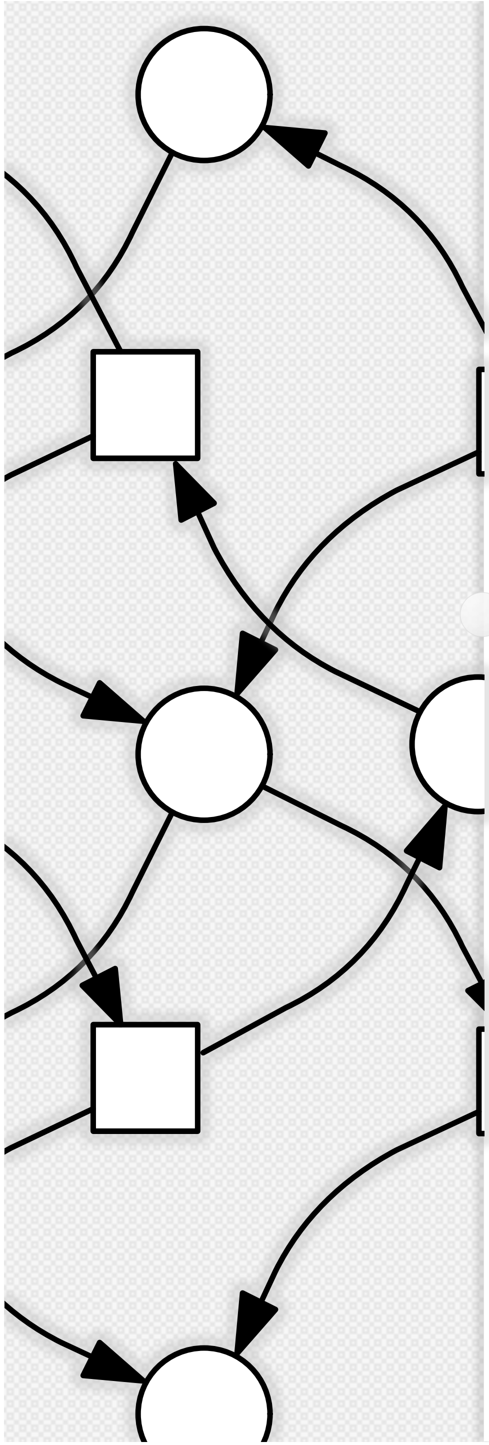

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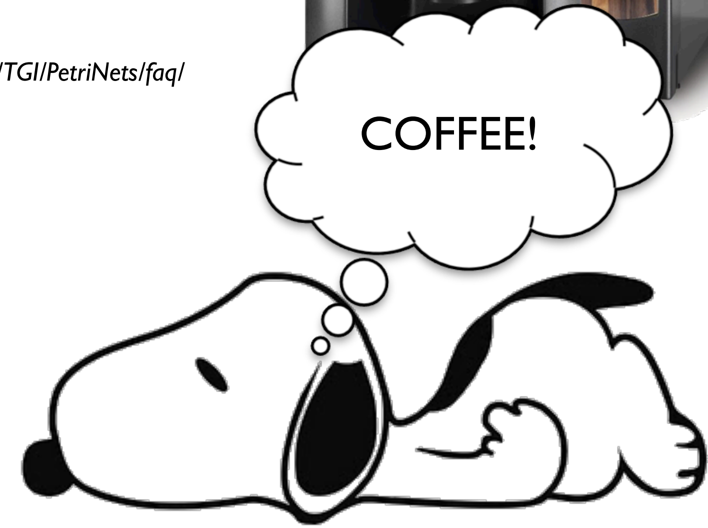
Petri Nets for Multiscale Systems Biology, 25TH June 2013, Milano

PETRI NETS IN BIOLOGY

What are Petri Nets for?

„Petri Nets is a formal and graphically appealing language which is appropriate for modelling systems with concurrency and resource sharing. Petri Nets have been under development since the beginning of the 60's, where Carl Adam Petri defined the language. It was the first time a general theory for discrete parallel systems was formulated. The language is a generalization of automata theory such that the concept of concurrently occurring events can be expressed."

http://www.informatik.uni-hamburg.de/TGI/PetriNets/faq/



12. July 1926 in Leipzig; † 2. July 2010

THE PETRI NET FORMALISM

Place

Transition

Arc

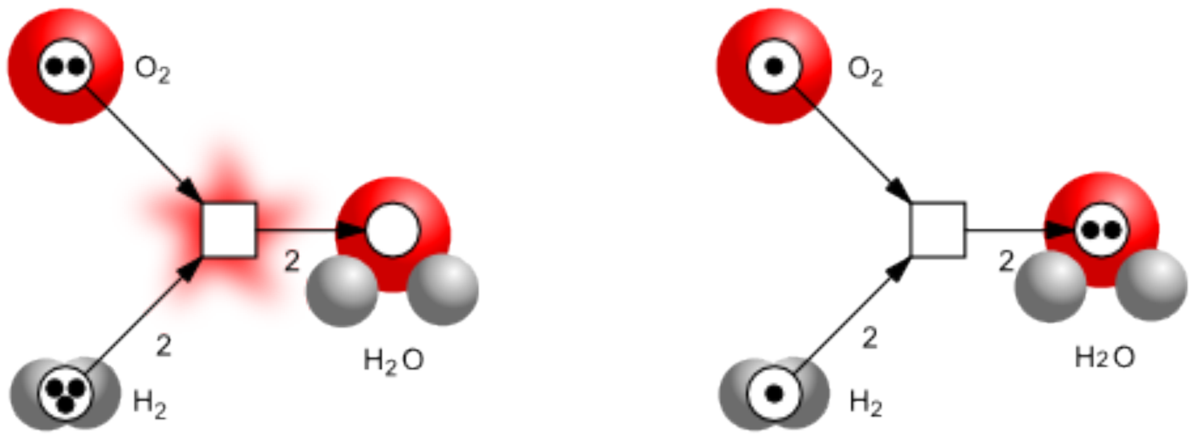
Token

Chemical reaction of the water formation:

$2\,H_2 + O_2 \rightarrow 2\,H_2O$

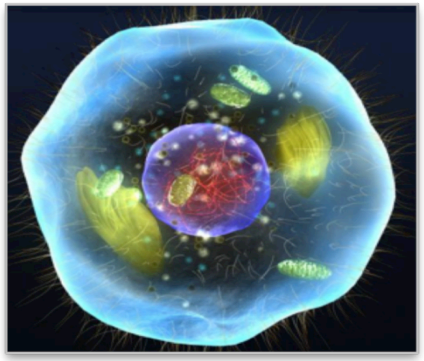
Before switch of t:

After switch of t:

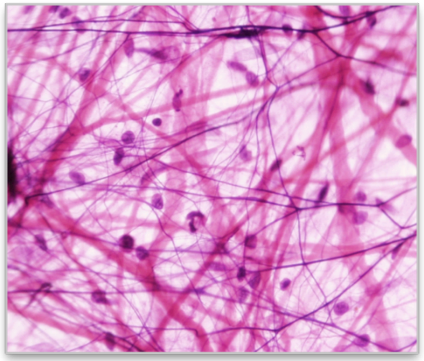


WHAT CAN BE REPRESENTED?

