

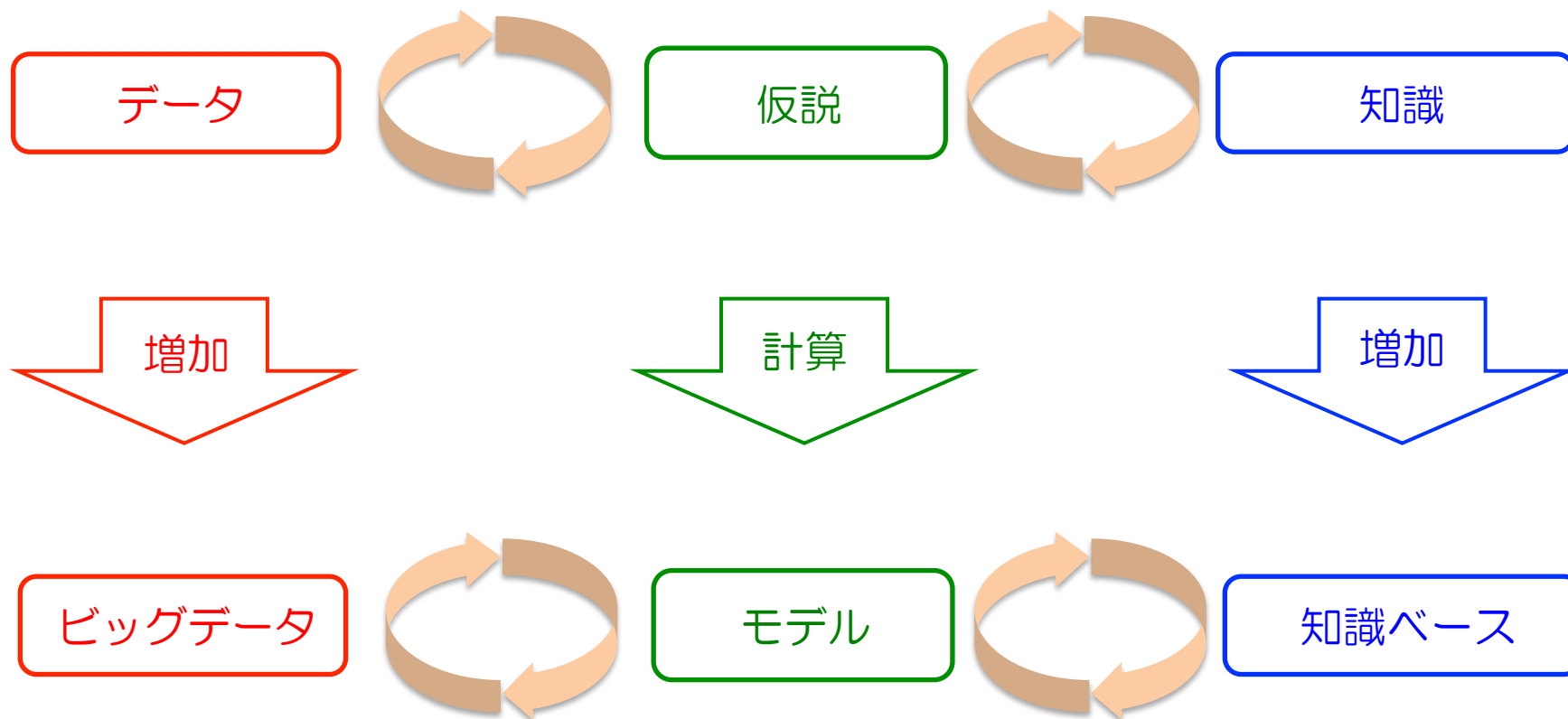
2015/10/21 計算生命科学の基礎Ⅱ

「生物システムの設計：システム生物学から合成生物学へ」

荒木 通啓 (Michihiro Araki)  
araki@port.kobe-u.ac.jp

神戸大学 自然科学系先端融合研究環  
Organization of Advanced Science and Technology  
Kobe University

- はじめに
- 遺伝子回路設計
- 代謝経路設計

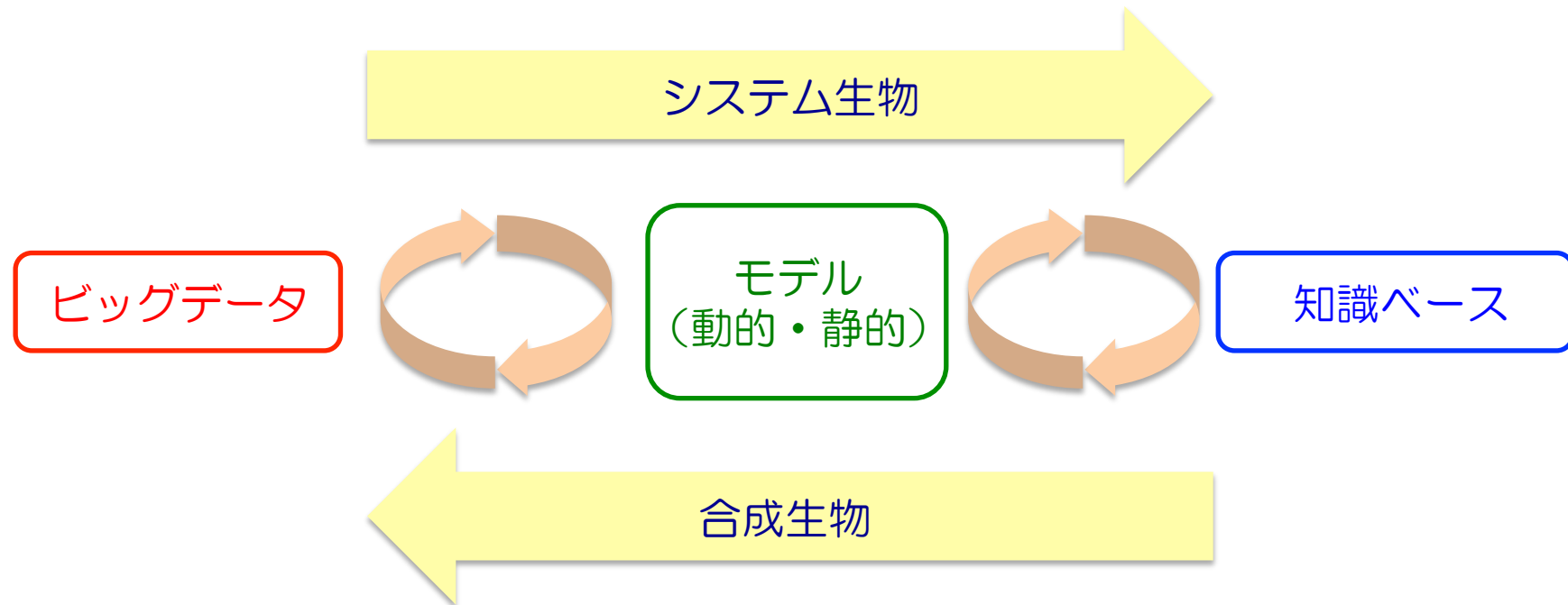


計算・情報科学の必要性

# はじめに

## キーワード)

要素同定、アノテーション、データベース、ネットワーク解析、システム解析、パラメータ同定、シミュレーション、階層性、モチーフなど

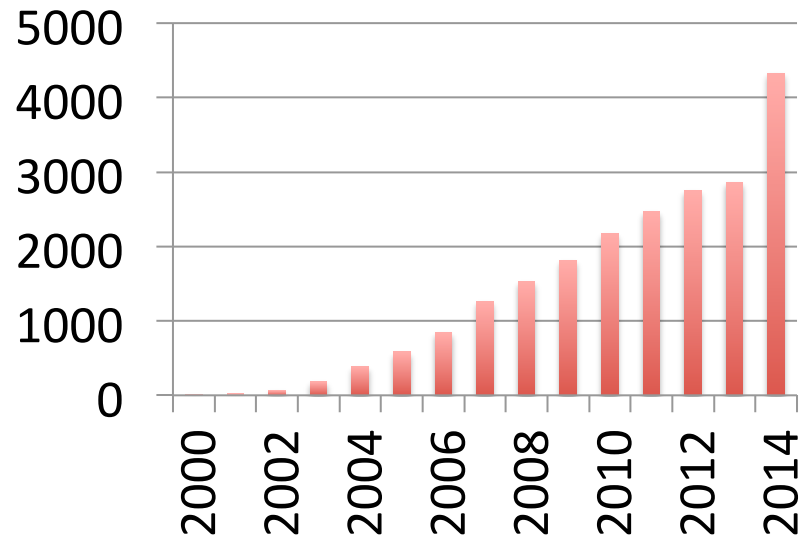


## キーワード)

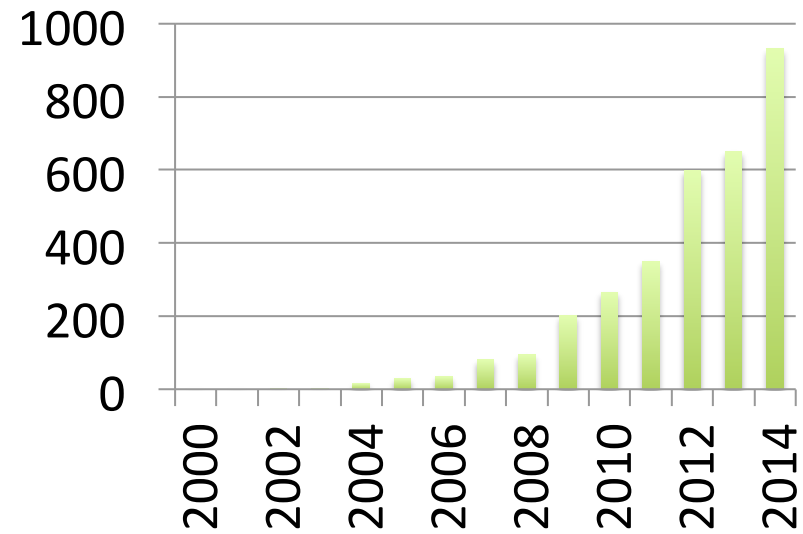
ゲノム細胞工学 (ミニマムゲノム、ゲノム合成)、非天然塩基・アミノ酸、ゲノム編集、BioBrick、人工細胞、遺伝子回路設計、代謝経路設計など

## PubMed検索の結果

システム生物学  
Systems Biology



合成生物学  
Synthetic Biology

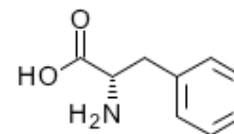
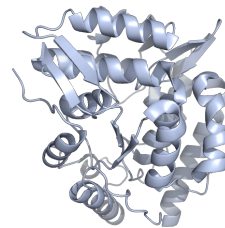


## 分子情報

- 塩基配列
  - DNA、RNA
- アミノ酸配列
  - タンパク質
- 立体構造
  - タンパク質
- 化学構造
  - 化合物

```
atgtccactgcggtcctggaaaaccaggcttgggc  
aggaaactctctgactttggacag
```

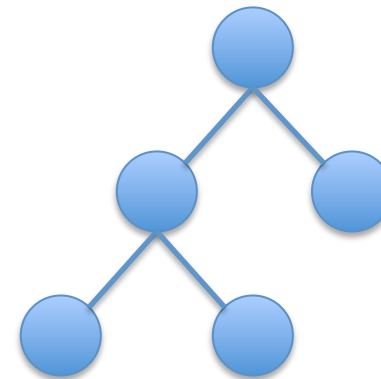
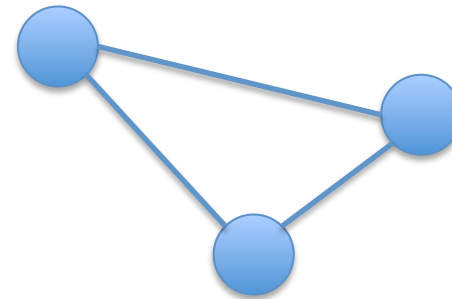
```
MSTAVLENPGLGRKLSDFGQETSYIED  
NCNQNGAISLIFSLKEEVGALAKVLRLF
```



C00079

## ネットワーク情報

- グラフ
  - ペア情報
  - パスウェイ
  
- ツリー
  - 分類情報
  - オントロロジー

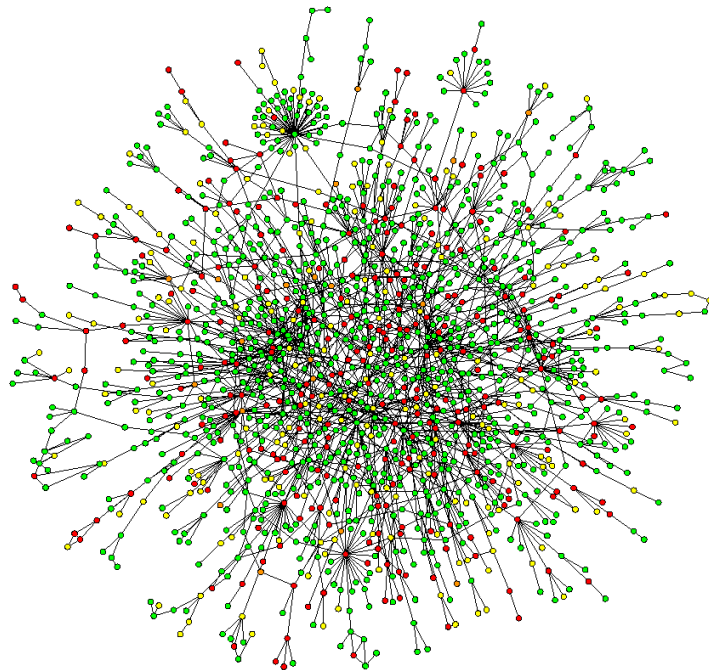


## 表現方法：データベース

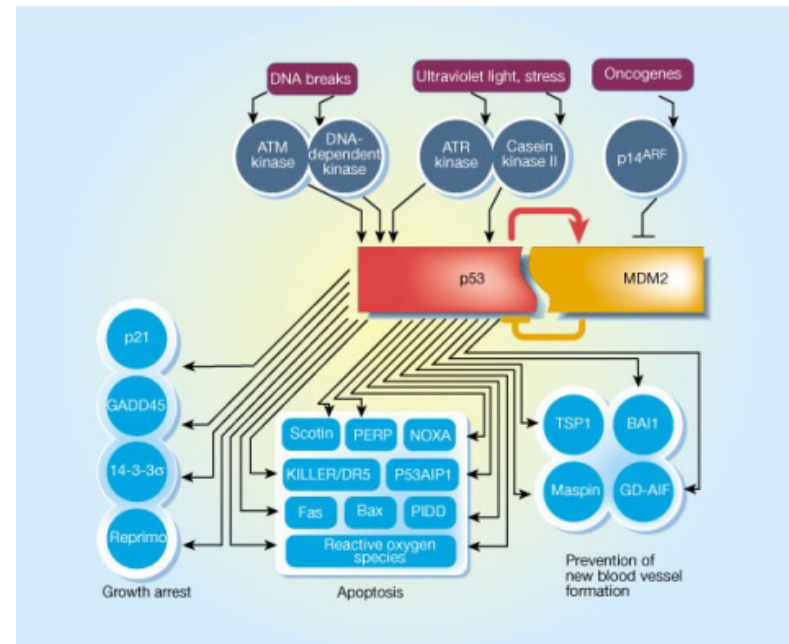
- 要素
  - 遺伝子、タンパク質、化合物
- ペア
  - 相互作用、制御関係、反応
- グラフ
  - パスウェイ
- 階層リスト
  - オントロジー



## 遺伝子回路



Barabasi A-L *et al.*

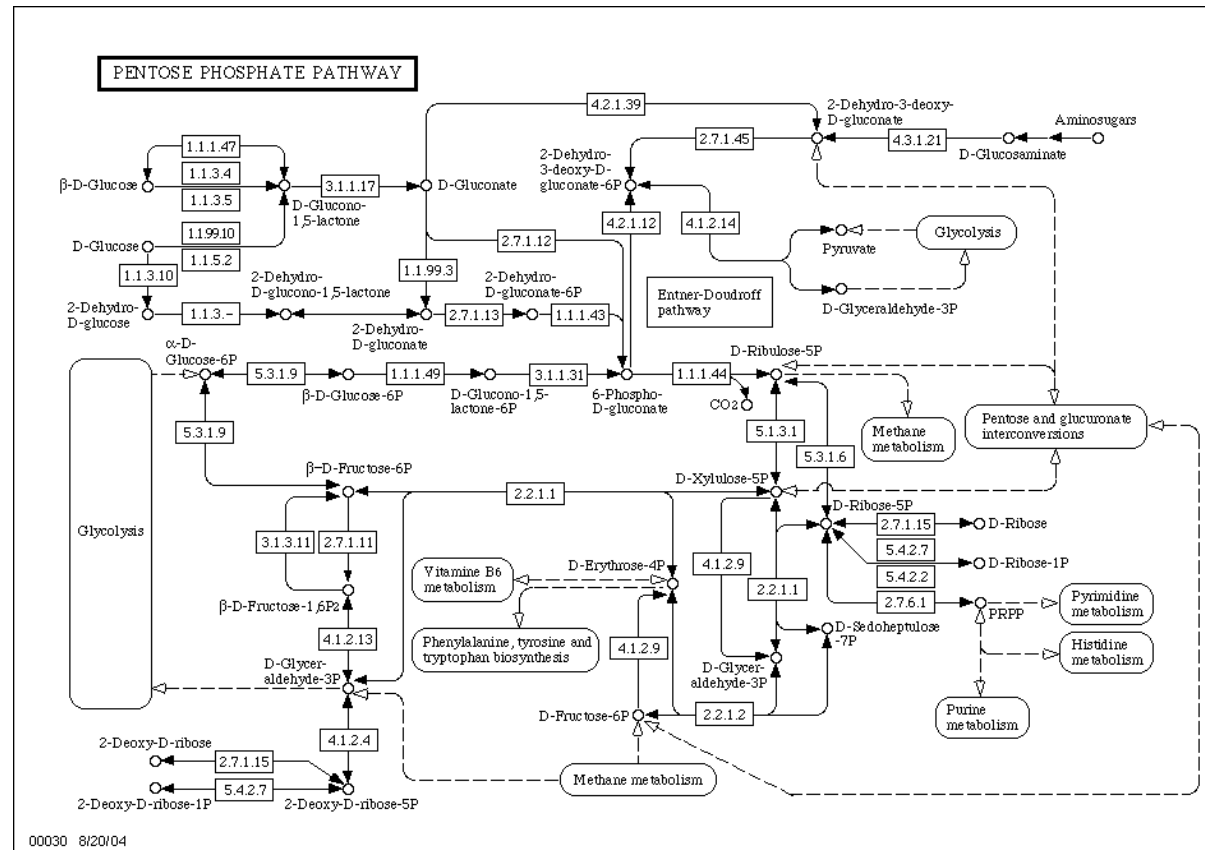


Vogelstein B *et al.*

ランダムな進化 → 一般的な法則・モデル? → 遺伝子回路設計?

## 代謝経路

## KEGG PATHWAY

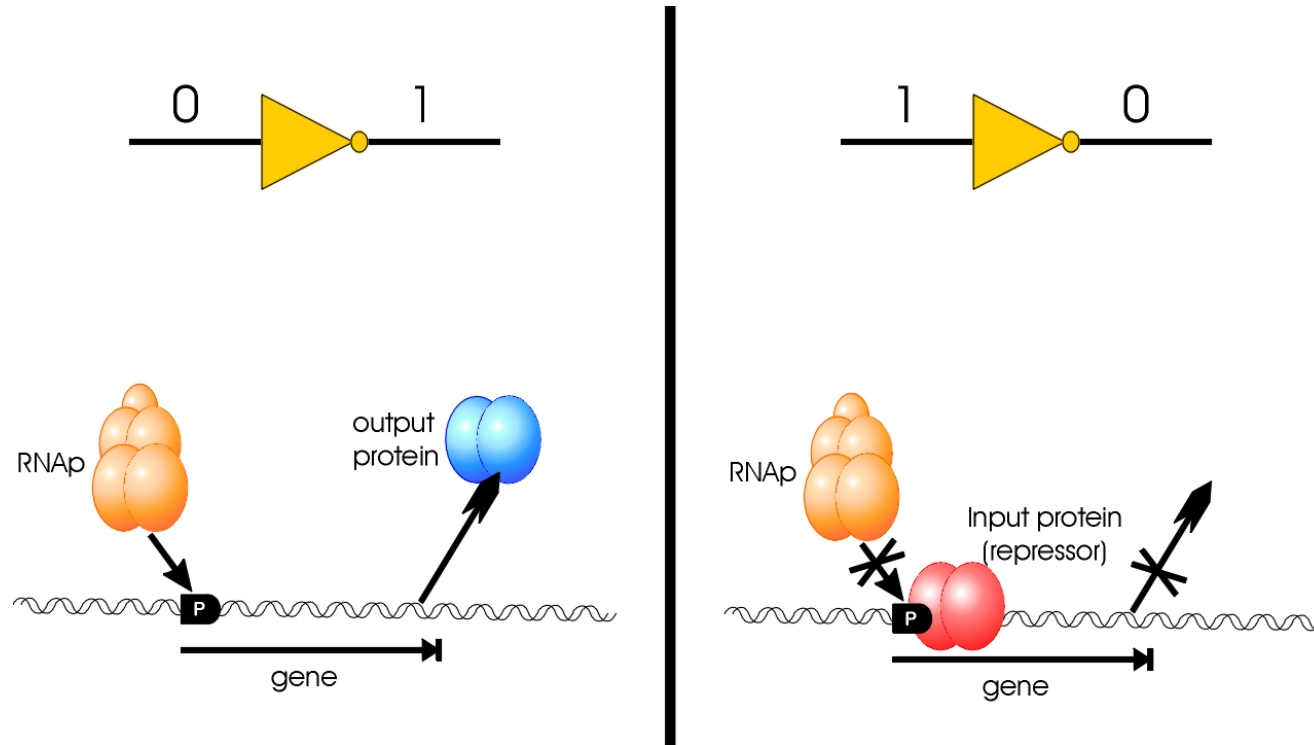


代謝経路制御・拡張 → 一般的な解析モデル? → 代謝経路設計?

