Robustness/plasticity of biochemical reaction systems and network topology

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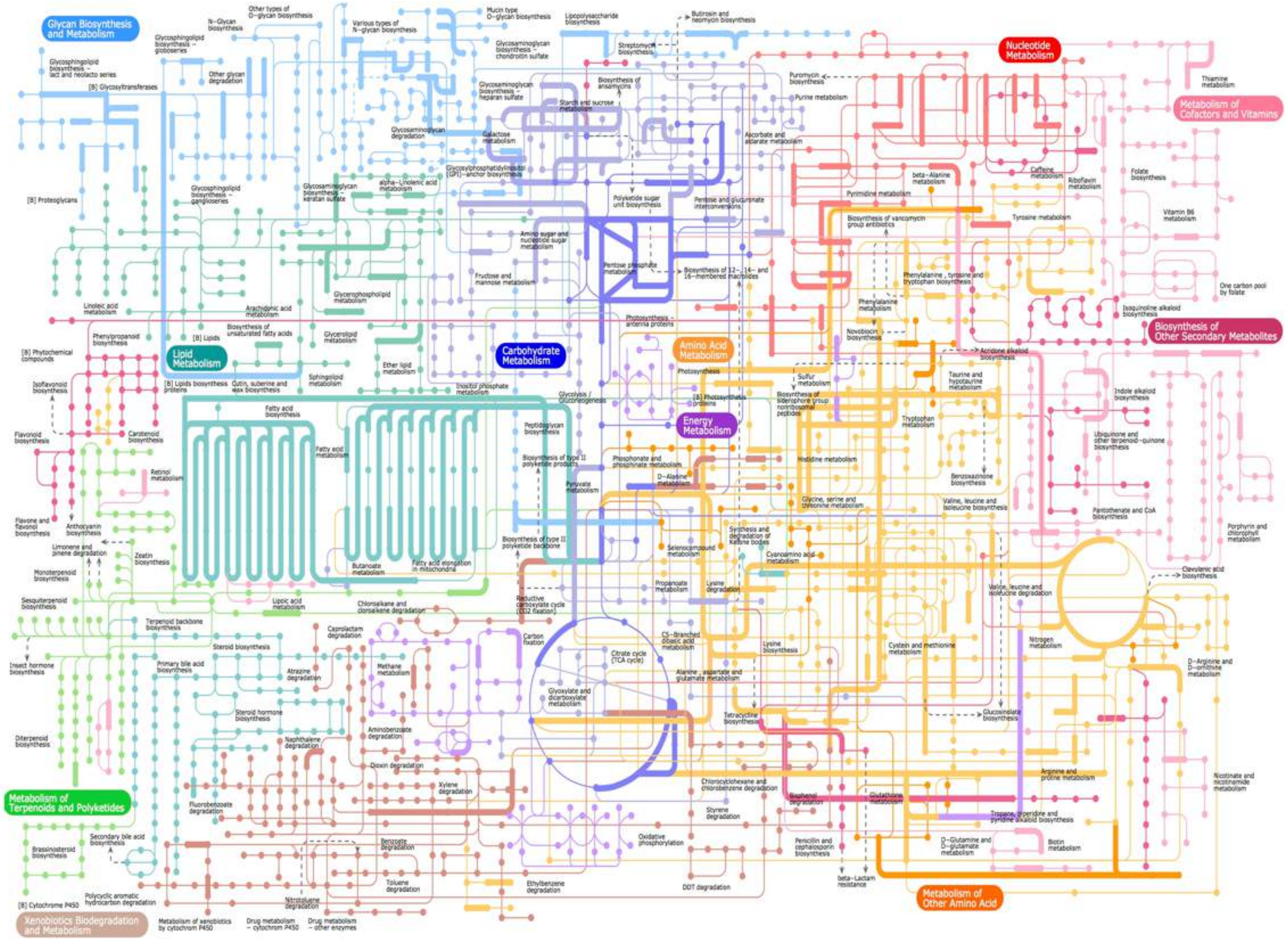
iCeMS-iTHEMS Joint Workshop on Interdisciplinary Biology

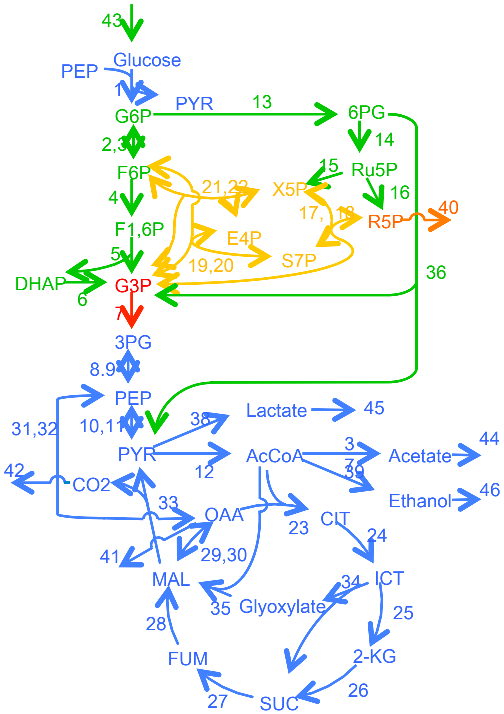
Mochizuki A, Fiedler B. JTB (2015),
Okada T., Mochizuki A. PRL (2016)
Okada T., Mochizuki A. PRE (2017)
Okada T., Tsai JC, Mochizuki A arXiv:1711.00250



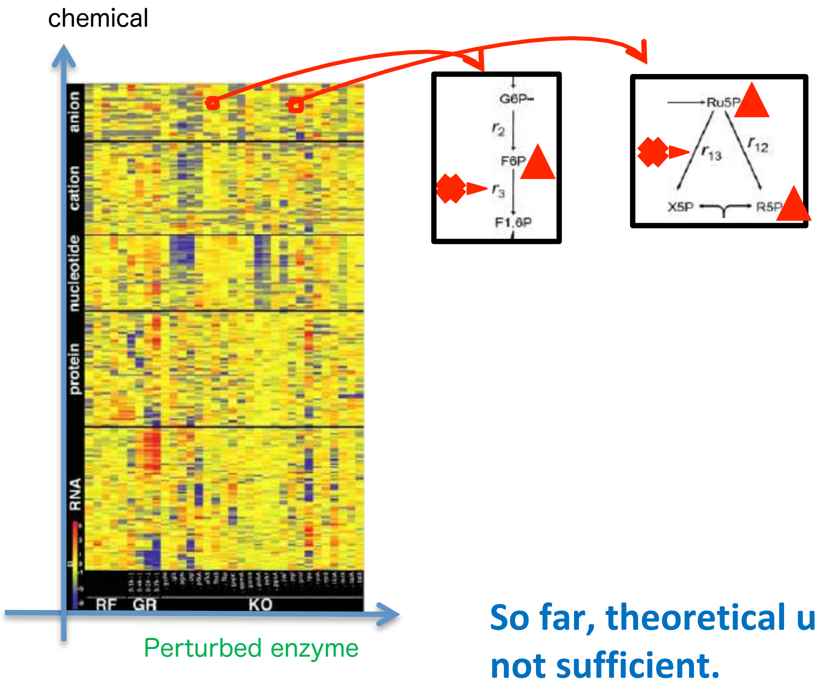
KEGG database

Enzyme knockdown experiment

Enzymes = proteins controlling reaction rates ("parameters").



