- **First Talk**
- **General Introduction to Complex Systems Biology**
- **Recursive Production of Cells**
- （A few Basic Problems in Origin of Life）
- **Development--Cell Differentiation**
- **Coupled Dynamical Systems**
- Summary

2nd; phenotype evolution; robustness, evolovability,….

Complex Systems Biology

cf. Life as Complicated System: （current trend)

Enumeration of molecules, processes

detailed models describing the life process

Life as Complex System:

Understand Universal features at a System with mutual dependence between parts and whole

Simplistic Physicists' Approach

Strategy:

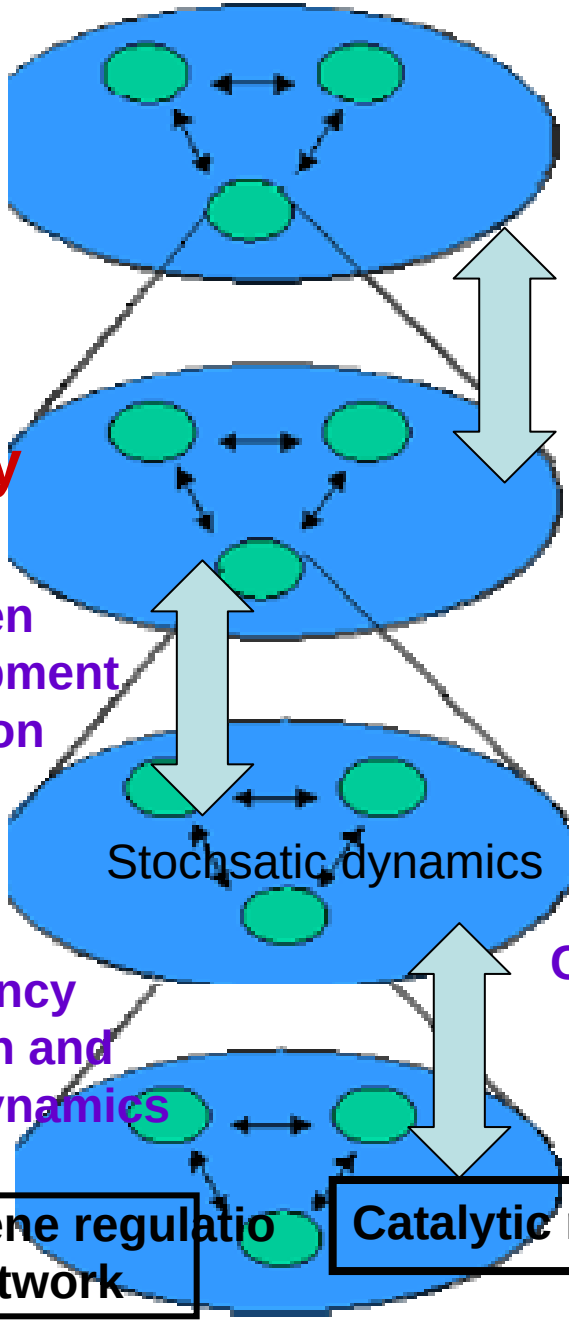
1) Dynamical Systems ++ & Statistical Physics ++

→ Catch consistency between micro-macro levels

2) Constructive Approach: (Exp & Theory)

` construct simple system to catch universal features'

as simple as possible



Ecosystem

Phenotypic Plasticity vs Symbiosis
Or Ecological diversification

Multicelluarity

Consistency between
Multicelluar development
and cell reprodcution

Evolutionary relationship on
Robustness and Fluctuation

Genotype ⟷ Phenotype

Cell

Stochsatic dynamics

Adaptation as
a result of consistency
between cell growth and
gene expression dynamics

Consisteny between Cell reproduction
nd molecule replication

Molecule

Gene regulatio
network

Catalytic reaction network

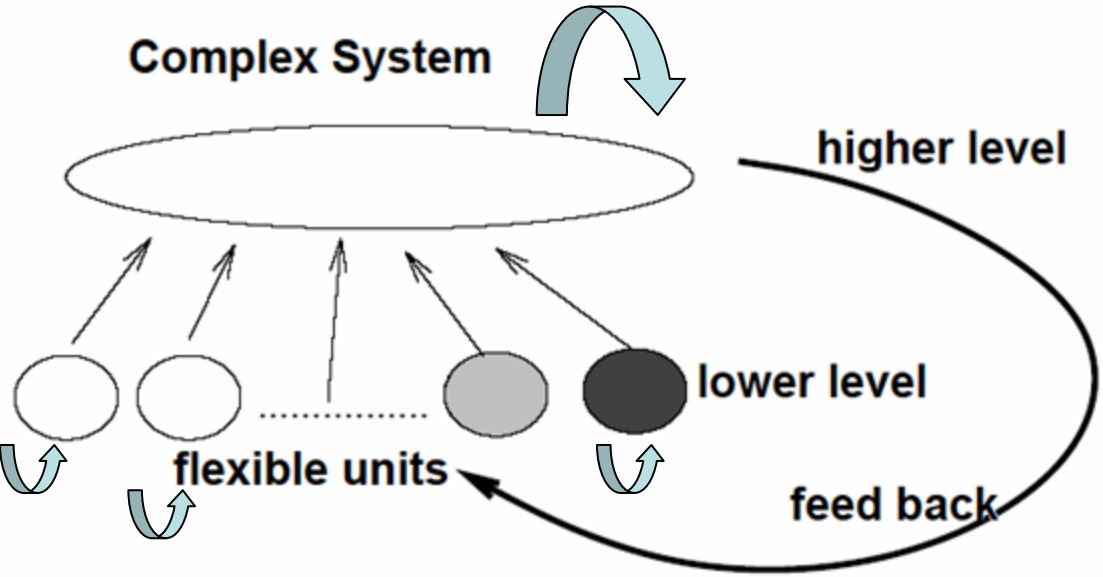
Consistency between different levels

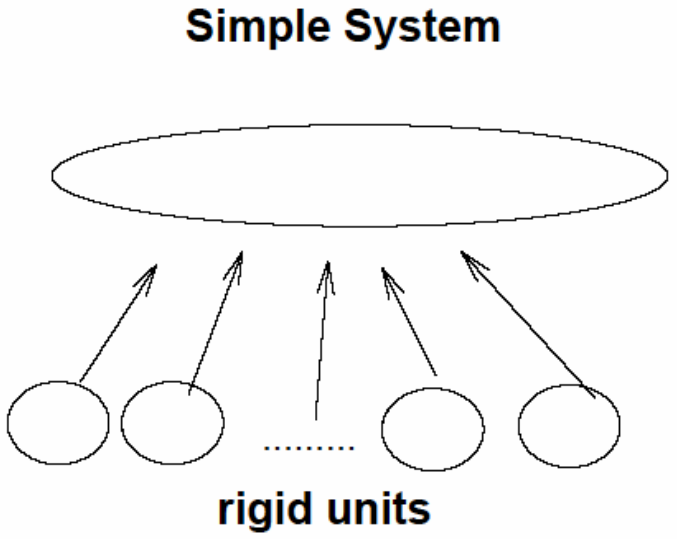
(1)Cell reproduction vs molecule replication (03-)

(2)Reproduction of multicellular organism vs of cells (97-

(3)Adaptation vs Reproduction (06-)

(4)Genetic change vs Phenotypic Fluctuation (03-



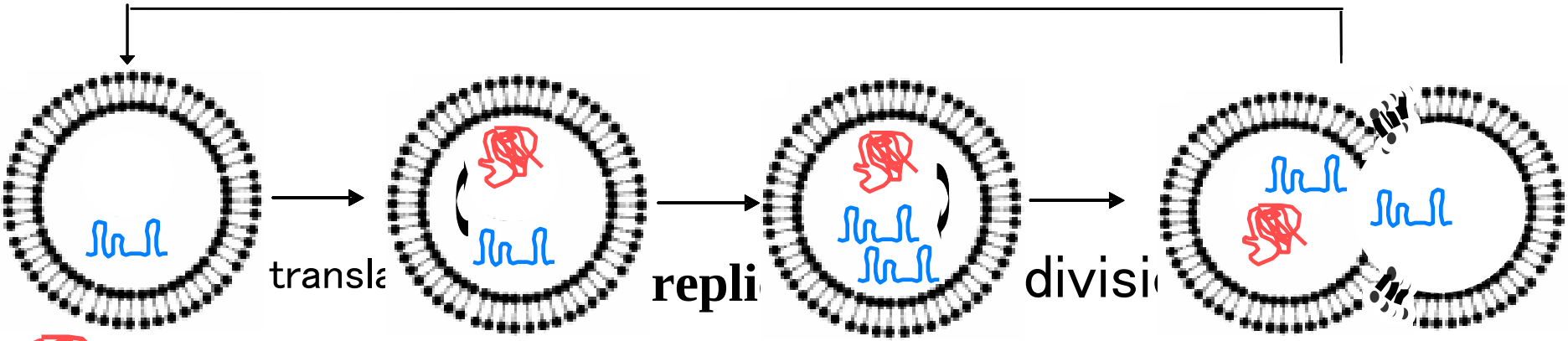


Constructive Biology Project

theme	experiment	theory	question
replicating system	in vitro replication with enzymatic reaction	minority control	origin of heredity; evolvability
cell system	replicating cell with internal reactions	universal statistics in reaction dynamics	condition for recursive growth
cell differentiation. development	differentiation of E Coil by interaction	emergence of differentiation rule from dynamics	irreversibility robustness
Spontaneous adaptation	Artificial gene network	Adaptive attractor selection by noise	Ubiquitous ability in adaptation
evolution	Laboratory evolution using bactreia	Fluctuation-response relationship	Robustness, evolvability

Complex Systems Biology Project (JST,ERATO; KK,Yomo,…)

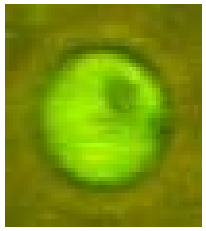
Replicating artificial cell (experiment)
(←→theory; fluctuation, minority control)



RNA polymerase

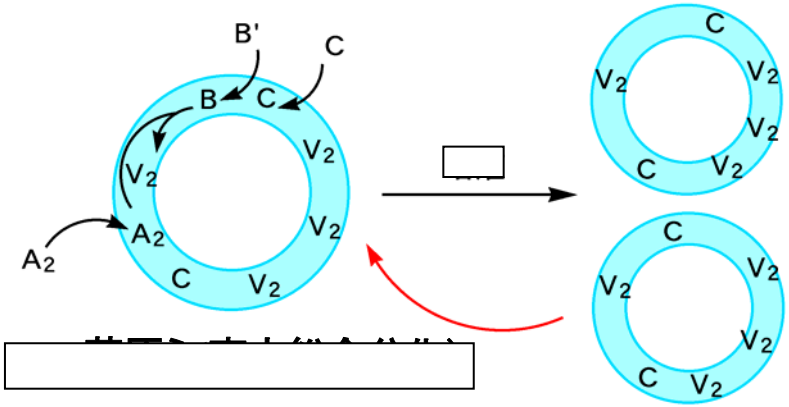
RNA polymerase geneRNA

(Yomo‘s group)



Tranlation in liposome

RNAreplication in liposome



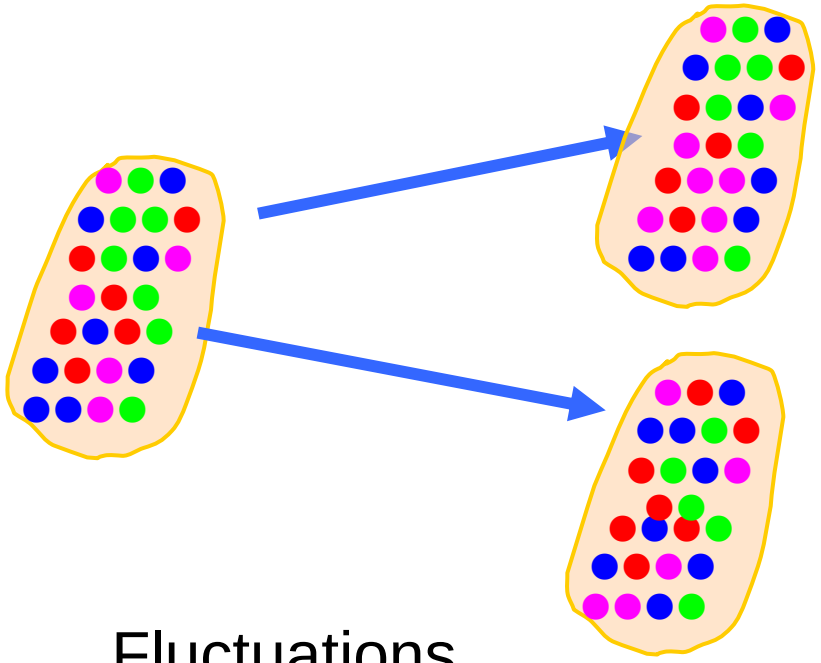
(Sugawara’s group)

Continouos division of liposomes

How is recursive production of a cell sustained ?

each cell complex reaction network with diversity of chemicals;

The number of molecules of each species not so large



?

Fluctuations

Naiive Physicist View

Toy Cell Model with Catalytic Reaction Network
‘Crude but whole cell model’

C.Furusawa & KK、PRL2003

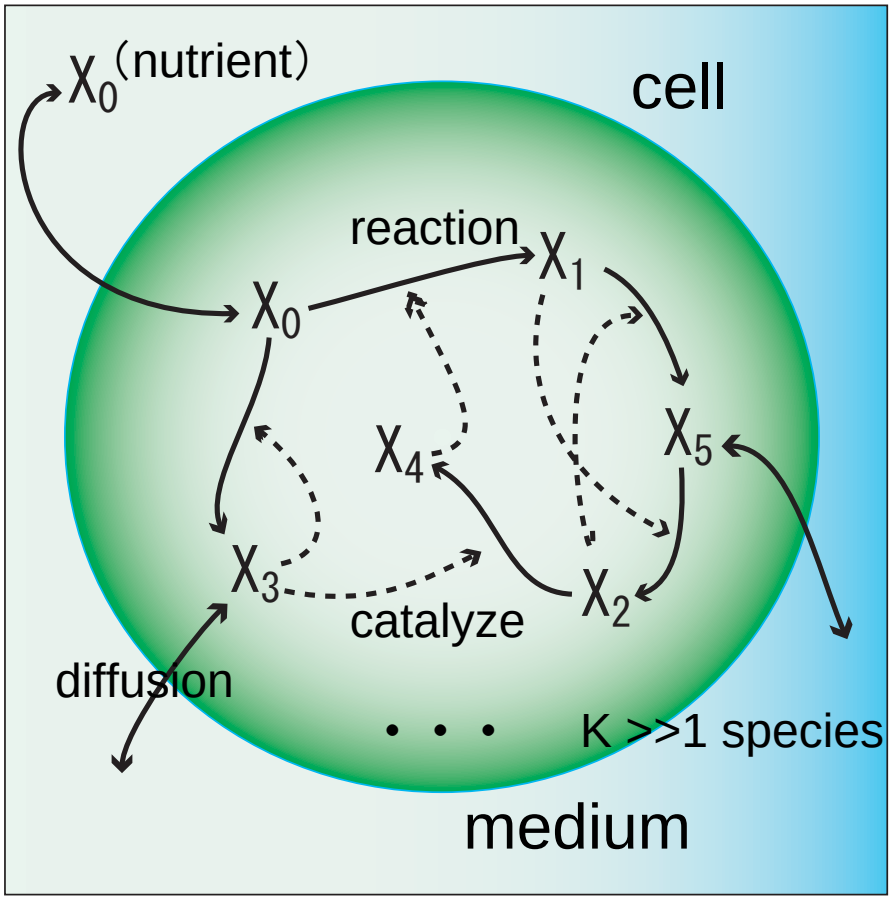
- **k species of chemicals 、$X_o \cdots X_{k-1}$**
number ---n_o 、n_1 … n_{k-1}

- random catalytic reaction network
with the path rate p
for the reaction $X_i + X_j -> X_k + X_j$

- some chemicals are penetrable through the membrane with the diffusion coefficient D

- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth in $N = \Sigma n_i$, when it exceeds N_{max}
the cell divides into two

model 細胞 (Cf. KK&Yomo 94,97)



dX1/dt ∝ X0X4; rate equation;
Stochastic model here

☆Simulation procedure

1 : Pick up randomly 2 molecules at each time step, if the pair reactions, change the substratre molecule into productt (with the probability of the reaction rate) otherwise leave as it is

2 With a certain rate per time step (≈1／D), exchange a molecule of inside in the cell by that in an enviromenment. If the molecule is impermeable, it stays

3 : If the total number of molecules N goes beyodn N_{max} cells are divided into two, eahc of which consists of molecules chosen randomly

In continuum description, the following rate eqn., but we mostly use stochastic simulation

$$dn_i/dt = \sum_{j,\ell} \mathrm{Con}(j, i, \ell)\epsilon n_j n_\ell / N^2 - \sum_{j',\ell'} \mathrm{Con}(i, j', \ell')\epsilon n_i n_{\ell'} / N^2 + D\sigma_i(\overline{n}_i/V - n_i/N),$$

where $\mathrm{Con}(i, j, \ell)$ is 1 if there is a reaction $i + \ell \rightarrow j + \ell$, and 0 otherwise, whereas σ_i takes 1 if the chemical i is penetrable, and 0 otherwise. The third term describes the transport of chemicals through the membrane, where $\overline{n}_i$ is

- Cf:
- Use of ODE (+ fluctuation)

versus stochastic model with discreteness of molecules

- Basically same if the number of molecules N therein is sufficiently large.

If N is small (in comparison with the number of species K), then several molecule species can be zero at some time, then there appears a qualitatively distinct behavior

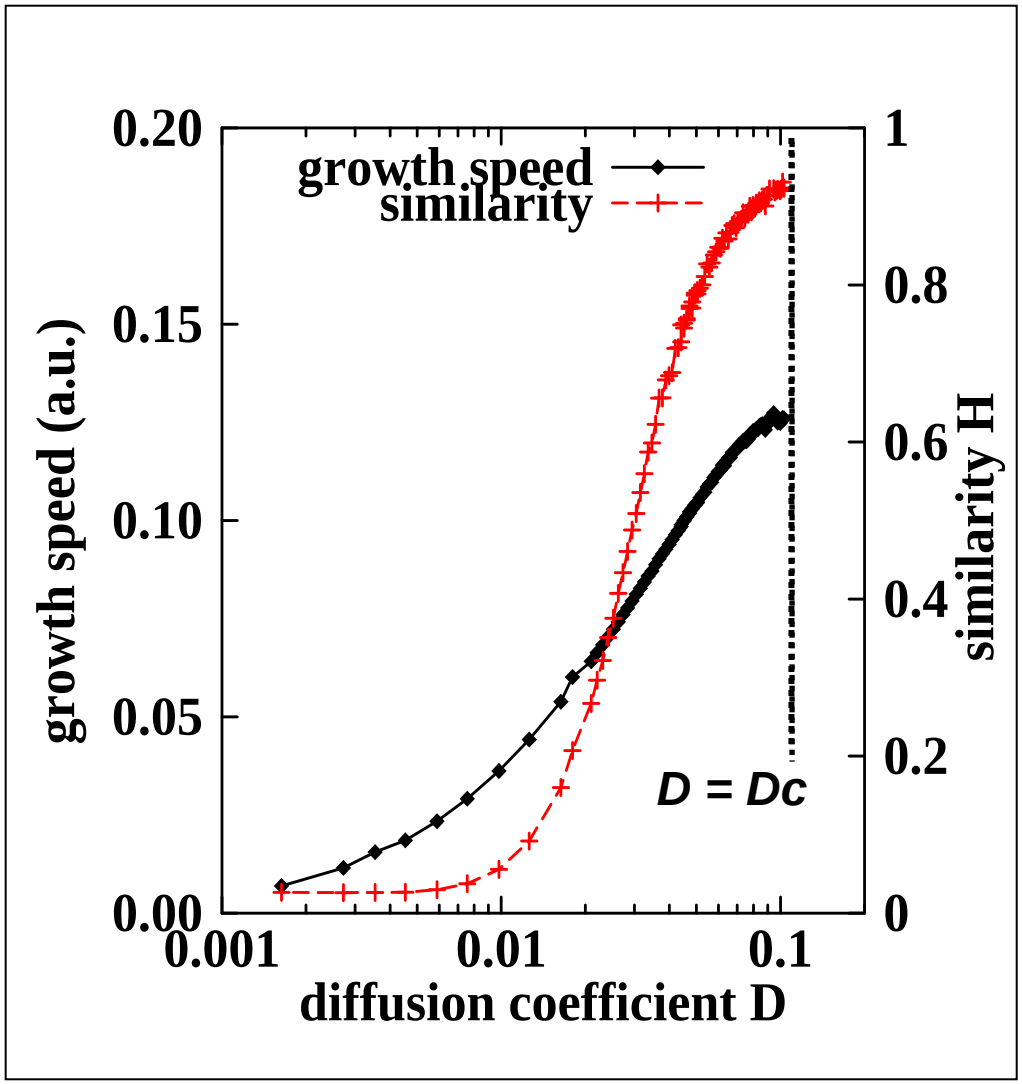
N>>K we are used in physics

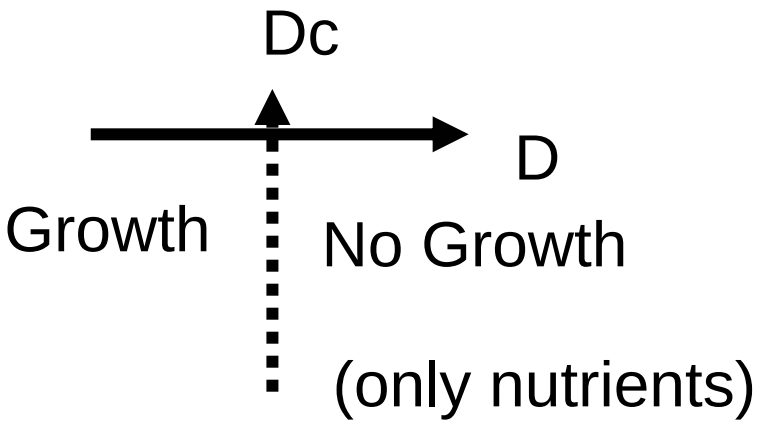
N ~K or N<<K needs different view

- --- Discreteness Induced Transition ---

(Togashi,KK, PRL 2002, Awazu, KK PRE 2007)

☆Growth speed and fidelity in replication are maximum at Dc

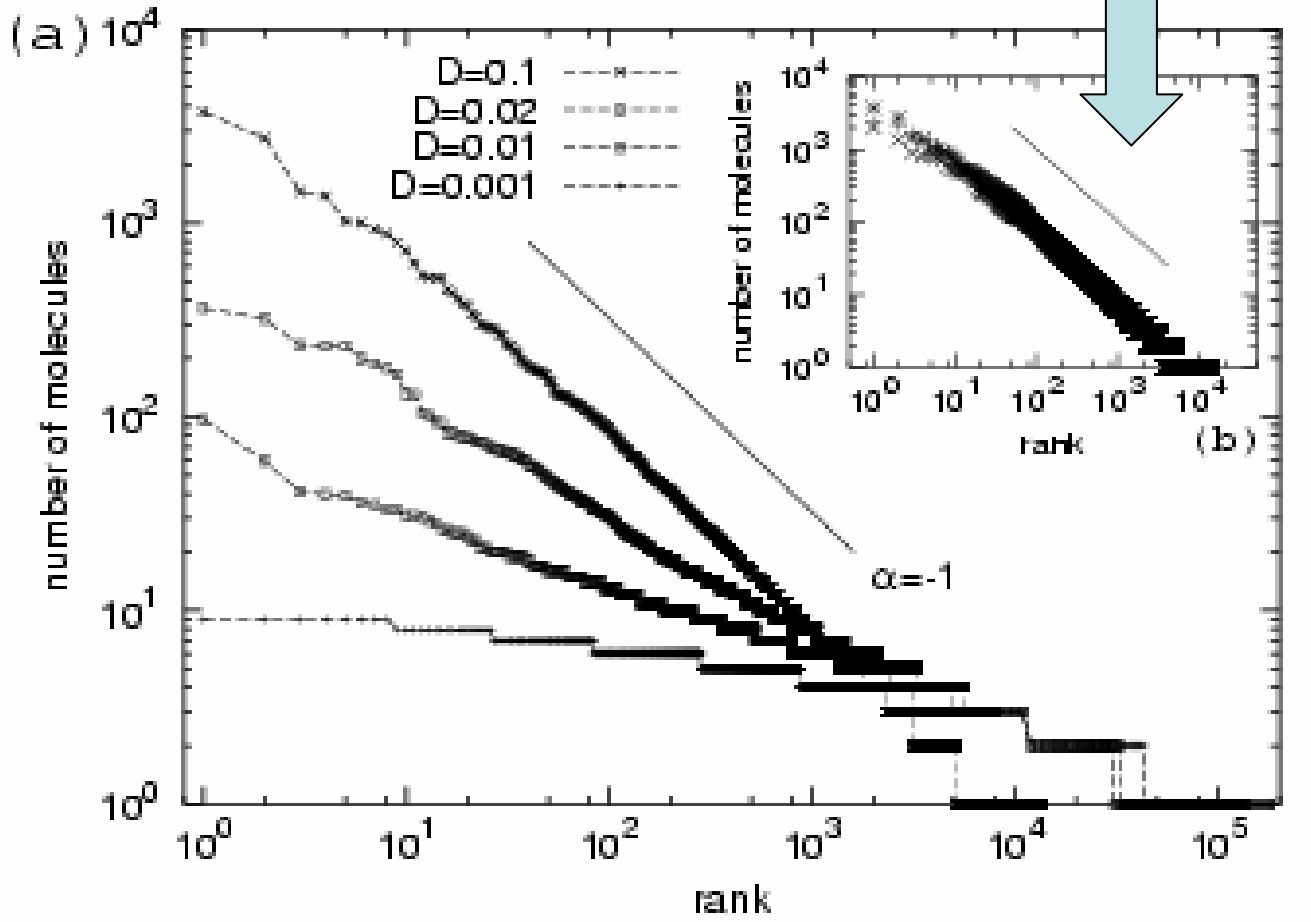




※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

Zipf's Law is oberved at D = Dc



n_i (number of molecules)