- はじめに
- 遺伝子回路設計
- 代謝経路設計

# 遺伝子回路：転写制御

例) リプレッサー



# 転写制御モデル

- 入力関数：転写因子の効果の強さ

Y の産生速度 =  $f(X^*)$

$\beta$  : 最大発現レベル  
 $K$  : 活性化係数  
 $n$  : ヒル係数  
 $\Theta$  : ステップ関数

- アクチベーターのヒル関数

$$f(X^*) = \frac{\beta X^{*n}}{K^n + X^{*n}}$$

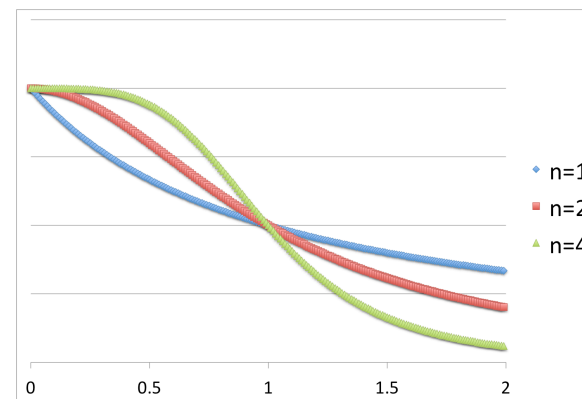
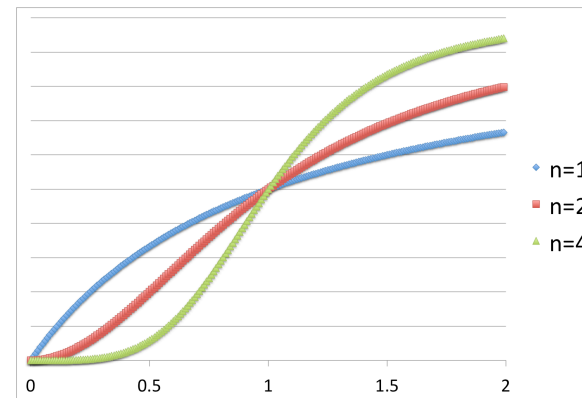
$$f(X^*) = \beta \theta(X^* > K)$$

- リプレッサーのヒル関数

$$f(X^*) = \frac{\beta}{1 + \left(\frac{X^*}{K}\right)^n}$$

$$f(X^*) = \beta \theta(X^* < K)$$

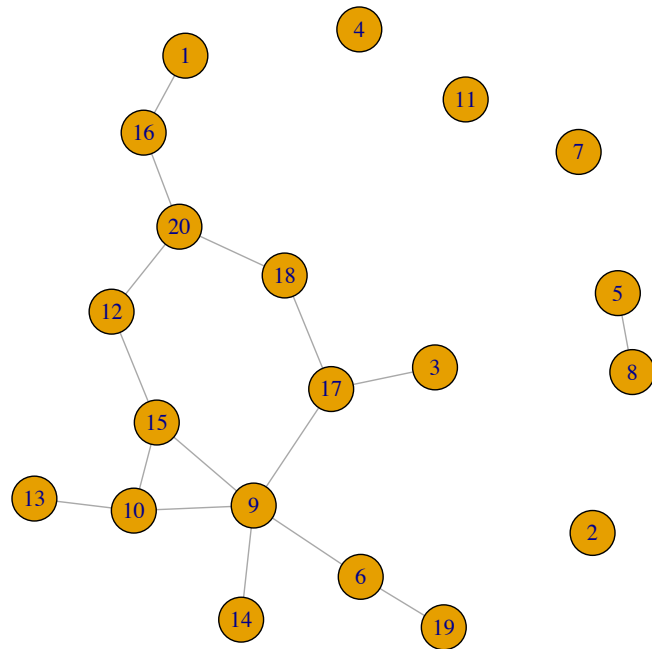
Yのプロモーター活性



$X^*/K$

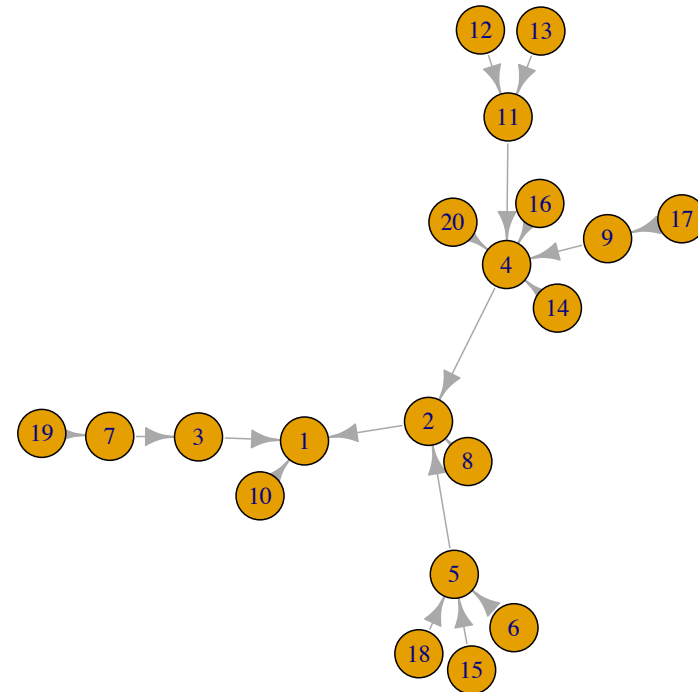
# ネットワーク

## ランダムネットワーク



$G(n,p)$  or  $G(n,m)$  graph:  
n個vertices  
任意の2vertices間にedgeがある確率p  
任意の2vertices間にm個のedgeがある

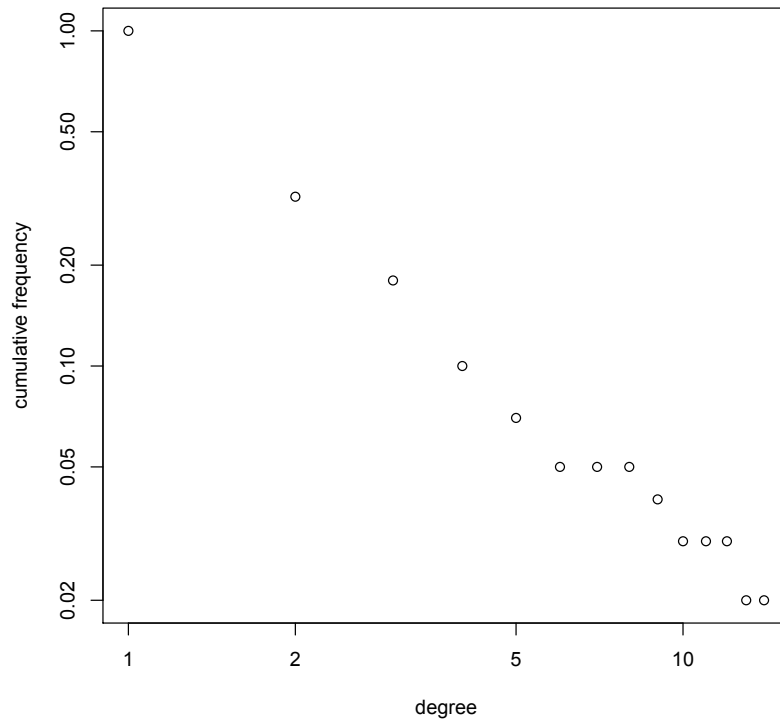
## 実際のネットワーク



一つのvertexからスタートしてvertexを追加  
vertexが選ばれる確率：  
 $P[i] \sim k[i]^\alpha + a$

## スケールフリー性

- エッジの数をノード毎に数えてプロット



例) WWW  
Social network  
Biological network

特徴) Modular structure  
ハブの存在  
短い経路  
冗長性

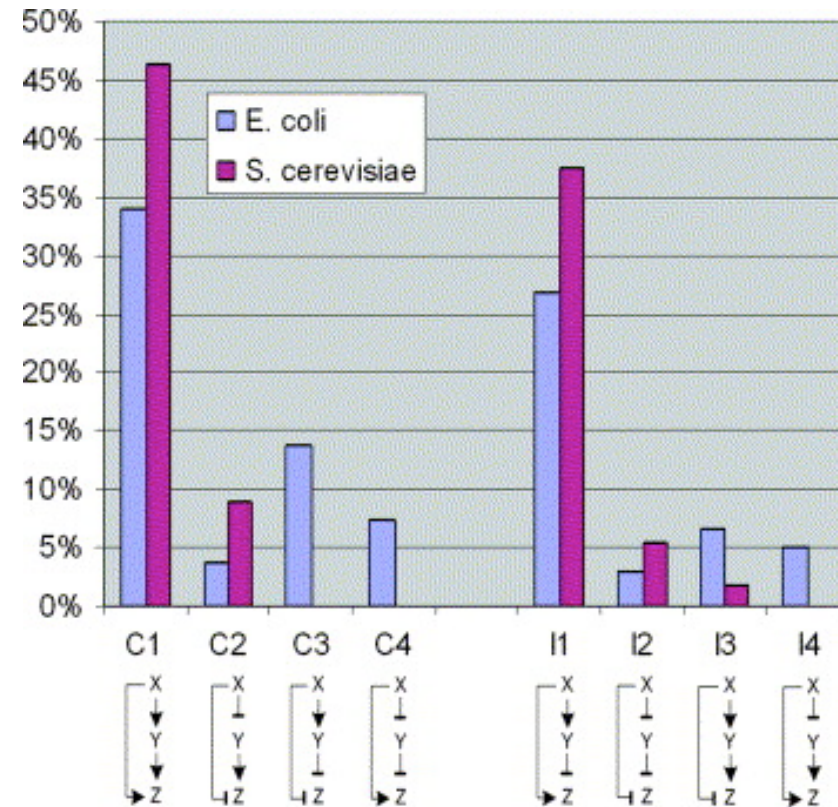
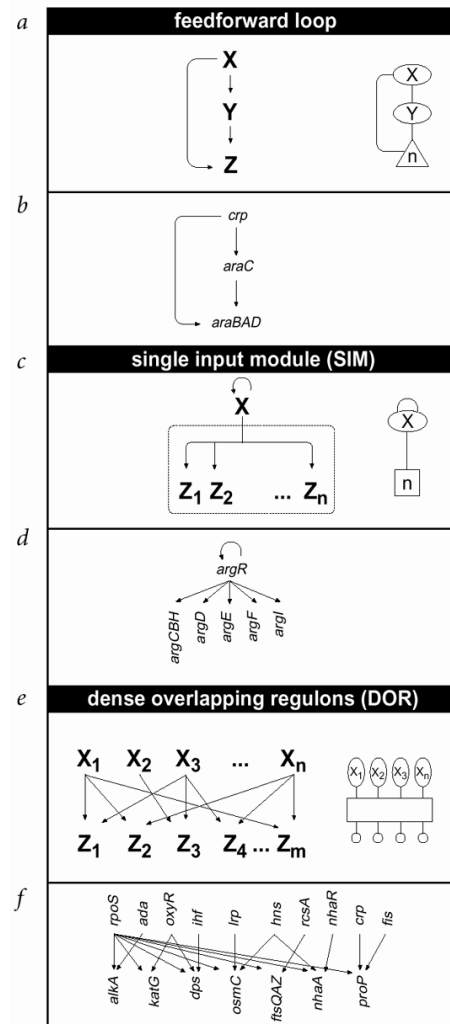




# ネットワークモチーフ

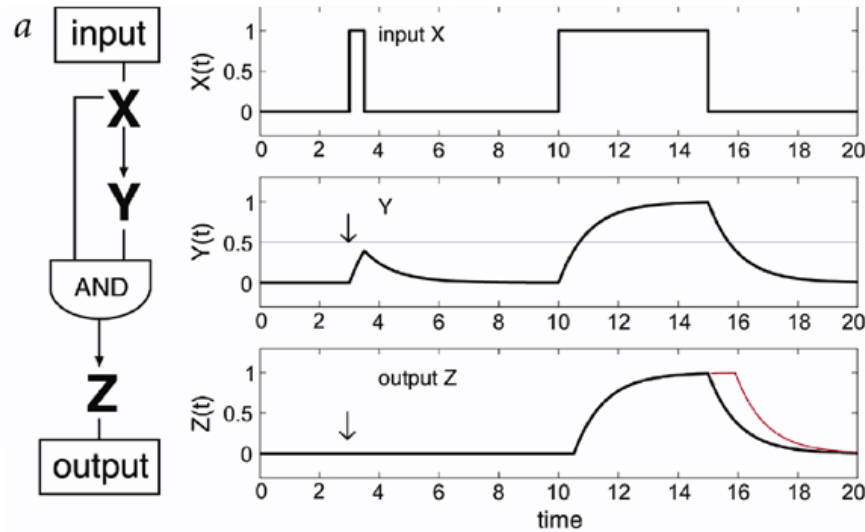
## モチーフ

## フィードフォワード



Shen-Orr *et al.* Nat Genet 31, 64-68 (2002)  
 Mangan and Alon JMB 356, 1073-1081 (2006)

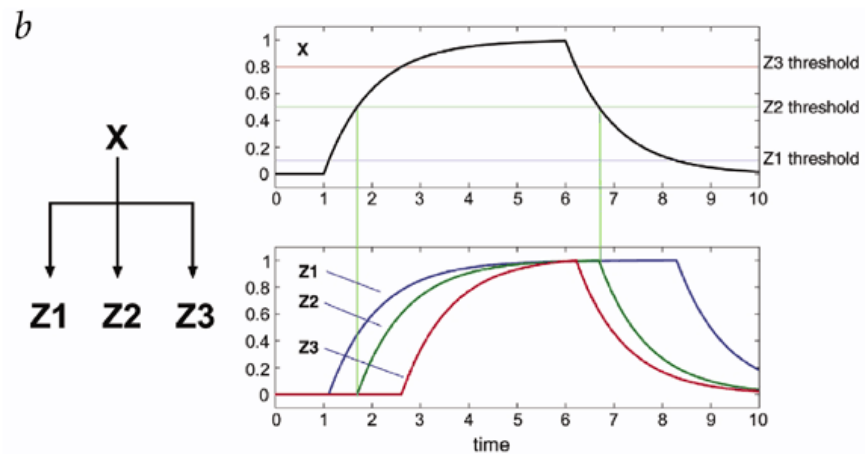
# ネットワークモチーフ



フィードフォワード (FFL)

$$\frac{dZ}{dt} = \beta_z \theta(X^* > K_{xz}) \theta(Y^* > K_{yz}) - \alpha_z Z$$

オンオフ感知性の遅延



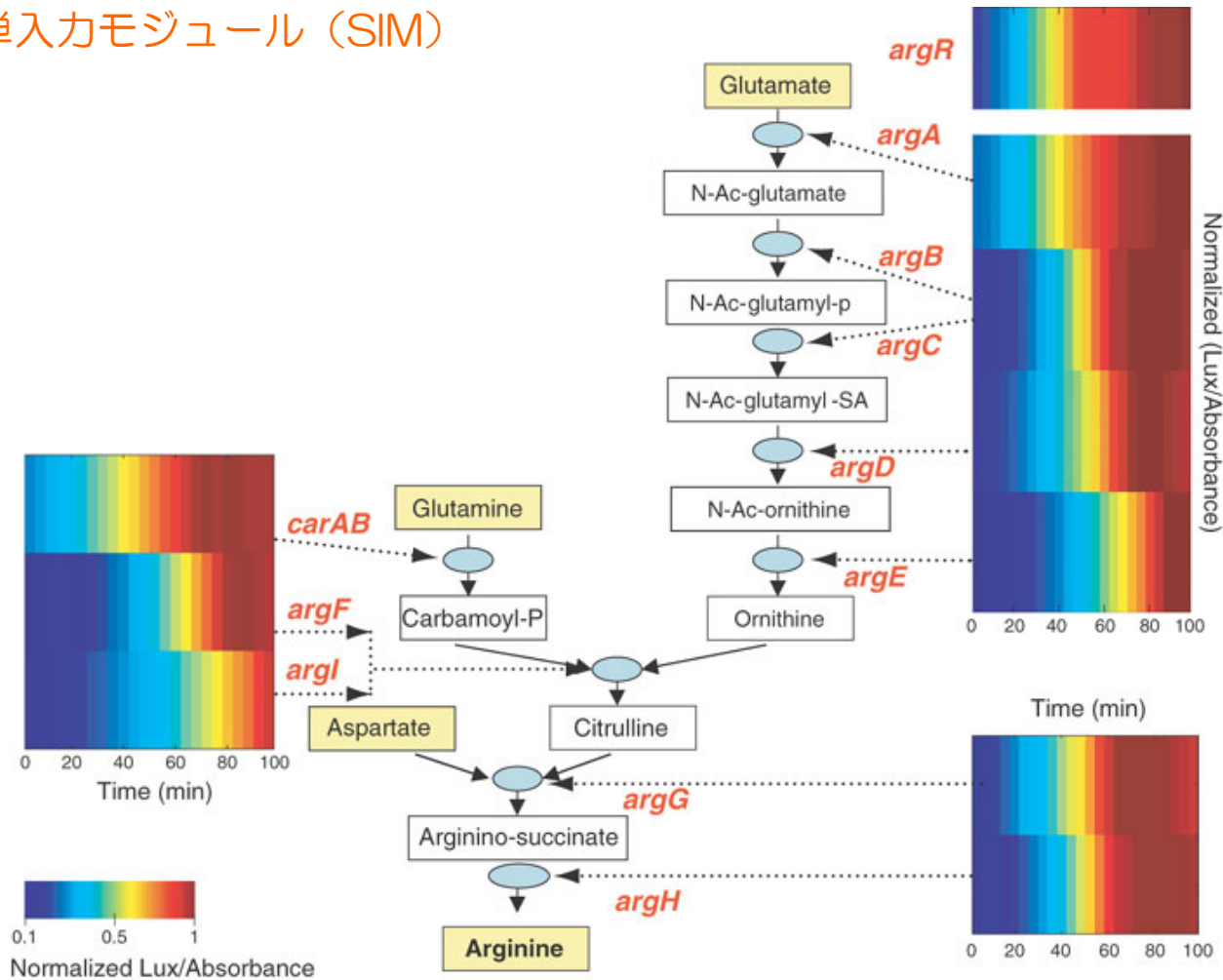
単入力モジュール (SIM)

$$\frac{dZ_i}{dt} = \beta_{zi} \theta(X^* > K_{xzi}) - \alpha_{z_i} Z_i$$

遺伝子発現の時間プログラム

# ネットワークモチーフ

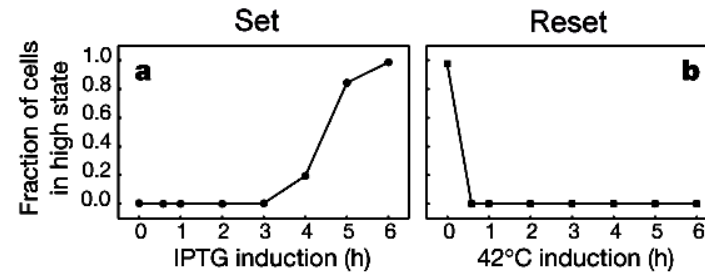
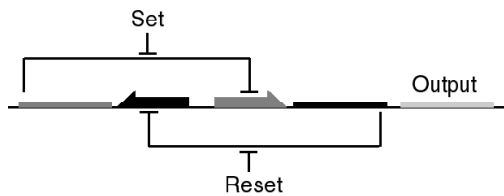
事例) 単入力モジュール (SIM)



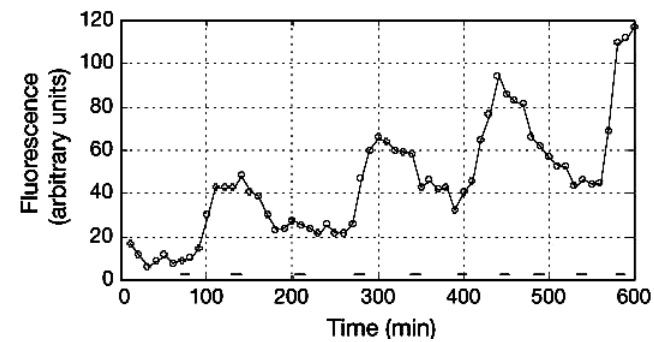
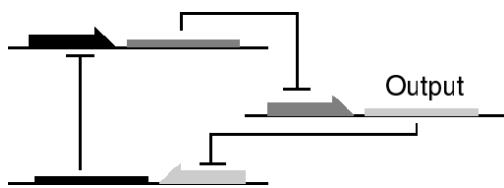
Zaslaver A *et al.* Nat Genet 36, 486-491 (2004)

# 遺伝子回路設計：Toy Model

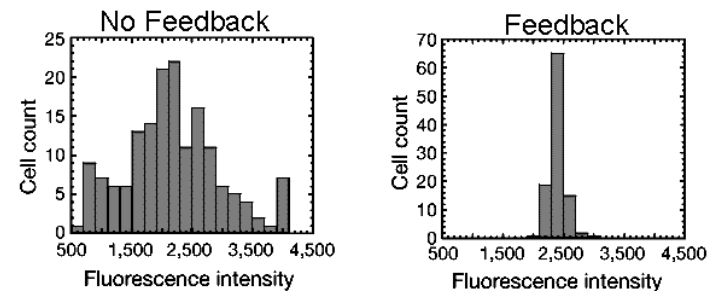
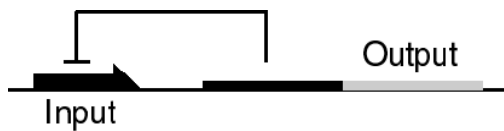
Memory (Gardner, *et al.*)



Clock (Elowitz, *et al.*)

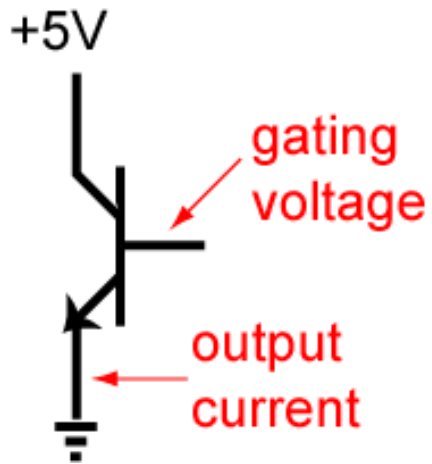


Noise Reduction (Becskei, *et al.*)

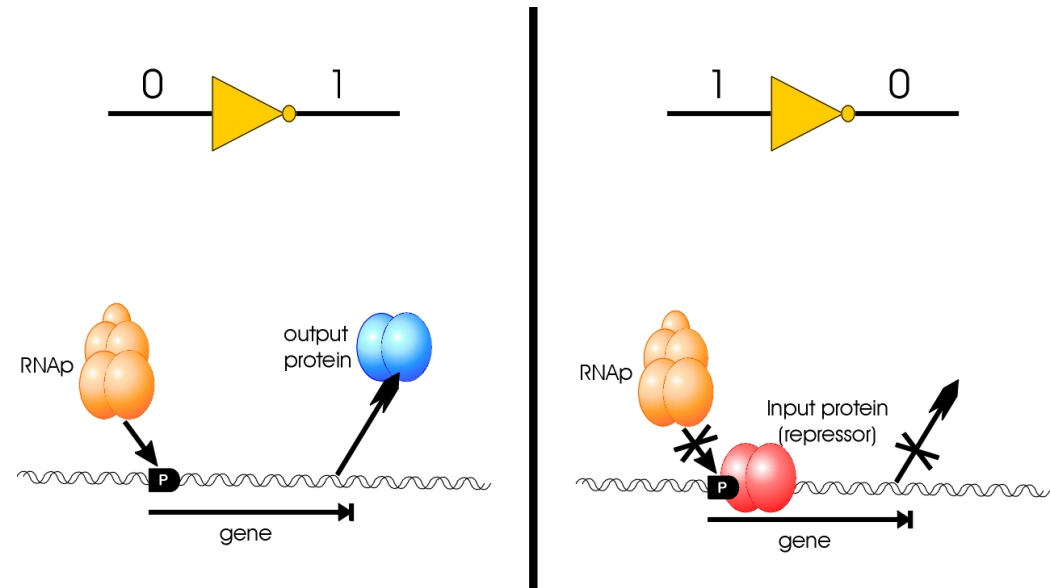


# 工学スイッチと遺伝子スイッチ

Electronic switch



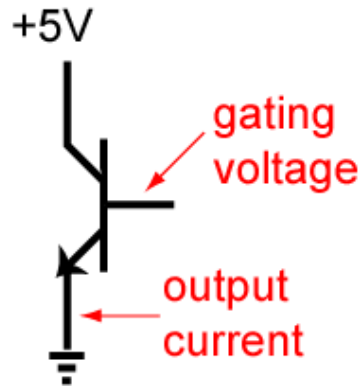
Genetic switch



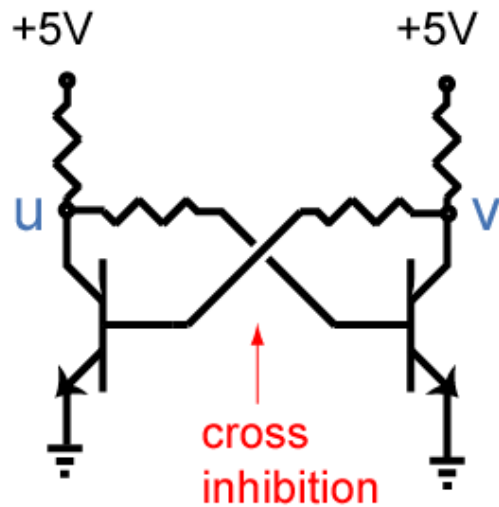
# 遺伝子トグルスイッチ

Electronic memory

Transistor

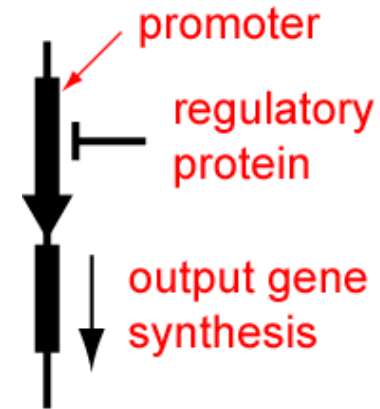


RS latch (bistable)