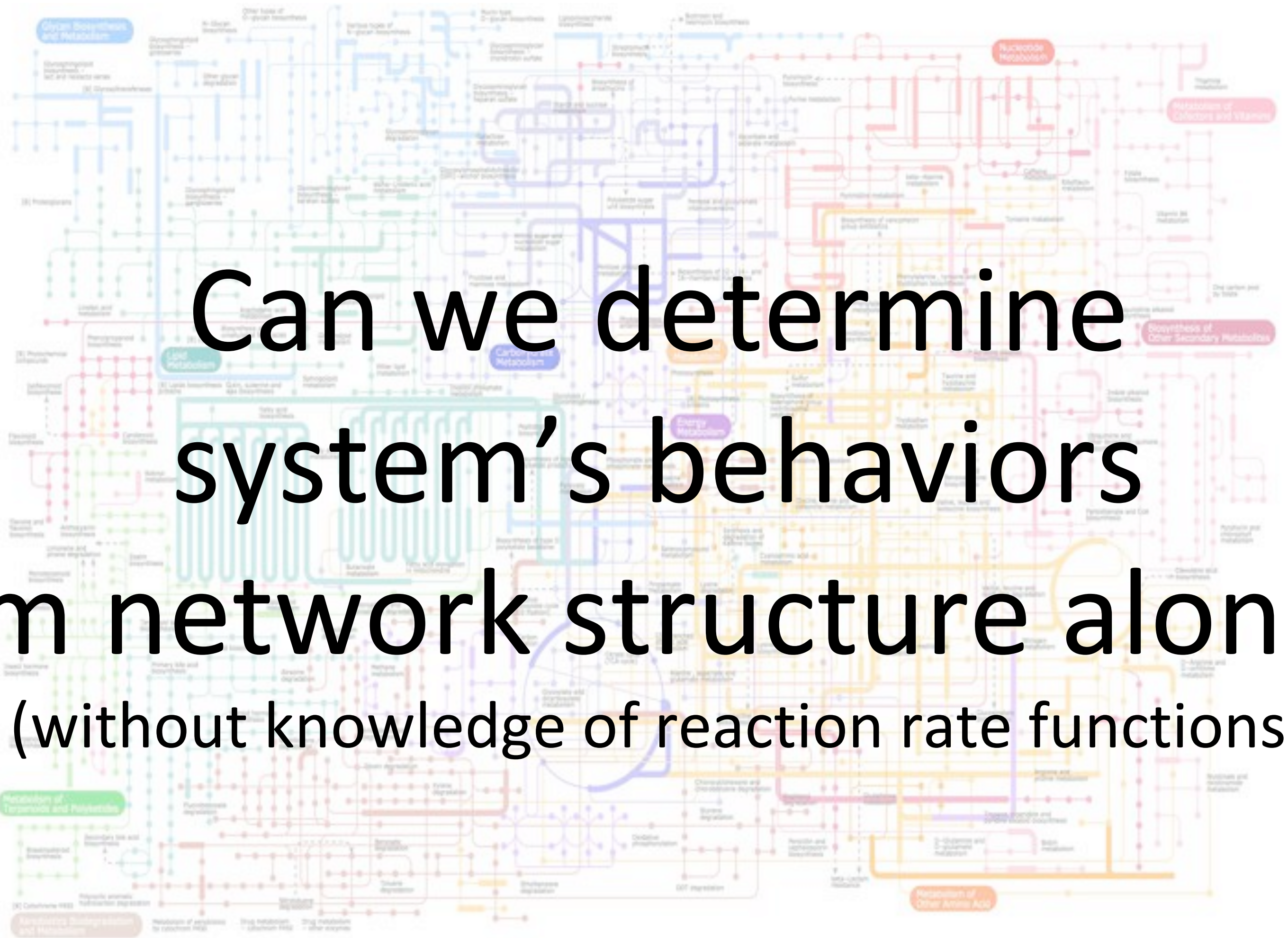
Reaction network of central carbon metabolism



Ishii *et al*. Science (2007)

So far, theoretical understandings are not sufficient.

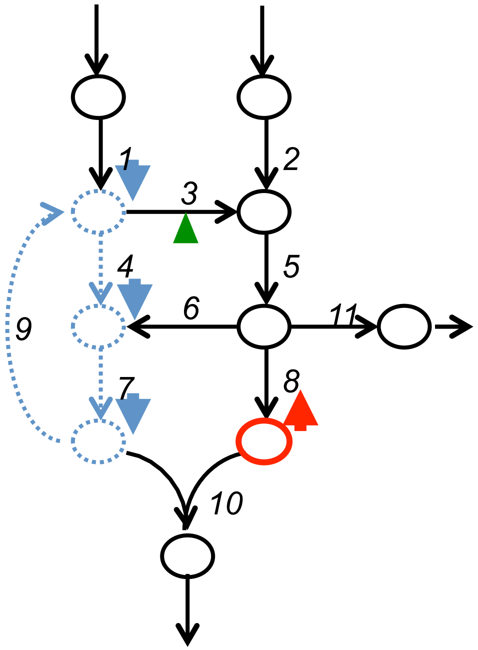
Reaction rate functions are not known precisely.



Can we determine system's behaviors from network structure alone???

(without knowledge of reaction rate functions)

OUTLINE



(1) Responses are determined from network structures

(2) Theorem connecting responses and network topology

(3) Bifurcation phenomena

Chemical Reaction systems Dynamics

Concentration of chemical *m*

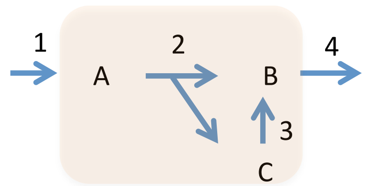
Rate (速度) of reaction *i*

$$\frac{dx_m}{dt} = \sum_i S_{mi} W_i(k_i, x)$$

Stoichiometric matrix
(化学量論行列)

parameter
(e.g. enzyme)

<u>example</u>



$$\frac{d}{dt}\begin{pmatrix} x_A \\ x_B \\ x_C \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & 1 & -1 \\ 0 & 1 & -1 & 0 \end{pmatrix} \begin{pmatrix} W_1(k_1) \\ W_2(k_2, x_A) \\ W_3(k_3, x_C) \\ W_4(k_4, x_B) \end{pmatrix}$$

stoichiometric matrix

<u>E.g.</u>

mass action type | Michaelis-Menten type

$W_2 = k_2 x_A$ | $W_2 = \frac{k_2 x_A}{x_A + K}$

We do not assume specific kinetics
because <u>we do not know the actual kinetics in living cells</u>

Q. **How does the steady state respond to parameter perturbation?** $\dfrac{\partial \bar{x}_m}{\partial k_j}$

A. Qualitative response is determined from network structure alone.

$$\left\{\begin{array}{l} \sum_i S_{mi} W_i(k_i, \bar{x}) = 0 \\ \sum_i S_{mi} W_i(k_i + \delta k, \bar{x} + \delta \bar{x}) = 0 \end{array}\right.$$

$$A \equiv \left(\begin{array}{c|c} J & \ker S \end{array} \right) \quad \Rightarrow \quad \boxed{\frac{\partial \bar{x}_m}{\partial k_j} = -(A^{-1})_{mj}}$$

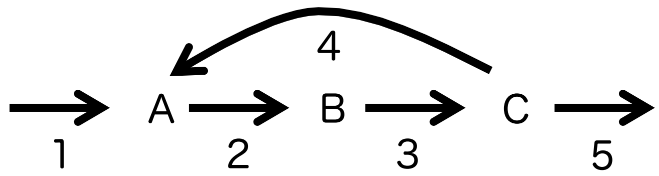
$$J_{im} = \frac{\partial W_i}{\partial x_m} = \begin{cases} + & (m \in \text{substrate}) \\ 0 & (\text{otherwise}) \end{cases}$$

※ The non-zero distribution in ***A*** is determined from network structure.

Example of a small network

$$\frac{dx_m}{dt} = \sum_i S_{mi} W_i(k_i, x)$$

$$A \equiv \left(\begin{array}{c|c} \dfrac{\partial W_i}{\partial x_m} & -\mathrm{ker} S \end{array} \right)$$



$$A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} \mathrm{A} & \mathrm{B} & \mathrm{C} & \mathrm{ker1} & \mathrm{ker2} \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & -1 & 0 \\ J_{2A} & 0 & 0 & -1 & -1 \\ 0 & J_{3B} & 0 & -1 & -1 \\ 0 & 0 & J_{4C} & 0 & -1 \\ 0 & 0 & J_{5C} & -1 & 0 \end{pmatrix} \end{array} \quad J_{im} = \frac{\partial W_i}{\partial x_m}$$

invert

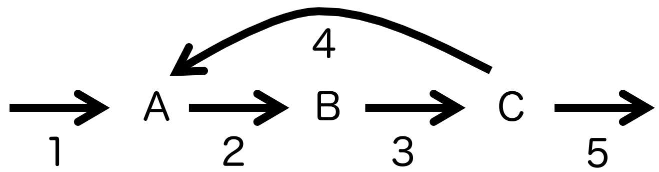
$$\begin{array}{c|ccccc} \text{perturbed reaction} & \Delta \mathrm{A} & \Delta \mathrm{B} & \Delta \mathrm{C} & \Delta \mathrm{ker1} & \Delta \mathrm{ker2} \end{array}$$

$$\begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{pmatrix} -\frac{J_{4C}+J_{5C}}{J_{2A}J_{5C}} & -\frac{J_{4C}+J_{5C}}{J_{3B}J_{5C}} & -\frac{1}{J_{5C}} & -1 & -\frac{J_{4C}}{J_{5C}} \\ \frac{1}{J_{2A}} & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{J_{3B}} & 0 & 0 & 0 \\ -\frac{1}{J_{2A}} & -\frac{1}{J_{3B}} & 0 & 0 & -1 \\ \frac{J_{4C}}{J_{2A}J_{5C}} & \frac{J_{4C}}{J_{3B}J_{5C}} & \frac{1}{J_{5C}} & 0 & \frac{J_{4C}}{J_{5C}} \end{pmatrix}$$

