Petri Net Based Descriptions for Systematic Understanding of Biological Pathways

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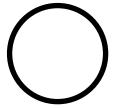
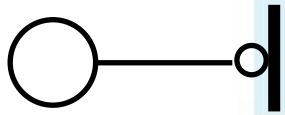
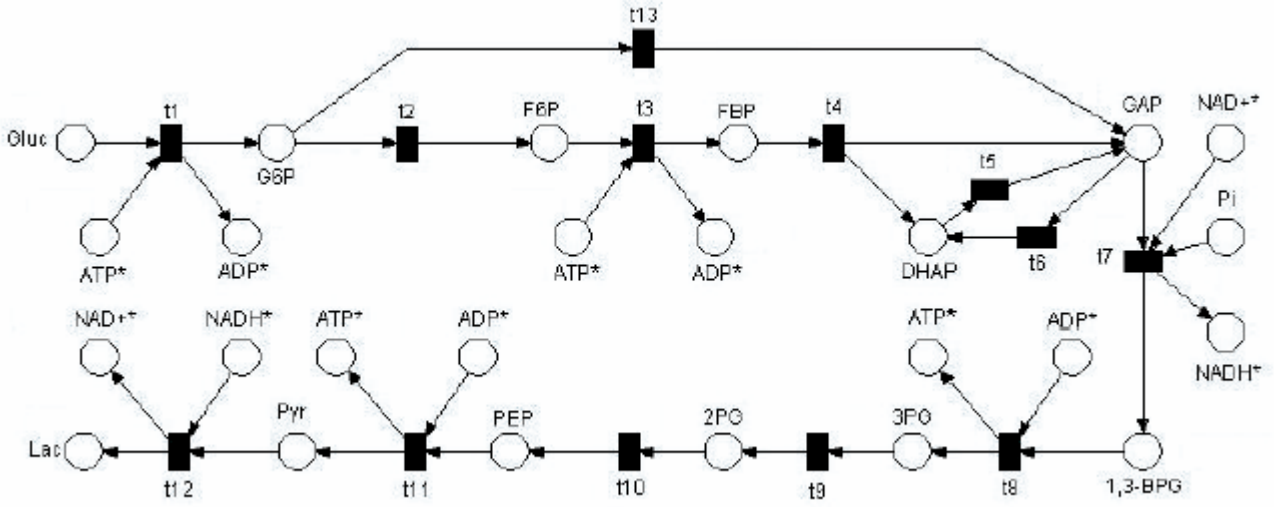
Element assignments

Biological pathways	Petri net
static elements (substances, states …)	
active elements (chemical reactions, interactions)	
relations, flows	
repression	

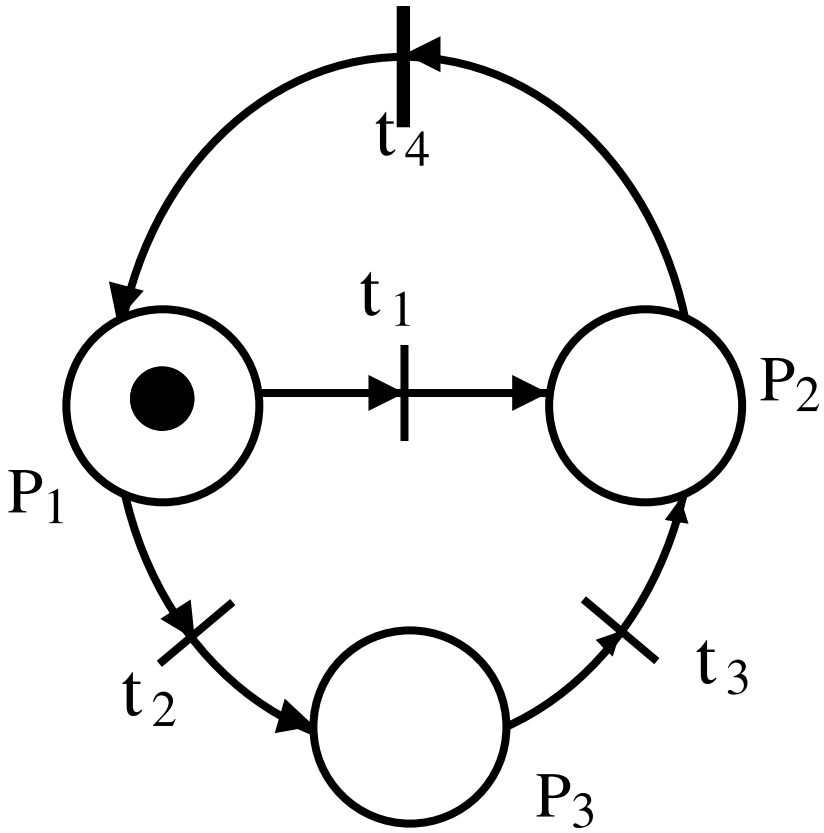
Metabolic pathway modeling with Petri nets

- Reddy et al. (1993) : The first application paper of Petri net to model biological pathway in 1st ISMB
  - ✓ place – amount of metabolite
  - ✓ transition – speed of enzymic reaction



