Bioinformatics: Network Analysis

Discrete Dynamic Modeling: Boolean and Petri Nets

COMP 572 (BIOS 572 / BIOE 564) - Fall 2013
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Gene Regulatory Networks

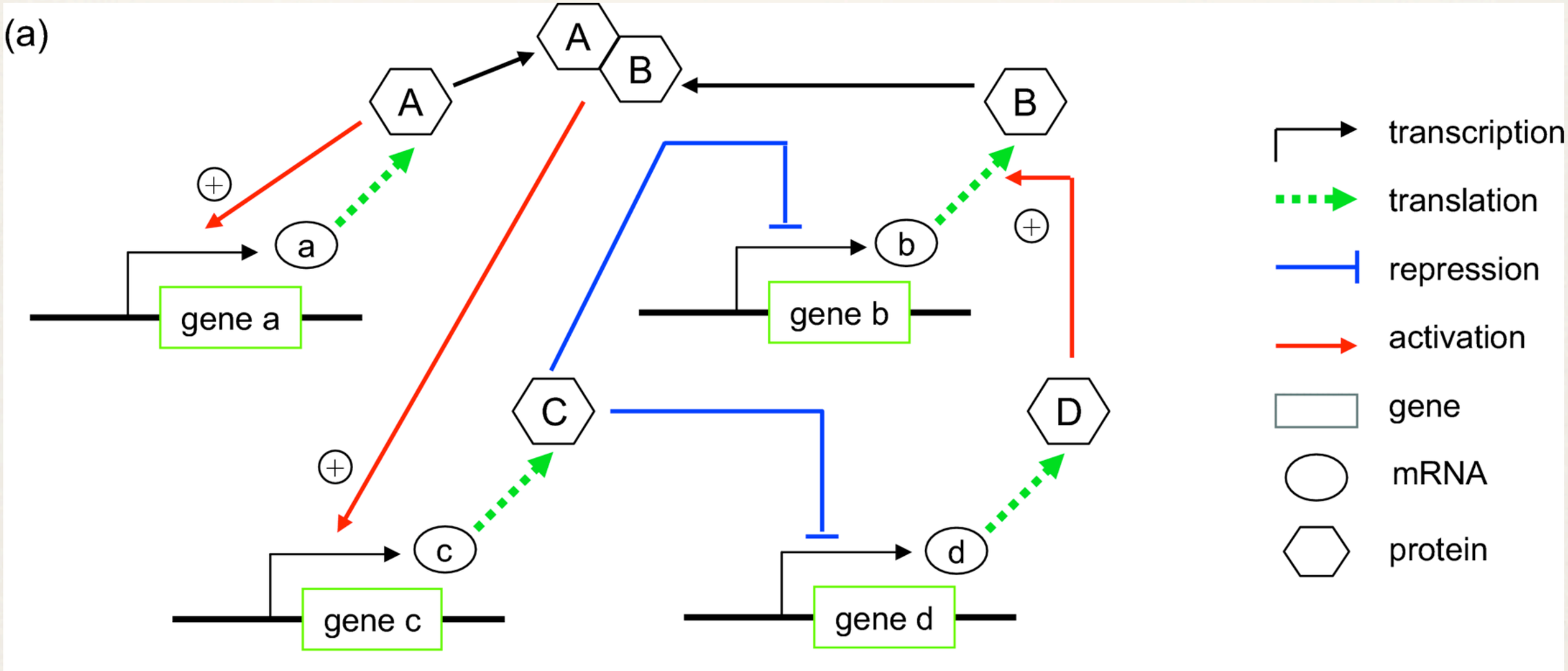
- We'll illustrate some of the graphical models using gene regulatory networks (GRNs).

- *Gene regulatory networks* describe the molecules involved in gene regulation, as well as their interactions.

- *Transcription factors* are stimulated by upstream signaling cascades and bind on *cis-regulatory* positions of their target genes.

- Bound transcription factors *promote* or *inhibit* RNA polymerase assembly and thus determine whether and to what extent the target gene is *expressed*.

Gene Regulatory Networks



Outline

- Graph representation
- Boolean networks
- Petri nets

Graph Representation

- A directed graph G=(V,E) is a tuple where V denotes a set of vertices (or nodes) and E a set of edges.

- An edge (i,j) in E indicates that i regulates the expression of j.

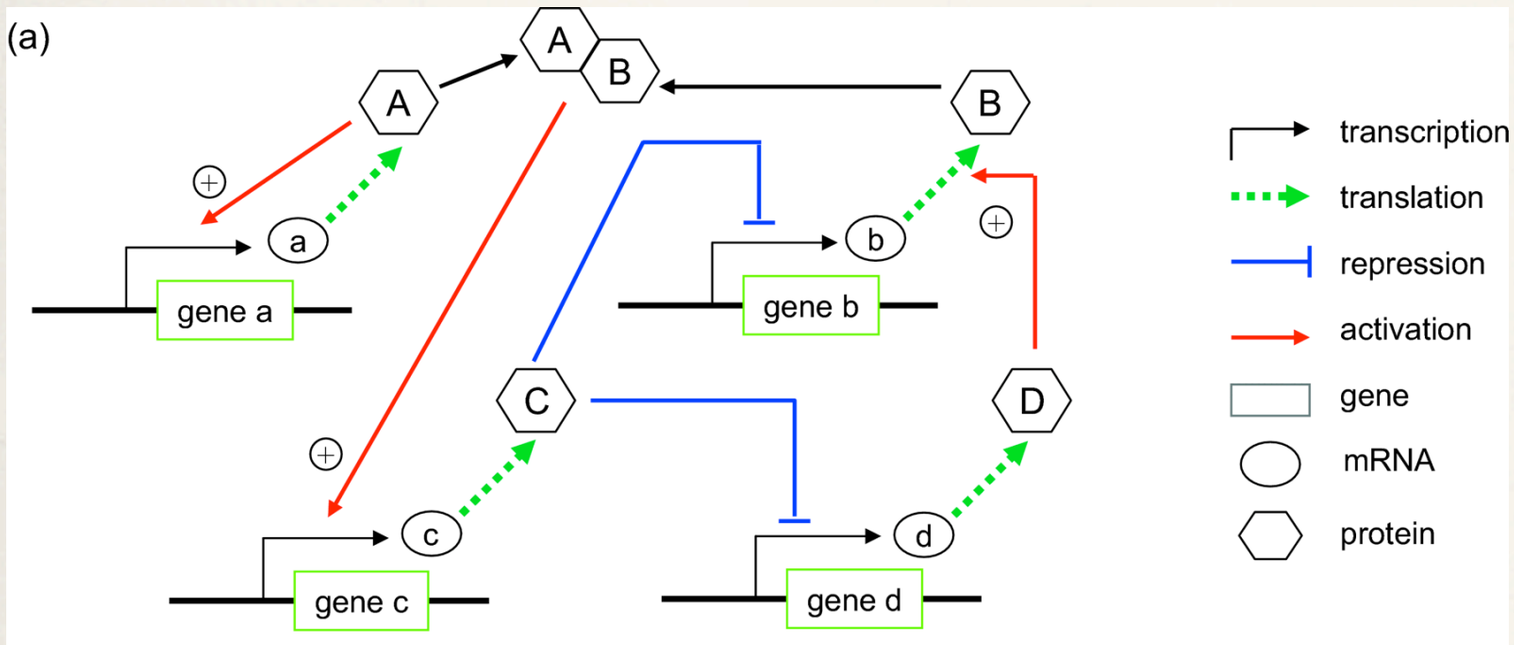
- Edges can have information about interactions. For example, (i,j,+) for “i activates j” and (i,j,-) for “i inhibits j”.

- Annotated directed graphs are the most commonly available type of data for regulatory networks.

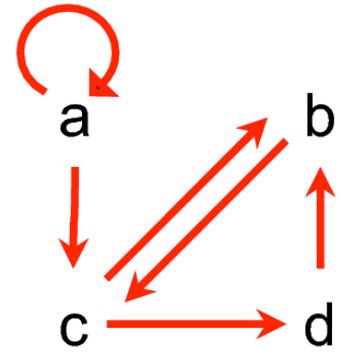
Graph Representation

- Directed graphs do not suffice to describe the dynamics of a network, but they may contain information that allows certain predictions about network properties:
  - Tracing paths between genes yields sequences of regulatory events, shows redundancy in the regulation, or indicates missing regulatory interactions (that are, for example, known from experiments).
  - A cycle may indicate feedback regulation.
  - Comparison of GRNs of different organisms may reveal evolutionary relations and targets for bioengineering and pharmaceutical applications.
  - The network complexity can be measured by the connectivity.

