

Reaction – perturbation and network topology in chemical reaction systems

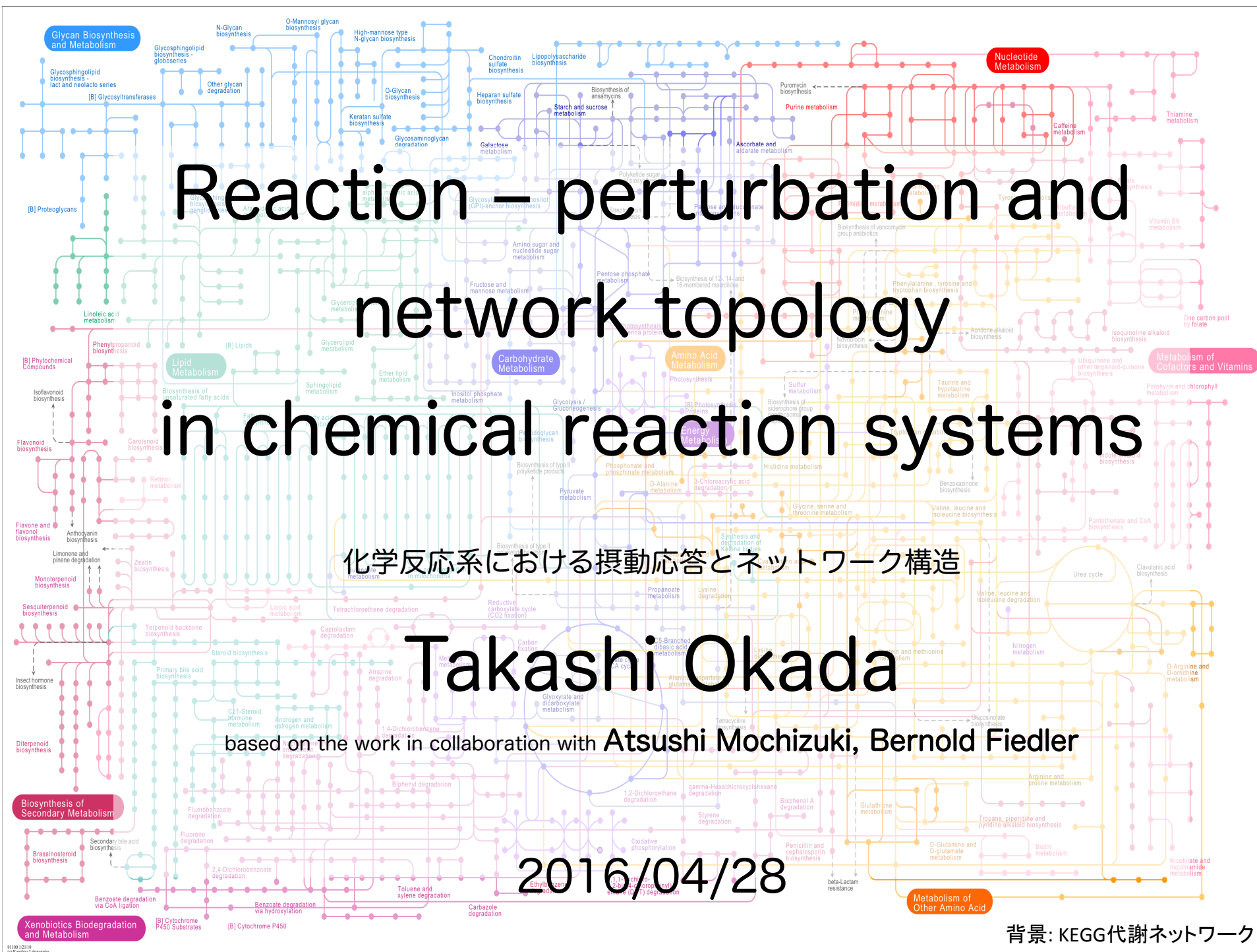
化学反応系における摂動応答とネットワーク構造

Takashi Okada

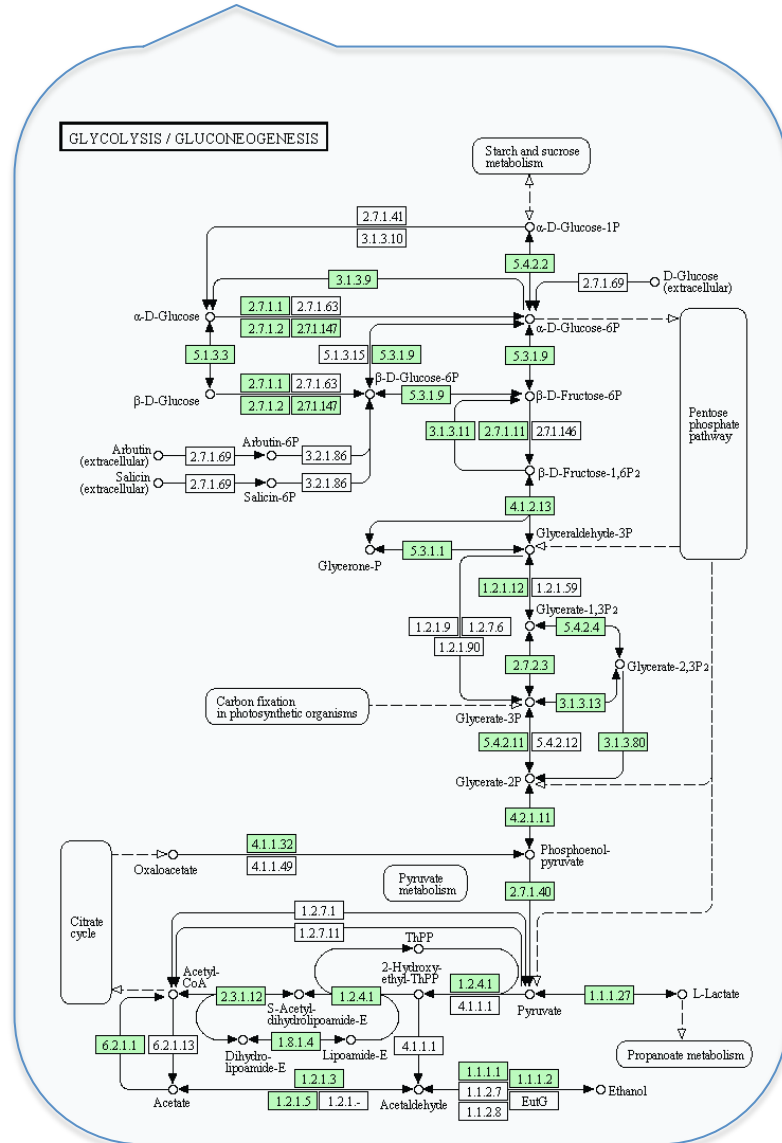
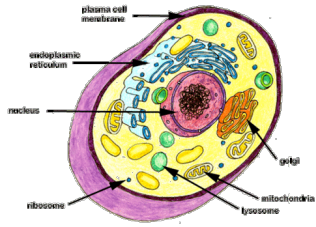
based on the work in collaboration with Atsushi Mochizuki, Bernold Fiedler

