Kinetic Memory

Cells -memorize the history of environmental inputs

（1）classic example

When the paramecium is placed in a culture environment with a temperature gradient, it moves toward its original temperature position. Internally, an adaptive process occurs. However, if exposed to a new temperature for a longer period of time, it will remember that temperature as the temperature to which it should return. (cf Fumio Osawa), in Biophysics of Complex Systems). In other words, the adaptation of adaptation process can be regarded as memory.

- Yeast memorizes internal states over 40 generations (Mark Segal)
- Epigenetically Heritable states of Fly (D melangoster), Stem,.,Braun, and Yoav Soen
- Unicellular organism: cellular states transferred to next generation. (eg protein abundances)

Still, the information on abundance is reduced by cell division, after 10 division, relaxes 2^{-10} ~1/1000

- ＊＊epigenetic—— ‘magic word?’

Methylation, histon modification etc…

Still how such molecular changes are maintained over generations?

Other long-term sustainment in cells

- Dormant state、 spore, seed

Almost closed, but “living state” sustained over years – nonequilibrium states?

Glass?

＊＊physical viscosity increased, molecules cannot move/react?

Water → trehalose

+ an alternative view before it (-> chemical net glass ?

Biological System:

*Adapt to variety of conditions while preserving its behavior ('homeostasis')

- Memory --tendency to stick to a certain state even after the change in external condition

→Atypical behavior in physico-chemical system

System-level property of catalytic reactions???

Core idea:catalytic reactions→ reaction-rate,thus, timescale, depends on catalyst concentration

Autonomous regulation in the concentration of catalysts → autonomous control of state → homeostasis and memory

Genuine Slow relaxation process in catalytic reaction network

external nonequlibrium but internal equilibrium?

inside → different class of nonequlibrium.

Enzyme --- autonomous regulation of time scale then again sustainment of non-equlibrium condition distinct from outside

Out-of-equilibrium: usually assumed in models of cells (cf dissipative structure)

Somehow sustained autonomously? At least somehow the system is kept off from easily falling to equilibrium?

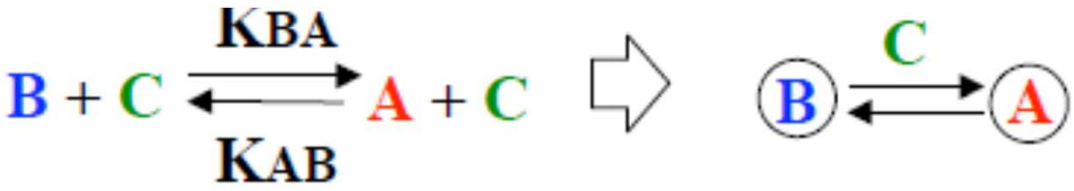
Long-term sustainment of non-equilibrium state

Proposal of 'Chemical Reaction Net Glass"

Simple catalytic reaction network **A.Awazu PRE 2009**

CLOSED SYSTEM

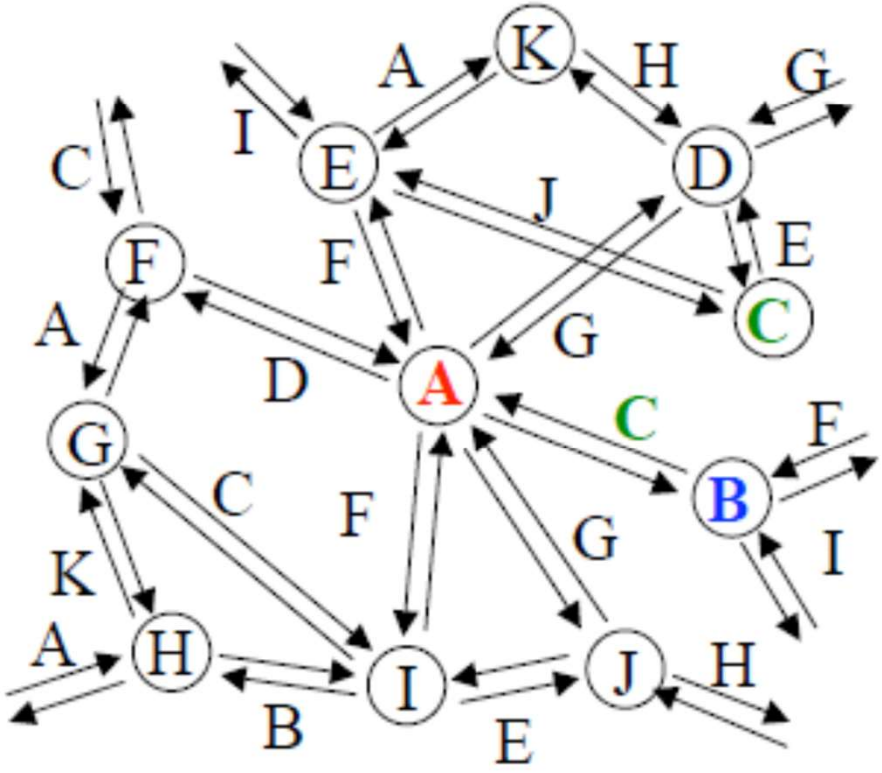
$$X_i + X_c \rightleftharpoons_{k_{j,i}}^{k_{i,j}} X_j + X_c.$$



$$\dot{x}_i = \sum_{j,c} Con(i,j;c) x_c (k_{j,i} x_j - k_{i,j} x_i),$$

$$k_{i,j}/k_{j,i} = \exp(-\beta(E_j - E_i))$$

$$k_{i,j} = \min\{1, \exp(-\beta(E_j - E_i))\}$$



Ei distributed : stnd deviation ε

RELEVANT parameter βε

Equilibrium distribution exp(-βEi) : (←detailed balance)

Relaxation process: Initial : β=0(high temp) for all species, i.e., equal probability for all chemical species.

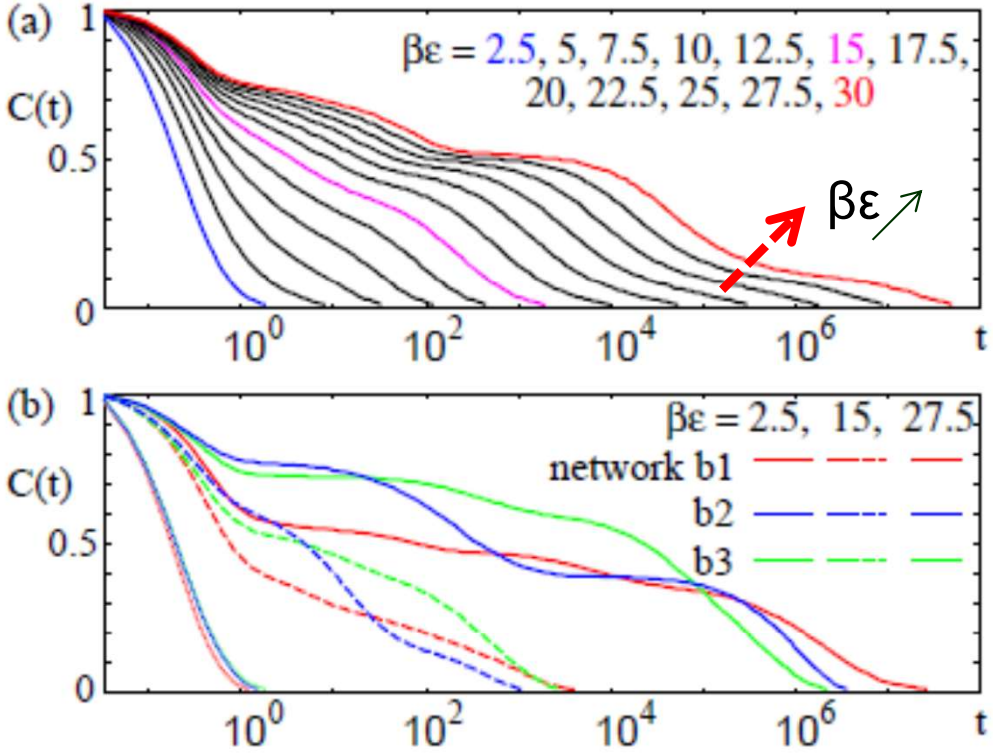


FIG. 1: (a)(b) Relaxation time course for four sets of networks ($M = 24$, $K = 8$) for several β.

