- **First Talk**
- **General Introduction to Complex Systems Biology**
- **Coupled Dynamical Systems**
- **Development--Cell Differentiation**
- **Self-consistent Bifurcation**
- **Dominance of Milnor Attractor > (5~7) dim**
- Summary

2nd; phenotype evolution as selection of dynamical systems; robustness, fluctuation,….

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:

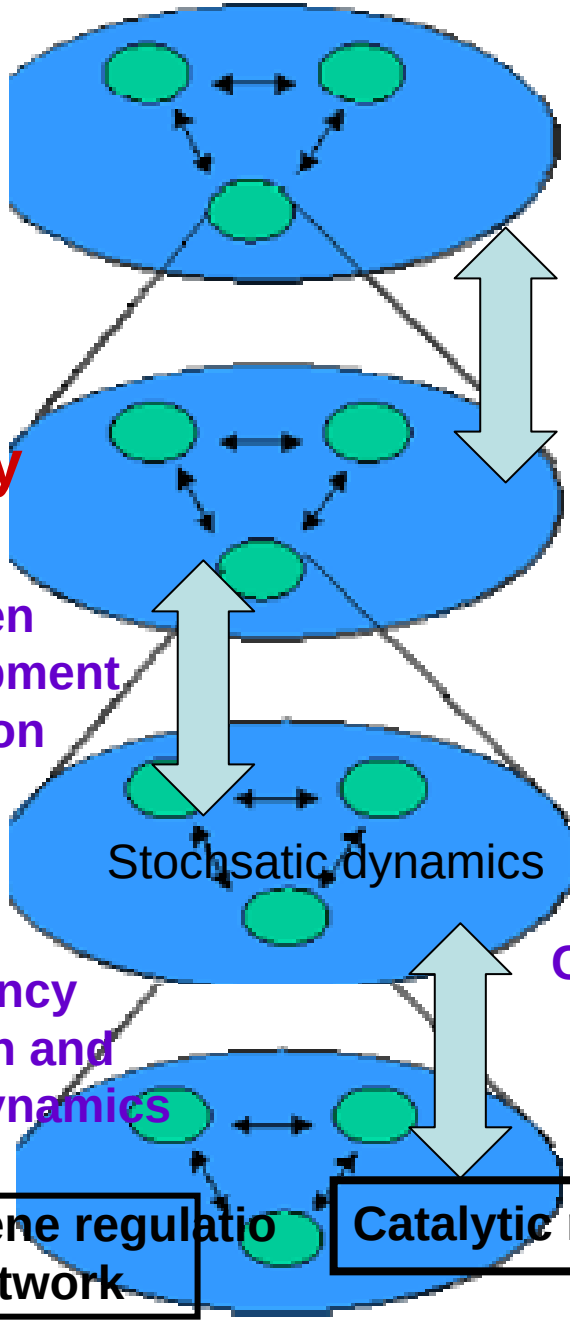
1) Dynamical Systems ++ & Statistical Physics ++

→ 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

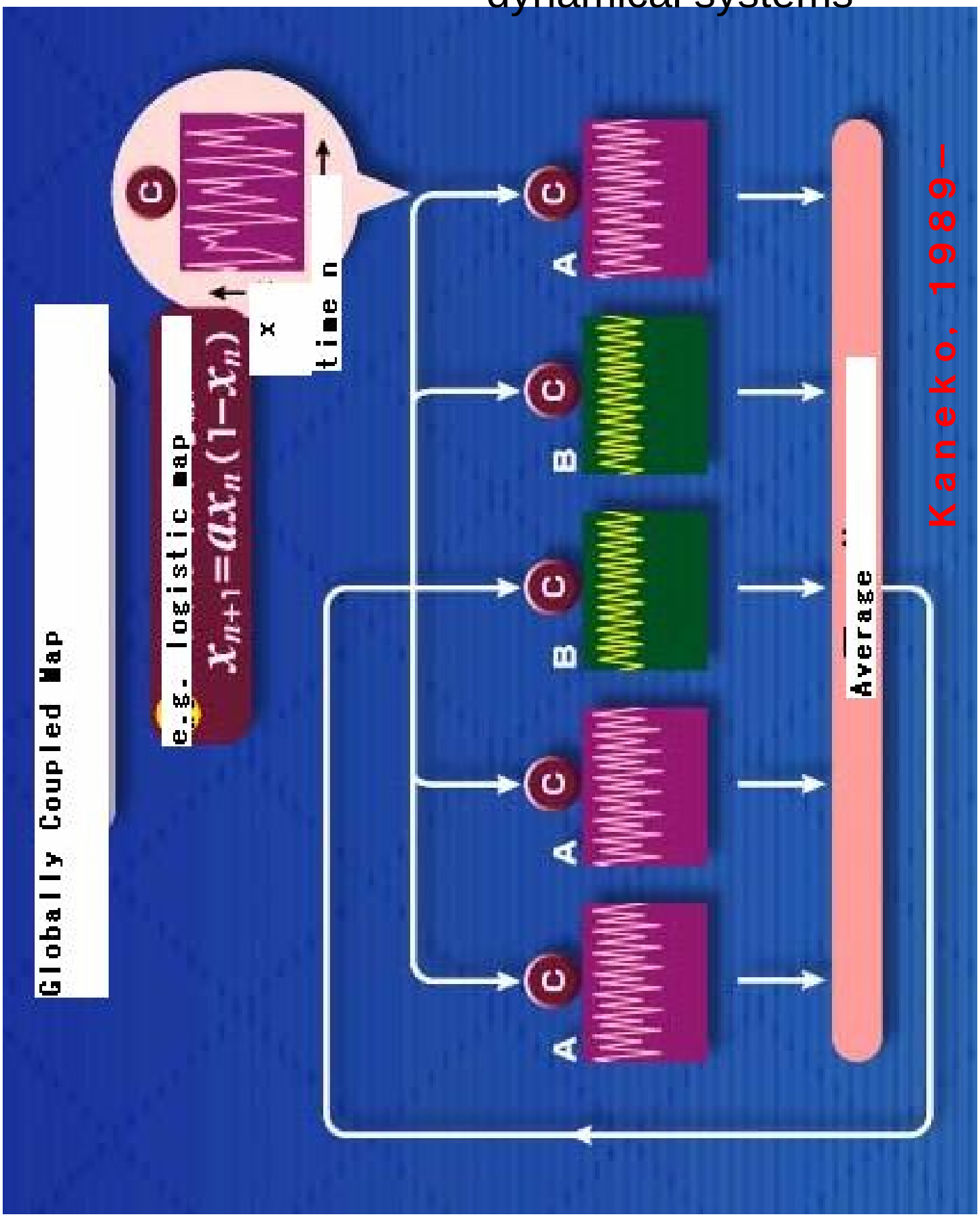
Consisteny between Cell reproduction
nd molecule replication

Molecule

Gene regulatio
network

Catalytic reaction network

20 years ago---- working on coupled dynamical systems



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

Globally coupled map (no spatial structure) [1] (1989,KK)

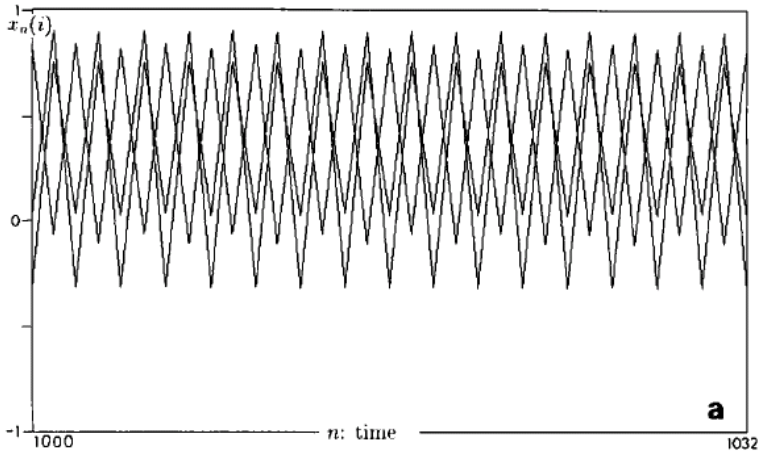
logistic map $f(x) = 1 - ax^2$

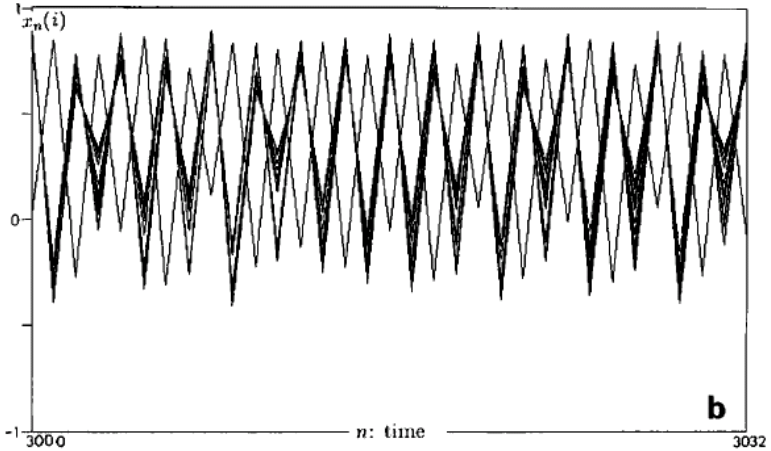
Cf Coupled map lattice → space-time chaos (1984,KK)

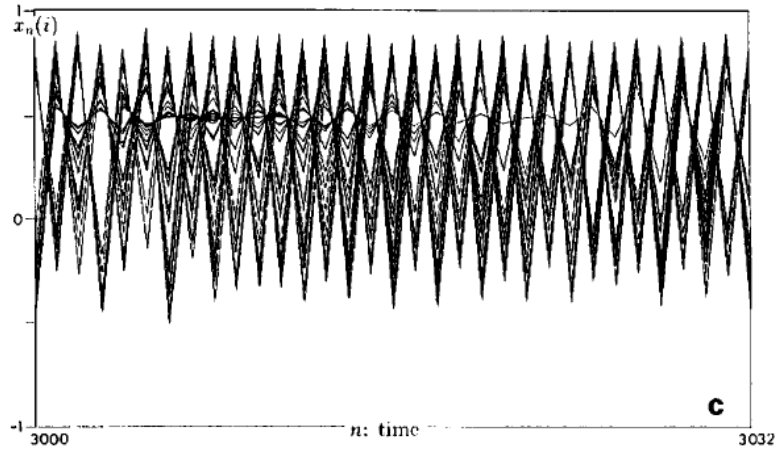
$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \tfrac{1}{2}\epsilon \left[f(x_n(i+1)) + f(x_n(i-1)) \right], \quad (2)$$