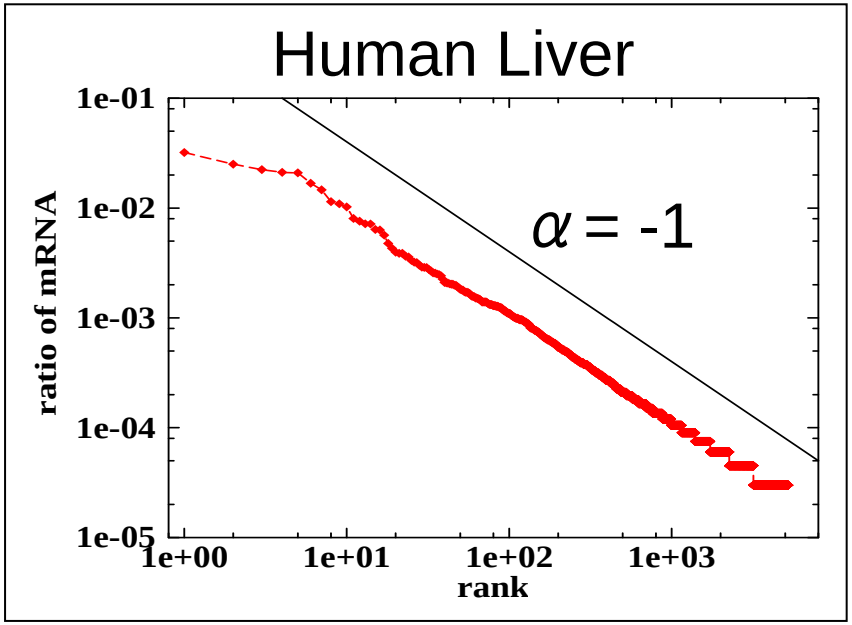
rank

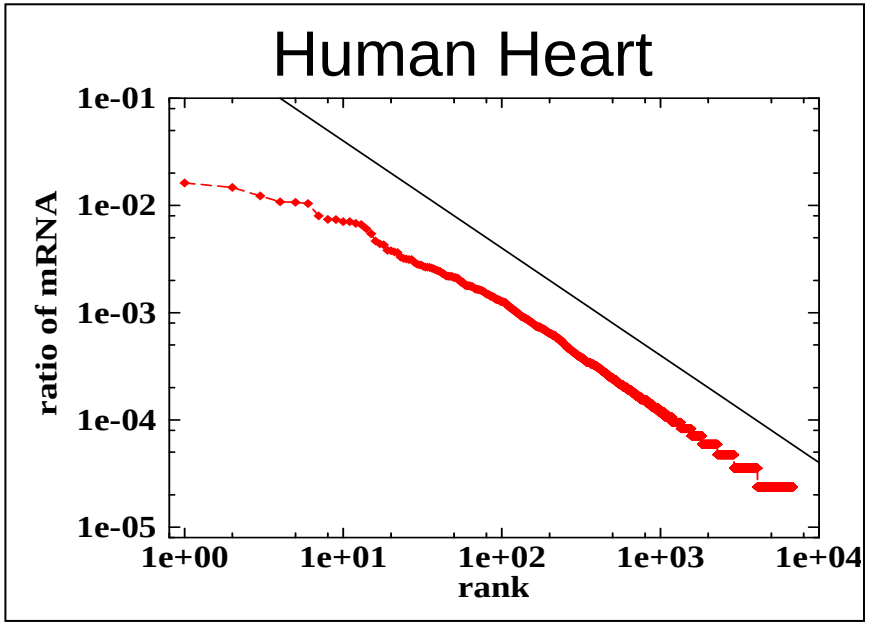
number rank
X1 300 5
X2 8000 1
X3 5000 2
X4 700 4
X5 2000 3
…… (for example)

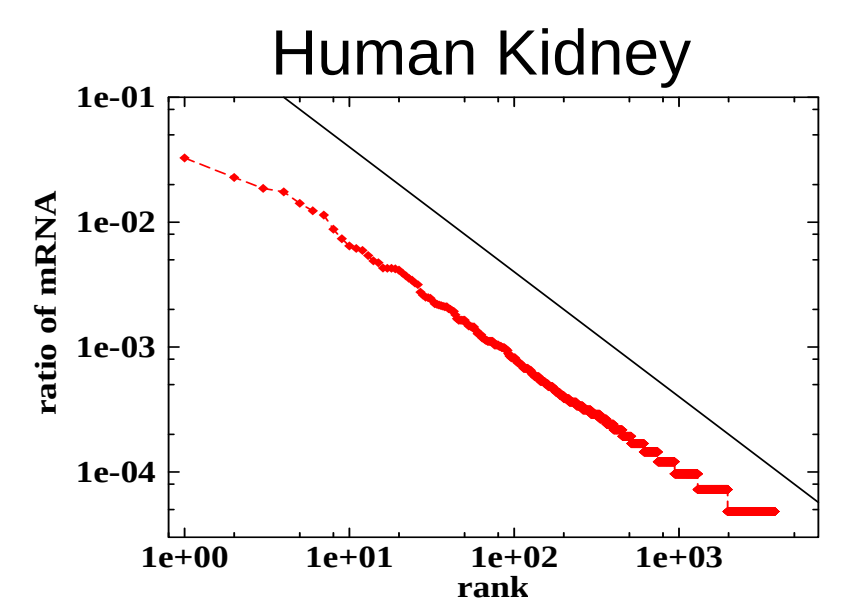
Average number of each chemical ∝ 1/(its rank)

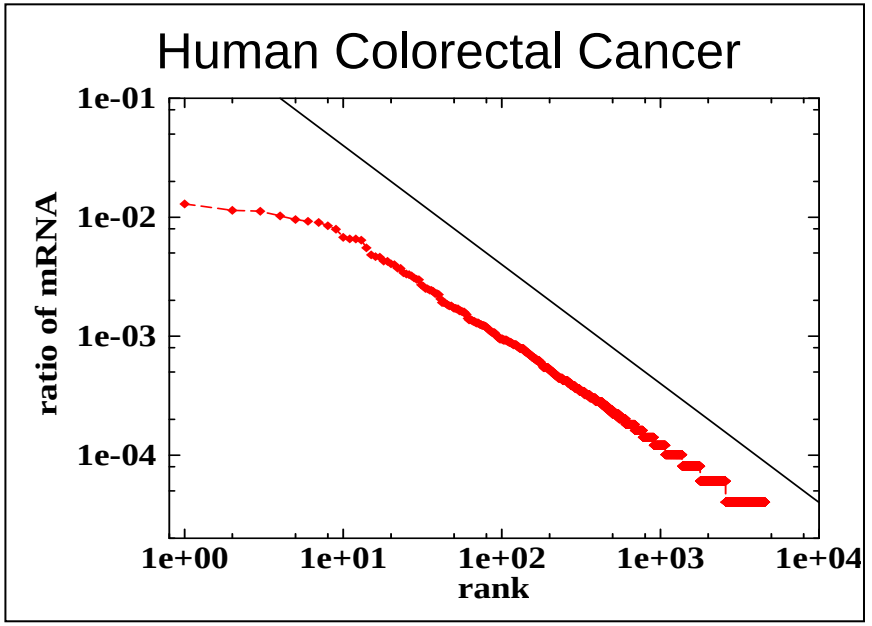
(distribution of x : $\rho(x) \propto x^{-2}$)

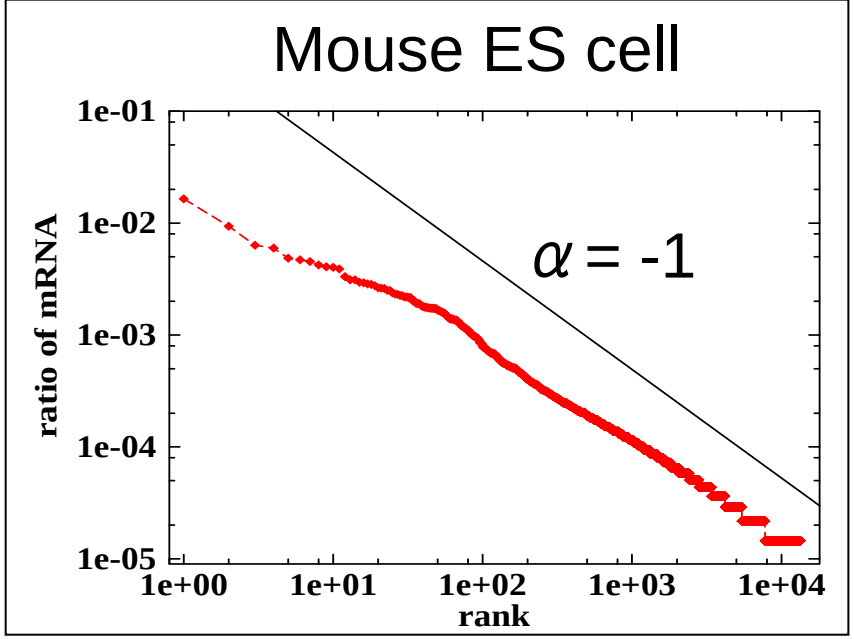
Confirmed by gene expression data

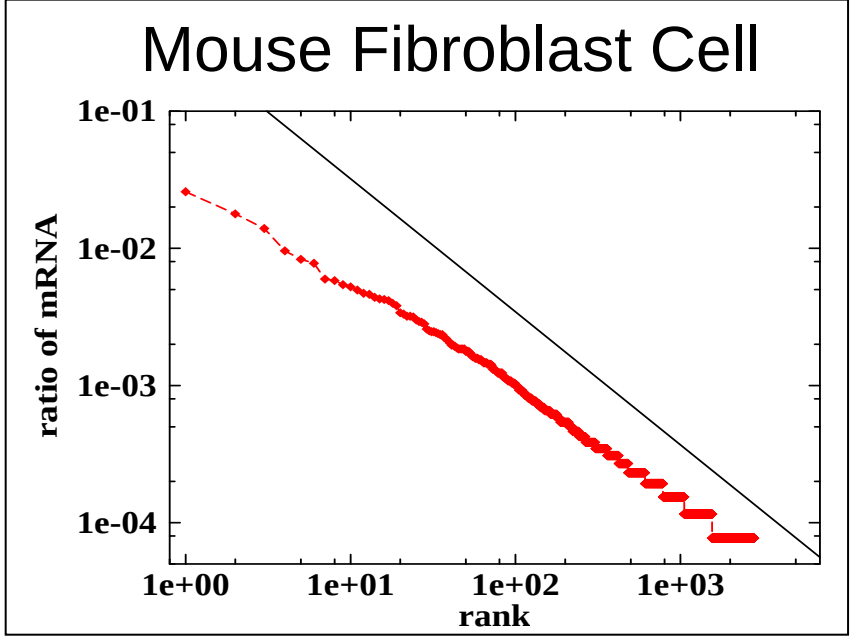


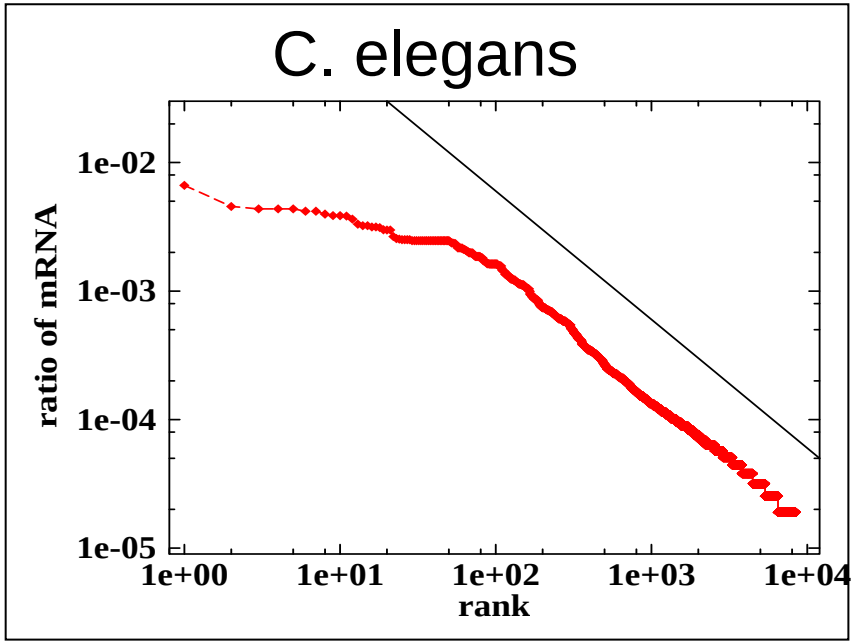


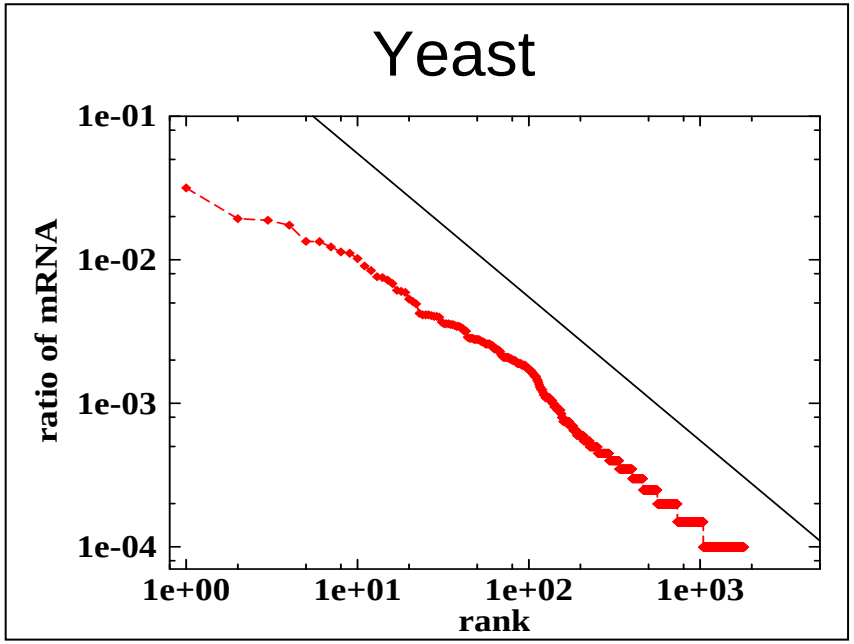






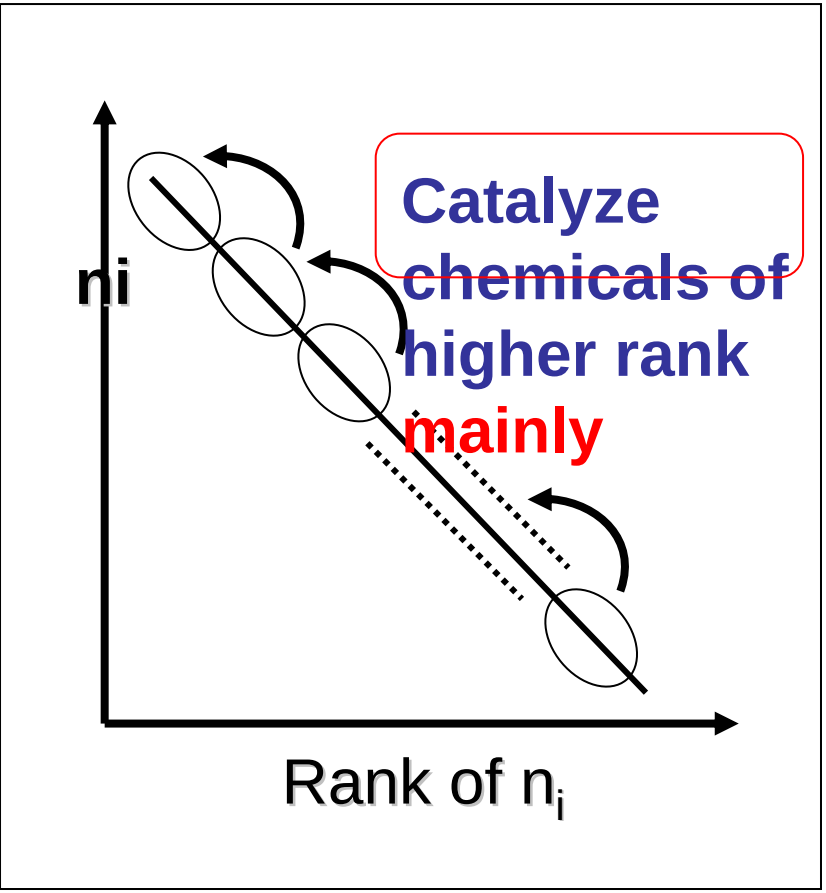


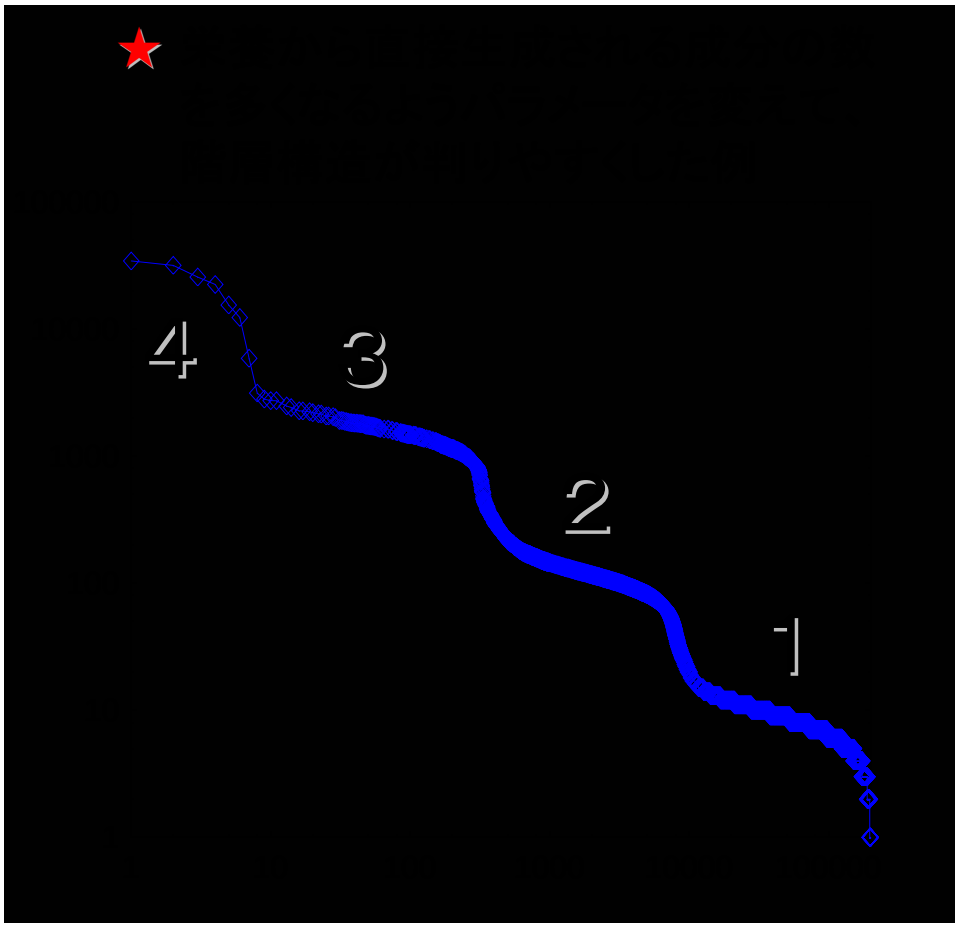




Later confirmed by several other groups

Formation of cascade catalytic reaction





1 : minority molecules

2 : catalyzed by 1, synthesized by resource

3 : catalyzed by 2

With conservation law,
The exponent -1 is explained

Mean-field theory in phase transition (self-consistent) calc.)

As a first step mean-field approximation;
assume that the nutrient chemicals have s

$$ds/dt = D(S_0 - s) - e\rho k' sx - sD(s_0 - s) \tag{1}$$

Recalling that $k'x + s = 1$,
fixed point solution is given by either $s = 1$ or

$$s^* = Ds_0/(D + e\rho) \tag{2}$$

The stability of this solution is computed by putting $s = s^* + \delta s(t)$, and
earize by $\delta s(t)$. This leads to the equation

$$s^* = (D(s_0 - 1) - e\rho)\delta s \tag{3}$$

Hecne the solution with $s \neq 1$ exists for

$$D < D_c \equiv= e\rho/(s_0 - 1) \tag{4}$$

As a next step to increase the mean-field approximation, we distinguish the chemicals that are directly synthesized from the nutrients and others. The number of the former chemicals are $\rho k'$ and the latter are $(1-\rho)k'$. Setting the concentrations of the former by x_0 and the latter x_1, the equations can be written as

$$dx_0/dt = exs + e\rho k'(x^2 - xx_0) - x_0 D(s_0 - s) \tag{5}$$

$$dx_1/dt = e\rho k'(x^2 - xx_1) - x_1 D(s_0 - s) \tag{6}$$

where x is the average concentration of non-nutrient chemicals, and thus given by $x = \rho x_0 + (1-\rho)x'$ (and again satsify $k'x + s = 1$).

$$dx_0/dt = \frac{Ds_0 e}{D + \rho e}(x - \rho x_0) + e\rho k' x(x - x_0) = 0 \tag{7}$$

The fixed point solution is computed from these equations. At $D \to D_c$, the solution satisfies $x_0 \to 1/\rho x$. Note that the fraction of chemicals at the first layer i_0 is ρ. Hence the relative abundance of chemicals is inversely

- Remarks:

（0）Universality

(1) Evolution to the critical state (with Zipf law) is confirmed numerically

(2) Evolution to scale-free network appears later as embedding of power-law abundances into network (Furusawa,KK, PRE 2006)

（3） Self-organization to critical state, if transport of ‘nutrition chemicals’ is catalyzed by some chemicals （no need for choice of D) (instead of simple diffusion) (Furusawa,KK,2007)

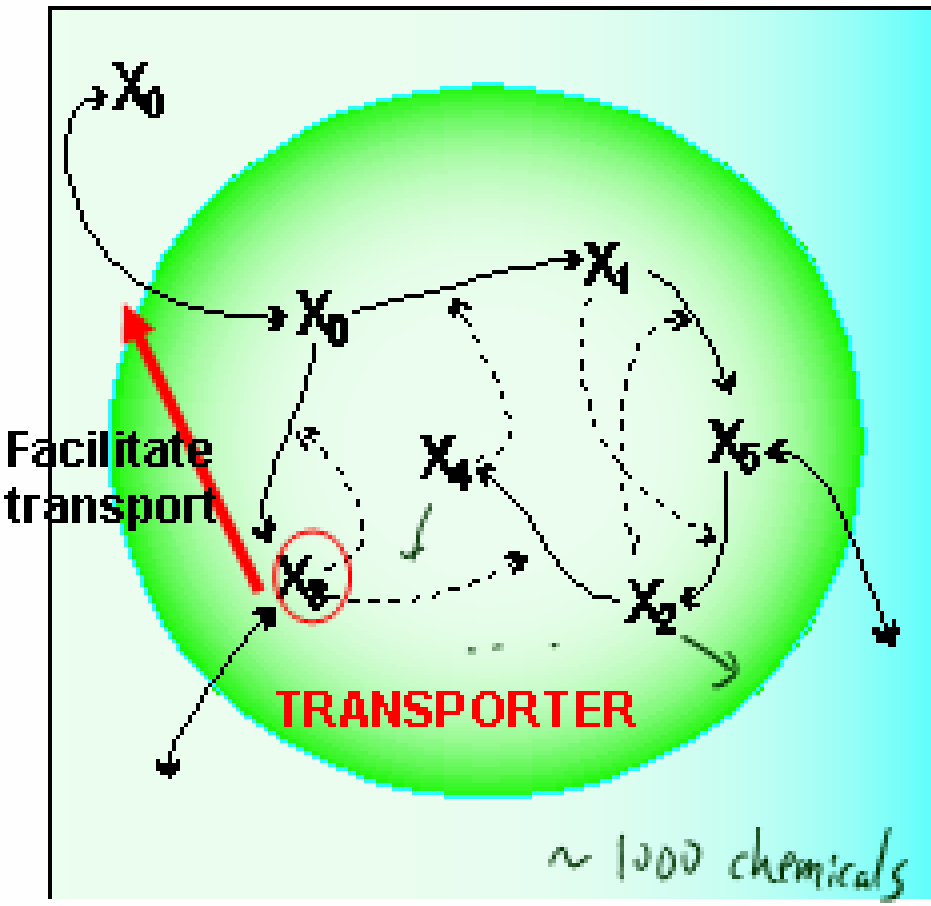
Adaptation to Criticality

Model with transporter facilitate transport of nutrient (active transport)

-→ self-tune the balance of concentrations of nutrient and catalytic chemicals

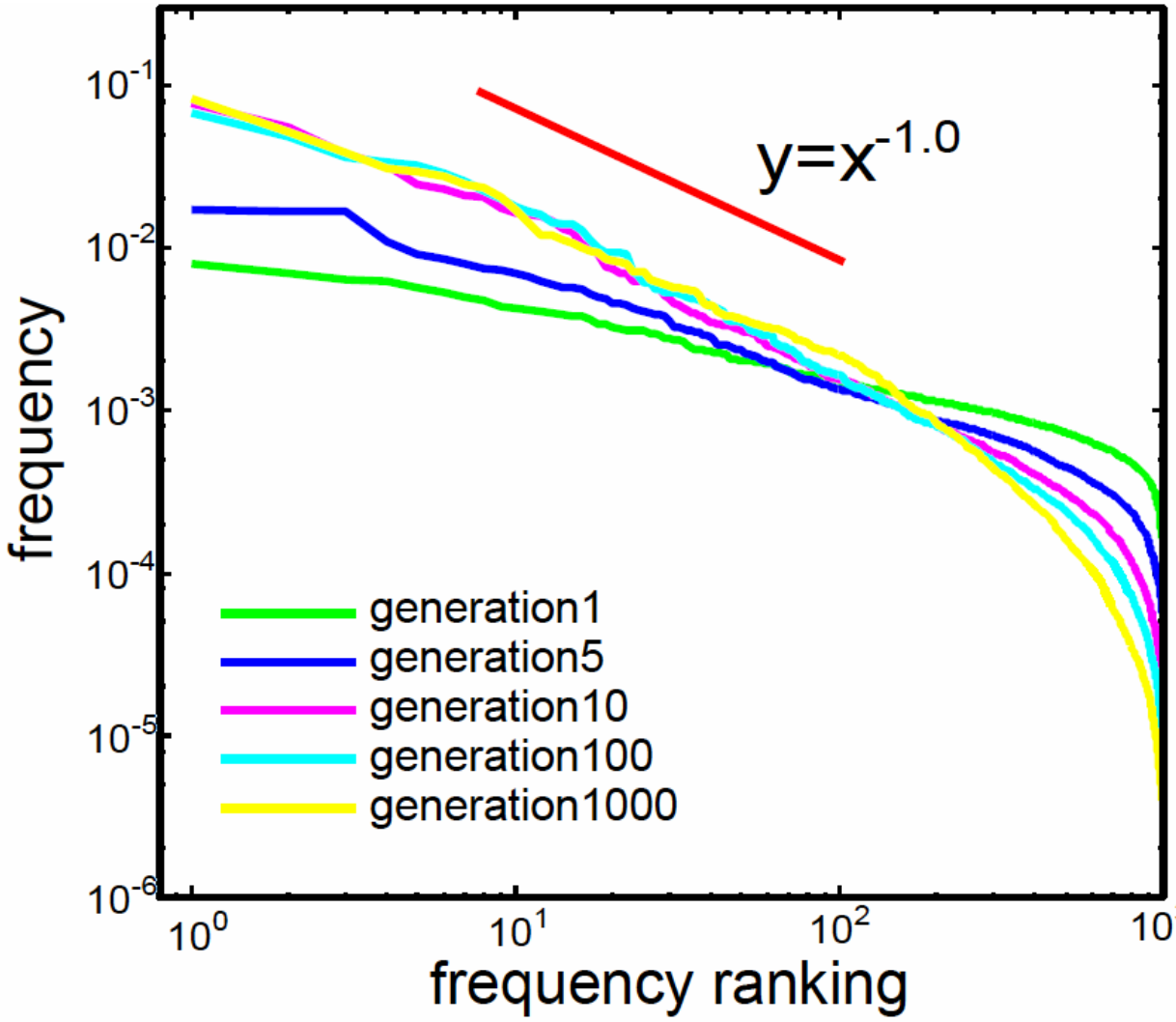
→ self-organize critical state, adaptive to environment

(Furusawa,KK, in prep)



Evolution of Network to satisfy Zipf's law? Yes

Critical D value depends on connectivity in the network;
mutation of network + selection → approaches Zipf's law



Furusawa

Fig1. rank distribution of chemical concentrations

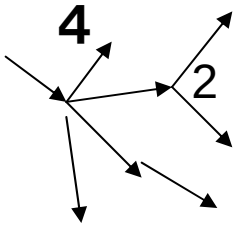
Zipf's law holds, irrespective of network structure, but

Later, the connectivity in the network approaches "scale-free" network through evolution.

statistical properties; embedded into network structure

Dynamics (abundance) first, structure (equation for dynamics) later

evolutionary embedding of dynamics into network



probability for a path to chemical with abundances x is selected; q(x) → transformation of abundance distrb. to connectivity distrib.