2016/04/28

背景: KEGG代謝ネットワーク



Introduction



- Metabolic network (代謝ネットワーク) : reactions producing energy, constructing cell components

node: metabolic molecules, edge: reactions

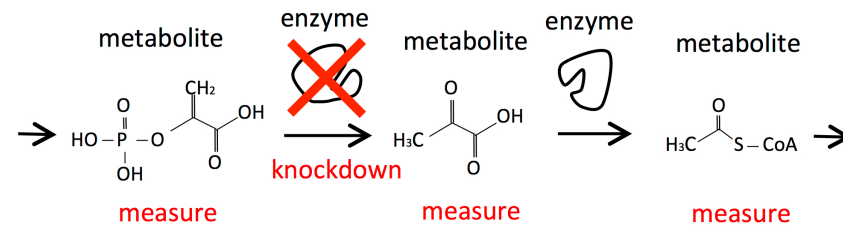
- Each reaction is catalyzed by specific enzyme (酵素によって触媒).



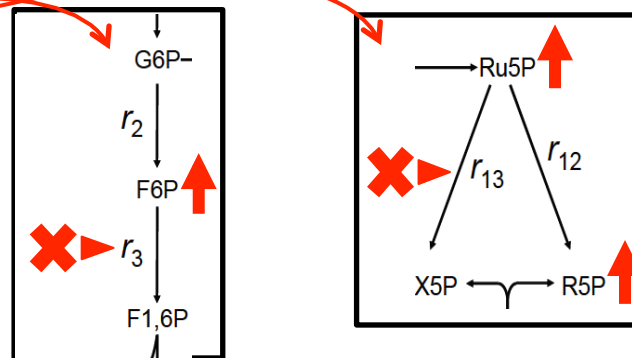
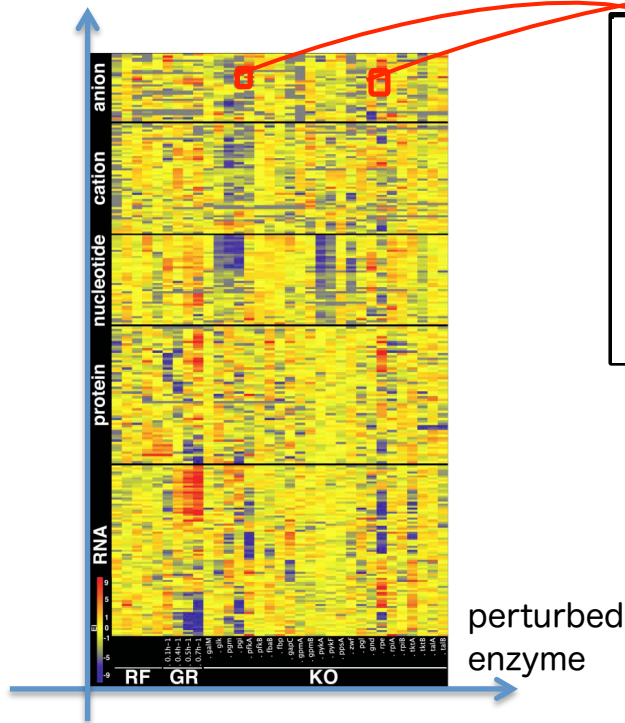
- How each enzyme influences the system?

Introduction

Experimental approach: 攪乱実験 (knockdown experiments)



molecule

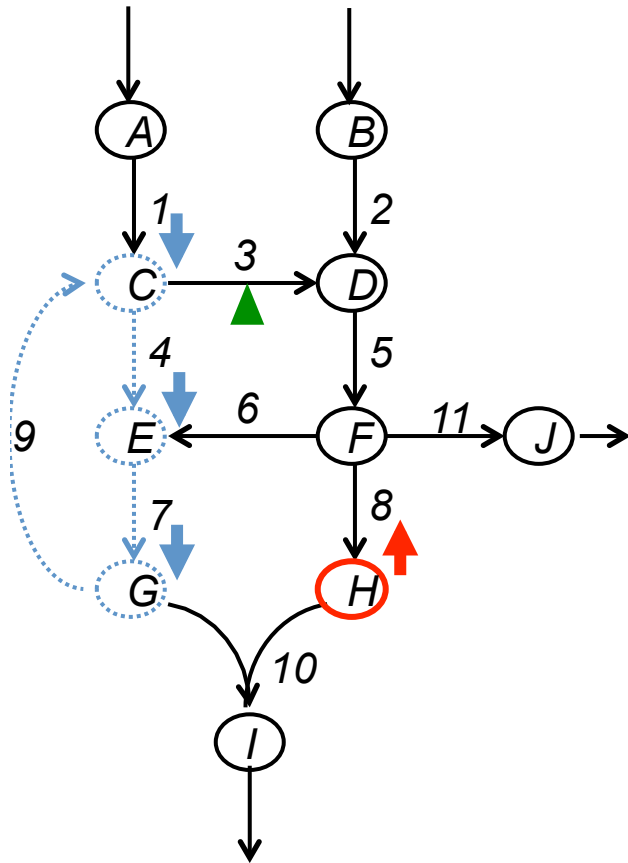


We want to construct theoretical frameworks for these experiments.