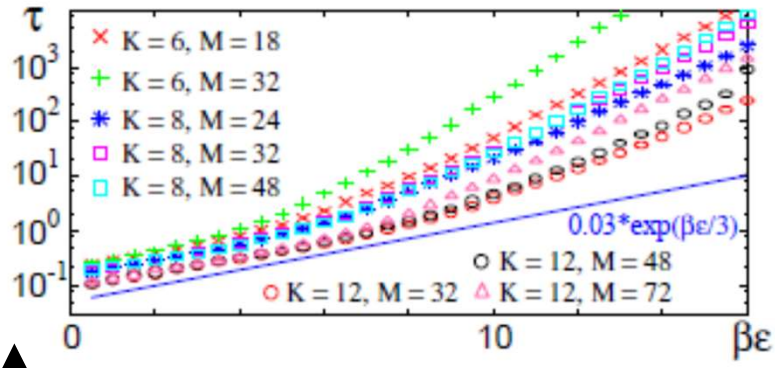


FIG. 2: Relaxation time as a function of β for the sampl reaction networks in Fig. 1(a)(b).

$$\tau = < \int_0^\infty |C(t)|\, dt >$$

$$C(t) = \frac{\left\langle (\vec{X}(t) - \vec{X}^{eq})(\vec{X}(0) - \vec{X}^{eq}) \right\rangle}{\left\langle (\vec{X}(0) - \vec{X}^{eq})^2 \right\rangle}$$

Deviation from equilibrium

Two salient features in relaxation analogous to 'glass'

(1) Log-t slow relaxation (rather than exponential)

(2) Existence of plateaus

Why Log-t slow relaxation?

due to energy distribution, the relaxation time (kinetic coefficients exp(-βE）) distribute extensively

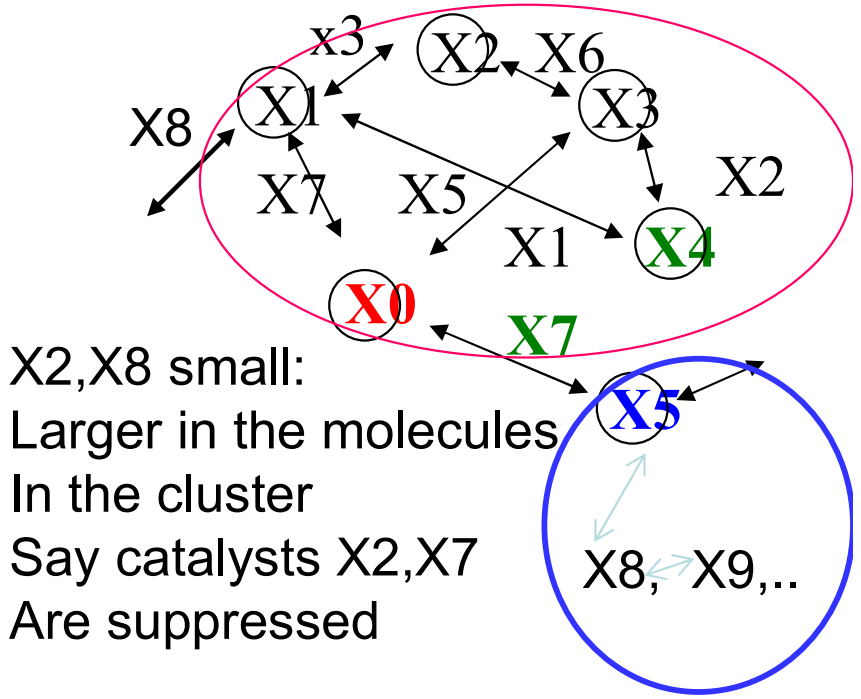
C(t)~ $\int_0^{\varepsilon} D(E)a(E)\exp(-e^{-\beta E}t)dE$

by $u=\exp(-\beta E)t$, $(1/\beta)\int_{te^{-\beta\varepsilon}}^{t}(1/u)e^{-u}du$ → log(t)

- Why plateaus?
- Local equilibrium within cluster
- Equilibrated with other clusters

is suppressed by deficiency of catalytic molecules

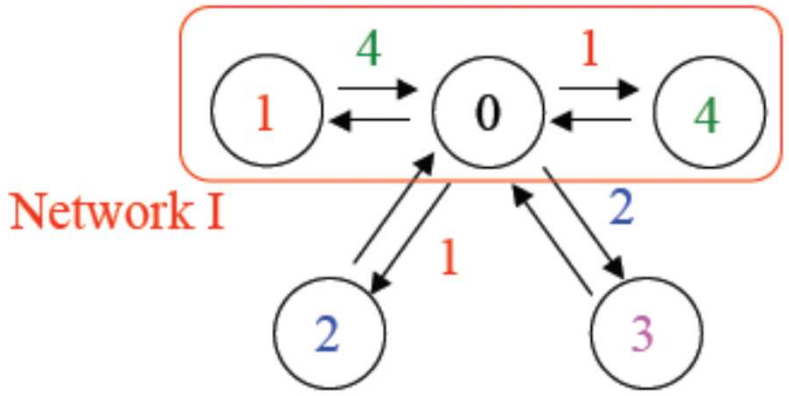
- negative-correlation with abundances versus catalysts
- ΔX ↑ → ΔJout ↓ ?



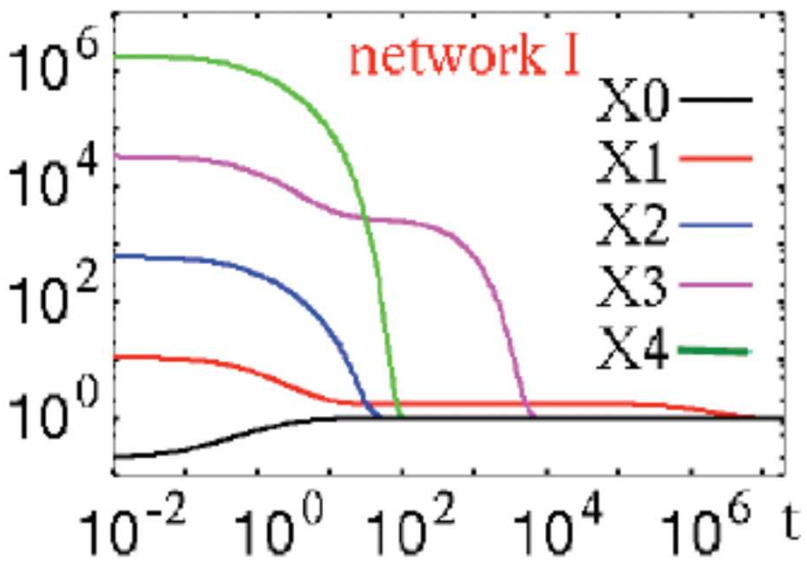
X2,X8 small:
Larger in the molecules
In the cluster
Say catalysts X2,X7
Are suppressed

General in catalytic networks → 'Chemical Net Glass'

A simple example



$x_i^{dev}(t) = x_i(t)/x_i^{eq}$



1 catalyzes decrease of 4 ;
4 catalyzes decrease of 1
→ mutual competition for relaxation

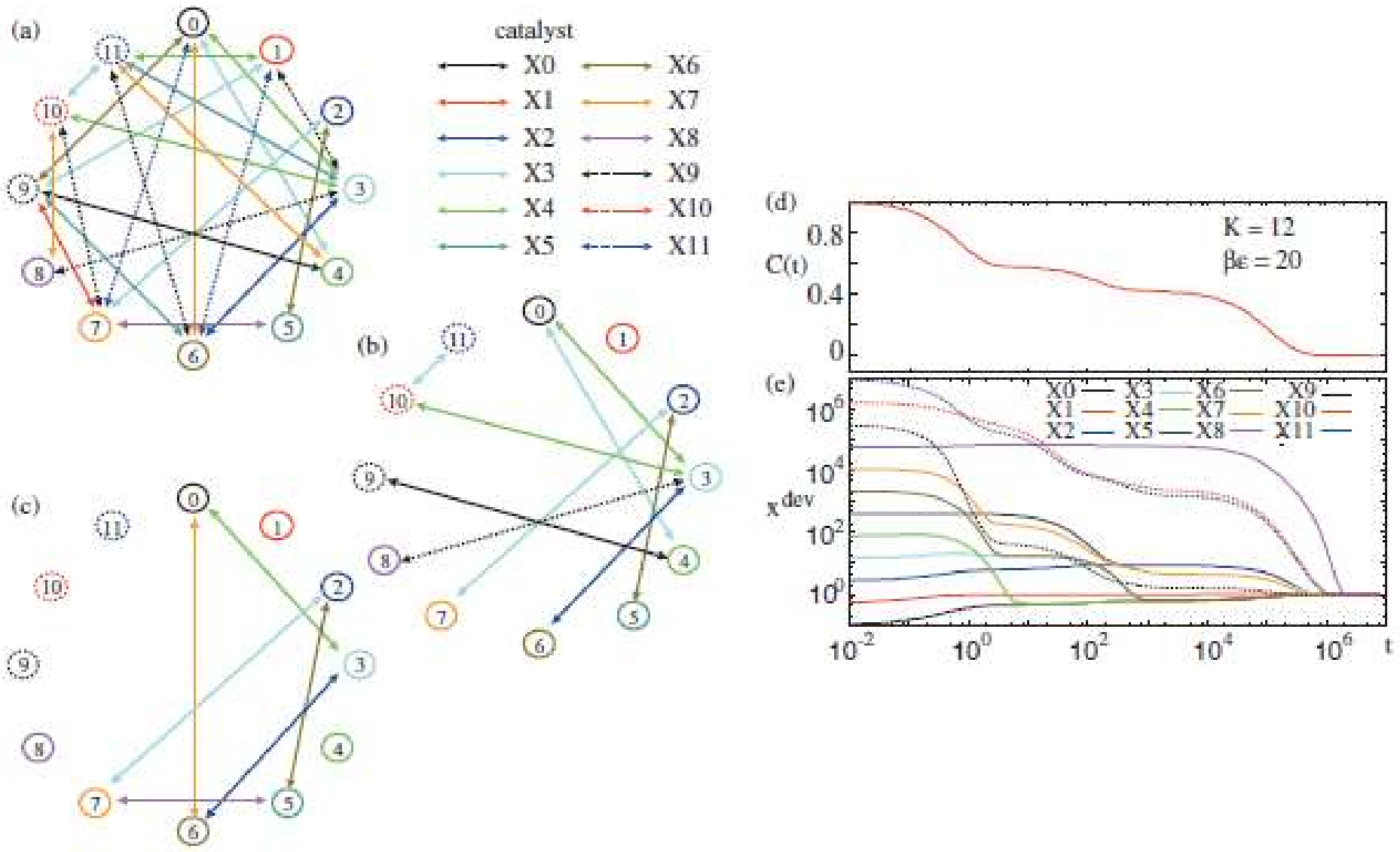
but 4 starts to decrease faster as exp(-βE4) is smaller
Then relaxation of 1 is further hindered

1 is not easily equilibrated
1—4 negative correlation

E0<E1<E2<E3<E4

→ x1,x2,x3,x4 decreases to increase x0

Xi ~ exp(-βEi)


(a)
(b)
(c)
(d)
catalyst
X0
X1
X2
X3
X4
X5
X6
X7
X8
X9
X10
X11
K = 12
βε = 20
C(t)
0.8
0.4
0
x dev
10^6
10^4
10^2
10^0
10^-2
10^0
10^2
10^4
10^6
t

Relevance of autonomous regulation of enzyme abundances to long-term dynamics

A proposal for kinetic memory based on enzyme-limited competition

Tetsuhiro S. Hatakeyama & KK

PLoS Comp Biol 2014

Cellular memory

Epigenetic Memory --- over dozens of generations
(yeast, E Coli)

Memorization of cultured temperature
(Oosawa, Nakaoka)

Origin? Molecular? How preserved?