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

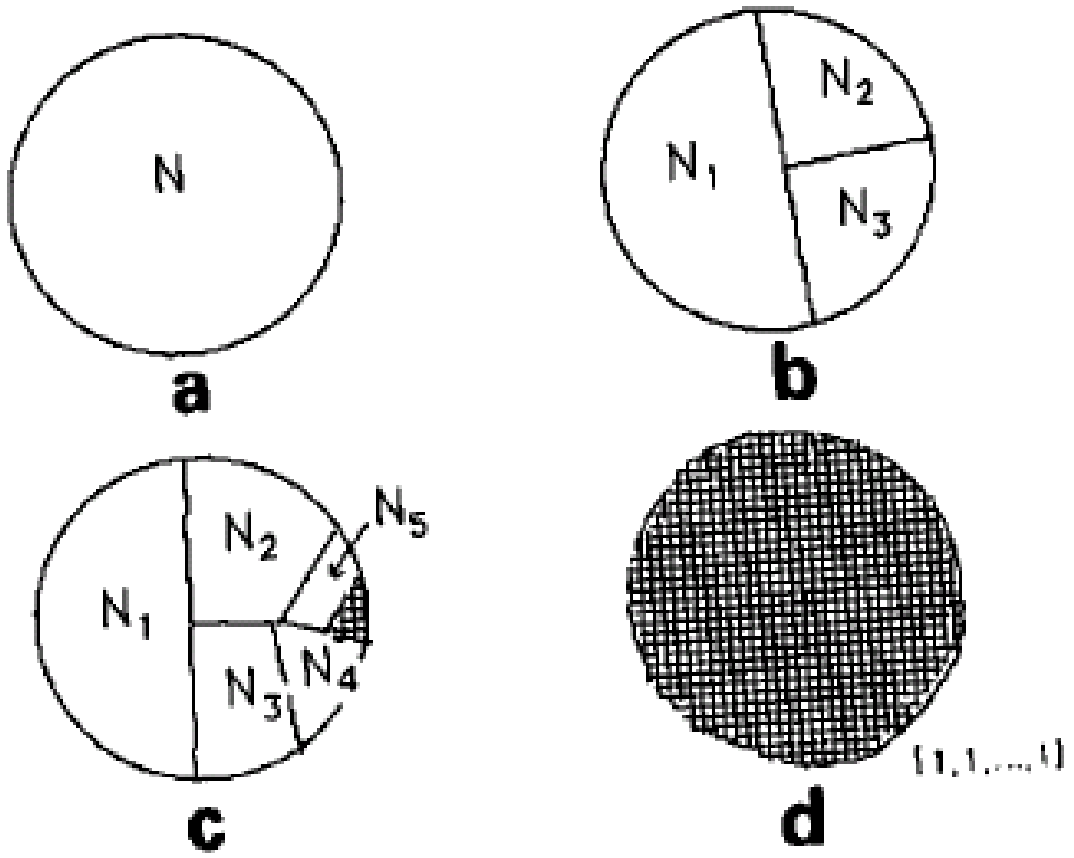
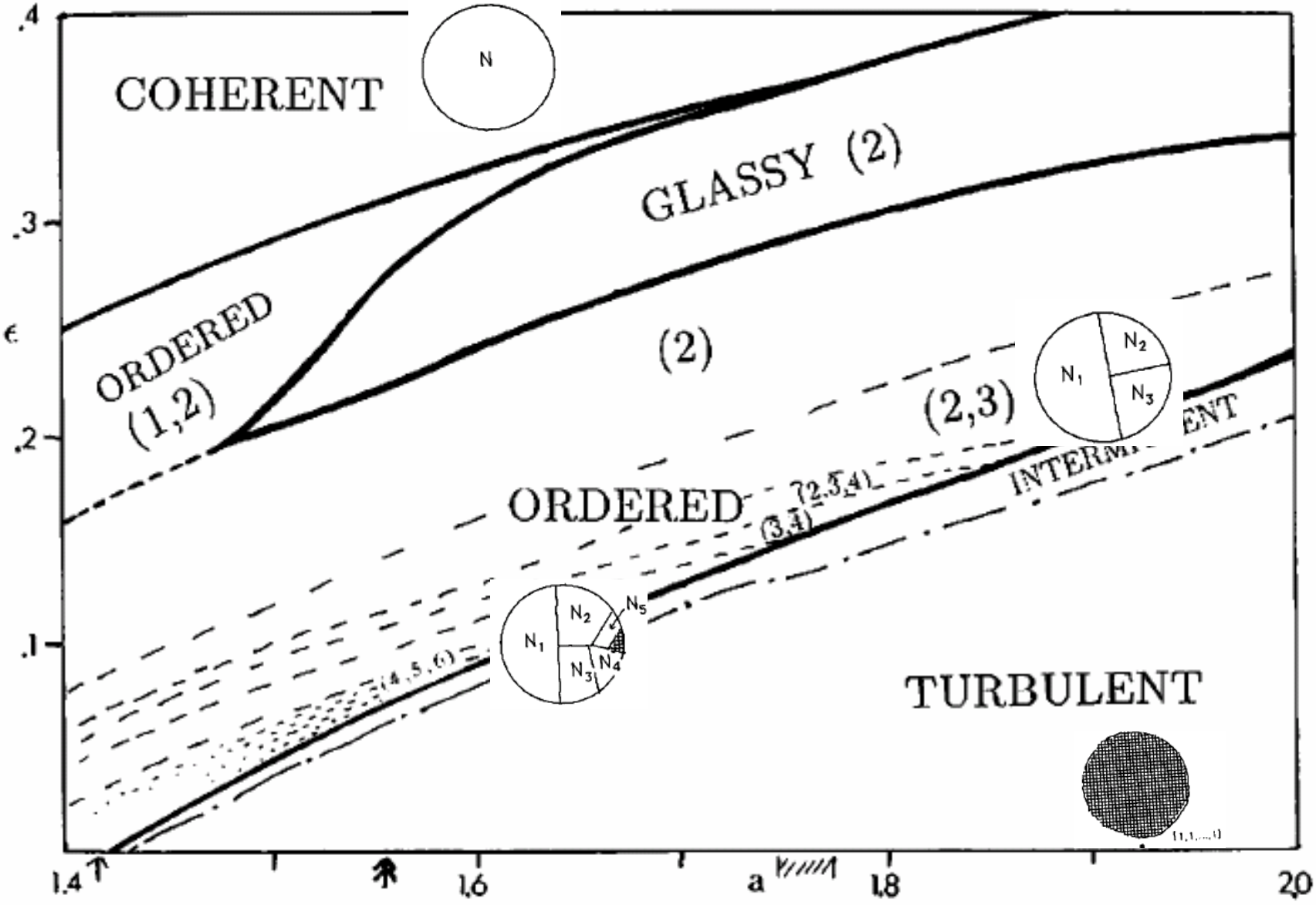
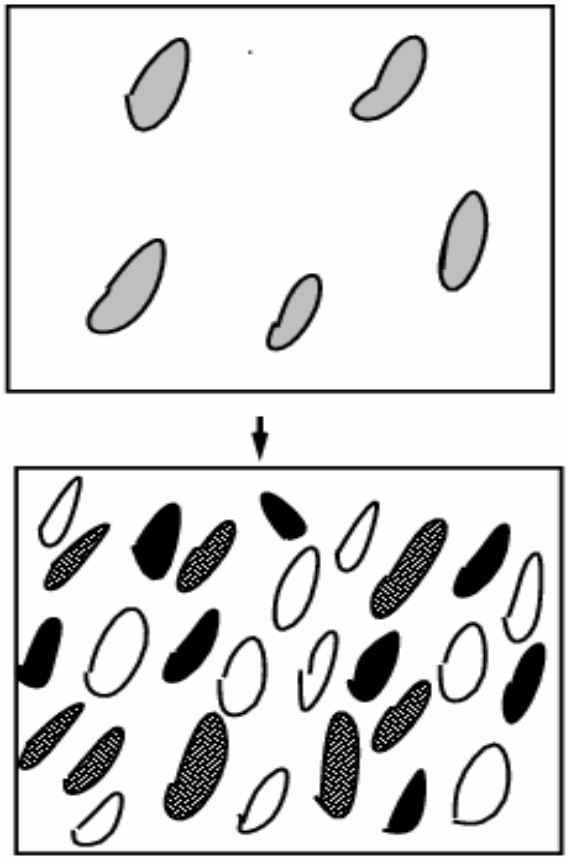


Fig. 1. Schematic figure for clusterings: (a) Coherent attractor. (b) Few clusters ($k = 3$). (c) Many-cluster attractor with unequal partition. (d) Many-cluster attractor with $k = N$.

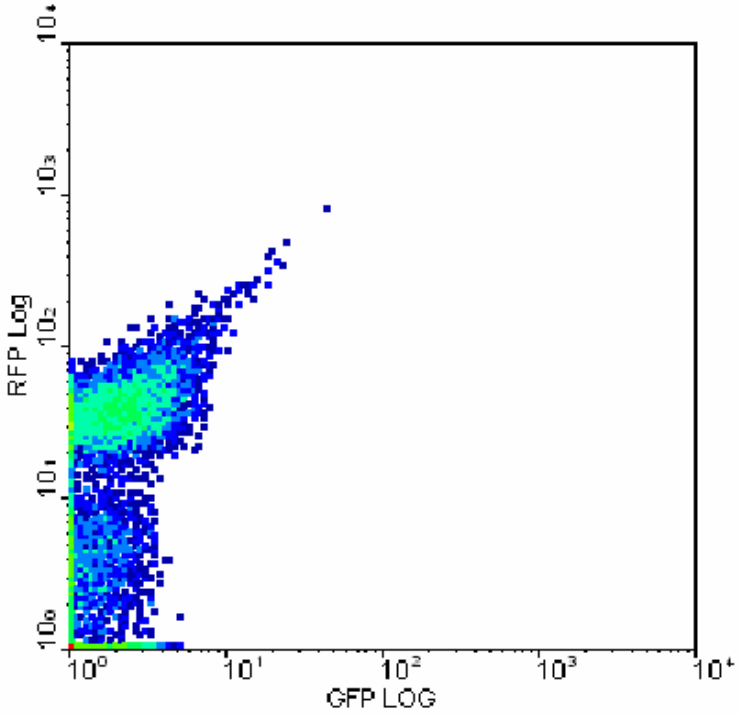


Onset of chaos

Around 1992, I met Tetsuya Yomo who was working on cell differentiation of Bacteria in a well stirred condition



Character of bacteria of identical genes differentiate in a crowded condition

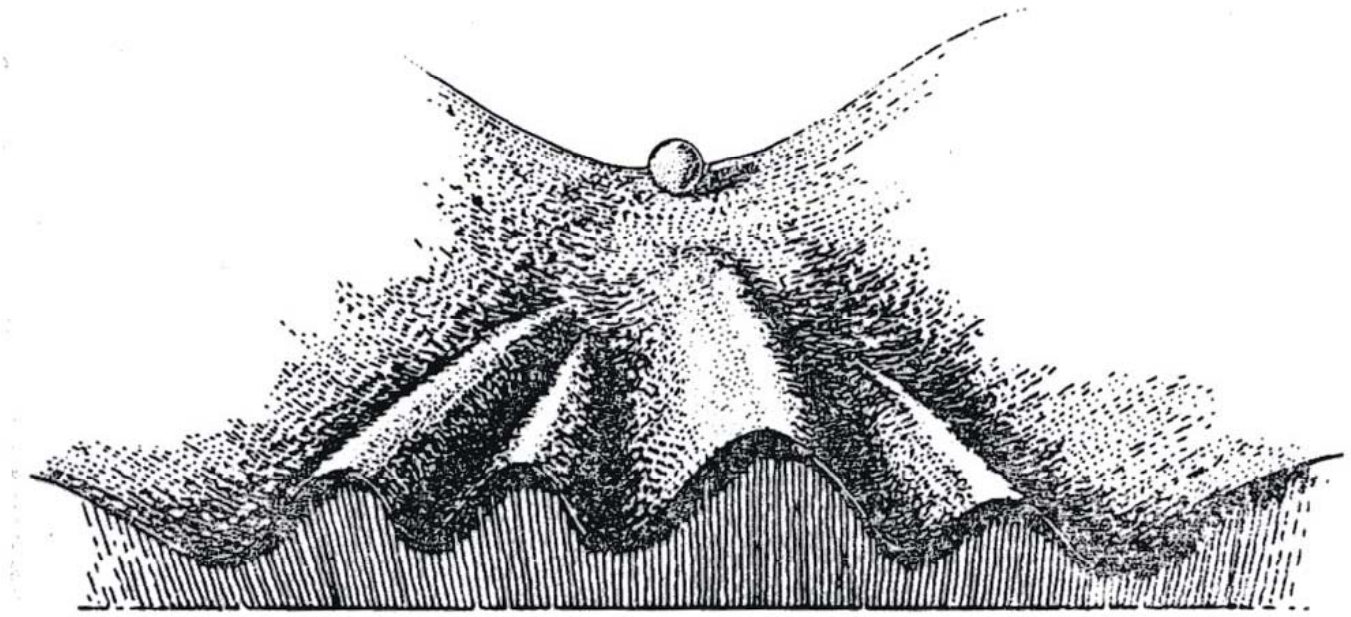


Measurement by fluoresecent proteins

Cell differentiation
--coupled dynamical systems?