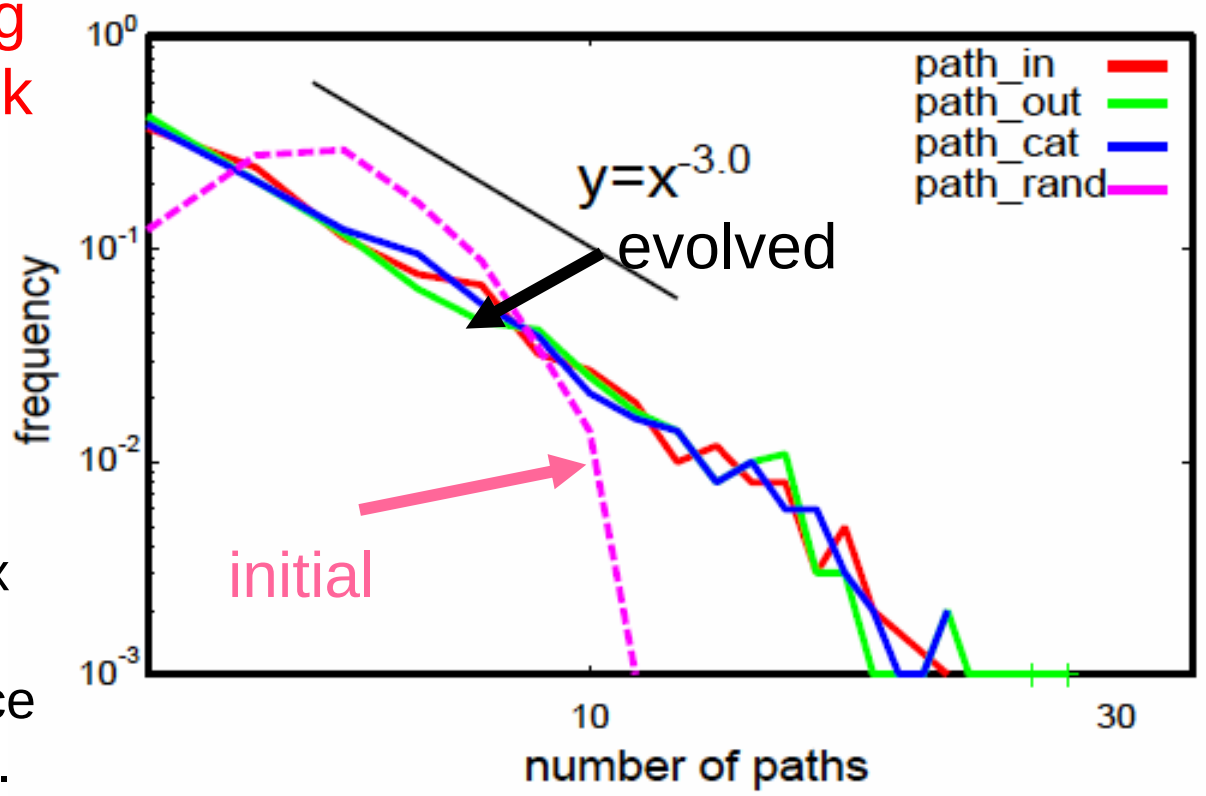


Fig2. connectivity distributions

Furusawa、KK, PRE, 2006

Relationship between Zipf's law (abundance) and scale-free network (structure): ???

(1) Abundance x: density $\rho(x) \propto x^{-2}$

(2) x; a path to molecule species with abundances x have more influence on growth speed: the simplest case

variation of growth speed to a path going out of a chemical with abundance x -> is x times higher ;

the evolution speed of a path from a chemical with x is effectively amplified by x: in general accelerated by some function q(x), say x^{α}

(3) as the path number is larger, there are some better networks. Then the distribution of paths k by transformation $q(x) \rightarrow k$

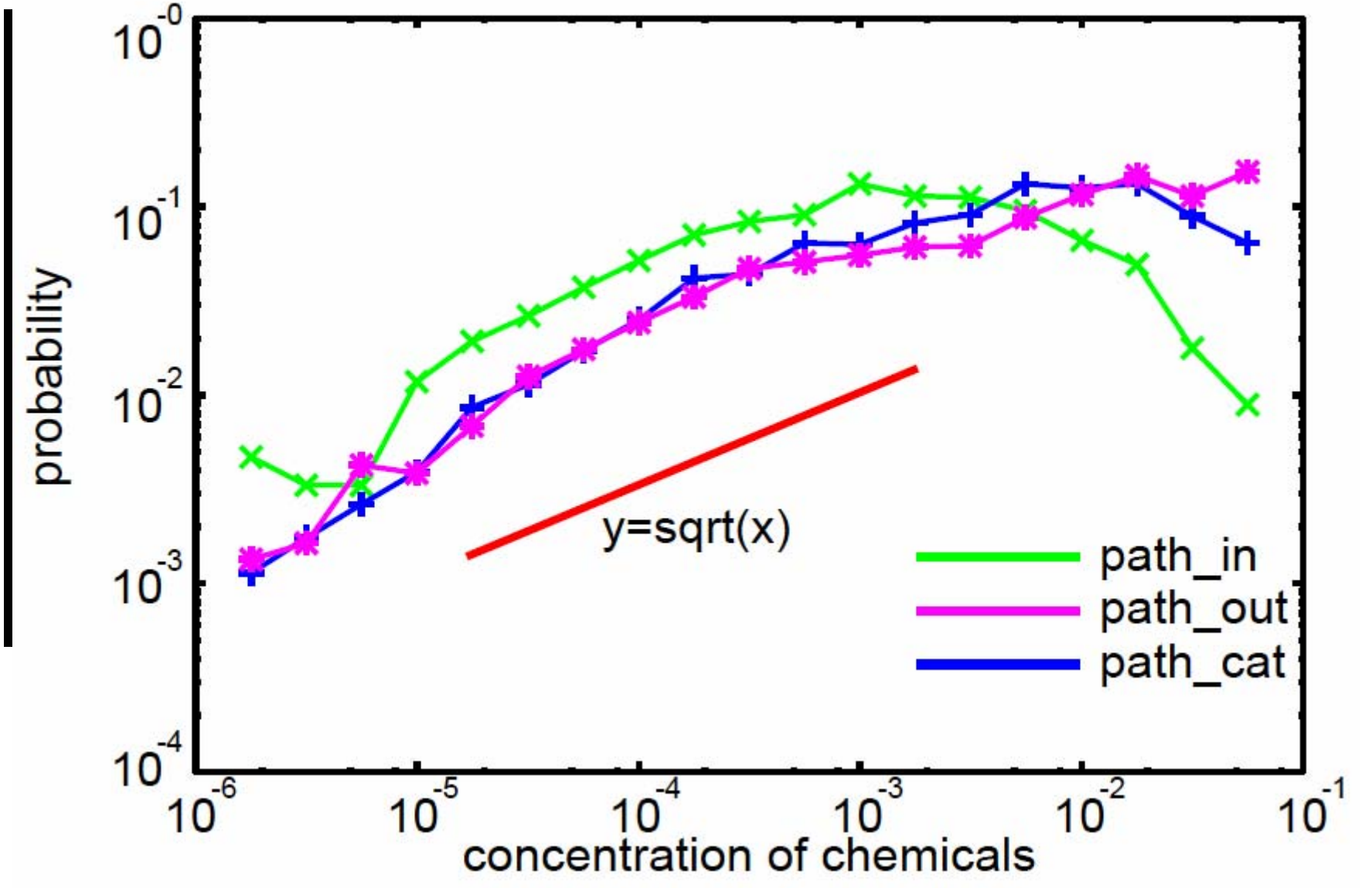
(4) Distribution of k ; $P(k) \propto (dx/dk)\ \rho(x)$

if $q(x) = x$, then $P(k)$ k^{-2}, if $\alpha = 1/2$ then k^{-3}

NOTE abundance dynamics first, topology of network (scale-free network) is later embedded accordingly

☆Distribution of paths in reaction network

Furusawa



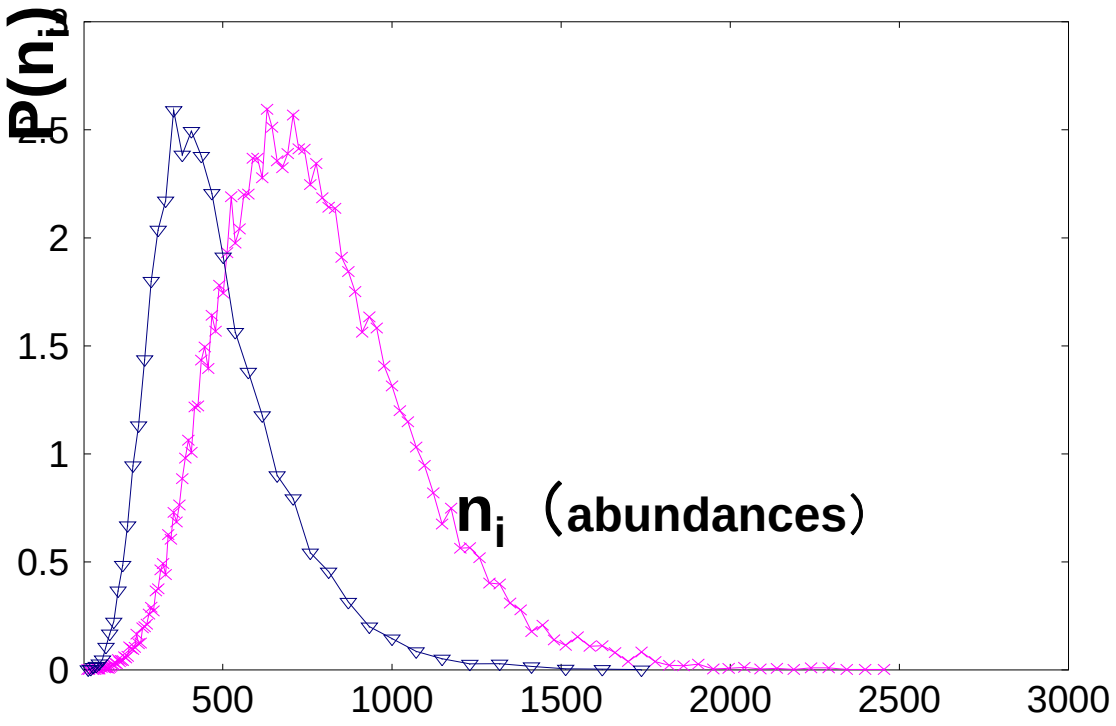
Fluctuation of each chemical Abundance;

→ long-tail to abundant size

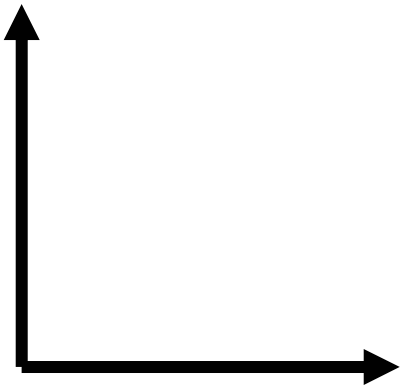
e.g.

cell1 X1 10000
cell2 8000
cell3 15000
cell4 20000
.....

histogrram



Frequency of n_i



n_i (abundances)

So far average quantity of all components;

Next question: fluctuation by cells:
distribution of each Ni by cells

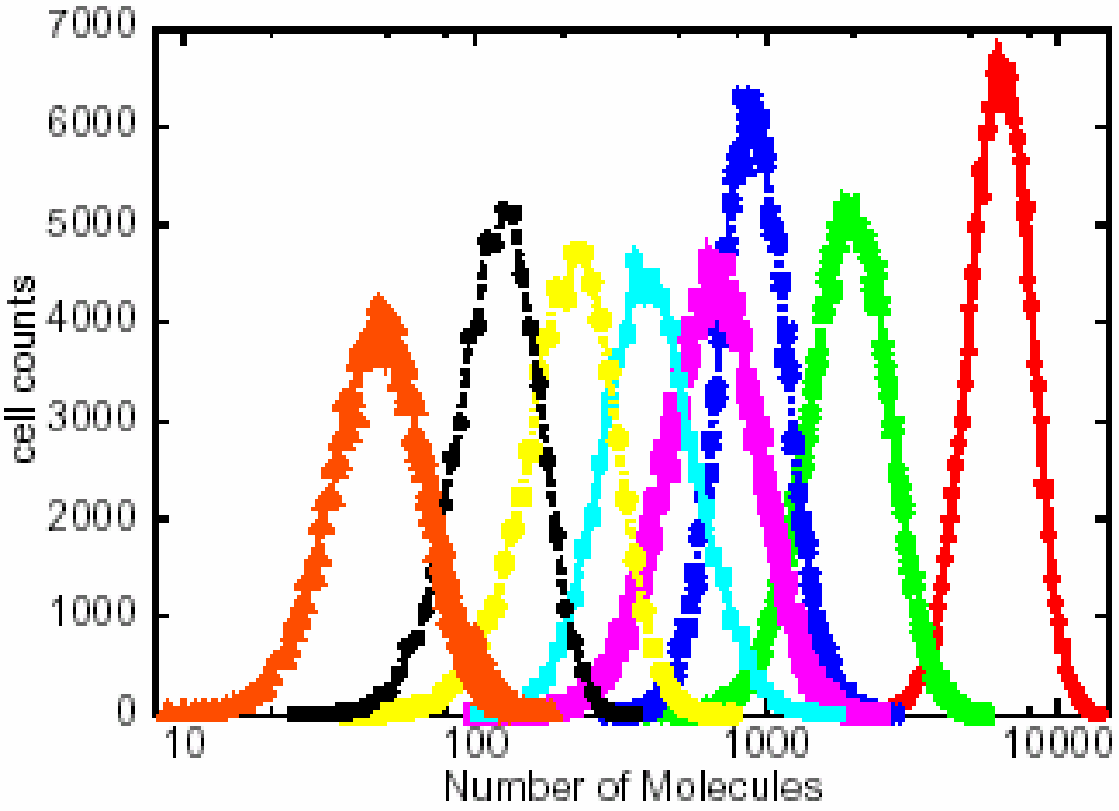
Furusawa,..
KK,
Biophysics2005

e.g.

cell1 X1	10000
cell2	8000
cell3	15000
cell4	20000

.....
histogrram

Log normal distribution !



Each color gives different chemical species

LOG SCALE

☆Heuristic explanation of log-normal distribution

Consider the case that a component X is catalyzed by other component A, and replicate; the number --N_X、N_A

$$d N_X /dt = N_X N_A$$

then

$$d \log(N_X)/dt = N_A$$

If、N_A fluctuates around its mean $<N_A>$, **with fluct.** η（t）

$$d \log(N_X)/dt = <N_A> + \eta(t)$$

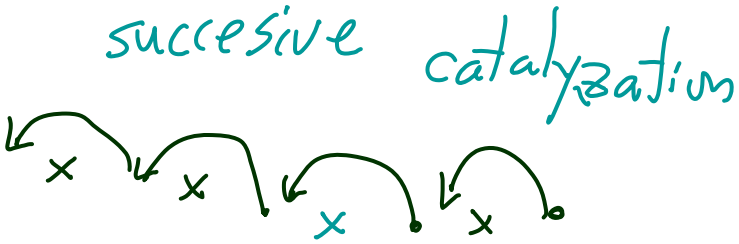
log(N_X) shows Brownian motion → N_X log-normal distribution

too, simplified, since no direct self-replication exists here

But with cascade catalytic reactions, fluctuations are successively multiplied, (cf addition in central limit theorem.);Hence after logarithm, central limit th. applied

☆Heuristic explanation of log-normal distribution

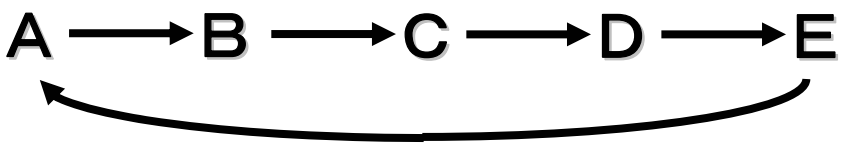
☆Cascade leads to multiplicative propagation of noise (at critical region)



d Nx/dt=Ny N **z**

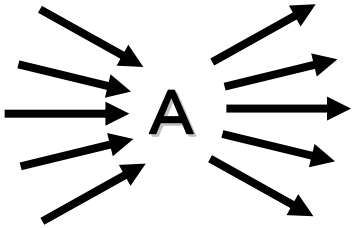
with cascade catalytic reactions, fluctuations are successively multiplied,
(cf addition in central limit theorem.);
Hence after logarithm, central limit th. applied

☆Cascade leads to multiplicative propagation of noise (at critical region)



Propagation of fluctuation, feedback to itself, leading to log-normal distribution tail.

Cf. If parallel,



Cf??

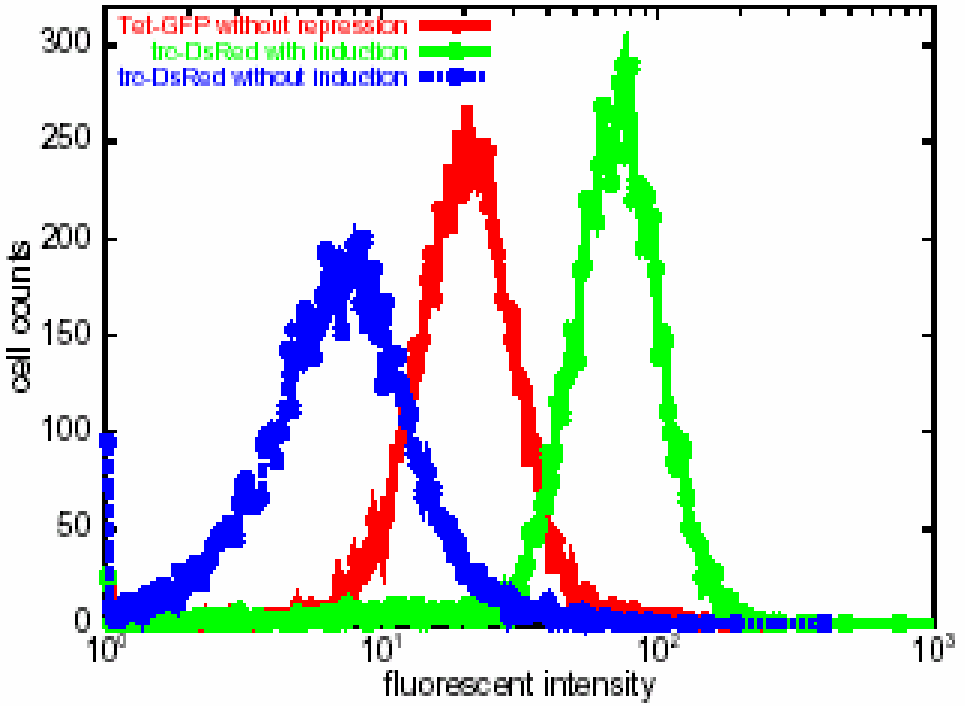
weight – log-normal
height -- normal

Fluctuations come in parallel:

Usual central limit theorem is valid;

normal distribution.

Experiment; protein abundances measured by fluorescence



+flow-cytometry

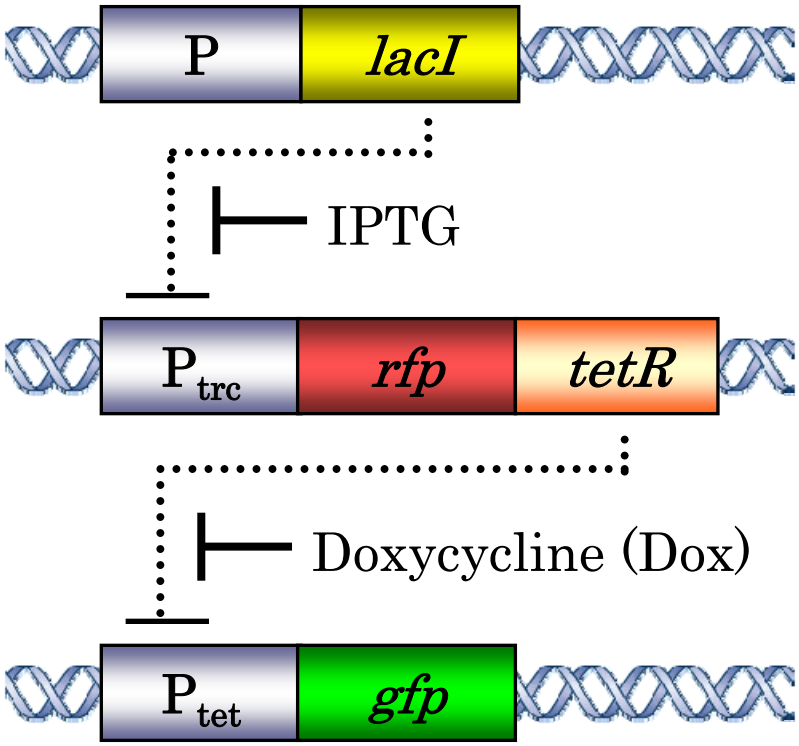
Log-normal Distribution Confirmed experimentally

Furusawa,Kashiwagi,,Yomo,KK

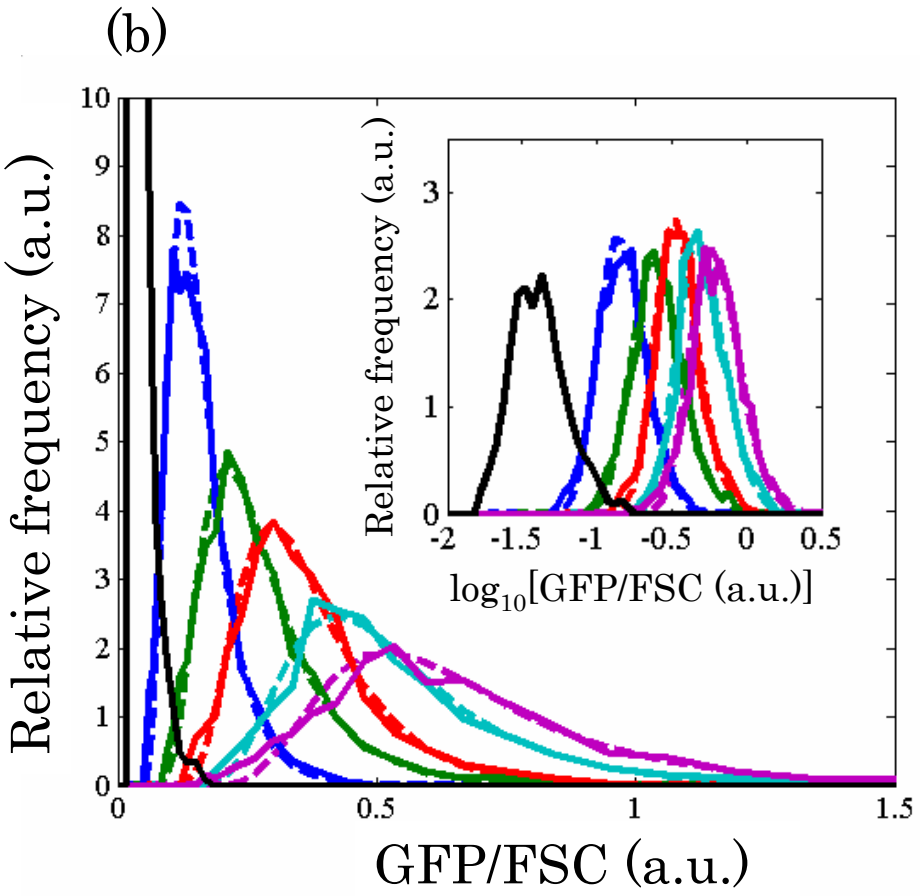
Figure 3: The number distribution of the proteins measured by fluorescent intensity. Distributions are obtained from three *Escherichia coli* cell populations containing different reporter plasmids, i.e., EGFP (enhanced green fluorescent protein) under the control of the tetA promoter, DsRed (red fluorescent protein) under the control of the trc promoter with and without IPTG induction. Note that, although the IPTG induction changes the average fluorescent intensity, both the distributions (with and without the induction) can be fitted by log-normal distributions well.