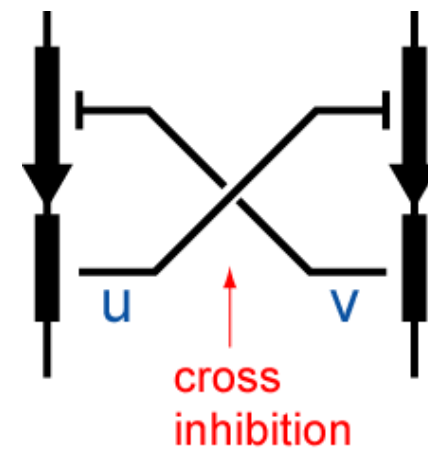


Biochemical memory

Repressible promoter

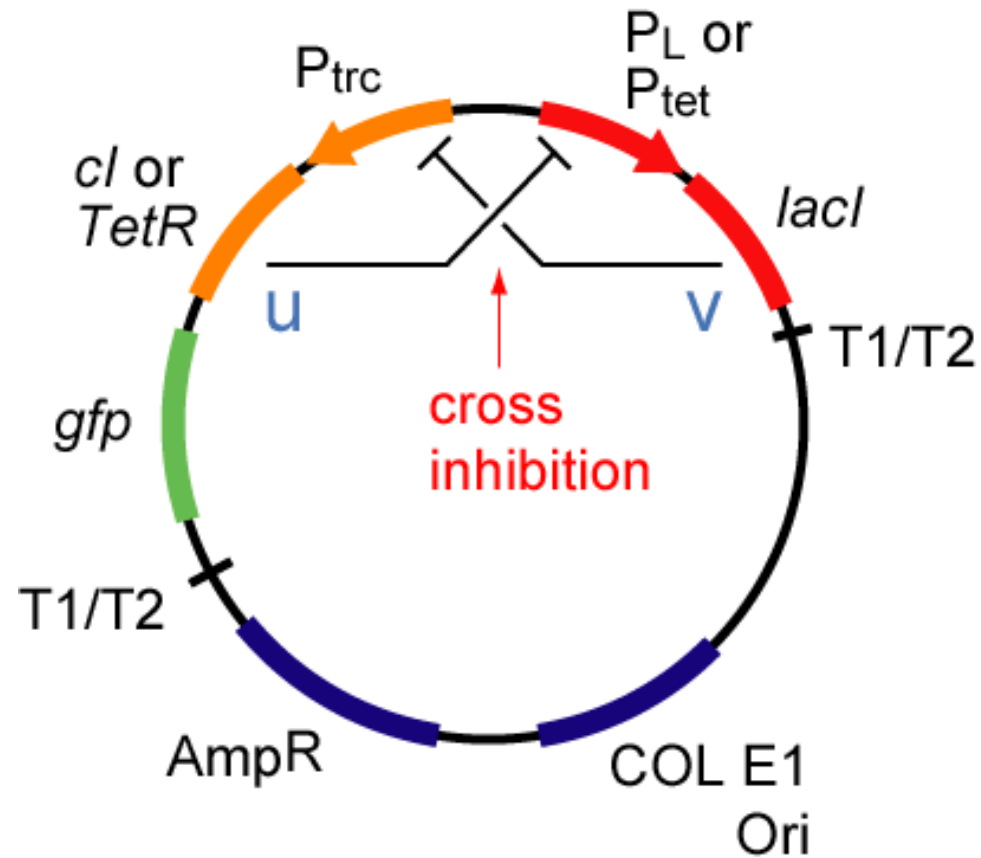


Genetic toggle switch (bistable)



# 遺伝子トグルスイッチ

Development of a genetic toggle switch in *E. coli* (biochemical memory)



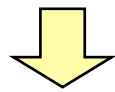
Gardner TS, Cantor CR, Collins JJ  
Nature 403, 339-342 (2000)

# トグルモデル

Nonlinear ODE model: reduced rate equations for transcription and translation

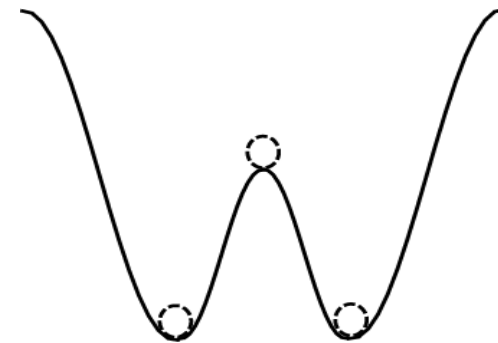
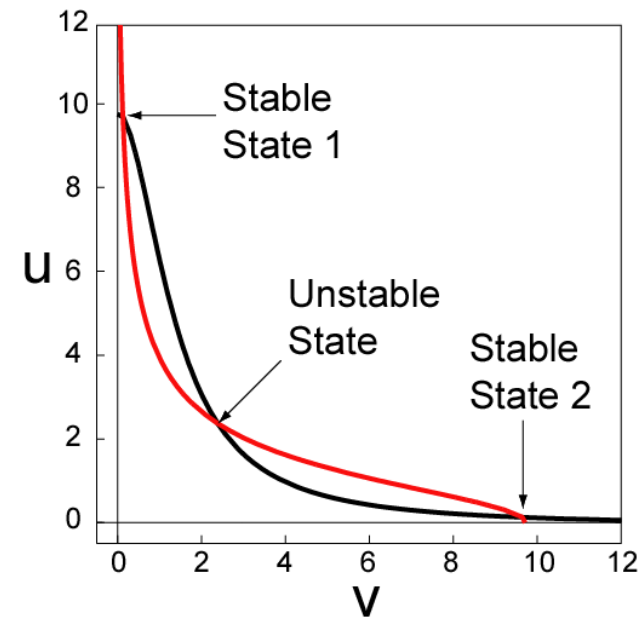
$$\dot{u} = \frac{\alpha_1}{1 + v^\beta} - u$$

$$\dot{v} = \frac{\alpha_2}{1 + u^\gamma} - v$$



$$u = \frac{\alpha_1}{1 + v^\beta}$$

$$v = \frac{\alpha_2}{1 + u^\gamma}$$

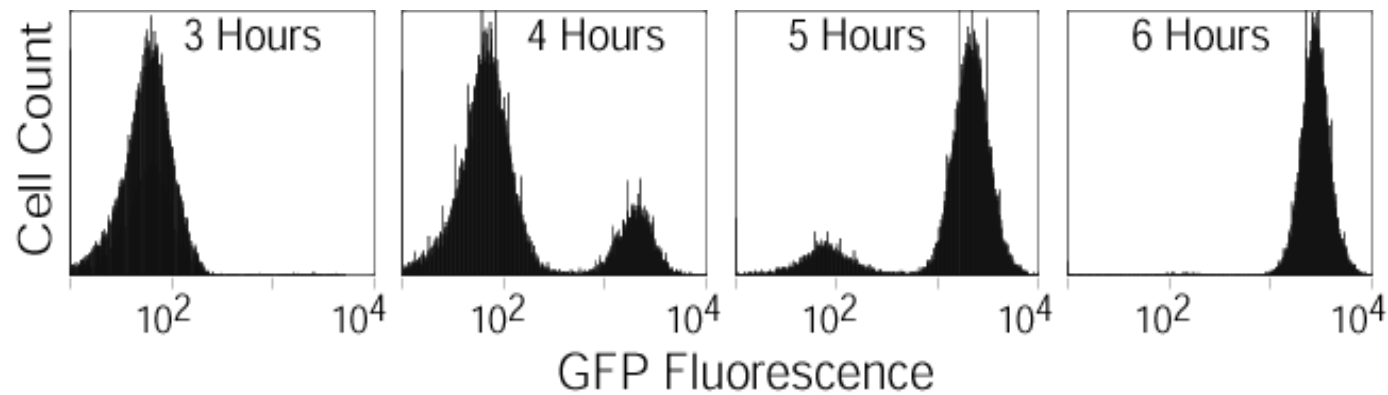
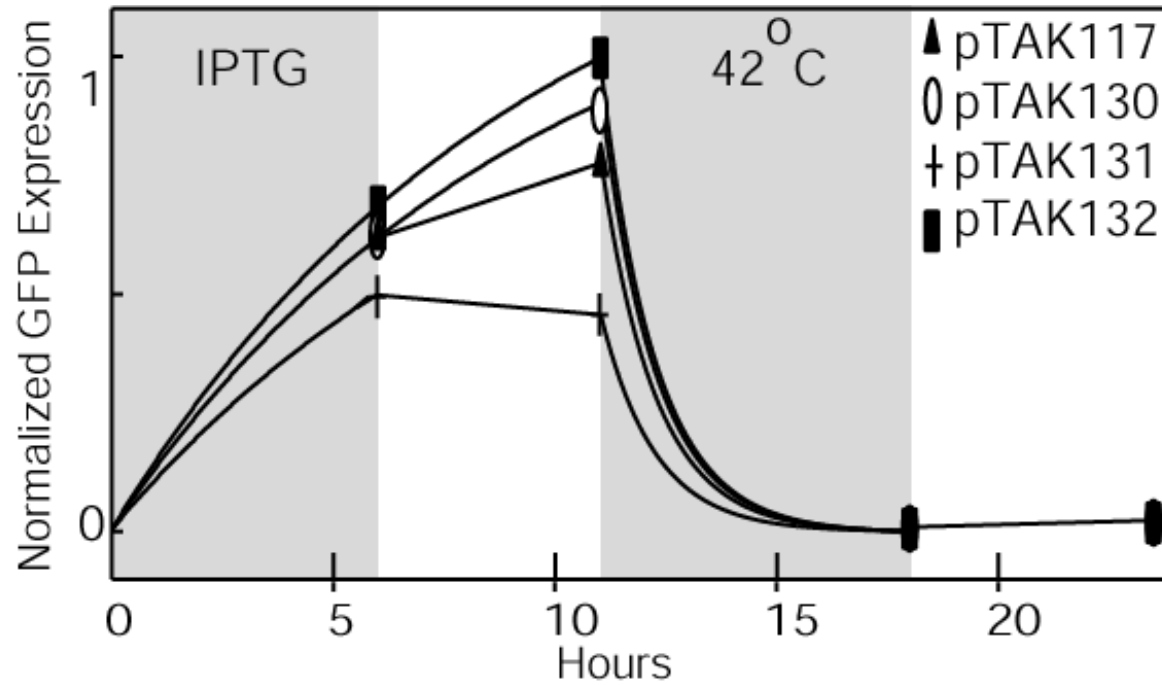


双安定状態 (Bistability)



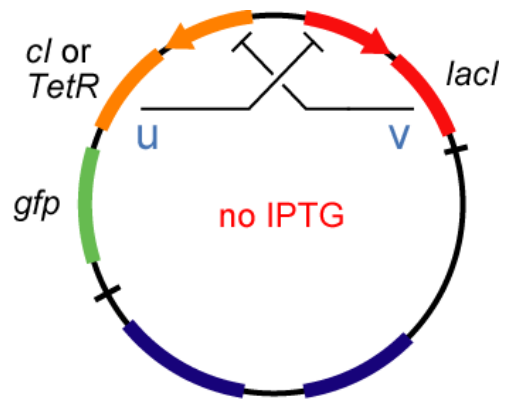
# Bistable Switch

LacI/CltS Toggle

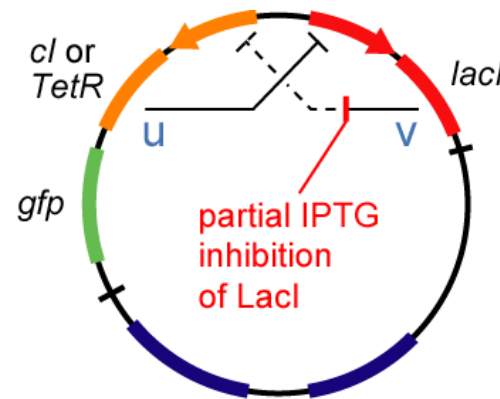


# Control of Bistability

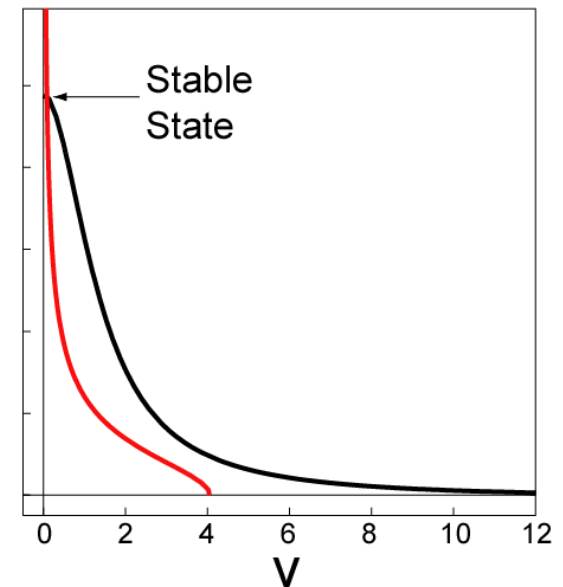
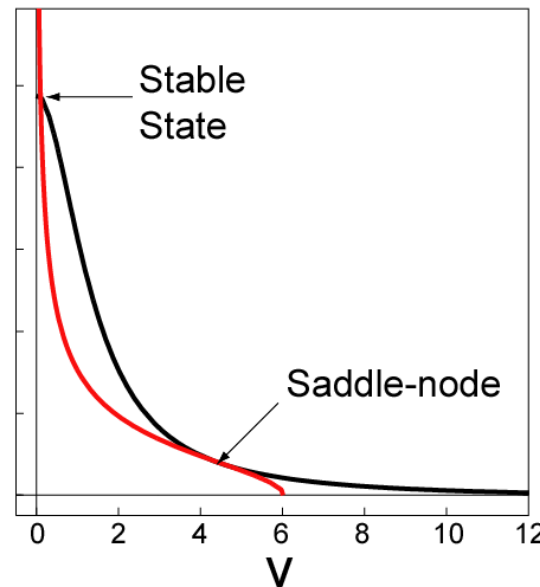
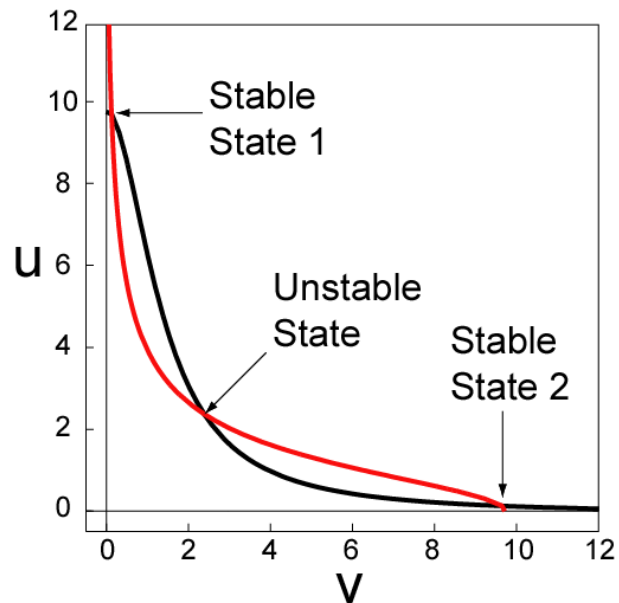
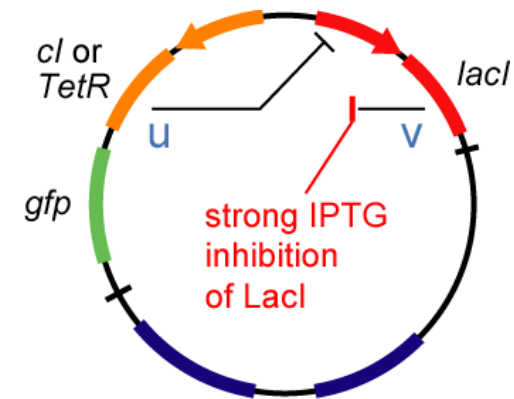
### Bistability



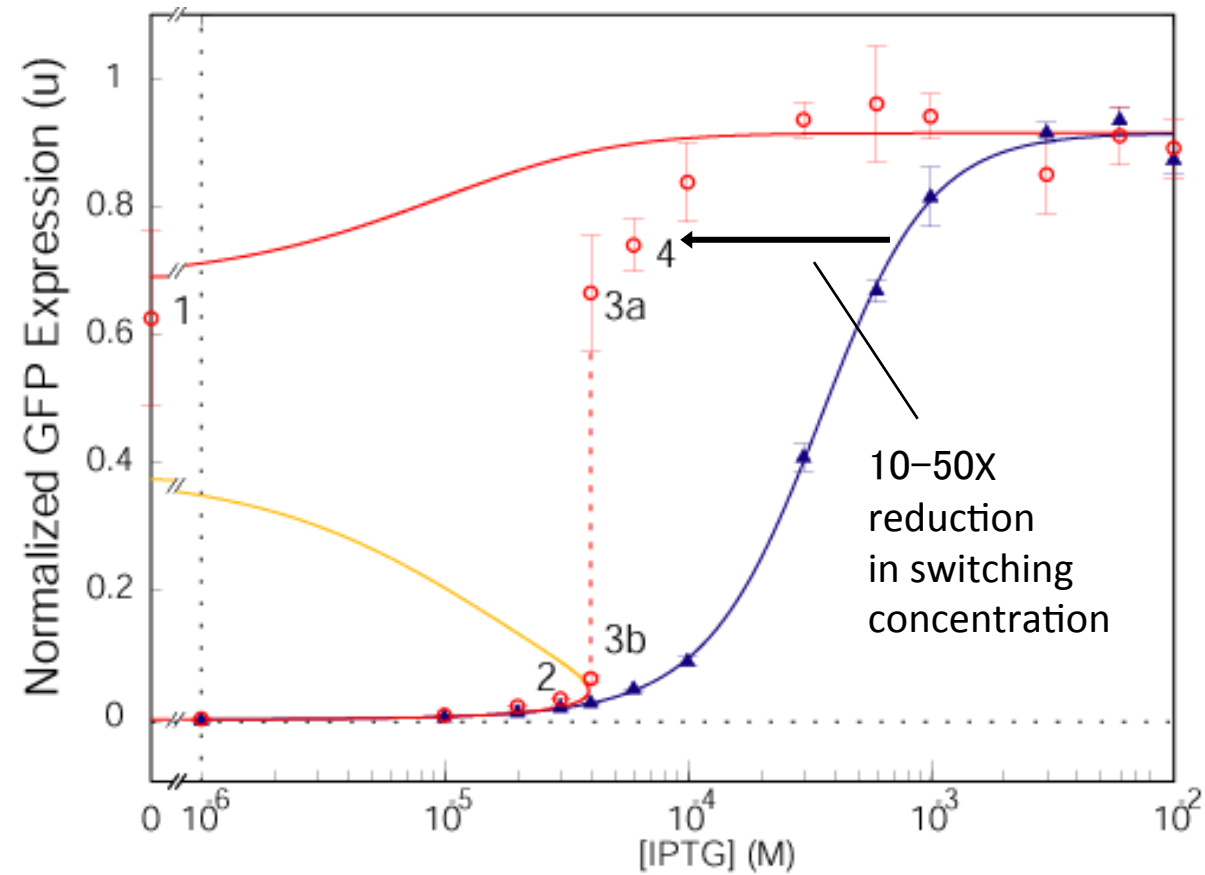
### Bifurcation



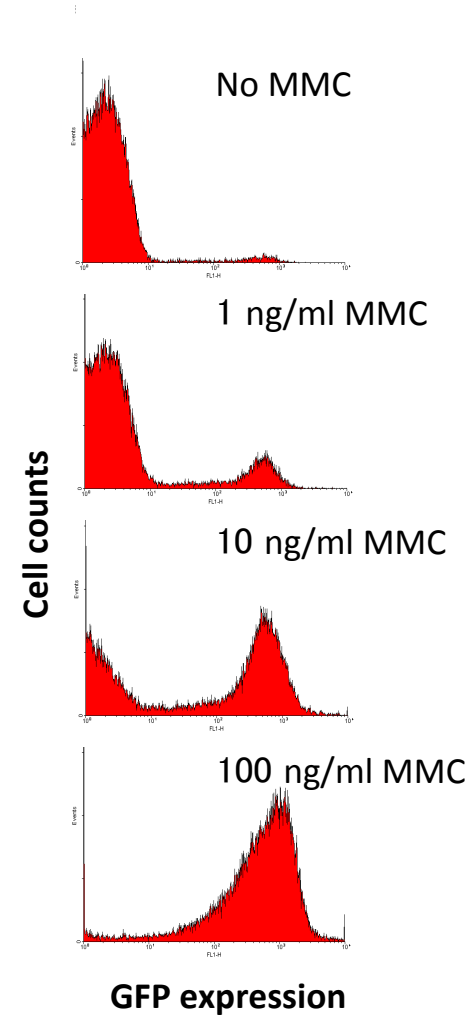
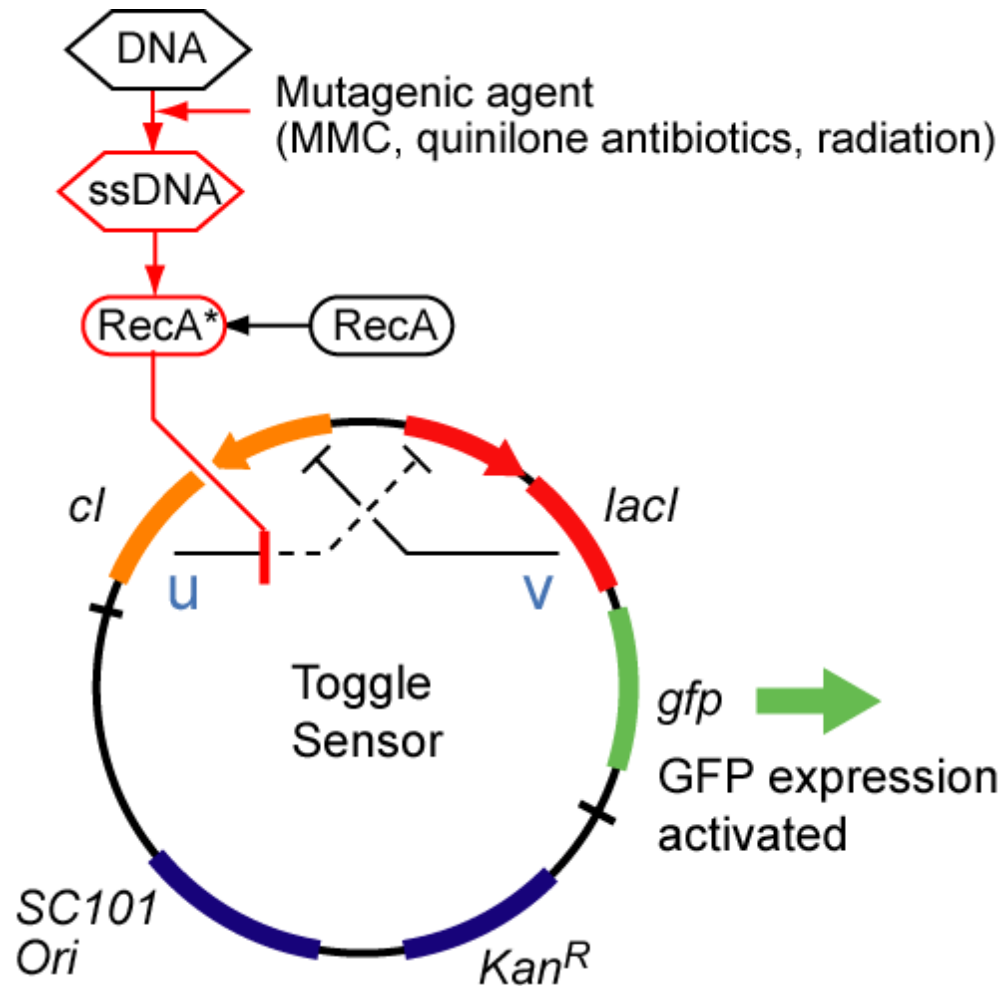
### Monostability