Graph Representation



Directed graphs



$V = \{a,b,c,d\}$

$E = \{(a,a,+),(a,c,+),(b,c,+),$
$(c,b,-),(c,d,-),(d,b,+)\}$

Boolean Networks

Boolean Networks

- Boolean networks are *qualitative* descriptions of gene regulatory interactions

- Gene expression has two states: on (1) and off (0)

- Let x be an n-dimensional binary vector representing the state of a system of n genes

- Thus, the state space of the system consists of 2^n possible states

Boolean Networks

- Each component, x_i, determines the expression of the i^{th} gene

- With each gene i we associate a Boolean rule, b_i

- Given the input variables for gene i at time t, this function determines whether the regulated element is active (1) or inactive (0) at time t+1, i.e.,

$$x_i(t+1) = b_i(x(t)), \quad 1 \leq i \leq n$$

Boolean Networks

- The practical feasibility of Boolean networks is heavily dependent on the number of input variables, k, for each gene
- The number of possible input states of k inputs is 2^k
- For each such combination, a specific Boolean function must determine whether the next state would be on or off
- Thus, there are 2^{2k} possible Boolean functions (or rules)
- This number rapidly increases with the connectivity

Boolean Networks

- In a Boolean network each state has a deterministic output state
- A series of states is called a *trajectory*
- If no difference occurs between the transitions of two states, i.e., output state equals input state, then the system is in a *point attractor*
- Point attractors are analogous to *steady states*
- If the system is in a cycle of states, then we have a *dynamic attractor*

Boolean Networks

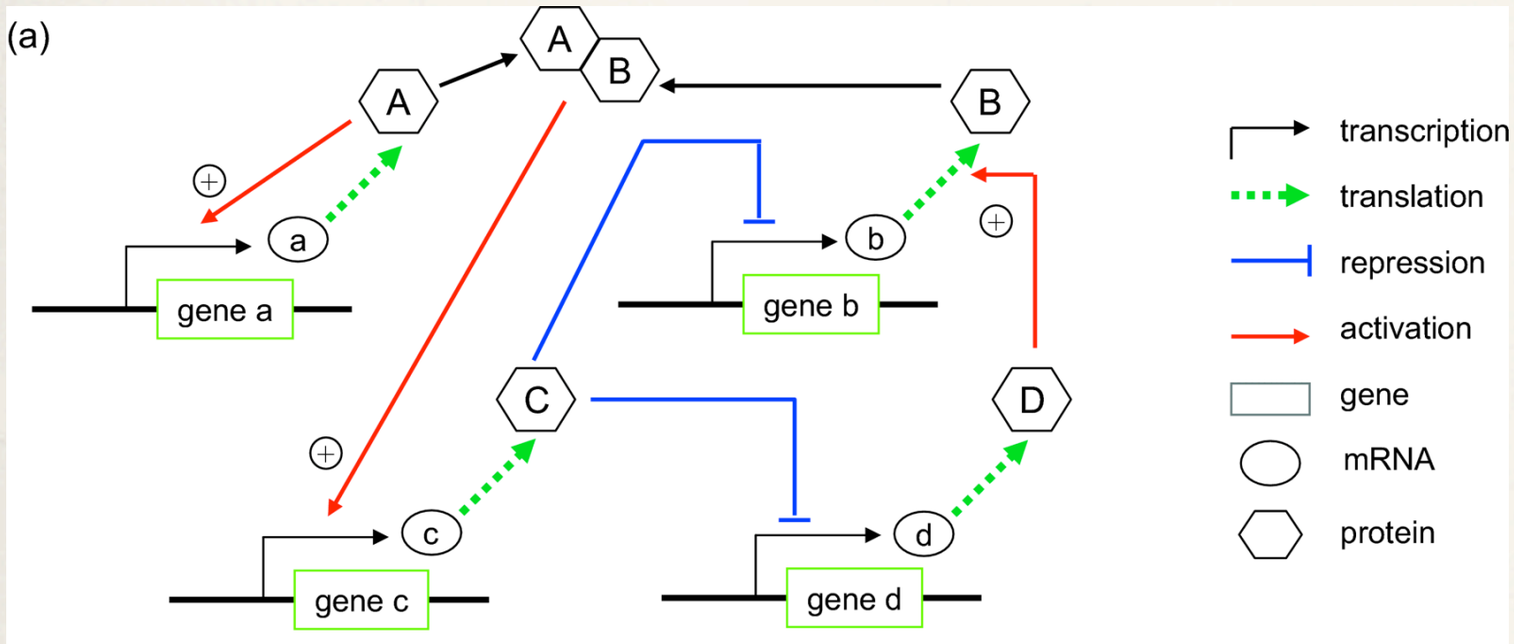
- Since the number of states in the state space is finite, the number of possible transitions is also finite.

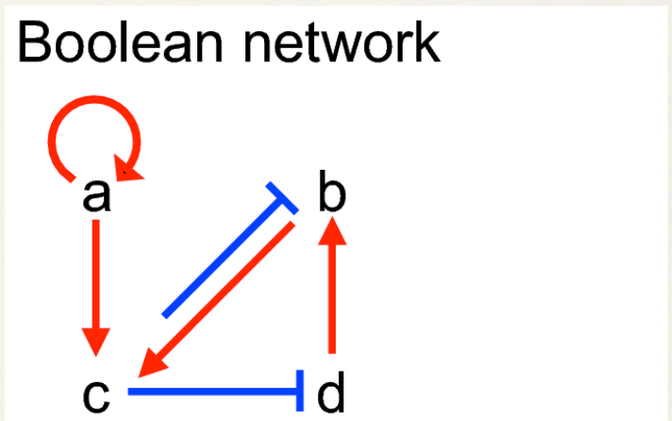
- Therefore, each trajectory will lead either to a steady state or to a state cycle. These state sequences are called *attractors*.

- *Transient states* are those states that do not belong to an attractor.

- All states that lead to the same attractor constitute its *basin of attraction*.

Boolean Networks





$a(t+1) = a(t)$

$b(t+1) = (\text{not } c(t)) \text{ and } d(t)$

$c(t+1) = a(t) \text{ and } b(t)$

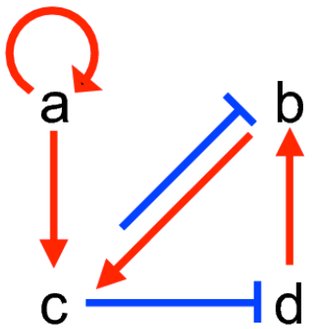
$d(t+1) = \text{not } c(t)$

Boolean Networks

- The temporal behavior is determined by the sequence of states (a,b,c,d) given in an initial state.

- What happens if the initial state of a is 0? If the initial state of a is 1?

Boolean network



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$c(t+1) = a(t) \text{ and } b(t)$

$d(t+1) = \text{not } c(t)$

Boolean Networks

a

b

A' = B

B' = A or C

C' = (A and B) or (B and C) or (A and C)

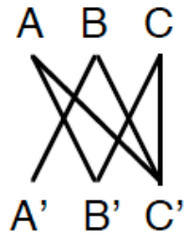
c

input			output		
A	B	C	A'	B'	C'
0	0	0	0	0	0
0	0	1	0	1	0
0	1	0	1	0	0
0	1	1	1	1	1
1	0	0	0	1	0
1	0	1	0	1	1
1	1	0	1	1	1
1	1	1	1	1	1

Fig. 1 A simple Boolean network. a) Wiring diagram. b) Logical (Boolean) rules. c) Complete state transition table defining network. The input column corresponds to the state at time=t, the output column (elements marked by prime) corresponds to the state at time=t+1.

Boolean Networks: The REVEAL Algorithm

a



b

A' = B
B' = A or C
C' = (A and B) or (B and C) or (A and C)

c

input			output		
A	B	C	A'	B'	C'
0	0	0	0	0	0
0	0	1	0	1	0
0	1	0	1	0	0
0	1	1	1	1	1
1	0	0	0	1	0
1	0	1	0	1	1
1	1	0	1	1	1
1	1	1	1	1	1

Fig. 1 A simple Boolean network. a) Wiring diagram. b) Logical (Boolean) rules. c) Complete state transition table defining network. The input column corresponds to the state at time=t, the output column (elements marked by prime) corresponds to the state at time=t+1.

