Adaptation: 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,

Keep 'micro-macro' consistency—Le Chatelier

(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

Model for adaptation

（cf）perfect vs partial adaptation

Koshland,Oosawa；Asakura-Honda model

‘Homeostasis’ after external change, most variables return to the original. Just few absorb the external change

Minimum model (1-degree of freedom)

du/dt=f(u,v;S)、dv/dt=g(u,v:S) if u*=indep’t of S

f=S-h(u,v) g=（uv-v）/τ：(eg. h=uv+u)→ u*=1

f=S-(u+v)、g=（S-v)/τ u*=1

f=S(1-u)-uv, g=(S-v)/τ u*=1/2

u shows perfect adaptation

→（more realistic models with gene expression, epigenetic modification, metabolic reaction）

Difference in time scale: fast response, slow relaxation to come back to the original

A simple example with catalytic reaction

PRL 107, 048301 (2011) PHYSICAL REVIEW LETTERS 22 JULY 2011

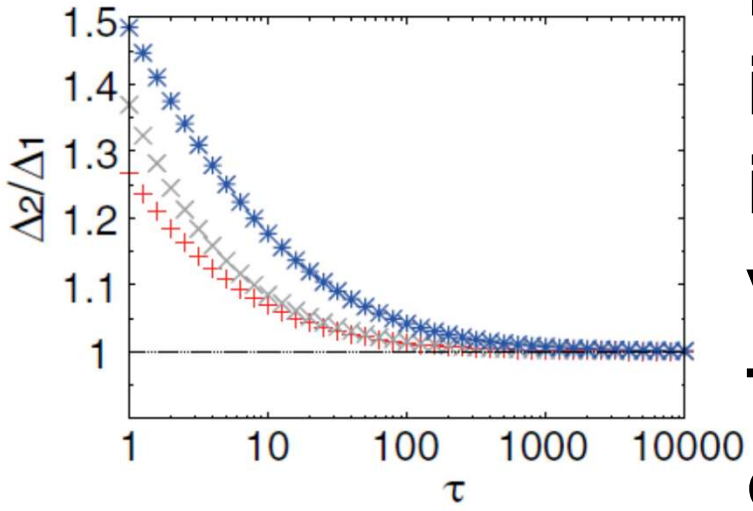
Weber's Law for Biological Responses in Autocatalytic Networks of Chemical Reactions

Masayo Inoue[1] and Kunihiko Kaneko[2]

introduced in [5]: $X_0 + X_1 \rightarrow 2X_1$; the model also includes (a) the synthesis of X_0 from an external resource chemical S as $S \rightarrow X_0$ and (b) the degradation of X_0 and X_1. By representing the concentrations of the two chemicals as x_0 and x_1 and suitably scaling the time and concentration variables, we get the rate equation as

$$dx_0/dt = S - x_0x_1 - x_0, dx_1/dt = (x_0x_1 - x_1)/\tau. \quad (1)$$

on the steady state $x_0^* = 1, x_1^* = S - 1$ [12]. According to a linear stability analysis, this state is stable when $S > 1$, i.e., as long as $x_1^* > 0$. It should be noted that x_0^* is independent of S. The chemical concentration responds to the



Fast variable changes initially while slow variable is insensitive. Later slow variable changes , and fast variable returns to te original

FIG. 1 (color online). Plot of ratio of maximum response amplitude Δ_2/Δ_1 (ordinate axis) versus τ(abscissa axis). $\Delta_i = x_0^{\text{peak}i} - x_0^*$ with the change $S_0^i \rightarrow pS_0^i$. $\Delta_2/\Delta_1 = 1$ implies the independence of the response amplitude from the S_0^i value, or

$(x_0^{\text{peak1}} - x_0^*)/(x_0^{\text{peak2}} - x_0^*)$ obtained by multiplying S $p-$ fold from S_0^1 or S_0^2, respectively, as a function of τ. The ratio is close to unity; it is independent of the initial S_0 as long as $\tau/t^{\text{peak}} \sim \tau S_0 \gtrsim 100$. In a previous study, we

Weber Law: change in Log --basic

Change S from S_0 to pS_0, peak change in x_0

We assume $\tau \gg 1$, which is required to ensure a fast response and slow adaptation. Under the adiabatic limit, x_1 changes more slowly than x_0 does. During the fast response of x_0 to the change in S, x_1 can be assumed to remain at the steady-state value under the condition of $S = S_0$. Then, the peak value of x_0 is obtained from $(dx_0/dt)_{x_0=x_0^{\text{peak}}} = 0$ by fixing the value of x_1 to $S_0 - 1$.

A straightforward calculation gives us $x_0^{\text{peak}} = p$. In a similar way, the peak time t^{peak} is estimated from $(dx_0/dt) \sim S - S_0 x_0$ and t^{peak} is given by $\sim 1/S_0$ [13].

The direct solution of $(dx_0/dt) = S - S_0 x_0$ is monotonic, but with inclusion of higher-order term in $1/(\tau S_0)$, x_0 shows a peak at t^{peak}.

If timescale τ is Separated the response is independent of the absolute value S

Fast change is absorbed by slow change (LeChatelier)

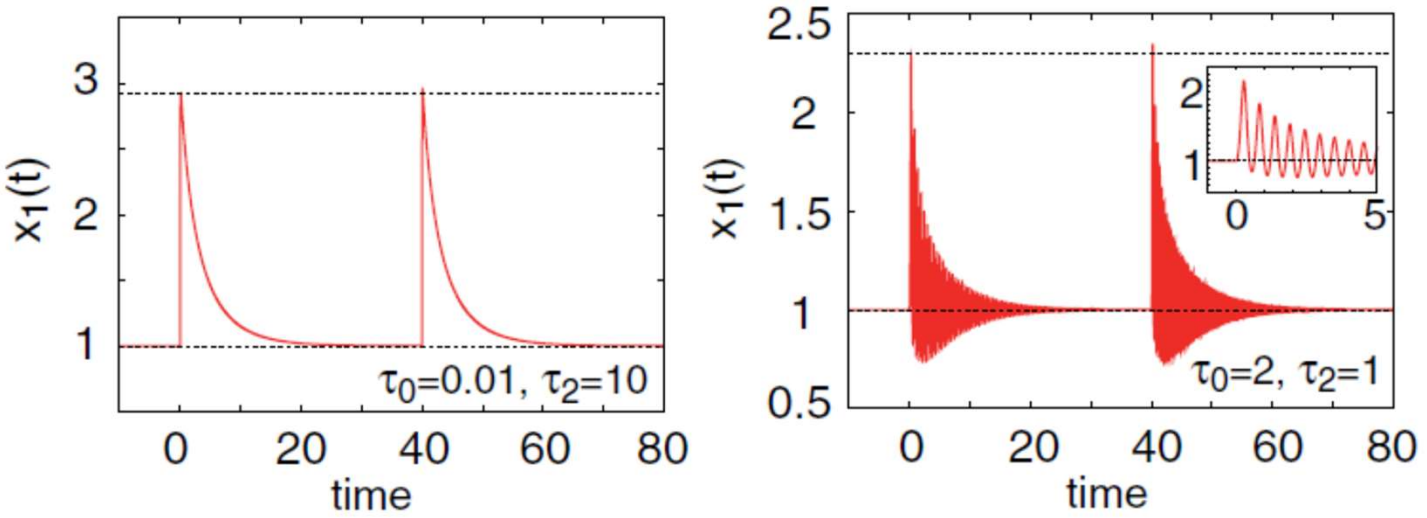
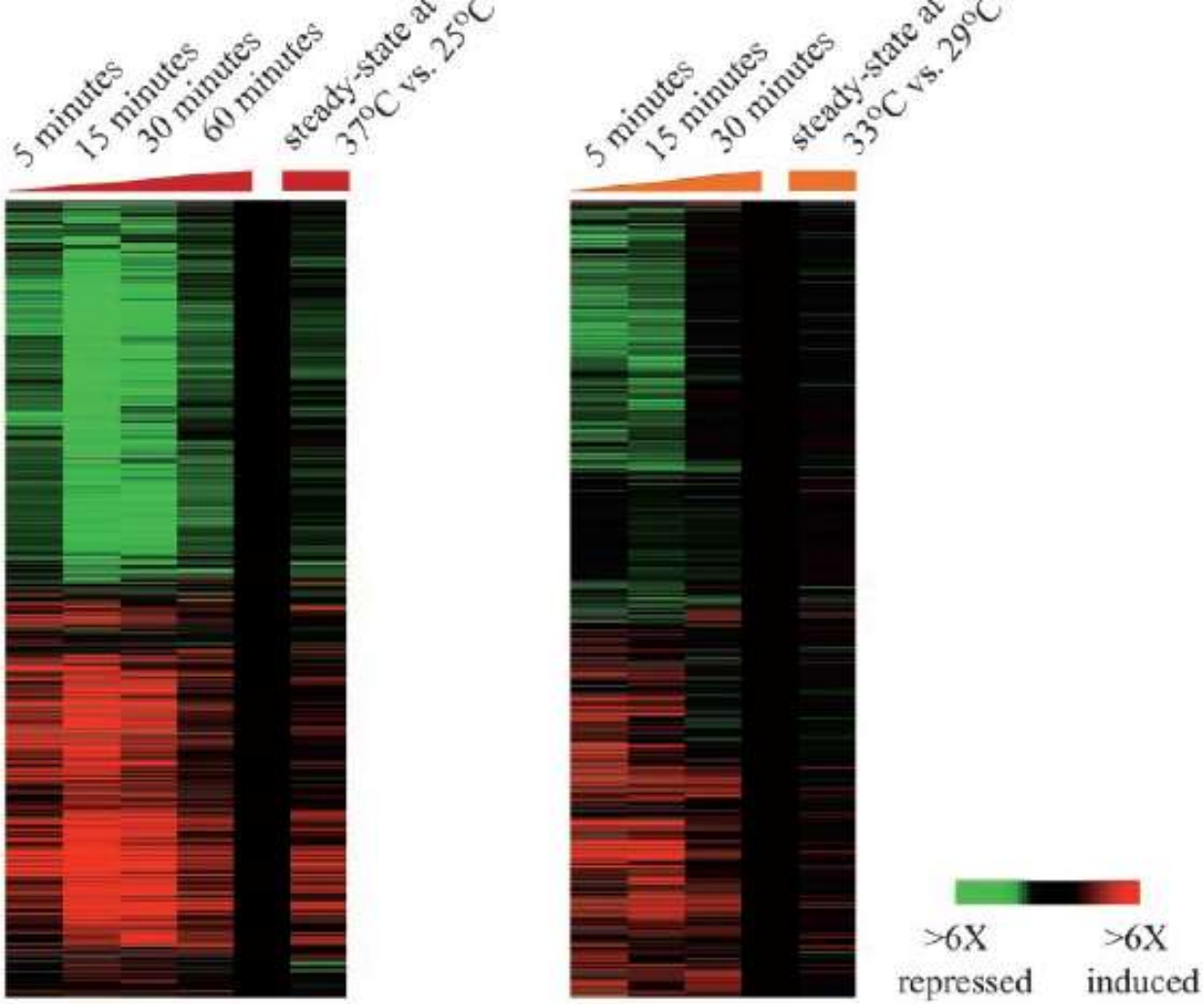
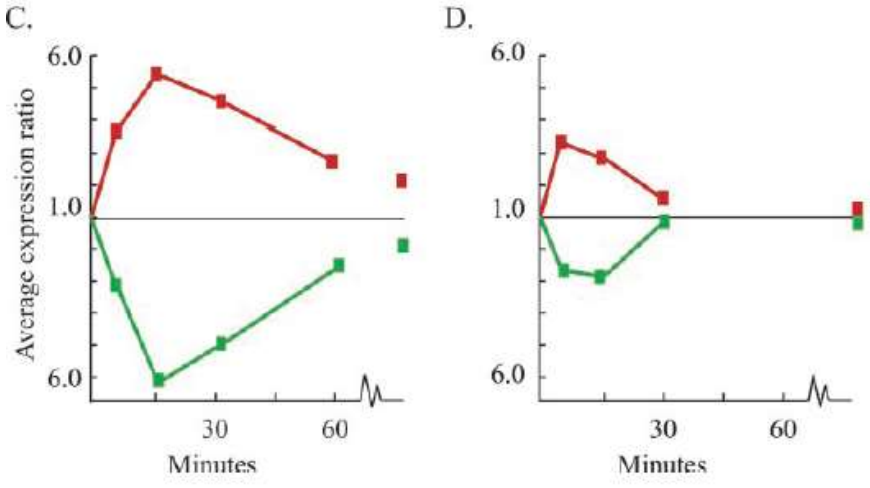


FIG. 2 (color online). Behaviors of an adaptive variable (x_1) in the $N = 3$ case. Responses corresponding to $S = 100 \rightarrow 200$ at $t = 0$ and $S = 200 \rightarrow 400$ at $t = 40$ are shown, respectively. (Left) $\tau_0 = 0.01$, $\tau_1 = 1$, $\tau_2 = 10$ and (Right) $\tau_0 = 2$, $\tau_1 = 1$, $\tau_2 = 1$, zoomed in the inset.