However, precise kinetics are unknown.

Ishii *et al.* Science (2007)

We found ...



(1) Network structure determines qualitative responses to perturbations.

(2) Patterns in responses.
- localization and hierarchy

(3) A theorem connecting network topology and system behaviors.

(4) Prediction of missing reactions in network

OUTLINE

1. Method
2. Example
3. Law of localization
4. Toward elucidating a true network

Dynamics of Chemical Reactions

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

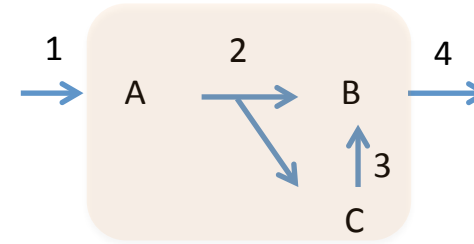
x_m : concentration of molecule m

W_i : flux of reaction i (fn. of substrates)

k_i : parameter such as enzyme amount

S_{mi} : Stoichiometric matrix

example



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

stoichiometric matrix

E.g.

mass action type

$$W_2 = k_2 x_A$$

Michaelis-Menten type

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

However, we do not assume specific kinetics

Q. How do concentrations (at steady state) change under enzyme knockdown (of reaction j)?

$$k_j \rightarrow k_j - \delta k$$

A. This can be answered from network structure alone !

- Steady state condition

$$\sum_i S_{mi} W_i(k_i, x) = 0 \quad (\text{before})$$

$$\sum_i S_{mi} W_i(k_i - \delta_{ij} \delta k, x + \delta x) = 0 \quad (\text{after})$$

$$A \equiv \left(\begin{array}{c} \text{sub-mat.} \\ J \end{array} \left| \begin{array}{c} \text{ker } S \end{array} \right. \right) \rightarrow \delta_j x_m = (A^{-1})_{mj} \rightarrow \text{flux } \delta_j W_i$$

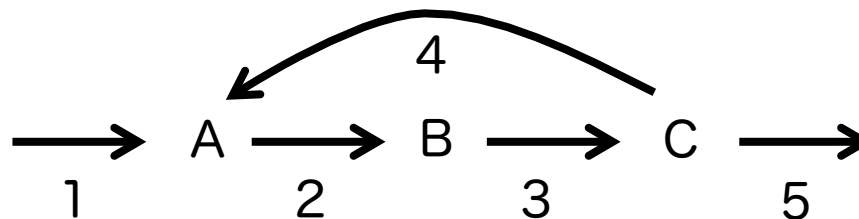
$$J_{im} = \frac{\partial W_i}{\partial x_m} = \begin{cases} + & (m \in \text{substrate}) \\ 0 & (\text{otherwise}) \end{cases}$$

※

non-zero distribution of A matrix.

$$A \equiv \left(\begin{array}{c|ccc} \frac{\partial W_i}{\partial x_m} & & & \\ \hline & \text{ker} S & & \end{array} \right)$$

Example of a small network



$$A = \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{pmatrix} & A & B & C & \text{ker1} & \text{ker2} \\ \begin{pmatrix} 0 & 0 & 0 & -1 & 0 \\ J_{2A} & 0 & 0 & -1 & -1 \\ 0 & J_{3B} & 0 & -1 & -1 \\ 0 & 0 & J_{4C} & 0 & -1 \\ 0 & 0 & J_{5C} & -1 & 0 \end{pmatrix} \end{pmatrix}$$

