Adaptation I: Universal Feature common to biological systems

- Two facets in adaptation

(1)adaptation --- ‘essential variables’ return to the original values (or within a range around them) independent of environmental conditions

Cannon’s Homeostasis

(eg. Body temperatures remains within a certain range) -- (‘Wisdom of the body’) → Wiener’s feedback,

(2) Change to a fitter state (higher survivability, growth) (here focus on the scale <<evolution)

- (1)(2) seemingly contradictory,,, but,,,somehow both are achieved
- For different time scales
- For different variables

Actually the two are studied rather independently

Dynamical systems view:

(1) Some variables respond and come back to the original

(2) Some variables change (switch to a different attractor, or by bifurcation) so that the ‘fitness’ is increased

- Adaptation in the 2nd sense:

standard picture

external signal from environment

→Signal transduction system

→Switch gene expression pattern

(jump to a different attractor or bifurcation by parameter change)

→Fitted state is achieved

Such signal-transduction/gene-expression networks are selected through the evolution

Indeed such examples are studied in depth in bacteria and other cells

- Generic Adaptation ??

* adaptation to a huger variety of environments

?? Signal transduction networks are prepared for all these?? ——hard to imagine

Some general, inefficient but non-specific, adaptation mechanism?

← (experimental suggestion) (cf Braun's group)

gene expression dynamics switch so that good metabolic state is achieved

consider gene expression dynamics (x)

with cell growth and fluctuation

** Fitted states are selected before selection by reproduction ("consistency"?),

Spontaneous Adaptation

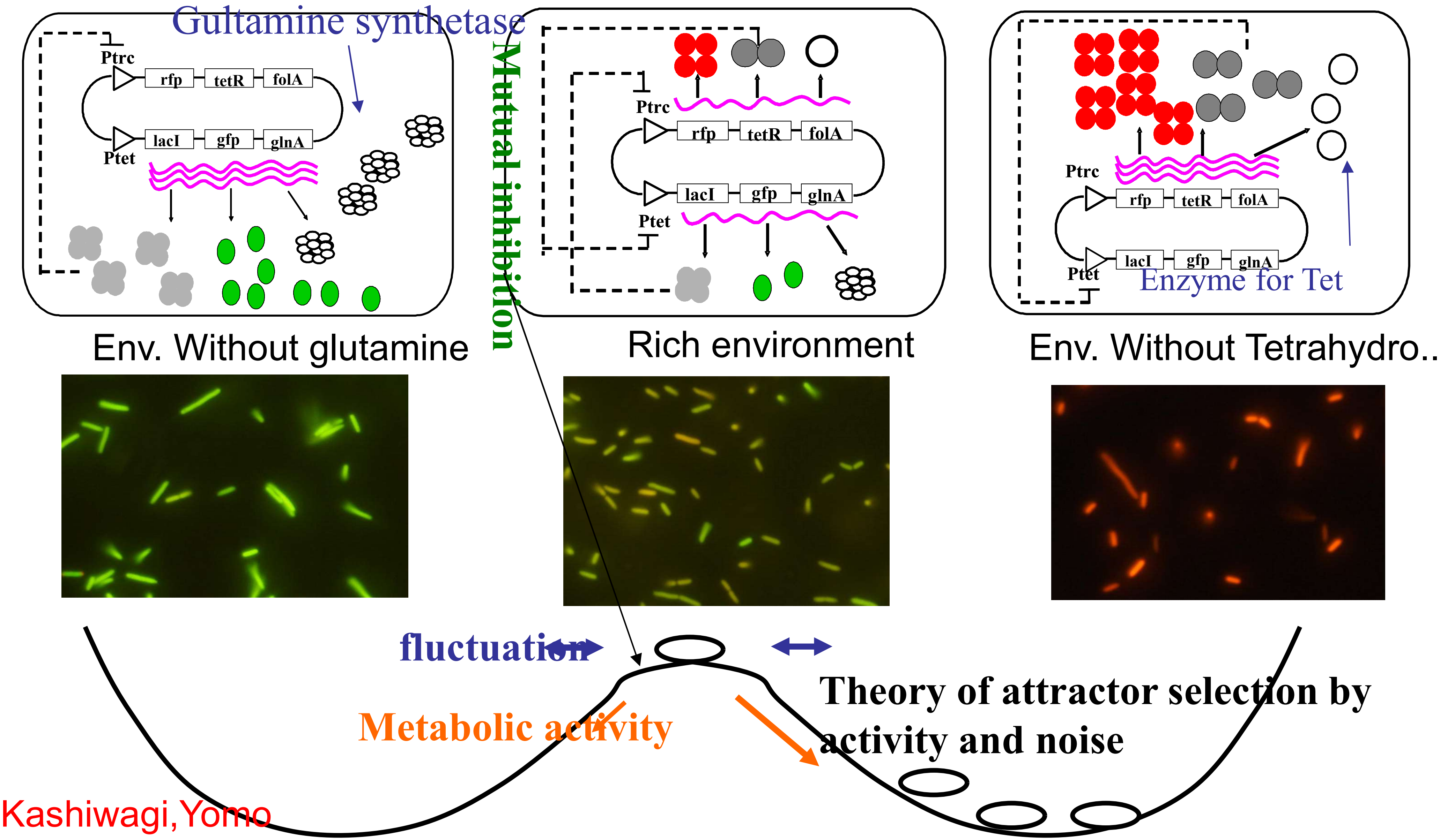
- For all possible changes in environment, signal transduction network is already provided?
- Or, is there any general (primitive) mechanism to make spontaneous adaptation?
- → Constructive Experiment with artificial Gene and theory assuming only growth condition and stochsticity

(ex) Adaptive response without signal transduction

Embedded gene network

Unexpected; beyond designed
Selection of preferable state

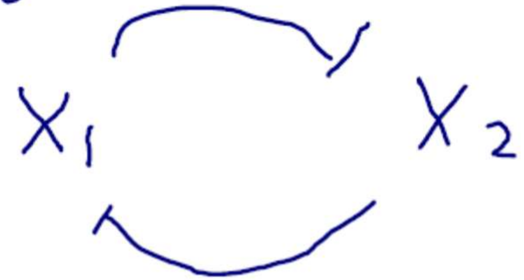
Phenomenological theory of attractor selection



Kashiwagi, Yomo

RECALL

Toggle Switch



mutually suppress the expression

$$\frac{dm_1}{dt} = \gamma\left(\frac{\alpha}{1+p_2^2} - m_1\right), \quad \frac{dp_1}{dt} = m_1 - p_1$$

$$\frac{dm_2}{dt} = \gamma\left(\frac{\alpha}{1+p_1^2} - m_2\right), \quad \frac{dp_2}{dt} = m_2 - p_2$$

mRNA (m_i) ⋯ faster timescale ($\gamma \gg 1$)

adiabatic elimination $\longrightarrow \frac{dm_1}{dt} \simeq 0, \ \frac{dm_2}{dt} \simeq 0$