- Exp: microarray analysis (gene expression dynamics) by measuring temporal changes after change in environmental condition
- Many expressions show perfect or partial adaptation; timescales to return are distributed
- ‘conservative tendency in a biological system’: to keep many components at the original level (probably ‘good’state for survival is rare, so that the life system tries to keep it)
- If sow variables regarded as parameters, the parameters have tendency for adaptation （cf Ashby’s ultrastability)
- ‘excitable system in a high-dimension?





Gesch etal, --Yeast, after stress, many expression levels have tendency to comeback towards the original

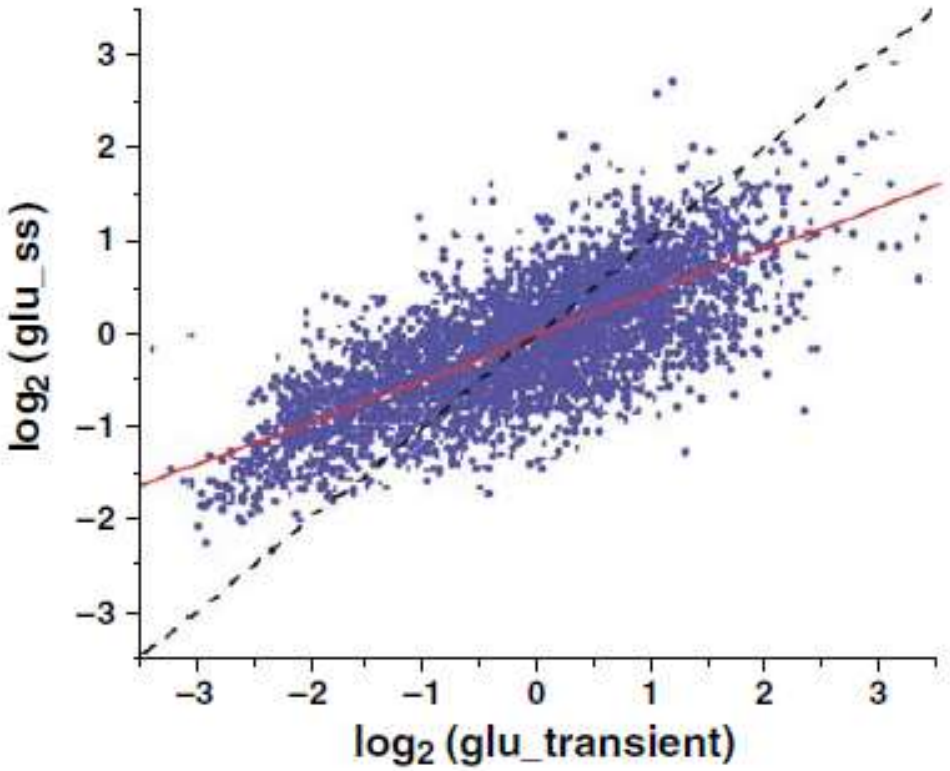
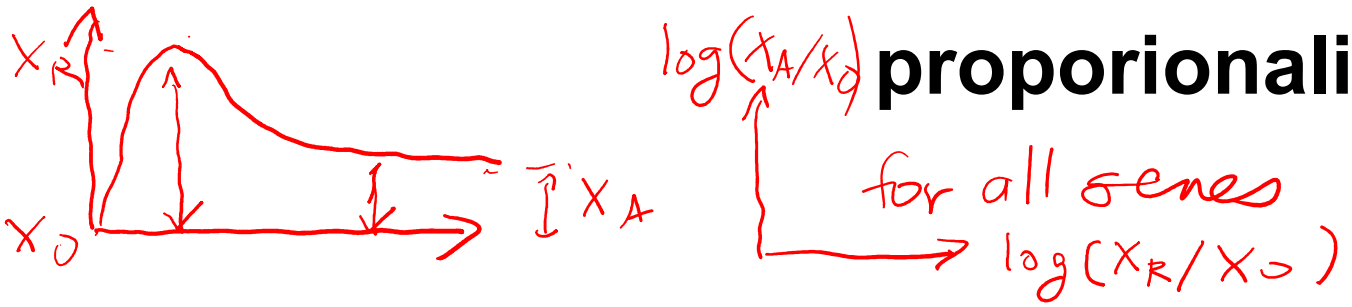


Figure 7 Steady-state transcriptional pattern is well predicted from the transient response. The steady-state expression level (average of the two measurement points in glucose steady state) versus the transient expression level (4th time point in Figure 1B) for the experiment with 40 mM *3AT*. The Pearson correlation between the transient response and steady state is 0.76. The slope deviation from the reference dashed black line represents the overshoot or undershoot in transient expression levels compared to the steady state.

Stern,,.Braun (MSB2007)
Yeast. Global trend in response/adaptation

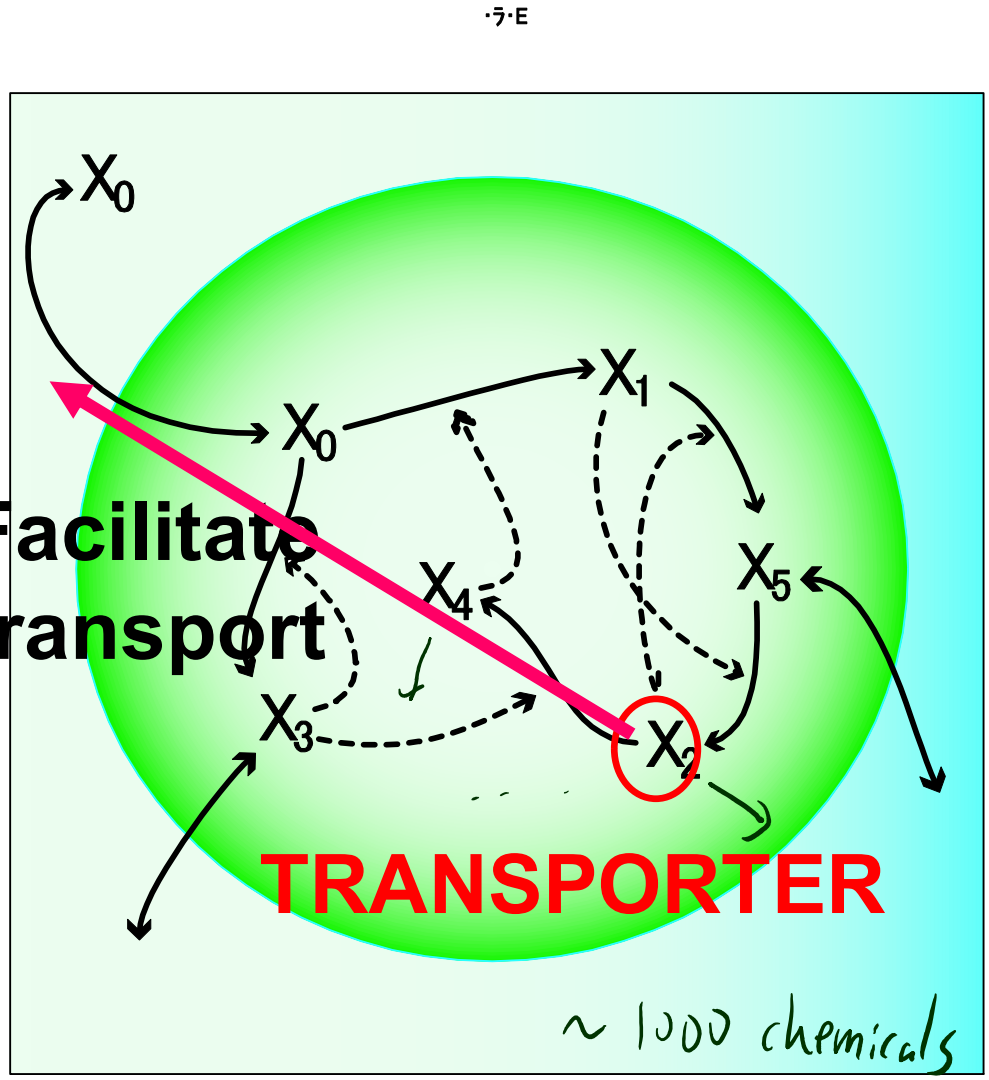
Thousands of gene expression levels show partial adaptation

Further there is common proporionality



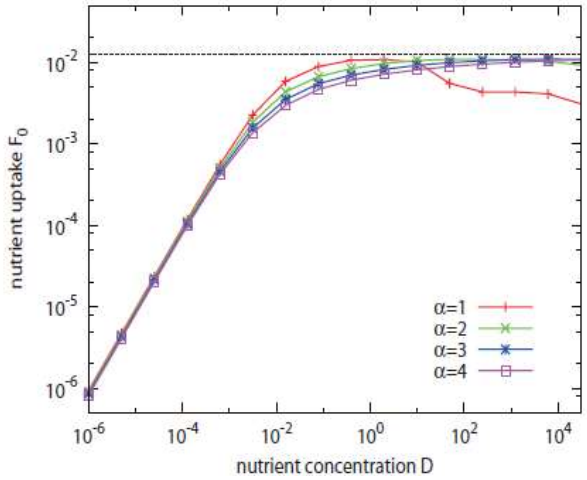
Microscopic Model → Adaptation to Criticality

Transport of resources is usually facilitated by 'transporter' molecule (active transport) instead of passive diffusion
→ self-tune the balance of concentrations of nutrient and catalytic chemicals
adaptive to environment
(Furusawa,KK, PRL,2012)

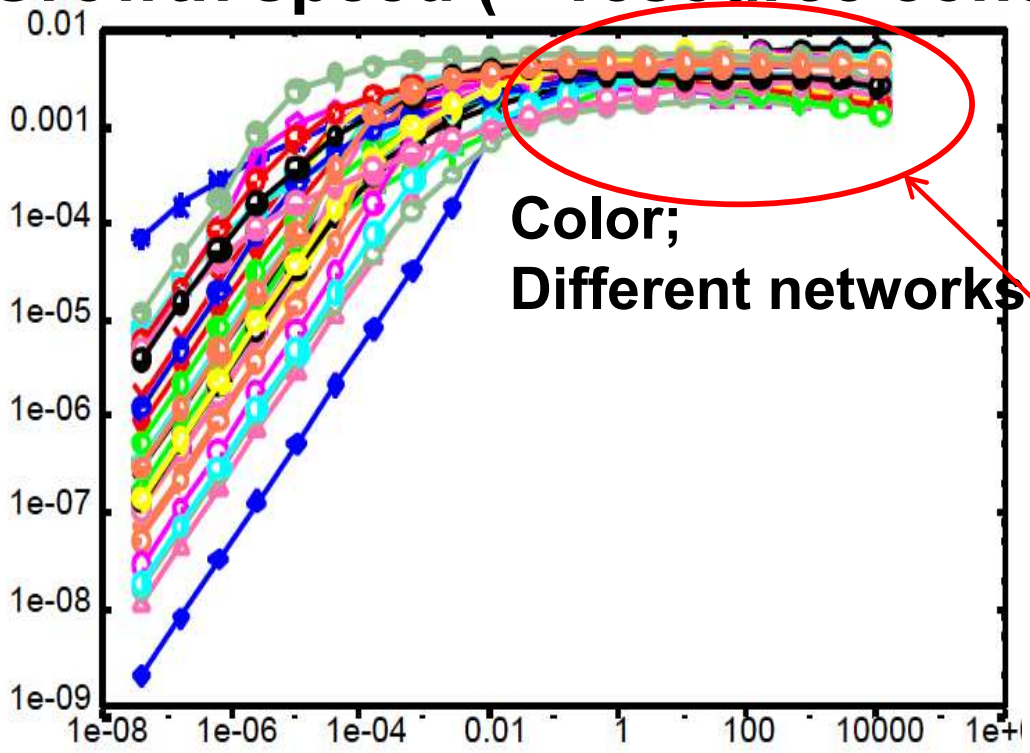


Mutual Dependency leads to maintenance of reproduc

As long as external resource concentration is sufficient, cellular system adapts to a 'critical' state



Growth speed (∝resource conc.)



