IV121: Computer science applications in biology

Qualitative Models in Biology

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March 5, 2012

Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

What is discrete? What does discrete mean?

- think of you communicating with your friends today
  - how many interactions have you noticed?
  - each one caused you a **discrete event**
- think of flies flying in the room
  - what interactions they have with each other?
  - what interactions they have with the room walls?
  - each one is a **discrete event**
- think of molecules in a solution or in a cell . . .

Is there something what is not discrete?

- think of movement around you
- think of you moving
- think of time passing
- think of current in the power supply
  - electron flow through or around the wire material
  - *is it discrete or continous?*

A way to understand the world...

- to understand (and capture) things happening around us we developed a modeling framework
  - discrete-time dynamics models
    - music "modeled" on CD
    - video clips filmed by your camera
    - ...
  - continuous-time dynamics models
    - mathematical model describing the flow of electrons in an electrical circuit
    - models of chemical reaction dynamics
    - ...
  - discrete-event models
    - model of a coffey machine
    - model of an elevator
    - models of chemical reaction dynamics
  - mixed models – e.g., hybrid systems ...

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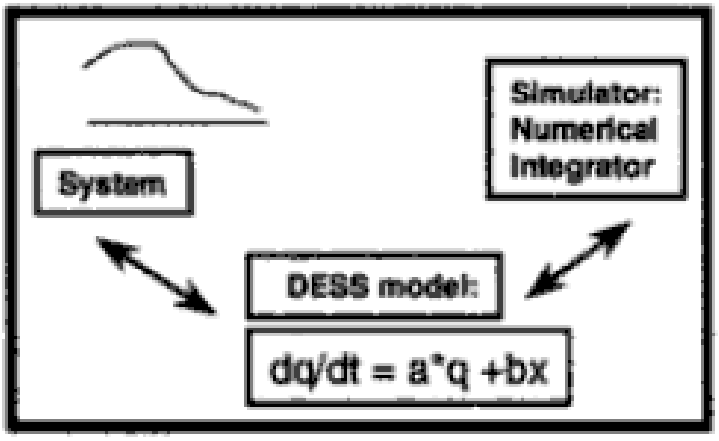
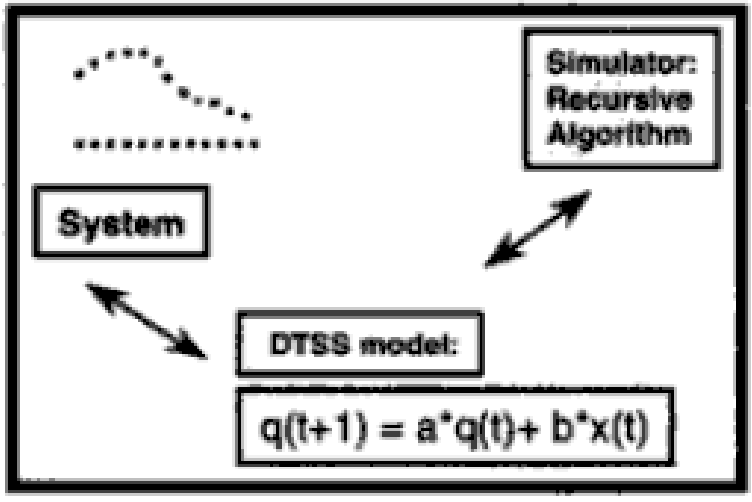


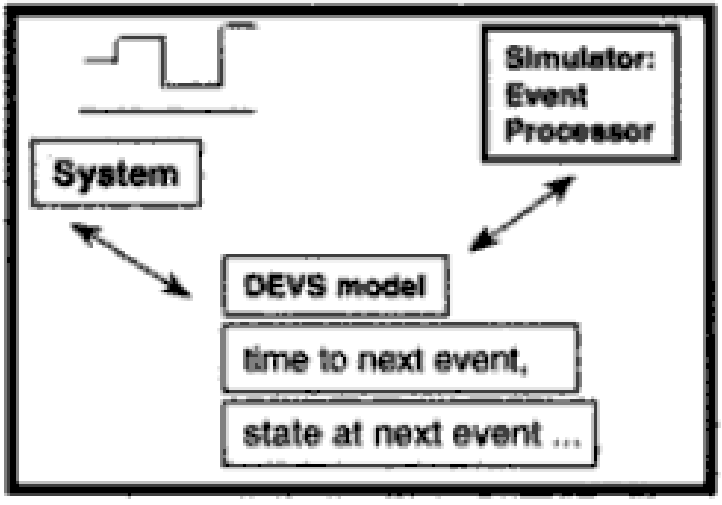
System Specification Formalism:

DESS: differential equation

DTSS: difference equation

DEVS: discrete event





B.P. Zeigler, H. Praehofer, T. Gon Kim. Theory of Modeling and Simulation: Integrating Discrete Event and Continuous Complex Dynamic Systems. Academic Press, 2000.

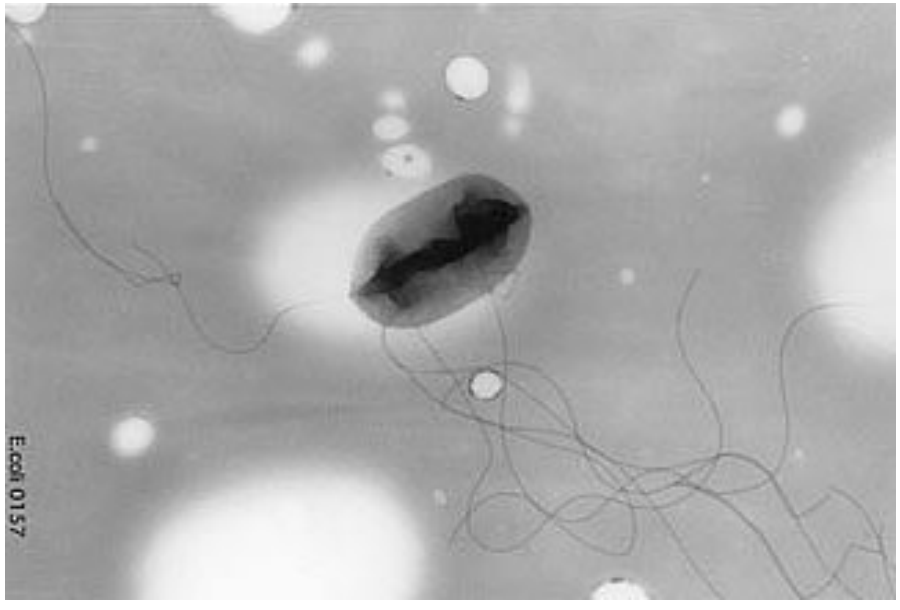
A way to understand the world...

Time scales

- think of a lightning causing a fire
  - very fast electron flow $\longrightarrow$ long-lasting fire
  - one of the views: a discrete event (lightning) changing the continuous world
  - is this a reasonable simplification?
- when modeling the world we have to abstract
- our abstract views (models) can make a hierarchy
- a drawback of simplifications: there can be feedbacks we silently omit ...

Time scales in a cell

Quantitative parameters	**Values in E.Coli**
cell size	$1\mu m^3$
number of protein molecules in a cell	$4 \cdot 10^6$
size of a protein molecule	$5nm$
concentration of a particular protein in a cell	$1nM$
amount of proteins in a cell	18%
time of protein diffusion	$0,1s$
time of other molecules diffusion	$1msec$
number of genes	4500



A way to understand the world...

Abstractions

- abstraction of time
  - think of ticks of the clock...
  - continuous-time domain sampled into the discrete-time domain
  - a single discrete time-step can abstract some notion of time
    - one generation of bacteria population
    - time abstracted to day/night phases or a.m./p.m.
    - the lowest time observed between any two event occurrences
- abstraction of quantities
  - large (possibly real) valued amounts abstracted by several discrete levels (e.g., light intensity, temperature, ...)
  - large valued amounts abstracted by real values (e.g., concentration of molecules in a cell of particular volume)
- abstraction of behaviour
  - neglecting some aspects (e.g., competitivness in transcription factors-to-DNA binding)
  - theoretical constraints (e.g., well-stirred solutions, fixed conditions – temperature, pressure)

A way to understand the world...

Abstractions

- in computer science abstraction is a formal notion:
  - identify what you add and what you lose by abstracting
- when doing models of life we use approximative abstractions
  - what is lost and what is added?
- note that abstractions between continuous and discrete views can be bidirectional

A way to understand the world...

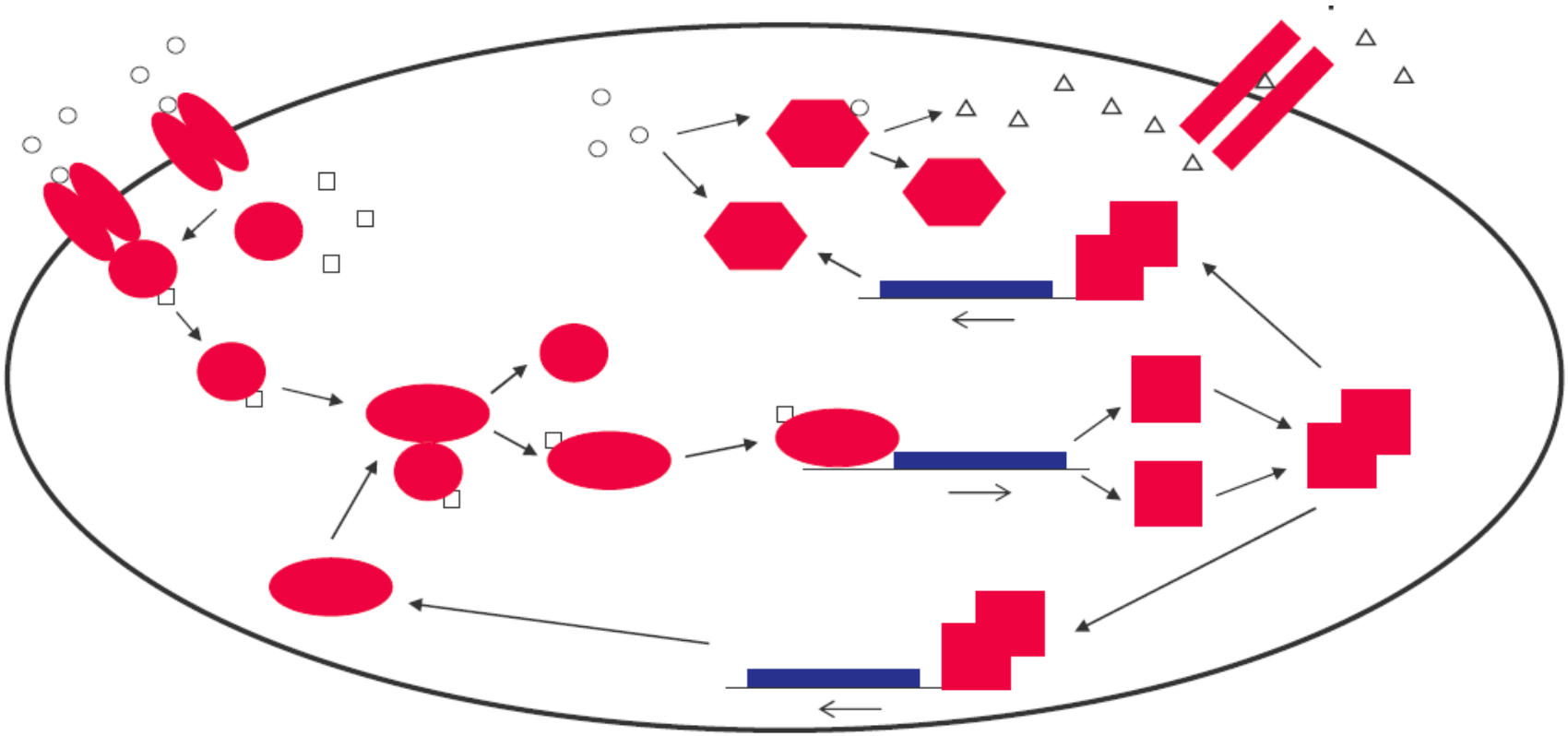
Using computers

- computation by computers is purely discrete
- quantities are stored in discrete memory
- memory has limited size
- computer-scientific abstractions are employed to automatically (technically) reduce the computational efforts

Systems View of the World

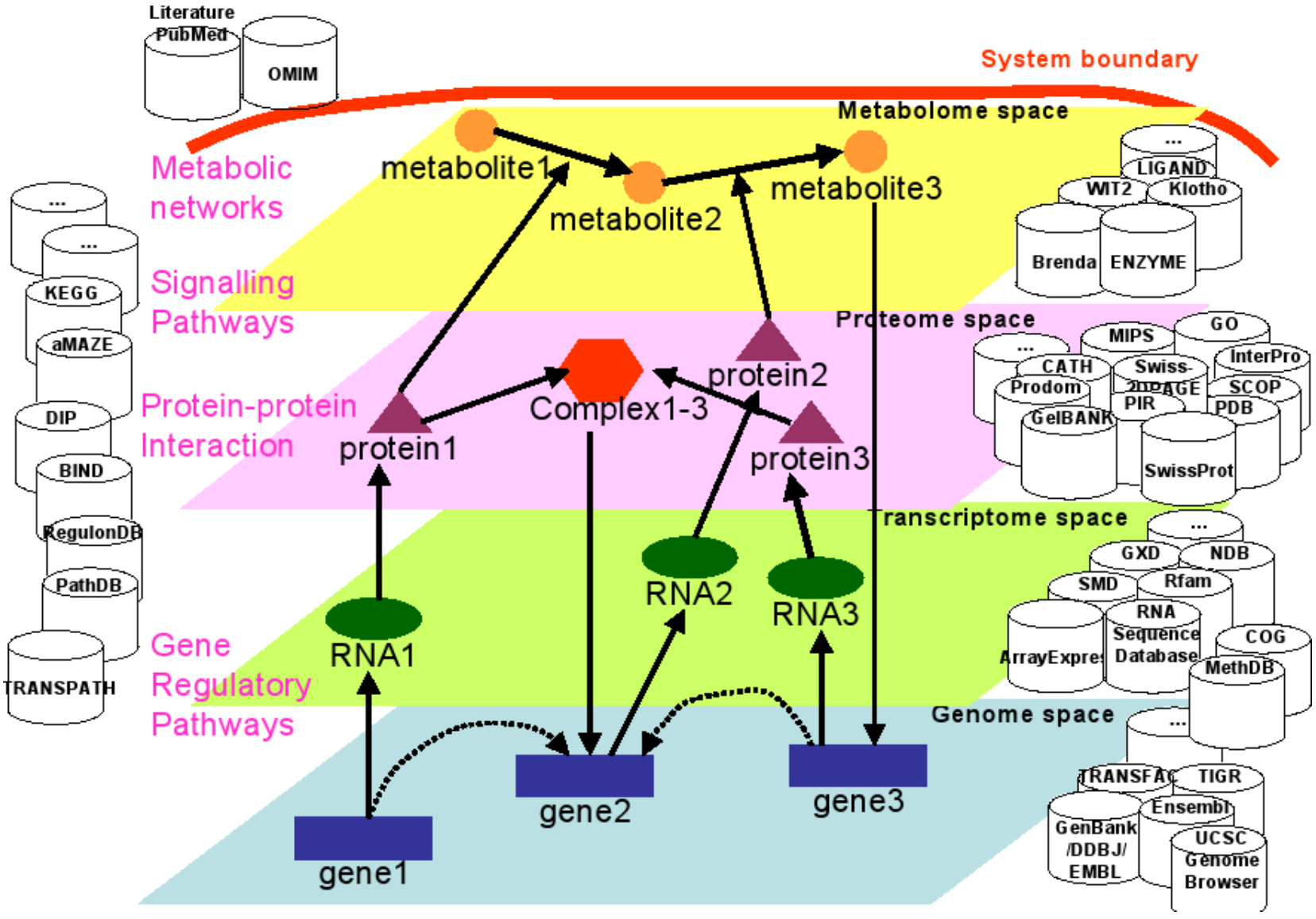
- systems models of the world (e.g., a living cell, a population)
- syntax of the systems model is a network:
  - components (nodes) – e.g. chemical substances
  - interactions (edges) – e.g. chemical reactions
- each component is assigned some quantity
  - discrete or continuous: number of particles, concentration
  - can be visualized by color intensity of a node
- dynamics is animation of colour intensity changing on nodes in time
  - driven by global rules (e.g., mass-action reactions)

Systems View of a Cell: Biological Networks

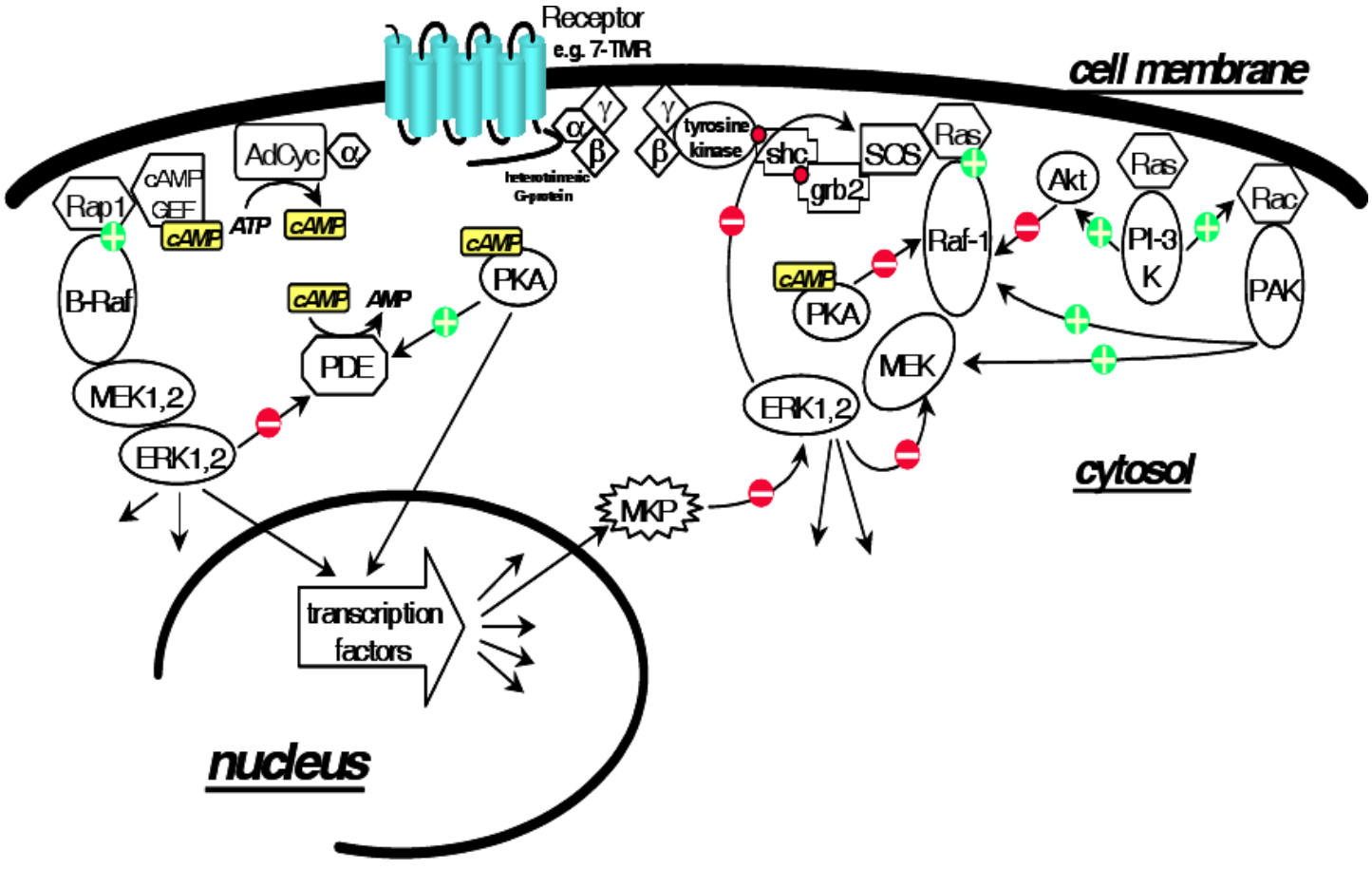


- identify substances (macromolecules, ligands, proteins, genes, . . .)
- identify interactions ((de)complexation, (de)phosphorylation, . . .)

