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

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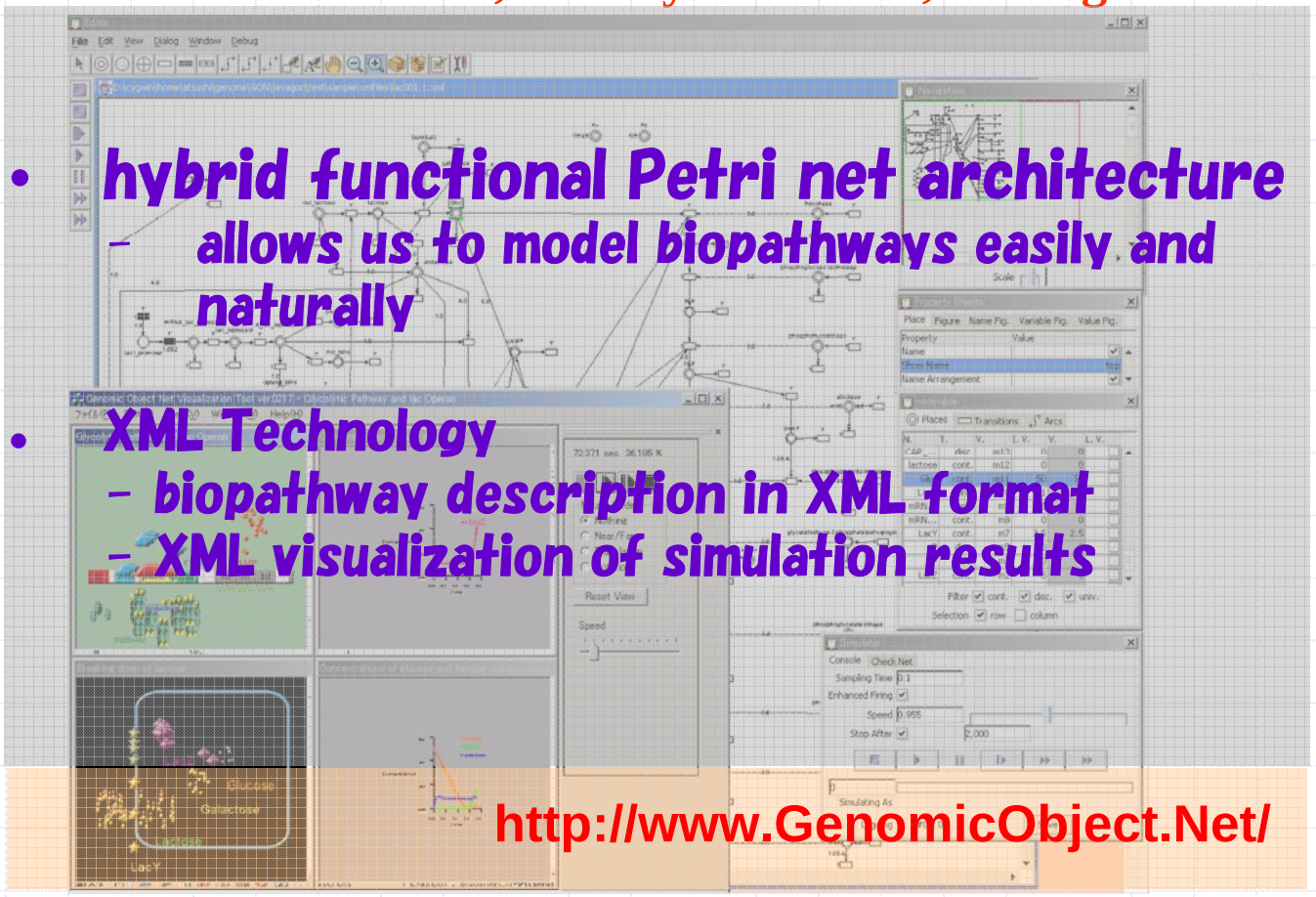
特別講演　システム生物学の最前線 2007年10月29日

Genomic Object Net Project

－Miyano lab. , Human Genome Center, U. of Tokyo

－Matsuno lab., Faculty of Science, Yamaguchi U.

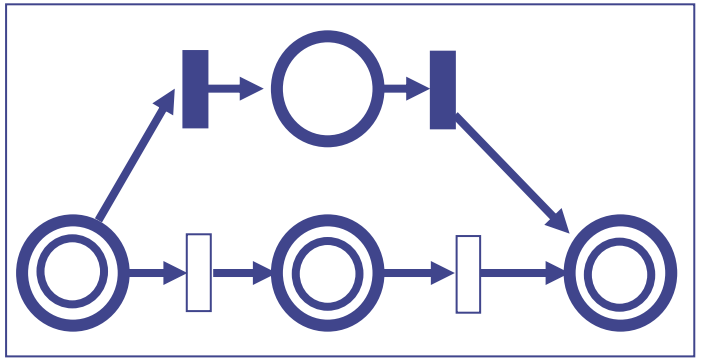


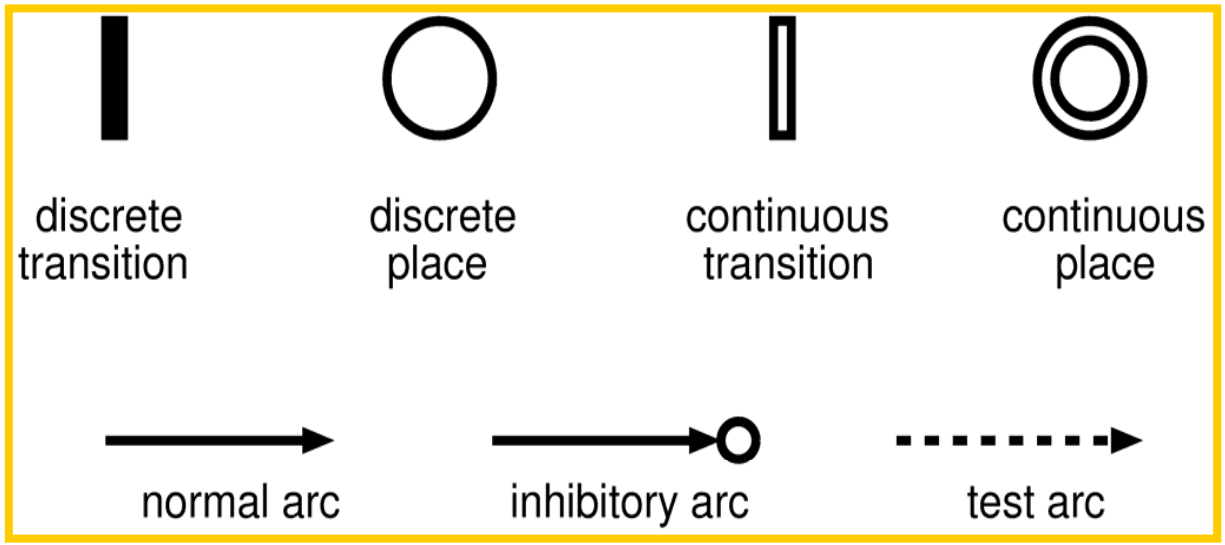
- **hybrid functional Petri net architecture**
  - allows us to model biopathways easily and naturally
- **XML Technology**
  - biopathway description in XML format
  - XML visualization of simulation results

