## Petri Net Tutorial – Part 1:

# Revision of basic qualitative Petri net concepts in the context of biological Application

Mary Ann Blätke

@ ICSB 2011, Heidelberg

# INTRODUCTION

REVISION OF BASIC QUALITATIVE PETRI NET CONCEPTS IN THE CONTEXT OF BIOLOGICAL APPLICATIONS

# Bioscience at the End of the 20th Century

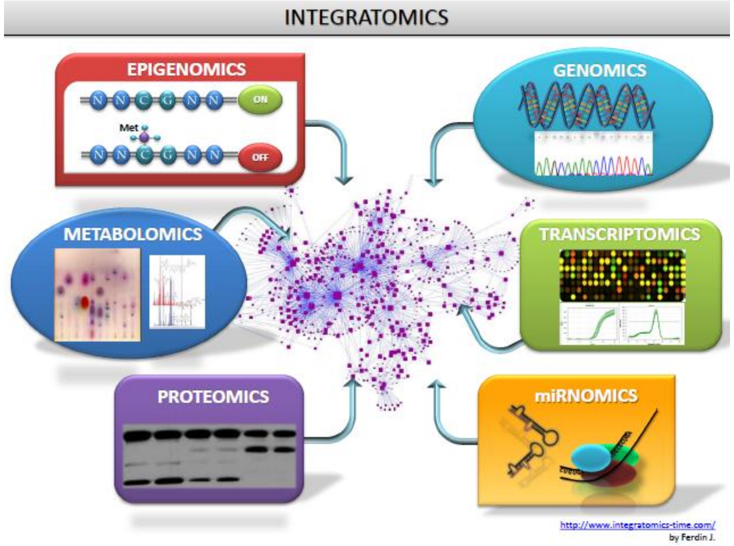
- Many genomes have been sequenced
- Additional high-throughput OMICS technologies

⇓

- How to interpret the data?
- What is the resulting functionality of the cell or entire organism?

⇓

- Systems biology may help to answer these questions




**Systems Biology**

www.integratomics-time.com/

# SYSTEMS BIOLOGY

- Several definitions:

To understand biology at the system level, we must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism.

[Kitano, H., Nature, 2002]

Systems biology does not investigate individual genes or proteins one at a time,[…]. Rather, it investigates the behavior and relationships of all of the elements in a particular biological system while it is functioning.

[Ideker, T. et al., Annu Rev Genomics Hum Genet, 2001]

Systems biology can be defined as a field of study that takes into account complex interactions in biological systems at different scales of biological organization, from the molecular to cellular, organ, organism, and even societal and ecosystem levels .

[Popel, A. et al., Wiley Interdiscip Rev Syst Biol Med, 2009]

# **Systems Biology**

- No widely accepted definition of Systems Biology :

To understand biology at the system level, we must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism.

[Kitano, H., Nature, 2002]

Systems biology does not investigate individual genes or proteins one at a [illegible] the elements in a part[illegible] while it is functioning.

**⇒ Systems biology investigates molecular life processes on a complex systems level**

[Ideker, T. et al., Annu Rev Genomics Hum Genet, 2001]

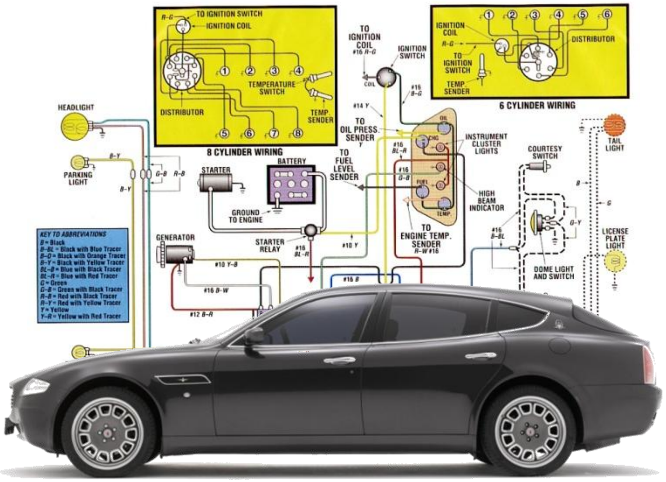
Systems biology can be defined as a field of study that takes into account complex interactions in biological systems at different scales of biological organization, from the molecular to cellular, organ, organism, and even societal and ecosystem levels .

[Popel, A. et al., Wiley Interdiscip Rev Syst Biol Med, 2009]

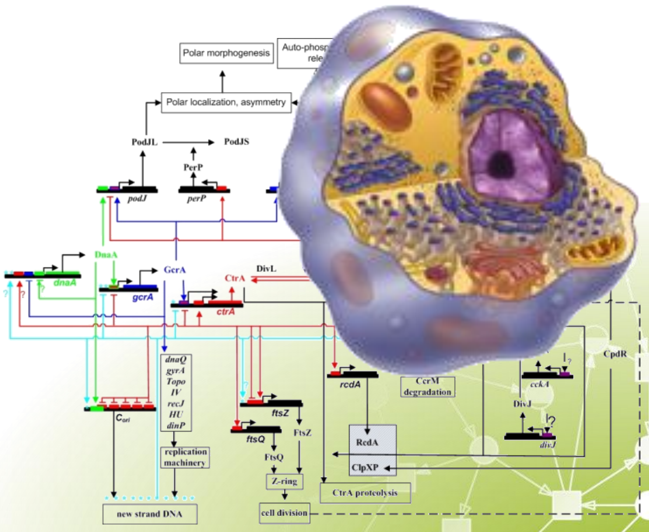
# Systems Biology

**⇒ Systems biology investigates molecular life processes on a complex systems level**

- Systems biology considers 4 key characteristics:
  - **Structure of the system:** Components of the biological system and their way of interacting with each other
  - **Dynamics of the system:** Time dependent behaviour of the biological system under different internal and external conditions
  - **Control principles of the system**: Mechanisms used to control the biological system
  - **Construction principals:** Identification of biological systems and their use for systems analysis




**Complex Systems**

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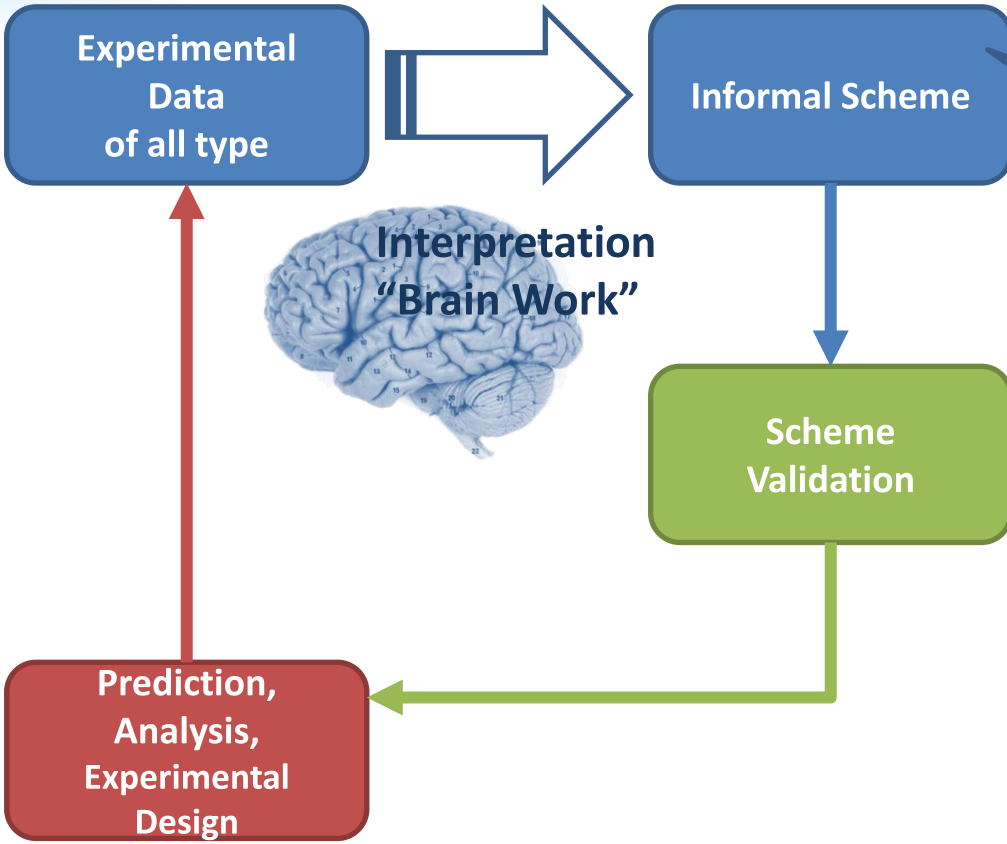
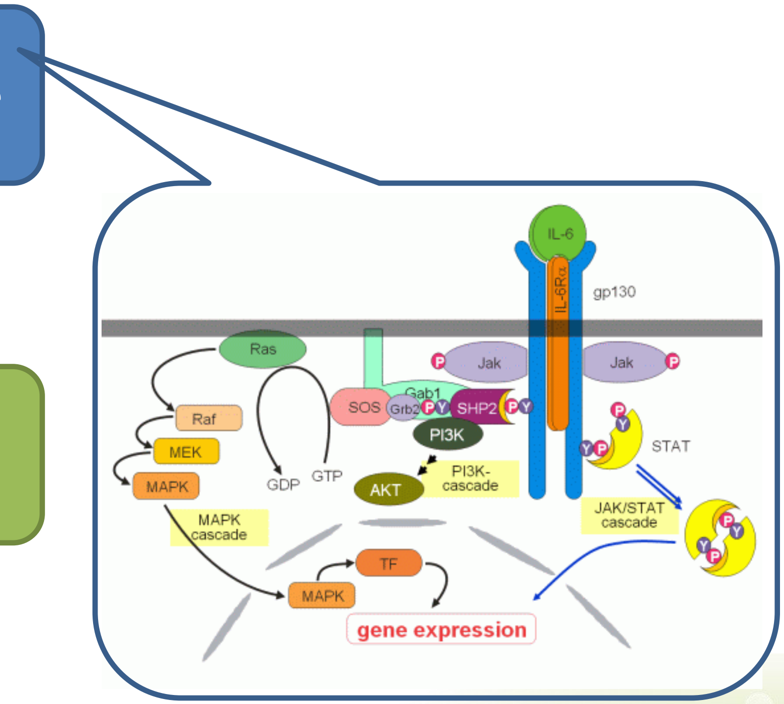
# Modeling and Model Validation in Bioscience

- Classical lab approach:



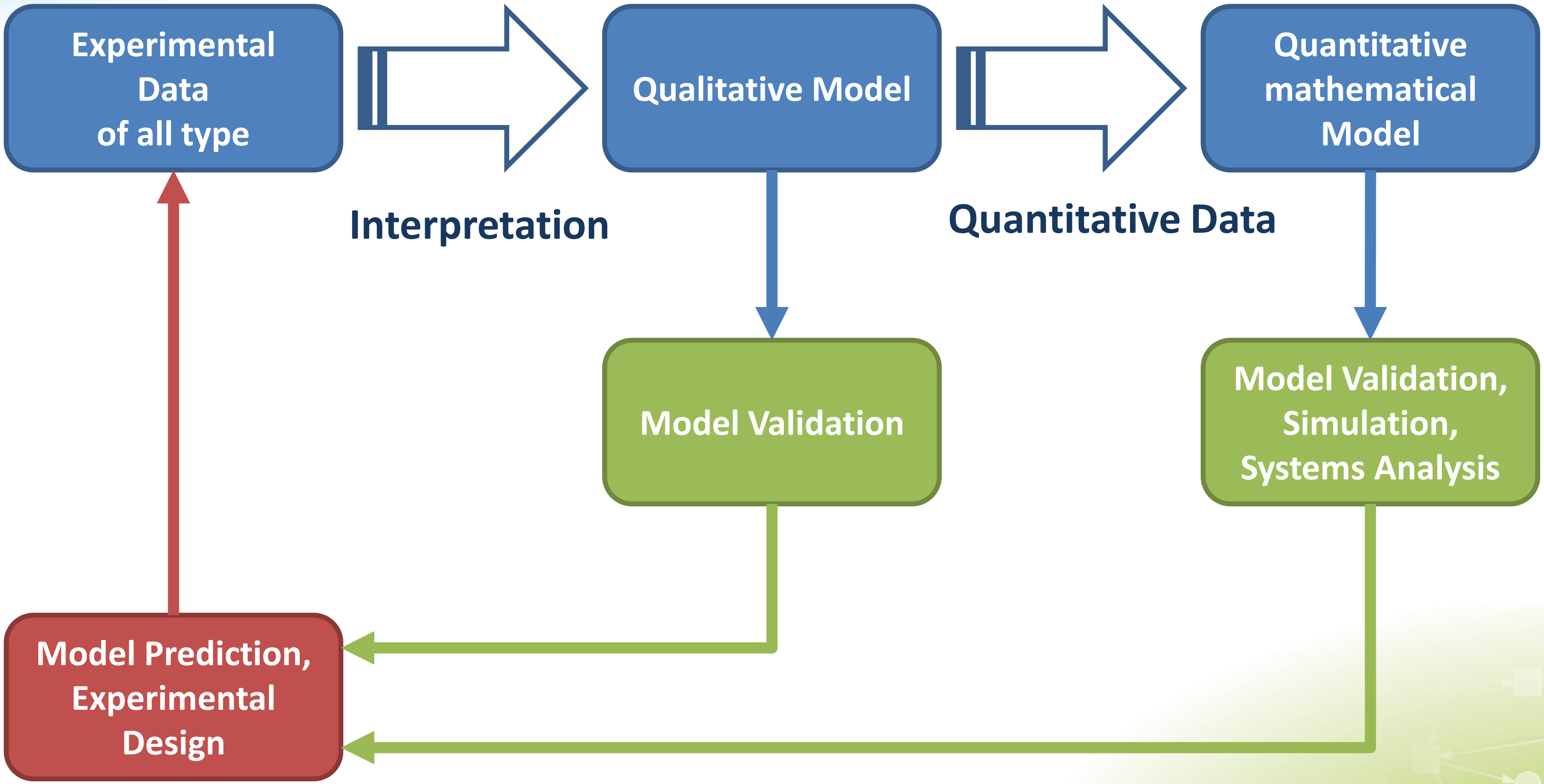

Heinrich, P.C. et al., Biochem. J., 1998

Repeat until the model correctly predicts all experimental results.