Example of a small network

$$\frac{dx_m}{dt} = \sum_i S_{mi} W_i(k_i, x)$$

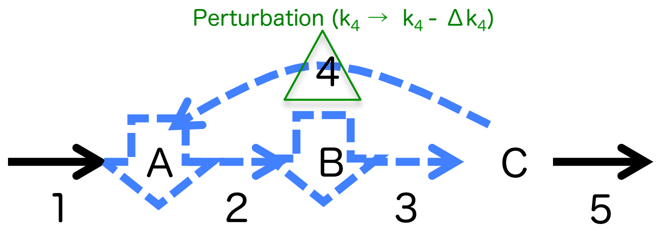
$$A \equiv \left(\frac{\partial W_i}{\partial x_m} \;\middle|\; -\mathrm{ker} S \right)$$

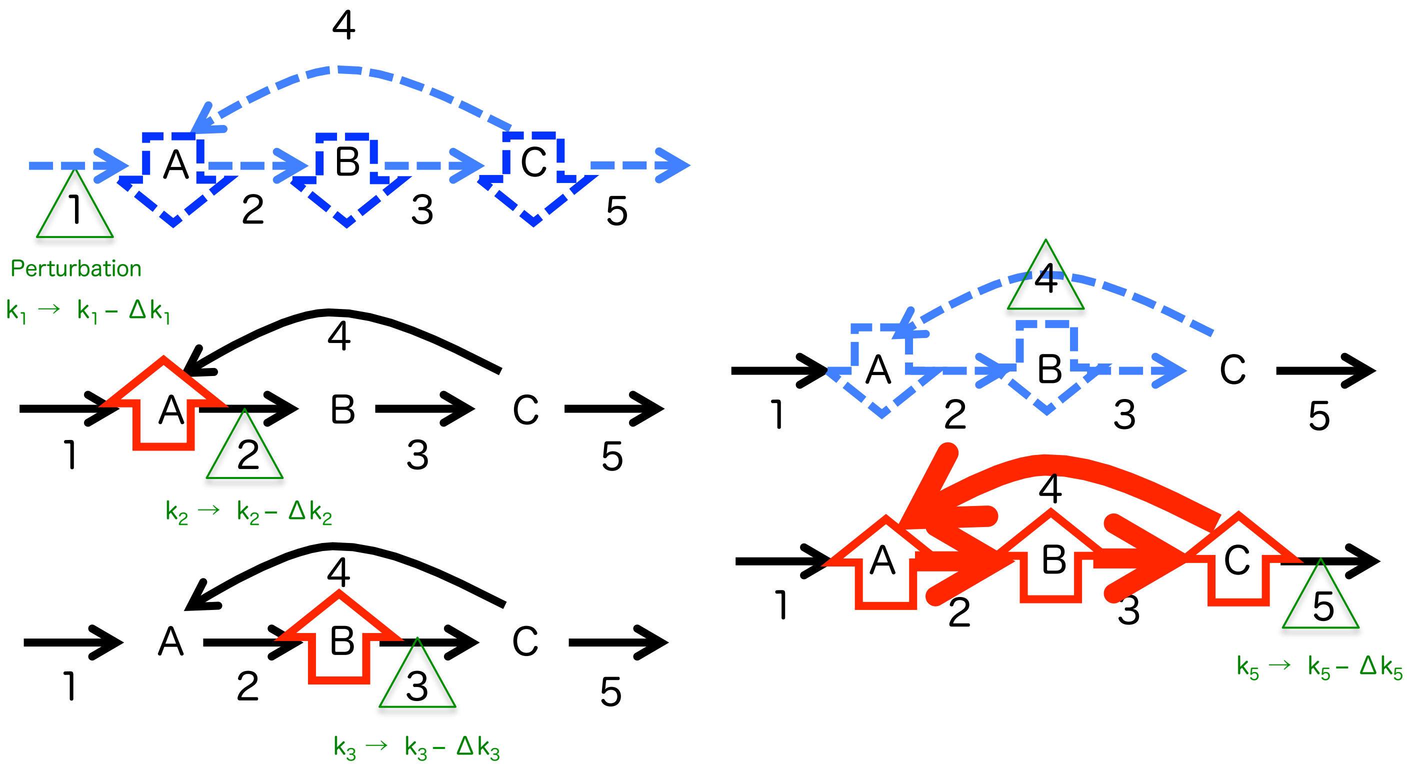


$$A = \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} A & B & C & \mathrm{ker1} & \mathrm{ker2} \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & -1 & 0 \\ J_{2A} & 0 & 0 & -1 & -1 \\ 0 & J_{3B} & 0 & -1 & -1 \\ 0 & 0 & J_{4C} & 0 & -1 \\ 0 & 0 & J_{5C} & -1 & 0 \end{pmatrix} \end{array} \qquad J_{im} = \frac{\partial W_i}{\partial x_m}$$

invert

$$\begin{array}{c} \text{perturbed reaction} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} \Delta A & \Delta B & \Delta C & \Delta \mathrm{ker1} & \Delta \mathrm{ker2} \end{array} \\ \begin{pmatrix} - & - & - & - & - \\ + & 0 & 0 & 0 & 0 \\ 0 & + & 0 & 0 & 0 \\ - & - & 0 & 0 & - \\ + & + & + & 0 & + \end{pmatrix} \end{array}$$



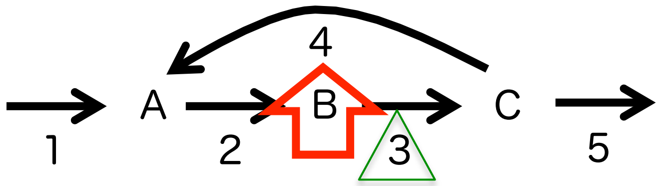


$$\frac{dx_m}{dt} = \sum_i S_{mi}\, W_i(k_i, x)$$

$$A \equiv \left(\begin{array}{c|c} \dfrac{\partial W_i}{\partial x_m} & -\mathrm{ker} S \end{array} \right)$$

$$\mathbf{A}^{-1} = \begin{array}{c} \text{perturbed reaction} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} \Delta A & \Delta B & \Delta C & \Delta \mathrm{ker1} & \Delta \mathrm{ker2} \end{array} \\ \begin{pmatrix} - & - & - & - & - \\ + & 0 & 0 & 0 & 0 \\ 0 & + & 0 & 0 & 0 \\ - & - & 0 & 0 & - \\ + & + & + & 0 & + \end{pmatrix} \end{array}$$