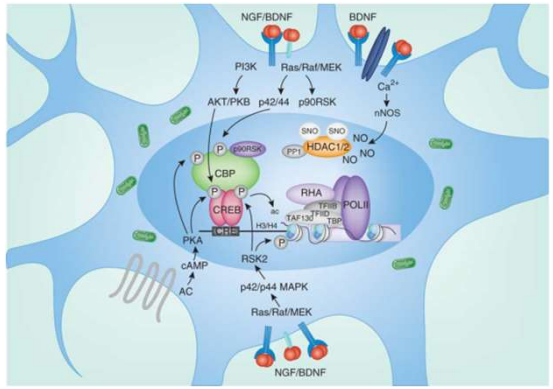
Standard Picture --- multiple attractors --OK?

1)continuous states are not memorized

2) dynamic processing for stimuli?

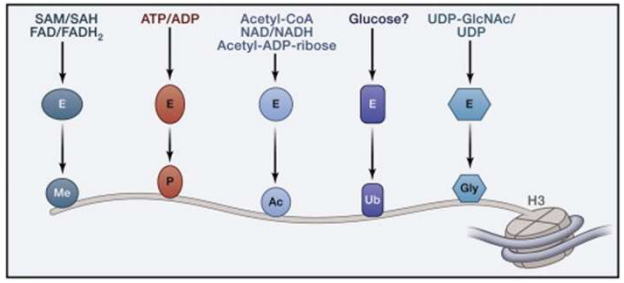
3) storage needs costs,

Phosphorylation of signaling molecule



Riccio A, Nat. Neurosci. (2010)

Chromatin modifications



Kotada S, et al., Cell (2012)

An Alternative: Proposal of Kinetic memory

not stored at attractors,
stored in a relaxation process

- Keeping memory for a long time
  - Slow relaxation dynamics
- Memorize history of continuous environment
- No cost, simple

← Autonomous change in time scale by Enzyme-limited Competition

Kinetic memory by ELC?

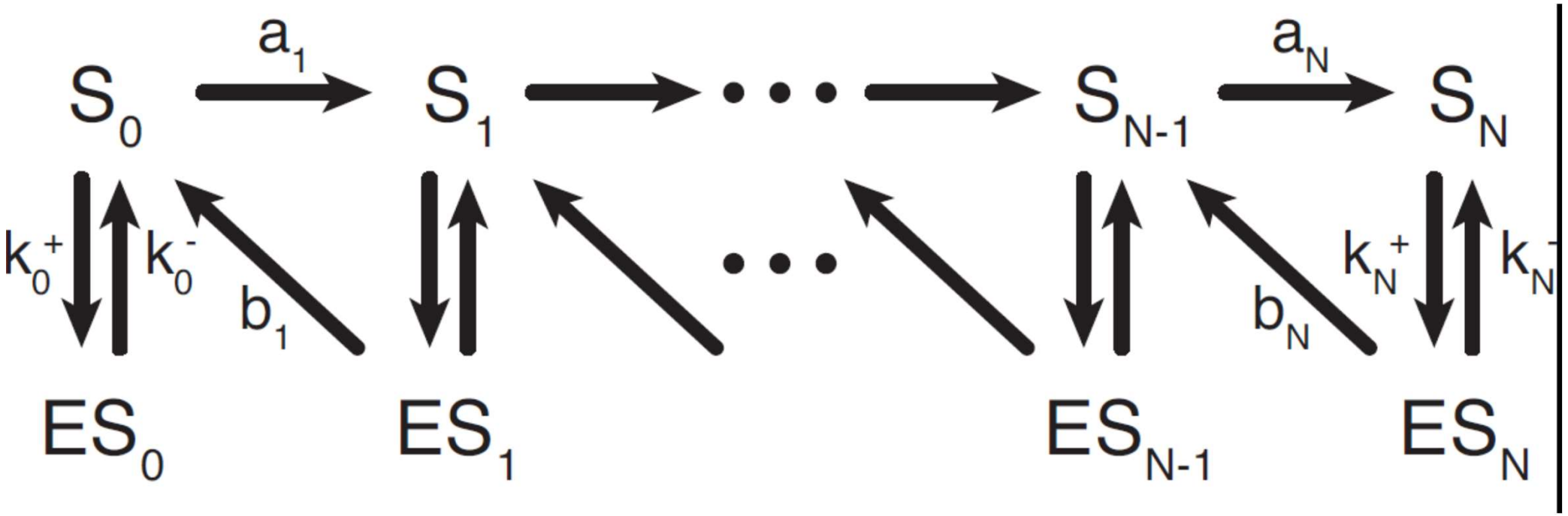
Hatakeyama,KK

Consider adaptation dynamics +ELC, instead of oscillation

E : Enzyme or Cofactor for site modification

(e.g., methylation etc)

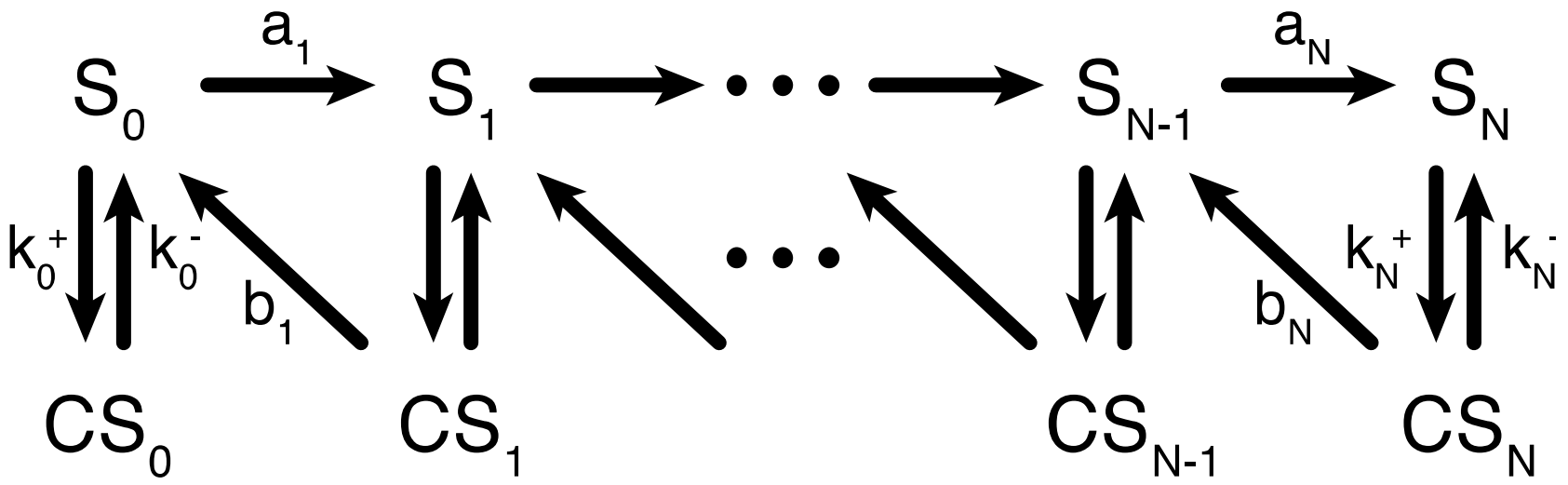
Each substrate competes for E



S_i : S form substrate with *i* modified sites

ES_i : S form substrate binding cofactor

Chained modification model



Stimulus $a_i = a(t)$

:

$$K_i = k_i^- / k_i^+ = K_o \times \gamma^i$$ Heterogeneity of affinity

Chained modification model

$$[\dot{S}_i] = -a_{i+1}[S_i] + b_{i+1}\frac{[C]_{free}[S_{i+1}]}{K_{i+1} + [C]_{free}}$$