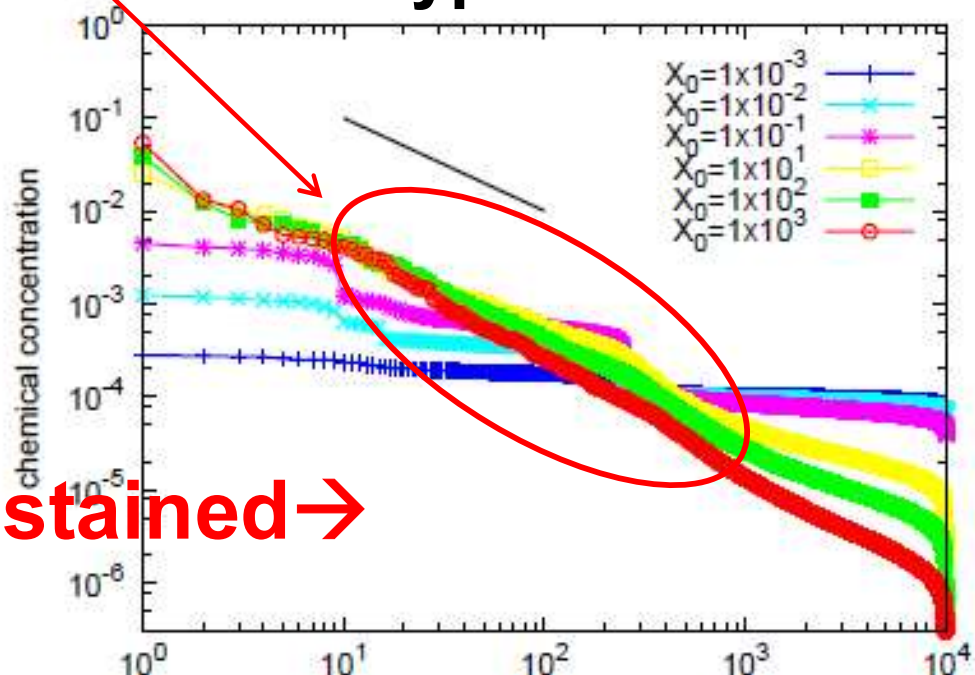
concentration of external resource

Dependence on order of catalysis 1,2,3,4

(for α=1 oscillatory dynamics can appear due to delay for high resource

Also dependence on initial conditions

- mean-field-type calculations



Power law abundances is sustained→

Layer-mean-field

M paths, N components

Layer 0 (resource) → L1 →L2→ …→Lk
catalyst : mean field

$$dm_0/dt = Sm_k^\alpha - (M/N)(1-m_0)m_0 - Sm_k^\alpha m_0$$

$$dm_j/dt = (M/N)((1-m_0)m_{j-1} - (1-m_0)m_j) - Sm_k^\alpha m_j,$$

$j = 1, \cdots, k$, and $M = \rho N$ indicates the mean number of reaction paths

By setting $dm_0/dt = 0$, we obtain $F_0 = Sm_k^\alpha = \rho m_0$, **Growth rate**

$dm_j/dt = 0$, we get $m_j = m_{j-1}(1-m_0)$. Thus, we get $m_k = m_0(1-m_0)^k$.

S is large, $m_k \propto (1-m_0)^k$ follows;

$F_0 \sim \rho$, i

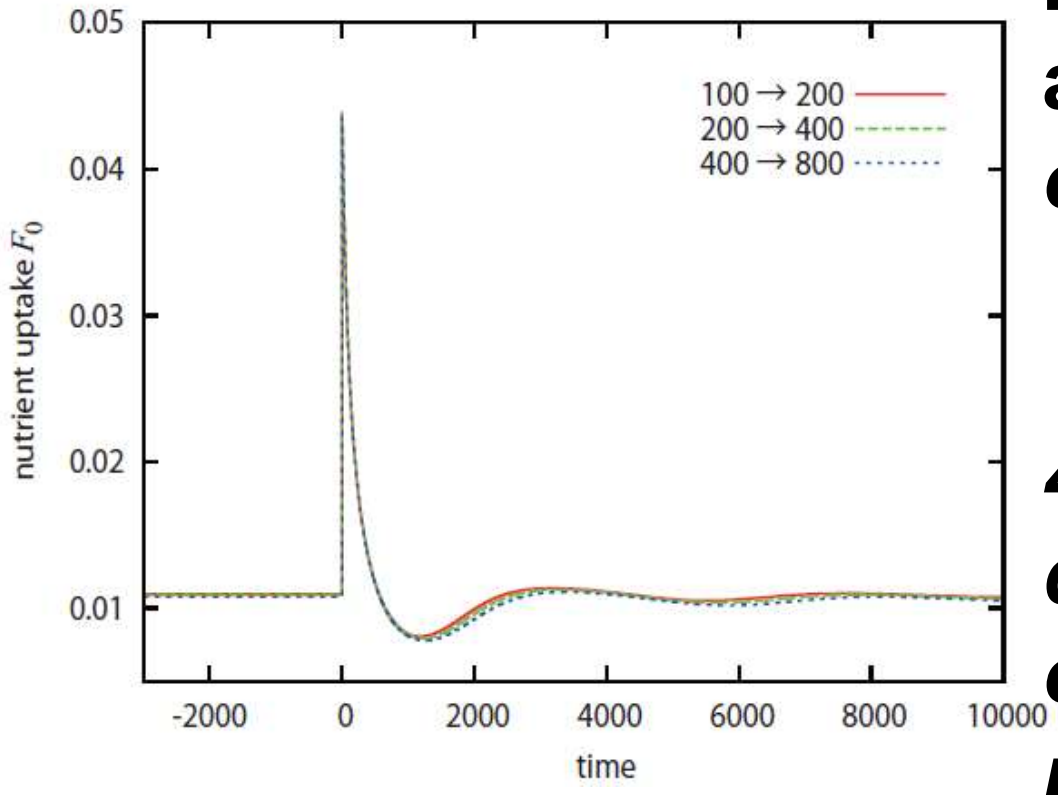
at k-th layer obeys $m_k = m_0(1-m_0)^k$. On the other hand, at each k-th layer, there are $\sim (\rho N)^k$ chemical species. Hence, the ranking of the chemical at k-th layer, denoted by r_k, in the order of abundances increases as $r_k \sim (\rho N)^k$ when ρN is enough large, and thus $k = \log(r_k)/\log(\rho N)$. From these equations, we obtain $m(r_k) = m_0(1-m_0)^{\log(r_k)/\log(\rho N)}$ where $m(r_k)$ represents the chemical concentration of r_k-th ranked chemical. Thus,

$$\log m_k = \log m_0 - \alpha \log(r_k) \qquad \text{(S1)}$$

Adaptation dynamics (Fold Change Detection)

Change in environment (Resource)

Adaptive dynamics (growth speed first changes and returns to the original



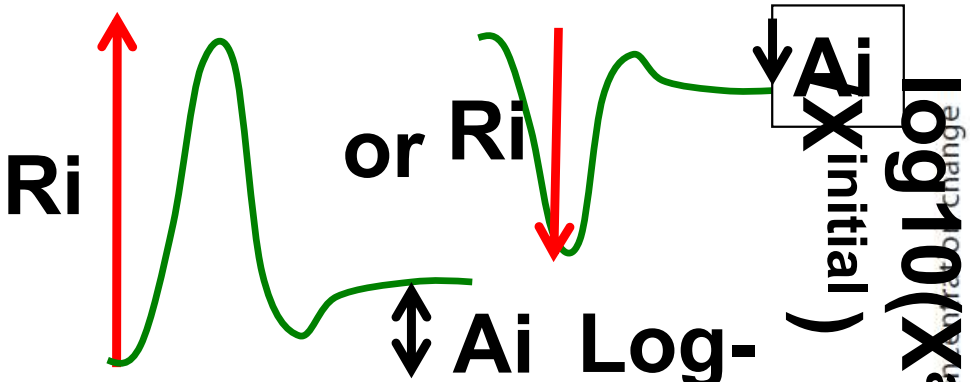
Fold-change detection:

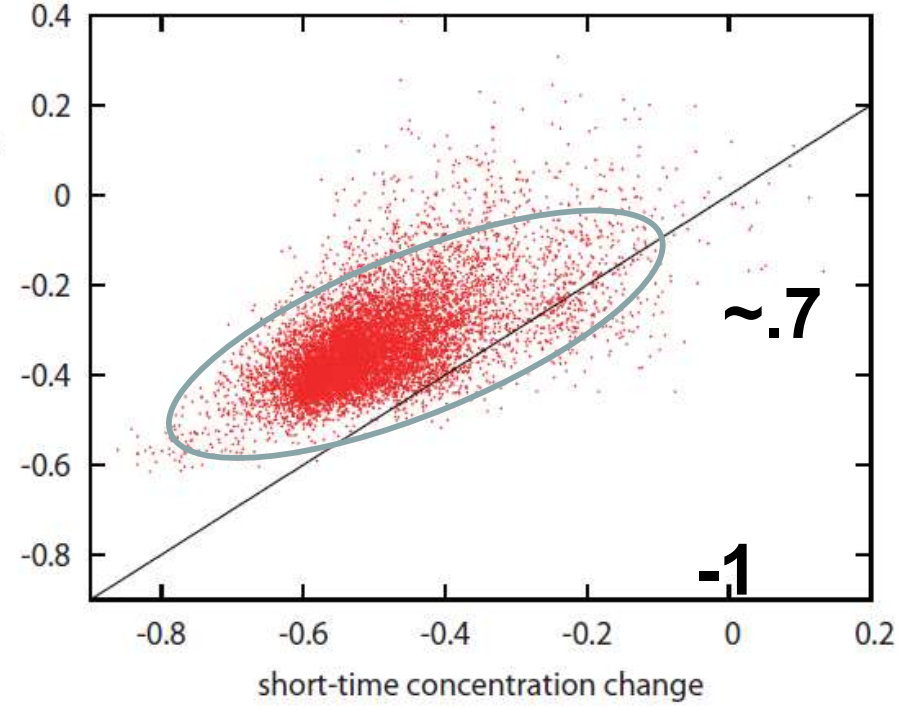
The adaptive dynamics depends only on the ratio of resources before and after. ***e.g., after change of external resources 100 → 200, 200 → 400, 400 → 800 , identical dynamics common in responses of present cells***

(Goentro-Kirschner, Alon et al

Common High-dimensional Adaptation dynamics

all chemicals show 'partial' adaptation



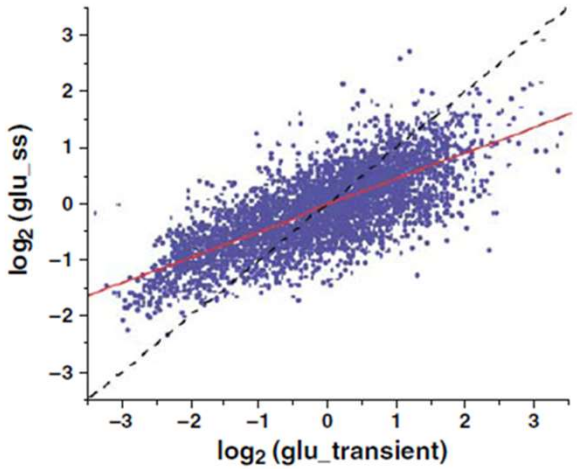


$\log_{10}(X_{adapt}/X_{initial})$

All of 10000 chemicals I show imperfect adaptation.

Response/Adapt

Ri= C * Ai with 1> C>0



$\log_{10}(X^{response}/X^{initial})$

Yeast, change in expression level of each gene by environmental change

Citation: *Molecular Systems Biology* 3:106

Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge

Shay Stern[1], Tali Dror[1], Elad Stolovicki[2], Naama Brenner[1] and Erez Braun[2,*]

- Ideal-Cell-Model of this version

(1)Optimal growth is achieved

(2)Power Law in abundances (Zipf's law)

(3)Adaptation dynamics of growth rate with FCD

(4)General trend of partial adaptation

just by catalytic reaction network +feedback from transporter(=enzyme).

