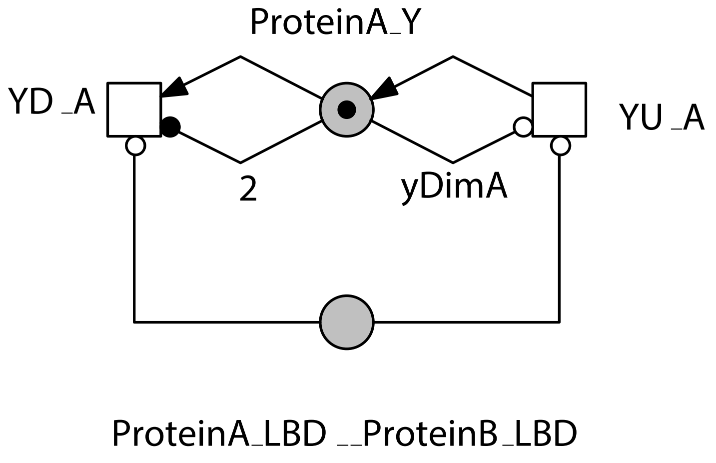
- add two transitions increase/decrease the value of the respective coordinate places in respect to the grid size

- connect places representing interaction states of the components via inhibitory arcs

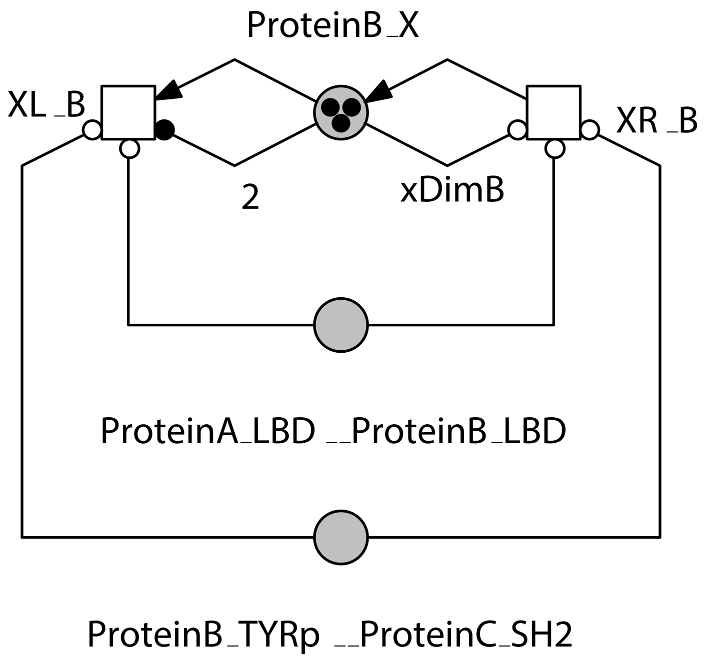
Case 1: Movement of components as a single entity