Multicelluarity: Question on Cell differentiation:

Insight by Conrad Waddington (1957)



Waddington's Canalization

Cell types as Attractors?

How genes guide this process?

If mutiple attractors, how initial conditions are chosen?
Relevance of cell-cell interaction?
–problem of coupled dynamical systems?

Isologous Diversification:

internal dynamics and interaction : development phenotype

instability

distinct phenotypes

interaction-induced

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

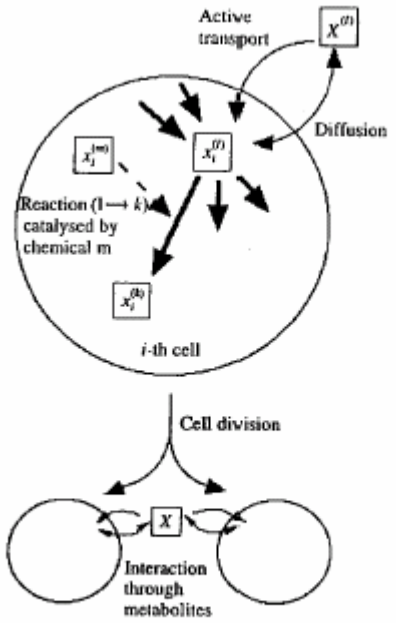


FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

Example: chemical reaction network

specialize in the use of some path

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

$$\mathrm{d}x_i^{(\ell)}(t)/\mathrm{d}t = \delta x_i^{(\ell)}(t) - x_i^{(\ell)}(t) \sum_{m=1}^{k} \delta x_i^{(m)}(t) \quad (1)$$

with

Dilution by the increase of cell volume

$$\delta x_i^{(\ell)}(t) = \sum_{m,j} Con(m, \ell, j)\ e\ x_i^{(m)}(t)\ (x_i^{(j)}(t))^{\alpha}$$

Catalytic reaction dynamics (or gene expression)

$$- \sum_{m',j'} Con(\ell, m', j')\ e\ x_i^{(\ell)}(t)\ (x_i^{(j')}(t))^{\alpha}$$

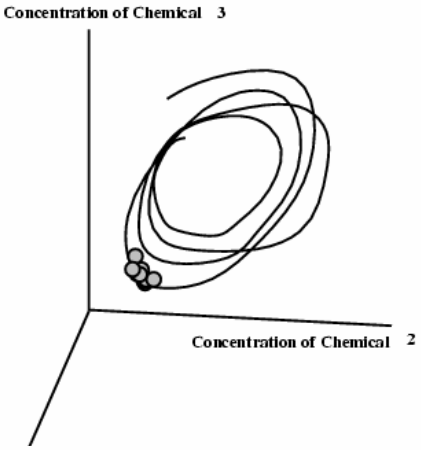
$$+ \sigma_{\ell} D(X^{(\ell)}(t) - x_i^{(\ell)}(t))$$

Diffusion to/from media; resource included

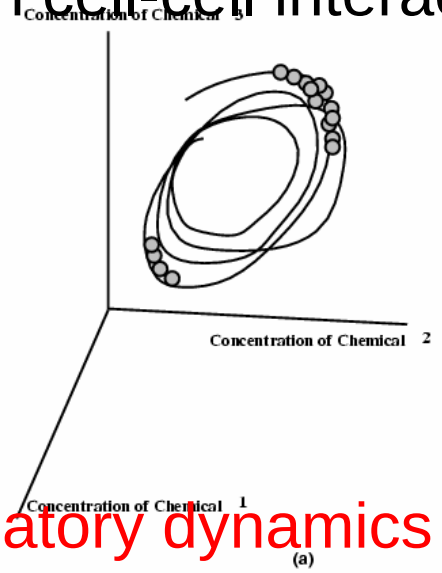
$$\left(+ \eta(t)\sqrt{x_i^{(\ell)}(t).} \right) \quad (2)$$

(noise by molceular fluctuation)

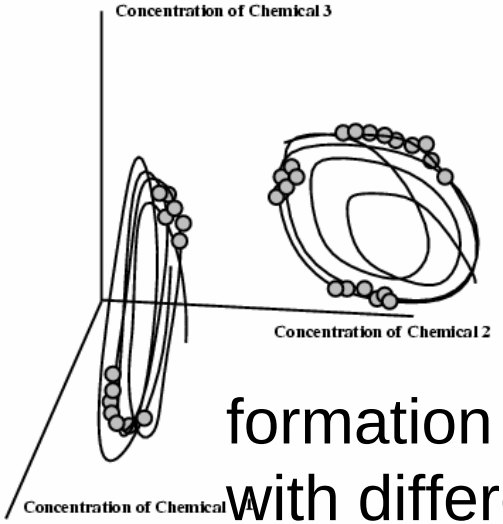
synchronous division:
no differentiation