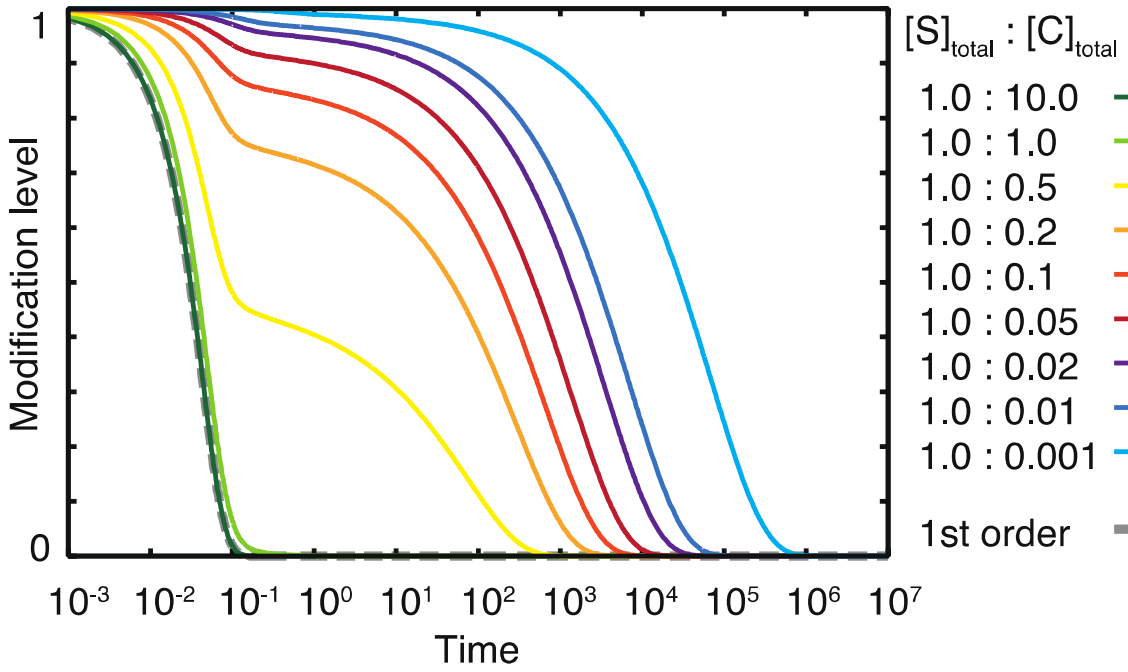
$$+ a_i[S_{i-1}] - b_i\frac{[C]_{free}[S_i]}{K_i + [C]_{free}}$$

$$[C]_{total} = \sum_{i=0}^{N}\frac{[C]_{free}[S_i]}{K_i + [C_{free}]} + [C]_{free}$$