# All-or-none switching

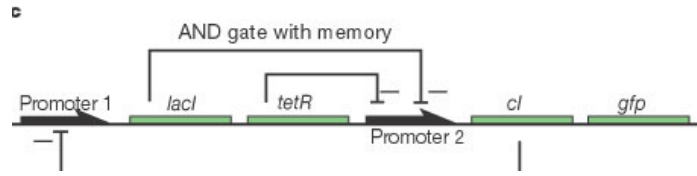
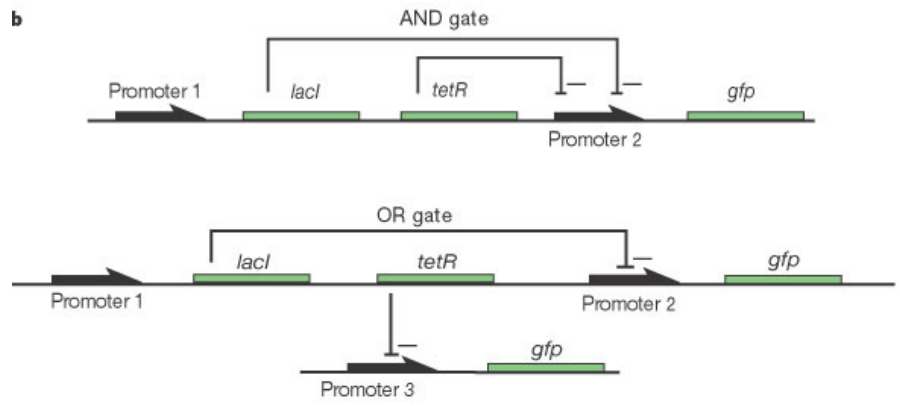
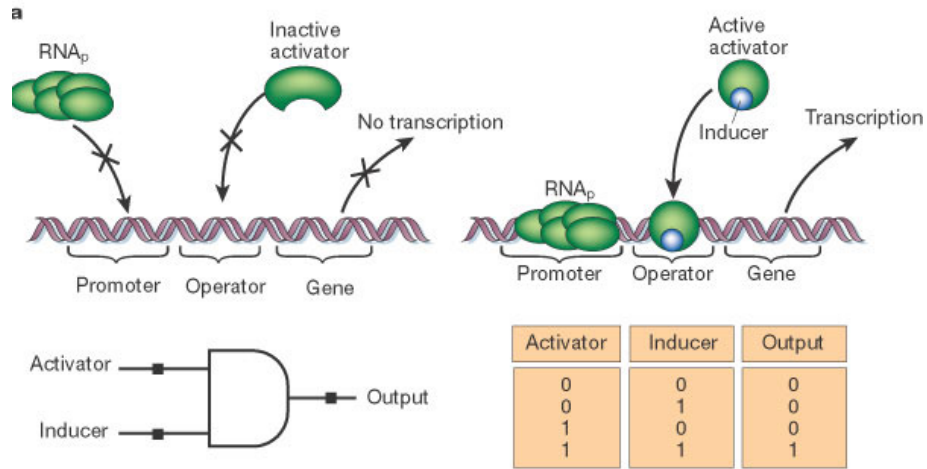


# Programmable Cells



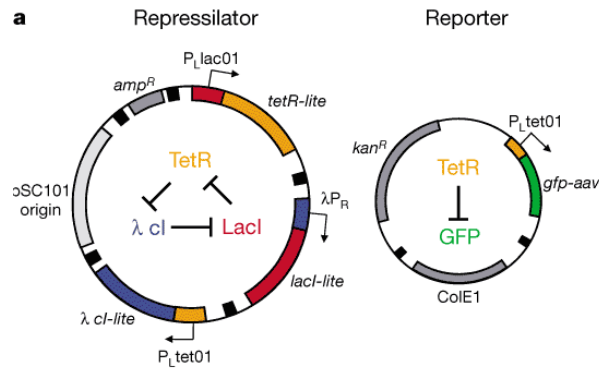
Kobayashi H, Kaern M, Araki M et al. PNAS 101(22):8414-8419 (2004)

# AND/OR GATE



Hasty J, McMillen D, Collins JJ  
 Nature 420, 224-230 (2002)

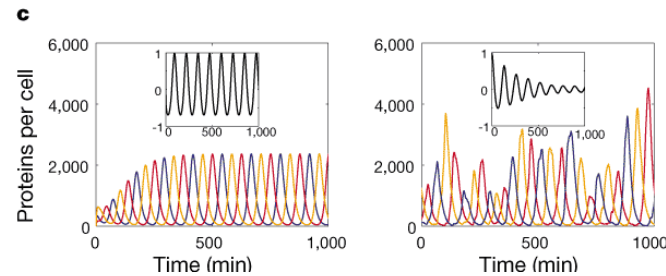
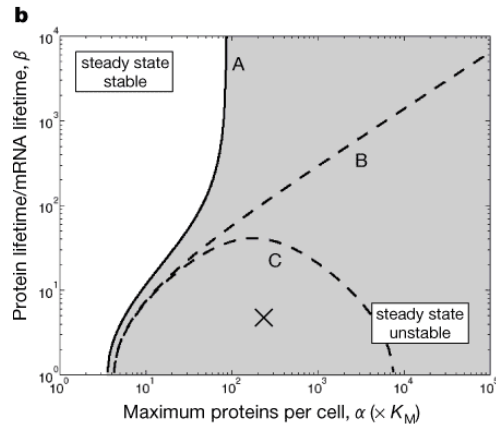
# Genetic Clock



$$\dot{m}_i = -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_0$$

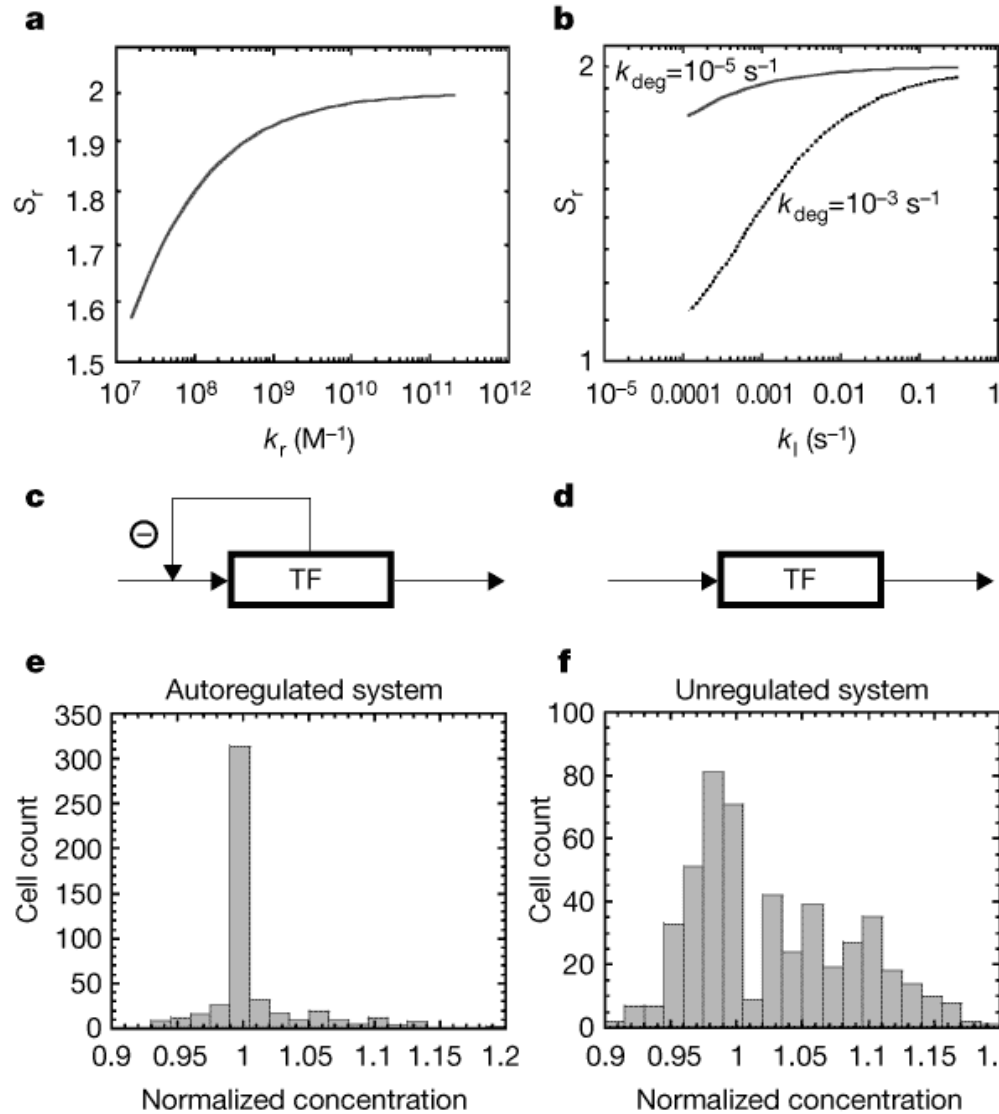
$$\dot{p}_i = -\beta(p_i - m_i)$$

Repressor-protein concentrations:  $p_i$   
 mRNA concentrations:  $m_i$   
 (where  $i$  is  $lacI$ ,  $tetR$  or  $cl$ )



Elowitz M, Leibler S  
 Nature 403, 335-338 (2000)

# Noise Reduction



$$S_{\text{unreg}} = f'_{\text{unreg}}(R^*) = -k_{\text{deg}}$$

$$S_{\text{auto}} = f'_{\text{auto}}(R^*) = -\frac{nk_p P k_i a k_r}{(1 + k_p P + k_r R^*)^2} - k_{\text{deg}}$$

$$S_r = \frac{S_{\text{auto}}}{S_{\text{unreg}}}$$


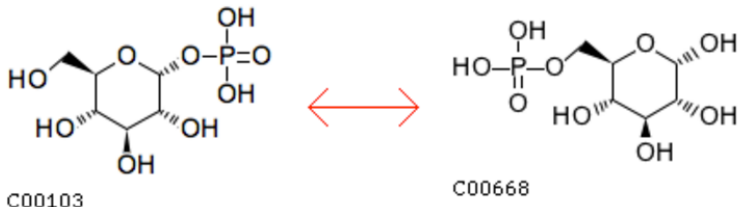
Repressor-protein concentrations: R  
 RNA polymerase concentrations: P  
 Binding constant of polymerase:  $k_p$   
 Binding constant of repressor:  $k_r$   
 Promoter isomerization rate:  $k_i$

Becskei A, Serrano L  
 Nature 405, 590-593 (2000)

- はじめに
- 遺伝子回路設計
- 代謝経路設計

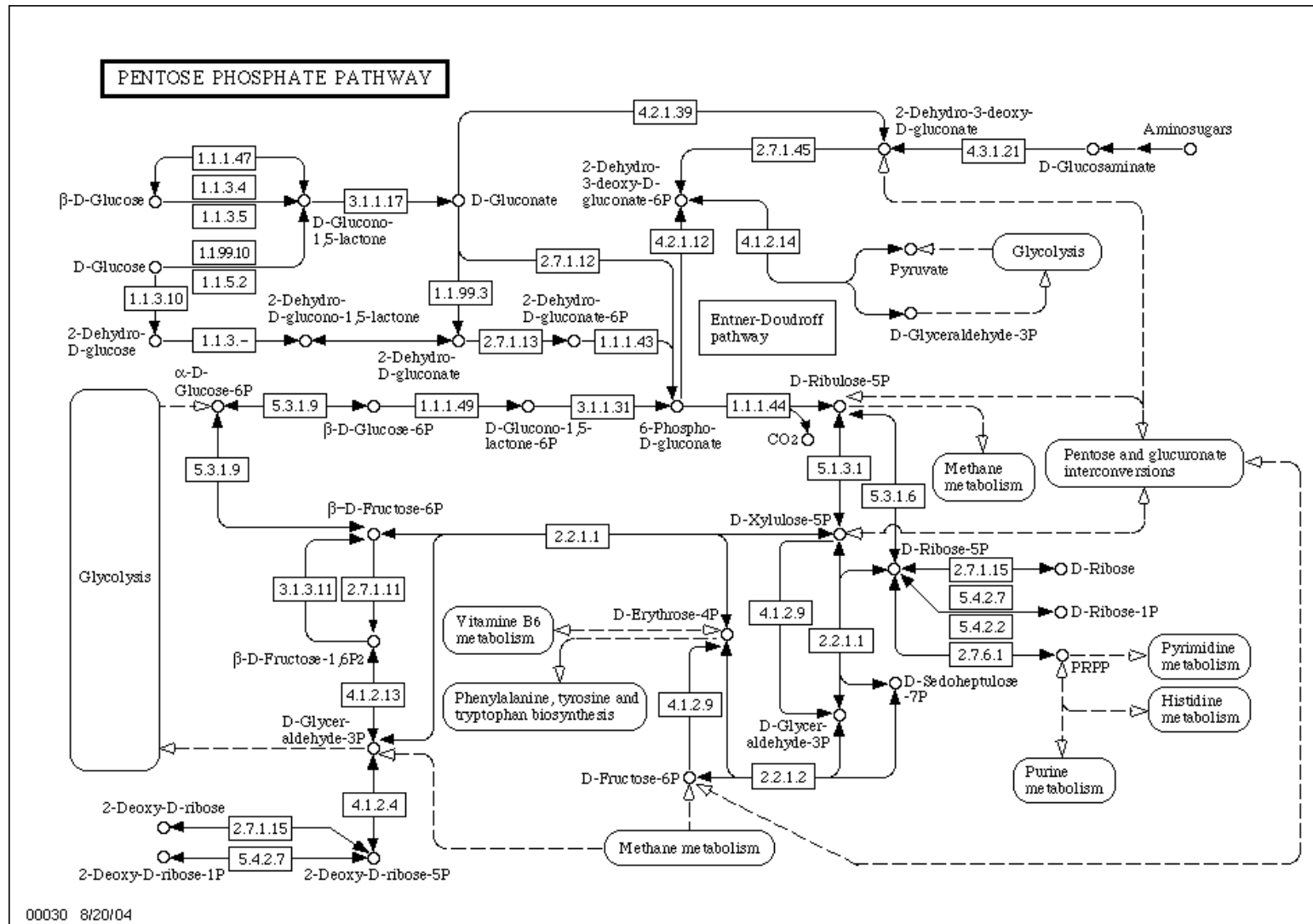


## KEGG REACTION

 <span style="float: right;">REACTION: R00959</span> <span style="float: right; border: 1px solid gray; padding: 2px;">Help</span>	
Entry	R00959 Reaction
Name	alpha-D-Glucose 1-phosphate 1,6-phosphomutase
Definition	D-Glucose 1-phosphate <=> alpha-D-Glucose 6-phosphate
Equation	C00103 <=> C00668
	
RPair	RP01197 C00103_C00668 main [RC:RC00408]
Enzyme	5.4.2.2 5.4.2.5
Pathway	<a href="#">rn00010</a> Glycolysis / Gluconeogenesis <a href="#">rn00052</a> Galactose metabolism <a href="#">rn00500</a> Starch and sucrose metabolism <a href="#">rn00520</a> Amino sugar and nucleotide sugar metabolism <a href="#">rn01100</a> Metabolic pathways <a href="#">rn01110</a> Biosynthesis of secondary metabolites <a href="#">rn01120</a> Microbial metabolism in diverse environments <a href="#">rn01130</a> Biosynthesis of antibiotics
Module	M00549 Nucleotide sugar biosynthesis, glucose => UDP-glucose
Orthology	<a href="#">K01835</a> phosphoglucomutase [EC:5.4.2.2] <a href="#">K15778</a> phosphomannomutase / phosphoglucomutase [EC:5.4.2.8 5.4.2.2] <a href="#">K15779</a> phosphoglucomutase / phosphopentomutase [EC:5.4.2.2 5.4.2.7]

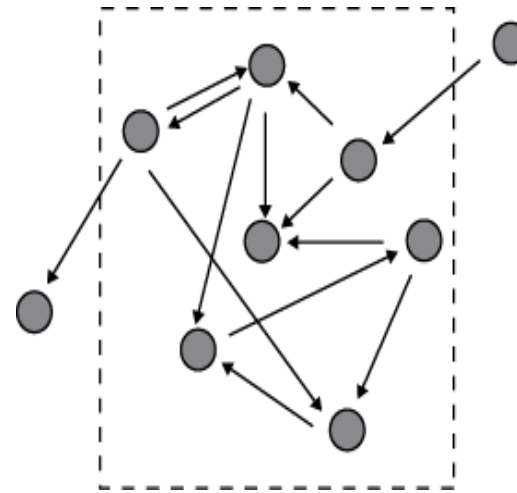
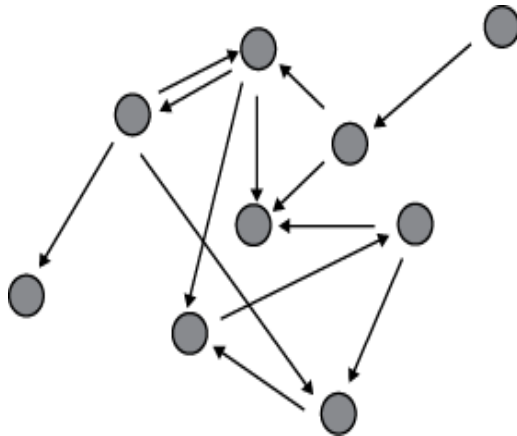
# 代謝パスウェイ

## KEGG PATHWAY

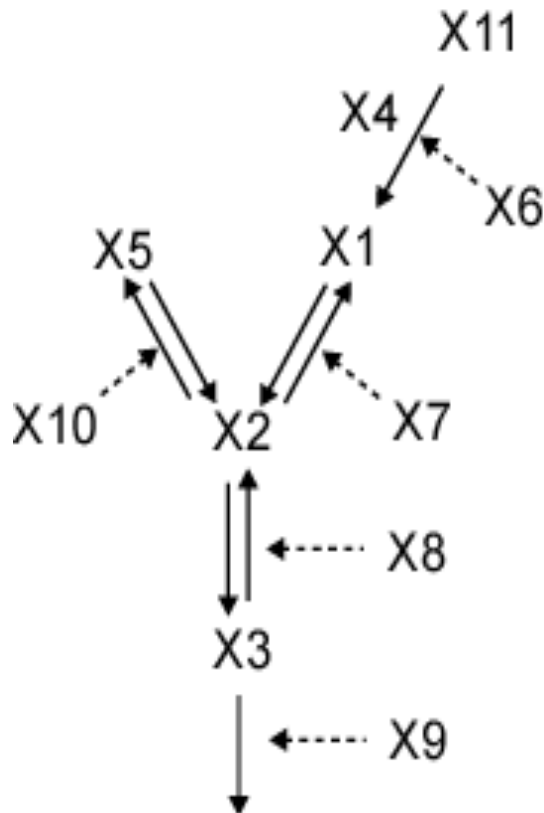


- 生化学反応系のモデル化
- 数学モデルの作成：仮定と近似
- パラメーター推定、感度解析
- 実験値と計算値の比較
- モデルの適否判定
- モデルの最適化

- 構成物質の決定
- 相互作用の決定
- 記述方法の決定



## Example of proper map: Glycolysis



### *Dependent Variables:*

- X1 = Glucose-1-phosphate
- X2 = Glucose-6-phosphate
- X3 = Fructose-1-phosphate
- X4 = Pi

### *Independent Variables:*

- X5 = Glucose
- X6 = Phosphorylase
- X7 = Phosphoglucomutase
- X8 = Phosphoglucose isomerase
- X9 = Phosphofructokinase
- X10 = Glucokinase
- X11 = Glycogen

## 数値解法

$$\begin{aligned} dy/dt &= f(y,t) \\ y(t_0) &= y_0 \end{aligned}$$

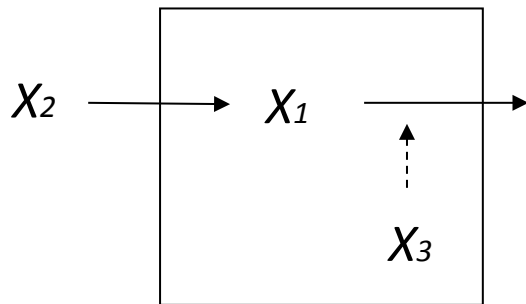
- 離散的な点列  $\{t_i\}$  上での正しい解  $\{y(t_i)\}$  の近似解  $\{y_i\}$
- 代表的な方法
  - オイラー法
  - 2次のルンゲークッタ法
  - 4次のルンゲークッタ法
  - など
- 数値解法は様々なソフトに組み込まれている

# S-system

## General equation

$$dX_i / dt = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \quad \text{for } i = 1, 2, \dots, n$$

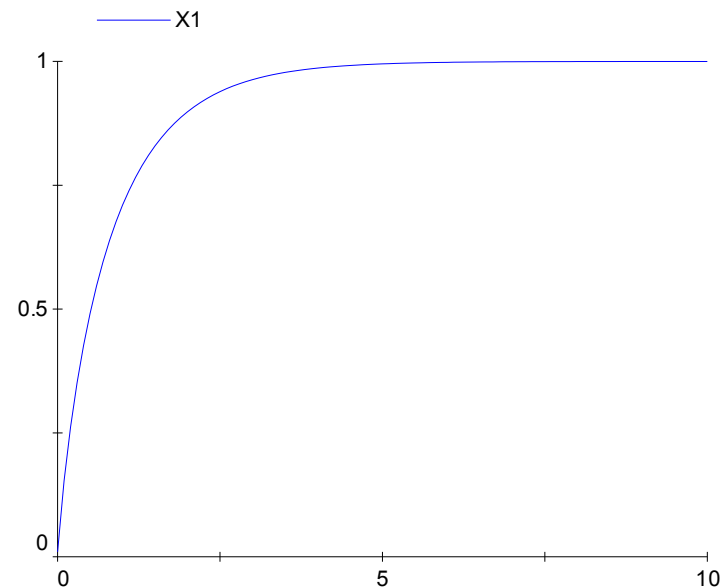
## Example



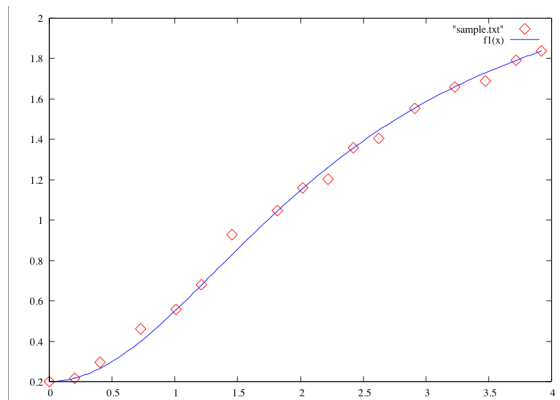
$$dX_1 / dt = \alpha_1 X_2 - \beta_1 X_1^{0.5} X_3^{-1}$$

$$dX_2 / dt = 2$$

$$dX_3 / dt = 0.5$$

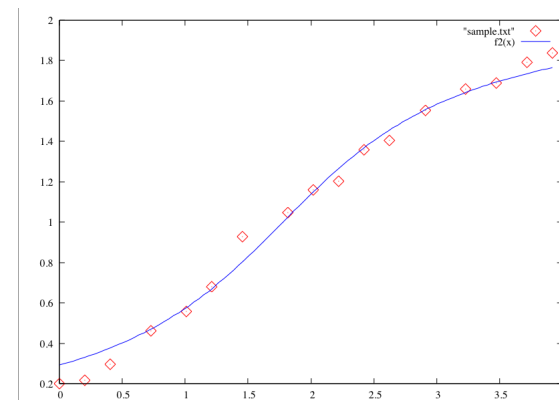


## Hill function



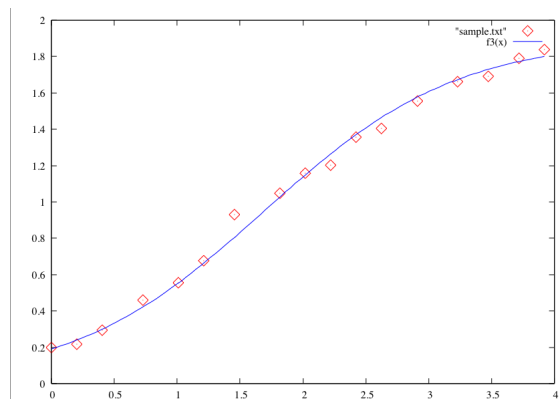
$$f_1(x) = 2.2x^2/(2.3^2+x^2)+0.2$$

## Arctangent function



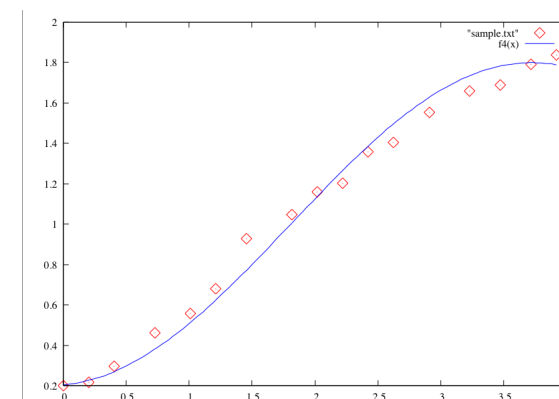
$$f_2(x) = 0.7*\text{arctg}(0.9x-1.6)+1$$