Interestingly, (1)-(4) agree well with the observations in the present cells

(1)-(3) is explained by layer-mean-field theory

Change in enzyme abundances → change in reaction rate → autonomous regulation in time scale? （→Next）

- Robustness of Circadian rhythm (period)

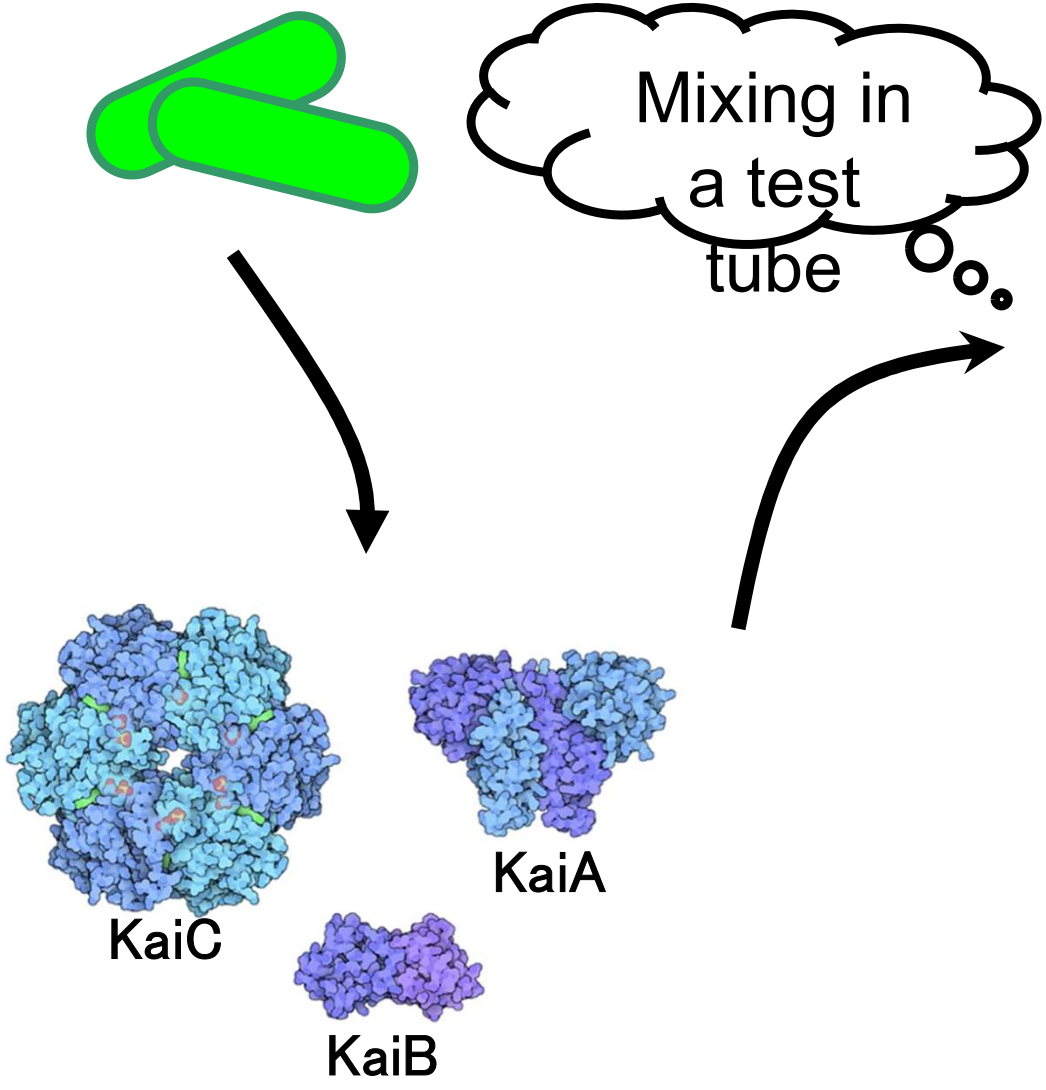
(*T.S.Hatakeyama and KK, PNAS, 2012*)

Circadian rhythm: generated in vitro by just a few proteins (KAI ABC experiments by Kondo)

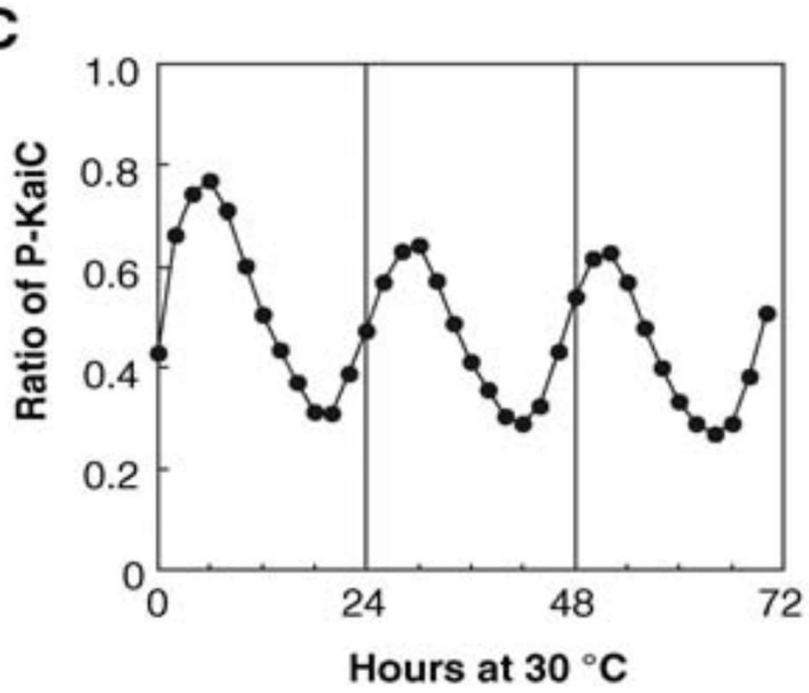
1. ~24 hour rhythm (Slow from protein timesclaes)
2. Period is insensitive to temperature change
3. But, synchronize with external periodic change (eg. 24-hr temperature change)

Response to external change + homeostasis =
Basic problem in biology, common to adaptation

In-vitro reconstruction of circadian rhythm (Takao Kondo's group)



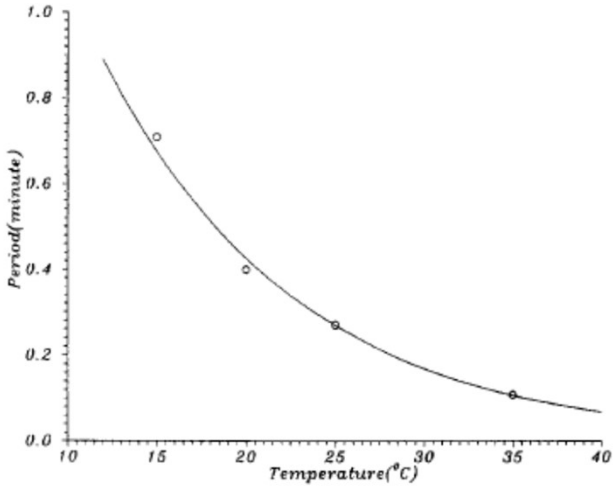
(Ilustrated by David Goodsell)



(Nakajima et al.,Science, 2005)

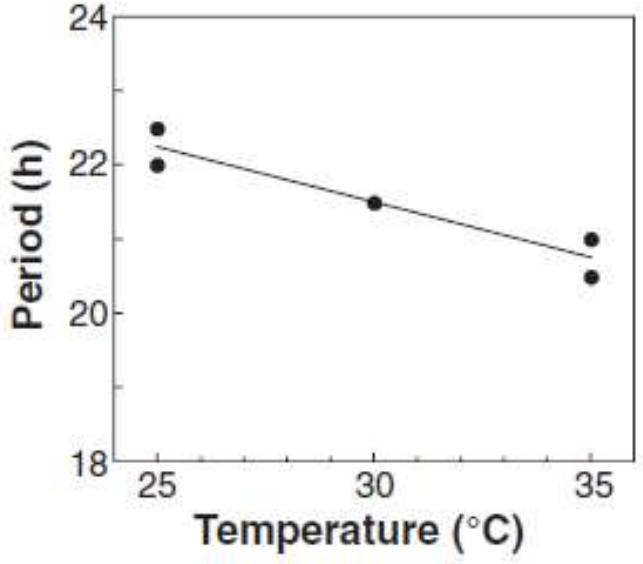
Temperature Compensation

B-Z reaction



In vitro Kai-protein oscillator

Extracted from cyanobacteria)



25℃	0.3 minute	21-22 hours
35℃	0.15 minute	
	50%	95%

(Dutt and Muller. J.Phys.Chem. 1993 ,Nakajima et al,. Science 2005)

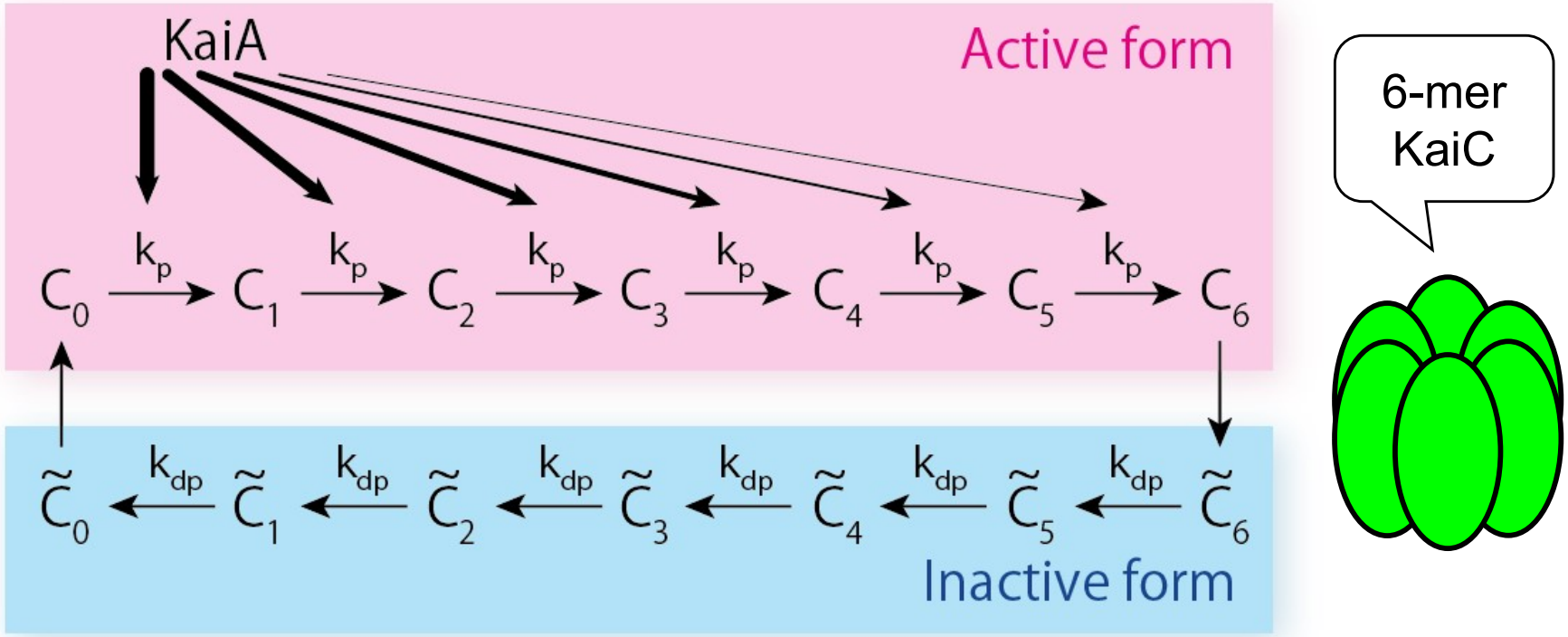
- Question: reaction rate typically changes with exp(-E/kT). How can the period be insensitive to temperature?
- Temperature affect to amplitude (entrainment) → $E \neq 0$
- Since the period is ‘long’, large E would be expected for some reactions
- →Slowness is not explained by smallness of exp(- E/kT)
- System-level compensation?

- Core Idea – enzyme limited competition
- The reaction rate by enzymatic reaction is given by r=A exp(-E/kT) A: concentration of free enzyme
- (i)rhythm consists of several reaction steps forming a circuit where abundances circulate
- (ii) Same enzyme is used by substrates in the circuit
- (iii) These enzymatic reactions rate-limit the cycle
- (iv) increasing T, substrates that bind enzyme increase with exp(-E/kT), so that

available free enzyme A decreases with exp(E/kT)

- Total reactionrate r is independent of temperature

Reaction process (phosphorylation/dephosphorylation)



$$k_p = A_p \exp(-\beta E_p) \qquad k_{dp} = A_{dp} \exp(-\beta E_{dp})$$

$$(E_p > E_{dp})$$

Adapted from (van Zon Lubensky, ten Wolde., PNAS 2007)

Model equation

$$C_i + A \underset{k_i^{Ab}}{\overset{k^{Af}}{\rightleftarrows}} AC_i \xrightarrow{k_p} C_{i+1} + A.$$