**Nagging Doubt: Would an alternative model do equally well?**

# Modeling and Model Validation in Bioscience

- Systems biological approach:

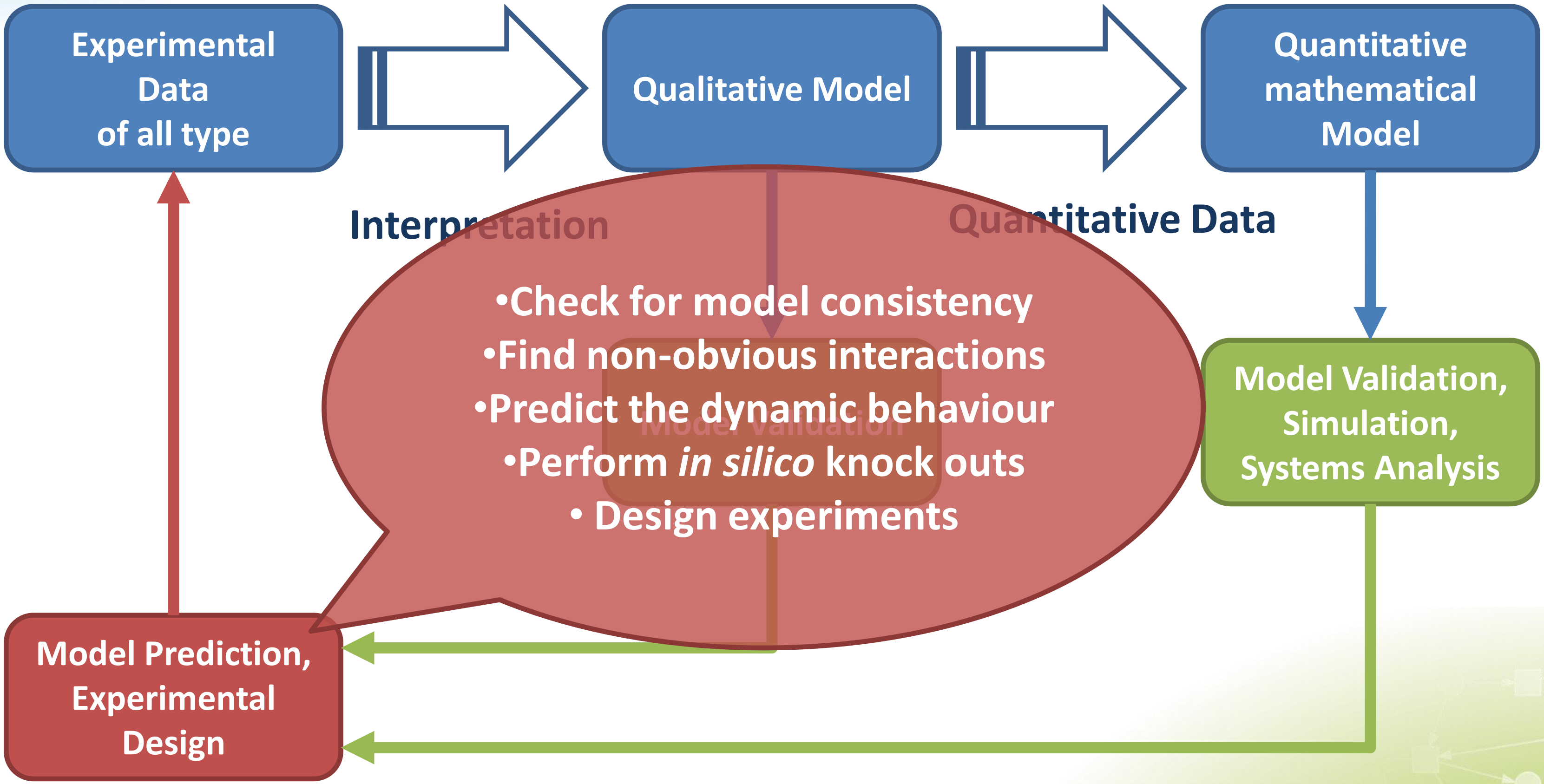



Repeat until the model correctly predicts all experimental results.

**Nagging Doubt: Would an alternative model do equally well?**

# Modeling and Model Validation in Bioscience

- Systems biological approach:




Repeat until the model correctly predicts all experimental results.

**Nagging Doubt: Would an alternative model do equally well?**

# COMPUTER SCIENCE MODELS

- Characteristics:
  - Formal language
  - Unambiguous, strict syntax
  - Model checking available
  - Executable

- Examples:
  - Boolean nets
  - **Petri nets**
  - Process algebras, e.g., Pi-calculus, β-binders and derivates
  - Other calculi or frameworks

Revision of basic qualitative Petri net concepts in the context of biological applications

# Workshop overview

Scaling up from single molecules to multicellular systems: modelling over time and space with advanced Petri net techniques

Day 1: Petri nets for systems biology

Day 2: Petri nets for multiscale Systems Biology

# DAY 1: PETRI NETS FOR SYSTEMS BIOLOGY

**14.00 – 14. 30:** Welcome Coffee

**14.30 – 16.10:**

1. Talk: Revision of basic qualitative Petri net concepts in the context of biological applications + Exercises [Mary Ann Blätke]

2. Talk: Qualitative analysis + Exercises [Monika Heiner]

**16.10 – 16.40:** Coffee Break and Sandwiches

**16.40 – 19.00:**

3. Talk: Introduction into advanced concepts:

   Stochastic, continuous and related analysis/simulation techniques [Monika Heiner]

   Hybrid Petri nets, and related simulation techniques, dynamic partitioning [Mostafa Herajy]+ Exercises

4. Talk: BioModel Engineering via modular, protein-oriented modeling [Mary Ann Blätke]

5. Talk: Behaviour checking techniques + Exercise [David Gilbert]

# DAY 2: MULTISCALE SYSTEMS BIOLOGY

**8.30 – 9.00:** Welcome Coffee

**9.00 – 11.10:**

1. Talk: Introduction: Moving to the multiscale in systems biology modeling. [David Gilbert]
2. Talk: Advanced modeling concepts: coloured, and hierarchically coloured Petri nets + Exercise [Monika Heiner]
3. Talk (1): Detailed discussion and analysis of examples:
   C.elegans and calcium channels [Fei Liu]
   Halobacterium salinarum [Wolfgang Marwan]

**11.10 – 11.40:** Coffee Break

**11.40 – 13.30:**

3. Talk (2): Detailed discussion and analysis of examples:
   Dictyostelium discoideum – cAMP diffusion & cell motility [Monika Heiner, David Gilbert]
   Drosophila melanogaster - planar cell polarity in tissues [Qian Gao, Ester Bamigboye]
4. Talk: Analysis techniques for multiscale models [Mary Ann Blätke, Daniele Maccagnola]
5. Discussion: Challenges in multi-scale modeling for systems biology: from single to multi-cell systems & wrap-up

**13.30 – 14.00:** Lunch

Revision of basic qualitative Petri net concepts in the context of biological applications

# Petri Net Basics

# Carl Adam Petri

„Petri Nets is a formal and graphical appealing language which is appropriate for modeling 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/*

K o m m u n i k a t i o n
m i t
A u t o m a t e n

Von der Fakultät für Mathematik und Physik
der Technischen Hochschule Darmstadt

zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer.nat.)

genehmigte
Dissertation

vorgelegt von
C a r l A d a m P e t r i

g

.rer.techn.A.Walther
.ing.H.Unger

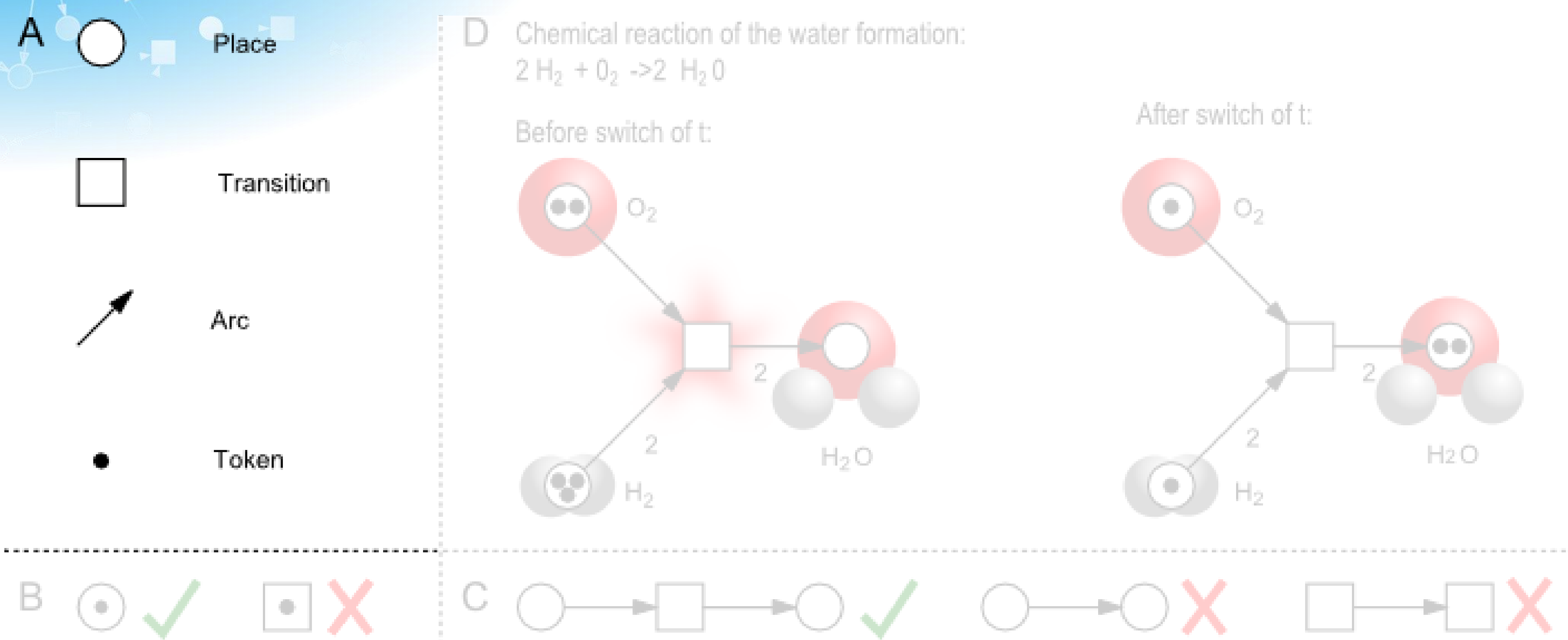
27.7.1961
rüfung: 20.6.1962
7
1962

**12. July 1926 in Leipzig; † 2. July2010**

# Advantages of Petri Nets

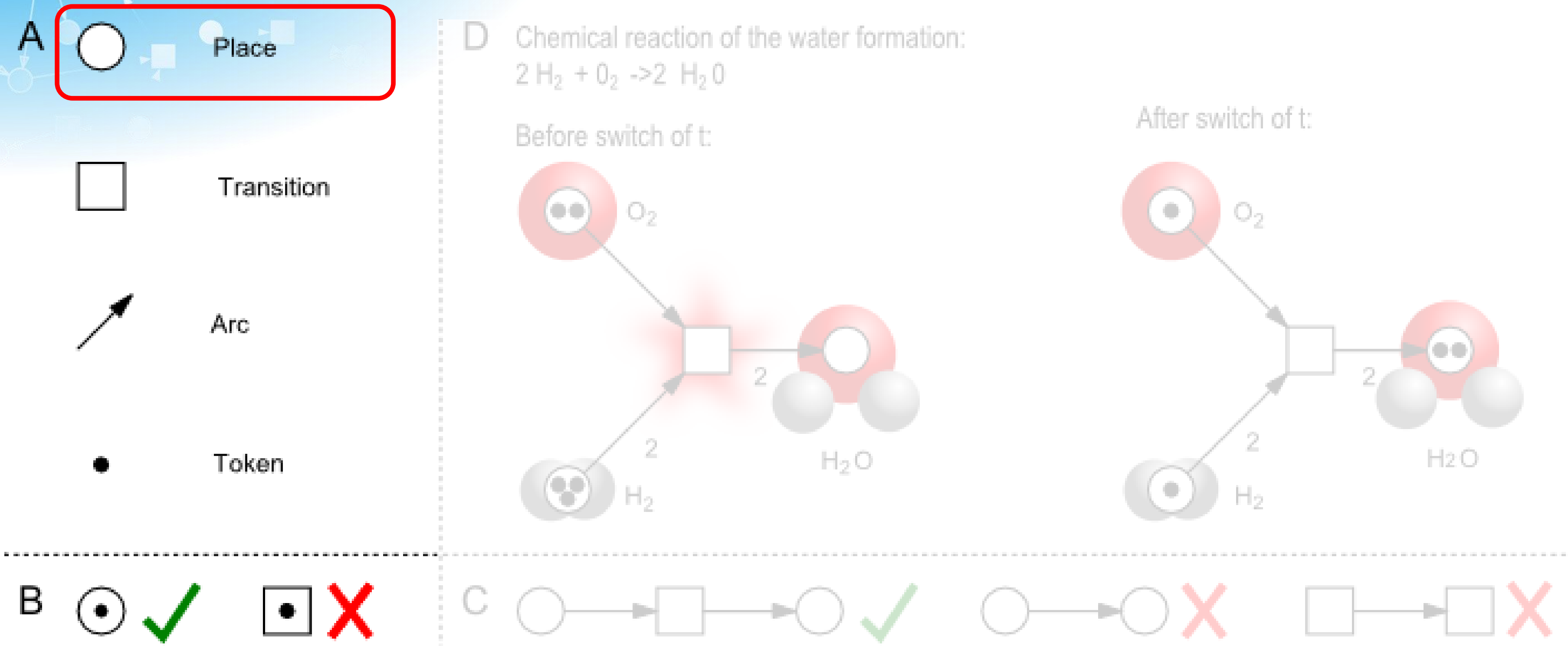
- Consistent representation of processes occurring at different levels of complexity within a single, coherent model while being formally and mathematically correct
- Intuitive language to describe experimental facts
- Generation, analysis and modification by a computer ⇒ SNOOPY
- Simulations of models (stochastic, deterministic, discrete, continuous) by executing the Petri Nets in ⇒ SNOOPY
- Structural Analysis supported by many reliable Petri net tools ⇒ Charlie, Marcie