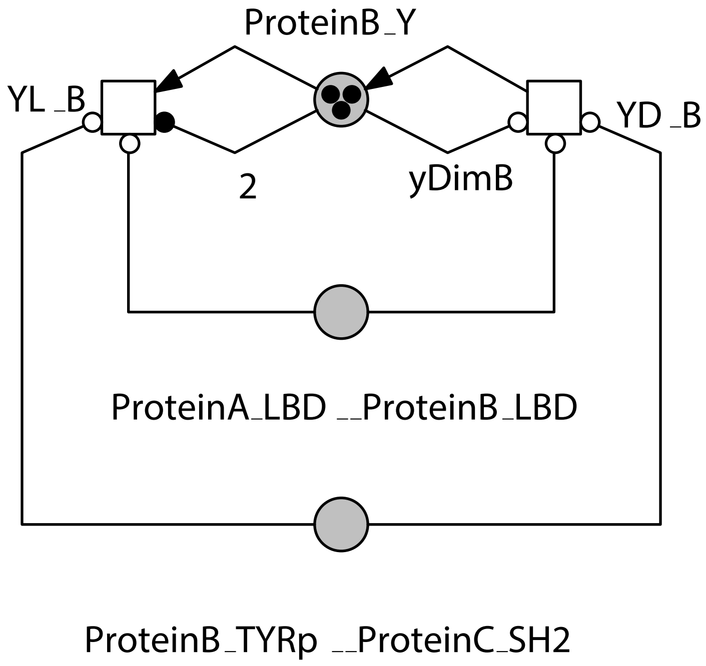
Movement of Protein A



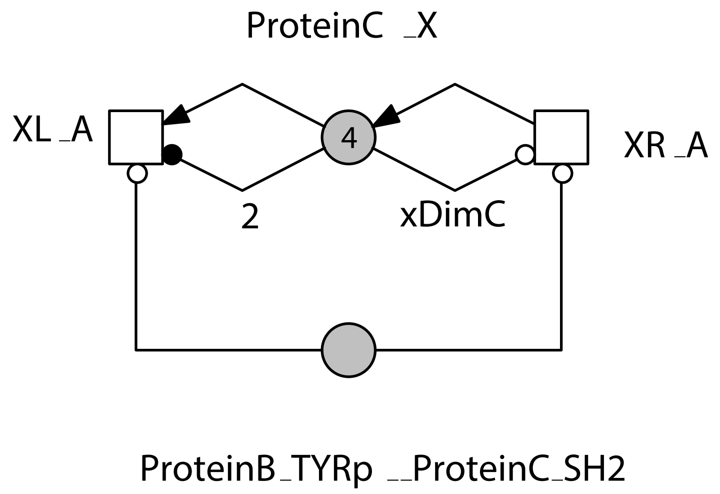


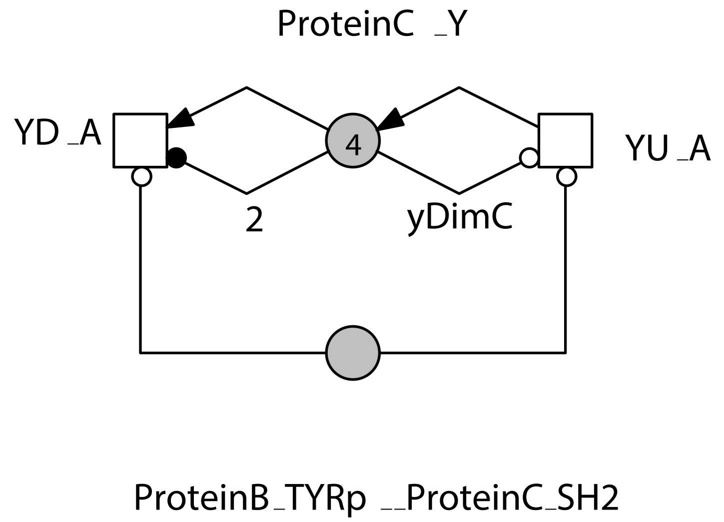
Movement of Protein B





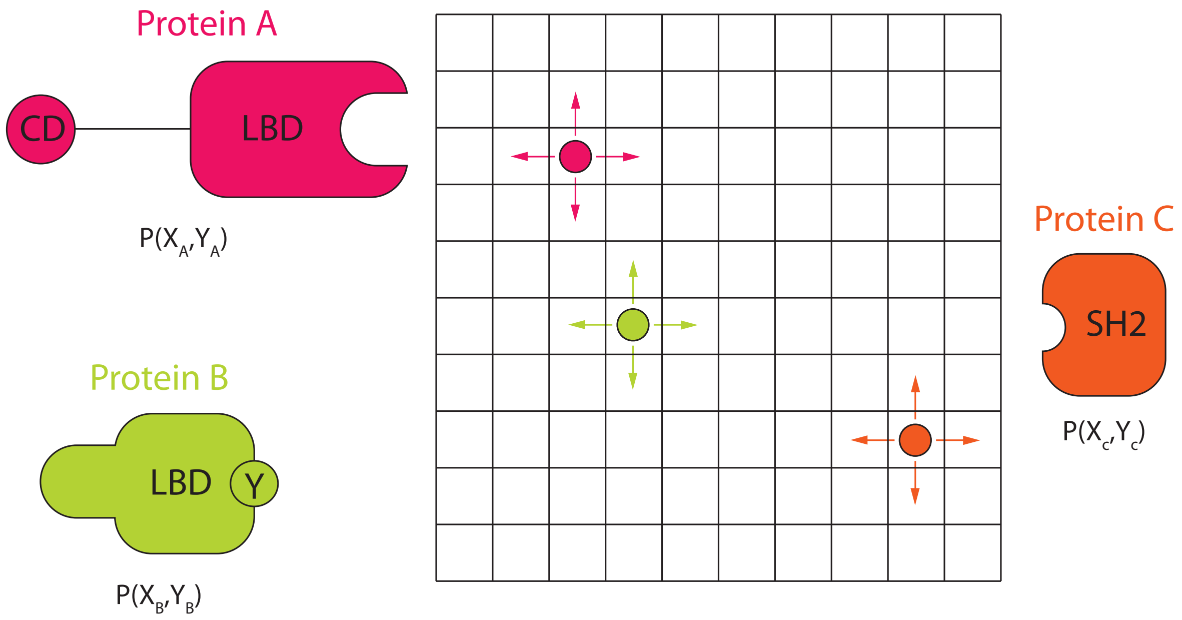
Movement of Protein C



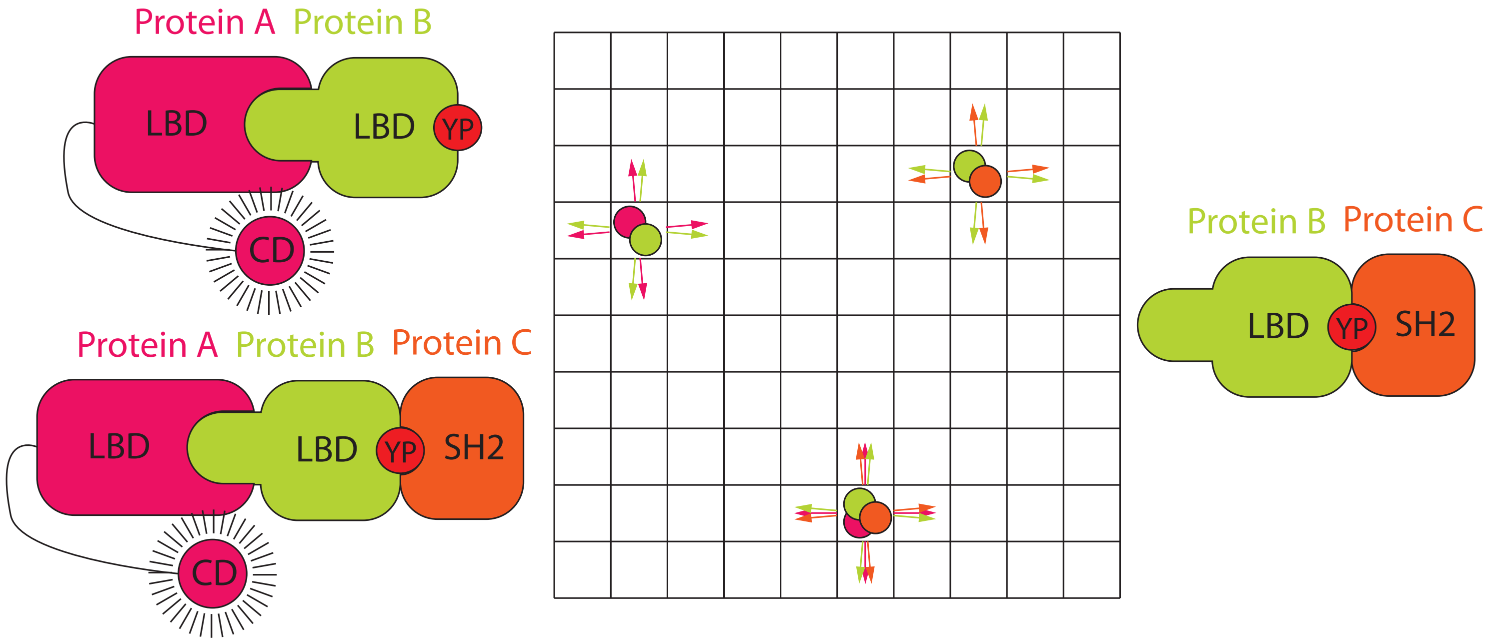


Step 3: Explicit Encoding of Local Position Changes

Case 1: Movement of components as a single entity

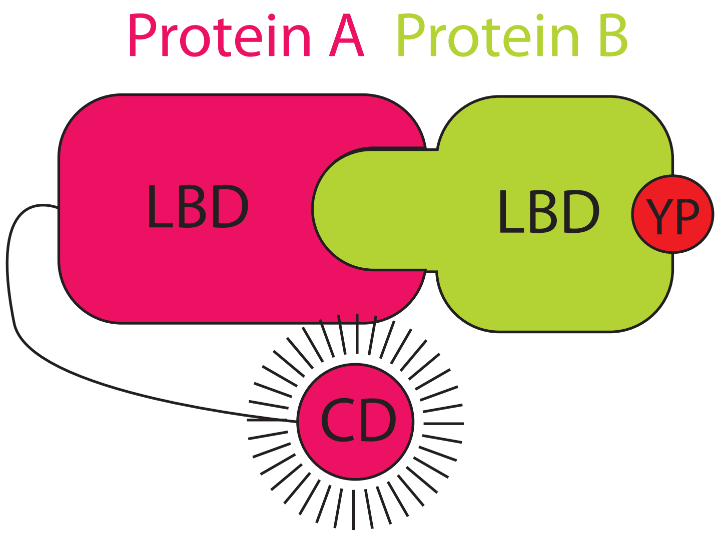


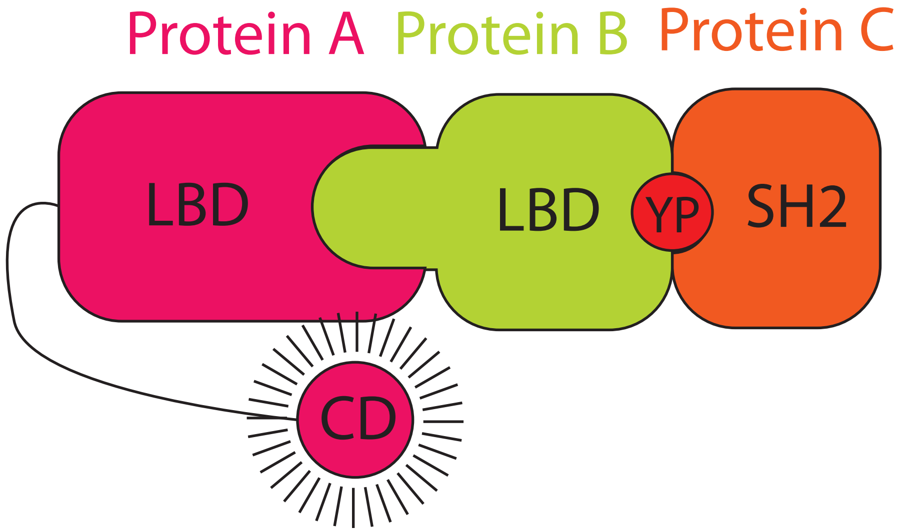
Case 2: Movement of components as complex

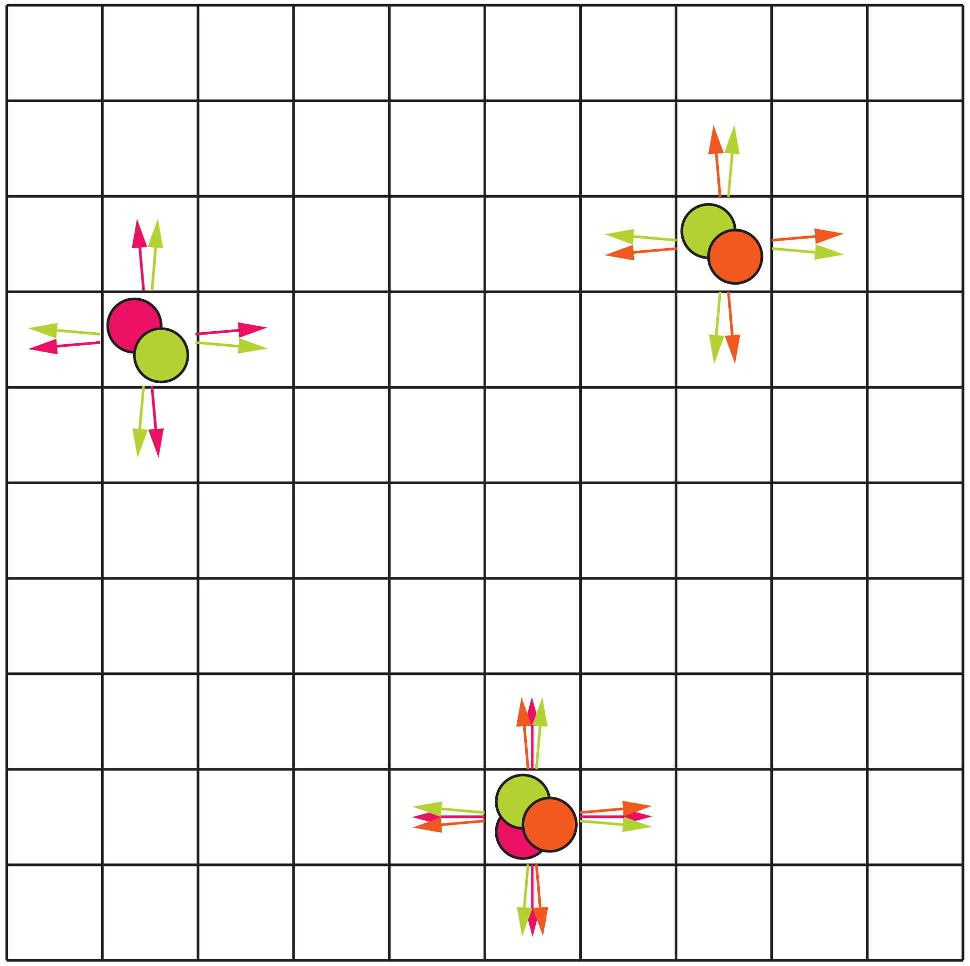


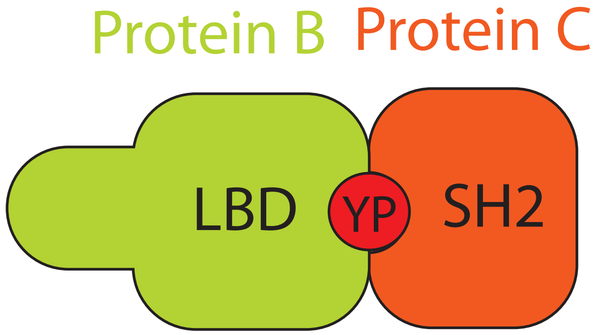
Case 2: Movement of components as complex

- Determine all possible complexes
    - e.g. Protein A + Protein B, Protein B + Protein C, Protein A + Protein B + Protein C
- Movement only if the corresponding interaction sites of interacting components in a complex are used and all other are unused
    - e.g. Protein A + Protein B can only move if they interact with each other, but not with Protein C
- Update local positions of all components forming a complex simultaneously









Case 2: Movement of components as complex

- Determine all possible complexes
  - e.g. Protein A + Protein B, Protein B + Protein C, Protein A + Protein B + Protein C
- Movement only if the corresponding interaction sites of a complex are used and all other are unused
  - e.g. Protein A + Protein B can only move if they interact with each other, but not with Protein C
- Update local positions of all components forming a complex simultaneously

For each complex:

- add two transitions per axis to increase/decrease the value of the coordinate places of the interacting components in respect to the grid size

- connect places representing the respective interaction via test arcs

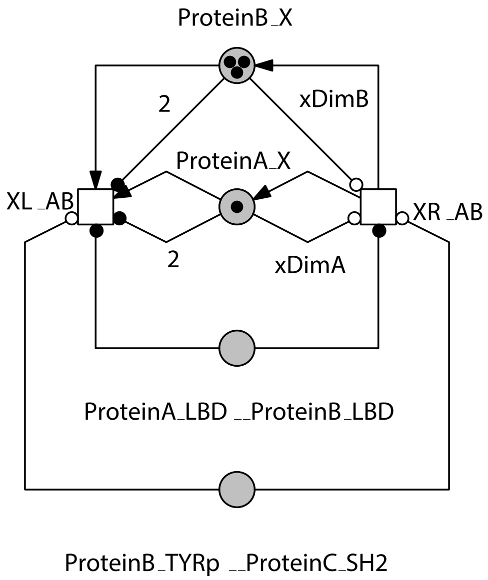
- connect places representing interaction with other components via inhibitory arcs