Can be modeled with simple rules

P-T incidence matrix

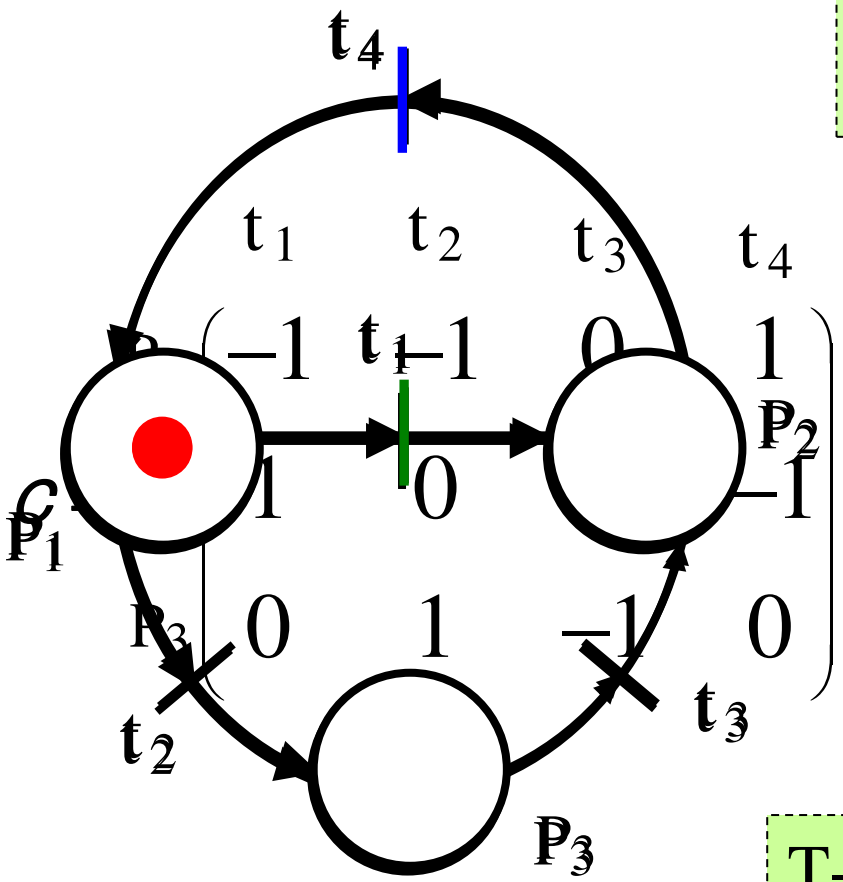


- P-T incidence matrix

express connections between places and transitions

$$C = \begin{array}{c} \\ P_1 \\ P_2 \\ P_3 \end{array} \begin{array}{c} \begin{array}{cccc} t_1 & t_2 & t_3 & t_4 \end{array} \\ \begin{pmatrix} -1 & -1 & 0 & 1 \\ 1 & 0 & 1 & -1 \\ 0 & 1 & -1 & 0 \end{pmatrix} \end{array}$$

T-invariant



T-invariant

Non-negative integer vector J satisfying $CJ=0$

$$
\begin{array}{l}
\qquad t_1\ t_2\ t_3\ t_4 \\
J_1=(1\ \ 0\ \ 0\ \ 1)^t \\
J_2=(0\ \ 1\ \ 1\ \ 1)^t \\
J_3=\ J_1+J_2 \\
\quad =(1\ \ 1\ \ 1\ \ 2)^t
\end{array}
$$

elementary T-invariant

elementary T-invariant

T-invariant that can not be expressed by non-negative rational linear combination of the other T-invariants.

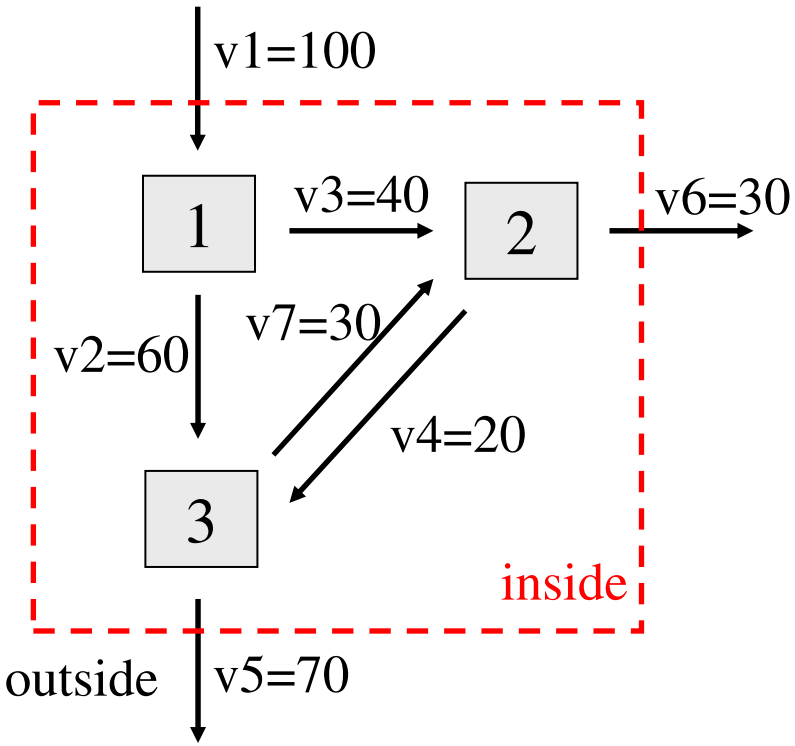
Metabolic pathways and elementary modes

Elementary Mode *

a minimum set of enzymic reaction paths, into which a metabolic pathway is decomposed so that it can keep steady state

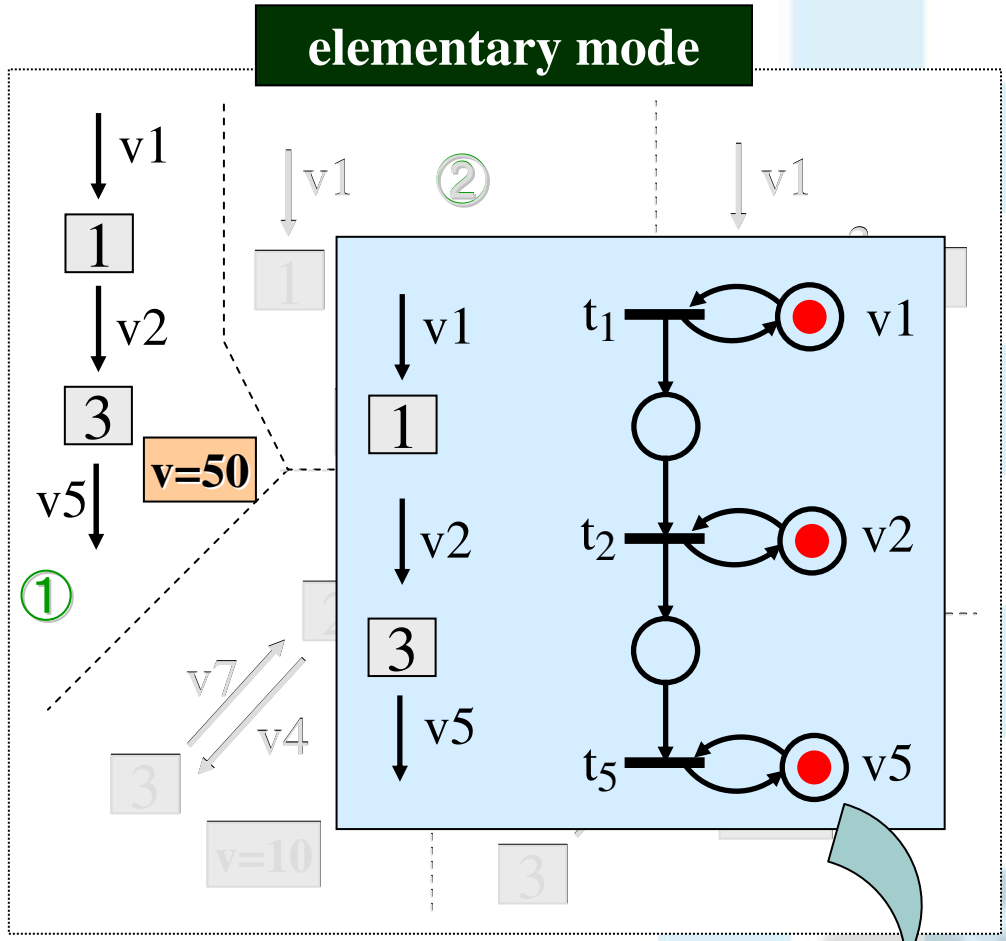
* S. Schuster, D.A. Fell, and T. Dandekar, "A general definition of metabolic pathways useful for systematic organization and analysis of complex metabolic networks.", *Nature America Inc.*, vol.18, 2000.