# OVERVIEW



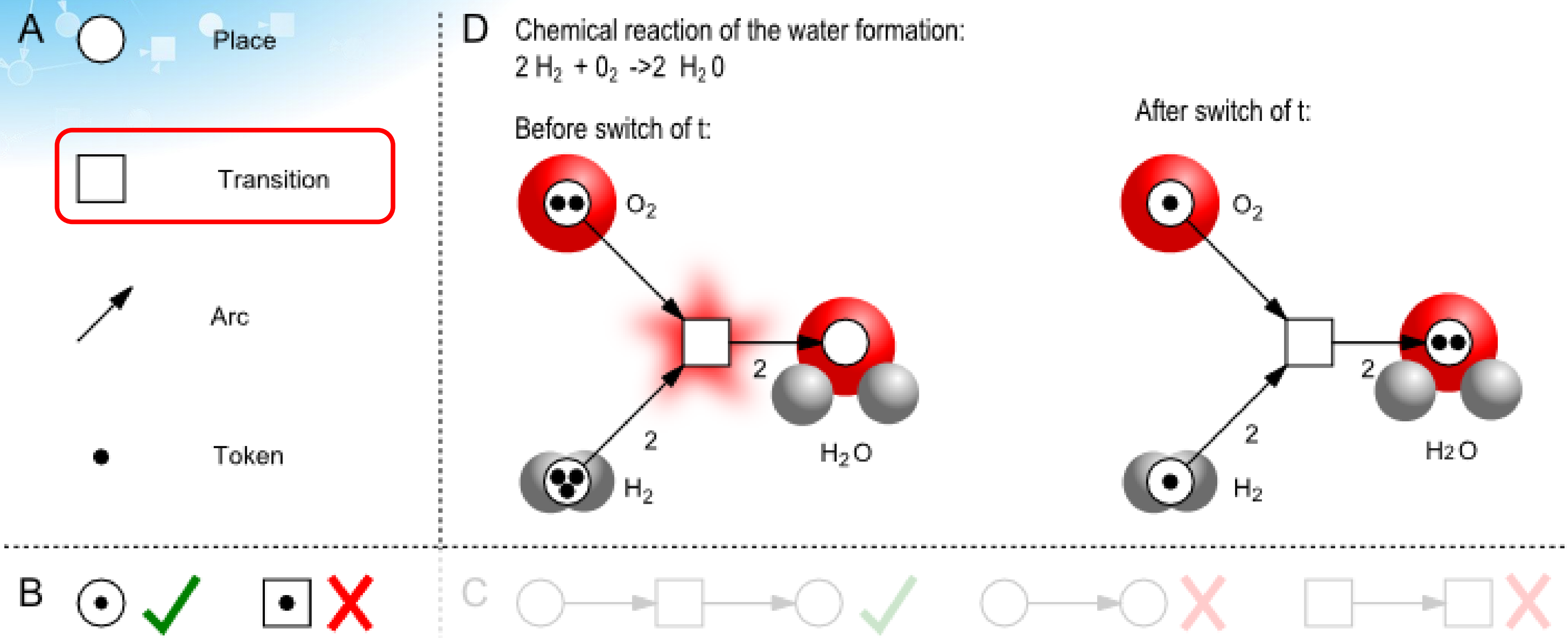

- 4 Standard Elements:
  - Place, transition, arc, token

# PLACES = INACTIVE ELEMENTS



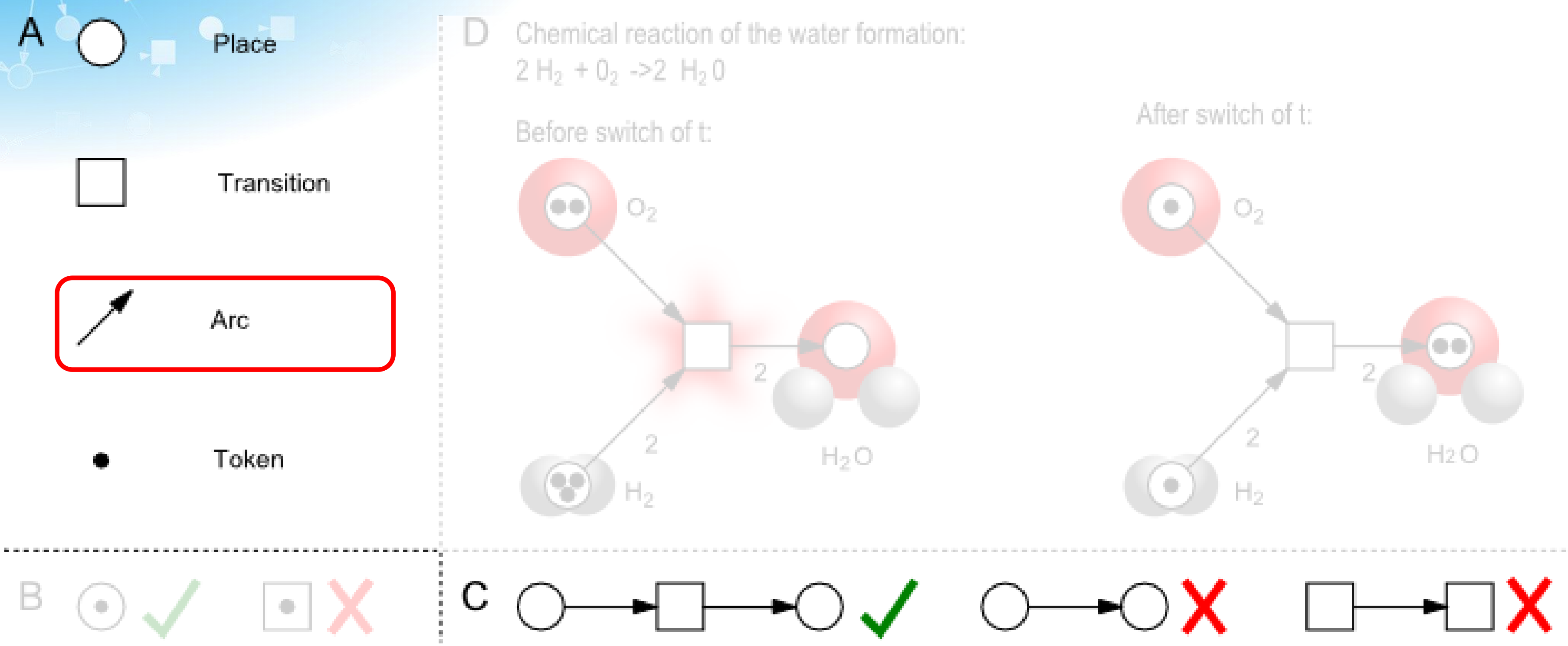

- Conditions, species or states of a system
- Carry tokens
- E.g.: atoms, ions, inorganic and organic molecules (Proteins, Carbohydrates, Fatty Acids)…

# Transitions = Active Element



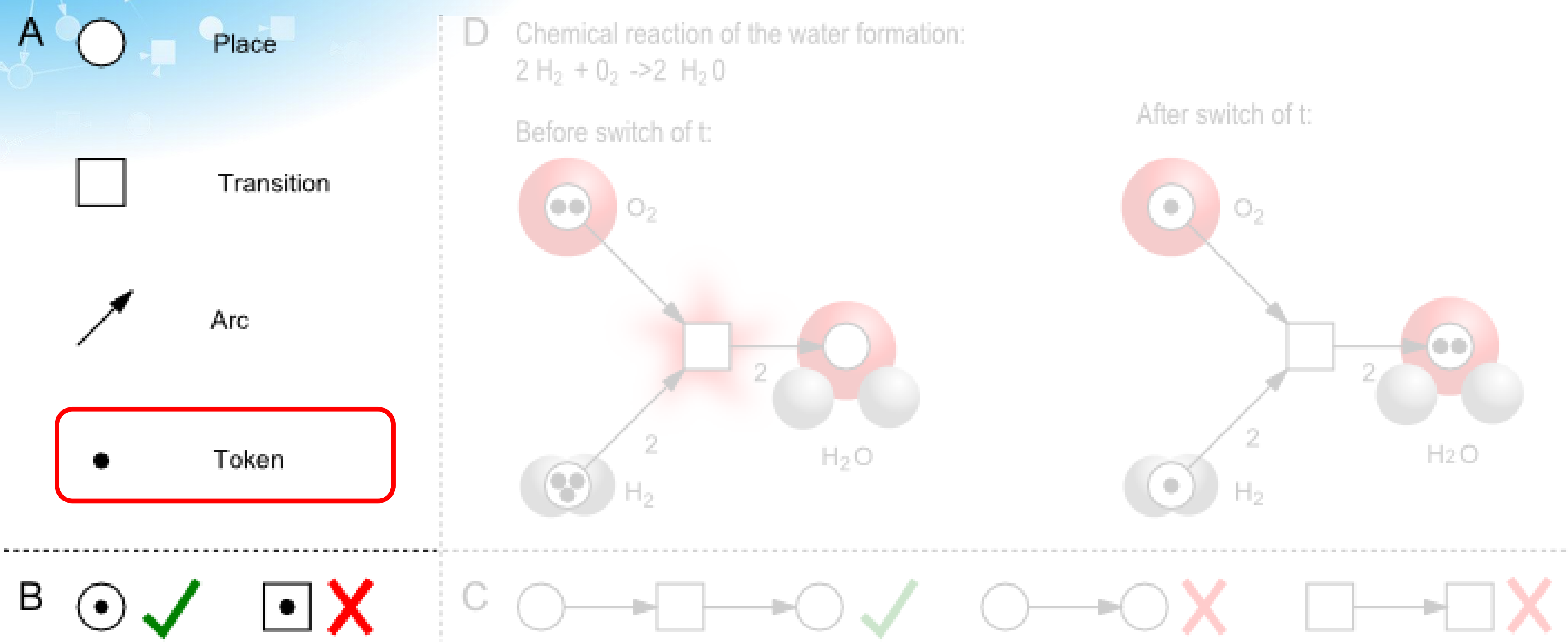

- State shifts, actions, system events
- Delete tokens from pre-places, produce tokens on post-places
- E.g.: reactions, dissociation, binding, phosphorylation

# Arcs = Inactive Elements



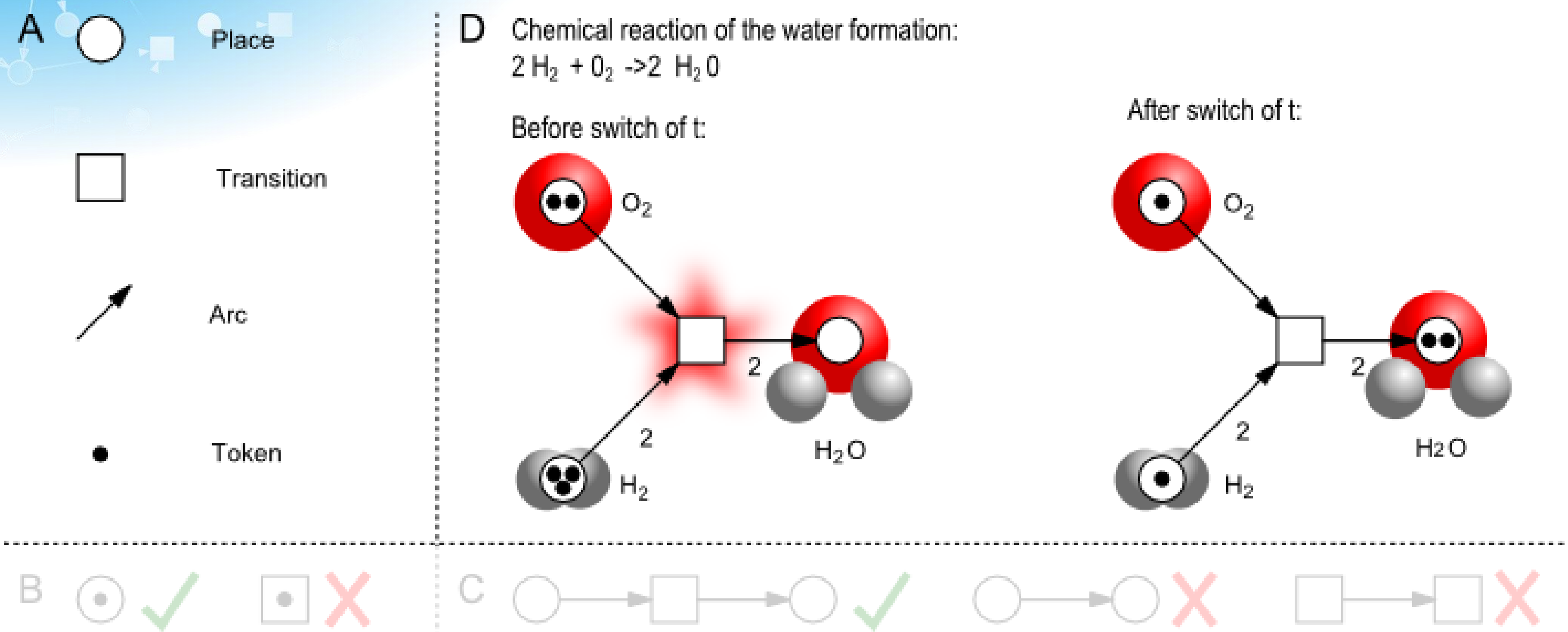

- Specification of relations between places and transitions
- Indicate how changes occur by a transition
- E.g.: stoichiometry of (bio-)chemical reactions