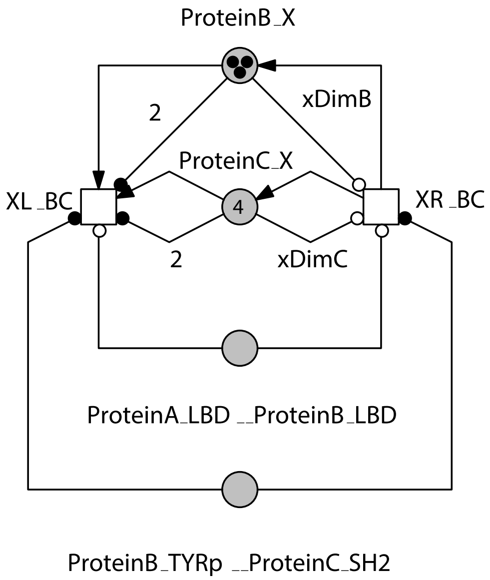
Case 2: Movement of components as complex

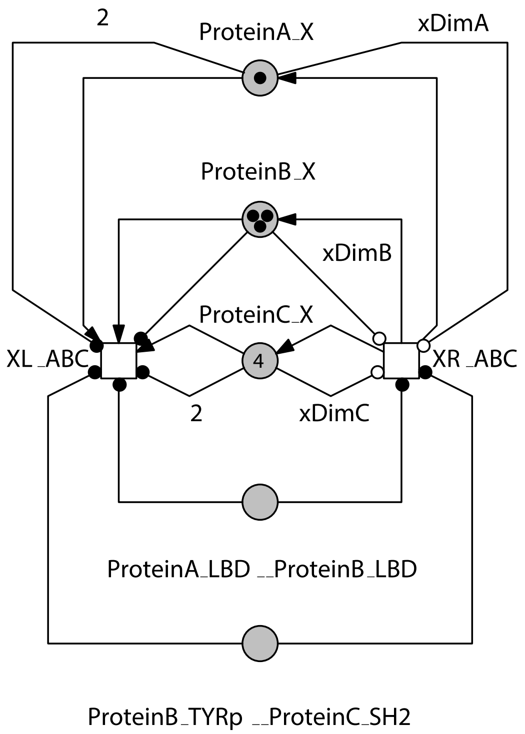
Movement of complex ProteinA_ProteinB

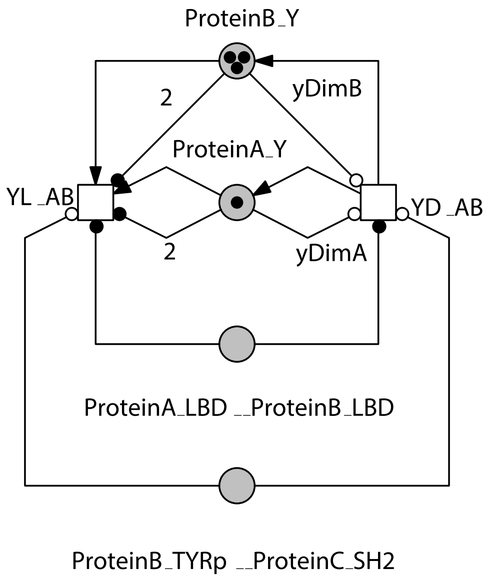
Movement of complex ProteinB_ProteinC

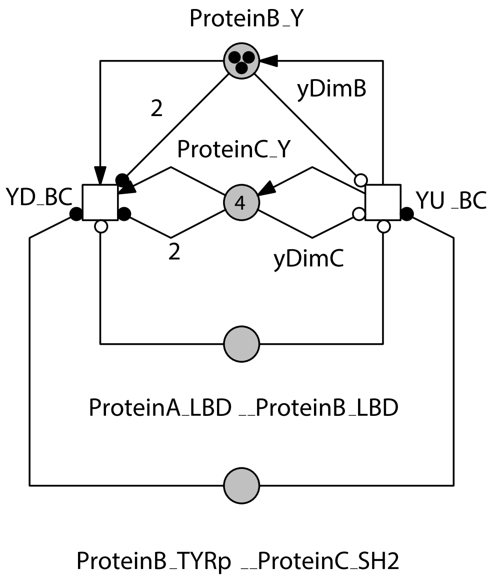
Movement of complex ProteinA_ProteinB_ProteinC

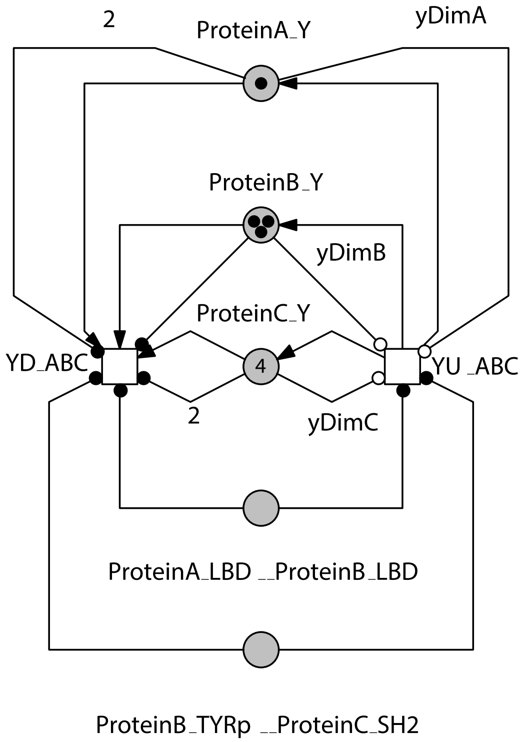






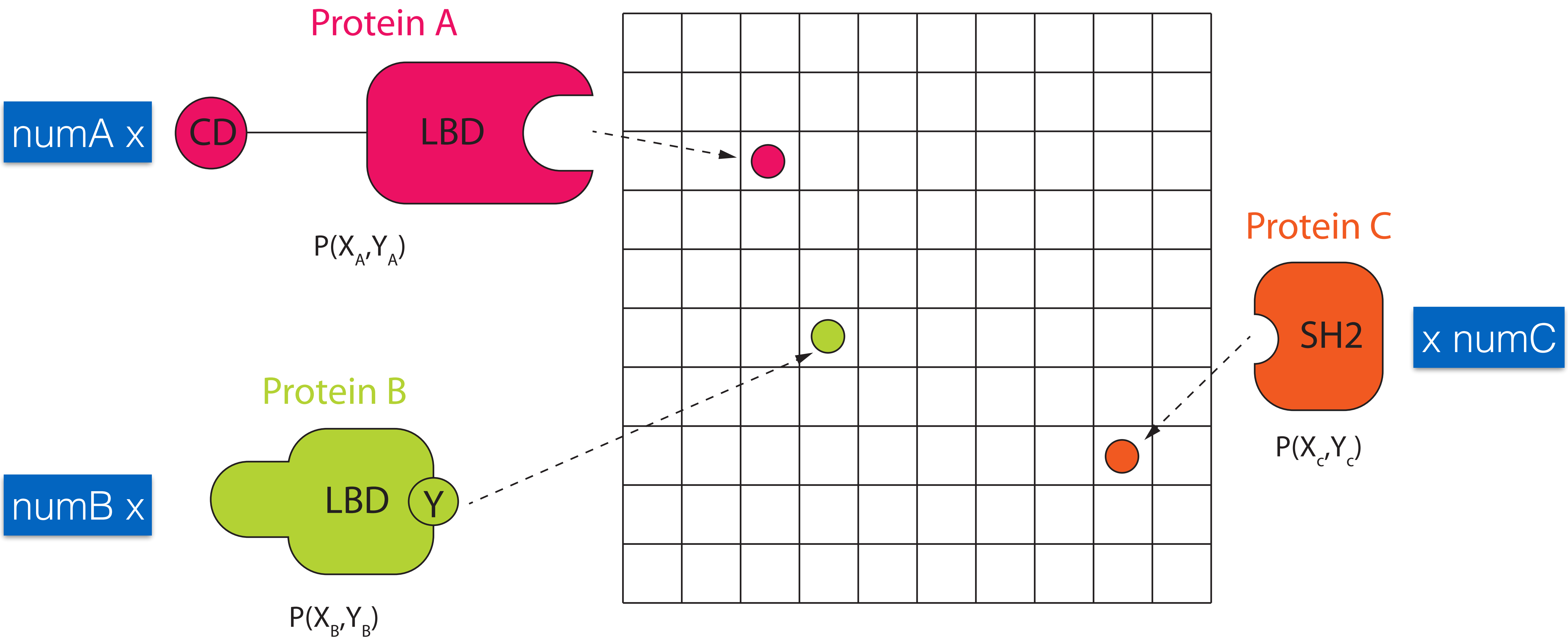






Explicit Encoding of Component Instances

- Define a number of instances for each component
  - e.g. numA = 3, numB= 3, numC = 3
- Duplicate the previously defined networks according to the number of instances



Explicit Encoding of Component Instances

- Define a number of instances for each component
  - e.g. numA = 3, numB= 3, numC = 3
- Duplicate the previously defined networks according to the number of instances

Application of coloured Petri nets:

- For each component define a simple colour-set and variable,

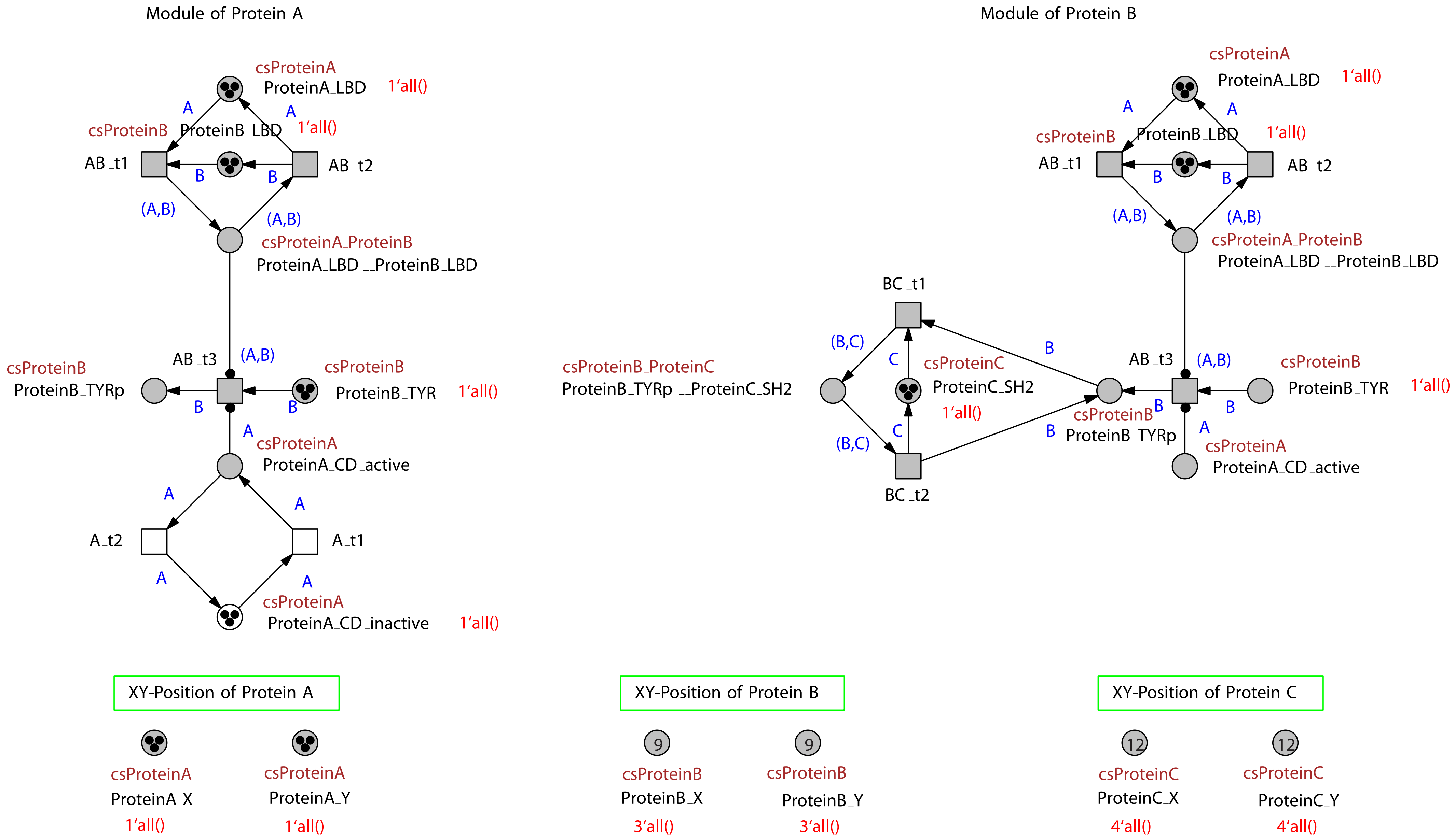
- Add simple colour-sets to places representing non-interaction states

- For each interaction define a product colour-set based on the respective simple colour-sets

- Add product colour-sets to all places representing the respective interaction

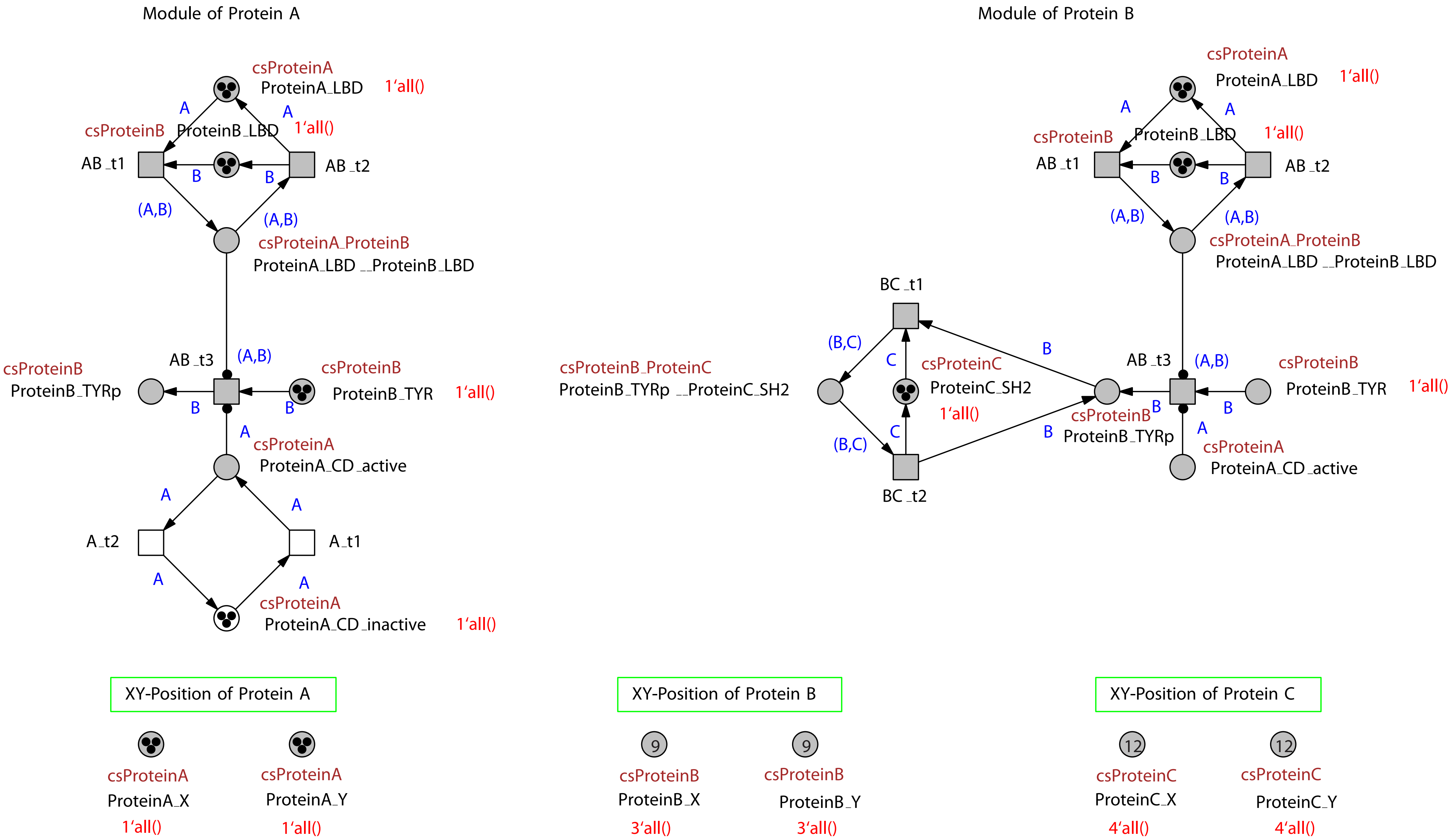
Applying Coloured Petri Nets

- Define a simple colour-set and a variable for each component
  - **Protein A** -> csProteinA:= int, 1-numA; csProteinA A
  - **Protein B** -> csProteinB:= int, 1-numB; csProteinB B
  - **Protein C** -> csProteinC:= int, 1-numC; csProteinC C



Applying Coloured Petri Nets

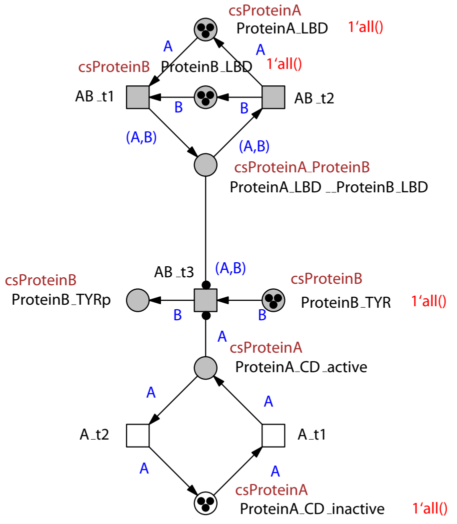
- Define a product colour-set for each interaction
  - **Protein A** + **Protein B** -> csProteinA__ProteinB := product csProteinA, csProteinB
  - **Protein B** + **Protein C** -> csProteinB__ProteinC := product csProteinB, csProteinC



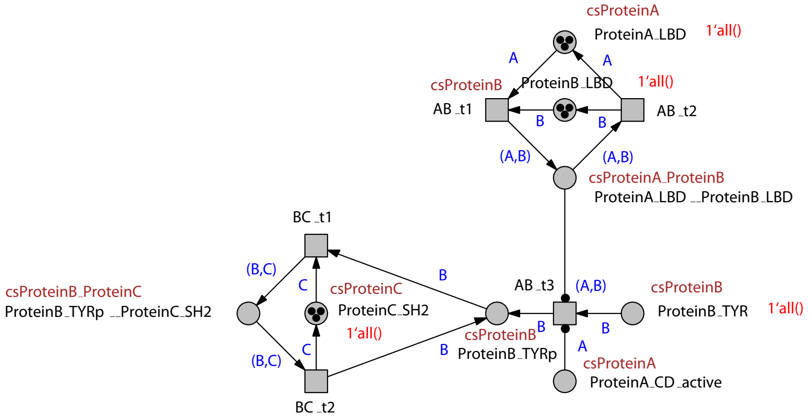
Mary-Ann Blätke, Sino-German Workshop, Bejing/China, 2015

Applying Coloured Petri Nets

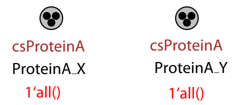
Module of Protein A



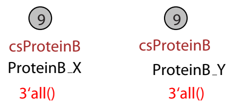
Module of Protein B



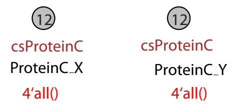
XY-Position of Protein A



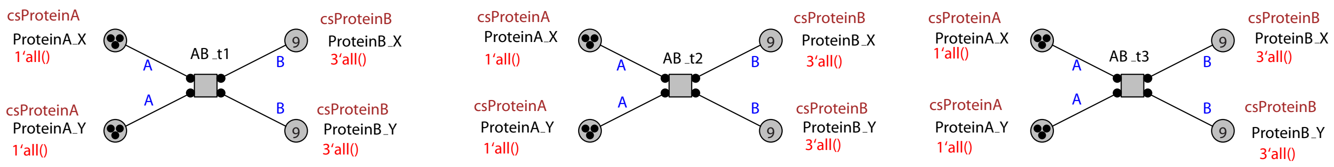
XY-Position of Protein B



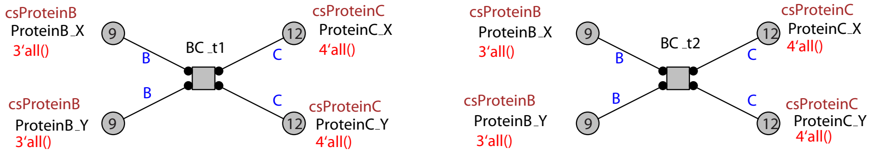
XY-Position of Protein C



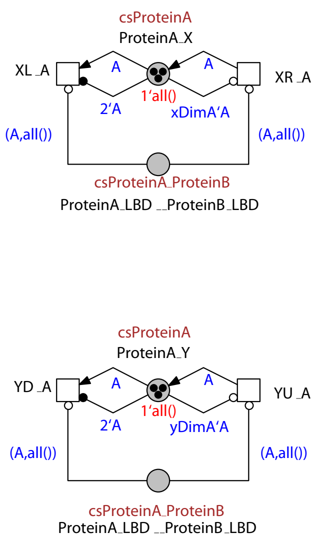
Restricted Interaction - Only if ProteinA (X,Y) = ProteinB (X,Y)