Systems Biology of a Cell



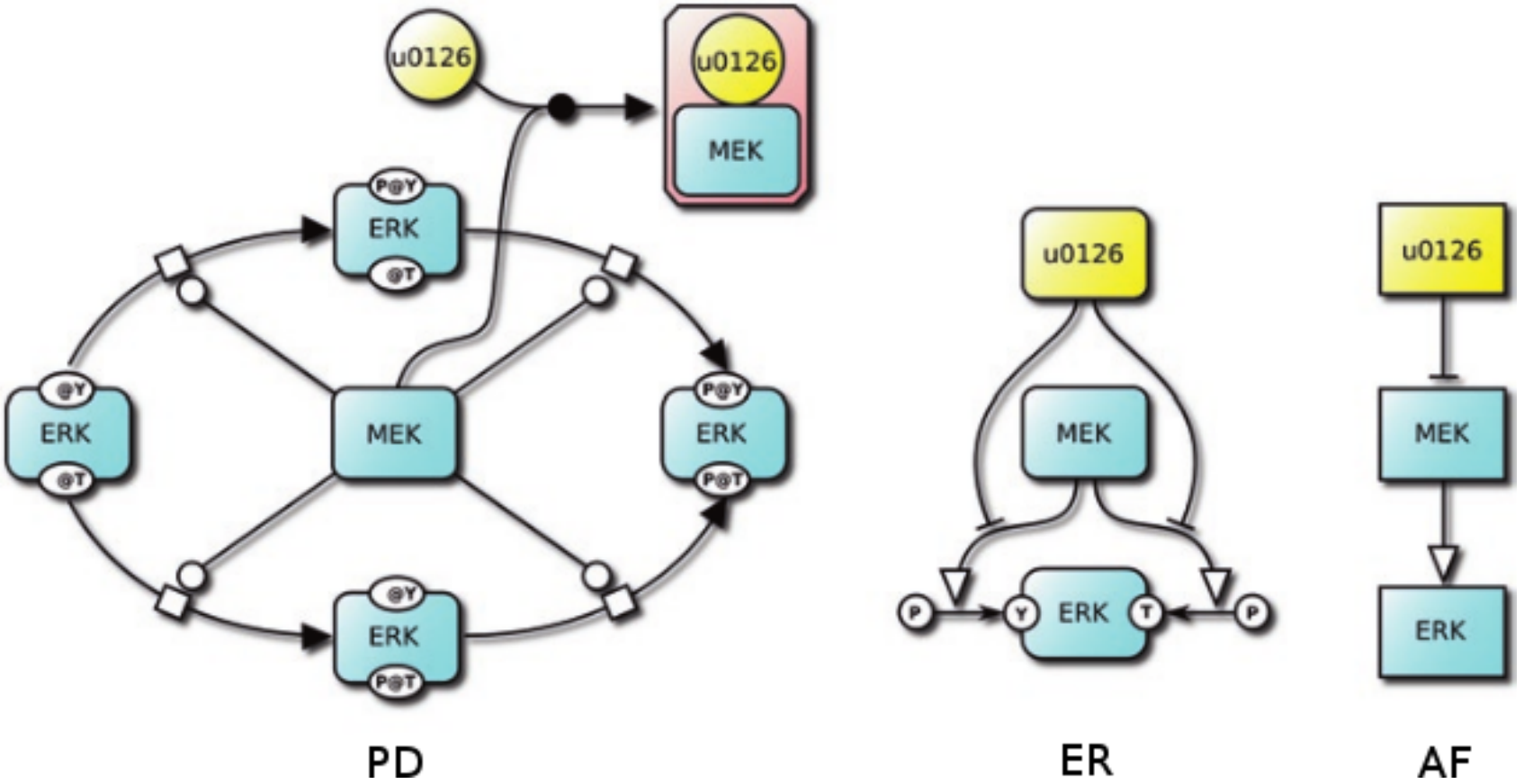
Biological Networks and Pathways



- what is the "right" meaning?
- in order to *analyse* we need to *formalise* a bit...

Graphical Specification in SBGN

Systems Biology Graphical Notation



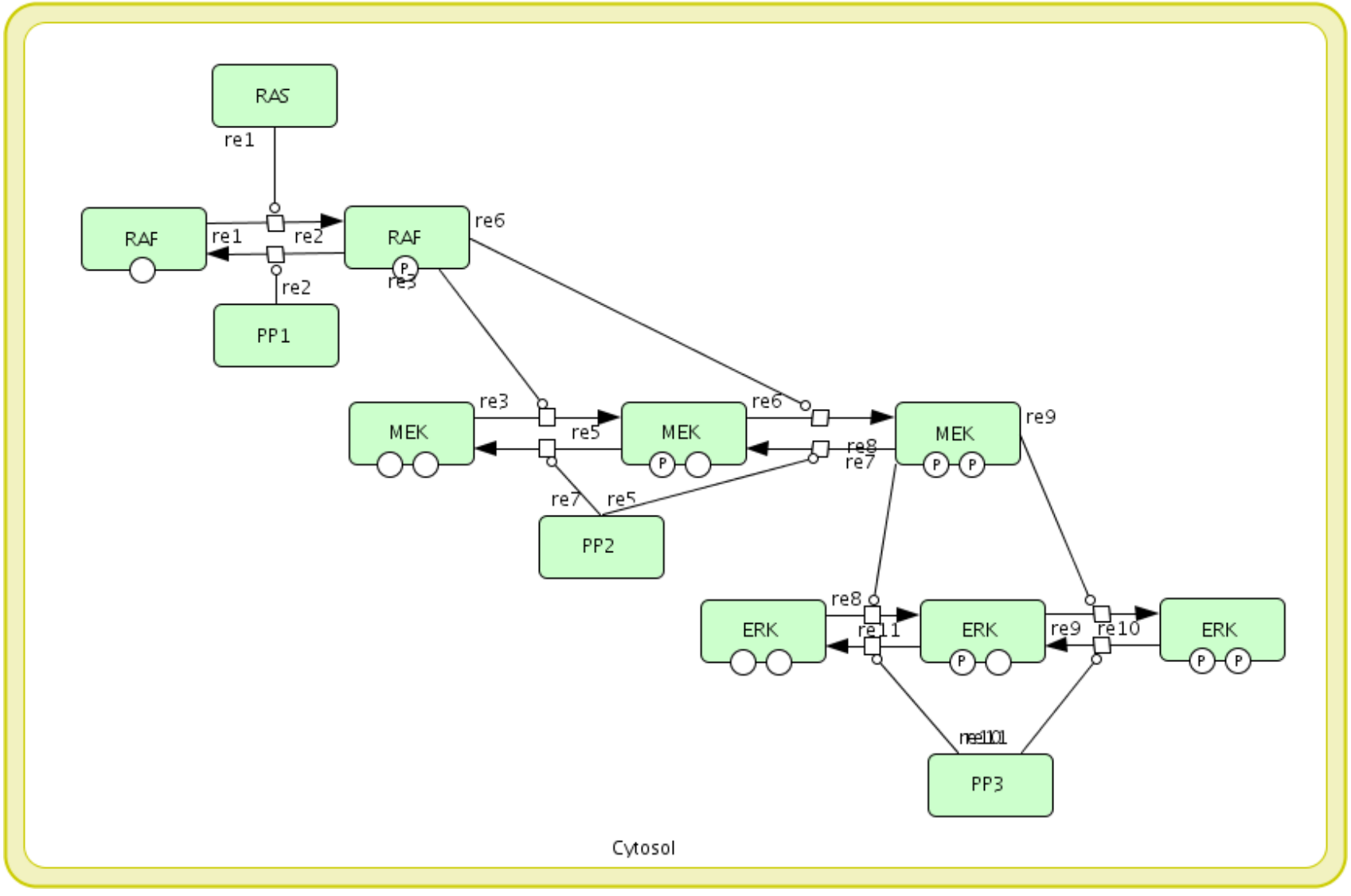
- PD: biochemical interaction level (the most concrete)
- ER: relations among components and interactions
- AF: abstraction to mutual interaction among activities

Graphical Specification in SBGN

Systems Biology Graphical Notation

- SBGN.org iniciative (from 2008)
- standard notation for biological processes
- `http://sbgn.org`
- Nature Biotechnology (doi:10.1038/nbt.1558, 08/2009)
- three sub-languages:
  - SBGN PD (Process Description) (doi:10.1038/npre.2009.3721.1)
  - SBGN ER (Entity Relationship) (doi:10.1038/npre.2009.3719.1)
  - SBGN AF (Activity Flow) (doi:10.1038/npre.2009.3724.1)
- tool support:
  - SBGN PD supported by CellDesigner
  - SBGN-ED (`http://www.sbgn-ed.org`)

Kinase Cascade in CellDesigner (SBGN)



From Systems Structure to Systems Dynamics

Discrete Events View

- once the systems structure is captured we want to animate . . .
- each node in SBGN PD represents some quantity of a particular species
- species are assumed to be well stirred in the cell
- interactions are events affecting related species (in amounts given by stoichiometry)
  - abstract from time (no information when the event occurred, events last zero time)
  - abstract from space (no information where the event occurred)
  - purely **qualitative model** of systems dynamics

Qualitative Model of a Reaction

$$AB \rightarrow A + B$$

- state configuration captures number of molecules:

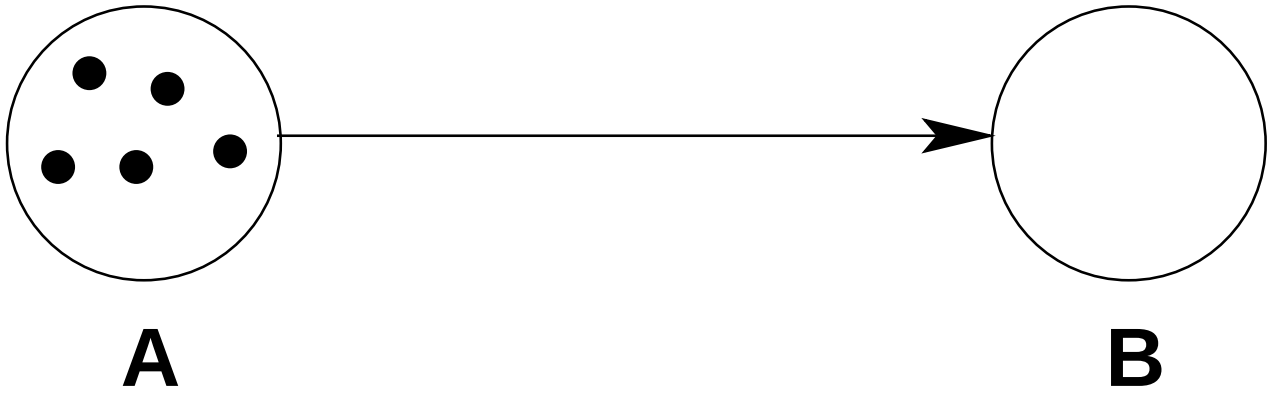
$$\langle \#[AB], \#[A], \#[B] \rangle$$

- global rule:
  - one molecule AB is removed from the solution
  - one molecule A is added to the solution
  - one molecule B is added to the solution

$$\begin{aligned} \#[AB](t+1) &= \#[AB](t) - 1 \\ \#[A](t+1) &= \#[A](t) + 1 \\ \#[B](t+1) &= \#[B](t) + 1 \end{aligned}$$

Example

Consider reaction: $A \rightarrow B$



$$\begin{pmatrix} 5 \\ 0 \end{pmatrix}$$

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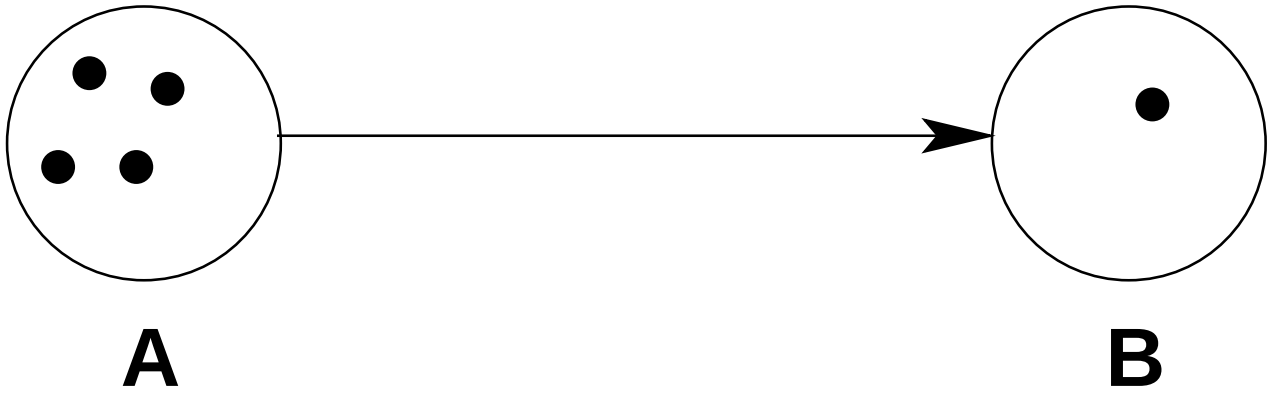
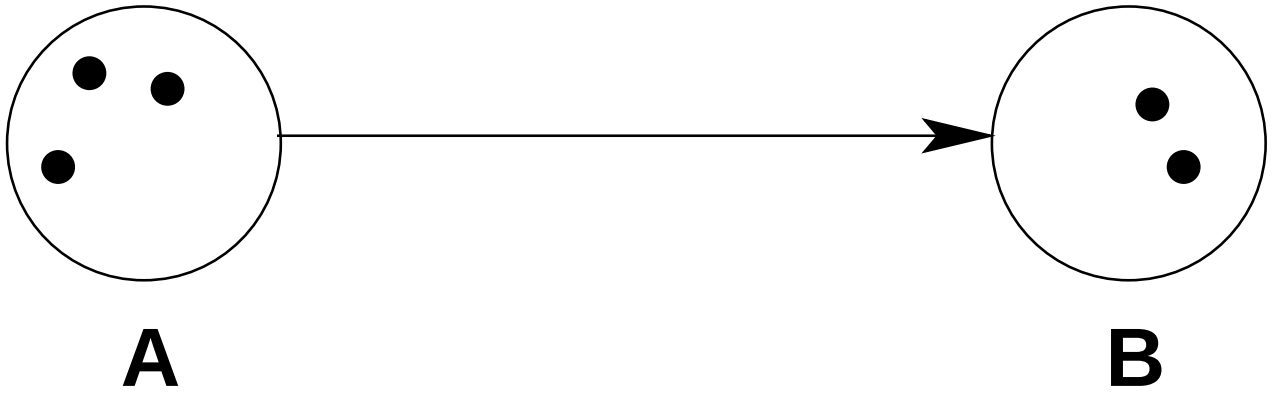


$$\begin{pmatrix} 5 \\ 0 \end{pmatrix} \rightarrow \begin{pmatrix} 4 \\ 1 \end{pmatrix}$$

Example

Consider reaction: $A \rightarrow B$



$$\binom{5}{0} \rightarrow \binom{4}{1} \rightarrow \binom{3}{2}$$

Example

Consider reaction: $A \rightarrow B$

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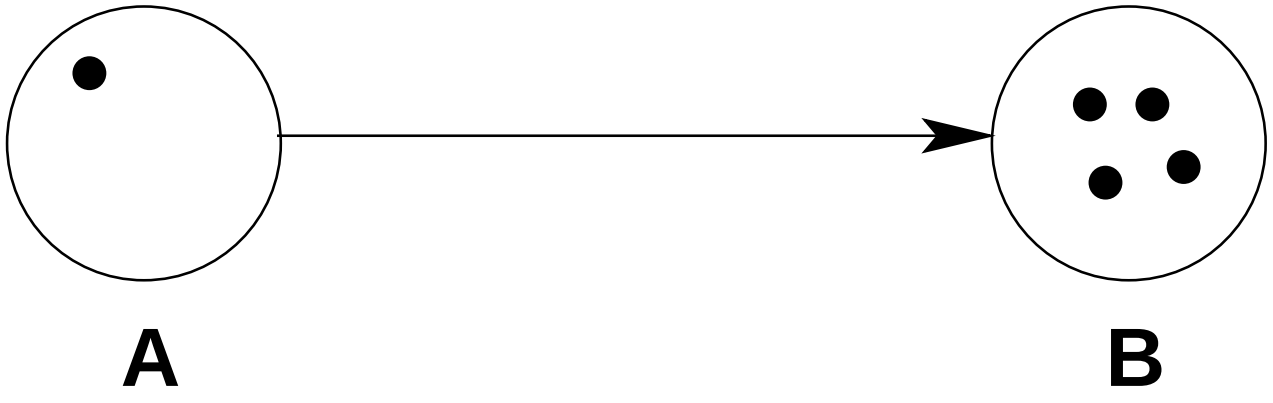
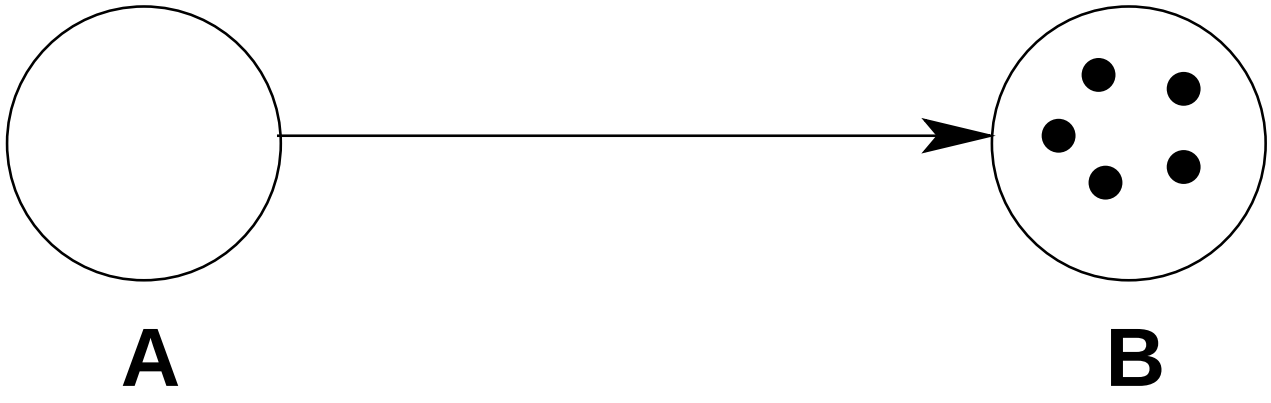


$$\binom{5}{0} \rightarrow \binom{4}{1} \rightarrow \binom{3}{2} \rightarrow \binom{2}{3} \rightarrow \binom{1}{4}$$

Example

Consider reaction: $A \rightarrow B$



$$\binom{5}{0} \rightarrow \binom{4}{1} \rightarrow \binom{3}{2} \rightarrow \binom{2}{3} \rightarrow \binom{1}{4} \rightarrow \binom{0}{5}$$

Example

Consider three reactions:

$$A \longrightarrow B$$
$$A + B \longrightarrow AB$$
$$AB \longrightarrow A + B$$

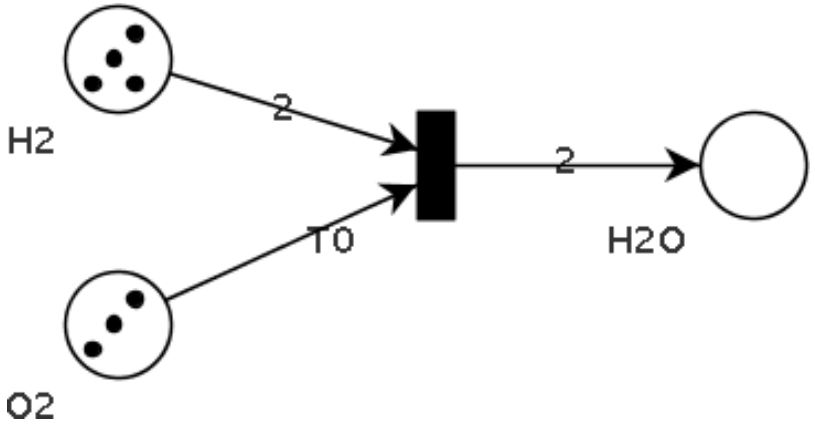
- state configuration has the form $\langle \#A, \#B, \#AB \rangle$
- consider, e.g., configuration $\langle 2, 2, 1 \rangle$
  $\Rightarrow$ what is the next configuration?
- reactions run in parallel ...