Numerical demonstration

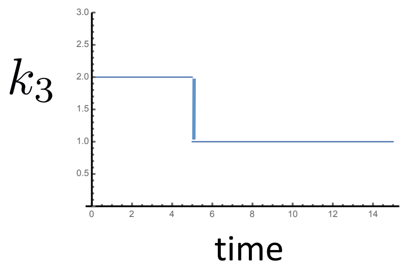


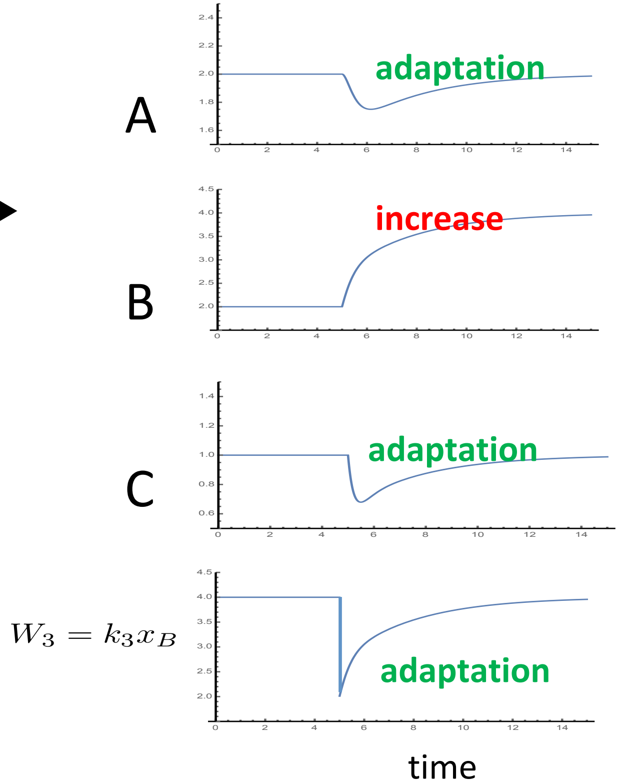
$$\dot{x}_A = k_1 - k_2 x_A + k_4 x_C$$

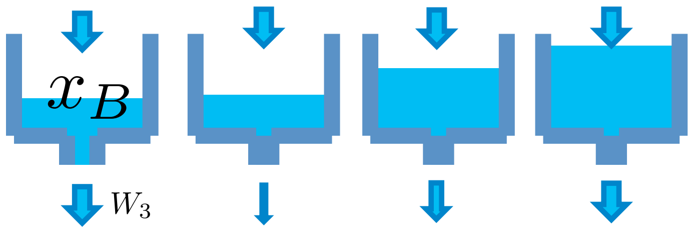
$$\dot{x}_B = k_2 x_A - k_3 x_B$$

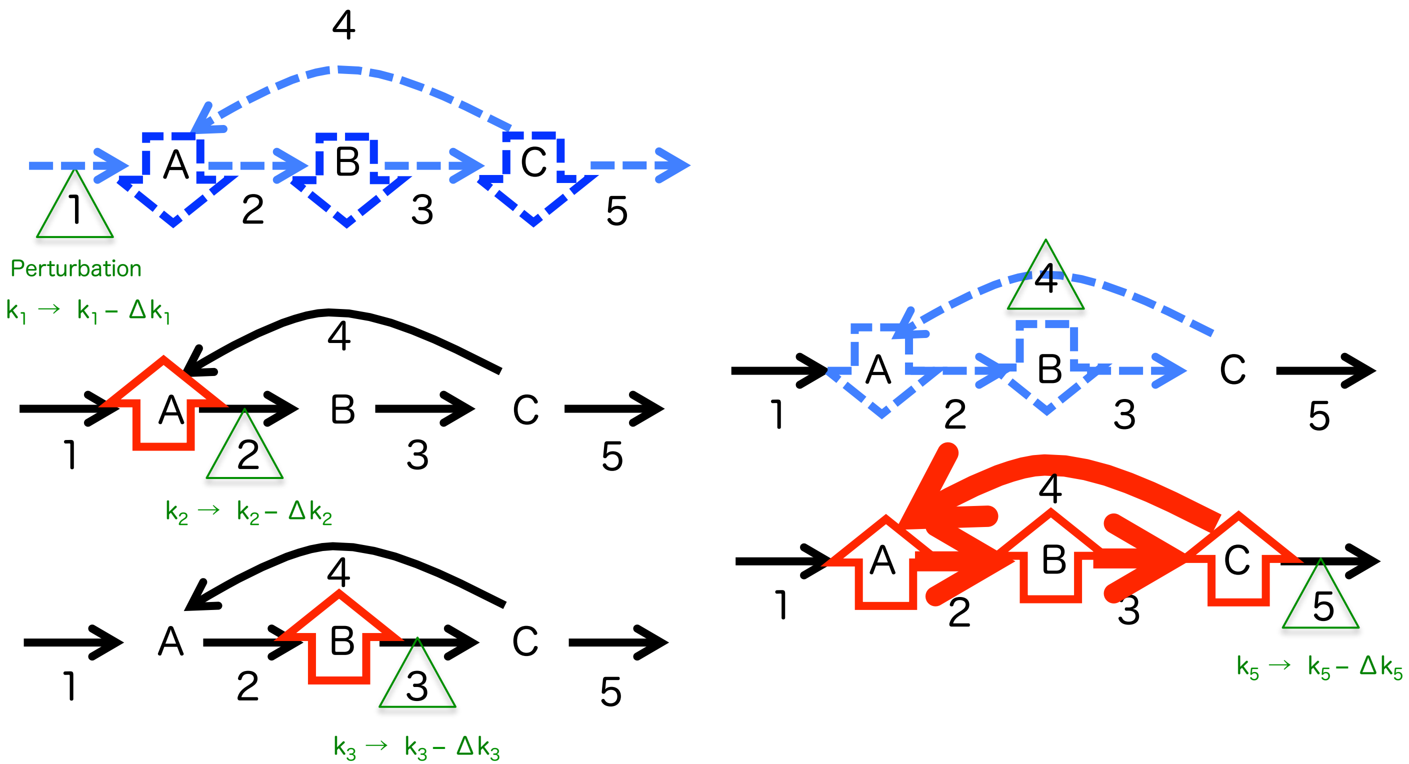
$$\dot{x}_C = k_3 x_B - k_4 x_C - k_5 x_C$$

$$k_3 = k_3^0 - k_3' \times \Theta(t - t_{perturb})$$









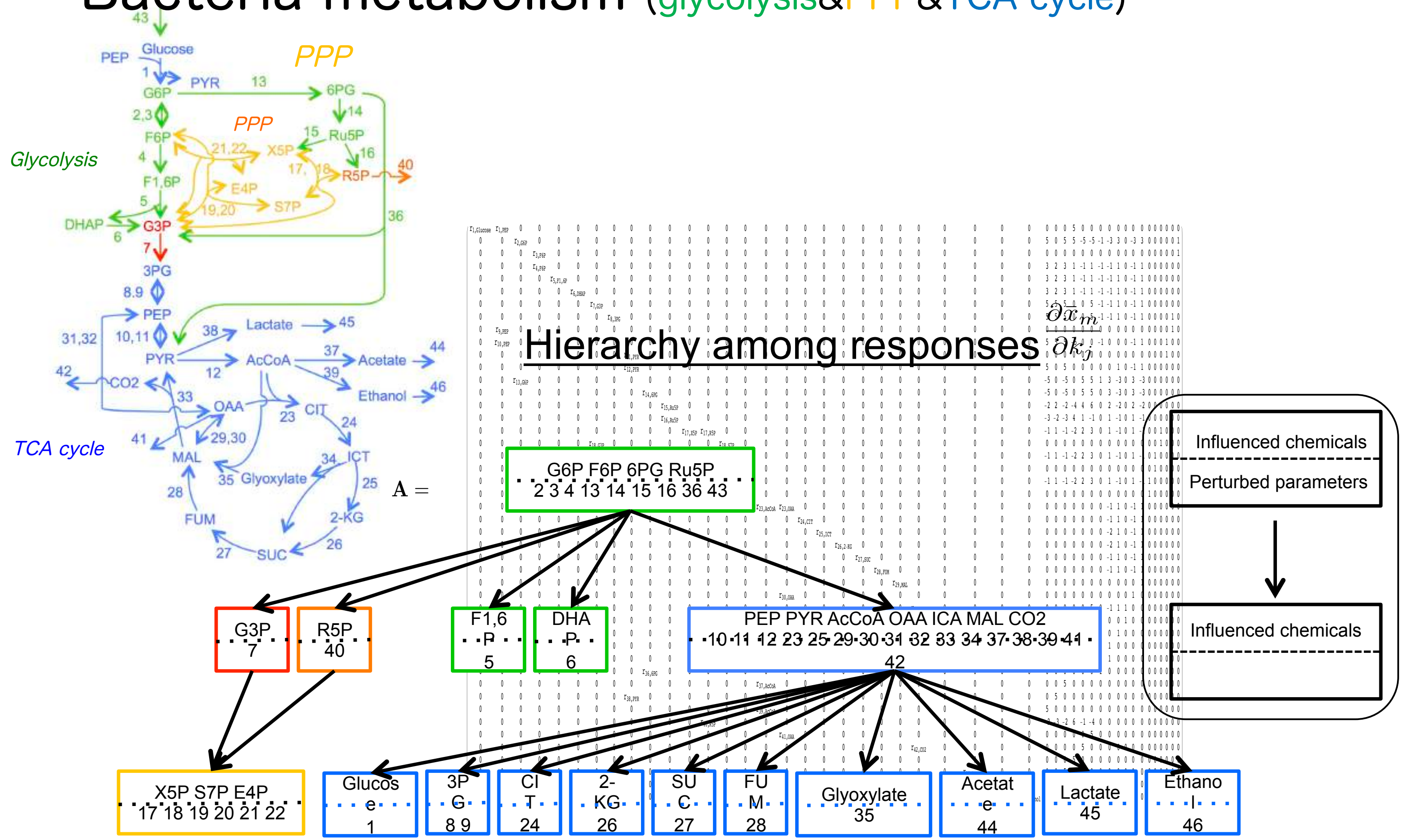
$$\frac{dx_m}{dt} = \sum_i S_{mi} W_i(k_i, x)$$

$$A \equiv \left(\begin{array}{c|c} \dfrac{\partial W_i}{\partial x_m} & -\ker S \end{array} \right)$$

$$\mathbf{A}^{-1} = \begin{array}{c} \text{perturbed reaction} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{ccccc} \Delta A & \Delta B & \Delta C & \Delta \mathrm{ker1} & \Delta \mathrm{ker2} \end{array} \\ \begin{pmatrix} - & - & - & - & - \\ + & 0 & 0 & 0 & 0 \\ 0 & + & 0 & 0 & 0 \\ - & - & 0 & 0 & - \\ + & + & + & 0 & + \end{pmatrix} \end{array}$$

Bacteria metabolism (glycolysis&PPP&TCA cycle)

Hierarchy among responses $\frac{\partial \bar{x}_m}{\partial k_j}$



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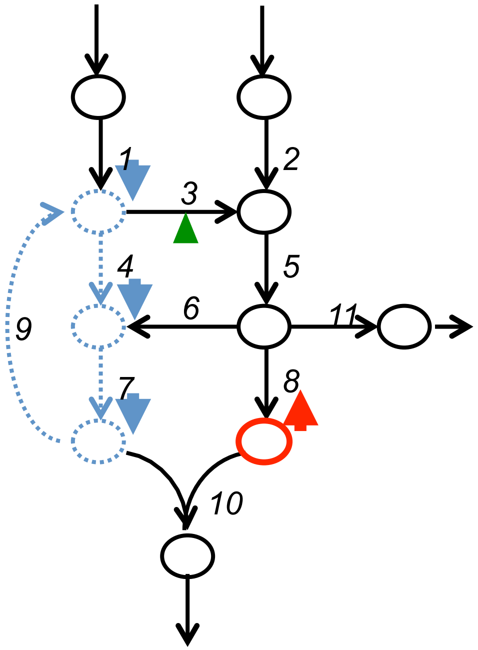


(1) Responses are determined from network structures

(2) Theorem connecting responses and network topology

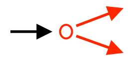
(3) Bifurcation phenomena

限局則 (*the law of localization)*

Okada T. & Mochizuki A. (2016) Phys. Rev. Lett. 117, 048101.