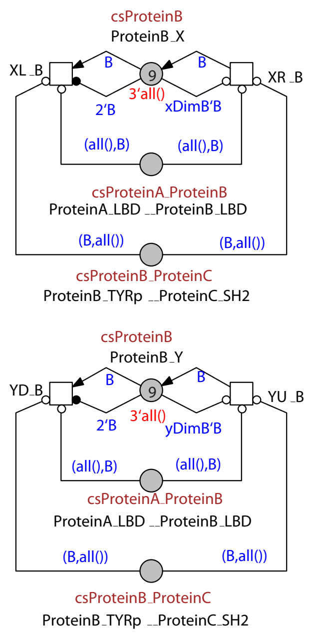
Restricted Interaction - Only if ProteinB (X,Y) = ProteinC (X,Y)



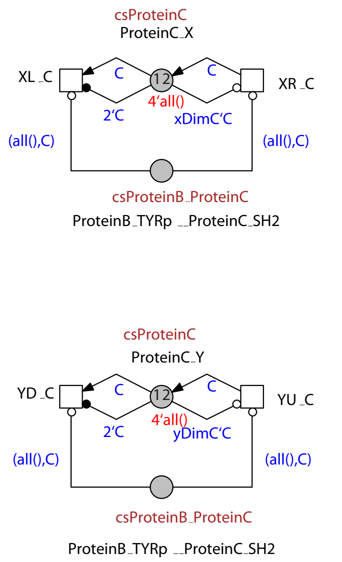
Movement of Protein A



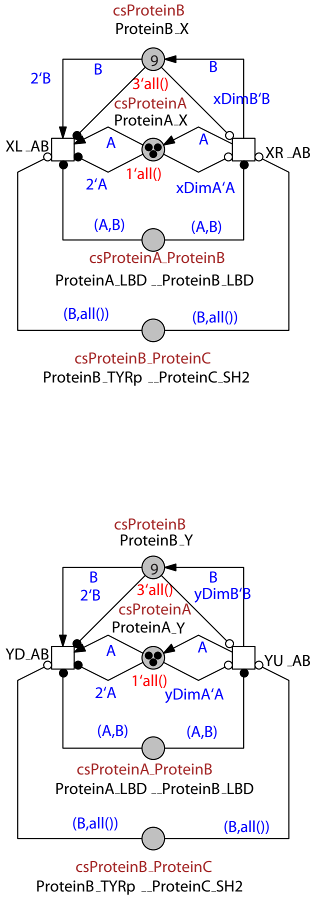
Movement of Protein B



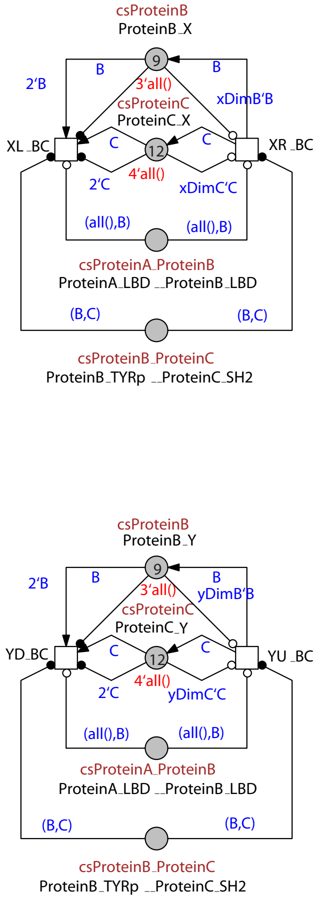
Movement of Protein C



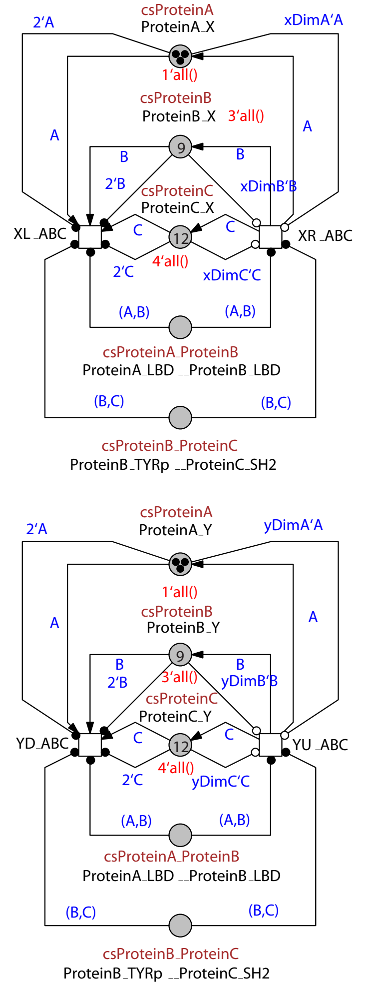
Movement of complex ProteinAProteinB



Movement of complex ProteinBProteinC

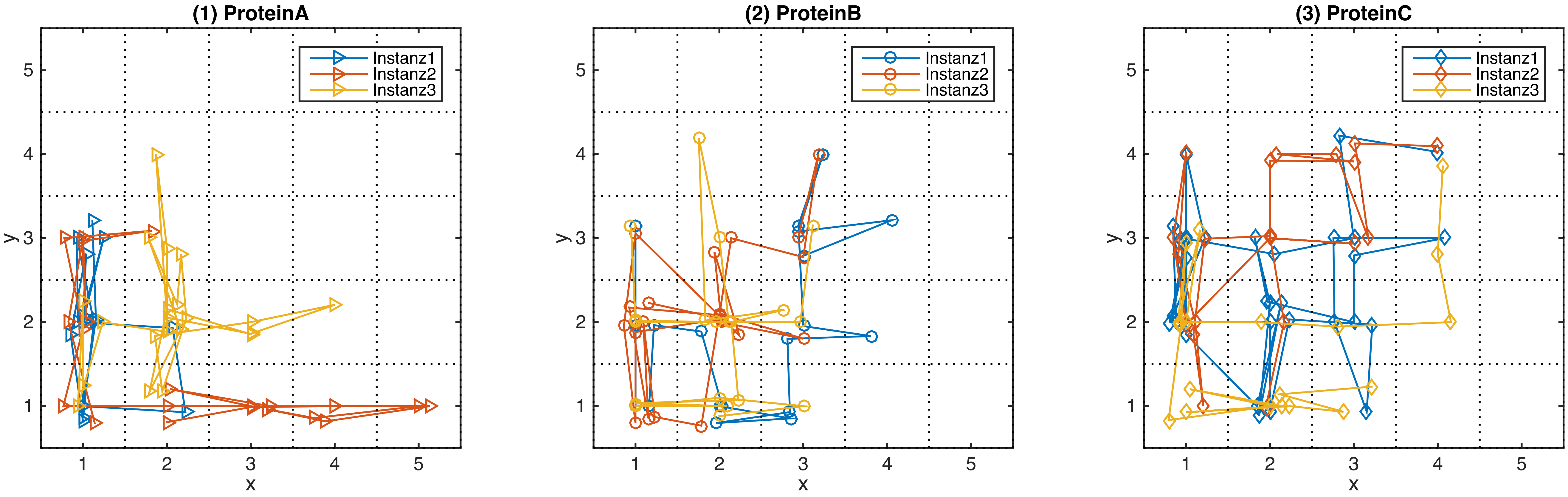


Movement of complex ProteinAProteinB_ProteinC



Stochastic Simulation

- Model parameter:
  - 5x5 2D-grid for each component
  - 3 instances per component
- Model size:
  - |P|=57, |T|=267, |A|=1992