Fast — — equilibrium

$$C_6 \xrightarrow{f} \tilde{C}_6, \qquad \tilde{C}_0 \xrightarrow{b} C_0, \qquad \tilde{C}_i \xrightarrow{k_{dp}} \tilde{C}_{i-1}$$

$$\frac{d[C_i]}{dt} = \frac{k_p[A]}{K_{i-1} + [A]}[C_{i-1}] - \frac{k_p[A]}{K_i + [A]}[C_i] + \delta_{i,0} b_i [\tilde{C}_i] - \delta_{i,N} f_i [C_i]$$

$$\frac{d[\tilde{C}_i]}{dt} = k_{dp}([\tilde{C}_{i+1}] - [\tilde{C}_i]) - \delta_{i,0} b_i [\tilde{C}_i] + \delta_{i,N} f_i [C_i]$$

$$K_i (= k_i^{Ab} / k^{Af})$$

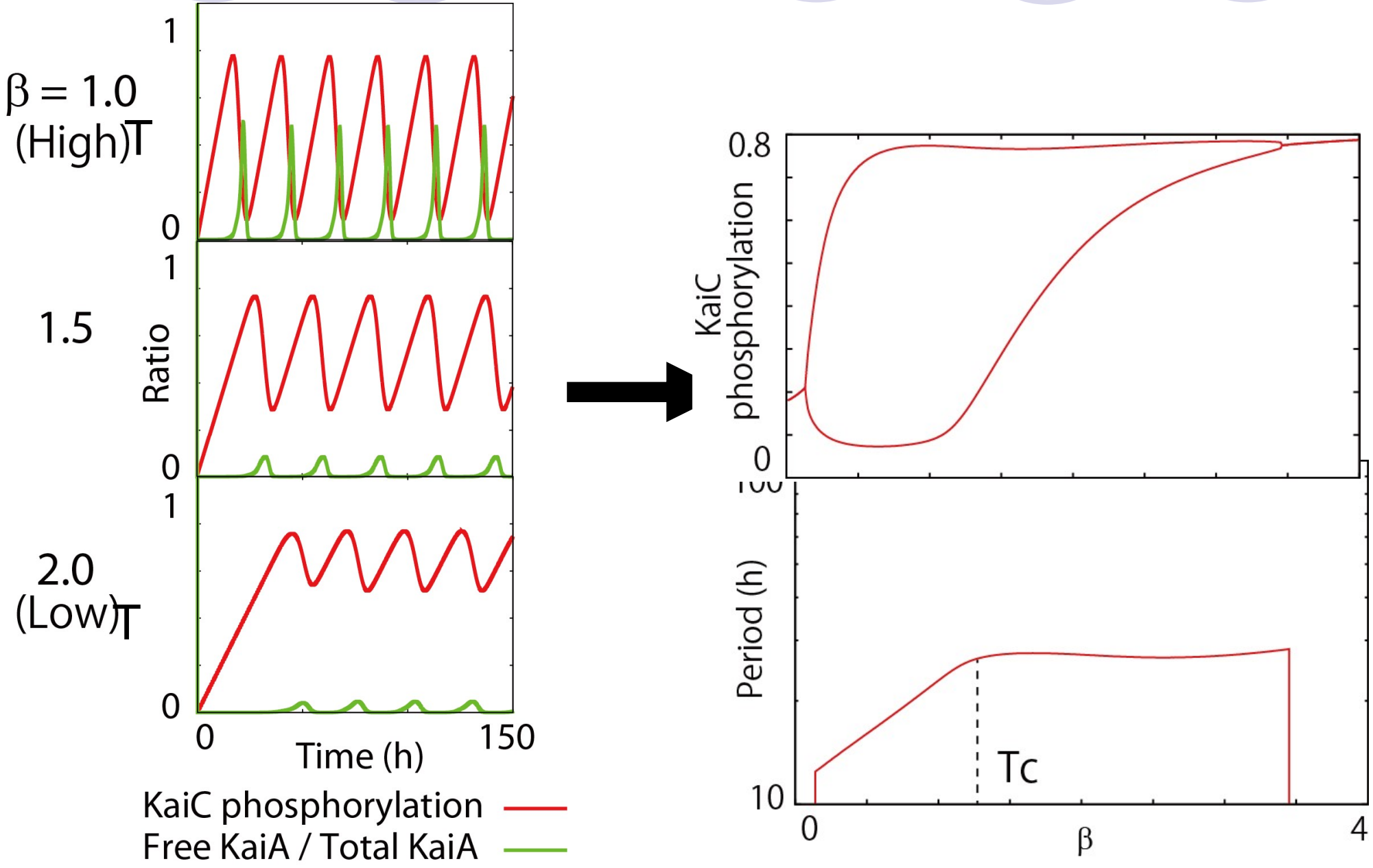
$$K_i = K_0 \alpha^i (\alpha > 1.0).$$

$$[A]_T = [A] + \sum_{i=0}^{N-1} \frac{[A][C_i]}{K_i + [A]}$$

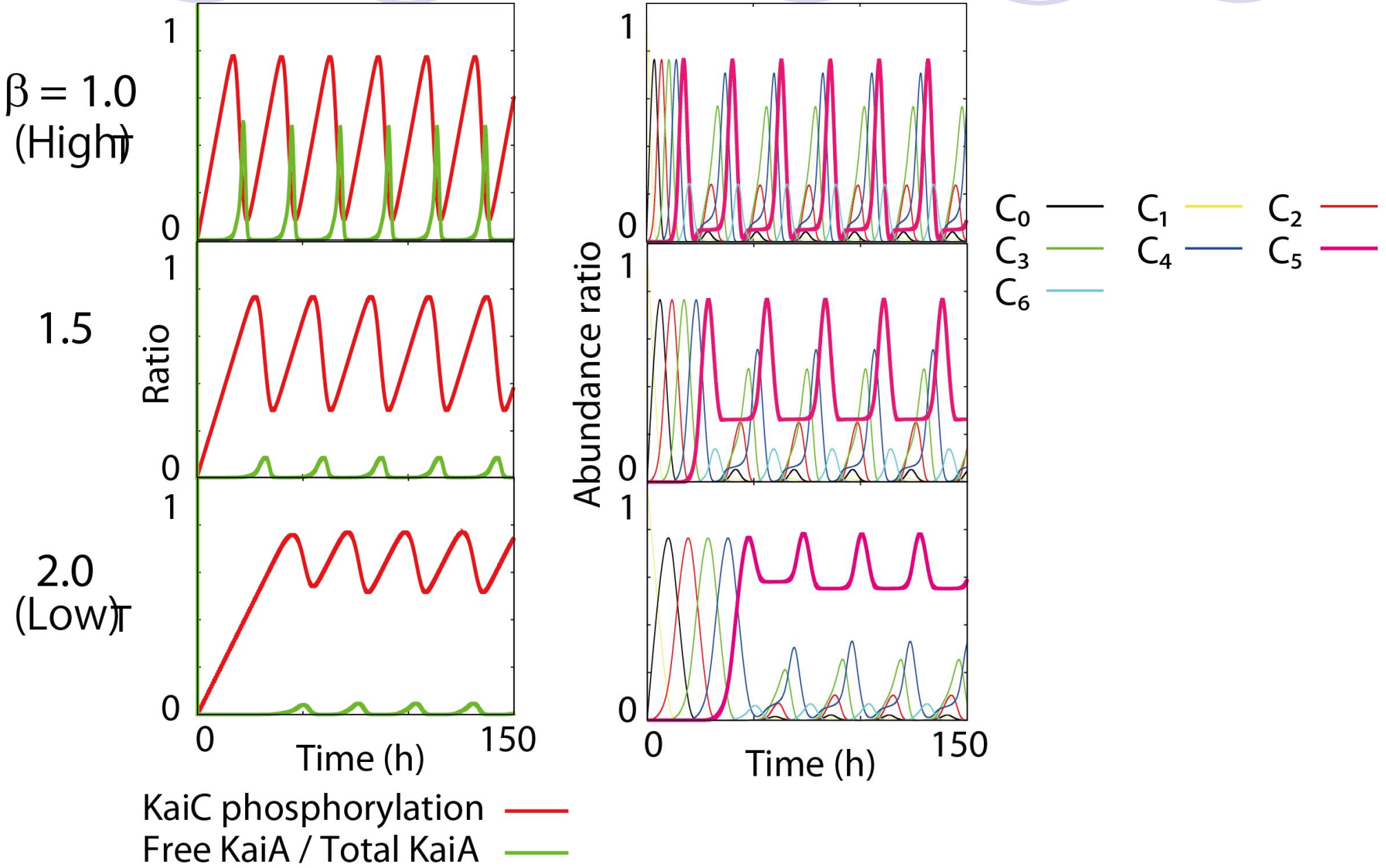
Total enzyme (const)
= Free+ Bound

$$k_p = A_p \exp(-\beta E_p) \qquad k_{dp} = A_{dp} \exp(-\beta E_{dp})$$

Below certain Tc, the period is insensitive to temperature, but the amplitude is lowered with lowering temperature

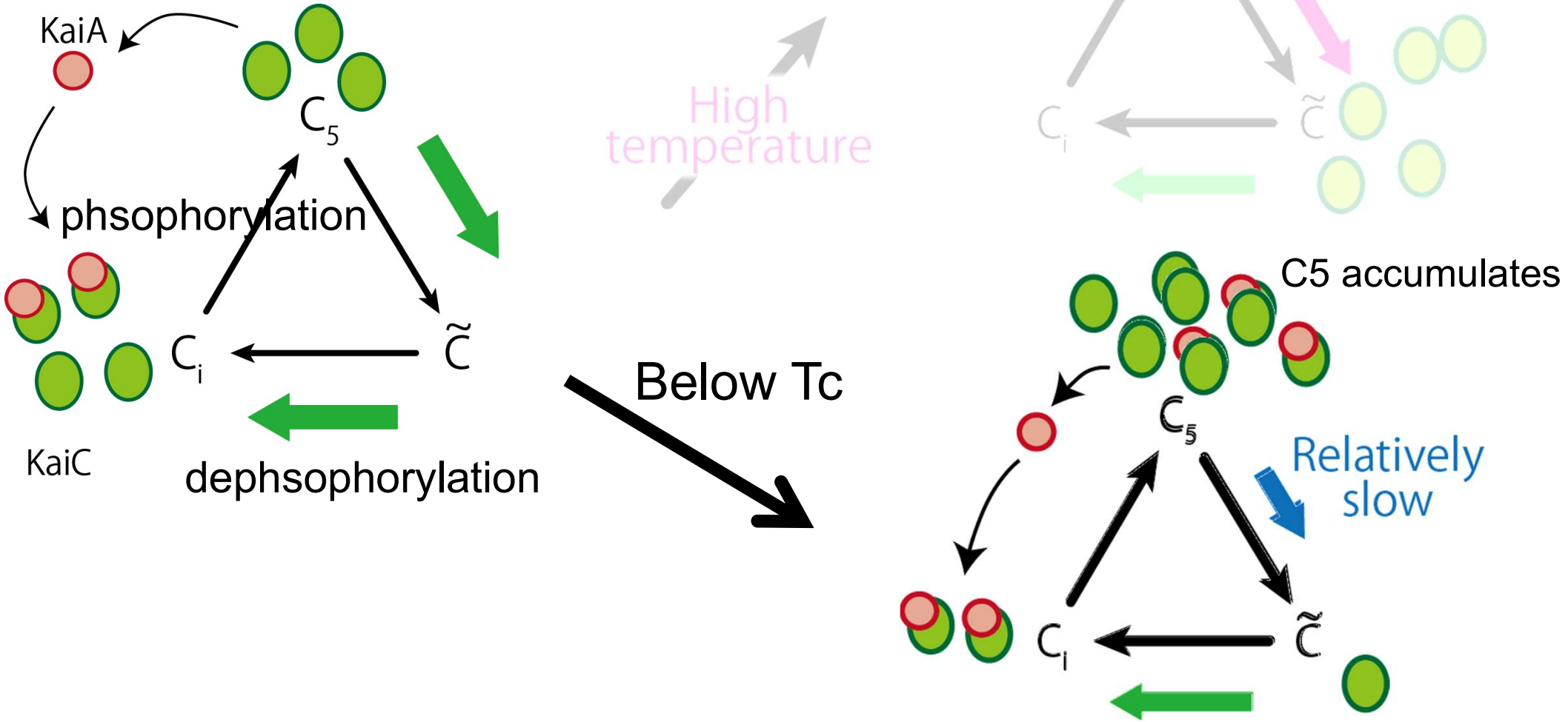


Below Tc, C_5 is accumulated, which leads to shortage of free Kai A enzyme



At the temperature-compensation region, phosphorylation is rate-limited ← Ep>Edp

At the critical temperature (Tc)

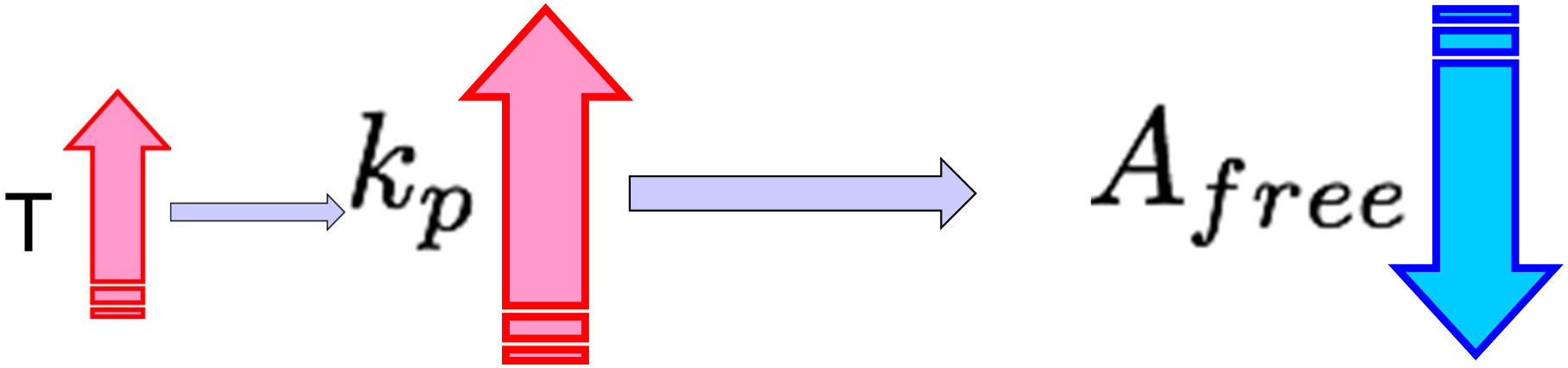


Enzyme-limited competition (ELC)