Also studied in GFP synthesis in liposome

Statistics in gene expression in the present cell



Chromosome in *E. coli*



Log-normal like distribution at each Doxycycline concentration

Tsuru,Ichinose,Kashiwagi,KK, Yomo (in prep.)

Cf. Recent studies on fluctuations:

log-normal or not?

Cell Growth has to be seriously considered

In theory and experiment.

X just stochastic gene expression

X condition suppressing cell growth

Condition for steady growth state --- should be carefully prepared in experiment

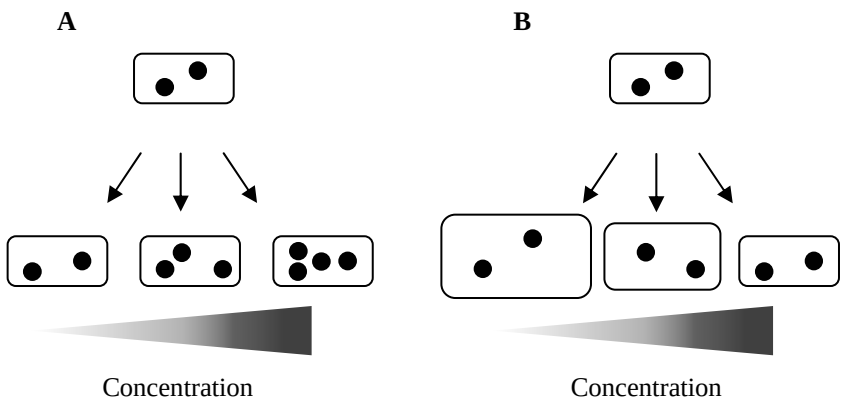
Size itself is lognormal: either selection by some size, or normalized by size

Analysis for all gene expressions in yeast（Bar－Even etal., 2006)

Growth Fluctuation induces log-normal-type distrb.

Figure 1

Fluctuations in a Cell; Cell Volume Growth effect



Stochastic gene expression that are current concern of many

Consequence of Cell volume growth fluctuation tha we are interested

Tsuru,Ichinose,Kashiwagi,Ying,KK,Yomo

Growth fluctuation can lead to Log-tailed phenotypic fluctuation

- protein concentration x
- dx/dt=f(x)-($\mu + \eta$)x

dilution term by cell volume growth

μ —— growth rate

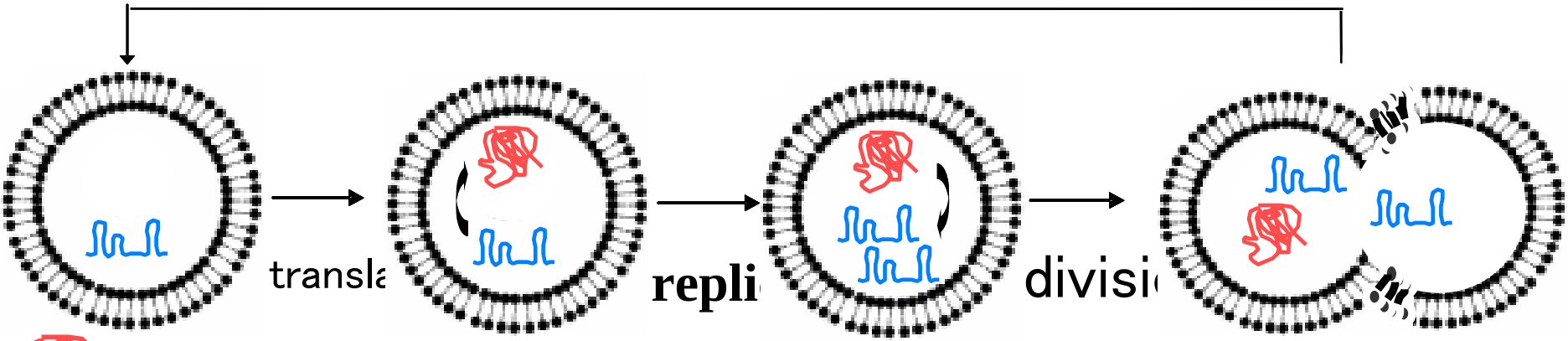
η —— fluctuation (noise)

multiplicative noise → log-tailed distribution

(exp; Tsuru etal)

Growth rate μ is a result of an ensemble of gene expression μ(x1,x2,x3,…) -- (consistency)?

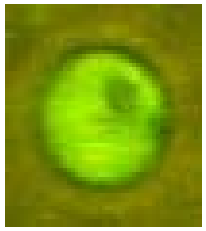
Replicating artificial cell (experiment)
(←→theory; fluctuation, minority control)



RNA polymerase

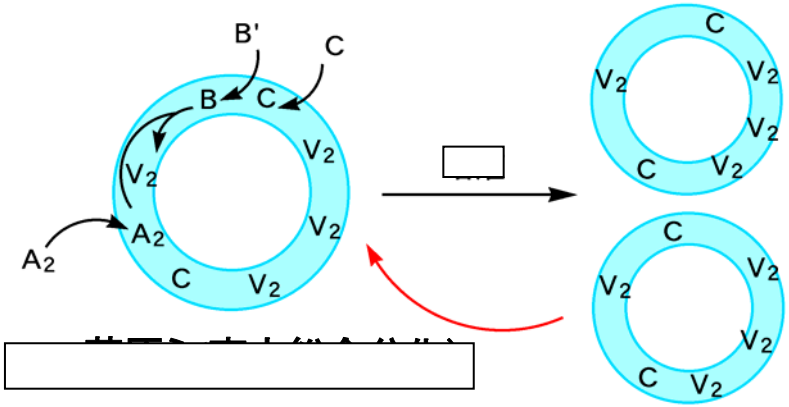
RNA polymerase geneRNA

(Yomo‘s group)



Tranlation in liposome

RNAreplication in liposome



(Sugawara’s group)

Continouos division of liposomes

- A Lesson:

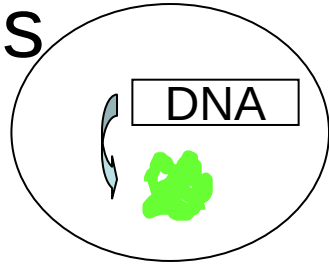
Necessity of mutual dependency to form self-consistent reproduction system

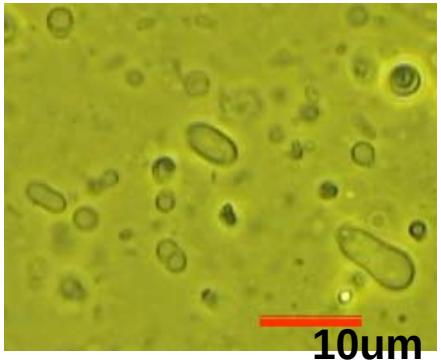
Liposome growth←→ synthesis of proteins

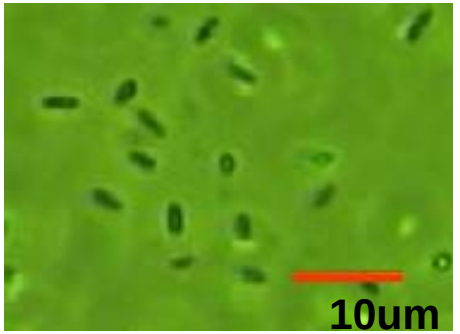
so far, not consistent→

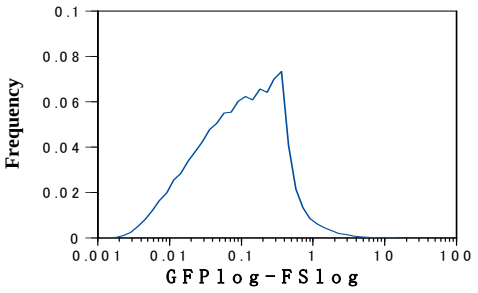
too large fluctuations

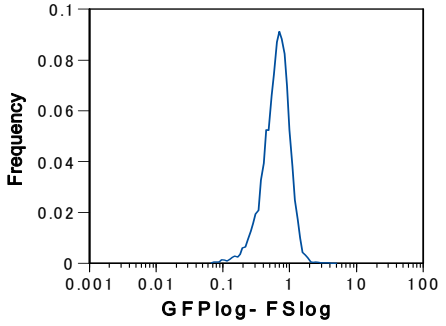
(not necessarily log-normal)











GFP synthesis in liposome and in bacteria

- Basic question related with Protocells (origin-of-life)

-- origin of genetic information (genetic take over?)

(Minority control, kk,Yomo JTB 2002,kk PRE2003,,,)

-- dynamics versus algorithmic: discreteness induces sequential procedure -- Discreteness Induced Transition, Togashi,kk; PRL2002, Awazu,kk 2007+)

-- 'jamming' problem in reaction dynamics?

(Awazu,kk; PRE 2007 +)

-- how non-equlibrium condition is sustained?

(Awazu,kk; PRL 2004, + arXiv2008)

Question :
All molecules have such large fluctuation?
Important ones are ‘protected’? (DNA?)

- Q: Origin of heredity?
- * some molecules in a cell are regarded as ‘’important’’, and control the behavior of cell

e.g., differentiation in roles between DNA and protein,

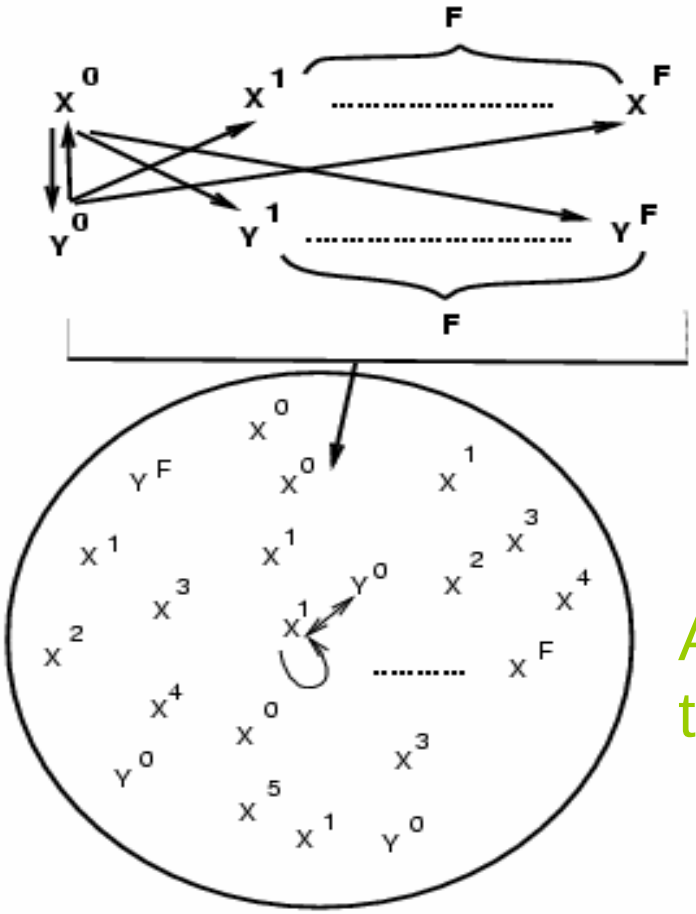
Minority Control hypothesis (KK & Yomo, 2002)

in a replicating system composing of mutually catalytic molecules, minority molecules play the role of heredity-carrier

Condition for heredity

preservation

controllability



X and Y mutually catalyze the synthesis of each other; Y is synthesized much slower than X molecules.

Rate equation may lead to (active) Y molecule of the concentr. < 1/N

A few Y molecules are necessary to continue reproduction

Selected are ‘rare’ states with a few Y molucules

Active Y molecules;
(i) Preserved well,
(ii)Control the behavior

Carrier of heredity

divsion

N molecules

N molecules

- Hypothesis based on Minority Control

minority (preservation+ control) →

evolution of

machinery of faithful transmission of minority molecule. →

more chemicals are synthesized with it

Package life-critical info. Into minority molecule.

From compositional information to sequence information

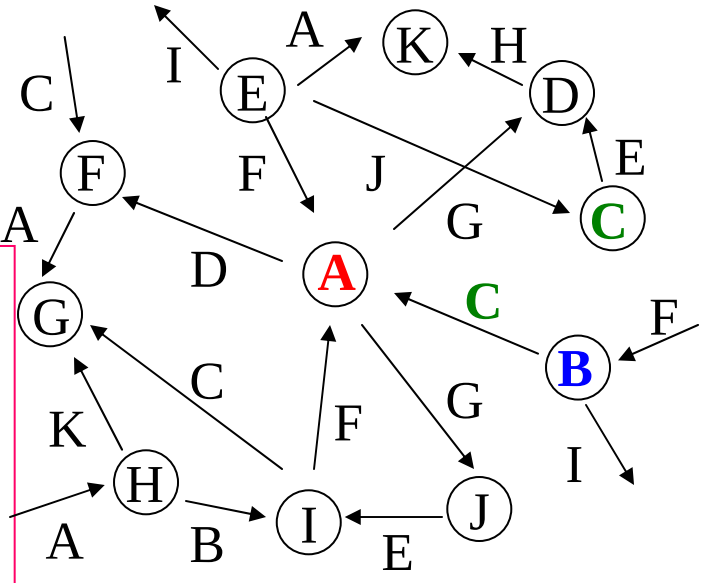
**Evolvablity: ‘’mutation’’ of minority molecule → large influence Genetic Takeover

(from loose reproduction to tight replication)

Mutual Catalytic Reaction network

Awazu,KK,PRE2007

Stochastic collision

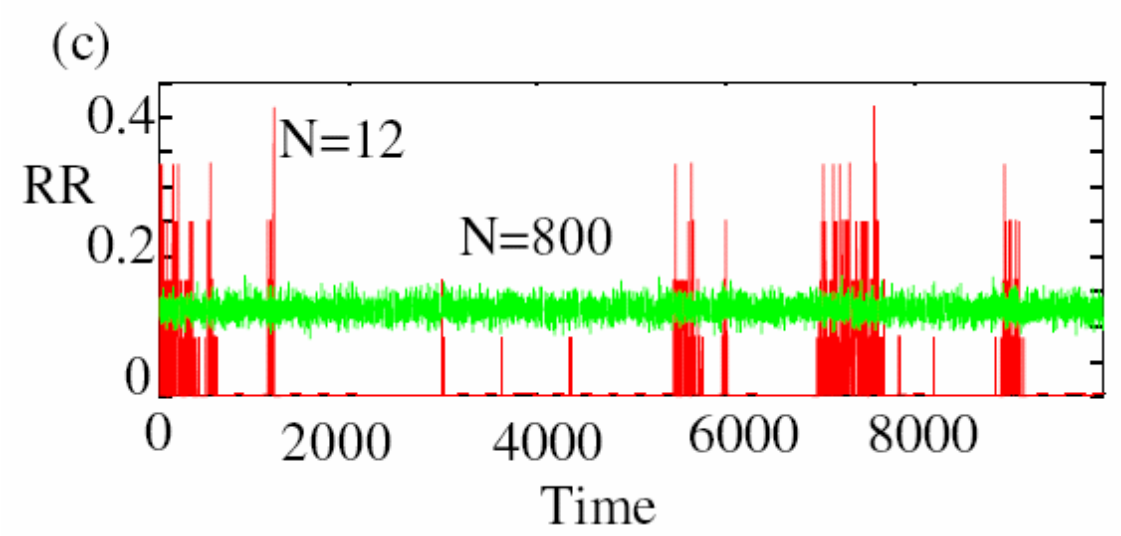


Random catalytic network

Total number of molecules N

Number of molecules species M

If not N >>M, the number of some species can be 0 → discreteness

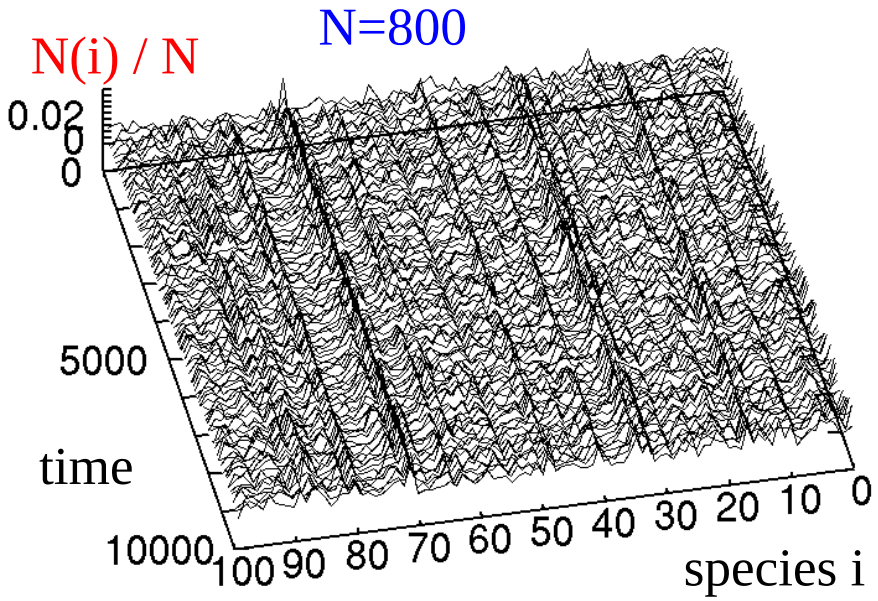


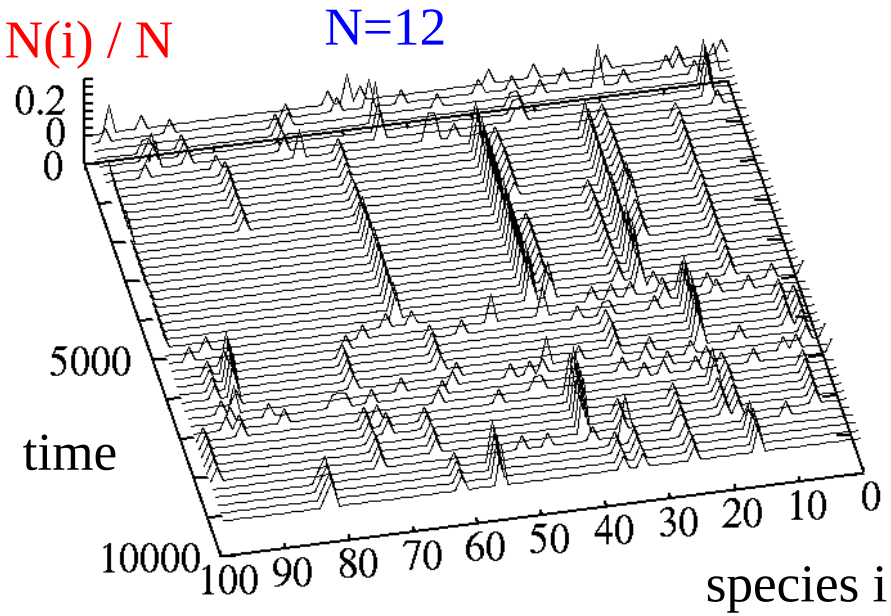
Reaction Rate RR =

reaction evens per time
total number of molecules

An example in network （Species：M=100、path：K=12）

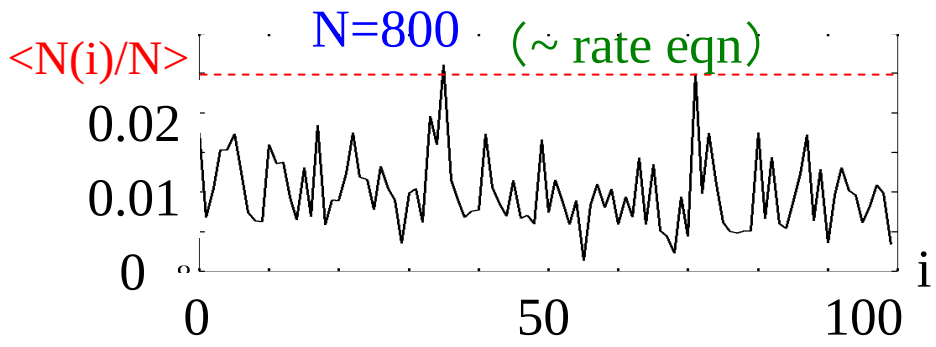
Plot of N(i) for species i same network, with different N

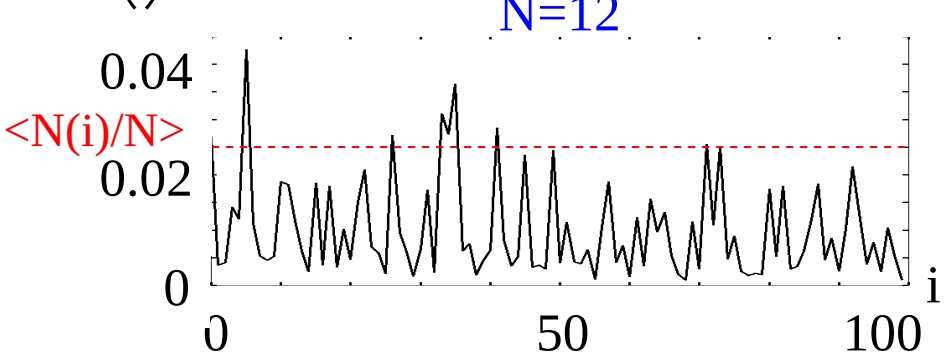




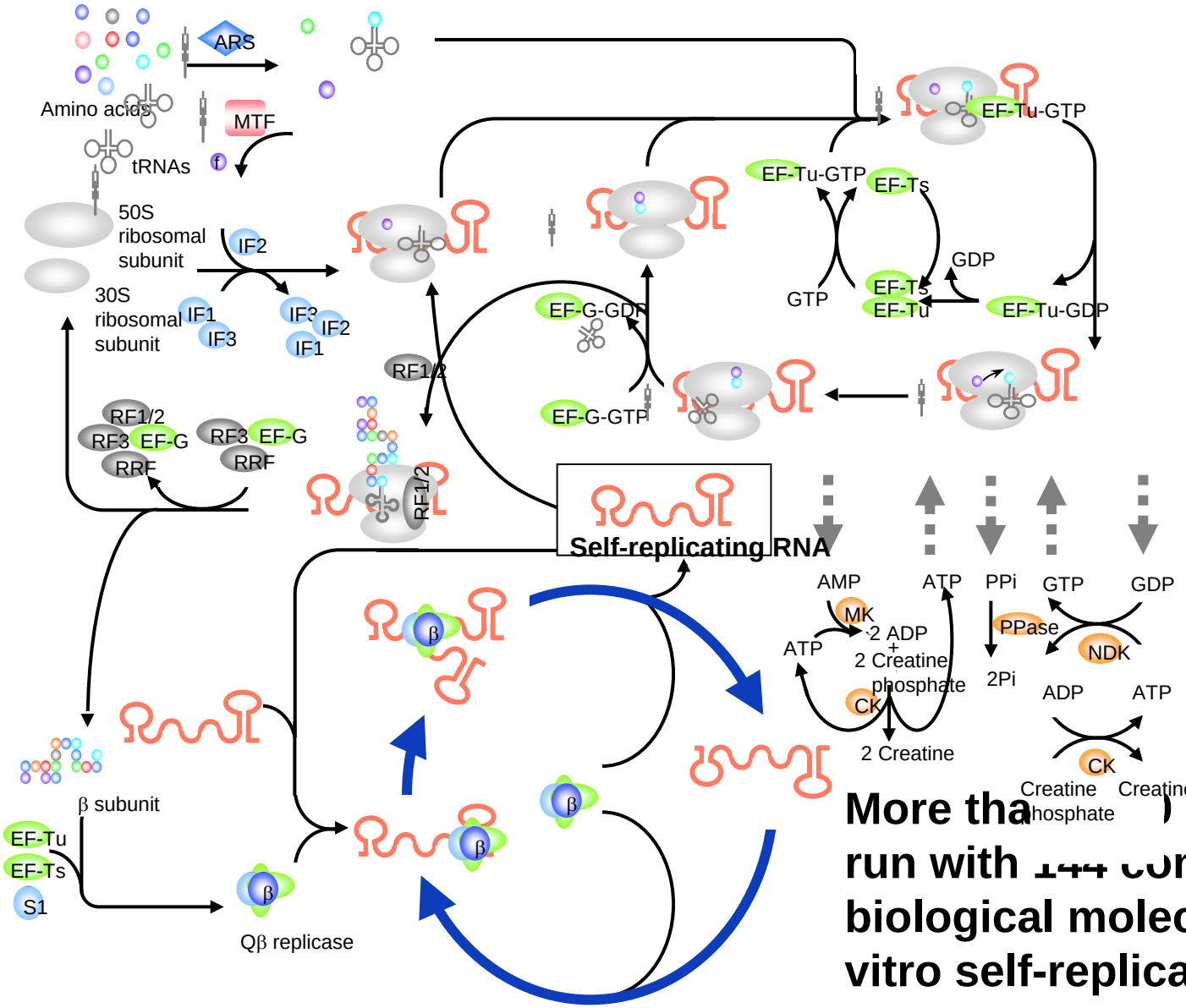
Steady state + small fluct. Intermittent switch among states

Average composition differs drastically





Jamming in reaction by crowding often suppresses the process, especially when complex reaction is put



Matsuura et al Yomo's group

More tha reaction steps run with 144 components of biological molecules for the in vitro self-replication.