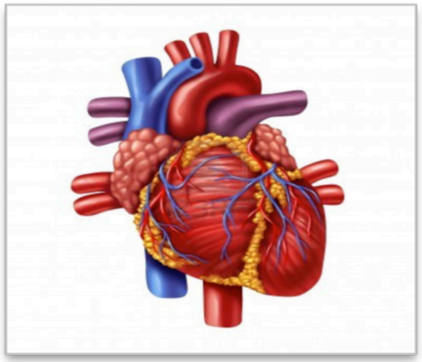
Molecules



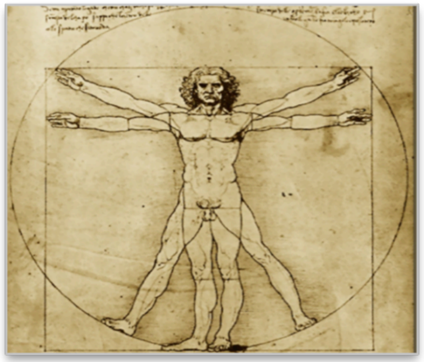
Cells



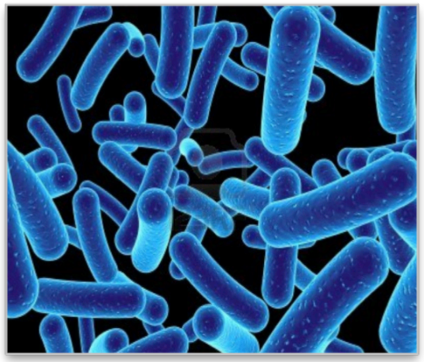
Tissues



Organs

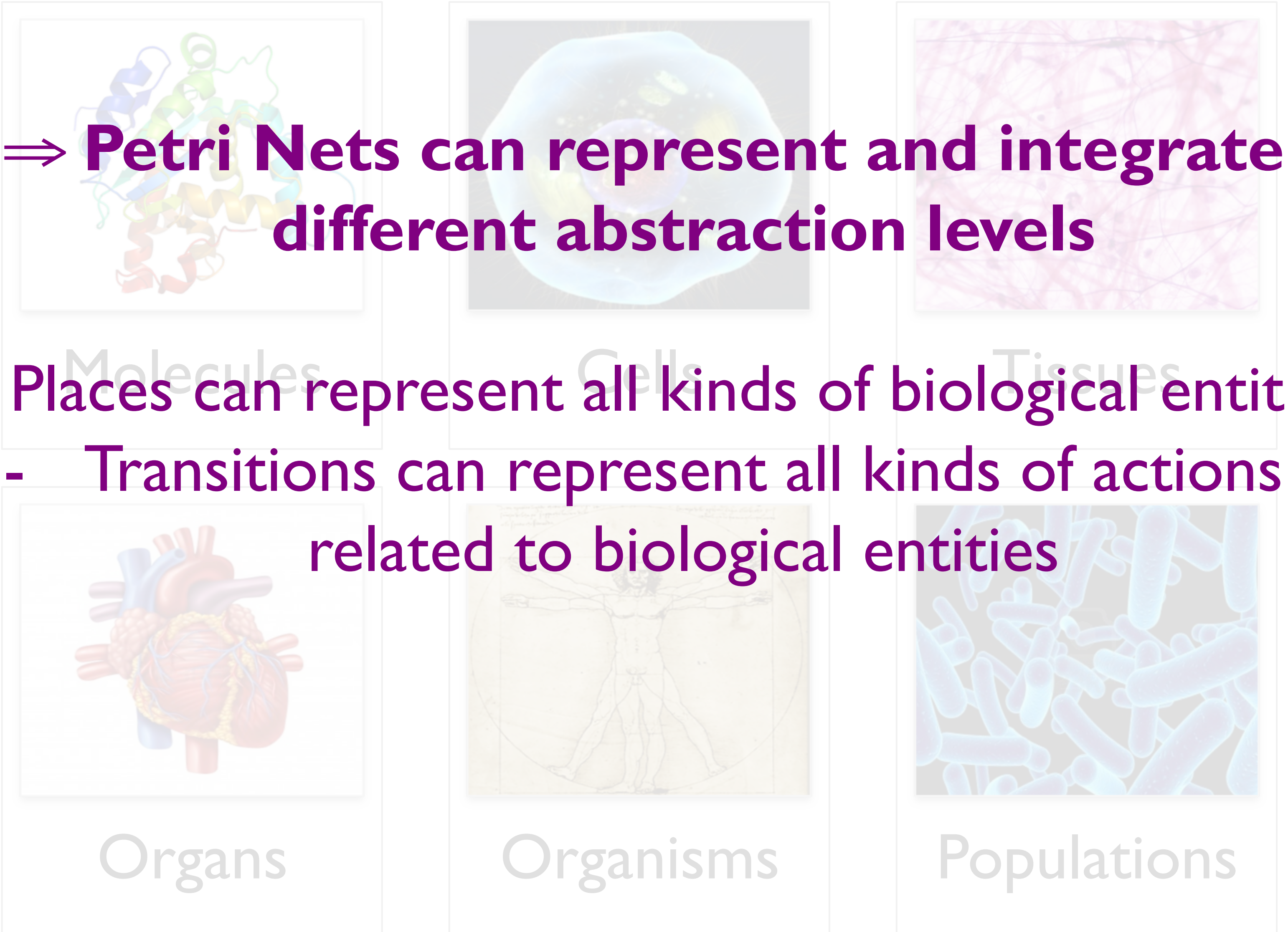


Organisms



Populations

WHAT CAN BE REPRESENTED?

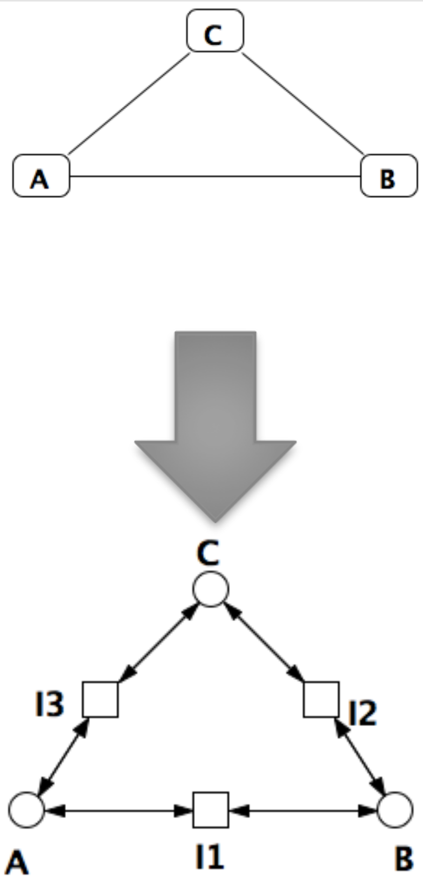


⇒ Petri Nets can represent and integrate different abstraction levels

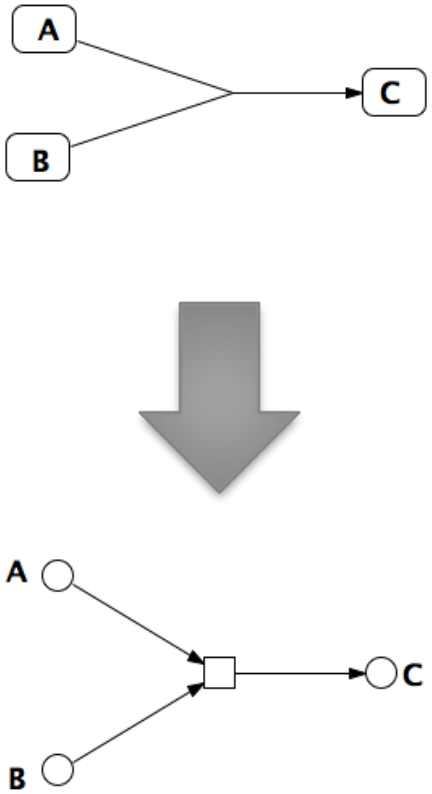
- Places can represent all kinds of biological entities
- Transitions can represent all kinds of actions related to biological entities

Which Network Types Can Be Represented?

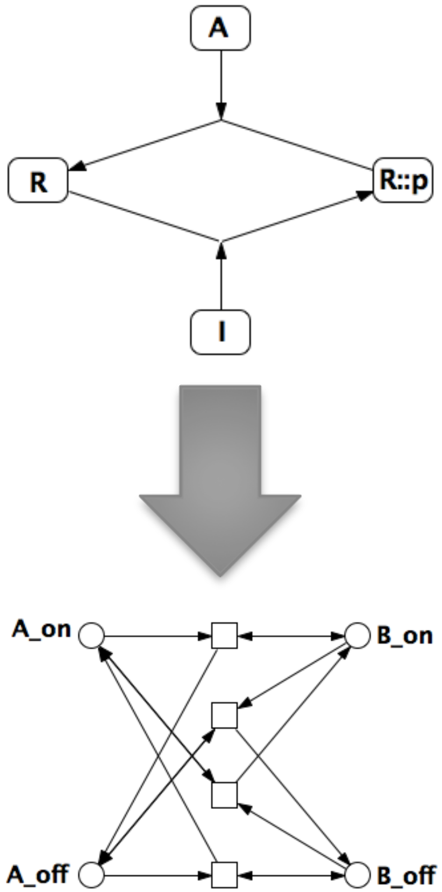
Protein/Gene Interaction Networks



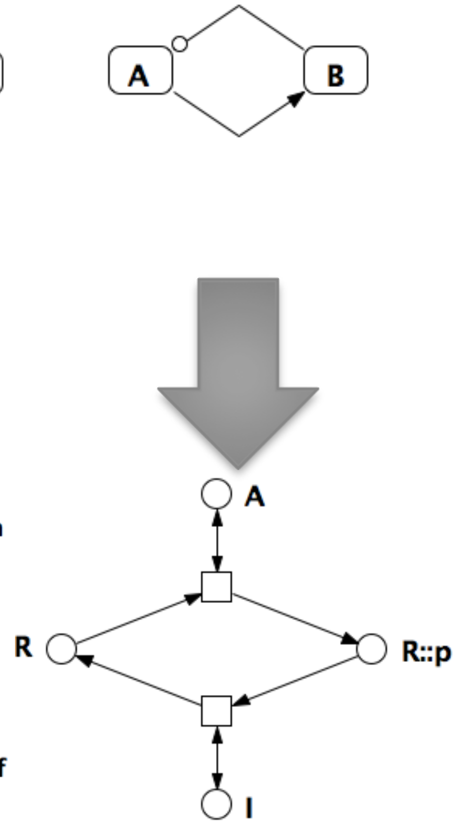
Metabolic Networks



Signaling Networks



Gene Regulatory Network



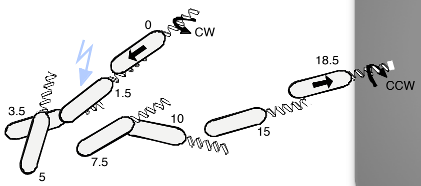
WHICH NETWORK TYPES CAN BE REPRESENTED?

⇒ Petri Nets can represent and integrate different Network Classes, and thus:

- Different OMICs data
- Different datatypes
- Different informations
- Different knowledge

How we generate Petri Nets?

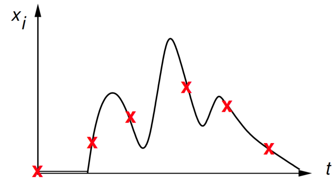
Functional Data and Biological response



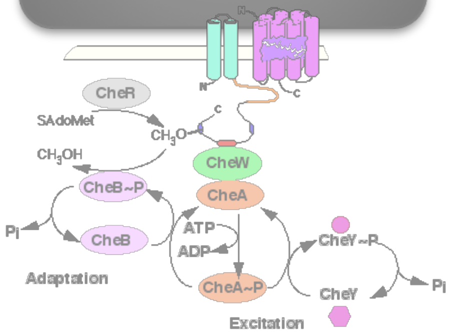
Top-Down = Reverse Engineering

Automatic Network Reconstruction

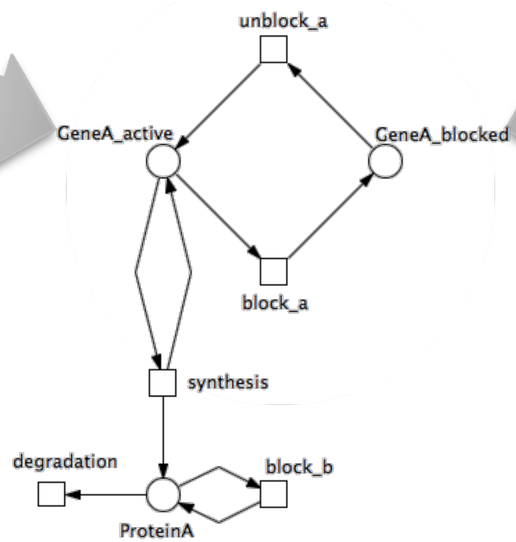
Time Series Data



Bottom-Up = Forward Engineering



Biochemical Reactions



Automatic Network Composition

Existing Models

How can we interpret a Petri Net?