Elementary mode in metabolic pathways



v*N*: speed of an enzymic reaction

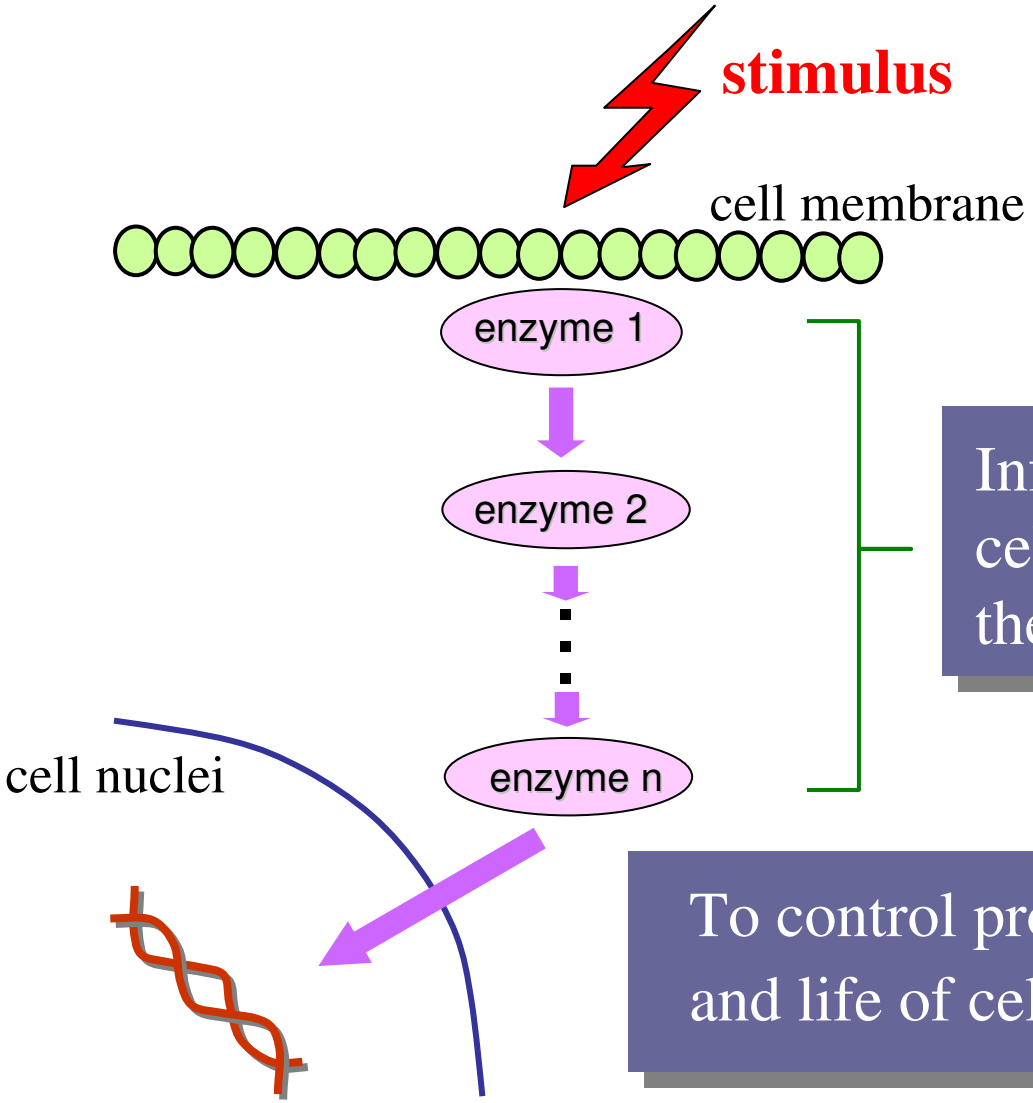
: metabolite



Elementary mode = Elementary T-invariant

** I. Zevedei-Oancea and S. Schuster,
"Topological analysis of metabolic networks based on Petri net theory," *In Silico Biology*, 3, 2003.

