

ペトリネットによる生命パスウェイ表現と シミュレーション

松野浩嗣

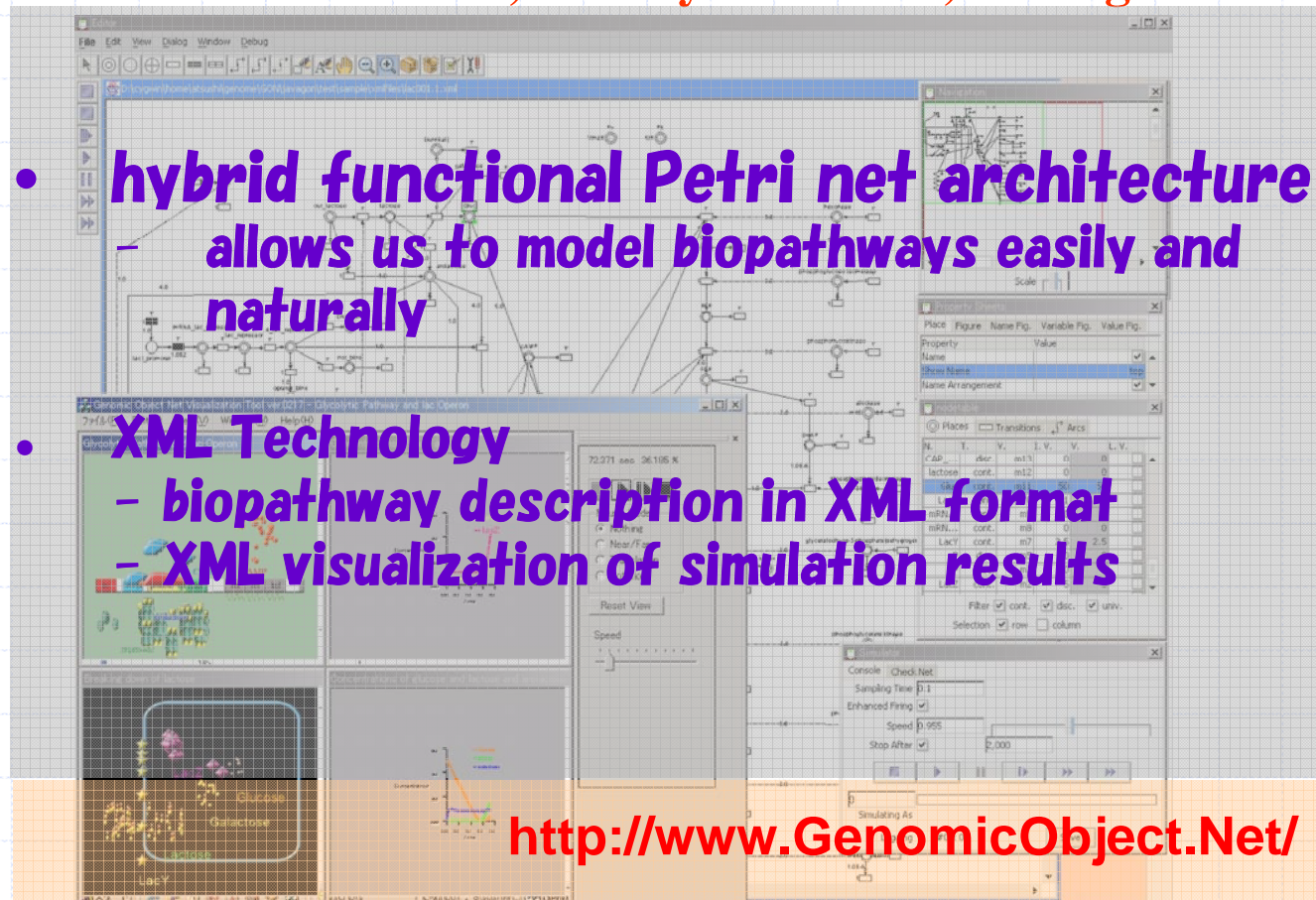
山口大学大学院理工学研究科

特別講演 システム生物学の最前線 2007年10月29日

Genomic Object Net Project

- Miyano lab., Human Genome Center, U. of Tokyo
- Matsuno lab., Faculty of Science, Yamaguchi U.

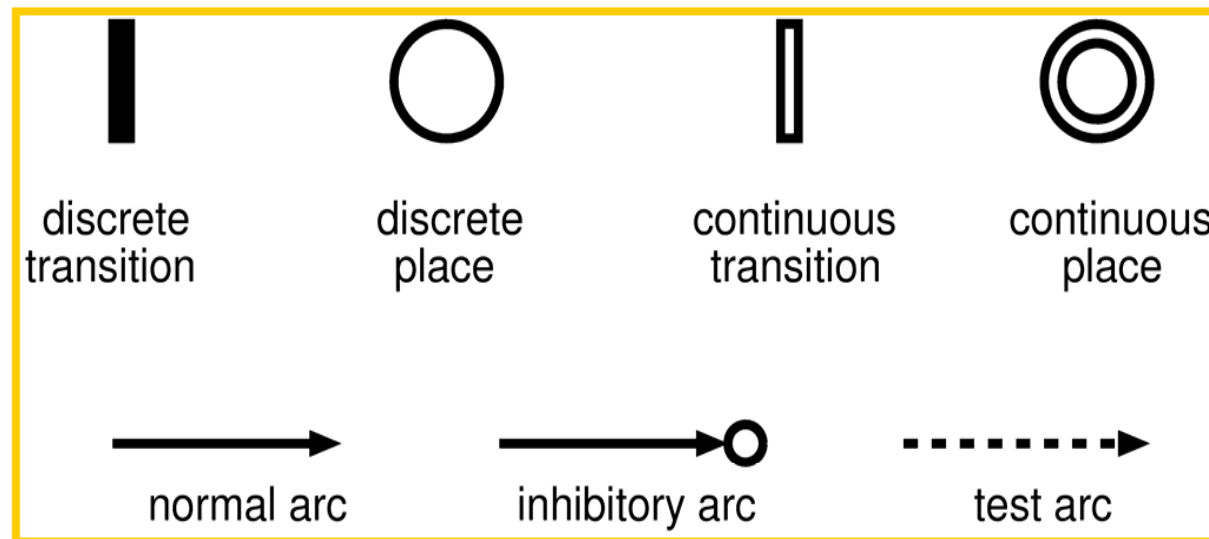
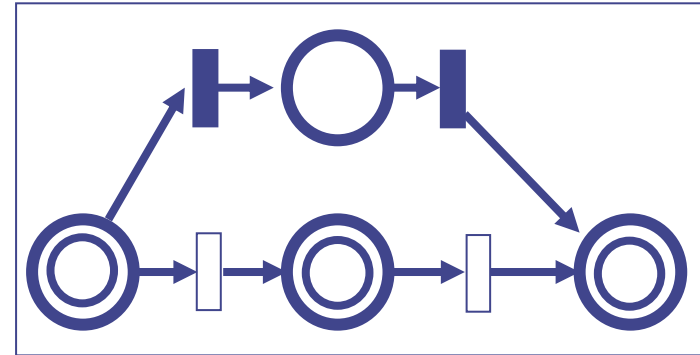
- **hybrid functional Petri net architecture**
 - allows us to model biopathways easily and naturally
- **XML Technology**
 - biopathway description in XML format
 - XML visualization of simulation results