Petri Nets – A Discrete Model of Chemichal World

Adam Carl Petri
1926–2010

- formal model for concurrent systems
- used for general modeling and simulation
- many simulation and analysis tools
- various semantics
- unambiguous system representation

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



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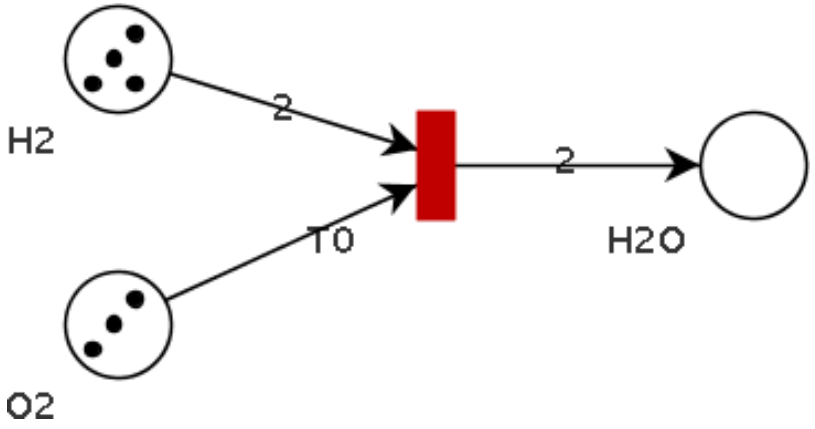

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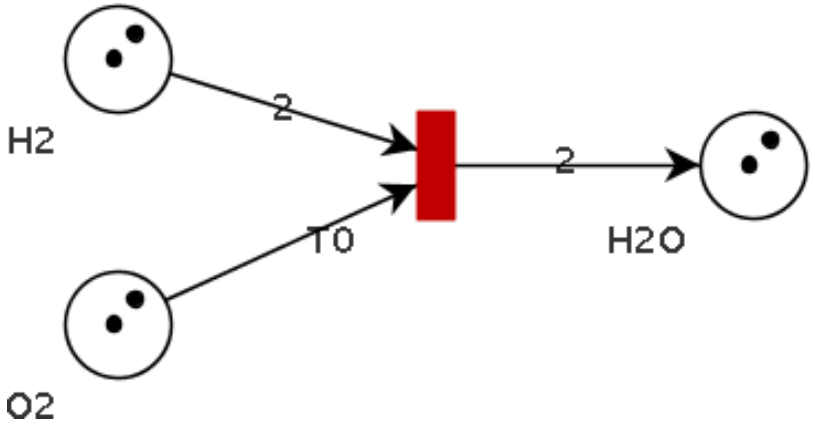

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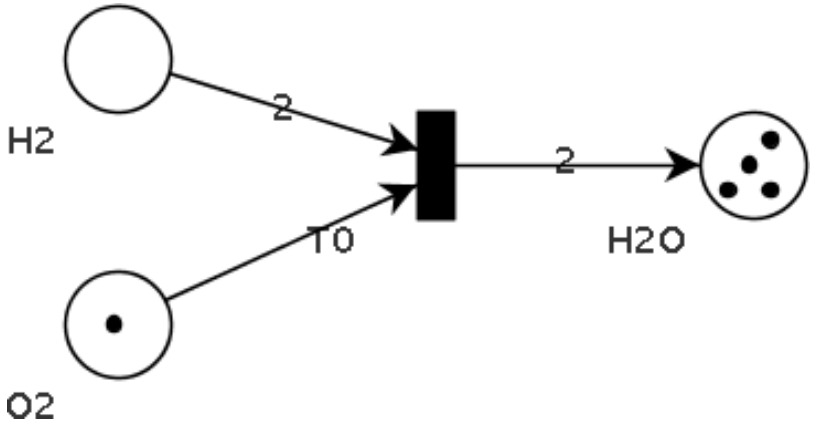
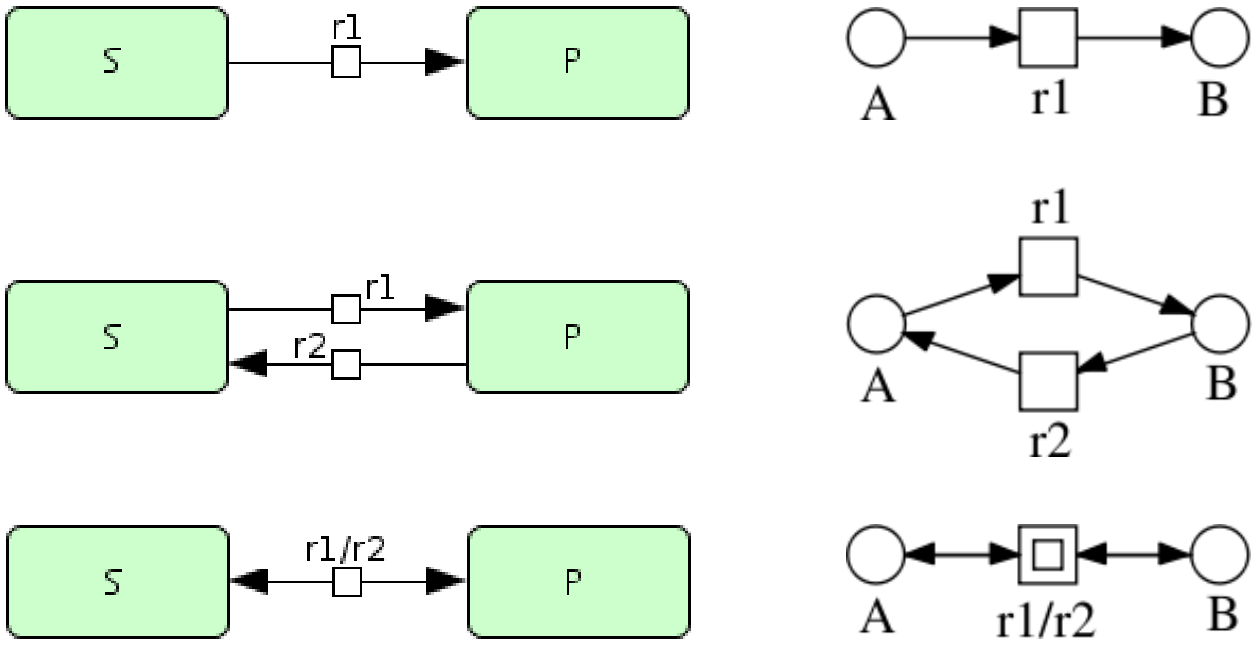


Petri Net Representation of Biological Networks



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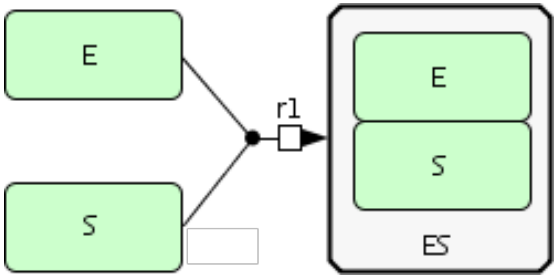
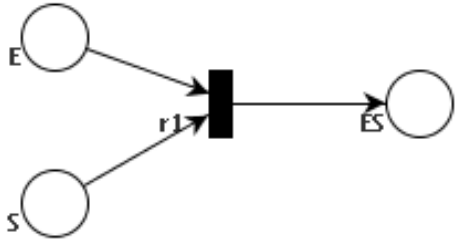
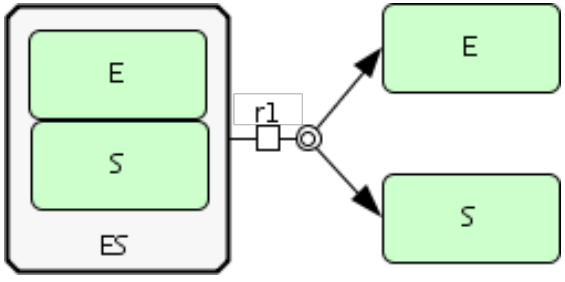
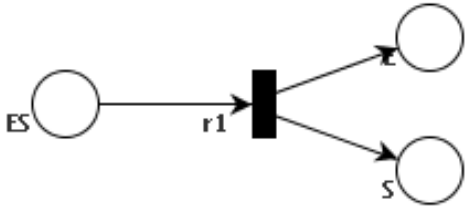
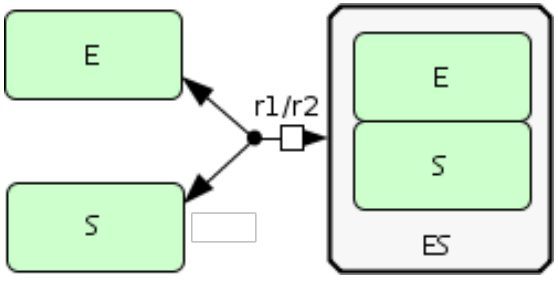
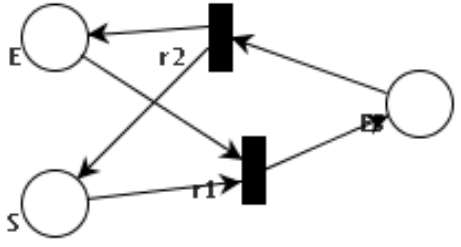




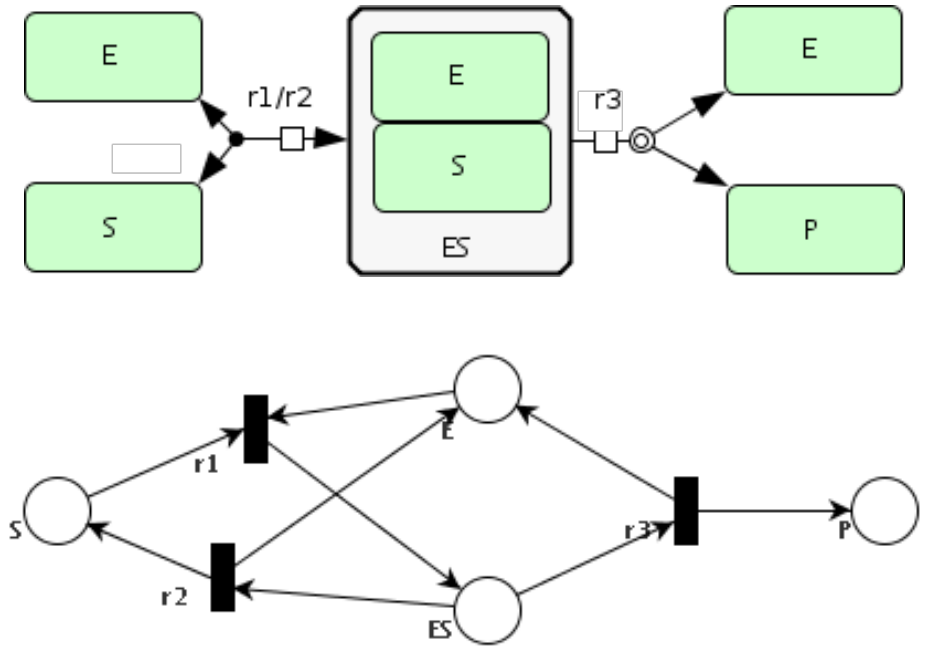








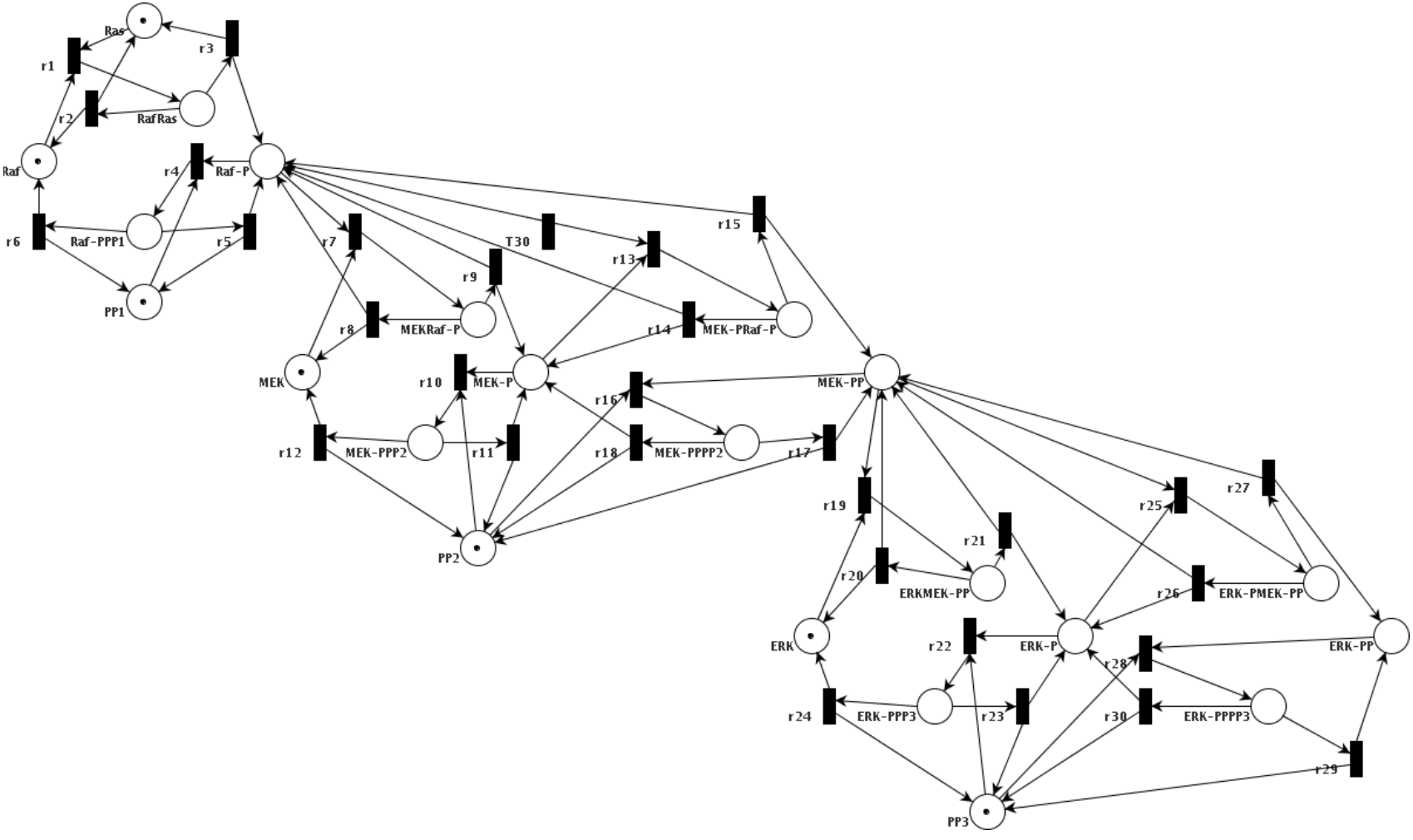
Petri Net Representation of Biological Networks



- visually infeasible but unambiguous, formal, and still graphical

Petri Net Representation of Biological Networks

Kinase Cascade in MAPK/ERK Signalling Network



Petri Net Representation of Biological Networks

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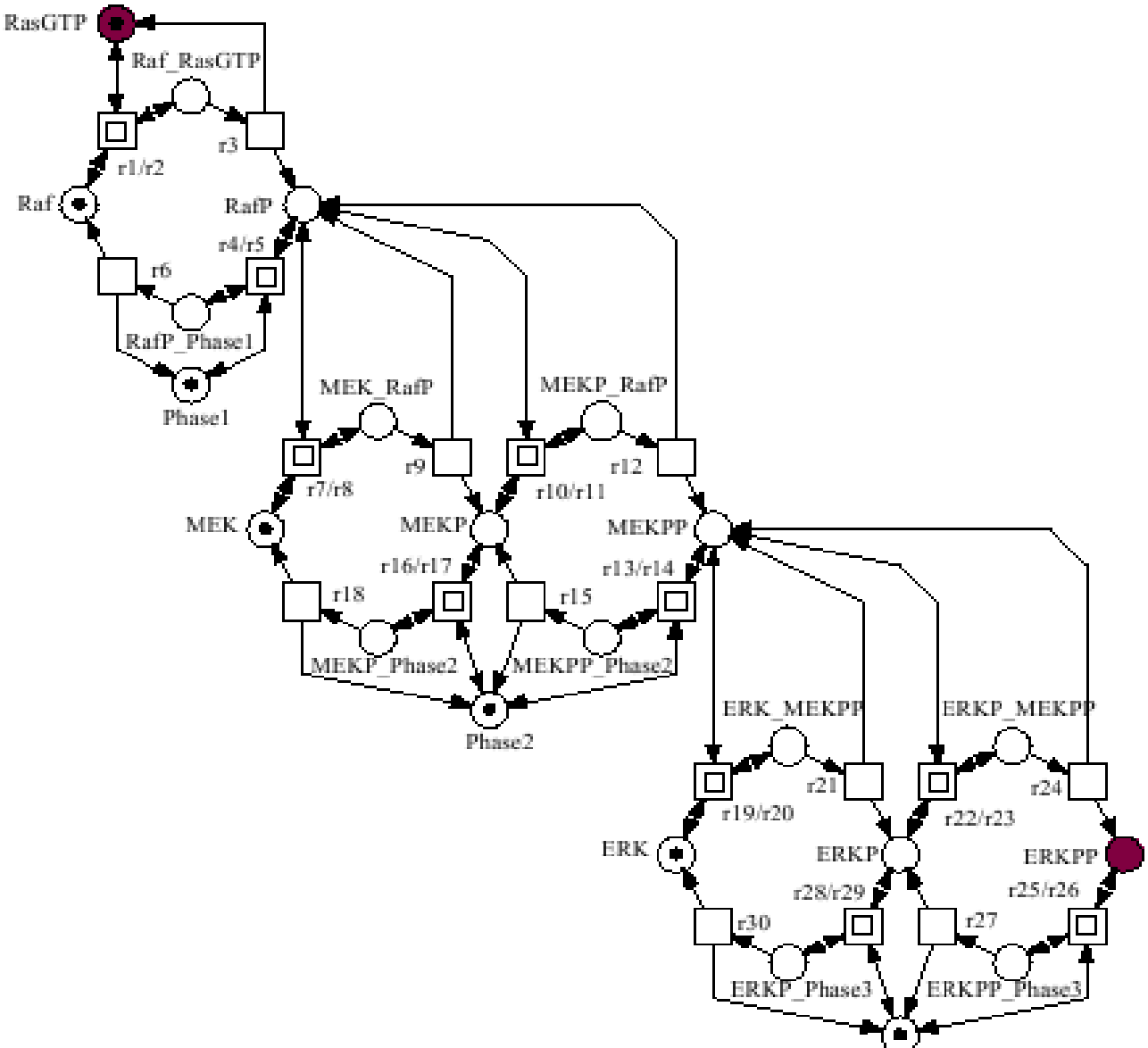
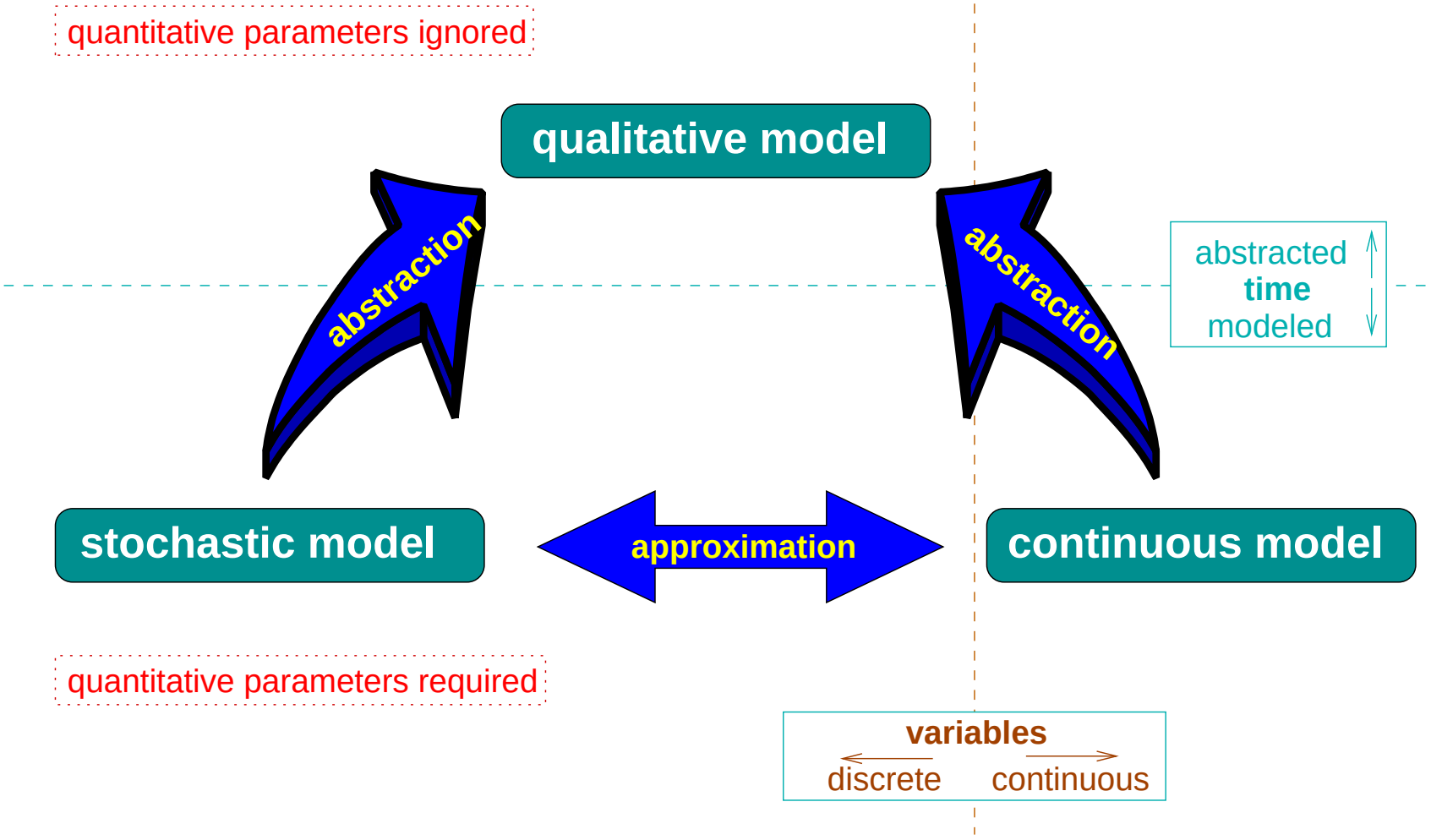


Petri Net Analysis Framework



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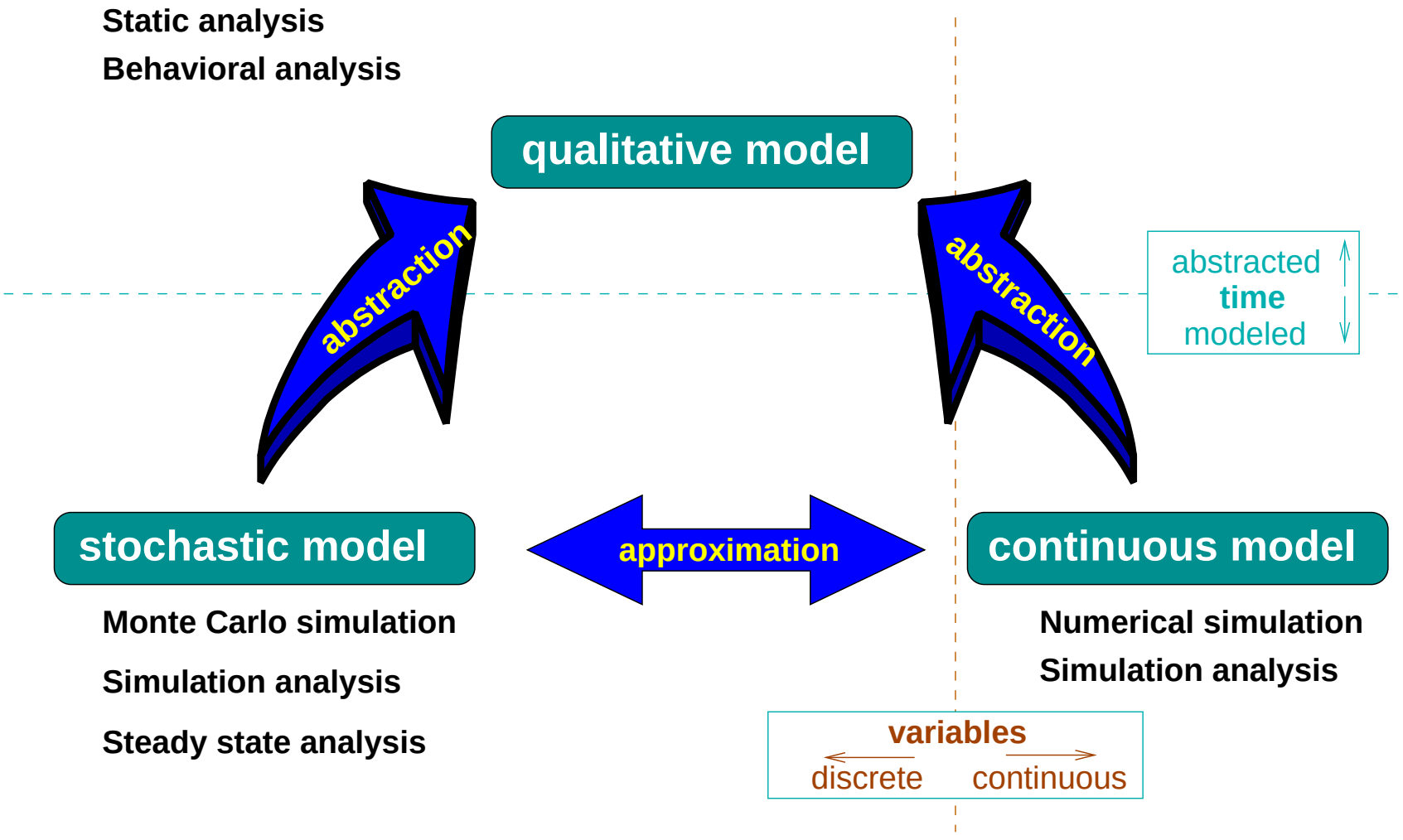


Petri Net Structure

(Place/Transition) Petri net is a quadruple $\mathcal{N} = \langle S, R, f, m(0) \rangle$ where

- S finite set of *places* (substances),
- T finite set of *transitions* (reactions),
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{N}_0$ set of weighted edges,
  - $x\bullet = \{y \in S \cup R \mid f(x, y) \neq 0\}$ denotes target of x
  - $\bullet x = \{y \in S \cup R \mid f(y, x) \neq 0\}$ denotes source of x
  - weight represents stoichiometric coefficients
- $m(0) : S \to \mathbb{N}_0$ is *initial marking* (initial condition).