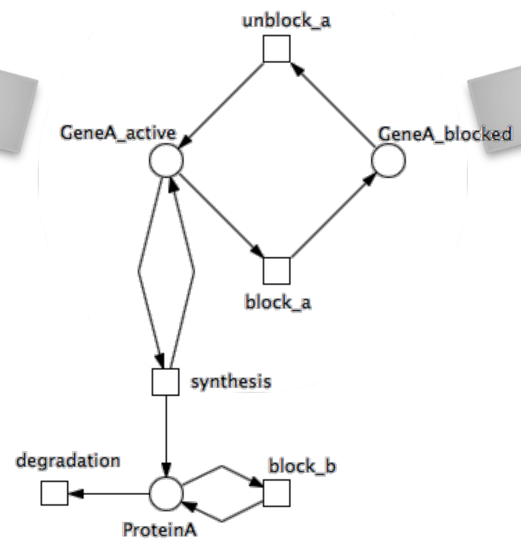
Discrete State Space
Timed
Molecules/Levels
Stochastic Rates

Stochastic Petri Nets

Continuous Petri Nets

Cont. State Space
Timed
Concentration
Deterministic Rates

Qualitative Petri Nets



Hybrid Petri Nets

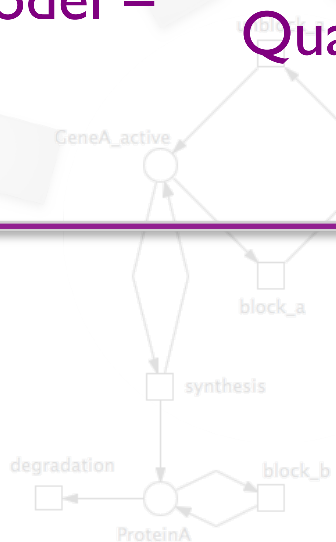
Discrete State Space
Time-free
Molecules/Levels

Mix of SPN and CPN

How can we interpret a Petri Net?

Four Models Sharing the **SAME** Structure

Quantitative Model = Qualitative Model + Quantitative Parameters (Kinetics)



General Characteristic of Petri nets

Formal language

- Strict syntax, no free-style description

Bipartite directed graphs

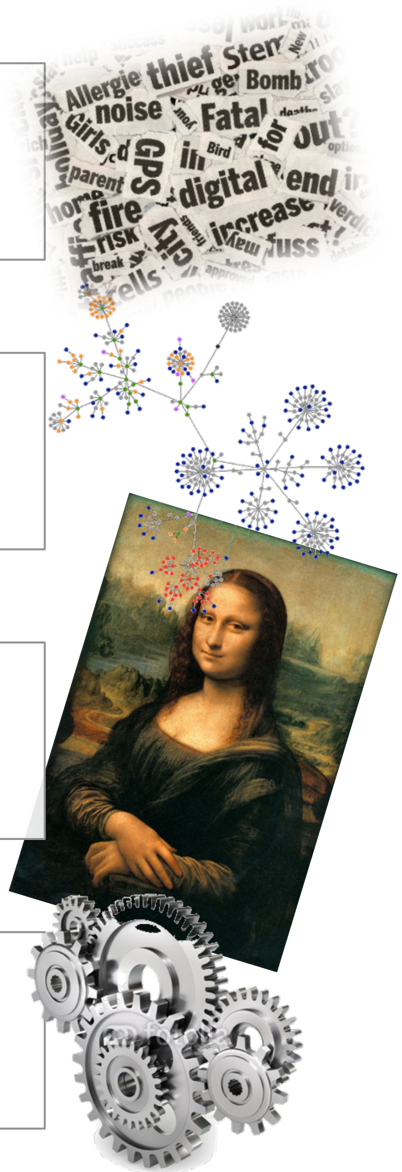
- Graph theory, linear algebra

Graphical

- Visualisation

Executable

- Simulation



General Characteristic of Petri nets

⇒ Advantages for Modelling in BME

- Easy and intuitive modelling framework
- Unambiguous translation of real systems into a formal model with operational semantics
- Explicitly formulating concurrency
- Support of hierarchical structuring

General Characteristic of Petri nets

Formal language

- Strict syntax, no free-style description

$\Rightarrow$ **Advantages for Analysis in BME**

- Network topology
- Structurally defined behavioural properties
- Simulative/analytical model checking
- Application of different modelling paradigms