・Take a subnetwork $\Gamma =$ (chemicals $\mathcal{M}$, reactions $\mathcal{R}$) satisfying

(i) $\mathcal{R}$ includes all reaction edges emanating from $\mathcal{M}$.



(ii) $\chi(\Gamma) \equiv |\mathcal{M}| - |\mathcal{R}| + \#cycles \text{ in } \Gamma = 0$

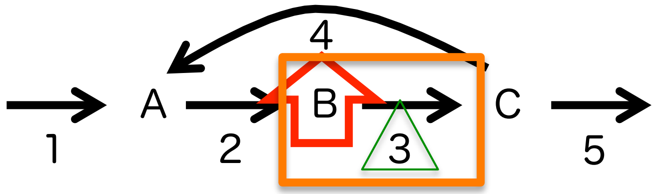
Γ : *buffering structure (BS), 緩衝構造*.

・Any parameters in a BS do not influence chemicals outside of the BS.

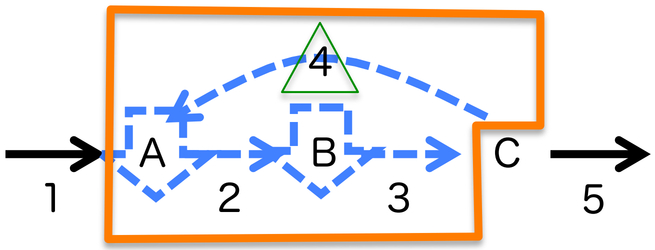
BS corresponds to a square submatrix

$$\mathbf{A} = \begin{array}{cc} & \overbrace{\phantom{\mathbf{A}_\Gamma}}^{|\mathcal{M}| + \#(cycles)} \\ |\mathcal{R}| & \begin{pmatrix} \boxed{\mathbf{A}_\Gamma} & * \\ 0 & \mathbf{A}_{\bar{\Gamma}} \end{pmatrix} \end{array} \xrightarrow{\text{inverse}} \left(\begin{array}{c|c} \mathbf{A}_\Gamma^{-1} & * \\ \hline \mathbf{0} & \mathbf{A}_{\bar{\Gamma}}^{-1} \end{array}\right)$$

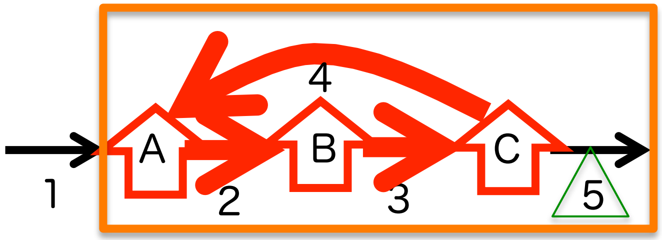
$$\chi(\Gamma) \equiv |\mathcal{M}| - |\mathcal{R}| + \#\text{cycle in } \Gamma \overset{???}{=} 0$$



$$\chi = 1 - 1 + 0$$

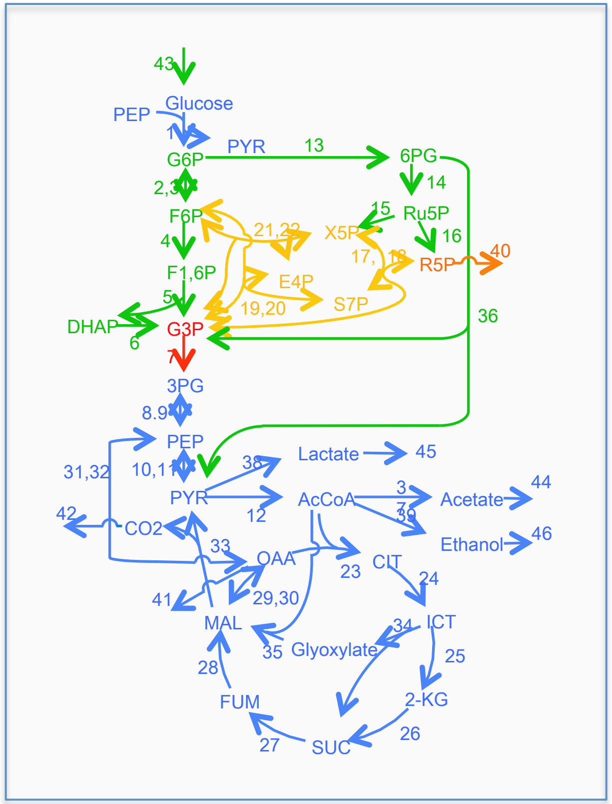


$$\chi = 2 - 3 + 1$$

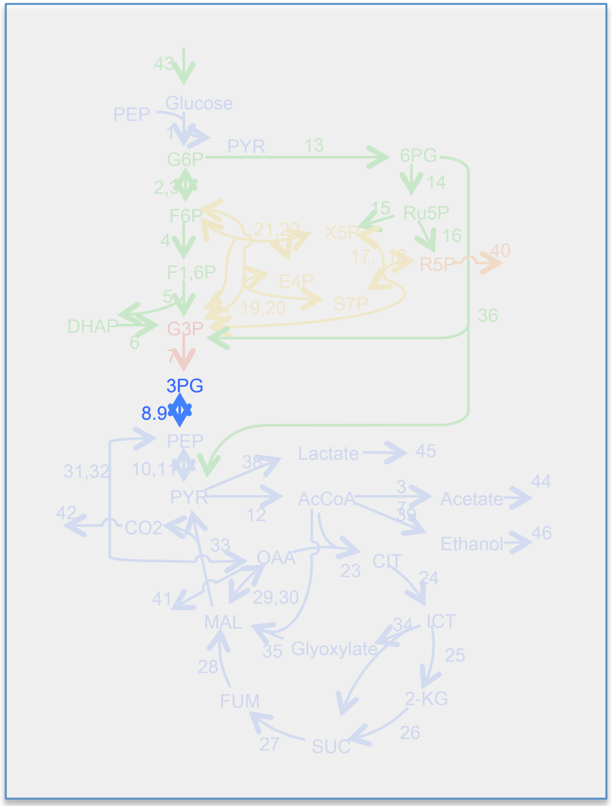


$$\chi = 3 - 4 + 1$$

$$\chi(\Gamma) \equiv \#\text{metabolite} - \#\text{reac.} + \#\text{cycle} \overset{???}{=} 0$$

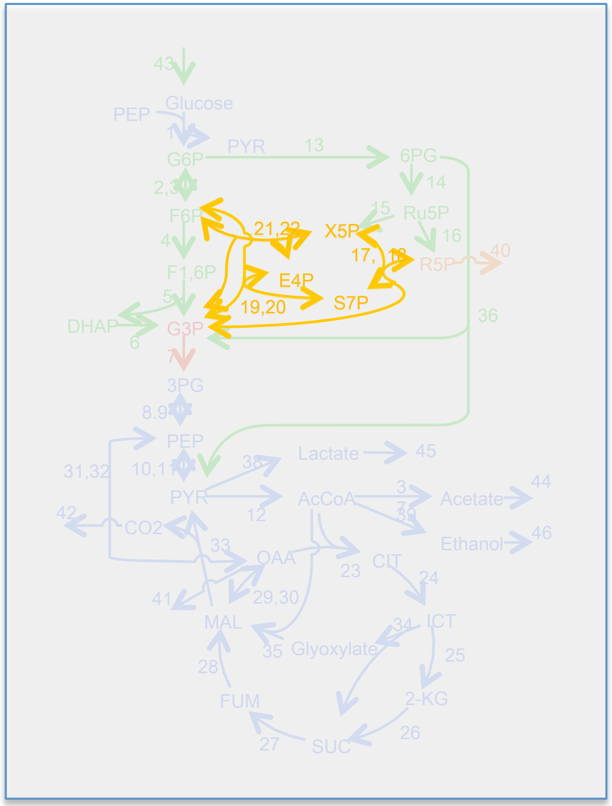


$$\chi(\Gamma) \equiv \#\text{metabolite} - \#\text{reac.} + \#\text{cycle} \overset{???}{=} 0$$