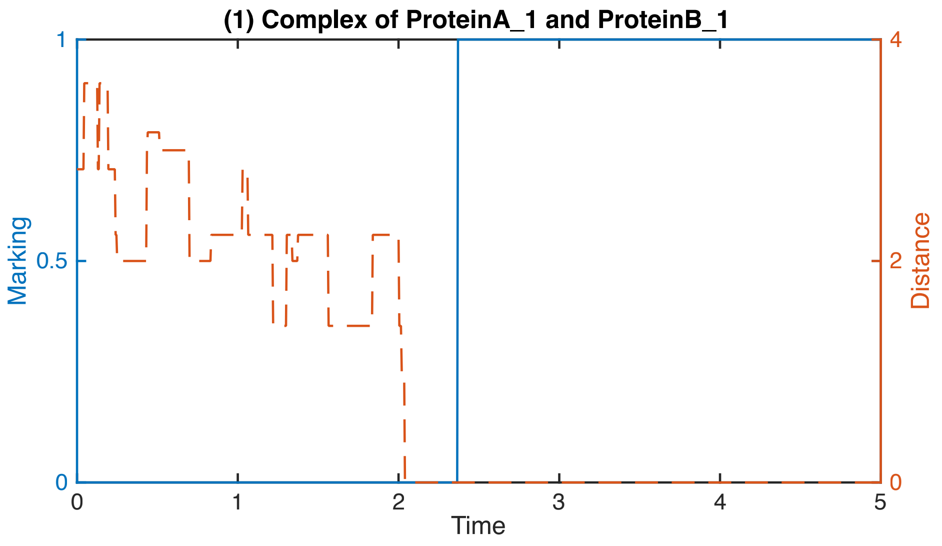


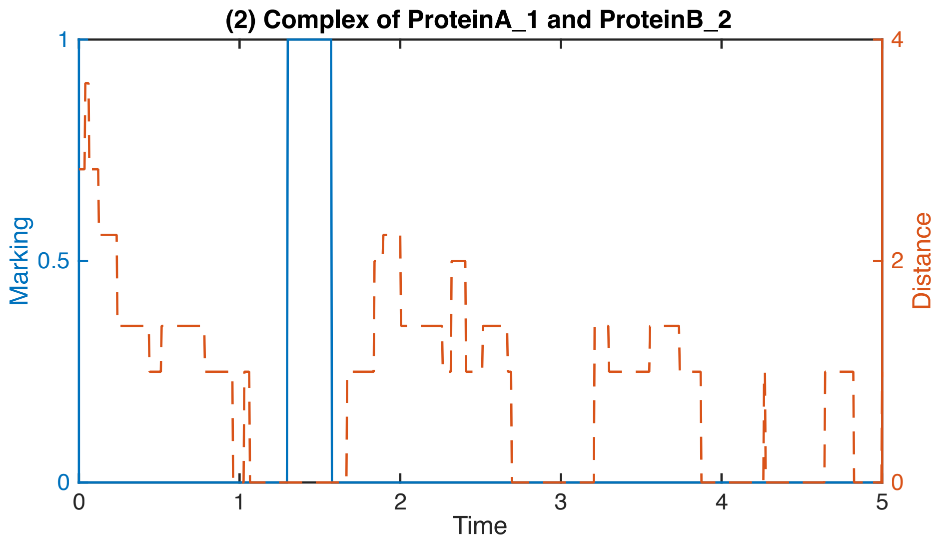
(1) ProteinA

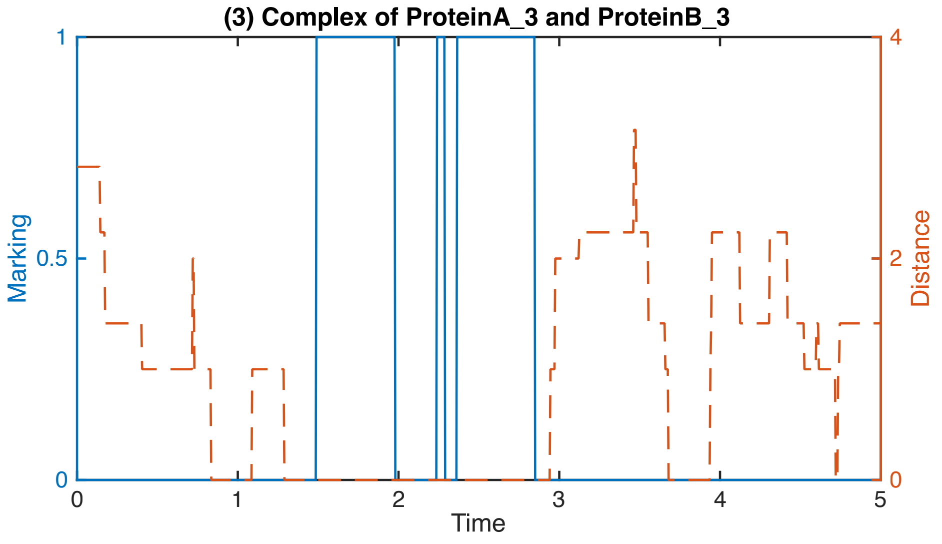
(2) ProteinB

(3) ProteinC

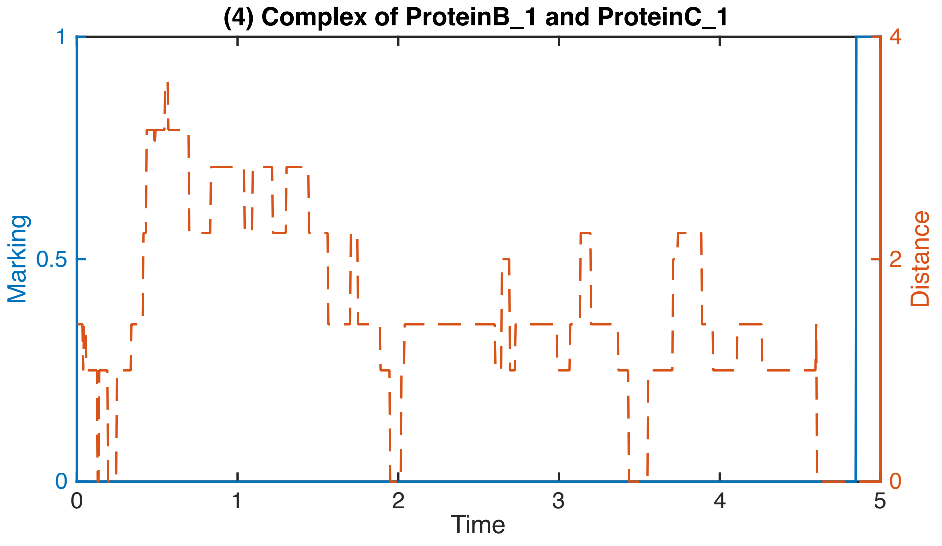
Stochastic Simulation

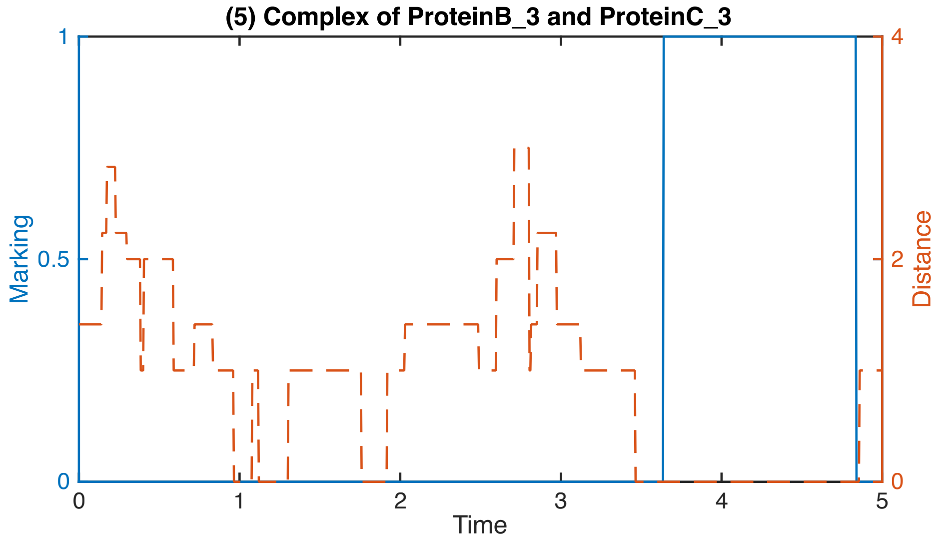

(1) Complex of ProteinA_1 and ProteinB_1


(2) Complex of ProteinA_1 and ProteinB_2


(3) Complex of ProteinA_3 and ProteinB_3

Components move as one entity while interacting


(4) Complex of ProteinB_1 and ProteinC_1


(5) Complex of ProteinB_3 and ProteinC_3

Summary

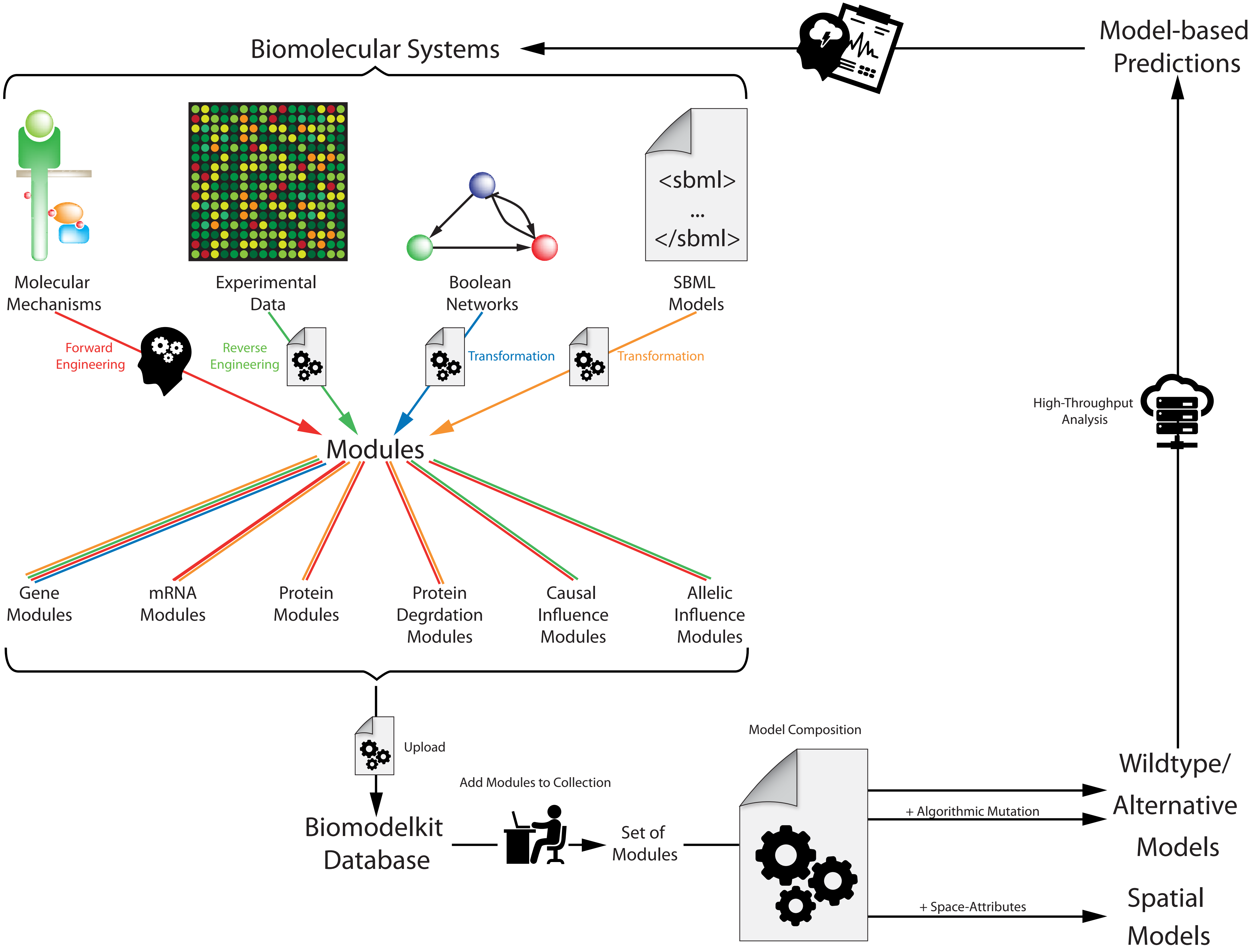
- Spatial Transformation Algorithm

    1. Explicit encoding of local positions
    2. Local restriction of interactions
    3. Explicit encoding of local position changes
    4. Explicit encoding of component instances using coloured Petri nets