Bipartite directed graphs

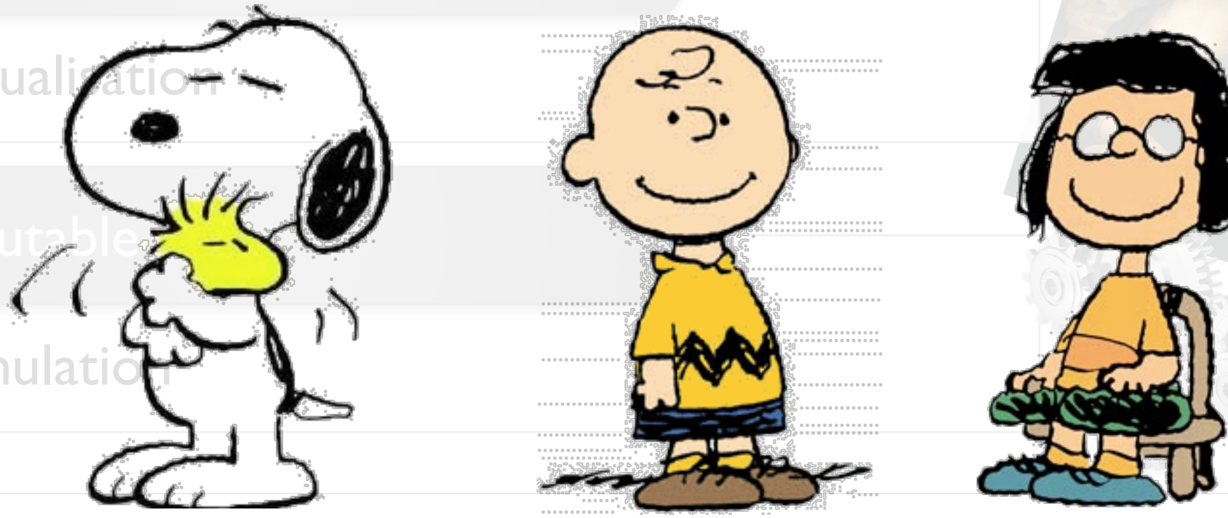
- Graph theory, linear algebra

Graphical

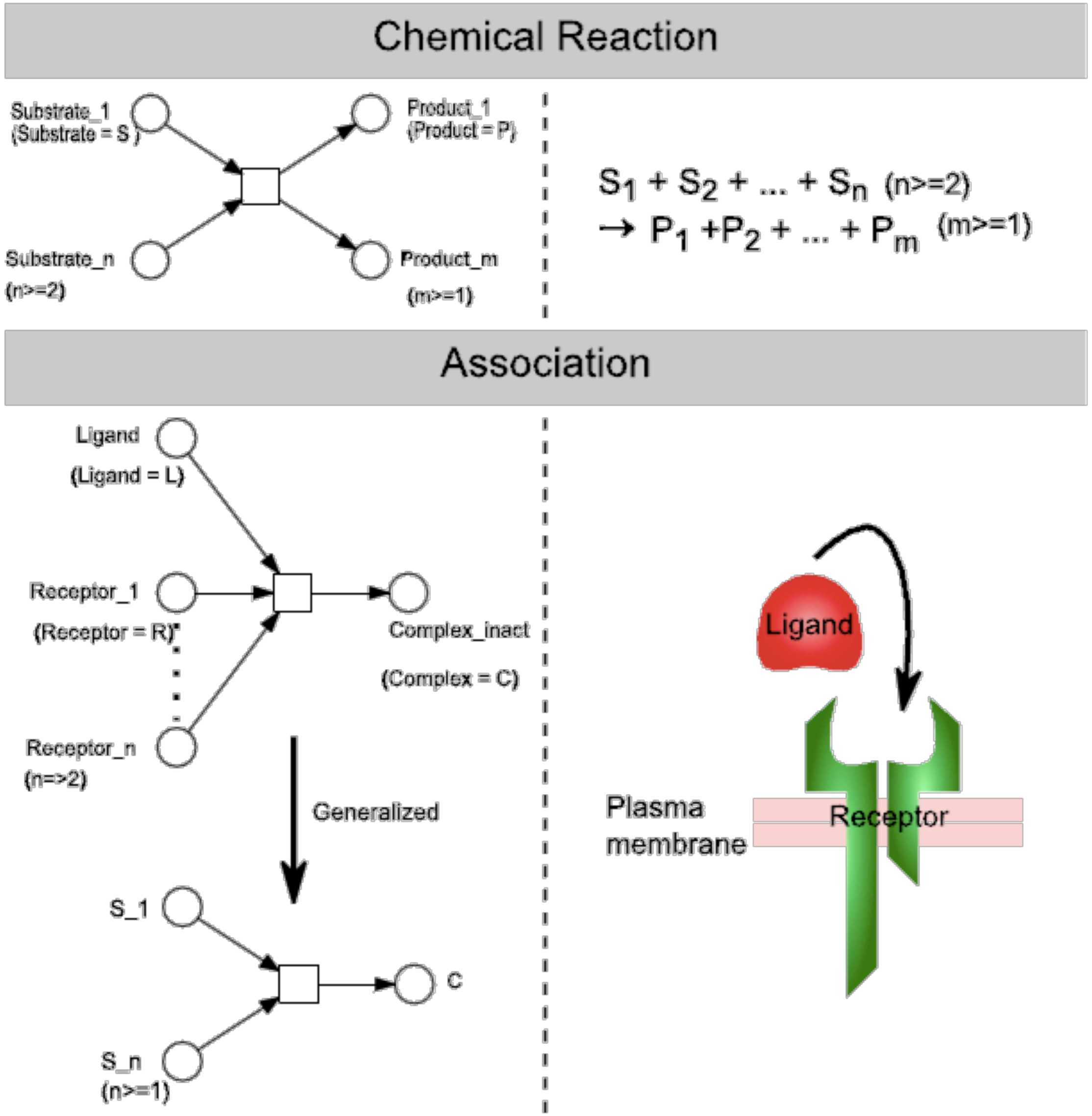
- Visualization

Executable

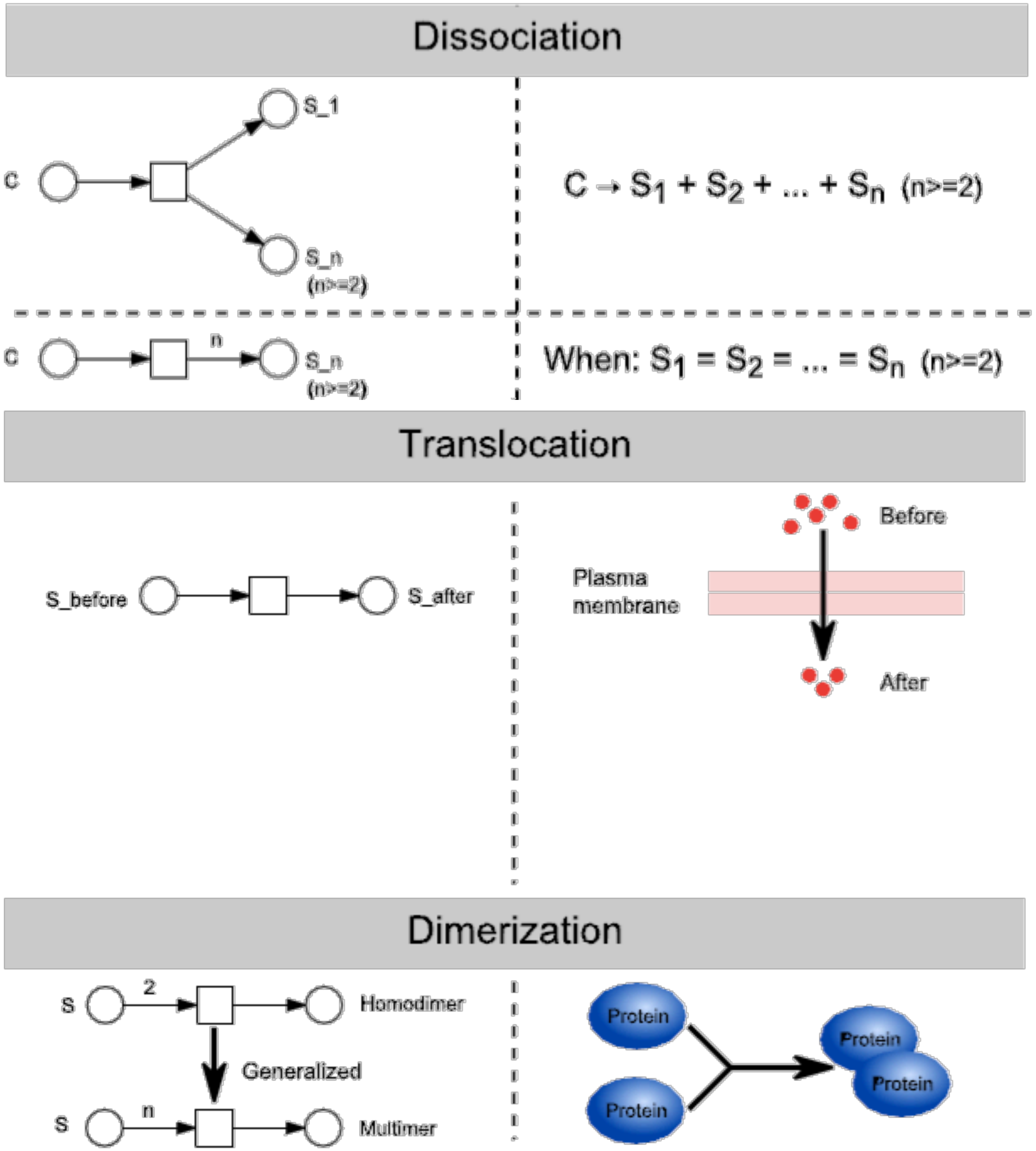
- Simulation



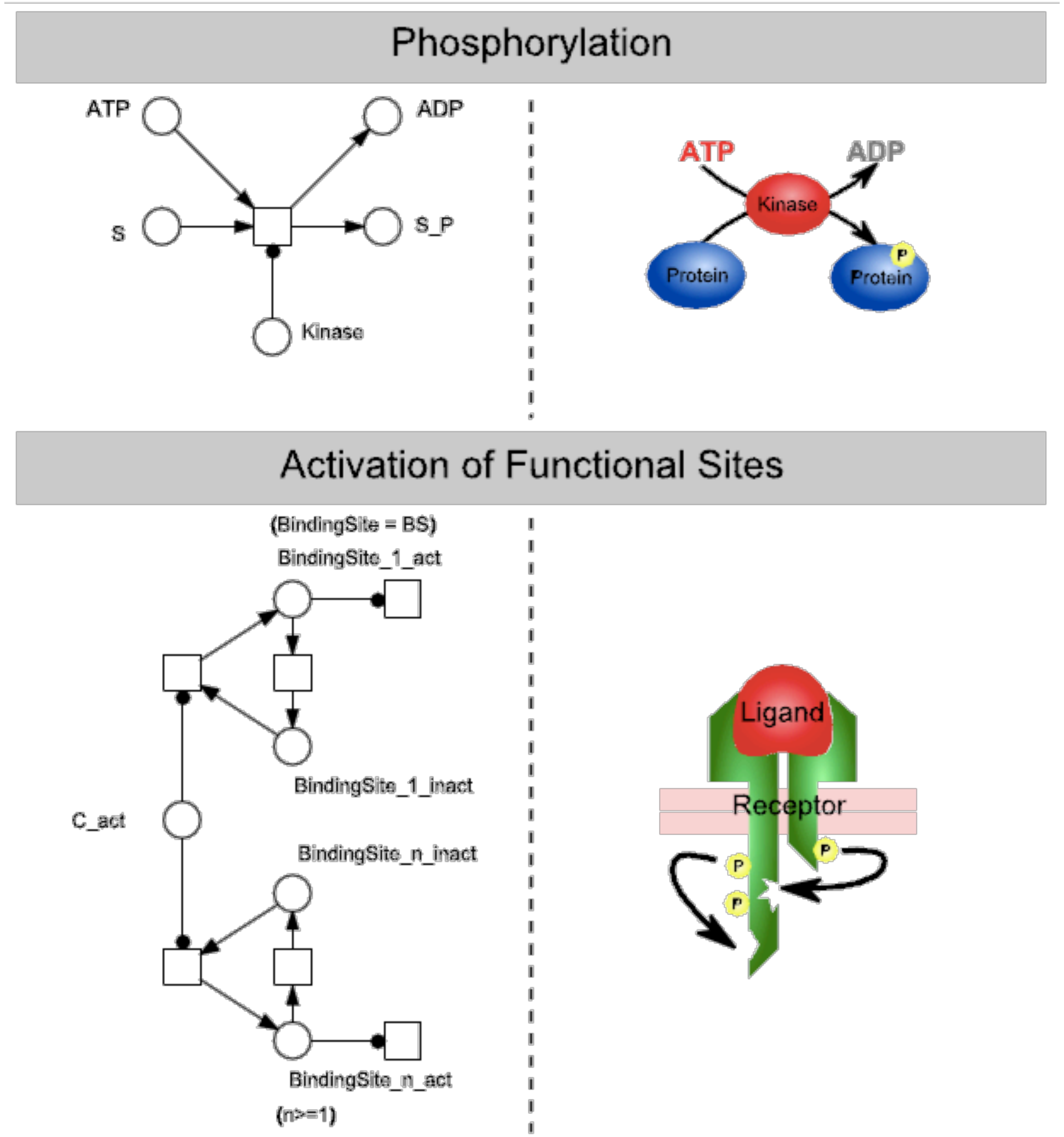
PROCESSES IN SIGNALING



PROCESSES IN SIGNALING

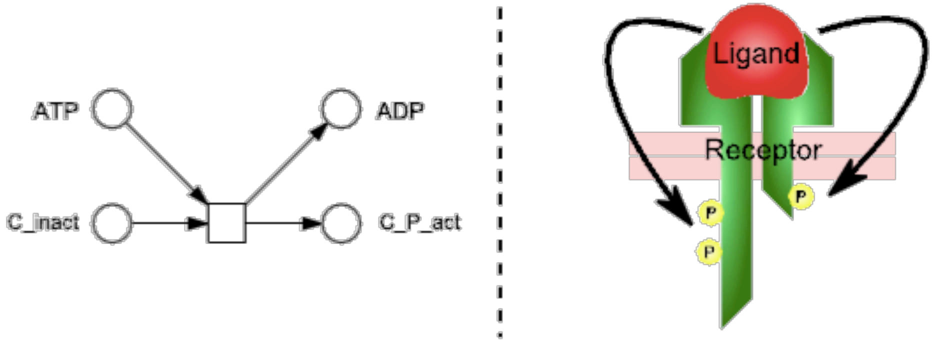


PROCESSES IN SIGNALING

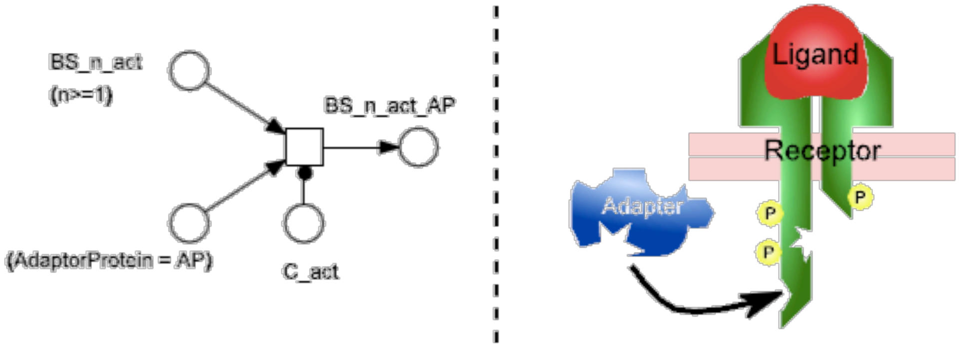


Processes in Signaling

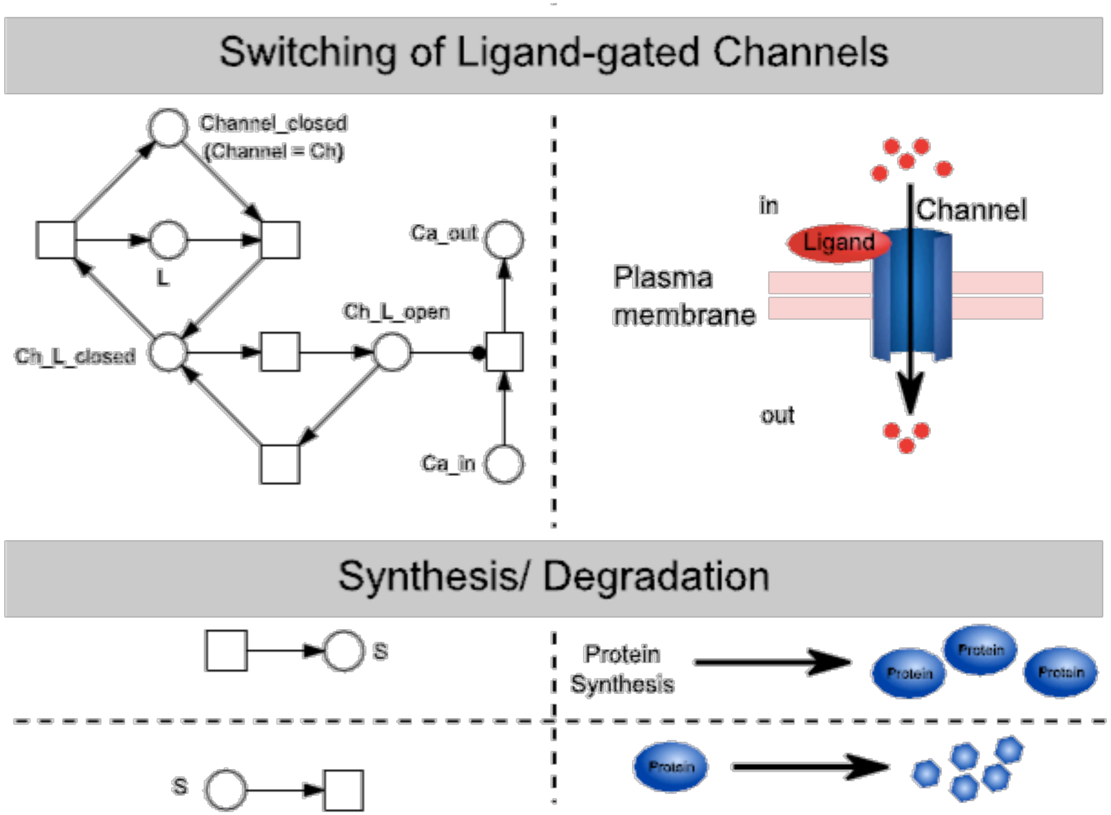
Autophosphorylation