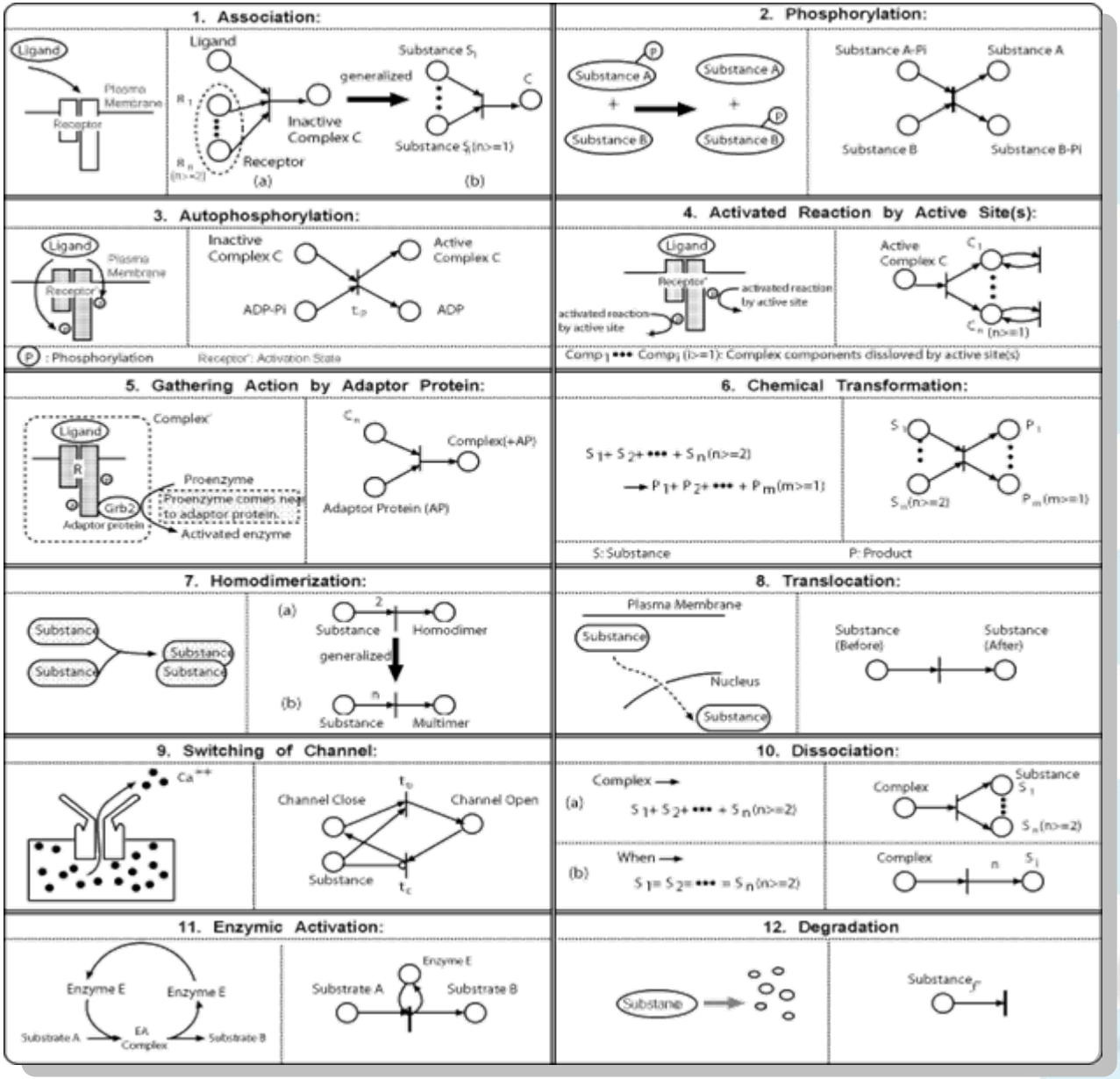
Signaling pathways



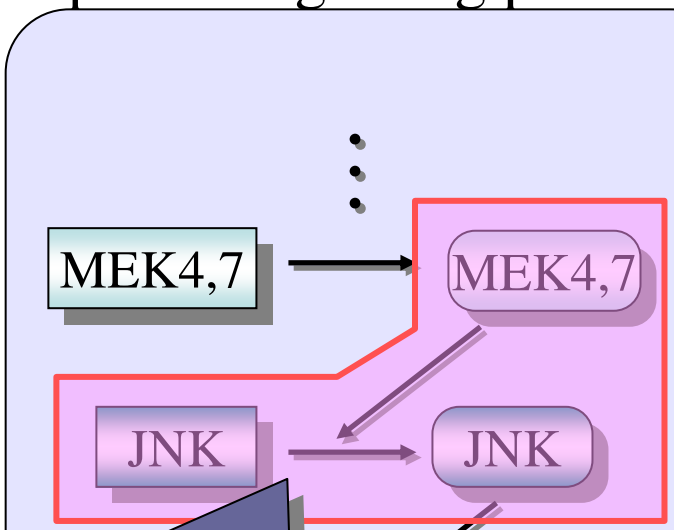
Information transmission from cell membrane to cell nuclei by the cascade of enzymes

To control proliferation, differentiation, and life of cells

signaling pathway components



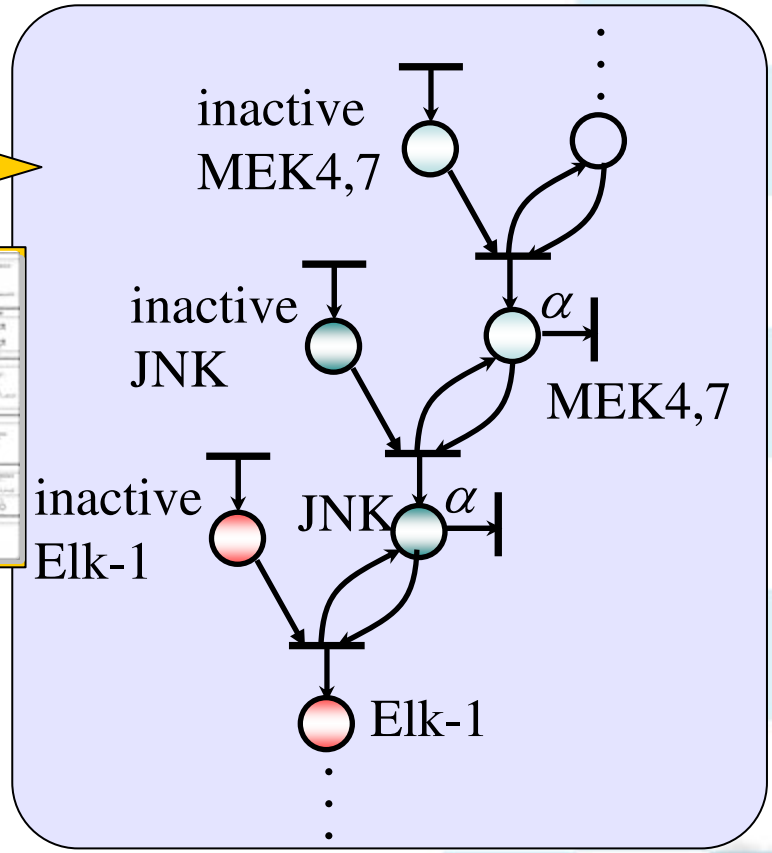
a part of signaling pathway



Activation Transduction Component (ATC)