http://www.GenomicObject.Net/

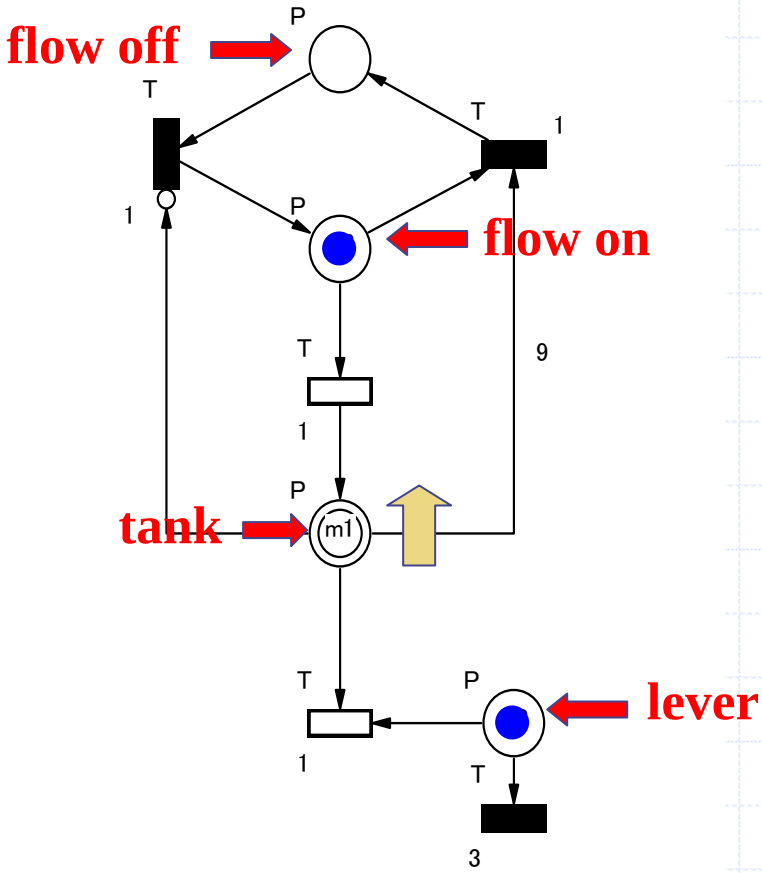
Genomic Object Net version 1.0

Hybrid Petri Net

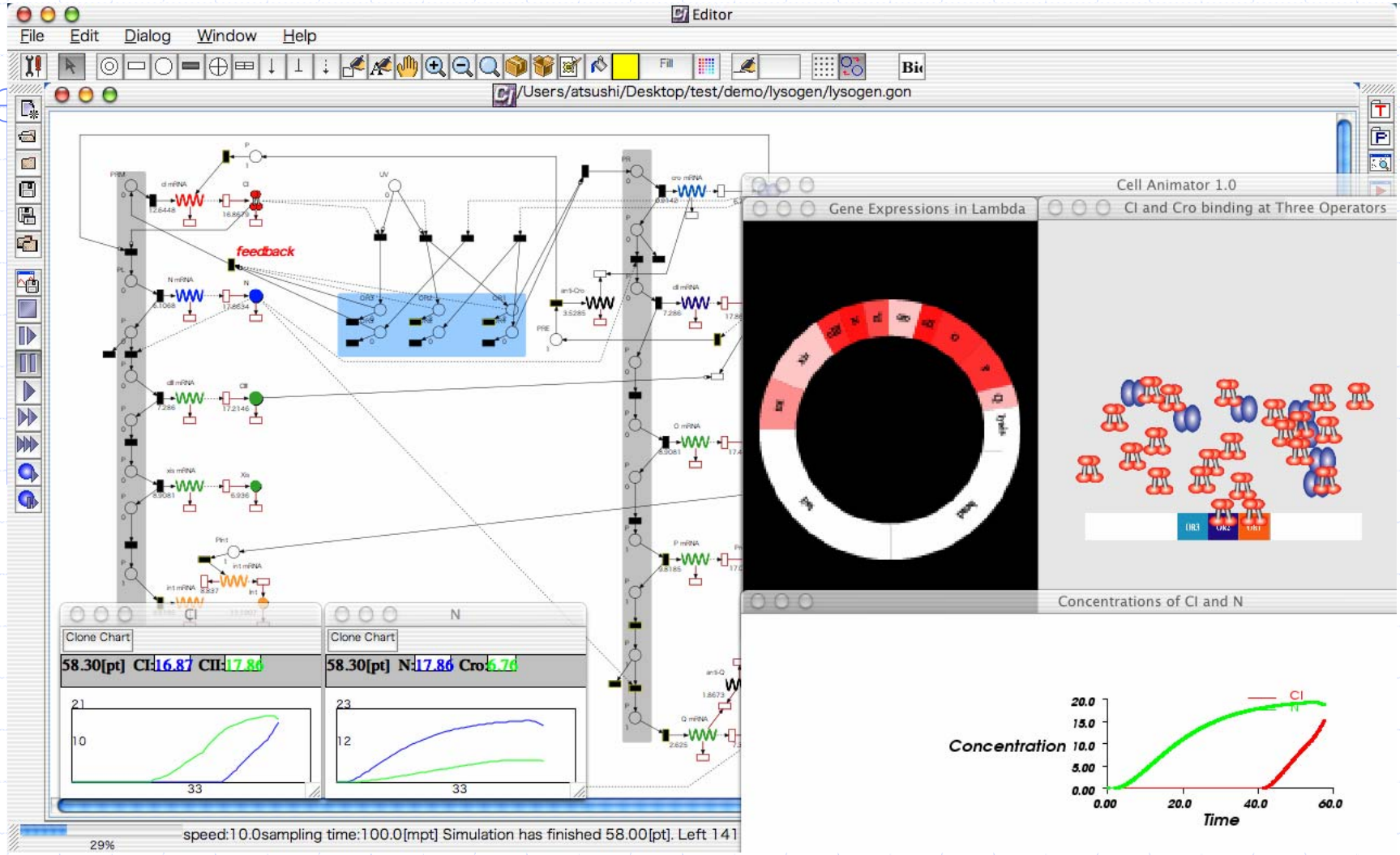




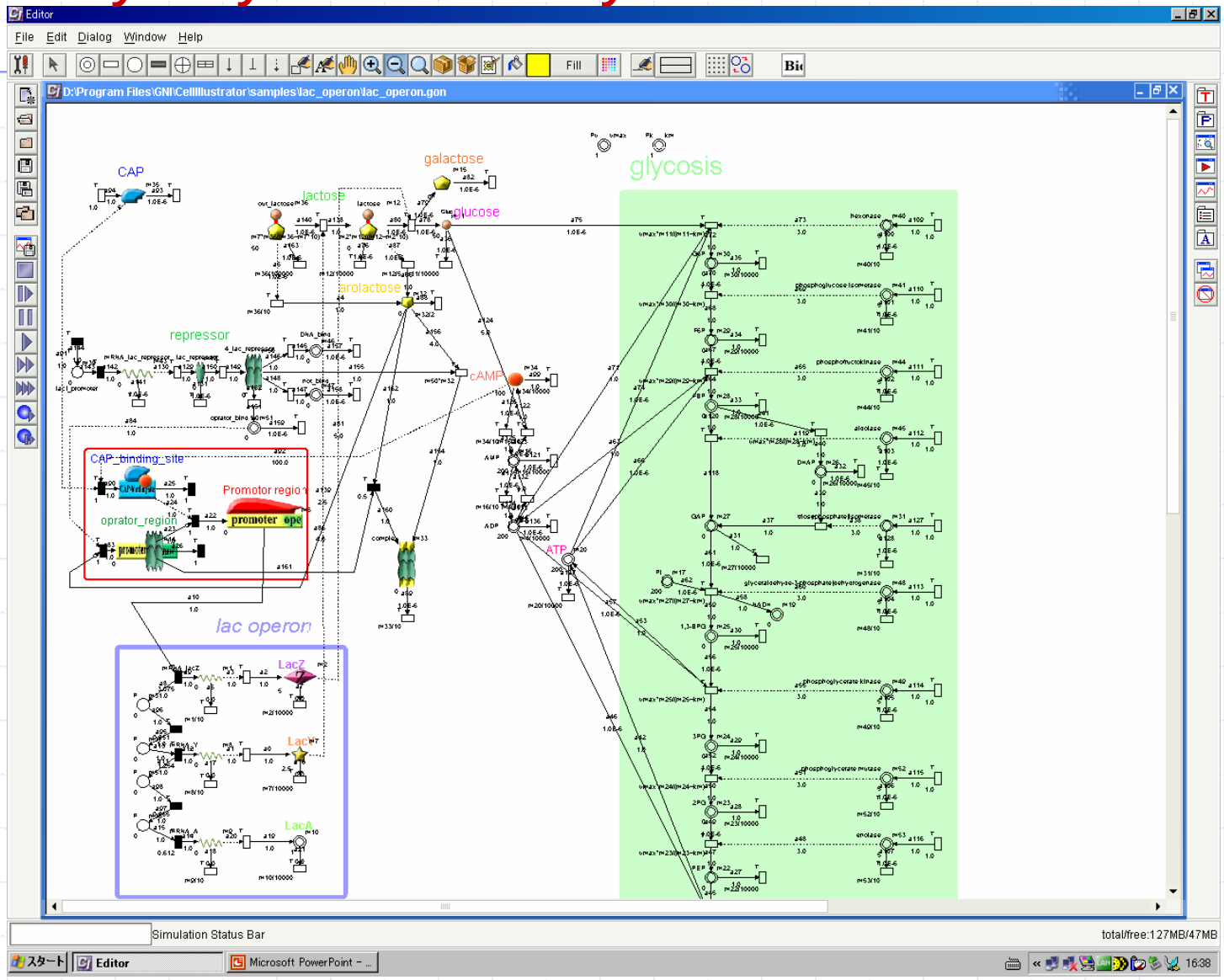
Example

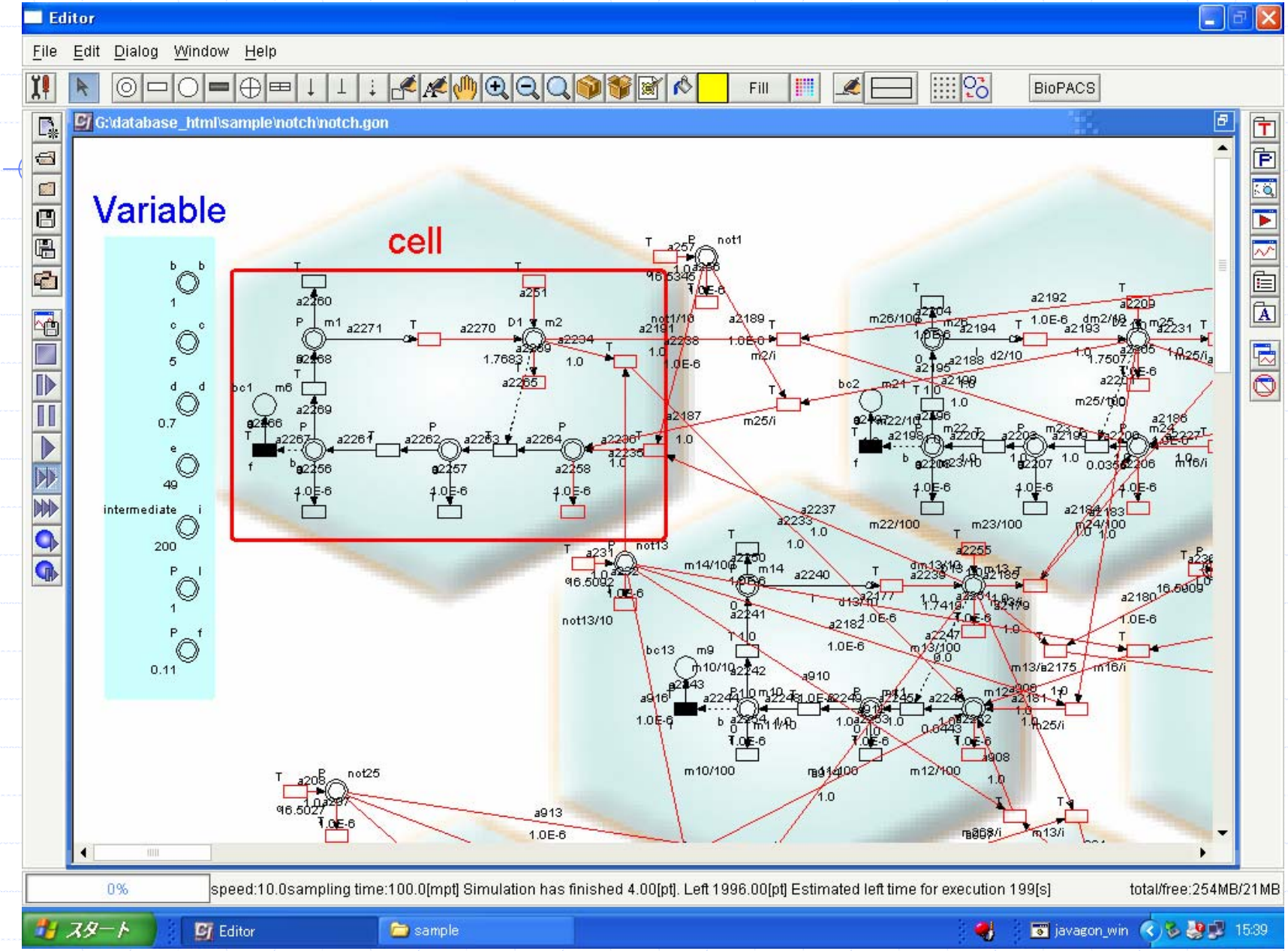


Lambda Phage Genetic Switch



lac Operon Gene Regulatory Mechanism and Glycolytic Pathway

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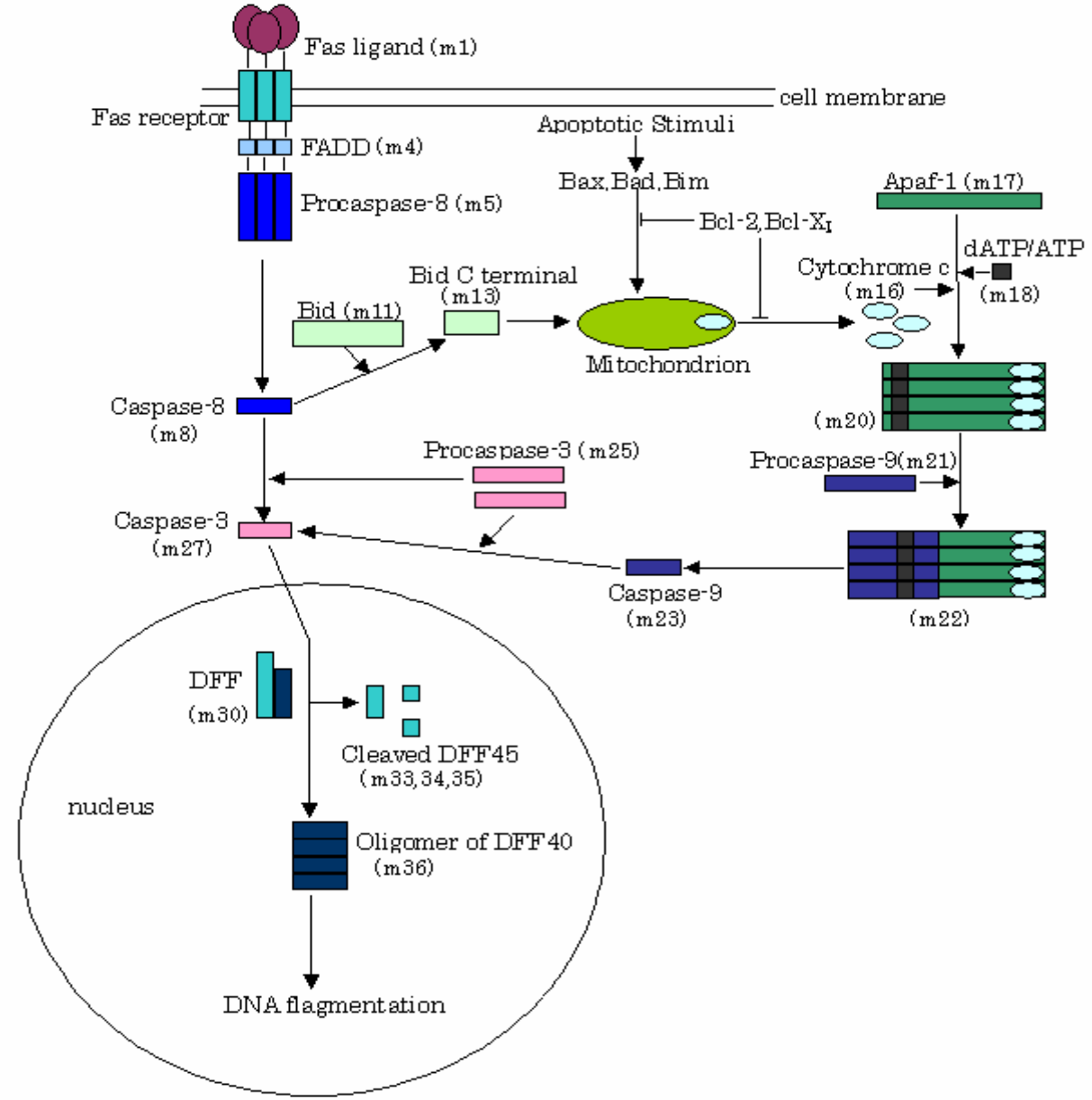
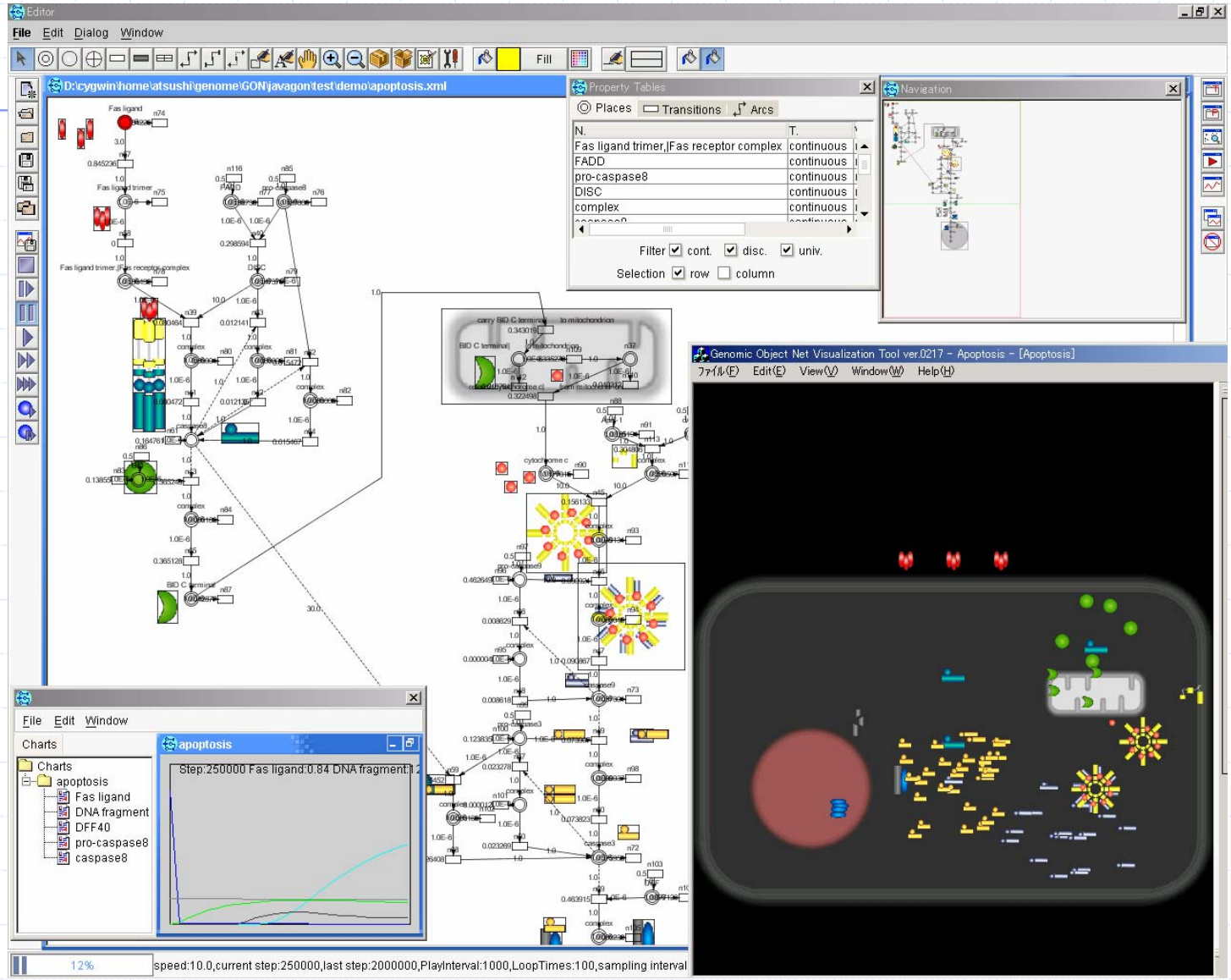
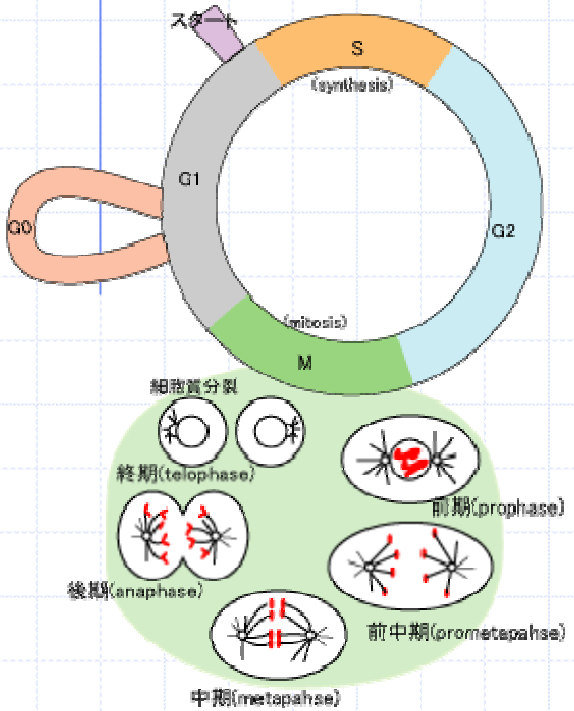
Apoptosis induced by Fas ligand

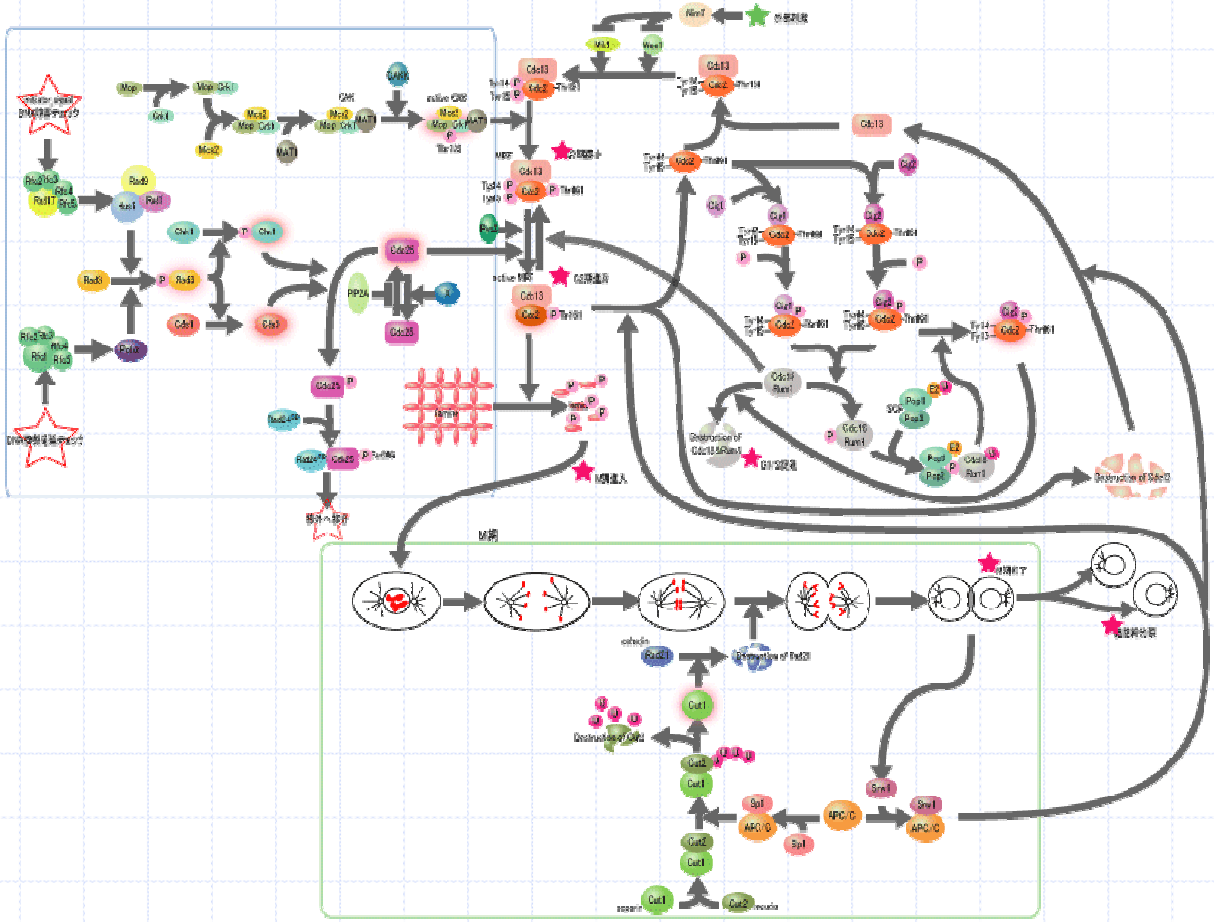


HFPN model of Apoptosis

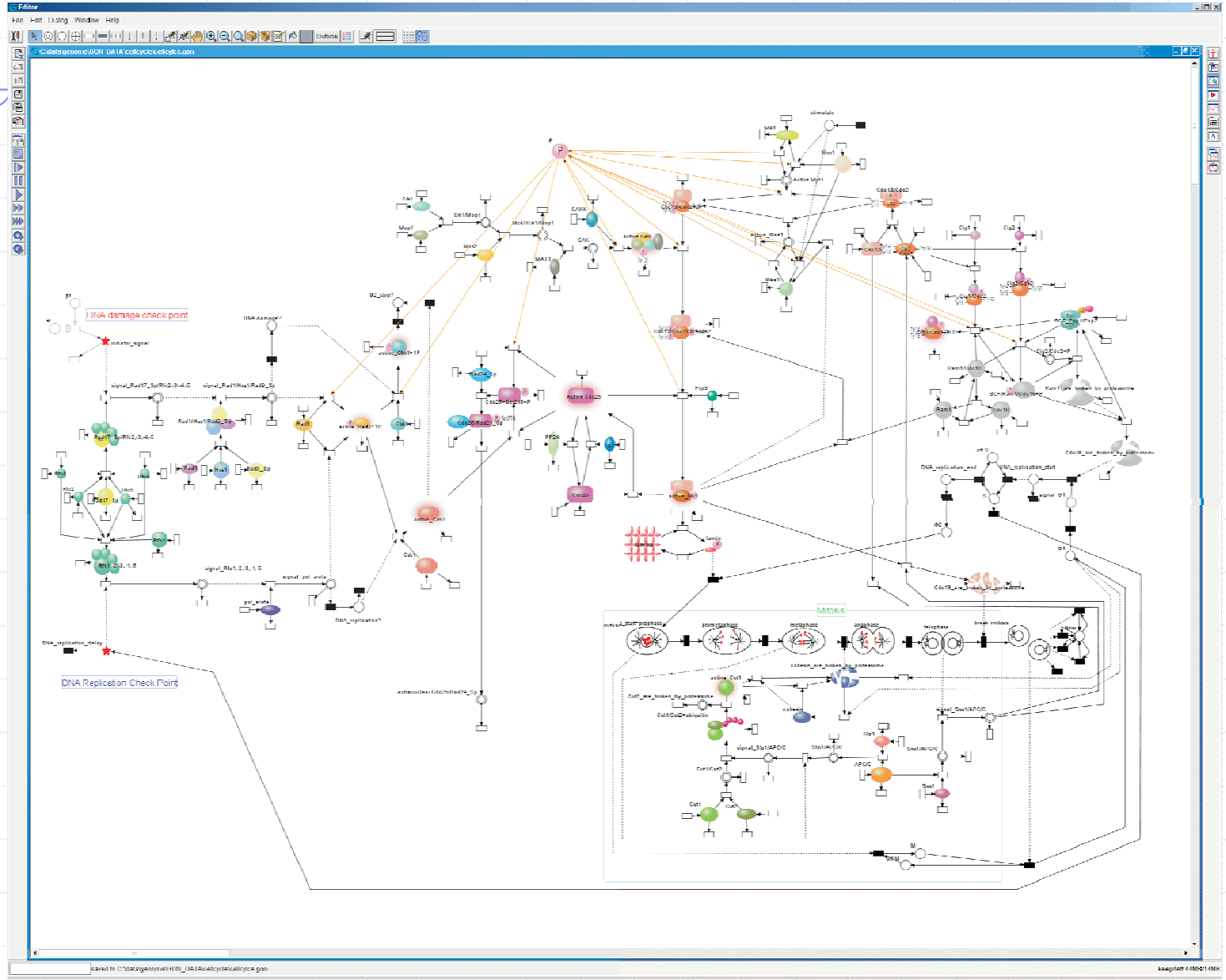


Regulatory Pathway for Cell Cycle of Budding Yeast

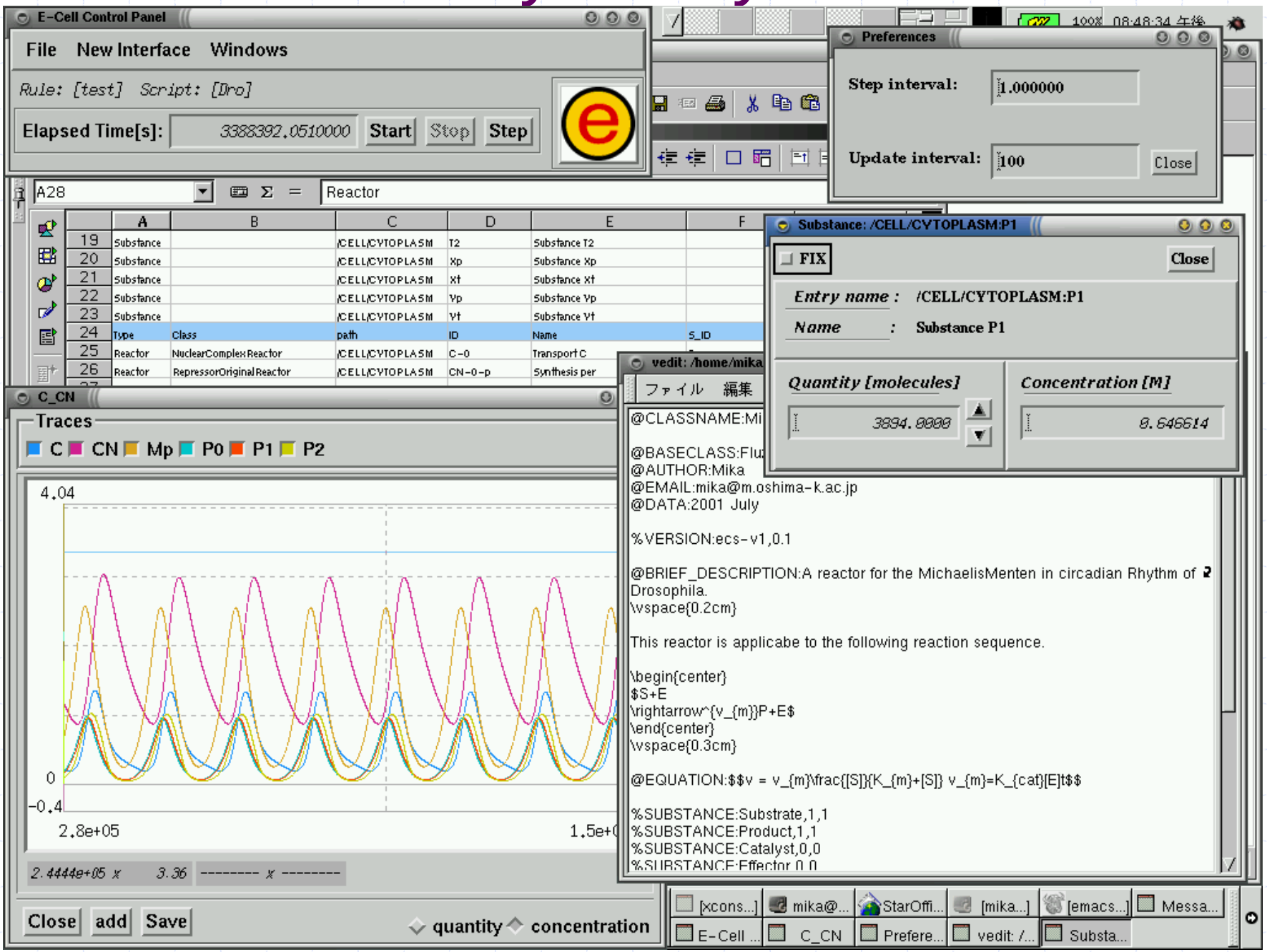




HFPN Model of Budding Yeast Cell Cycle

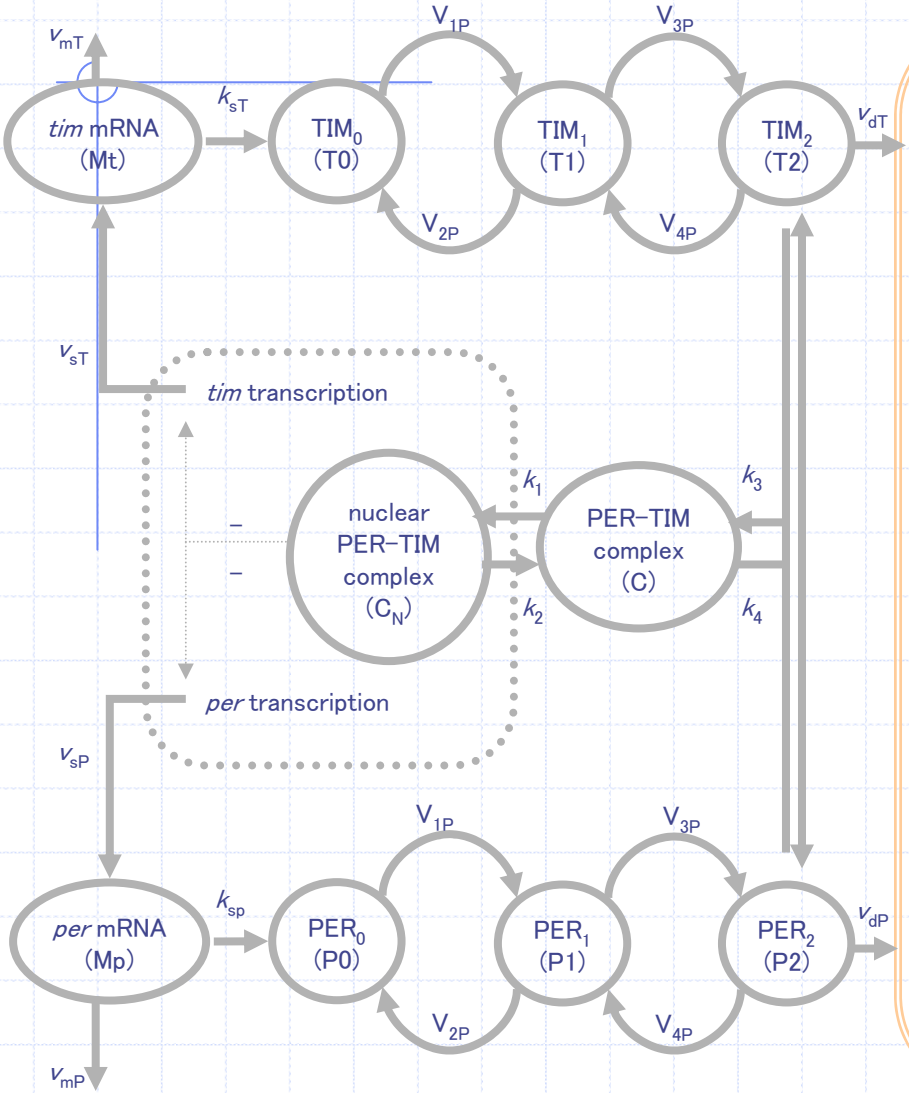


Circadian Rhythm by E-CELL



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 *Pi* to *Ti (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	MichaelisUniUniReactor	/CELL/CYTOPLASM	A-0	Isomerization of A
Reactor	MichaelisUniUniReversibleReactor	/CELL/CYTOPLASM	B-0	Isomerization of B