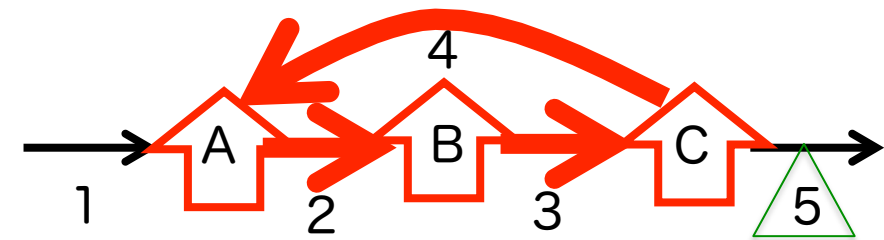
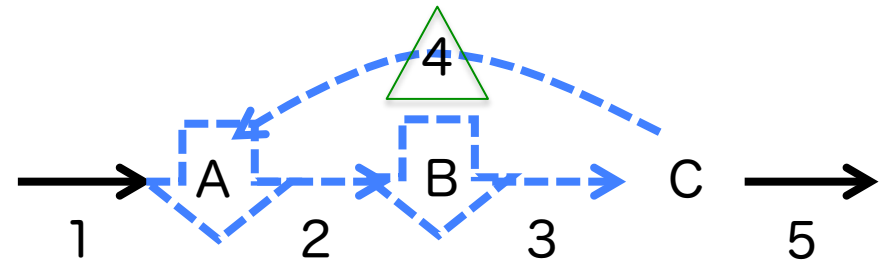
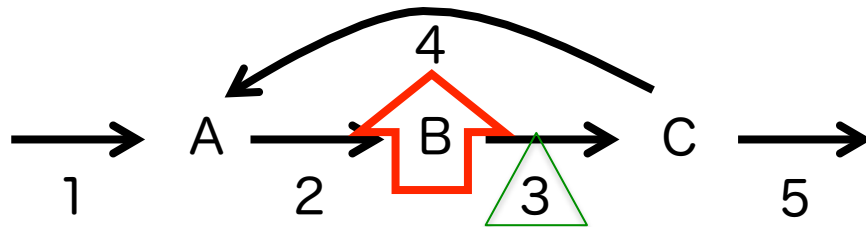
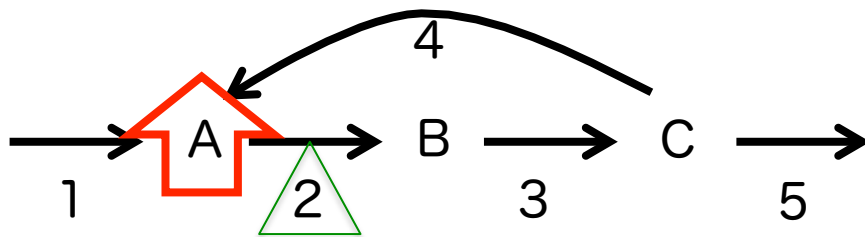
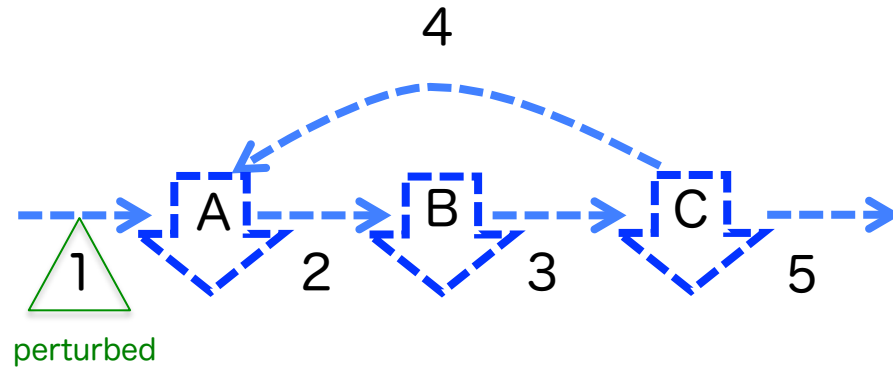
$$J_{im} = \frac{\partial W_i}{\partial x_m}$$

invert

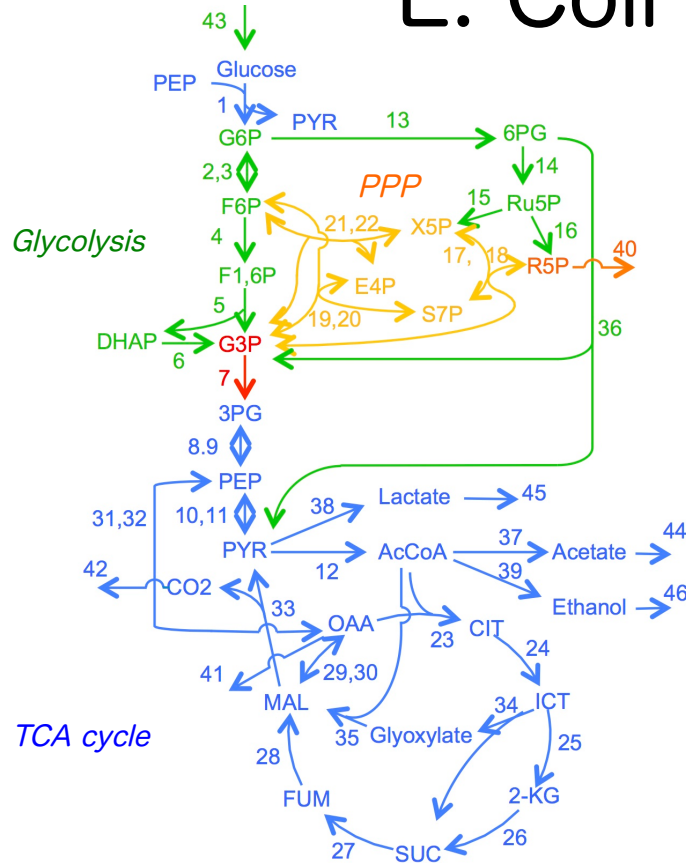


$$\begin{array}{c} \text{perturbed} \\ \text{reaction} \end{array} \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{pmatrix} \Delta A & \Delta B & \Delta C & \Delta \text{ker1} & \Delta \text{ker2} \\ \begin{pmatrix} -\frac{J_{4C}+J_{5C}}{J_{2A}J_{5C}} & -\frac{J_{4C}+J_{5C}}{J_{3B}J_{5C}} &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

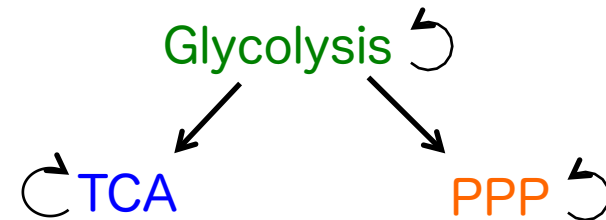
Responses to enzyme perturbation are *localized*