How is non-equilibrium condition sustained?

Our tentative answer: a large class of Catalytic network exhibits ‘glassy’ (slow,)relaxation with bottlenecks

← negative correlation between substrate and catalysts

General in catalytic networks → ‘Chemical Net Glass’ (Awazu-kk)

with spatial pattern -- further hindered --good news

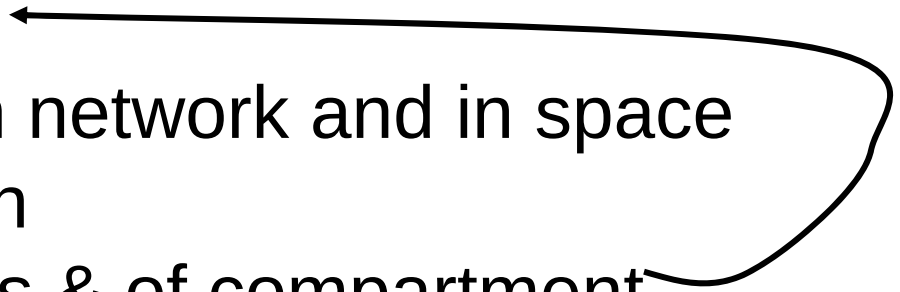
Reinforcement？

nonequilibrium condition

←→ Structure formation in network and in space

→ Compartmentalization

→reproduction of molecules & of compartment



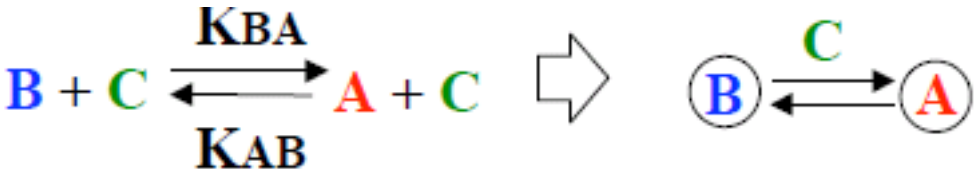
Reproduction of Non-equilibrium Condition Itself？？

But there appear reaction bottlenecks (bad news) + successive switch --- may underlie ‘slow dynamics’ in present cells?

Proposal of 'Chemical Reaction Net Glass''

Simple catalytic reaction network

With A.Awazu

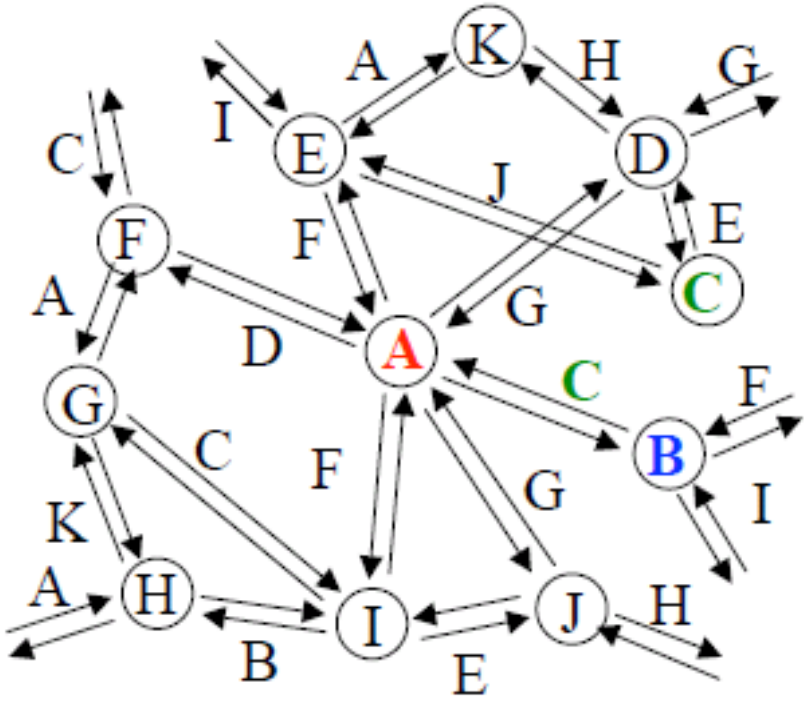


$$X_i + X_c \rightleftharpoons_{k_{j,i}}^{k_{i,j}} X_j + X_c.$$

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

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

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



Ei distributed : stnd deviation ε

RELEVANT parameter β ε

Equilibrium distribution exp(- β Ei) : (←detailed balance)

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

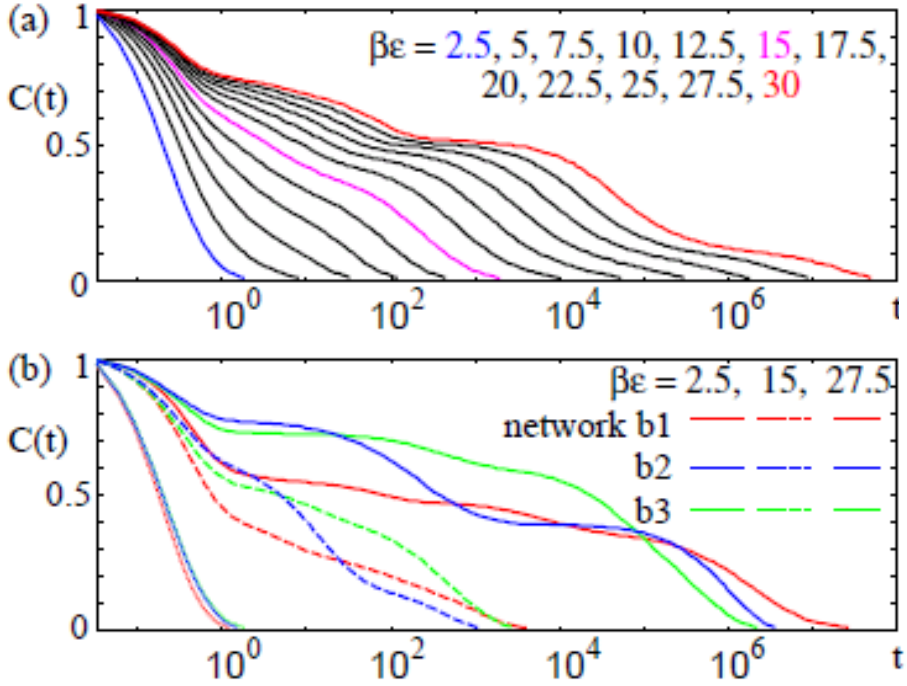


FIG. 1: (a)(b) Relaxation time course for four sets of networks ($M = 24$, $K = 8$) for several β.

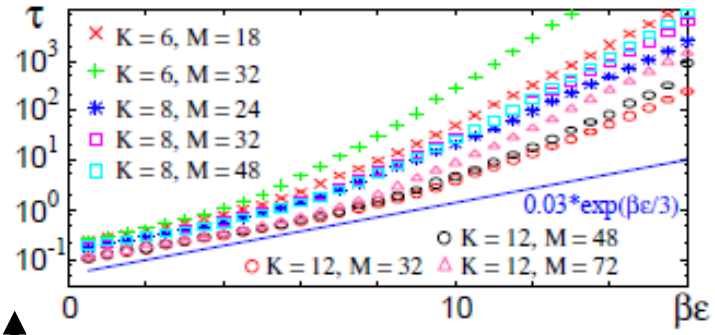


FIG. 2: Relaxation time as a function of β for the samp
reaction networks in Fig. 1(a)(b).

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

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

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(- β E)) 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)

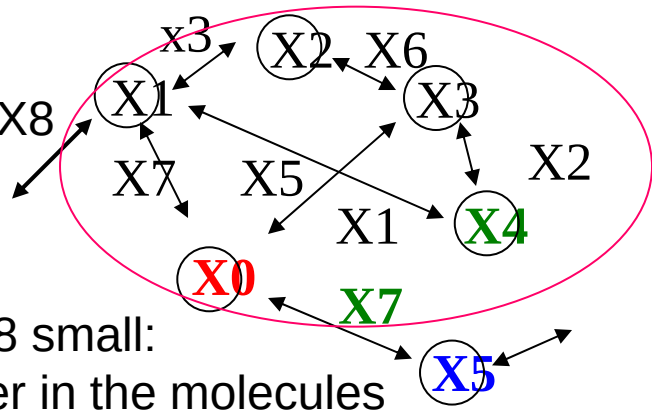
- Why plateaus?
- Local equilibrium within cluster
- Equilibrated with other clusters

is suppressed by deficiency of catalytic molecules

- negative-correlation with

abundances versus catalysts

- $\Delta X \uparrow \rightarrow \Delta Jout \downarrow$?



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

General in catalytic networks → 'Chemical Net Glass'

Consolidation (Reinforcement)?

nonequilibrium condition

←→ Structure formation in network and in space

→ Compartmentalization

→reproduction of molecules & of compartment

→ increase inhomegeneity in space

Reproduction of Non-equilibrium Condition Itself

But reaction can be easily stopped (bad news?)

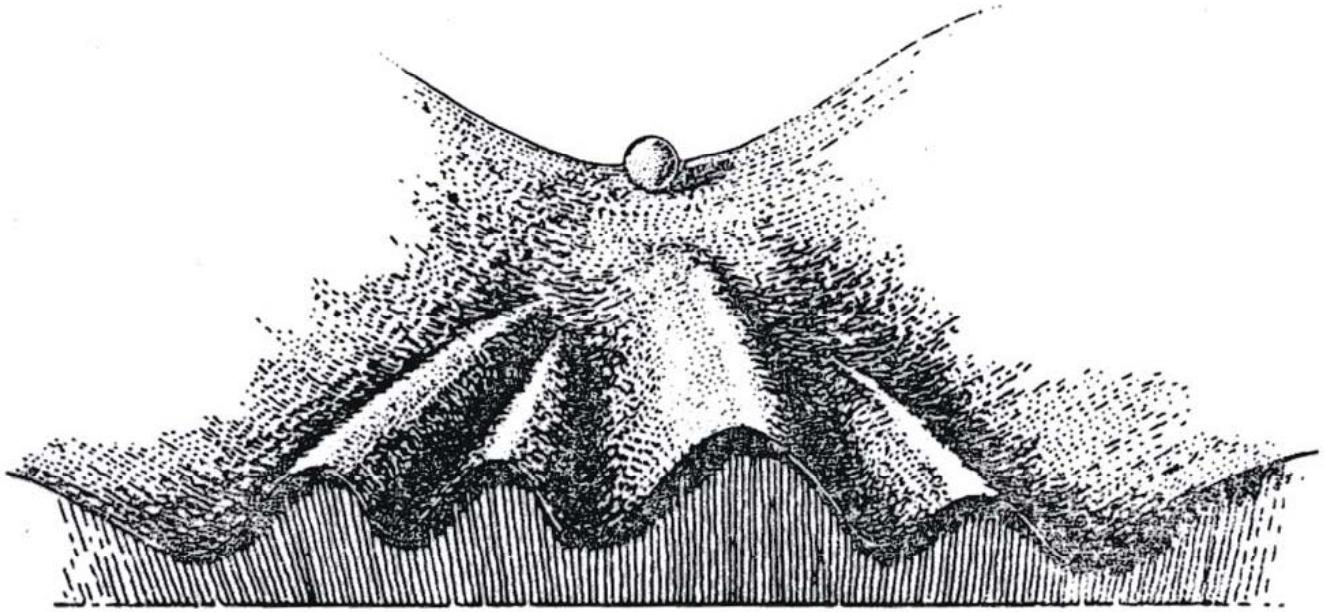
Bottlenecks in reactions + successive switch --- may underlie ‘slow dynamics’ in present cells?

True in irreversible reactions/ open systems?

→ Study irreversible Catalytic Reaction Network

Multicelluarity: Question on Cell differentiation:

Insight by Conrad Waddington



Waddington's Canalization

Cell types as Attractors?

How genes guide this process?

Multicelluarity:Question on Cell differentiation:

$$\frac{dx^m}{dt} = f_m(x^1, x^2, .., x^k)$$

1 diversification of cell types

2 Loss of Pluripotency (plasticity)

('time's arrow'?)

3 Robustness in cell types and Their distribution

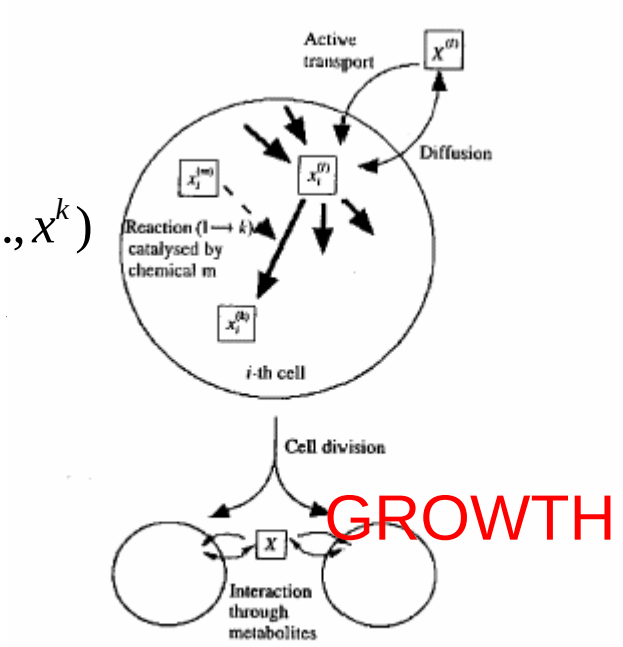


FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

GROWTH

Coupled Dynamical Systems with growth in dimension

Proposal of Isologous Diversification:

(KK,Yomo,Furusawa1997-)

(Oscillatrory) Gene expression dynamics

* cell-cell interaction + Reproduction of a cell

Growth as a multicellular organism

→ irreversible and robust developmental process

Isologous Diversification:

internal dynamics and interaction : development phenotype

instability

distinct phenotypes

interaction-induced

$$\frac{dx^m}{dt} = f_m(x^1, x^2, .., x^k)$$

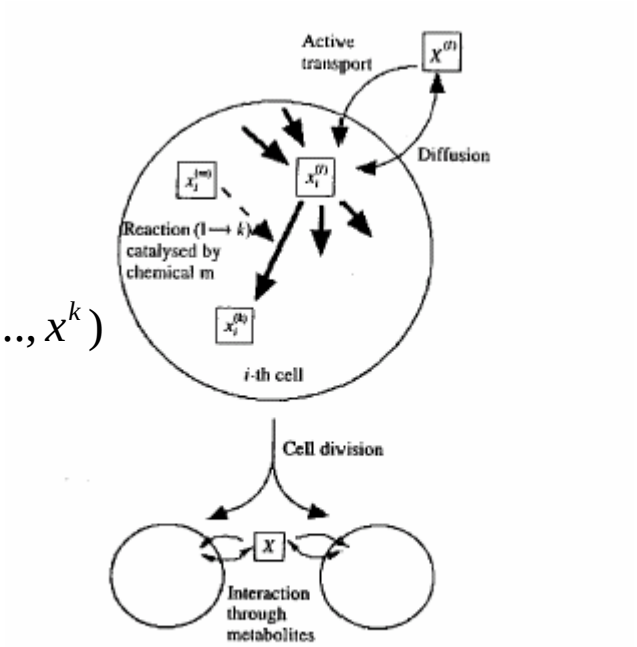


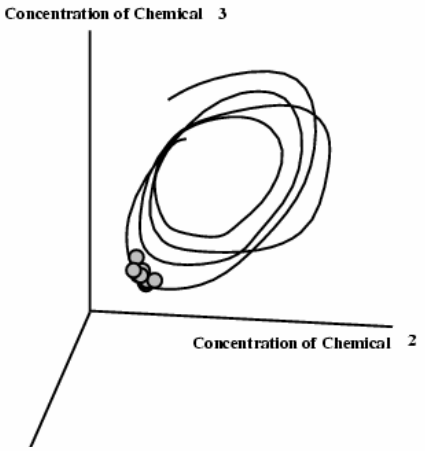
FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

Example: chemical reaction network

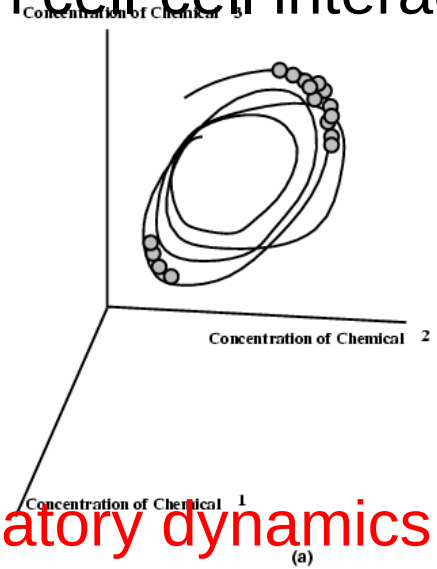
specialize in the use of some path

Coupled Dynamical Systems
→ development
Internal chemical reaction dynamics
and interaction and cell division

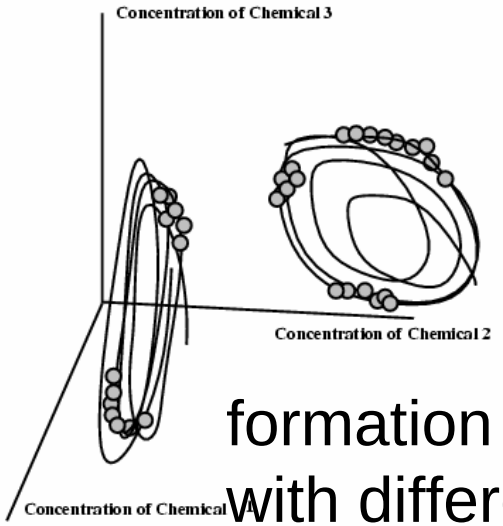
synchronous division:
no differentiation



Instability of homogeneous state
through cell-cell interaction

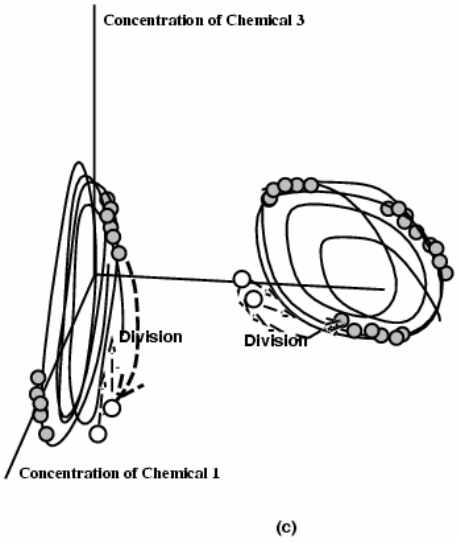


Assuming oscillatory dynamics as a single cell



formation of discrete types
with different chemical
compositions:
stabilize each other

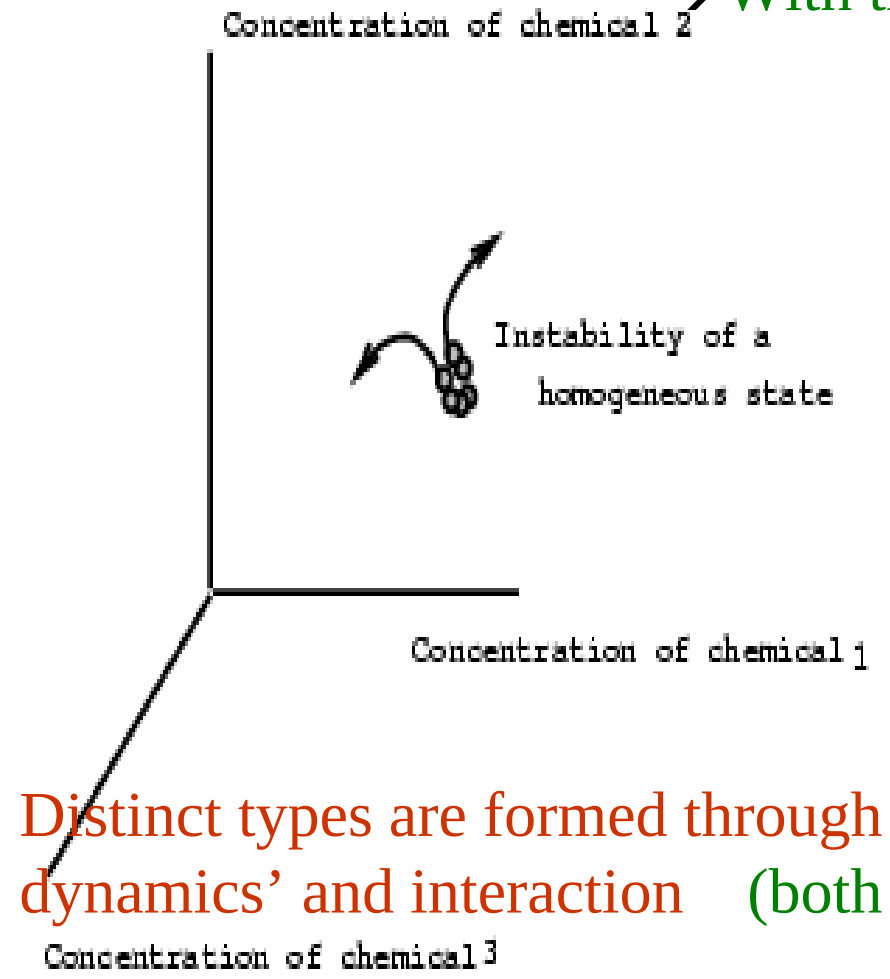
recursive production

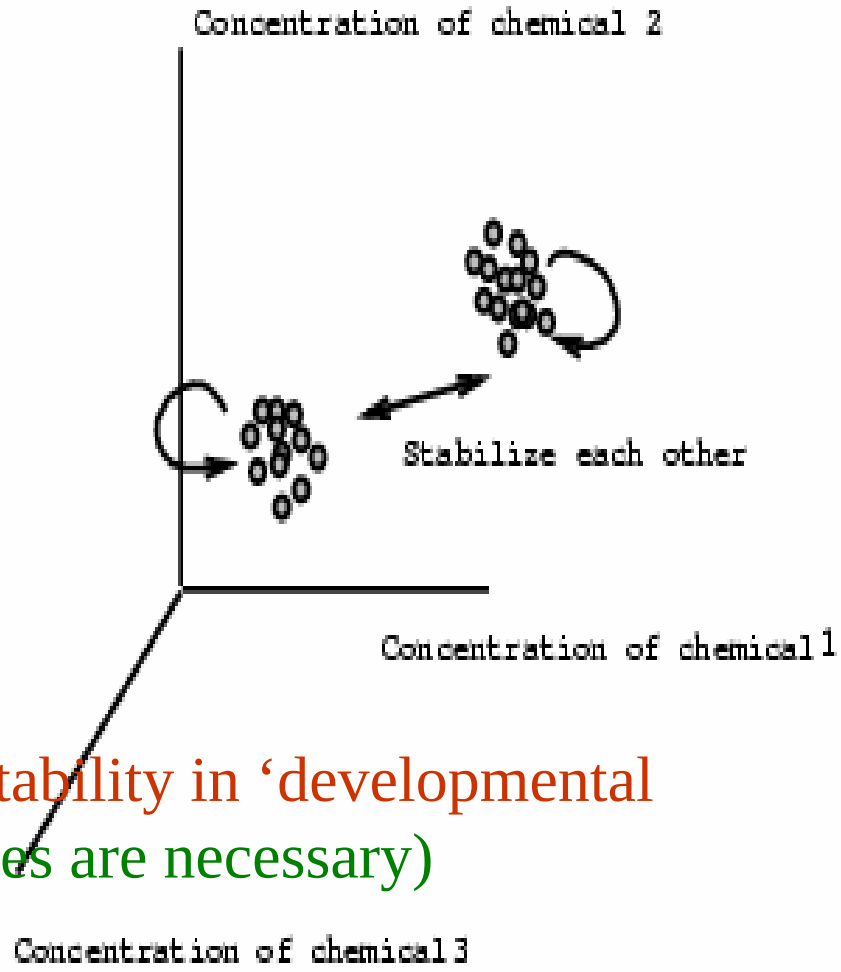


- (1) Synchronous oscillations of identical units

  Up to some threshold number of units, all of them oscillate synchronously, and their states are identical.}
- (2) Differentiation of the phases of oscillations of internal states. When the number of units exceeds the threshold, they lose identical and coherent dynamics. Although the state of units are different at an instance, averaged behaviors over periods are essentially the same. Only the phase of oscillations differs by units.
- (3) Differentiation of the amplitudes of internal states. At this stage, the states are different even after taking the temporal average over periods. It follows that the behavior of states (e.g., composition of chemicals, cycles of oscillations, and soon) are differentiated.
- (4) Transfer of the differentiated state to the offspring by reproduction. This ``memory'' is made possible through the transfer of initial conditions (e.g., of chemicals) during the reproduction (e.g., cell division).
- (5) Hierarchy of organized groups. This stage is the result of successive differentiation with time. Thus, the total system consists of units of diverse behaviors, which forms a cooperative society.