Enzyme competition

$$K_i = k_i^- / k_i^+ = K_0 \times \gamma^i$$

Memory maintenance and erasure

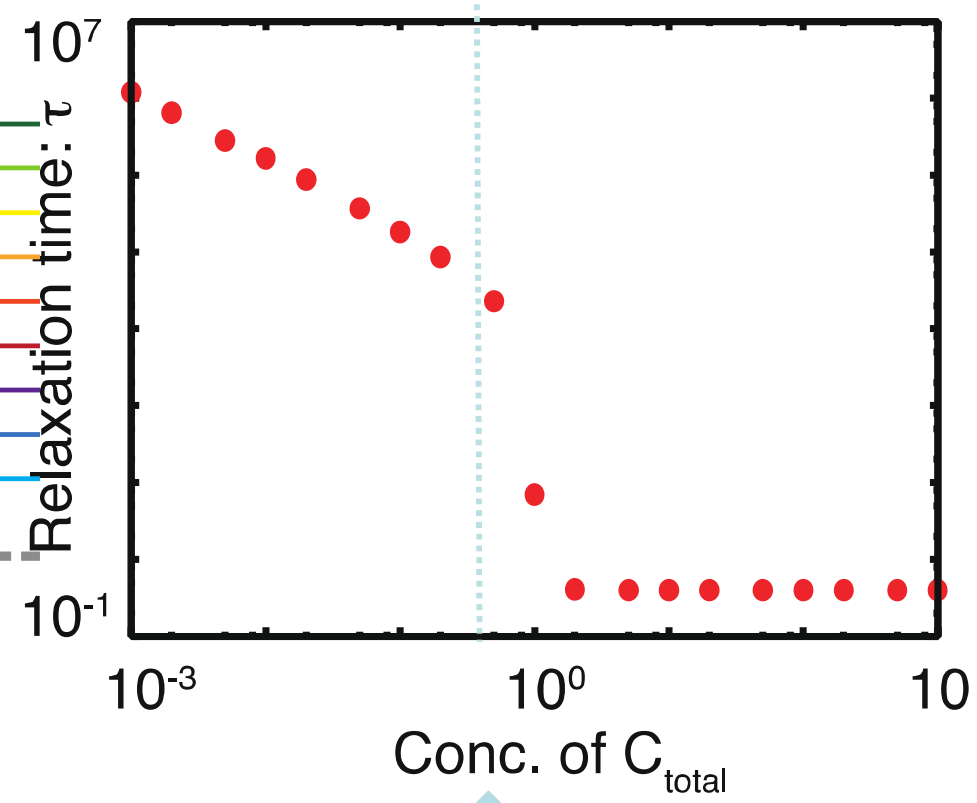


Maintenance

Slow log relaxation

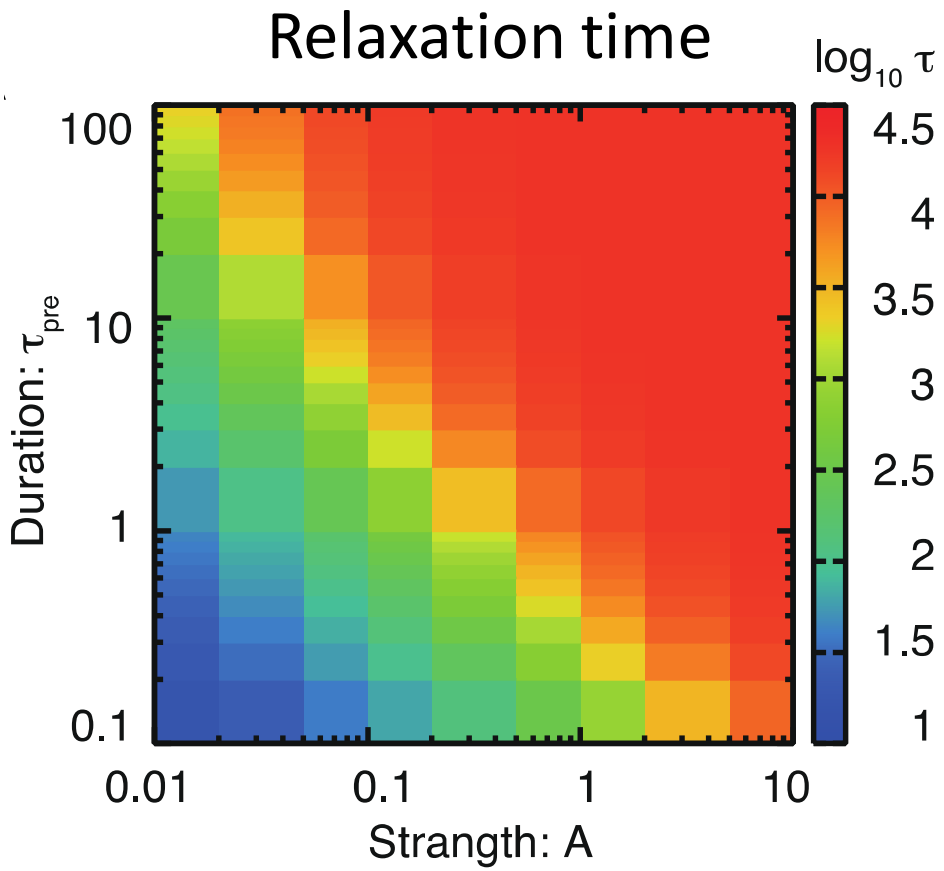
erasure

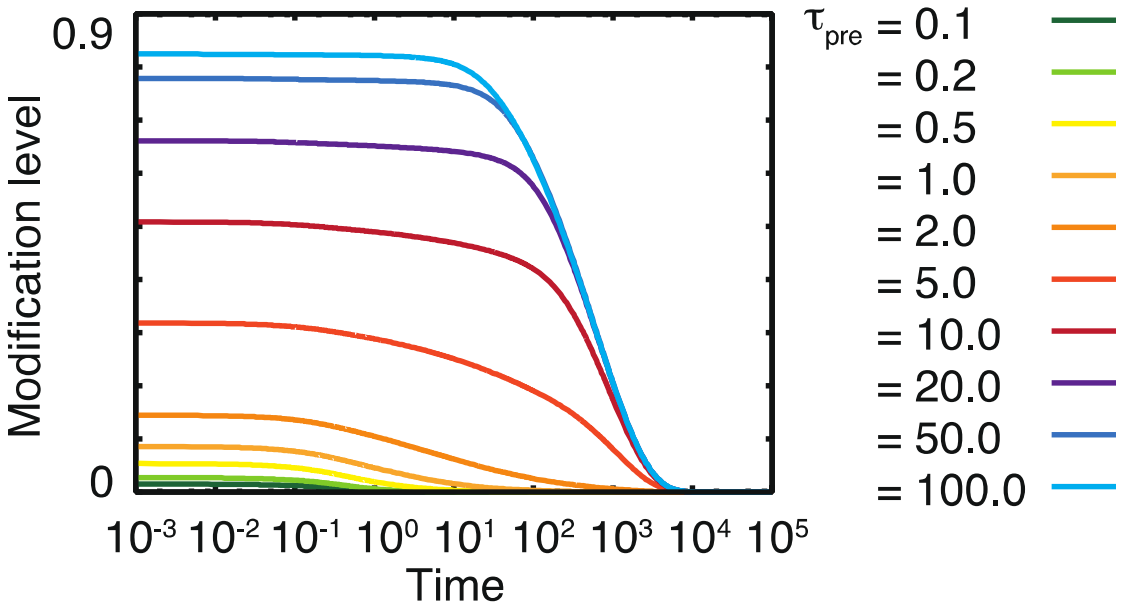
fast exp relaxatio



$$[S]_{total} : [C]_{total} = 1 : 1$$

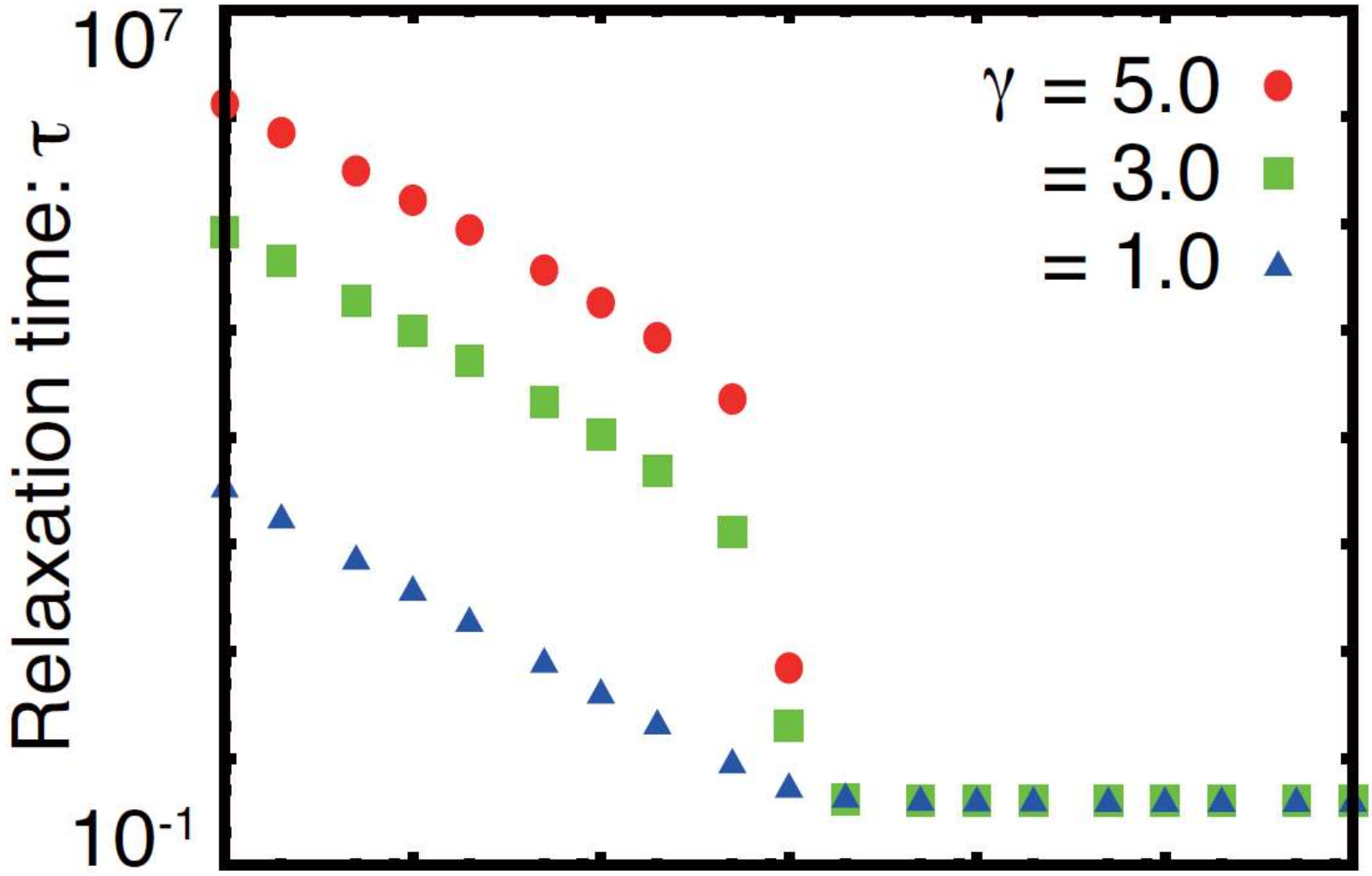
Continuous Memory



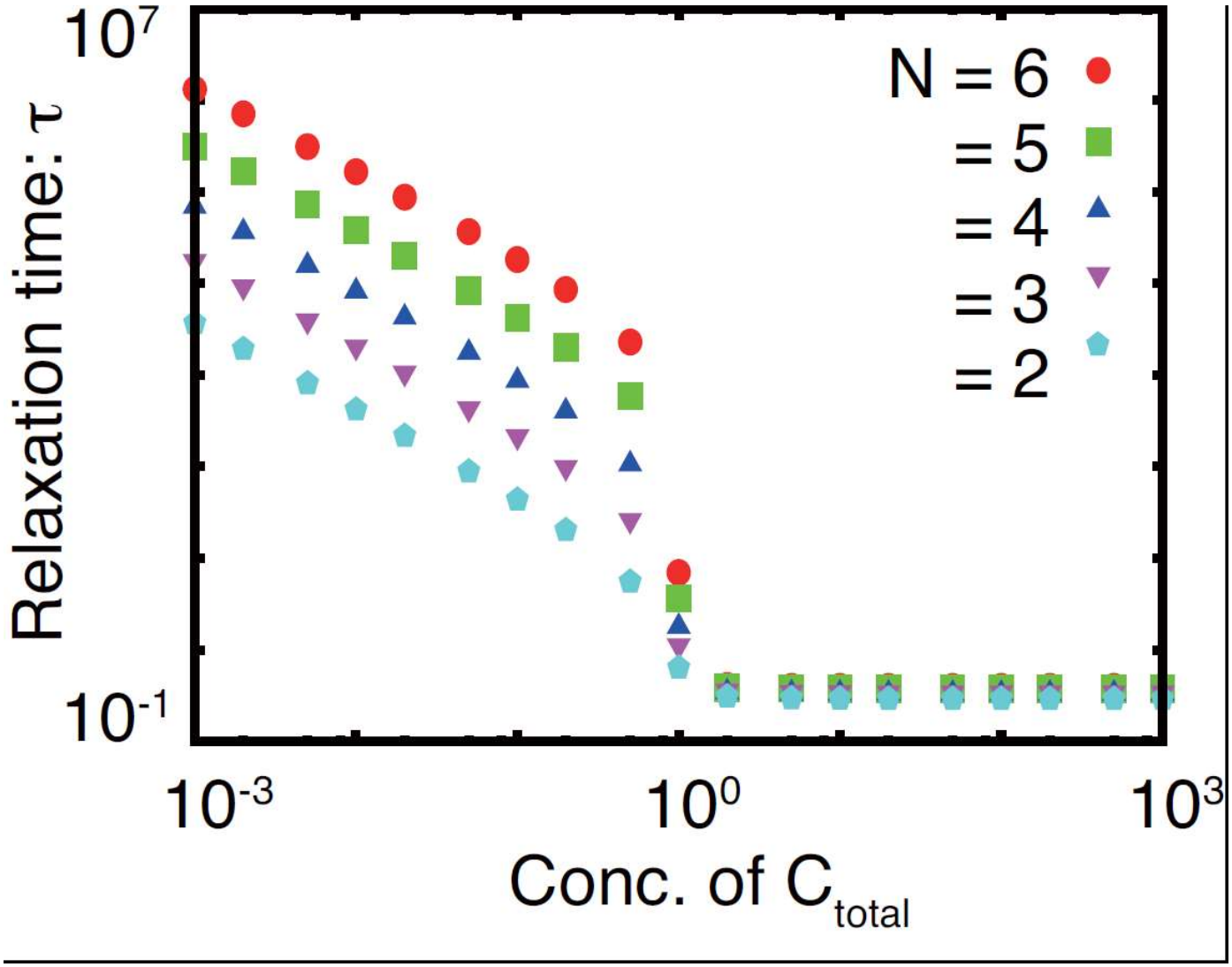


Modification level and relaxation time continuously changes with the stimulus strength and lenbth