A range of an activation process influenced by an enzyme reaction

Petri net model

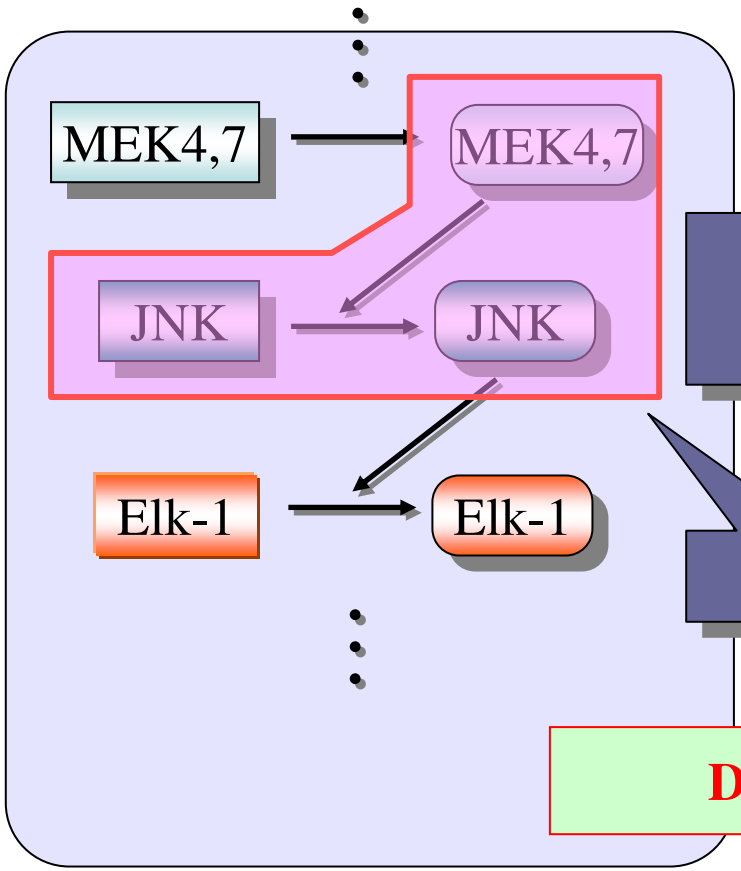


ATC = Elementary T-invariant

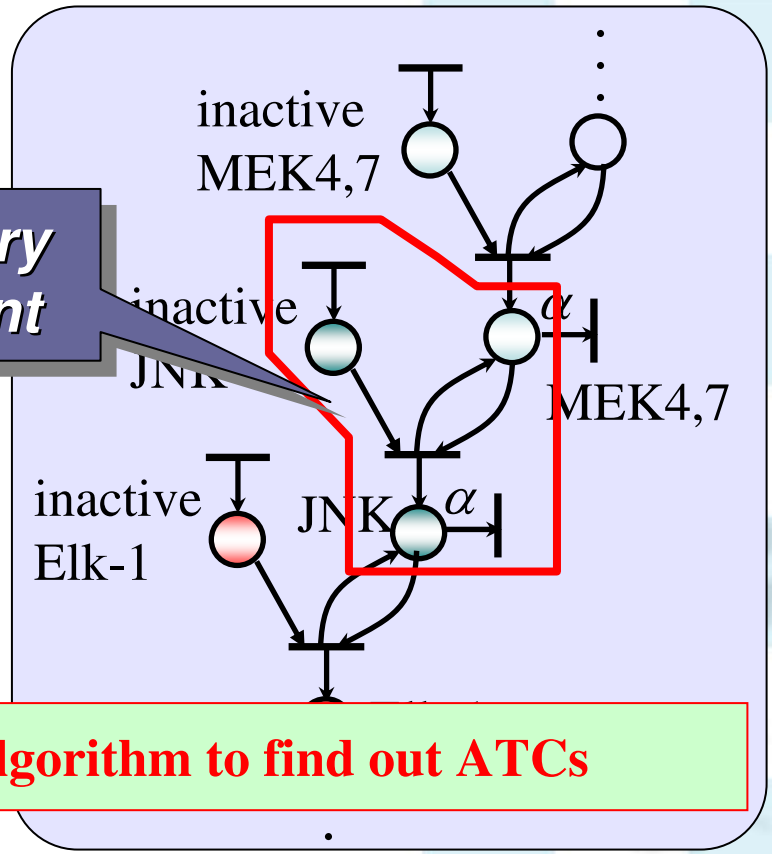
Signaling Pathway TERM

Petri net TERM

A part of signaling pathway



Petri net model



Elementary T-invariant

ATC

Develop an algorithm to find out ATCs

Algorithm to find ATC

C. Li, S. Suzuki, Q.-W.Ge, M. Nakata, H. Matsuno, S. Miyano, Structural modeling and analysis of signaling pathways based on Petri nets, J. Bioinfo. Comput. Biol. in press. 2006.

≪Searching Activation Transduction Components≫

1° Let PN be a given Petri net, and L_s be a list of sink transitions (except sink output transitions of enzyme places) in PN. Do $SN_J \leftarrow \phi$, $T_{sink} \leftarrow \{t | t \in L_s\}$, $T_{gen} \leftarrow \phi$ and initialize $FIFO$ queue $Q \leftarrow \phi$.

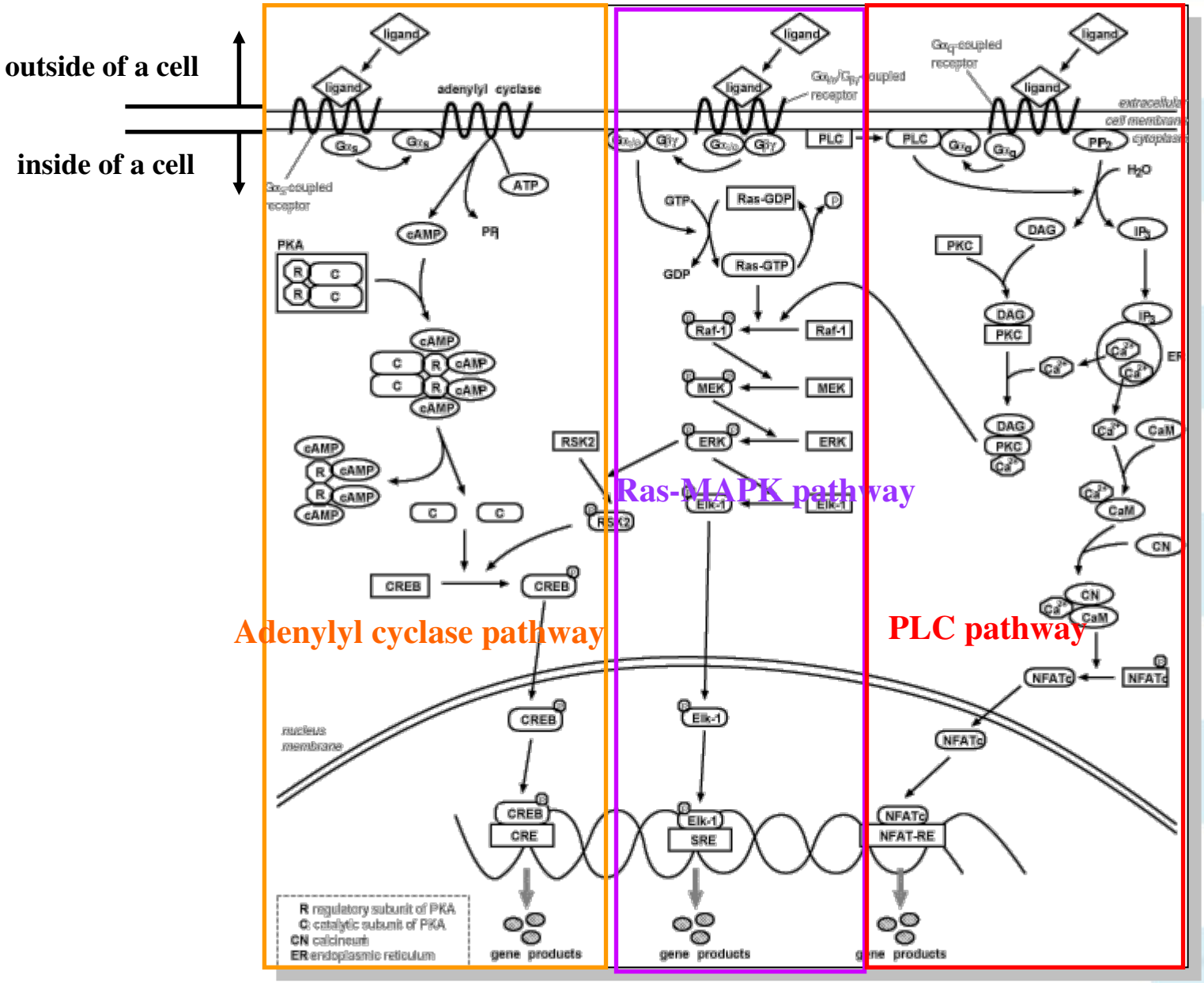
2° If $Q \neq \phi$, pull a subnet N_{J_i} from Q and do the followings:
(i) let P_e and T_e be a set of enzyme places in N_{J_i} and a set of transitions providing tokens to the places of P_e, respectively;
(ii) let L_e be a list of transitions in $T_e - T_{gen}$, and do $L_s \leftarrow L_s \cdot L_e$, $T_{gen} \leftarrow T_{gen} \cup T_e$ and $PROV(N_{J_i}) = \{t | t \in T_e\}$.