Petri Net Dynamics

Each place $s \in S$ is marked by a value in $\mathbb{N}_0$ (representing number of molecules of the respective species):

- in Petri net terminology the state configuration (configuration of places) is called *marking*: $m : S \to \mathbb{N}_0$
- marking is represented as an n-dimensional vector $m \in \mathbb{N}_0^n$

Dynamics of each *transition* $r \in R$ is the following:

- a transition $r \in R$ must be *enabled* iff $\forall s \in {\bullet r}.\, m(s) \geq f(s, r)$
- enabled transition can be fired, causing an update of related places (marking m is updated to marking m'):

$$\forall s \in S.\, m'(s) = m(s) - f(r, s) - f(s, r)$$

Static Analysis

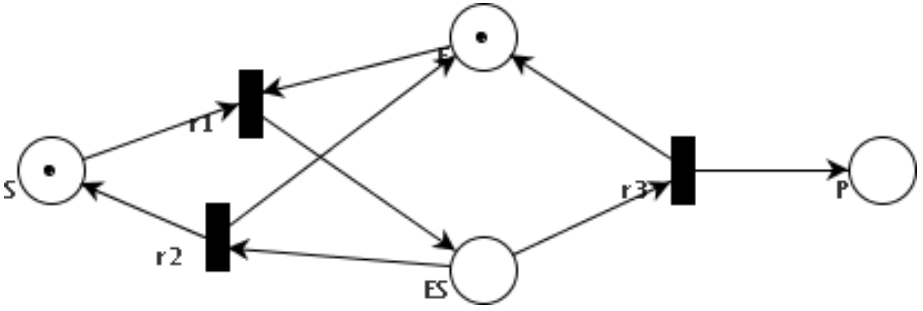
Matrix Representation

- Petri Net can be represented by *incidence matrix* $\mathbb{M} : S \times R \to \mathbb{Z}$ defined as follows:

$$\mathbb{M}(s, r) = f(r, s) - f(s, r)$$

- equivalent to stoichiometric matrix

Note: If reversible reactions are considered, forward and backward matrices must be distinguished.



$$\mathbb{M} = \begin{pmatrix} -1 & 1 & 1 \\ -1 & 0 & 1 \\ 1 & -1 & -1 \\ 0 & 1 & 0 \end{pmatrix}$$

species indices: $s_1 ... E, s_2 ... S, s_3 ... ES, s_4 ... P$

reaction indices: $r_1 : E + S \to ES$, $r_2 : ES \to E + S$, $r_3 : ES \to P + E$

Static Analysis

Invariant Analysis – P-invariants

- species vector x is called *P-invariant* iff

$$x\mathbb{M} = 0$$

- characteristic property of P-invariant x:

$$\forall r \in R. \sum_{i=1}^{n} \mathbb{M}(i, r) x_i = 0$$

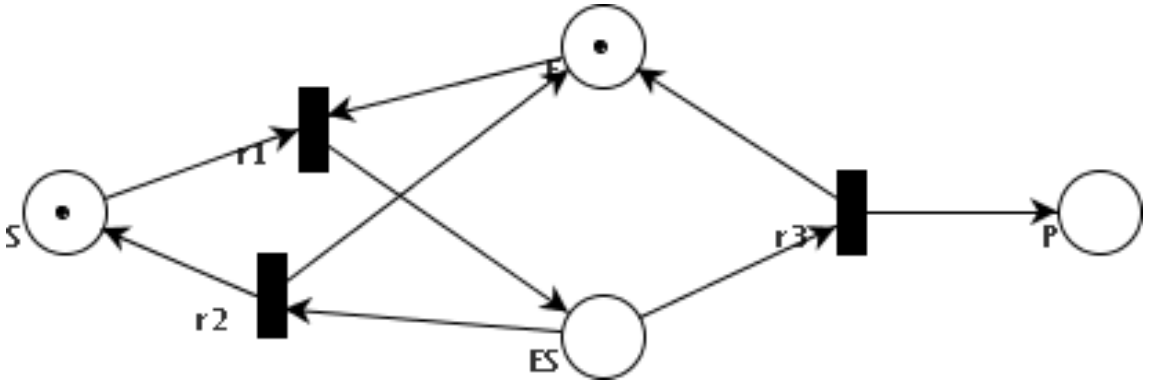
- Petri Net terminology translates the P-invariant property to:

$$\forall r \in R. \sum_{s \in \bullet r} x_s = \sum_{s \in r \bullet} x_s$$

- interpretation: conserved mass

Static Analysis

Invariant Analysis – P-invariants



$$E + S \leftrightarrow ES \rightarrow P + E$$

species indices: $s_1 ... E, s_2 ... S, s_3 ... ES, s_4 ... P$

- minimal P-invariants:
  - $(1, 0, 1, 0)$: $m_E + m_{ES} = \text{const.}$
  - $(0, 1, 1, 1)$: $m_S + m_{ES} + m_P = \text{const.}$
- minimal P-invariants make the basis of $\mathbb{M}$ left-null space
- non-minimal P-invariant example:
  - $(1, 1, 2, 1)$: $m_E + m_S + 2m_{ES} + m_P = \text{const.}$

Static Analysis

Invariant Analysis – T-invariants

- species vector y is called *T-invariant* iff

$$\mathbb{M}y = 0$$

- characteristic property of T-invariant y:

$$\forall s \in S. \sum_{j=1}^{|R|} \mathbb{M}(s,j)y_j = 0$$

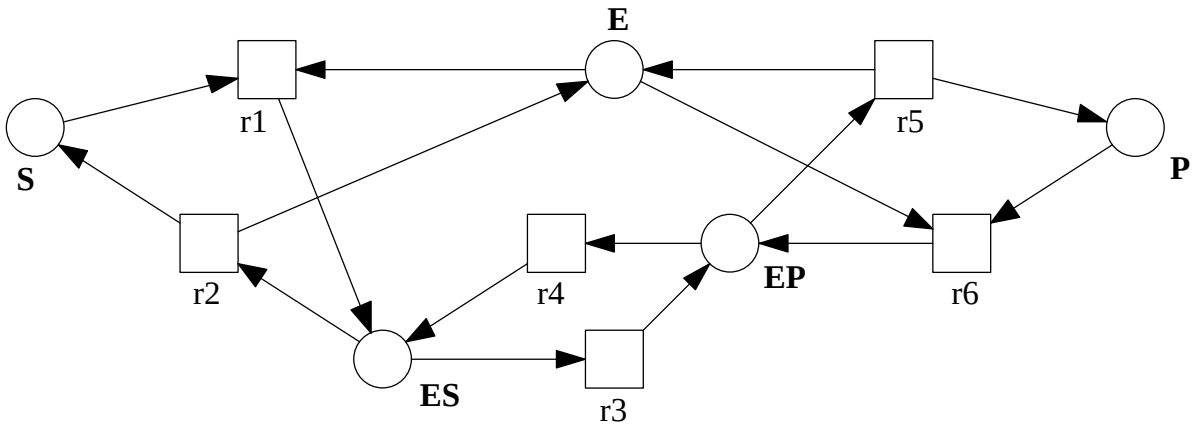
- Petri Net terminology translates the T-invariant property to:

$$\forall s \in S. \sum_{r \in {}^\bullet s} y_r = \sum_{r \in s^\bullet} y_r$$

- interpretation: stable flux mode

Static Analysis

Invariant Analysis – T-invariants



$$E + S \leftrightarrow ES \leftrightarrow EP \leftrightarrow P + E$$

- minimal T-invariants:
  - $(1, 1, 0, 0, 0, 0)$: $r_1; r_2$ (trivial – reversibility)
  - $(0, 0, 1, 1, 0, 0)$: $r_3; r_4$ (trivial – reversibility)
  - $(0, 0, 0, 0, 1, 1)$: $r_5; r_6$ (trivial – reversibility)
- minimal T-invariants make the basis of $\mathbb{M}$ null space
- non-minimal (and non-trivial) T-invariant example:
  - $(1, 1, 1, 1, 1, 1)$: $r_1; r_2; r_3; r_4; r_5; r_6$
  - this T-invariant represents significant input/output behaviour of the network ($S \longrightarrow P$)

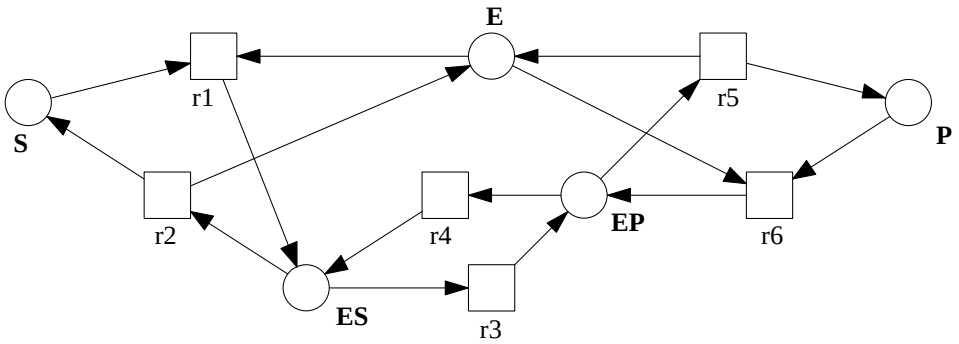
Static Analysis

Initial Marking Construction

- what species have to be set with non-zero concentration initially?
- follow the following rules:
  - each P-invariant contains at least one non-zero species
  - each non-trivial T-invariant is realizable
  - there is only minimal number of species set non-zero
  - in each P-invariant choose non-zero the least active species (or monomer)

Static Analysis

Initial Marking Construction Example



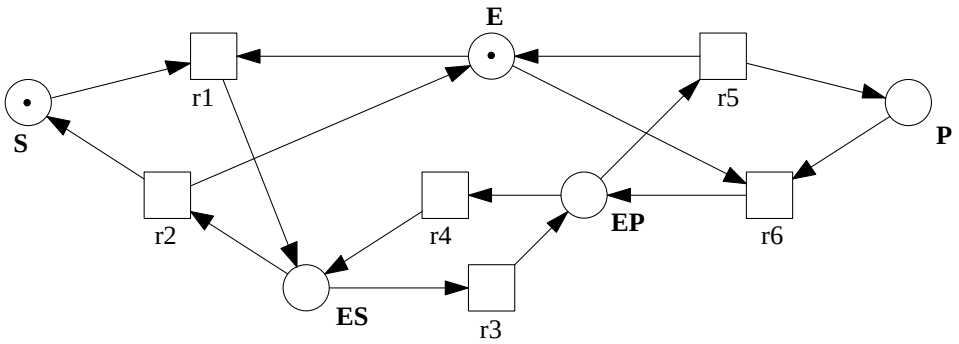
$$E + S \leftrightarrow ES \leftrightarrow EP \leftrightarrow P + E$$

indexace: $s_1 ... E, s_2 ... S, s_3 ... ES, s_4 ... P, s_5 ... EP$

- P-invariants: $(1, 0, 1, 0, 1)$, $(0, 1, 1, 1, 1)$
- T-invariants: $(1, 1, 0, 0, 0, 0)$, $(0, 0, 1, 1, 0, 0)$, $(0, 0, 0, 0, 1, 1)$
- initial marking (m_0) construction:
  - set non-zero one in $\{E, ES, EP\}$ and one in $\{S, ES, P, EP\}$
  - choose E and S (monomers)
  - non-trivial T-invariant $(1, 1, 1, 1, 1)$ is realizable in m_0: reaction sequence $r_1; r_3; r_5; r_6; r_4; r_2$

Static Analysis

Initial Marking Construction Example



$$E + S \leftrightarrow ES \leftrightarrow EP \leftrightarrow P + E$$

indexace: $s_1 ... E, s_2 ... S, s_3 ... ES, s_4 ... P, s_5 ... EP$

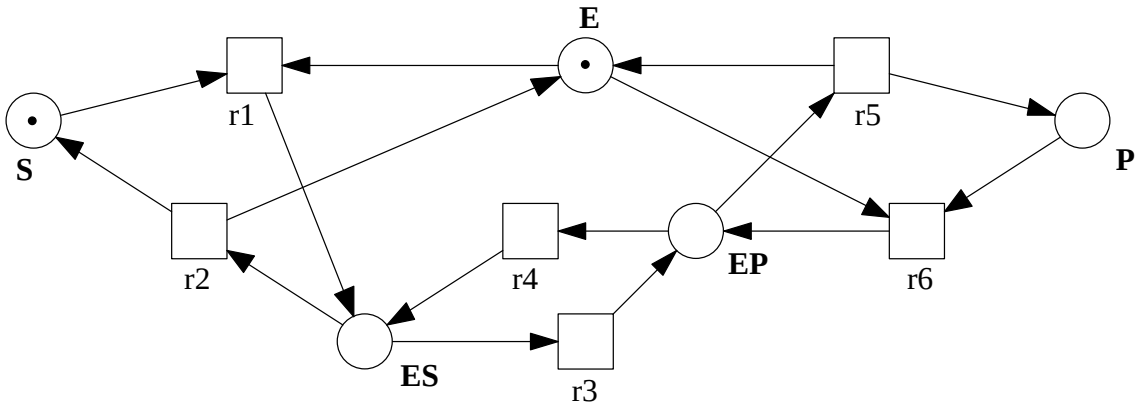
- P-invariants: $(1, 0, 1, 0, 1)$, $(0, 1, 1, 1, 1)$
- T-invariants: $(1, 1, 0, 0, 0, 0)$, $(0, 0, 1, 1, 0, 0)$, $(0, 0, 0, 0, 1, 1)$
- initial marking (m_0) construction:
  - set non-zero one in $\{E, ES, EP\}$ and one in $\{S, ES, P, EP\}$
  - choose E and S (monomers)
  - non-trivial T-invariant $(1, 1, 1, 1, 1)$ is realizable in m_0: reaction sequence $r_1; r_3; r_5; r_6; r_4; r_2$

Qualitative Behavioral Properties

- boundedness
  - no species concentration expands indefinitely
  - can be decided statically (P-invariant coverability)
- liveness
  - weak form – always at least one reaction is working
    – can be decided statically in some cases
  - strong form – every reaction is always eventually working
    – can be decided statically in some cases (T-invariant coverability)
- reversibility
  - reversible process (each flux mode keeps realizing)
  - can be decided only by dynamical analysis
- dynamic properties independent of time and quantity

Qualitative Behavioral Properties

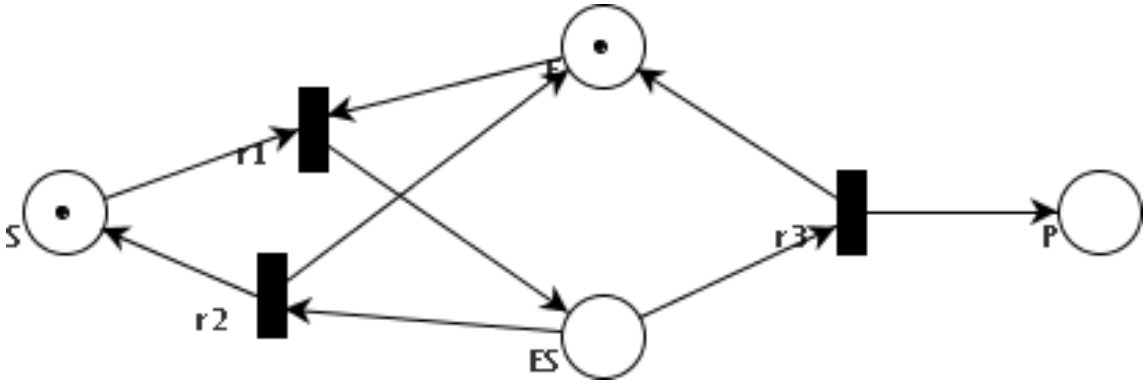
Example Michaelis Menten Reversible



- bounded, strongly live, reversible
- S and E is never finaly consumed (marked zero)
- P finally marked non-zero

Qualitative Behavioral Properties

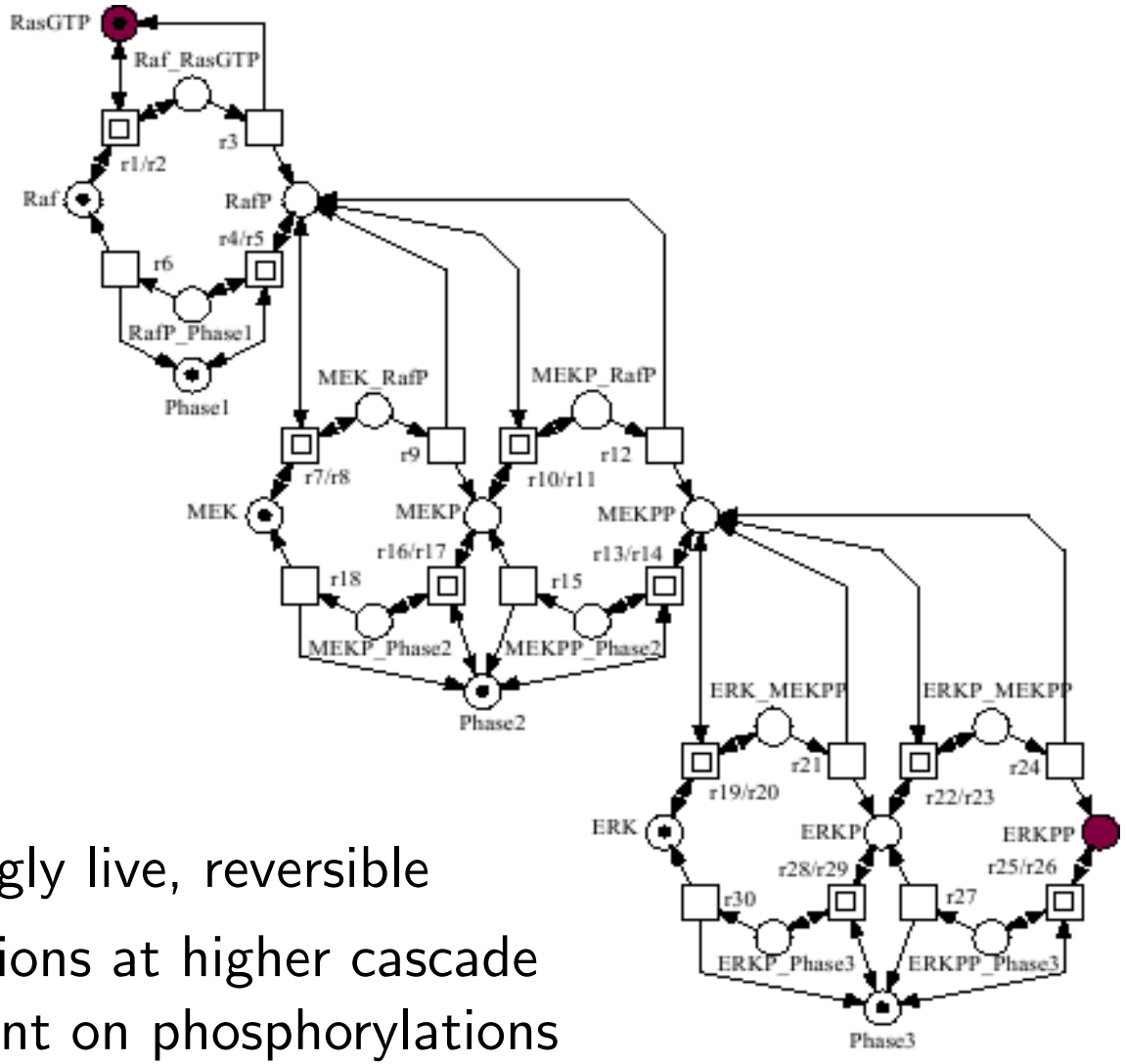
Example Michaelis Menten Kinetics



- bounded, not live, not reversible
- S finally consumed
- E consumed but recovered finally