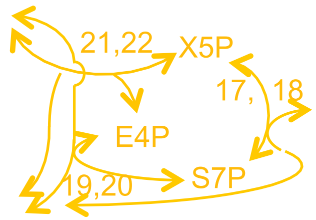


$$\chi = 1 - 2 + 1 = 0$$

$$\chi(\Gamma) \equiv \#\text{metabolite} - \#\text{reac.} + \#\text{cycle} \overset{???}{=} 0$$

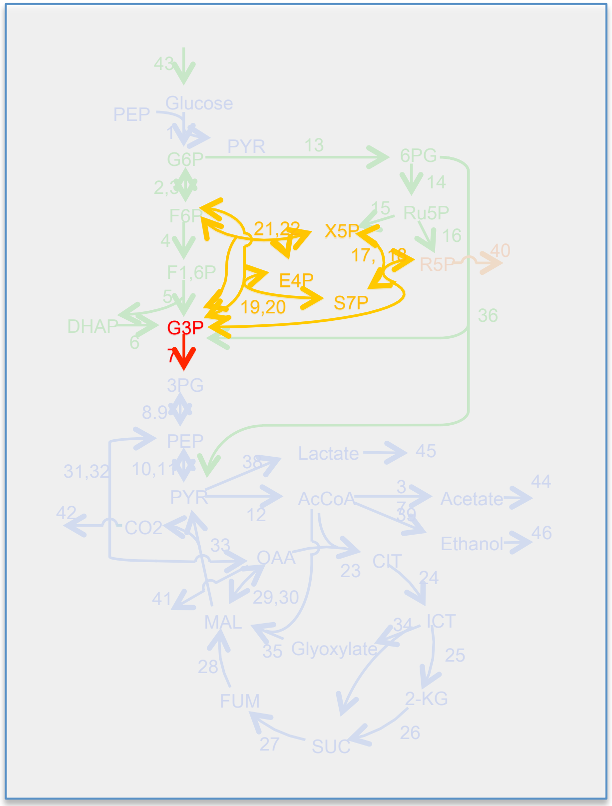


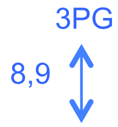
$$\chi = 1 - 2 + 1 = 0$$



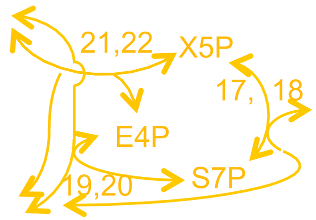
$$\chi = 3 - 6 + 3 = 0$$

$$\chi(\Gamma) \equiv \#\text{metabolite} - \#\text{reac.} + \#\text{cycle} \overset{???}{=} 0$$

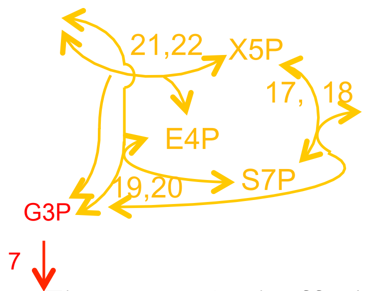




$$\chi = 1 - 2 + 1 = 0$$

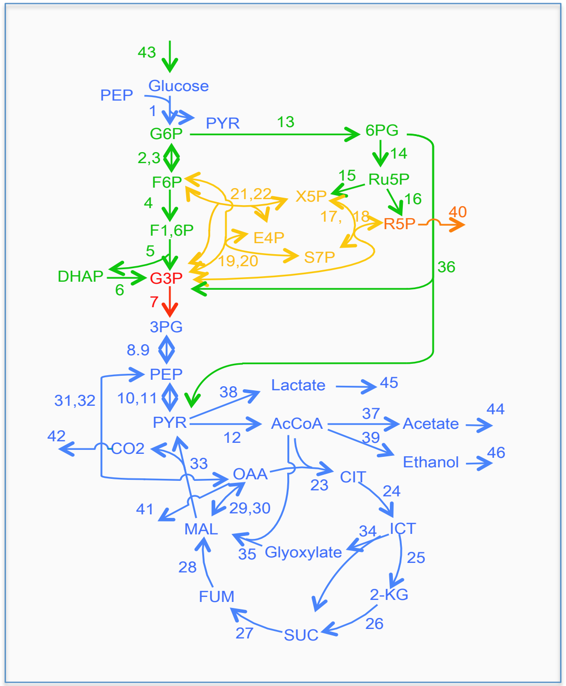


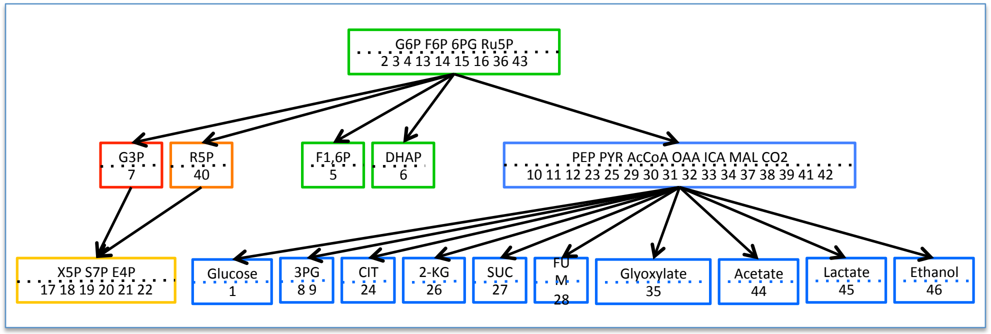
$$\chi = 3 - 6 + 3 = 0$$



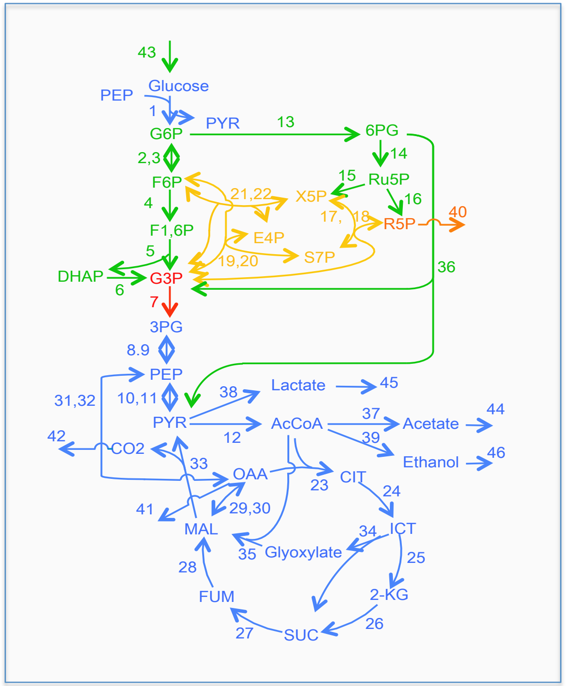
$$\chi = 4 - 7 + 3 = 0$$

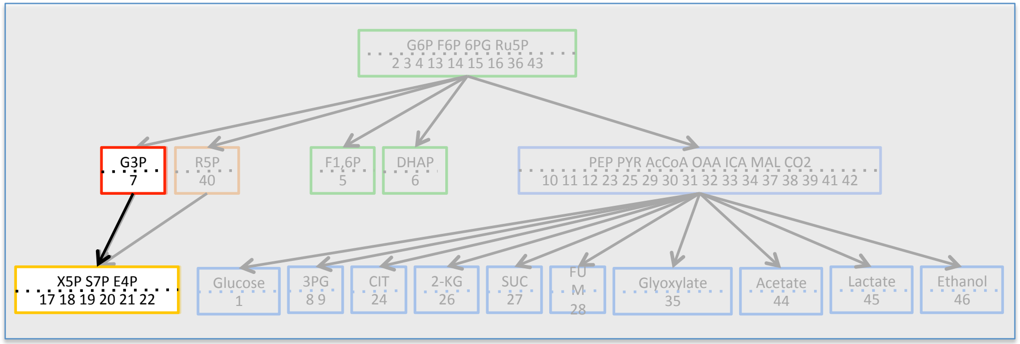
note: There are 17 buffering structures in total.