"REVEAL, A general reverse engineering algorithm for inference of genetic network architectures"
Liang et al., PSB 1998

Input entropies

H(A)	1.00
H(B)	1.00
H(C)	1.00
H(A,B)	2.00
H(B,C)	2.00
H(A,C)	2.00
H(A,B,C)	3.00

$$H(X) = -\sum p(x) \log p(x)$$
$$H(X,Y) = -\sum p(x,y) \log p(x,y)$$
$$M(X,Y) = H(X) + H(Y) - H(X,Y)$$
$$M(X,[Y,Z]) = H(X) + H(Y,Z) - H(X,Y,Z)$$

Determination of inputs for element A ①

H(A')	1.00			
H(A',A)	2.00	M(A',A)	0.00	M(A',A) / H(A') 0.00
H(A',B)	1.00	M(A',B)	1.00	**M(A',B) / H(A') 1.00**
H(A',C)	2.00	M(A',C)	0.00	M(A',C) / H(A') 0.00

② **Rule table for A**
rule no. 2

input	output
B	A'
0	0
1	1

Determination of inputs for element B ③

H(B')	0.81			
H(B',A)	1.50	M(B',A)	0.31	M(B',A) / H(B') 0.38
H(B',B)	1.81	M(B',B)	0.00	M(B',B) / H(B') 0.00
H(B',C)	1.50	M(B',C)	0.31	M(B',C) / H(B') 0.38
H(B',[A,B])	2.50	M(B',[A,B])	0.31	M(B',[A,B]) / H(B') 0.38
H(B',[B,C])	2.50	M(B',[B,C])	0.31	M(B',[B,C]) / H(B') 0.38
H(B',[A,C])	2.00	M(B',[A,C])	0.81	**M(B',[A,C]) / H(B') 1.00**

④ **Rule table for B**
rule no. 14

input		output
A	C	B'
0	0	0
0	1	1
1	0	1
1	1	1

Determination of inputs for element C ⑤

H(C')	1.00			
H(C',A)	1.81	M(C',A)	0.19	M(C',A) / H(C') 0.19
H(C',B)	1.81	M(C',B)	0.19	M(C',B) / H(C') 0.19
H(C',C)	1.81	M(C',C)	0.19	M(C',C) / H(C') 0.19
H(C',[A,B])	2.50	M(C',[A,B])	0.50	M(C',[A,B]) / H(C') 0.50
H(C',[B,C])	2.50	M(C',[B,C])	0.50	M(C',[B,C]) / H(C') 0.50
H(C',[A,C])	2.50	M(C',[A,C])	0.50	M(C',[A,C]) / H(C') 0.50
H(C',[A,B,C])	3.00	M(C',[A,B,C])	1.00	**M(C',[A,B,C]) / H(C') 1.00**

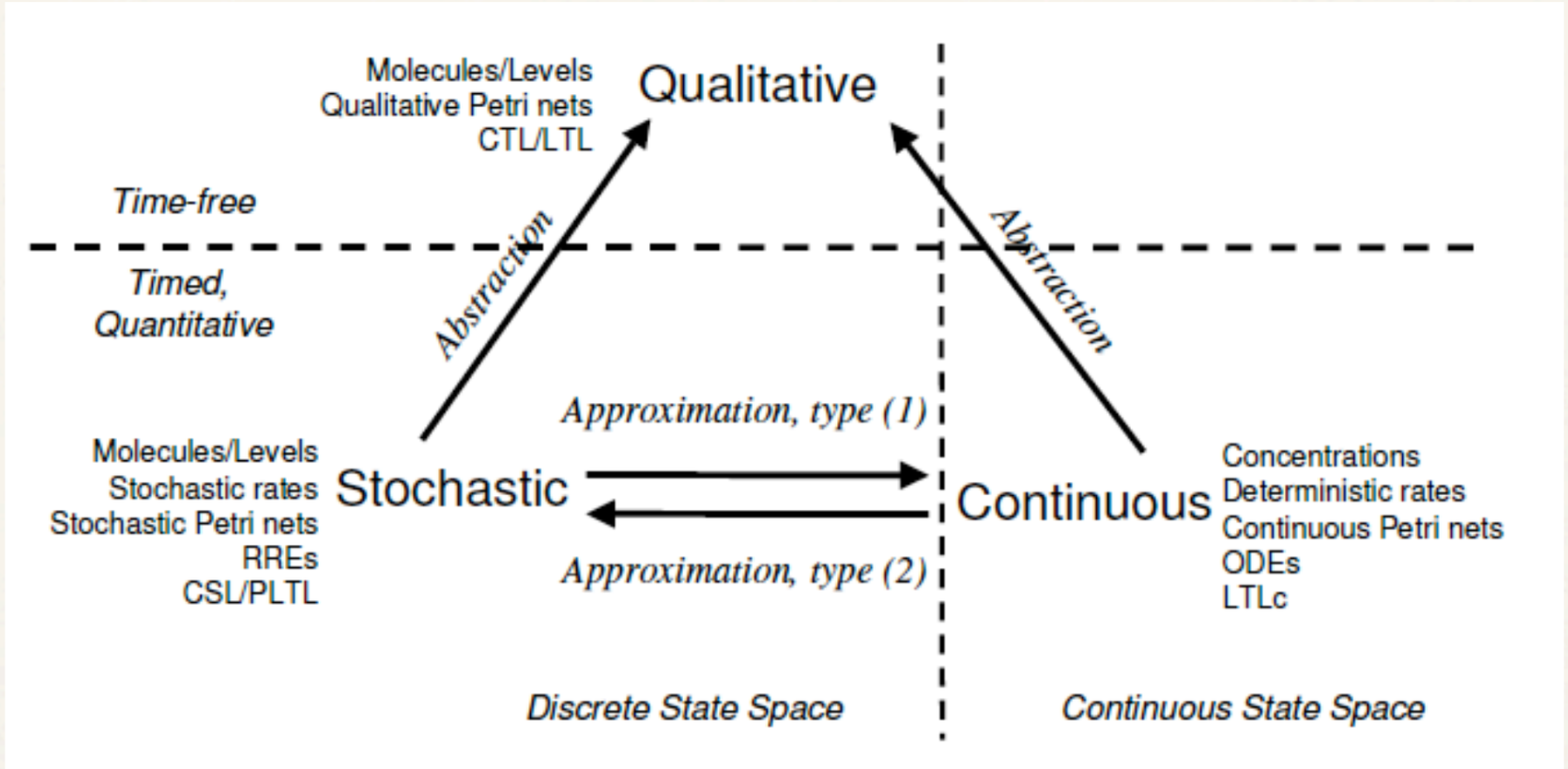
⑥ **Rule table for C**
rule no. 170

input			output
A	B	C	C'
0	0	0	0
0	0	1	0
0	1	0	0
0	1	1	1
1	0	0	0
1	0	1	1
1	1	0	1
1	1	1	1

Fig. 5 Outline of progressive M-analysis underlying REVEAL for network example shown in Fig. 1. Hs and Ms are calculated from the look-up tables according to the definitions (shaded). The network wiring is extracted by M-analysis (left, odd steps). Rule tables are then determined directly from the trajectory (right, even steps).

Petri Nets

Three Major Ways of Modeling



- Biochemical reaction systems are inherently (1) bipartite, (2) concurrent, and (3) stochastic

- *Stochastic Petri nets* have all these three characteristics

- Analyzing stochastic Petri nets is very hard

- Two abstractions are used: qualitative models (removing time dependencies) and continuous models (approximating stochasticity by determinism)

Outline

- The qualitative approach: Petri nets
- The stochastic approach: Stochastic Petri nets
- The continuous approach: Continuous Petri nets

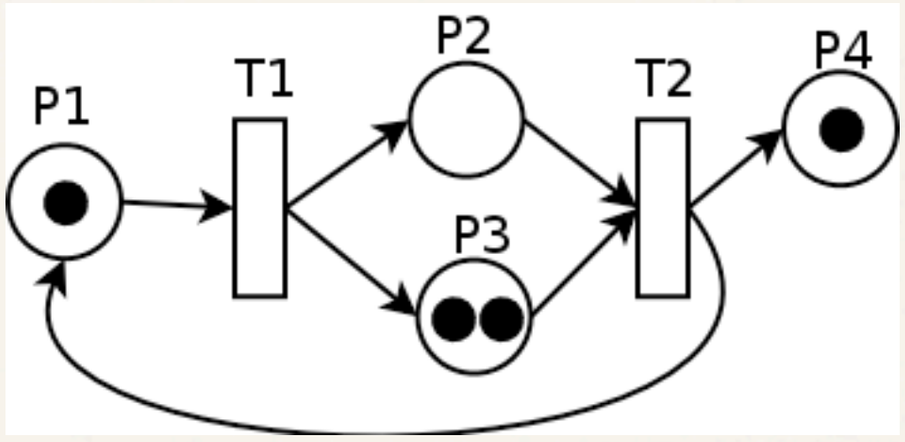
The Qualitative Approach

Petri Nets

Definition 1 (Petri net, Syntax). *A* Petri net *is a quadruple* $\mathcal{N} = (P, T, f, m_0)$, *where*

- P *and* T *are finite, non empty, and disjoint sets.* P *is the set of* places *(in the figures represented by circles).* T *is the set of* transitions *(in the figures represented by rectangles).*
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{N}_0$ *defines the set of directed* arcs, *weighted by nonnegative integer values.*
- $m_0 : P \to \mathbb{N}_0$ *gives the* initial marking.