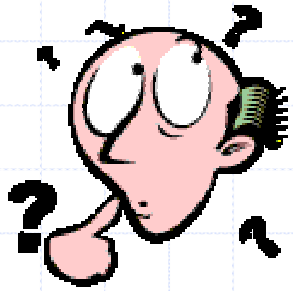
Reactor(rd-file)

- MichaelisUniUniReactor.rd

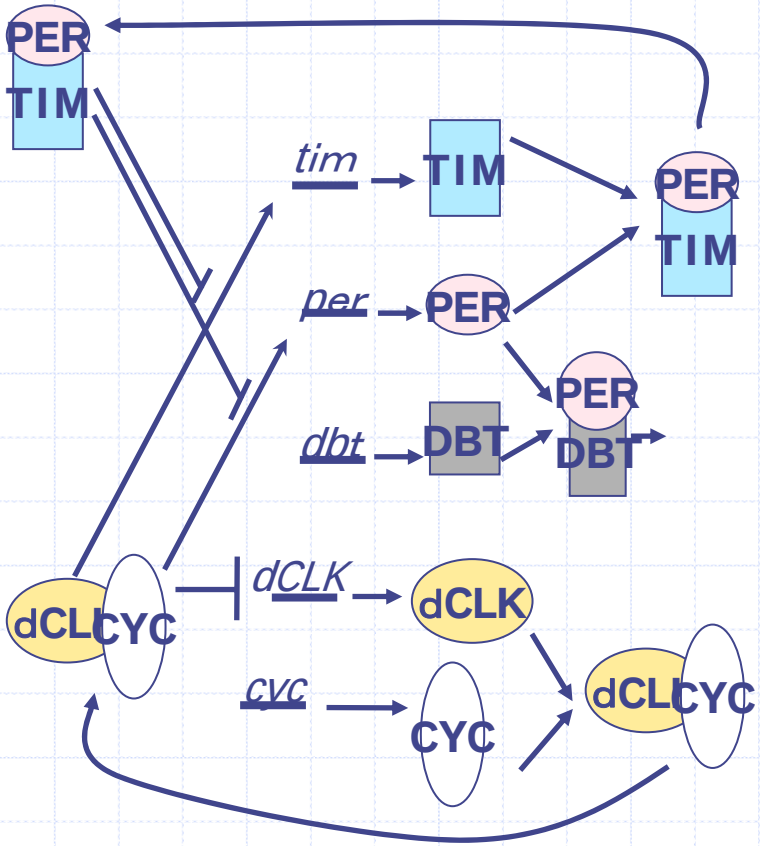
$$v = \frac{K_{cF}[E][S]}{K_{mS} + [S]}$$

- 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

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

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

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

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

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

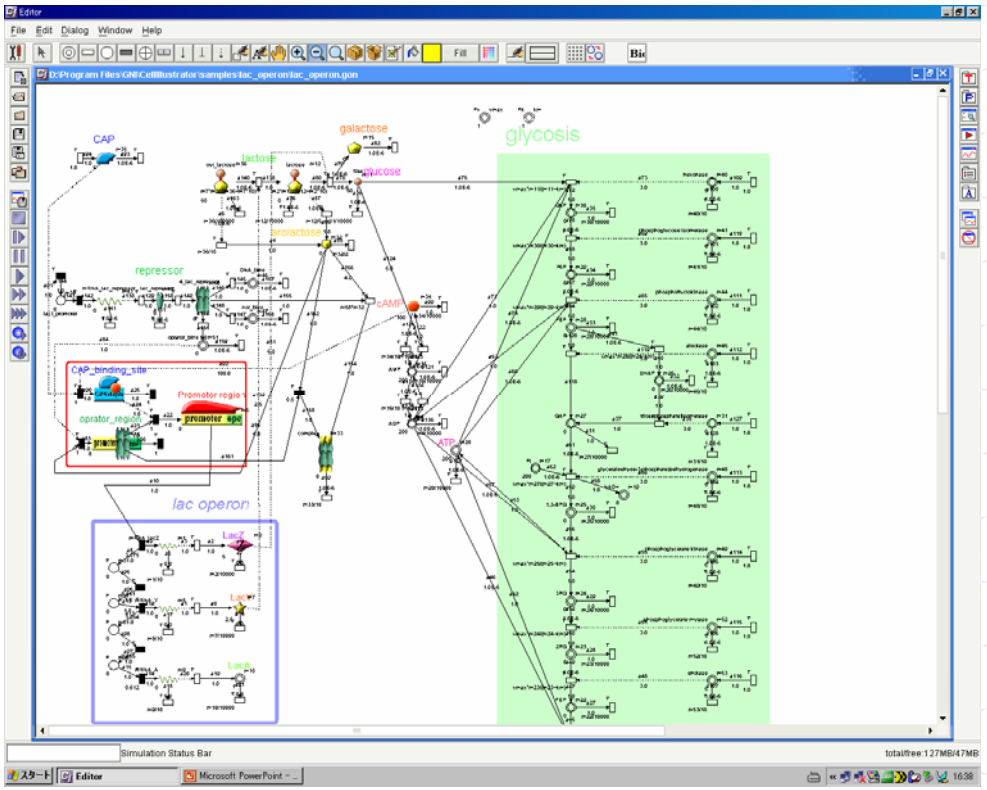
$$\frac{dC_N}{dt} = k_1 C - k_2 C_N - k_{dN} C$$

Top-down approach

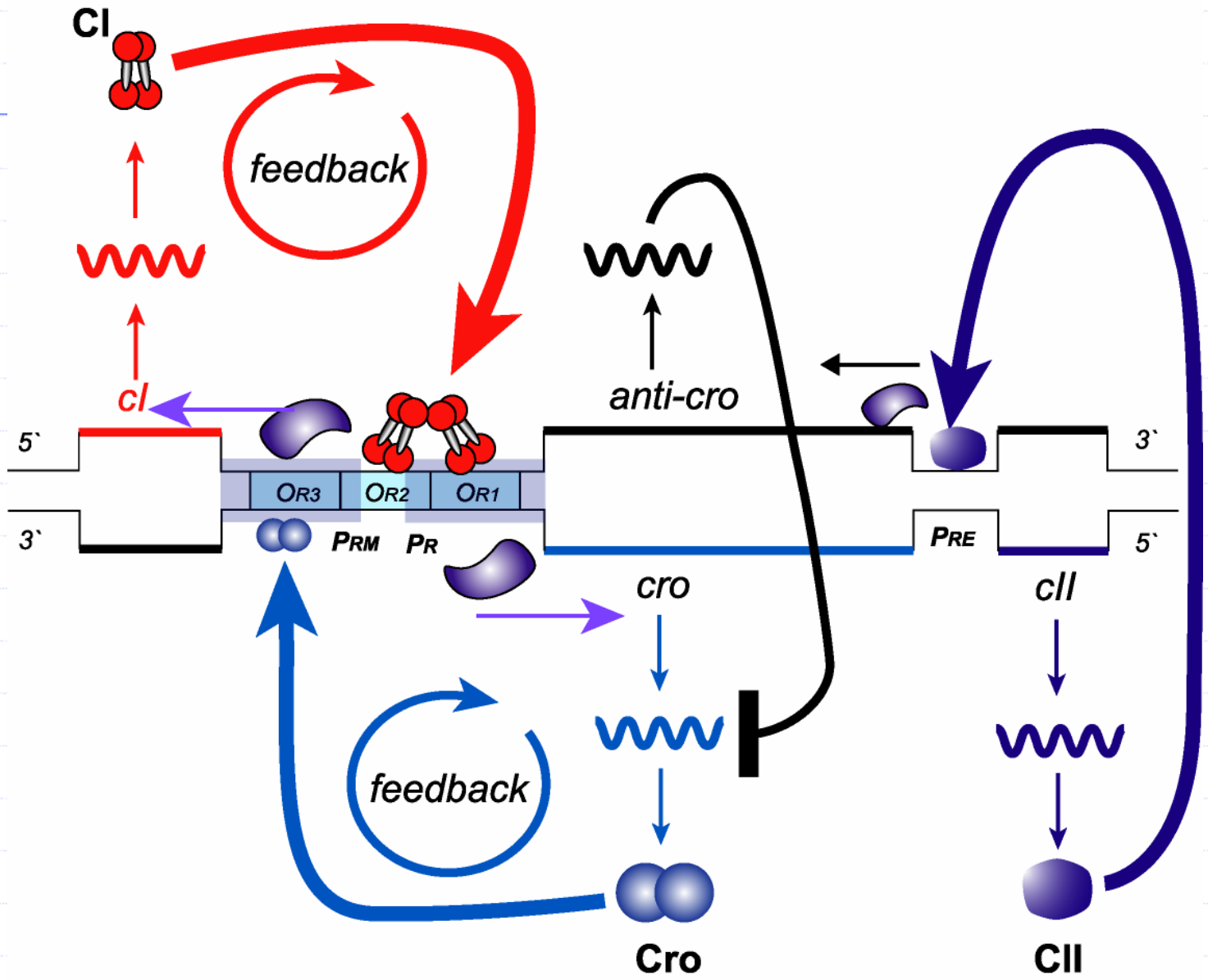
biological pathway map

describe a structure of biological pathway

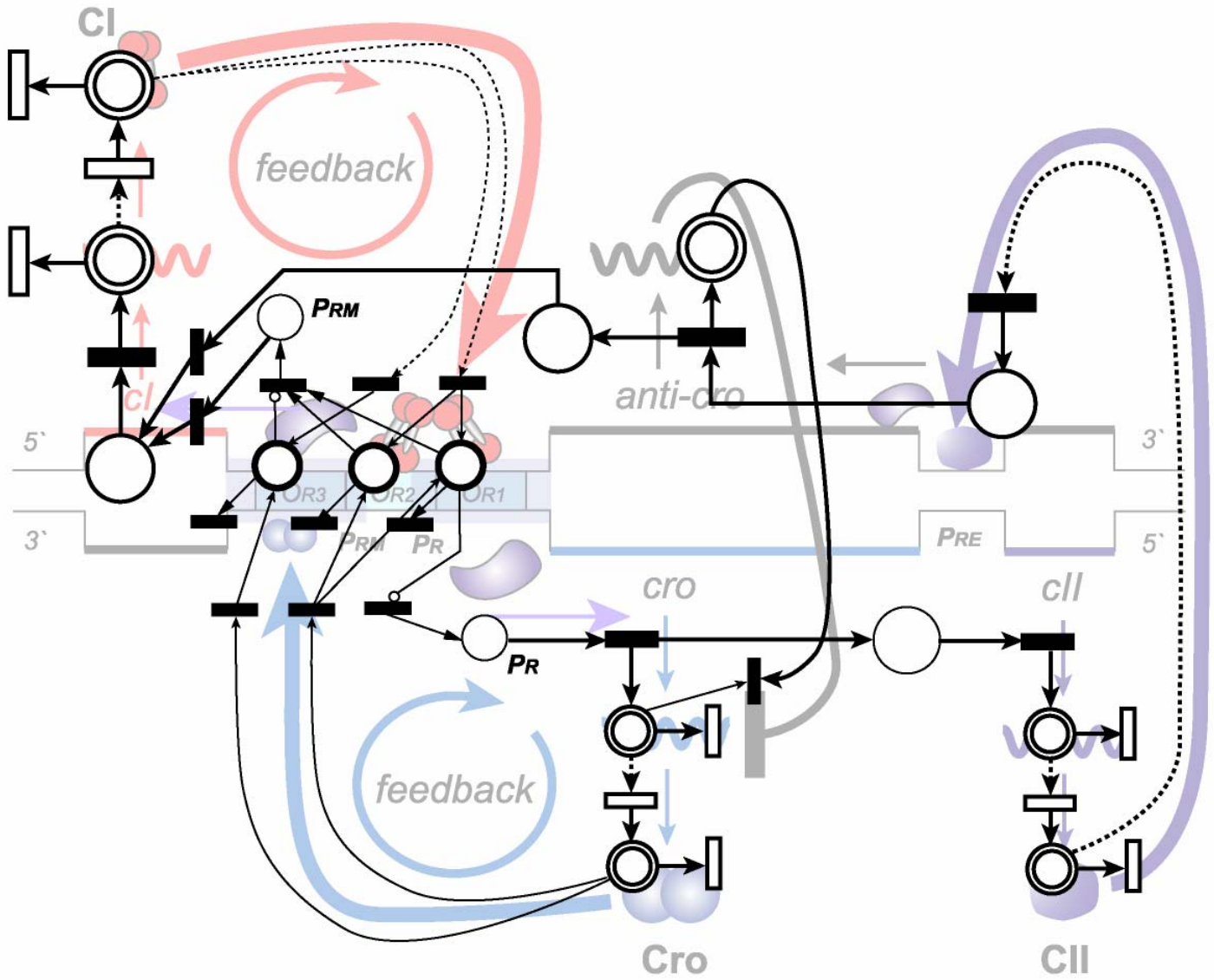
tuning parameters with repeating simulations



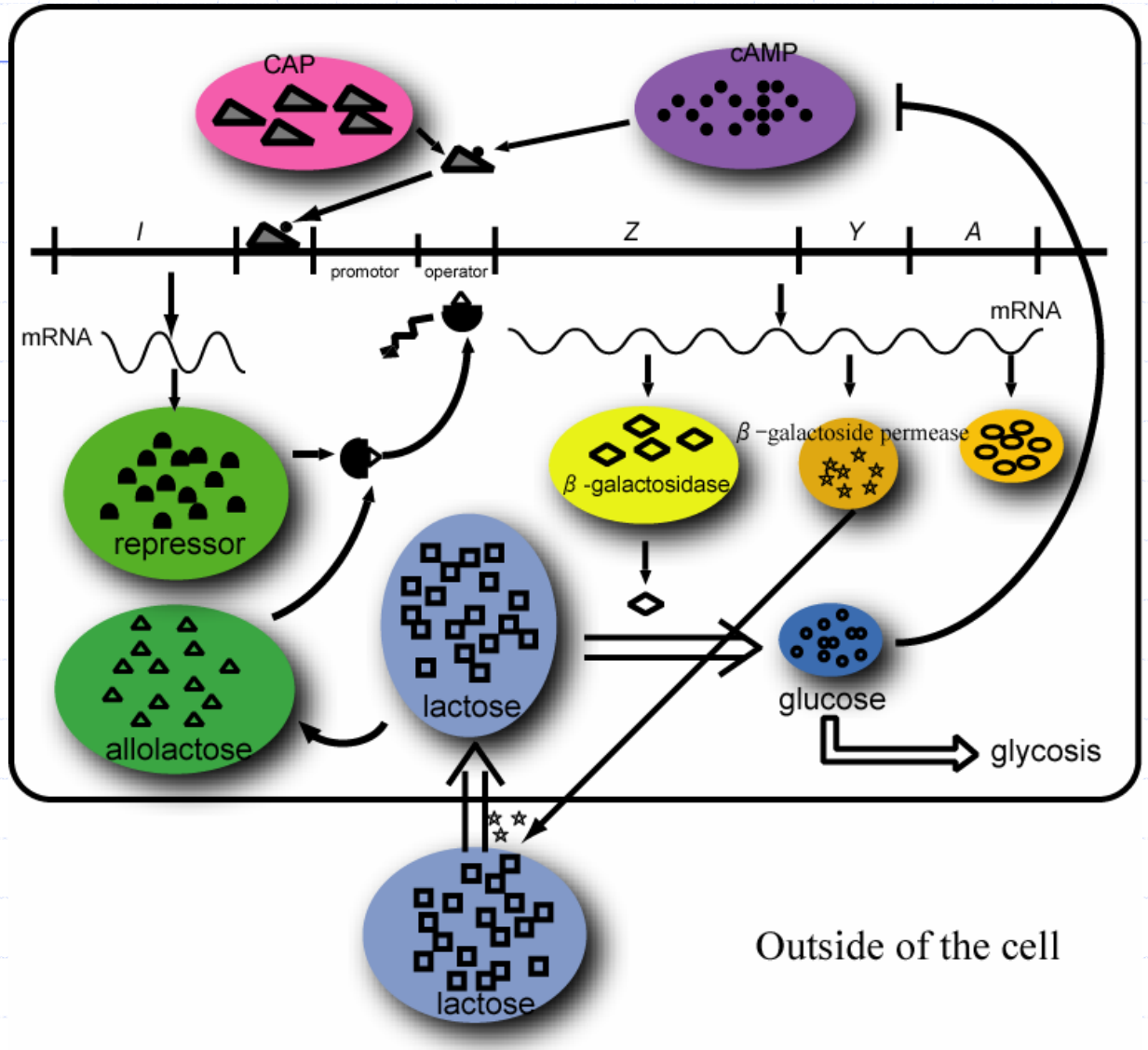
Lambda phage genetic switch feedback mechanism



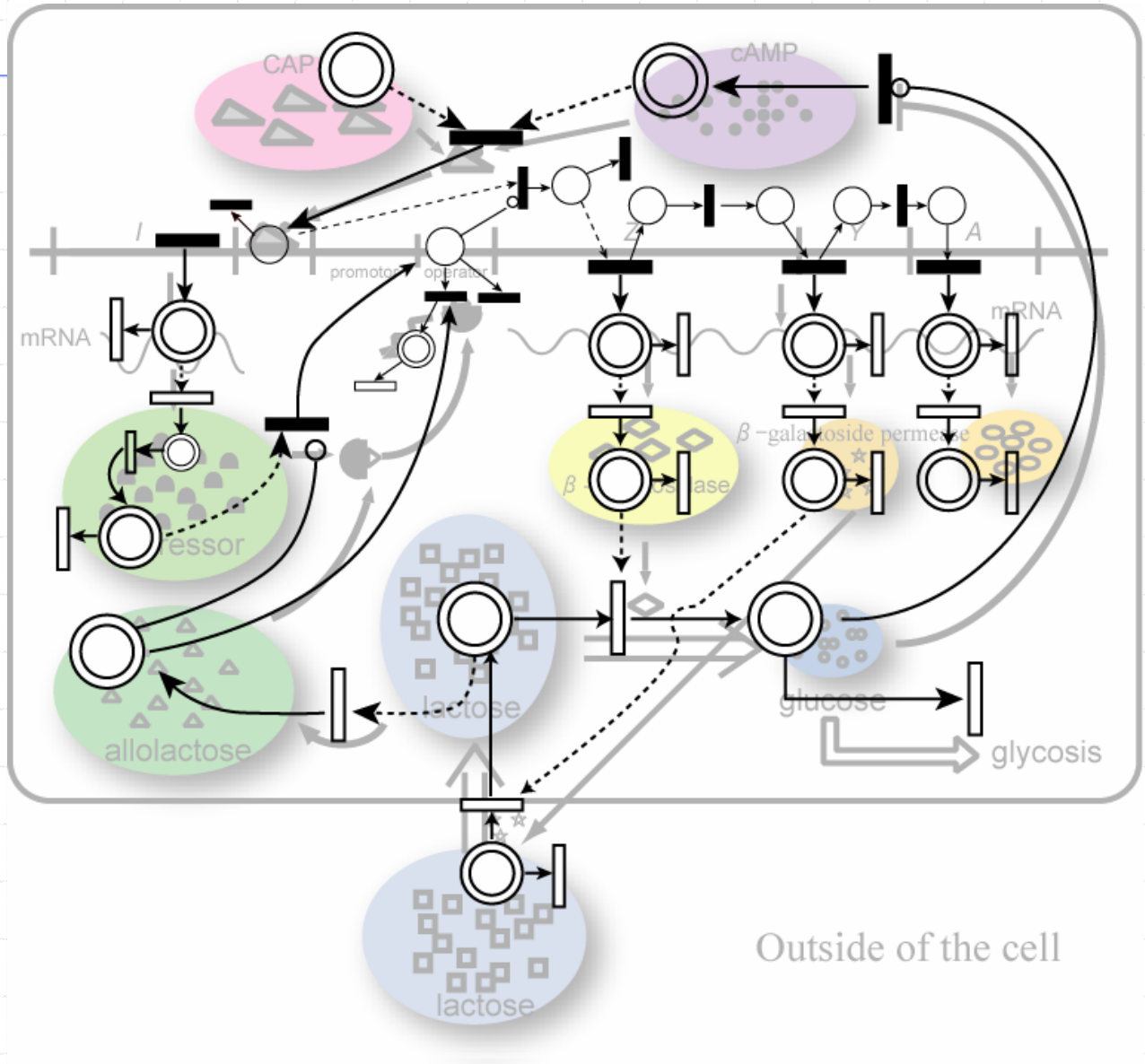
Lambda phage genetic switch feedback mechanism