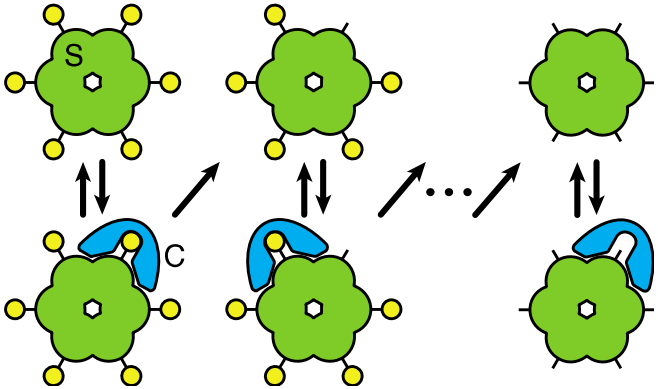
Condition: affinity depends on sites



Enhanced as the number of sites is larger



How Slow relaxtion occurs

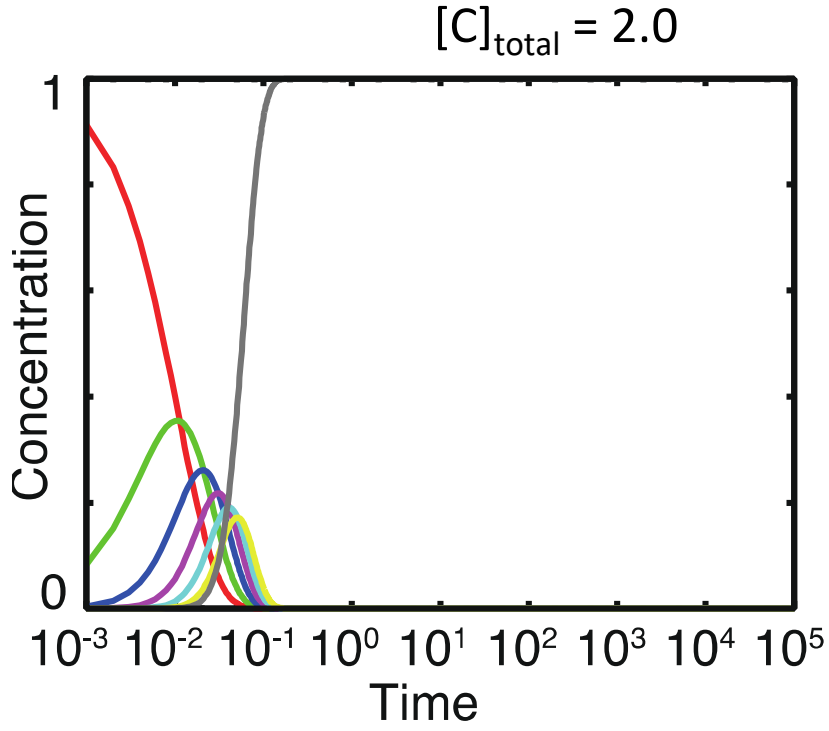


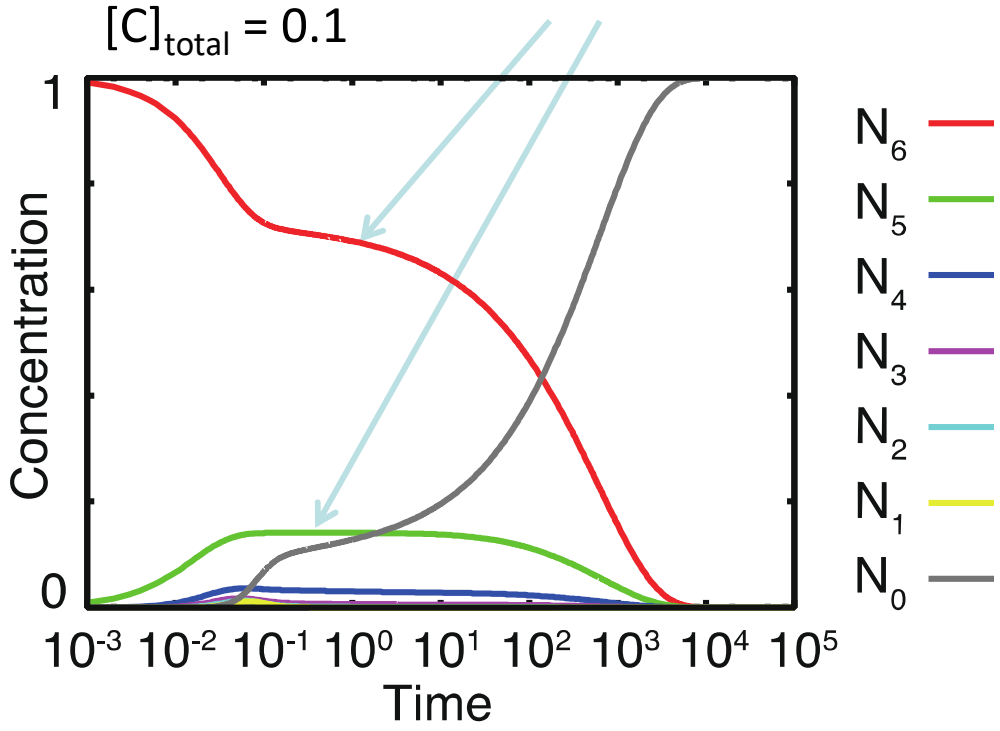
S_{i-1} has higher affinity than S_i

$\rightarrow S_i$ cannot get the enzyme successively

For relaxation of each component

There emerges a plateau





Enzyme limit competition is a key

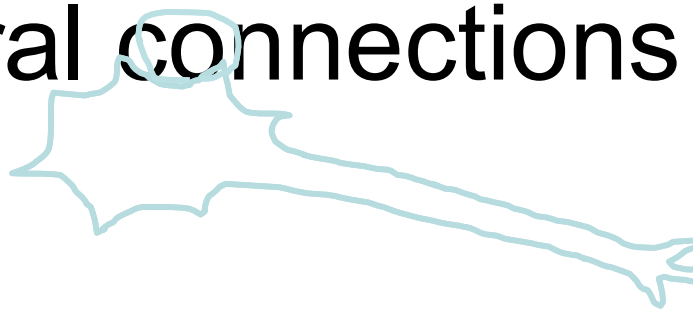
Requirements for kinetic memory

- Enzyme-limited competition by multiple modification sites
- Different affinity among substrate states
  - –Leading to glassy relaxation

By decreasing the concentration of catalysts, current state is memorized, while, memory is erased by increasing the concentration

Relevance of ‘kinetic memory’

Long term potentiation in neural connections



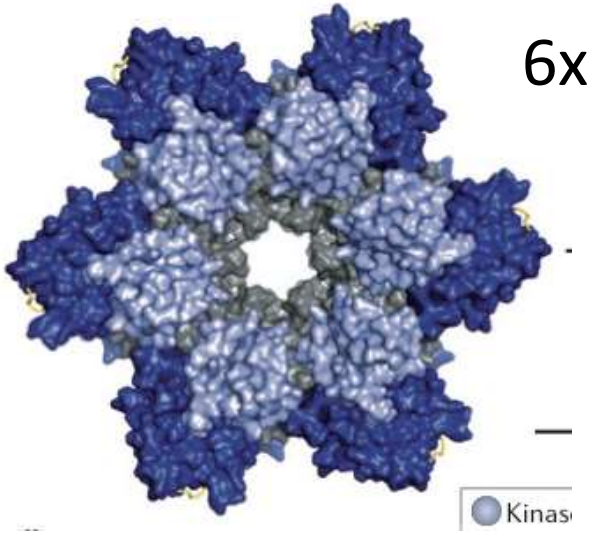
Molecules concerning LTP

- Early LTP (without protein synthesis)
  - Ca^{2+}/calmodulin-dependent kinase II (CaMKII)
  - Protein Kinase C (PKC)
- Late LTP (with protein synthesis)
  - cAMP-responsive element-binding protein (CREB)

With multiple phosphorylation sites
(eg, CaMKII CREB)

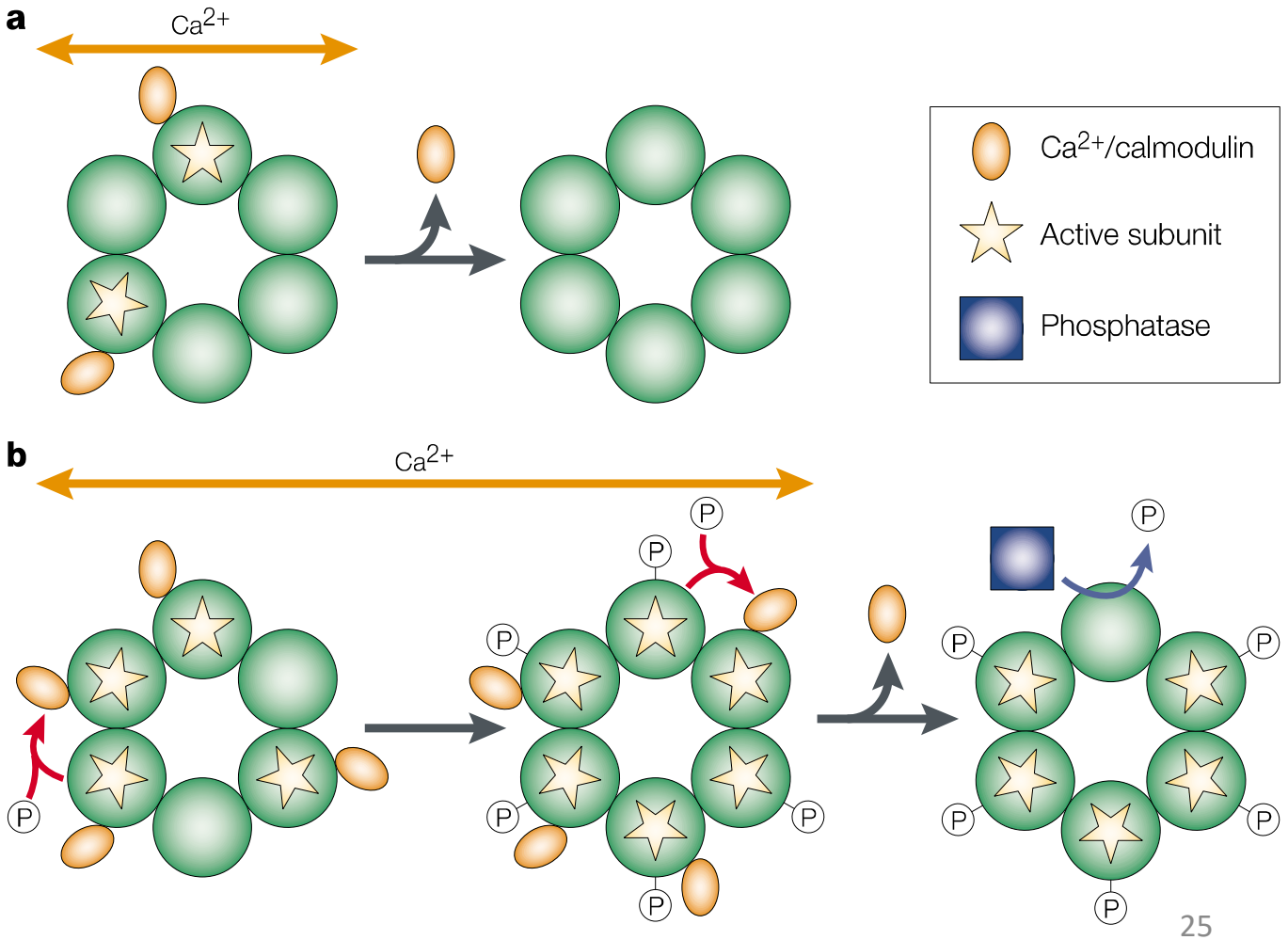
Long-term phosphorylaton needed

CaMKII



6x2 mer

Lisman et al.,
Nat Rev Neurosci (2012)



Lisman et al., Nat Rev Neurosci (2002)

Attractor memory: limitation?