## Logistic function



$$f_3(x) = 1.9/(1+\exp(2.2-1.3x))$$

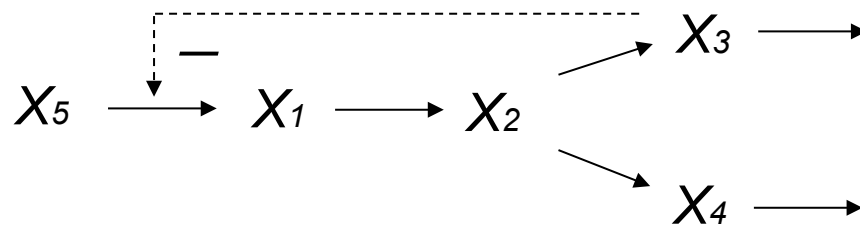
## Sine function



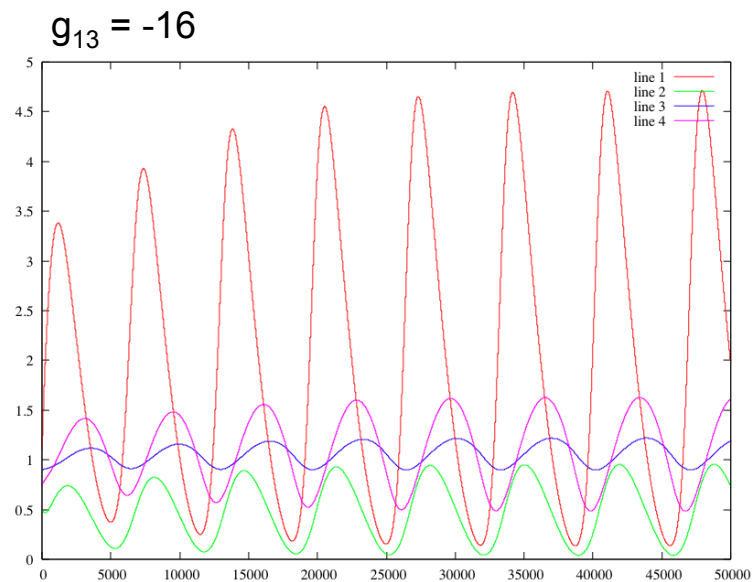
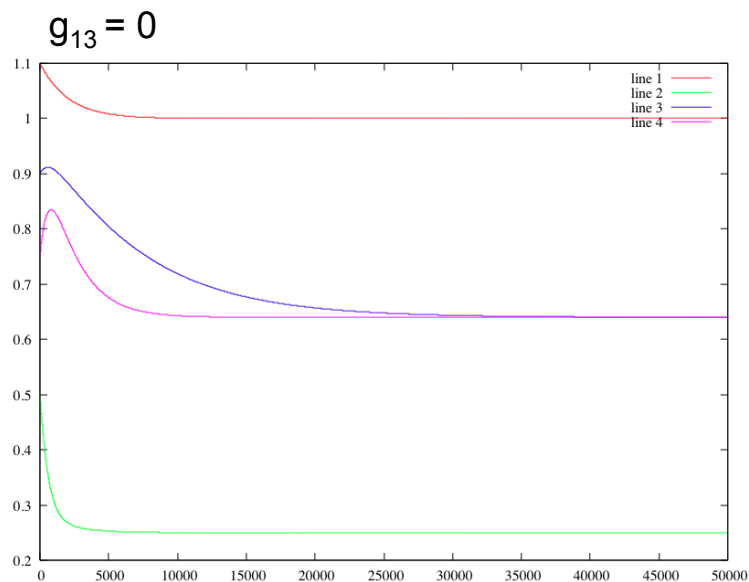
$$f_4(x) = 0.8\sin(0.82x+4.8)+1$$



# パラメータ依存性

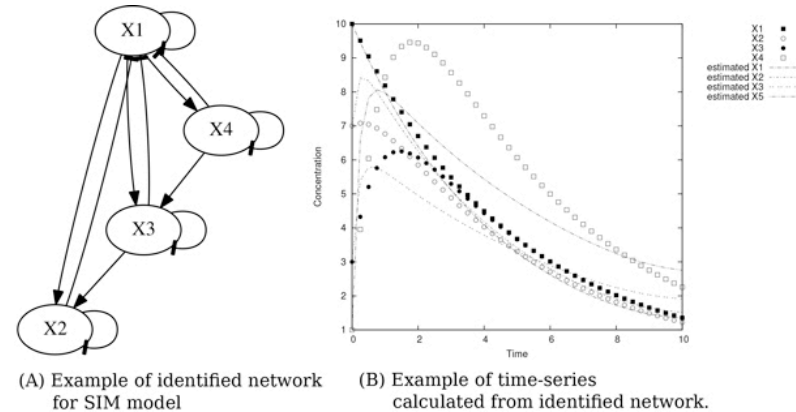
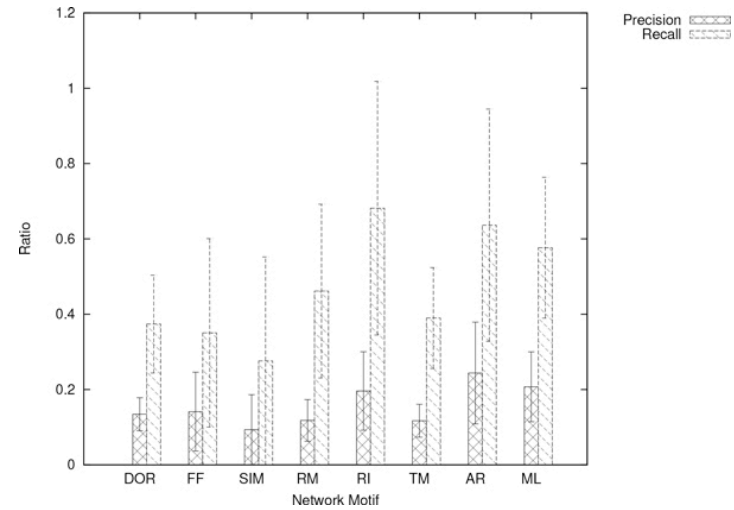
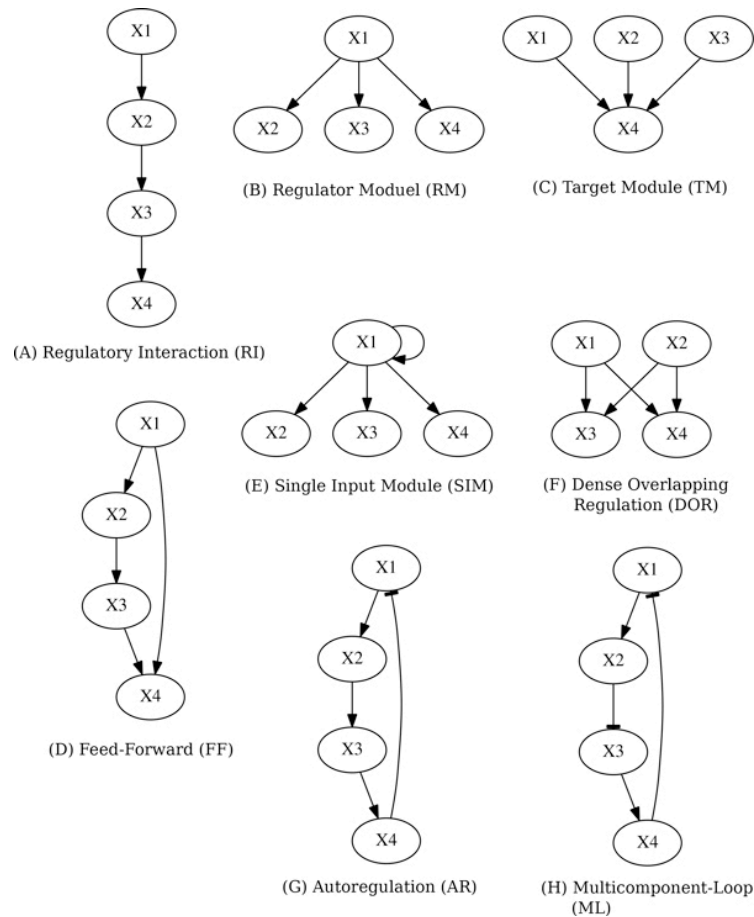


$$\begin{aligned}
 dX_1 / dt &= 10X_3^{g_{13}} X_5 - 5X_1^{0.5} \\
 dX_2 / dt &= 5X_1^{0.5} - 10X_2^{0.5} \\
 dX_3 / dt &= 2X_2^{0.5} - 1.25X_3^{0.5} \\
 dX_4 / dt &= 8X_2^{0.5} - 5X_4^{0.5} \\
 dX_5 / dt &= 0.5
 \end{aligned}$$



# パラメータ推定

## S-system解析：時系列データからのパラメータ最適化・ネットワーク推定



(C) Example of estimated S-system parameter values.

7.50	-2.58	-0.87	-1.28	-1.49	0.22	1.00	0.00	0.00	0.00
8.98	1.96	-1.68	0.75	0.00	8.60	0.00	1.00	0.00	0.00
7.93	1.59	0.00	-2.90	1.28	3.74	0.00	0.00	1.00	0.00
9.59	0.94	0.00	0.00	-0.60	2.56	0.00	0.00	0.00	1.00

## Systems Biology Markup Language (SBML)

XML形式で生化学反応を記述

Compartment  
Species  
Reaction  
Parameter  
Unit Definition  
Rule

$$k = \frac{k_3}{k_2}, \quad s_2 = \frac{kx}{1 + k_2}, \quad A = 0.10x$$

```
<model>
...
<listOfRules>
  <assignmentRule variable="k">
    <notes>
      <xhtml:p>
        k = k3/k2
      </xhtml:p>
    </notes>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <divide/>
        <ci> k3 </ci>
        <ci> k2 </ci>
      </apply>
    </math>
  </assignmentRule>
  <assignmentRule variable="s2">
    <notes>
      <xhtml:p>
        s2 = (k * x)/(1 + k2)
      </xhtml:p>
    </notes>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <divide/>
        <apply>
          <times/>
          <ci> k </ci>
          <ci> x </ci>
        </apply>
        <apply>
          <plus/>
          <cn> 1 </cn>
          <ci> k2 </ci>
        </apply>
      </apply>
    </math>
  </assignmentRule>
</listOfRules>
```

---

Process	Phenomena	Models
Metabolism	Enzymatic reaction	ODE, S-systems, FBA
Signal transduction	Molecular binding Enzymatic reaction	DAE Stochastic algorithms
Gene expression	Molecular binding Polymerization Degradation	DAE, S-systems Boolean networks Stochastic algorithms

---

# シミュレータ

	Capabilities					Frameworks							API	Dep.	Platforms	SBML		Availabil.		
	Creation	Simulation	Analysis	Database	Utility	ODE	DAE	PDE	Stochastic	Events	Logical	Other				Import	Export	Open source	Academic use	Commercial use
<b>acslXtreme</b>	•														W	•		•	•	•
<b>ALC</b>	•					•	•		•			•			L, W, M, B	•		•	•	•
<b>Asmparts</b>	•				•	•									L,W	•	•	•	•	•
<b>Antimony</b>	•				•								C, C++		L, W, M	•	•	•	•	•
<b>AutoSBW</b>			•			•							SBW	SBW	L, W, M	•	•	•	•	•
<b>AVIS</b>														various	L	•		•	•	•
<b>BALSA</b>	•													Sigtran						
<b>BASIS</b>	•	•		•					•	•			WS		B	•	•	•	•	•
<b>BetaWB</b>	•	•	•						•	•					L,W,M		•		•	•
<b>BiGG</b>				•											B		•		•	
<b>BiNoM</b>	•		•		•										L, W, M	•	•	•	•	•
<b>BiNoM Cytoscape Plugin</b>	•		•		•									Cytoscape	L, W, M	•	•	•	•	•
<b>BIOCHAM</b>		•			•	•									L,W,M		•	•	•	•
<b>BioCharon</b>	•	•	•		•	•								CHARON						
<b>Biological Networks</b>	•		•		•										L,W,M	•	•		•	•
<b>BioCyc</b>				•													•		•	•
<b>BioGrid</b>																				

## フラックスバランス解析 (FBA)

**I. Reaction network formalism**

**Chemical reactions**

Internal	Exchange
R1: -1 A → 1 B	R4: 1 A
R2: -1 B → 1 C	R5: -1 B
R3: -1 C → 1 B	R6: -1 C
	R7: 1 C

→ S =

	R1	R2	R3	R4	R5	R6	R7
A	-1	0	0	1	0	0	0
B	1	-1	1	0	-1	0	0
C	0	1	-1	0	0	-1	1

**II. FBA formulation**

Dynamic mass balance

$$\frac{dC}{dt} = Sv$$

C : Concentration  
t : Time  
S : Stoichiometric matrix  
v : Flux vector

Steady-state assumption

$$Sv = 0$$

LP formulation

Objective: max Z = v<sub>5</sub>

Constraints:

$$\begin{matrix}
 A \\
 B \\
 C
 \end{matrix}
 \begin{bmatrix}
 R1 & R2 & R3 & R4 & R5 & R6 & R7 \\
 -1 & 0 & 0 & 1 & 0 & 0 & 0 \\
 1 & -1 & 1 & 0 & -1 & 0 & 0 \\
 0 & 1 & -1 & 0 & 0 & -1 & 1
 \end{bmatrix}
 \begin{bmatrix}
 v_1 \\
 \vdots \\
 v_7
 \end{bmatrix}
 = 0
 \quad 0 \leq v_1, \dots, v_7 \leq 10$$
  

**III. Hypothetical flux distribution at steady-state**

Z = 10  
v = [6.67 3.33 6.67 6.67 10.0 3.33 6.67]<sup>T</sup>

反応マトリックス記述

定常状態仮定  
定式化

線形計画法

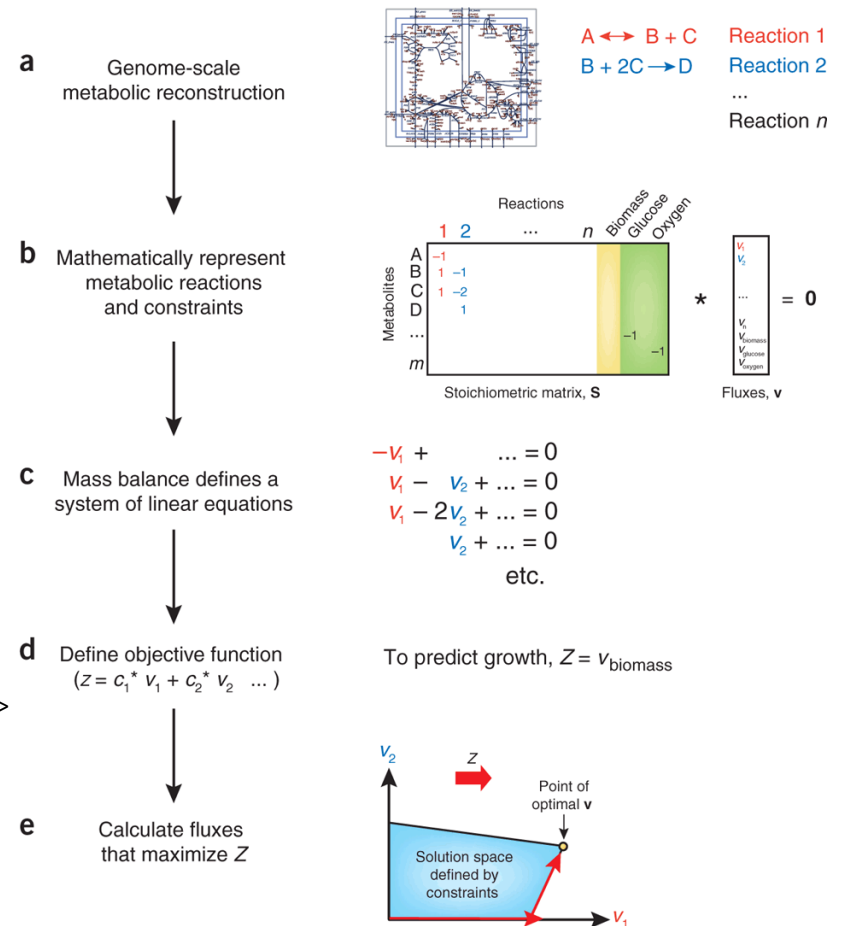
# ゲノムスケールモデル

## SBMLによる記述

```

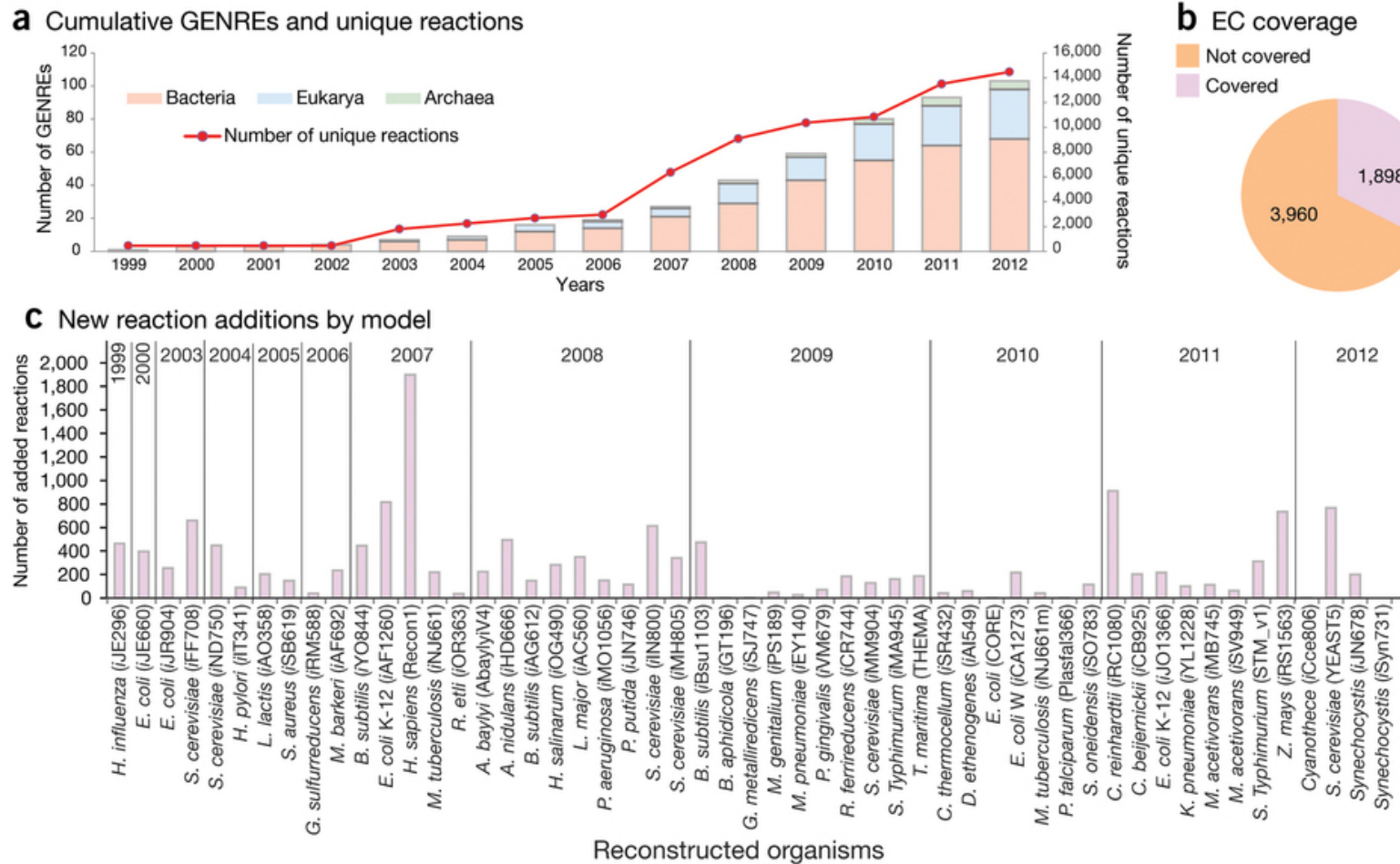
<reaction id="R_ACKr" name="acetate kinase">      反応 (酵素名称)
<notes>
  <html xmlns="http://www.w3.org/1999/xhtml">
    <p>GENE_ASSOCIATION: (b3115 or b2296 or b1849)</p>      遺伝子ID
    <p>GENE_LIST: b1849 b2296 b3115</p>
    <p>SUBSYSTEM: Pyruvate Metabolism</p></html>
  </notes>
  <listOfReactants>
    <speciesReference species="M_ac_c"/>
    <speciesReference species="M_atp_c"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="M_actp_c"/>
    <speciesReference species="M_adp_c"/>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <ci> FLUX_VALUE </ci>
    </math>
    <listOfParameters>
      <parameter id="LOWER_BOUND" value="-1000" units="mmol_per_gDW_per_hr"/>
      <parameter id="UPPER_BOUND" value="1000" units="mmol_per_gDW_per_hr"/>
      <parameter id="OBJECTIVE_COEFFICIENT" value="0"/>
      <parameter id="FLUX_VALUE" value="0" units="mmol_per_gDW_per_hr"/>
    </listOfParameters>
  </kineticLaw>
</reaction>
  
```

## ゲノムスケールモデル



# ゲノムスケールモデル

## Genome-scale network reconstruction (GENRE)

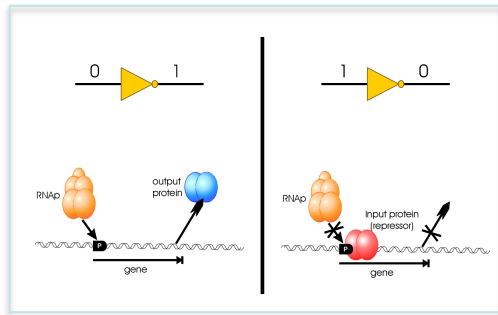


Monk J, Nogales J, Palsson BO  
 Nature Biotechnology 32, 447-452(2014)