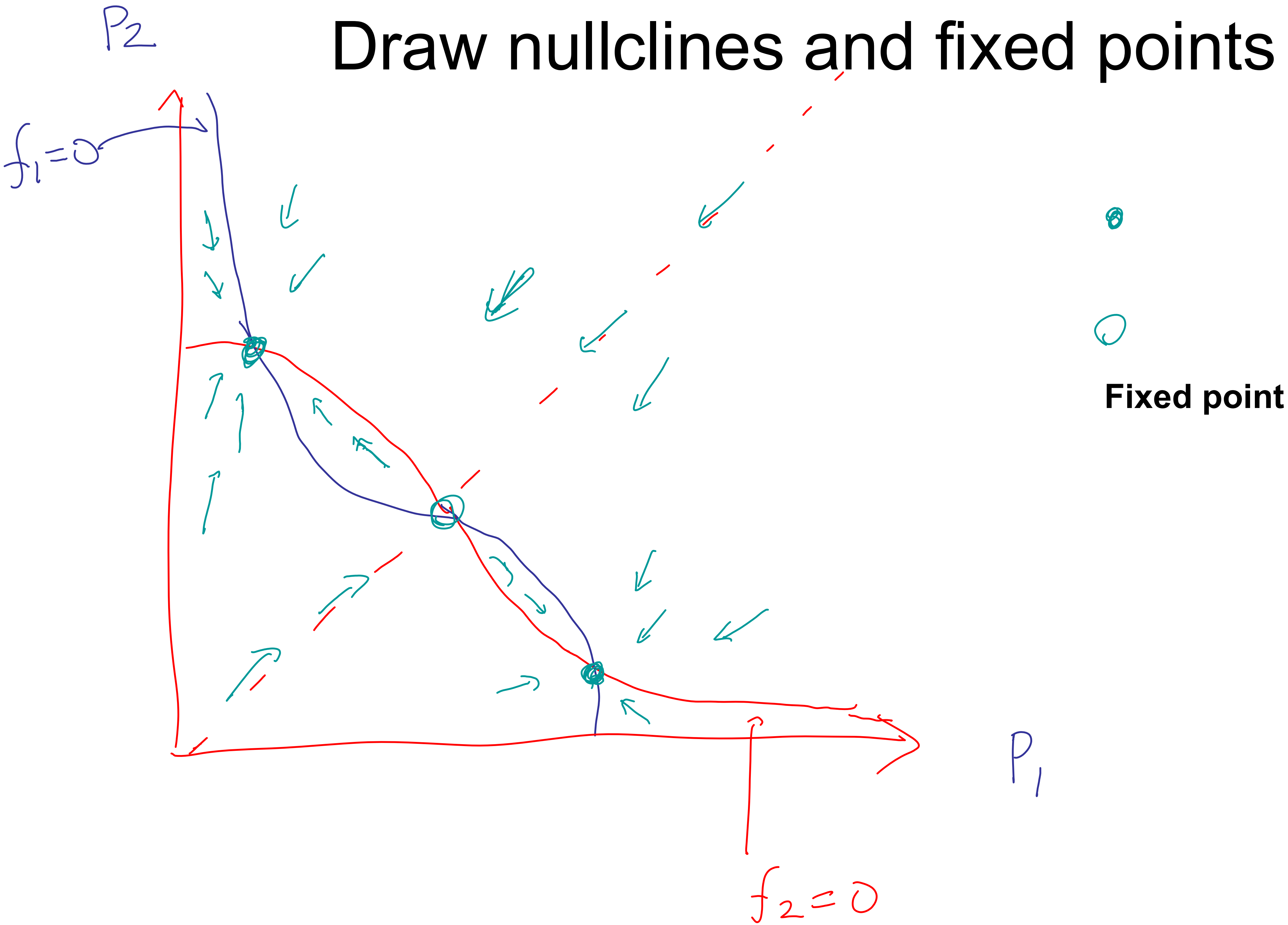
$$\frac{dP_1}{dt} = \frac{\alpha}{1+P_2^2} - P_1 \equiv f_1(P_1, P_2), \quad \frac{dP_2}{dt} = \frac{\alpha}{1+P_1^2} - P_2 \equiv f_2(P_1, P_2)$$

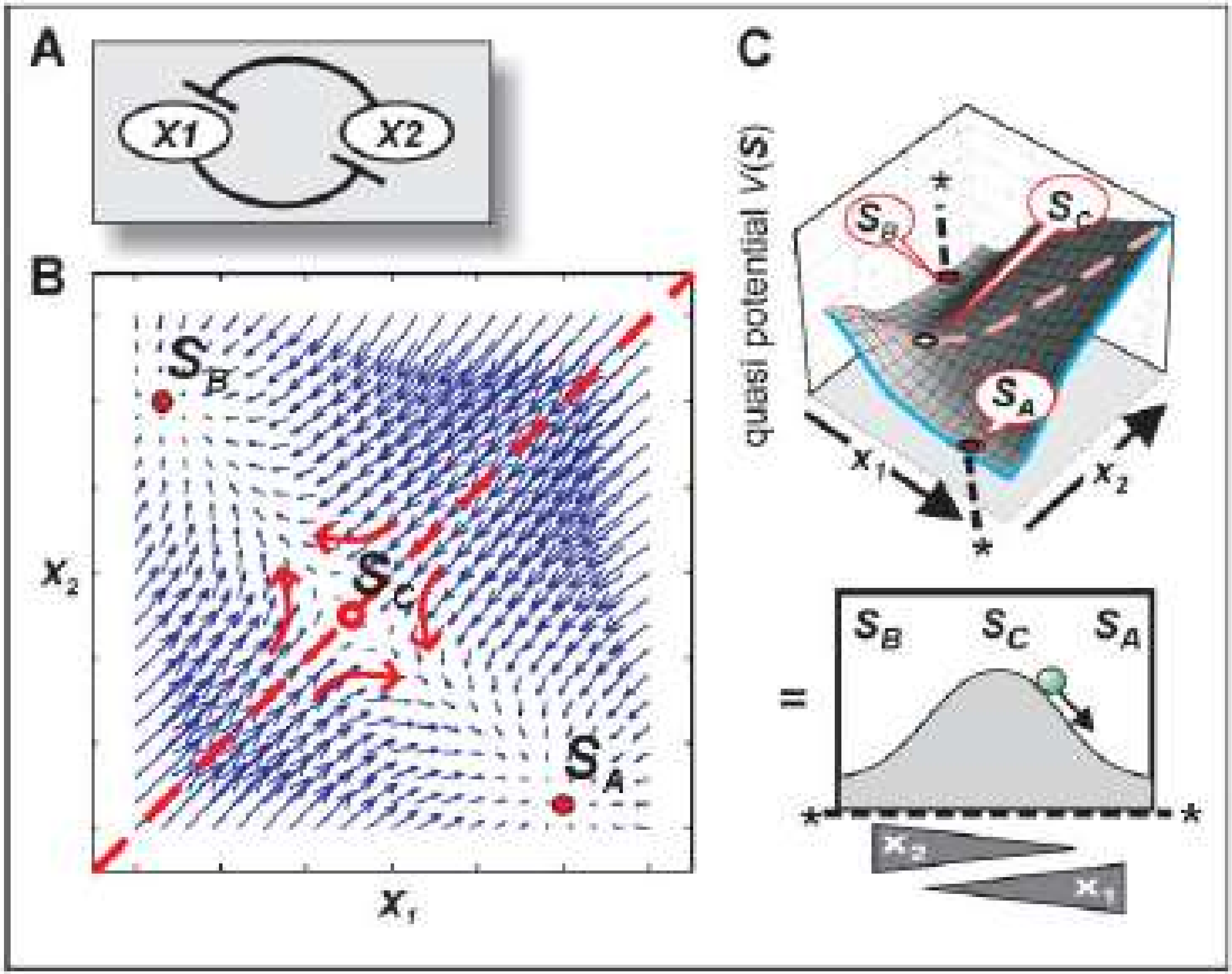
mullcline

$$f_1 = 0 \qquad P_1 = \frac{\alpha}{1+P_2^2}$$

$$f_2 = 0 \qquad P_2 = \frac{\alpha}{1+P_1^2}$$

Draw nullclines and fixed points





Sui Huang
Bioessay
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- Embedded network: each of the two can be selected equally. However, ‘good’ attractor in each environment is selected. Why?
- Due to hidden signal network?