- Memory in multiple-attractor system
  - requires a number of modification sites

    (e.g., memory $\propto$ n or less)
  - Need to isolated each site (then read/write has difficulty?)
  - Erasure needs cost?
  - or need to design complex network structure
  - hard to store the memories against various stimuli
- Some form of ‘Kinetic memory ‘

preferable to adapt to a various dynamic stimuli?
Also low cost to read/write/ erase?

Relevance of continuous, kinetic memory?

Flexibility?

Controllability, continuous

by inputs/ enzyme abundances

continuous dependence on inputs

→ LTP/LDP, Hebb/antiHebb

Erasable without thermodynamic costs?

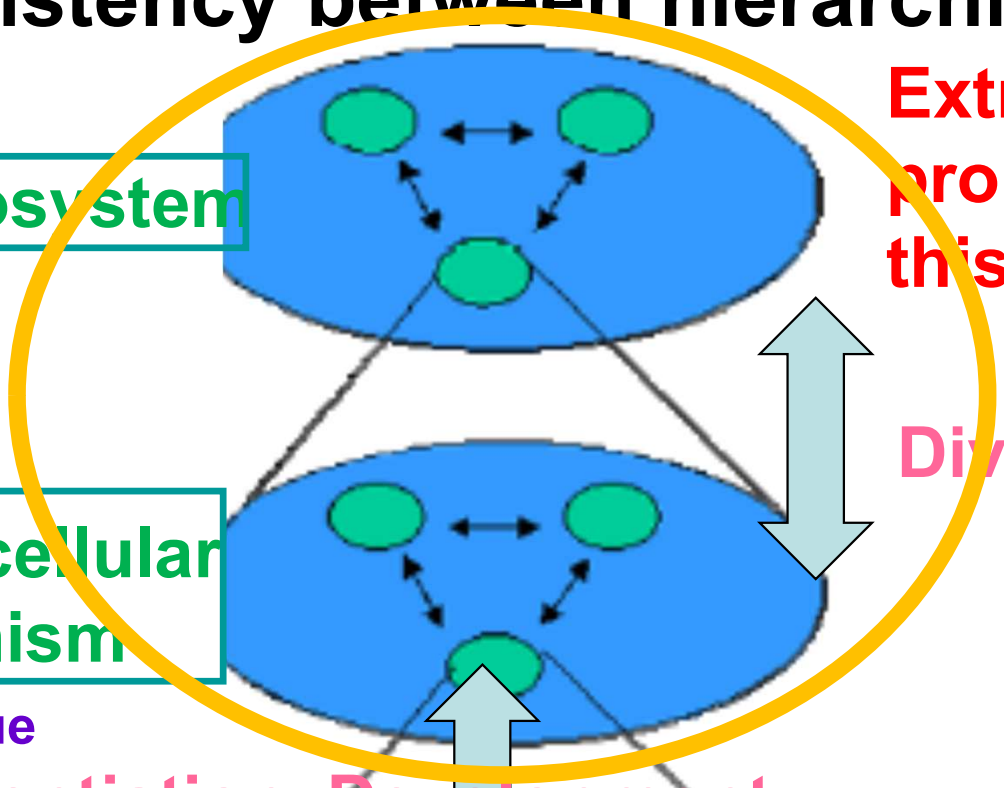
- Processing of temporak information
- Memory in Synapse（continuous /by number？）

  metaplasticity?
- Epigenetic Memory on DNA?

  (copy? Feedback?)

- OtherTopics that I have no time to talk this time…

Consistency between hierarchical levels (+collapse)



Extract general basic properties of life, based on this consistency principle

Ecosystem

Diversity, Symbiosis

Multicellular organism

Cell-Tissue

Differentiation, Development

Evolution

Genotype ⟷ Phenotype

Cell

Molecule replication vs cell reproducti

Reproduction

Cell-growth vs Intracellular dynamics

Adaptation→

Molecule

Gene-expression/metabolic networks

Consistency with such distinct spatiotemporal scales?

○Ecosystem: further hierarachy --Theory for interaction-induced diversity

traditional studies --population dynamics

In reality (eg microbial ecosystem such as biofilm)

intracellular dynamics + interaction

-- multi-level dynamics (eg Yamagishi Saito, KK PLoSCB2021)

Growth rate μ -- as a function of intra-cellular components {X*} as μ=g({Xj})

Balance condition among types

KK,2015

$$\frac{dX_i(\alpha)}{dt} = F_i^\alpha(\{X_j(\alpha)\}) + H_i([X_i(\alpha), \rho^\beta]) - \mu^\alpha$$

$$\rho^\alpha = N^\alpha / N_{tot}$$

$$\frac{d\rho^\alpha}{dt} = (g^\alpha(\{X_j^*(\alpha)\}) - \overline{\mu})\rho^\alpha$$

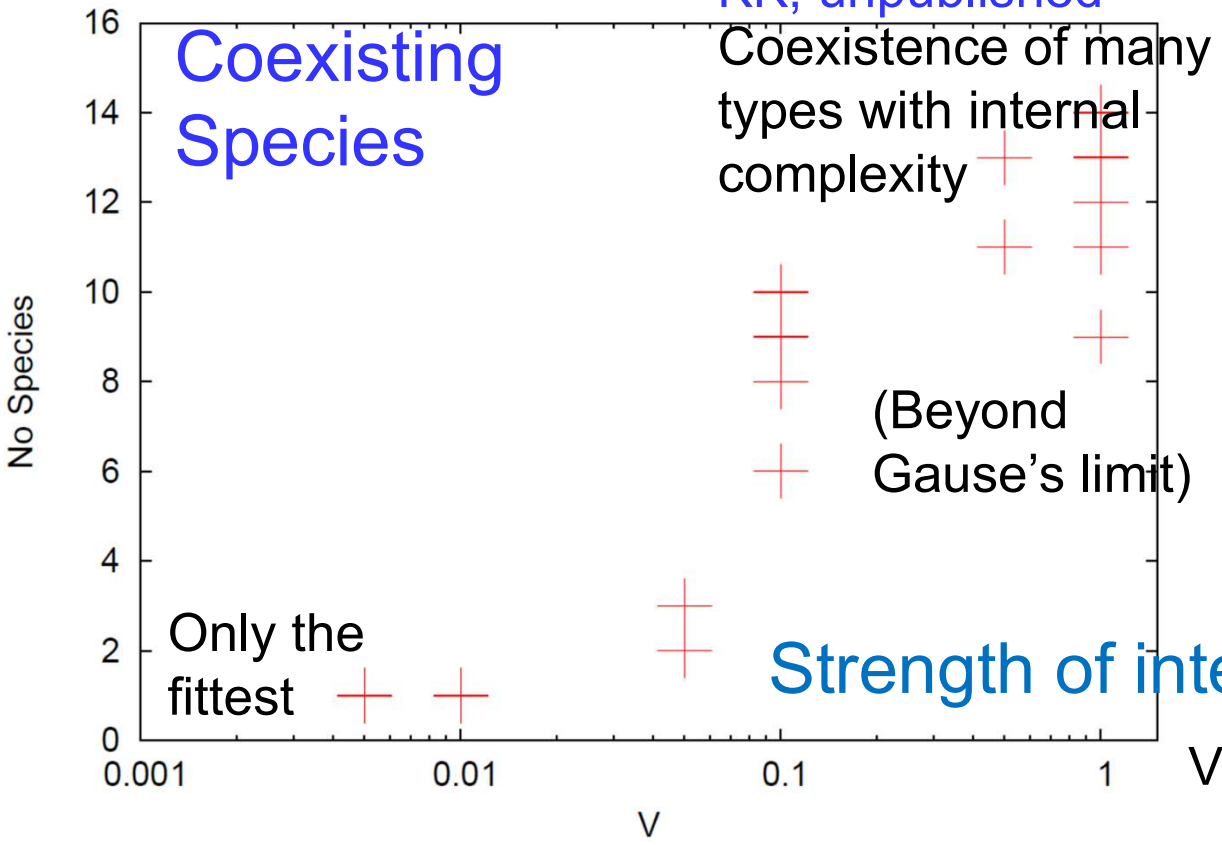
$$\mu^\alpha = \mu^\beta$$

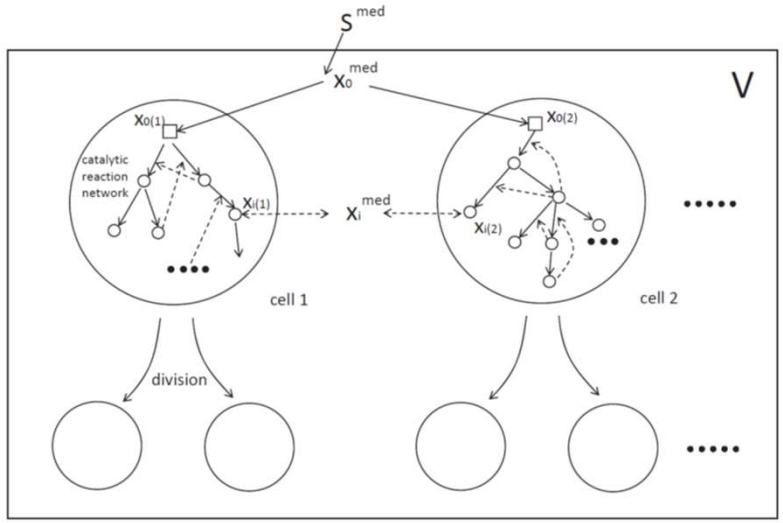
$$g^\alpha(\{X_j(\alpha)\}) = g^\alpha(\{X_j(\beta)\}$$