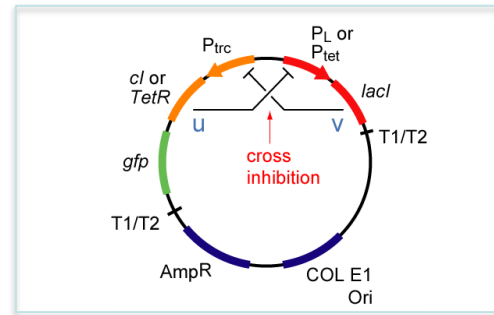
# 代謝経路設計：化学情報解析

単位/部品



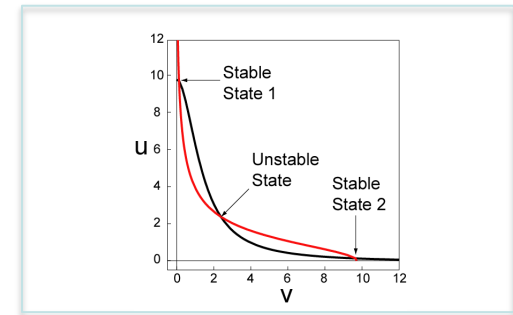
遺伝子/プロモータ

組合せ/再構築



遺伝子回路

表現型/構造



スイッチ

基質

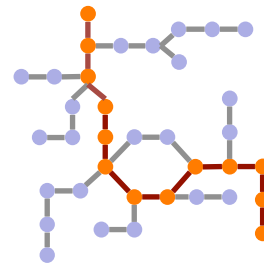
生成物



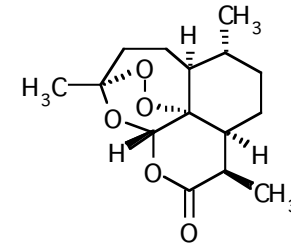
酵素/遺伝子



反応/酵素

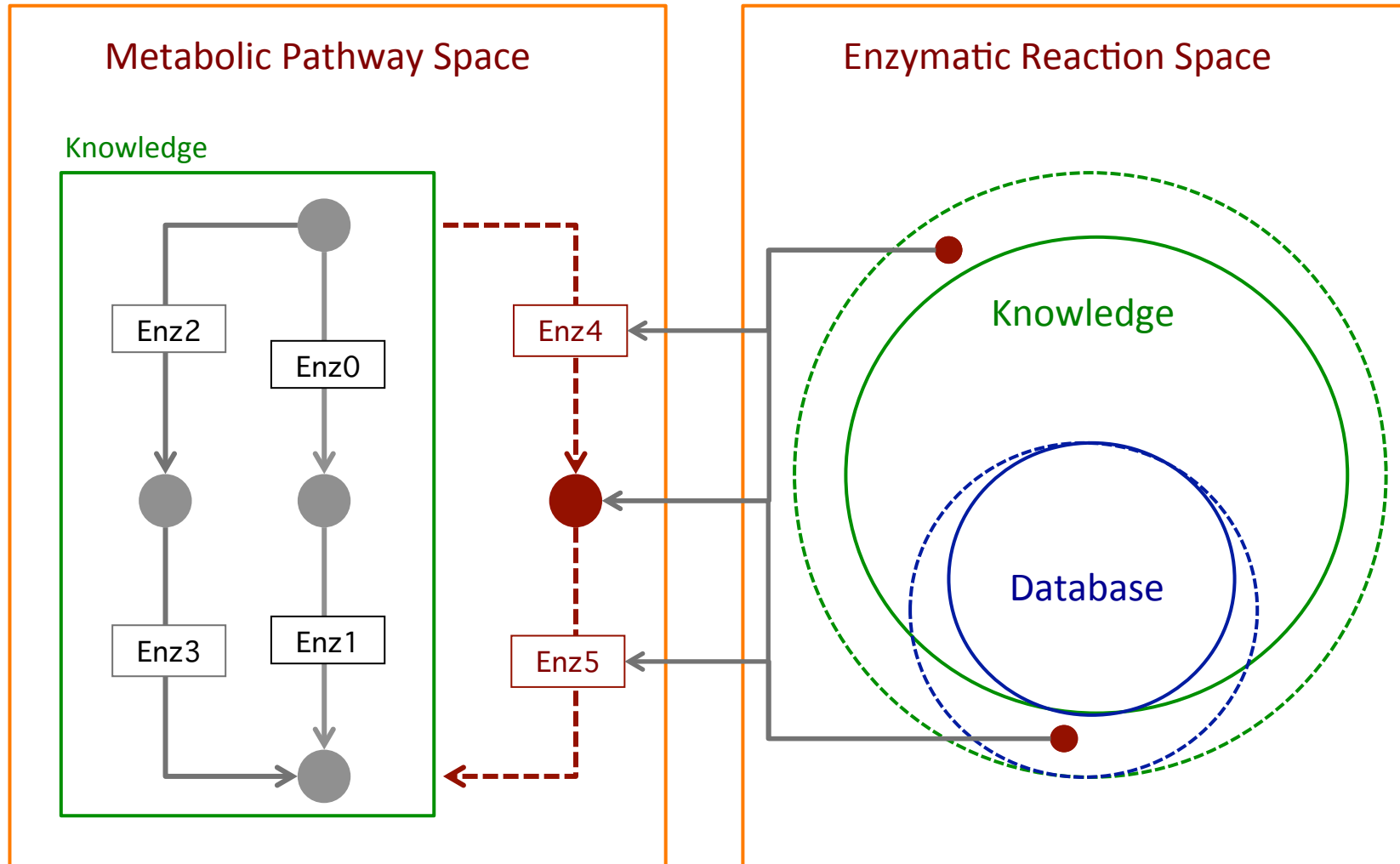


代謝経路



代謝化合物

# 代謝パスウェイの知識拡張



# 代謝反応データベース

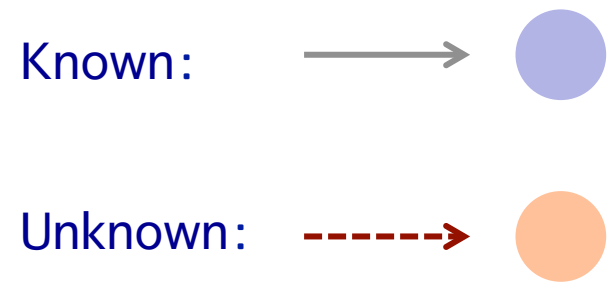
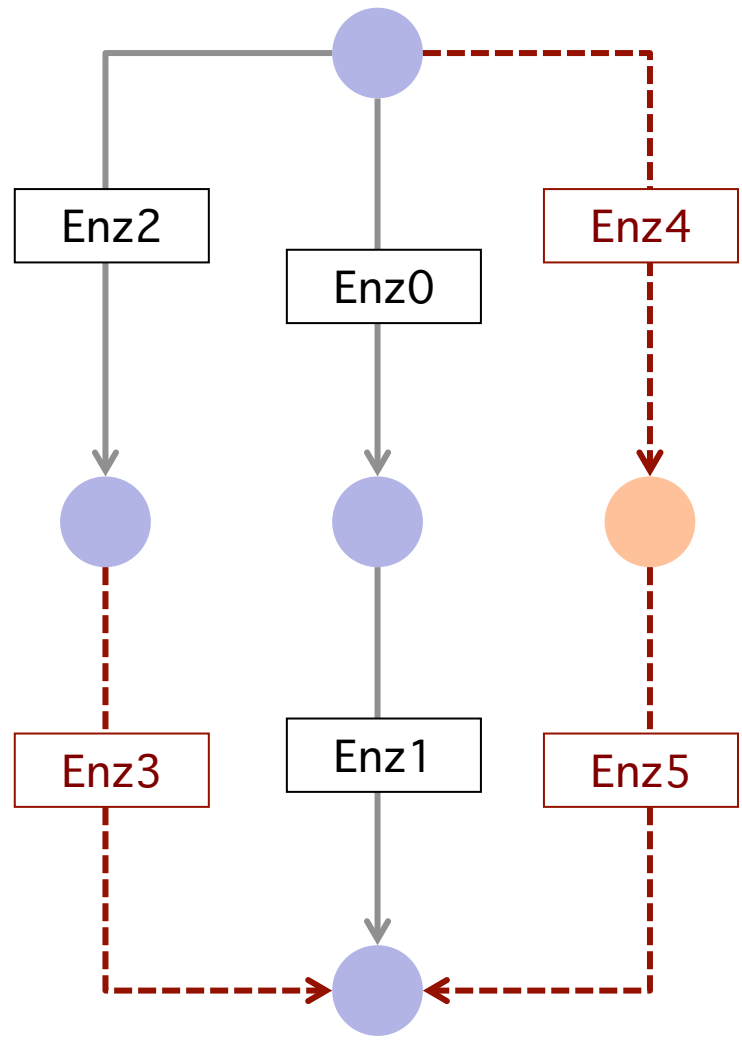
51

---

Database	Entries	Description
KEGG COMPOUND	17,091	Compounds
PubChem	~50,000,000	Compounds
KEGG REACTION	9,400	Reactions
KEGG RPAIR	14,218	Reactant Pairs
KEGG ENZYME	6,118	EC Numbers
BRENDA	6,130	Different Enzymes

---

# 代謝經路設計



PATH\_0 (Enz0\_Enz1): Known

PATH\_1 (Enz2\_Enz3): Unknown Ez

PATH\_2 (Enz4\_Enz5): Unknown Ez, Co

The screenshot shows the OMICtools website. At the top is the logo "OMICtools" with a grid of blue dots. Below the logo is a navigation bar with links: Home, Reviews, News, FAQ, Media, About, and Submit tools. To the right of the navigation bar is a search box with a "Search" button. Below the navigation bar is a blue header for a featured article: "A workflow for omic data analysis (NGS, microarray, PCR, MS, NMR)". The article text states: "OMICtools can help a) experimental researchers/clinicians find appropriate tools for their needs b) developers to stay up to date and to avoid redundancy c) funding agencies to ensure that the submitted projects are high value-added. Do you want help us to improve OMICtools? [Call for curators](#) (Henry et al., 2014) [OMICtools: an informative directory for multi-omic data analysis](#). Database." Below the article is a blue header for "Browse by omic applications". This section contains a grid of 9 categories, each with an icon and a count: Sequencing (2256), Microarray (504), Mass spectrometry (349), NMR spectroscopy (98), PCR (113), nCounter System (4), Cytometry (70), Thermal shift assay (4), and Common omic tools (290). Below this is another blue header for "Browse by functional analysis". This section contains a grid of 12 categories, each with an icon and a count: Functional analysis (1361), Drug discovery (417), Genome editing (38), Transcriptomics (344), Proteomics (364), Epigenomics (35), Fluxomics (41), Biomolecular structure (386), Health & Diseases (203), Immunology (72), and Educational resources (198).

omictools.com/

Home > Functional analysis > Synthetic biology > Metabolic pathways

## Synthetic metabolic pathway tools



### M-path NEW



A computational platform, M-path, to explore synthetic metabolic pathways including putative enzymatic reactions and compounds. M-path is an iterative random algorithm which makes efficient use of chemical and...



### Metabolic tinker



Aims to guide the design of synthetic metabolic pathways between any two desired compounds.



### MetRxn NEW



A knowledgebase that includes standardized metabolite and reaction descriptions by integrating information from BRENDA, KEGG, MetaCyc, Reactome.org and 44 metabolic models into a single unified data set. All...

## Related sites M-path

### [PathPred](#)

*A web-based server to predict plausible enzyme-catalyzed reaction pathways from a query compound...*

### [Desharky](#)

*A Monte Carlo algorithm that finds a metabolic pathway from a target compound by exploring a...*

### [FMM](#)

*It can reconstruct metabolic pathways from one metabolite to another metabolite among different...*

### [MetRxn](#)

*A knowledgebase that includes standardized metabolite and reaction descriptions by integrating...*

### [MRSD](#)

*A tool to search and design routes based on the weighted compound transform diagraph.*

### [SobolHDMR](#)

*A general purpose metamodeling software.*

### [FindPath](#)

*An unified system predicting and ranking the possible pathways according to their metabolic...*

### [XTMS](#)

*A web-based pathway analysis platform which provides full access to the set of pathways that can...*

### [Metabolic tinker](#)

*Aims to guide the design of synthetic metabolic pathways between any two desired compounds.*

## Network (knowledge) based approaches

- Handorf *et al.*, 2005; Noor *et al.*, 2010; Chou *et al.*, 2009; McClymont and Soyer, 2013; Kumar *et al.*, 2012; Xia *et al.*, 2011; Rodrigo *et al.*, 2008

*The methods are effective in finding known heterologous enzymatic reactions, but it ignores any pathway with an unknown reaction step.*

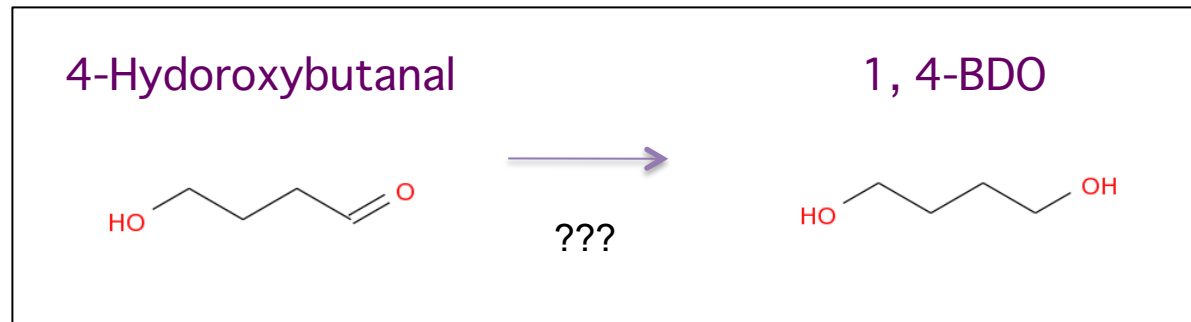
## Reaction (chemical) rule based approaches

- Yim *et al.*, 2011; Hatzimanikatis *et al.*, 2005; Carbonell *et al.*, 2012, 2014; Henry *et al.*, 2010; Cho *et al.*, 2010
- Araki *et al.*, 2015

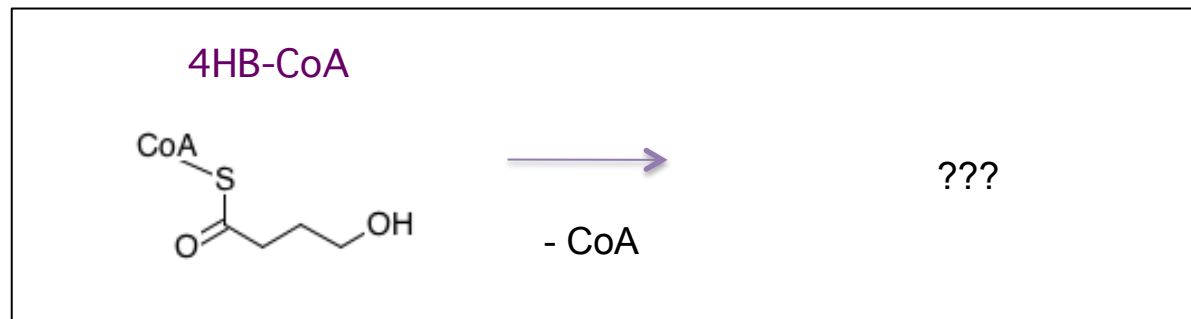
*These methods have been limited to a small number of either reactions or compounds to avoid combinatorial explosion in reconstructing synthetic metabolic pathways.*



## Reaction



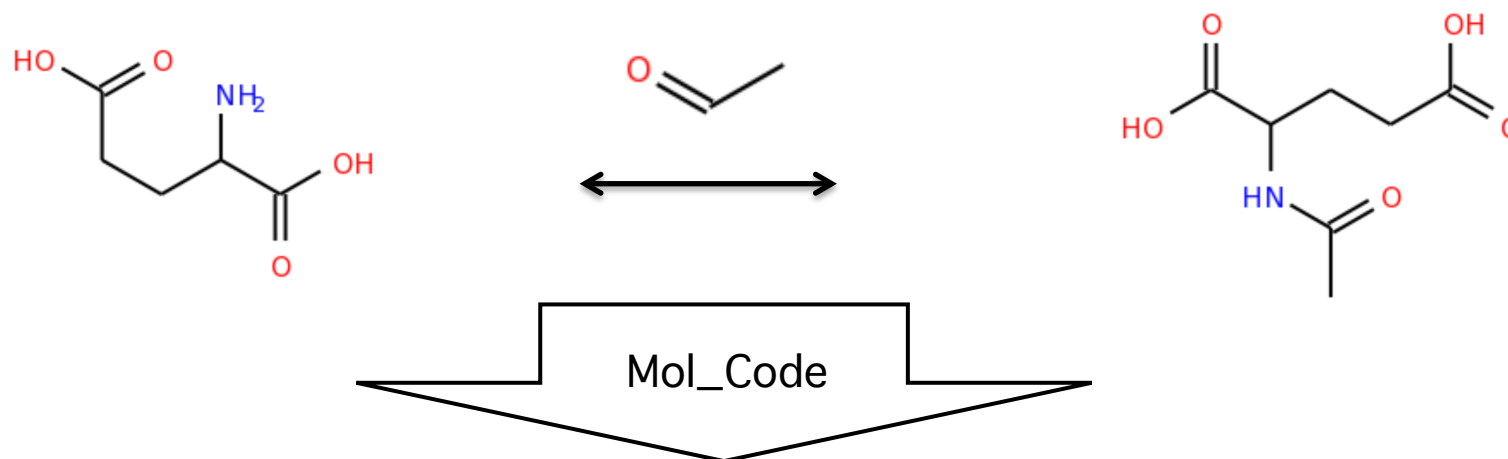
## Compound



① Glutamate

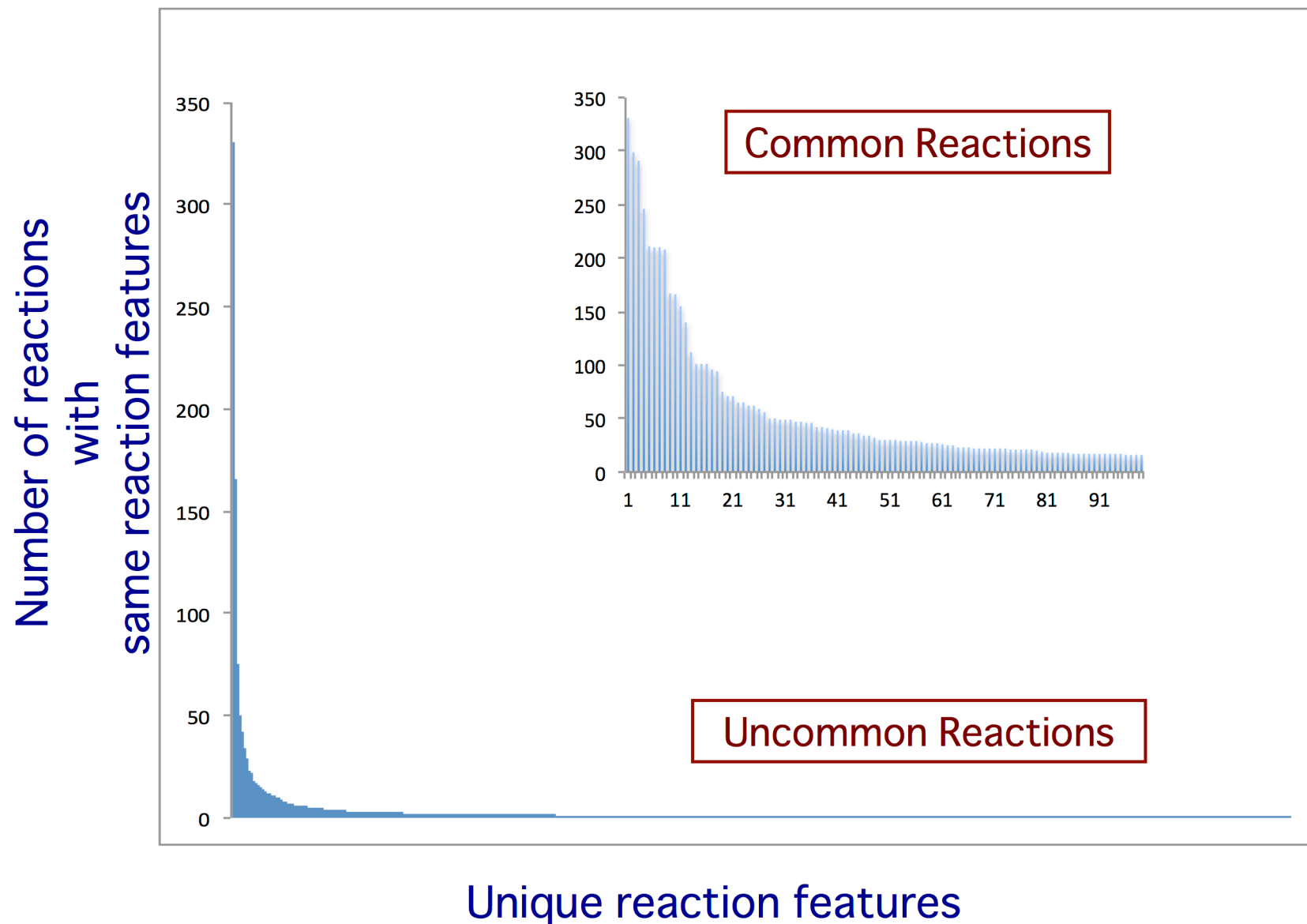
② Acetyl group

③ N-acetyl glutamate

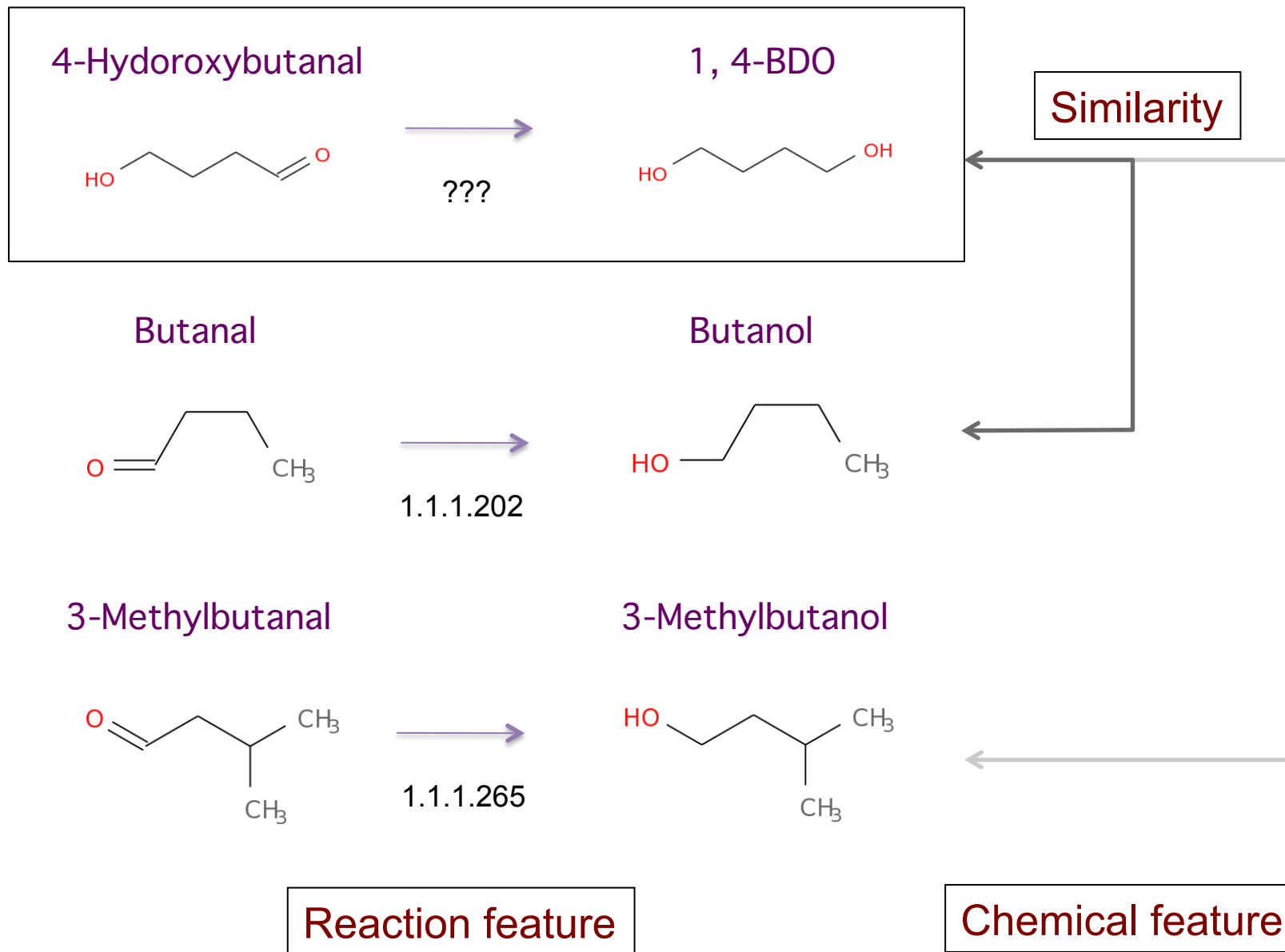


Glutamate	Acetylation	N-acetyl glutamate
(2 3 0 0 ······ 1 2 0)	(1 1 0 0 ······ 0 0 1)	(3 4 0 0 ······ 1 2 1)
Feature vector (Chemical feature)	←····→ Deacetylation	Feature vector (Chemical feature)
	Feature vector differences (Reaction feature)	

# 反応バリエーション



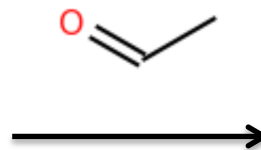
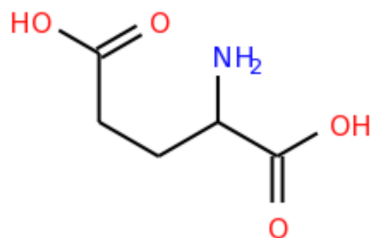
# 反应推定



# 化合物推定

① Glutamate

② Acetyl group



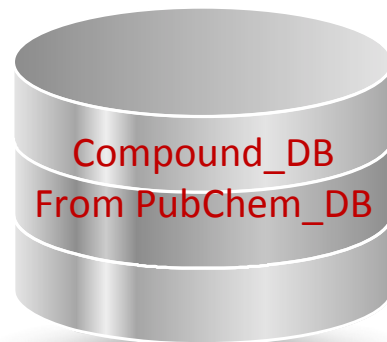
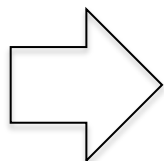
???