Summary

- No interference with the model structure
  - ➡ *Transformation is reversible*
- Scalable
  - ➡ *Grid size/dimensions, Number of Instances*
- Common grid or individual grids
  - ➡ *Adapt Neighbourhood Relation*
- Not restricted to discrete space
  - ➡ *Representation of continuous space by the use of continuous places*

Summary



Biomolecular Systems

Model-based Predictions

Molecular Mechanisms

Experimental Data

Boolean Networks

SBML Models

Forward Engineering

Reverse Engineering

Transformation

Transformation

High-Throughput Analysis

Modules

Gene Modules

mRNA Modules

Protein Modules

Protein Degrdation Modules

Causal Influence Modules

Allelic Influence Modules

Upload

Biomodelkit Database

Add Modules to Collection

Set of Modules

Model Composition

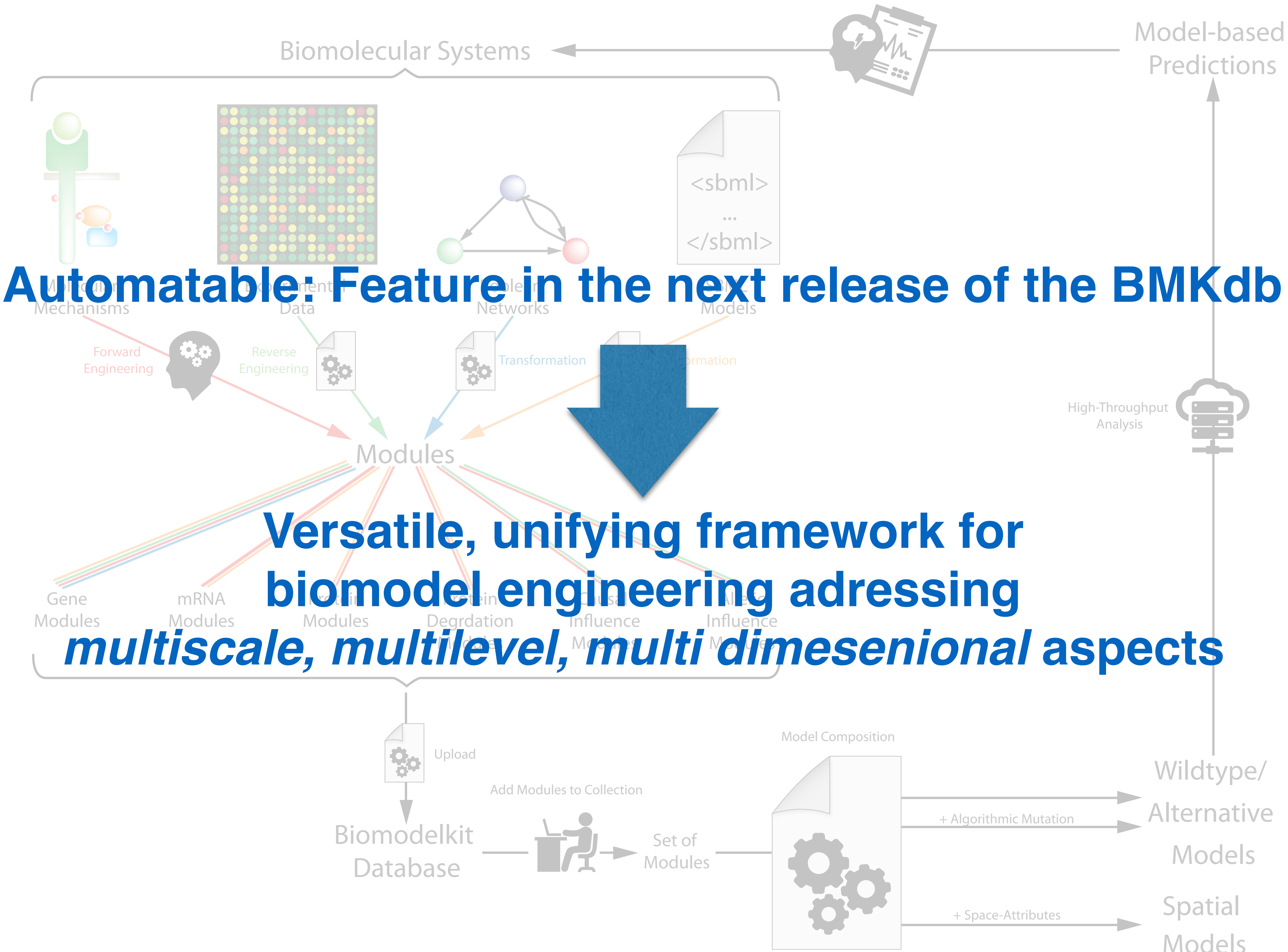
+ Algorithmic Mutation

+ Space-Attributes

Wildtype/ Alternative Models

Spatial Models

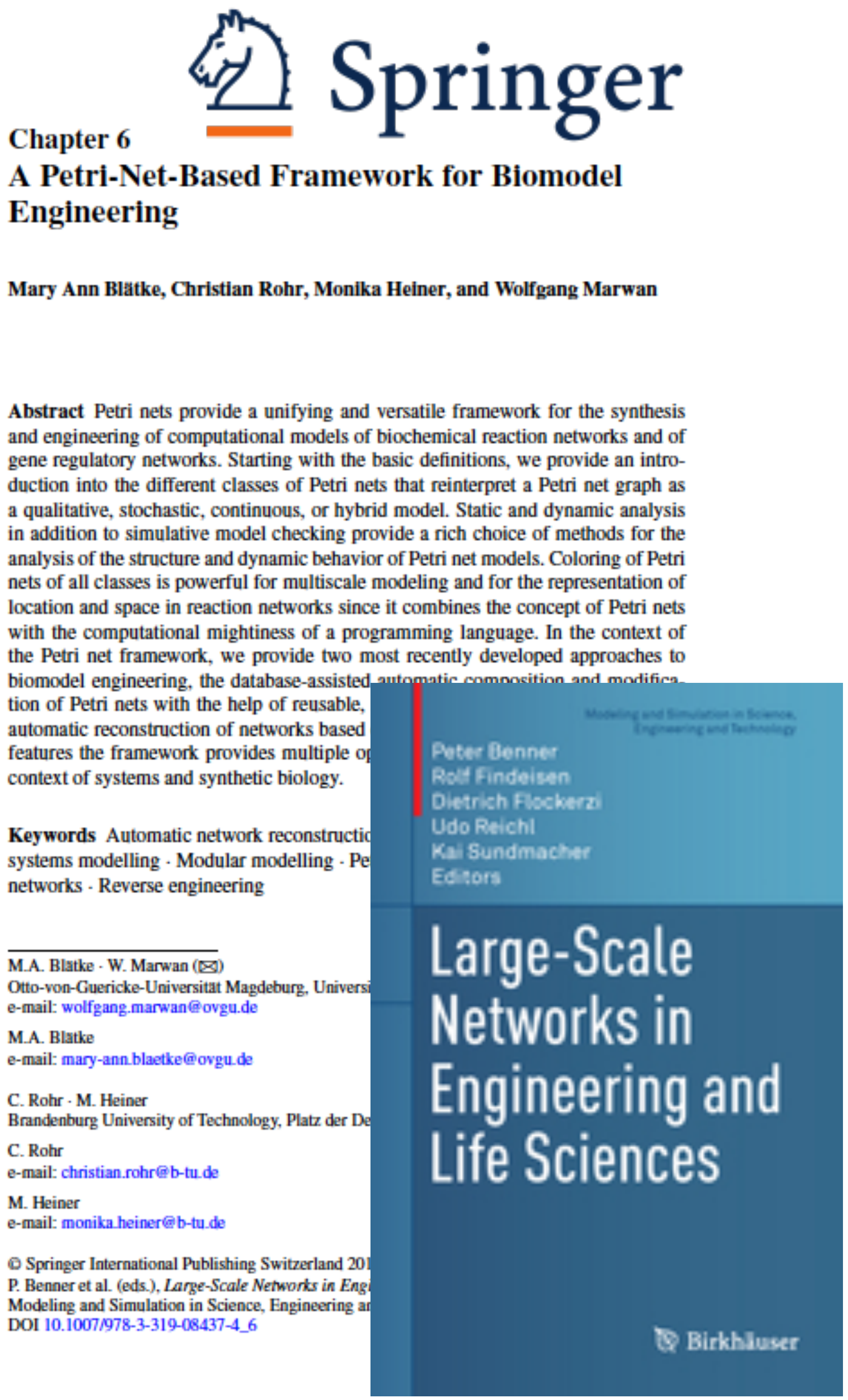
Summary



Automatable: Feature in the next release of the BMKdb

Versatile, unifying framework for biomodel engineering adressing *multiscale, multilevel, multi dimesenional* aspects

Recent Publications



Springer

Chapter 6
A Petri-Net-Based Framework for Biomodel Engineering

Mary Ann Blätke, Christian Rohr, Monika Heiner, and Wolfgang Marwan

Abstract Petri nets provide a unifying and versatile framework for the synthesis and engineering of computational models of biochemical reaction networks and of gene regulatory networks. Starting with the basic definitions, we provide an introduction into the different classes of Petri nets that reinterpret a Petri net graph as a qualitative, stochastic, continuous, or hybrid model. Static and dynamic analysis in addition to simulative model checking provide a rich choice of methods for the analysis of the structure and dynamic behavior of Petri net models. Coloring of Petri nets of all classes is powerful for multiscale modeling and for the representation of location and space in reaction networks since it combines the concept of Petri nets with the computational mightiness of a programming language. In the context of the Petri net framework, we provide two most recently developed approaches to biomodel engineering, the database-assisted automatic composition and modifica-
tion of Petri nets with the help of reusable,
automatic reconstruction of networks based
features the framework provides multiple op
context of systems and synthetic biology.