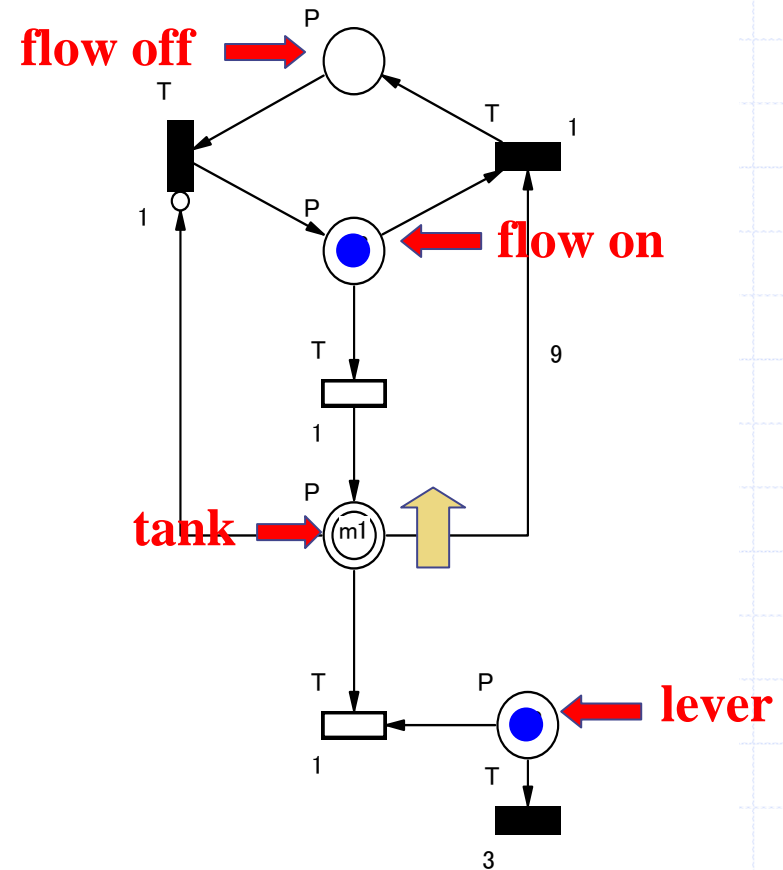
<http://www.GenomicObject.Net/>

Genomic Object Net version 1.0

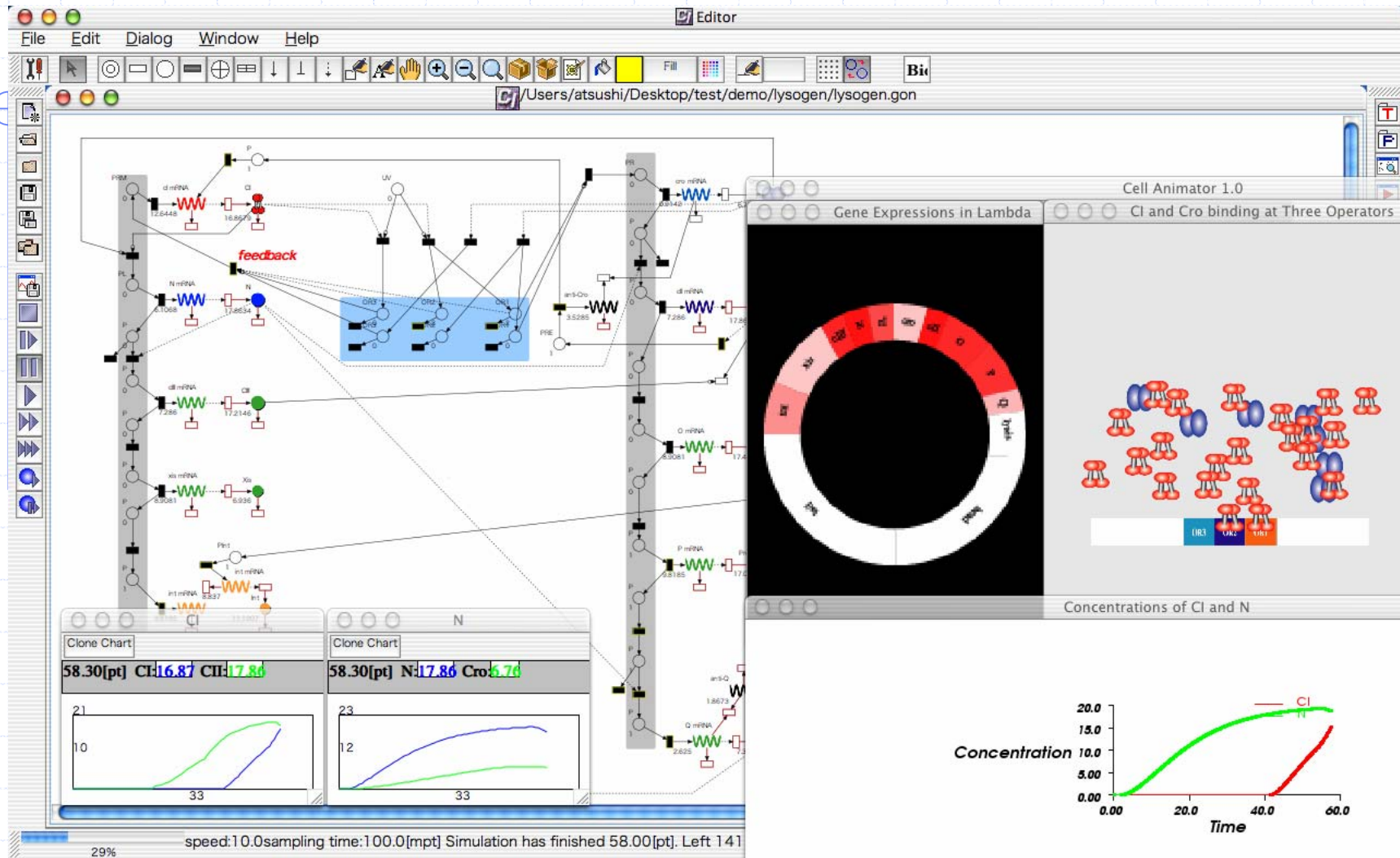
Hybrid Petri Net



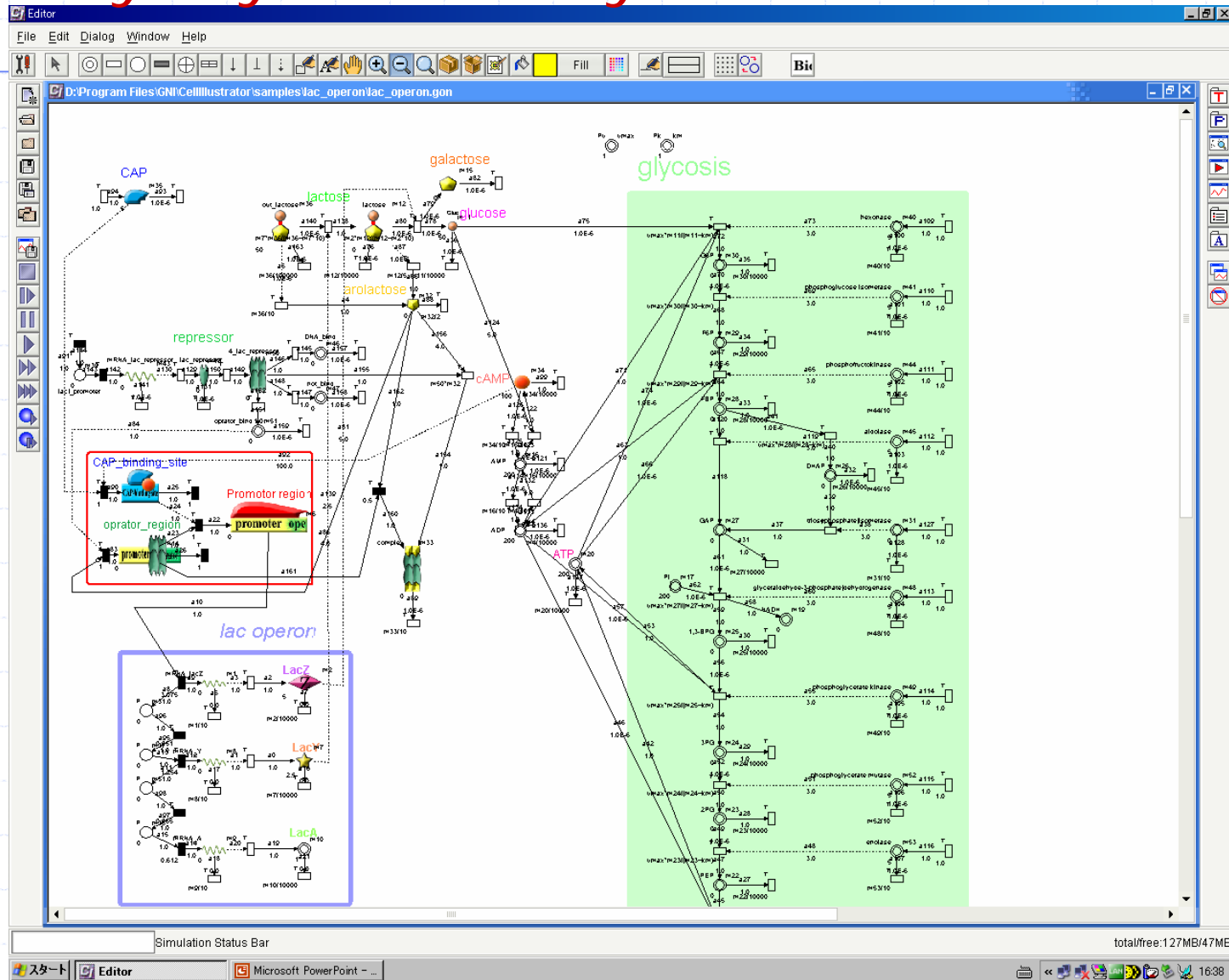
Example



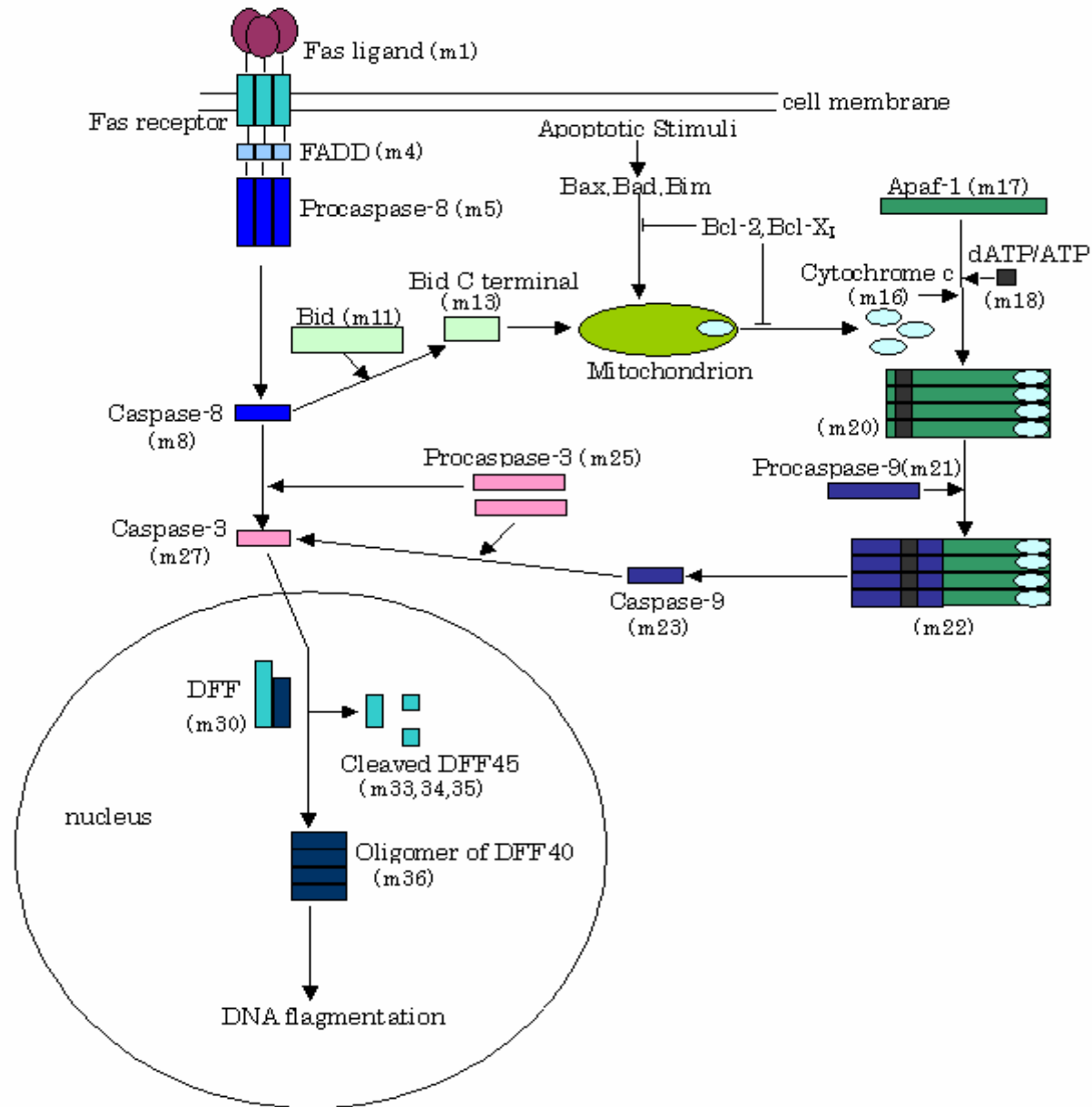
Lambda Phage Genetic Switch



lac Operon Gene Regulatory Mechanism and Glycolytic Pathway



Apoptosis induced by Fas ligand



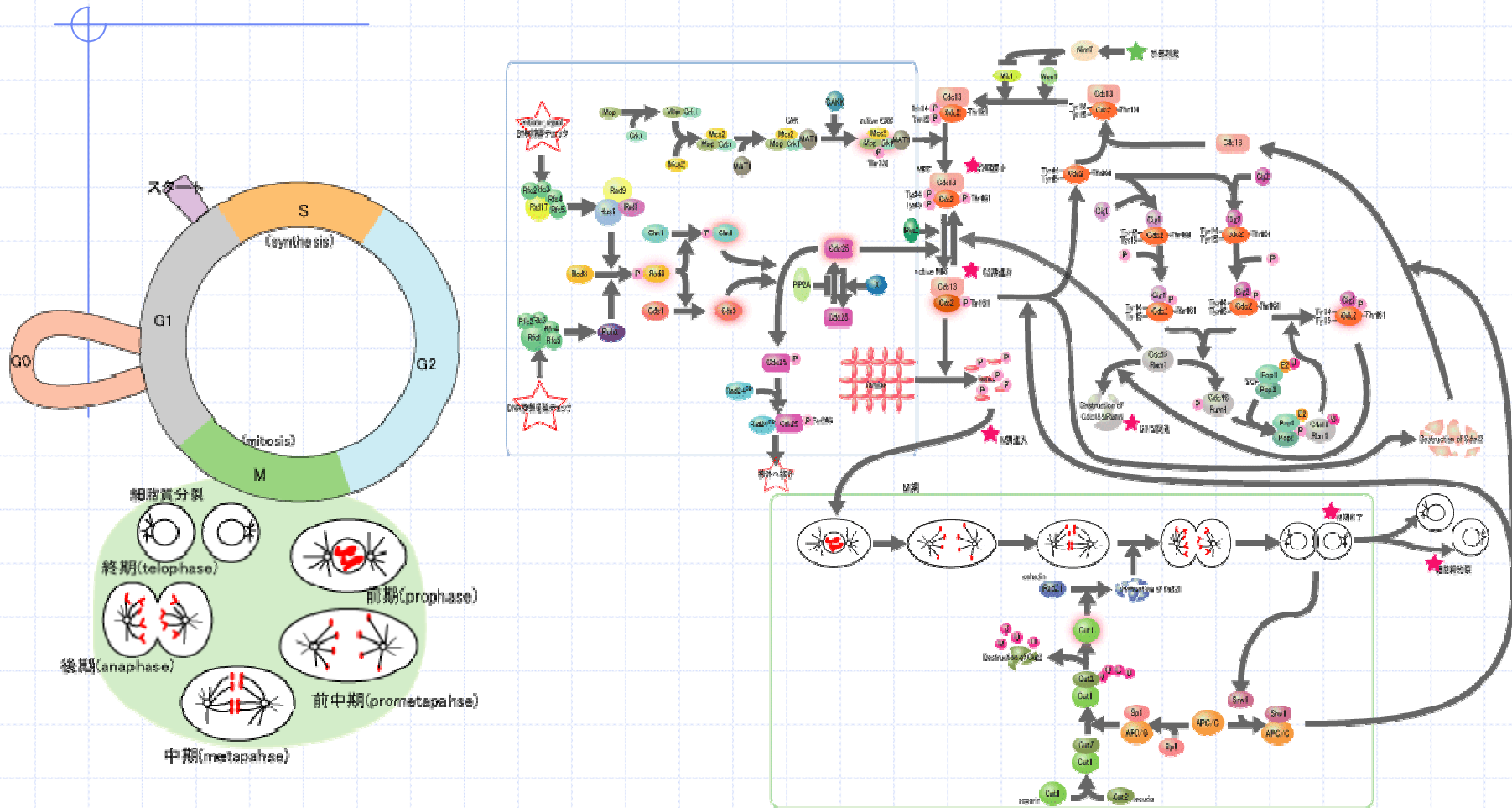
HFPN model of Apoptosis

The screenshot displays the HFPN model of Apoptosis software interface, which includes several key components:

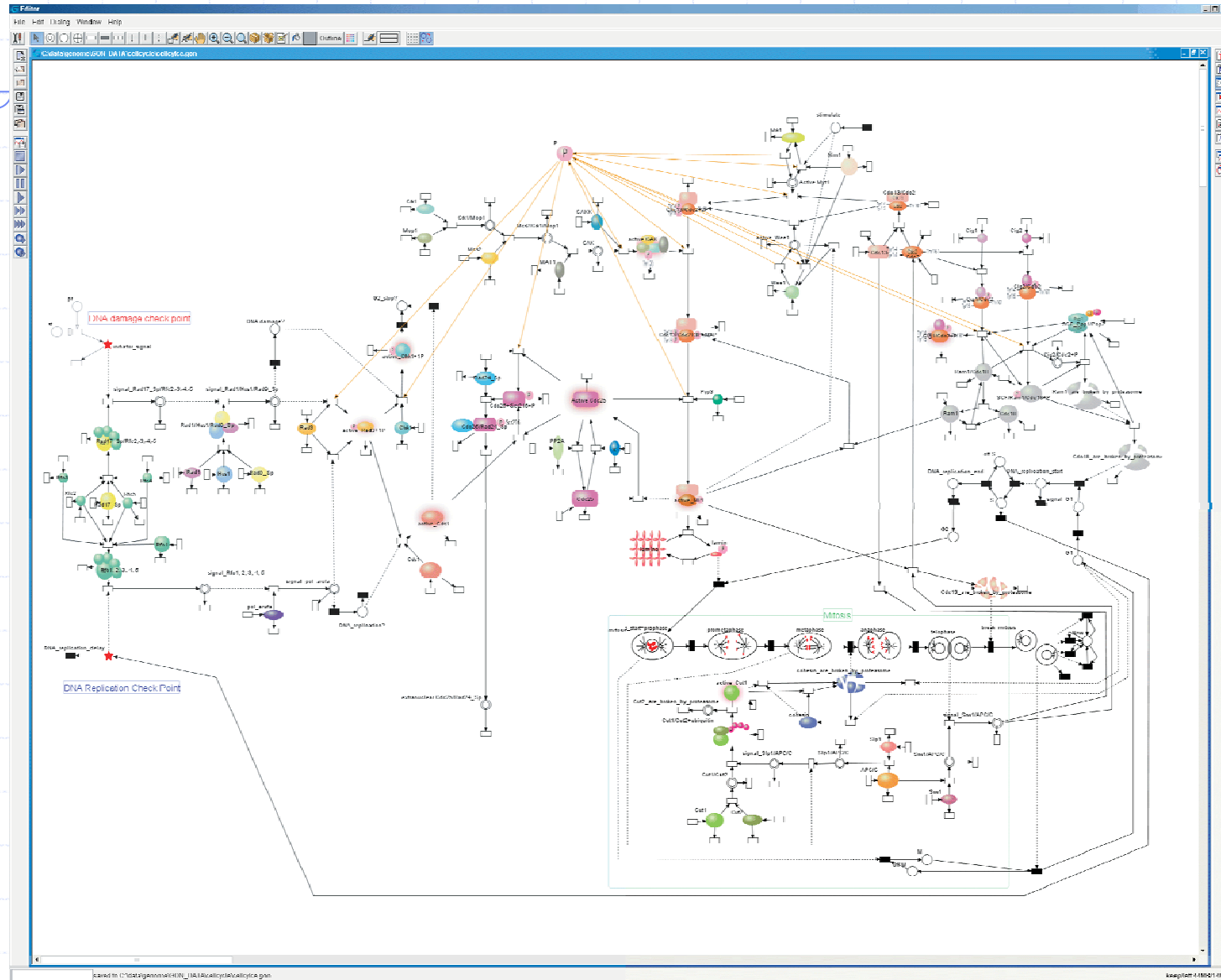
- Editor:** The main workspace showing a Petri net diagram with nodes (places and transitions) and arcs. The diagram is titled "D:\cygwin\home\atsushi\genome\GON\javagon\test\demo\apoptosis.xml".
- Property Tables:** A table listing the properties of the model's components.

N.	T.
Fas ligand trimer,IFas receptor complex	continuous
FADD	continuous
pro-caspase8	continuous
DISC	continuous
complex	continuous
cytochrome c	continuous
mitochondrion	continuous
- Navigation:** A window showing a hierarchical tree of the model's components.
- Simulation Window:** A window titled "Genomic Object Net Visualization Tool ver 0217 - Apoptosis - [Apoptosis]" showing a 3D visualization of the cell and its internal components. The simulation is running at "Step: 250000" with "Fas ligand: 0.84" and "DNA fragment: 1.0".
- Charts:** A window titled "apoptosis" showing a line graph of the simulation results. The graph plots the concentration of Fas ligand (red line), DNA fragment (green line), DFF40 (blue line), pro-caspase8 (yellow line), and caspase8 (purple line) over time. The x-axis represents time, and the y-axis represents concentration.

Regulatory Pathway for Cell Cycle of Budding Yeast



HFPN Model of Budding Yeast Cell Cycle



Circadian Rhythm by E-CELL

The screenshot displays the E-Cell software interface with several windows open:

- E-Cell Control Panel:** Shows the menu (File, New Interface, Windows), the current rule and script (Rule: [test] Script: [Dro]), and the elapsed time (3388392.051000). It includes Start, Stop, and Step buttons and a logo with the letter 'e'.
- Preferences:** A dialog box with 'Step interval' set to 1.000000 and 'Update interval' set to 100.
- Table:** A table listing substances and reactors. The highlighted row is:

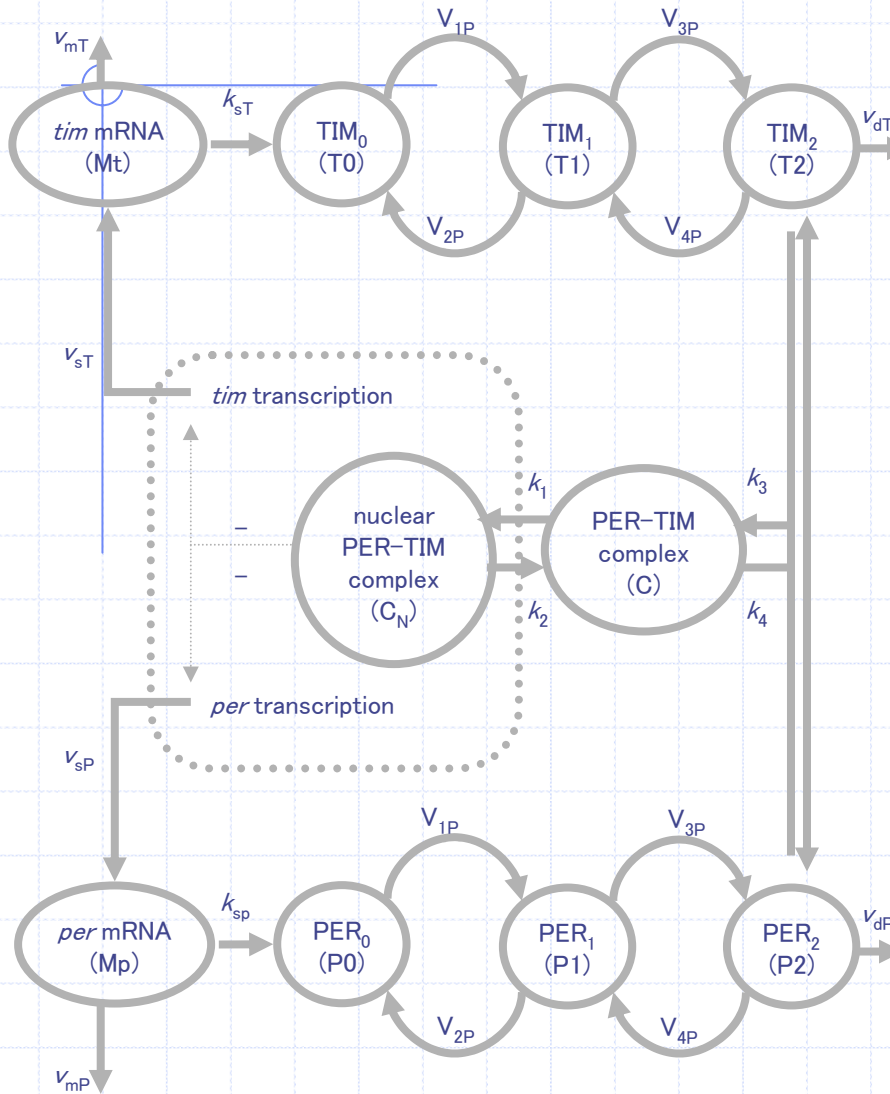
Type	Class	path	ID	Name	S_ID
Reactor	NuclearComplex	/CELL/CYTOPLASM	C-0	Transport C	
- Substance: /CELL/CYTOPLASM:P1:** A detail window for Substance P1, showing its entry name, name, quantity (3394.8888), and concentration (8.646614).
- Traces:** A plot showing the time evolution of various substances (C, CN, Mp, P0, P1, P2) over time. The x-axis ranges from 2.444e+05 to 1.5e+06, and the y-axis ranges from -0.4 to 4.04. The plot shows oscillatory behavior for several substances.
- vedit:** A text editor window displaying the model's metadata and description, including the author's name (Mika), email (mika@m.oshima-k.ac.jp), and a brief description of the reactor for the Michaelis-Menten reaction in circadian rhythm of Drosophila. It also shows the chemical equation:

$$S + E \rightleftharpoons v_m P + E$$
 and the rate equation:

$$v = v_m \frac{[S]}{K_m + [S]} \quad v_m = K_{cat} [E] t$$

Circadian Rhythm in *Drosophila*

(Leloup and Goldbeter, 1998)



Kinetic Equations

$$\frac{dM_P}{dt} = v_{sP} \frac{K_{IP}^n}{K_{IP}^n + C_N^n} - v_{mP} \frac{M_P}{K_{mP} + M_P} - k_d M_P$$

$$\frac{dP_0}{dt} = k_{sP} M_P - V_{1P} \frac{P_0}{K_{1P} + P_0} + V_{2P} \frac{P_1}{K_{2P} + P_1} - k_d P_0$$

$$\frac{dC}{dt} = K_3 P_2 T_2 - k_4 C - k_1 C + k_2 C_N - k_{dC} C$$

$$\frac{dP_1}{dt} = V_{1P} \frac{P_0}{K_{1P} + P_0} - V_{2P} \frac{P_1}{K_{2P} + P_1} - V_{3P} \frac{P_2}{K_{3P} + P_2} + V_{4P} \frac{P_2}{K_{4P} + P_2} - k_d P_1$$

$$\frac{dP_2}{dt} = V_{3P} \frac{P_2}{K_{3P} + P_2} - V_{4P} \frac{P_2}{K_{4P} + P_2} - K_3 P_2 T_2 + k_4 C - v_{dP} \frac{P_2}{K_{dP} + P_2} - k_d P_2$$

$$\frac{dC_N}{dt} = k_1 C - k_2 C_N - k_{dN} C$$

Equations for *tim mRNA* and TIM_i are obtained by substituting P_i to T_i ($i=0,1,2$) and suffix p to t .

making E-CELL file

Rule file (Spread Sheet)

Type	path	ID	Name
Substance	/CELL/CYTOPLASM	A	Substance A
Substance	/CELL/CYTOPLASM	B	Substance B
Substance	/CELL/CYTOPLASM	C	Substance C
Substance	/CELL/CYTOPLASM	D	Substance D
Substance	/CELL/CYTOPLASM	E	Substance E

Type	Class	path	ID	Name
Reactor	<u>MichaelisUniUniReactor</u>	/CELL/CYTOPLASM	A-0	Isomerization of A
Reactor	<u>MichaelisUniUniReversibleReactor</u>	/CELL/CYTOPLASM	B-0	Isomerization of B

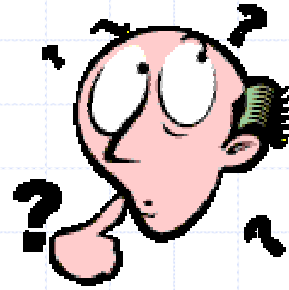
Reactor(rd-file)

MichaelisUniUniReactor.rd

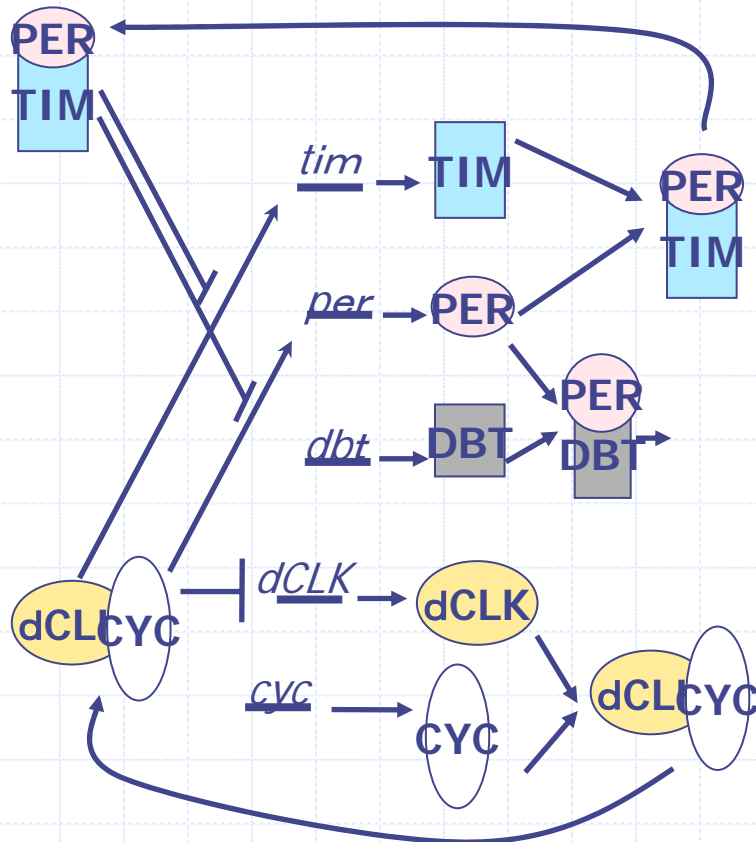
$$v = \frac{K_{cF} [E][S]}{K_{mS} + [S]}$$

MichaelisUniUniReversibleReactor.rd

$$v = \frac{(K_{cF} K_{mP} [S] - K_{cR} K_{mS} [P])[E]}{K_{mS} [P] + K_{mP} [S] + K_{mS} K_{mP}}$$