A hierarchy appears
from a nest of buffering structures





A hierarchy appears
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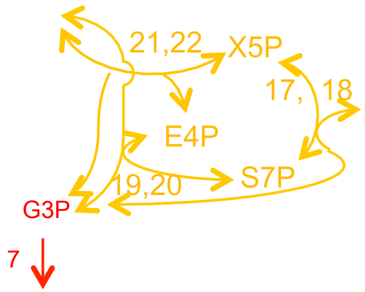
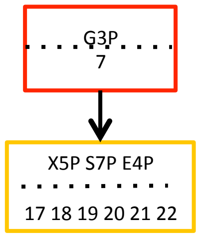
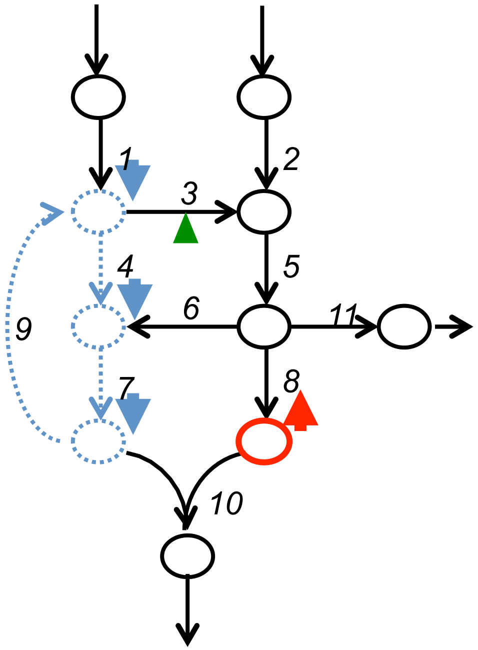






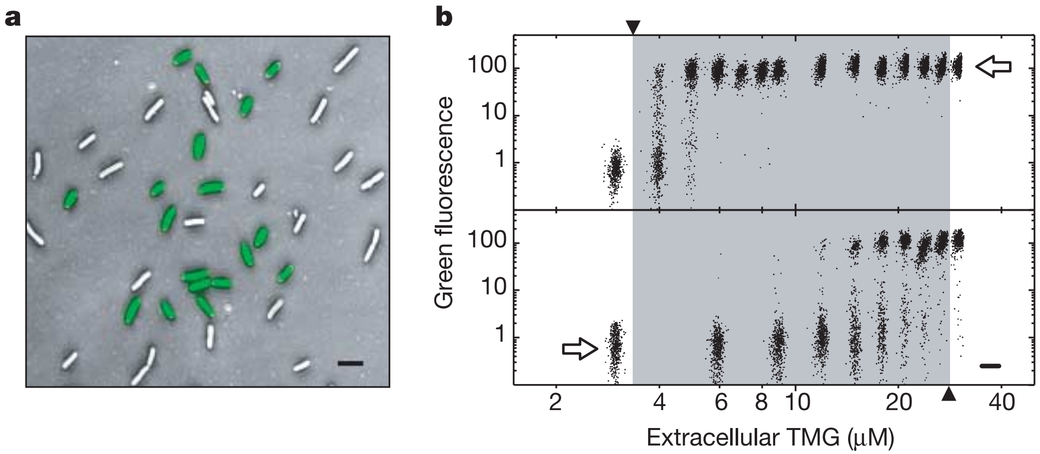
(1) Response patterns from network structures

(2) Theorem connecting responses and network topology

(3) Bifurcation phenomena and network structures

Plasticity and Bifurcation Phenomena

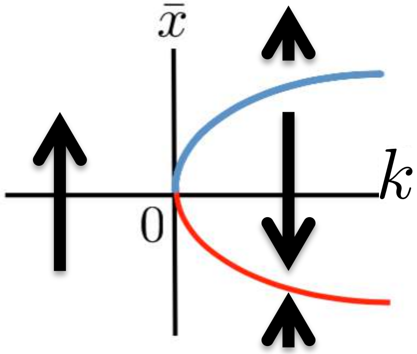
Ertugrul M. Ozbudak, et al, Nature, 2004



The concentration of the protein (necessary to utilize the nutrient) change discontinuously.

Bifurcation theory

$$\frac{dx}{dt} = f(x) = -k + x^2$$



$$J = \frac{\partial f}{\partial x}\Big|_{x=x^*} = 2x^* = \pm 2\sqrt{k}$$

At bifurcation point (k=0), the Jacobian *J* becomes 0.

In a multivariate case,
bif point ⇔ det J =0

$$\dot{x} = f(x,y) \qquad \mathbf{J} = \left.\begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial y} \end{pmatrix}\right|_{\vec{x}=\vec{x}^*}$$
$$\dot{y} = g(x,y)$$

$$\det \mathrm{J} = \frac{\partial f}{\partial x}\frac{\partial g}{\partial y} - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}$$

Bifurcation analysis based on the matrix A

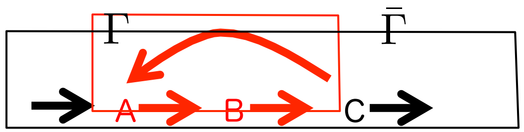
At bif. point, $\det \mathrm{J} = 0$

$$\mathbf{A} = \left(\frac{\partial \boldsymbol{r}}{\partial \boldsymbol{x}}\Big|_{\boldsymbol{x}=\boldsymbol{x}^*} \;\vdots\; \ker S \right)$$

$$\frac{d\mathbf{x}}{dt} := S\mathbf{r}(x)$$

$$\mathbf{J} := S\frac{\partial \mathbf{r}}{\partial \mathbf{x}}|_{x=x^*}$$

$$\boxed{\det \mathrm{J} = \det \mathrm{A}}$$



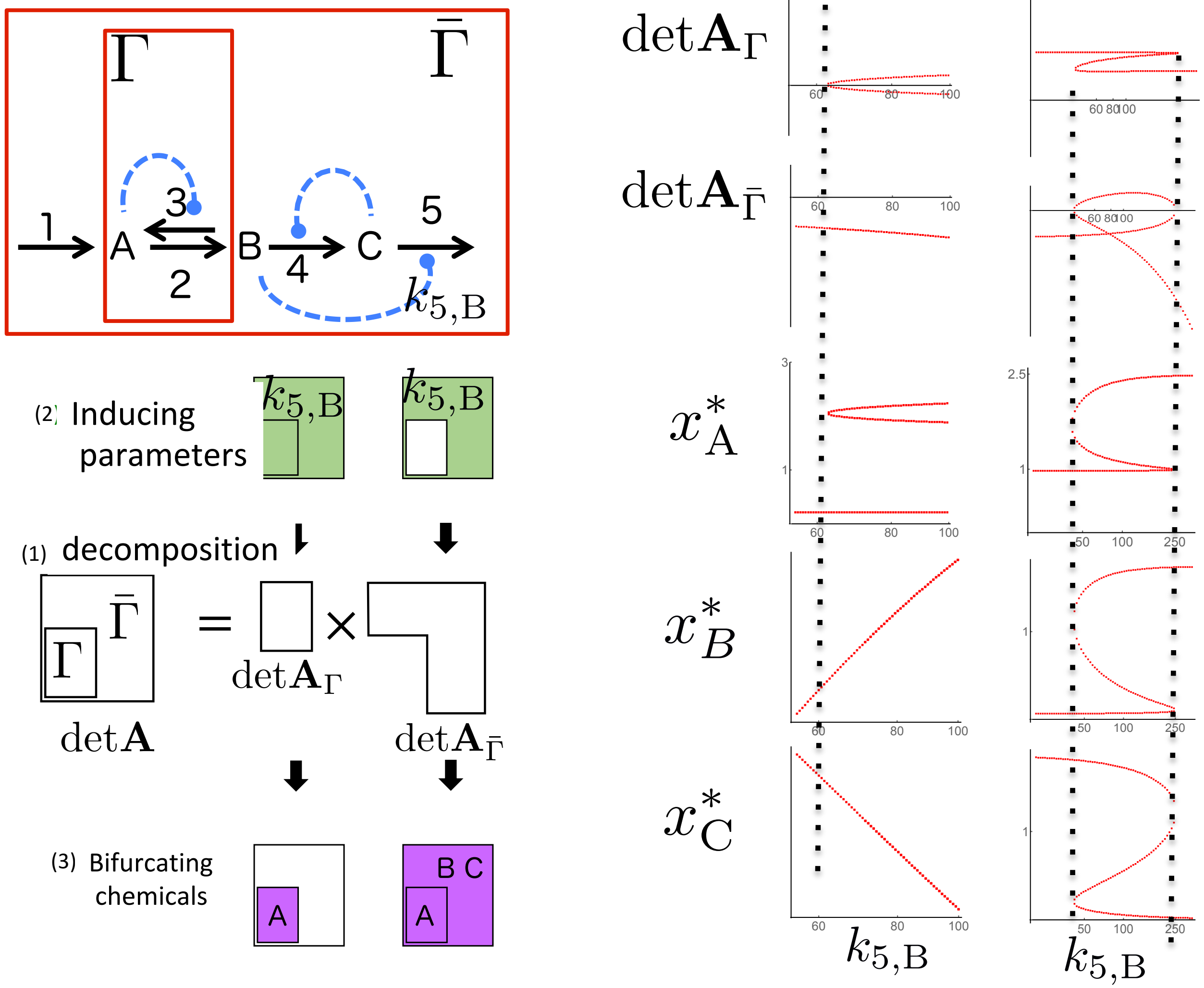
Buffering Structure

$$\mathbf{A} = \left(\begin{array}{c|c} \boxed{\mathbf{A}_\Gamma} & * \\ \hline 0 & \mathbf{A}_{\bar{\Gamma}} \end{array} \right)$$