(2 3 0 0 ..... 1 2 0)

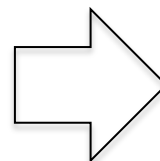
(1 1 0 0 ..... 0 0 1)

(3 4 0 0 ..... 1 2 1)

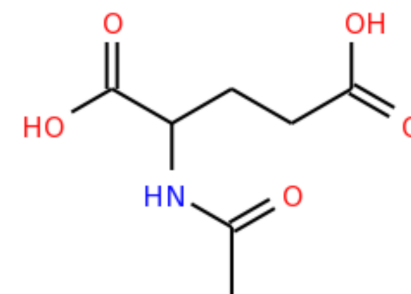
Structure Search



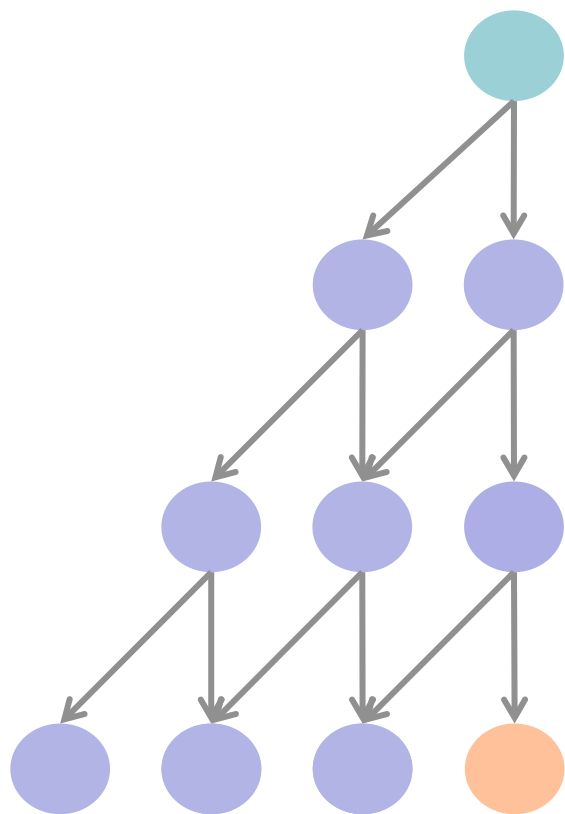
Assignment



③ N-acetyl glutamate



## Brute-force method



Reaction

Compound

1,000

1,000

1,000

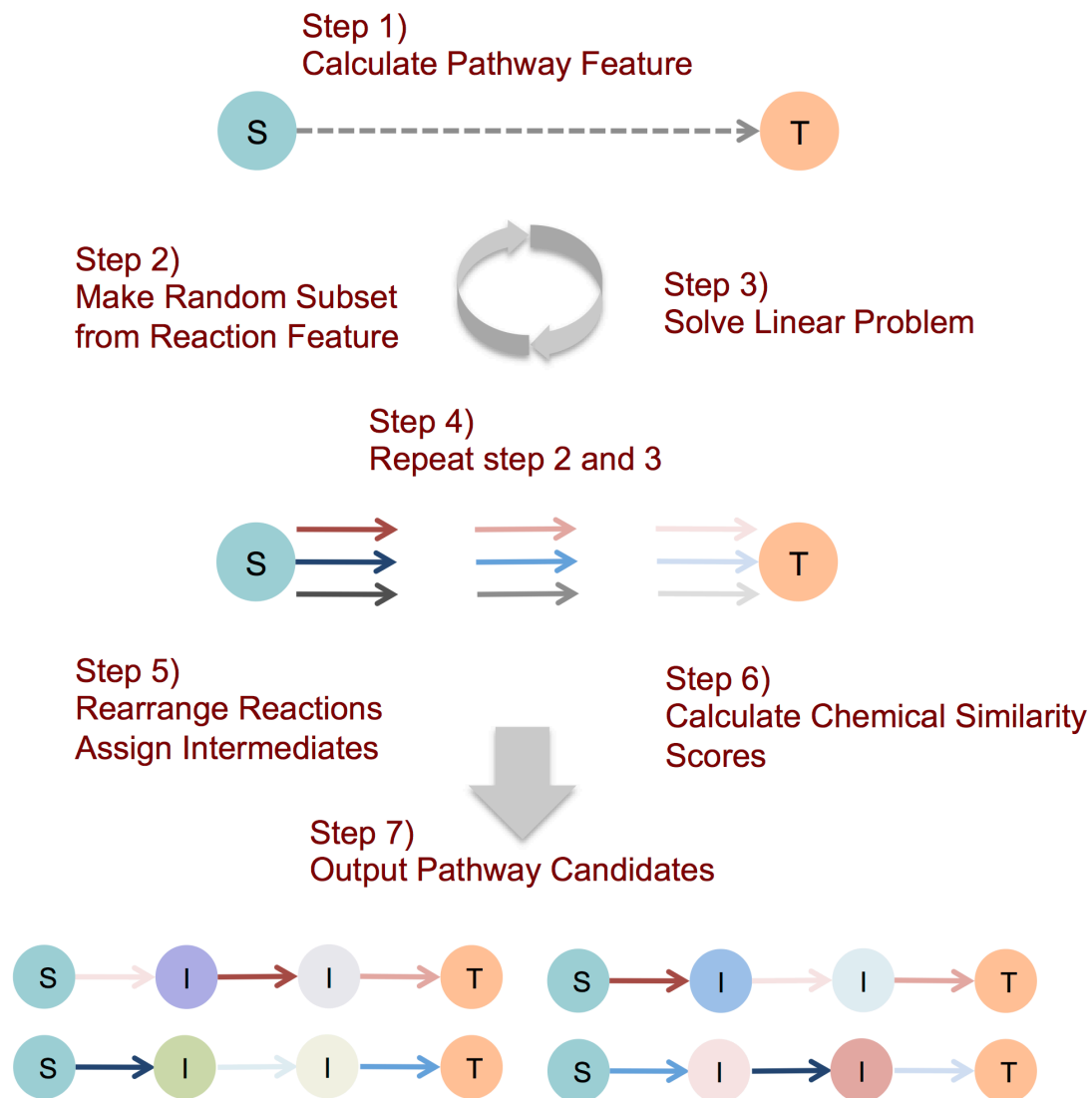
1,000,000

1,000

1,000,000,000

Incorrect

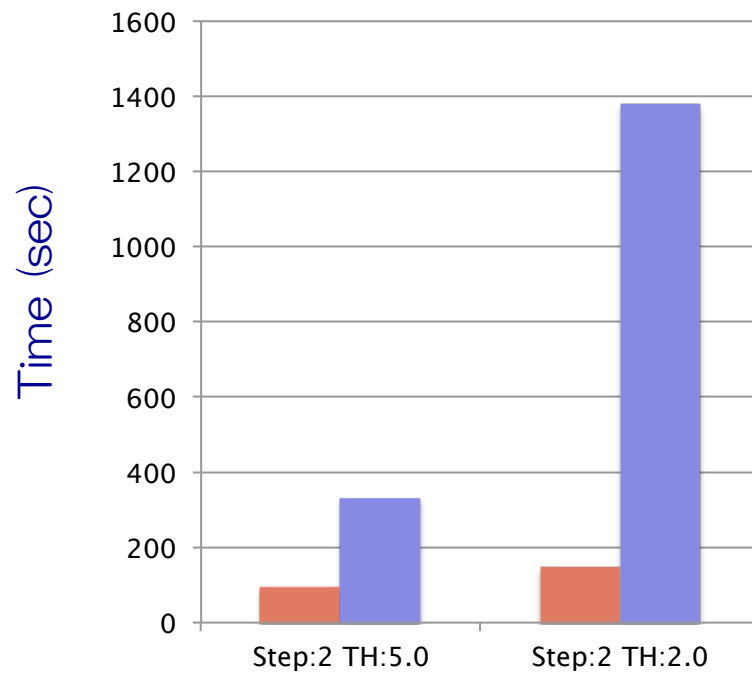
Correct



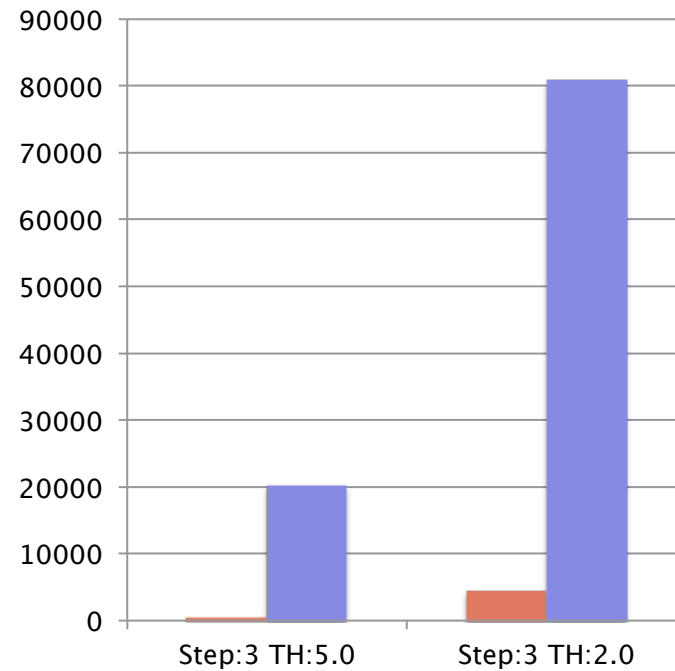
## Example) Glucose ~ Succinate

Proposed (■) vs Sequential (■)

Reaction Data  
- 1553 (TH: 2)  
- 599 (TH: 5)



Reaction Steps : 2



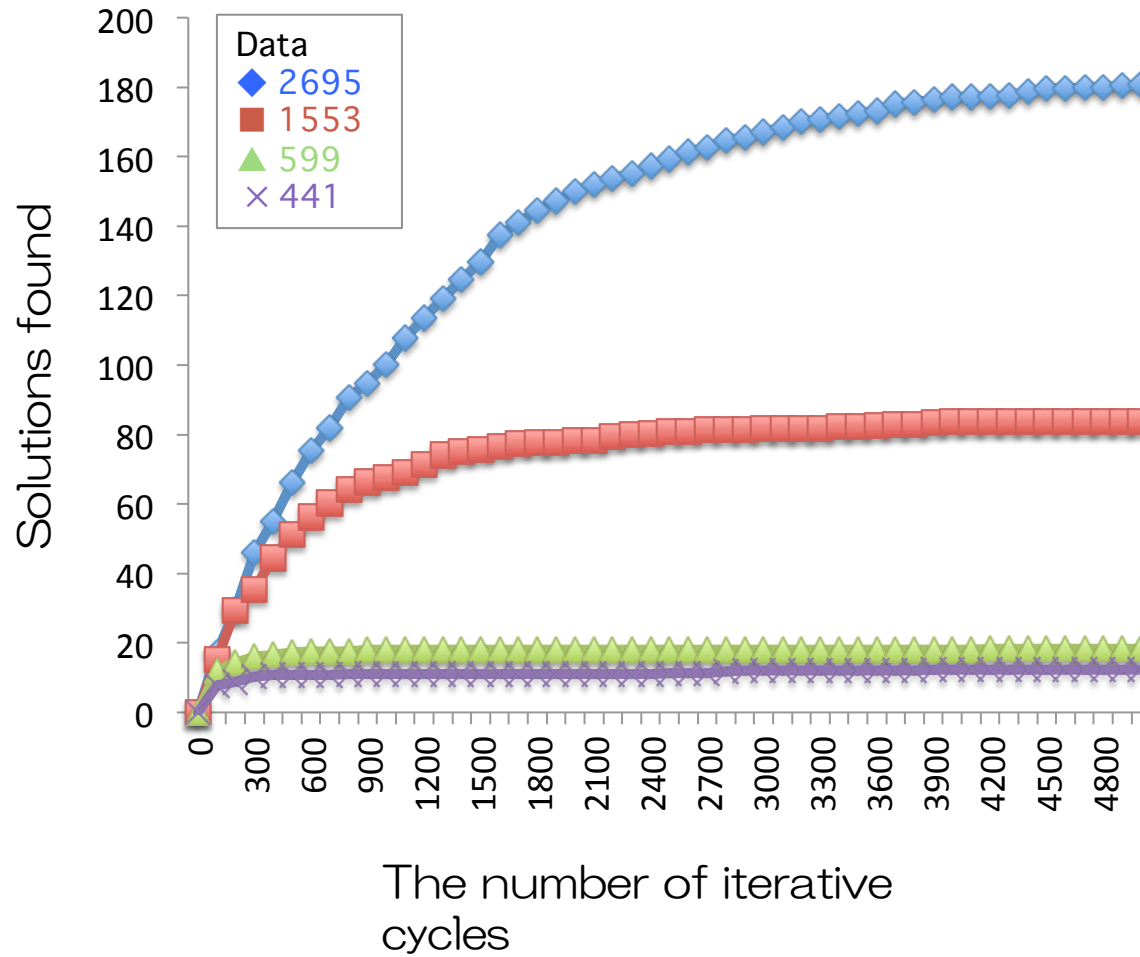
Reaction Steps : 3



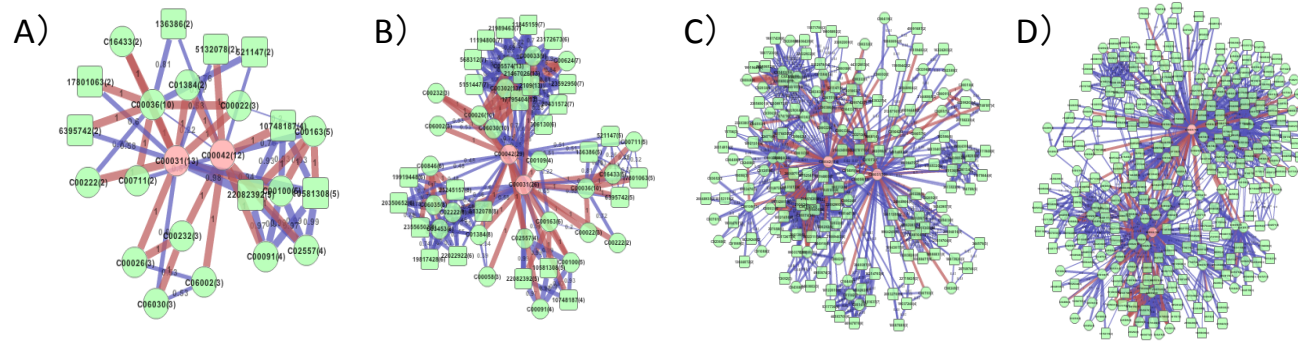
# Iterative Enumeration

Example) Glucose  $\sim$  Succinate

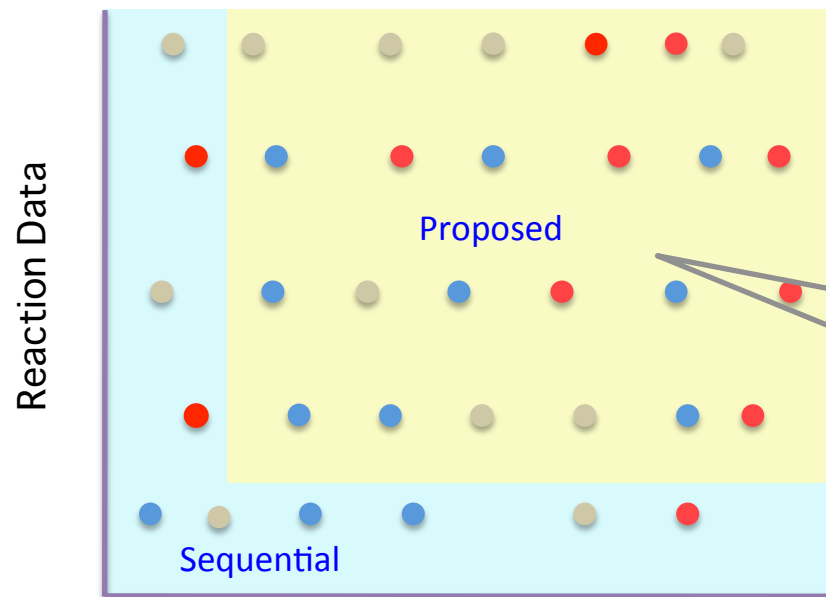
Reaction step: 3



# Advantage



Reaction Data:  $A < B < C < D$



Increasing network diversity with putative compounds and reactions

Expanding the diversity of chemical and reaction information available for finding novel metabolic pathways

Compound Data

● : Feasible Path

## Input interface

The screenshot displays the 'Job Register Form' and 'Compound List' sections of the M-path web application. The 'Job Register Form' includes input fields for 'CompoundID (Start): C00031', 'CompoundID (Last): C00042', 'Step Num: 3', 'Threshold: 2', and 'Cycle Num: 1000'. The 'Hub' section has radio buttons for 'First' (selected), 'All', and 'non'. The 'Option' section includes 'Feature Type' (radio buttons for 'mol2', 'mol2+' (selected), 'mol2c+'), 'Mode' (radio buttons for 'Standard' (selected), 'Sequential'), 'Rand Num: 500', and 'Limit Num: 500'. There are also 'Add Reaction' and 'Del Reaction' fields. The 'Submit' button is highlighted in green. The 'Compound List' section shows a table with columns 'CompoundID', 'SMILES', and 'Type'. A blue box labeled 'KEGG\_ID PubChem\_ID' points to the 'CompoundID' column. A green box labeled 'Start\_Calculation' points to the 'Submit' button. Red boxes label various fields: 'Reaction\_Step' (Step Num), 'Reaction\_Diversity' (Threshold), 'Iteration\_Number' (Cycle Num), 'Hub\_Compound' (Hub), and 'Options' (Option section).

KEGG\_ID  
PubChem\_ID

Reaction\_Step

Reaction\_Diversity

Iteration\_Number

Hub\_Compound

Options

Start\_Calculation

CompoundID	SMILES	Type
TestCase	<chem>OC(=O)CC/C=C/C(=O)O</chem>	mol2+
CR00011	<chem>CC(=O)CCC</chem>	mol2+
CR00010	<chem>CC(=O)C=C</chem>	mol2+
CID8065	<chem>C(C=CCO)O</chem>	mol2+
CID8064	<chem>C(CCO)CO</chem>	mol2+

# M-path

Example) Glucose ~ Succinate

**Start Compound**      **Hub Compound**

**Pathway List**

pid	Name	Score
PATH:1-1		
Total Score: 1, Step: 2		
1	C00031 -- C00122	1
1	C00122 -- C00042	1
PATH:4-2		
Total Score: 1, Step: 3		
PATH:6-1		
Total Score: 0.99, Step: 3		
PATH:6-2		
Total Score: 0.92, Step: 3		
PATH:3-2		
Total Score: 0.74, Step: 3		
PATH:5-2		
Total Score: 0.74, Step: 3		
PATH:2-2		
Total Score: 0.65, Step: 3		
PATH:3-1		
Total Score: 0.65, Step: 3		
PATH:7-1		
Total Score: 0.61, Step: 2		

**Path View**

RE: C00031 → C00122 → C00042

VC: C00031, C00031, 18664281, C00042, C00042

**Reaction**      **Chemical Transition**

**Last Compound**

**Reaction List**

ID	RE	Name	Score	EC
1	C00042_00122	Fumarate -- Succinate	1.0	1.3.1.6 1.3.99.1 1.3.5.1
2	C00846_02222	2-Maleylacetate -- 3-Oxoadipate	0.704348	1.3.1.32
10	C16470_016468	(2E)-5-Methylhexa-2,4-dienoyl-Co -- 5-Methylhex-4-en...	0.1145276	1.3.99.-
7	C05432_015867	3,4-Dehydrolycopene -- Lycopene	0.10054965	1.14.99.-
3	C05413_005414	Phytofluene -- Phytoen	0.09411205	1.14.99.-
4	C05414_005430	zeta-Caroten -- Phytofluene	0.09411205	1.14.99.-
5	C05430_005431	Neurosporen -- zeta-Caroten	0.09411205	1.14.99.30
6	C05431_005432	Lycopene -- Neurosporen	0.09411205	1.14.99.30
8	C05411_005435	gamma-Caroten -- beta-Zeacaroten	0.0787879	1.14.99.30
9	C14146_C08586	delta-Caroten -- alpha-Zeacaroten	0.07545455	1.14.99.30

**Compound List**

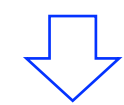
ID	KEGG	CID	Name	Similarity	C match
1	C00042	1110	butanedioic acid	1.0	1

# M-path

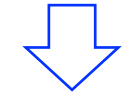
Enzymatic Reactions

ID	RE	Name	Score	EC
40	C11062_C00989	4-Hydroxybutanoic acid – 4-Hydroxybutyryl-Co...	1.0	3.1.2.6.2.1.2.8.3 u...
42	C05668_C01013	3-Hydroxypropanoate – 3-Hydroxypropionyl-...	1.0	3.1.2.6.2.1.2.8.3 u...
44	C04047_C01188	3-Hydroxy-2-methylpropanoate – 3-Hydroxy-2...	1.0	3.1.2.6.2.1.2.8.3 u...
69	C06000_C06001	(S)-3-Hydroxyisobutyrate – (S)-3-Hydroxyisobu...	1.0	3.1.2.6.2.1.2.8.3 u...
9	C00136_C00246	Butanoic acid – Butanoyl-CoA	0.990338	3.1.2.6.2.1.2.8.3 u...
95	C16268_C16267	Cyclopropanecarboxylate – Cyclopropanecarb...	0.990338	3.1.2.6.2.1.2.8.3 u...
2	C00091_C00042	Succinate – Succinyl-CoA	0.985714	3.1.2.6.2.1.2.8.3 u...
4	C00083_C00383	Malonate – Malonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
16	C00827_C00186	(S)-Lactate – Lactoyl-Co	0.985646	3.1.2.6.2.1.2.8.3 u...
34	C00683_C02170	Methylmalonate – (S)-Methylmalonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
45	C01213_C02170	Methylmalonate – (R)-Methylmalonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
60	C03188_C04025	alpha,omega-Dicarboxylic acid – omega-Carb...	0.985646	3.1.2.6.2.1.2.8.3 u...
6	C00100_C00163	Propanoate – Propanoyl-CoA	0.980583	3.1.2.6.2.1.2.8.3 u...
10	C04348_C00149	(S)-Malate – (3S)-3-Carboxy-3-hydroxypropan...	0.976636	3.1.2.6.2.1.2.8.3 u...
36	C00904_C00815	Citramalate – Citramalyl-Co	0.976636	3.1.2.6.2.1.2.8.3 u...
37	C01011_C00815	Citramalate – (3S)-Citramalyl-CoA	0.976636	3.1.2.6.2.1.2.8.3 u...
41	C01011_C02614	(S)-2-Methylmalate – (3S)-Citramalyl-CoA	0.976636	3.1.2.6.2.1.2.8.3 u...
14	C00332_C00164	Acetoacetate – Acetoacetyl-CoA	0.97619	3.1.2.6.2.1.2.8.3 u...
22	C00356_C03761	3-Hydroxy-3-methylglutarate – (S)-3-Hydroxy...	0.972093	3.1.2.6.2.1.2.8.3 u...
55	C03058_C02630	2-Hydroxyglutarate – 2-Hydroxyglutaryl-Co	0.972093	3.1.2.6.2.1.2.8.3 u...