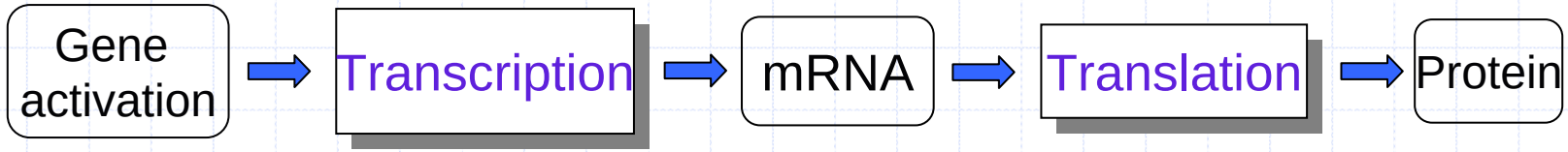
lac operon genetic switch control

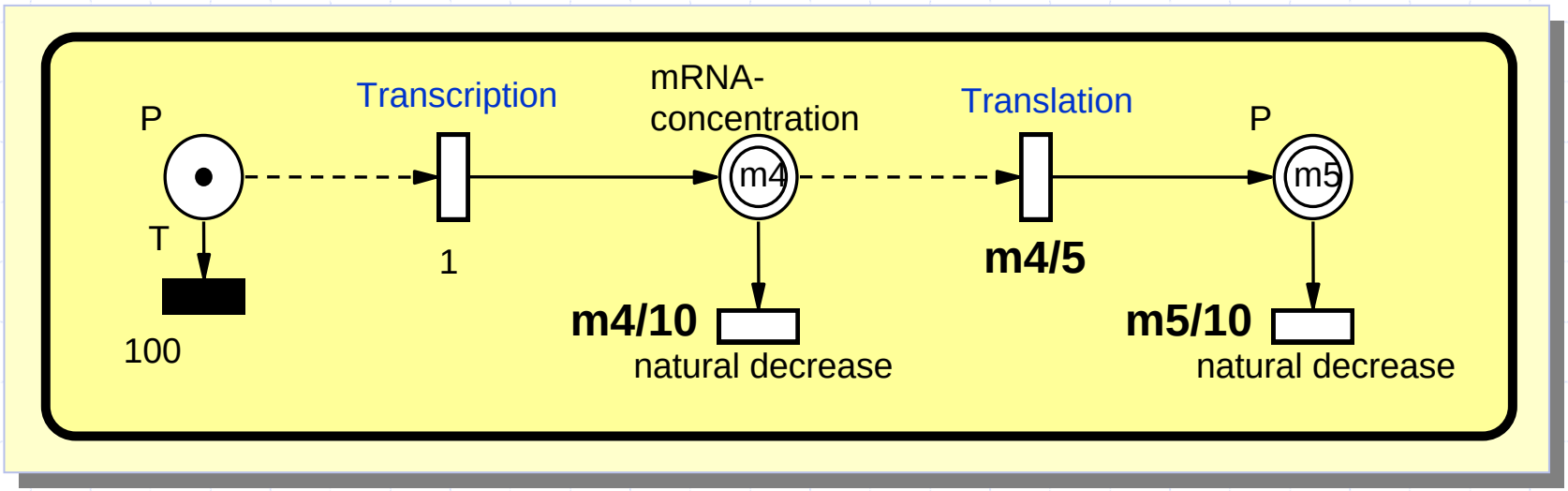


lac operon genetic switch control

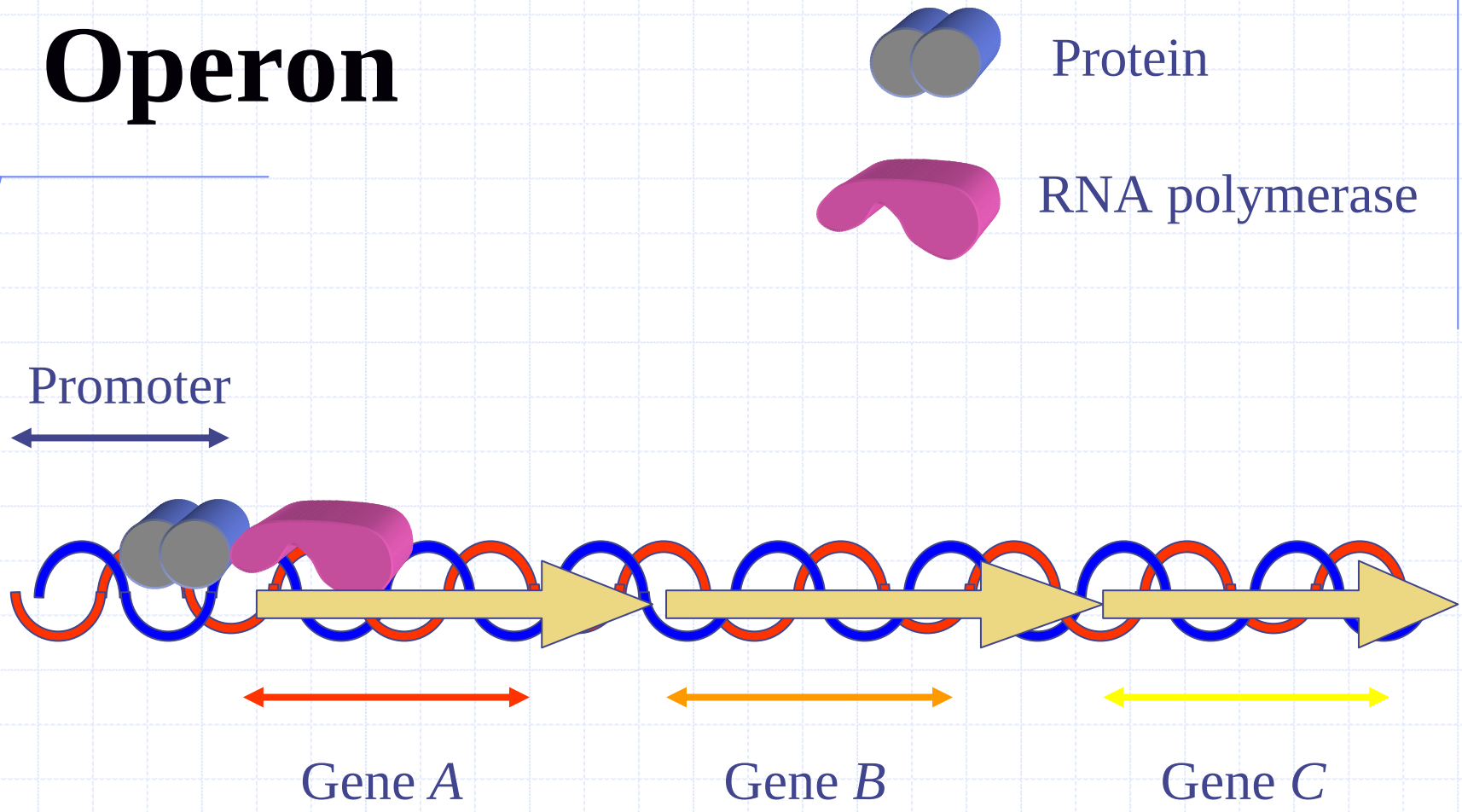


Modeling of the protein production process

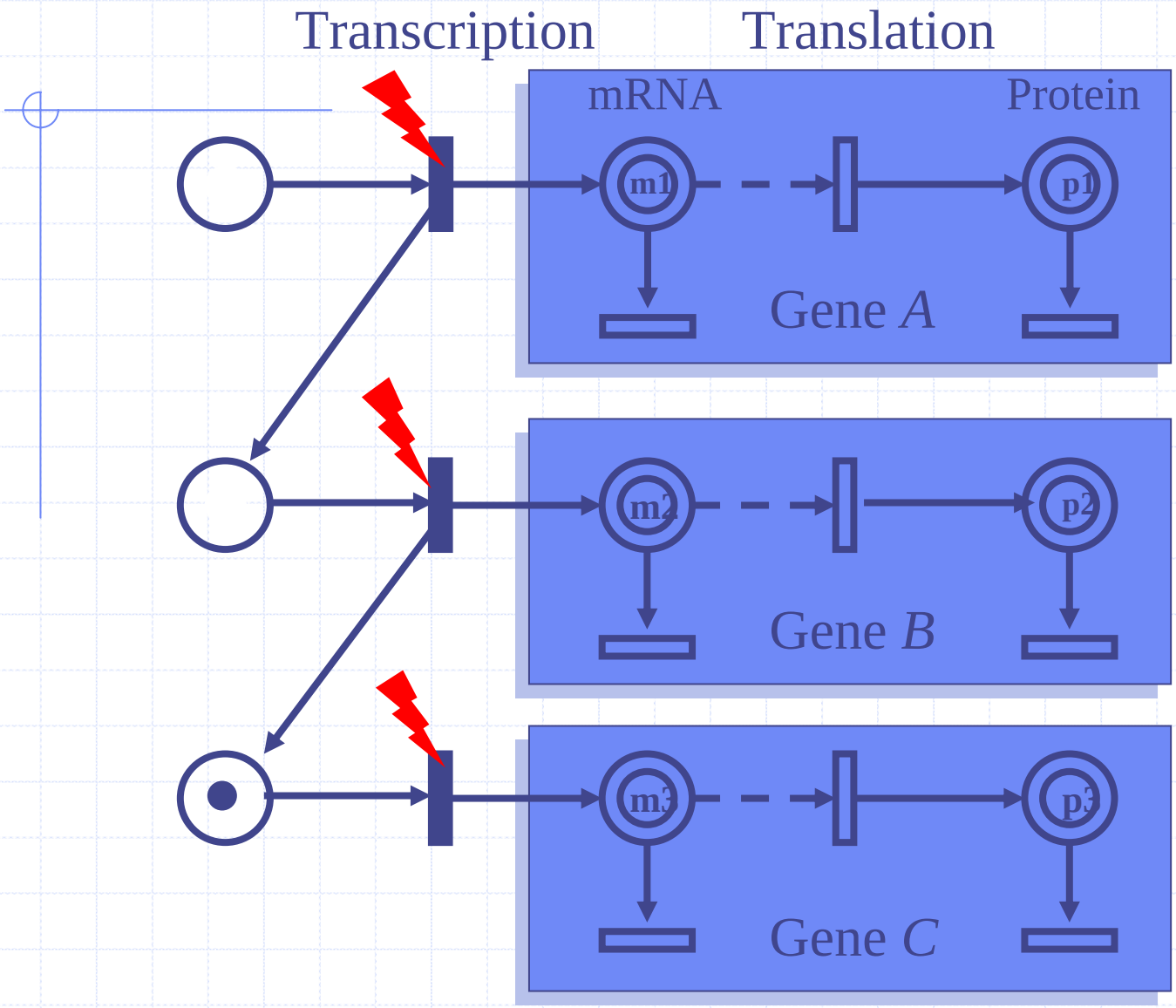




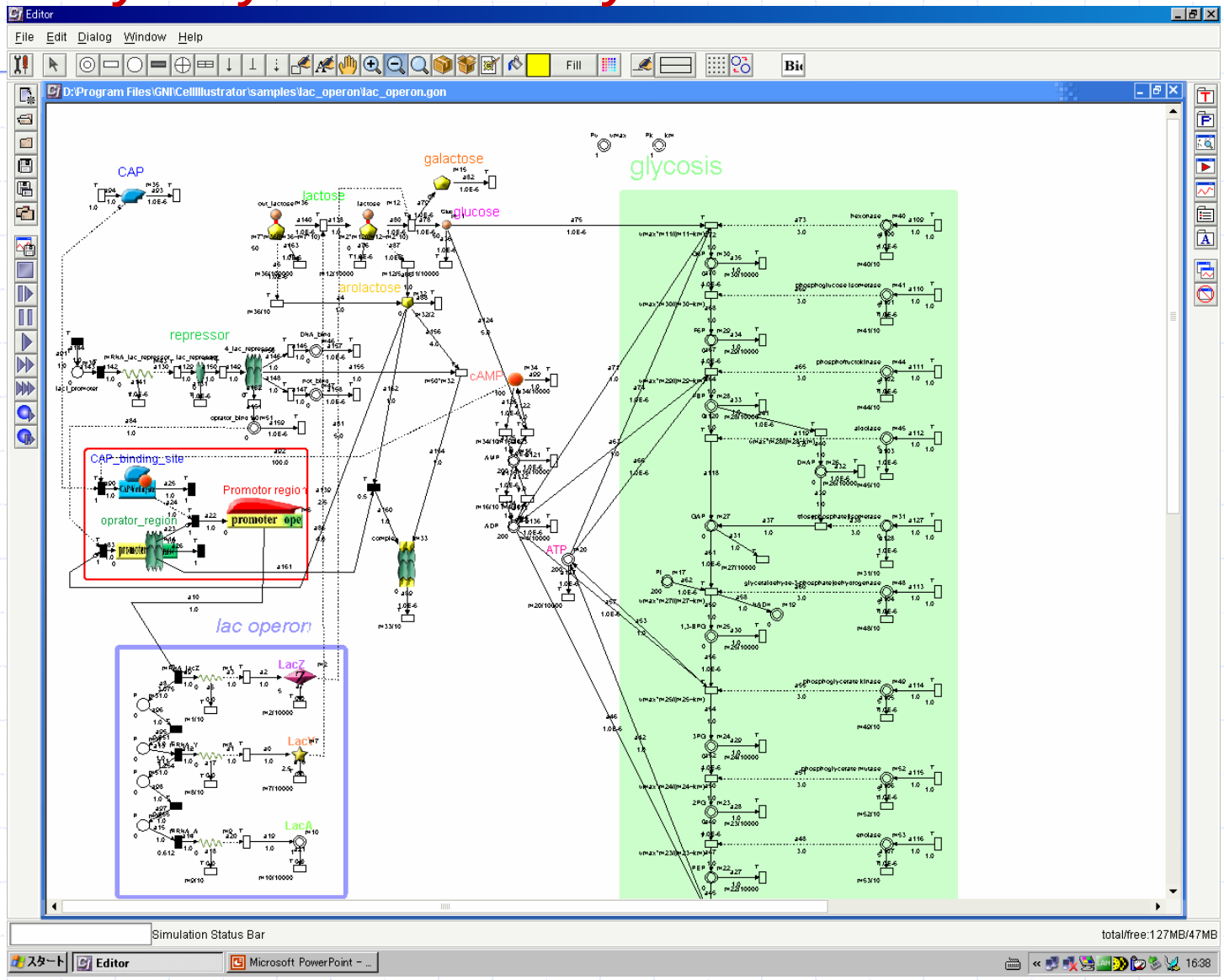
Operon



Operon

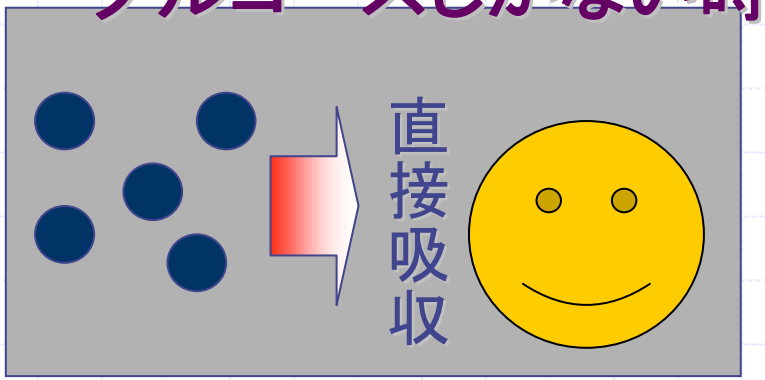

Transcription
Translation
mRNA
Protein
m1
p1
Gene A
m2
p2
Gene B
m3
p3
Gene C

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



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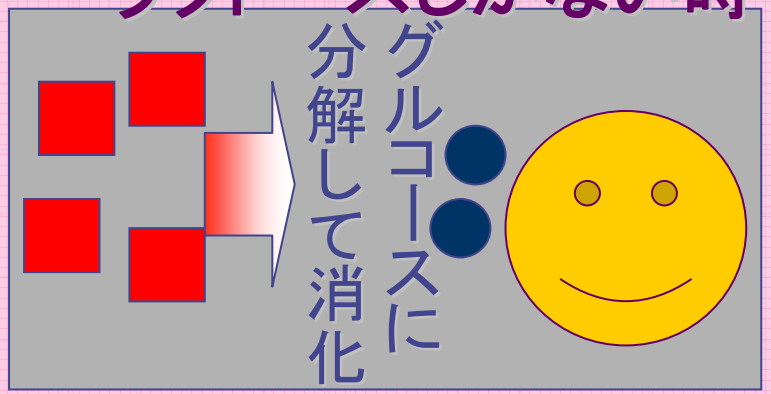
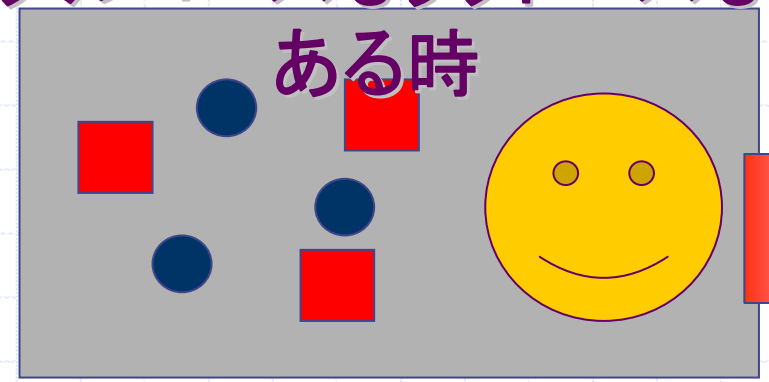
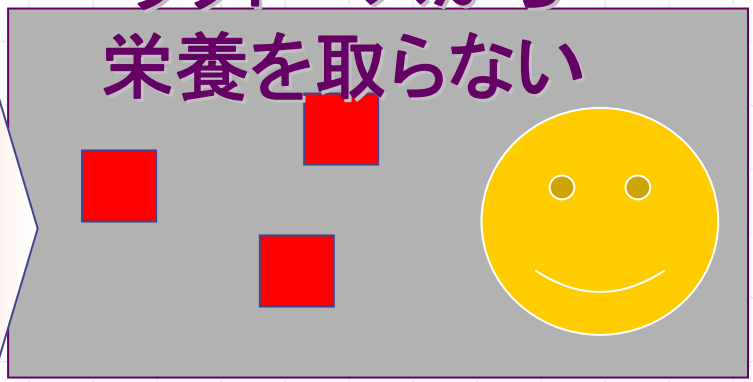