Instability of homogeneous state
through cell-cell interaction

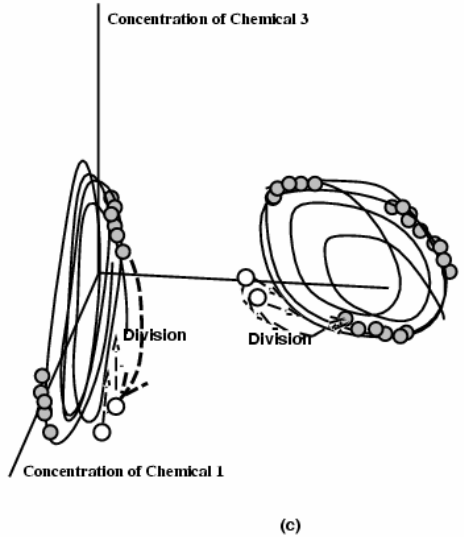


Assuming oscillatory dynamics as a single cell



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

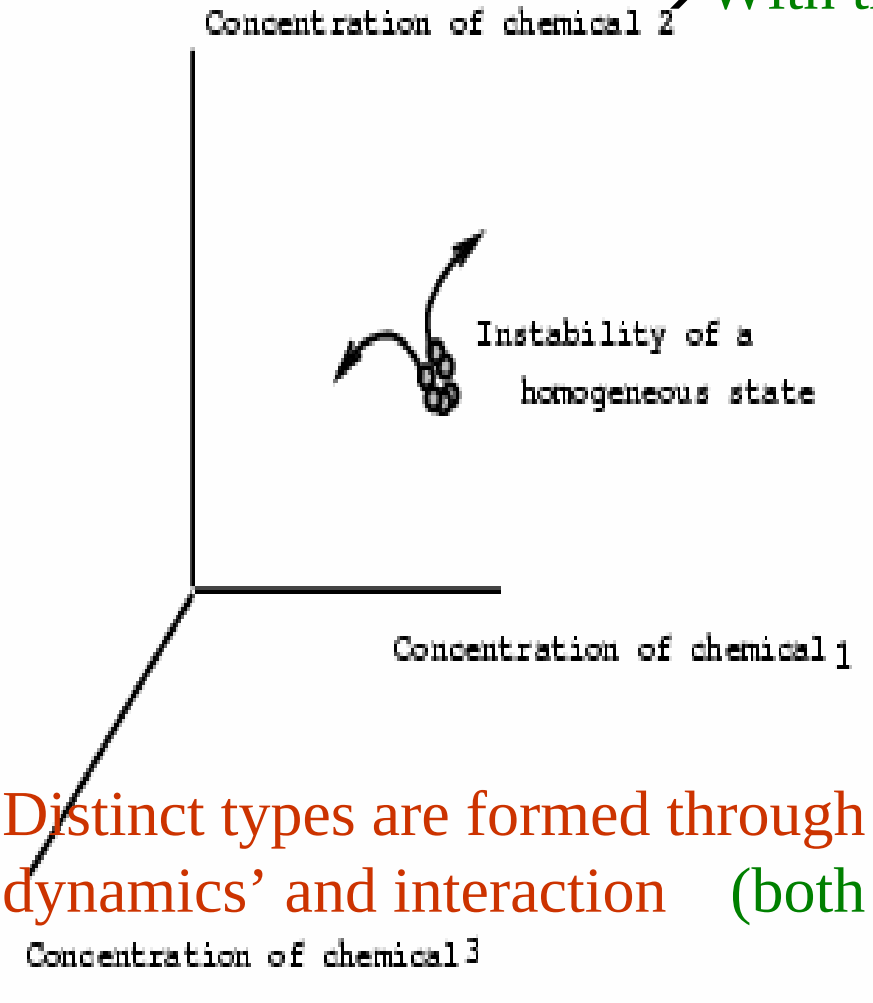
recursive production

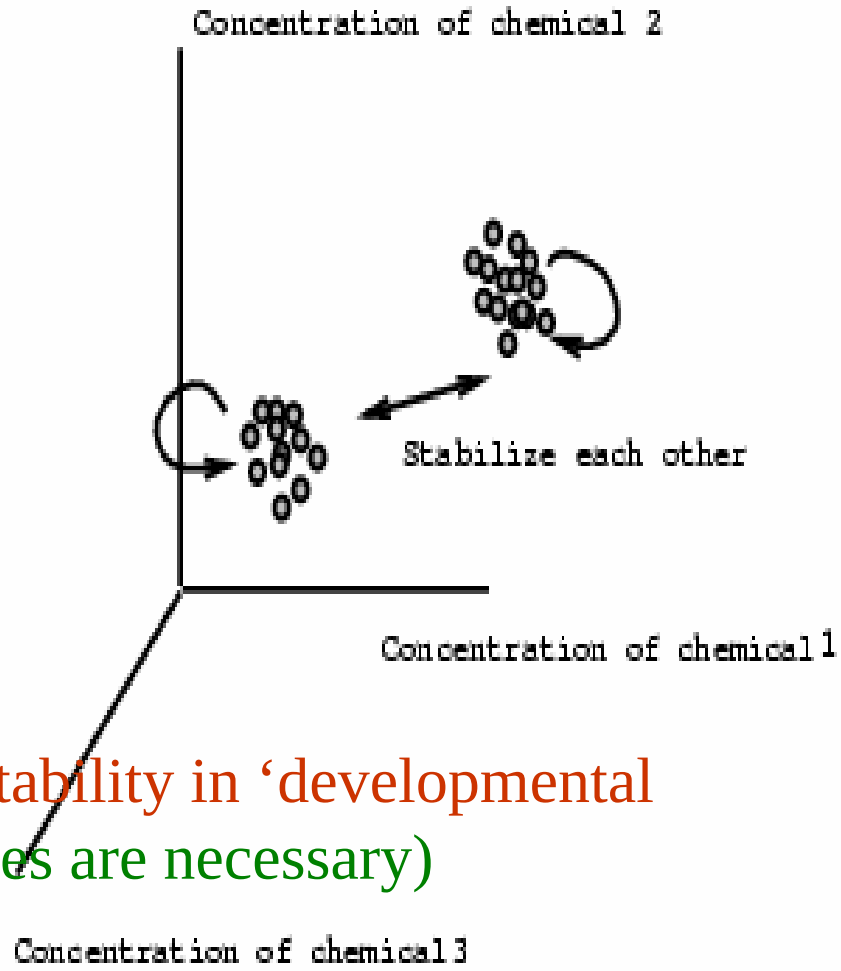


- (1) Synchronous oscillations of identical units

  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





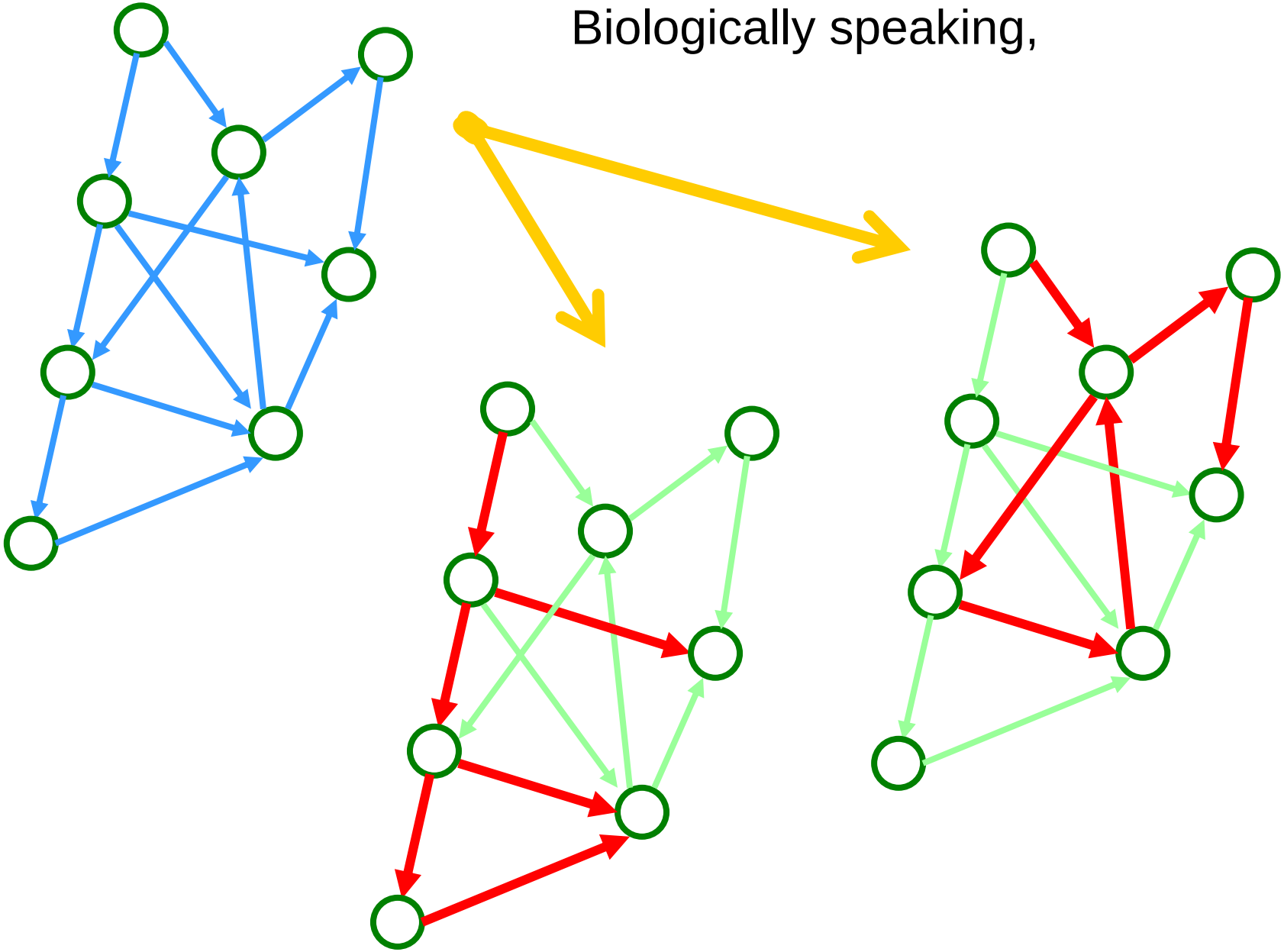
Distinct types are formed through instability in ‘developmental dynamics’ and interaction (both types are necessary)

As Single cell dynamics --- bifurcation

Interaction term works as bifurcation parameter

Self-consistent choice of bifurcation parameter

Biologically speaking,



Robustness of developmental process

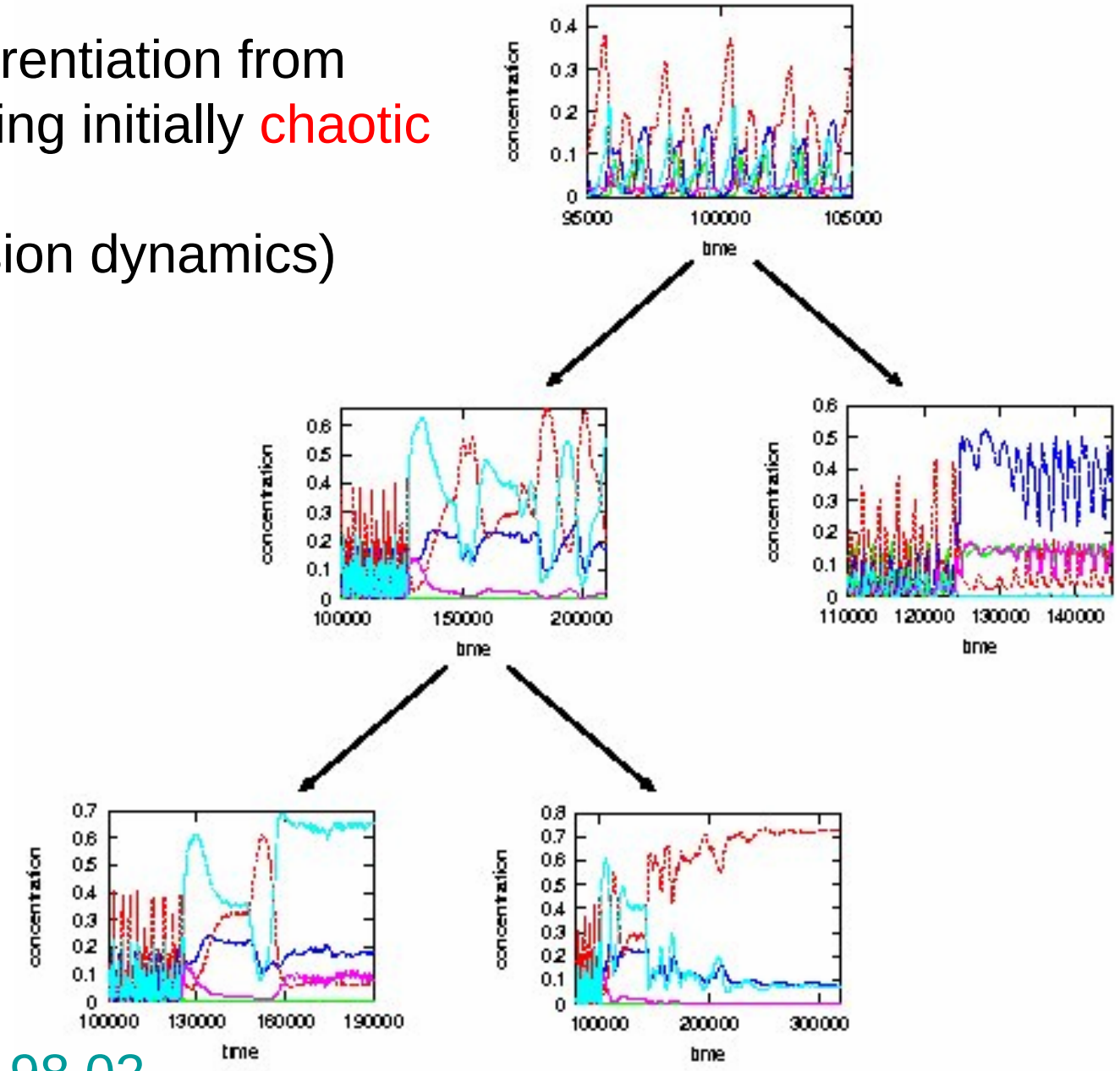
both states of each cell type and number distribution of each cell type

(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)

Hierarchical differentiation from ‘stem cell’;by taking initially chaotic dynamics

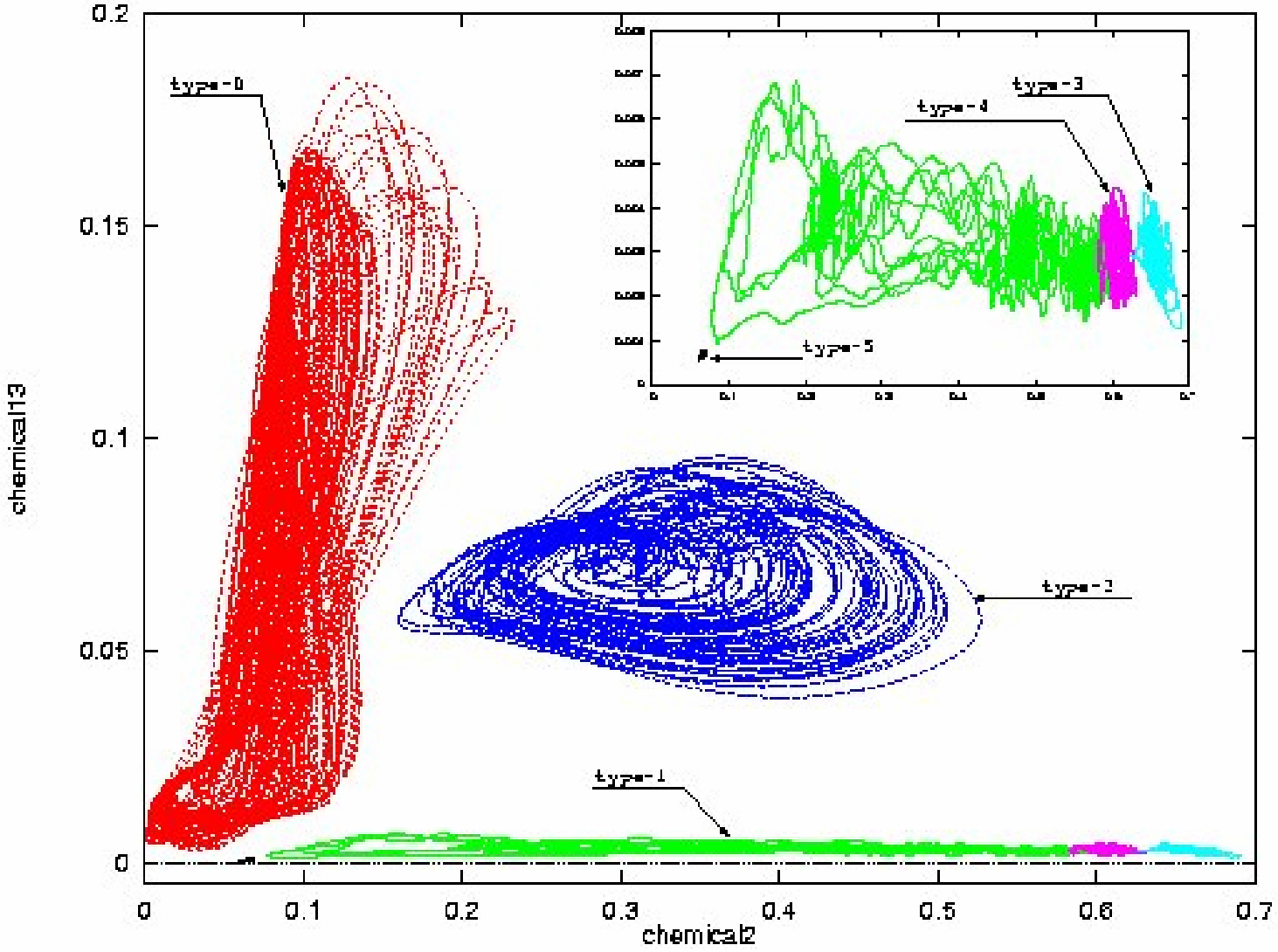
(or gene exression dynamics)