Petri Nets



Petri Nets

- *Places* model passive system components, such as conditions, species, or chemical compounds

- *Transitions* model active system components, such as atomic actions, or any kind of chemical reactions (phosphorylation, dephospohorylation, etc.)

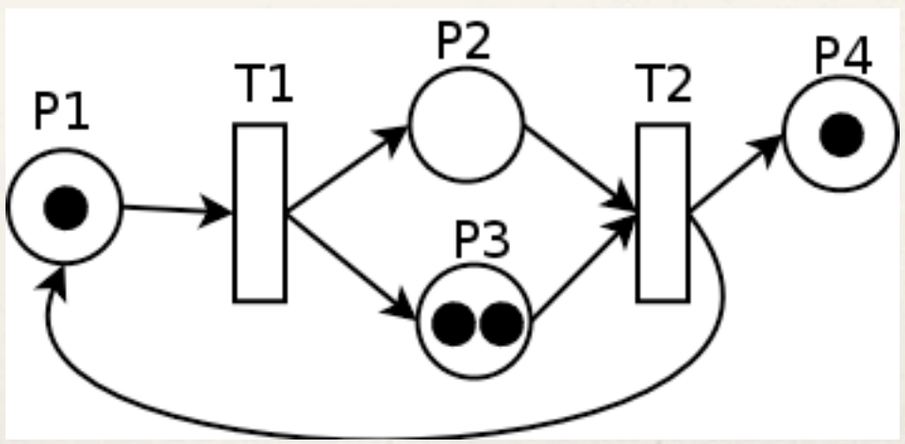
Petri Nets

- In the most abstract way, a concentration can be thought of as being ‘high’ or ‘low’ (‘present’ or ‘absent’)

- This boolean approach can be generalized to any continuous concentration range by dividing the range into a finite number of equally sized sub-ranges (equivalence classes), so that the concentrations within each sub-range can be considered equivalent

Petri Nets

- A particular arrangement of tokens over the places of the net is called a *marking*, modeling a system state



Petri Net Notations

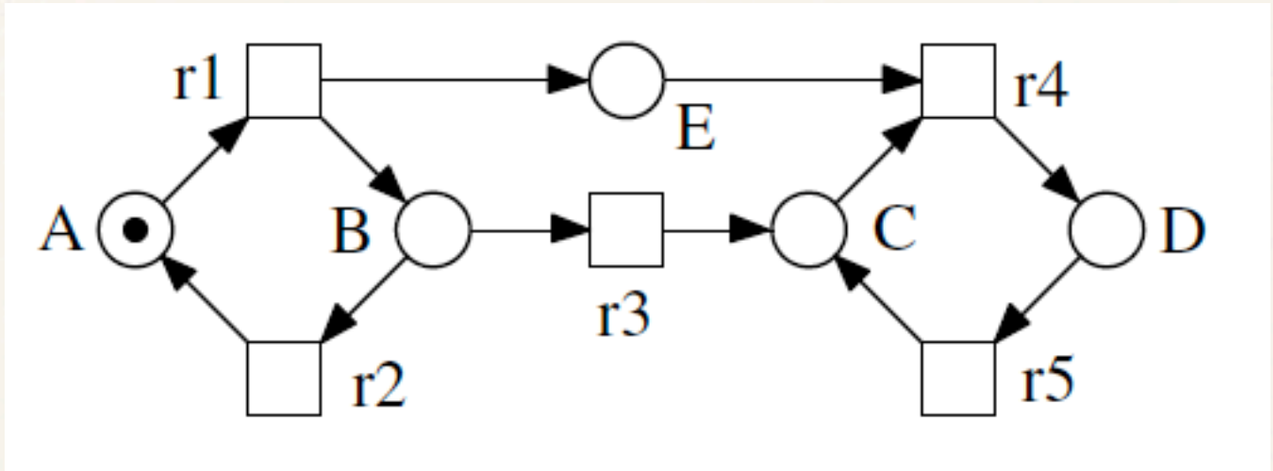
- m(p) is the number of tokens on place p in the marking m
- A place p with m(p)=0 is called *clean* in m; otherwise, it is called *marked*

Petri Net Notations

- $\bullet t$, the preplaces of a transition t, consisting of the reaction's precursors,
- $t\bullet$, the postplaces of a transition t, consisting of the reaction's products,
- $\bullet p$, the pretransitions of a place p, consisting of all reactions producing this species,
- $p\bullet$, the posttransitions of a place p, consisting of all reactions consuming this species.

We extend both notions to a set of nodes $X \subseteq P \cup T$ and define the set of all prenodes $\bullet X := \bigcup_{x \in X} \bullet x$, and the set of all postnodes $X\bullet := \bigcup_{x \in X} x\bullet$.

Petri Net Notations



pretransitions: $\bullet\{\mathrm{A},\mathrm{B}\} = \{\mathrm{r1},\mathrm{r2}\}$ posttransitions: $\{\mathrm{C},\mathrm{D},\mathrm{E}\}\bullet = \{\mathrm{r4},\mathrm{r5}\}$

posttransitions: $\{A,B\}\bullet = \{\mathrm{r1},\mathrm{r2},\mathrm{r3}\}$ pretransitions: $\bullet\{\mathrm{C},\mathrm{D},\mathrm{E}\} = \{\mathrm{r1},\mathrm{r3},\mathrm{r4},\mathrm{r5}\}$

Petri Net Semantics

Definition 2 (Firing rule). *Let $\mathcal{N} = (P, T, f, m_0)$ be a Petri net.*

- *A transition t is* enabled *in a marking m, written as $m[t\rangle$, if $\forall p \in {}^\bullet t : m(p) \geq f(p,t)$, else* disabled.
- *A transition t, which is enabled in m, may fire.*
- *When t in m* fires, *a new marking m' is reached, written as $m[t\rangle m'$, with $\forall p \in P : m'(p) = m(p) - f(p,t) + f(t,p)$.*
- *The firing happens atomically and does not consume any time.*