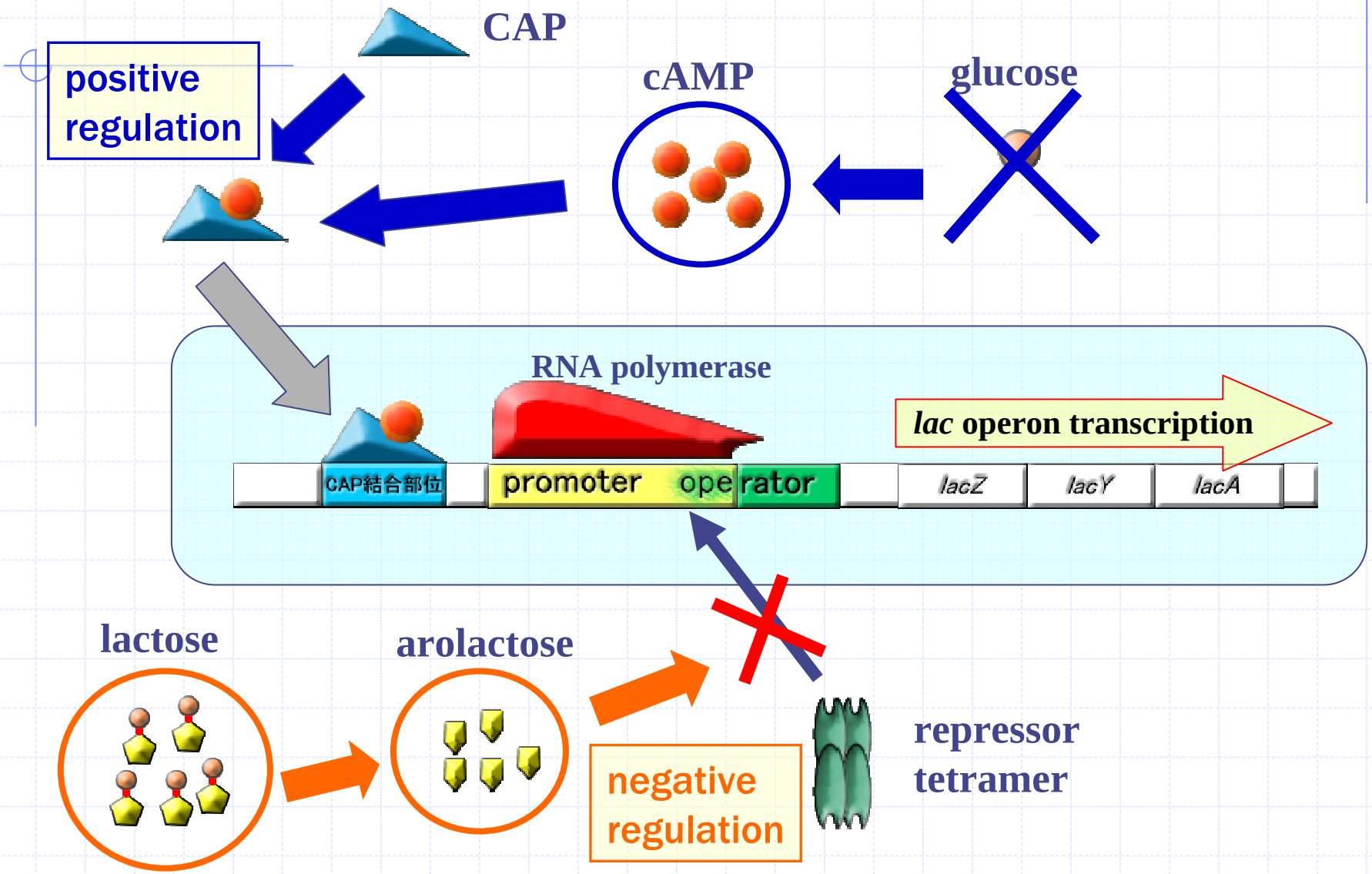
グルコースもラクトースもある時

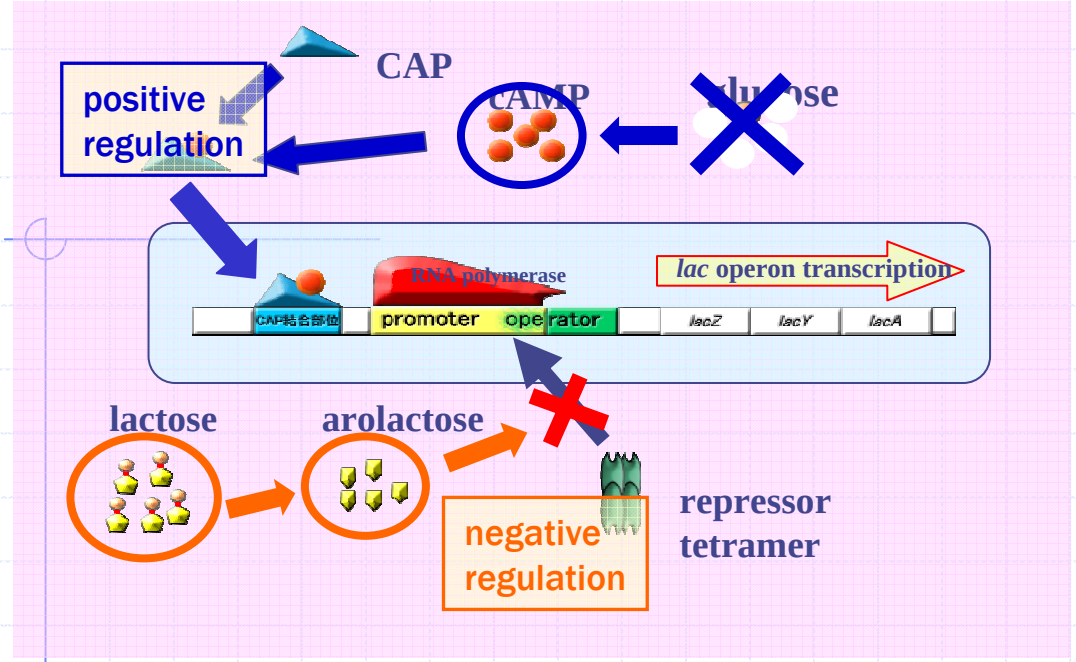


ラクトースから栄養を取らない



Positive regulation and Negative regulation

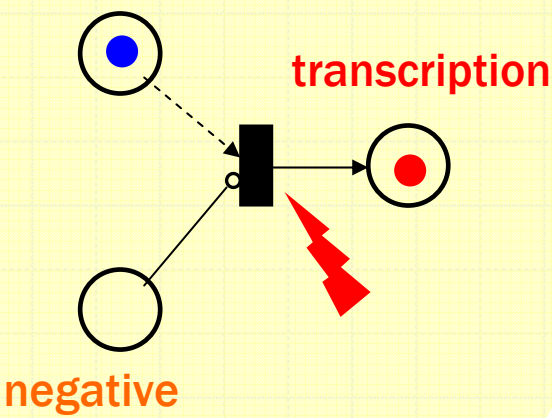




Transcription control switch

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

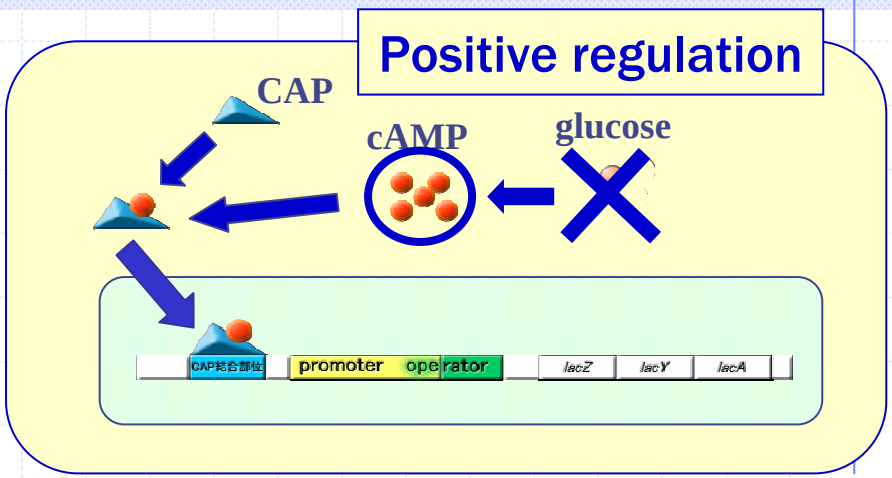
Petri net reprentation

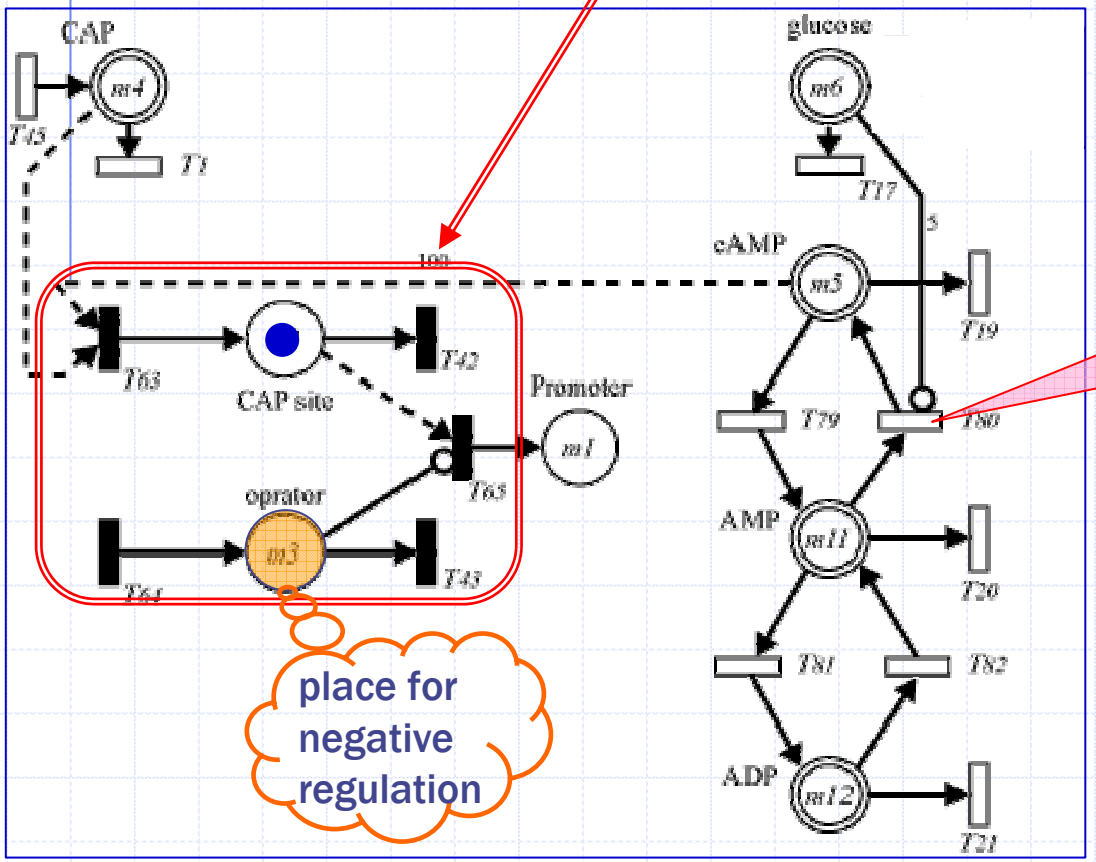


Transcription control switch

and

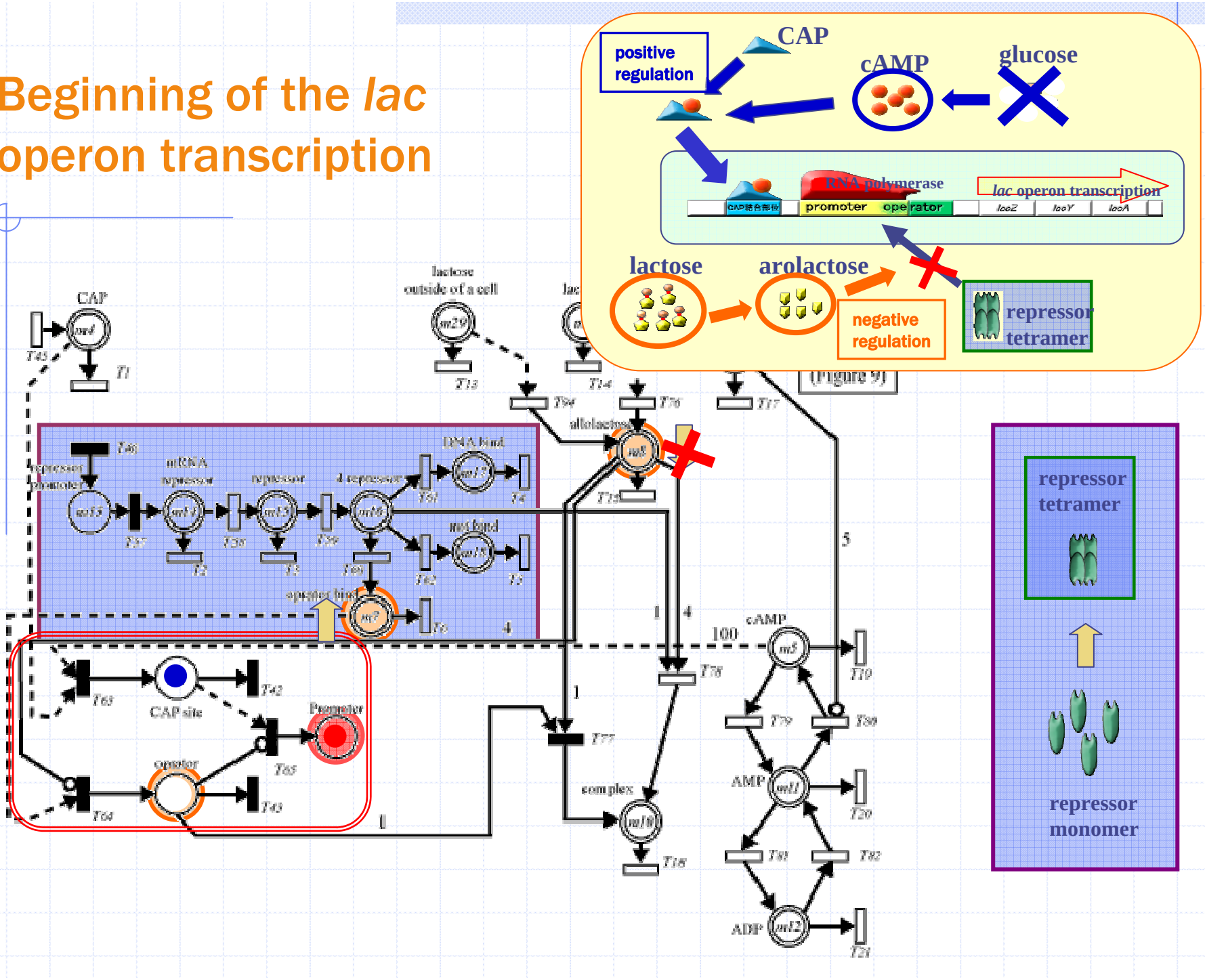
Positive regulation



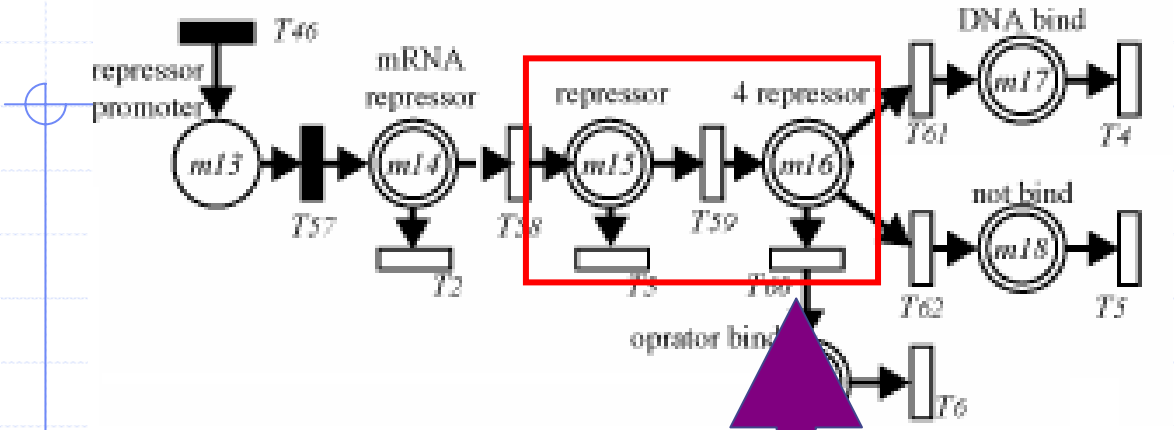


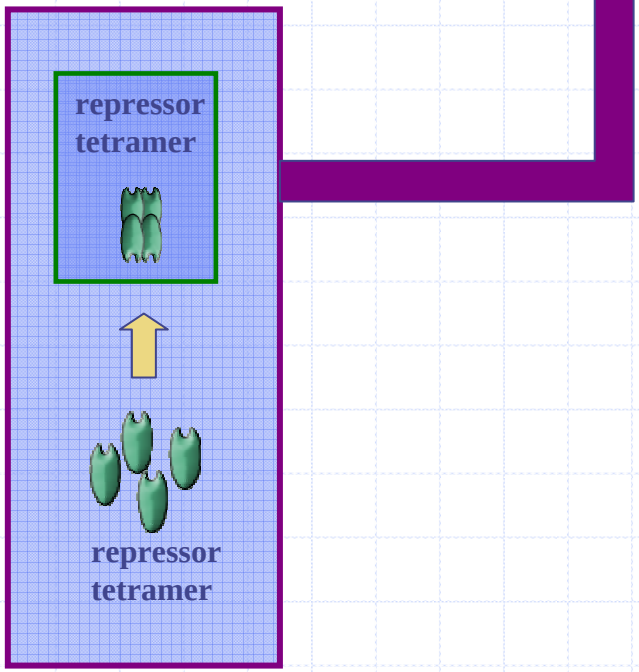
become active

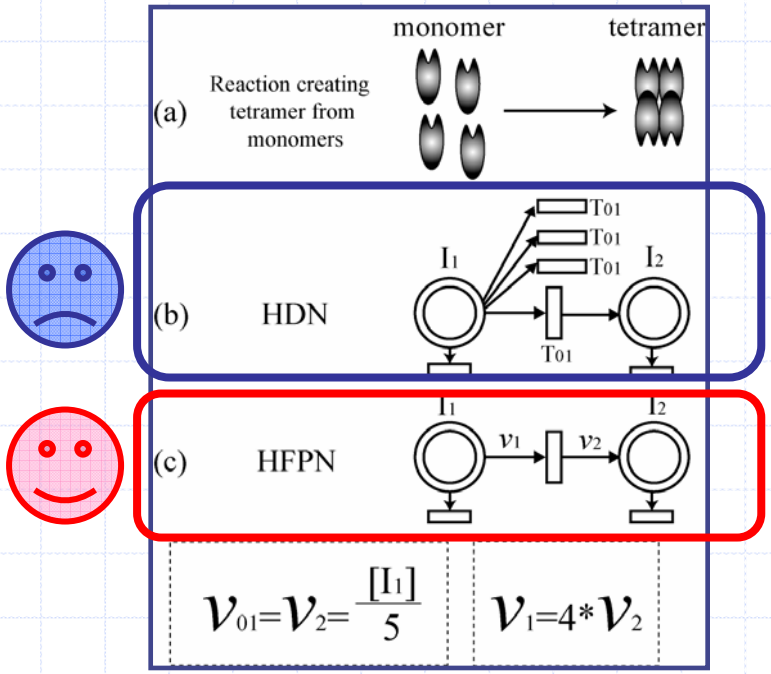
Beginning of the *lac* operon transcription