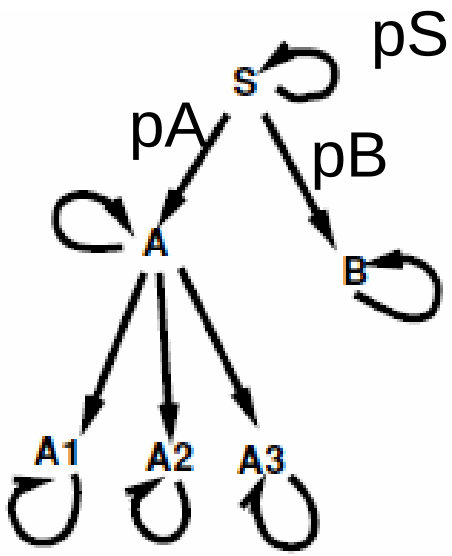
Furusawa & KK,98,02

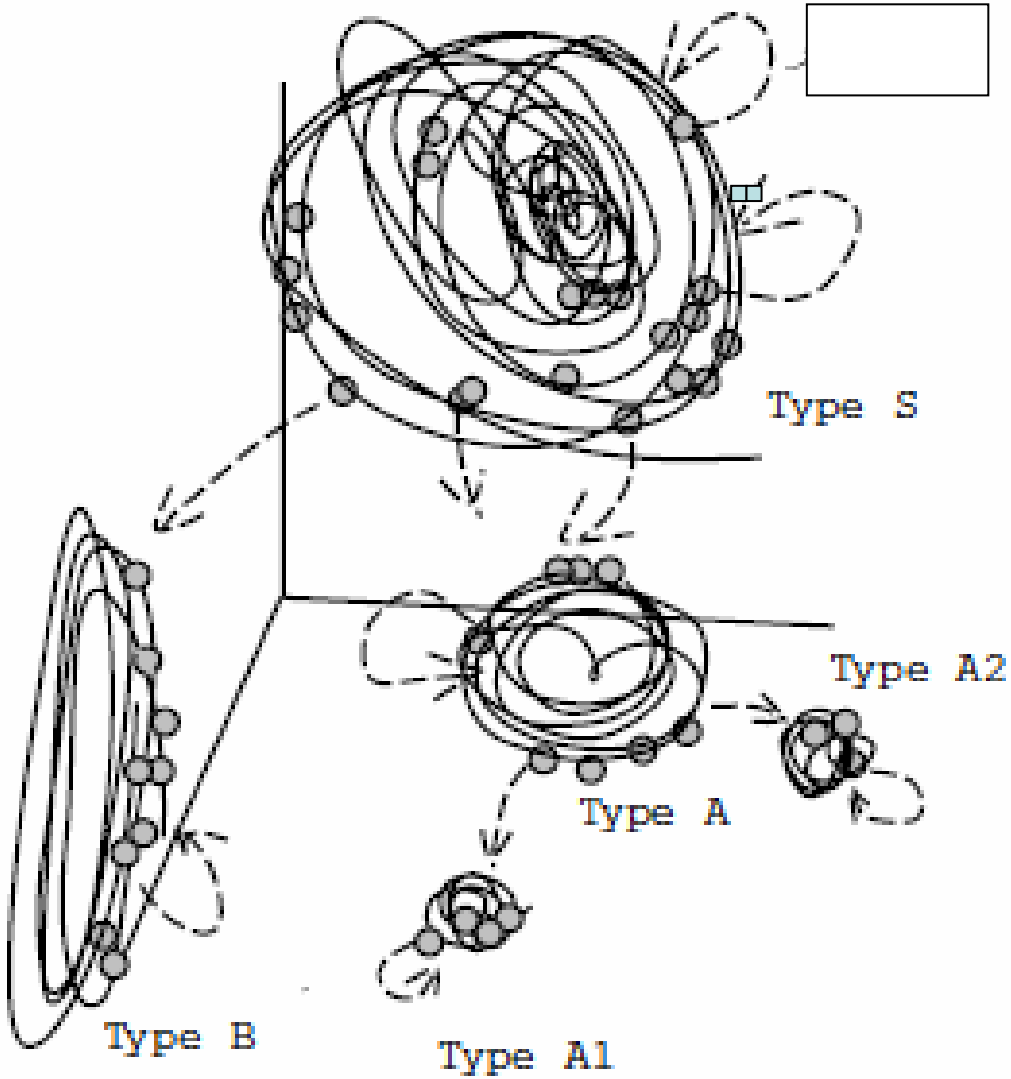
Hierarchical differentiation from ‘stem cell’; by taking initially chaotic dynamics (higher order catalysis)

Furusawa&KK



Hierarchical differentiation from ‘stem cell’;by taking initially chaotic dynamics



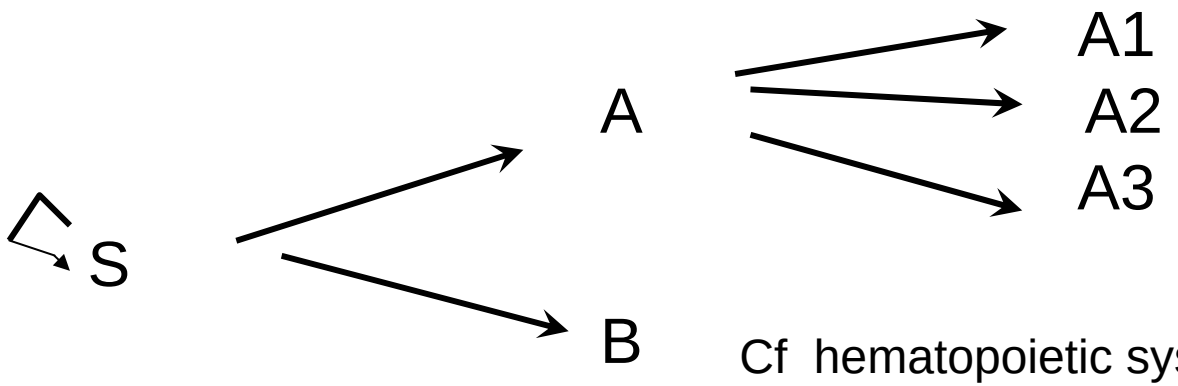


probability depends on # distrib. of cell types

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

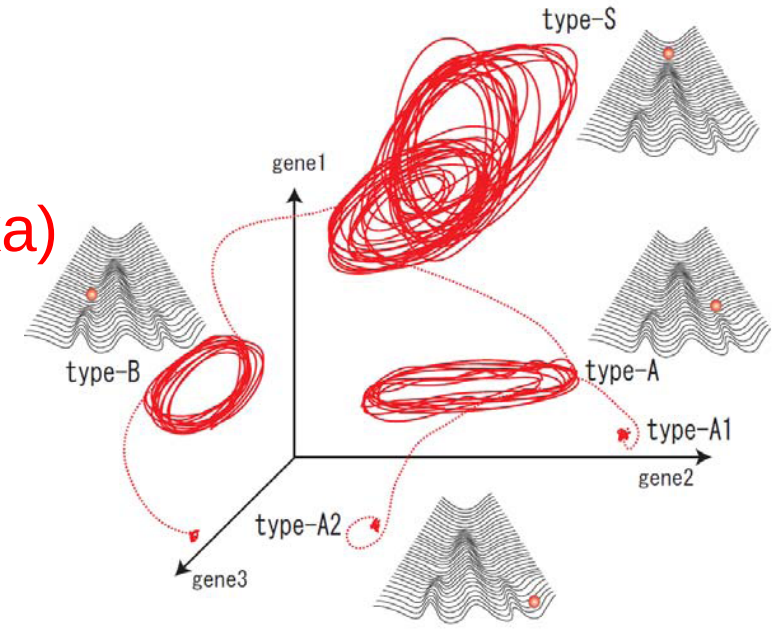
- Loss of pluripotency is characterized by

  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 group (Nature 2008)

Mechanism: approach to ``Milnor attractor''?

(that touches with basin boundary)

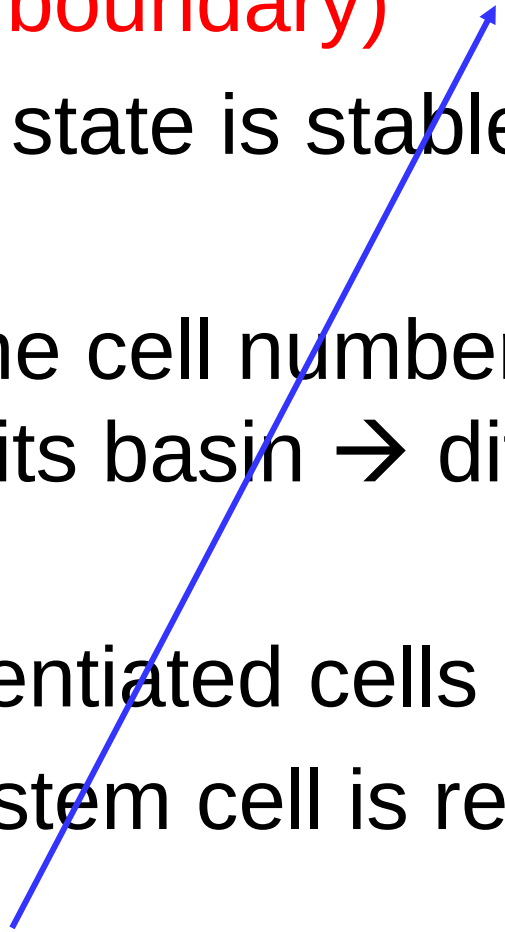
As long as the stem cell state is stable, it reproduces itself

→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



``Milnor attractor'' : attractor by Milnor's definition(positive measure of basin) − attractor with asymptoric stability

- Toward ‘mathematical Representation’