# Tokens = Variable Elements



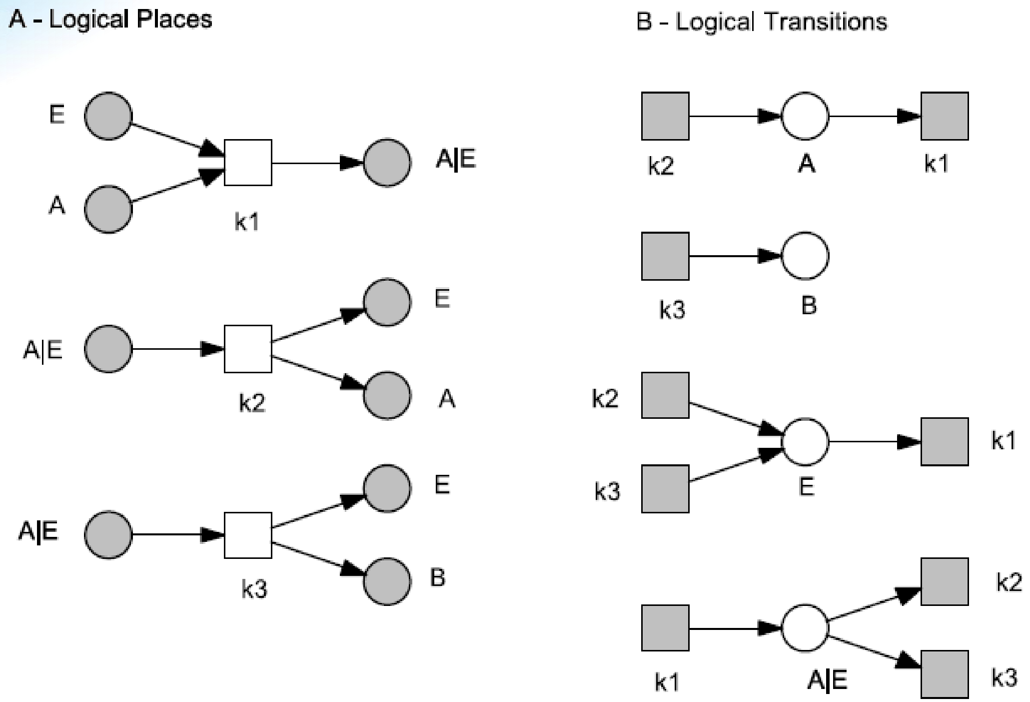

- Value of a condition
- E.g.: discrete number or concentration of a molecule, membrane voltage, temperature…

# Petri Net Semantics



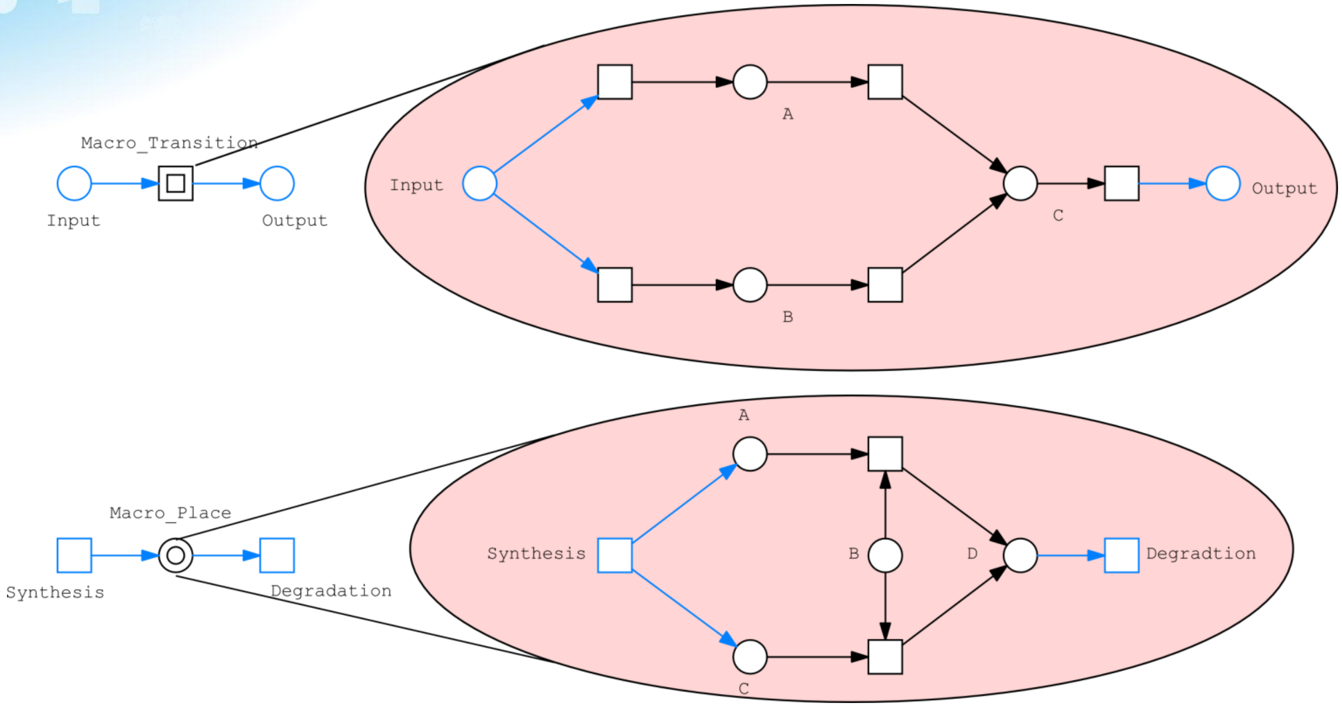

- Firing of a transition:
  - A transition is enabled to fire if all its pre-places are sufficiently marked
  - Tokens on pre-places are consumed and new tokens are produced on its post-places if a transition fires

# EXTENSION OF VISUALISATION – LOGIC NODES



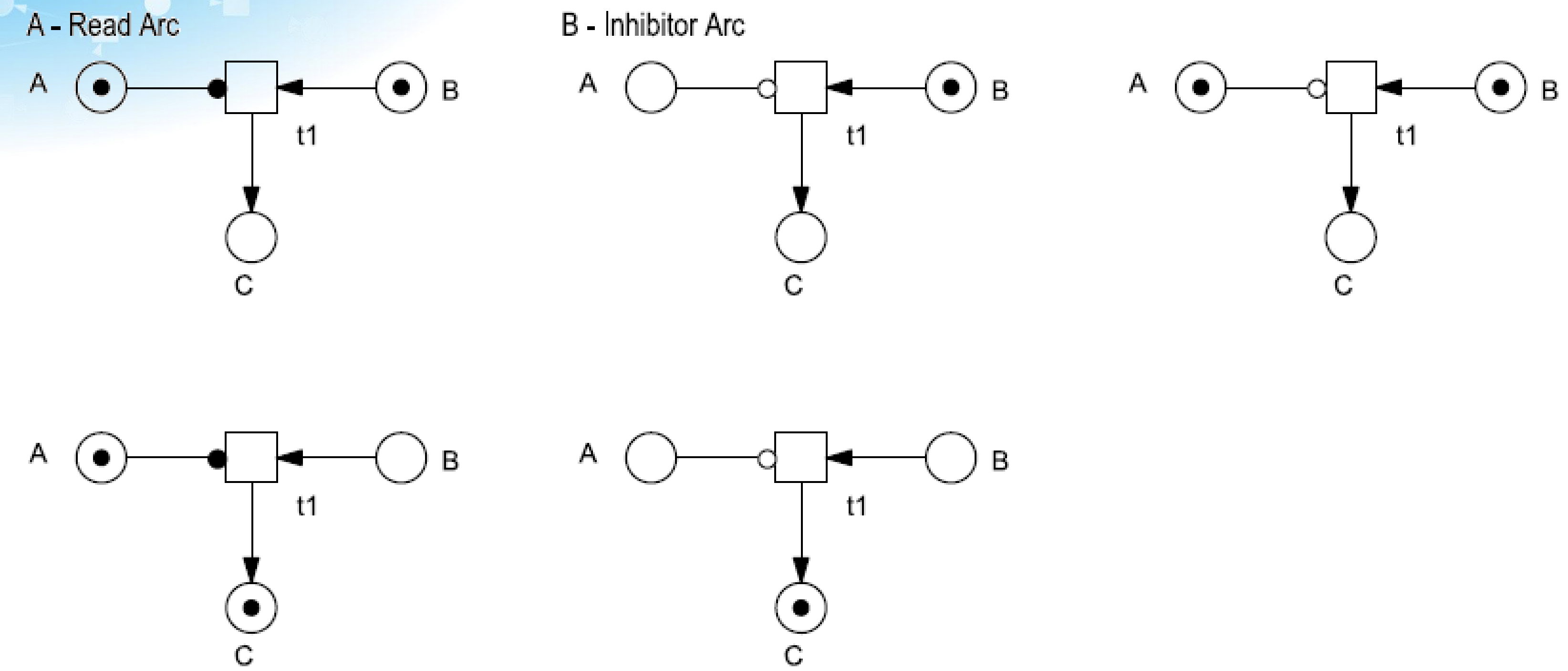

- Shaded nodes (places, transitions)
- Connection of multiple identical spread nodes
- A logical node is represented by multiple graphical copies

# Extension of Visualisation – Coarse Nodes




- Boxed nodes (places, transitions)
- Refine the structure by using coarse nodes to model a node in more detail (≠ extension of the model)
- Structuring of complex networks

# Extension of Expressiveness




- **Read Arc:** The transition is enabled/fires if pre-places A and B are sufficiently marked. No Tokens are deleted on place A by firing.
- **Inhibitor Arc:** The transition is enabled/fires if pre-places A <u>**is not**</u> and B is sufficiently marked. No Tokens are deleted on place A by firing.

# USING PETRI NETS TO MODEL BIOLOGICAL SYSTEMS

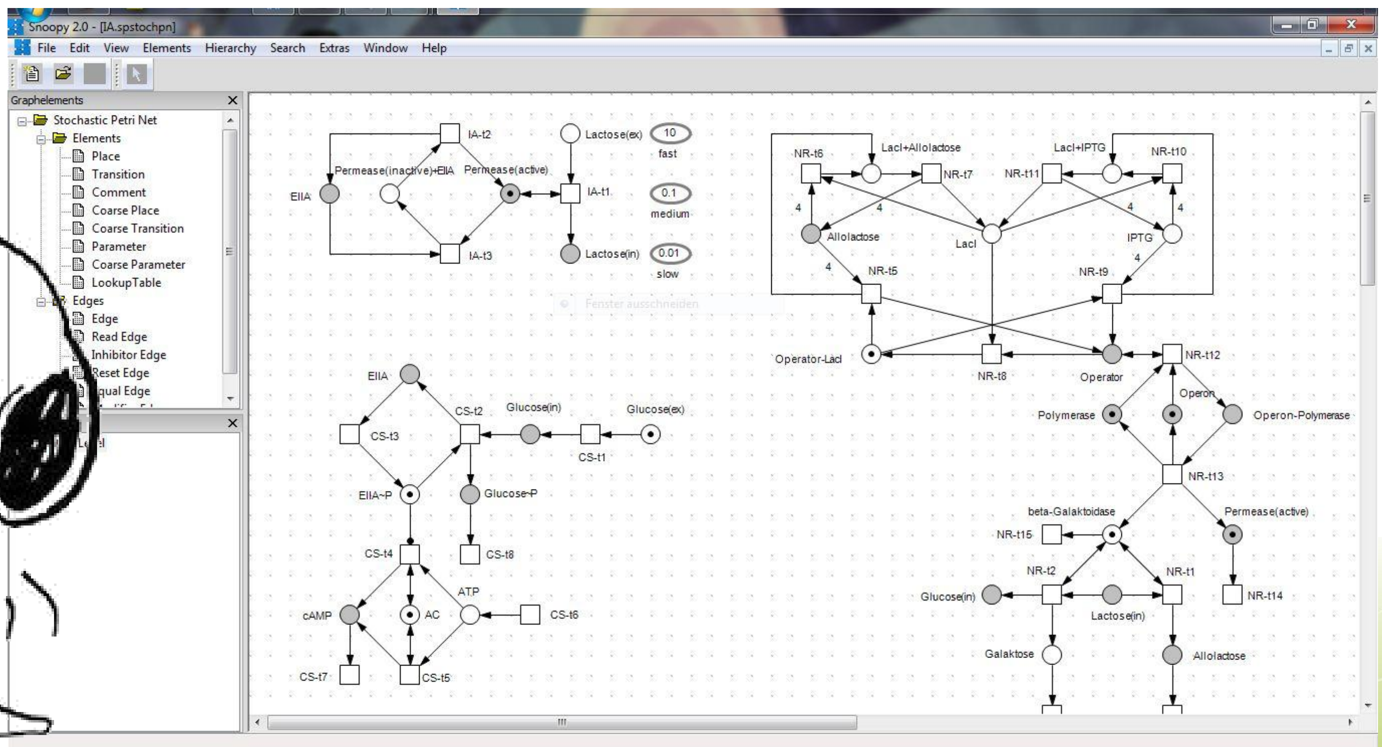
- A Petri net may represent
  - Stochastic (discrete) and/or kinetic (continuous) processes at arbitrary resolution of molecular detail within a single, coherent model;
  - Chemical or biochemical reactions at any resolution of kinetic detail,
  - Localization of biomolecules in different spatial compartments and the translocation between them;
  - Signaling states of molecules, circuits or networks;
  - Physiological state, behaviour or response of a cell.