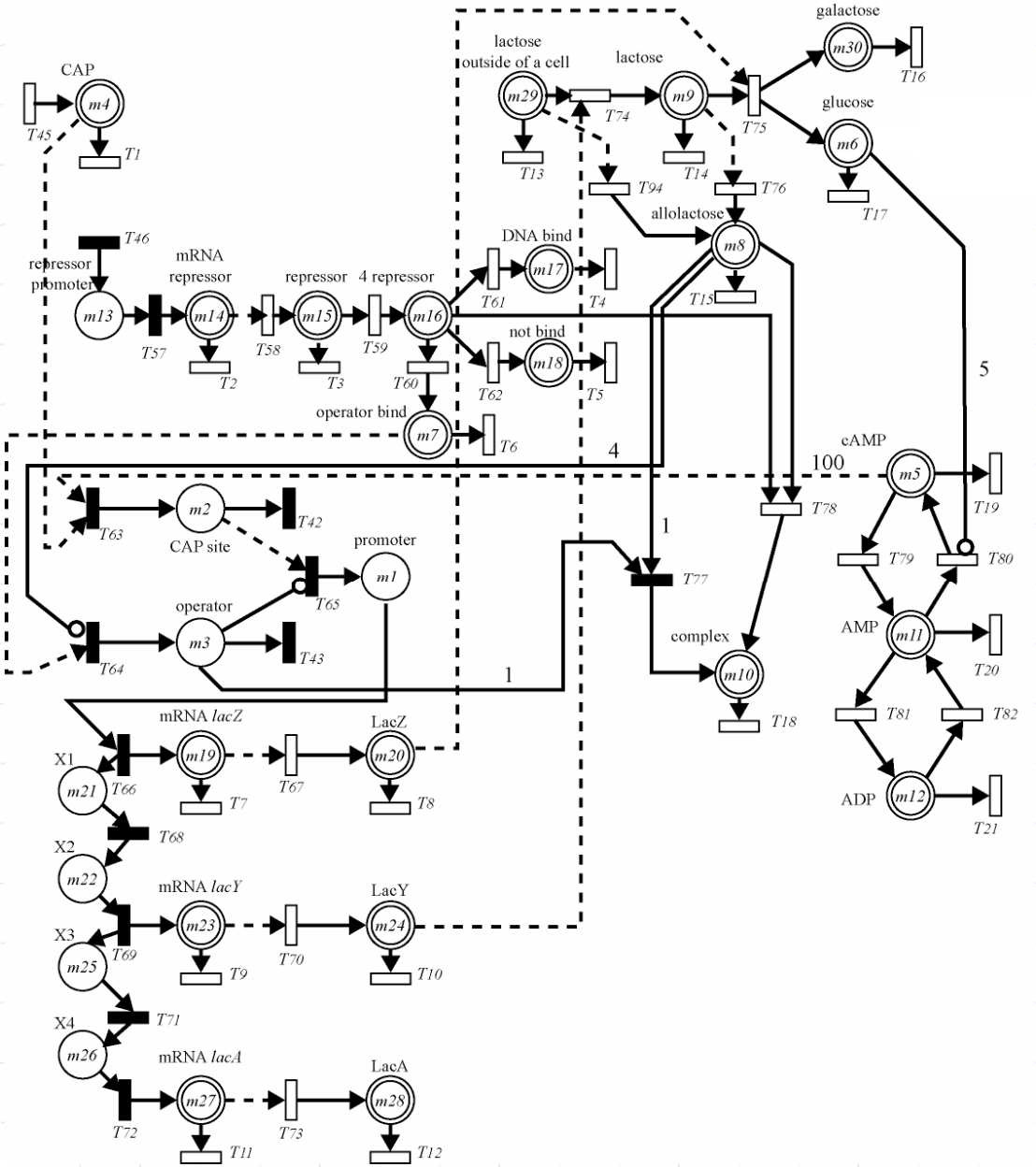
Usage of hybrid functional Petri net





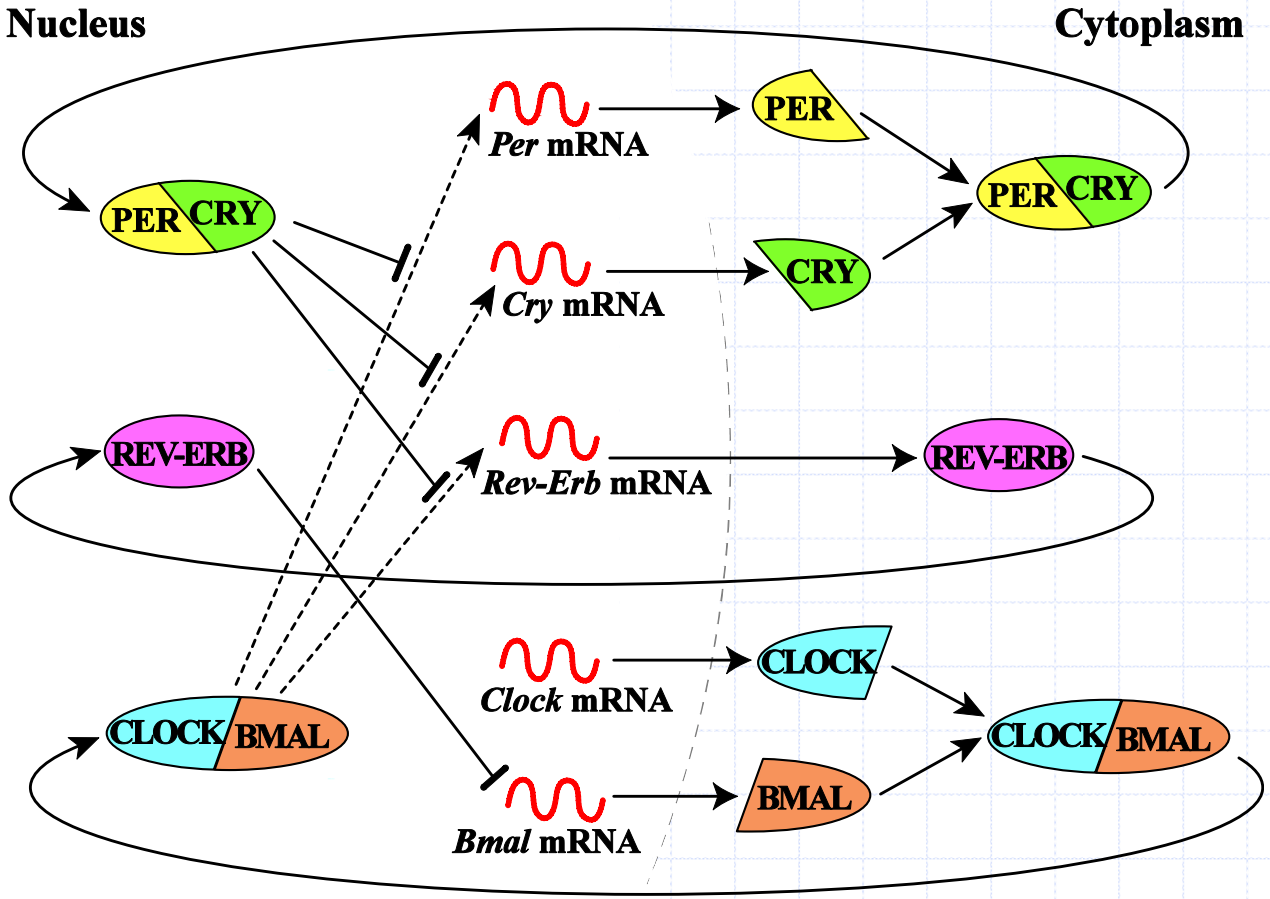


HFPN model of lac operon genetic control mechanism

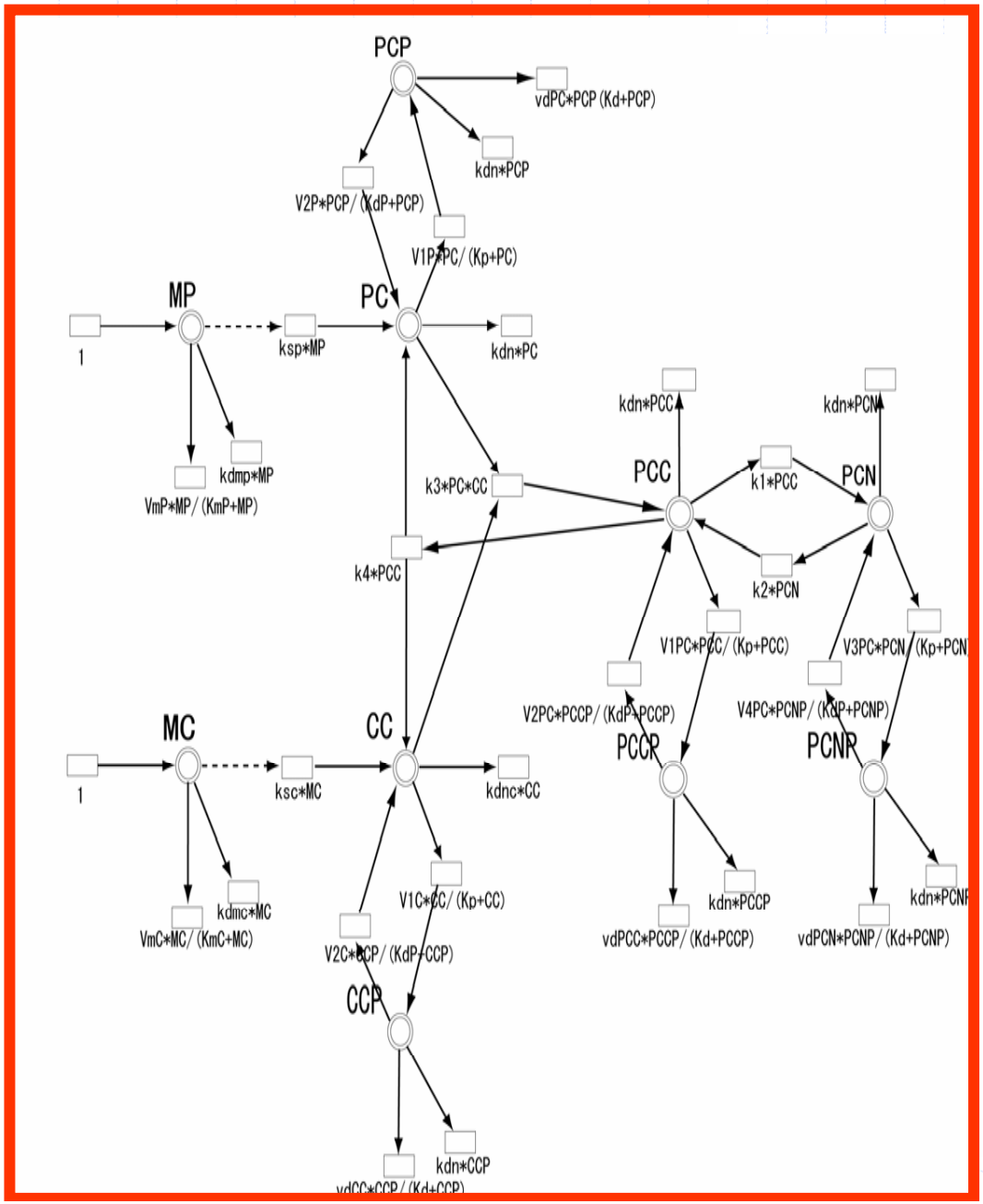


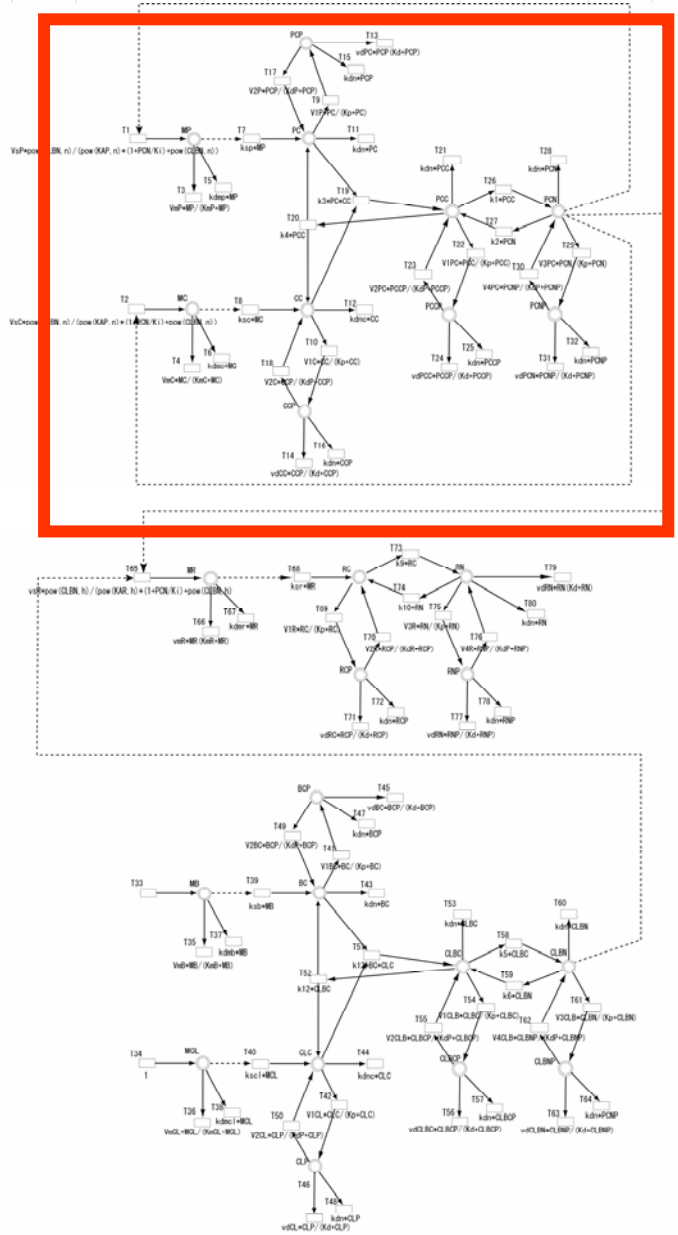
ウス　日リ　ム

山口大 理　　研との



分　　による　　ル化 (Leloup & Goldbeter, 2003)





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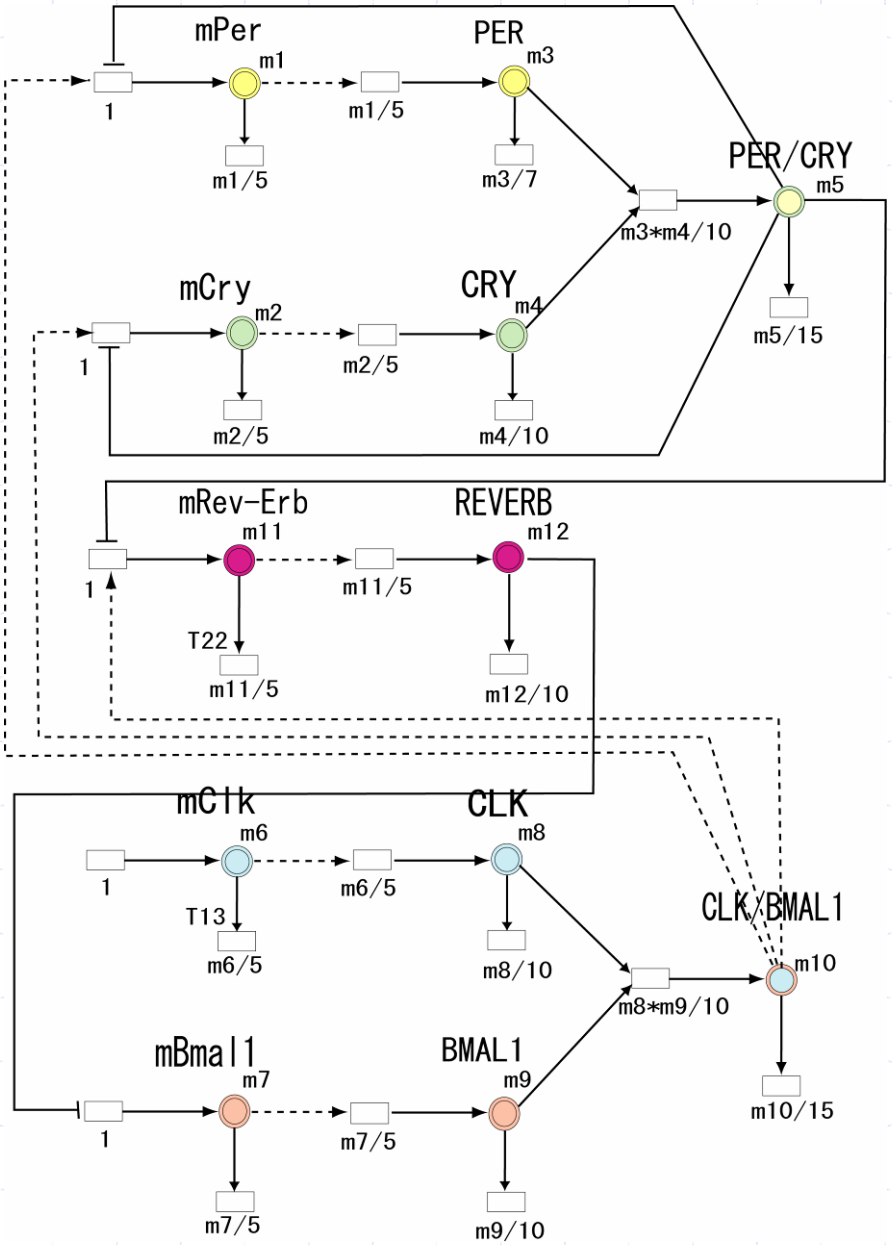
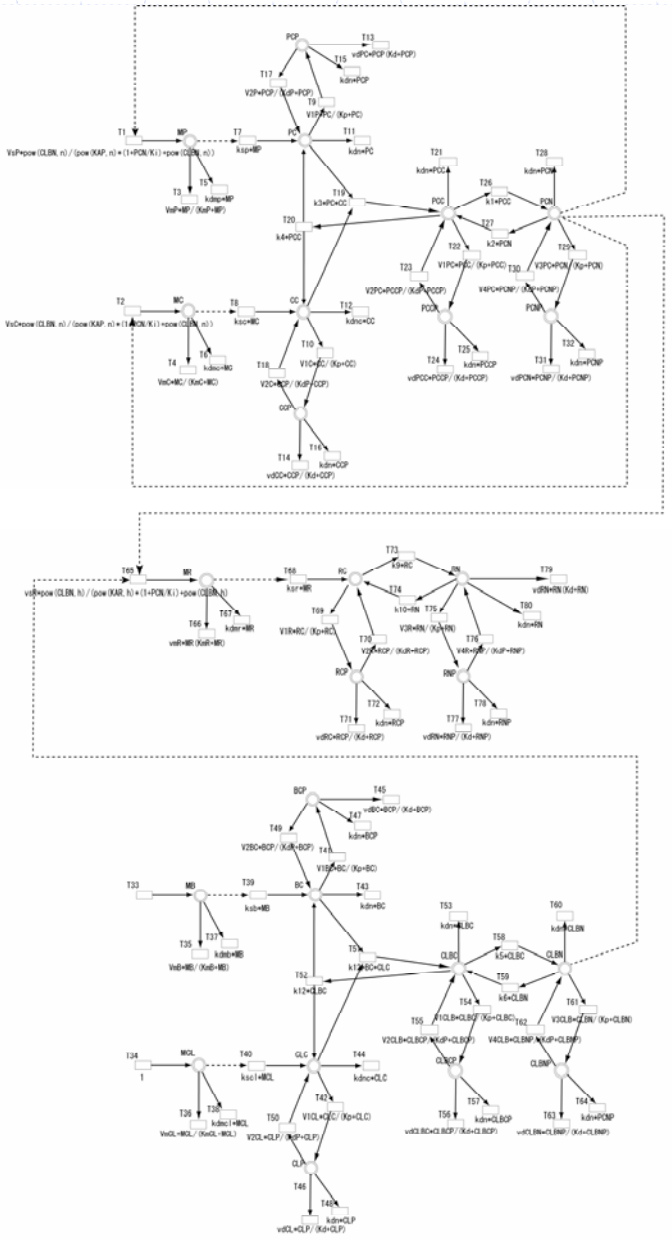
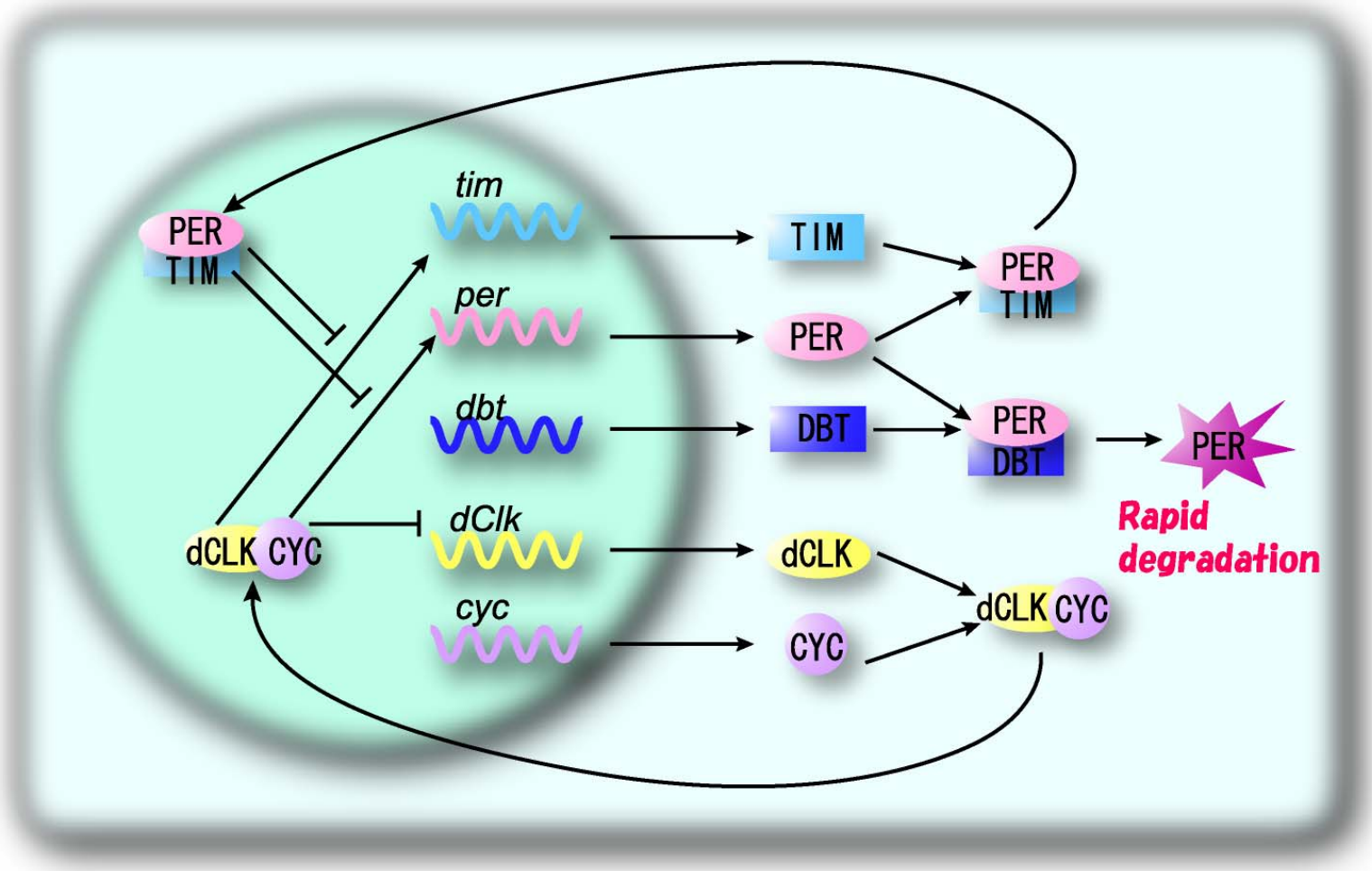
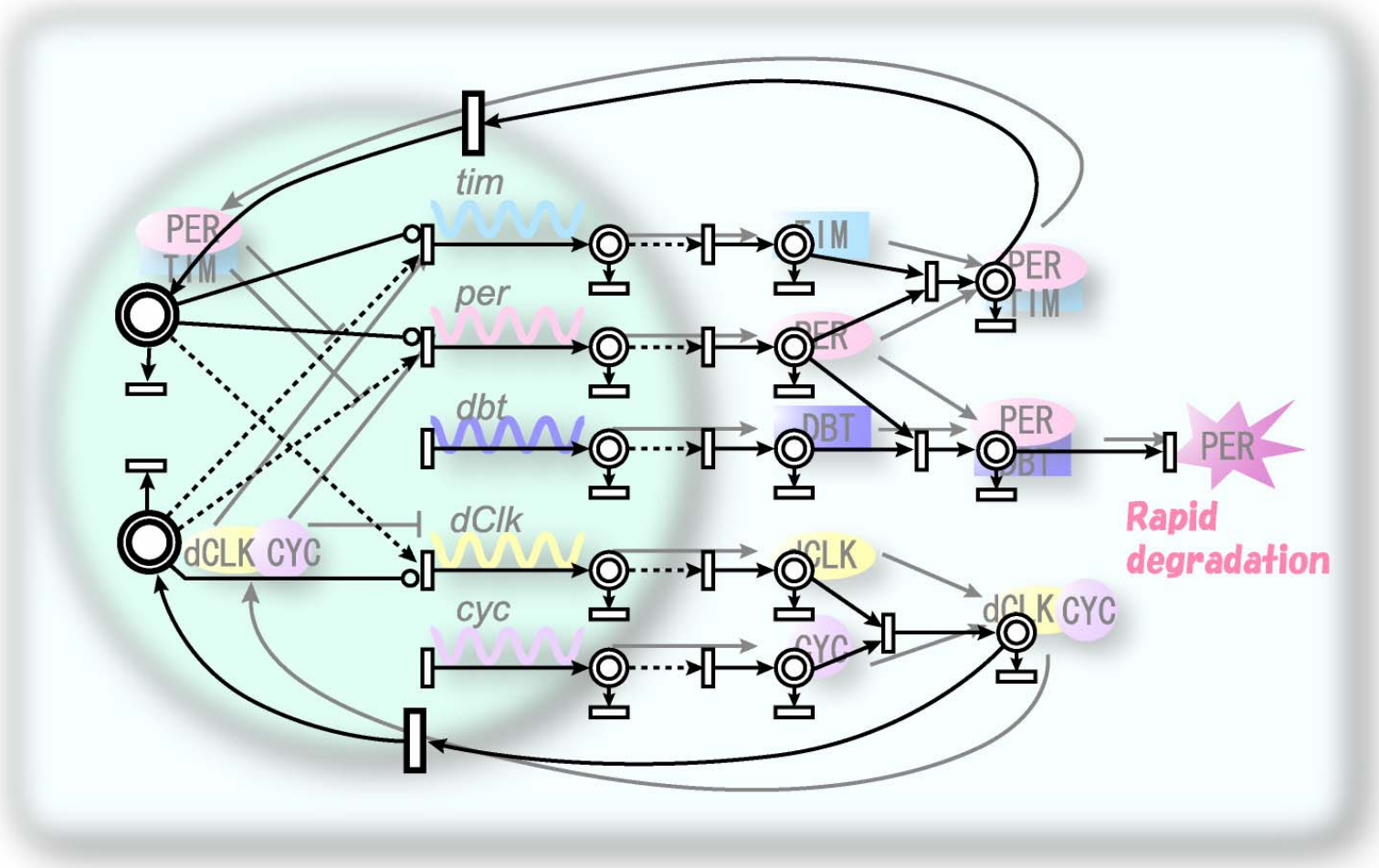