  NO!: verified by swapping the promoter
- After each state is attracted with 50%,

cells in a ‘bad’ attractor cannot grow,

cells in a good attractor can grow, so that

good attractors are selected?

NO!; the process occurs without (or before) the cell division process

Novel Mechanism of Spontaneous Adaptation (without the use of signal transduction) should exist!

- Possible Generic Mechanism

$dx_i/dt=F(Activity)f(x_i)-G(Activity)x_i+\eta(t)$

F,G: increase with activity.

active: synthesis, degradation both are fast

η → (external) noise

Active state : both Ff and Gx are large

deterministic part >> noise

Poor state : both Ff and Gx are small

deterministic part ~ noise

Switch from Poor state to Active state by noise

(Kashiwagi,Urabe,kk,Yomo; PLoS One 2006)

Simplest example of attractor selection by noise
Bistability+Growth-dilution+Noise

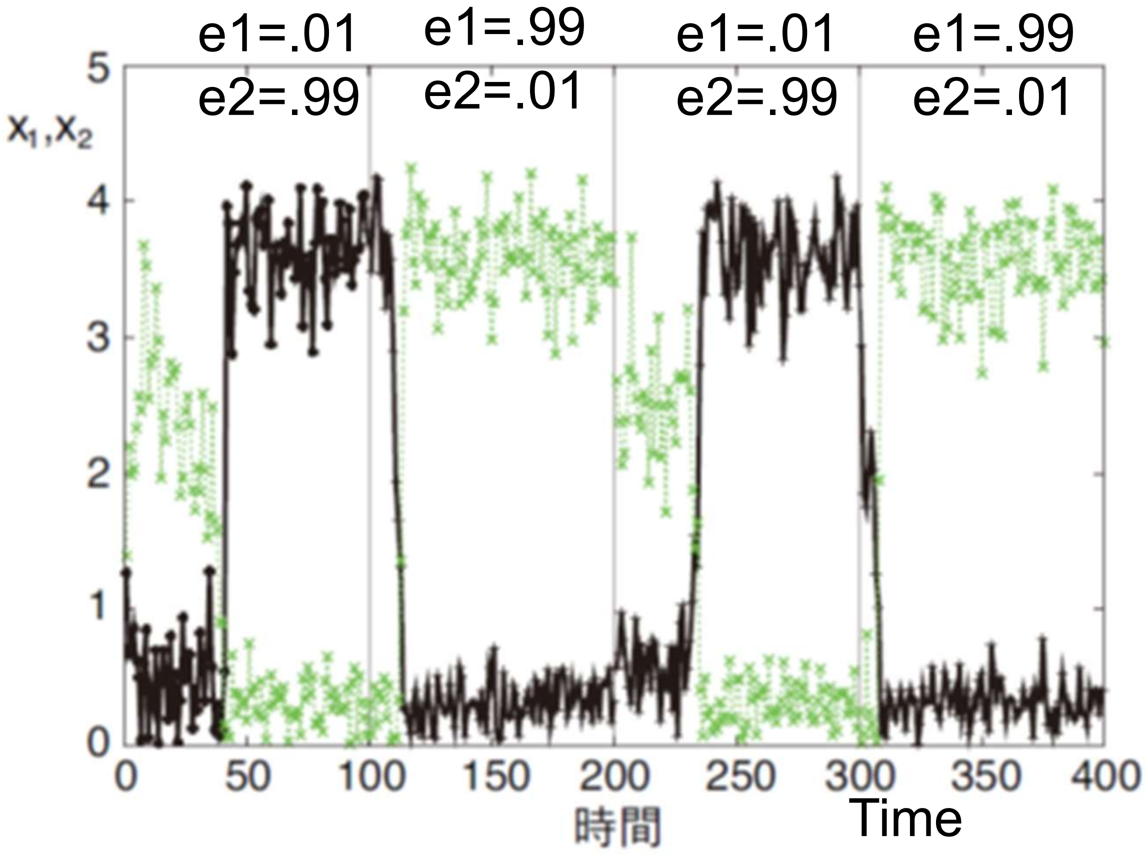
Growth rate μ → dilution –μx

Synthesis increases with μ Simplest example: synthesis ∝ μ

$$dx_1/dt = f_1(x_1,x_2) = \mu_g(\alpha/(1+x_2^2) - x_1) + \eta_1(t)$$

Still, bistable system

$$dx_2/dt = f_2(x_1,x_2) = \mu_g(\alpha/(1+x_1^2) - x_2) + \eta_2(t)$$



Environment 1:
 if x1 is expressed,
 higher growth μ

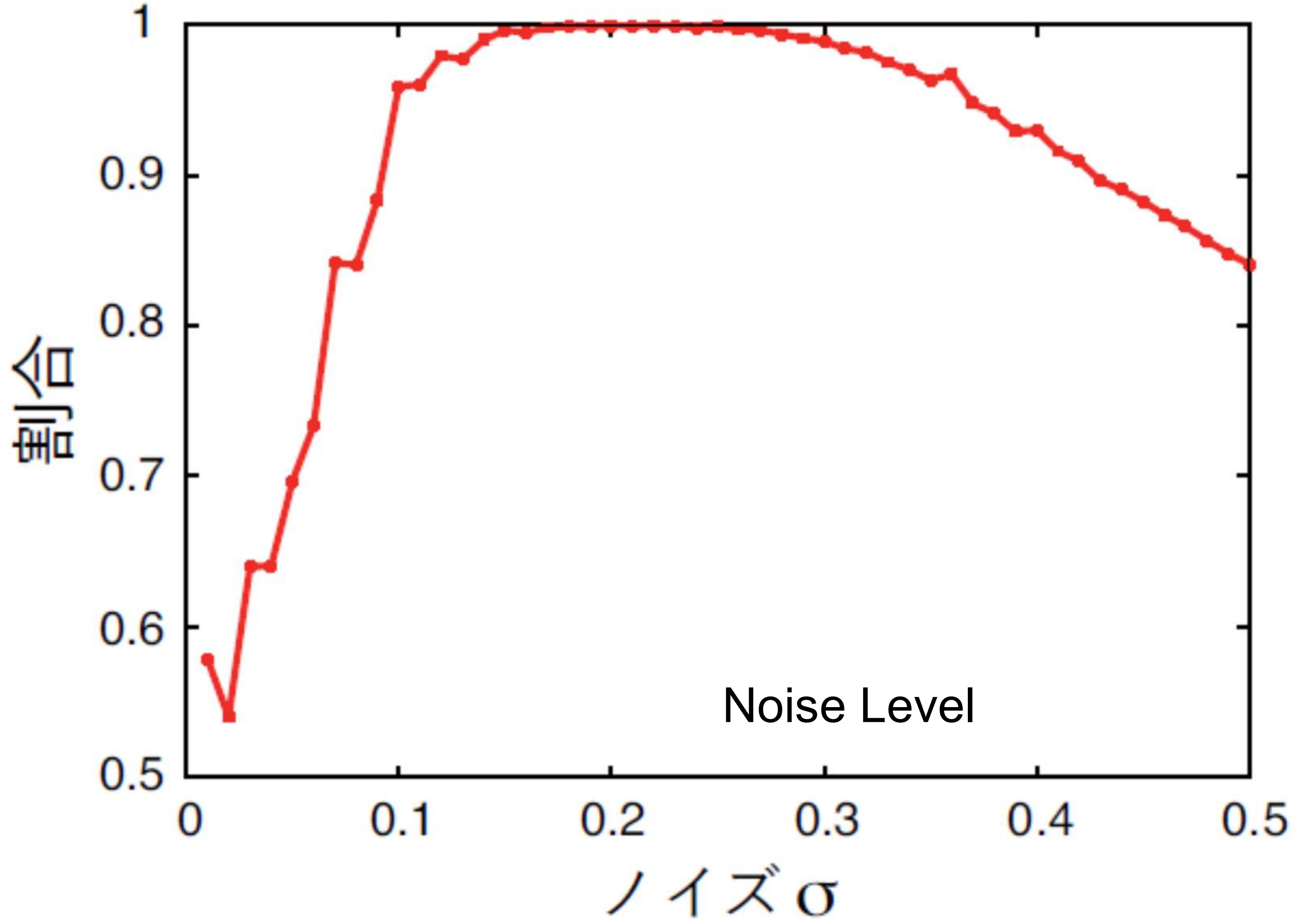
Environment 2:
 if x2 is expressed,
 higher growth μ

Under appropriate noise level adapted attractor is selected

$$\mu = \frac{0.1A^4}{1+A^4}$$

A＝e1x1+e2x2

The fraction that cells select and stay at an adapted state with higher growth



- Growth-Induced-Attractor-Selection in General
- Basic Logic (Furusawa kk, PLoSCompBiol 2008)

$dx_i/dt=f(x_i)-S(\{x_j\})x_i+\eta(t)$

f: synthesis, S→ dilution effect η → noise

Both synthesis and dilution ∝ Growth

Active state : both f and S are large

deterministic part >> noise

Poor state : both f and S are small

deterministic part ~ noise

Switch from Poor state to Active state by noise

Selection before reproduction.