3° If $L_s = \phi$ go to 4°, otherwise take out a transition t from the beginning of L_s and do $gen(t) \leftarrow \phi$. Obtain all the elementary T-invariants $\{J_i\}$ with $J_i(t) > 0$ by applying **≪Searching Basic-Feasible Solution with $x_s > 0$≫**[23]. For each J_i, do the followings:
(i) obtain its corresponding subnet N_{J_i} (generated by the support T_{J_i} of J_i);
(ii) do $gen(t) \leftarrow gen(t) \cup \{N_{J_i}\}$;
(iii) if $N_{J_i} \notin SN_J$ is satisfied, then $SN_J \leftarrow SN_J \cup \{N_{J_i}\}$ and push N_{J_i} to Q.

4° If $Q = \phi$ then output T_{gen}, T_{sink}, $gen(t)$ for $t \in T_{gen} \cup T_{sink}$ and $PROV(N_{J_i})$ for $N_{J_i} \in SN_J$, and stop; otherwise go to 2°. □

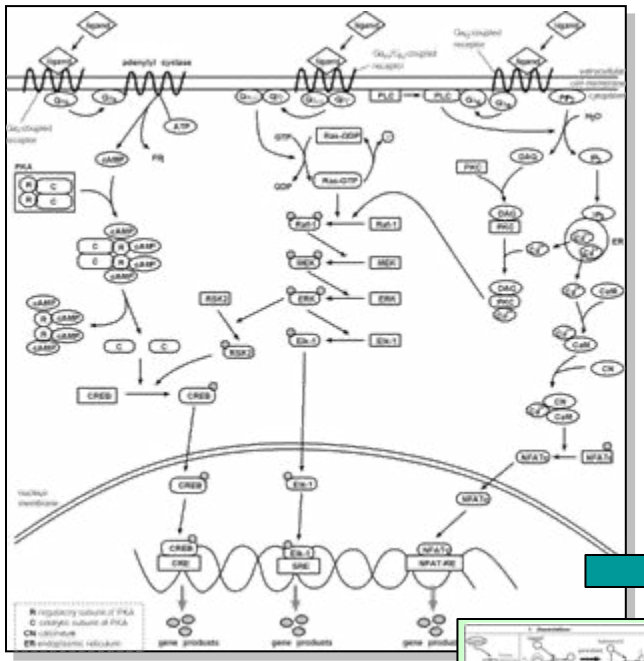
Q.-W.Ge, Fukunaga, T., Nakata, M., On generating elementary T-invariants of Petri nets by linear programming, Proc. ISCA2005, pp.168-171, 2005.