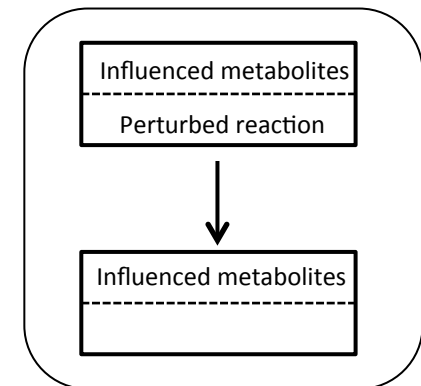
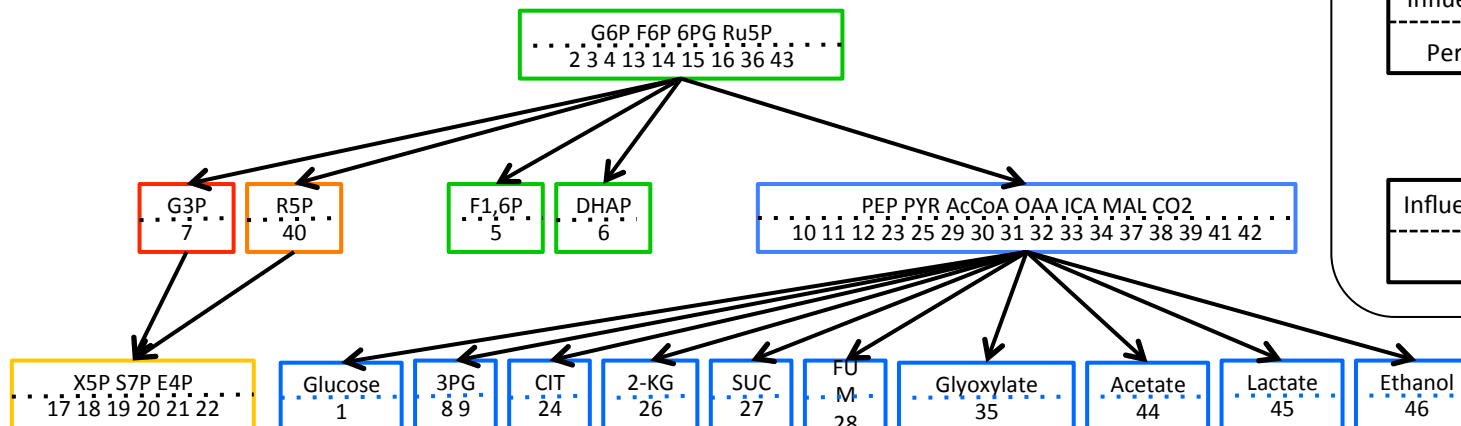
E. Coli network (glycolysis&PPP&TCA cycle)



Schematically,



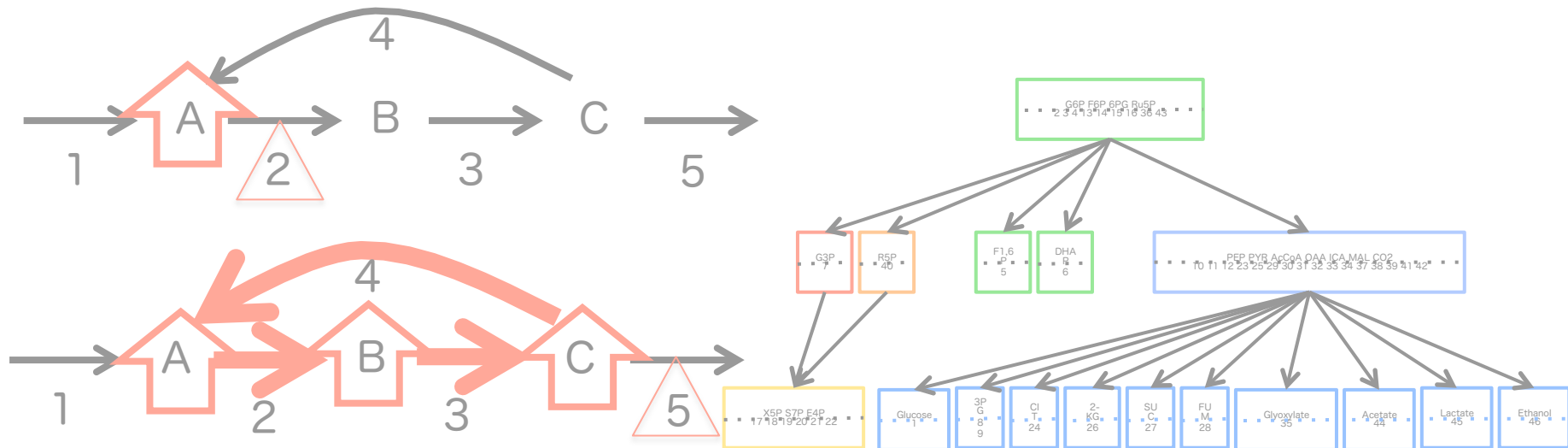
Hierarchy of response



General features in response patterns

- Responses to enzymes perturbation are *localized* in some regions of networks.
- Responses form a *hierarchy*.

Why?
Relation to network structure?



限局則 (*the law of localization*)

Okada T., Mochizuki A.

- Take a subnetwork $\Gamma = (\text{metabolites } \mathcal{M}, \text{ reactions } \mathcal{R})$ such that $\mathcal{R}$ includes all reaction edges emanating from $\mathcal{M}$.