Self-consistent bifurcation

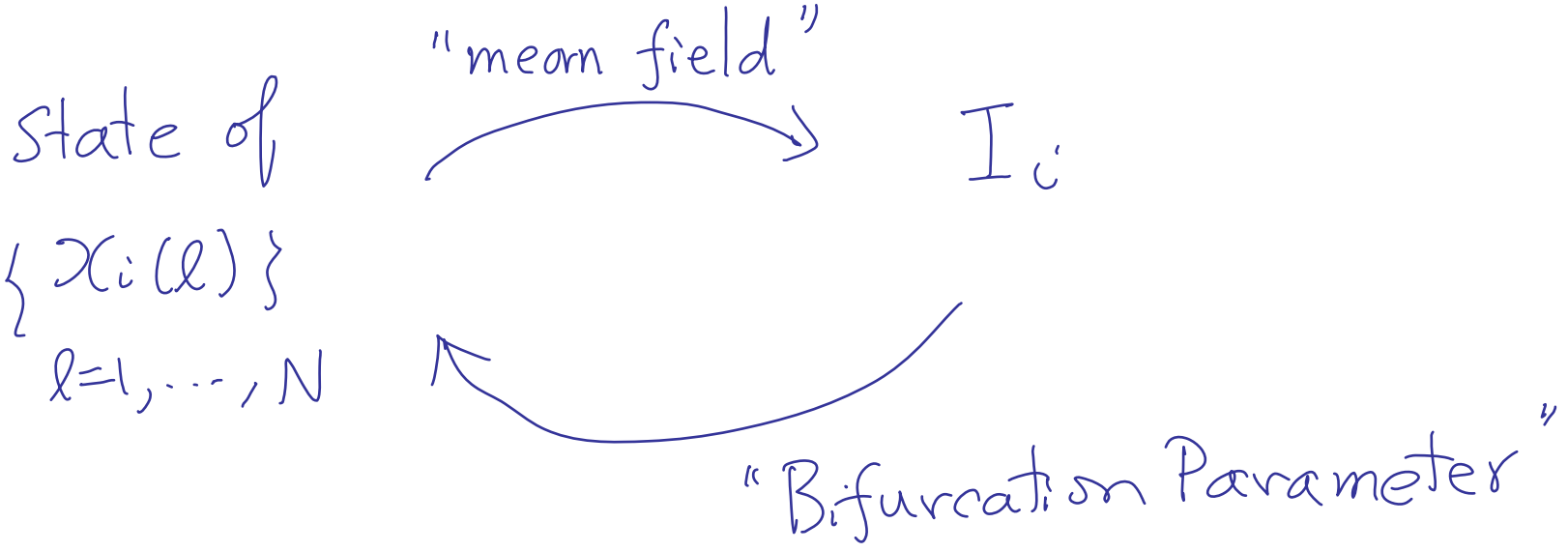
$$\frac{dx_i}{dt} = f_i(\{x_j\}) \quad \leftarrow \text{Internal dynamics}$$

element (cell) $k = 1, 2, \cdots, N$

$$\frac{dx_i(k)}{dt} = f_i(\{x_j(k)\}) + \underbrace{\sum_{l=1}^{N} g_i(\{x_i(l)\})}_{\text{Interaction term } I_i}$$

I_i .... "Bifurcation Parameter"

determined by $\{x_i(l)\}$



"Differentiation"

$\{x_i(\ell)\}$ $\ell=1,\cdots,N$ differentiate

→ different attractor for dynamics

$f_i(\{x\}) + I_i \Leftarrow$ Bf. Parameter

cf. in general I_i can be time dependent $I_i(t)$ if $\{x_i\}$ falls on periodic / chaotic attractor

For the moment we consider the case with constant I_i

Cell differentiation

cell # ↗ $\Rightarrow$ change in interaction term $\Rightarrow$ change in I_i

For cell differential

$\{x_i(1)\} \rightarrow \{x_i(1) = x_i(2)\} \rightarrow \cdots$

$\rightarrow \left\{ \#\ \begin{array}{l} x_i(1) = x_i(2) = \\ x_i(\ell) = \cdots\ x_i(N) \end{array} \right.$ ⟲ differentiate

as $N \nearrow \Rightarrow$ I_i ("bifurcation parameter") changes

bifurcate to have more than one attractor

"Types of Bifurcation" — classification

[Set up]

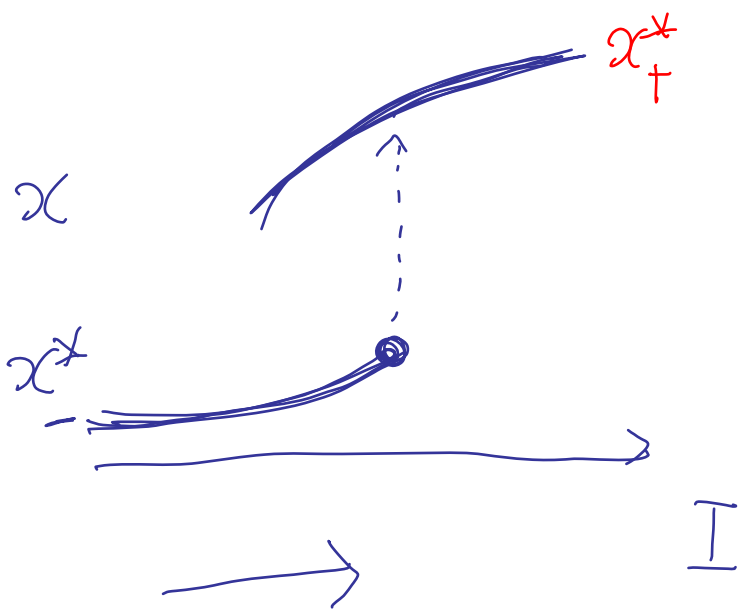
1) $N \nearrow$ $\Rightarrow \sum g(\{x\})$ changes $\Rightarrow I_i$ changes

2) $N \to N+1$: add a state with same x_i value (+ perturbation)

3) self-consistent solution

$I_i \rightleftarrows$ attractor $\{x_i\}$

A-I. Saddle-Node



$N=1$ x_-^*

$\downarrow N\nearrow \Rightarrow I\nearrow$

"x_+^*"

$\sum g_\ell(x_-^*) + \sum g_\ell(x_+^*)$

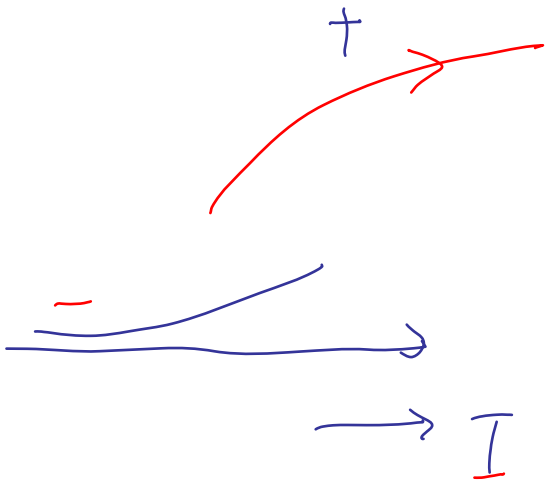
$\ell \in x_-^*$ $\ell \in x_+^*$

existence of $g(x_+^*)$ { $I\nearrow$? A-ii

$I\searrow$? A-i

Self-consistent determination of distribution of x-*,x+* and I

A-i

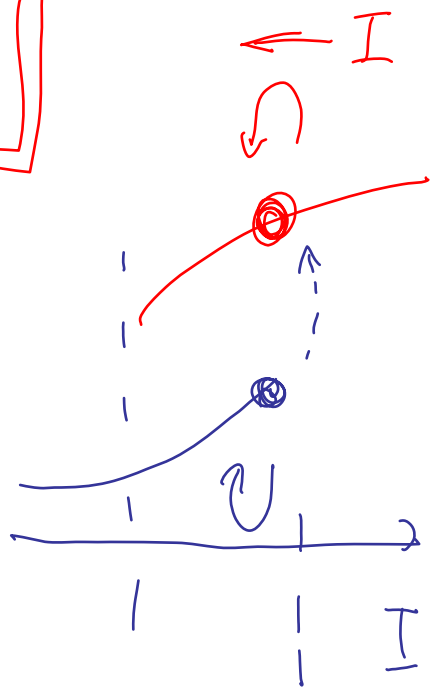


N ↗

I ↗

switch from − to + type

A-ii



N ↗

x_-^* ↺ I ↗

x_+^* ↻ I ↘

(−) (+) coexist

regulation of ratio −/+

Bifurcation parameter is given by interaction –self-consistent state

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

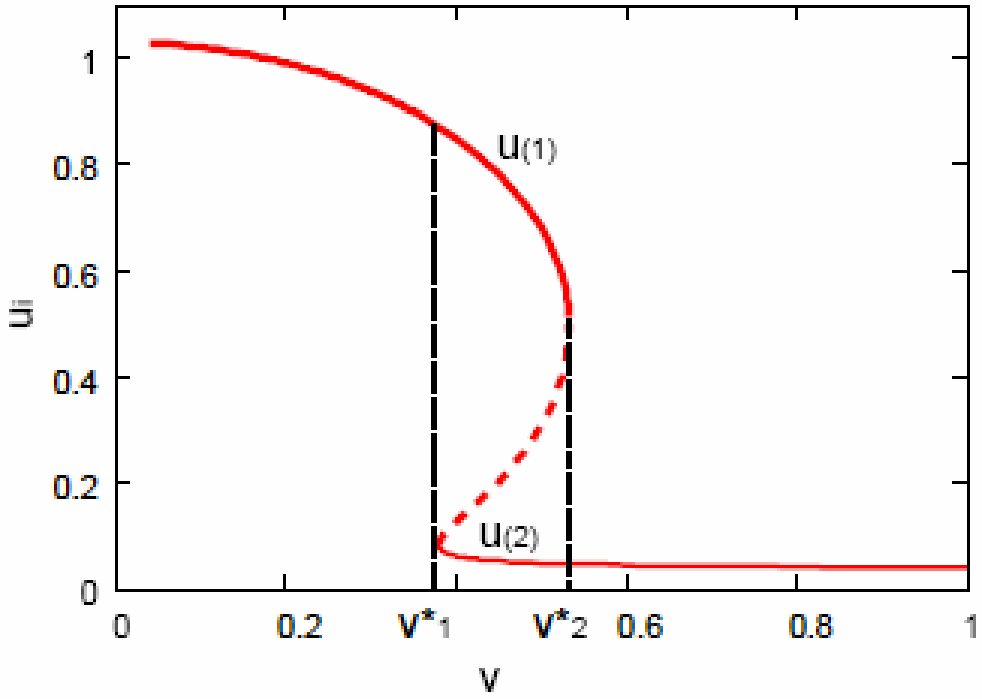
$$\frac{dv(t)}{dt} = g(u_1, \ldots, u_N, v). \qquad (2)$$

（α＝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)

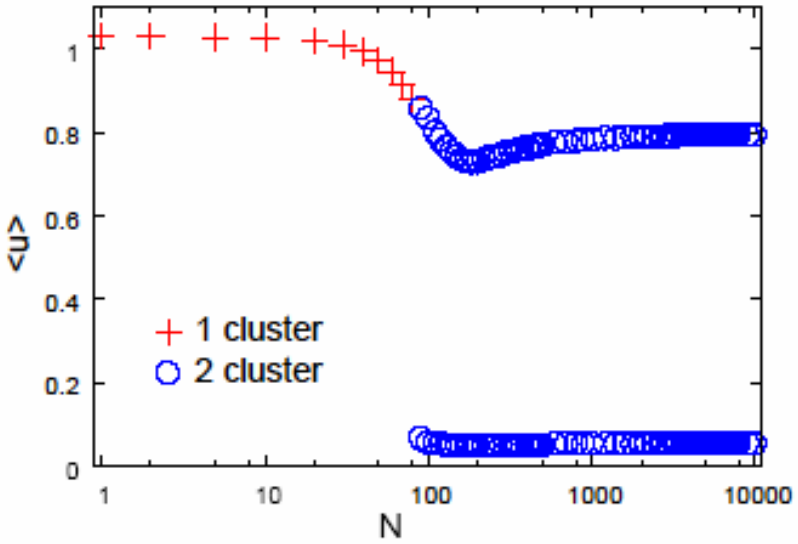


Figure 8: The fixed point solutions of model III plotted against the total cell number N.