Gene Regulatory mechanism of *Drosophila* Circadian Clock



Gene Regulatory mechanism of *Drosophila* Circadian Clock



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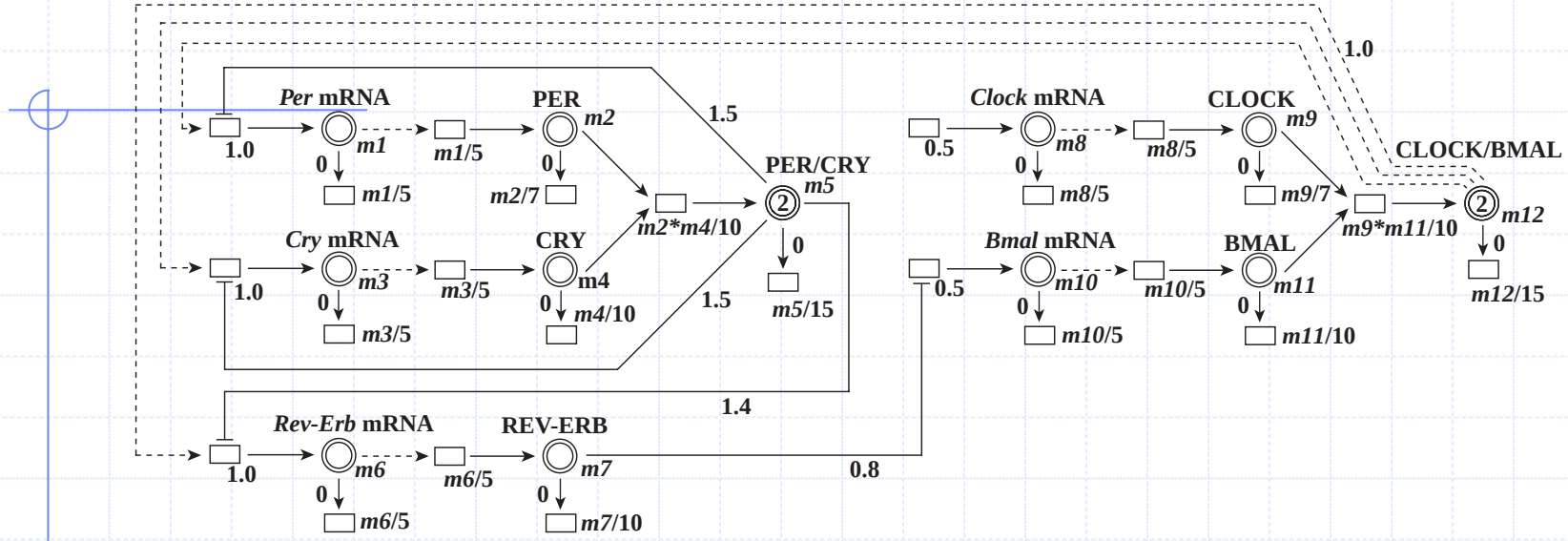
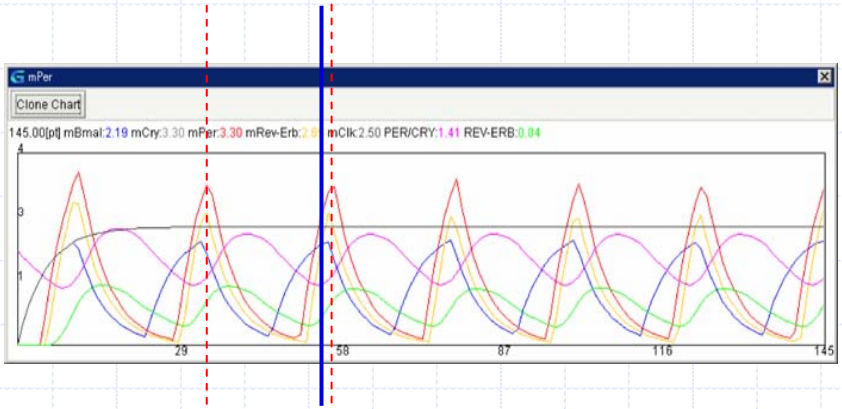
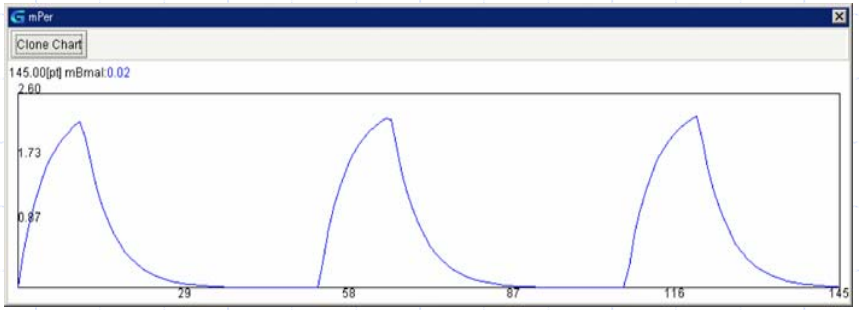


*Cry*を　ック　ウト　ると

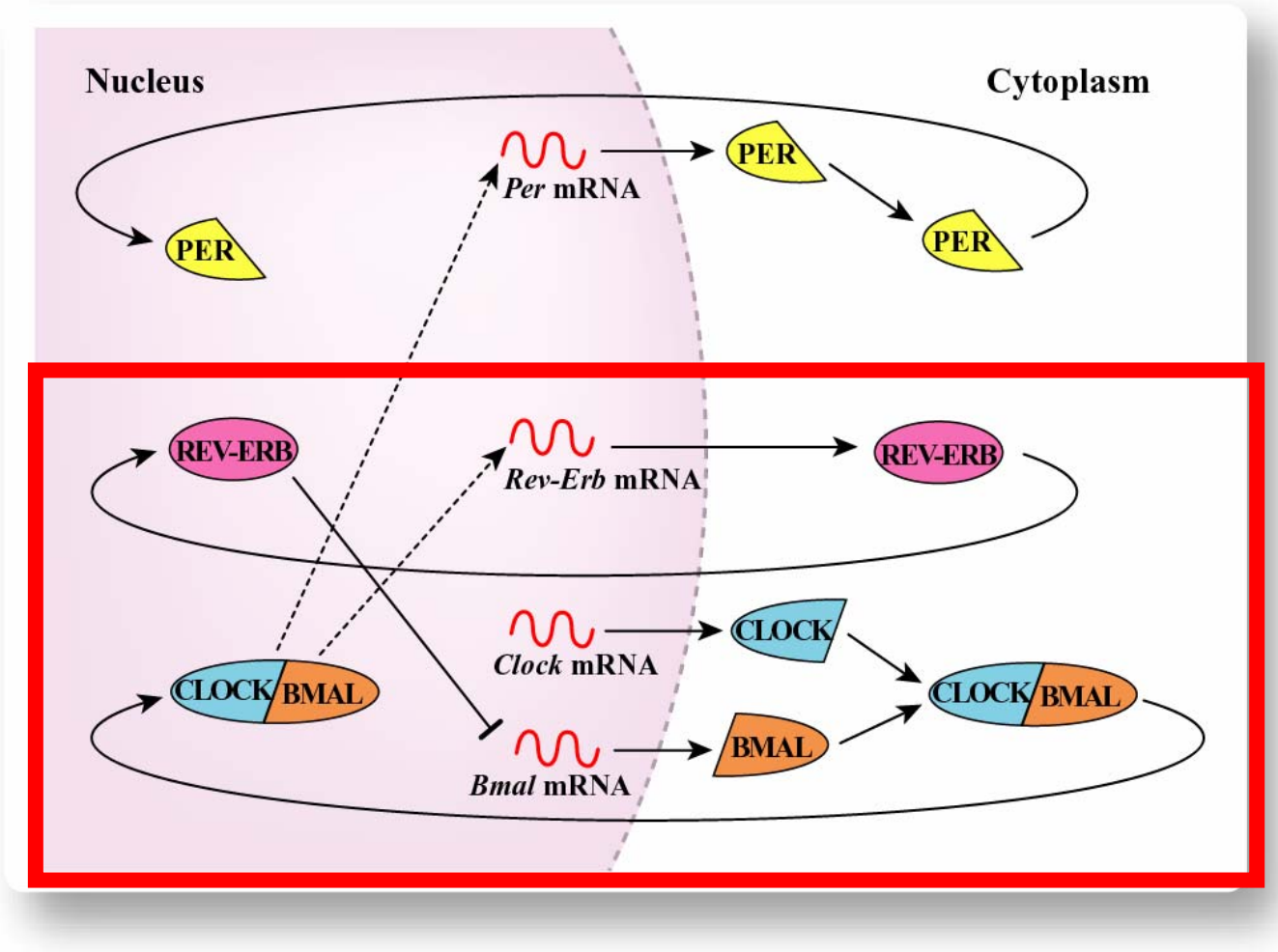


*Bmal1*mRNAの　ーク　*Per*mRNAの　ークの　に　　しい

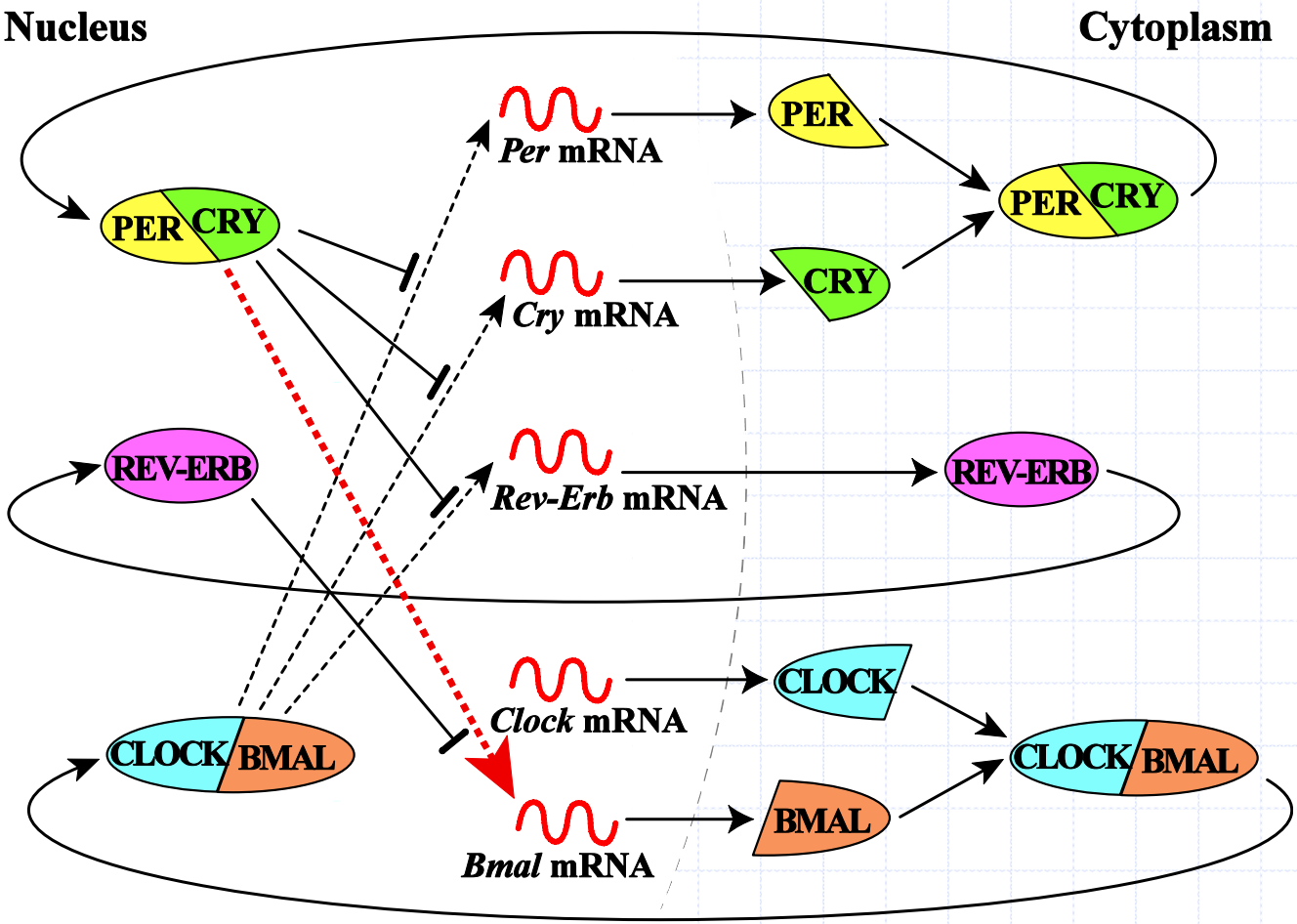


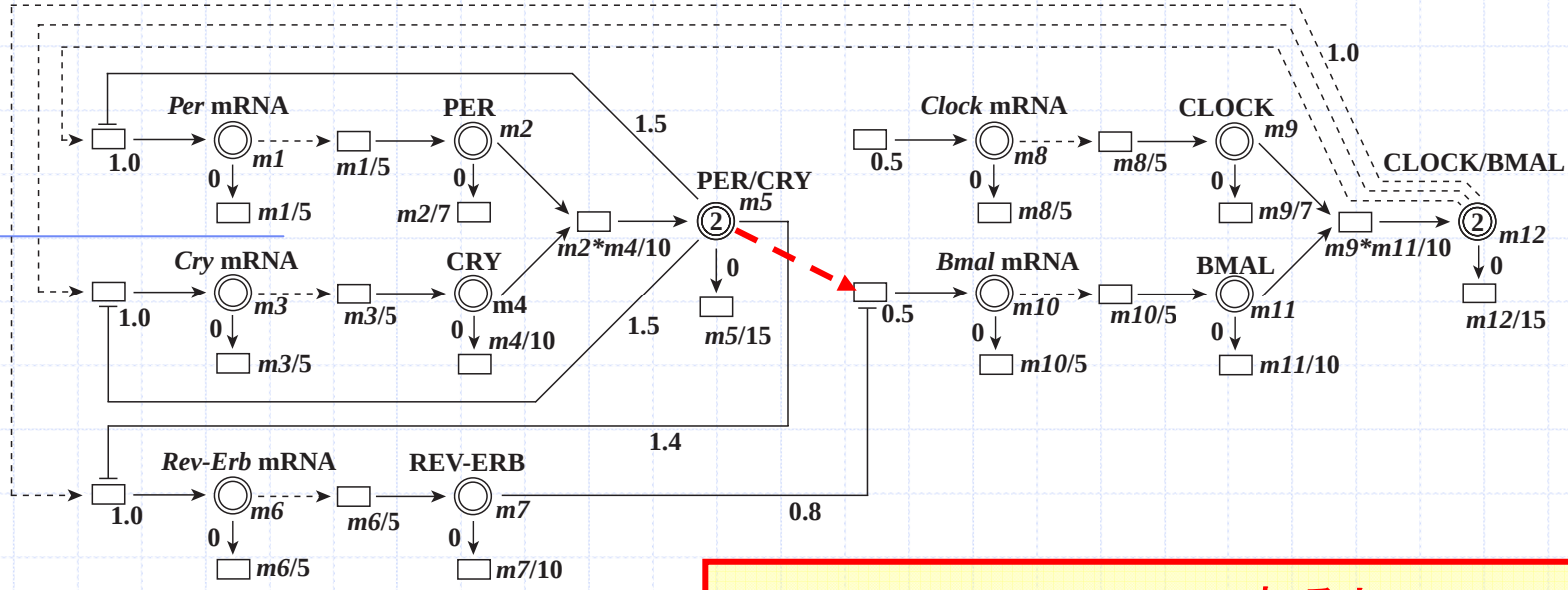
*Bmal1*mRNA　　しない　　しい

Cry　ック　ウト


Nucleus
Cytoplasm
PER
Per mRNA
PER
PER
REV-ERB
Rev-Erb mRNA
REV-ERB
CLOCK
BMAL
Clock mRNA
CLOCK
CLOCK
BMAL
BMAL
Bmal mRNA