Biological Pathways



Differential Equations

$$\frac{dM_P}{dt} = v_{sP} \frac{K_{IP}^n}{K_{IP}^n + C_N^n} - v_{mP} \frac{M_P}{K_{mP} + M_P} - k_d M_P$$

$$\frac{dP_0}{dt} = k_{sP} M_P - V_{1P} \frac{P_0}{K_{1P} + P_0} + V_{2P} \frac{P_1}{K_{2P} + P_1} - k_d P_0$$

$$\frac{dC}{dt} = K_3 P_2 T_2 - k_4 C - k_1 C + k_2 C_N - k_{dC} C$$

$$\frac{dP_1}{dt} = V_{1P} \frac{P_0}{K_{1P} + P_0} - V_{2P} \frac{P_1}{K_{2P} + P_1} - V_{3P} \frac{P_2}{K_{3P} + P_2} + V_{4P} \frac{P_2}{K_{4P} + P_2} - k_d P_1$$

$$\frac{dP_2}{dt} = V_{3P} \frac{P_2}{K_{3P} + P_2} - V_{4P} \frac{P_2}{K_{4P} + P_2} - K_3 P_2 T_2 + k_4 C - v_{dP} \frac{P_2}{K_{dP} + P_2} - k_d P_2$$

$$\frac{dC_N}{dt} = k_1 C - k_2 C_N - k_{dN} C$$

Top-down approach

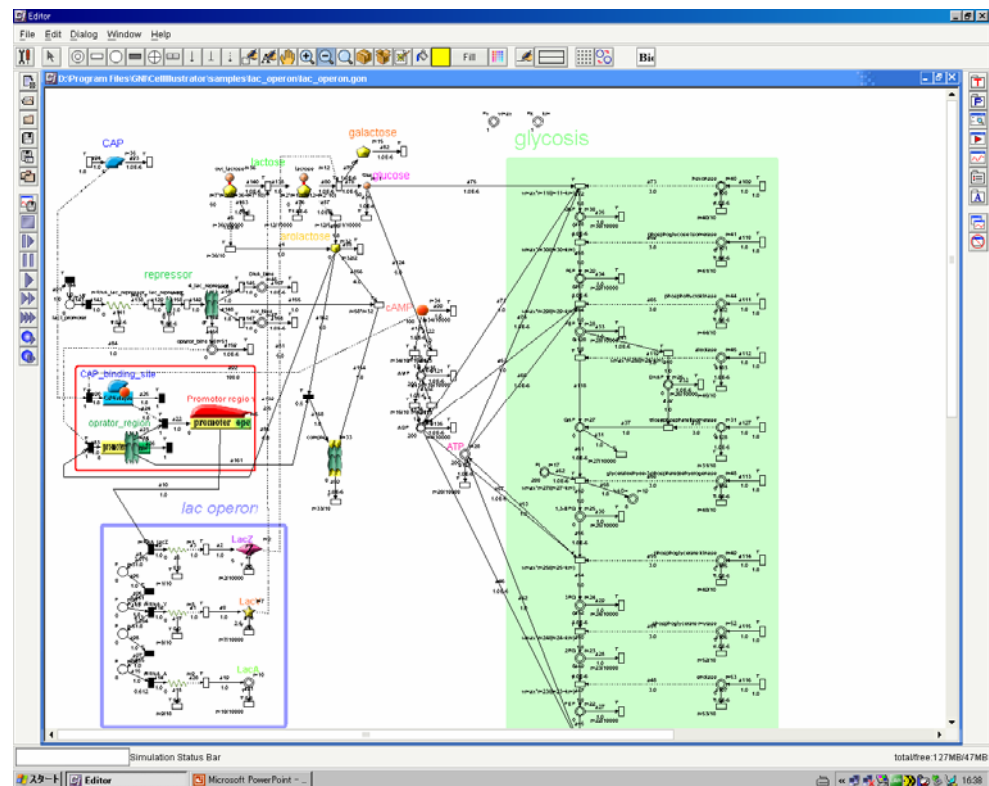
biological
pathway map



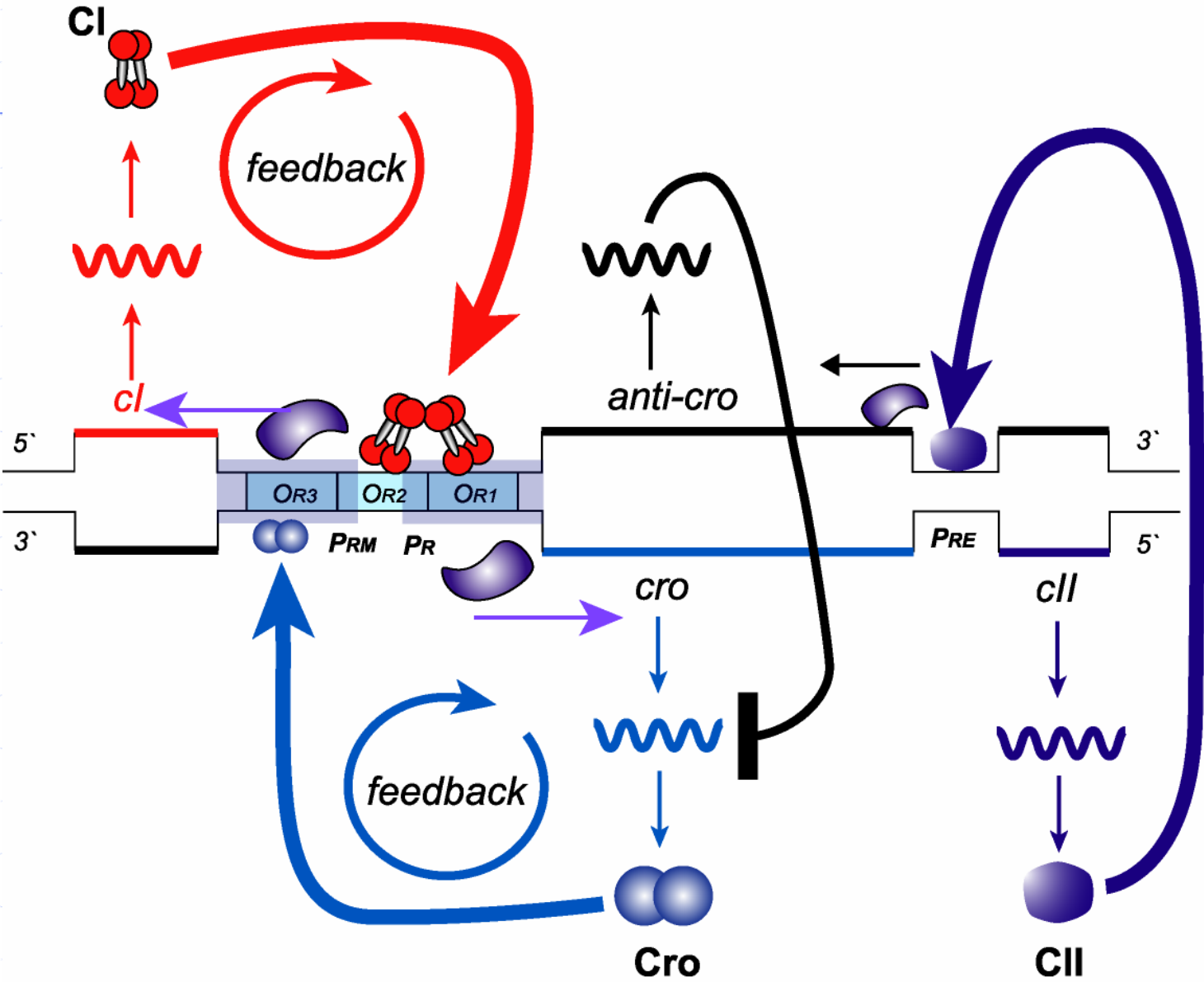
describe a structure
of biological pathway



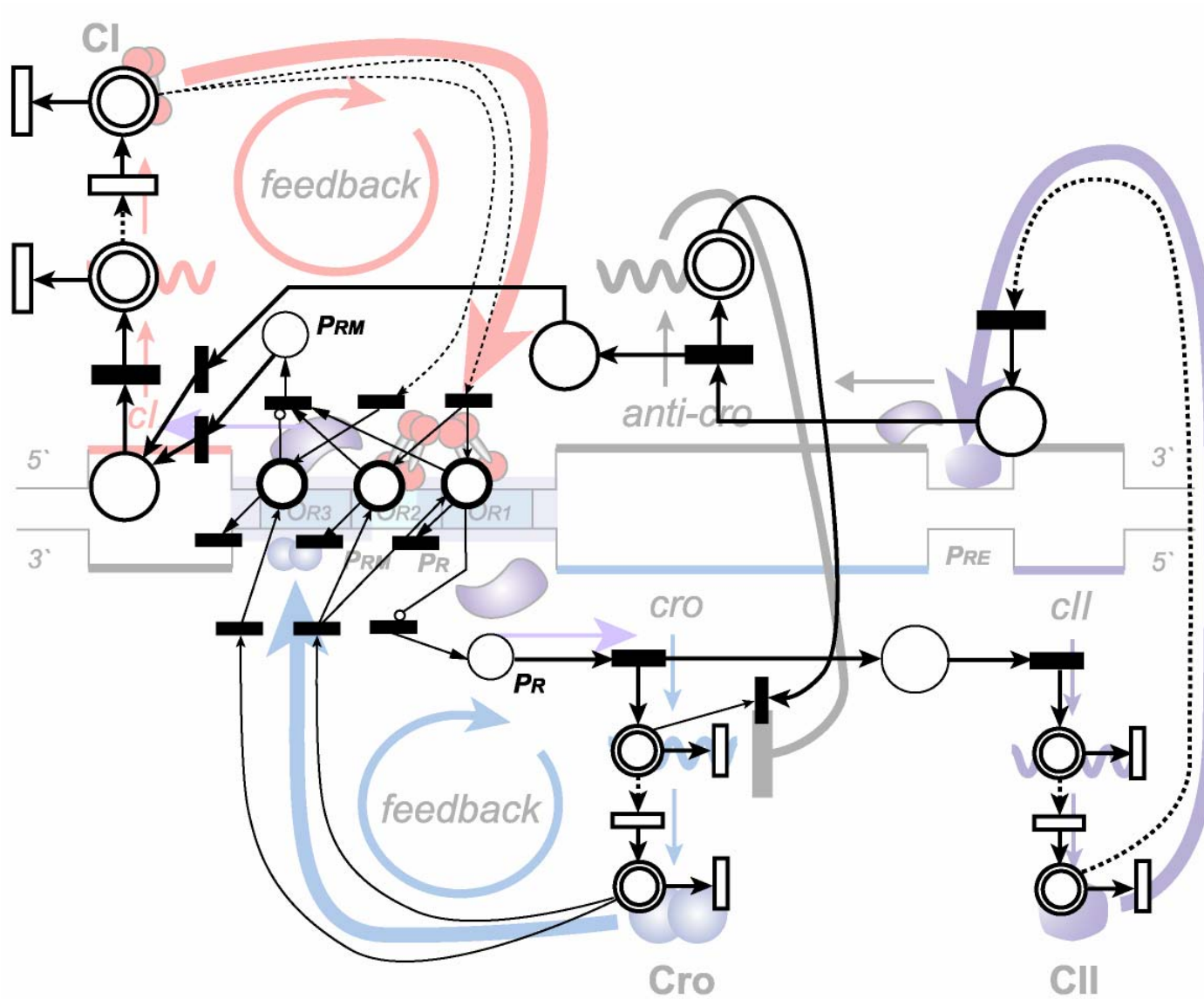
tuning parameters
with repeating
simulations



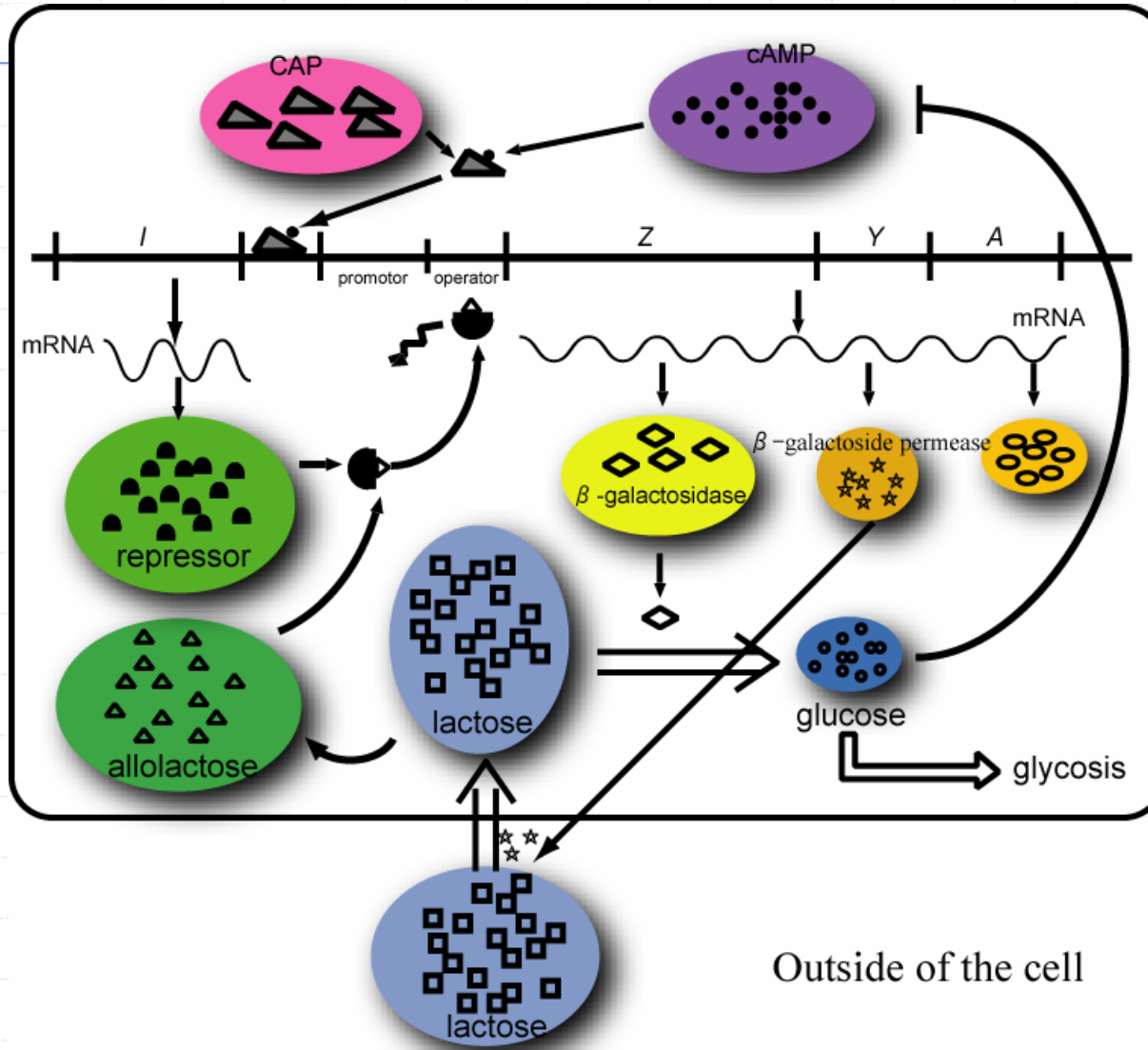
Lambda phage genetic switch feedback mechanism



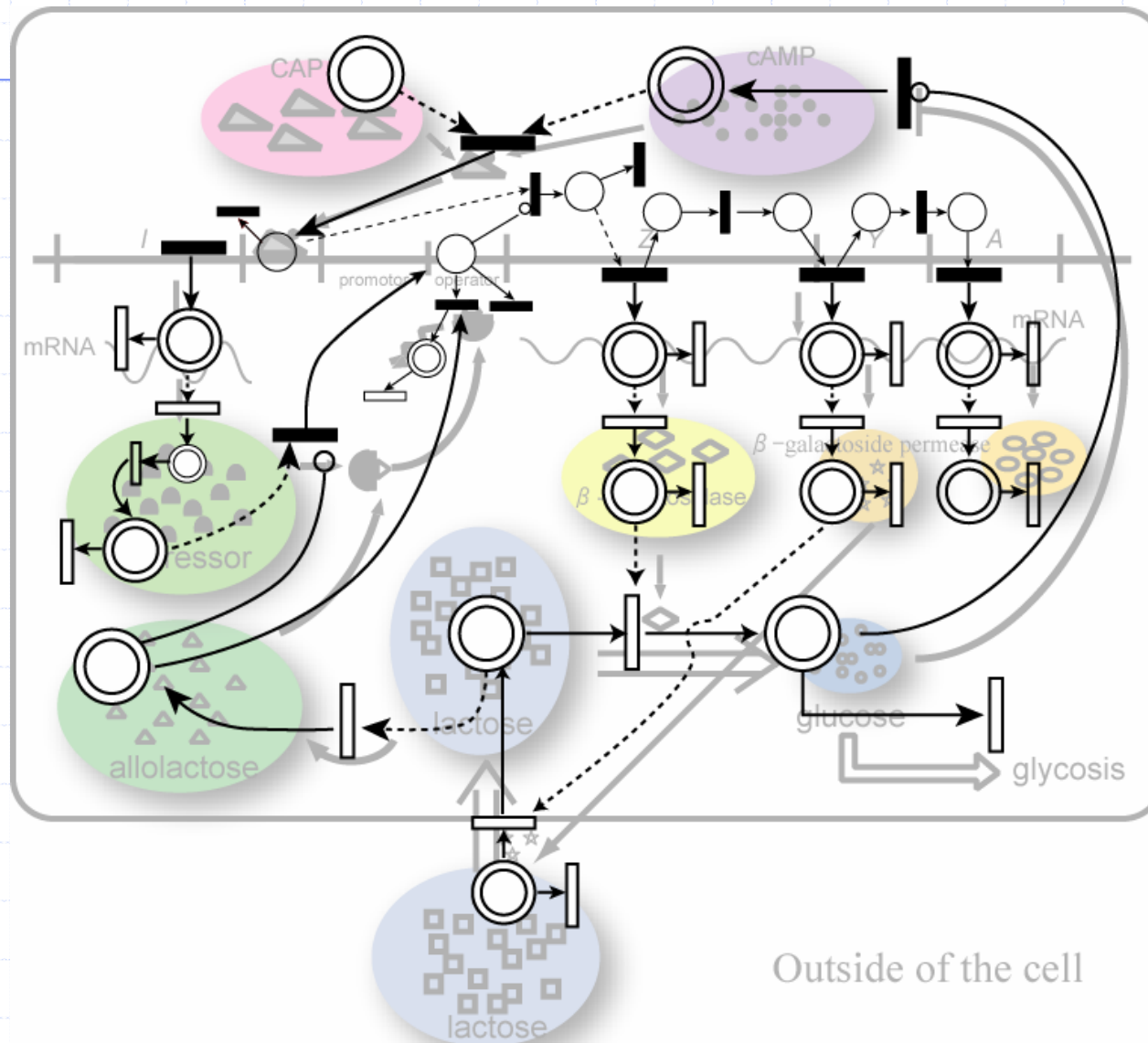
Lambda phage genetic switch feedback mechanism



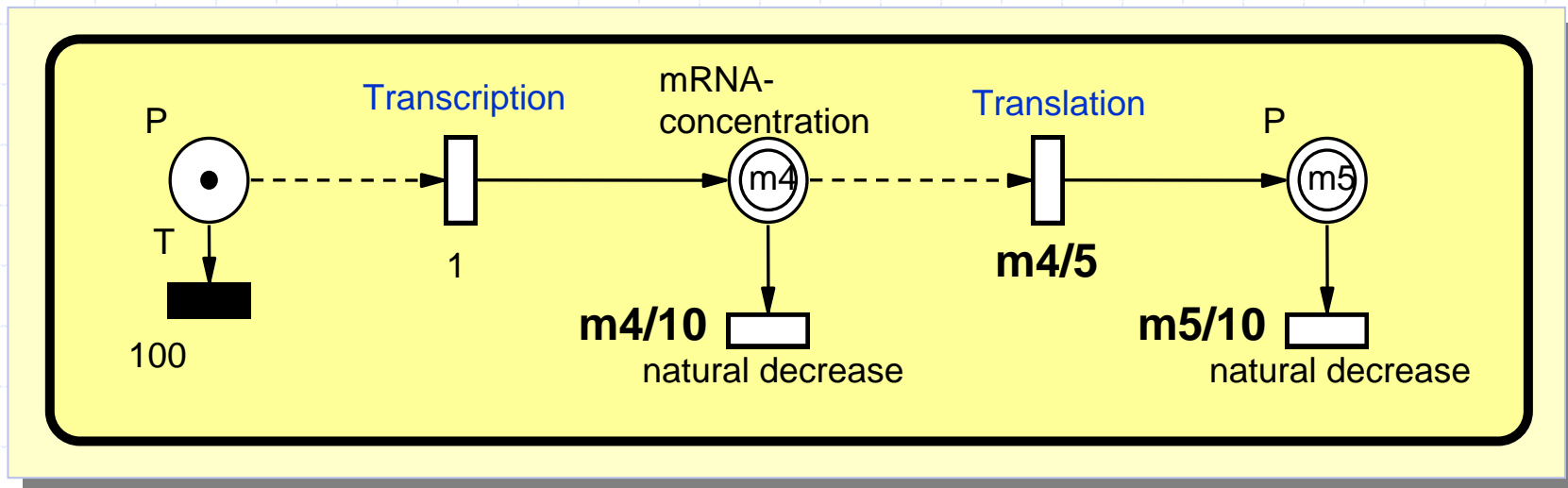
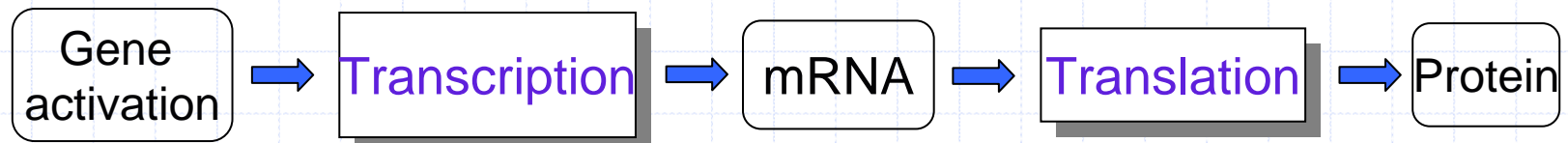
lac operon genetic switch control