Petri Net Semantics

- The repeated firing of transitions establishes the behavior of the Petri net

Petri Net Semantics

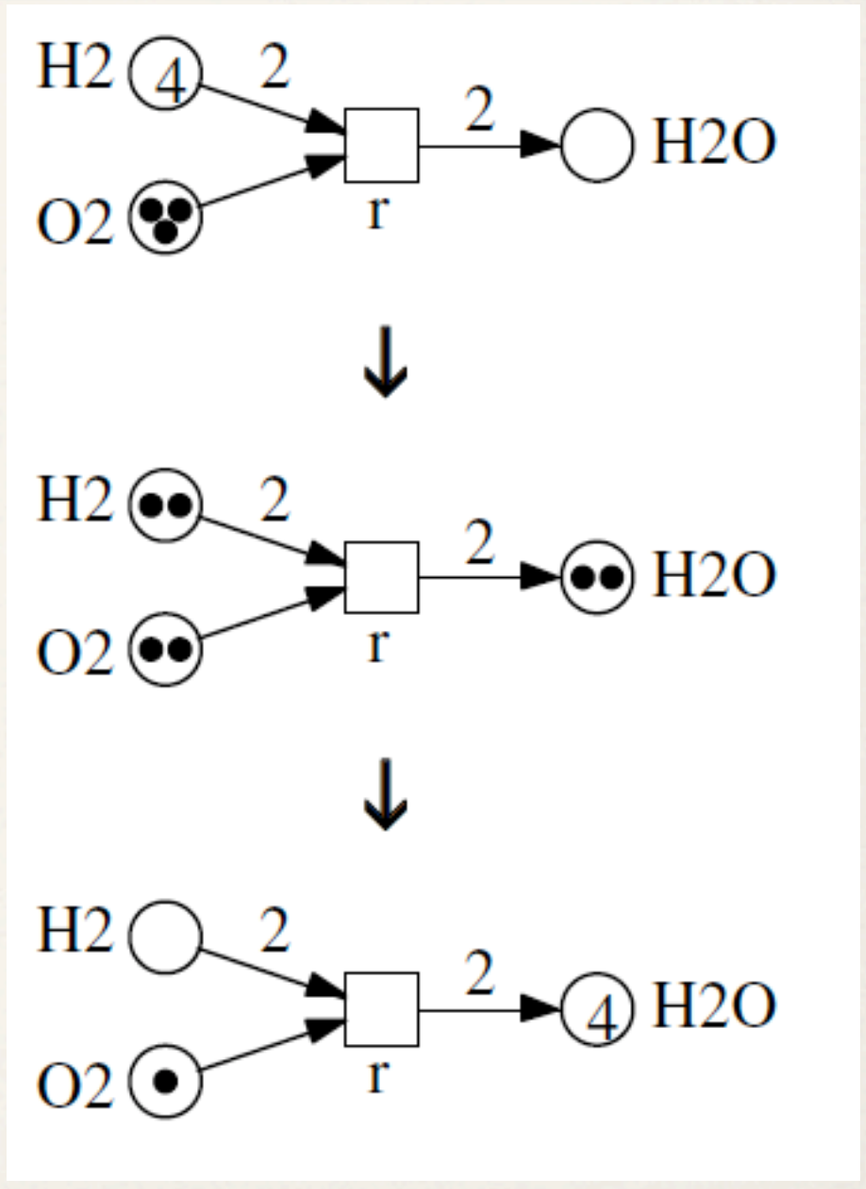
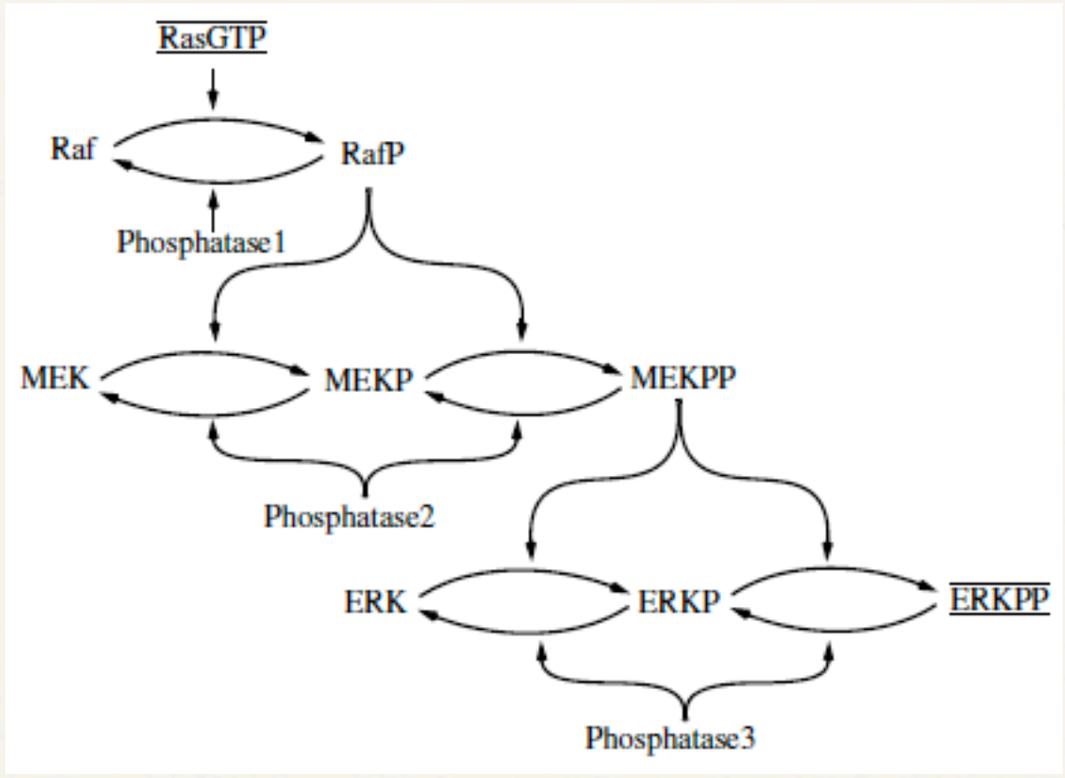


Fig. 4. The Petri net for the well known chemical reaction r: $2H_2 + O_2 \rightarrow 2H_2O$ and three of its markings (states), connected each by a firing of the transition r. The transition is not enabled anymore in the marking reached after these two single firing steps.

Petri Nets: Reachability and State Space

Every marking is defined by the given token situation in all places $m \in \mathbb{N}_0^{|P|}$, whereby $|P|$ denotes the number of places in the Petri net. All markings, which can be reached from a given marking m by any firing sequence of arbitrary length, constitute the *set of reachable markings* $[m\rangle$. The set of markings $[m_0\rangle$ reachable from the initial marking is said to be the *state space* of a given system.