General logic in a system with growth and fluctuation

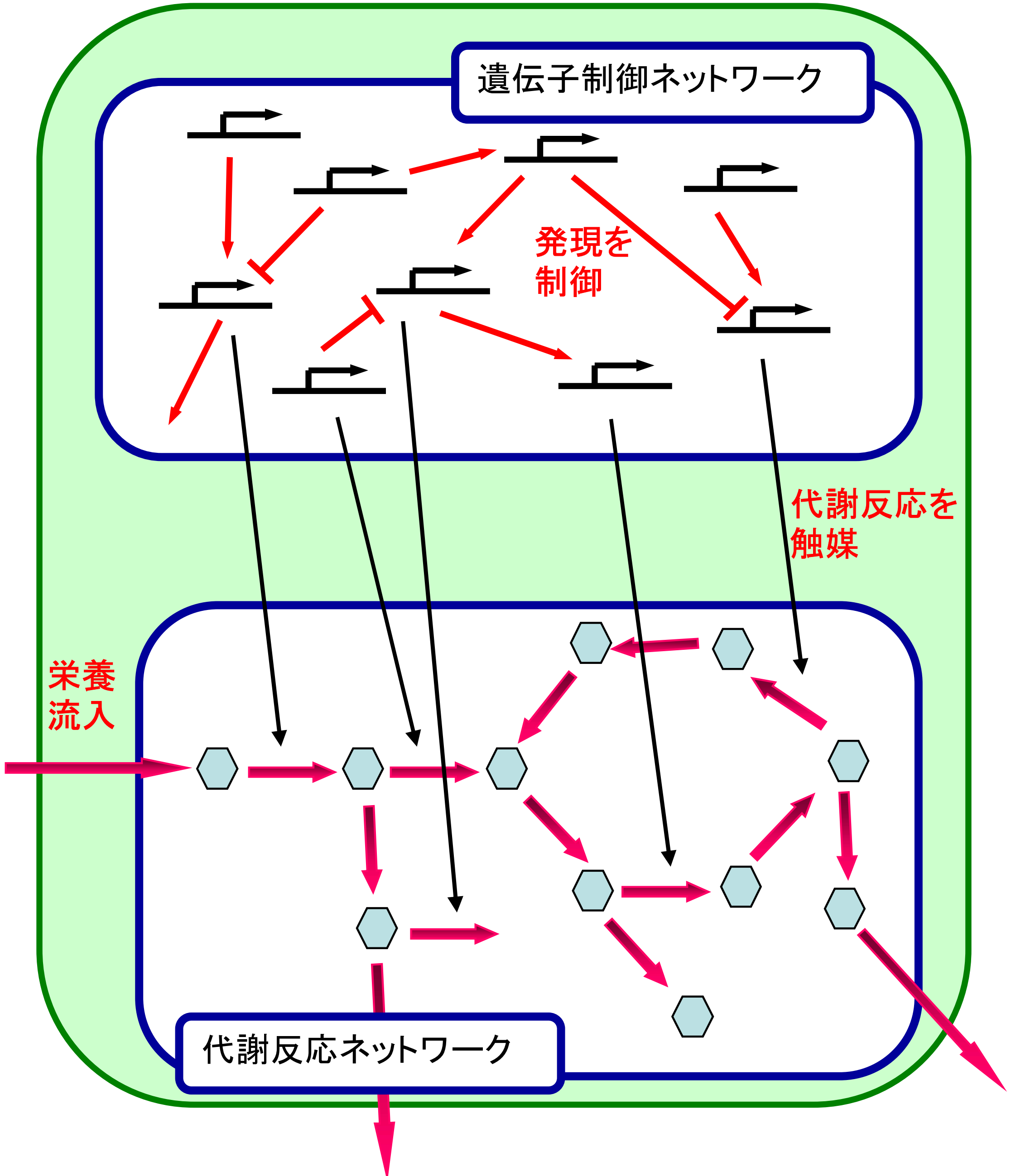
Gene-regulation+metabolic net model

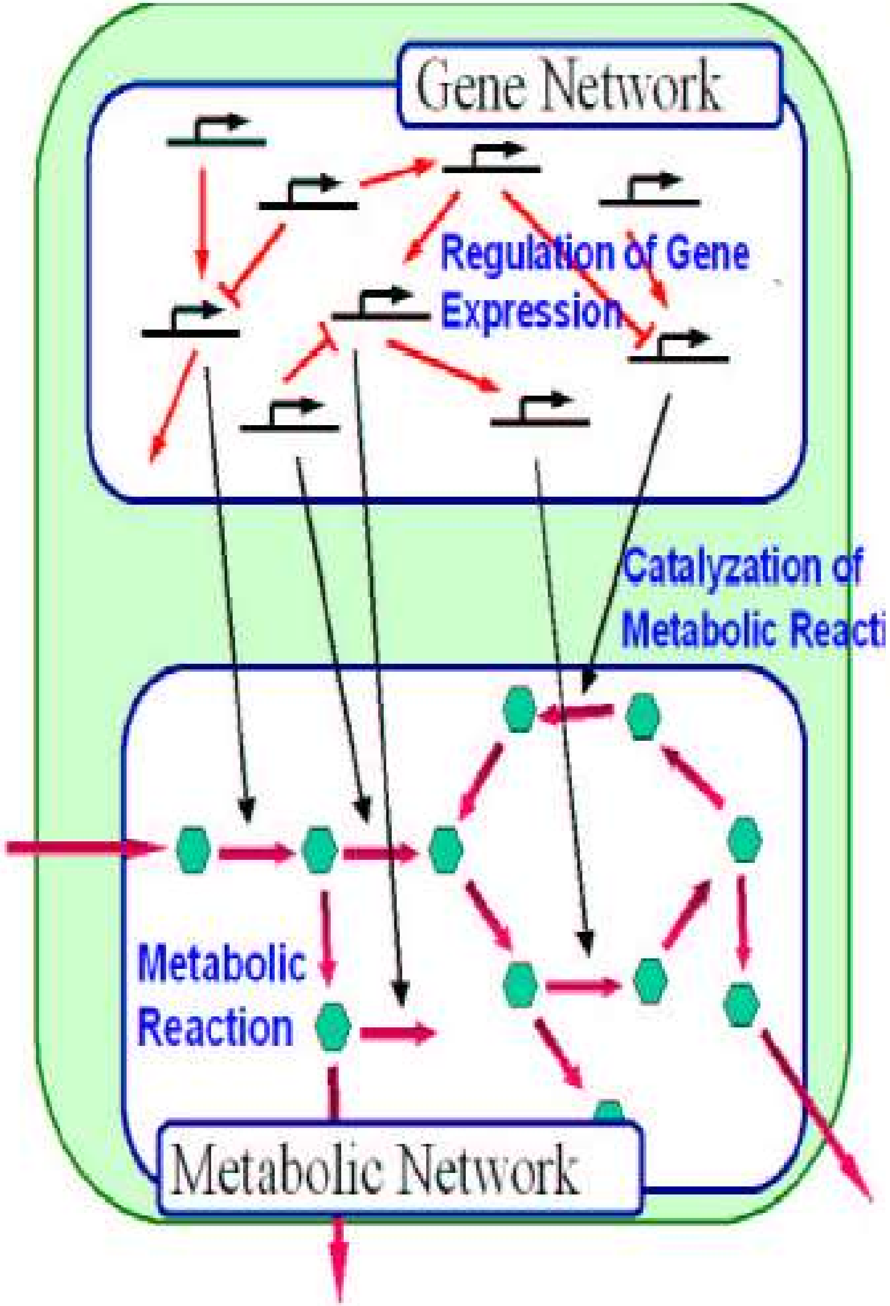
Furusawa,KK2008

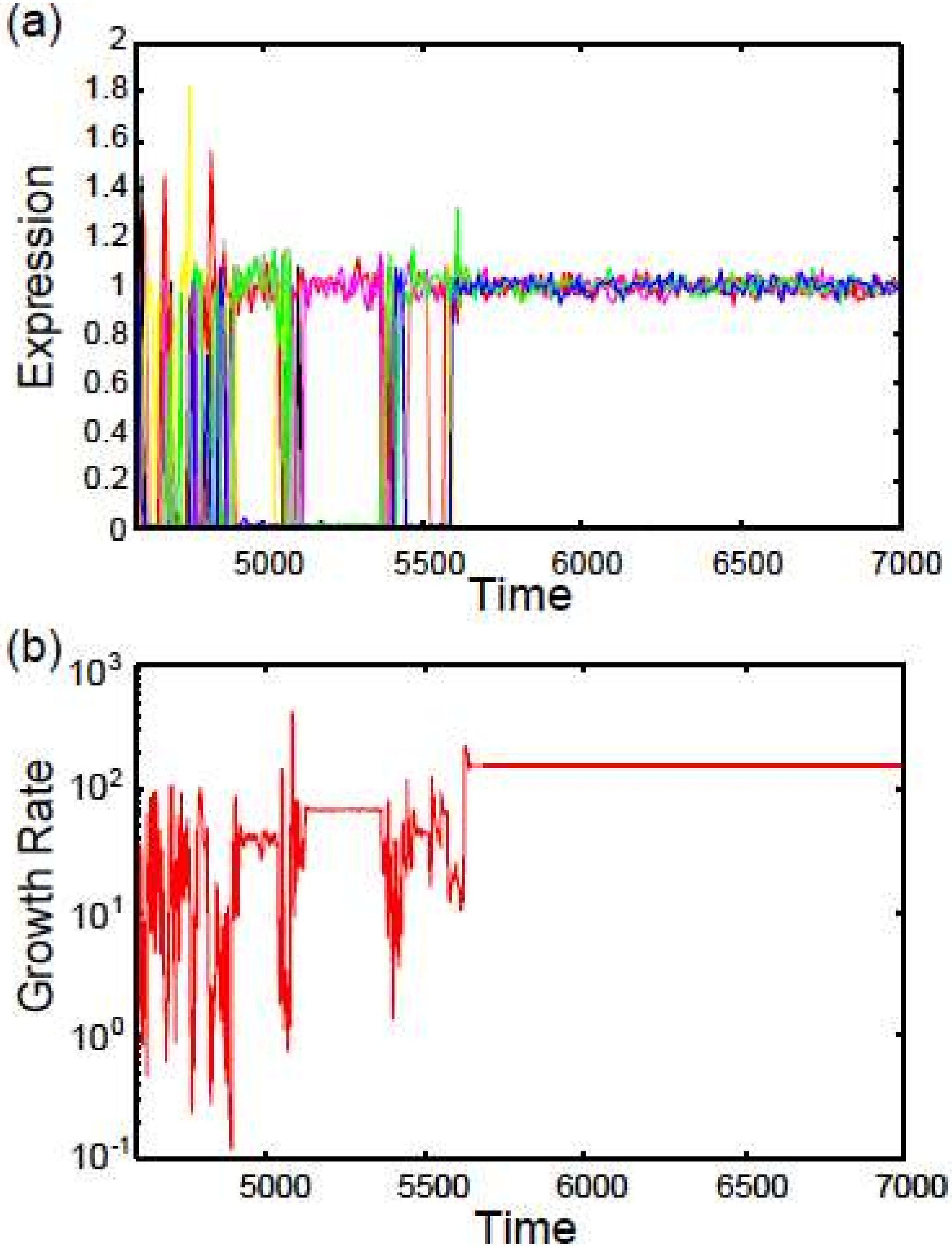
- Both gene regulation + metabolic networks
- Gene regulation : activate /repress mutually → many attractors
- Each gene (protein) catalyzes one metabolic path
- Resource cpmes in and flow out,