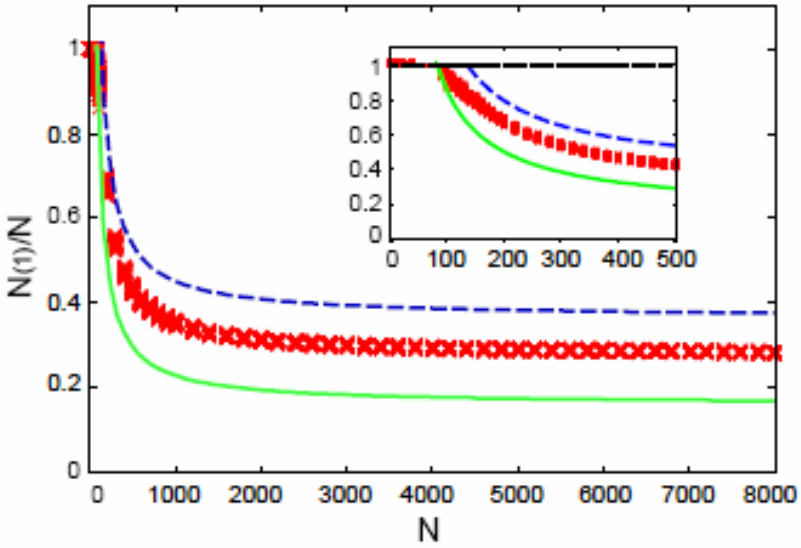
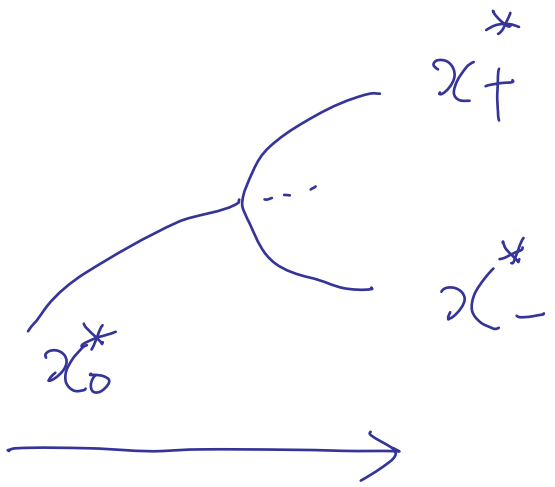


Figure 9: The ratio of the number cell type 1 $N_{(1)}$ to the total cell number N is plotted against N for model III. The initial condi-

B : pitchfork (not so relevant to differentiation)

$N \nearrow$ $I \nearrow$



B-i $\begin{cases} x_+ \\ x_- \end{cases}$ $I \nearrow$

$\xrightarrow{I}$ from 0 to $\begin{Bmatrix} + \\ - \end{Bmatrix}$

no cexistence of +/− unless one assumes complicated function of I (# of +, # of −)

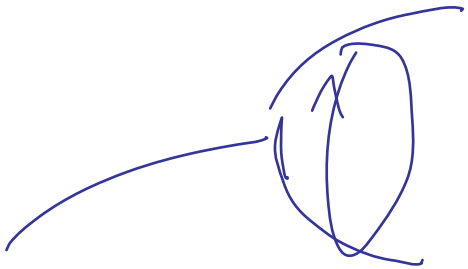
B-ii $\begin{cases} x_+ \\ x_- \end{cases}$ $I \searrow$ stay near bifurcation pt. (no coexistence)

- By considering coupling depending on the sum of state variables, it wourd be possible to consider the self-consistent pitchfork bifurcation say,

$$dXi/dt = aXi - Xi^3 - (\Sigma_j Xj)^2 Xi$$

C : Hopf bifurcation

(depend on super/sub critical)

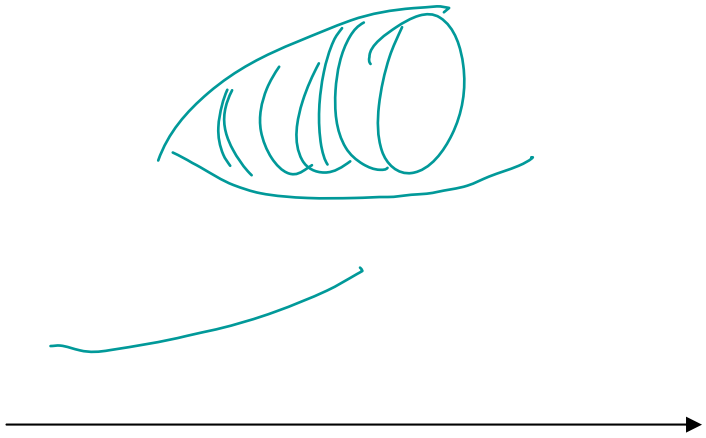


not relevant

(as in the case of pitchfork)

Ii (bifurcation parameter)

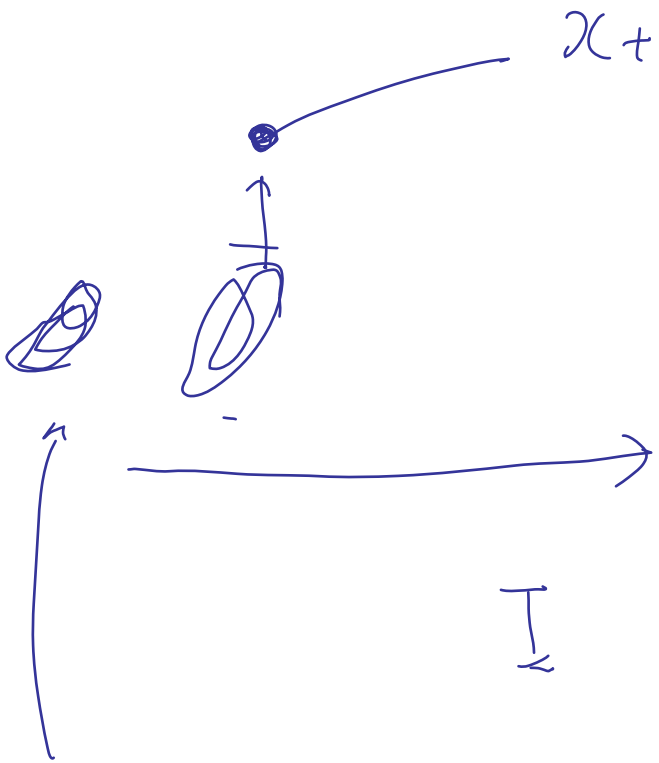
Cf Oscillation death



→ ~ case A-ii (SN)

D : Nonlocal bifurcation

crisis etc



x_c N↗ I↗

x_+

I↘

D-ii

(x_c, x_+) coexist

"Milnor Attractor" "Stem" all

$x_+^1, x_+^2, \cdots \Rightarrow$ many types

- Bifurcation to plural cell types –

possible for nonlocal bifurcation (crisis)

∗ Successive bifurcation → hierarchical differentiation

*For cell differentiation, we also need to consider the speed for cell division

*** Dynamical systems theory to ‘classify’ possible self-consistent bifurcation scenario needed?

Which types are most plausible evolutionarily?

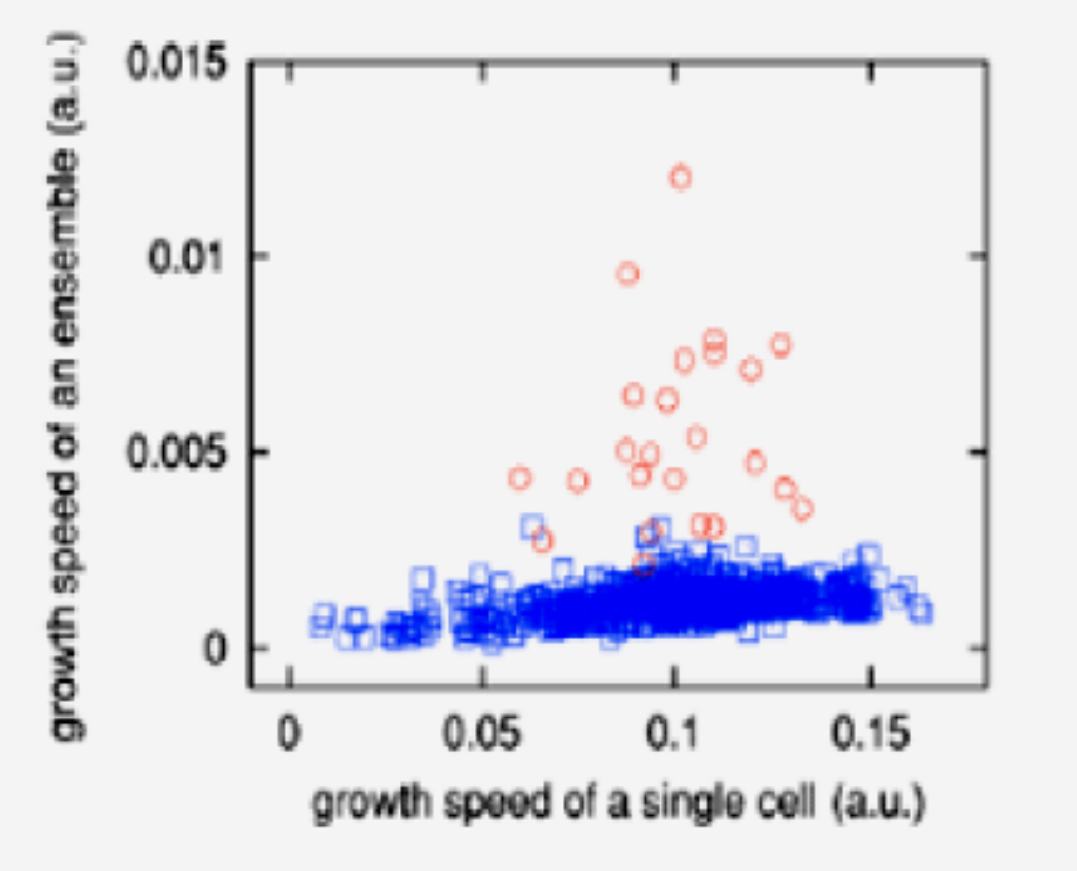
One needs ‘plausible measure for ‘model space’ and dynamics over model space (→ 2nd talk)

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

A remark on prevalence of Milnor attractor

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

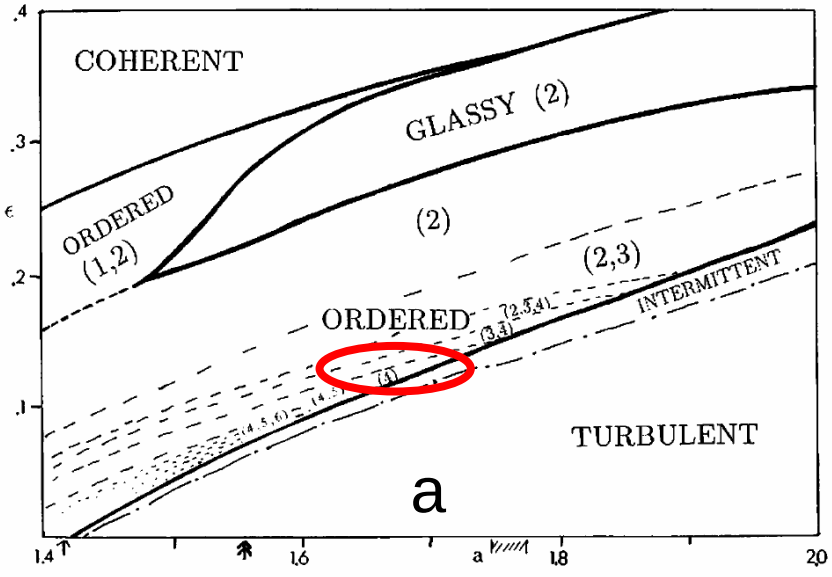
attractor and its basin boundary touches,

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)

GCM

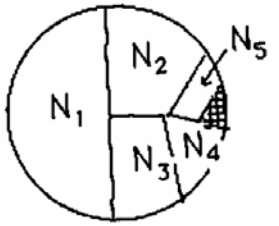
$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \frac{\epsilon}{N} \sum_j f(x_n(j)),$$



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)

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 ….