Modeling of a MAPK Signaling Pathway Using a Petri Net



Basic Building Blocks

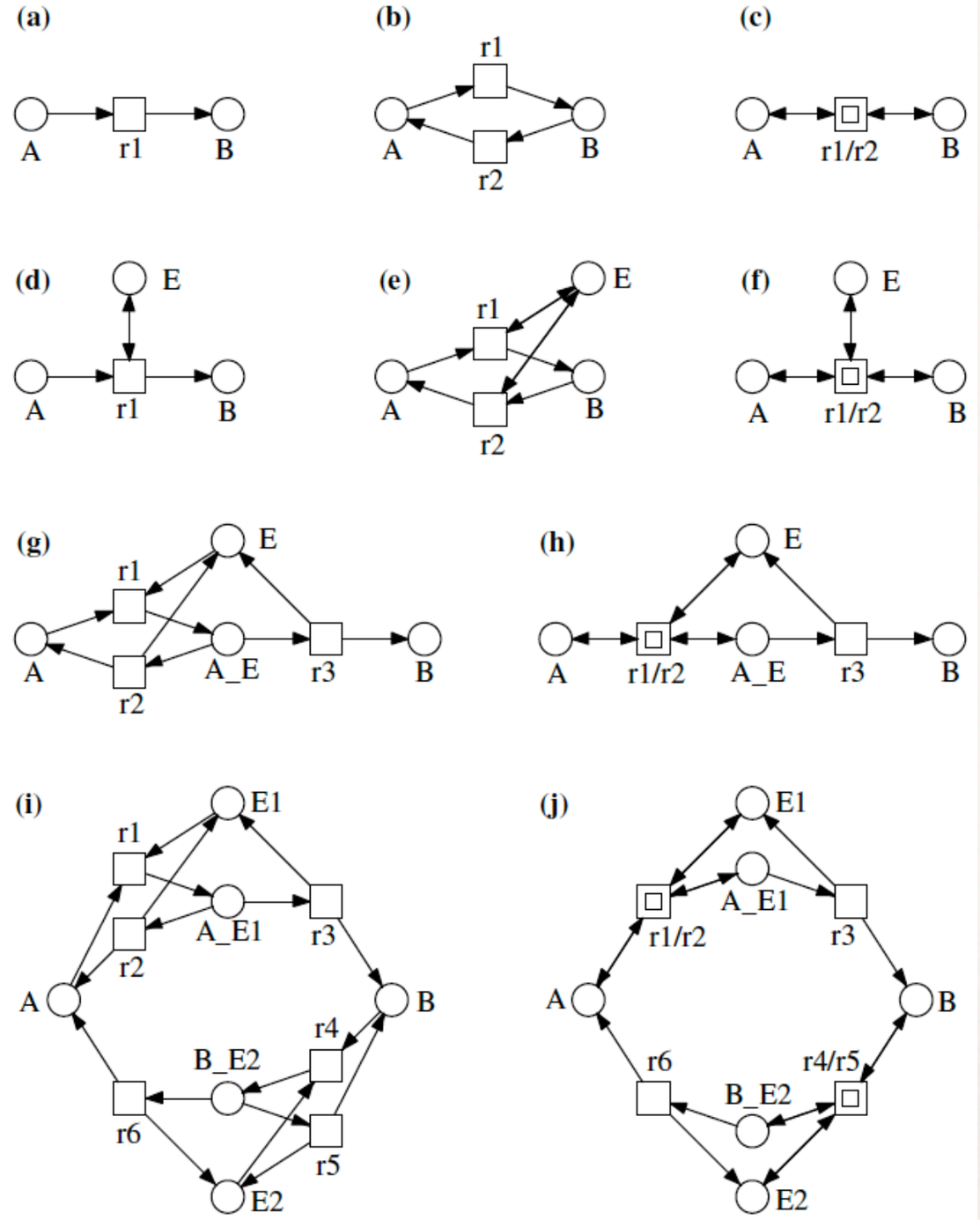
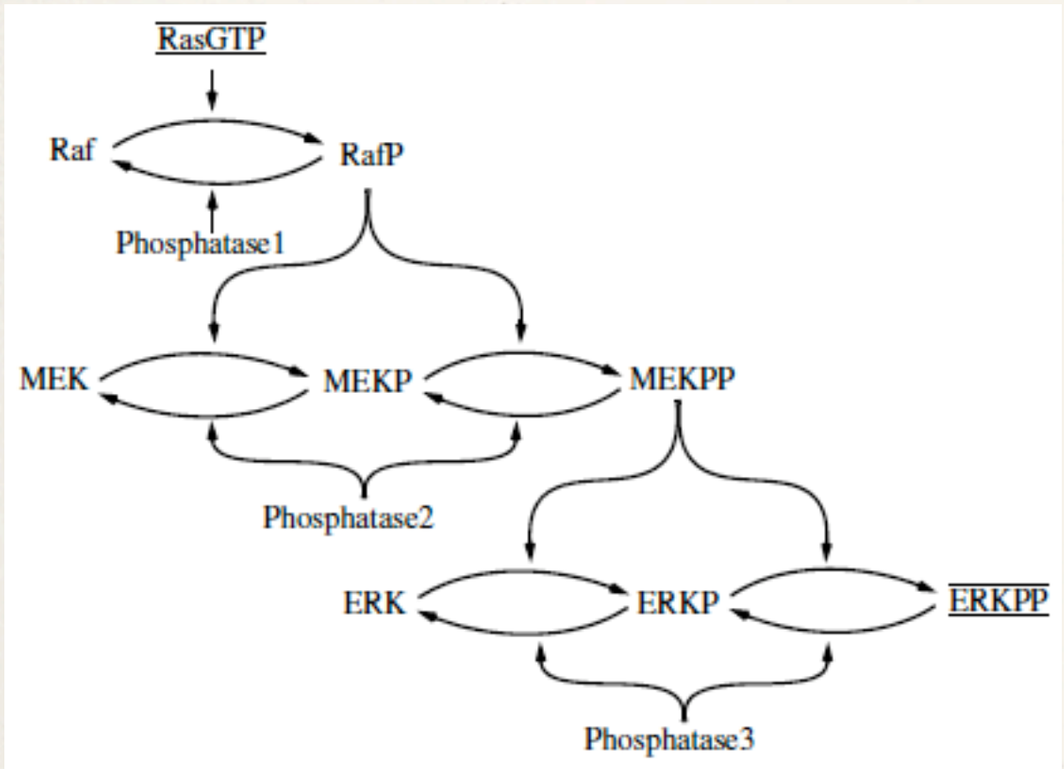
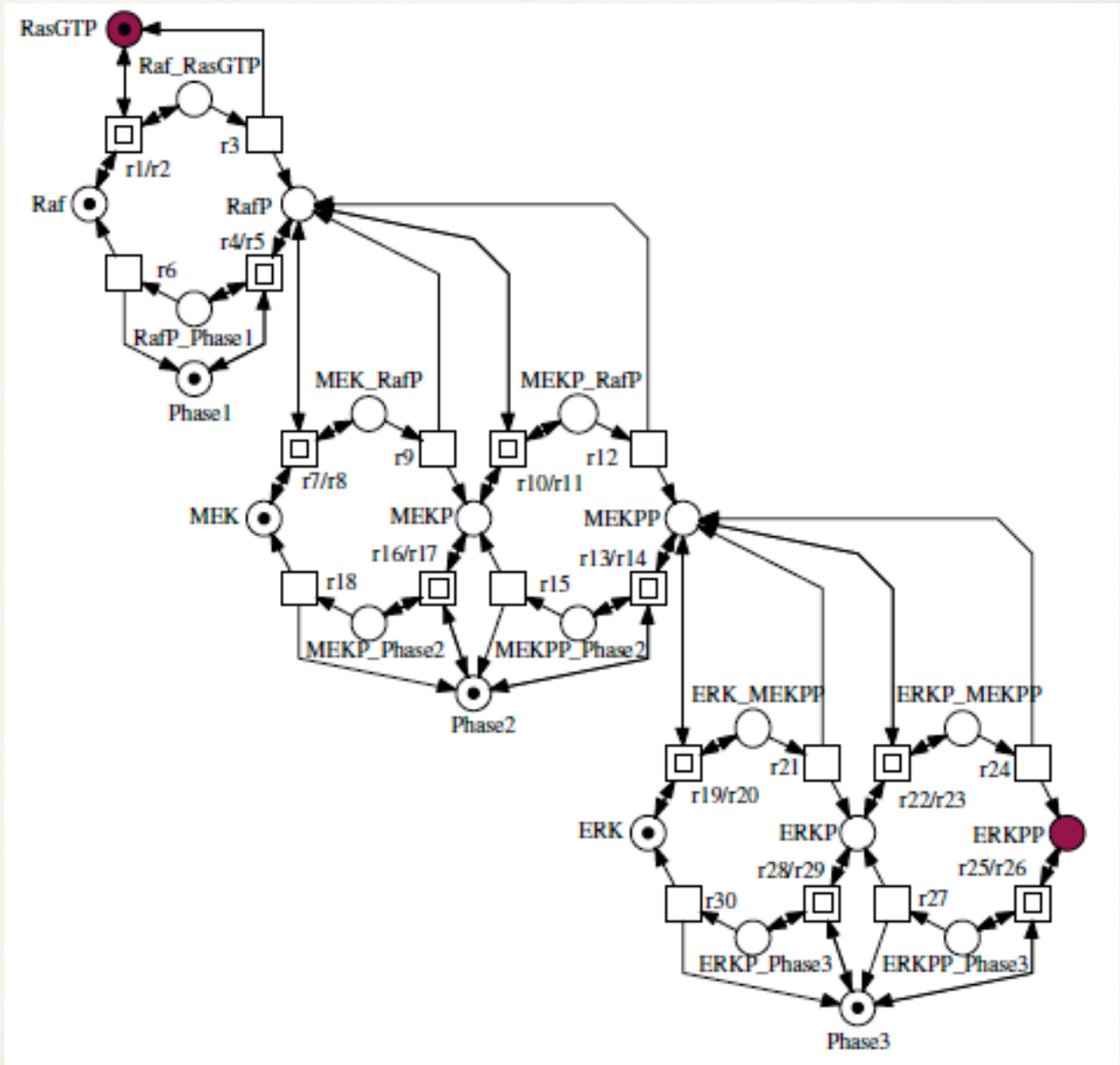


Fig. 5. The Petri net components for some typical basic structures of biochemical reaction networks. **(a)** simple reaction $A \rightarrow B$; **(b)** reversible reaction $A \rightleftharpoons B$; **(c)** hierarchical notation of (b); **(d)** simple enzymatic reaction, Michaelis-Menten kinetics; **(e)** reversible enzymatic reaction, Michaelis-Menten kinetics; **(f)** hierarchical notation of (e); **(g)** enzymatic reaction, mass action kinetics, $A + E \rightleftharpoons A\_E \rightarrow B + E$; **(h)** hierarchical notation of (g); **(i)** two enzymatic reactions, mass action kinetics, building a cycle; **(j)** hierarchical notation of (i). Two concentric squares are macro transitions, allowing the design of hierarchical net models. They are used here as shortcuts for reversible reactions. Two opposite arcs denote read arcs, see (d) and (e), establishing side conditions for a transition's firing.

Modeling of a MAPK Signaling Pathway Using a Petri Net





Analyzing Properties of Petri Nets

- Beside simulating a Petri net, by observing the flow of tokens, formal analyses of Petri net properties help reveal properties of the underlying biochemical system that is being modeled

- Analyses include
  - General behavioral properties
  - Structural properties
  - Static decision of marking-independent behavioral properties
  - Initial marking construction
  - Static decision of marking-dependent behavioral properties
  - Dynamic decision of behavioral properties

1. General Behavioral Properties

- *boundedness* For every place it holds that: Whatever happens, the maximal number of tokens on this place is bounded by a constant. This precludes overflow by unlimited increase of tokens.
- *liveness* For every transition it holds that: Whatever happens, it will always be possible to reach a state where this transition gets enabled. In a live net, all transitions are able to contribute to the net behaviour forever, which precludes dead states, i.e. states where none of the transitions are enabled.
- *reversibility* For every state it holds that: Whatever happens, the net will always be able to reach this state again. So the net has the capability of self-reinitialization.

1. General Behavioral Properties

Finally we introduce the general behavioural property *dynamic conflict*, which refers to a marking enabling two transitions, but the firing of one transition disables the other one. The occurrence of dynamic conflicts causes alternative (branching) system behaviour, whereby the decision between these alternatives is taken nondeterministically. See Figure 7 for an illustration of these behavioural properties.