Revision of basic qualitative Petri net concepts in the context of biological applications

# Snoopy – Versatile Petri Net Tool

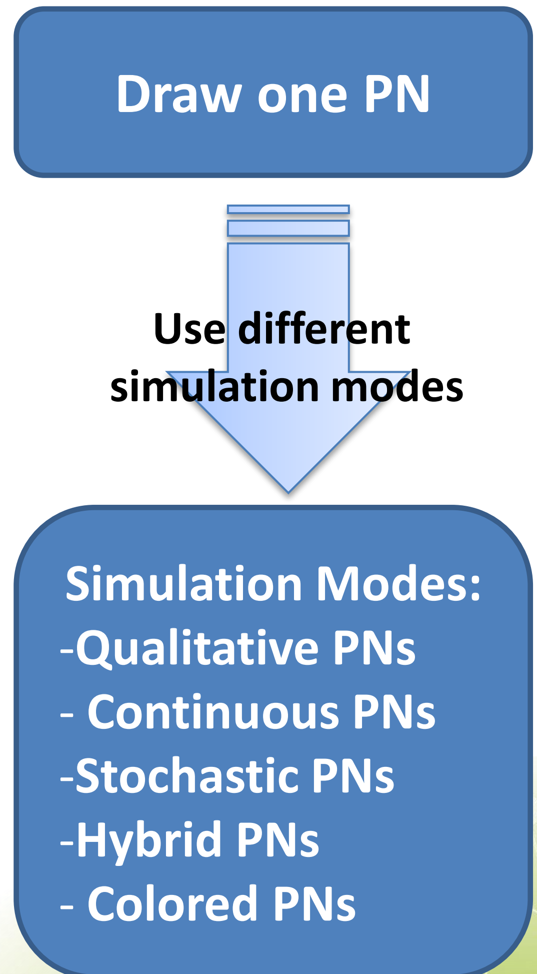
# Snoopy – Versatile Petri Net Tool

- Developed at BTU Cottbus by Monika Heiner and co-workers
- Freely available at: http://www-dssz.informatik.tu-cottbus.de/DSSZ/




# MAIN FEATURES

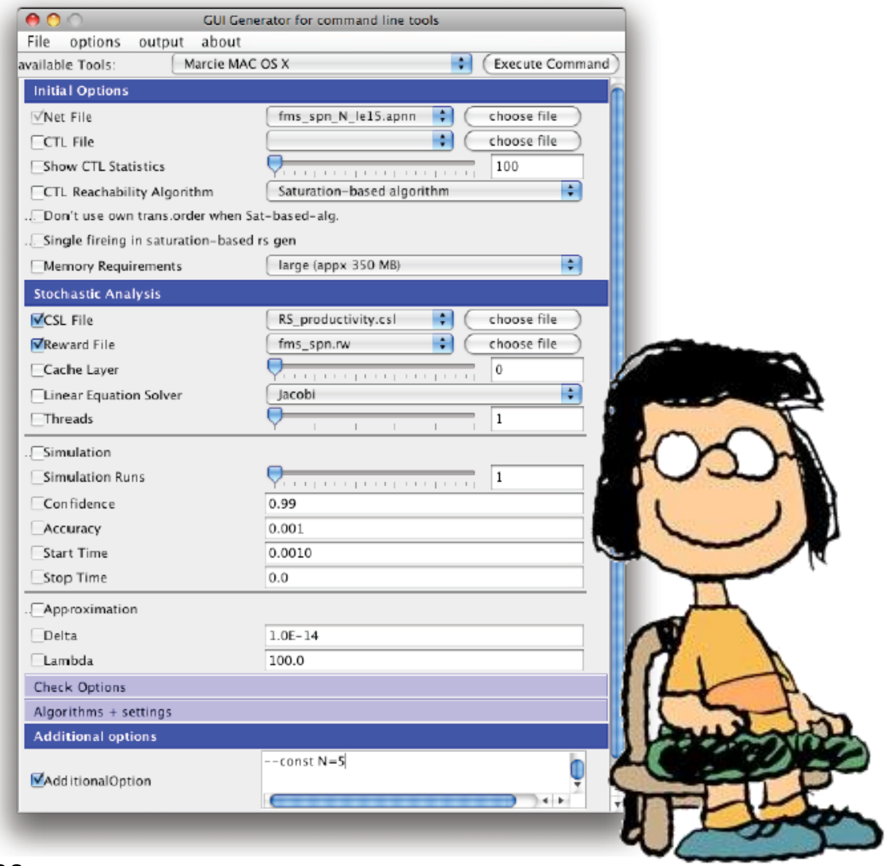
- The three outstanding main characteristics of Snoopy are:
  1. it is *extensible*; its generic design facilitates the implementation of new Petri net classes.
  2. it is *adaptive*; several models can be used simultaneously, the graphical user interface adapts dynamically to the network class in the active window.
  3. All Petri nets classes are *interconvertible.*
  4. it is *platform independent*; it is executable on all popular operating systems (linux, mac, windows).



# RELATED PROGRAMS

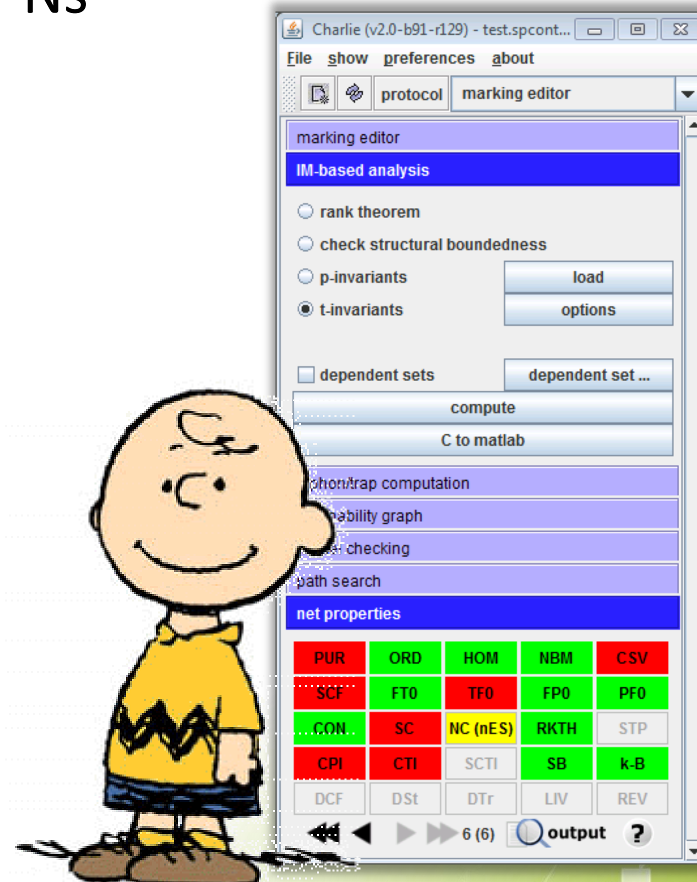
## MARCIE

- Advanced simulator and model checker for PNs




## Charlie

- Structural analysis tool for PNs

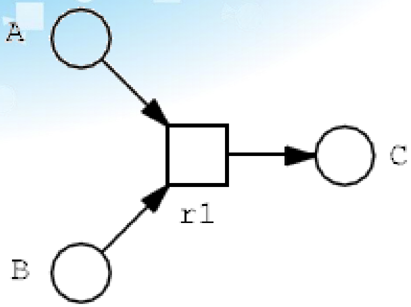


REVISION OF BASIC QUALITATIVE PETRI NET CONCEPTS IN THE CONTEXT OF BIOLOGICAL APPLICATIONS

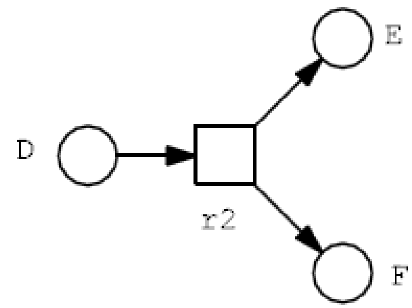
# PETRI NET PATTERN OF ELEMENTARY BIOMOLECULAR REACTIONS

# Chemical Reactions

A

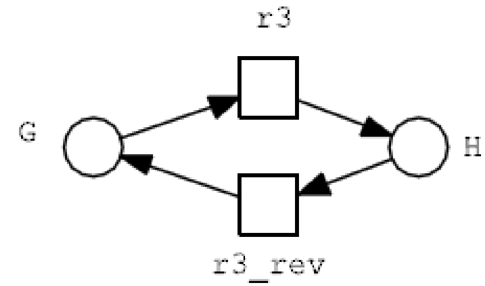



complexation:
r1: A + B --> C



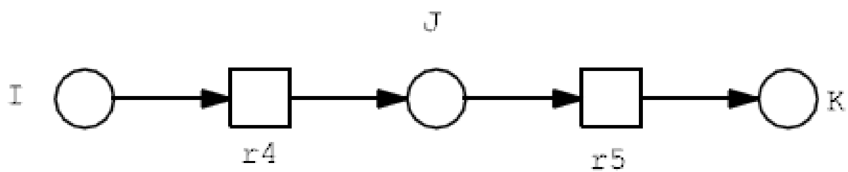

decomplexation:
r2: D --> E + F

B



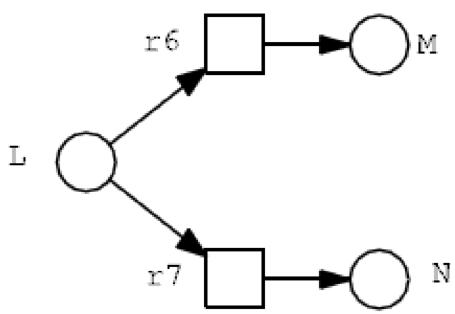

reversible reaction:
r3: G <--> H

C



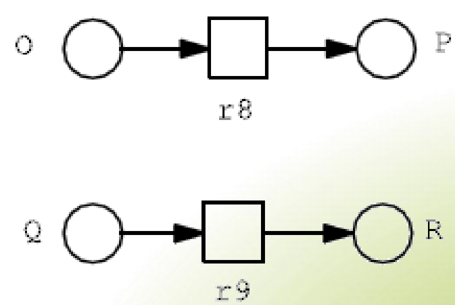

sequence:
r4: I --> J, r5: J -->K

D




alternative:
r6: L --> M
r7: L --> N

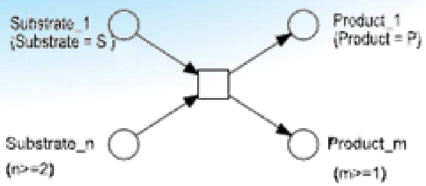
E




concurrency:
r8: O --> P
r9: Q --> R

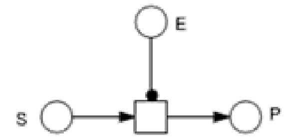
# Processes in Signaling

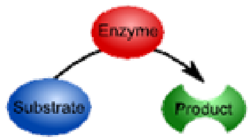
## Chemical Reaction



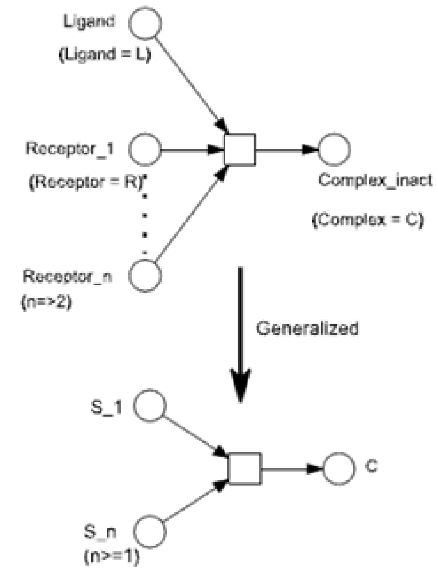

$S_1 + S_2 + \ldots + S_n$ (n>=2)
$\rightarrow P_1 + P_2 + \ldots + P_m$ (m>=1)

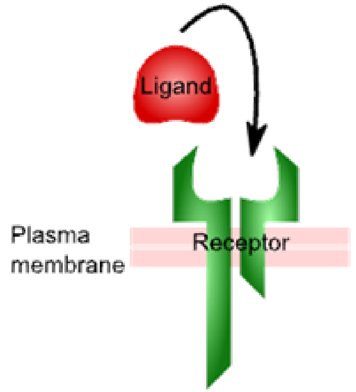
## Enzymatic Reaction



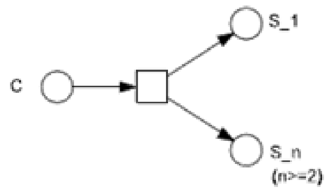




## Association

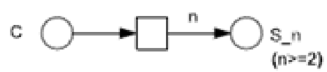



## Dissociation



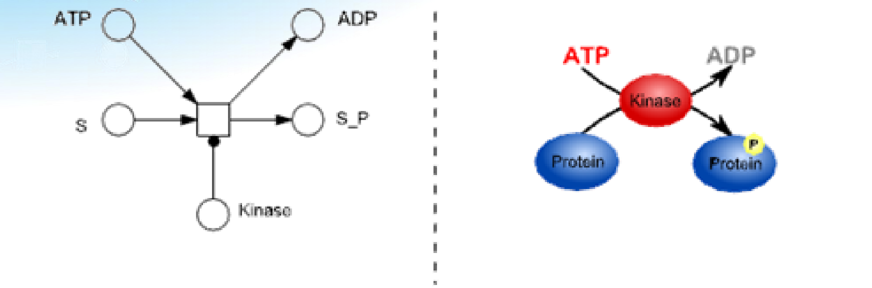

$C \rightarrow S_1 + S_2 + \ldots + S_n$ (n>=2)