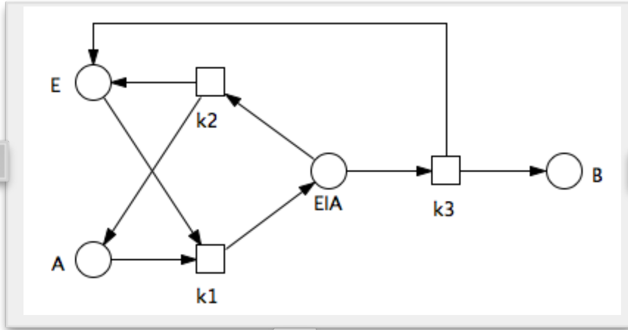
Gathering Functionality by Adaptor Proteins



PROCESSES IN SIGNALING



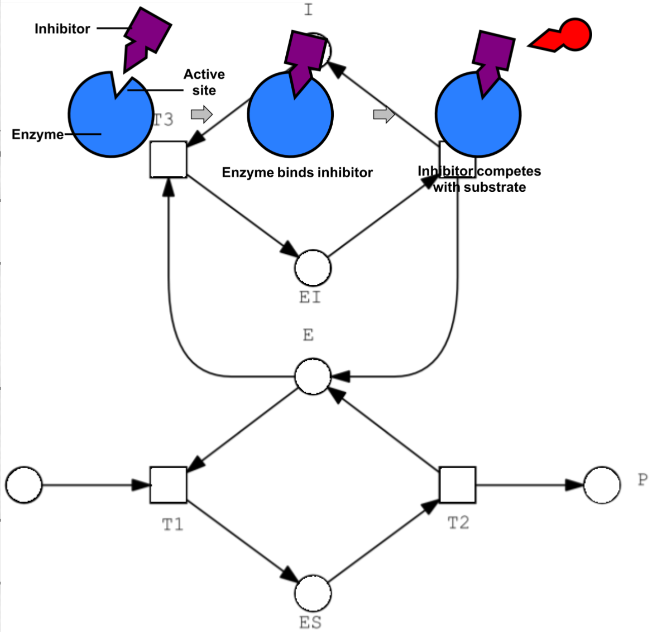
ENZYMATIC REACTIONS



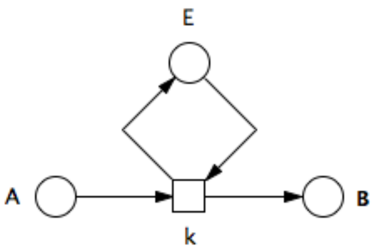
Extension

Extension

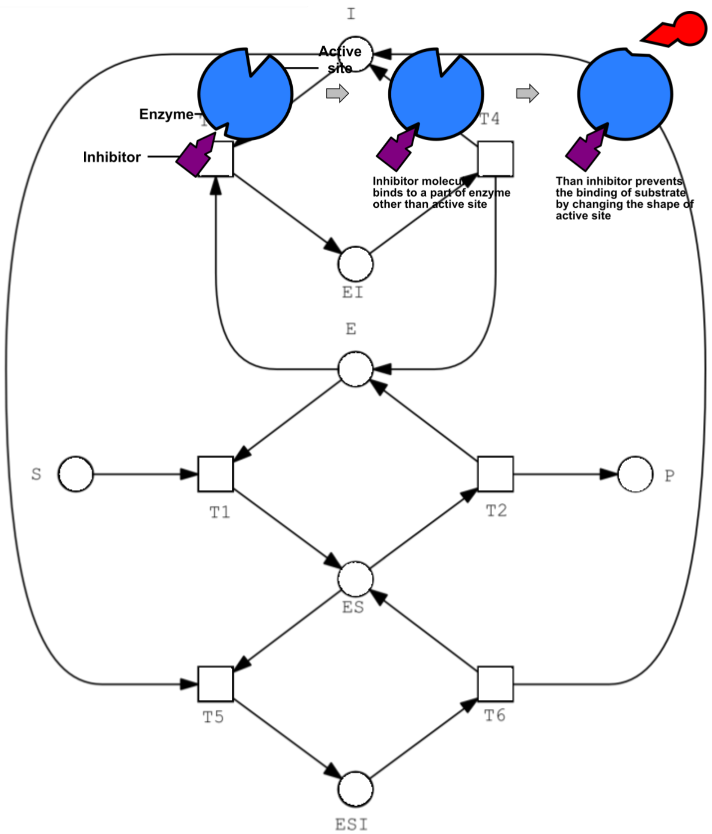
Competitive Inhibition



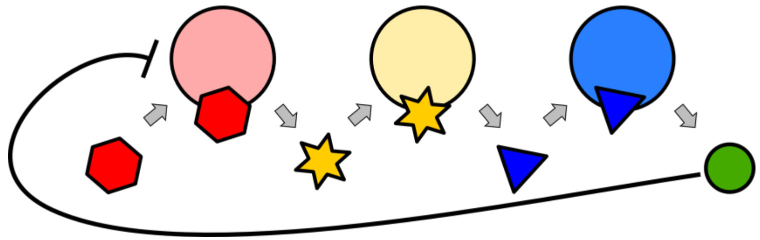
Simplification

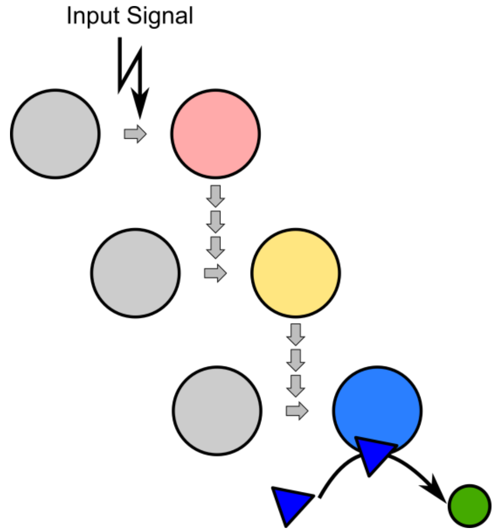


Allosteric Inhibition



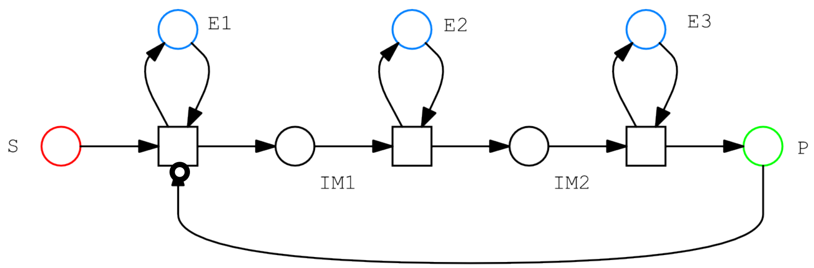
FEEDBACK INHIBITION VS. SIGNAL AMPLIFICATION