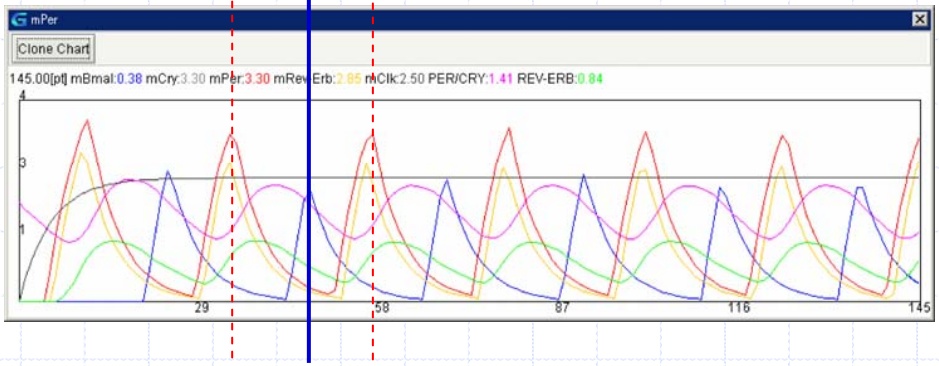
Drosophila　ら　いる　PER/TIM　*dClk* を

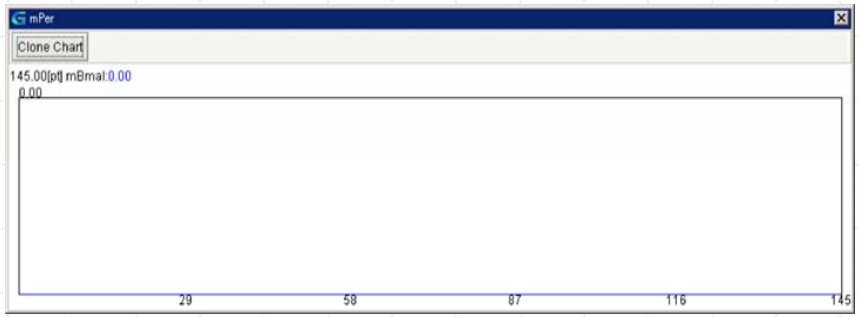




PER CR *mal1* あると る

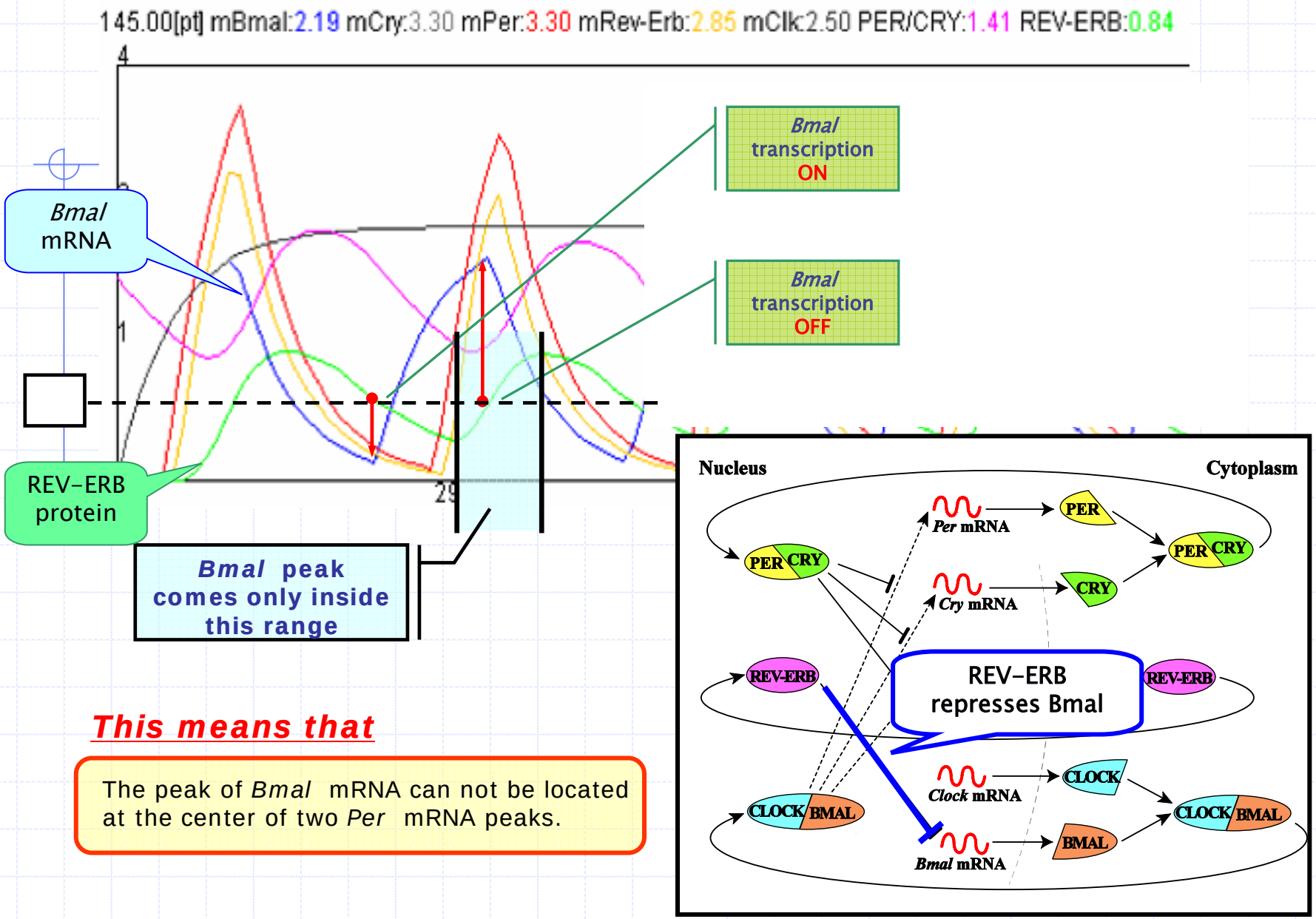
*Cry*を ック ウト ると





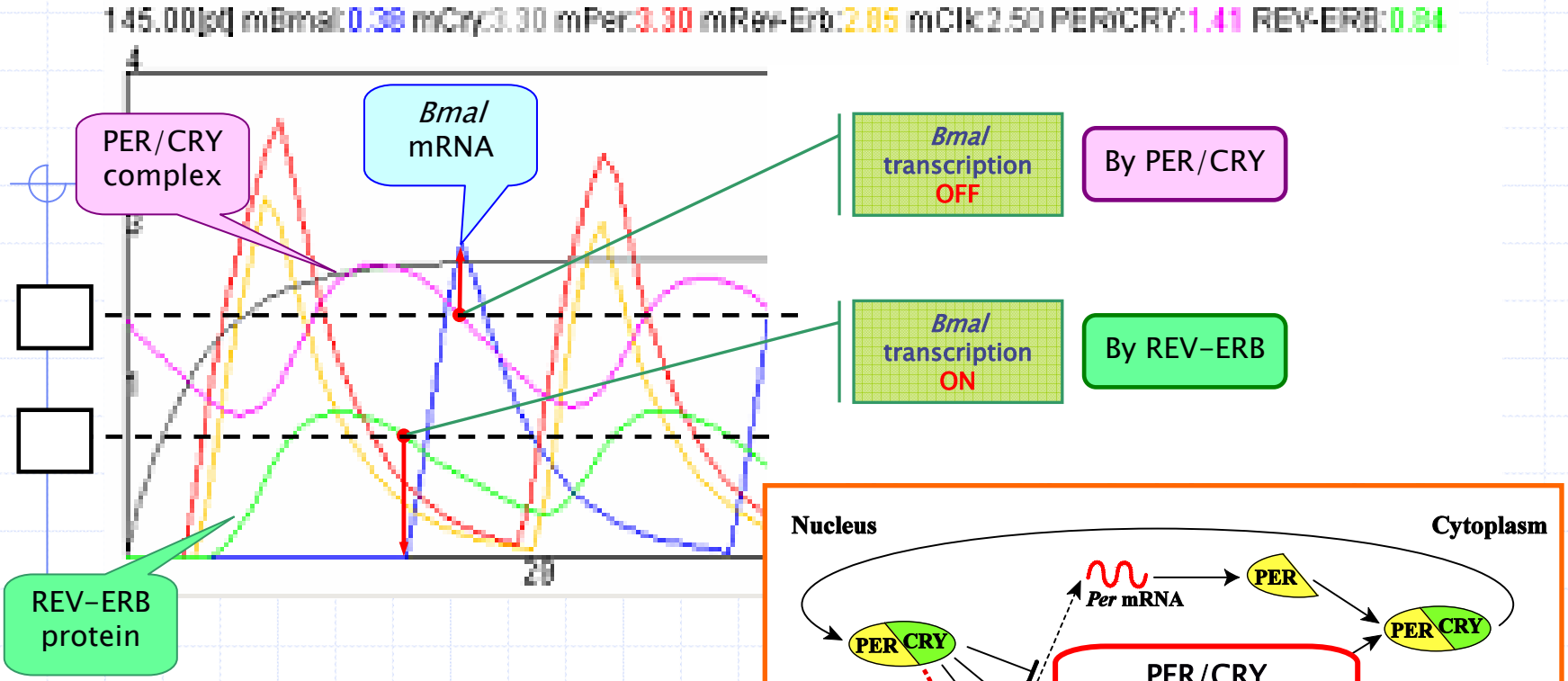
*Bmal1*mRNAの ーク PermRNAの
ークの に

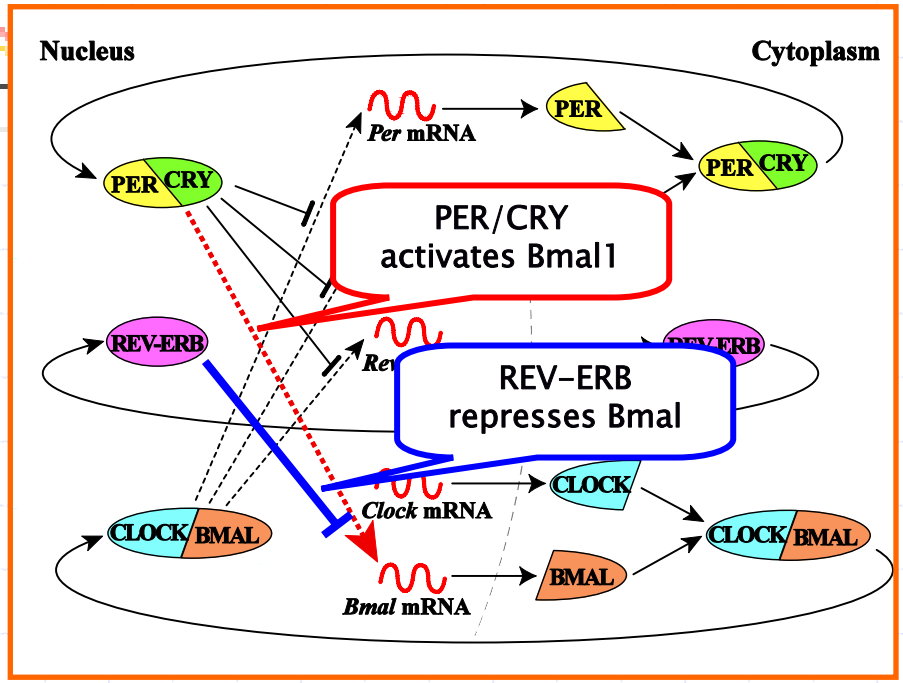
Bmal1mRNAの



This means that

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



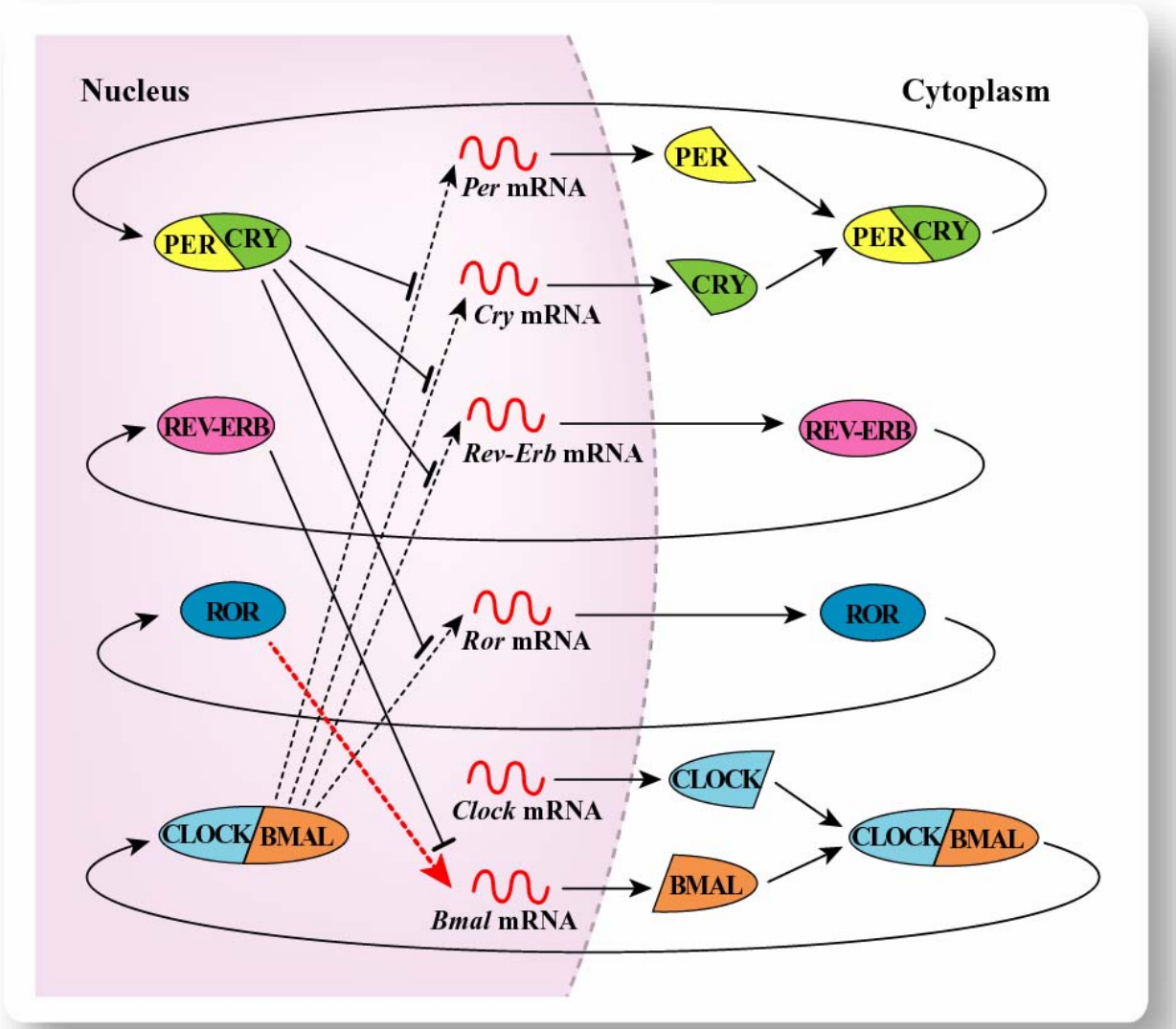


Two switches of PER/CRY and REV-ERB allow *Bmal* mRNA peak to locate at the center of two *Per* mRNA peaks.

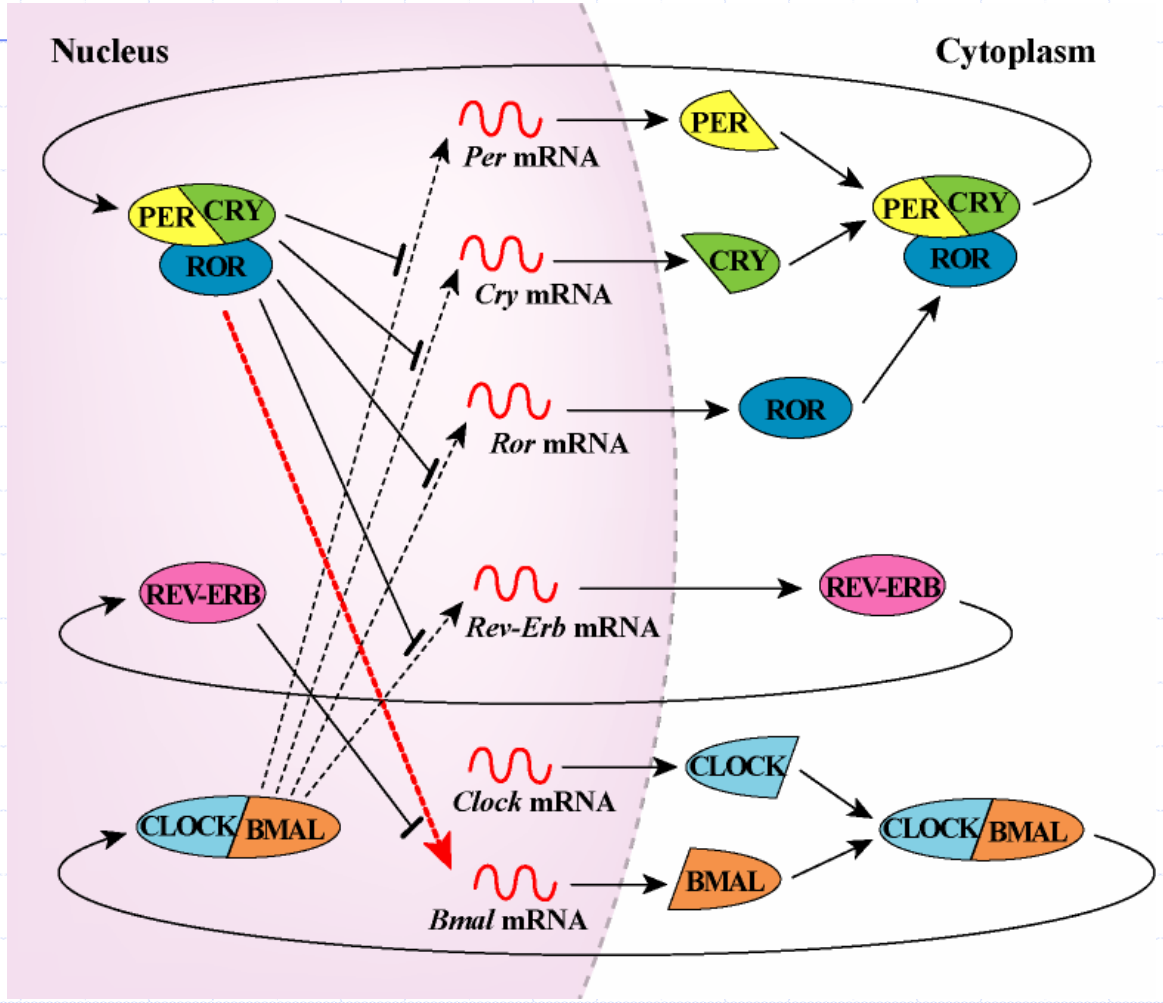
- Sato, T.K., *et al*., A functional genomics strategy reveals Rora as a component of the mammalian circadian clock, *Neuron*, 43, pp.527-537, 2004.

- Akashi, M., Takumi, T., The orphan nuclear receptor ROR 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.

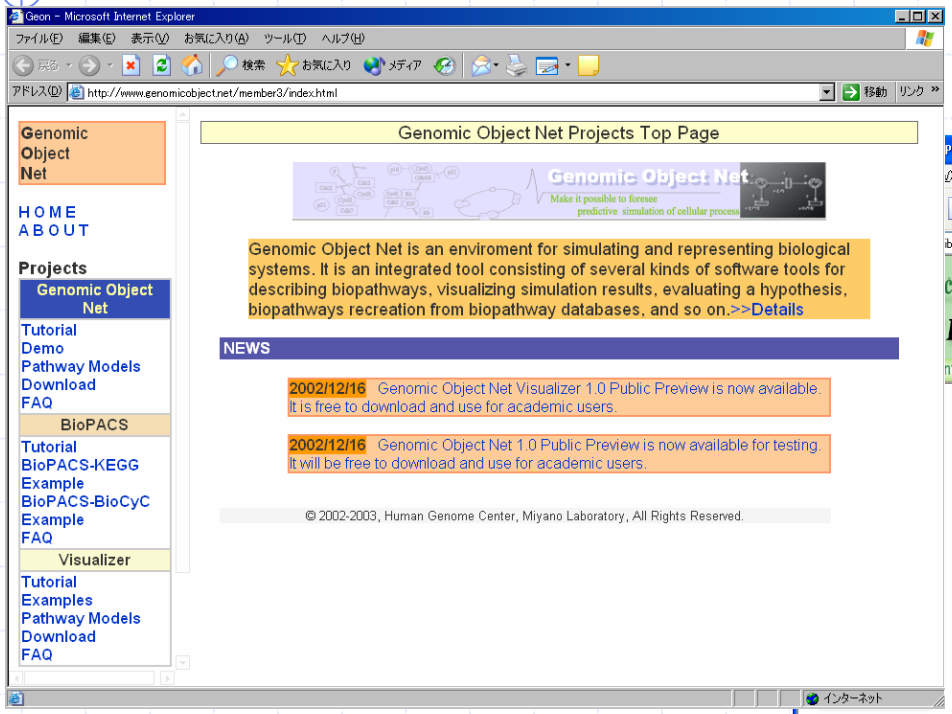
Ror の


Nucleus
Cytoplasm
PER
CRY
PER CRY
Per mRNA
Cry mRNA
REV-ERB
Rev-Erb mRNA
ROR
Ror mRNA
CLOCK
BMAL
CLOCK BMAL
Clock mRNA
Bmal mRNA

*Ror*の　　PER/CRYとの　　化

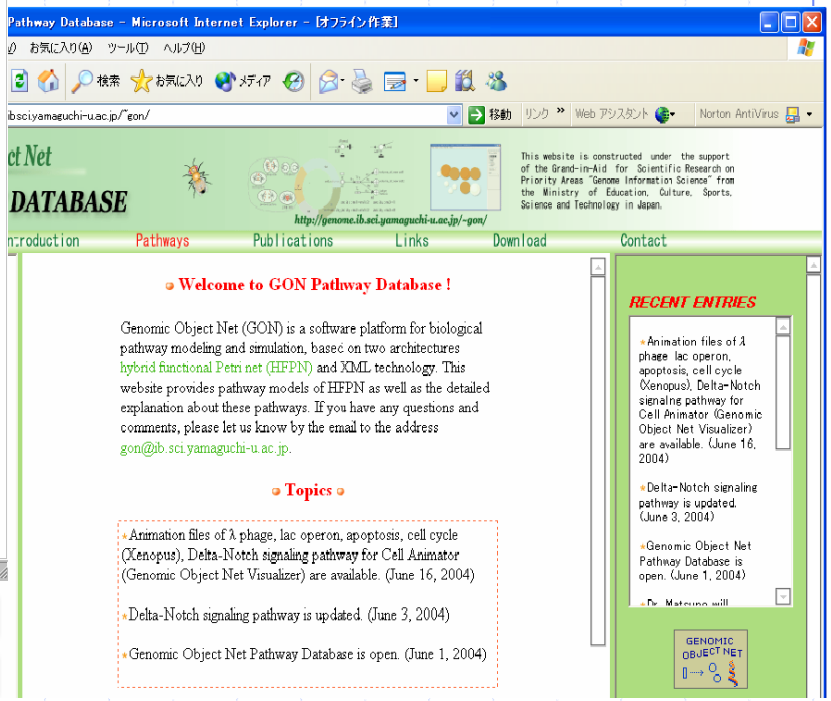


Genomic Object Net



http://www.GenomicObject.Net/

GON Pathway DB



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