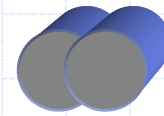
lac operon genetic switch control



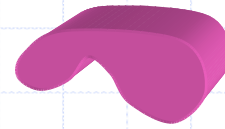
Modeling of the protein production process



Operon

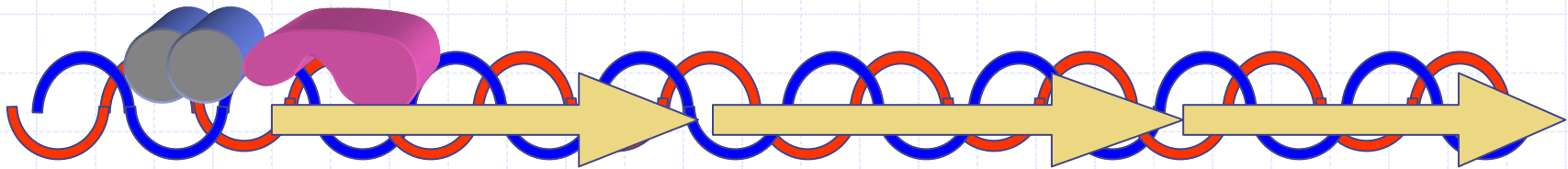


Protein



RNA polymerase

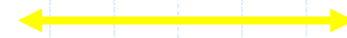
Promoter



Gene A

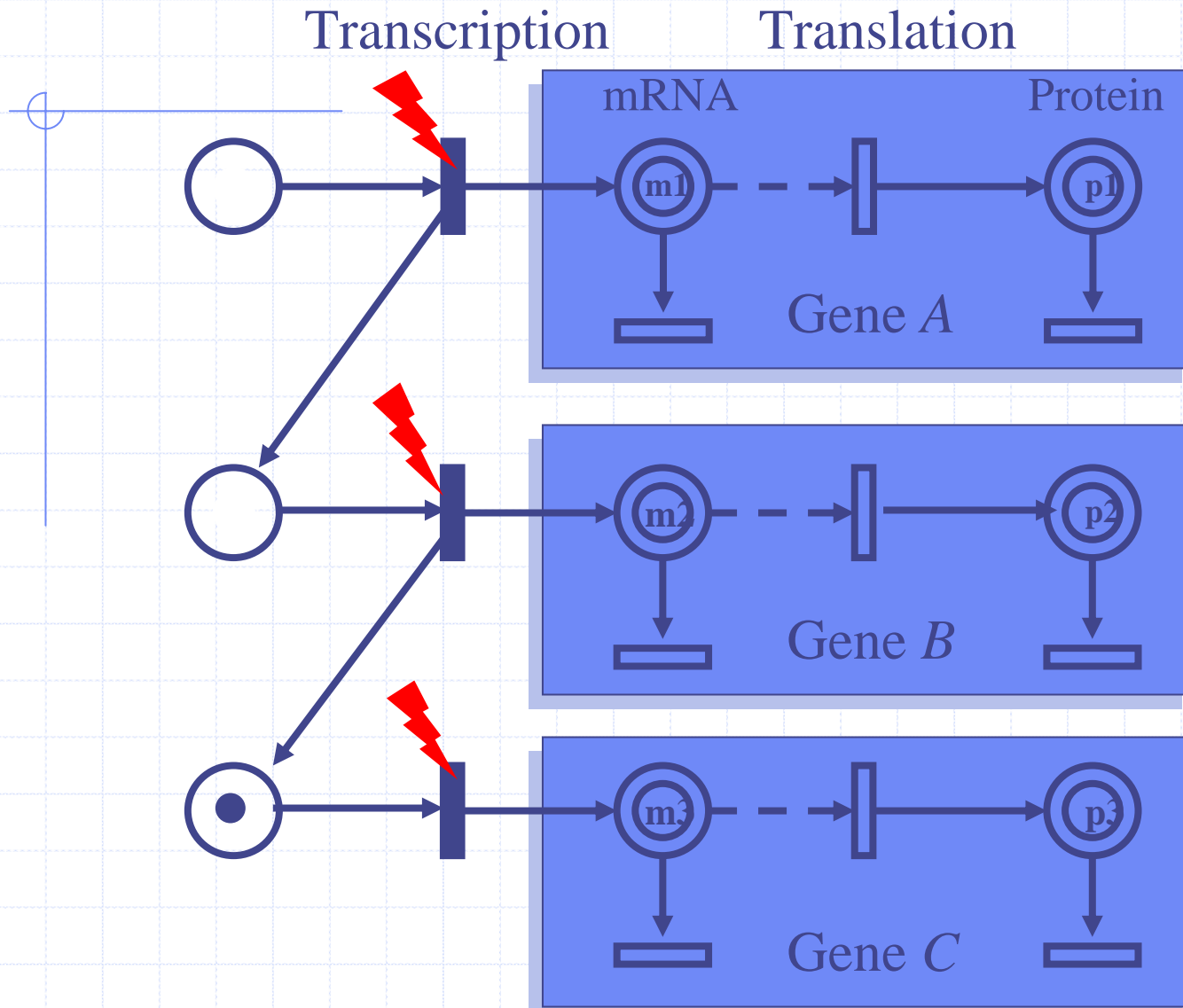


Gene B

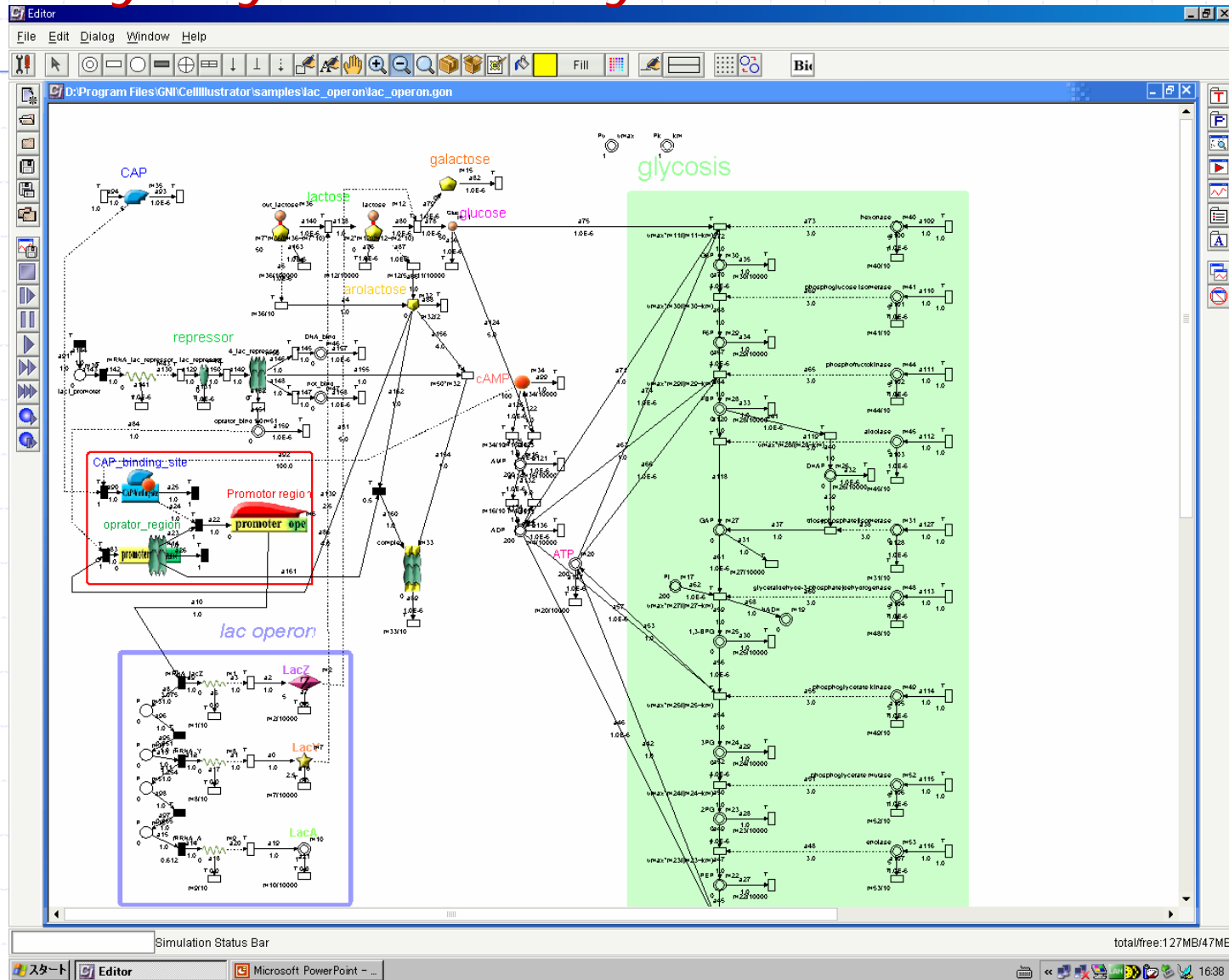


Gene C

Operon

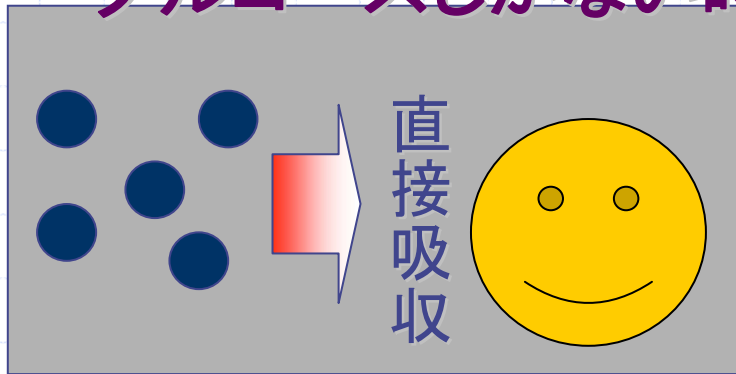


lac Operon Gene Regulatory Mechanism and Glycolytic Pathway

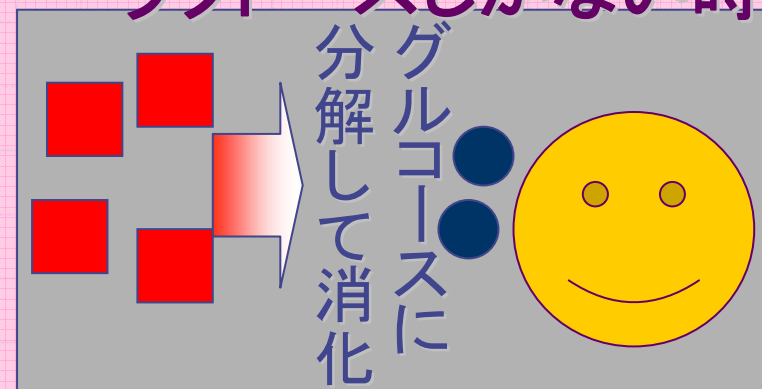


大腸菌の食生活

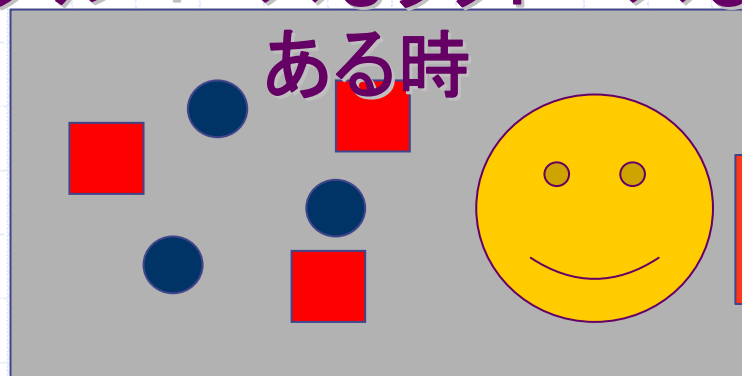
グルコースしかない時



ラクトースしかない時



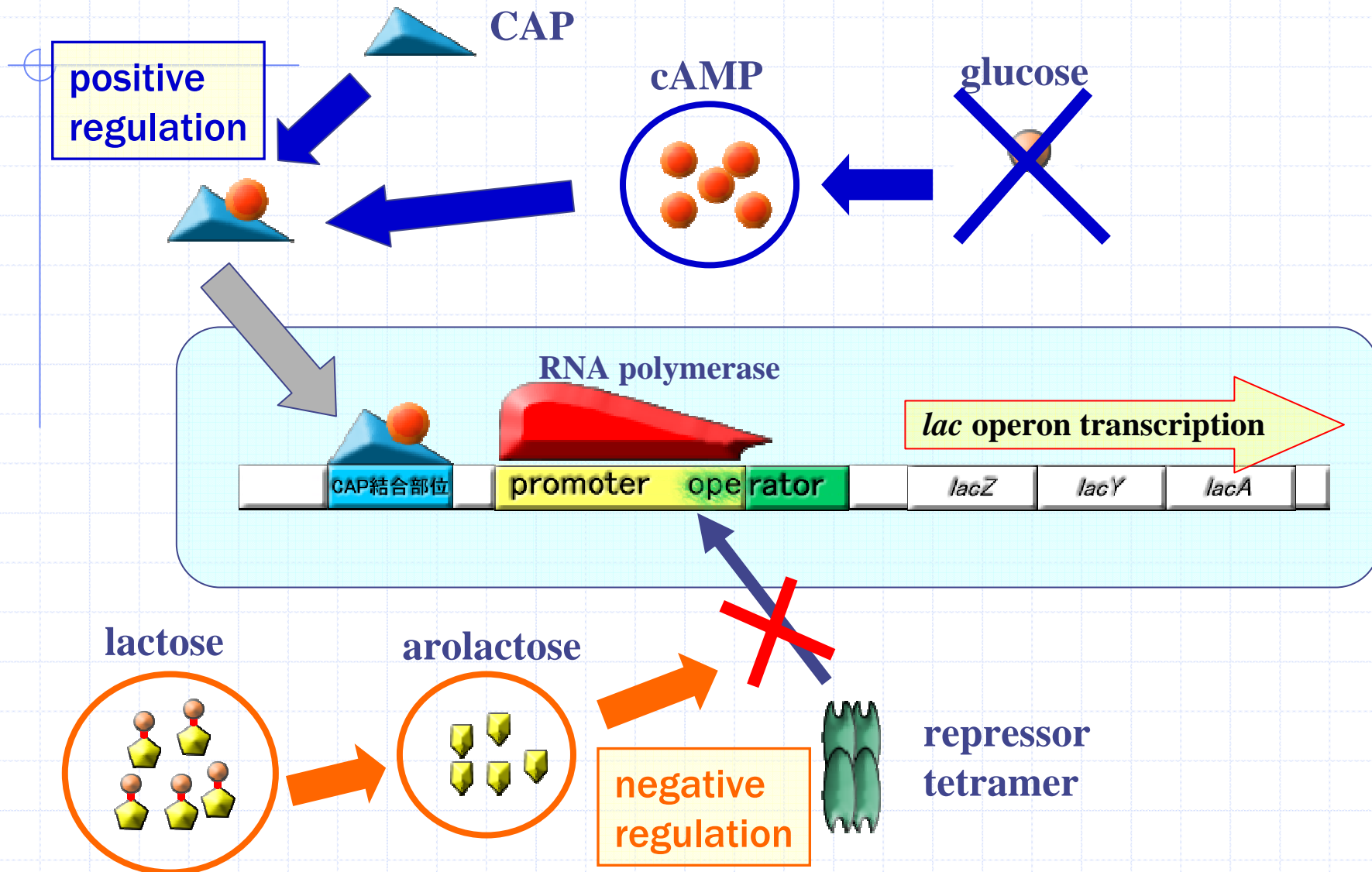
グルコースもラクトースもある時

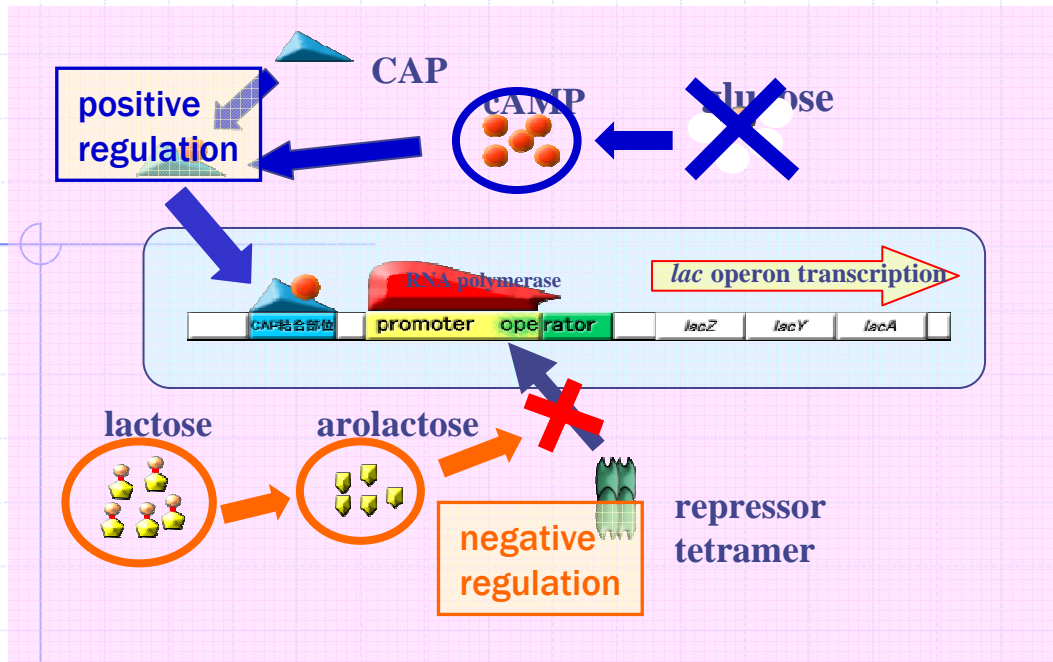


ラクトースから栄養を取らない



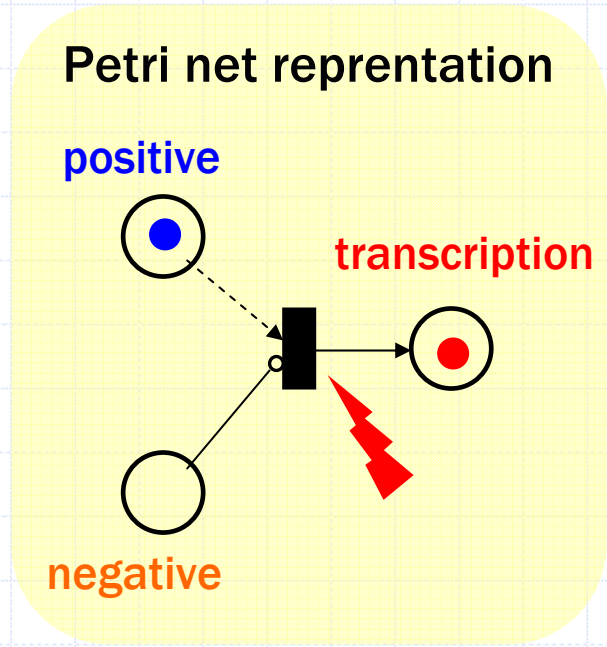
Positive regulation and Negative regulation