- “Character” defined as

$$\chi(\Gamma) \equiv |\mathcal{M}| - |\mathcal{R}| + \#\text{cycle in } \Gamma \quad (\text{generally nonpositive})$$

- if $\chi(\Gamma) = 0$,

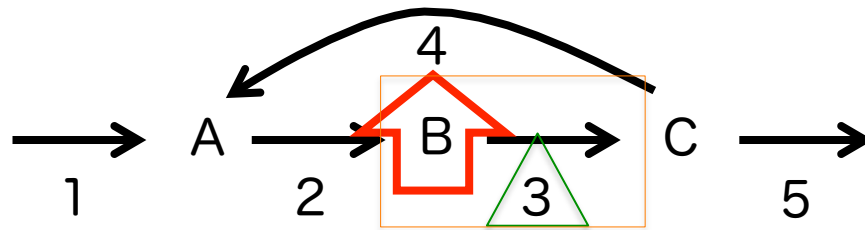
any enzyme perturbation in Γ does not influence the outside of Γ

(Γ : *buffering structure*, 限局構造).

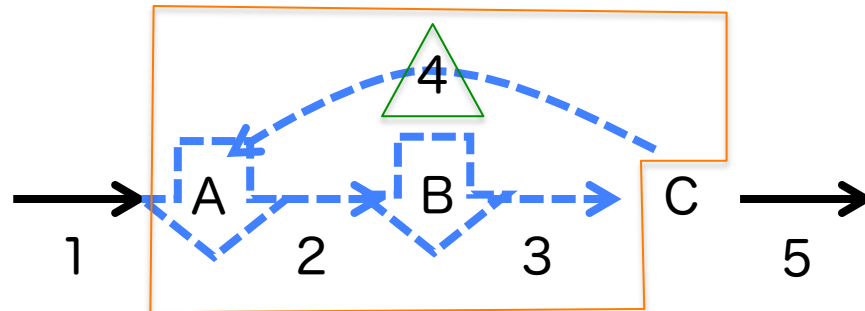
指数 χ の計算例 (previous example)

???

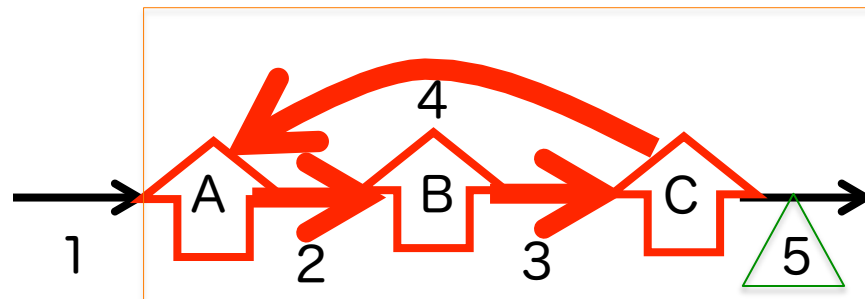
$$\chi(\Gamma) \equiv |\mathcal{M}| - |\mathcal{R}| + \#\text{cycle in } \Gamma = 0$$



metabolite = 1
reaction = 1
cycle = 0

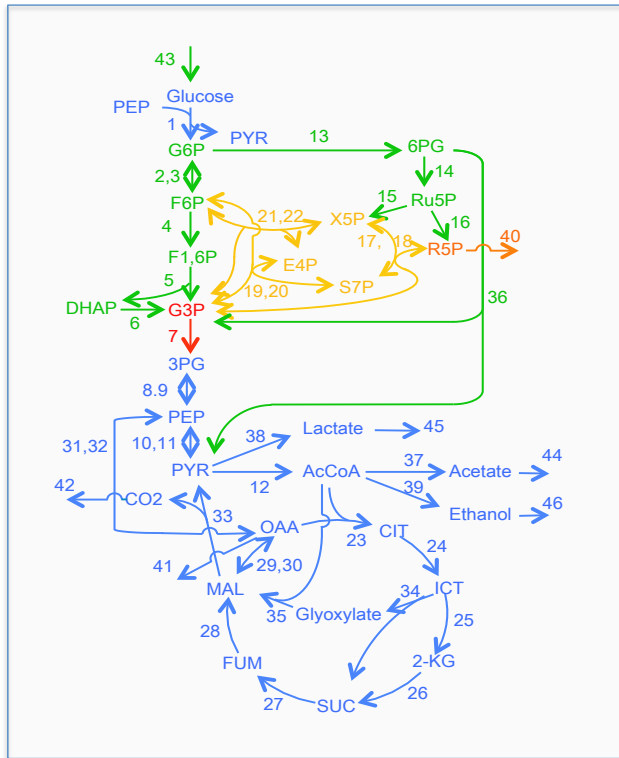


metabolite = 2
reaction = 3
cycle = 1



metabolite = 3
reaction = 4
cycle = 1

Response patterns revisited



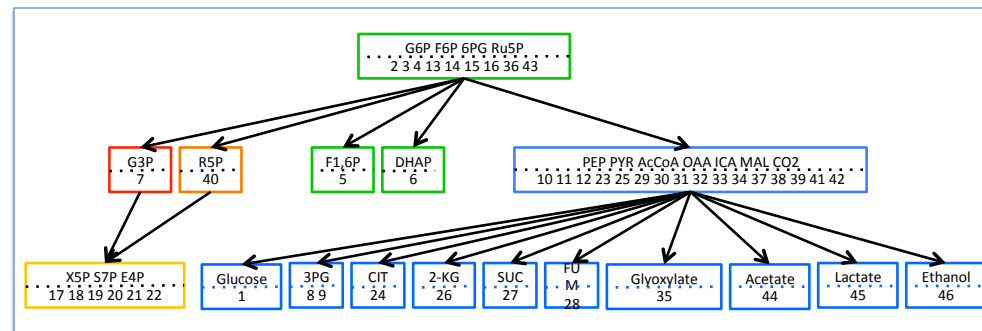
Why localized ?

← Existence of buffering strs.

$$\chi(\Gamma) = 0$$

Why hierarchy appears?

← Nest of buffering strs.