Keywords Automatic network reconstructio
systems modelling · Modular modelling · Pe
networks · Reverse engineering

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Modeling and Simulation in Science, Engineering ar
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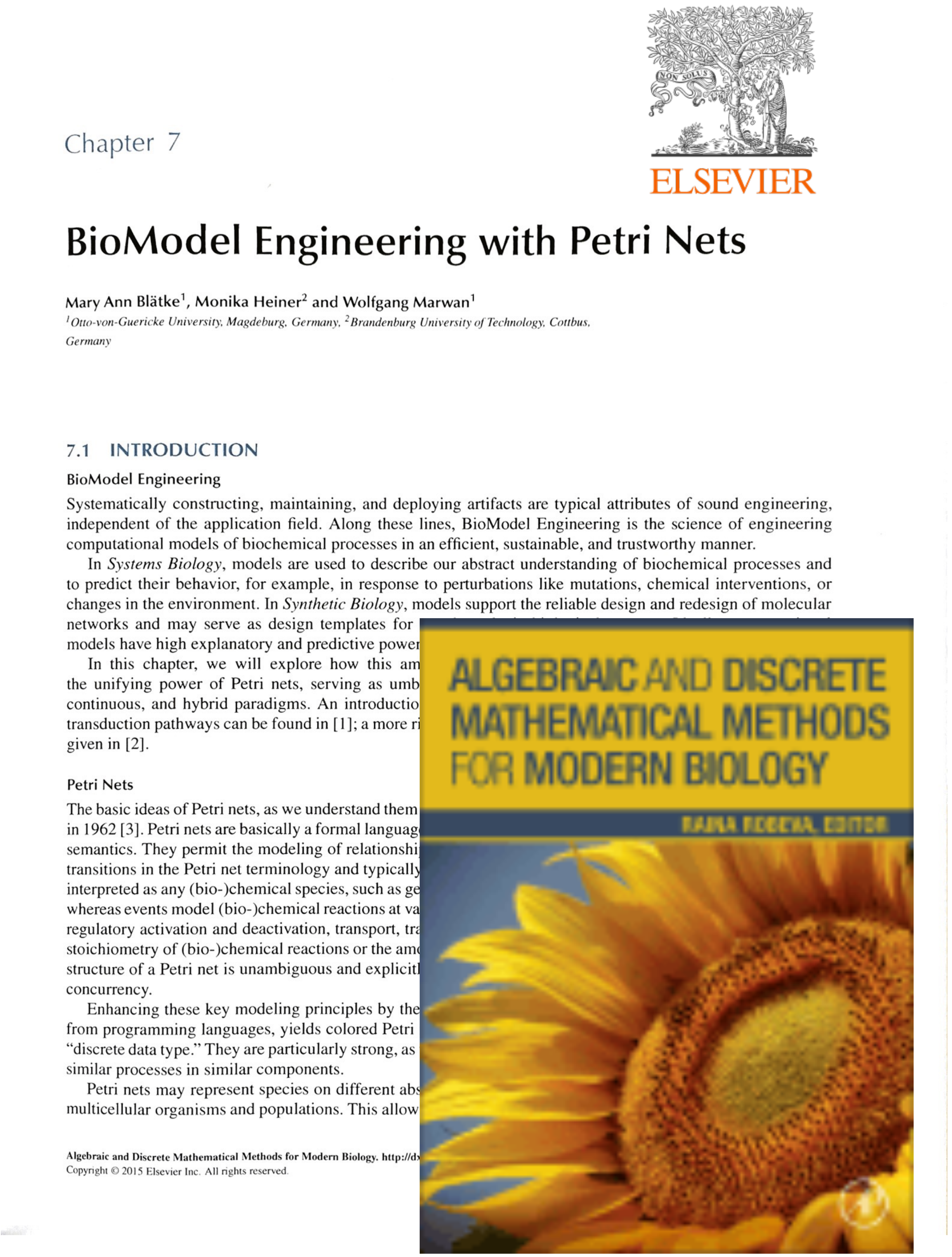
Modeling and Simulation in Science, Engineering and Technology

Peter Benner
Rolf Findeisen
Dietrich Flockerzi
Udo Reichl
Kai Sundmacher
Editors

Large-Scale Networks in Engineering and Life Sciences

Birkhäuser



Chapter 7

ELSEVIER

BioModel Engineering with Petri Nets

Mary Ann Blätke[1], Monika Heiner[2] and Wolfgang Marwan[1]
[1] *Otto-von-Guericke University, Magdeburg, Germany,* [2] *Brandenburg University of Technology, Cottbus, Germany*

7.1 INTRODUCTION

BioModel Engineering

Systematically constructing, maintaining, and deploying artifacts are typical attributes of sound engineering, independent of the application field. Along these lines, BioModel Engineering is the science of engineering computational models of biochemical processes in an efficient, sustainable, and trustworthy manner.

In *Systems Biology*, models are used to describe our abstract understanding of biochemical processes and to predict their behavior, for example, in response to perturbations like mutations, chemical interventions, or changes in the environment. In *Synthetic Biology*, models support the reliable design and redesign of molecular
networks and may serve as design templates for
models have high explanatory and predictive power

In this chapter, we will explore how this am
the unifying power of Petri nets, serving as umb
continuous, and hybrid paradigms. An introductio
transduction pathways can be found in [1]; a more ri
given in [2].

Petri Nets

The basic ideas of Petri nets, as we understand them
in 1962 [3]. Petri nets are basically a formal languag
semantics. They permit the modeling of relationshi
transitions in the Petri net terminology and typically
interpreted as any (bio-)chemical species, such as ge
whereas events model (bio-)chemical reactions at va
regulatory activation and deactivation, transport, tra
stoichiometry of (bio-)chemical reactions or the amo
structure of a Petri net is unambiguous and explicitl
concurrency.

Enhancing these key modeling principles by the
from programming languages, yields colored Petri
"discrete data type." They are particularly strong, as
similar processes in similar components.

Petri nets may represent species on different abs
multicellular organisms and populations. This allow

Algebraic and Discrete Mathematical Methods for Modern Biology. http://dx
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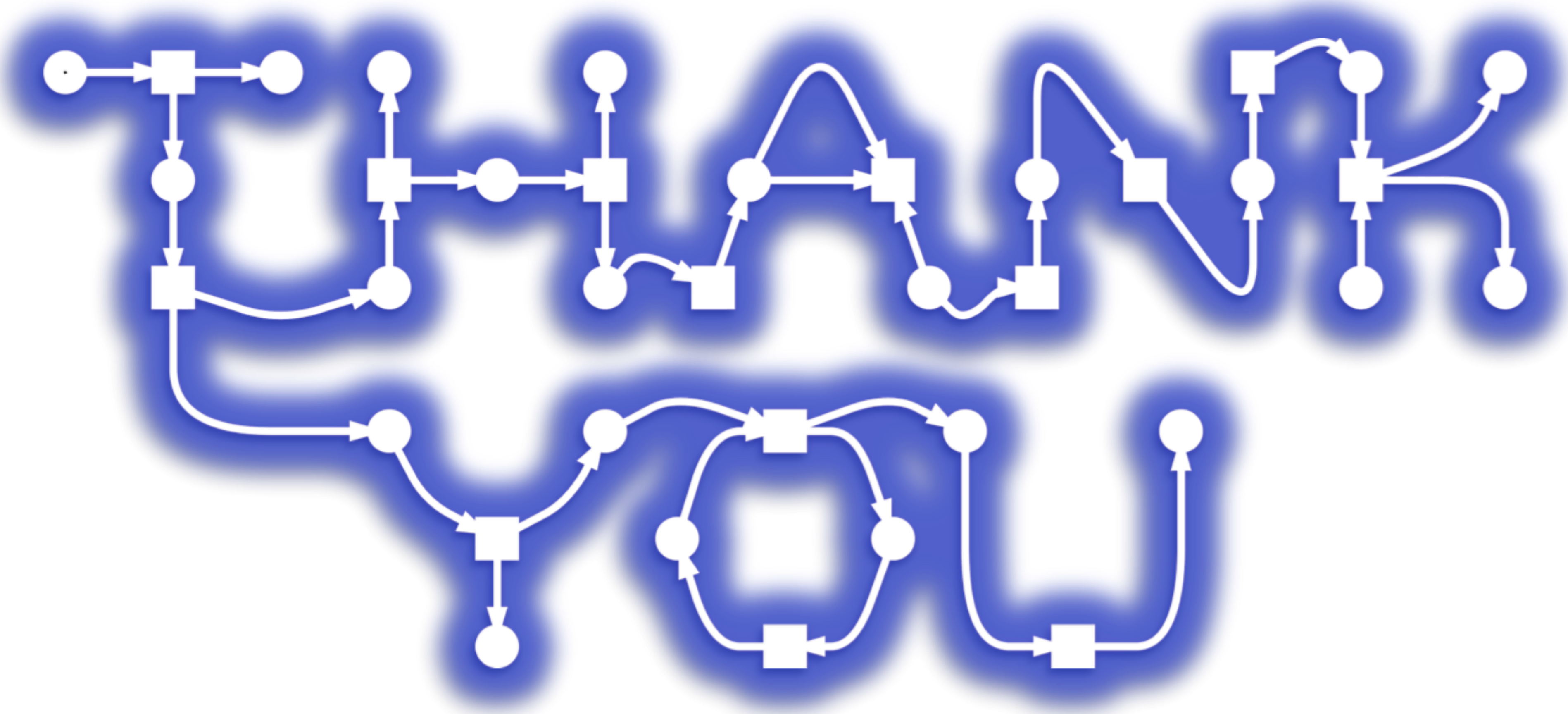
ALGEBRAIC AND DISCRETE MATHEMATICAL METHODS FOR MODERN BIOLOGY

RAINA ROBEVA, EDITOR



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
Fei Liu, Harbin Institute of Technology

Projects

Consortium „Modelling of Pain Switches” 2009-2011
Consortium „NoPain” 2013-2015

Graduate School

IMPRS Magdeburg

Sachsen-Anhalt

Federal Ministry
of Education
and Research

FORSYS
Research Units for Systems Biology

Magdeburg Centre for Systems Biology
MaCS

btu
Brandenburg
University of Technology
Cottbus

IMPRS ProEng
International Max Planck Research School for Advanced Methods in Process and Systems Engineering
Magdeburg

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UNIVERSITÄT
MAGDEBURG

DFG Deutsche Forschungsgemeinschaft