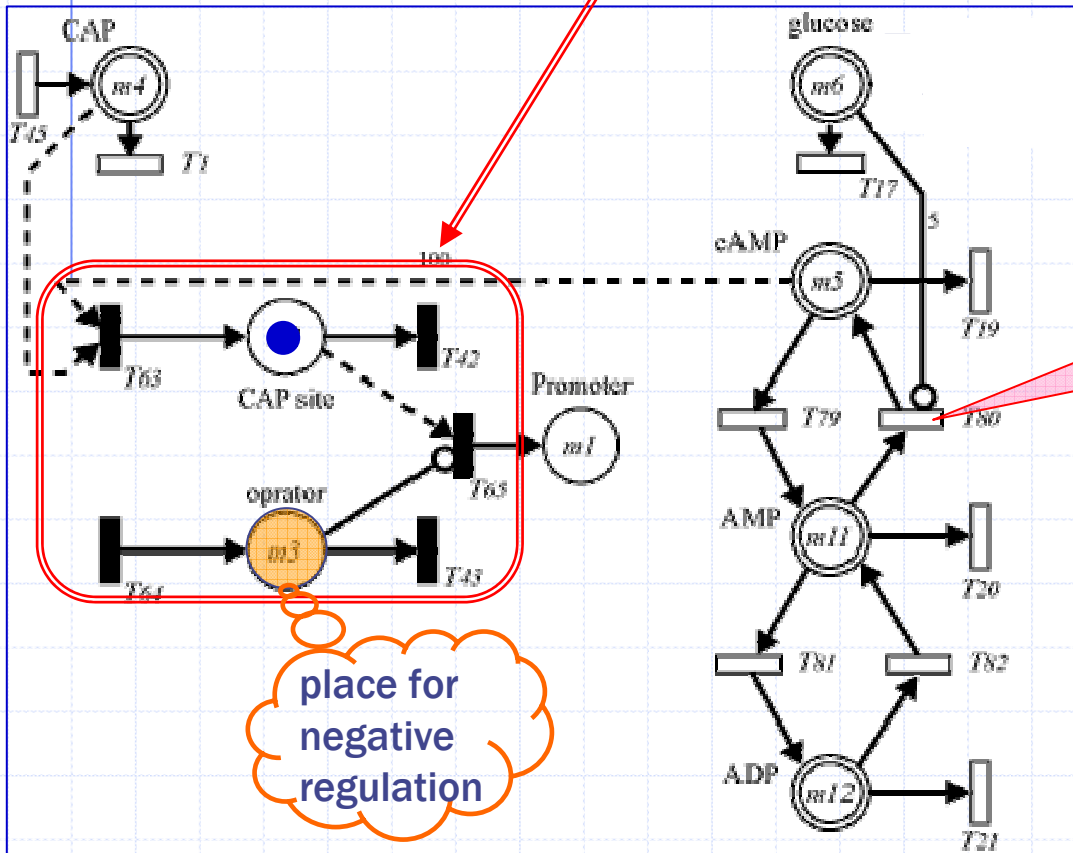
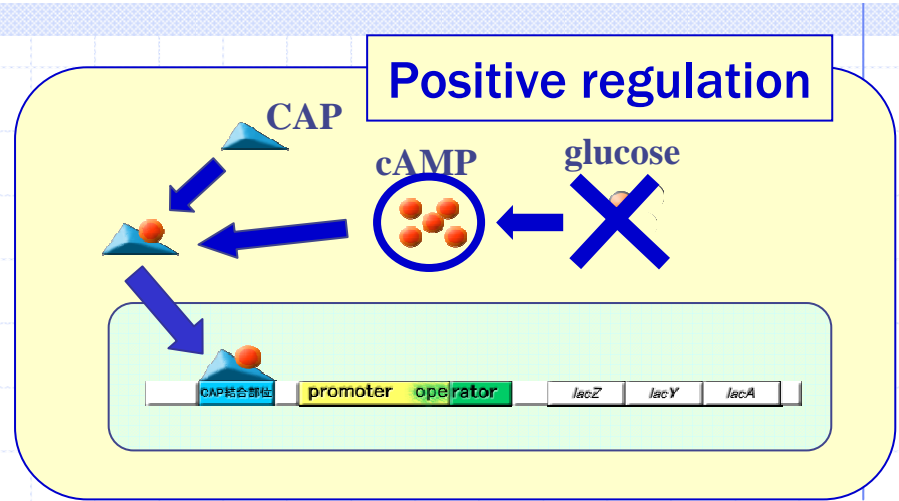


Transcription control switch

CAP with cAMP (positive factor)	repressor tetramer (negative factor)	transcription
yes	yes	no
yes	no	yes
no	yes	no
no	no	no

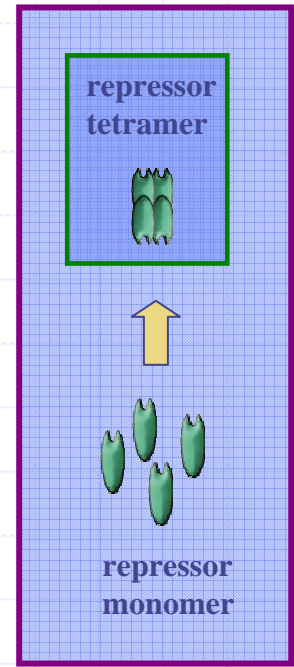
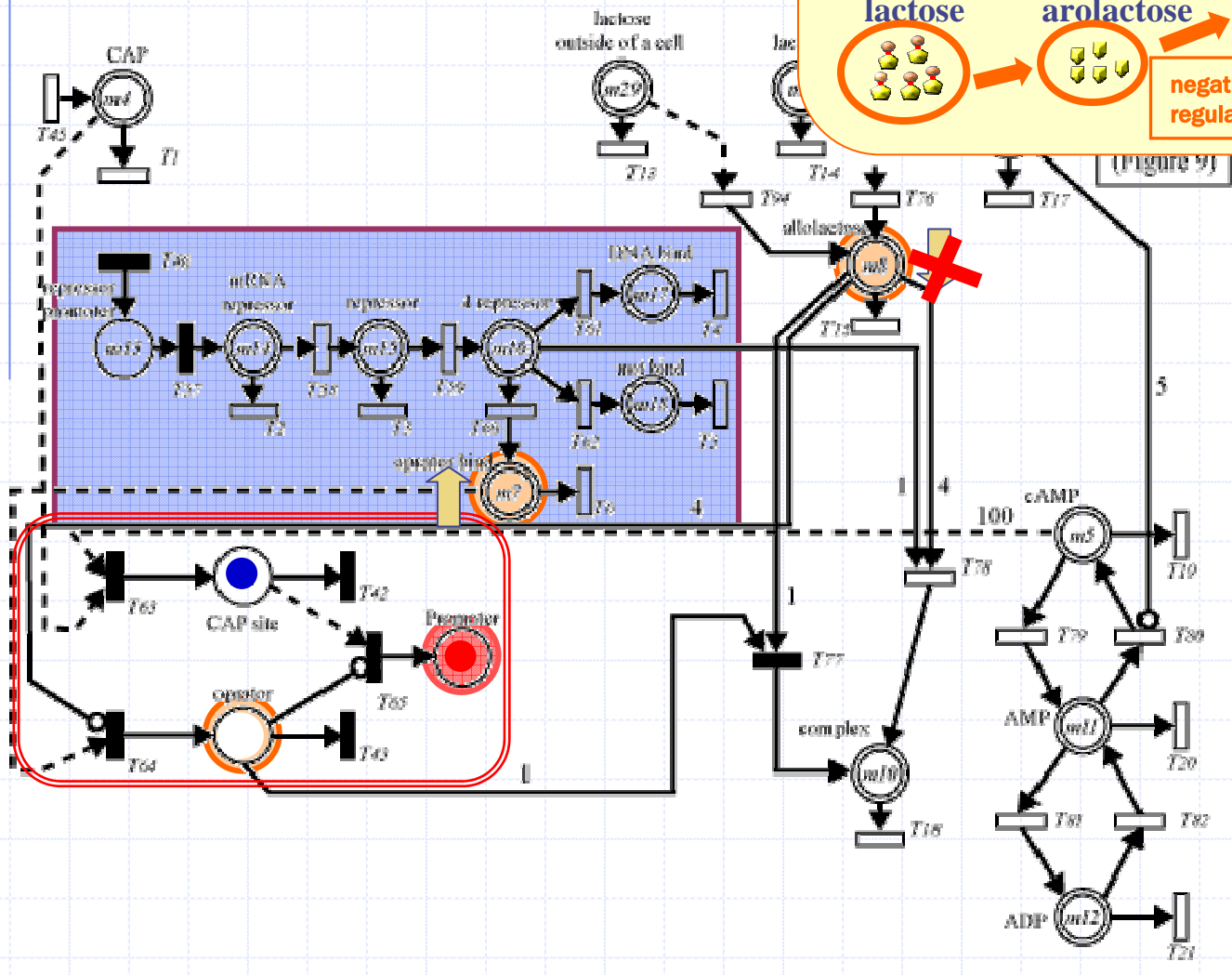
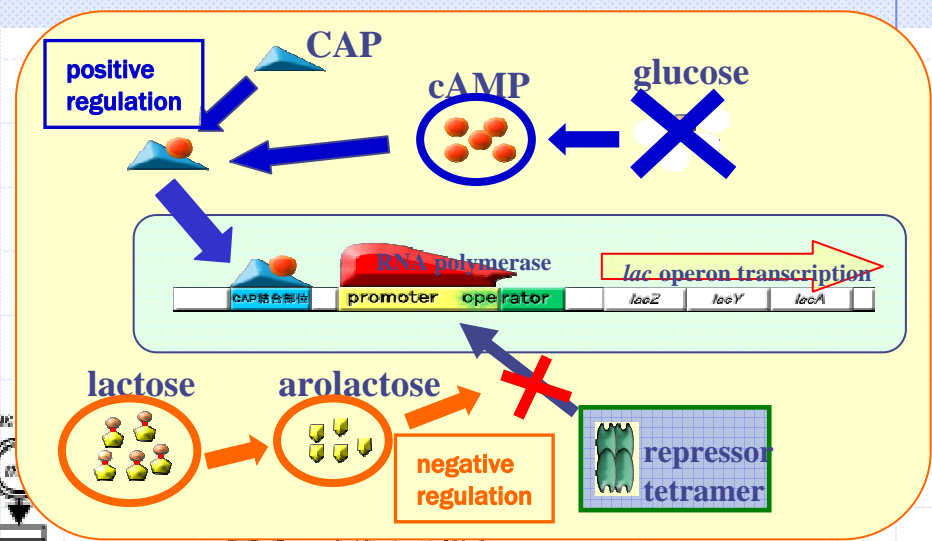


Transcription control switch and Positive regulation

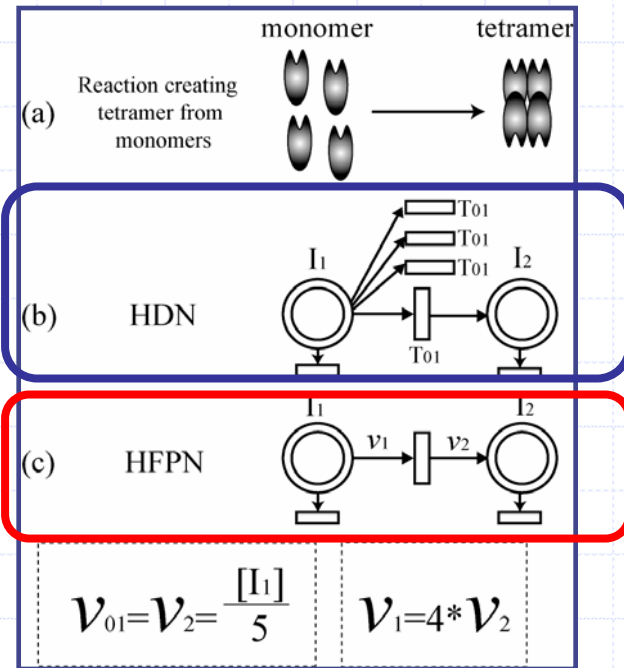
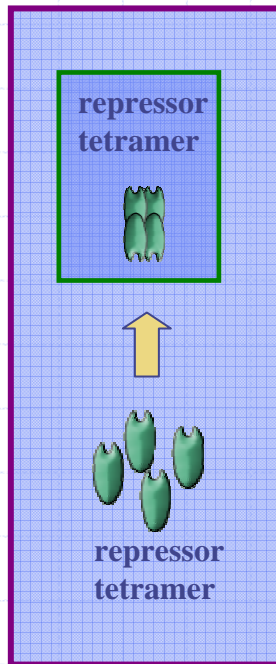
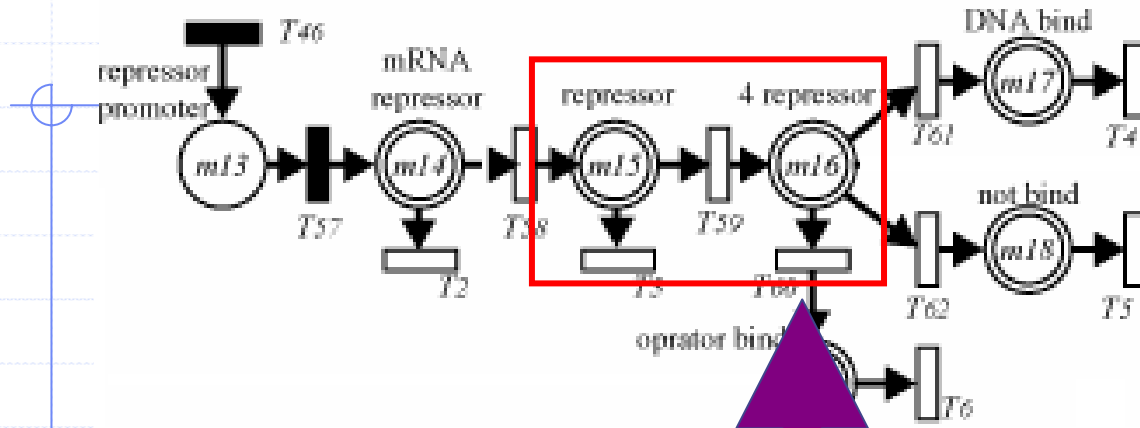


become active

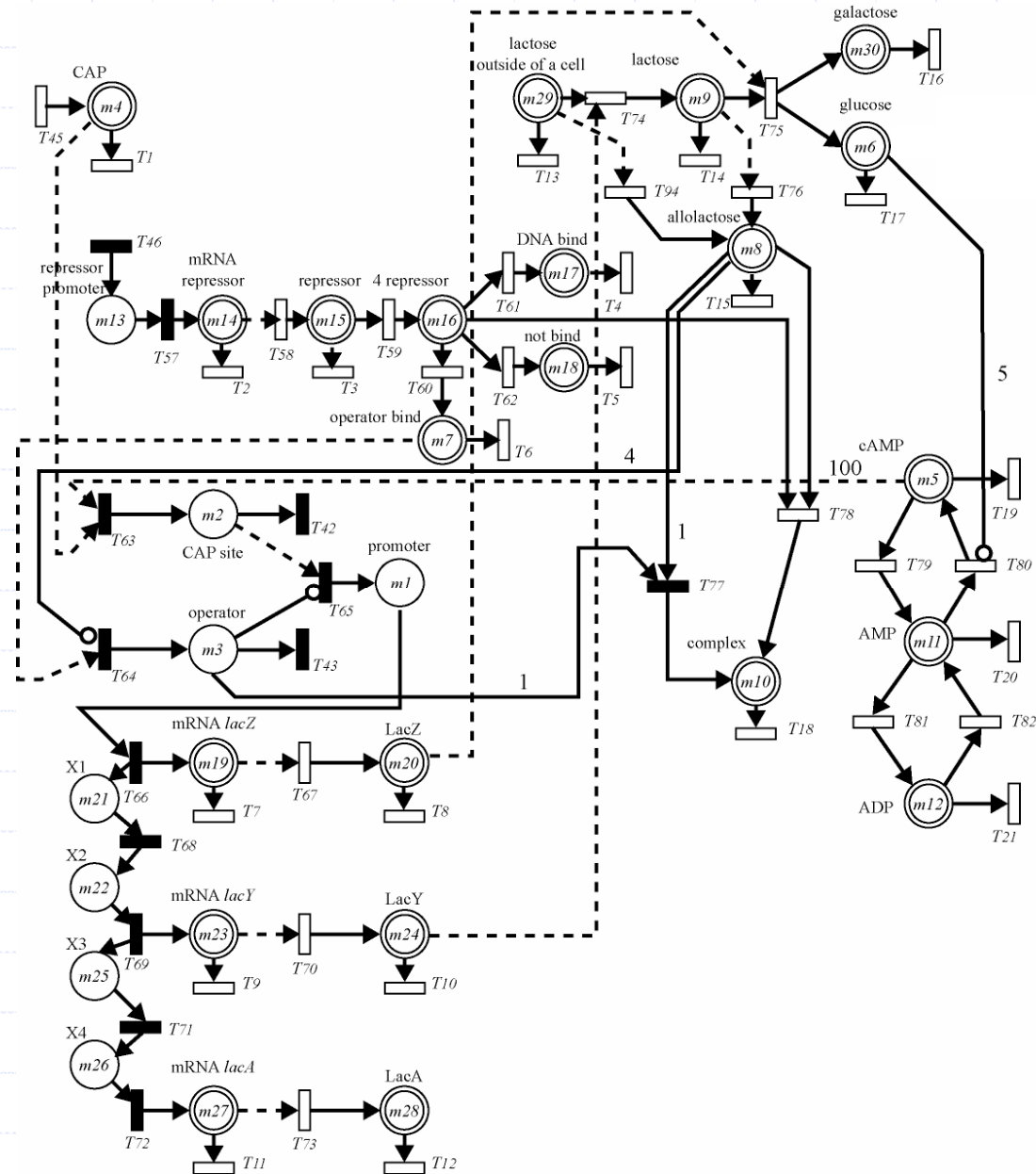
Beginning of the *lac* operon transcription