Glycolysis

PPP

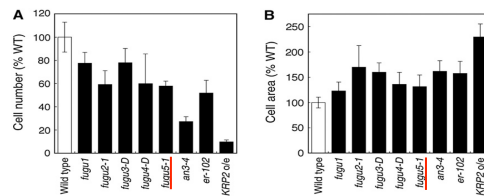
TCA

Biological meanings

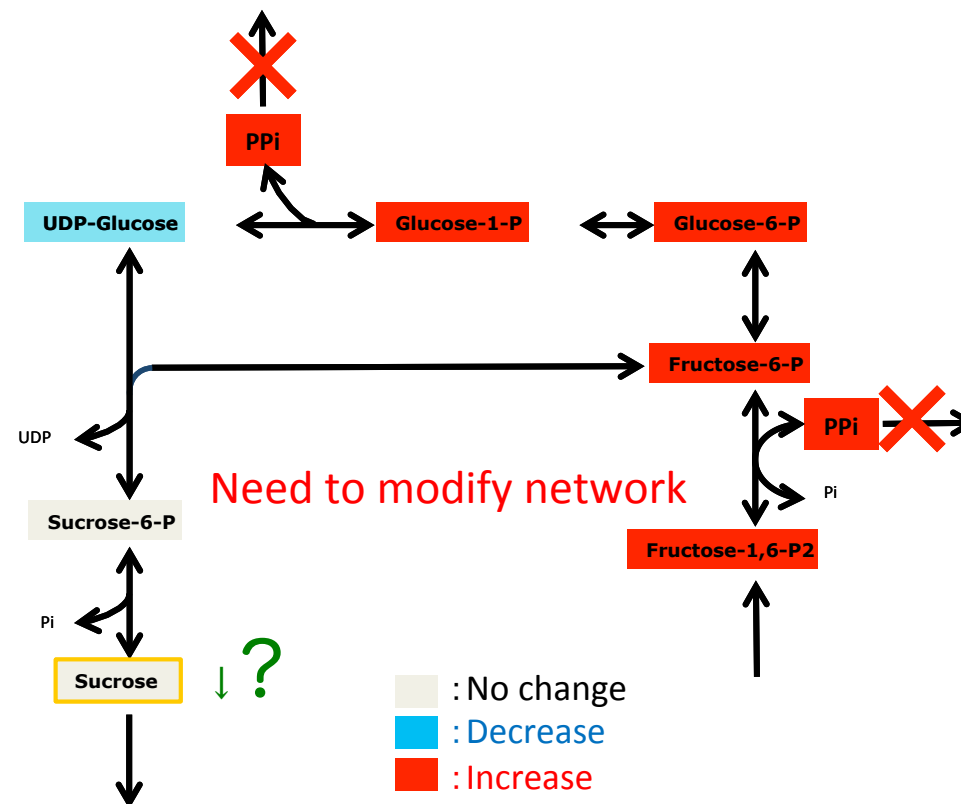
- “Firewalls” against enzyme fluctuations
→ biological advantage?

- Units of biological functions (PPP, TCA cycle)
↔ buffering structures

collaboration with
Ali Ferjani (Gakugei Univ),
Hirokazu Tsukaya (Univ Tokyo),
Masami Y. Hirai (RIKEN)

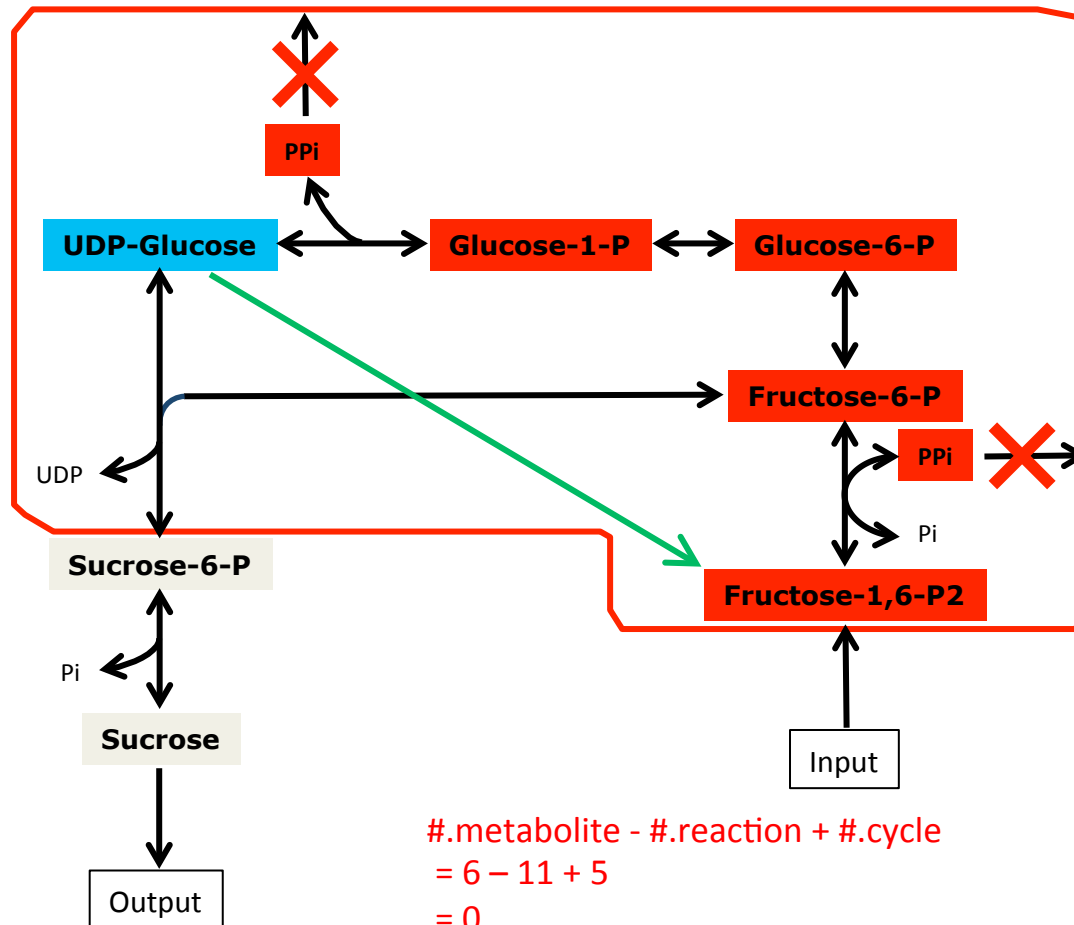


Defect of H⁺-Ppase ⇒ [Sucrose]↓



Why do all networks predict **insensitive** [sucrose]?