By lowering (increasing) temperature→

Abundances of reacting substrates at the phosphorylation circuit decrease (increase) →

Abundances of free enzyme (that is not bound with substrates) increase (decrease)

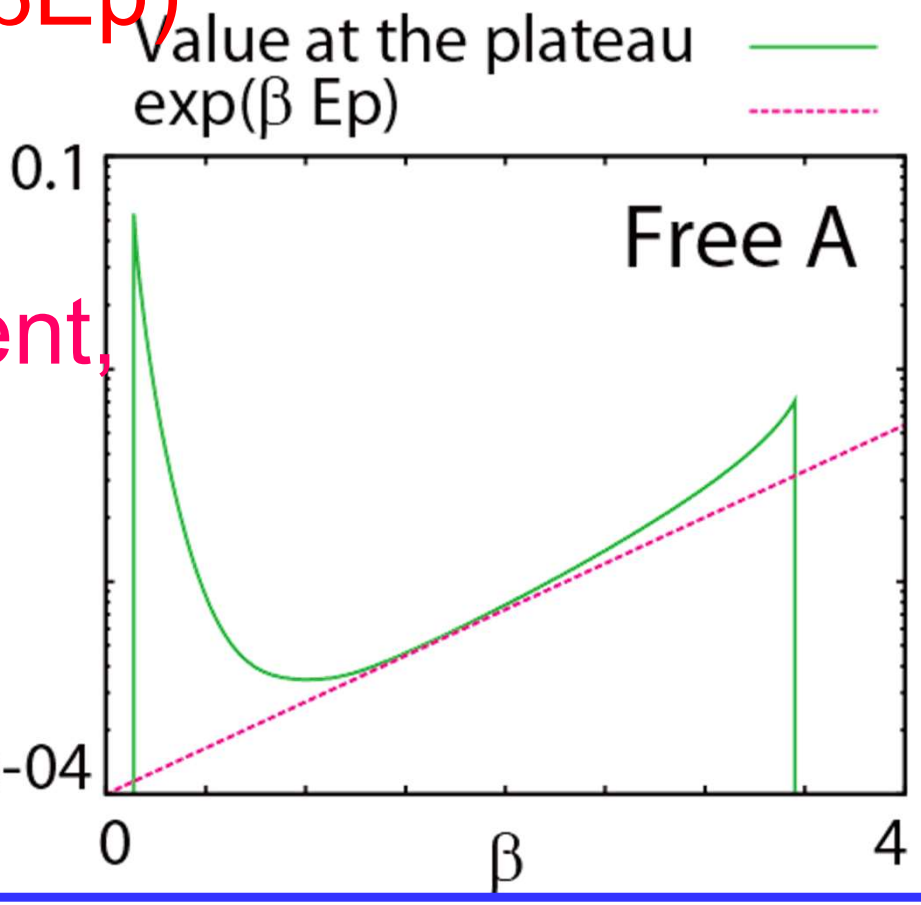


(details)Enzyme-limited competition (ELC)

(1)Flow at phosphorylation process change with exp(-βEp)

$$\Sigma\tilde{C} \propto \exp(-\beta(E_p - E_{dp}))$$

$$C_i \sim k_{dp}\Sigma\tilde{C} \propto \exp(-\beta E_p)$$



(2)When A_{total} is not sufficient, due to ELC, available free enzyme decreases with exp(βEp) against T↗

Phosphorylation process slows down at phosphorylation level m ∼2, while C5 is accumulated

$$A \simeq \frac{A_{\text{total}}}{1 + C_m/K_m} \simeq \frac{A_{\text{total}}K_m}{C_m} \propto \exp(\beta E_p).$$

$$A_{free} \sim \exp(\beta E_p)$$

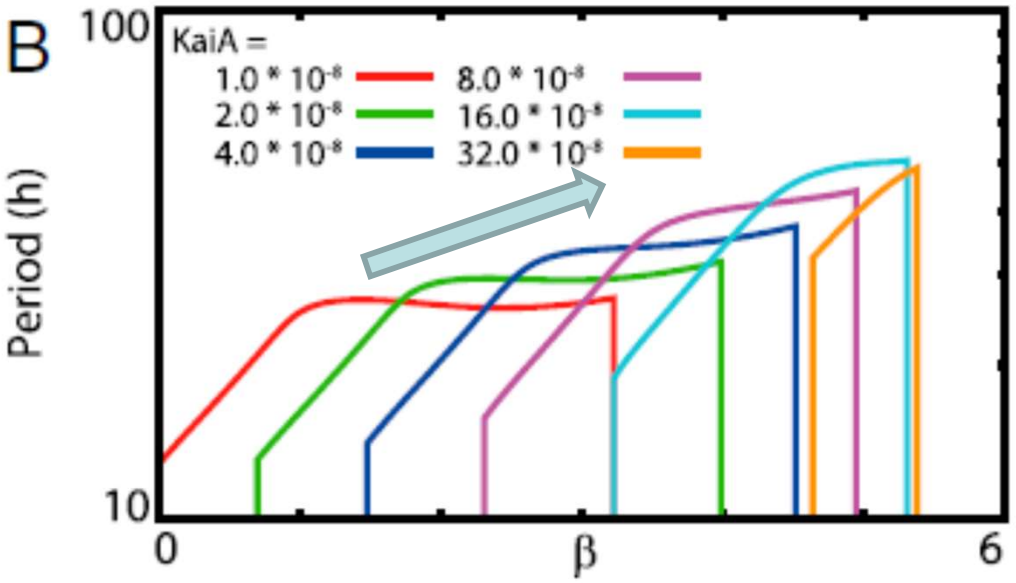
$$k_p A_{free} \sim \exp(-\beta E_p)\exp(\beta E_p) \sim 1$$

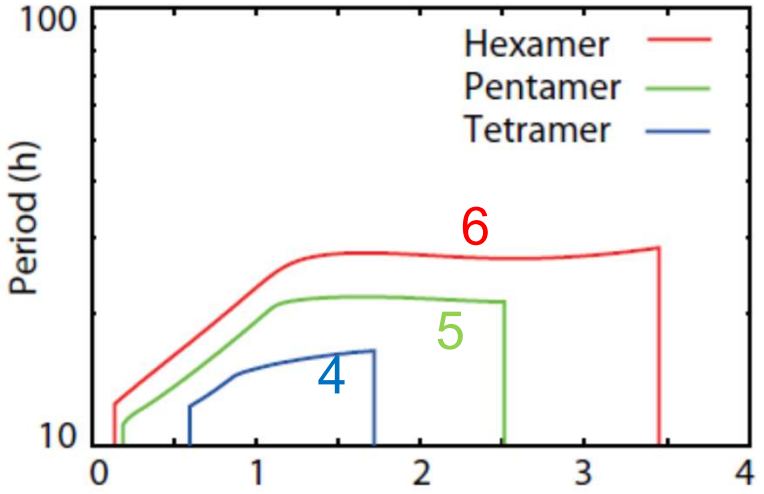
A bit more…

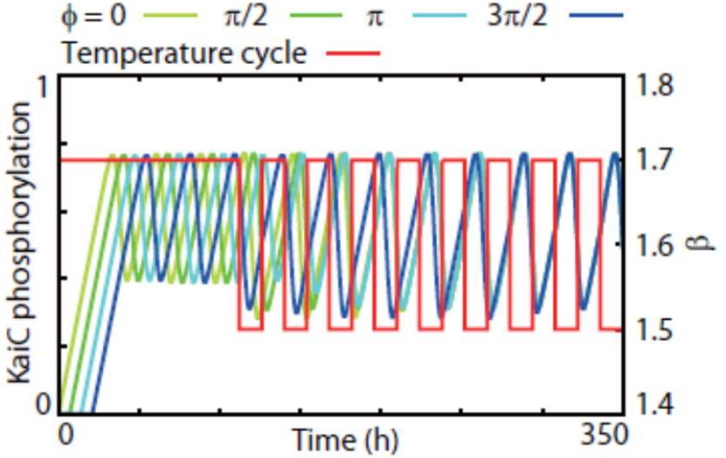
(i)As the total Kai A increases, the temperature compensation region decreases

(ii) If phosphorylation sites are less, temperature compensation (and limit cycle) region decreases, >3 required

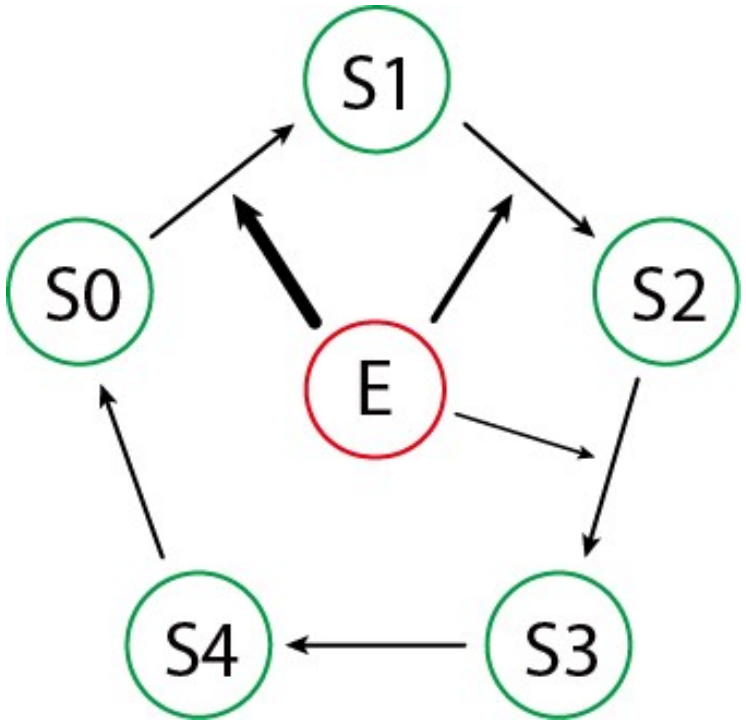
(iii) Against cyclic change in temperature, the entrainment occurs (as in experiments)

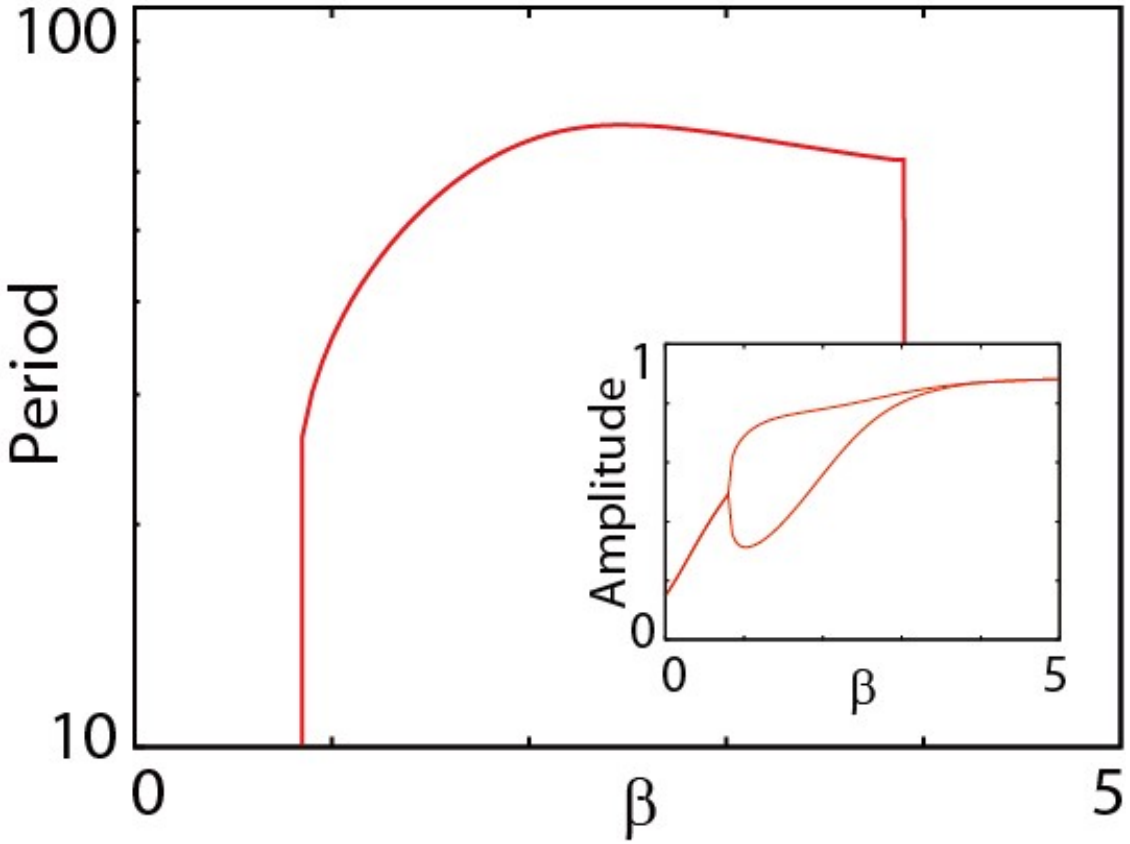






Generality:The ELC mechanism is confirmed for much simpler cyclic reaction to lead to temperature compensation