Qualitative Behavioral Properties

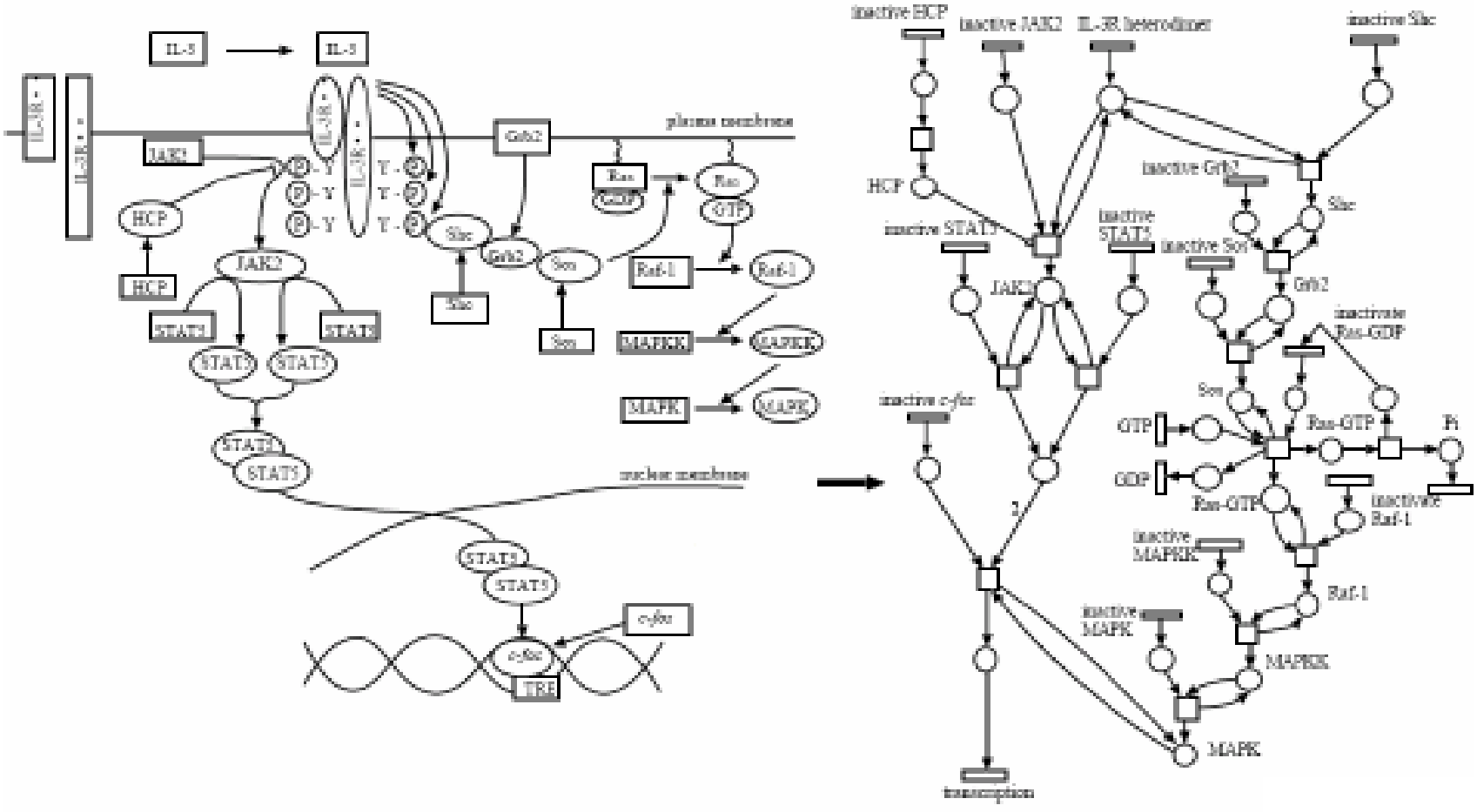
Example MAPK/ERK pathway



- bounded, strongly live, reversible
- dephosphorylations at higher cascade level independent on phosphorylations at lower level

Petri Net Representation

Example of complex signalling network



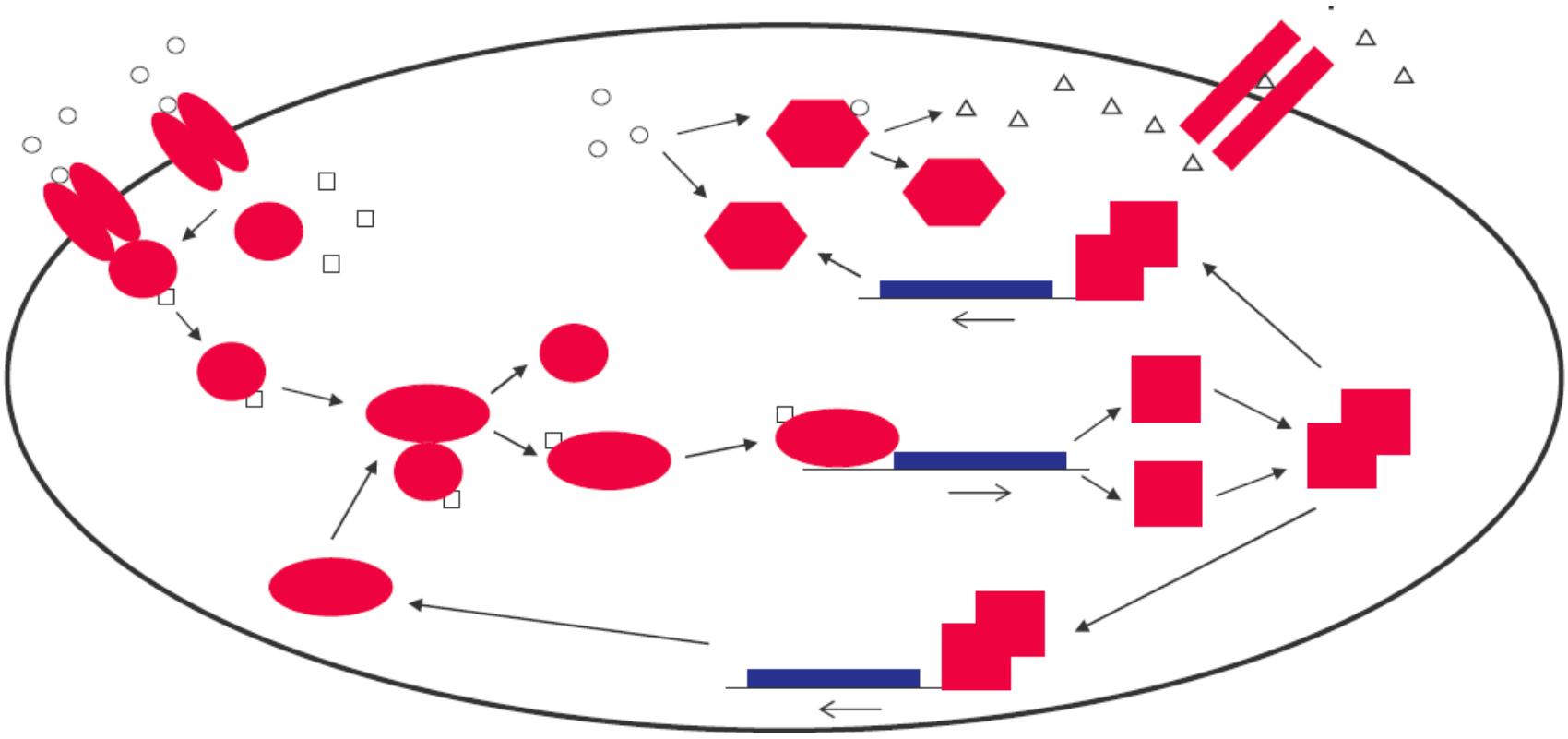
Tool Support

- format transformation and editing
  - Snoopy – visual editing, SBML export/import, Petri net variants transformation
  - PIPE – visual editing
- static analysis
  - Charlie (Petri Net invariant analysis)
  - also can be used: Matlab/Octave (stoichiometric analysis)
- qualitative behavioral analysis
  - Charlie (liveness, boundedness, and more ...)
  - MARCIE (qualitative dynamics analysis)
- Petri Net simulation
  - Snoopy – simulation of qualitative and stochastic nets
  - Cell Illustrator – proffesional tool, hybrid semantics

Literature

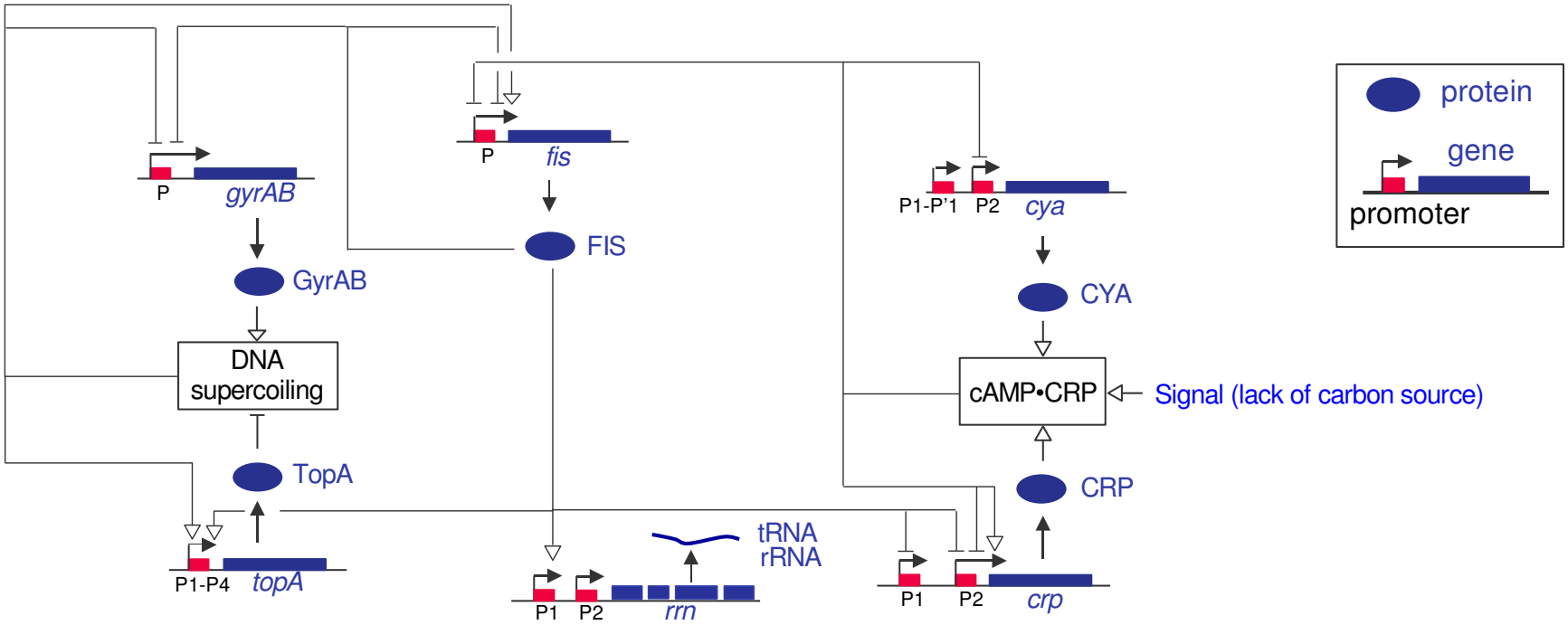
- M. Heiner & D. Gilbert. *How Might Petri Nets Enhance Your Systems Biology Toolkit.* Petri Nets 2011: 17-37
- M. Heiner, D. Gilbert & R. Donaldson. *Petri Nets for Systems and Synthetic Biology.* SFM 2008: 215-264
- Koch, I., Reisig, W. & Schreiber, F. *Modeling in Systems Biology: The Petri Net Approach.* Computational Biology, Vol. 16, Springer-Verlag, 2011.
- Pinney, J.W., Westhead, D.R. & McConkey, G.A. *Petri Net representations in systems biology.* Biochem Soc Trans. 2003 Dec;31(Pt 6):1513-5.
- Reddy, V.N., Mavrovouniotis M.L.& Liebman M.N. *Petri net representation in metabolic pathways.* Proc Int Conf Intell Syst Mol Biol 1993, 328-336.

Regulatory Networks of Cellular Processes

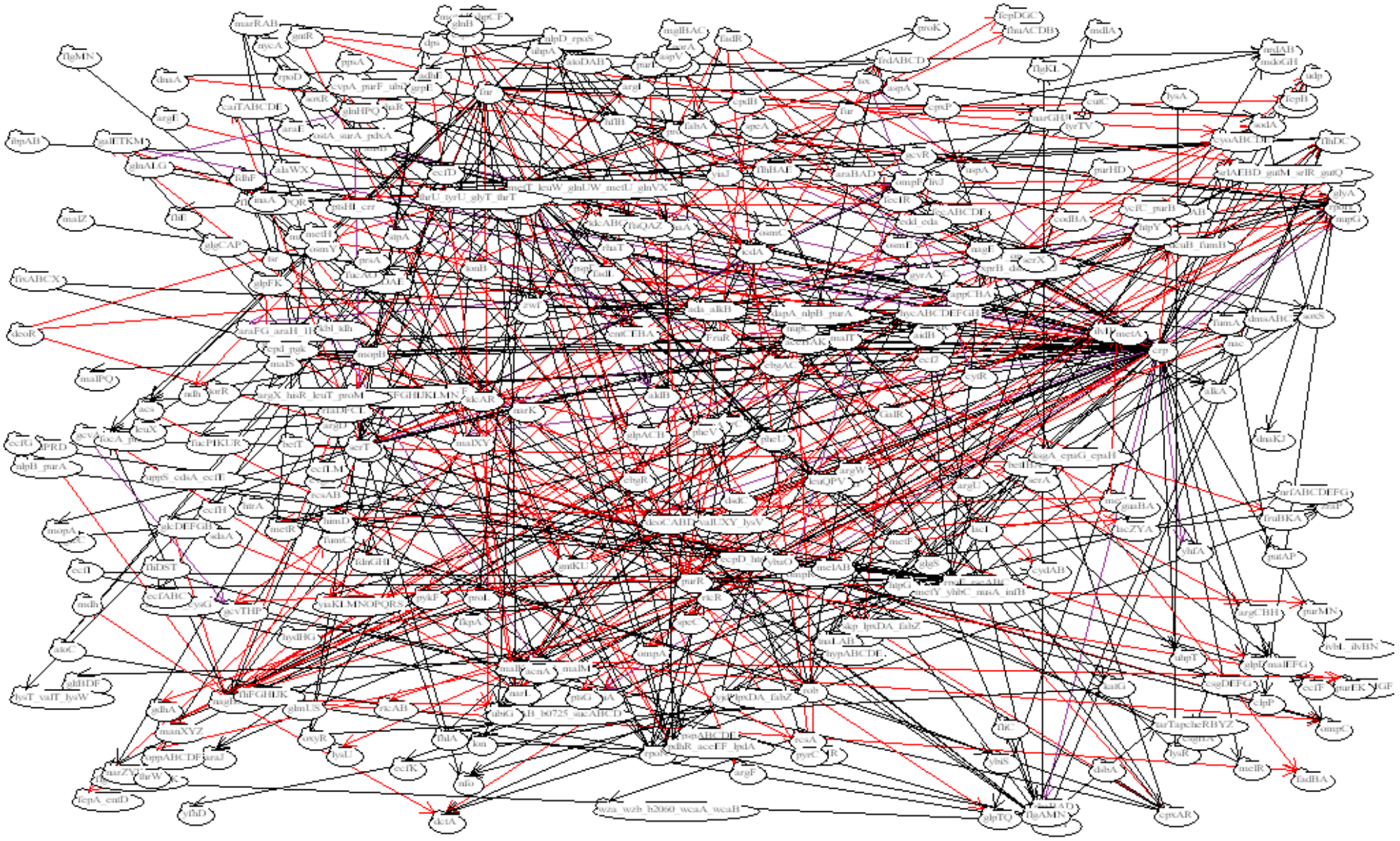


- identify substances (proteins, genes)
- identify interactions (transcriptory activation, repression – do we know reactions behind?)

Example of a gene regulatory network

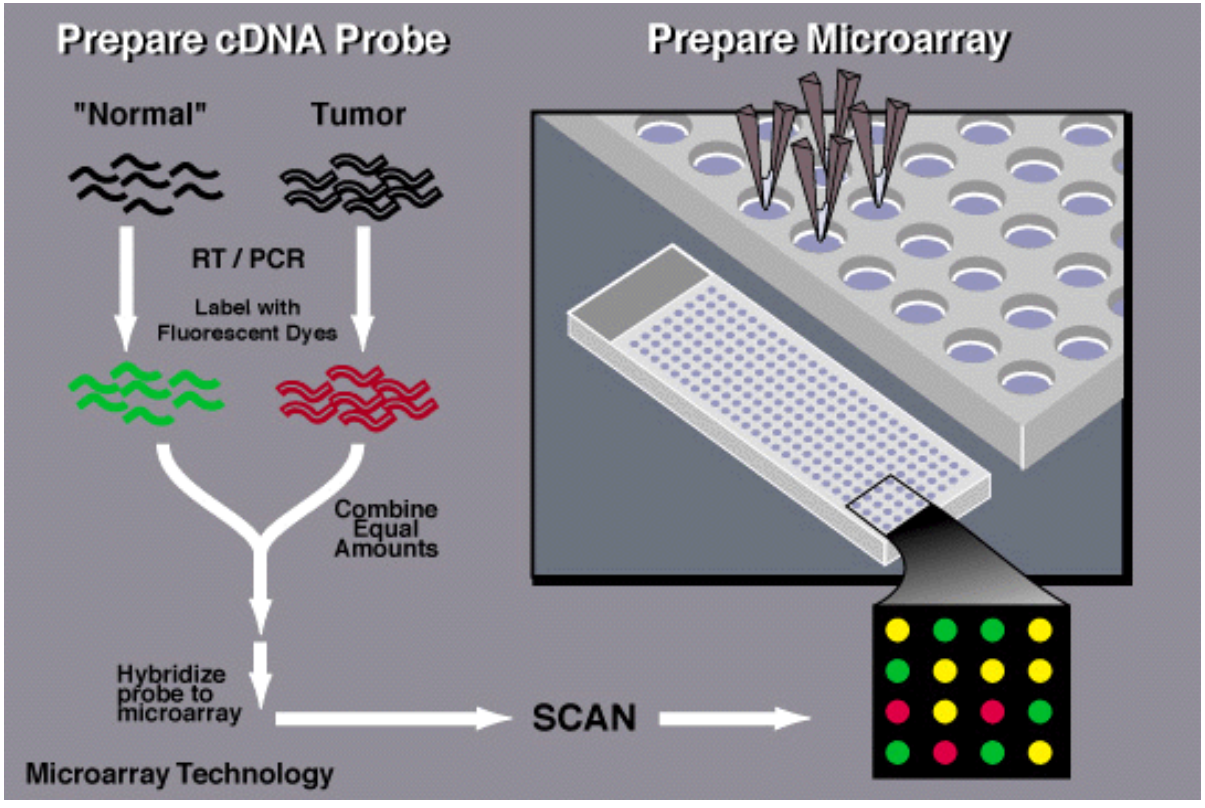


Gene regulatory network of E. Coli

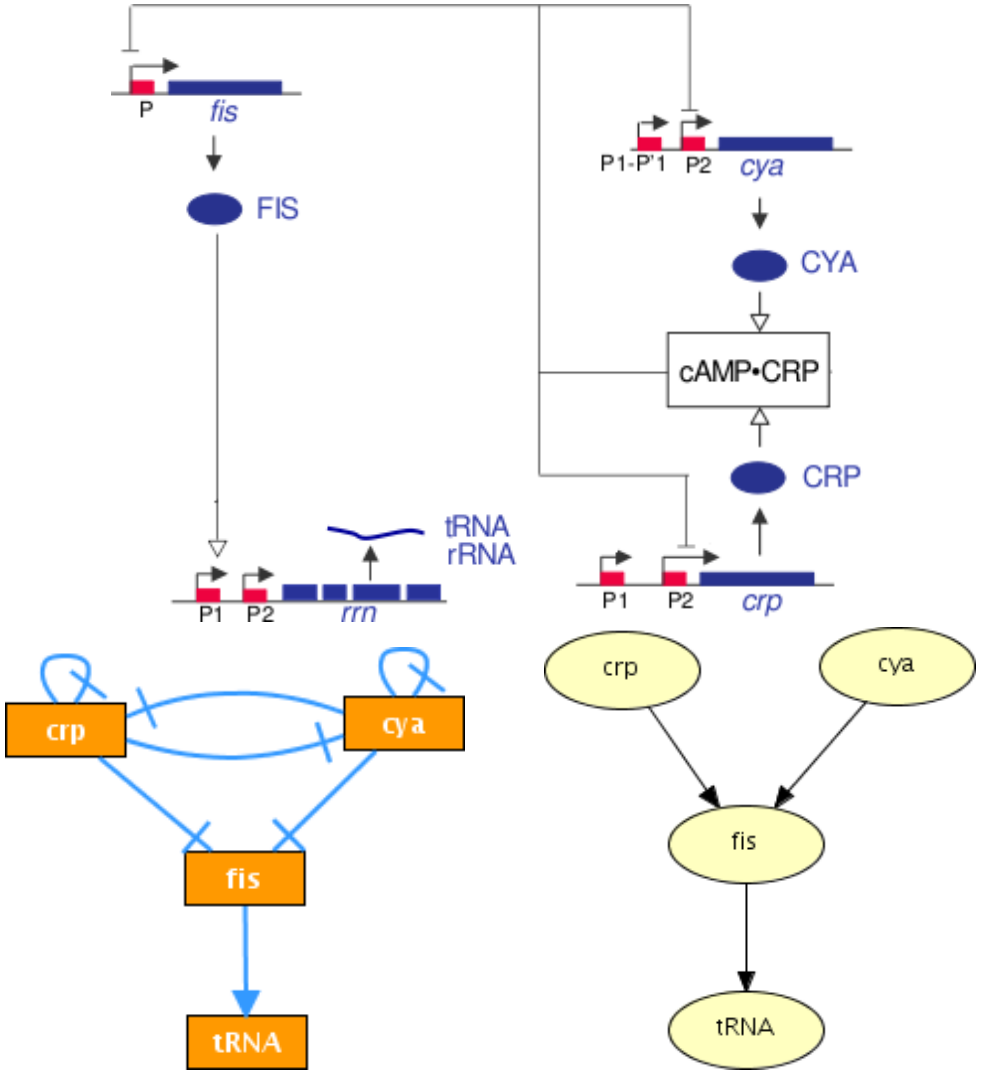


Identification of regulatory dynamics

- systems measurement of transcriptome (mRNA concentration) is imprecise and discrete!
- interactions can be partially identified by analysis of transcriptor factor binding sites (e.g., TRANSFAC)
- microarray experiments can be reversed engineered