1. General Behavioral Properties

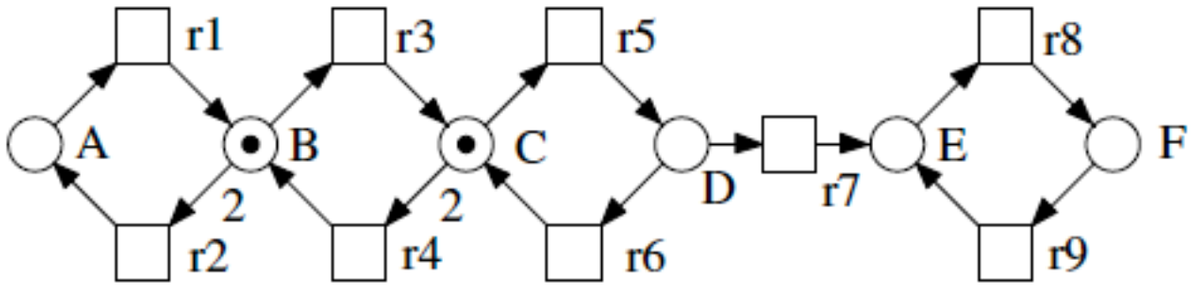


Fig. 7. A net to illustrate the general behavioural properties. The place A is 0-bounded, place B is 1-bounded and all other places are 2-bounded, so the net is 2-bounded. The transitions r1 and r2 in the leftmost cycle are dead at the initial marking. The transitions r8 and r9 in the rightmost cycle are live. All other transitions are not live; so the net is weakly live. The net is not reversible, because there is no counteraction to the token decrease by firing of r4. There are dynamic conflicts, e.g. between r4 and r5 in a marking with m(C)=2.

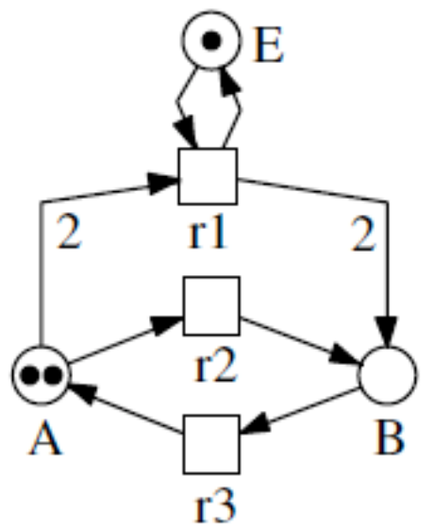
3. Static Decision of Marking-independent Behavioral Properties

The *incidence matrix* of a Petri net is an integer matrix $\mathbb{C}$ with a row for each place and a column for each transition. A matrix entry $\mathbb{C}(p,t)$ gives the token change on place p by the firing of transition t. Thus, a preplace of t, which is not a postplace of t, has a negative entry, while a postplace of t, which is not a preplace of t, has a positive entry, each corresponding to the arc multiplicities. The entry for a place, which is preplace as well as postplace of a transition, gives the difference of the multiplicities of the transition's outgoing arc minus the transition's ingoing arc. In this case we lose information; the non-ordinary net structure cannot be reconstructed uniquely out of the incidence matrix.

r1: $2\ \mathrm{A} \xrightarrow{E} 2\ \mathrm{B}$

r2/3: $\mathrm{A} \rightleftharpoons \mathrm{B}$

	r1	r2	r3
A	−2	−1	1
B	2	1	−1
E	0	0	0



3. Static Decision of Marking-independent Behavioral Properties

A *P-invariant* x is a nonzero and nonnegative integer place vector such that $x \cdot \mathbb{C} = 0$; in words, for each transition it holds that: multiplying the P-invariant with the transition's column vector yields zero. Thus, the total effect of each transition on the P-invariant is zero, which explains its interpretation as a token conservation component. A P-invariant stands for a set of places over which the weighted sum of tokens is constant and independent of any firing, i.e. for any markings m_1, m_2, which are reachable by the firing of transitions, it holds that $x \cdot m_1 = x \cdot m_2$. In the context of metabolic networks, P-invariants reflect substrate conservations, while in signal transduction networks P-invariants often correspond to the several states of a given species (protein or protein complex). A place belonging to a P-invariant is obviously bounded.

3. Static Decision of Marking-independent Behavioral Properties

Analogously, a *T-invariant* y is a nonzero and nonnegative integer transition vector such that $\mathbb{C} \cdot y = 0$; in words, for each place it holds that: multiplying the place's row with the T-invariant yields zero. Thus, the total effect of the T-invariant on a marking is zero. A T-invariant has two interpretations in the given biochemical context.

- The entries of a T-invariant specify a multiset of transitions which by their partially ordered firing reproduce a given marking, i.e. basically occurring one after the other. This partial order sequence of the T-invariant's transitions may contribute to a deeper understanding of the net behaviour. A T-invariant is called *feasible* if such a behaviour is actually possible in the given marking situation.
- The entries of a T-invariant may also be read as the relative firing rates of transitions, all of them occurring permanently and concurrently. This activity level corresponds to the steady state behaviour.

3. Static Decision of Marking-independent Behavioral Properties

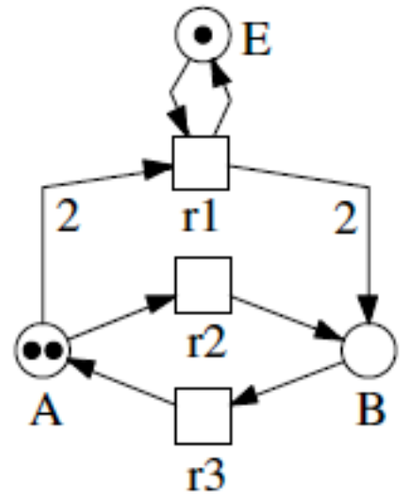
Definition 8 (P-invariants, T-invariants).

- *The* incidence matrix *of* $\mathcal{N}$ *is a matrix* $\mathbb{C} : P \times T \to \mathbb{Z}$, *indexed by* P *and* T, *such that* $\mathbb{C}(p,t) = f(t,p) - f(p,t)$.
- *A* place vector (transition vector) *is a vector* $x : P \to \mathbb{Z}$, *indexed by* P *(*$y : T \to \mathbb{Z}$, *indexed by* T*).*
- *A place vector (transition vector) is called a* P-invariant (T-invariant) *if it is a nontrivial nonnegative integer solution of the linear equation system* $x \cdot \mathbb{C} = 0$ *(*$\mathbb{C} \cdot y = 0$*).*
- *The set of nodes corresponding to an invariant's nonzero entries are called the* support *of this invariant* x, *written as* $supp(x)$.
- *An invariant* x *is called* minimal *if* $\nexists$ *invariant* $z : supp(z) \subset supp(x)$, *i.e. its support does not contain the support of any other invariant* z, *and the greatest common divisor of all nonzero entries of* x *is 1.*
- *A net is* covered by P-invariants, shortly CPI, (covered by T-invariants, shortly CTI) *if every place (transition) belongs to a P-invariant (T-invariant).*

3. Static Decision of Marking-independent Behavioral Properties

r1: $2\,\mathrm{A} \xrightarrow{E} 2\,\mathrm{B}$
r2/3: $\mathrm{A} \rightleftharpoons \mathrm{B}$

	r1	r2	r3
A	−2	−1	1
B	2	1	−1
E	0	0	0



$x_1 = (1, 1, 0) = (\mathrm{A}, \mathrm{B}),$
$x_2 = (0, 0, 1) = (\mathrm{E})$

$y_1 = (1, 0, 2) = (\mathrm{r1}, 2 \cdot \mathrm{r3}),$
$y_2 = (0, 1, 1) = (\mathrm{r2}, \mathrm{r3})$

$y_3 = (1, 1, 3) = y_1 + y_2$

Fig. 8. Two reaction equations with the corresponding Petri net, its incidence matrix, and the minimal P-invariants x_1, x_2, and the minimal T-invariants y_1, y_2, and a non-minimal T-invariant y_3. The invariants are given in the standard vector notation as well as in a shorthand notation, listing the nonzero entries only. The net is not pure; the incidence matrix does not reflect the dependency of r1 on E.

4. Initial Marking Construction

The following criteria are considered in a systematic construction of the initial marking

- Each P-invariant needs at least one token.
- All (nontrivial) T-invariants should be feasible, meaning, the transitions, making up the T-invariant's multi-set can actually be fired in an appropriate (partial) order.
- Additionally, it is common sense to look for a minimal marking (as few tokens as possible), which guarantees the required behaviour.
- Within a P-invariant, choose the species with the most *inactive* or the *monomeric* state.