→With the increase of the number





Distinct types are formed through instability in ‘developmental dynamics’ and interaction (both types are necessary)

Single cell dynamics --- bifurcation

interaction term works as bifurcation parameter

Self-consistent choice of bifurcation parameter

Bifurcation parameter is given by interaction –self-consistent state

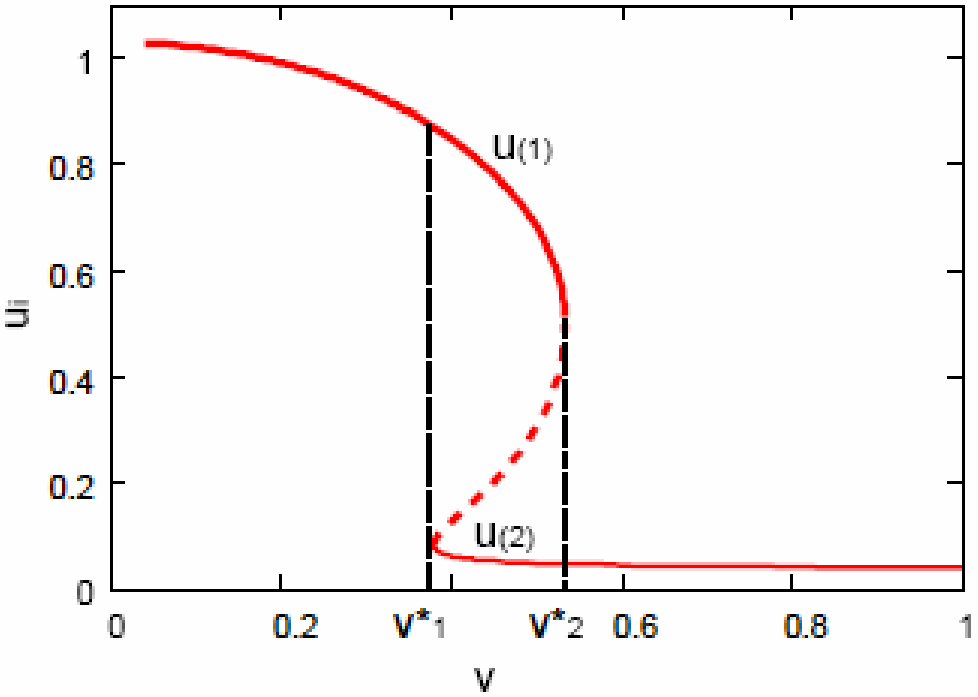
$$\frac{du_i(t)}{dt} = f(u_i, v) = \frac{1}{\tau}\left(\frac{u_i^{\alpha}(t)}{K_u^{\alpha} + v^{\alpha}(t) + u_i^{\alpha}(t)} - u_i(t) + A_u\right) \qquad \text{for } i = 1, \ldots, N, \qquad (1)$$

$$\frac{dv(t)}{dt} = g(u_1, \ldots, u_N, v). \qquad (2)$$

$$\frac{dv(t)}{dt} = g_3(u_1, \ldots, u_N, v)$$

$$= c_{v1} \sum_{i=1}^{N} \frac{u_i^{\beta}(t)}{\tilde{K}_v^{\beta} + u_i^{\beta}(t)} - c_{v2} v(t) \sum_{i'=1}^{N} \frac{\tilde{K}_v^{\beta}}{\tilde{K}_v^{\beta} + u_{i'}^{\beta}(t)} - v(t)$$

For fixed v ---Bifurcation



Self-consistent choice of Bifurcation parameter

A.Nakajima,KK(2007)

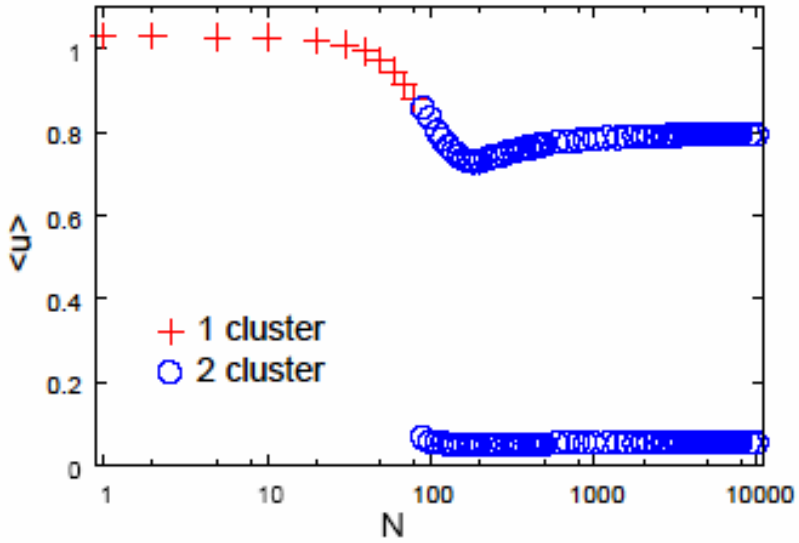


Figure 8: The fixed point solutions of model III plotted against the total cell number N.

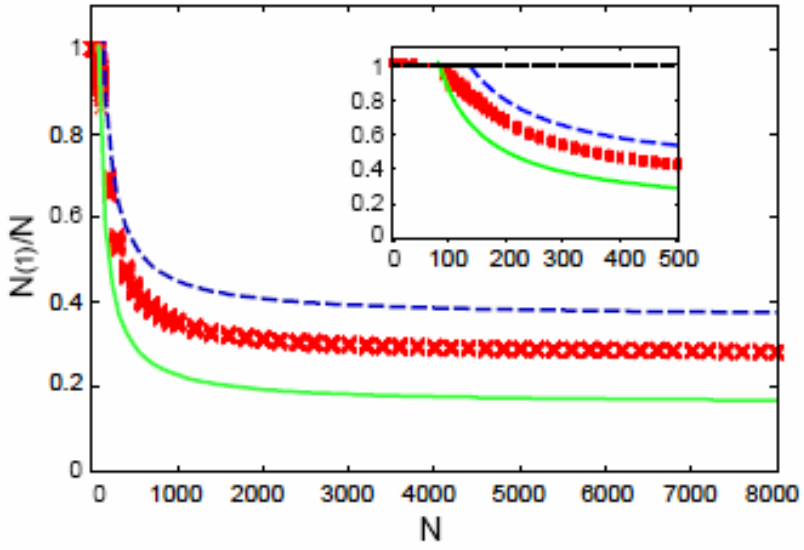
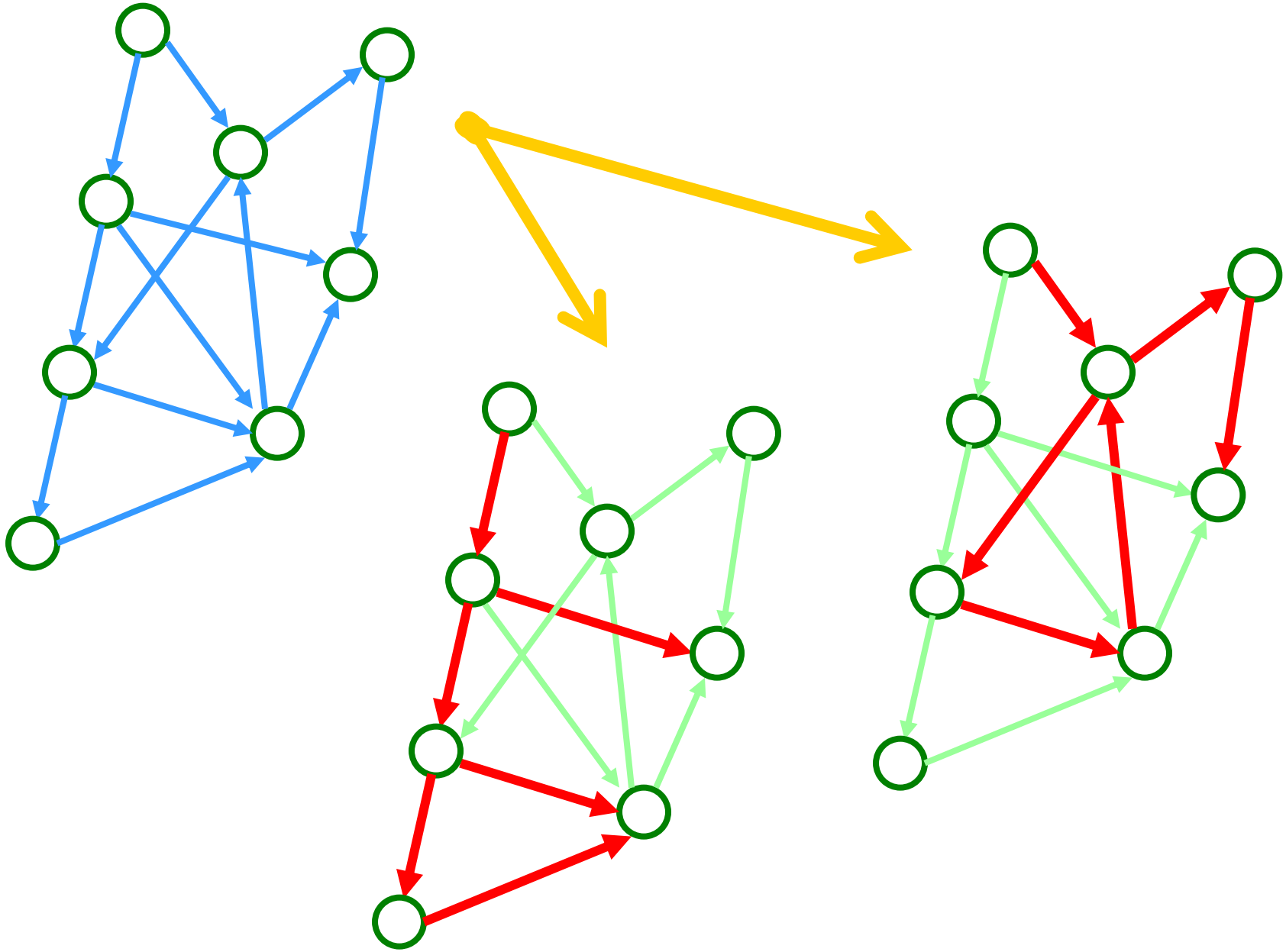


Figure 9: The ratio of the number cell type 1 $N_{(1)}$ to the total cell number N is plotted against N for model III. The initial condi-



Robustness of developmental process

both states of each cell type and number distribution of each cell type

(1) against molecular fluctuations;

(a few % fluctuations, (~ 100-1000 molecules))

(2) against macroscopic damage;

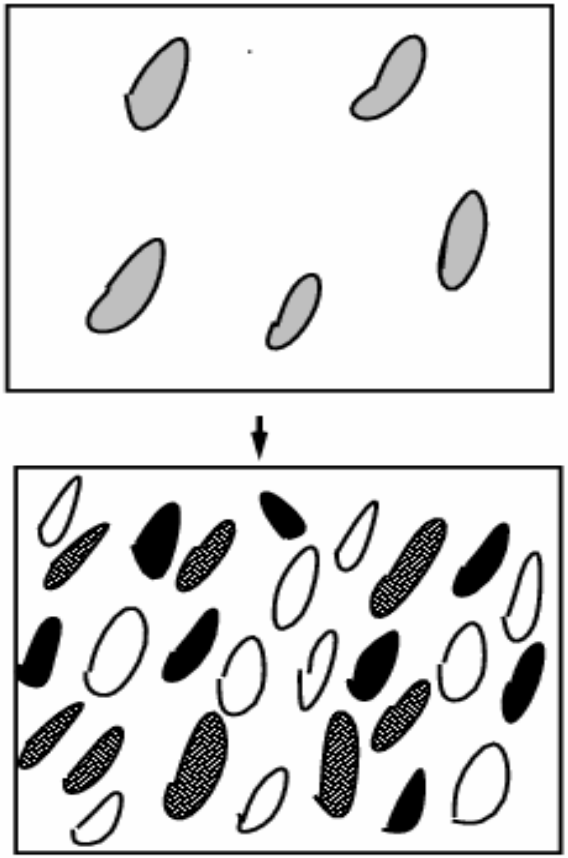
i.e., type A and type B, determined

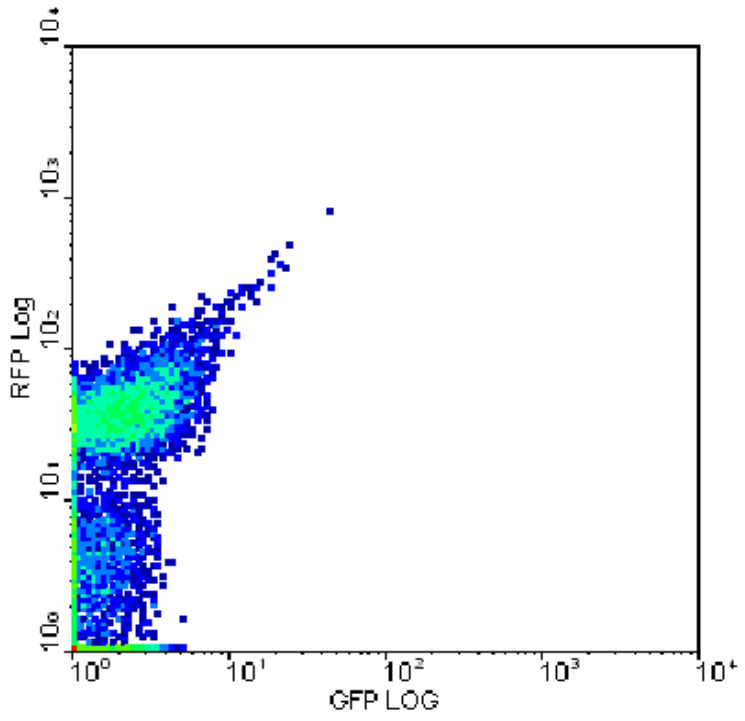
but if type A is eliminated, then B de-differentiates

and initial A-B cell ensemble is recovered

(since A,B is stabilized each other)

Differentiation of E Coli



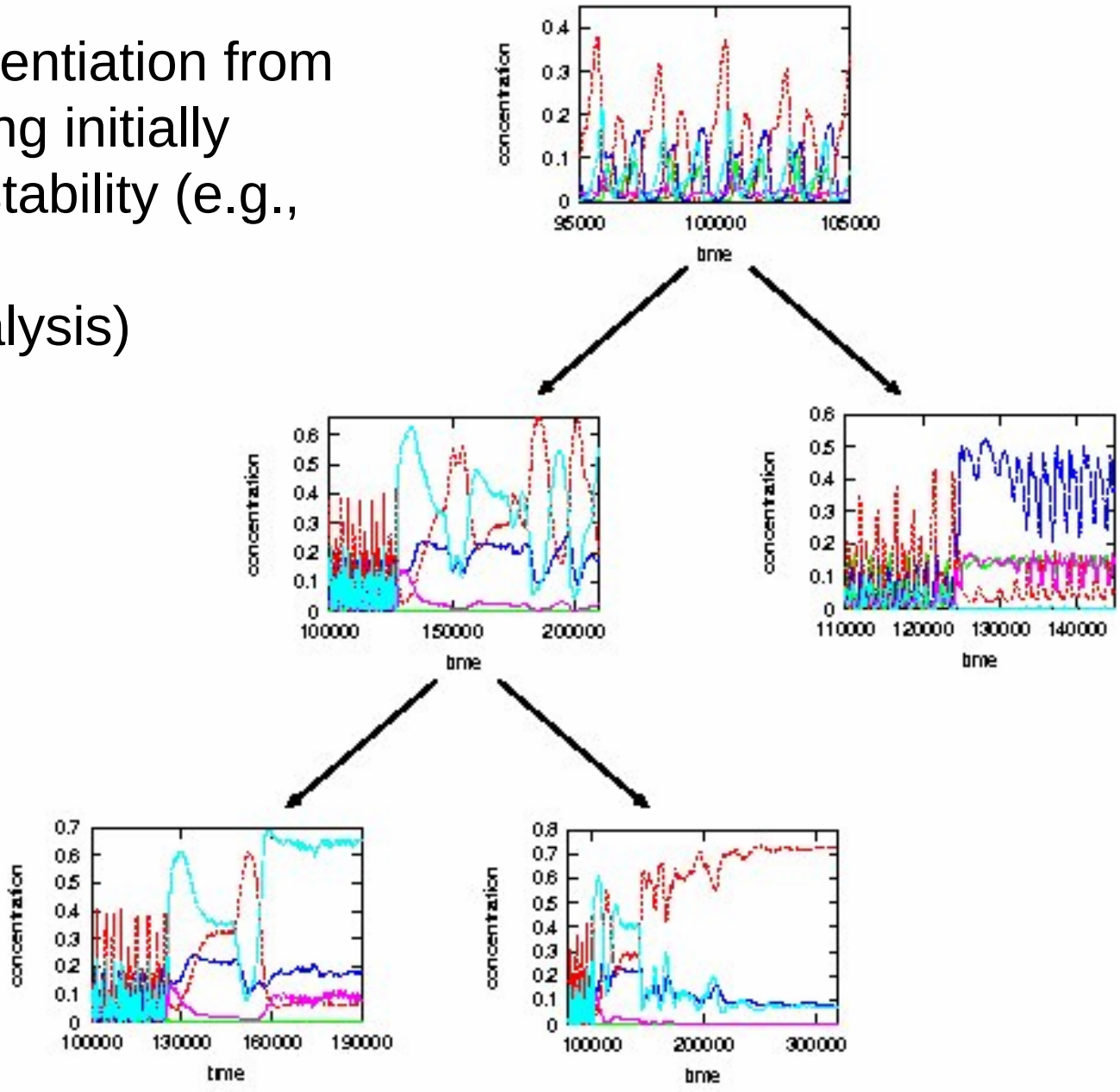


Measurement by fluoresecent proteins

Character of bacteria differentiate in a crowded condition

(Kashiwagi, Yomo,…)

Hierarchical differentiation from ‘stem cell’;by taking initially dynamics with instability (e.g., chaotic)
(higher order catalysis)



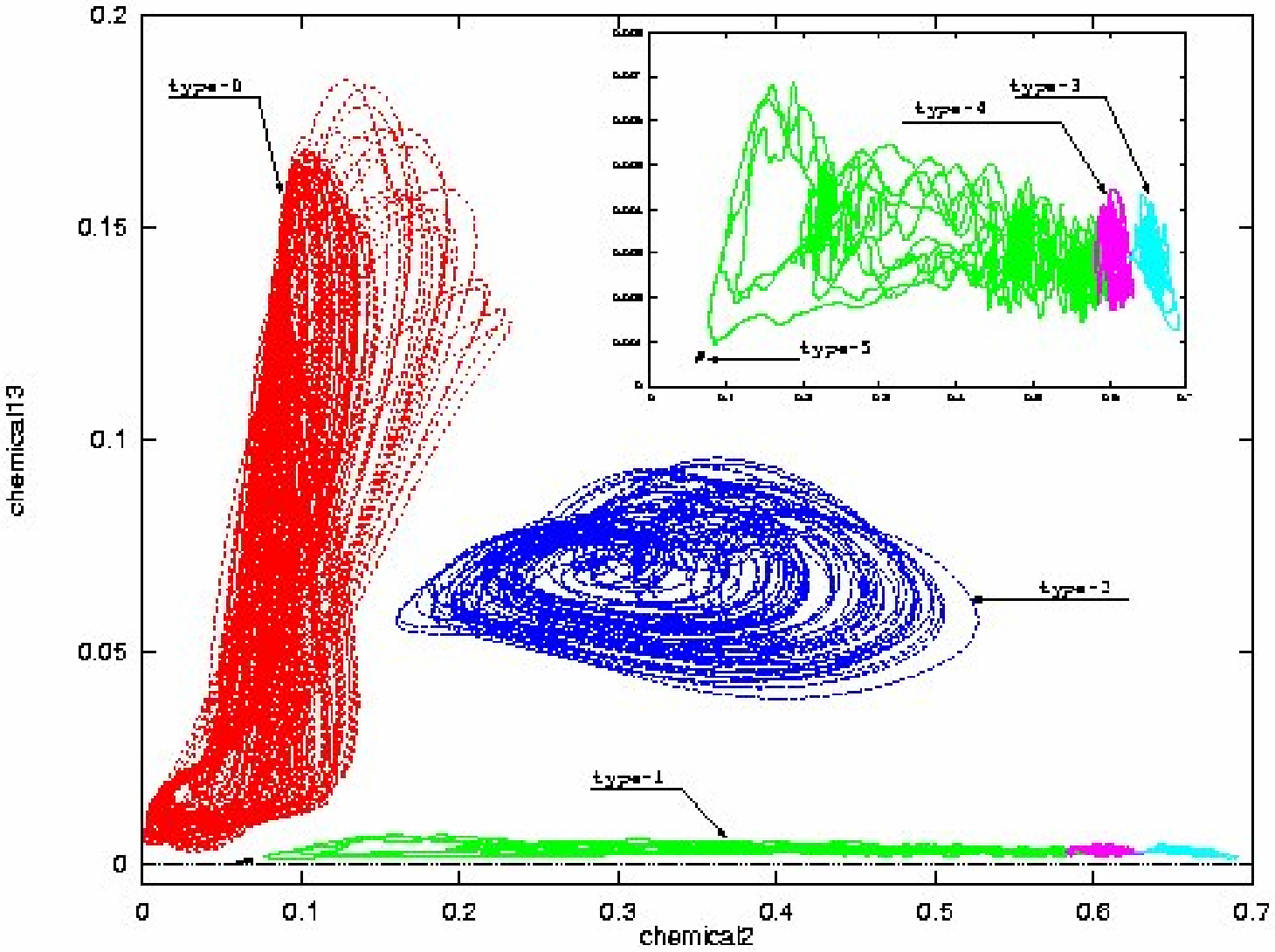
Furusawa & KK

$$dc_i^{(\ell)}(t)/dt = \Delta c_i^{(\ell)}(t) - c_i^{(\ell)}(t) \sum_{\ell=1}^{k} \Delta c_i^{(\ell)}(t), \qquad (1)$$

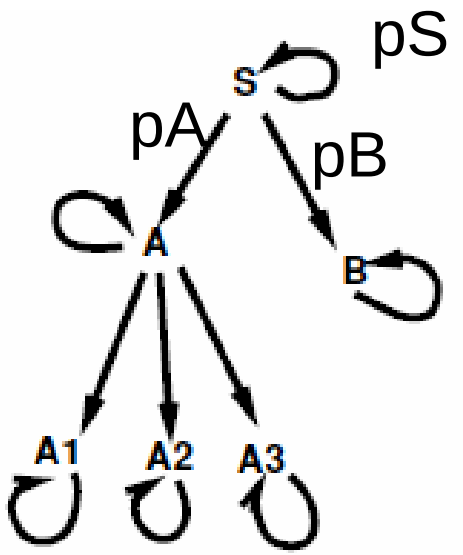
with

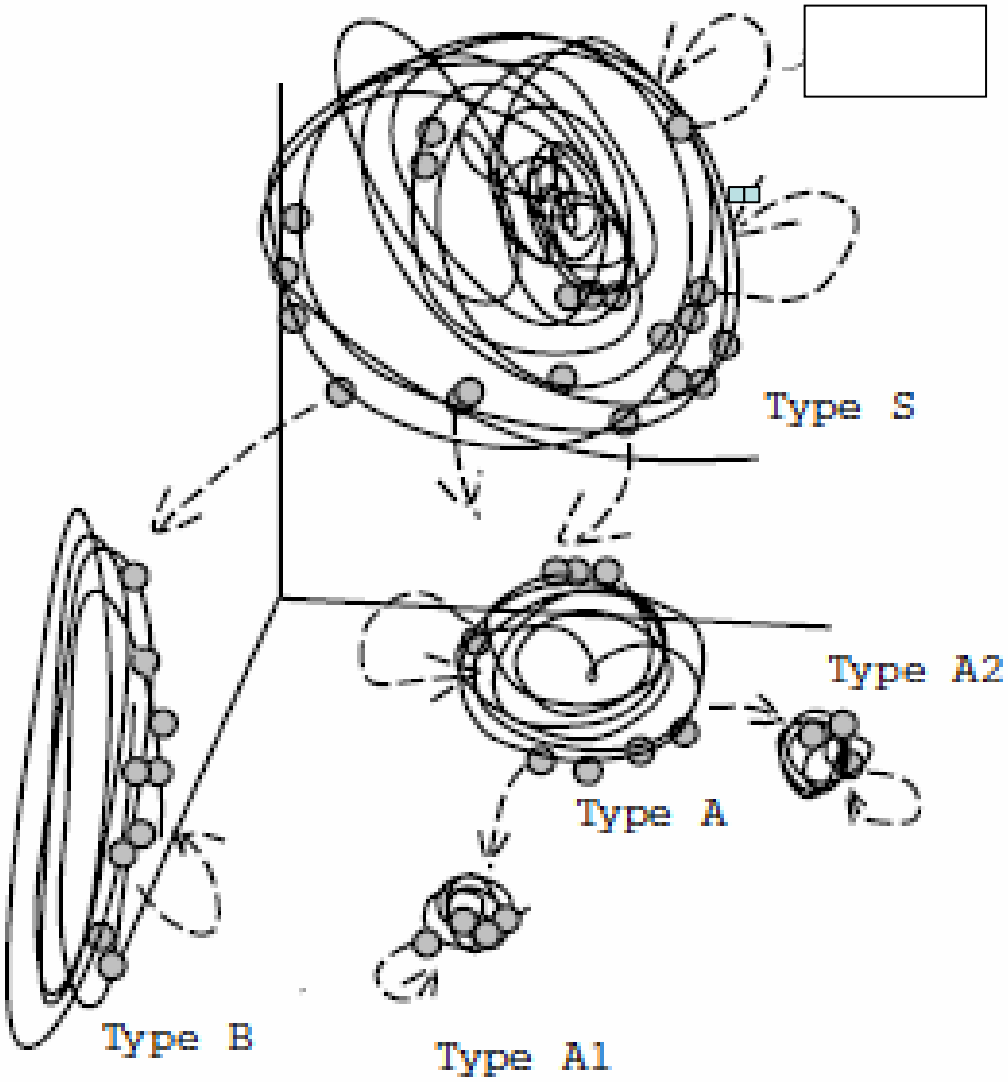
$$\begin{aligned}\Delta c_i^{\ell}(t) = & \sum_{m,j} \mathrm{con}(m, j, \ell) e_1 c_i^{(m)}(t) [c_i^{(j)}(t)]^n \\ & - \sum_{m',j'} \mathrm{con}(\ell, j', m') e_1 c_i^{(\ell)}(t) [c_i^{(j')}(t)]^n \\ & + \sigma_\ell D[C^{(\ell)}(p_i^x, t) - c_i^{(\ell)}(t)]. \qquad (2)\end{aligned}$$