Resource-limitation+ Strong Interaction (Exchange of chemicals)

- Coexistence of diverse celltypes

KK, unpublished





V= cell volume/ medium volume

"Strong cell type in isolation" secrets out useful chemical→ Coexistence of diverse species

Cf Kashiwahi,..,Yomo coexistence of multiple E Coli types
J Mol Ev 2001

＊＊Theory for interaction-induced diversity

traditional studies --population dynamics
(random matrix+alfa)

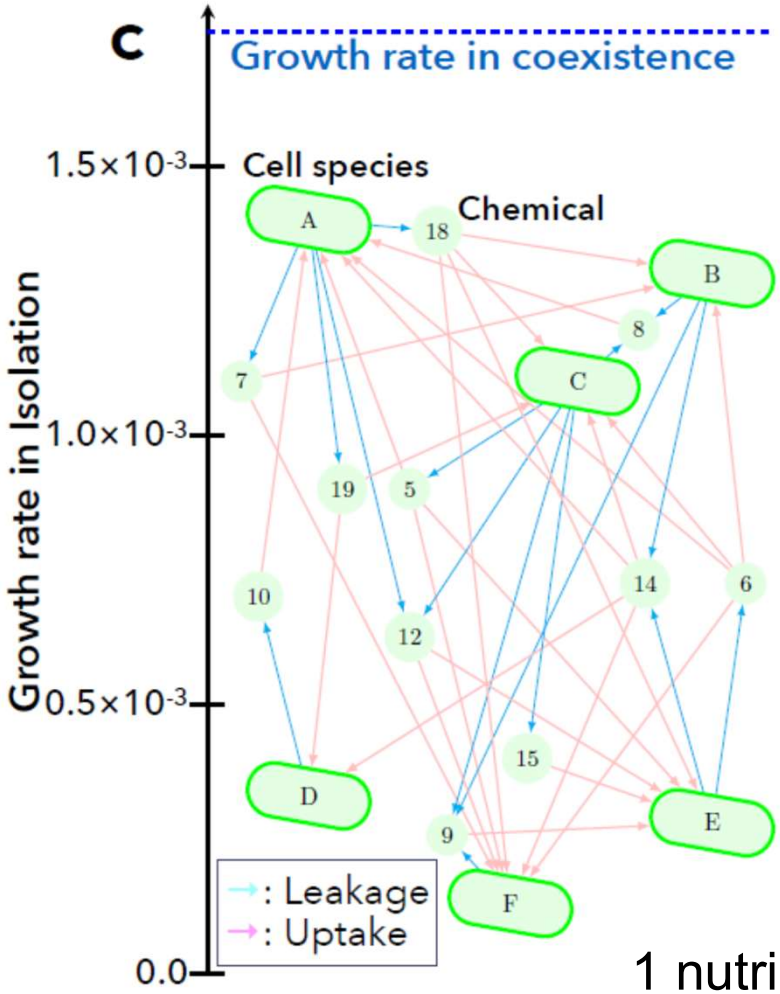
In reality (eg microbial ecosystem such as biofilm)
intracellar dynamics + interaction
-- multi-level dynamics model (eg Yamagishi Saito, KK PLoSCB2021), not a single layer) Species other than the fittest at a single-level coexist due to interaction

NEED

Simple model with internal states + interaction
e.g., spin model + interaction
Statistical-physica Theory?

for each unit + population dynamics

Multiple Species Interaction → Intra-Inter Dynamics (Exchange of Chemicals) → Coexistence of multiple species (Macro-micro-consistency) → Each cell-types increase the growth-speed by interaction → Resilient "ecosystem"



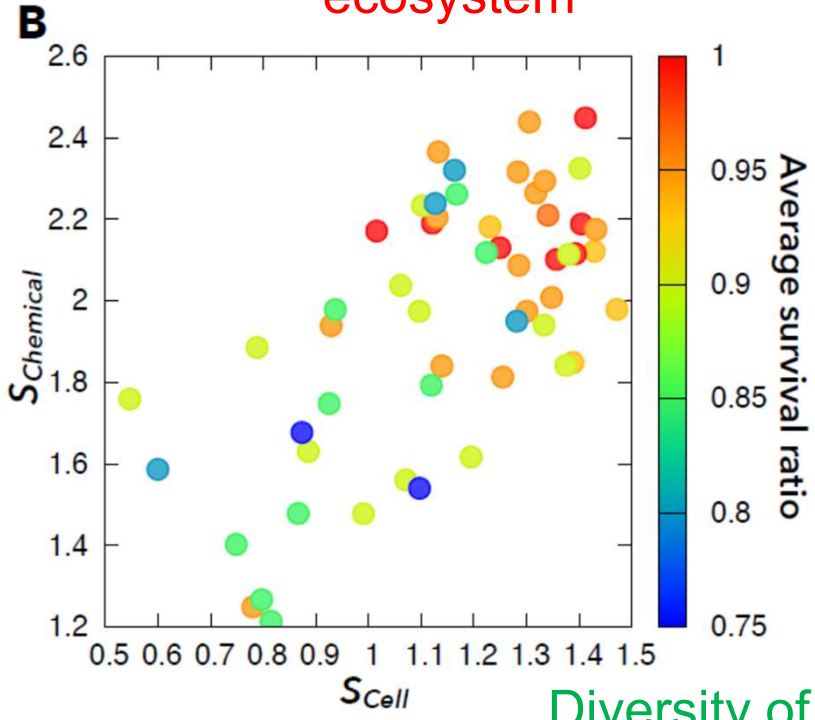
1 nutrient component

A-E: different celltypes with reaction nets

Yamagishi,Saito,KK, PLoS CB 2021.

Diversity of exchanged chemicals

Color: resilience of "ecosystem"



Diversity of cells

Diversity enhances Resilience

(no trophic level, entangled)

○Neural Dynamics: from dynamics to symbol

Chaotic Itinerancy in layered coupled map (KK unpub 90's, 2017)

i)"?"state →slow-fast interfere → slow-mode controll: Fast changes are successively embedded into slower (to generate prior) :

←Brain as Timescale Machine

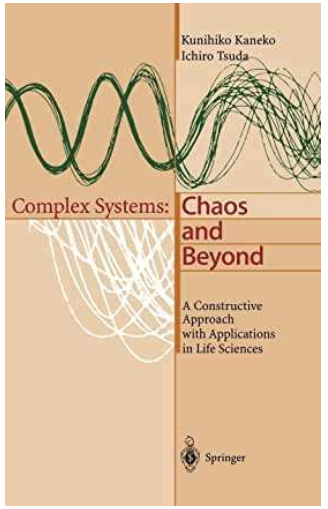
Fast input –Embed by Slow Learning →Output (Kurikawa,KK 2011…,21;Ichikawa, KK) --memory dynamics

ii) Learning ←recent view of phenotypic evolution (constraint, dim-reduction, fluctuation-response)

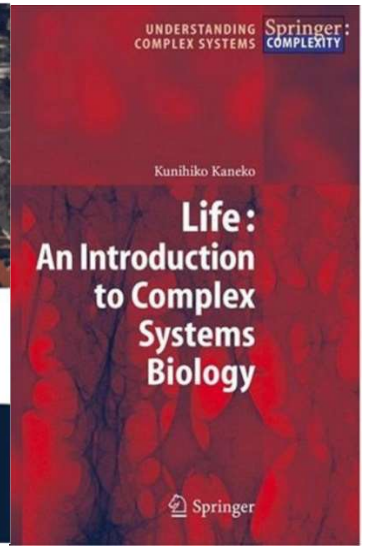
iii) Revisit to MagicNo7?? (cf Ishihara,KK 2005)

etcetc……

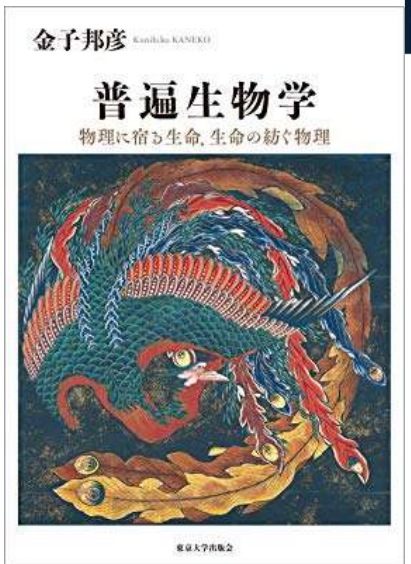
Complex Systems; High-dimensional Dynamical Systems



→ Complex-systems Biology



→ Universal Biology



Translation in Progress