Usage of hybrid functional Petri net

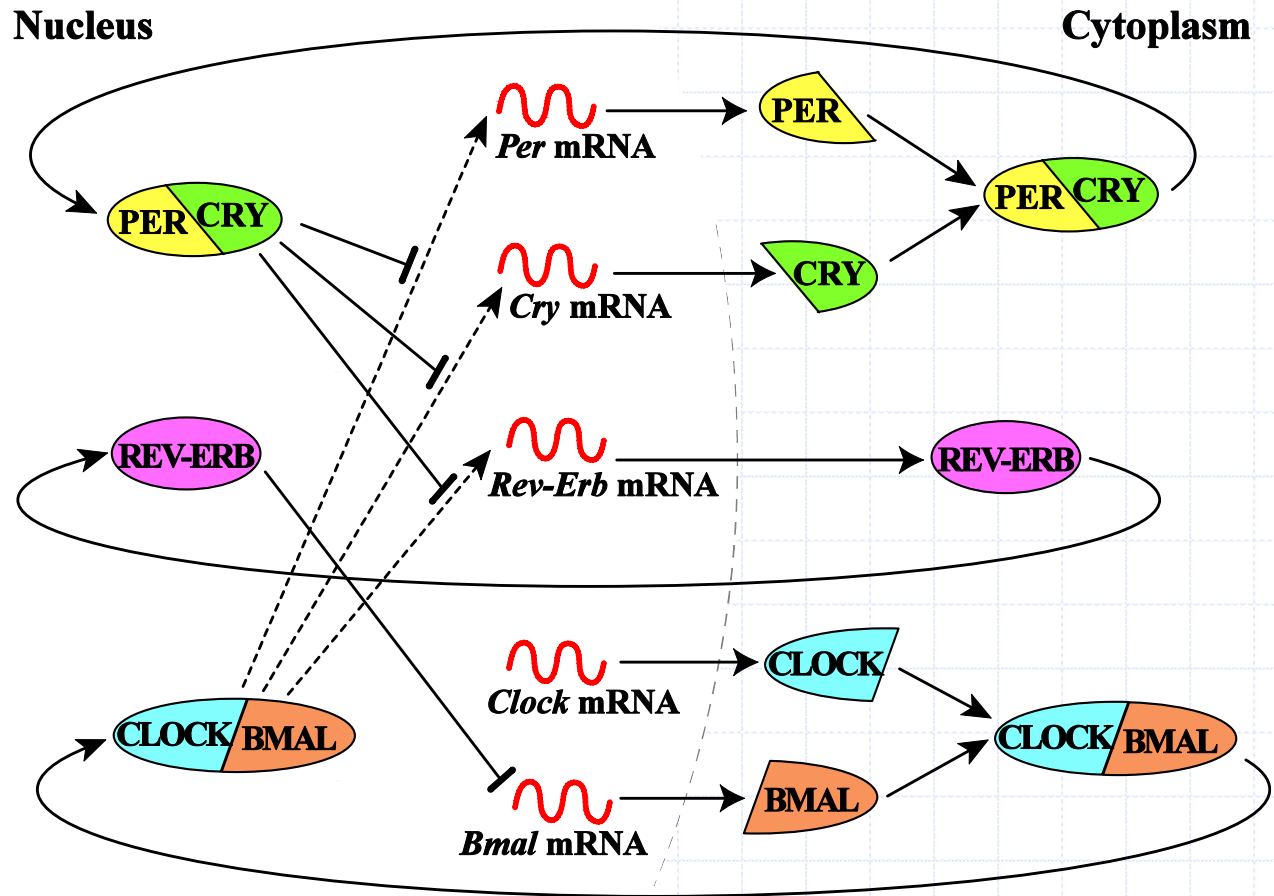


HFPN model of lac operon genetic control mechanism

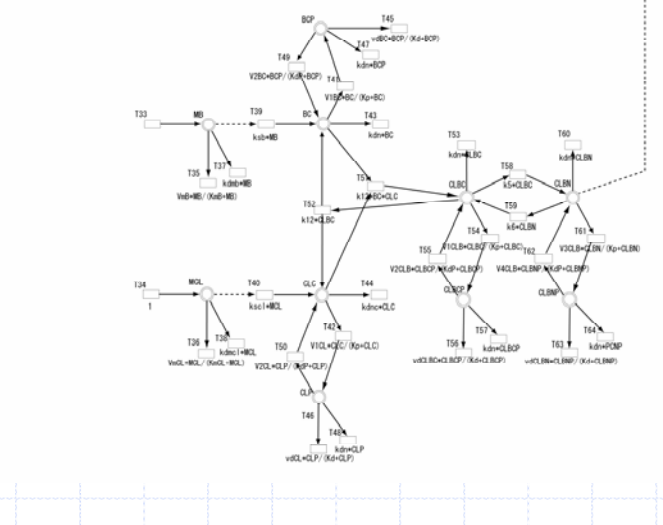
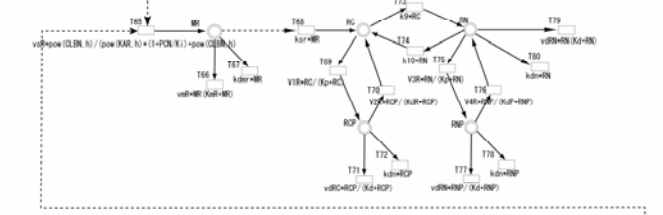
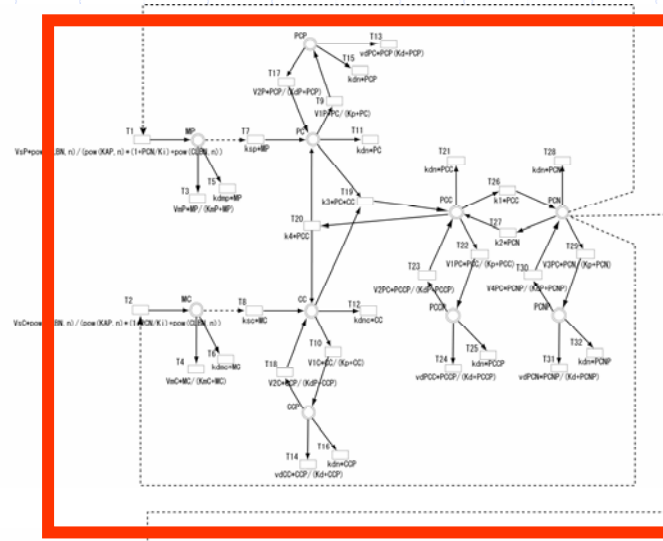
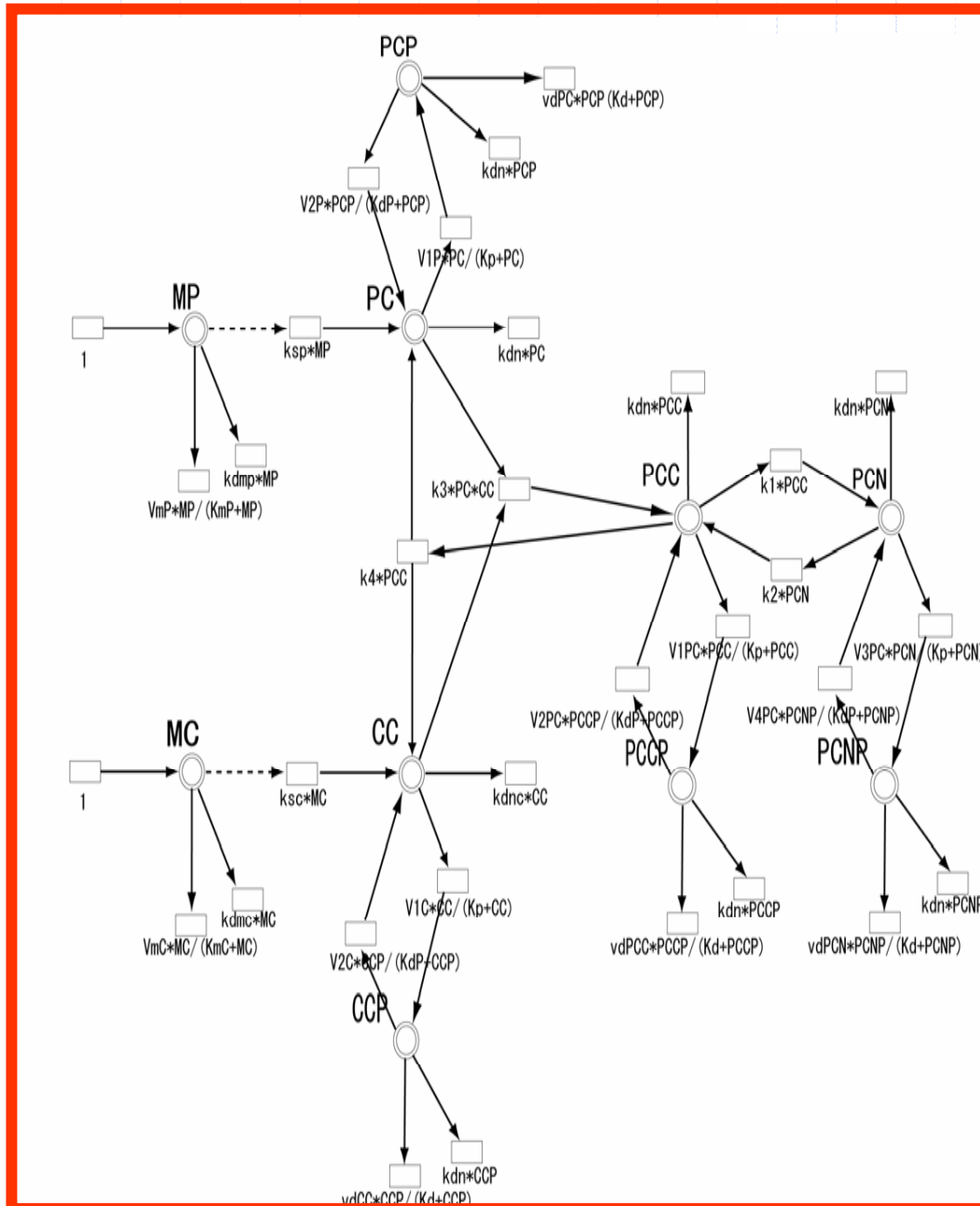


リズム

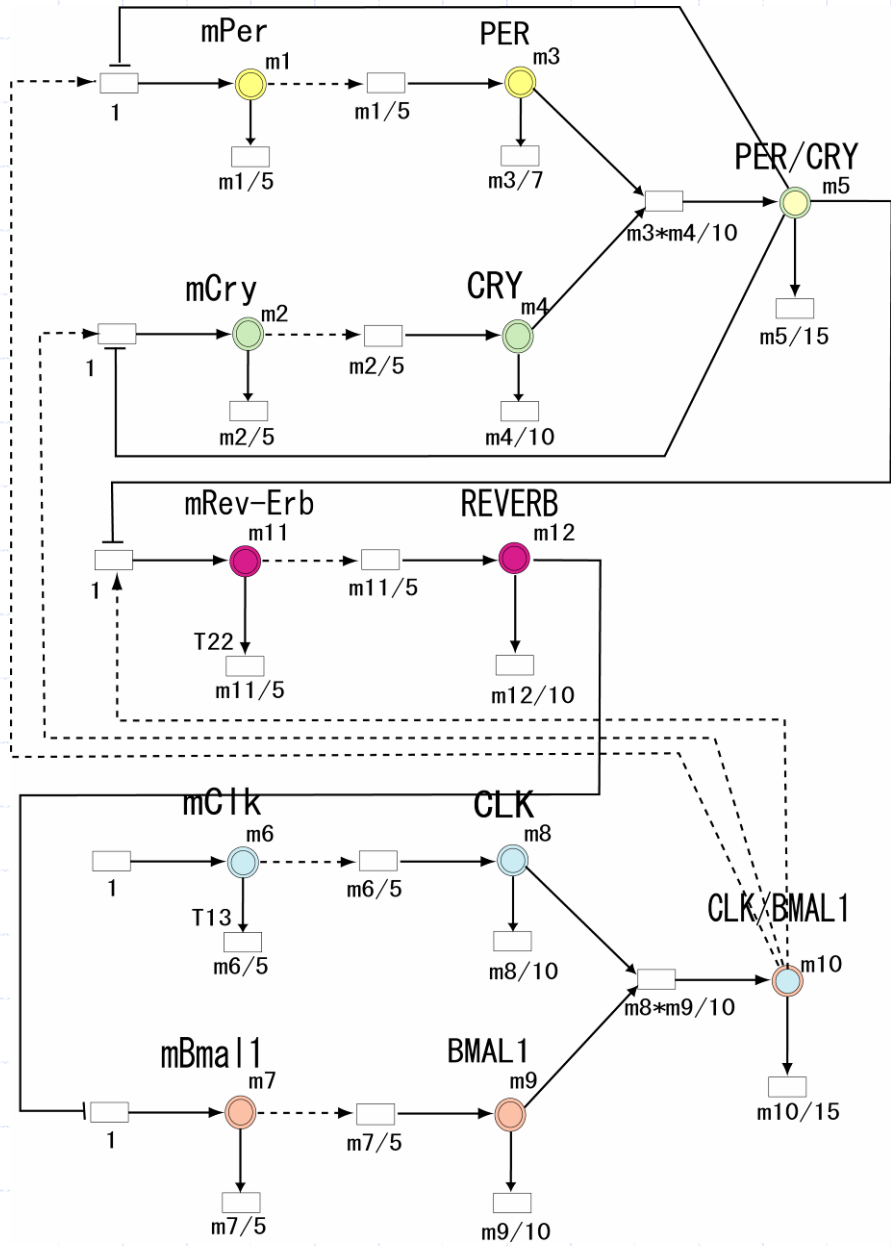
山口大 理 研との



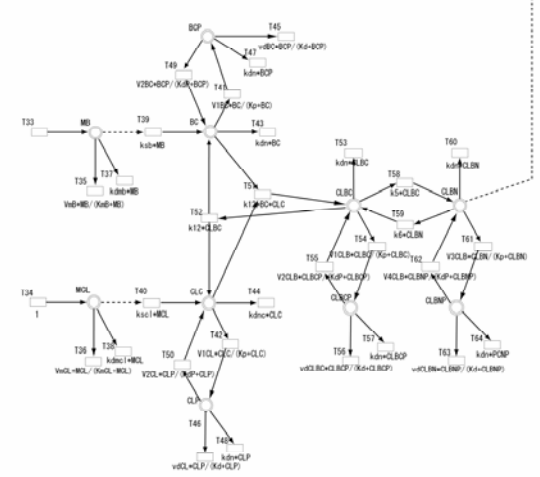
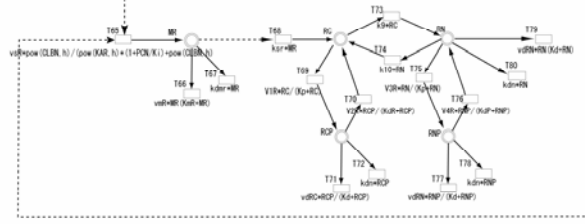
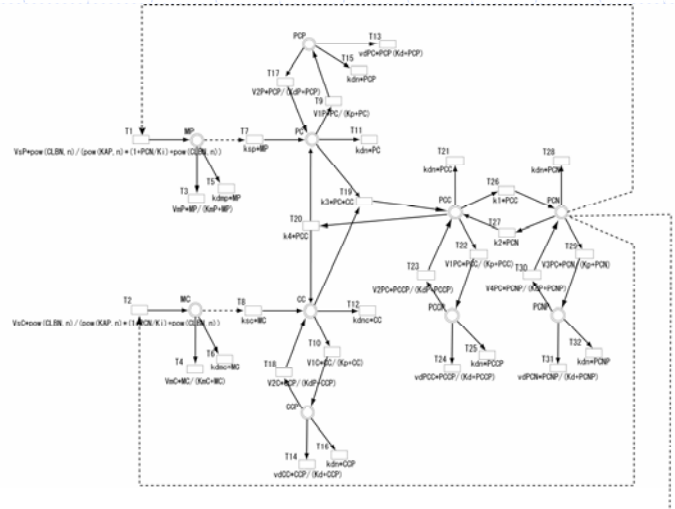
分によるル化 (Leloup & Goldbeter, 2003)