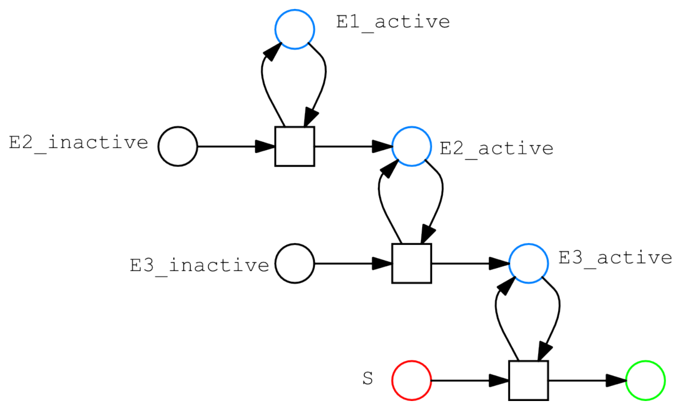




(e) Feed-back Inhibition

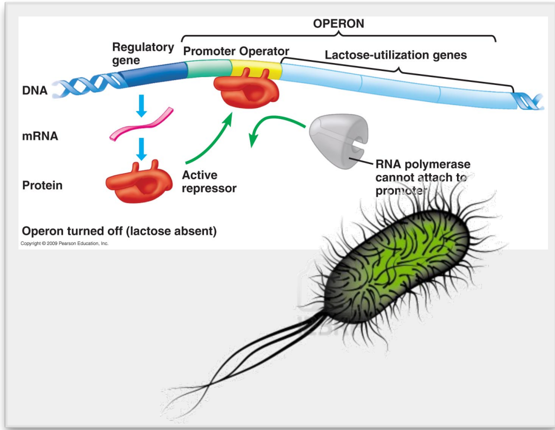
(f) Amplification of an input signal





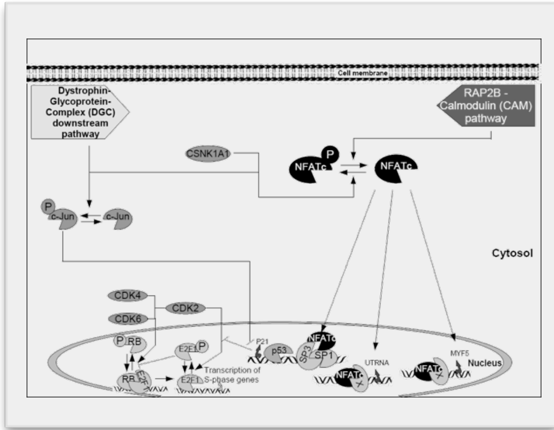
Examples

Lac Operon



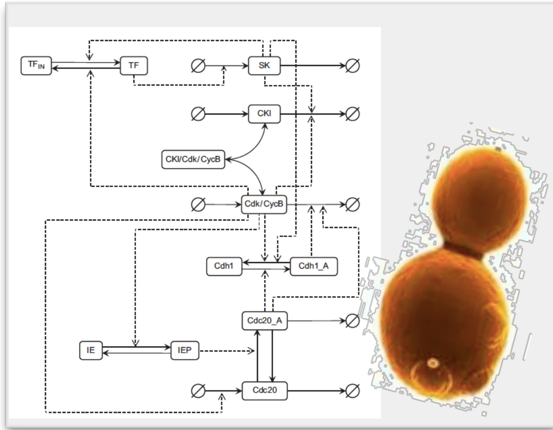
Sackmann et al, 2006

Duchenne Musclar Dystrophy



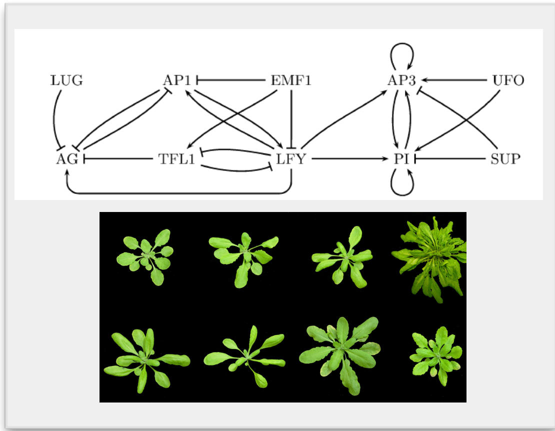
Grunwald et al, 2008

Yeast Cell Cycle



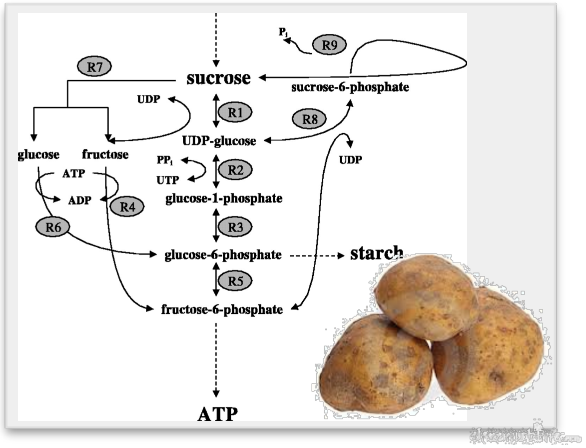
Mura et al, 2008

Morphogenesis in Arabidopsis thaliana



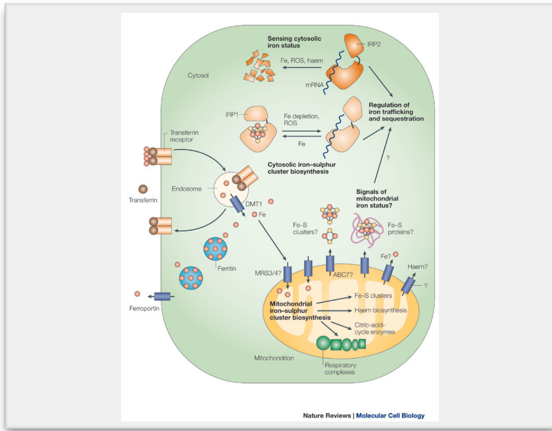
Chaouiya et al, 2004

Sucrose breakdown in the potato tuber



Koch et al, 2005

Iron homoeostasis



Sackmann et al, 2007

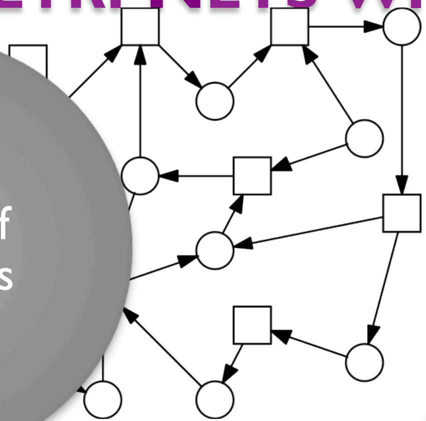
But…

Standard Petri nets do not scale

But…

Coloured
Petri nets
do scale

Extending Petri Nets with Colour



Power of Petri nets

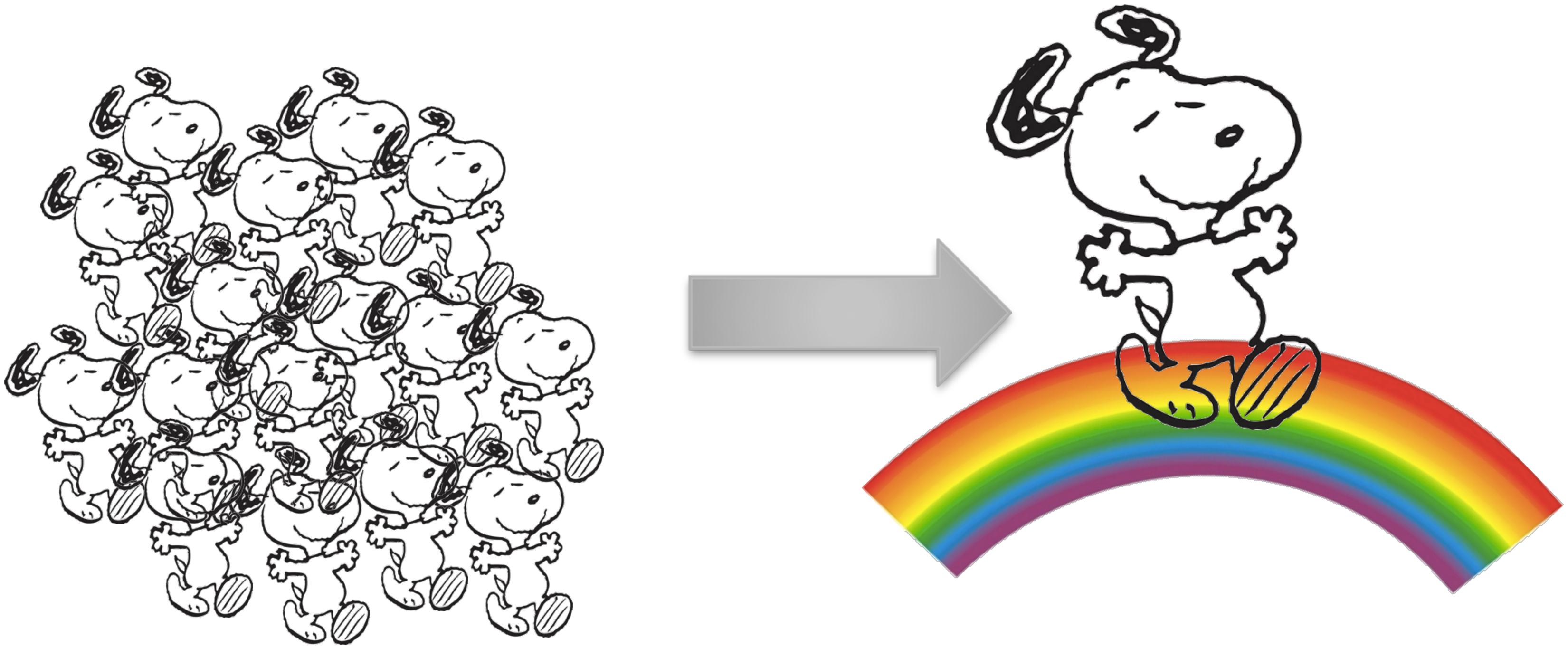
+

Capability of programming to describe data types and operations

→ **Coloured Petri nets**

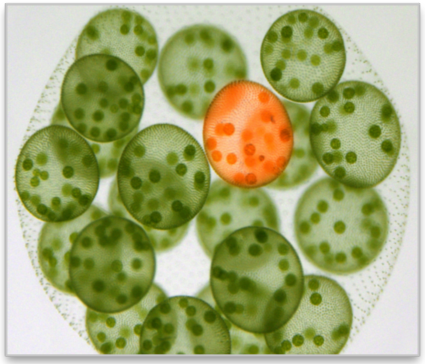
What is Colour?