An Example of signaling pathway modeling

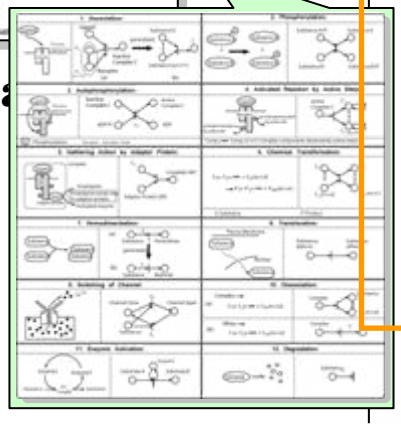


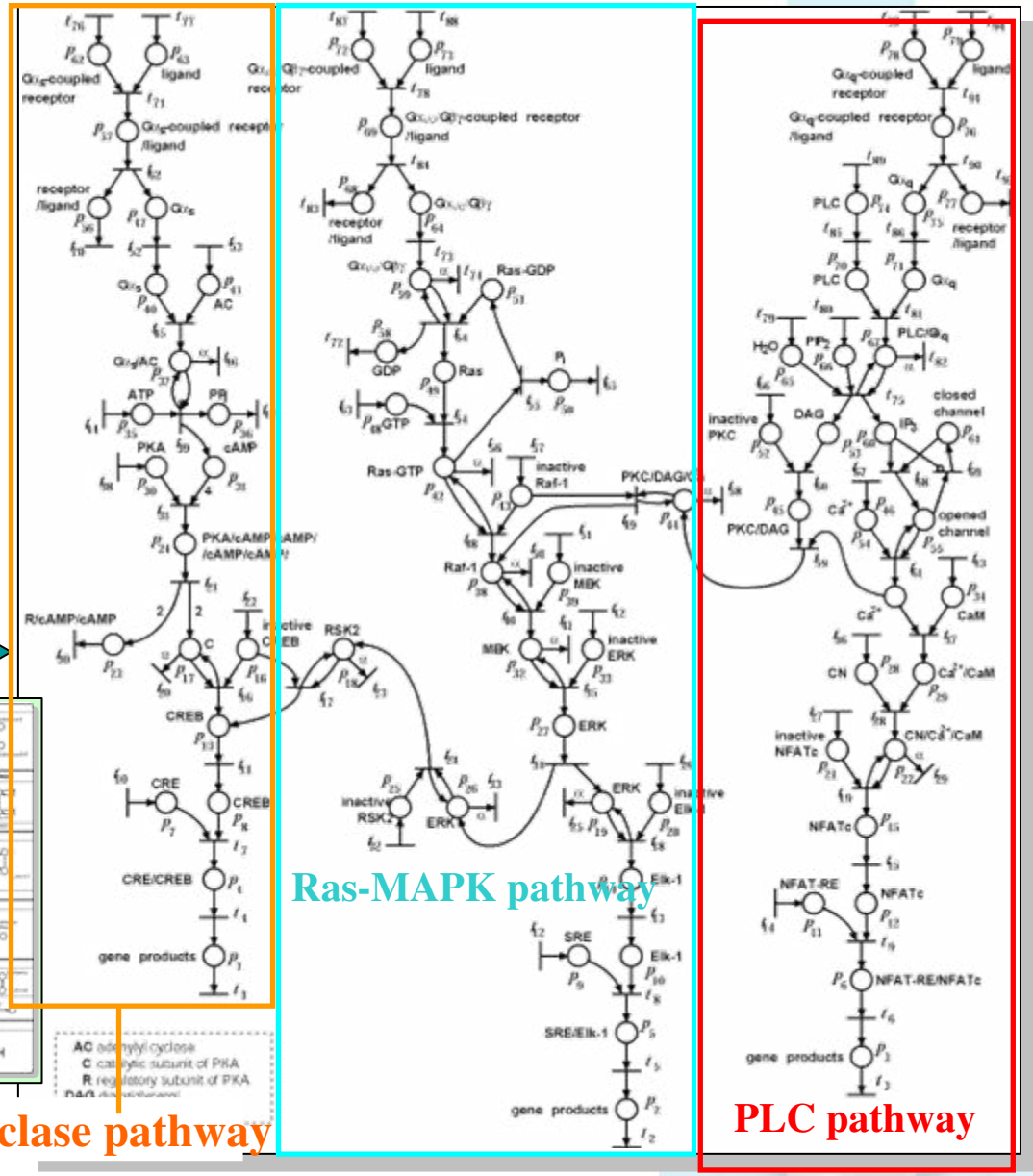
G protein signaling pathways

Petri net model of signaling pathway



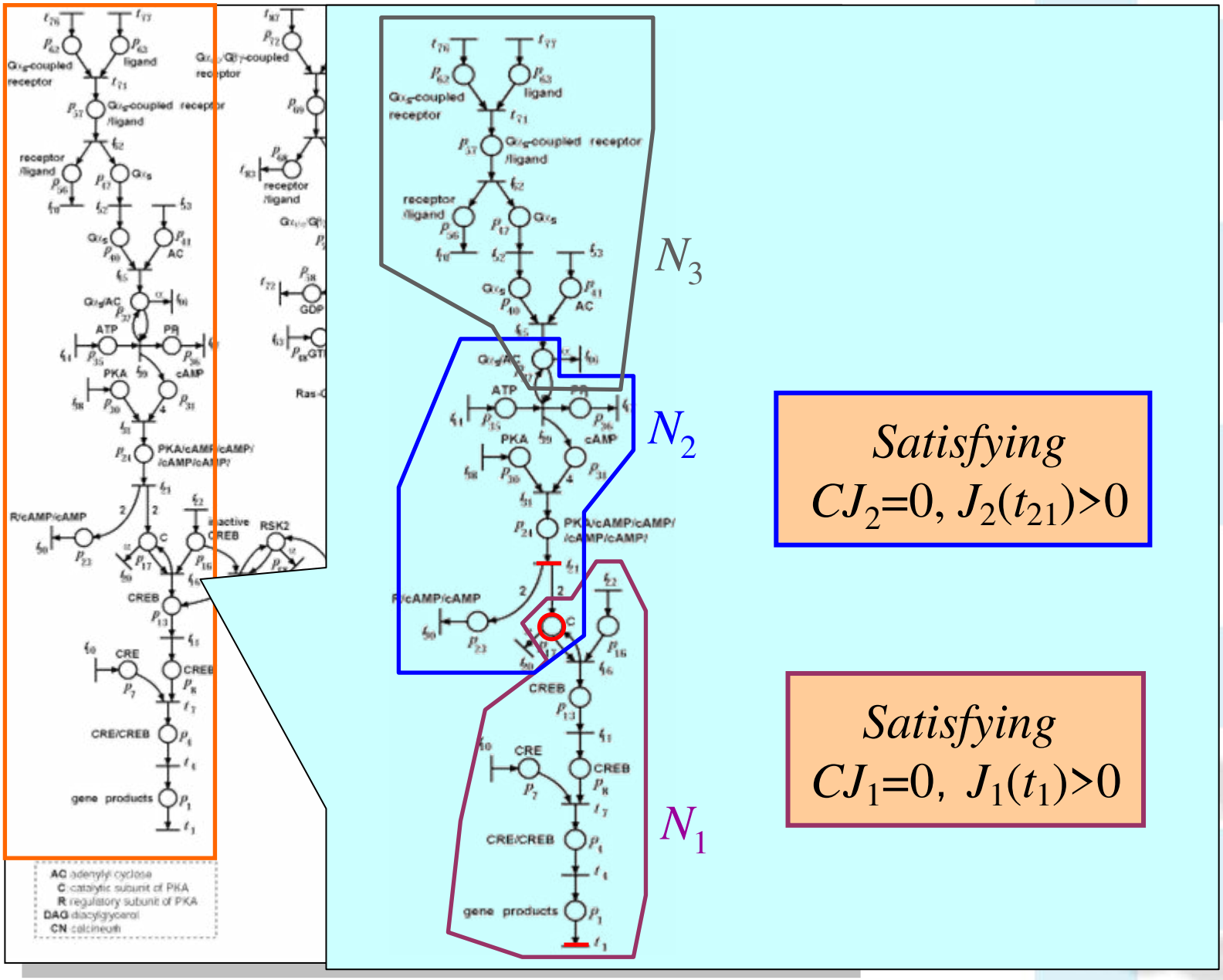
G protein signaling pa





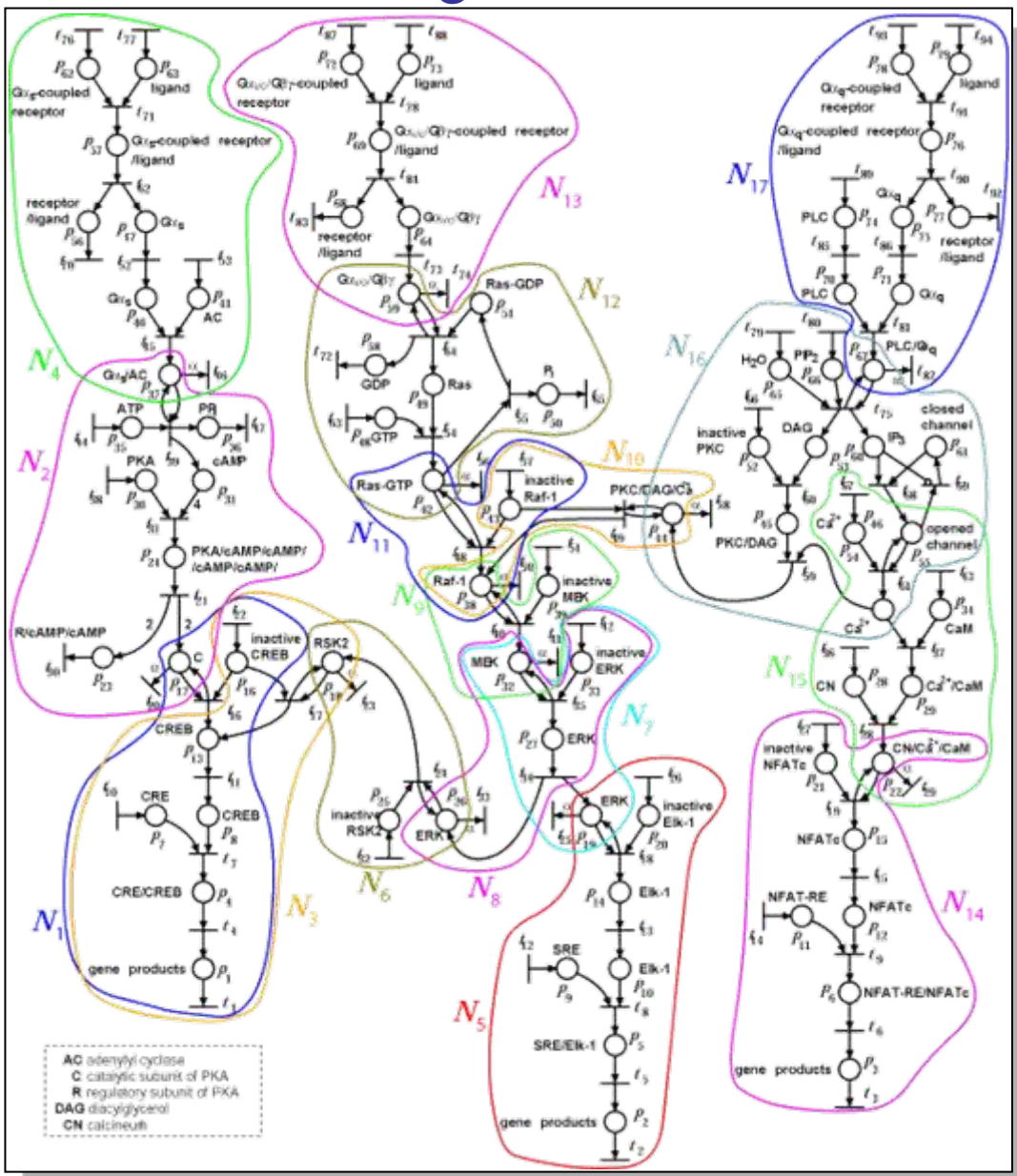
Petri net model of G protein signaling pathway

Searching ATC by the proposed algorithm



G protein signaling pathway

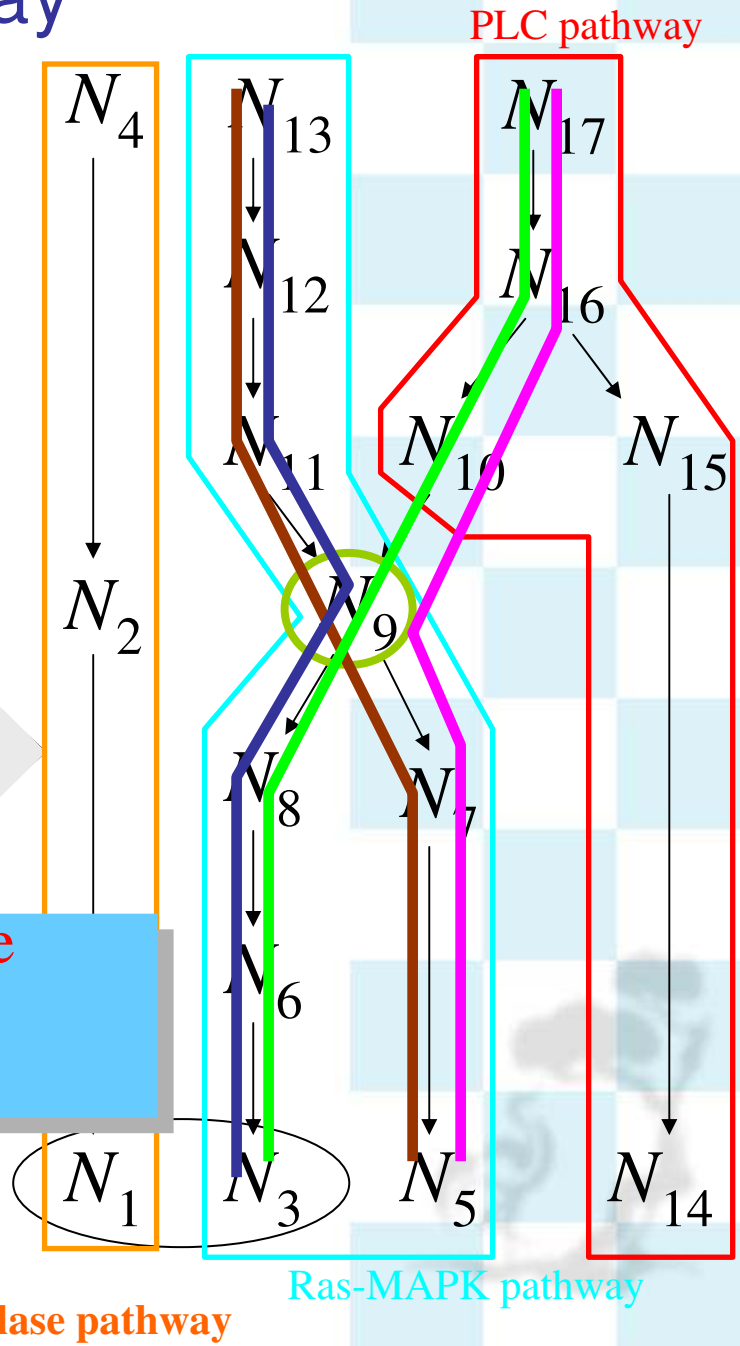
Result of ATC searching



ATC representation of pathway

- Subnet N_9 (MEK activation by Raf-1) is an important reaction in the pathway.
- More than one pathways are working for producing the same gene product.

Easy to acquire the characteristics on the structure of signaling pathways



Summary

- We present Petri net models of various reactions in cells, with which signaling pathways can be modeled.
  - Modeled pathways are open to the public by the web site "Petri Net Pathways".

- We define the new notation "activation transduction component (ATC)" and propose a new algorithm to search ATCs, and show that
  - ATC corresponds to elementary T-invariant in Petri net theory,
  - signaling pathways can be expressed by chains of ATC (=elementary T-invariants), and
  - network representation of signaling pathways with ATC gives a new view for clarifying the characteristics of signaling pathways based on these structures.