components can diffuse out

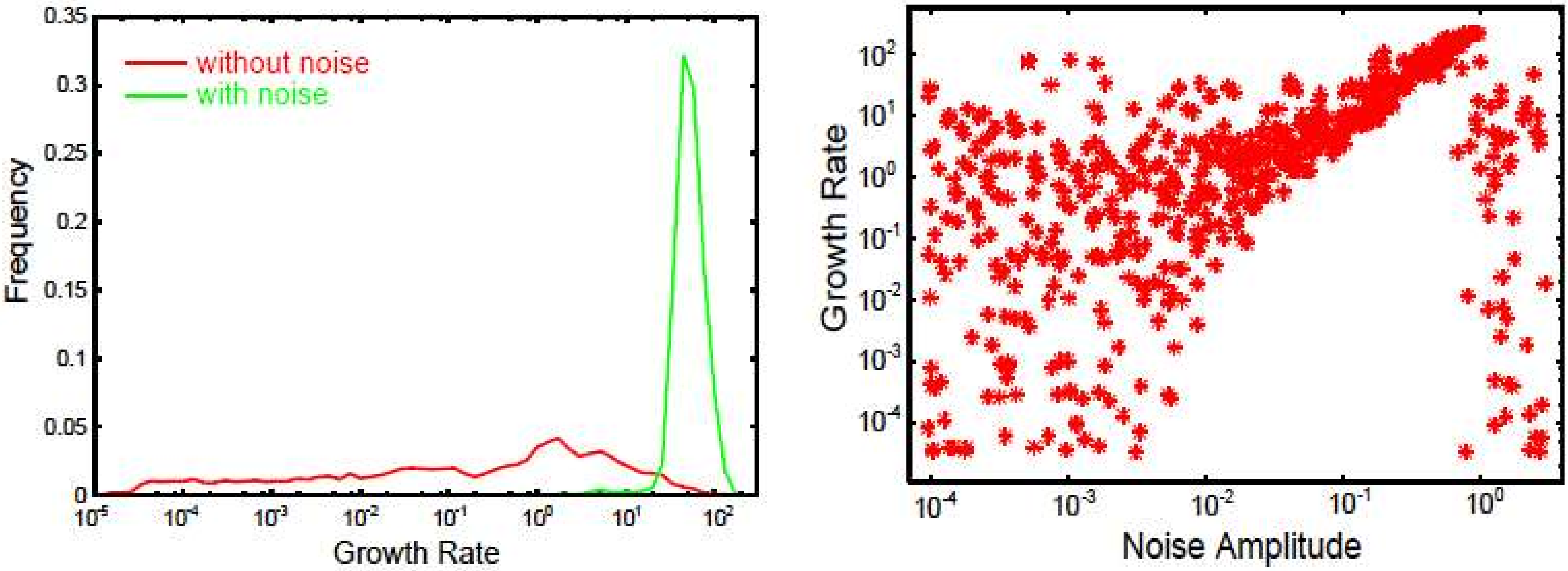
- Growth rate determined by the chemical required (e.g., minimum concentration of metabolic components)







Gene network -> a huge number of attractors coexist with different growth speeds



Spontaneous selection of optimal growth states

General in a system with noise and growth

(1) Existence of some compensation of dilution by growth

If synthesis rate is totally indep't of growth rate, then this mechanism should not work. Even if the compensation is partial, the mechanism works (exp/ partial ~50%: Tsuru et al. 2009MSB)

This compensation means the 'adaptaion in the 1st sense', as the concentration of each chemical comes back to the original, indep't of external condition that alters the growth rate.

- (2)Noise:

if the variance of noise ∝ growth speed

this does not work; if noise amplitude ∝ √μthis mechanism should not work

Still, as long as noise does not vanish as growth-rate →0, it works

- Usually noise remains for μ->0

- （3） Similarity and Difference with Simulated Simulated Annealing; noise strength is changed in time: In contrast

noise strength is fixed , but strength (speed) of deterministic part change autonomously (due to the change in growth rate)

→higher-growth state is spontaneously selected

- Limitation;

resolution (Δ(growth) ~ noise)

speed --- not good

(4) Need to assume multiple attractors?

Originally single-attractor, but environment change → growth-rate change generates new attractors?

If synthesis is not fully compensated, possible:

Bifurcation to multi-attractors and then

Switch from Poor to Active attractor by noise

e.g.. Combine bifurcation and attractor slection

(5) Later evolution of signal transduction network for frequently encountered environment

initially noise—induced attractor selection then Evolution of signal network??

Note: evolution works only after cells survived→ some generic mechanism for survival needed

(6) Further experimental confirmation needed

← Checking correlation between growth-rate and expression

Cf immune system, revolution from prepared to generic system leads to paradigm change

Epigenetic feedback for Adaptation   Furusawa-KK

Epigenetic change (methylation, histon modification) →

Slower change in feasibility of expression →Threshold for expression changes → Fixed point attractors are generated
Simplify: if expressed, then it is easier to be expressed
 'Hebbain dynamics' for epigenetic process

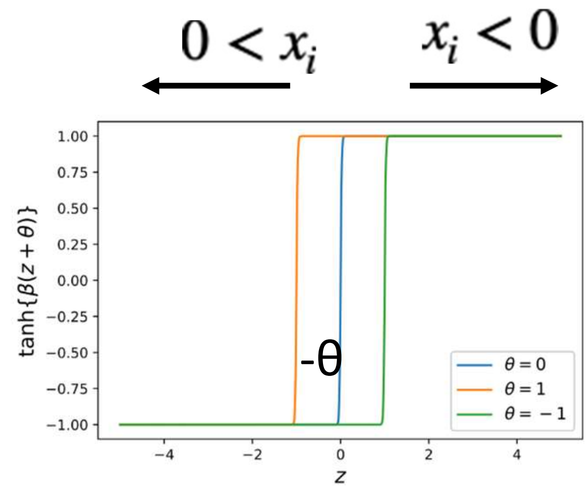
→ Adaptation to novel conditions are possible by noise (Furusawa, KK, PLoS One 2013) or by chaotic dynamics (Matsushita, KK, Phys Rev Res 2023)