- A group of similar components is represented by **one** component
- Single components are defined and thus distinguished through their specific colour



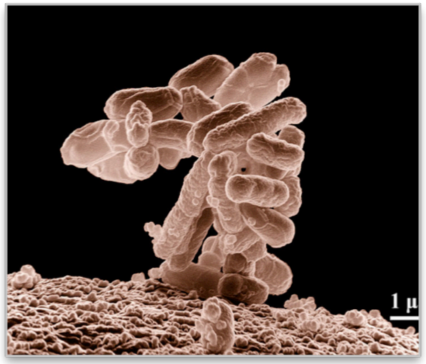
MULTISCALE/ MULTILEVEL/ MULTIDIMENSIONAL MODELLING

Repetition of components

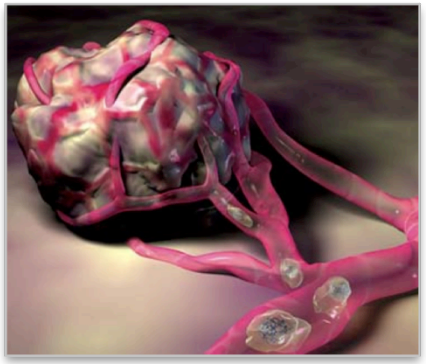


Variation of components

Organisation of components

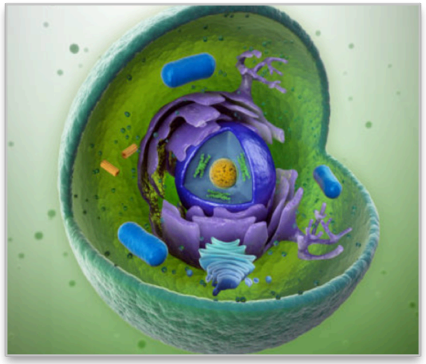


Communication between components

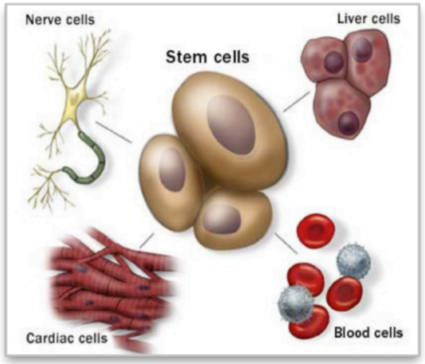


Movement of components

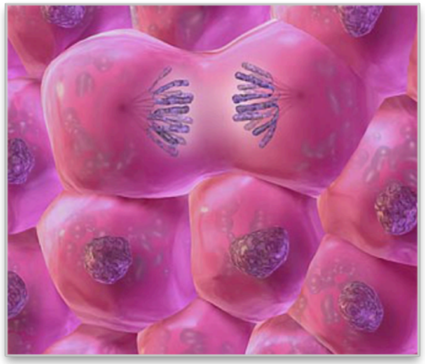
MULTISCALE/ MULTILEVEL/ MULTIDIMENSIONAL MODELLING



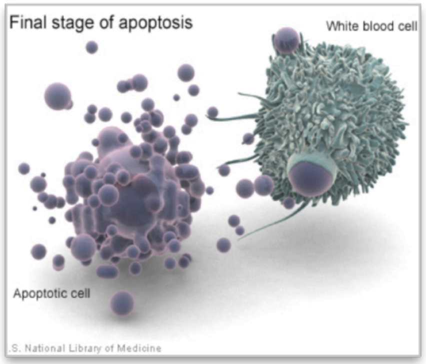
Hierarchical organisation of components



Differentiation of components



Replication of components

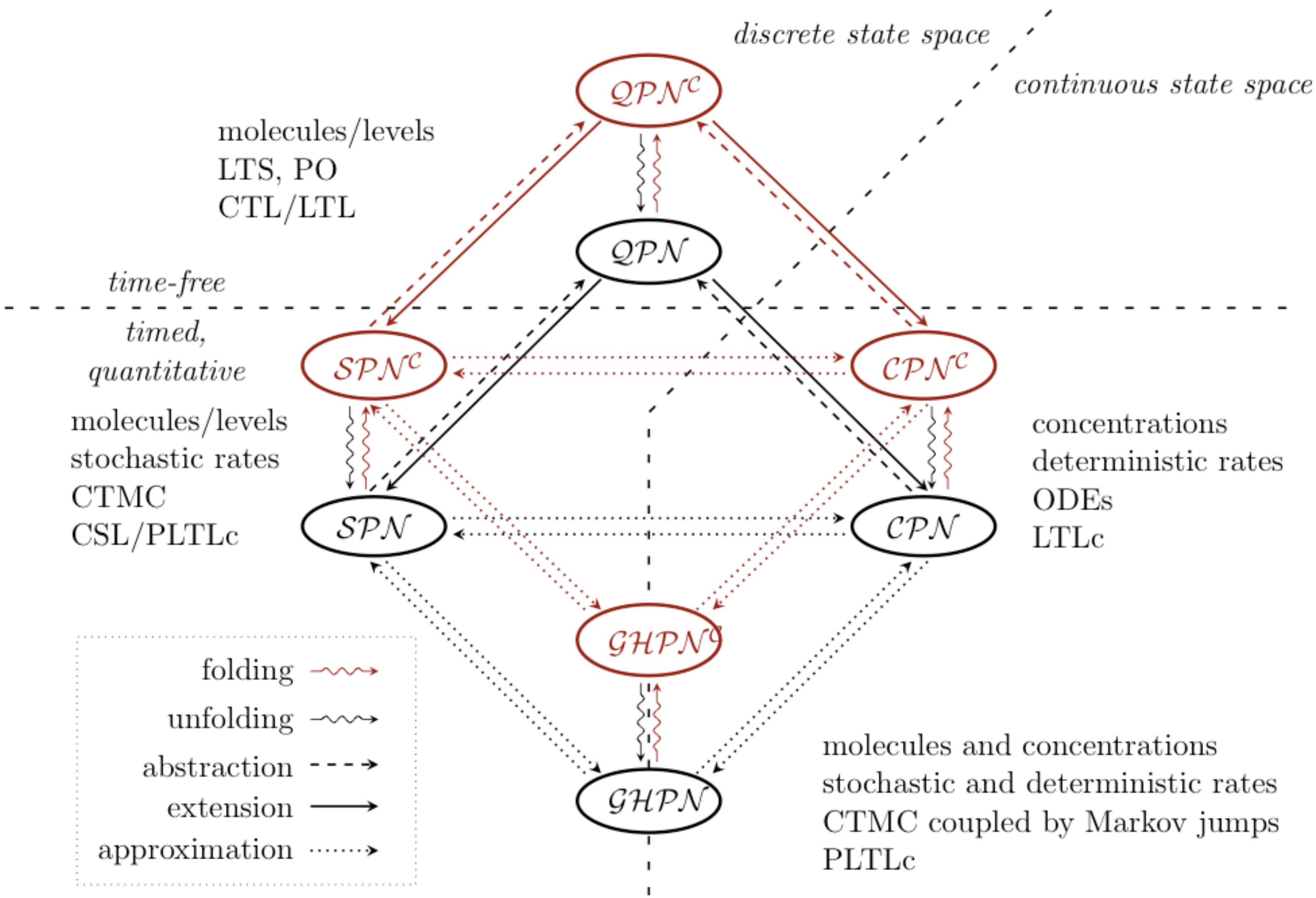


Deletion of components

Pattern formation of components

Components, e.g., genes, molecules, cellular compartment, cells, multicellular complex, tissues, organs, organisms, populations