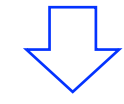
EC\_number



Multiple Alignment Find Motifs

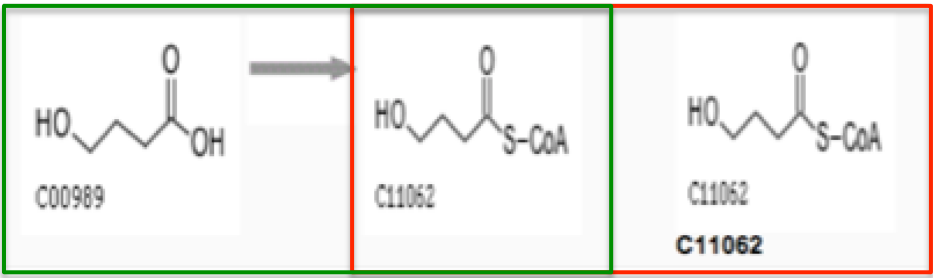


Genome mining



Enzyme/Gene Selection

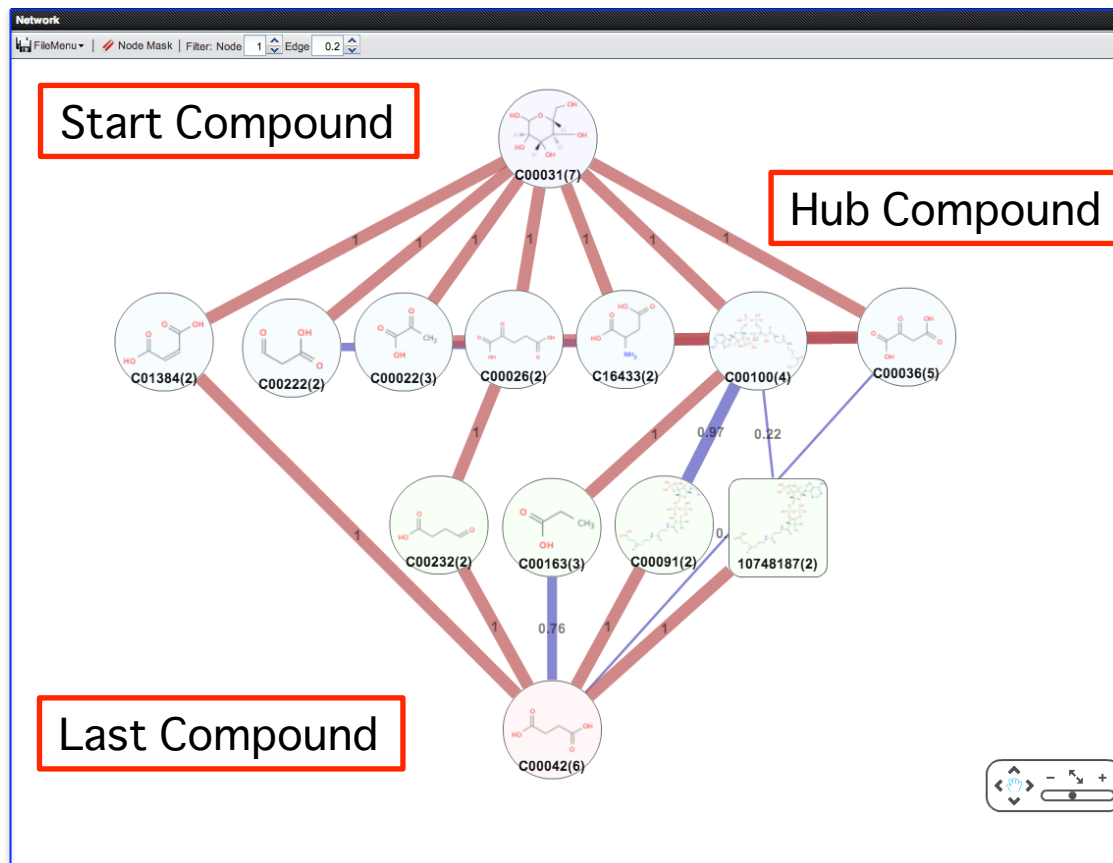
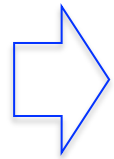
Chemical Similarity Scores



# M-path

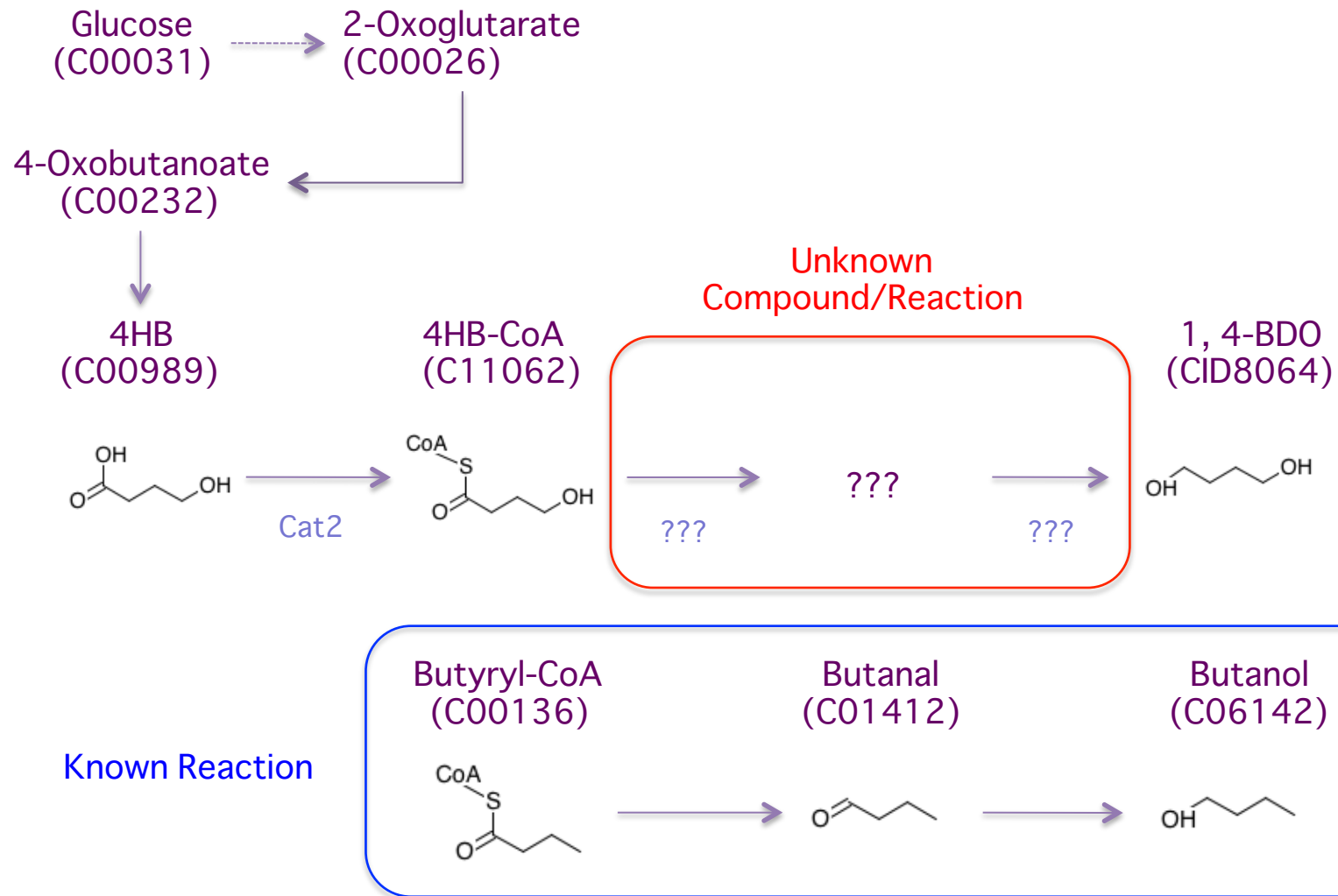
Example) Glucose ~ Succinate

pid	Name	Score
<input type="checkbox"/> PATH:1-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 1, Step: 2		
<input type="checkbox"/> PATH:4-2		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 1, Step: 3		
<input type="checkbox"/> PATH:6-2		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.92, Step: 3		
<input type="checkbox"/> PATH:3-2		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.74, Step: 3		
<input type="checkbox"/> PATH:5-2		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.74, Step: 3		
<input type="checkbox"/> PATH:6-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.74, Step: 3		
<input type="checkbox"/> PATH:2-2		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.65, Step: 3		
<input type="checkbox"/> PATH:3-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.65, Step: 3		
<input type="checkbox"/> PATH:7-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.61, Step: 2		
<input type="checkbox"/> PATH:4-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.63, not hit: 1, Step: 3		
<input type="checkbox"/> PATH:5-1		<input type="checkbox"/> passed <input type="checkbox"/> failed
Total Score: 0.59, not hit: 1, Step: 3		



- 1) Design metabolic pathways for specified target compounds
- 2) Enumerate reachable compounds from specified start compounds
- 3) Expand the scope of metabolic pathways
- 4) Find genes/metabolites using omics data

# 事例) 1,4-Butanediol





# 事例) 1,4-Butanediol

73

**Path Tree**

path\_vc\_C00031\_CID8064\_50000 ScoreReset

Name	Score
2-Aminomalonate semialdehyde -- 2-Oxoglutarate Total Score: 1, Yield: 150	
2-Aminomalonate semialdehyde -- 2-Oxoglutarate Total Score: 1, Yield: 150	
2-Aminomalonate semialdehyde -- 2-Oxoglutarate Total Score: 1, Yield: 150	
2-Aminomalonate semialdehyde -- 2-Oxoglutarate Total Score: 0.97, Yield: 150	
D-Glucose -- 2-Oxoglutarate	1
Pyruvate -- Acetaldehyde	1
2-Aminomalonate semialdehyde -- L-Serine	1
Acetate -- Acetyl-CoA	1
Acetyl-CoA -- Acetaldehyde	0.82
2-Aminomalonate semialdehyde -- L-Serine	1

**Path View**

RE VC

**Reaction**

**Chemical Transition**

**Assigned Reaction**

**Assigned Compound**

**Control**

**Reaction List**

ID	RE	Name	Score	EC
40	C11062_C00989	4-Hydroxybutanoic acid -- 4-Hydroxybutyryl-Co	1.0	3.1.2.6.2.1.2.8.3 u...
42	C05668_C01013	3-Hydroxypropanoate -- 3-Hydroxypropionyl-...	1.0	3.1.2.6.2.1.2.8.3 u...
44	C04047_C01188	3-Hydroxy-2-methylpropanoate -- 3-Hydroxy-2...	1.0	3.1.2.6.2.1.2.8.3 u...
69	C06000_C06001	(S)-3-Hydroxyisobutyrat -- (S)-3-Hydroxyisobu...	1.0	3.1.2.6.2.1.2.8.3 u...
9	C00136_C00246	Butanoic acid -- Butanoyl-CoA	0.990338	3.1.2.6.2.1.2.8.3 u...
95	C16268_C16267	Cyclopropanecarboxylat -- Cyclopropanecarb...	0.990338	3.1.2.6.2.1.2.8.3 u...
2	C00091_C00042	Succinate -- Succinyl-CoA	0.985714	3.1.2.6.2.1.2.8.3 u...
4	C00083_C00383	Malonate -- Malonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
16	C00827_C00186	(S)-Lactate -- (S)-Lactyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
34	C00683_C02170	Methylmalonate -- (S)-Methylmalonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
45	C01213_C02170	Methylmalonate -- (R)-Methylmalonyl-CoA	0.985646	3.1.2.6.2.1.2.8.3 u...
60	C03188_C04025	alpha,omega-Dicarboxylic aci -- omega-Carb...	0.985646	3.1.2.6.2.1.2.8.3 u...
6	C00100_C00163	Propanoate -- Propanoyl-CoA	0.980583	3.1.2.6.2.1.2.8.3 u...
10	C04348_C00149	(S)-Malate -- (3S)-3-Carboxy-3-hydroxypropan...	0.976636	3.1.2.6.2.1.2.8.3 u...
36	C00904_C00815	Citramalate -- Citramalyl-Co	0.976636	3.1.2.6.2.1.2.8.3 u...
37	C01011_C00815	Citramalate -- (3S)-Citramalyl-CoA	0.976636	3.1.2.6.2.1.2.8.3 u...
41	C01011_C02614	(S)-2-Methylmalate -- (3S)-Citramalyl-CoA	0.976636	3.1.2.6.2.1.2.8.3 u...
14	C00332_C00164	Acetoacetate -- Acetoacetyl-CoA	0.97619	3.1.2.6.2.1.2.8.3 u...
22	C00356_C03761	3-Hydroxy-3-methylglutarate -- (S)-3-Hydroxy...	0.972093	3.1.2.6.2.1.2.8.3 u...
55	C03058_C02630	2-Hydroxyglutarat -- 2-Hydroxyglutaryl-Co	0.972093	3.1.2.6.2.1.2.8.3 u...

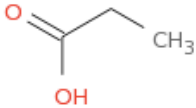
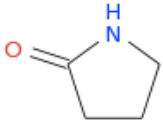

**Virtual Compound**

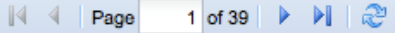
ID	KEGG	CID	Name	Similarity
1		4487557	S-[2-[3-[4-[[[5-(6-aminopurin-9-yl)-4-hydroxy-3-phosphono...	1.0
6		11966192	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	1.0
18	C11062	443062	S-[2-[3-[4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydrox...	1.0
3		9543037	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
4		11966146	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
7		24798719	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
8		25246084	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
11		46936728	S-[2-[3-[[(2S)-4-[[[(2S,3R,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
13		521	S-[2-[3-[[(2S)-4-[[[(2S,3R,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
14	C01144	439419	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydro...	0.971564
15	C03561	440045	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydro...	0.971564
17	C05116	440563	S-[2-[3-[4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydrox...	0.971564
19		644065	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.971564
2	C06000	6857371	S-[2-[3-[4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydrox...	0.957346
5		11966163	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.957346
9		45259165	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.957346
10		46173171	S-[2-[3-[[(2R)-4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hy...	0.957346
12		88	S-[2-[3-[4-[[[5-(6-aminopurin-9-yl)-4-hydroxy-3-phosphono...	0.957346
16	C04047	440205	S-[2-[3-[4-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-4-hydrox...	0.957346

# Reachable compounds

74

Calculate N steps from start compounds (eg. glutamate)

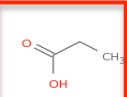
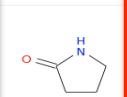
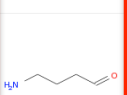
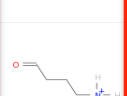

Glutamate List						
Structure	CompoundID	SMILES	MW <small>▲</small>	TotalScore	M-Score	Pathway
	CID1032	<chem>CCC(=O)O</chem>	74.07854	0.83	0.6515155	<a href="#">25</a>
	CID12025	<chem>C1CC(=O)NC1</chem>	85.10448	0.86	0.7104465	<a href="#">4</a>
	CID118	<chem>C(CC=O)CN</chem>	87.12036	1.0	1.0	<a href="#">8</a>

Page 1 of 39 |  Displaying Compounds 1 - 50 of 1928

# Reachable compounds

Integrate all pathways from glutamate

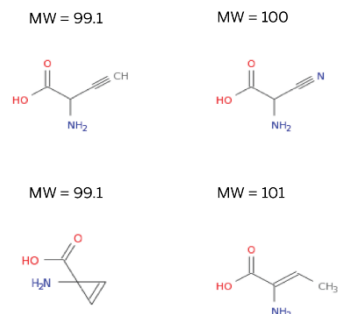
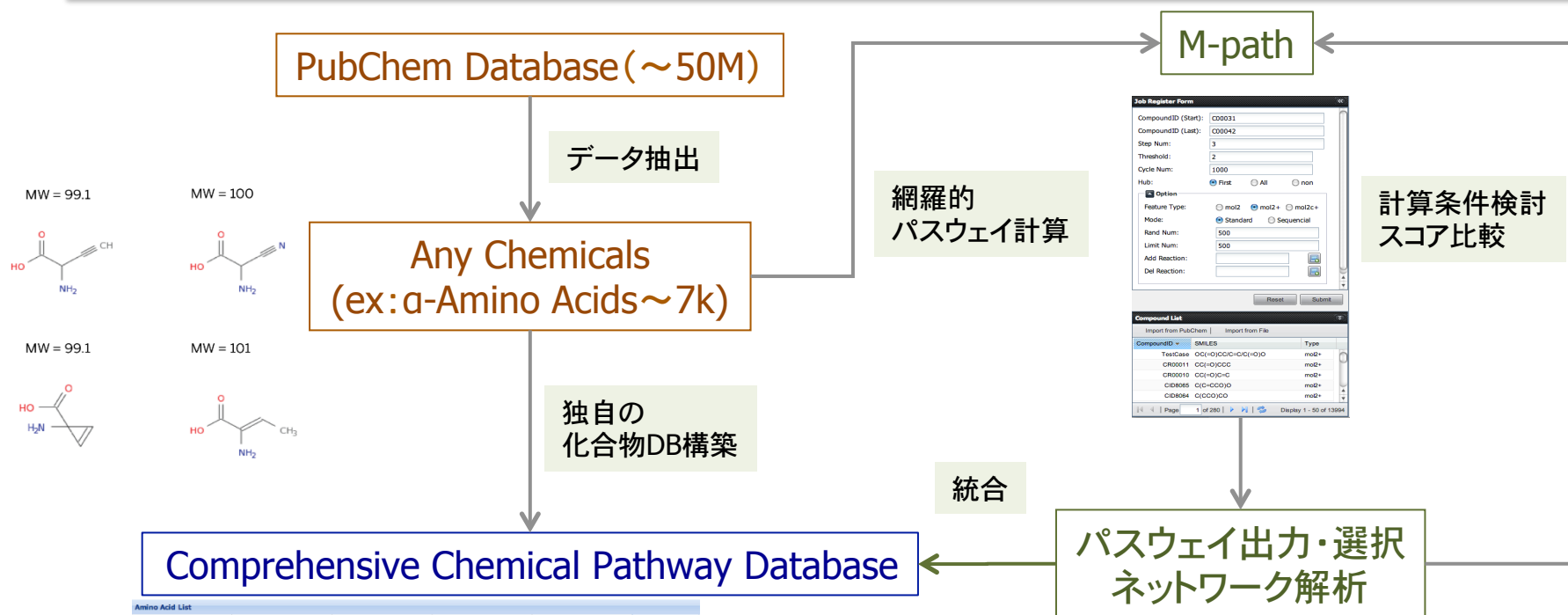
The image displays a software interface for chemical network analysis. On the left, a table titled "Glutamate List" shows a list of compounds with their SMILES, molecular weights, and scores. A red box highlights the first entry, which is linked to a chemical structure. An arrow points from this structure to a specific cluster in a larger network graph on the right. The network graph shows a central node labeled "Start (Glutamate)" in a red box, with numerous other nodes and edges radiating outwards. A red box also highlights one of these peripheral clusters, labeled "Reachable Compound".

Structure	CompoundID	SMILES	MW	TotalScore	M-Score	Pathway
	CID1032	CCC(=O)O	74.07854	0.83	0.6515155	25
	CID12025	C1CC(=O)NC1	85.10448	0.86	0.7104465	4
	CID116					
	CID25245200					
	CID239					

Start (Glutamate)

Reachable Compound

# Expanding Metabolic Pathway



Structure	CompoundID	SMILES	MW	BP-WEB	PickUp
	9964226	CC(=O)SC[Co]	174.19766	on	9964226

PathID	Name	Score	Status
PATH:1-1	D-Glucose - Acetyl-CoA	0.97	passed
1	Acetyl-CoA - Acetate	1	failed
1	Acetate - N-Acetylmethine	0.91	failed

PathID	Name	Score	Status
PATH:11-1	D-Glucose - Acetyl-CoA	0.97	passed
PATH:20-1	D-Glucose - Acetyl-CoA	0.97	passed
PATH:27-1	D-Glucose - Acetyl-CoA	0.97	passed
PATH:29-1	D-Glucose - Acetyl-CoA	0.97	passed
PATH:38-2	D-Glucose - Acetyl-CoA	0.97	passed
PATH:39-2	D-Glucose - Acetyl-CoA	0.97	passed
PATH:13-2	D-Glucose - Acetyl-CoA	0.96	failed
PATH:14-2	D-Glucose - Acetyl-CoA	0.96	failed

Network

FileMenu | NodeMask | Filter: Node | 0 | Edge | 0

Information

(2S)-2-amino-3-(6-hydroxy-1H-indol-3-yl)propionic acid

Compound ID: 49867758

Formula: C11H12N2O3

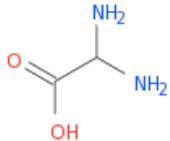
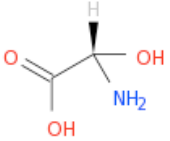
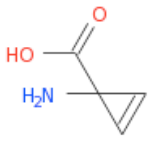
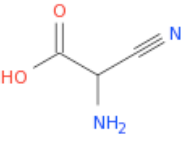
SMILES: C1=CC=C(C=C1O)NC=C[C@@H](C=O)ON

MW: 220.22458

# Expanding Metabolic Pathway

77

<http://bp.scitec.kobe-u.ac.jp/m-path/db/>

Amino Acid List						
Structure	CompoundID	SMILES	MW	TotalScore	M-Score	Pathway
	CID18976960	<chem>C(C(=O)O)(N)N</chem>	90.08124		0.430622	<a href="#">yes</a>
	CID16744473	<chem>[C@H](C(=O)O)(N)O</chem>	91.066	0.88		<a href="#">yes</a>
	CID10996968	<chem>C1=CC1(C(=O)O)N</chem>	99.088	0.77	0.3058555	<a href="#">yes</a>
	CID533486	<chem>C(#N)C(C(=O)O)N</chem>	100.07606	0.86	0.6555185	<a href="#">yes</a>

# Expanding Metabolic Pathway

78

<http://bp.scitec.kobe-u.ac.jp/m-path/db/>

### Path List

Score Step PathName

pid	Name	Score
<b>PATH:3-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.97, Step: 3		
4	D-Glucose -- L-Serine	1
4	L-Serine -- L-Tryptophan	1
4	C00078 -- C00643	0.92
<b>PATH:8-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.97, Step: 3		
9	D-Glucose -- Formate	1
9	C00058 -- C05648	1
9	C05648 -- C00643	0.92
<b>PATH:10-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.71, Step: 3		
<b>PATH:15-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.66, Step: 3		
<b>PATH:11-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.58, Step: 3		
<b>PATH:7-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.57, Step: 3		
<b>PATH:4-1</b> <span style="float: right;"><input type="checkbox"/> passed <input type="checkbox"/> failed</span>		
Total Score: 0.47, not hit: 1, Step: 3		

### Path View

Export ExportSelect Score Histogram Histogram TXT

RE VC

C00031 C00065 C00716 C00806

589768

### Control

#### Reaction List

ID	RE	Name	Score	EC
1	C00643_C00078	L-Tryptophan -- 5-Hydroxy-L-tryptophan	0.92406	<a href="#">1.14.16.4</a>
2	C00082_C00079	L-Phenylalanine -- L-Tyrosine	0.6013515	<a href="#">1.14.16.1</a>
67	C05643_C01598	Melatonin -- 6-Hydroxymelatonin	0.6001985	<a href="#">1.14.14.1</a>
3	C00355_C00082	L-Tyrosine -- 3,4-Dihydroxy-L-phenylalanine	0.595226	<a href="#">1.10.3.1</a> <a href="#">1.14.18.1...</a>
16	C03227_C00328	L-Kynurenine -- 3-Hydroxy-L-kynurenin	0.559275	<a href="#">1.14.13.9</a>
22	C05658_C00463	Indole -- Indoxyl	0.5027315	<a href="#">1.14.16.-</a>
69	C01717_C06325	2-Quinolonecarboxylic acid -- 4-Hydroxy-2-quinol...	0.494649	<a href="#">1.3.99.18</a>
94	C11457_C05629	Phenylpropanoate -- 3-(3-Hydroxy-phenyl)-prop...	0.4627745	
57	C15986_C01297	6-Hydroxypseudooxynicotine -- 2,6-Dihydroxyps...	0.4550825	<a href="#">1.14.18.-</a>
115	C09239_C11635	10-Deoxysarpagine -- Sarpagin	0.4489245	<a href="#">1.14.13.91</a>
55	C04044_C01198	3-(2-Hydroxyphenyl)propanoate -- 3-(2,3-Dihydr...	0.4460225	<a href="#">1.14.13.4</a>
86	C04044_C11457	3-(3-Hydroxy-phenyl)-propanoic acid -- 3-(2,3-Di...	0.4460225	<a href="#">1.14.13.-</a>
5	C00632_C00108	Anthranilate -- 3-Hydroxyanthranilate	0.4431685	<a href="#">1.14.16.3</a>
102	C06330_C06343	Quinolin-4-o -- Quinoline-3,4-diol	0.43378	<a href="#">1.14.13.62</a>

#### Compound List

ID	KEGG	CID	Name	Similarity	C match
11		589768	2-amino-3-(4-hydroxy-1H-indol-3-yl)propanoic acid	0.92406	0.27

# Expanding Metabolic Pathway

79

<http://bp.scitec.kobe-u.ac.jp/m-path/aa/>

Network

FileMenu Node Mask Filter: Node 0 Edge 0

Data from amino acids with top 100 M-scores

Information

**(2S)-2-amino-3-(6-hydroxy-1H-indol-3-yl)propionic acid**

**Compound ID:** 49867758  
**Formula:** C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>  
**SMILES:**  
C1=CC2=C(C=C1O)NC=C2[C@@H](C(=O)O)N  
**MW:** 220.22458

ありがとうございました

荒木 通啓 (Michihiro Araki)  
araki@port.kobe-u.ac.jp

神戸大学 自然科学系先端融合研究環  
Organization of Advanced Science and Technology  
Kobe University