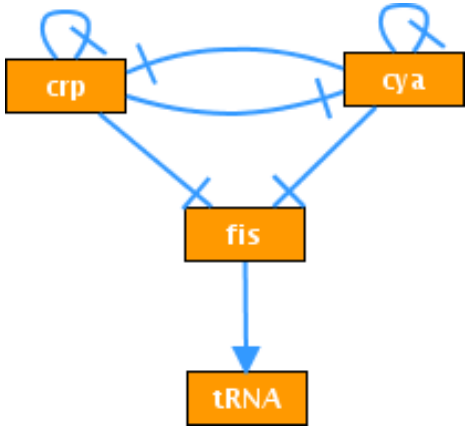


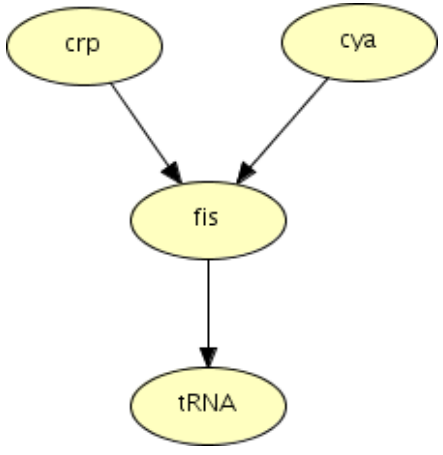
Identification of regulatory dynamics



Identification of regulatory dynamics

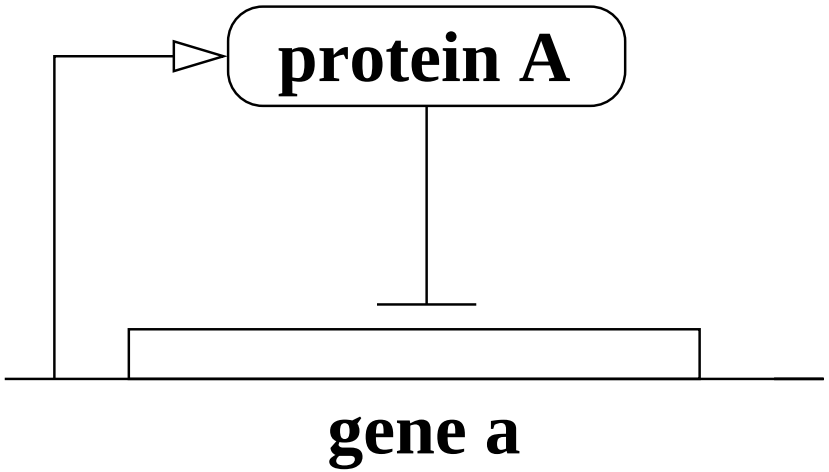
Boolean and Bayesian networks



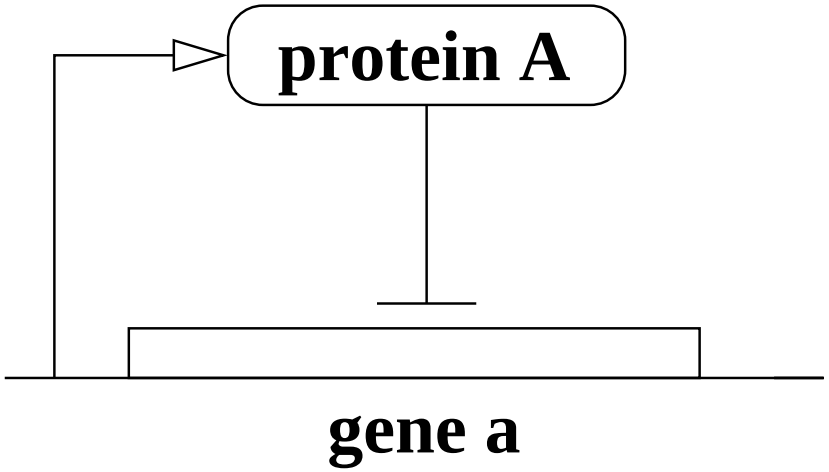


$$
\begin{aligned}
crp(t+1) &= \neg crp(t) \wedge \neg cya(t) \\
cya(t+1) &= \neg cya(t) \wedge \neg crp(t) \\
fis(t+1) &= \neg crp(t) \wedge \neg cya(t) \\
tRNA(t+1) &= fis(t)
\end{aligned}
\qquad
\begin{aligned}
P(X_{crp}) \\
P(X_{cya}) \\
P(X_{fis}|X_{crp}, X_{cya}) \\
P(X_{tRNA}|X_{fis})
\end{aligned}
$$

Model example – autoregulation

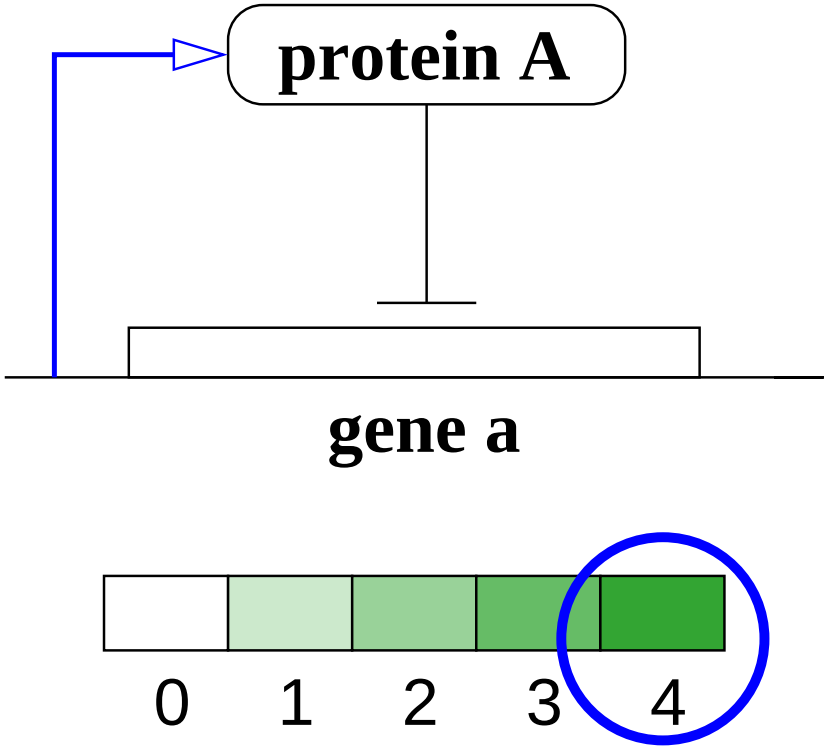


Model example – autoregulation



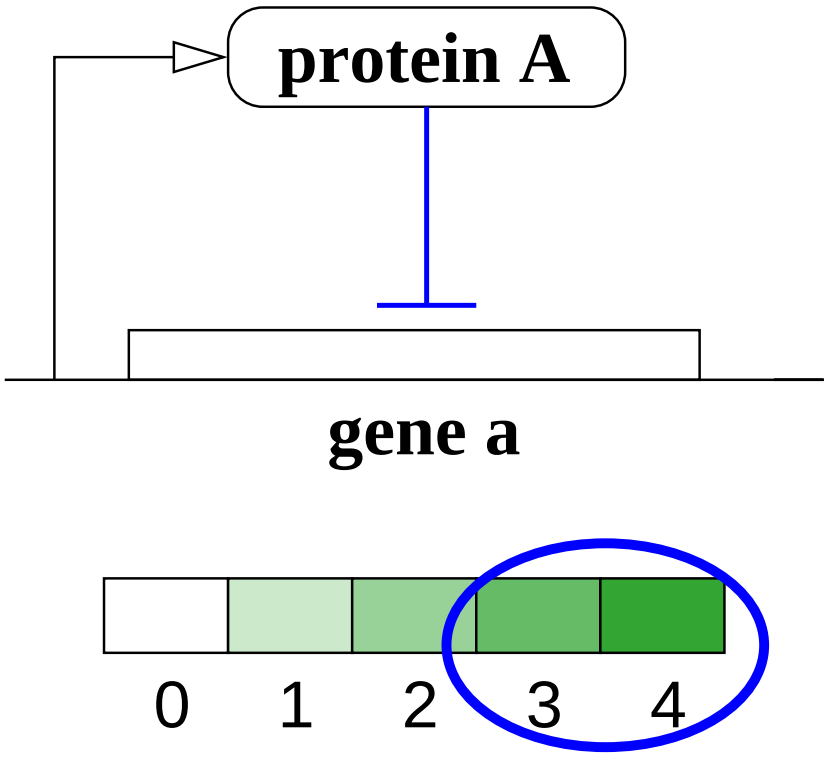
- identification of discrete expression levels

Model example – autoregulation



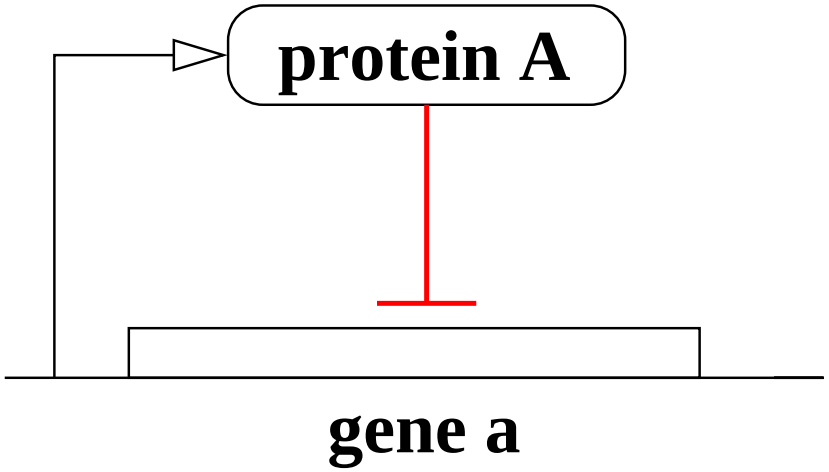
- spontanneous (basal) transcription: $A \rightarrow 4$

Model example – autoregulation



- range of regulatory activity ($A \in \{3, 4\} \Rightarrow$ regulation active)

Model example – autoregulation



- target level ($A \in \{3, 4\} \Rightarrow A \to 0$)

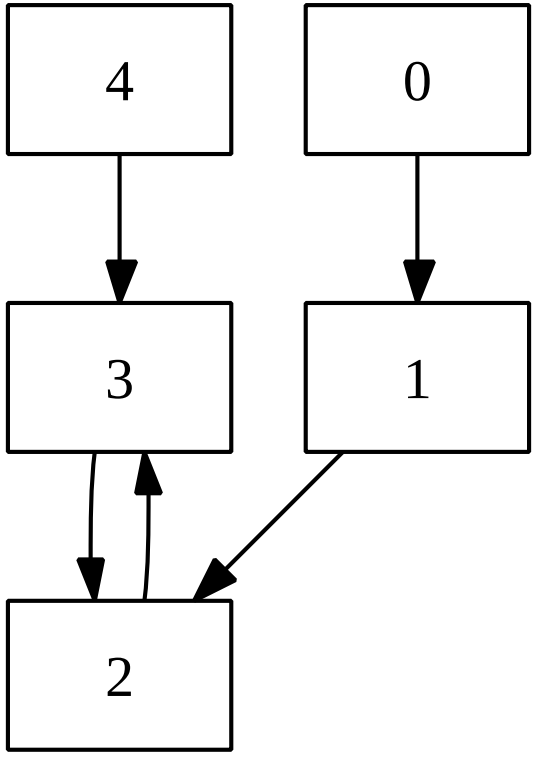
State space – autoregulation

- state transition system $\langle S, T, S_0 \rangle$
  - S state set, $S \equiv \{0, 1, 2, 3, 4\}$
  - $S_0 \subseteq S$ initial state set
  - $T \subseteq S \times S$ transition function:

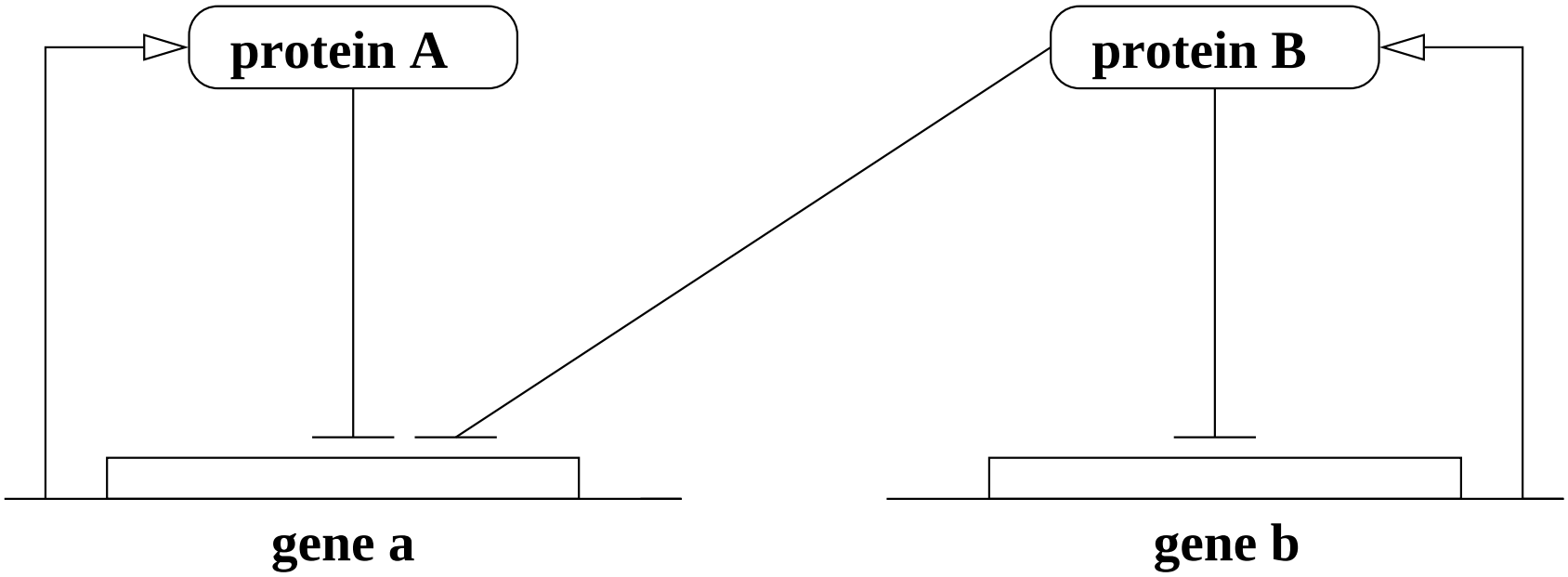
source state	active regulation	target state
0	$\emptyset; [A \rightarrow 4]$	1
1	$\emptyset; [A \rightarrow 4]$	2
2	$\emptyset; [A \rightarrow 4]$	3
3	$A \rightarrow^{-} A; [A \rightarrow 0]$	2
4	$A \rightarrow^{-} A; [A \rightarrow 0]$	3

State space – autoregulation

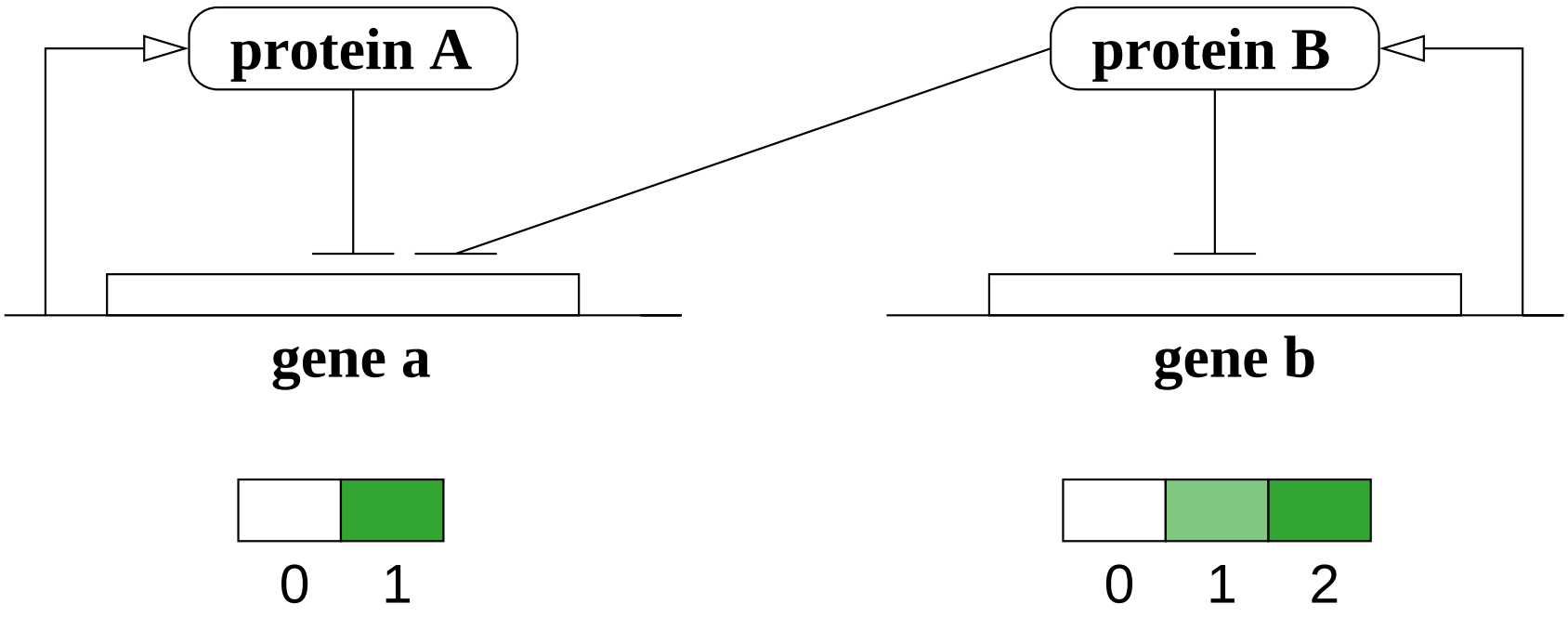
state transition system for negative autoregulation $\langle S, T, S_0 = S \rangle$:



Combined regulation

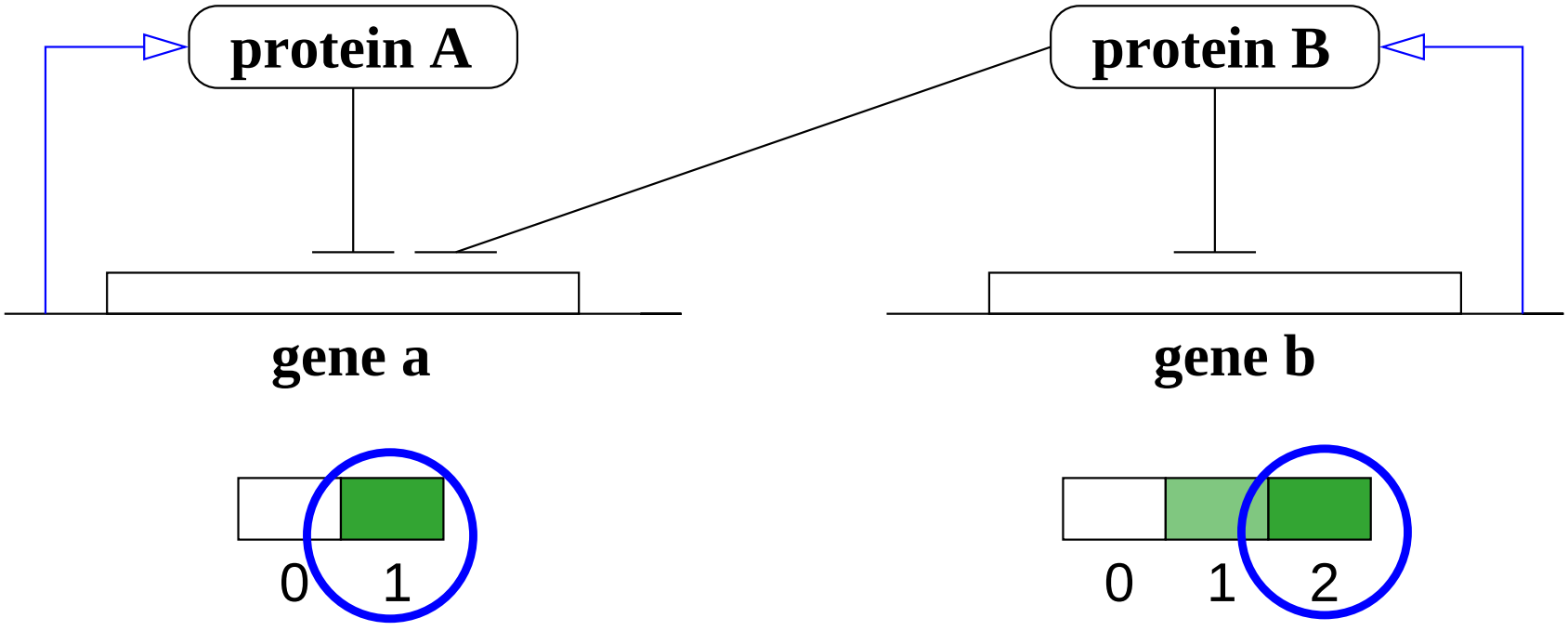


Discrete characteristics of dynamics



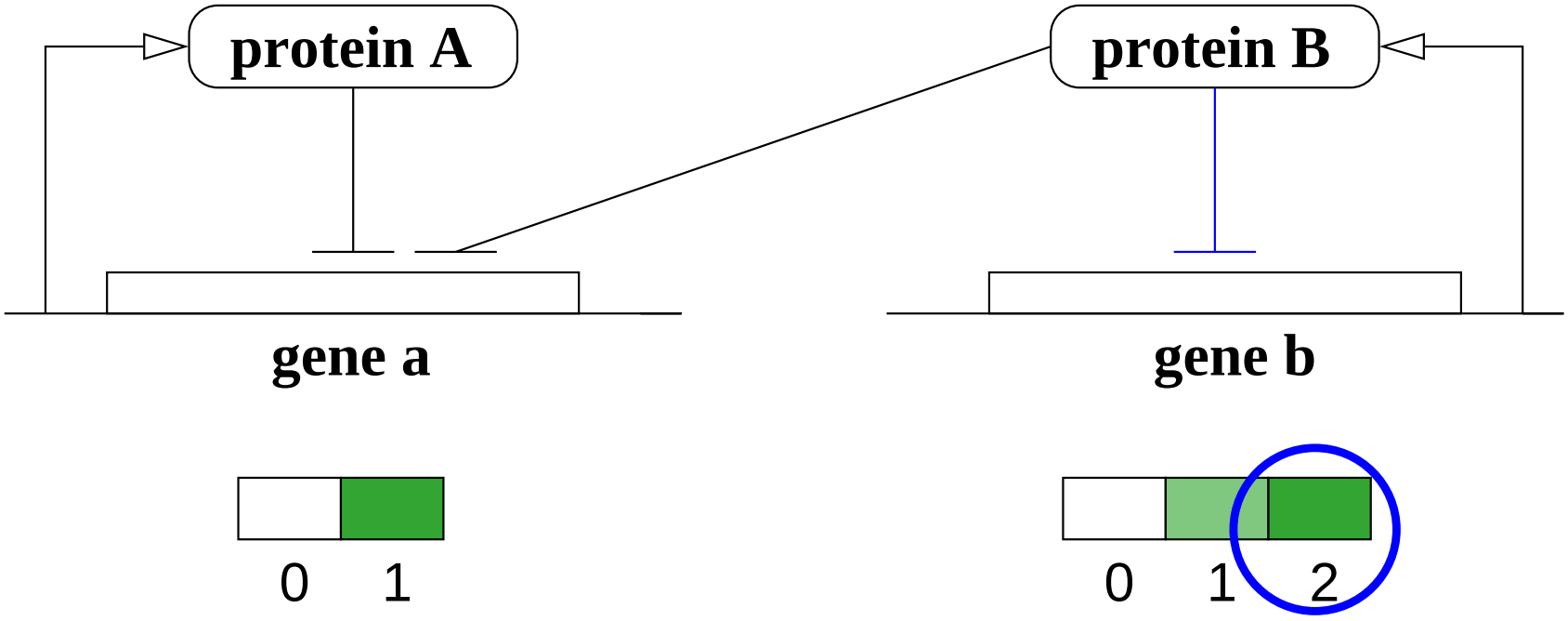
- identification of dicrete levels of expression