6. Dynamic Decision of Behavioral Properties

Definition 11 (Reachability graph). *Let $\mathcal{N} = (P, T, f, m_0)$ be a Petri net. The* reachability graph *of $\mathcal{N}$ is the graph $\mathcal{RG}(\mathcal{N}) = (V_\mathcal{N}, E_\mathcal{N})$, where*

- $V_\mathcal{N} := [m_0\rangle$ *is the set of nodes,*
- $E_\mathcal{N} := \{\, (m, t, m') \mid m, m' \in [m_0\rangle, t \in T : m[t\rangle m' \}$ *is the set of arcs.*

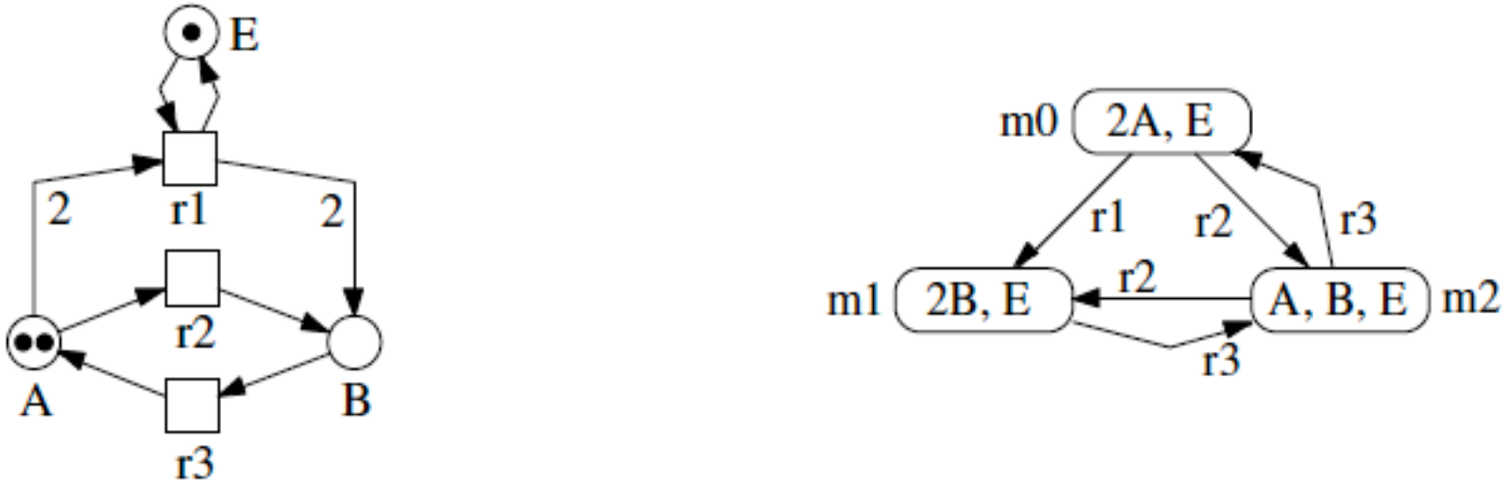


Fig. 12. A Petri net (left) and its reachability graph (right). The states are given in a shorthand notation. In state m0, transitions r1 and r2 are in a dynamic conflict; the firing of one transition disables the other one. In state m2, transitions r2 and r3 are concurrently enabled; they can fire independently, i.e. in any order. In both cases we get a branching node in the reachability graph.

6. Dynamic Decision of Behavioral Properties

If the reachability graph can be constructed explicitly, then many properties of the Petri net can be tested easily

However, the reachability graph of a Petri net modeling almost any realistic system tends to be huge (the state explosion problem)

The Stochastic Approach

Stochastic Petri Nets

- Each place maintains a discrete number of tokens

- A firing rate (waiting time) is associated with each transition t, which are random variables $X_t \in [0,\infty)$, defined by probability distributions

- When a transition is enabled, a timer is set, and starts decreasing at a constant rate. When the timer value is 0, the transition fires

Stochastic Petri Nets

Definition 12 (Stochastic Petri net, Syntax). *A* biochemically interpreted stochastic Petri net *is a quintuple* $\mathcal{SPN}_{Bio} = (P, T, f, v, m_0)$, *where*

- P *and* T *are finite, non empty, and disjoint sets.* P *is the set of* places, *and* T *is the set of* transitions.
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{N}_0$ *defines the set of directed* arcs, *weighted by nonnegative integer values.*
- $v : T \to H$ *is a function, which assigns a* stochastic hazard function h_t *to each transition* t, *whereby* $H := \bigcup_{t \in T} \left\{ h_t \mid h_t : \mathbb{N}_0^{|{}^\bullet t|} \to \mathbb{R}^+ \right\}$ *is the set of all stochastic hazard functions, and* $v(t) = h_t$ *for all transitions* $t \in T$.
- $m_0 : P \to \mathbb{N}_0$ *gives the* initial marking.

Stochastic Petri Nets

The stochastic hazard function h_t defines the marking-dependent transition rate $\lambda_t(m)$ for the transition t. The domain of h_t is restricted to the set of preplaces of t to enforce a close relation between network structure and hazard functions. Therefore $\lambda_t(m)$ actually depends only on a sub-marking.

Stochastic Petri Net Semantics

- Transitions become enabled as usual, i.e., if all preplaces are sufficiently marked

- However, there is a time, which has to elapse, before an enabled transition t fires

- The transition's waiting time is an exponentially distributed random variable X_t with the probability density function

$$f_{X_t}(\tau) = \lambda_t(m) \cdot \mathrm{e}^{(-\lambda_t(m)\cdot\tau)}, \qquad \tau \geq 0$$

Stochastic Petri Net Semantics

- Specialized biochemically interpreted stochastic Petri nets can be defined by specifying the required kind of stochastic hazard function

- Two examples

  - *Stochastic mass-action hazard function*, which tailors the general SPN definition to biochemical mass-action networks, where tokens correspond to molecules

  - *Stochastic level hazard function*, which tailors the general SPN definition to biochemical mass-action networks, where tokens correspond to concentration levels

Stochastic Petri Net Semantics: Stochastic Mass-action Hazard Function

$$h_t := c_t \cdot \prod_{p \in {}^\bullet t} \binom{m(p)}{f(p,t)}$$

where c_t is the transition specific stochastic rate constant, and m(p) is the current number of tokens on the preplace p of transition t. The binomial coefficient describes the number of unordered combinations of the f(p,t) molecules, required for the reaction, out of the m(p) available ones

Stochastic Petri Net Semantics: Stochastic Level Hazard Function

$$h_t := k_t \cdot N \cdot \prod_{p \in {}^\bullet t} \left(\frac{m(p)}{N}\right)$$

where k_t is the transition specific deterministic rate constant, and N is the number of the highest level.

The Continuous Approach

Continuous Petri Nets

- The marking of a place is no longer an integer, but a positive real number, called token value, which can be interpreted as the concentration of the species modeled by the place

- The instantaneous firing of a transition is carried out like a continuous flow

Continuous Petri Nets

Definition 13 (Continuous Petri net, Syntax). *A* continuous Petri net *is a quintuple* $\mathcal{CON}_{Bio} = (P, T, f, v, m_0)$, *where*

- P *and* T *are finite, non empty, and disjoint sets.* P *is the set of* continuous places. T *is the set of* continuous transitions.
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{R}_0^+$ *defines the set of directed* arcs, *weighted by nonnegative real values.*
- $v : T \to H$ *is a function which assigns a* firing rate function h_t *to each transition* t, *whereby* $H := \bigcup_{t \in T} \left\{ h_t | h_t : \mathbb{R}^{|^\bullet t|} \to \mathbb{R} \right\}$ *is the set of all firing rate functions, and* $v(t) = h_t$ *for all transitions* $t \in T$.
- $m_0 : P \to \mathbb{R}_0^+$ *gives the* initial marking.

Continuous Petri Nets

- Note that a firing rate may be negative, in which case the reaction takes place in the reverse direction

- This feature is commonly used to model reversible reactions by just one transition, where positive firing rates correspond to the forward direction, and negative ones to the backward direction

Continuous Petri Net Semantics

- Each continuous marking is a place vector, containing |P| non-negative real values, and m(p) yields the marking on place p, which is a real number

- A continuous transition t is enabled in m, if for every preplace p of t, we have m(p)>0

- Due to the influence of time, a continuous transition is forced to fire as soon as possible

Continuous Petri Net Semantics

- The semantics of a continuous Petri net is defined by a system of ODEs, whereby one equation describes the continuous change over time on the token value of a given place by the continuous increase of its pretransitions' flow and the continuous decrease of its posttransitions' flow

- In other words, each place p gets its own equation

$$\frac{dm(p)}{dt} = \sum_{t \in {}^\bullet p} f(t,p)\, v(t) - \sum_{t \in p^\bullet} f(p,t)\, v(t)$$

Tools for Petri Nets

- Snoopy: design, animate, and simulate qualitative, stochastic, and continuous Petri nets
  http://www-dssz.informatik.tu-cottbus.de/index.html?/software/snoopy.html

- Charlie: analyzes properties of Petri nets
  http://www-dssz.informatik.tu-cottbus.de/software/charlie/charlie.html

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  - "Systems Biology in Practice: Concepts, Implementation and Applications", by E. Klipp et al., Wiley-VCH, 1st Edition, 2nd Reprint, 2006.
  - "Petri Nets for Systems and Synthetic Biology", by M. Heiner, D. Gilbert, and R. Donaldson, SFM 2008, LNCS 5016, 215-264, 2008.