$$\det \mathbf{A} = \det \mathbf{A}_\Gamma \times \det \mathbf{A}_{\bar{\Gamma}} = 0$$

decomposition

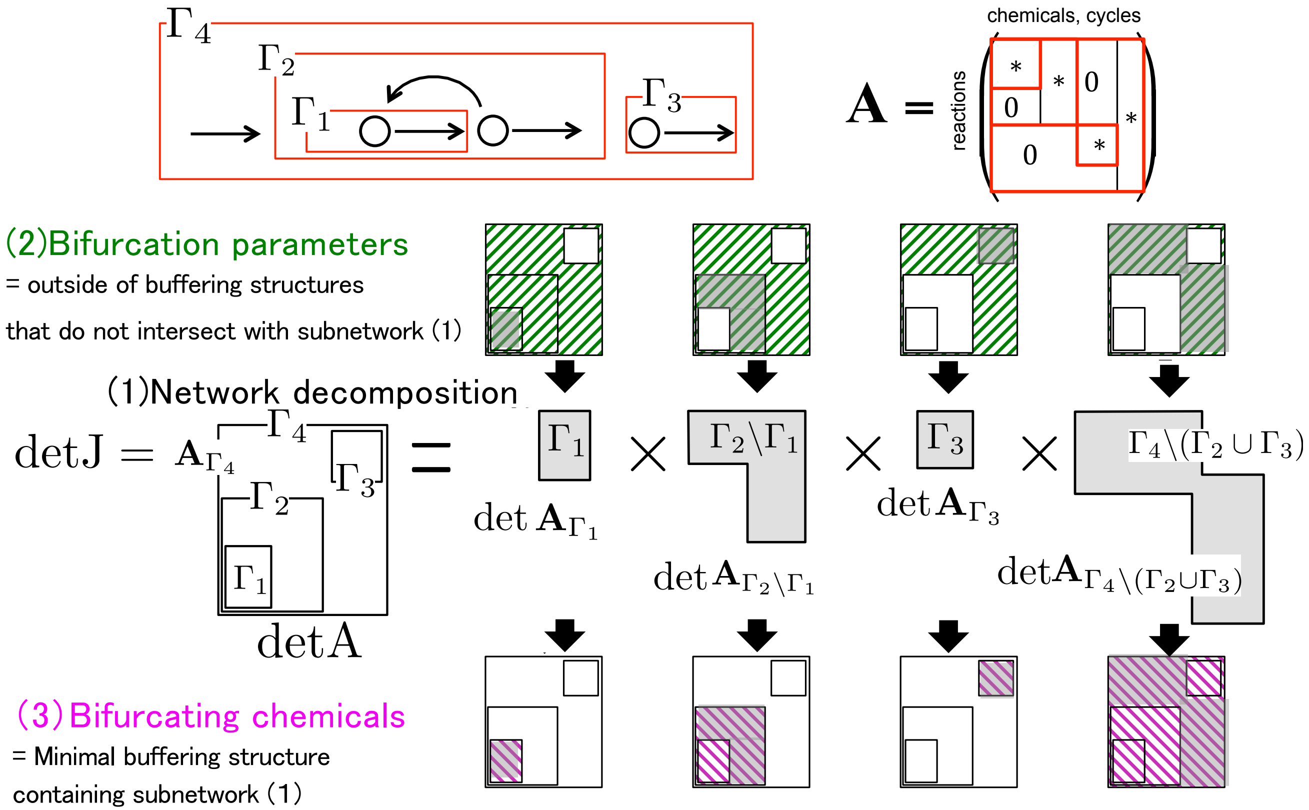
Example 1



Γ
Γ̄
1
A
3
2
B
4
C
5
$k_{5,B}$
(2) Inducing parameters
(1) decomposition
$\det \mathbf{A}$
$\det \mathbf{A}_\Gamma$
$\det \mathbf{A}_{\bar{\Gamma}}$
(3) Bifurcating chemicals
A
B C
x^*_A
x^*_B
x^*_C
60
80
100
50
250
2.5
3
1

Bifurcation analysis of reaction systems based on network structures

Okada T., Tsai JC, Mochizuki A. arXiv:1711.00250



Example. E.coli central carbon network

(2) Bifurcation parameters

(1) Network decomposition

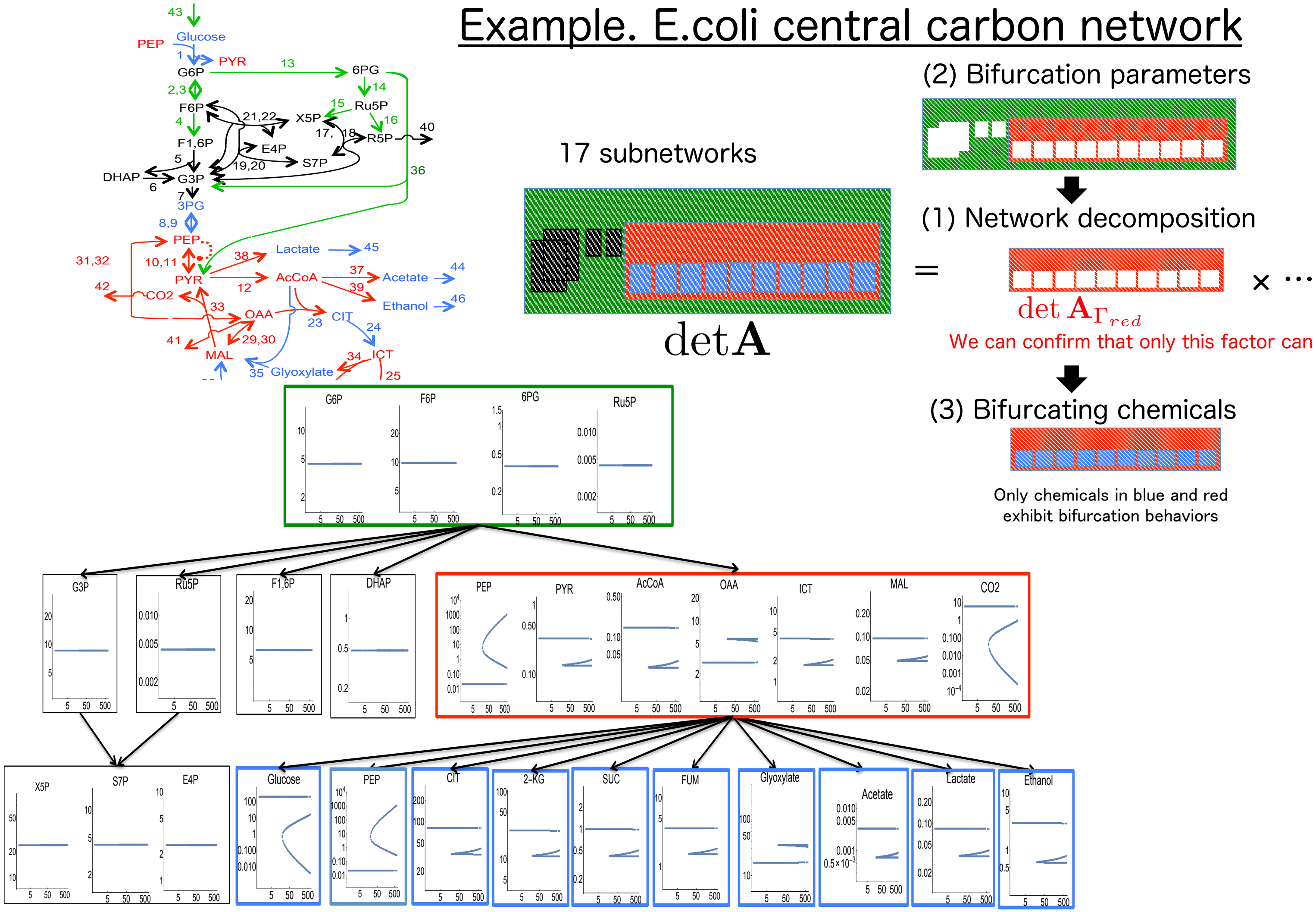
17 subnetworks

$\det \mathbf{A}$ = $\det \mathbf{A}_{\Gamma_{red}}$ × ⋯

We can confirm that only this factor can become zero

(3) Bifurcating chemicals

Only chemicals in blue and red exhibit bifurcation behaviors



Summary

Mochizuki A, Fiedler B. JTB (2015),
Okada T., Mochizuki A. PRL (2016)
Okada T., Mochizuki A. PRE (2017)

- Responses and network topology
  - Responses are determined from network topology
  - Buffering structures explain response patterns

- Bifurcation and network topology
  - *Det J = Det A*

Okada T., Tsai JC, Mochizuki A arXiv:1711.00250