Buffering structure



$$\begin{aligned} \#.\text{metabolite} - \#.\text{reaction} + \#.\text{cycle} \\ &= 6 - 11 + 5 \\ &= 0 \end{aligned}$$

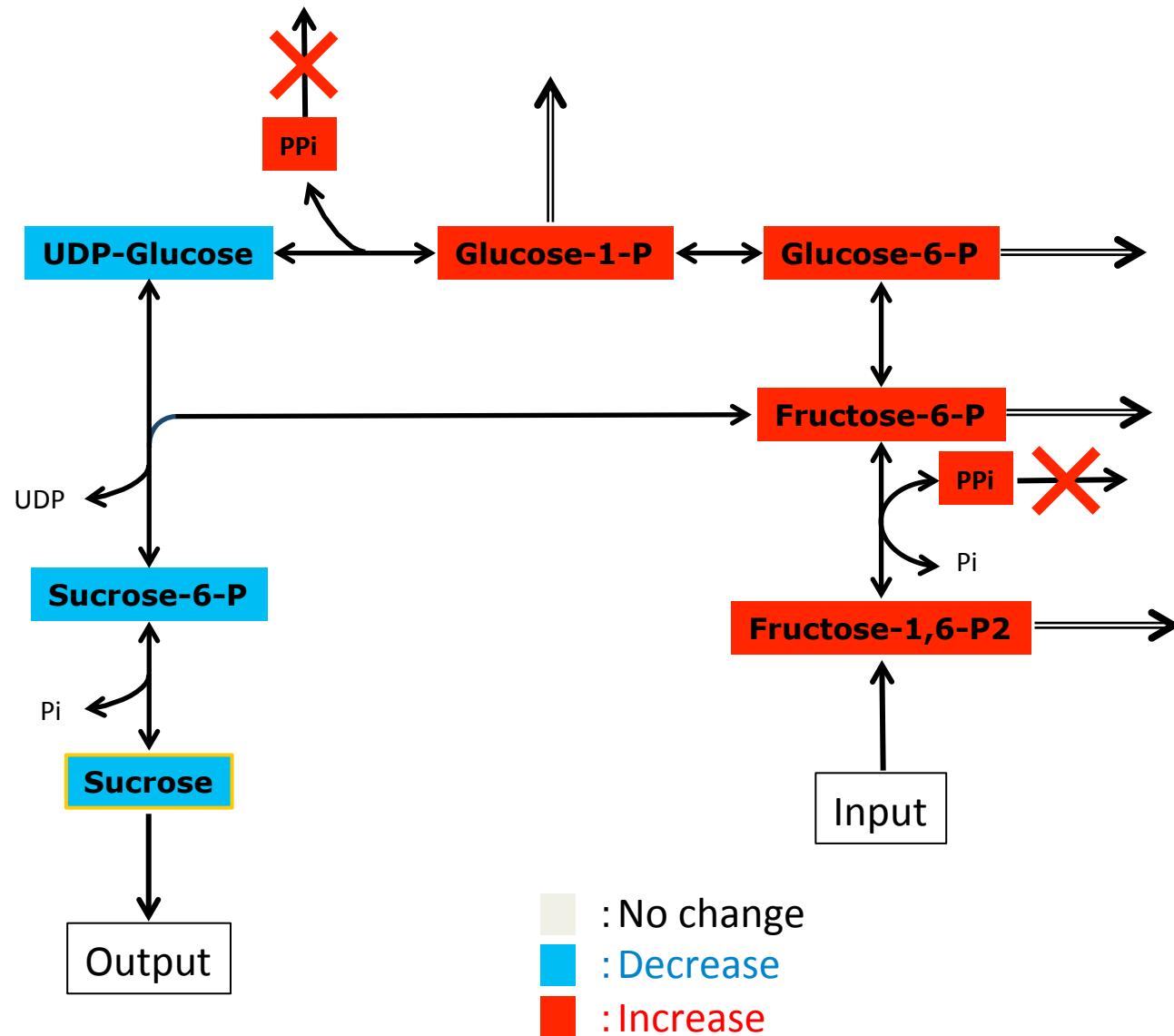
$$\begin{aligned} \#.\text{metabolite} - \#.\text{reaction} + \#.\text{cycle} \\ &= 6 - 12 + 6 \\ &= 0 \end{aligned}$$

: No change
 : Decrease
 : Increase

Additional internal reactions cannot break $\chi(\Gamma) = 0$

Does defect of PPI degradation decreases [sucrose] ?

Modification 2: add outflow pathways



We can predict necessary reactions. ← Thm. depends on *local* network info.

Summary

- ✓ Theoretical framework which predicts the responses to enzyme perturbations form network structures.

- ✓ A theorem governing response patterns (localization, hierarchy)

- ✓ Collaborations

 - Nakayama Lab @ Kyushu Univ. (cancer metabolism)

 - Kuroda Lab @ Univ. Tokyo (insulin action)

 - Tsukaya Lab @Univ. Tokyo (plant metabolism)

 - Sako Lab @ Riken (ErbB receptor network)

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