EXTENDED PETRI NET FRAMEWORK



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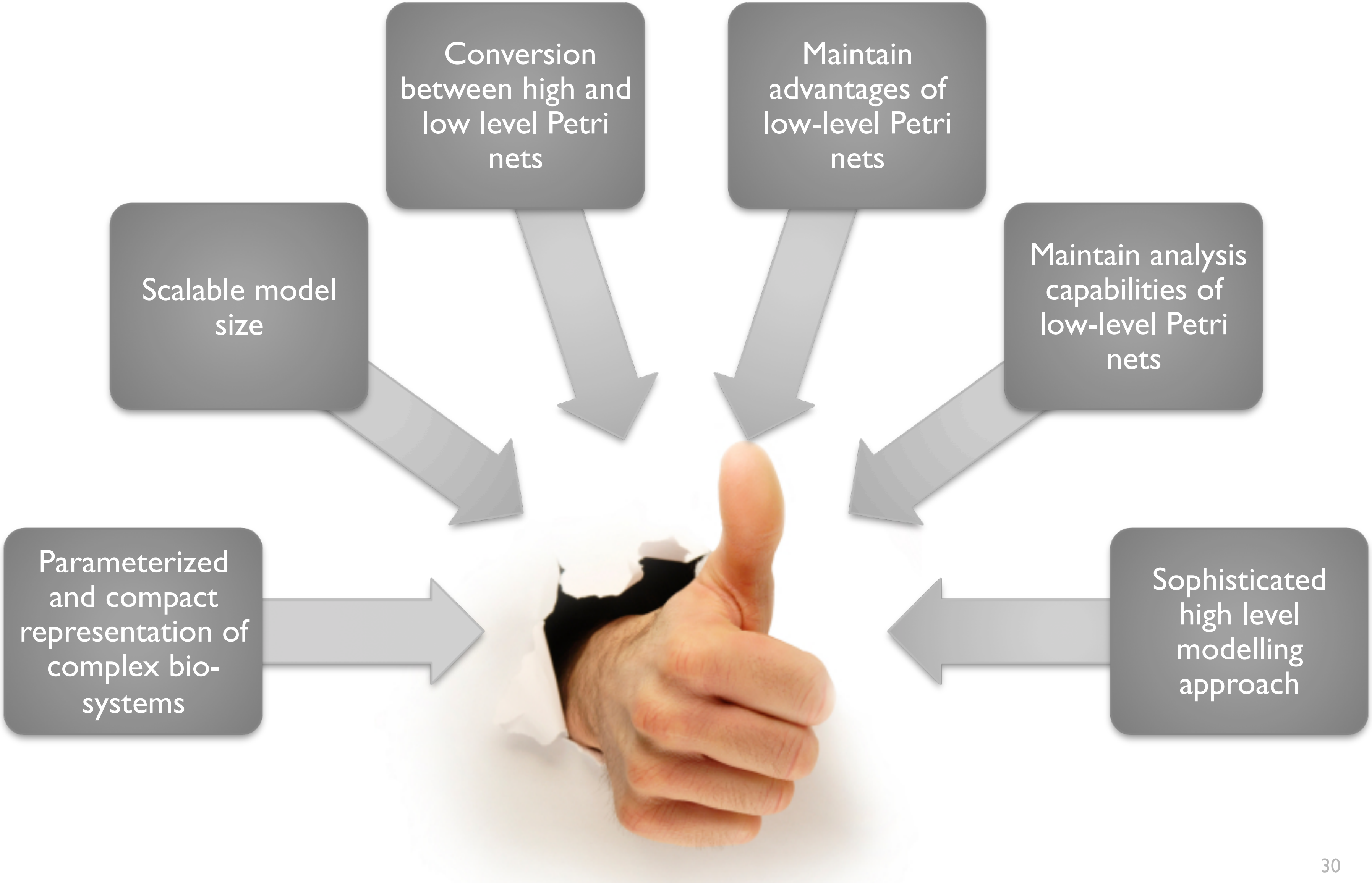
EXTENDED PETRI NET FRAMEWORK

Eight Models Sharing the **SAME** Structure

(Coloured) Quantitative Model = (Coloured) Qualitative Model + Quantitative Parameters (Kinetics)

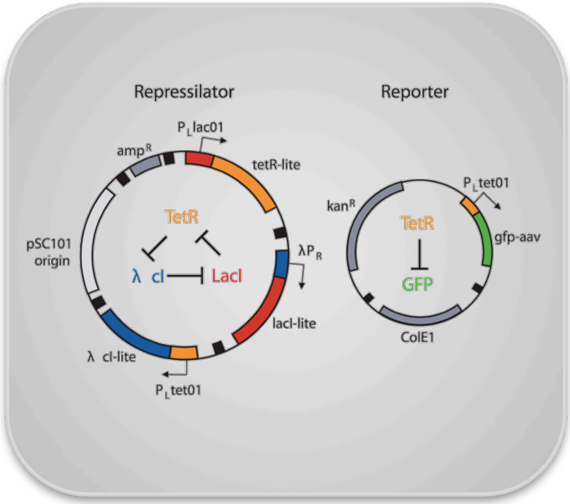
Coloured Models ← Folding — Unfolding → Low-Level Models

ADVANTAGES OF PETRI NETS

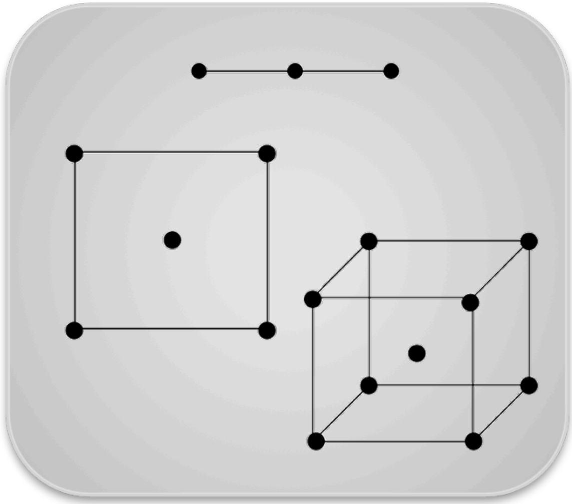


Coloured Examples in this Tutorial...

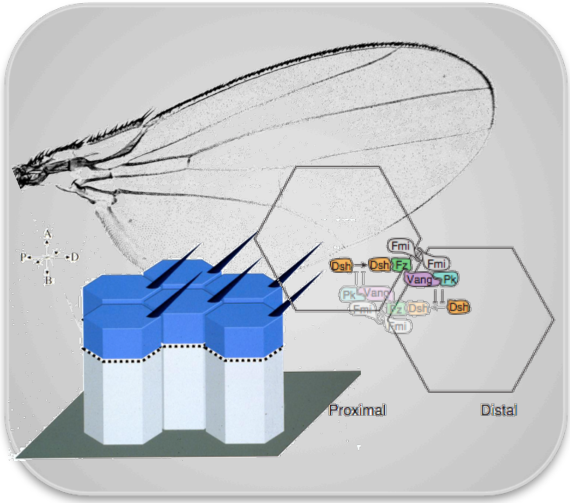
Lotka-Volterra



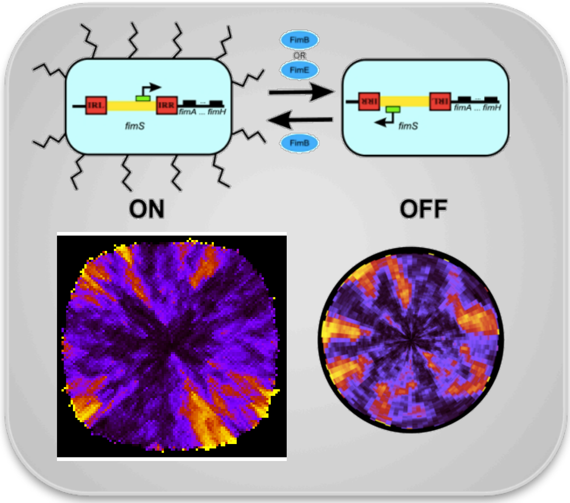
Repressilator



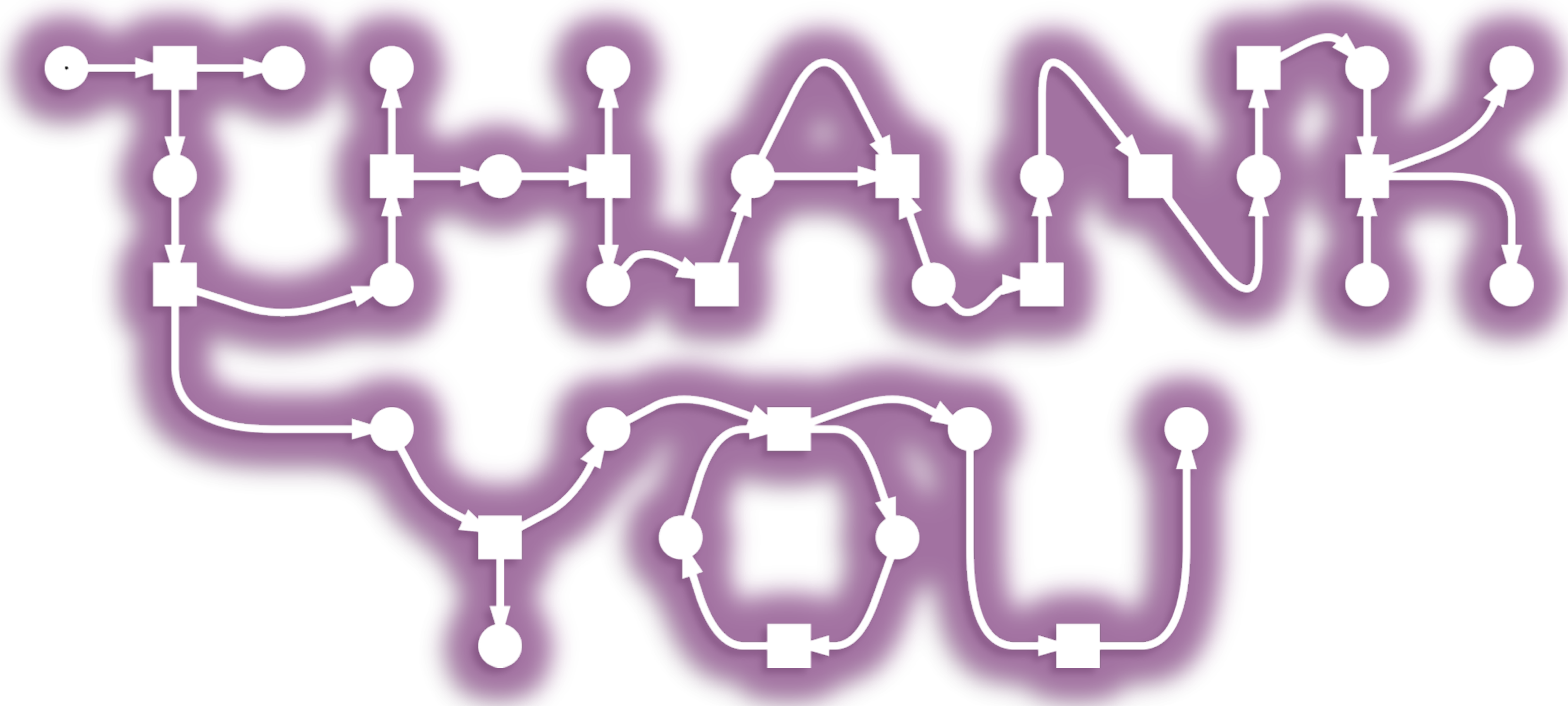
1D, 2D, 3D



Drosophila Fly Wing



Phase Variation in Bacterial Colony



- **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

Federal Ministry of Education and Research

FORSYS Research Units for Systems Biology

Magdeburg Centre for Systems Biology MaCS

IMPRS Magdeburg International Max Planck Research School for Analysis, Design, and Optimization in Chemical and Biochemical Process Engineering

btu Brandenburg University of Technology Cottbus

Otto von Guericke Universität Magdeburg