Hierarchical differentiation from ‘stem cell’;
by taking initially dynamics with instability (e.g., chaotic)
(higher order catalysis) Furusawa&KK



Hierarchical differentiation from ‘stem cell’;by taking initially dynamics with instability (e.g., chaotic) (higher order catalysis)



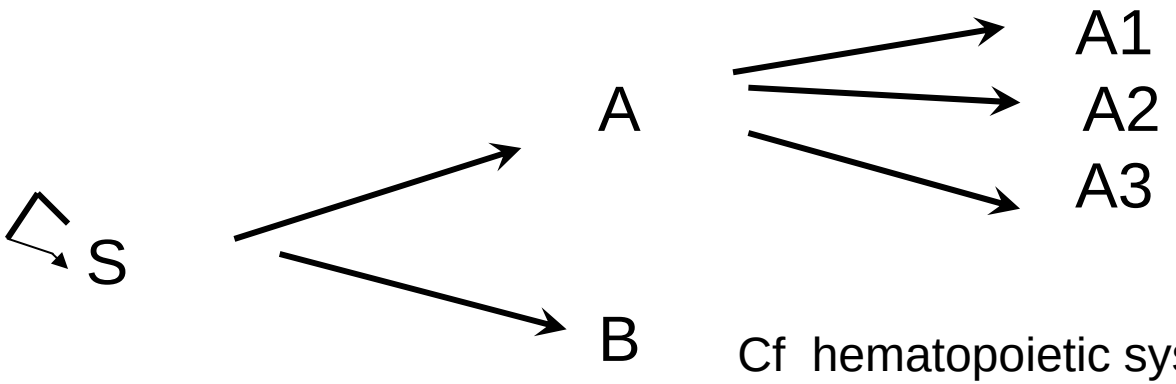


probability depends on # distrib. of cell types

with prob. *pA* for *S* → *A*

if #(A) decreases then *pA* increases: **STABILITY**

Generated Rule of Differentiation (example)



Cf hematopoietic system

(1)hierarchical differentiation: stem cell system

(2) Stochastic Branching:

stochastic model proposed in hematopoietic system

(3) probability depends on # distrib. of cell types

with prob. *pA* for *S* → *A*

if #(A) ↘ then *pA* ↗

—— global info. is embedded into internal cell states

→STABILITY

(4) Differentiation of cell ensemble (tissue)

——multiple stable distrib. { *Ni* }

Explained:

Robustness in development under large fluctuation in molecule numbers

Recall: (signal) molecules of few number -- relevant;

Loss of potency from totipotent cell (ES),
to multipotent stem cell, and to determination

Irreversibility in cell differentiation process
characterized by the loss of phenotypic variation

- Loss of pluripotency is characterized by

  Decrease in the degrees of expressed genes (chemical diversity)

  Decrease in cell-cell variation

  Decrease in temporal variation in gene expression (loss of chaos)

To recover pluripotency

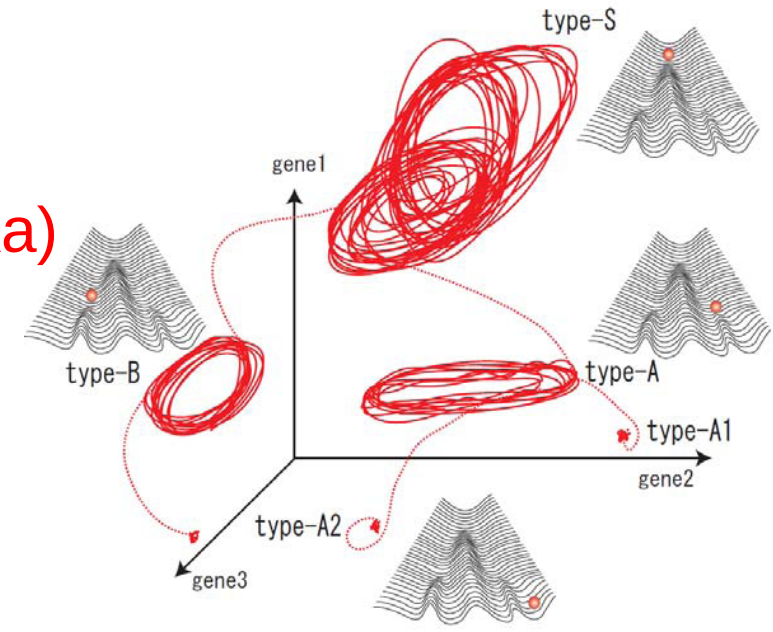
increase the degrees of freedom (# of excpressed genes)

prediction confirmed by iPS (Yamanaka)

To confirm the theory

Measure gene expression dynamics (oscillatory gene expression and its change through differentiation)

partially observed by Sui Huang's (Nature 2008)

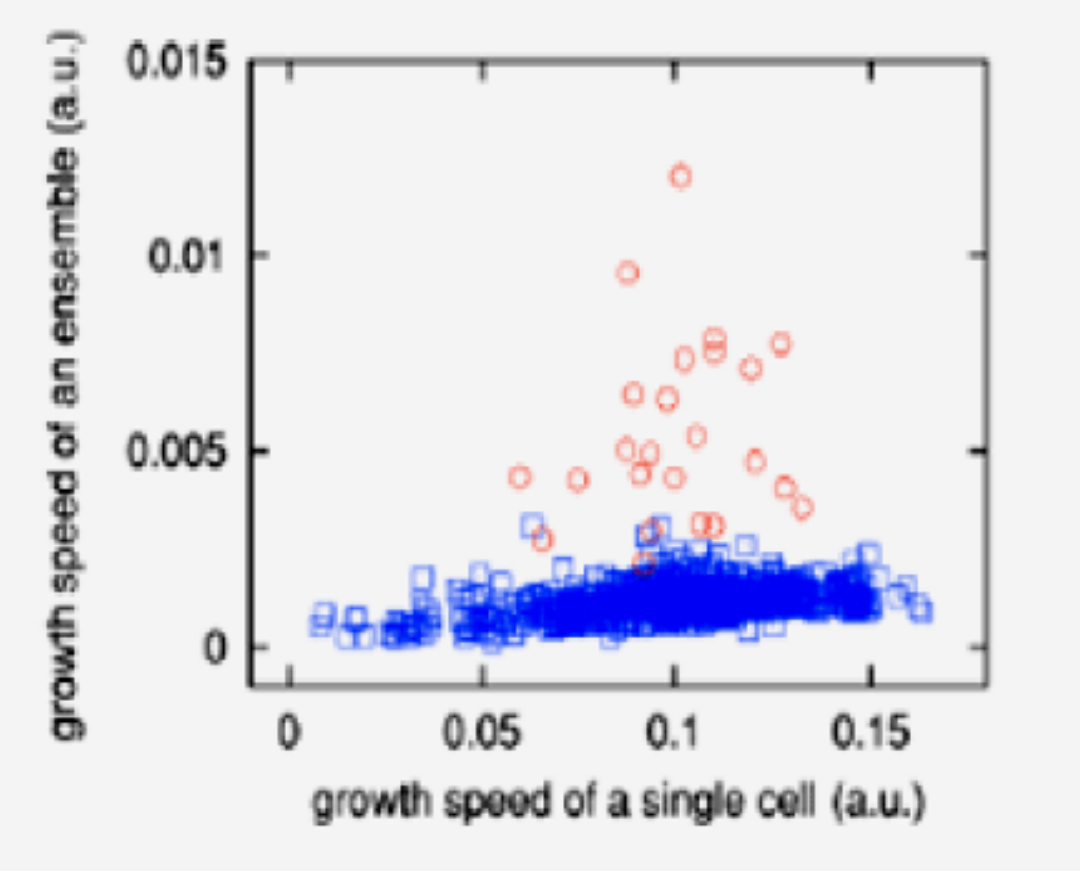


Universality?

checked a huge number of networks; only some fraction of them show chaotic dynamics & differentiation

Cells with such networks with differentiation

higher growth speed as an ensemble



Such networks are selected

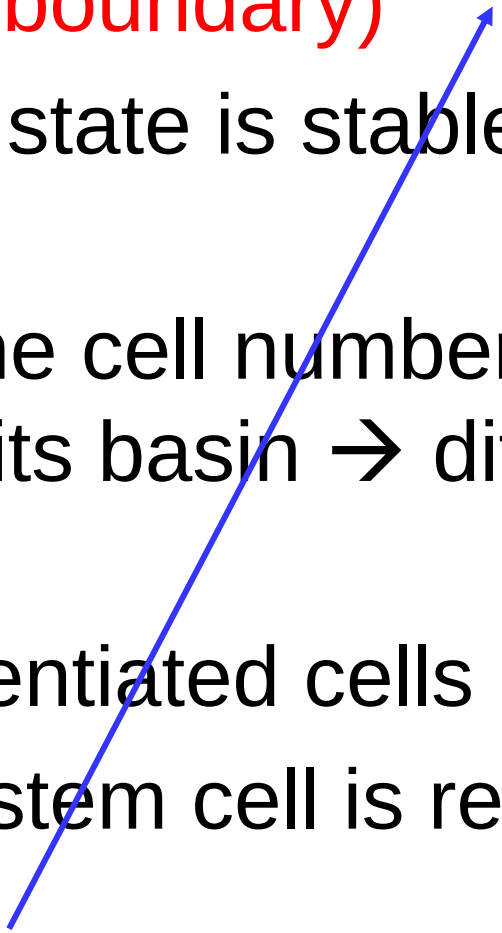
Mechanism: approach to Milnor attractor?

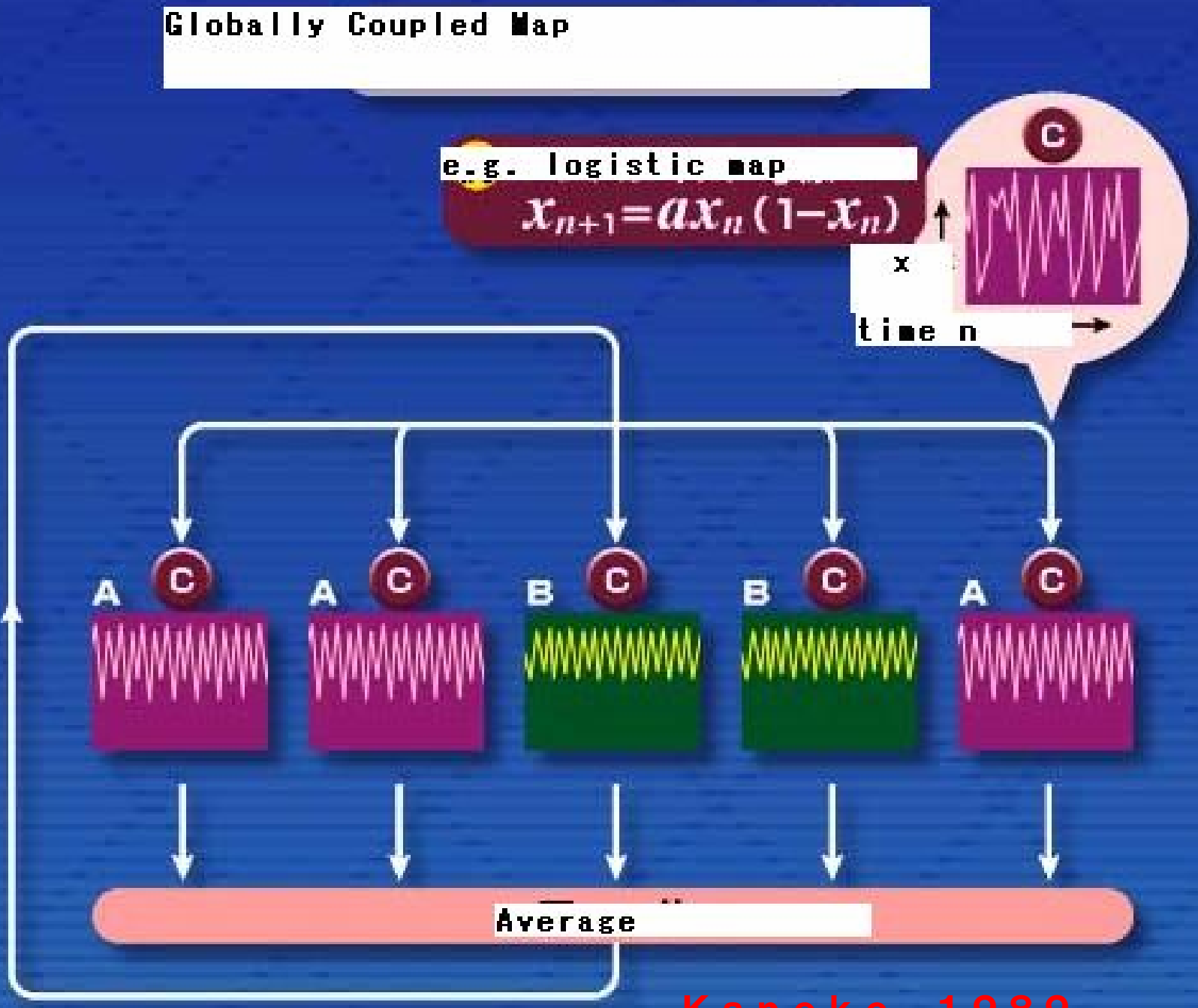
(that touches with basin boundary)

As long as the stem cell state is stable, it reproduces itself

→With the increase in the cell number, the attractor touches with its basin → differentiate to other types

→If the number of differentiated cells increases then the stability of the stem cell is recovered, and it reproduces itself




Globally Coupled Map
e.g. logistic map
$x_{n+1}=ax_n(1-x_n)$
C
x
time n
A C
A C
B C
B C
A C
Average

Kaneko, 1989–

$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \frac{\epsilon}{N} \sum_{j=1}^{N} f(x_n(j)),$$

Globally coupled map (no spatial structure) (1)

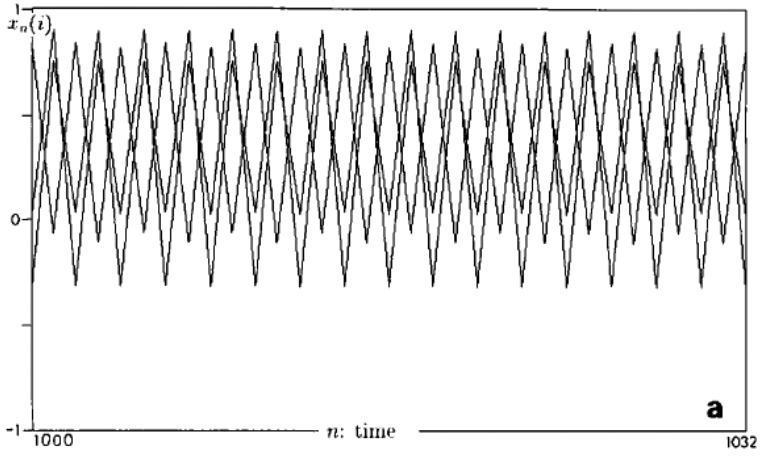
logistic map $f(x) = 1 - ax^2$

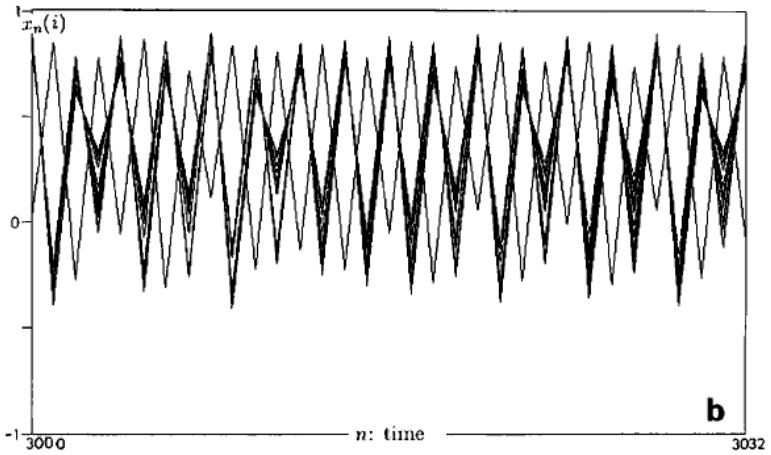
Cf Coupled map lattice → space-time chaos

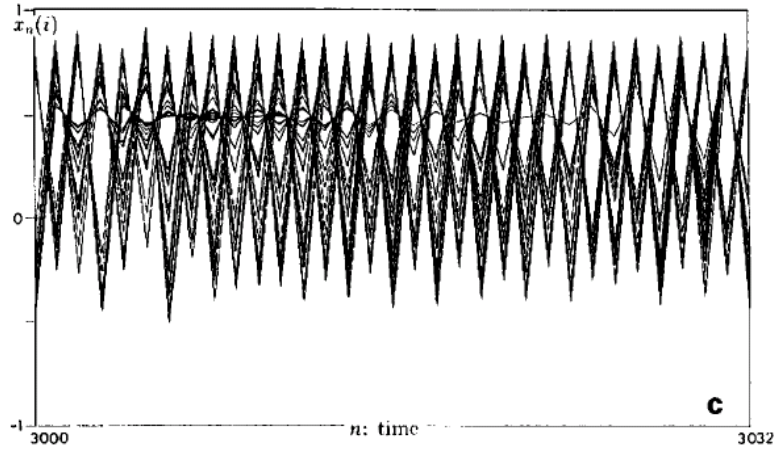
$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \tfrac{1}{2}\epsilon \left[f(x_n(i+1)) + f(x_n(i-1)) \right], \quad (2)$$

Cf. synchronized state is stable if $\lambda_0 + \log(1-\epsilon) < 0.$

Synchronization of all elements with chaos is possible







Clustering

Example 1
3-clusters, with each synchronized oscillatios

Differentiation of behavior from identical elements and identical interaction

Cluster of synchrnoized elemens
+ non-synchronized elements

Desycnhronized

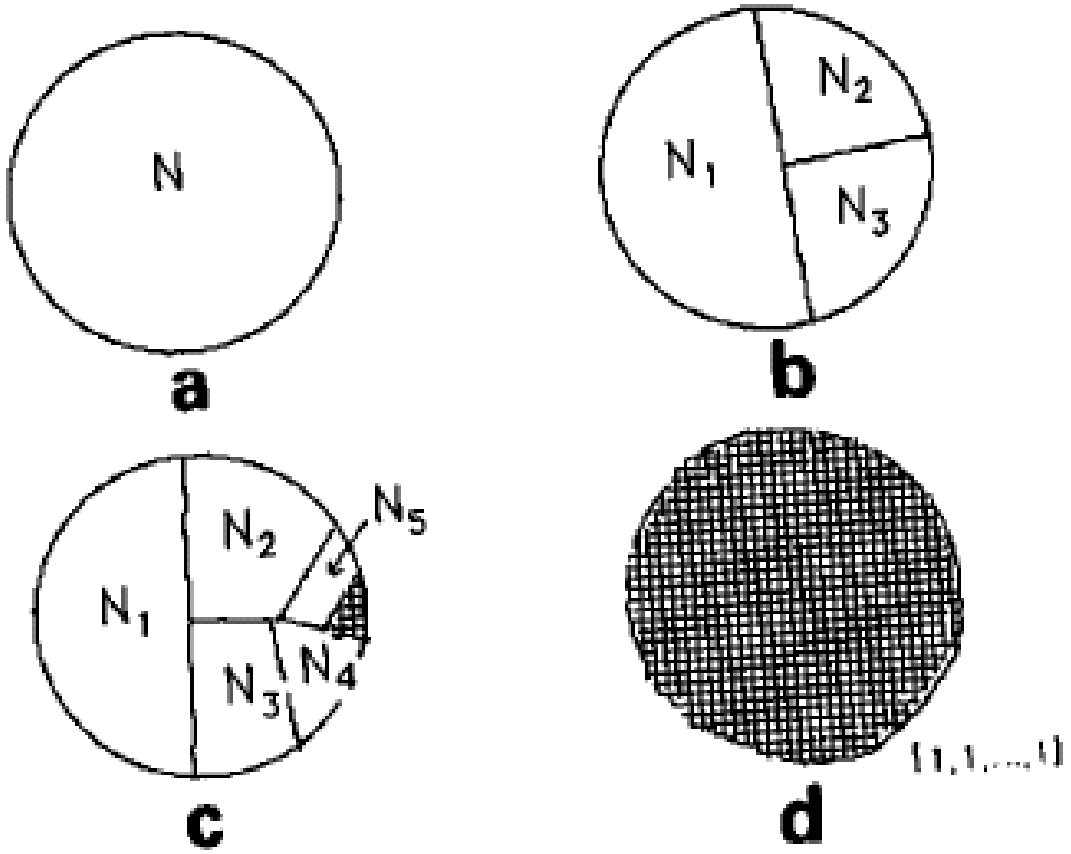
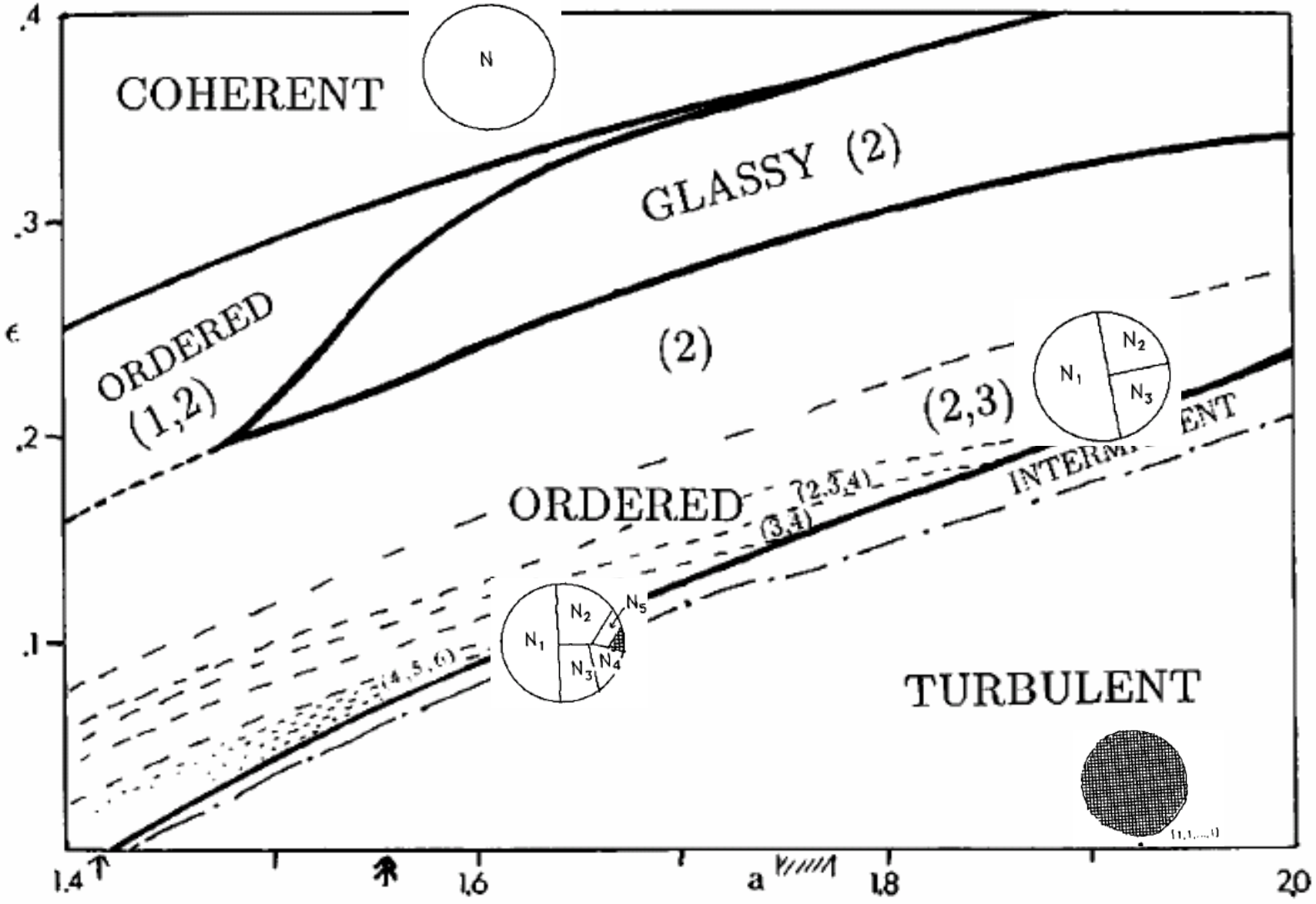


Fig. 1. Schematic figure for clusterings: (a) Coherent attractor. (b) Few clusters ($k = 3$). (c) Many-cluster attractor with unequal partition. (d) Many-cluster attractor with $k = N$.