Cell model (GRN + epigenetic modification)

x_i $(i = 1,2,\ldots,N)$ Gene expression

x_i + expressed (max 1) On
- Repressed Off

$$\frac{dx_i}{dt} = \tanh \beta(\sum J_{ij}x_j + \theta_i) - x_i$$



$-\theta_i$ Threshold for expression

Gene regulatory network (GRN)
: regulation matrix

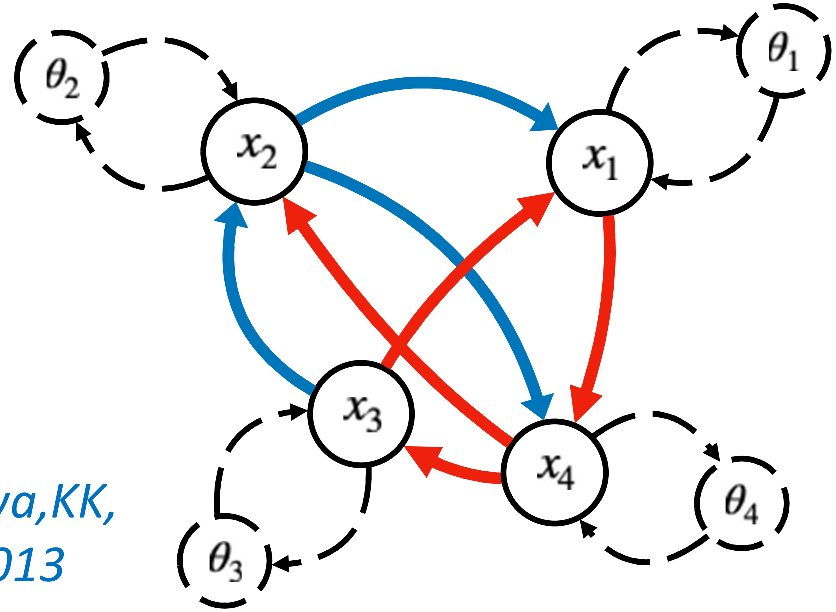
J_{ij} + : activate
:- inhibit

θ_i → Variable for epigenetic modification

+Positive feedback from Expression

$$\frac{d\theta_i}{dt} = v(ax_i - \theta_i)$$

If expressed, easier to be expressed: If repressed, harder to be expressed



Cf: Furusawa,KK, PLoS One 2013

a: strength of feedback

***v:* rate of epigenetic feedback dep on μ**

Generic Optimization by Fast Chaotic Exploration and Slow Feedback Fixation

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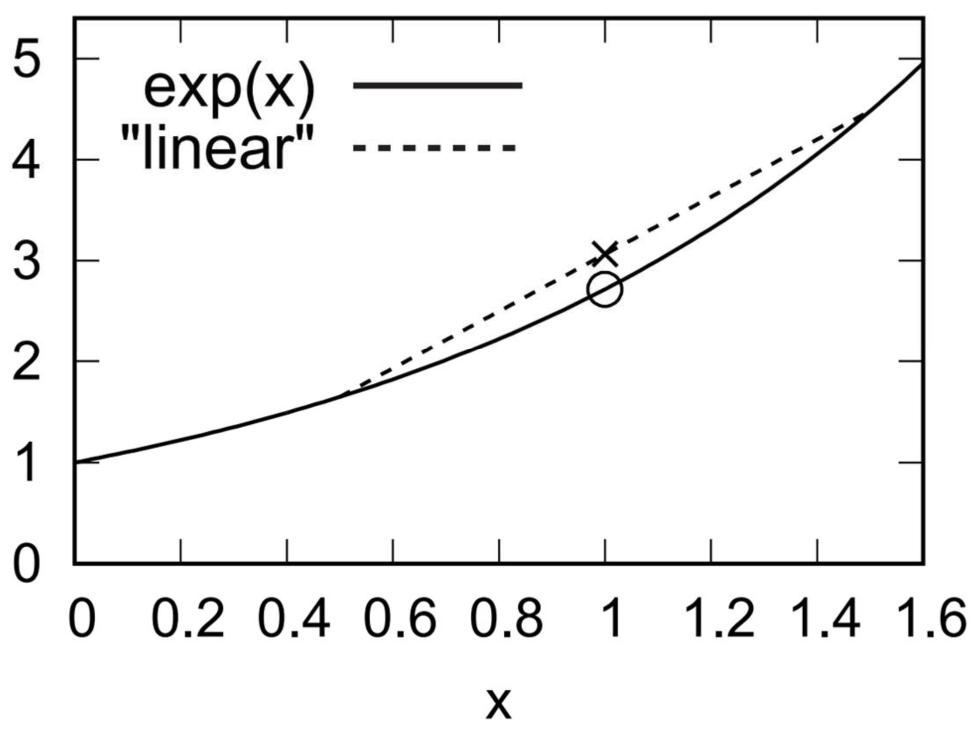
(Dated: February 23, 2023)

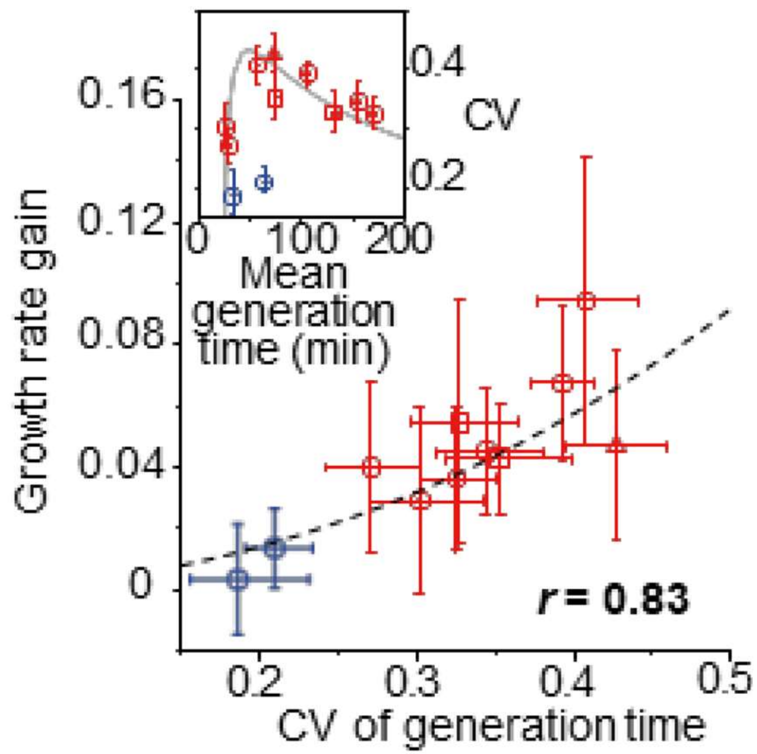
Living systems adapt to various environmental conditions by changing their internal states through processes such as gene expression and epigenetic modification. In this paper, we propose a generic mechanism for optimization that combines fast oscillatory dynamics with a slower feedback fixation process. Through extensive model simulations, we demonstrate that the fast chaotic dynamics serve as a global search for optimal states, which are then fixed by the slower dynamics. This mechanism becomes more effective as the number of elements is increased. We also discuss the potential relevance of this optimization mechanism to problems in artificial neural networks.