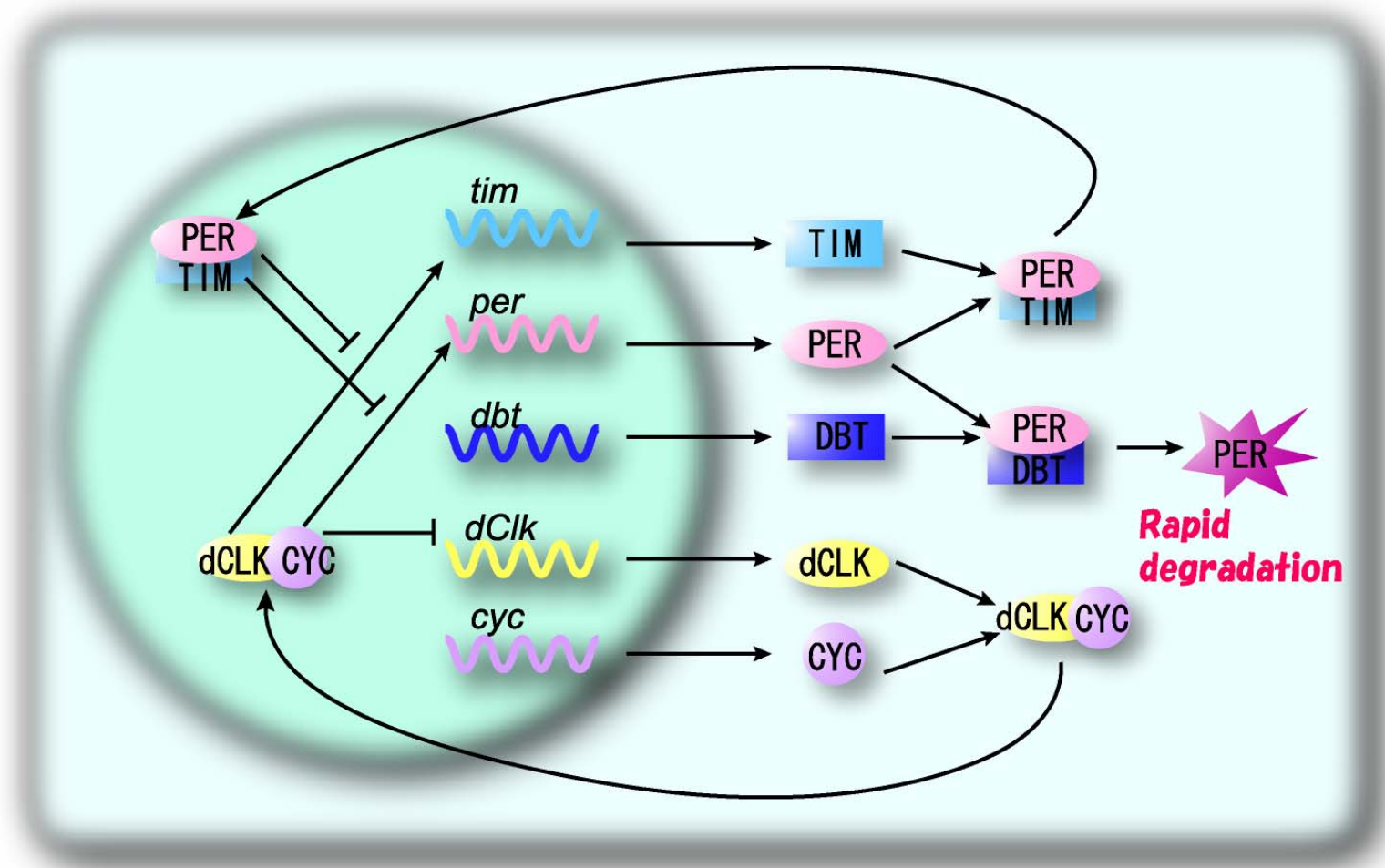
ル



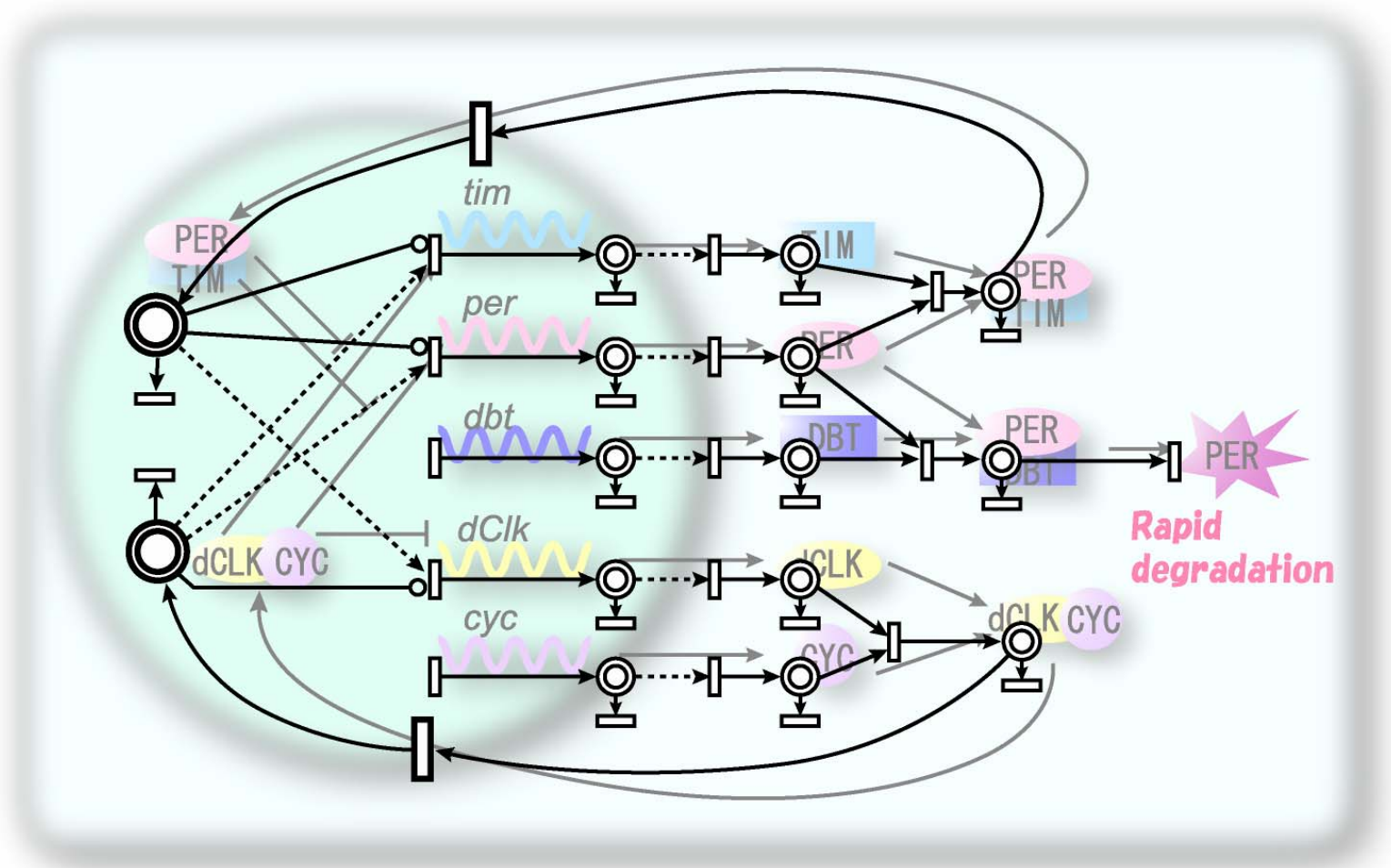
e
ース
oldbeter
ル



Gene Regulatory mechanism of *Drosophila* Circadian Clock

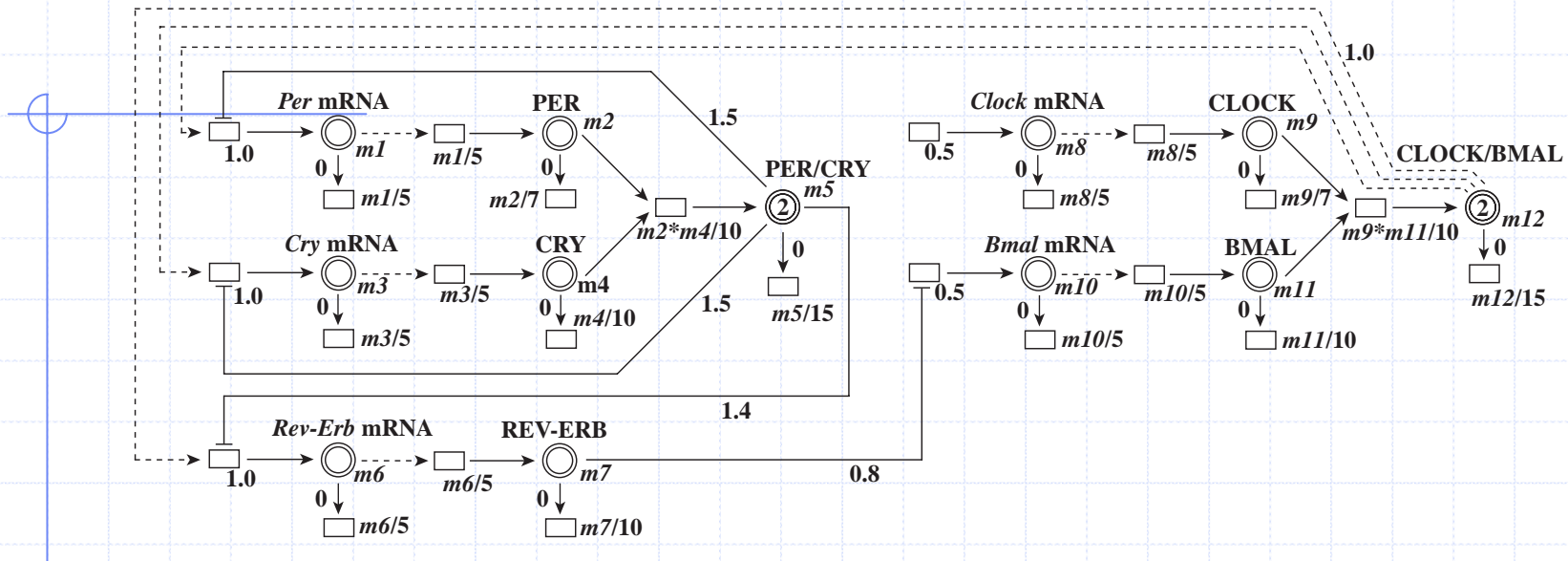


Gene Regulatory mechanism of *Drosophila* Circadian Clock

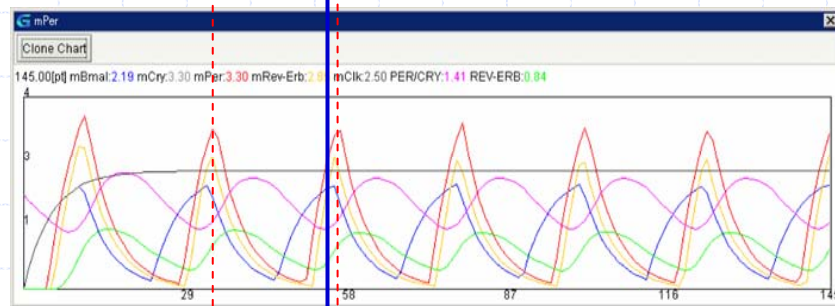


ウ ス 日 リ ム

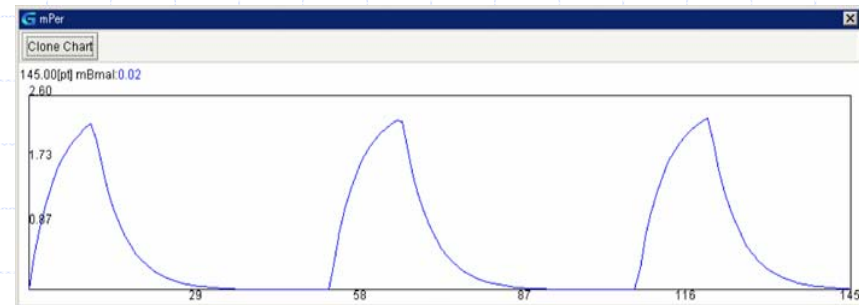
の イ リ ッ ペ ト リ ネ ッ ト ル



Cryを ッ ク ウ ト る と

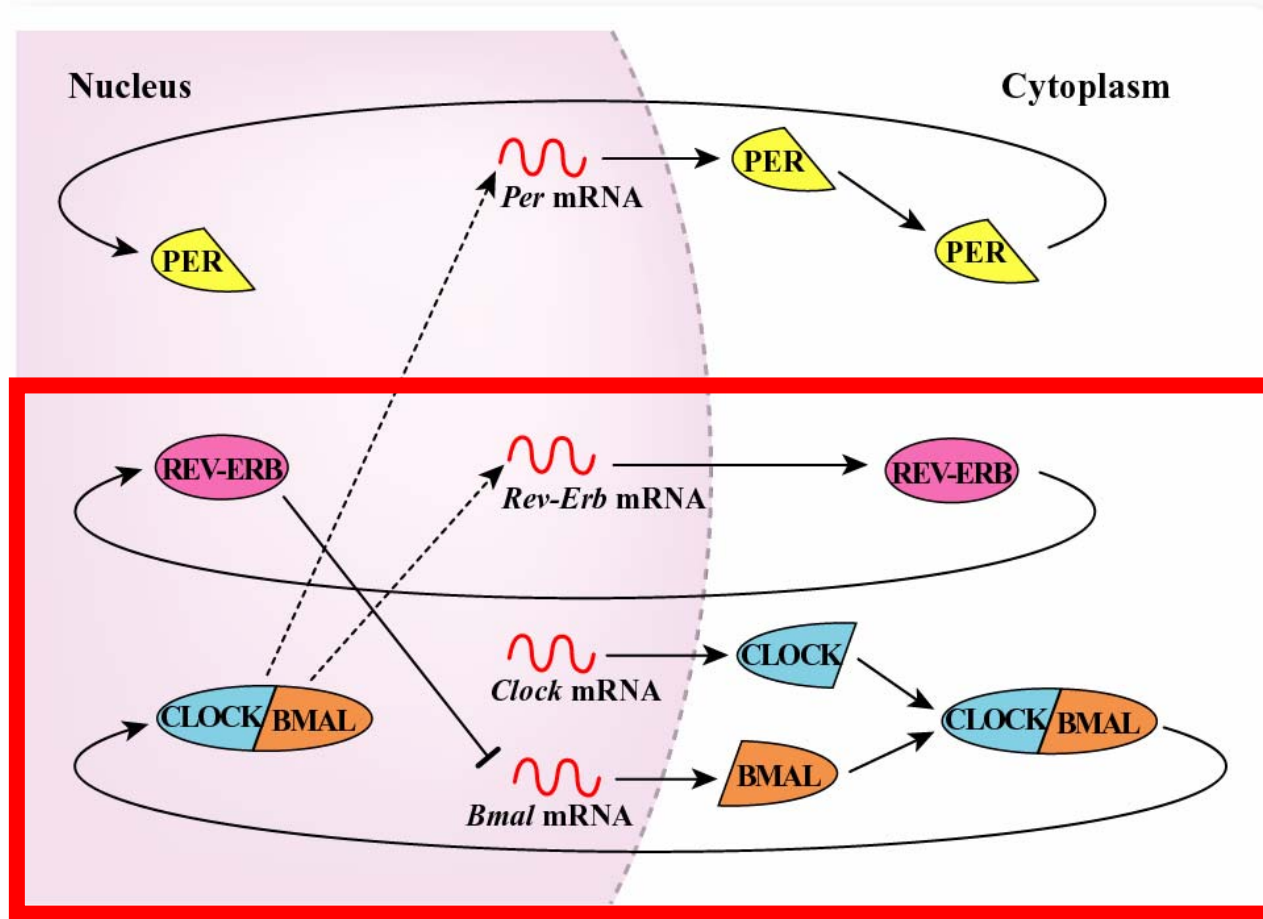


Bmal mRNAの 一ク Per mRNAの 一クの に しい

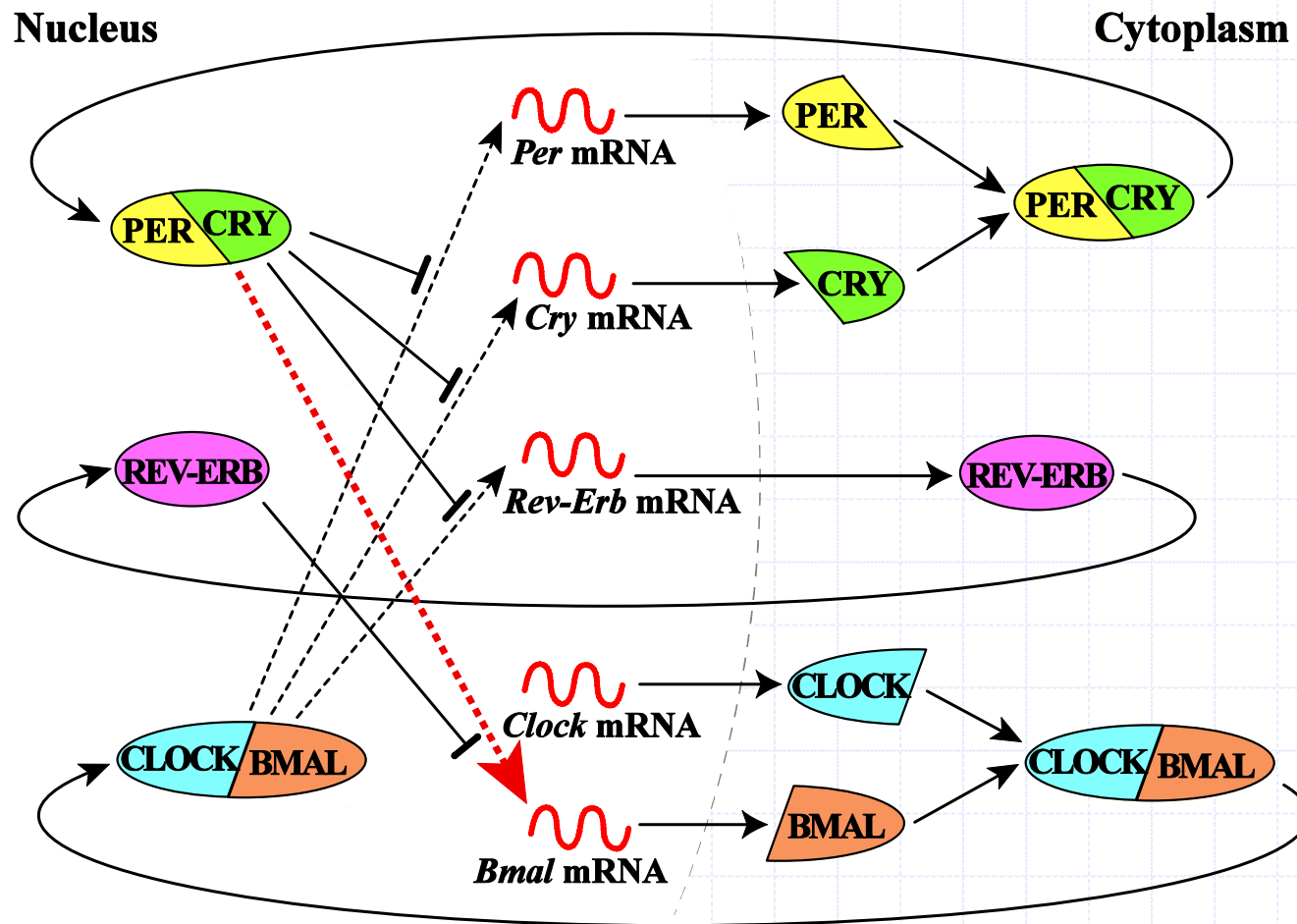


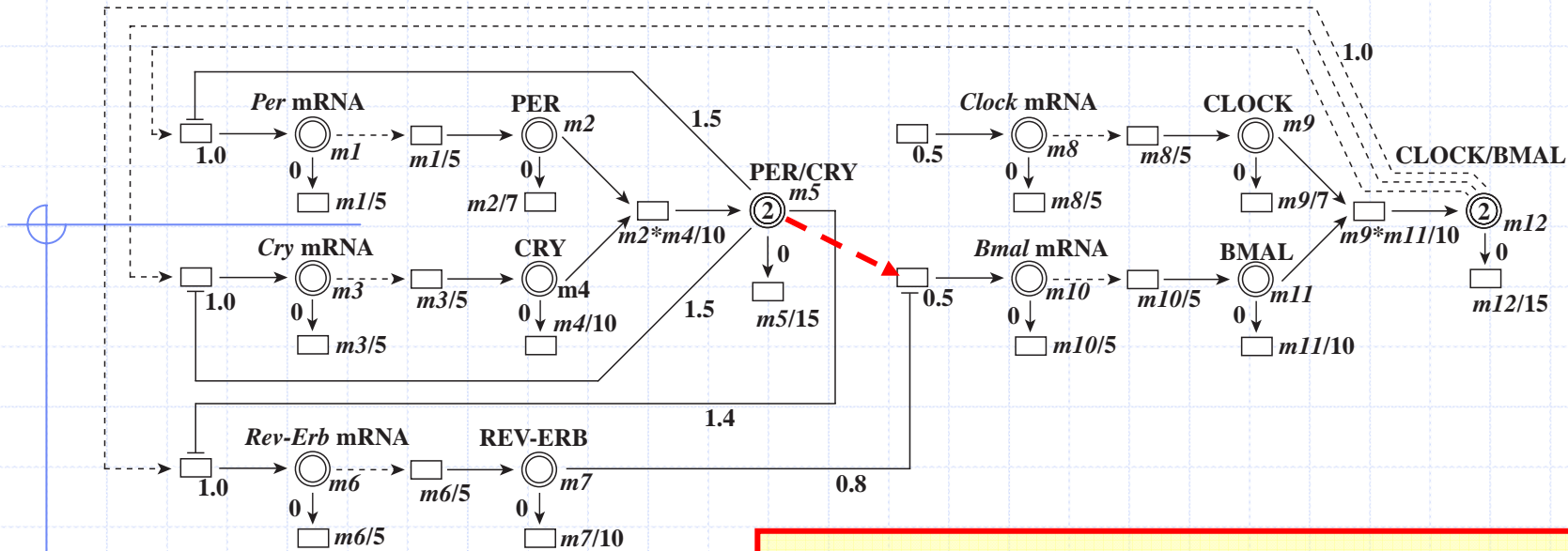
Bmal mRNA しない しい

Cry ック ウト



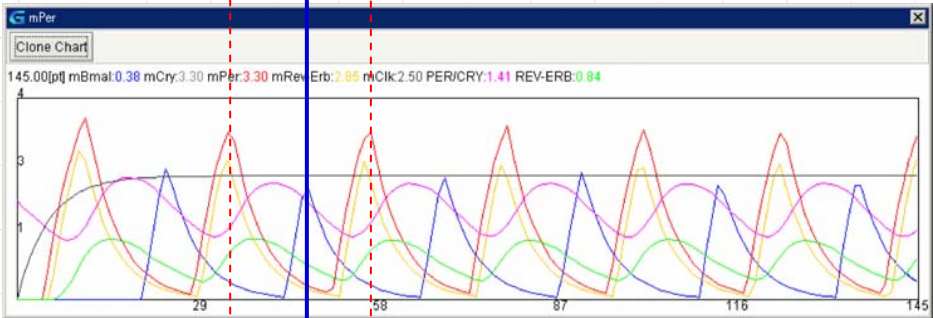
Drosophila における PER/TIM *dClk* を



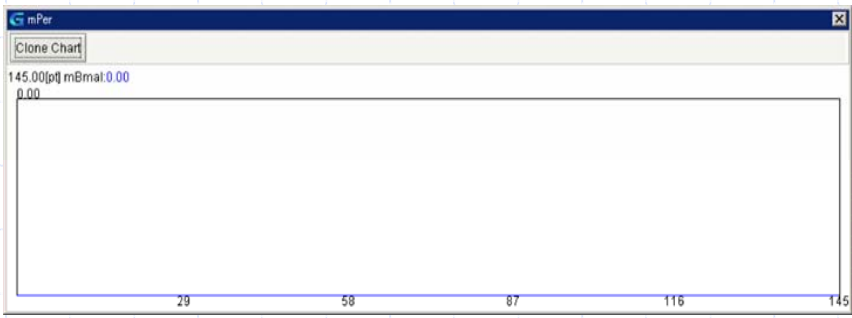


PER CR *mal1* あると る

*Cry*を ック ウト ると

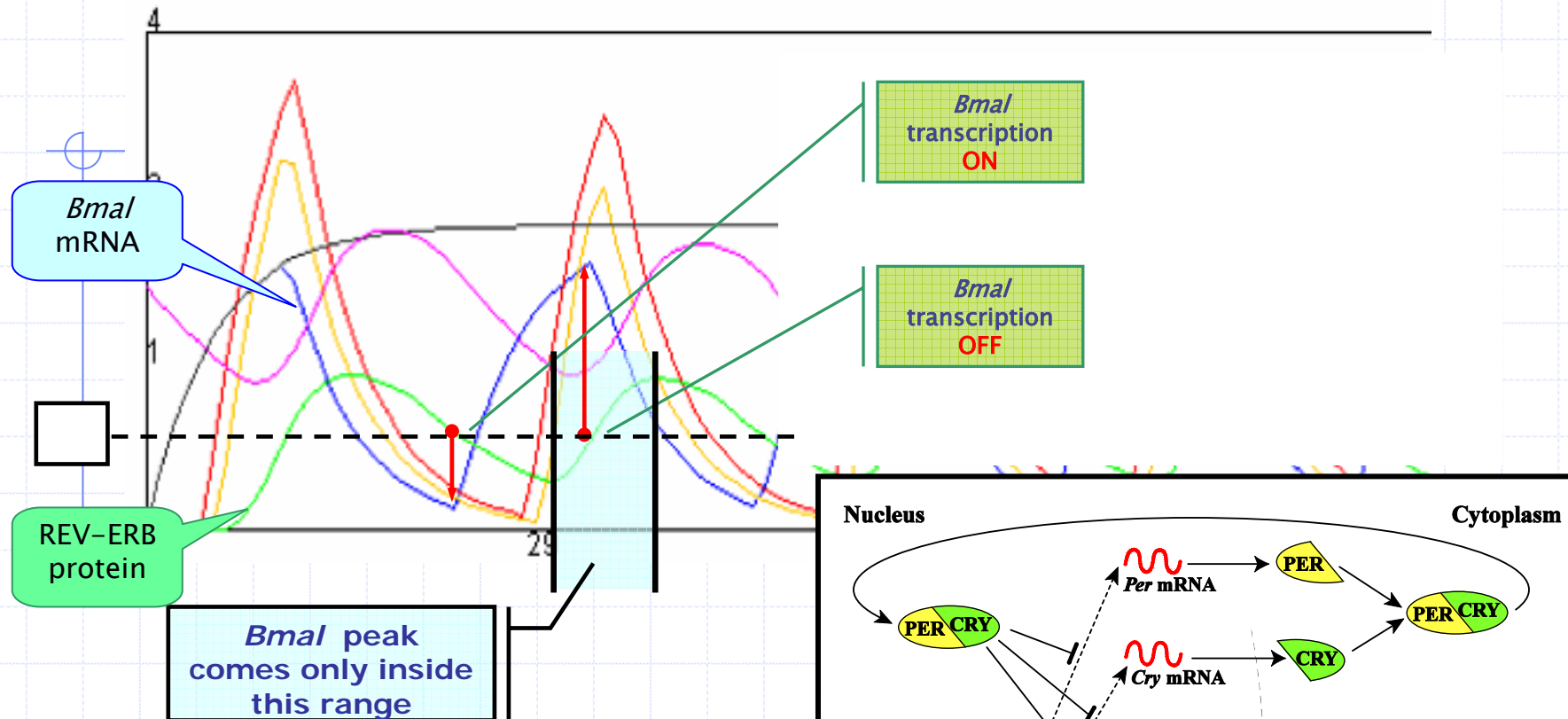


*Bmal1*mRNAの 一ク PermRNAの 一クの に



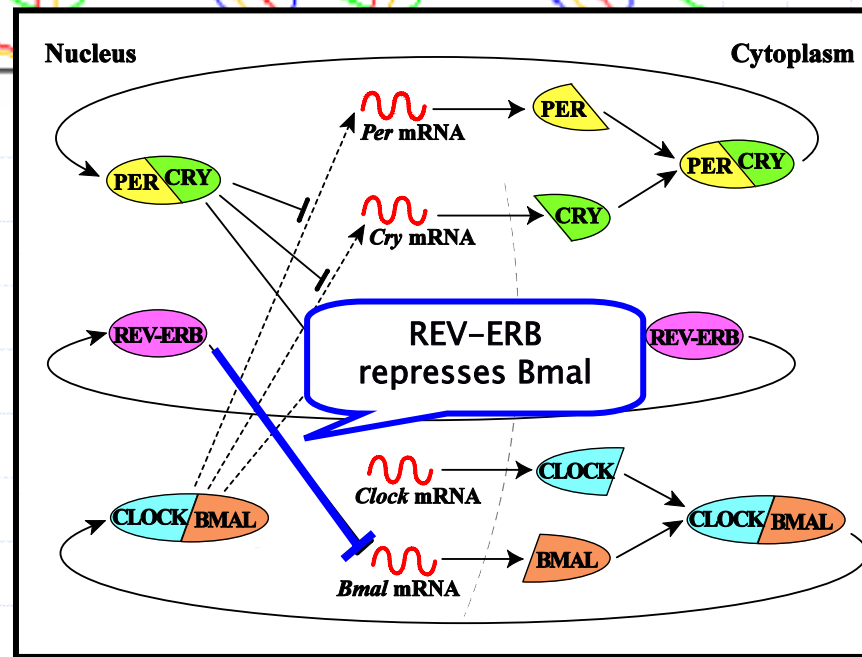
*Bmal1*mRNAの

145.00[pt] mBmal:2.19 mCry:3.30 mPer:3.30 mRev-Erb:2.85 mClk:2.50 PER/CRY:1.41 REV-ERB:0.84