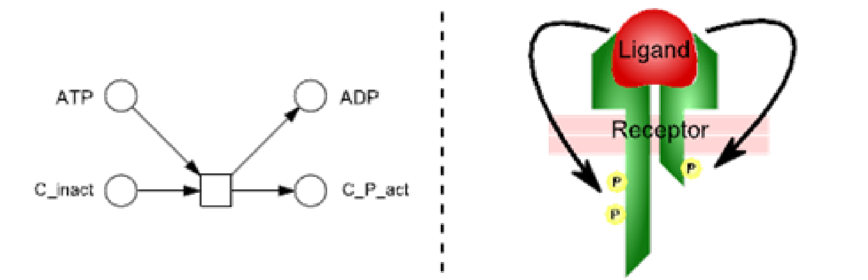

When: $S_1 = S_2 = \ldots = S_n$ (n>=2)

# PROCESSES IN SIGNALING

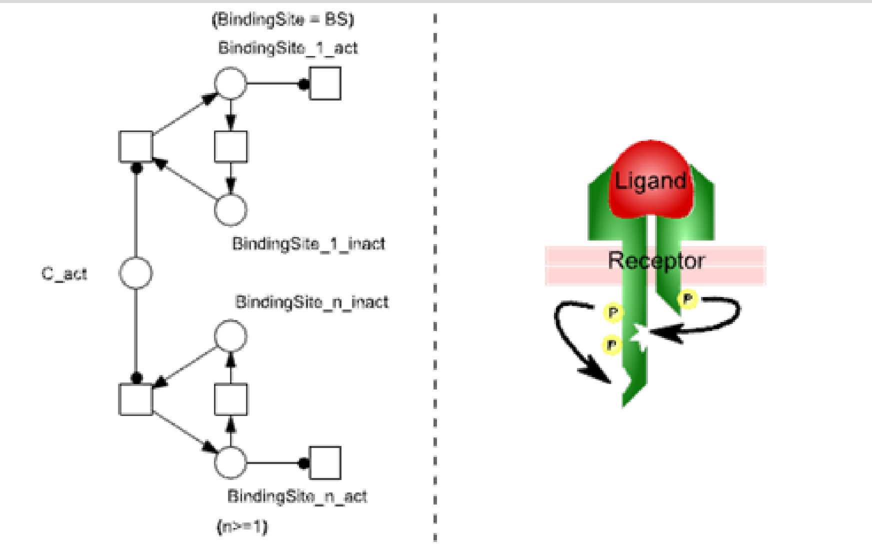
## Phosphorylation



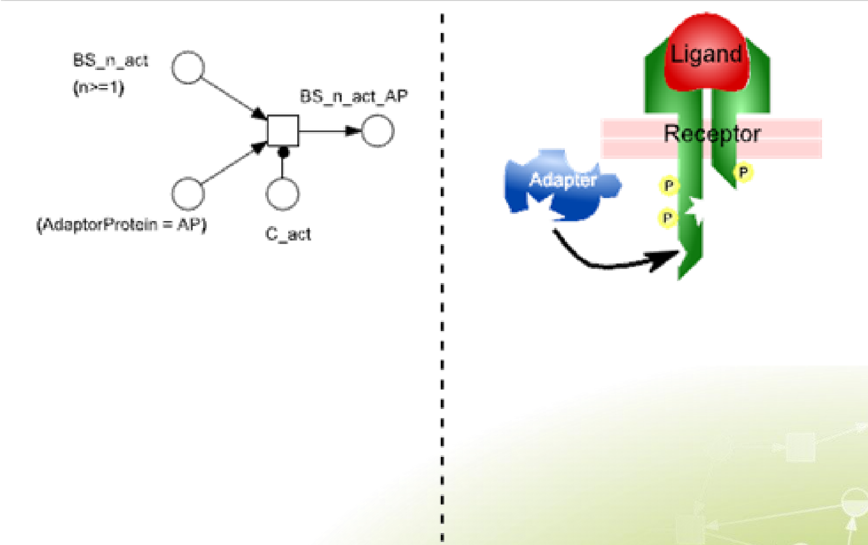

## Autophosphorylation



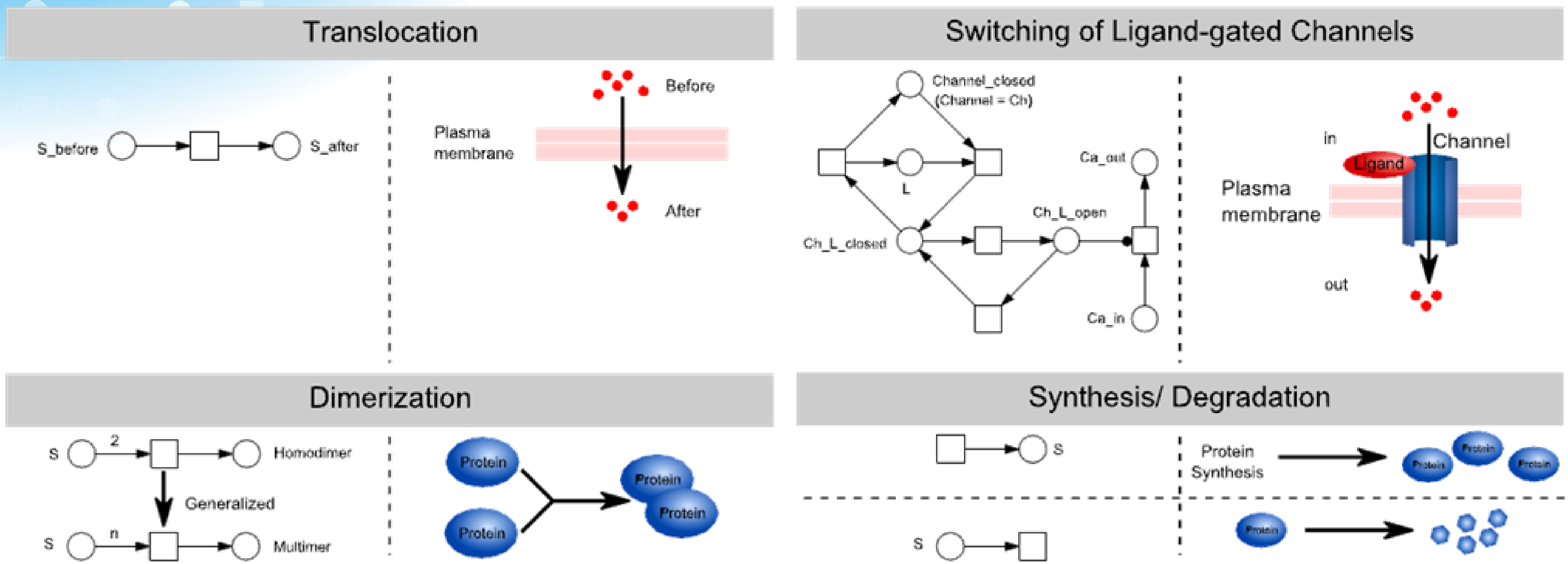

## Activation of Functional Sites



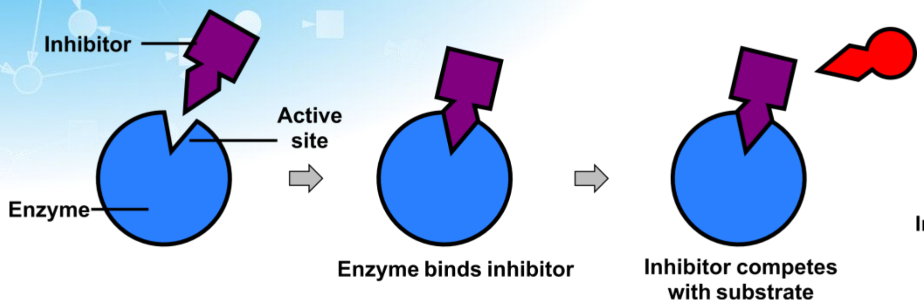

## Gathering Functionality by Adaptor Proteins

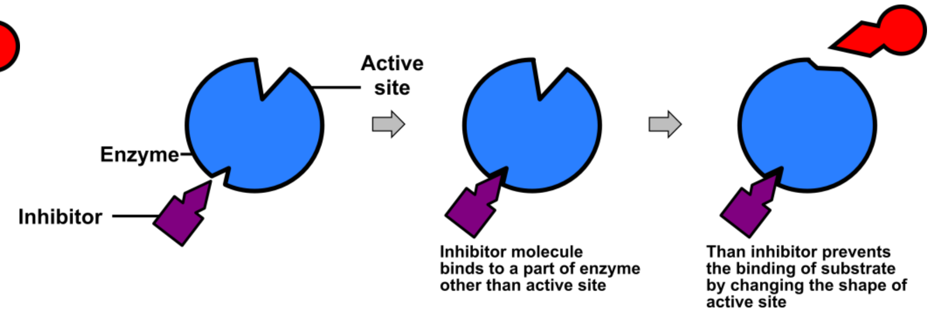


# PROCESSES IN SIGNALING

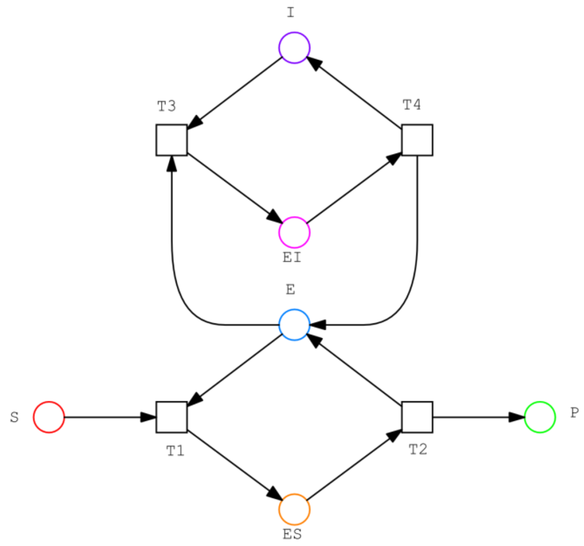


# Competitive vs. Allosteric Enzyme Inhibition

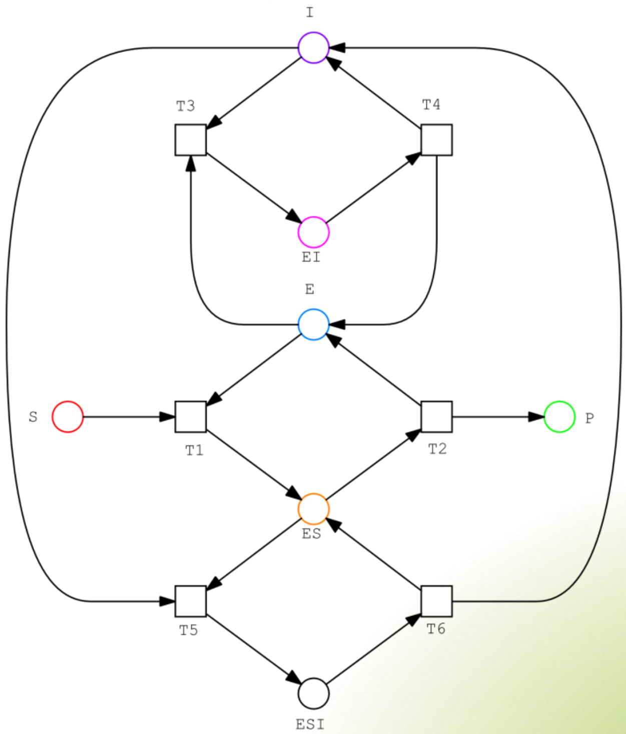


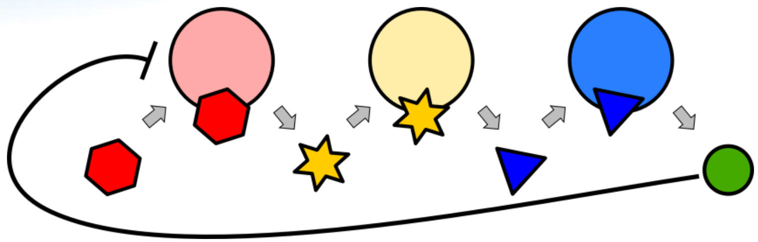

(c) Competitive Inhibition



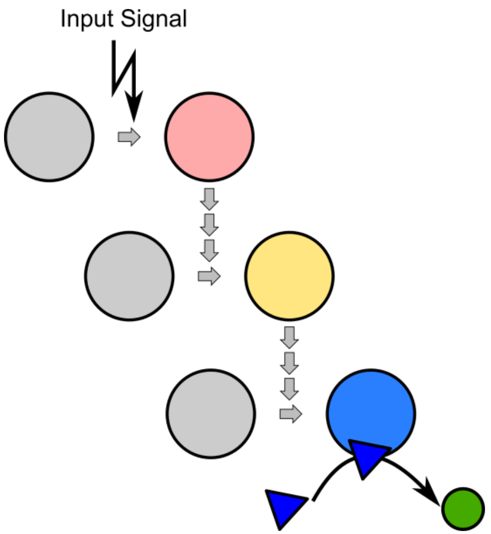

(d) Allosteric Inhibtion



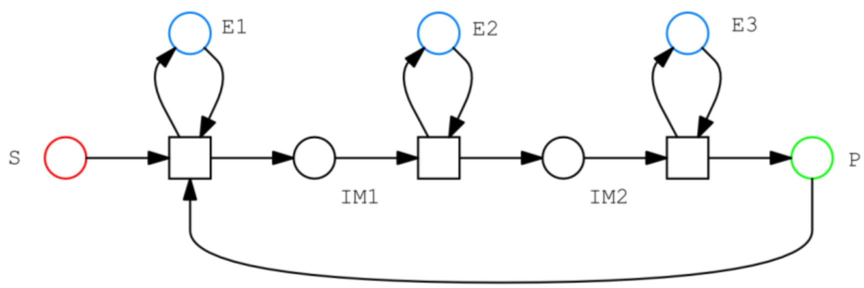
# FEEDBACK INHIBITION VS. SIGNAL AMPLIFICATION