Onset of chaos

カオス的遍歴

Chaotic Itinerancy

High-dimensional disordered

Almost-2 cluster

High-dimensional disordered

Almost-3 cluster

自由度の大きいダイナミクスでの普遍的現象
（e.g., 津田の非平衡神経回路系、池田らの光乱流）

秩序が出来るのとこわれるのが組み

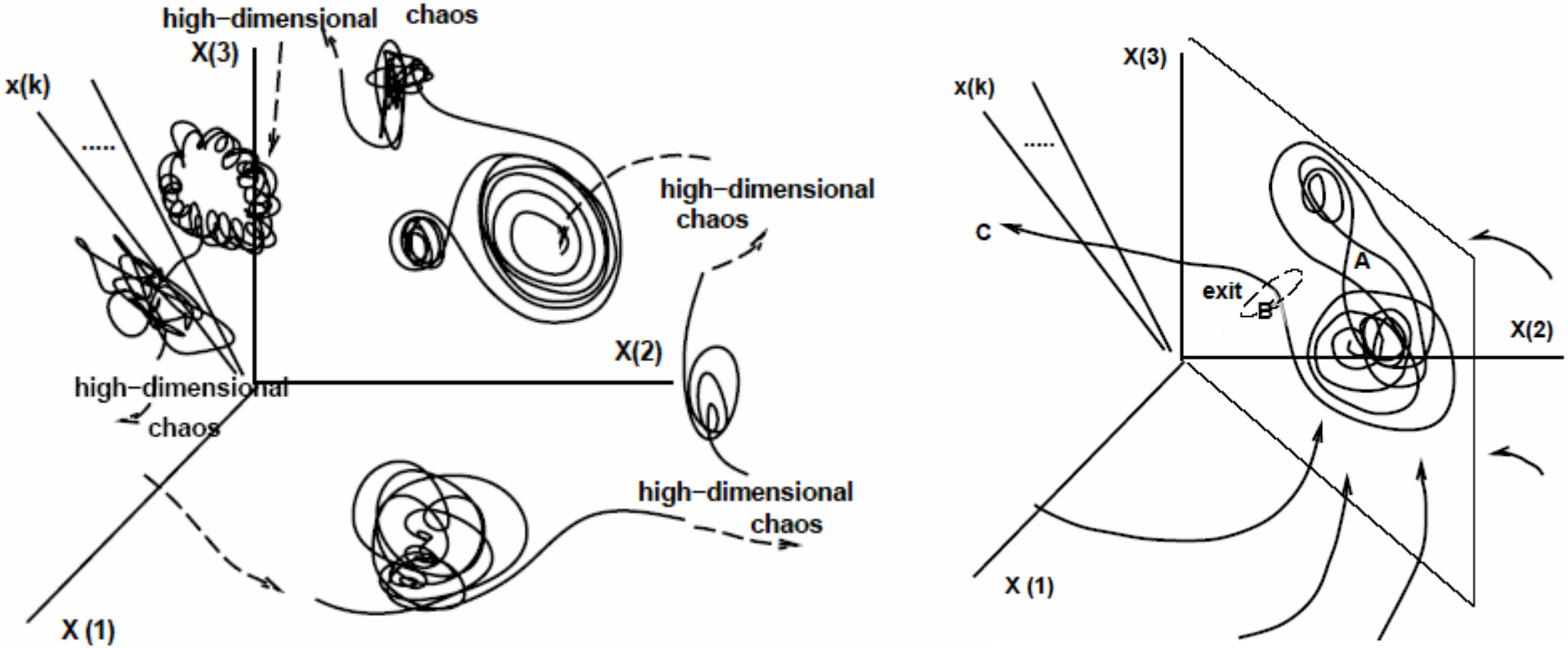
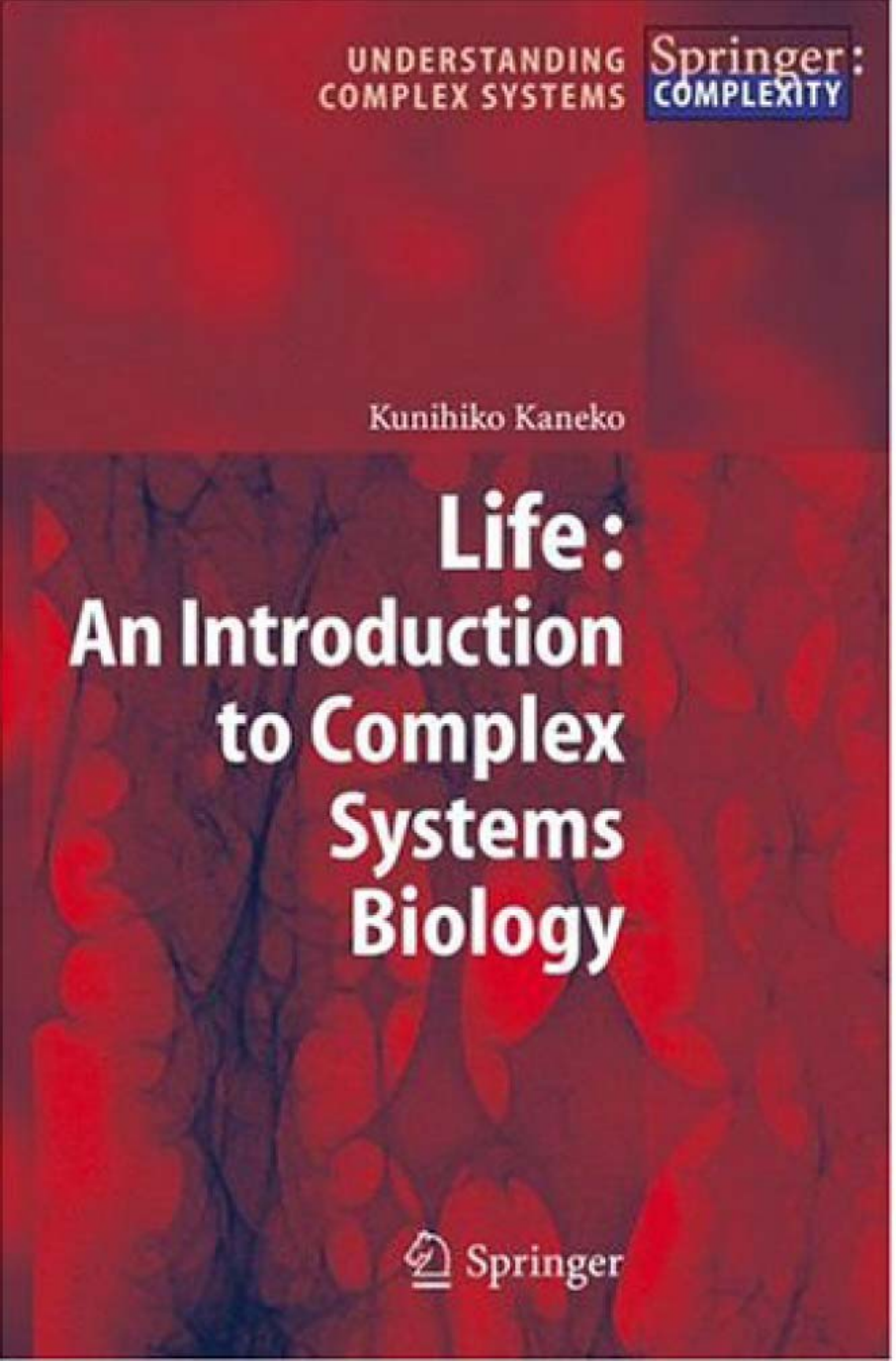


図 14: カオス的遍歴の模式



Collaborators

Chikara Furusawa

experiment

Tetsuya Yomo
Saburo Tsuru
Akiko Kashiwagi

Most papers (biology, Dynamical systems) Available at
http://chaos.c.u-tokyo.ac.jp

ERATO Complex Systems Biology Project

(**2006,August**)

- Why?

  Conjecture by combinatorial explosion of basin boundaries

Simple separation x(i)>x* or x(i)<x*; one can separate 2 ^N attractors by N planes.

In this case the distance between attractor and the basin boundary does not change with N ---- Order of (N-1)!

The boundary makes combinatorial explosion

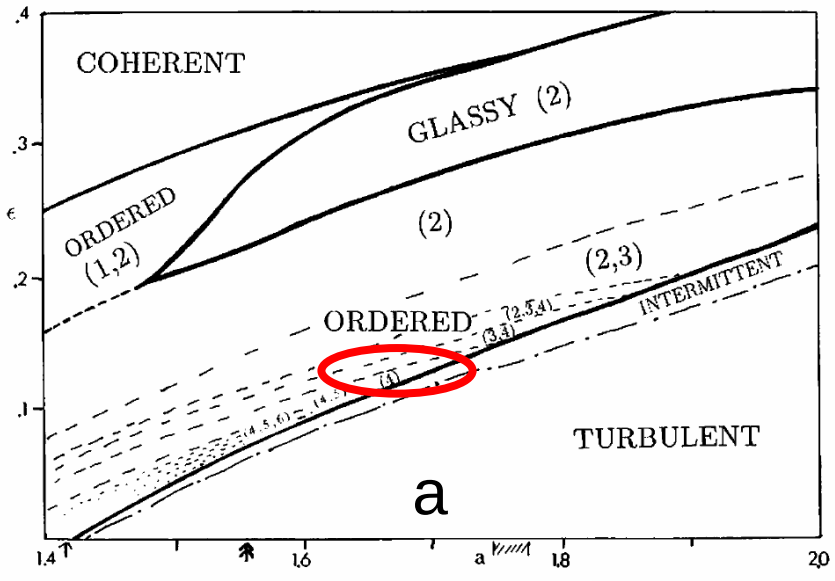
On the other hand, consider a boundary given by some condition for $[x(1), \ldots, x(N)]$. In the present system with global (all-to-all) couplings, many of permutational change of $x(i)$ in the condition give also basin boundaries. Here the condition for the basin can also have clustering $(N_1, \ldots, N_k)$, since the attractors are clustered as such. Then there are $M(N_1, \ldots, N_k)$ partitions by boundaries equivalent by permutations. The number of regions parti-

$$M(N_1, \ldots, N_k) = (N!/\Pi_{i=1}^{k} N_i!)\Pi_{\text{over sets of } N_i = N_j}(1/m_\ell!)$$

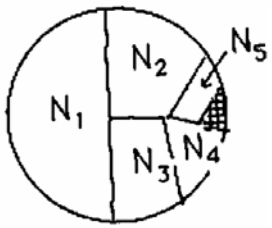
GCM

$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \frac{\epsilon}{N} \sum_j f(x_n(j)),$$

where n is the discrete time and i being the index for elements ($i = 1,2,\ldots,N$ = dimension of the system). For elements we choose $f(x) = 1 - ax^2$, since the model has been



Cluster: group of elements such that x(i)=x(j);
Number of elements in each cluster; N1,N2,…,Nk



•at some parameter region many attractors with different clusterings

Due to the symmetry there are

$$M(N_1, \ldots, N_k) = (N!/\Pi_{i=1}^{k} N_i!)\, \Pi_{\text{oversets of } N_i = N_j} (1/m_\ell!)$$

attractors of the same clusterings --
combinatorially many increase with the order of (N-1)!
or so (KK,PRL89)

Milnor attractor

(i.e., Attractor in the sense of Milnor minus usual attractor with asymptotic stability);

attractor and its basin boundary touches,

i.e., any small perturbation from it can kick the orbit out of the attractor, while it has a finite measure of basin (orbits from many initial conditions are attracted to it)

Observed; Milnor attractors large portion of basin for the partially ordered phase in GCM (kk,97,98)

The fraction of basin (i.e. initial values) for Milnor attractors,
Plotted as a function of Logistic map parameter

Note! Fraction is almost 1 for some region

Result for N=10,50,100 ….

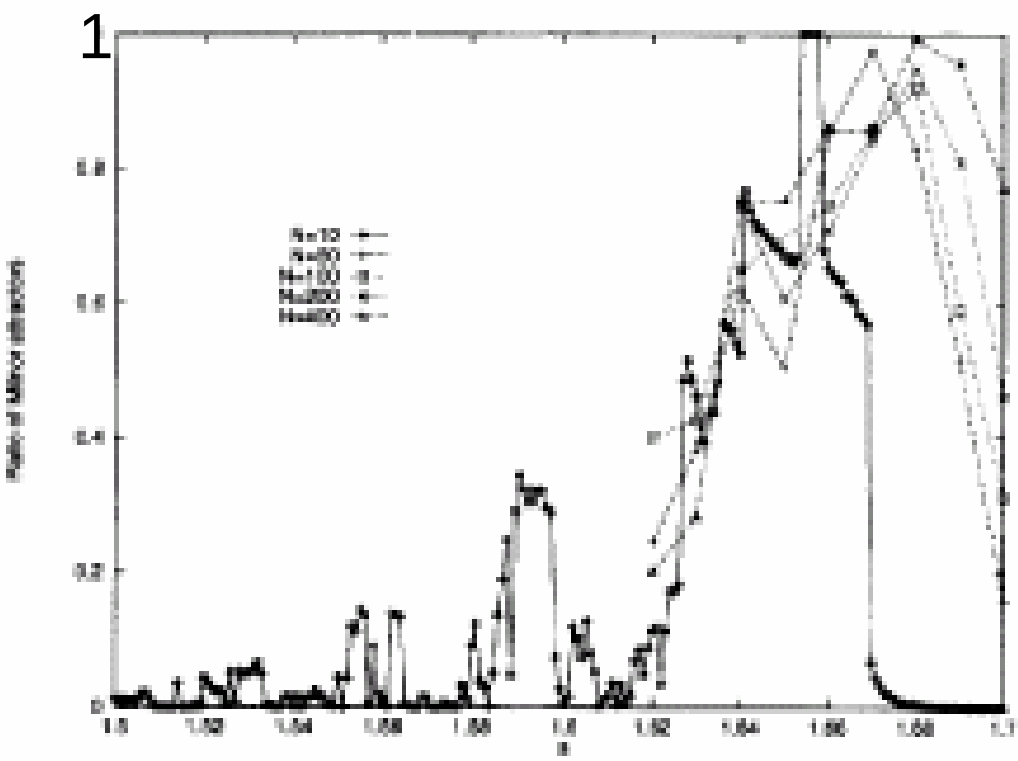
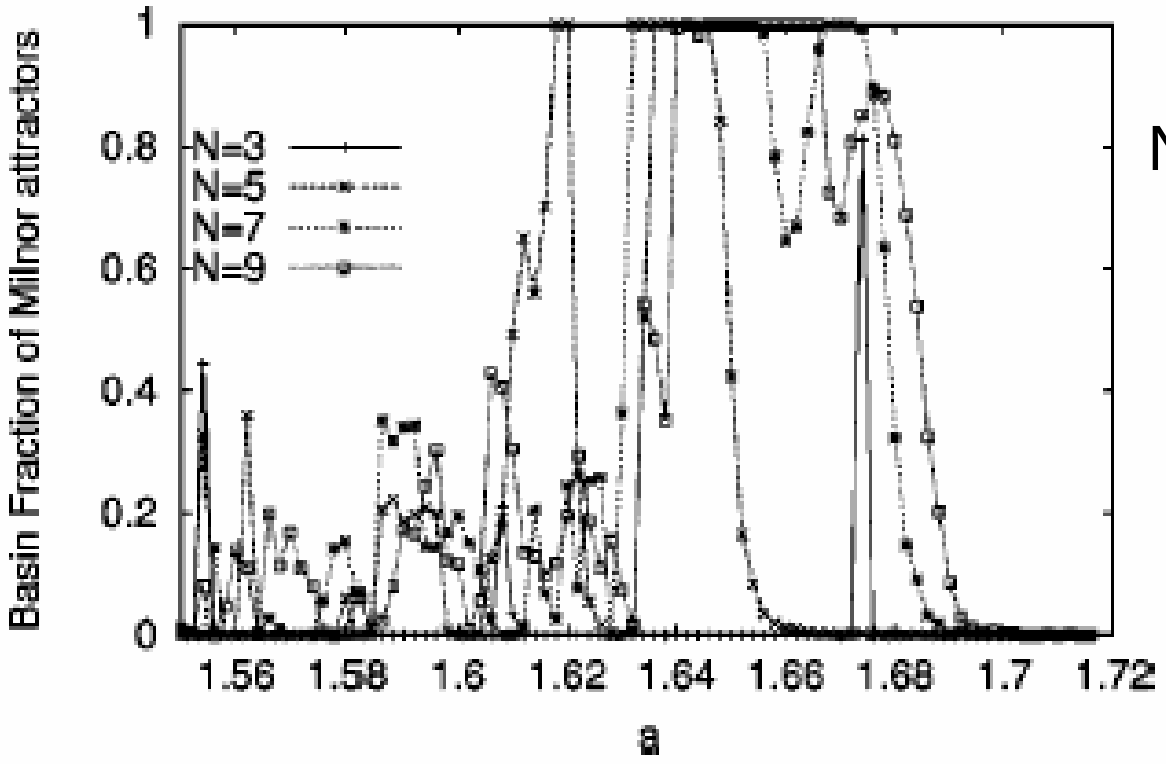


Fig. 9. The basin volume ratio of Milnor attractors with the change of a. For each a, we take 1000 initial conditions, and iterate the dynamics over 100 000 steps to get an attractor. We check if the orbit returns to the original attractor, by perturbing each attractor by $\sigma = 10^{-7}$ over 100 trails. If the orbit does not return at least for one of the trails, the attractor is counted as a Milnor one. For $N = 10$, the ratio is measured for $1.5 < a < 1.7$ with the increment 0.001, while for larger sizes it is measured only for $1.62 < a < 1.7$ with the increment 0.01.

The Milnor attractors become dominant around N＞~（7－8）



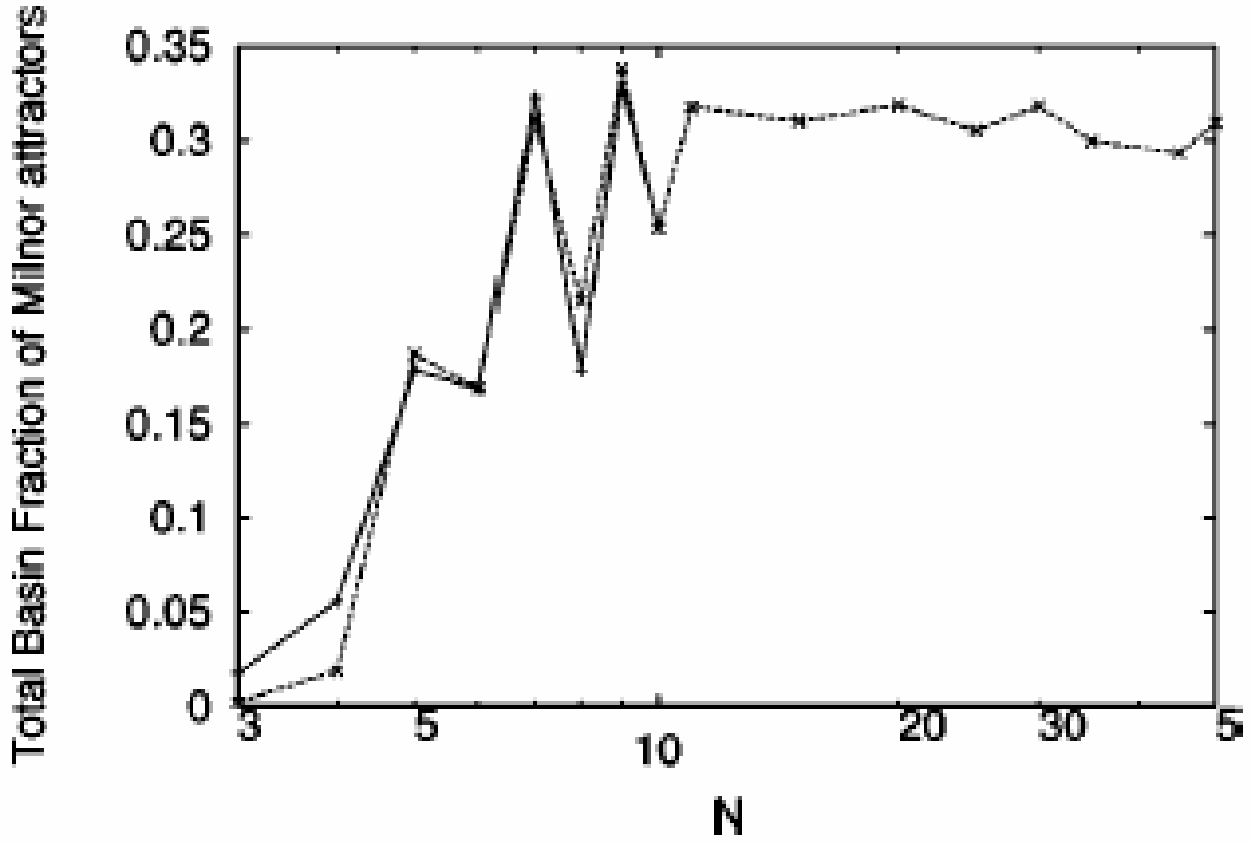
N=3, almost 0

5, few cases

7,8,9,.. dominant

FIG. 1. The basin fraction of Milnor attractors plotted as a function of the parameter a, for $N=3$, 5, 7, and 9. For the present simulations, we take 1000 randomly chosen initial conditions, and iterate 10^5 steps. Then the orbit is perturbed as $x_n(i)+10^{-10}\sigma_i$,

The Milnor attractors become dominant around N ＞~（５－８）



Dependence On the Number of Elements N

(accumulation over 1.55<a<1.72)

FIG. 2. The average fraction of the basin ratio of Milnor attractors. After the basin fraction of Milnor attractor is computed as in Fig. 1, the average of the ratios for parameter values $a = 1.550, 1.552, 1.554, \ldots, 1.72$ is taken. This average fraction is

（kk、PRE,2002）

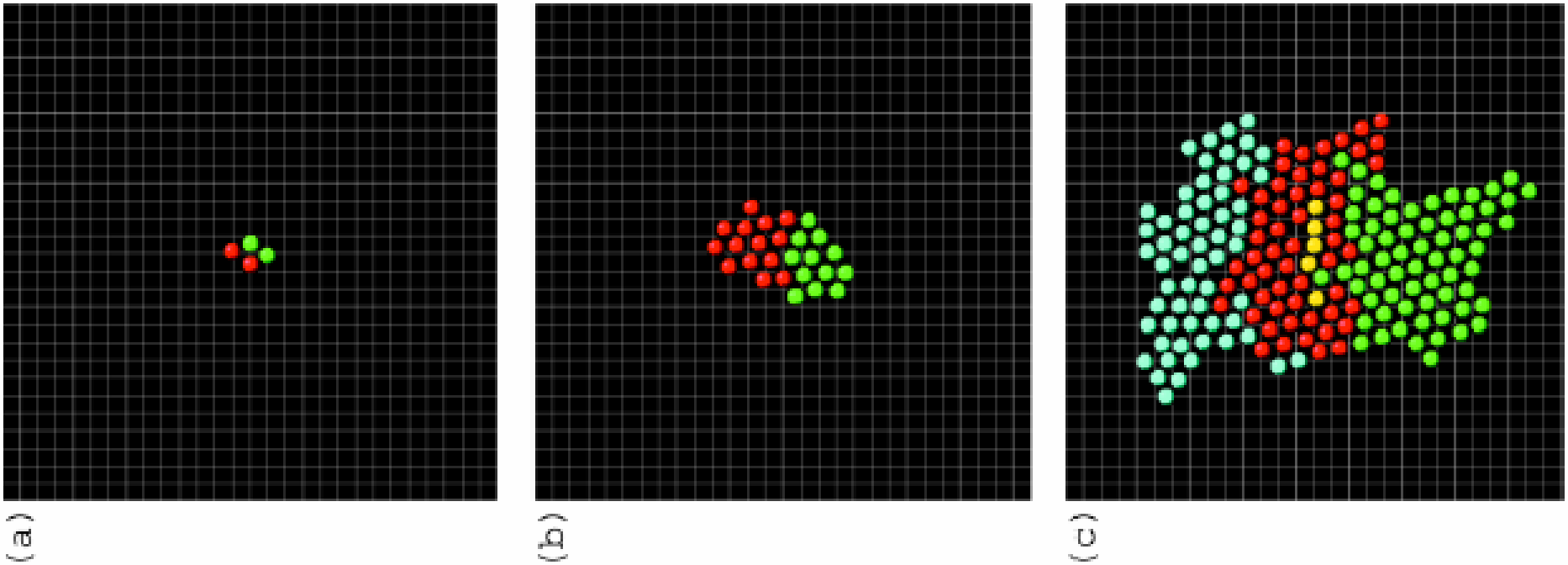
- Why?

  Conjecture by combinatorial explosion

changes with N. Consider a one-dimensional phase space, and a basin boundary that separates the regions of $x(1) > x^*$ and $x(1) < x^*$, while the attractor in concern exists at around $x(1) = x_A < x^*$, and the neighboring one at around $x(1) = x_B > x^*$. Now consider a region of N-dimensional phase space $x_A < x(i) < x_B$. If the region is partitioned by (basin) boundaries at $x(i) = x^*$ for $i = 1, \ldots N$, it is partitioned into 2^N units. Since this partition is just a direct prod-

On the other hand, consider a boundary given by some condition for $[x(1), \ldots, x(N)]$. In the present system with global (all-to-all) couplings, many of permutational change of $x(i)$ in the condition give also basin boundaries. Here the condition for the basin can also have clustering $(N_1, \ldots, N_k)$, since the attractors are clustered as such. Then there are $M(N_1, \ldots, N_k)$ partitions by boundaries equivalent by p

$$M(N_1, \ldots, N_k) = (N!/\Pi_{i=1}^{k} N_i!)\Pi_{\text{overset of } N_i = N_j}(1/m_\ell!)$$



Chemical Gradient for Positional Information is generated

cell differentiation ←→ graidient for pattern

図9．5

Consolidation to Patterns