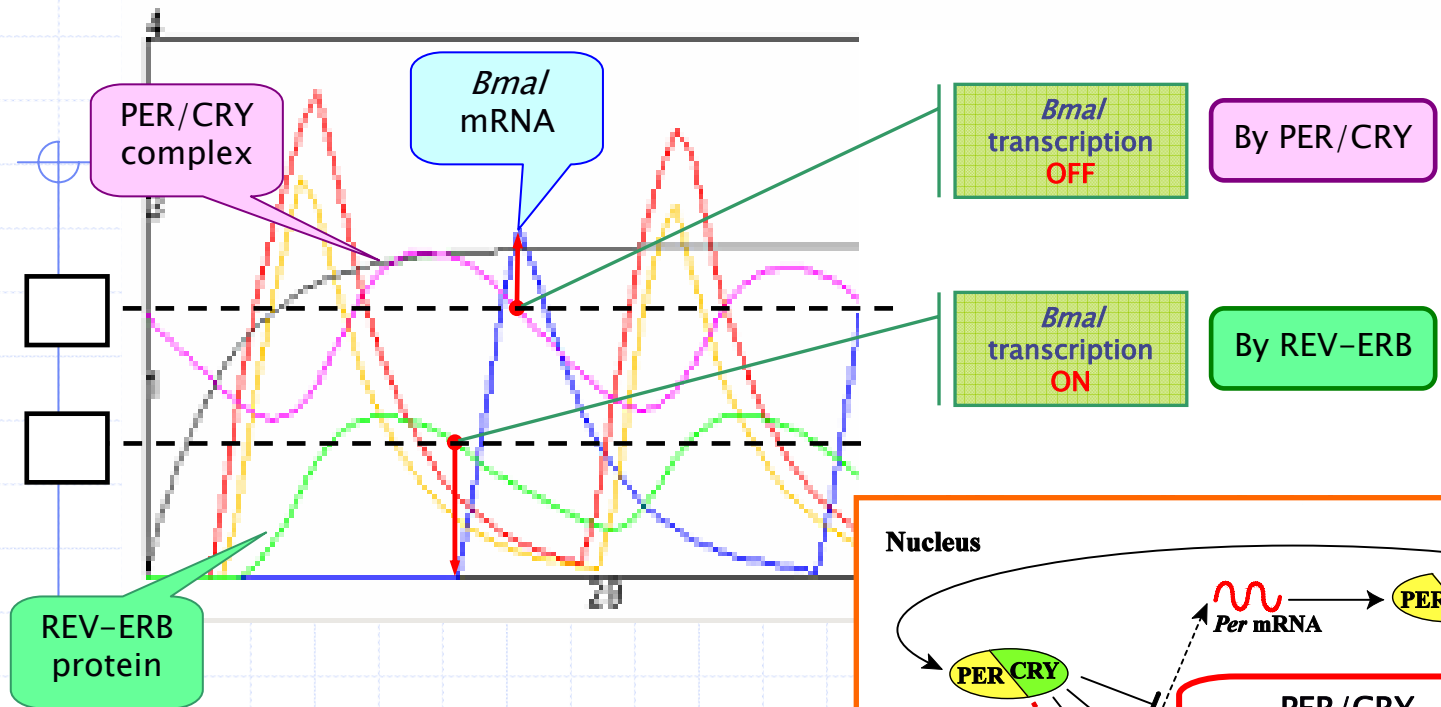


This means that

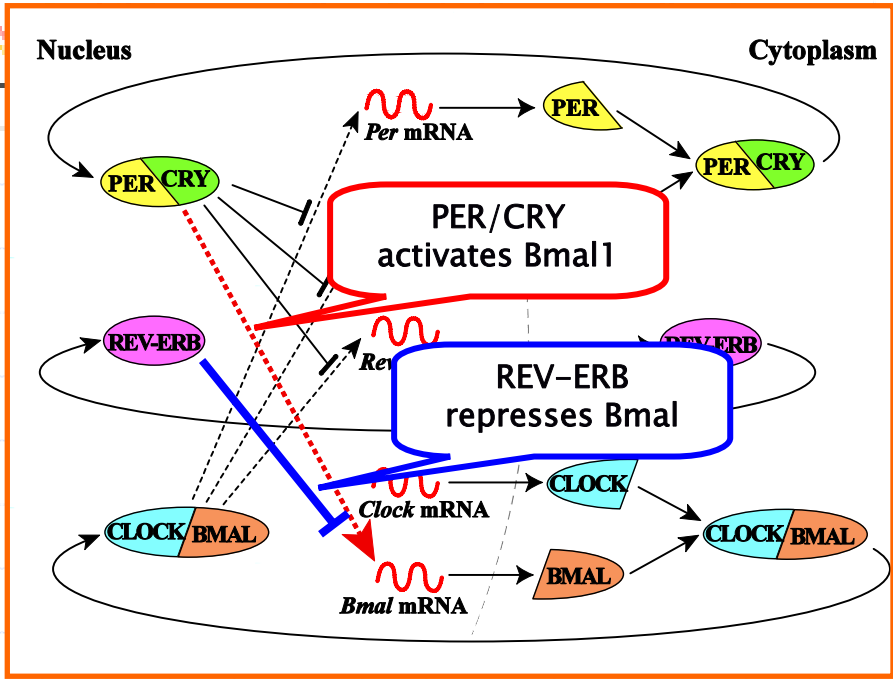
The peak of *Bmal* mRNA can not be located at the center of two *Per* mRNA peaks.



145.00]p] mBmal1:0.38 mCry:3.30 mPer:3.30 mRev-Erb:2.85 mCik:2.50 PER/CRY:1.41 REV-ERB:0.84

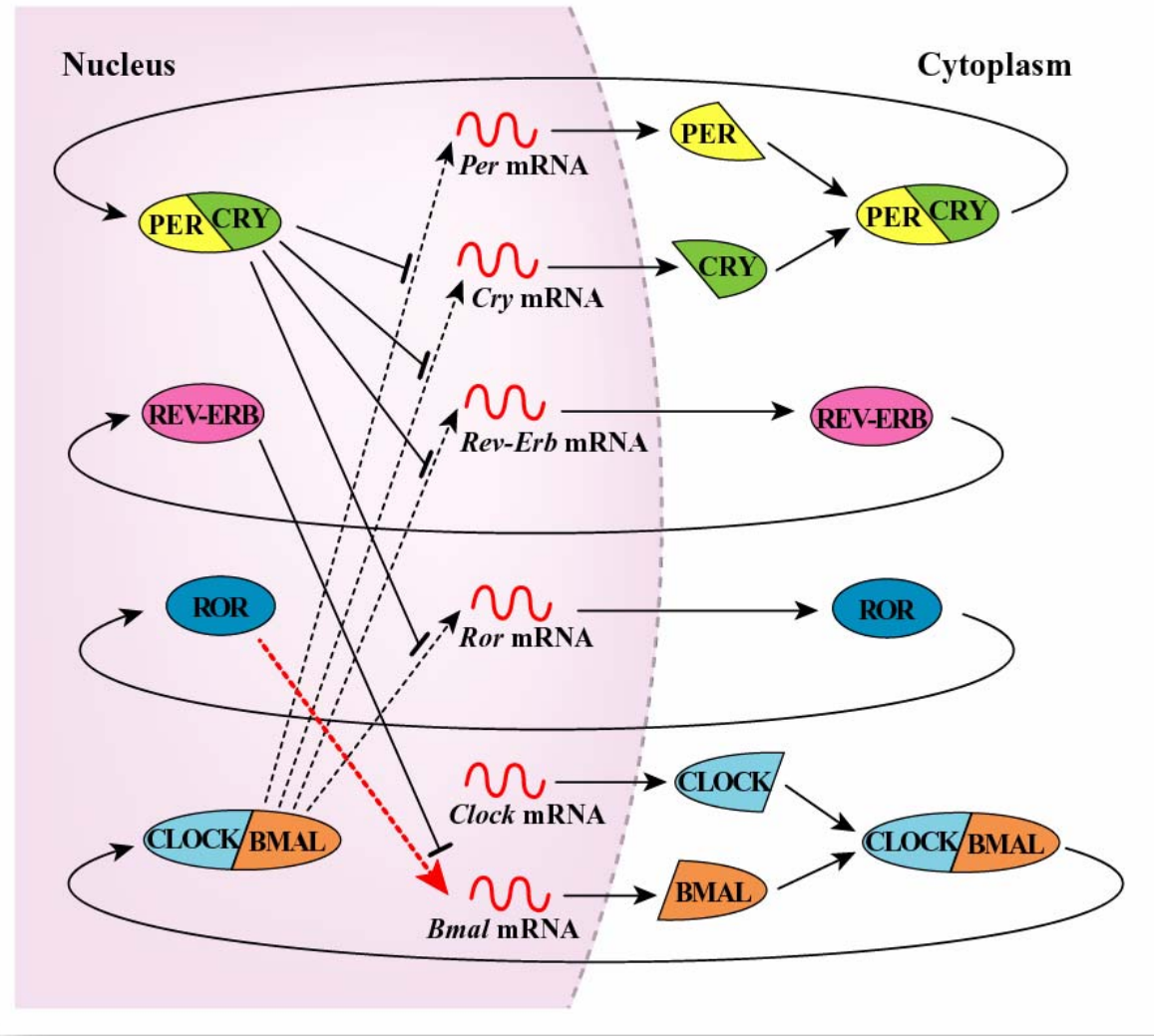


Two switches of **PER/CRY** and **REV-ERB** allow *Bmal* mRNA peak to locate at the center of two *Per* mRNA peaks.



- ◆ Sato, T.K., *et al.*, A functional genomics strategy reveals Rora as a component of the mammalian circadian clock, *Neuron*, 43, pp.527-537, 2004.
- ◆ Akashi, M., Takumi, T., The orphan nuclear receptor ROR α regulates circadian transcription of the mammalian core-clock *Bmal1*, *Nature Structural Molecular Biology*, Published online: 10 April 2005, <http://www.nature.com/nsmb/journal/vaop/ncurrent/abs/nsmb925.html>.

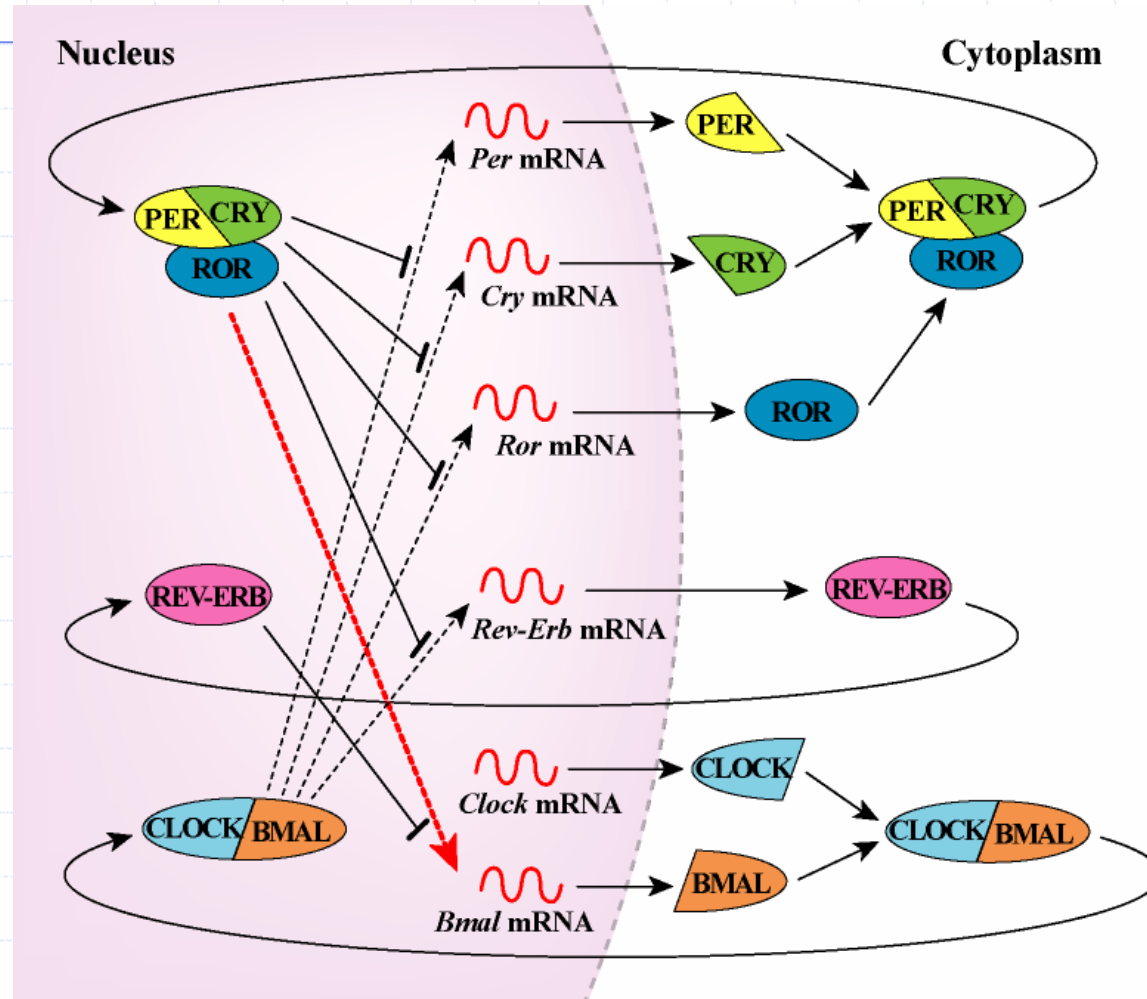
Ror



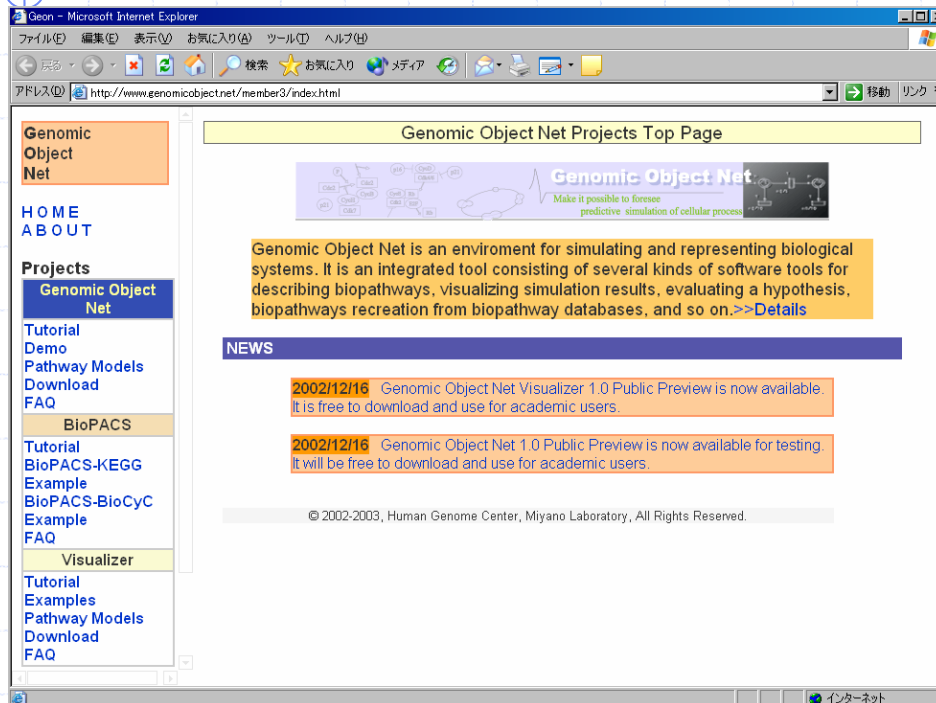
Rorの

PER/CRYとの

化



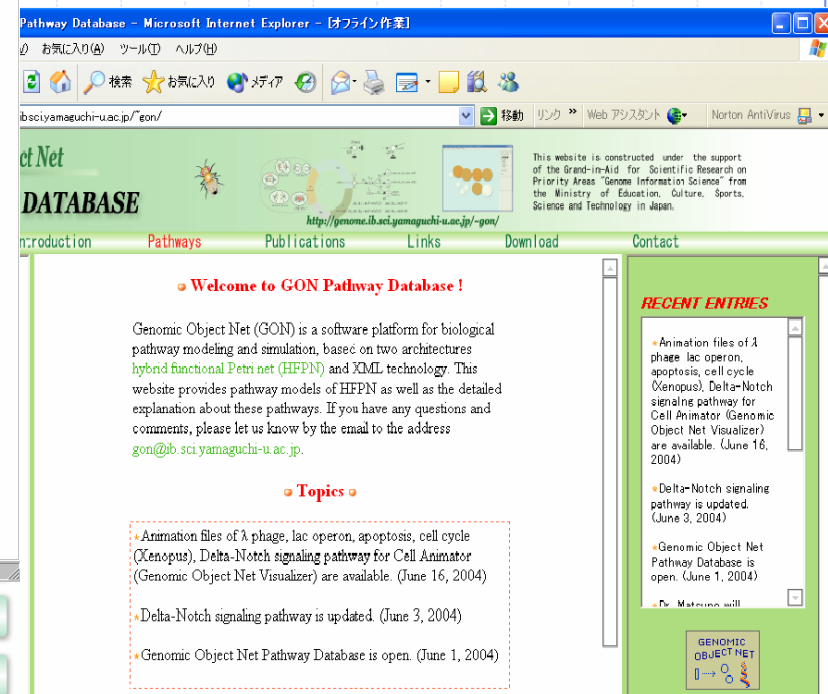
Genomic Object Net



<http://www.GenomicObject.Net/>



GON Pathway DB



<http://genome.ib.sci.yamaguchi-u.ac.jp/~gon/>