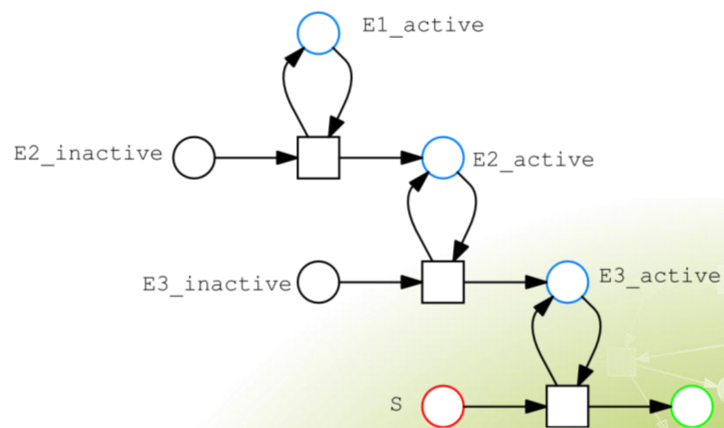


(e) Feed-back Inhibition




(f) Amplification of an input signal

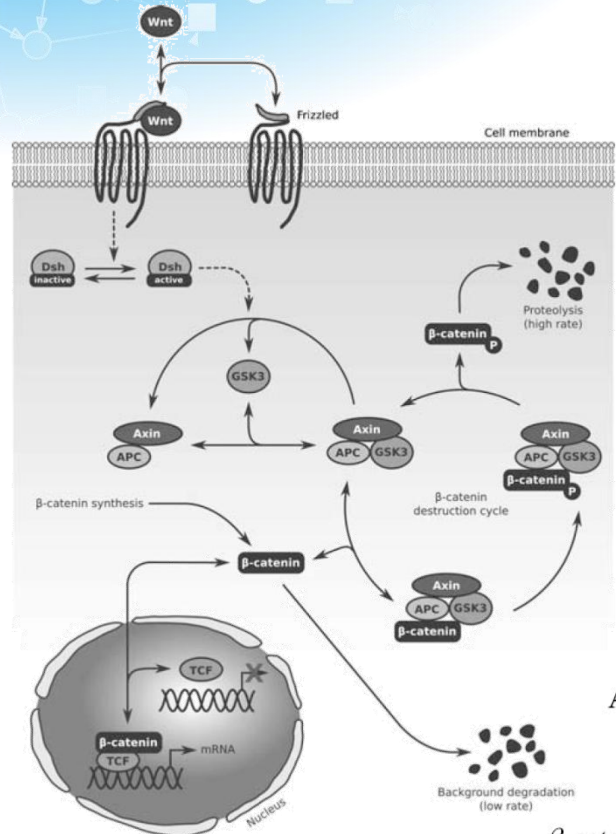


Revision of basic qualitative Petri net concepts in the context of biological Applications

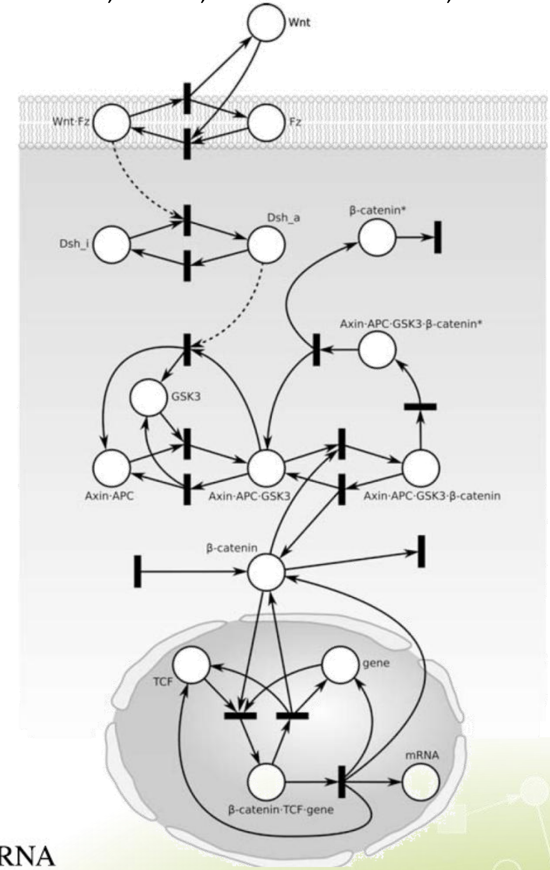
# Advanced Petri Net Models of Biomolecular Systems

# WNT-SIGNALING



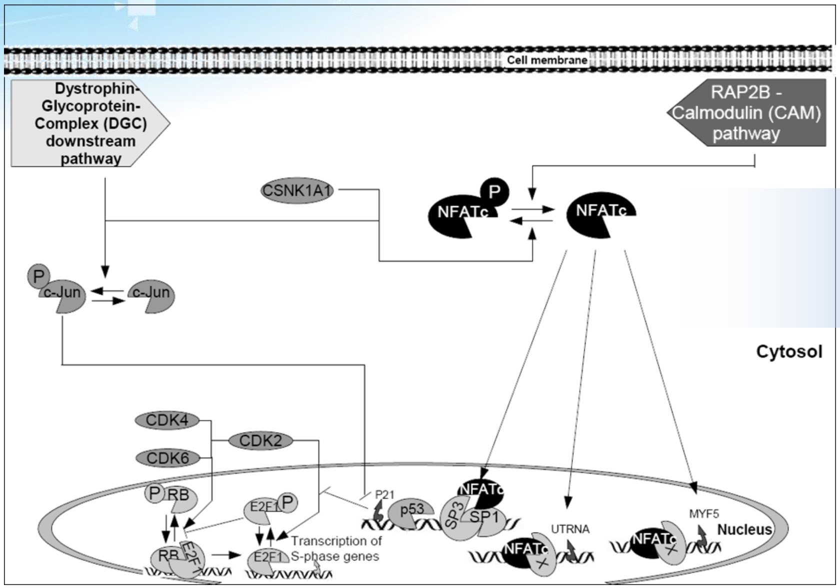

$$
\begin{aligned}
\text{Wnt} + \text{Fz} &\Longleftrightarrow \text{Wnt}\cdot\text{Fz} \\
\text{Dsh}_i &\xrightarrow{\text{Wnt}\cdot\text{Fz}} \text{Dsh}_a \\
\text{Dsh}_a &\longrightarrow \text{Dsh}_i \\
\text{Axin}\cdot\text{APC}\cdot\text{GSK3} &\xrightarrow{\text{Dsh}_a} \text{Axin}\cdot\text{APC} + \text{GSK3} \\
\text{Axin}\cdot\text{APC} + \text{GSK3} &\Longleftrightarrow \text{Axin}\cdot\text{APC}\cdot\text{GSK3} \\
\emptyset &\longrightarrow \beta\text{-catenin} \\
\beta\text{-catenin} &\longrightarrow \emptyset \\
\beta\text{-catenin} + \text{TCF} + \text{gene} &\Longleftrightarrow \beta\text{-catenin}\cdot\text{TCF}\cdot\text{gene} \\
\beta\text{-catenin}\cdot\text{TCF}\cdot\text{gene} &\longrightarrow \beta\text{-catenin} + \text{TCF} + \text{gene} + \text{mRNA} \\
\text{Axin}\cdot\text{APC}\cdot\text{GSK3} + \beta\text{-catenin} &\Longleftrightarrow \text{Axin}\cdot\text{APC}\cdot\text{GSK3}\cdot\beta\text{-catenin} \\
\text{Axin}\cdot\text{APC}\cdot\text{GSK3}\cdot\beta\text{-catenin} &\longrightarrow \text{Axin}\cdot\text{APC}\cdot\text{GSK3}\cdot\beta\text{-catenin}^* \\
\text{Axin}\cdot\text{APC}\cdot\text{GSK3}\cdot\beta\text{-catenin}^* &\longrightarrow \text{Axin}\cdot\text{APC}\cdot\text{GSK3} + \beta\text{-catenin}^* \\
\beta\text{-catenin}^* &\longrightarrow \emptyset
\end{aligned}
$$

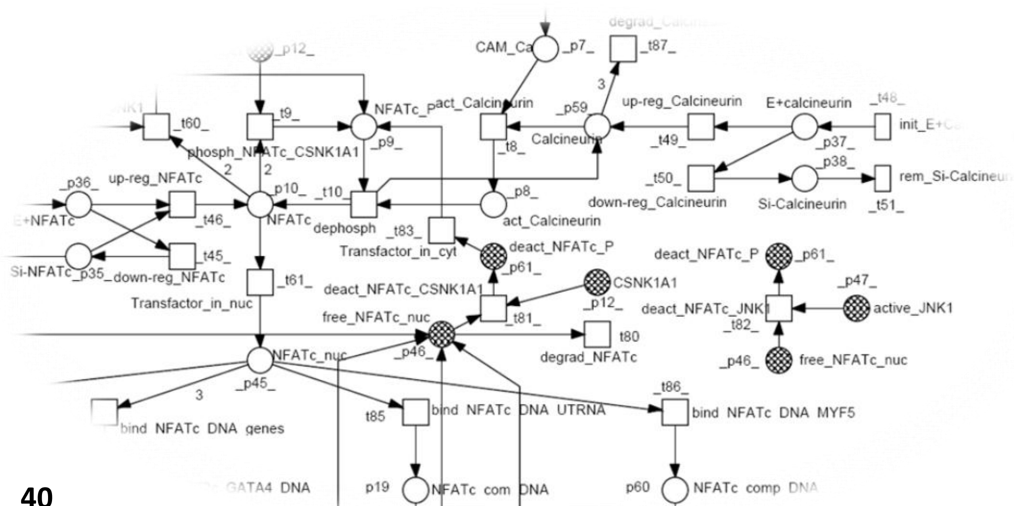
Ewald, R. et al., Journal of Simulation, 2007



# DUCHENNE MUSCLE DYSTROPHY

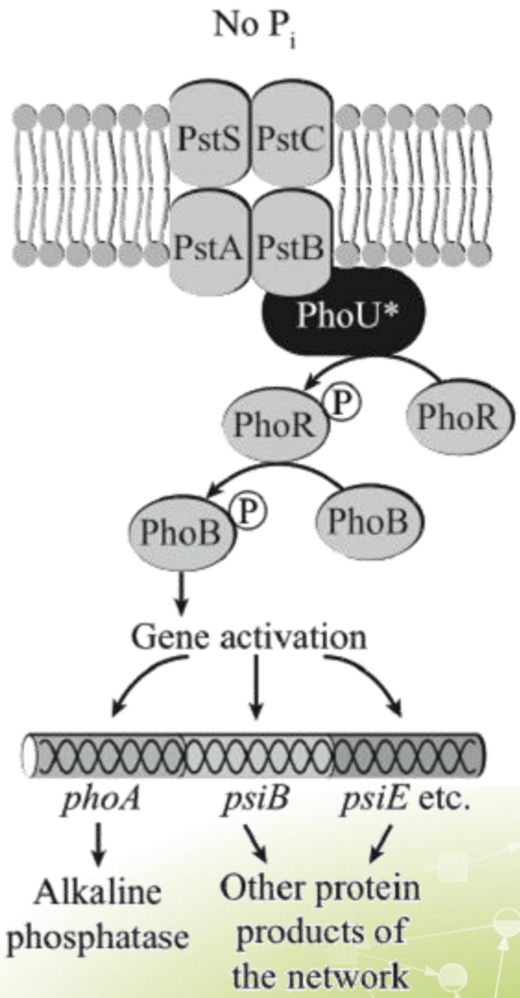
Grunwald et al., Biosystems, 2008



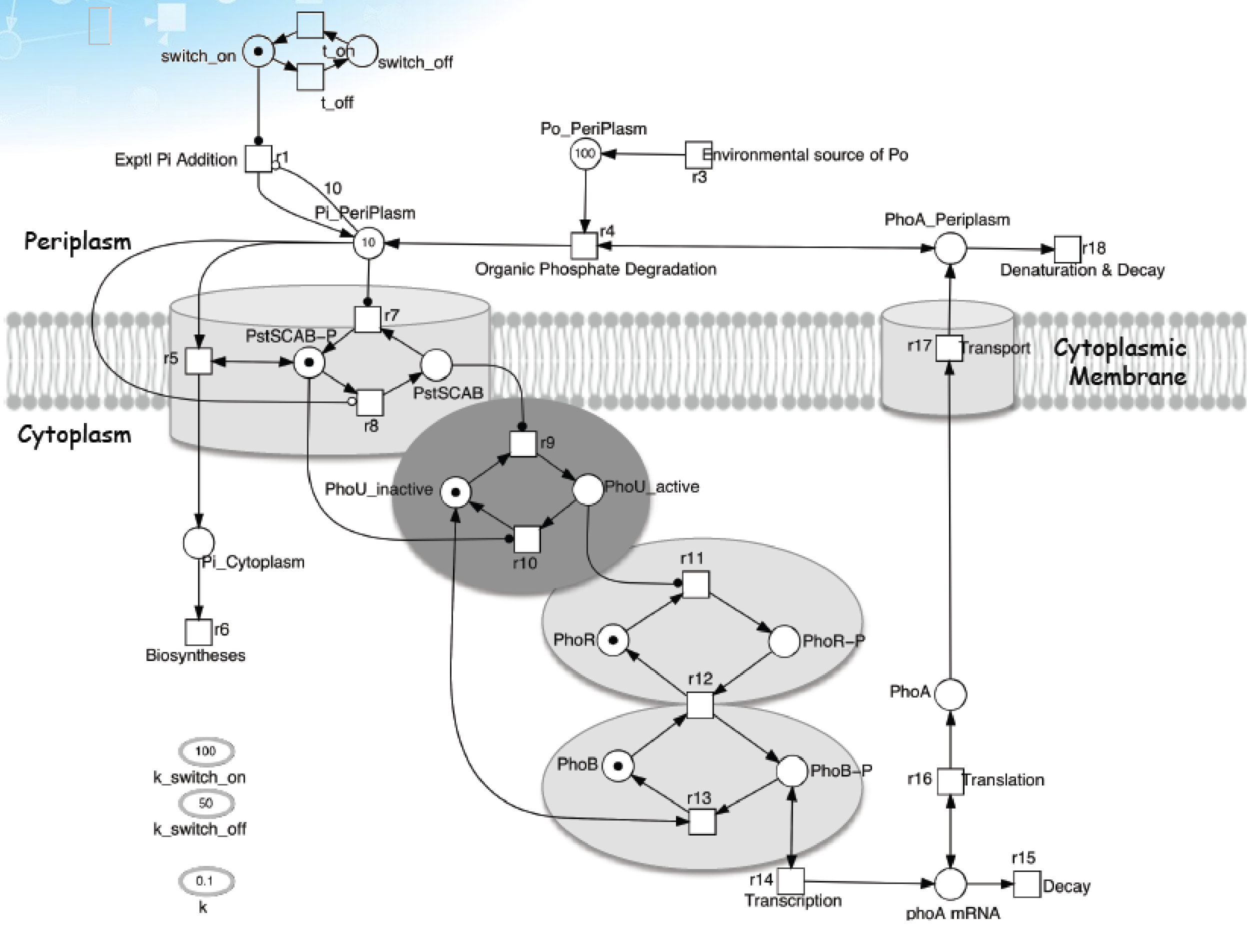
# Phosphate Regulation in Entero Bacteria