Discrete characteristics of dynamics



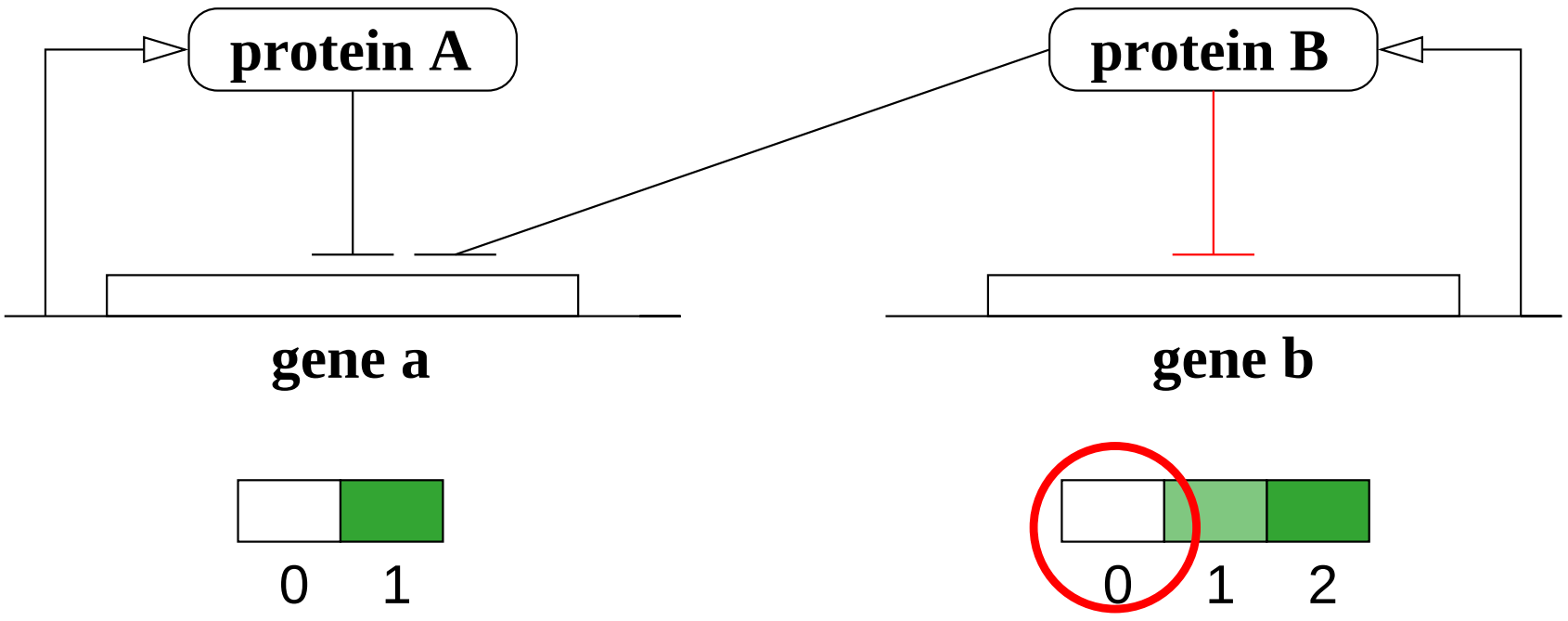
- spontanneous (basal) transcription: $A \rightarrow 1$, $B \rightarrow 2$

Characteristics of regulation



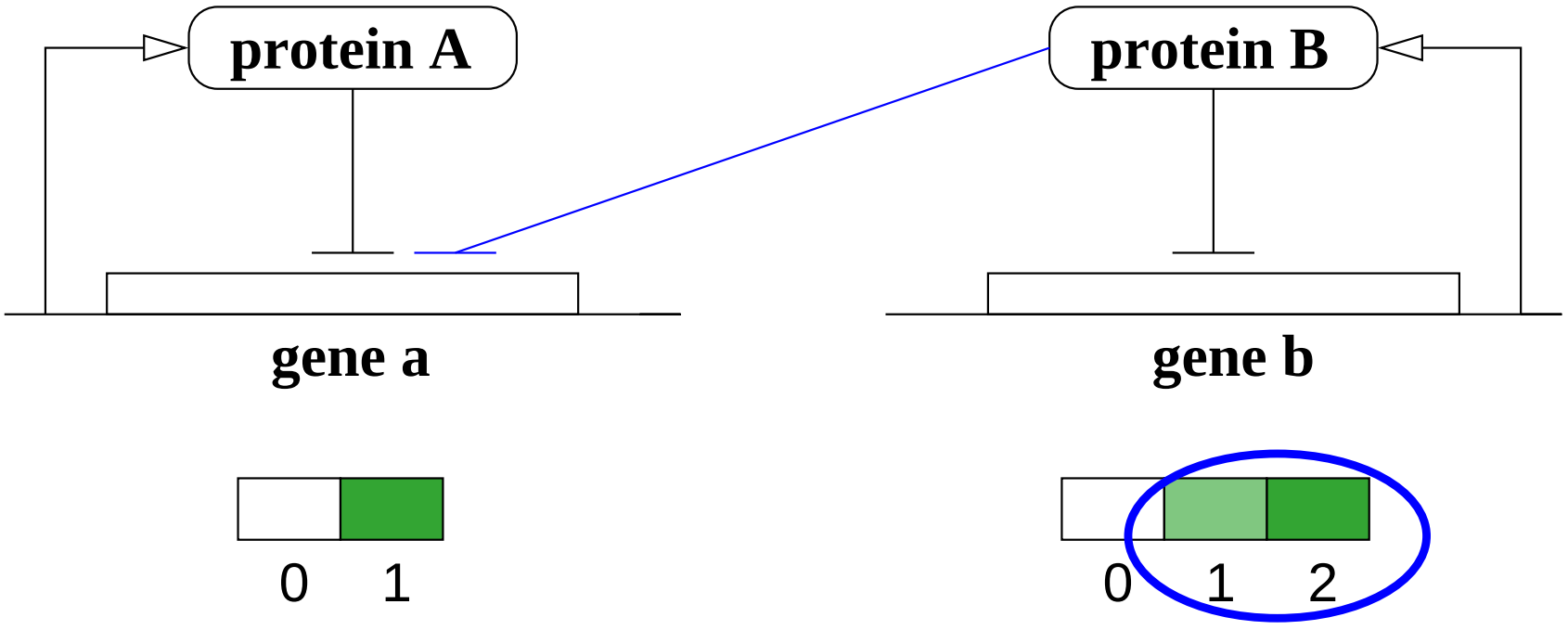
- range of regulatory activity $B \rightarrow^{-} B$ ($B = 2 \Rightarrow$ regulation active)

Characteristics of regulation



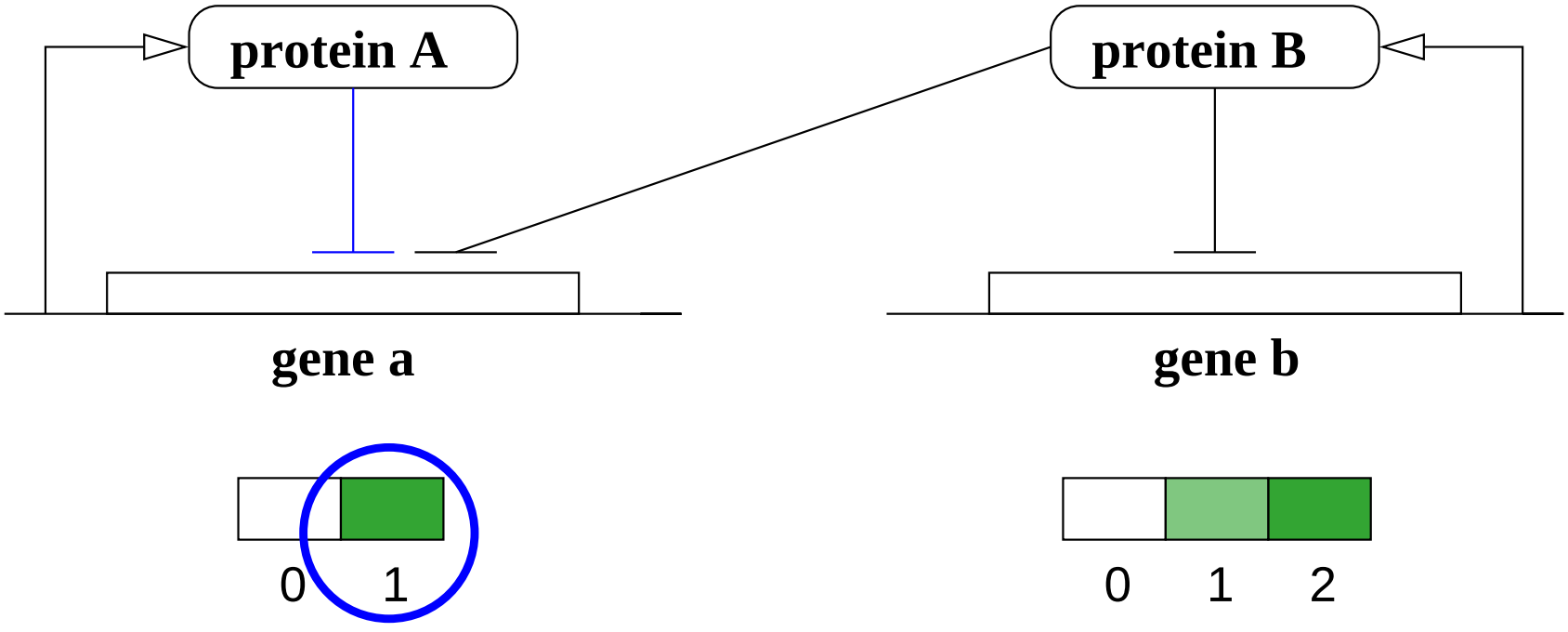
- target level $B \rightarrow^{-} B$ $(B = 2 \Rightarrow B \rightarrow 0)$

Characteristics of regulation – input function



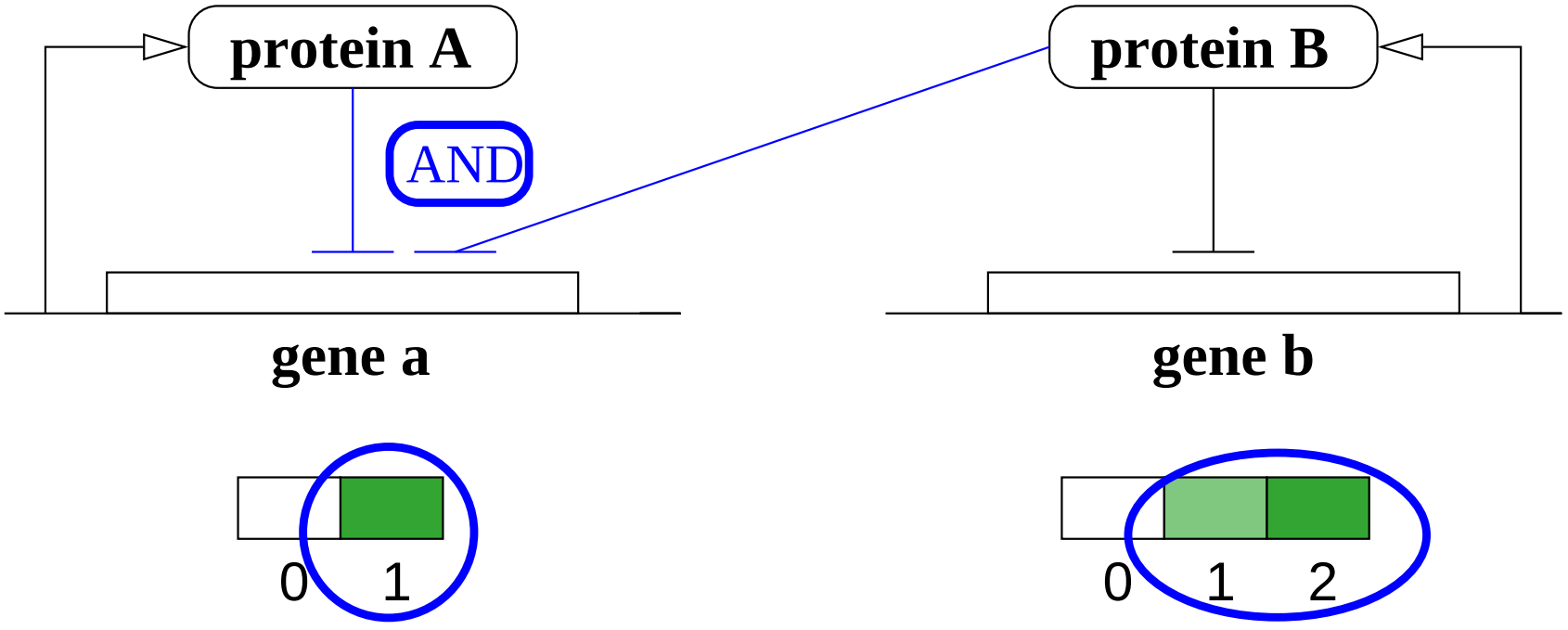
- range of regulatory activity $B \rightarrow^{-} A$ ($B \in \{1, 2\} \Rightarrow$ reg. active)

Characteristics of regulation – input function



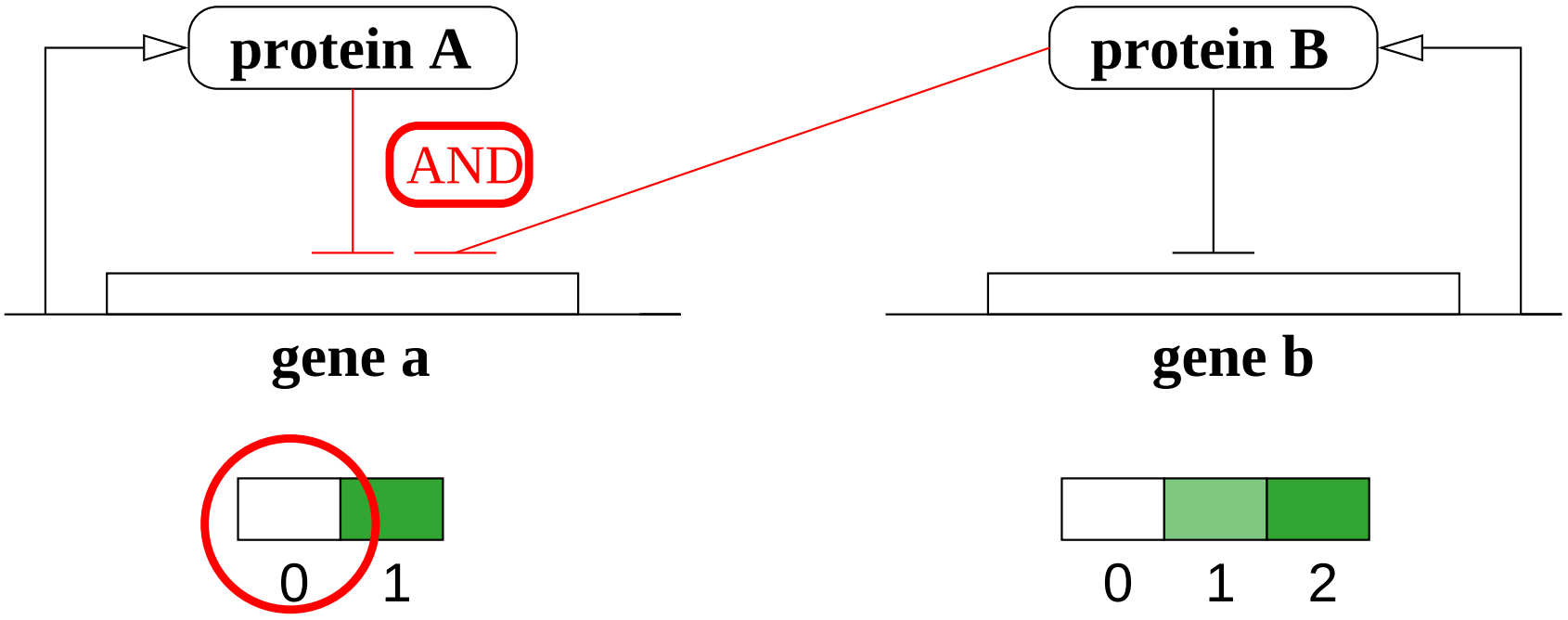
- range of regulatory activity $A \rightarrow^{-} A$ ($A = 1 \Rightarrow$ reg. active)

Characteristics of regulation – input function



- AND-combined regulation $A \rightarrow^{-} A \wedge B \rightarrow^{-} A$:
  $A = 1 \wedge B \in \{1, 2\} \Rightarrow$ regulation active

Characteristics of regulation – input function



- target levels of combined regulation $A \rightarrow^{-} A \wedge B \rightarrow^{-} A$:
  $A = 1 \wedge B \in \{1, 2\} \Rightarrow A \rightarrow 0$

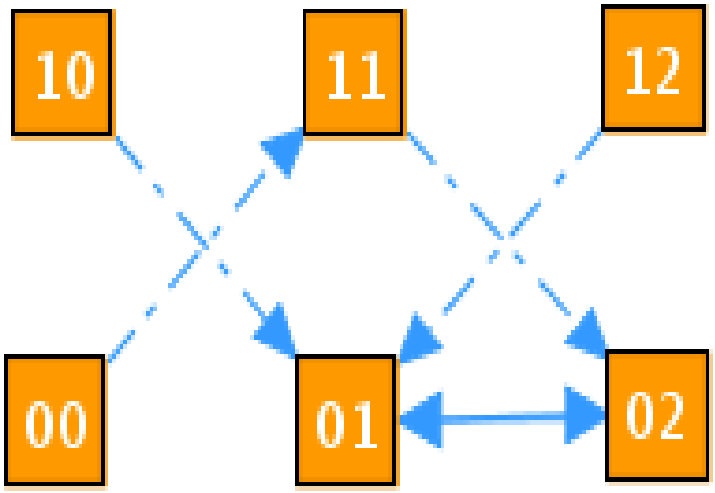
State space – synchronnous semantics

- state transition system $\langle S, T, S_0 \rangle$
  - $S \equiv \{0,1\} \times \{0,1,2\}$
  - $S_0 \subseteq S$, we consider $S_0 = S$
  - $T \subseteq S \times S$ transition function:

source state	active regulation	target state
$[0,0]$	$\emptyset$; $[A \to 1, B \to 2]$	$[1,1]$
$[0,1]$	$B \to^- A$; $[A \to 0, B \to 2]$	$[0,2]$
$[0,2]$	$B \to^- B \wedge B \to^- A$; $[A \to 0, B \to 0]$	$[0,1]$
$[1,0]$	$A \to^- A$; $[A \to 0, B \to 2]$	$[0,1]$
$[1,1]$	$A \to^- A \wedge B \to^- A$; $[A \to 0, B \to 2]$	$[0,2]$
$[1,2]$	$A \to^- A \wedge B \to^- A \wedge B \to^- B$; $[A \to 0, B \to 0]$	$[0,1]$

State space – synchronnous semantics

state transition system $\langle S, T, S_0 = S \rangle$:



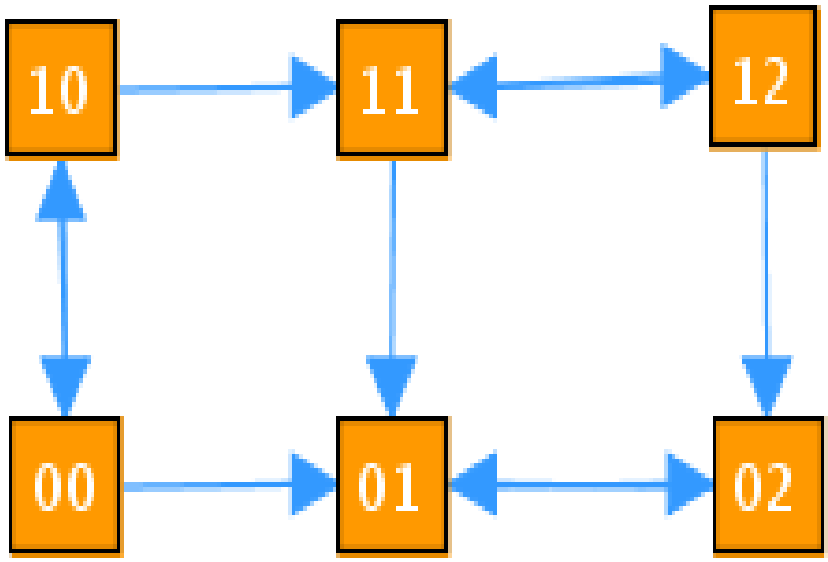
State space – asynchronnous semantics

- state transition system $\langle S, T, S_0 \rangle$
  - $S \equiv \{0,1\} \times \{0,1,2\}$
  - $S_0 \subseteq S$, we consider $S_0 = S$
  - $T \subseteq S \times S$ transition function:

source state	active regulation	target states
$[0,0]$	$\emptyset$; $[A \to 1, B \to 2]$	$[1,0]$, $[0,1]$
$[0,1]$	$B \to^- A$; $[A \to 0, B \to 2]$	$[0,2]$
$[0,2]$	$B \to^- B \wedge B \to^- A$; $[A \to 0, B \to 0]$	$[0,1]$
$[1,0]$	$A \to^- A$; $[A \to 0, B \to 2]$	$[0,0]$, $[1,1]$
$[1,1]$	$A \to^- A \wedge B \to^- A$; $[A \to 0, B \to 2]$	$[0,1]$, $[1,2]$
$[1,2]$	$A \to^- A \wedge B \to^- A \wedge B \to^- B$; $[A \to 0, B \to 0]$	$[0,2]$, $[1,1]$

State space – asynchronnous semantics

state transition system $\langle S, T, S_0 = S \rangle$:



Properties of discrete semantics

- synchronous semantics
  - effect of active regulations is realized in terms of a single event
  - strong approximation leading to deterministic state transition system
- asynchronnous semantics
  - effect of active regulations is realized for each gene/protein individually in terms of single events
  - nondeterminism models all possible serializations (so called interleaving)
  - approximation is rather conservative

Free Tool Support

- Gene Interaction Network simulation (GINsim)
  `http://gin.univ-mrs.fr/GINsim/accueil.html`
- asynchronous and synchronous simulation
  - allows to get rough understanding of regulatory logic
  - allows to identify potential steady states of regulation
  - purely qualitative modelling and analysis
- directly allow application of a large set of computer scientific tools
  - graph algorithms for state space graph analysis
  - model checking

Literature

- Thomas, R. *Regulatory networks seen as asynchronous automata : a logical description.* J. Theor. Biol. 153 ,(1991) 1-23.
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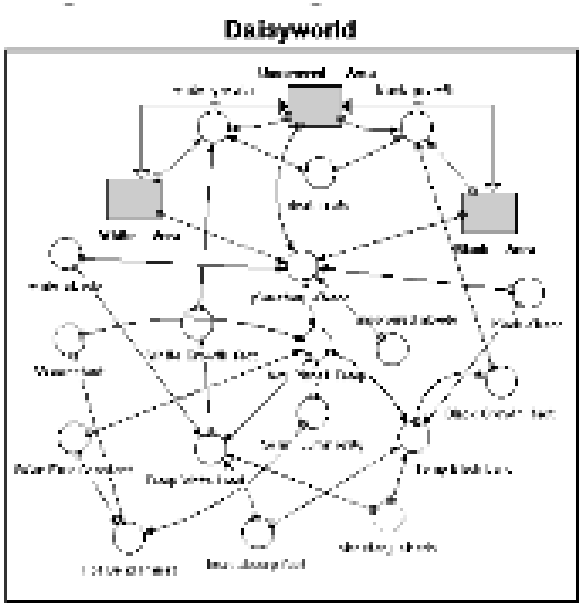
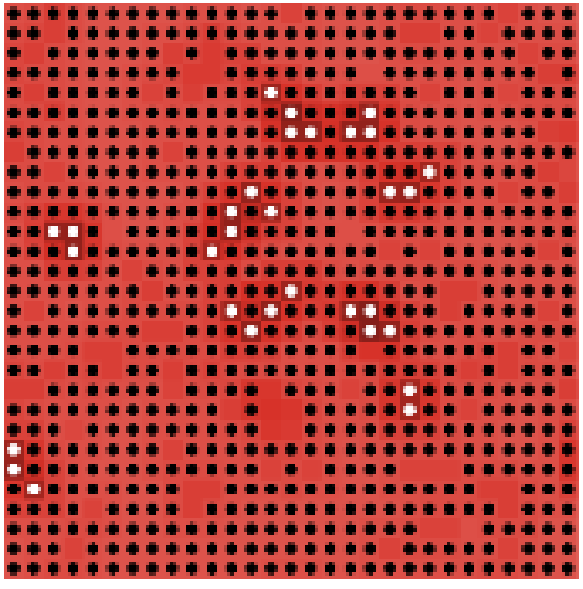
- Bower, J.M. & Bolouri, H. *Computational Modeling of Genetic and Biochemical Networks.* Bradford Book, 2001.
- A.G. Gonzalez, A. Naldi, L. Sanchez, D.Thieffry, C. Chaouiya. *GINsim: a software suite for the qualitative modelling, simulation and analysis of regulatory networks*. Biosystems (2006), 84(2):91-100

Top-down vs. bottom-up view



top-to-bottom modeling
systems view



bottom-to-top modelling
agent-based view

Agent-based modeling

- discrete time and discrete space
- strictly local interactions
- dynamics driven by local rules

Agent-based modeling – history

- 1940-60: studying self-reproduction (von Neumann)
  - found a theoretical machine that copies itself
- 1970: Game of Life (Conway)
  - strong simplification of von Neumann machine
  - preserves theoretical computational power of a Turing machine
- 1983: formalization of **cellular automata and applications in physics**

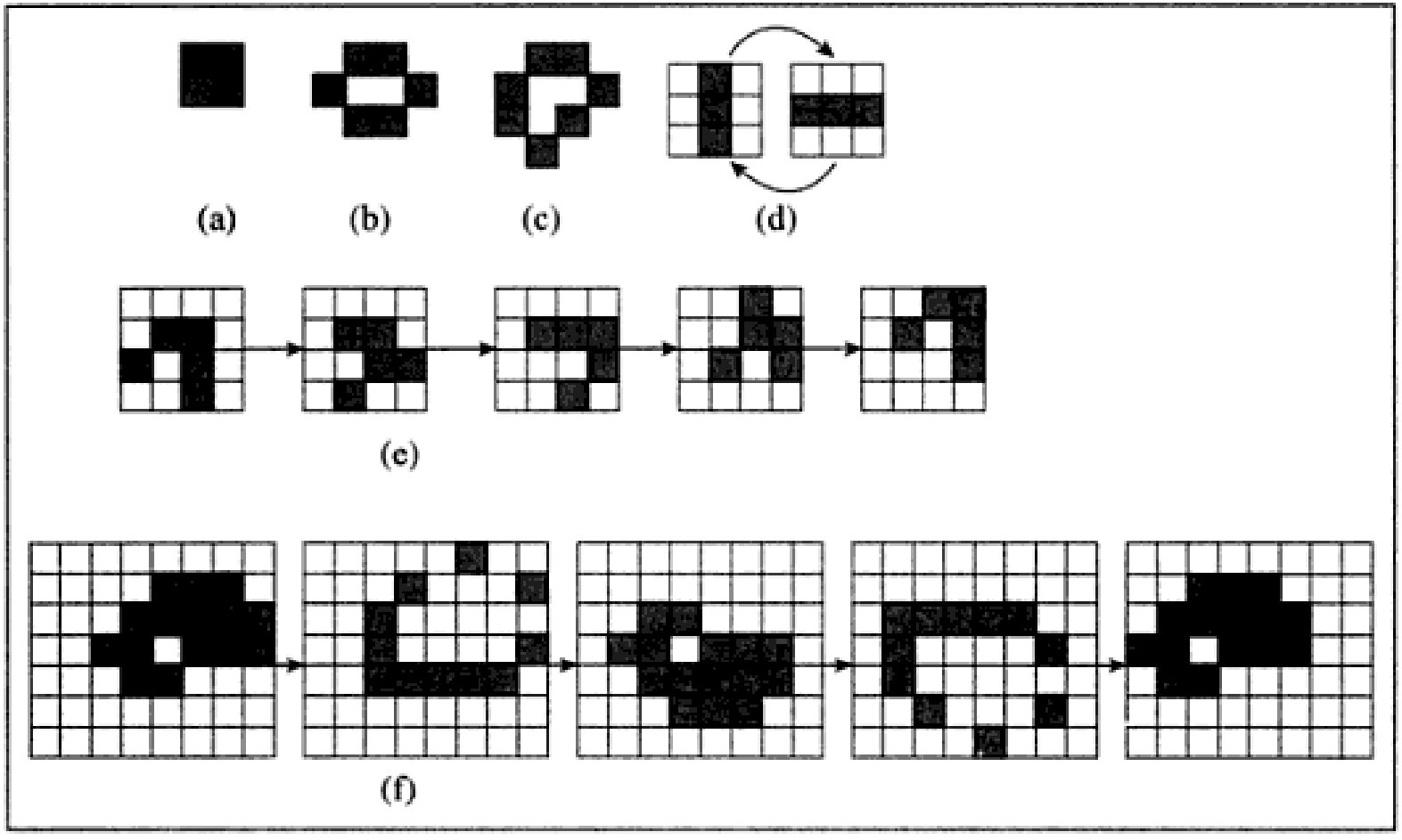
Agent-based modeling – cellular automata

- discrete space (a grid of cells)
- homogenity (all cell identical)
- finite discrete states of a cell
- interaction strictly local – next state of a cell depends on its nearest neighbours
- discrete-time dynamics – system evolves in discrete time-steps

Game of Life

- 2D grid of cells
- each cell has two states: dead or live
- dynamics evolves in turns
- local rules for a living cell:
  - **if** less than two neighbours **then** die from loneliness
  - **if** more than three neighbours **then** die from congestion
  - stay alive, **otherwise**
- local rules for a dead cell:
  - **if** just three neighbours **then** go alive
  - stay dead, **otherwise**

Game of Life



B.P. Zeigler, H. Praehofer, T. Gon Kim. Theory of Modeling and Simulation: Integrating Discrete Event and Continuous Complex Dynamic Systems. Academic Press, 2000.

Game of Life

- problem: is an infinite behaviour possible in the game of life?
- proven true!
- game of life has universal Turing power (a computer with unlimited memory and no time contraints)

Cellular automata – Wolfram's classification

class I dynamics always leads to a stable (non-changing) state

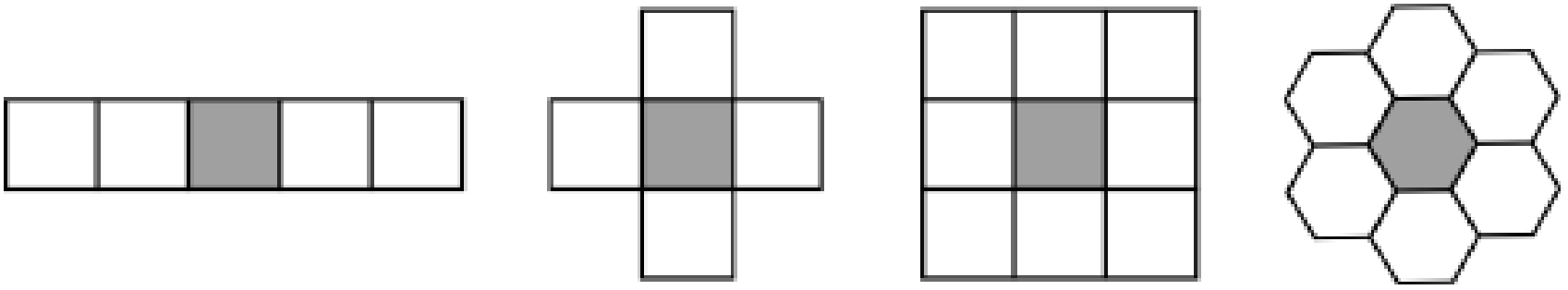
class II dynamics leads to simple repeating (periodical) situations

class III dynamics leads to aperiodic, chaotic behaviour

class IV complex patterns moving in the space

Examples:
`http://www.youtube.com/watch?v=XcuBvj0pw-E`

Cellular automata – definition



- each cell i has a neighbourhood $N(i)$
- finite set of local states $\Sigma = \{0, ..., k-1\}$
- state of cell i in time t is denoted $\sigma_i(t) \in \Sigma$
- local dynamics rule Φ:
  - $\Phi : \Sigma^n \rightarrow \Sigma$
  - $\sigma_i(t+1) = \Phi(\sigma_j(t), j \in N(i))$

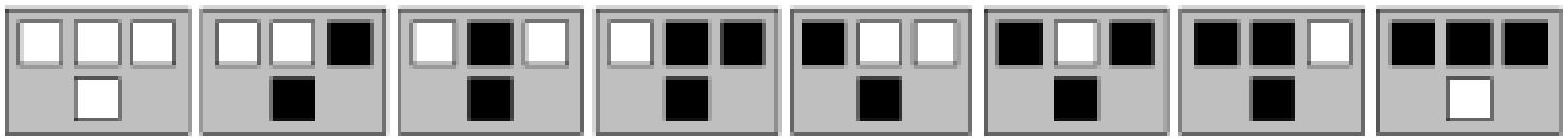
Cellular automata – definition

- semantics is defined by a state transition system (automaton)
- a configuration is determined as the current state of all cells
- state update (discrete transition event) is defined by (synchronous) application of local rule to each cell of the source configuration
- automaton is deterministic
- finite grid implies finite number of configurations

Cellular automata – example

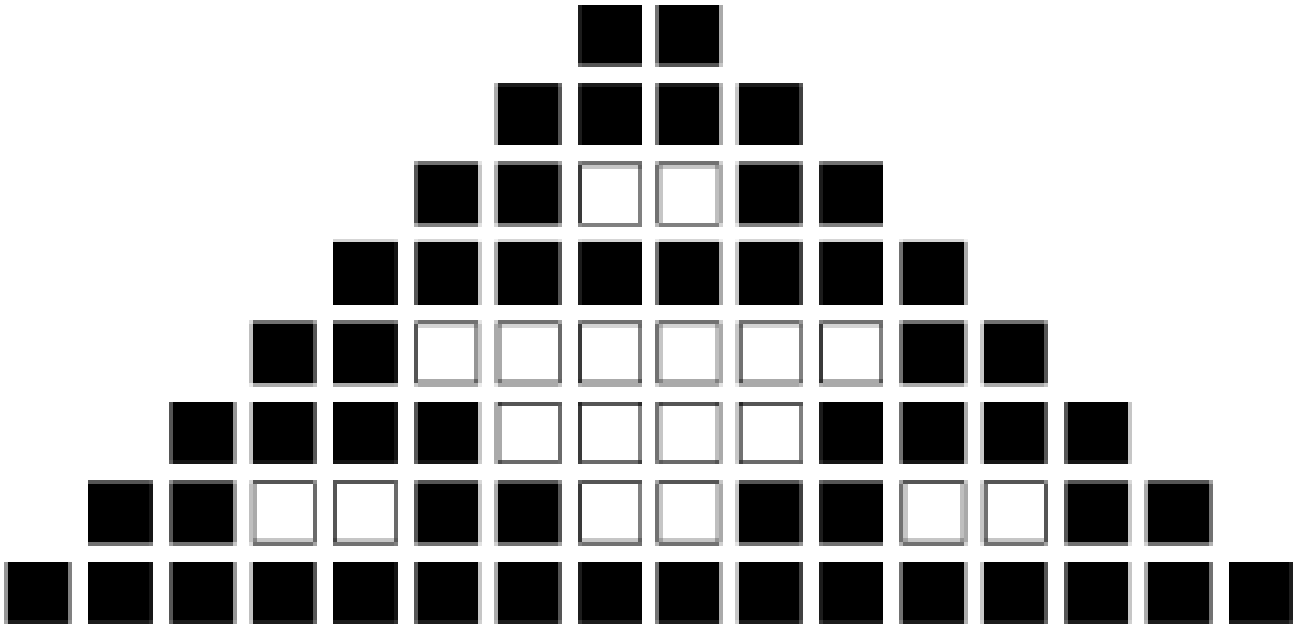
Example of a state update on a 1D grid

$c_{i-1}(t-1)$	$c_i(t-1)$	$c_{i+1}(t-1)$	$c_i(t)$
0	0	0	0
0	0	1	1
0	1	0	1
0	1	1	1
1	0	0	1
1	0	1	1
1	1	0	1
1	1	1	0



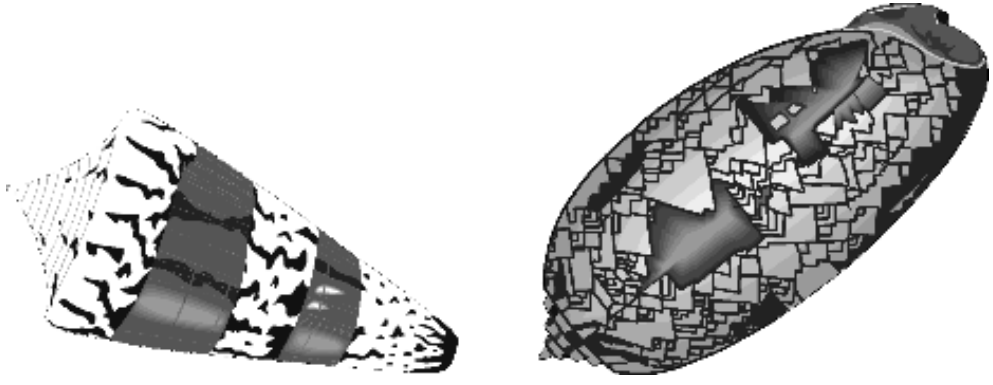
Cellular automata – example

Example of dynamics on a 1D grid



Cellular automata – application in biology

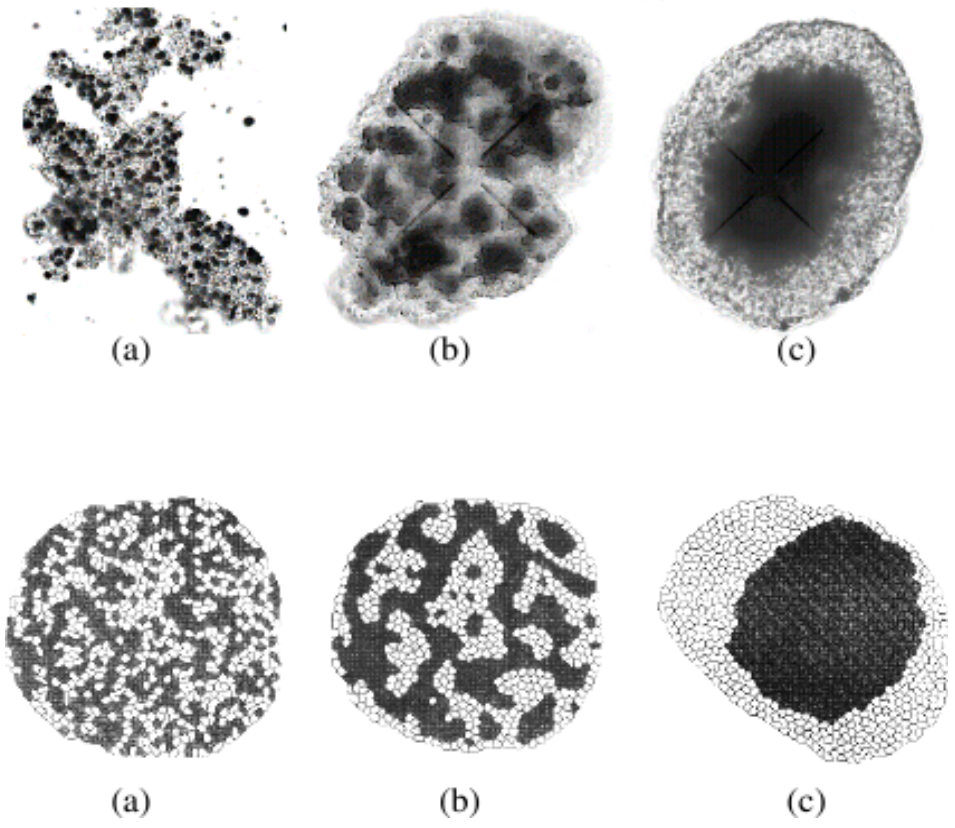
- models in developmental biology
- pattern forming simulation



- modeling and simulation of population models (e.g., sheeps and wolfs)

Cellular automata – example

Retinal Cell Development in Chicken Embryo



- light cells – neural retinal cells
- dark cells – pigmented retinal cells
- dynamics – (a) 10 hours, (b) 40 hours, (c) 72 hours

Free Tool Support

- CelLab – library for cellular automata programming
  `http://www.fourmilab.ch/cellab/`
- NetLogo – multi-agent programmable modeling environment
  - education platform for agent-based modelling
  - large library of models
  - many extensions (continuous and stochastic simulation)
  - `http://ccl.northwestern.edu/netlogo/`

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- M. Alber, M. Kiskowski, J. Glazier & Y. Jiang. *On cellular automaton approaches to modeling biological cells.*, 2002.