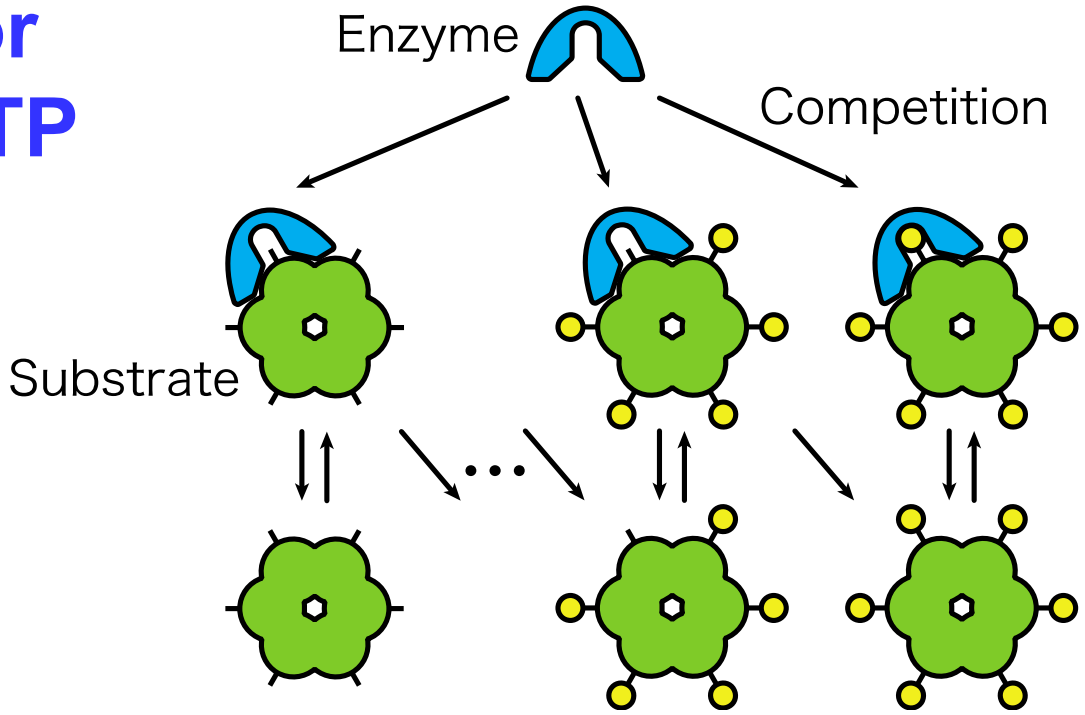
Summary of this part

- Temperature compensation is achieved by autonomous change in free enzyme
- →No need for balance mechanism by fine tuning (through evolution)

Enzyme-limited competition (ELC)

→Other robust behavior (e.g., to the change in ATP concentration)

homeostasis in biological system?



Robustness vs plasticity in biological clocks

PRL 115, 218101 (2015) PHYSICAL REVIEW LETTERS week ending 20 NOVEMBER 2015

Reciprocity Between Robustness of Period and Plasticity of Phase in Biological Clocks

Tetsuhiro S. Hatakeyama* and Kunihiko Kaneko

- Robustness
  - Temperature compensation
  - Nutrient compensation
- Plasticity
  - Temperature-entrainability
  - Food-entrainability
  - Light/dark-entrainability

APS physics | Physics

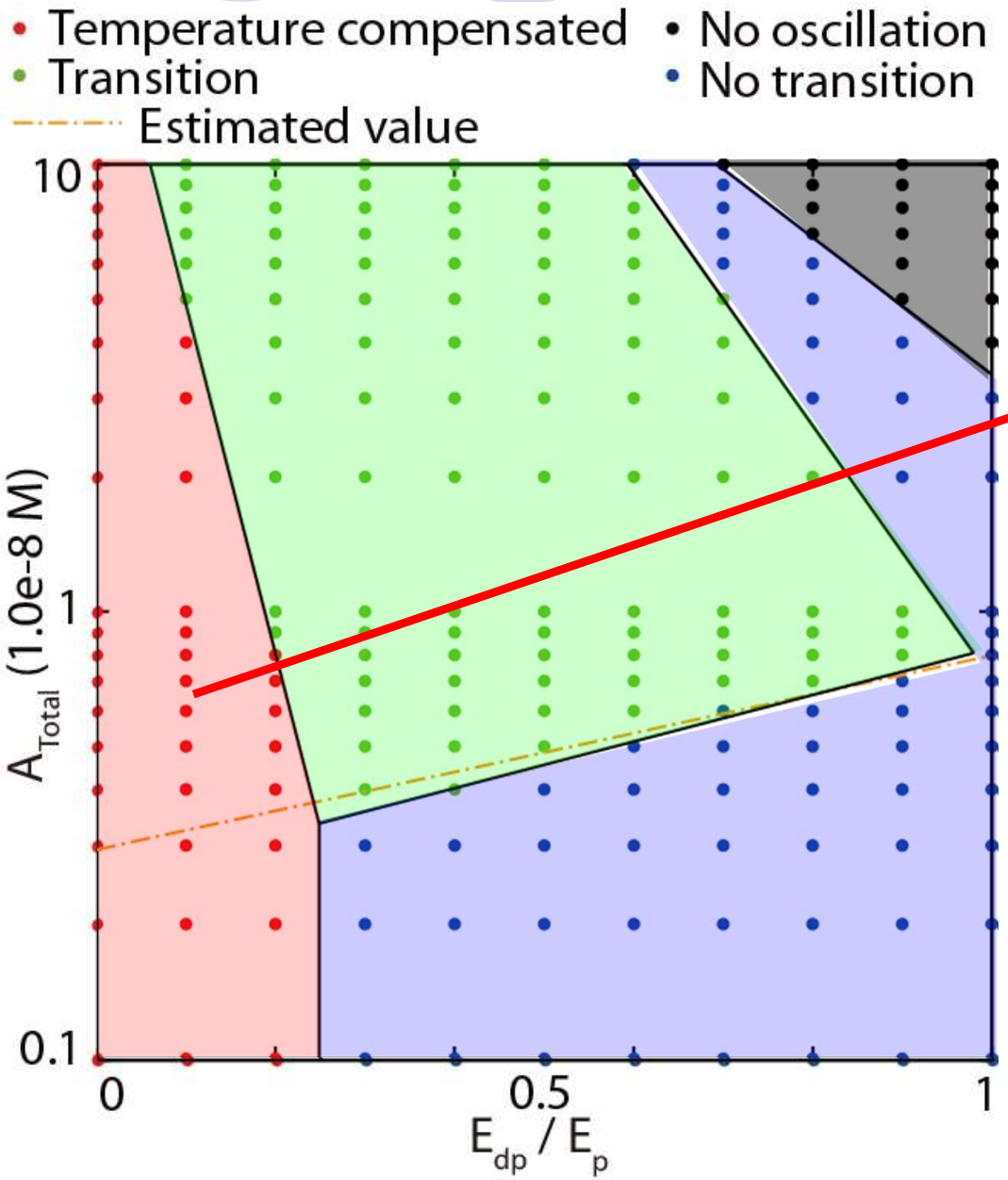
Synopsis: Robust Yet Flexible Clocks

November 19, 2015

A theoretical analysis explains why circadian clocks can be robust but also able to adapt to environmental changes.

iStockphoto.com/MarkSwallow

Phase Diagram



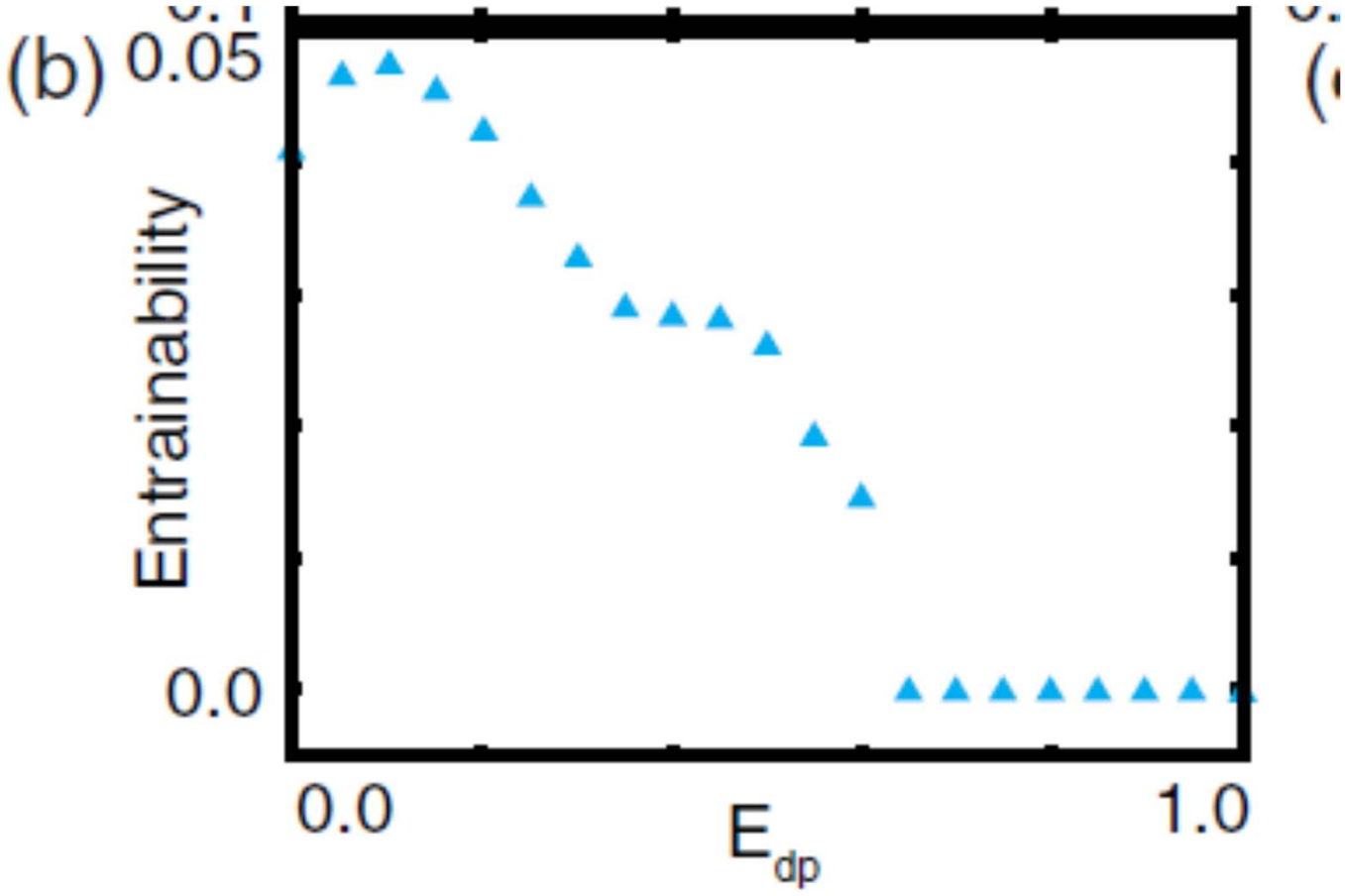
Condition for the present Temperature Compensation

1 E_{dp} / E_p small （Ep>>Edp）

2 A_{total} small

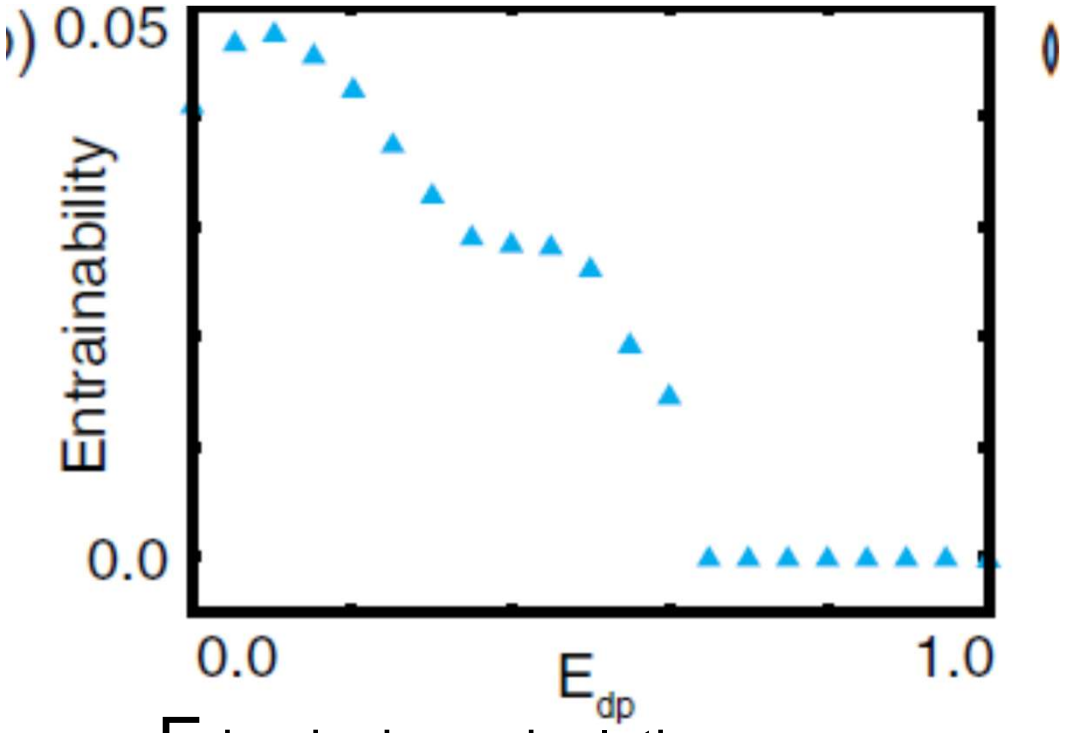
As the condition is relaxed, period robustness gets worse