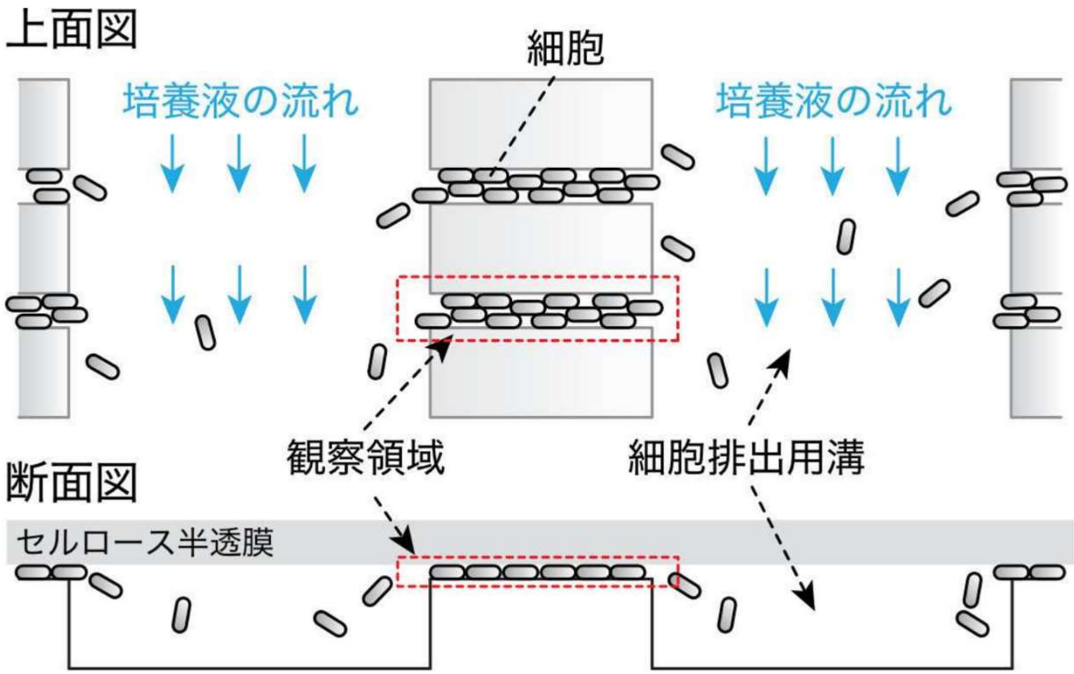
Cf　Significance of fluctuations (Passive role)

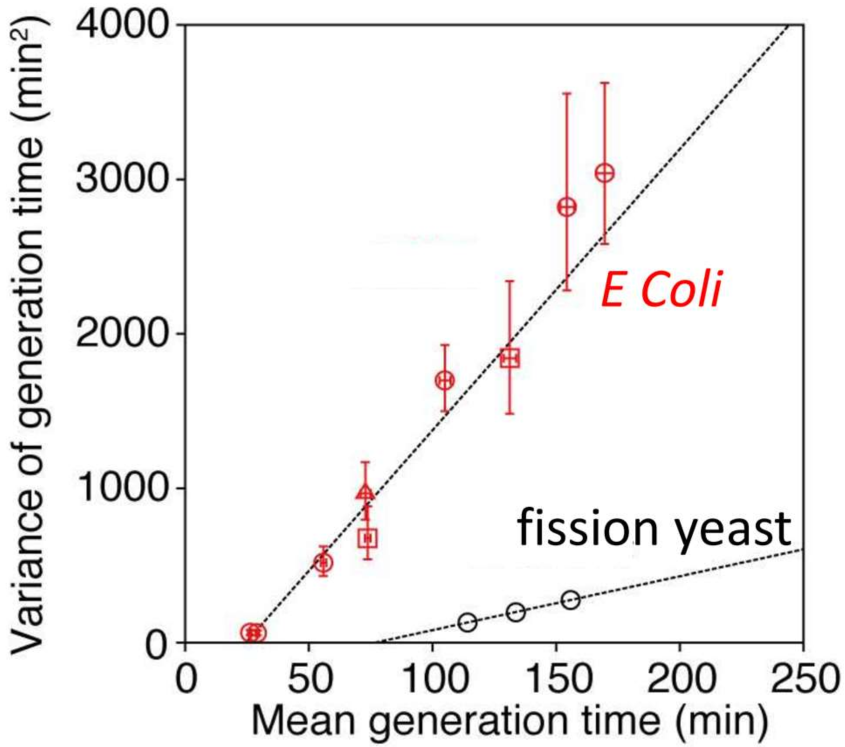
if the growth-rate is distributed, cells that happen to grow faster brings more offspring. The growth-rate as an ensemble of cells is enhanced by fluctuation (just because exp(t) is a convex function)

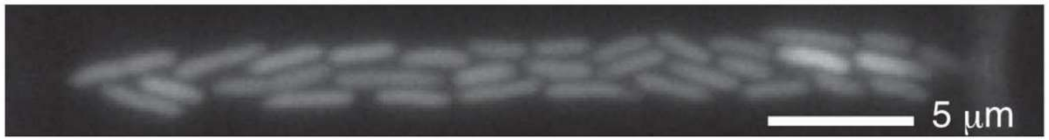
Confirmed by single-cell measurement (Wakamoto)



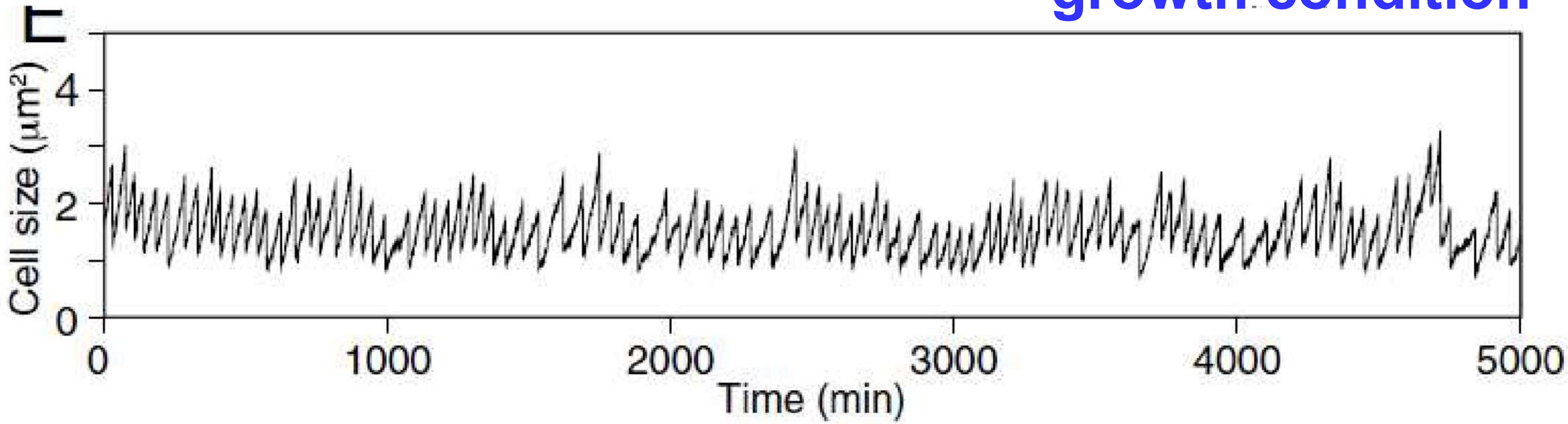








→ Larger CV for low-growth condition



Wakamoto's group