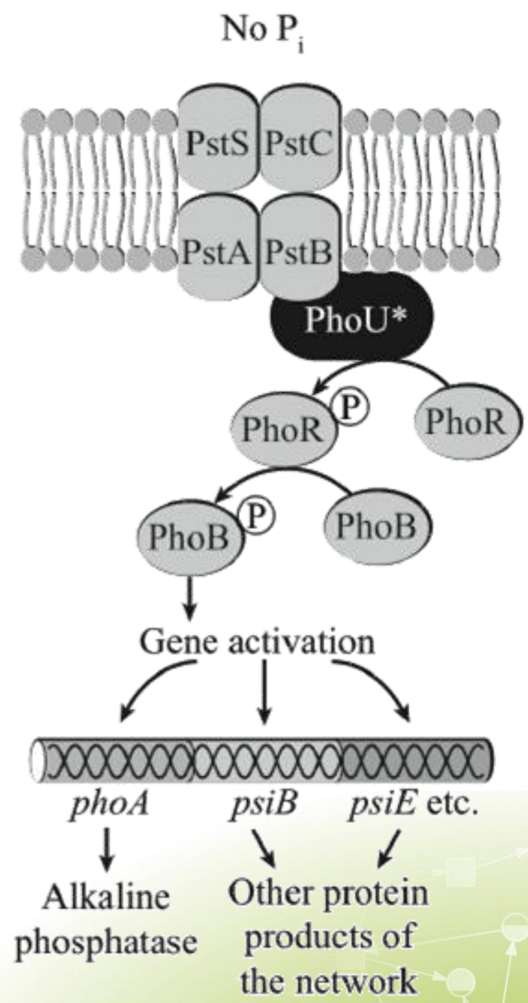
- Inorganic phosphate is needed for the synthesis nuclide acids
- Inorganic phosphate is a growth- limiting factor for microorganism
- In enterobacteria phosphate limitation leads to the synthesis of alkaline phosphatase (PhoA) and its export into the periplasma
- PhoA hydrolyses exogenous organic phosphate to inorganic phosphate, which can be imported by the cell
- The biosynthesis of PhoA is strictly regulated and depends on the availability of inorganic phosphate




Marwan, W. et al., Humana Press, 2011

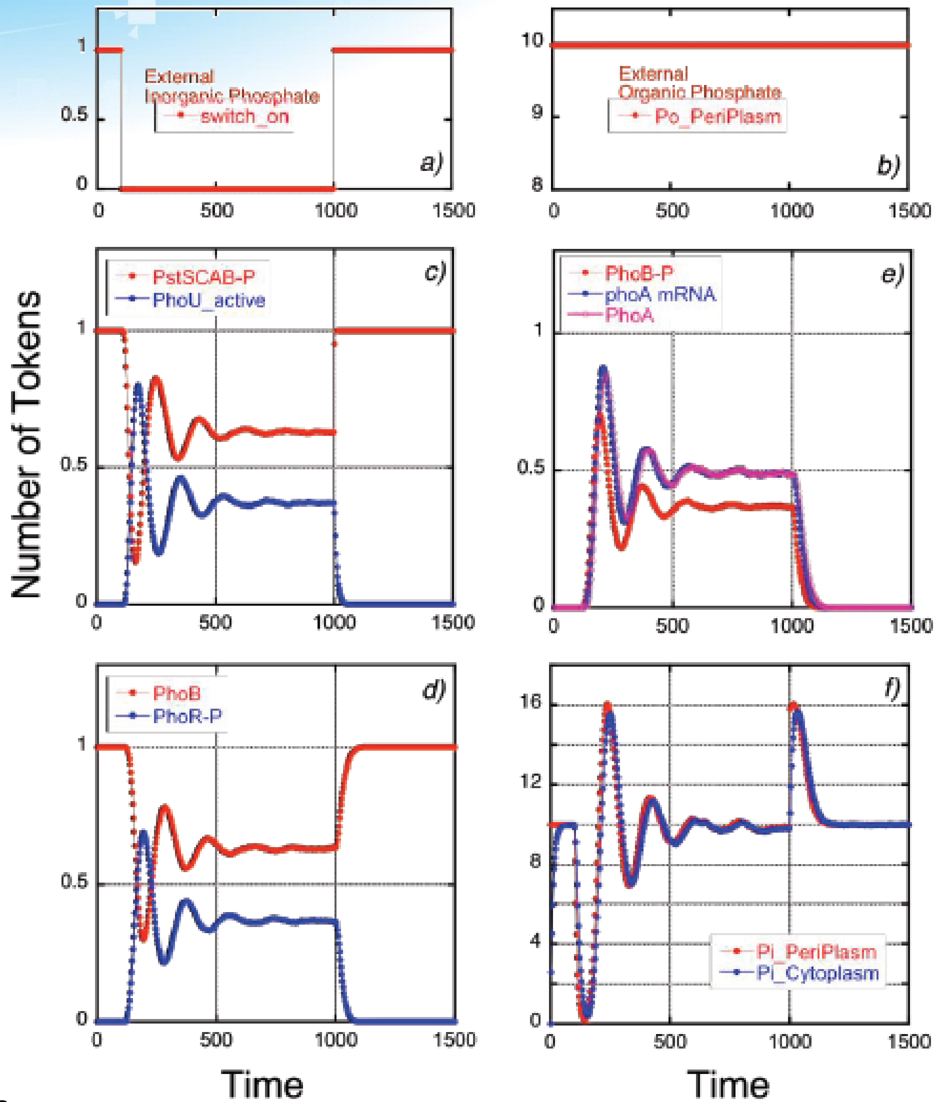
# Phosphate Regulation in Entero Bacteria

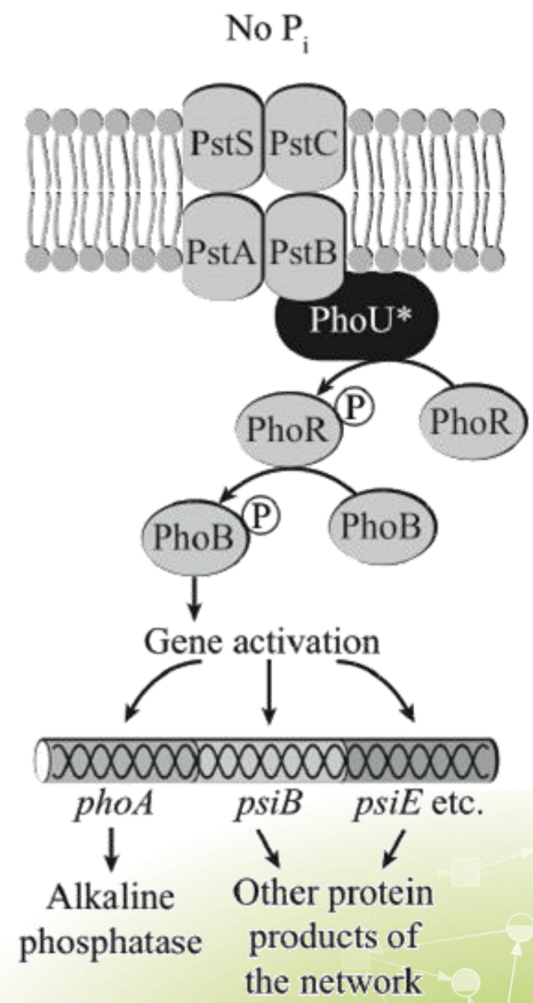



Marwan, W. et al., Humana Press, 2011

# Phosphate Regulation in Enterobacteria




Marwan, W. et al., Humana Press, 2011

Revision of basic qualitative Petri net concepts in the context of biological applications

# Summary

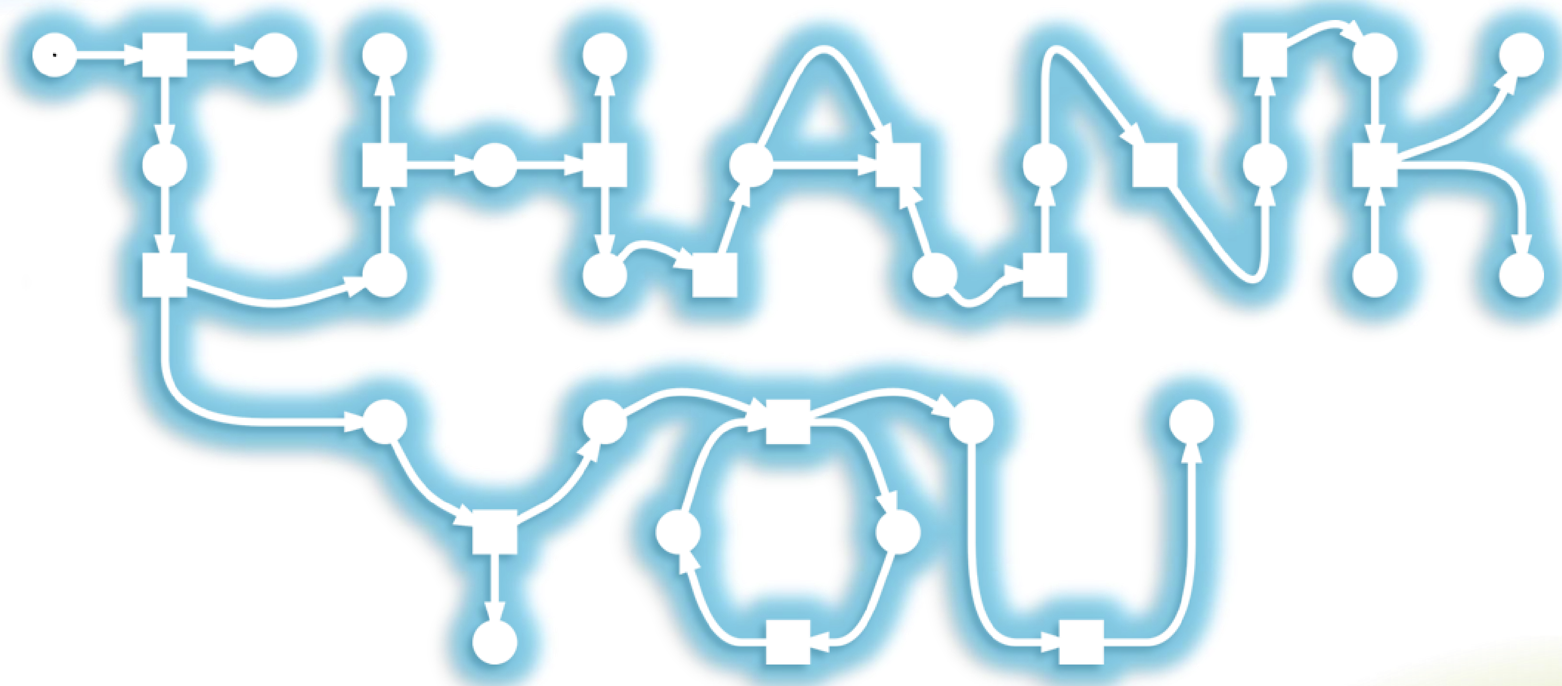
# Petri Nets for Systems Biology

- A Petri net is a well-defined mathematical structure/graph
  - Intuitively understandable formal language  with a strictly defined syntax  where graphically represented models that can be directly run,
  - Representation of processes at the molecular and cellular level
  - Consistent  representation of processes occurring at different levels of complexity within a single cell in a coherent model
  - Capable for different types of simulations (stochastic, continuous, hybrid, etc.)
  - Generation, analysis and modification by a computer

**⇒Enhances understanding between experimentalists and theoreticians**

# Petri Net Applications in Systems Biology

- WNT Signaling
- Duchenne muscle dystrophy
- Phosphate regulation enterobacteria
- Regulation of the *lac* operon
- Circadian clock
- Regulation of the switching process of rotating flagella in *Halobacterium salinarum*
- Regulatory network of *Physarum polycephalum*
- Yeast cycle
- Response of *S. cerevisiae* to mating hormones
- Mitogen activated protein kinase cascade
- Many more…

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