Entrainability=inverse of time needed to entrain



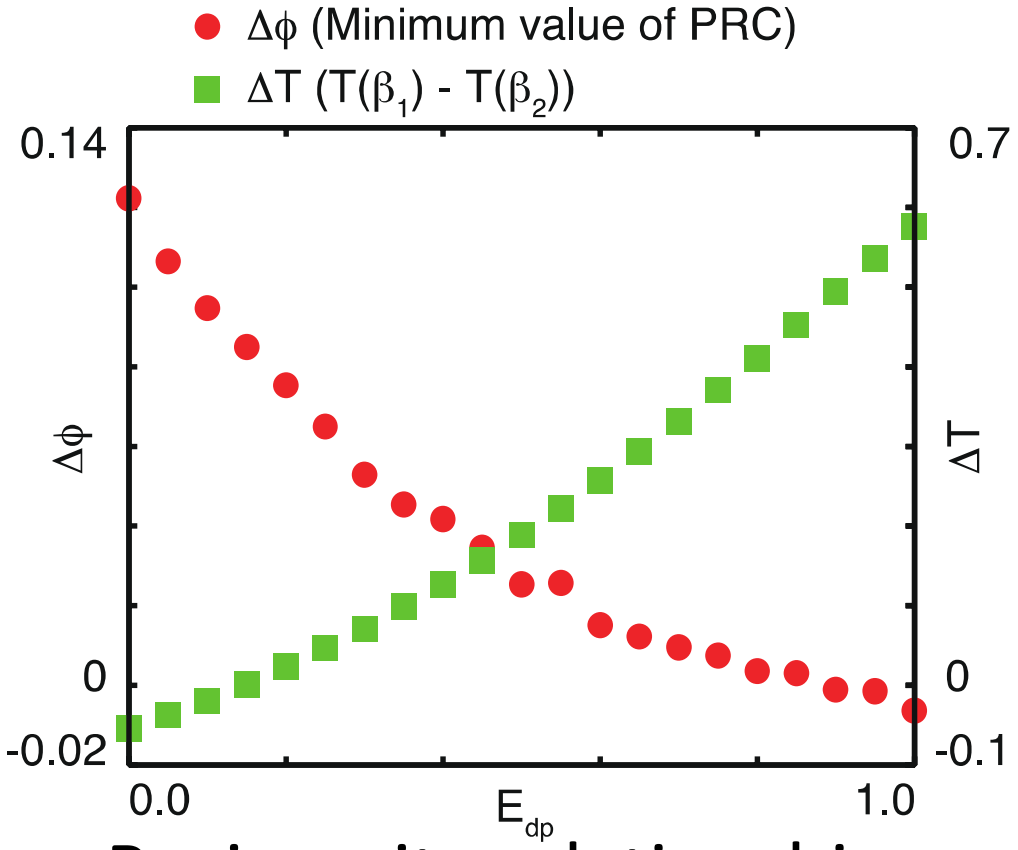
Well temperature-compensated clock shows high temperature-entrainability

Entrainability=inverse of time needed to entrain



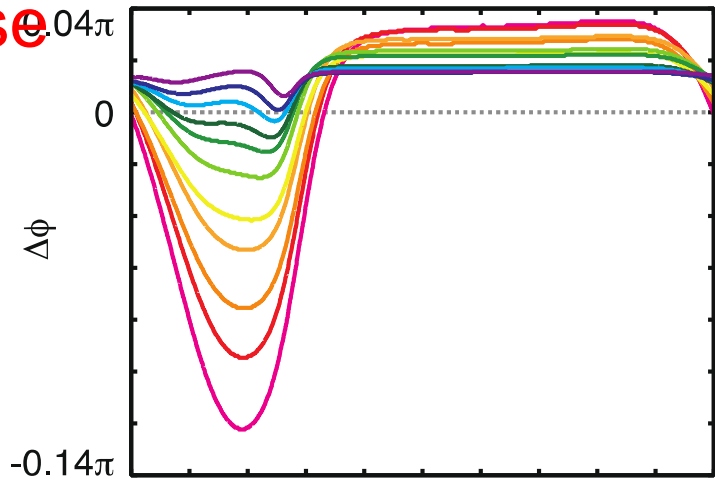
Edp: dephosophrylation energy, smaller → temp compensation

Reciprocity relationship

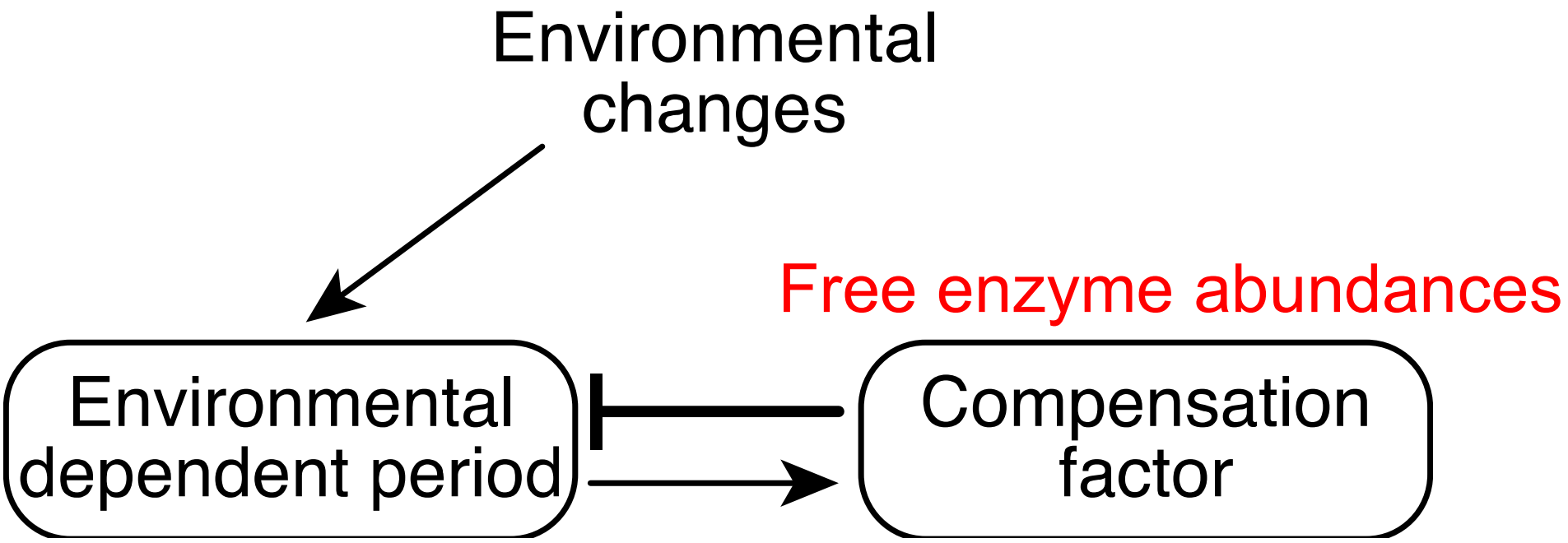


Reciprocity relationship b etween Δϕ and ΔT

Phase Response curve→ degree of plasticity in phase ⊿φ



Reciprocity relationship – general. – compensation needs time



compensation needs time (delay),
during which phase is shifted,
Strong compensation
→ Low environmental dependence
and large phase shift ：

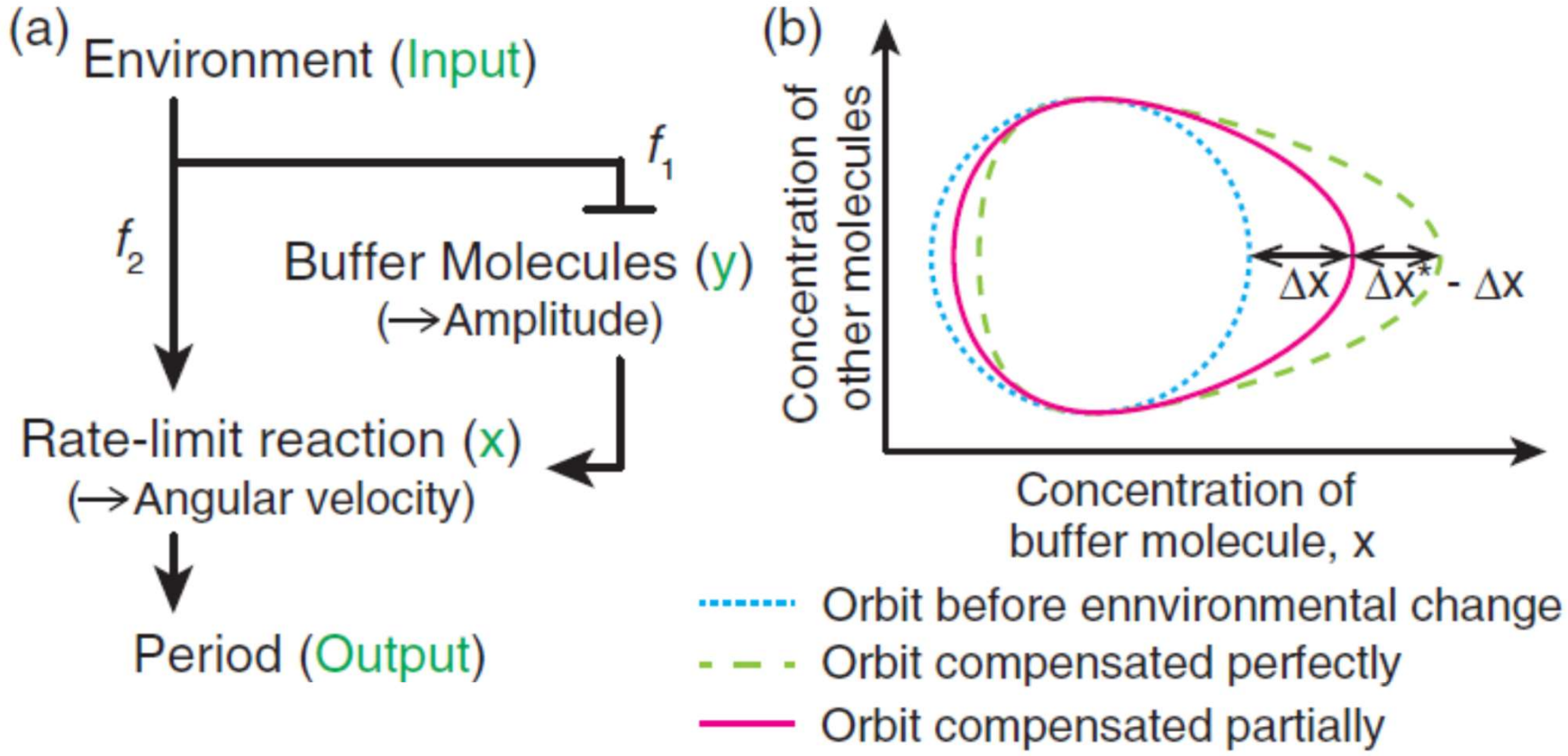


FIG. 3 (color online). Schemes of the reciprocity between the robustness of period and plasticity of phase. (a) Schematic networks of a generic (bio)chemical oscillator exhibiting homeostasis of period. Pointed and flat arrowheads indicate positive and negative regulation, respectively. Correspondences with a simple feedforward adaptation motif are represented by green characters in parentheses. (b) Scheme of limit-cycle orbits with compensation of the period against environmental change. Blue dotted line

Summary of this part

- Robustness & Plasticity: Two important features in biological systems
- But they seem to be in opposite direction (consider a process deepening the potential valley)
- Possible answer:

1) Conjugate variable (eg phase and period), robustness to one variable ~ plasticity to the other (reciprocity)
2) Buffer process for adaptation (robustness) provides the basis for reciprocity

→ Generalized?

Q

Consider a model that shows the adaptation in the sense of robustness (homeostasis), in which most variables have tendency to return to the original. Then, examine if there is a ‘plastic’ variable. Discuss, if possible, relationship between robustness and plasticity