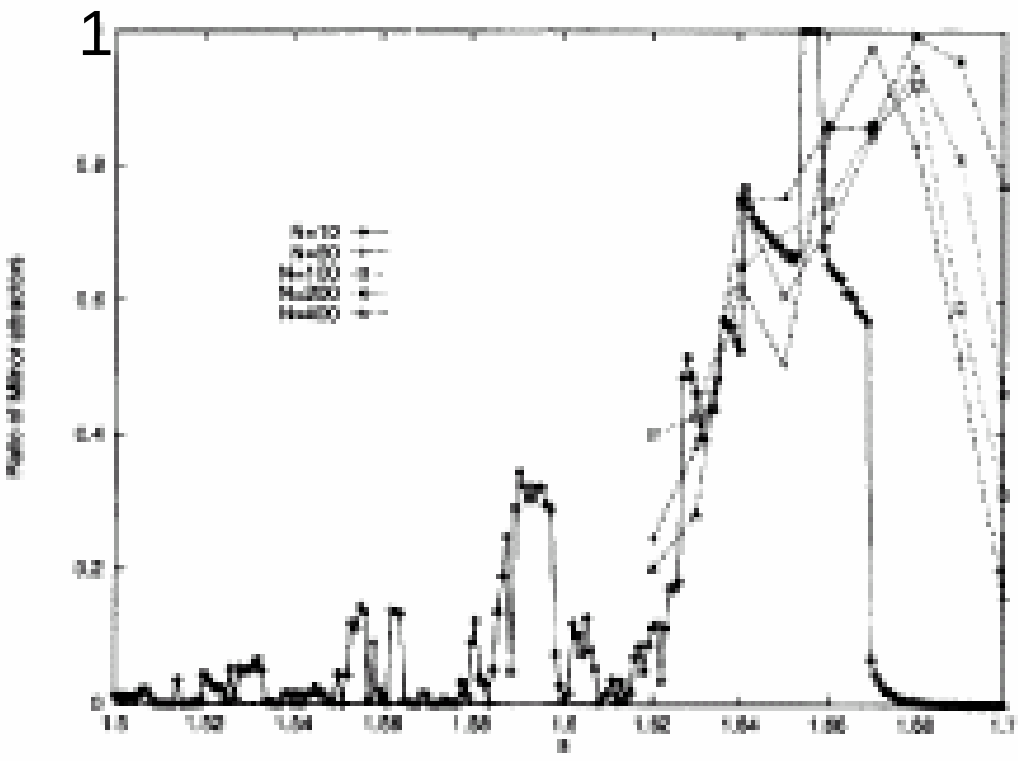
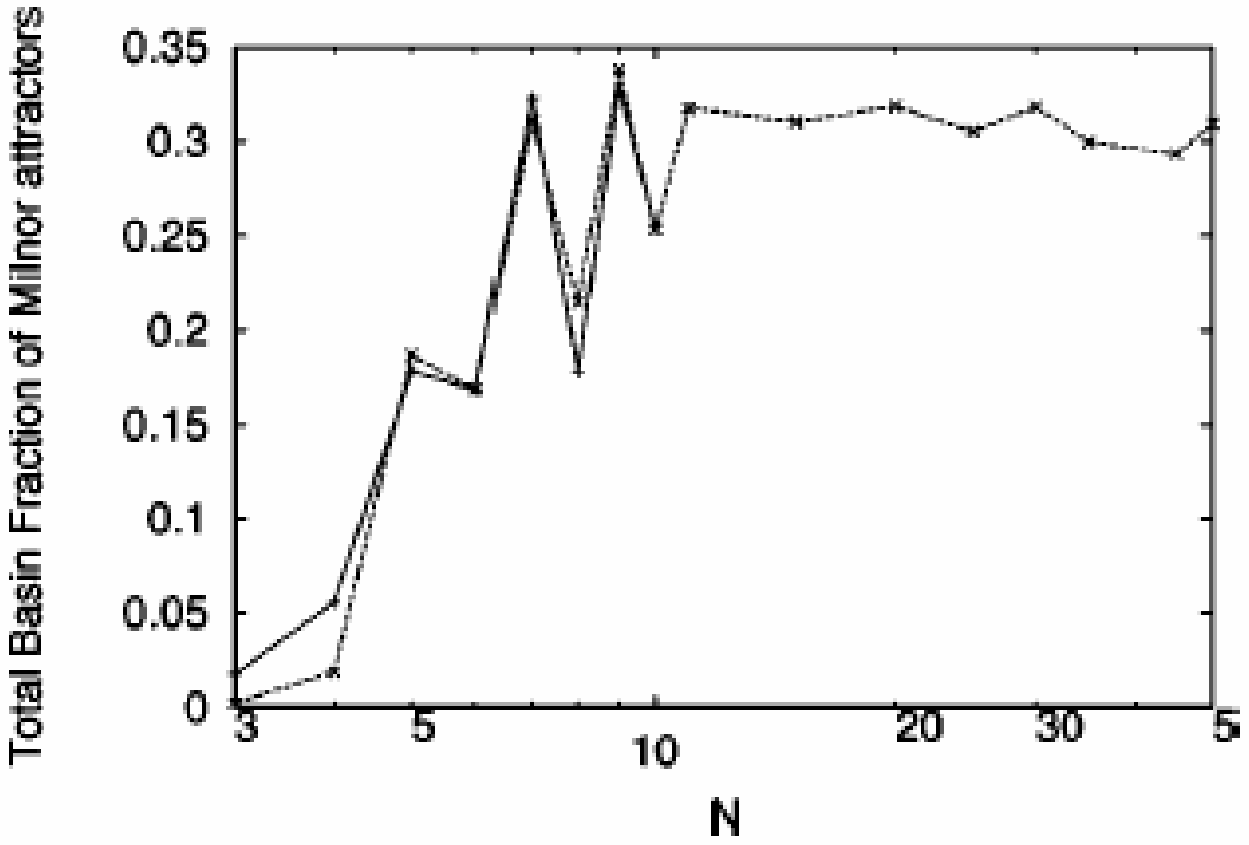


Fig. 9. The basin volume ratio of Milnor attractors with the change of a. For each a, we take 1000 initial conditions, and iterate the dynamics over 100000 steps to get an attractor. We check if the orbit returns to the original attractor, by perturbing each attractor by $\sigma = 10^{-7}$ over 100 trails. 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 ＞~（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 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

but The boundary makes combinatorial explosion ---- Order of (N-1)!

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-

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

- The number of basin boundary planes has combinatorial explosion, as factorial wins over exponential (around N ≒7). Then, the basin boundary is ‘crowded’ in the phase space. Thus often attractors touch with basin boundaries

  → dominance of Milnor attractors here

  (complete symmetry is unnecessary)

When combinatorial variety wins over exponential increase of the phase space, ‘complex dynamics’

(also in neural net model, Ishihara,kk 2006,PRL).

Magic number 7 + － 2 in dynamical systems？

If elements more than 7 are entangled, clear separation behavior is difficult

→A solution could be use of modules with each

<7 elements

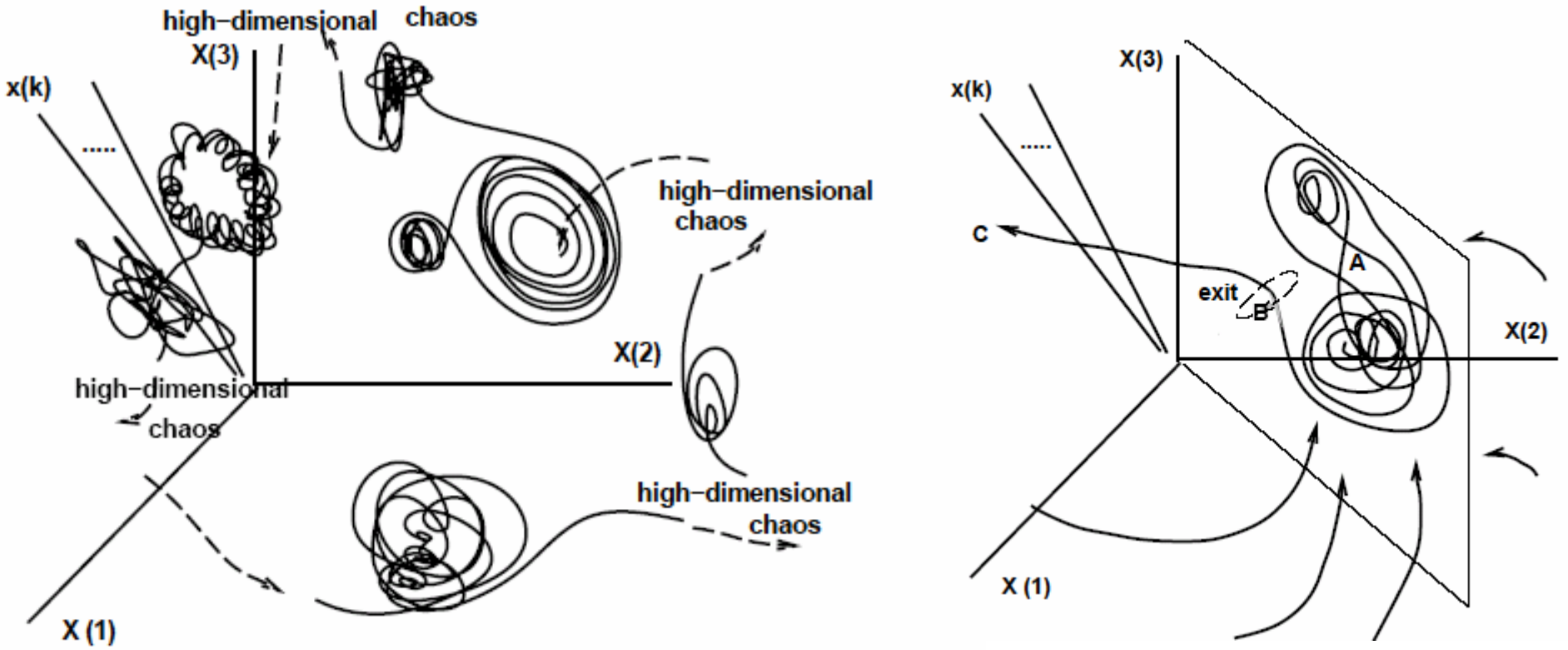
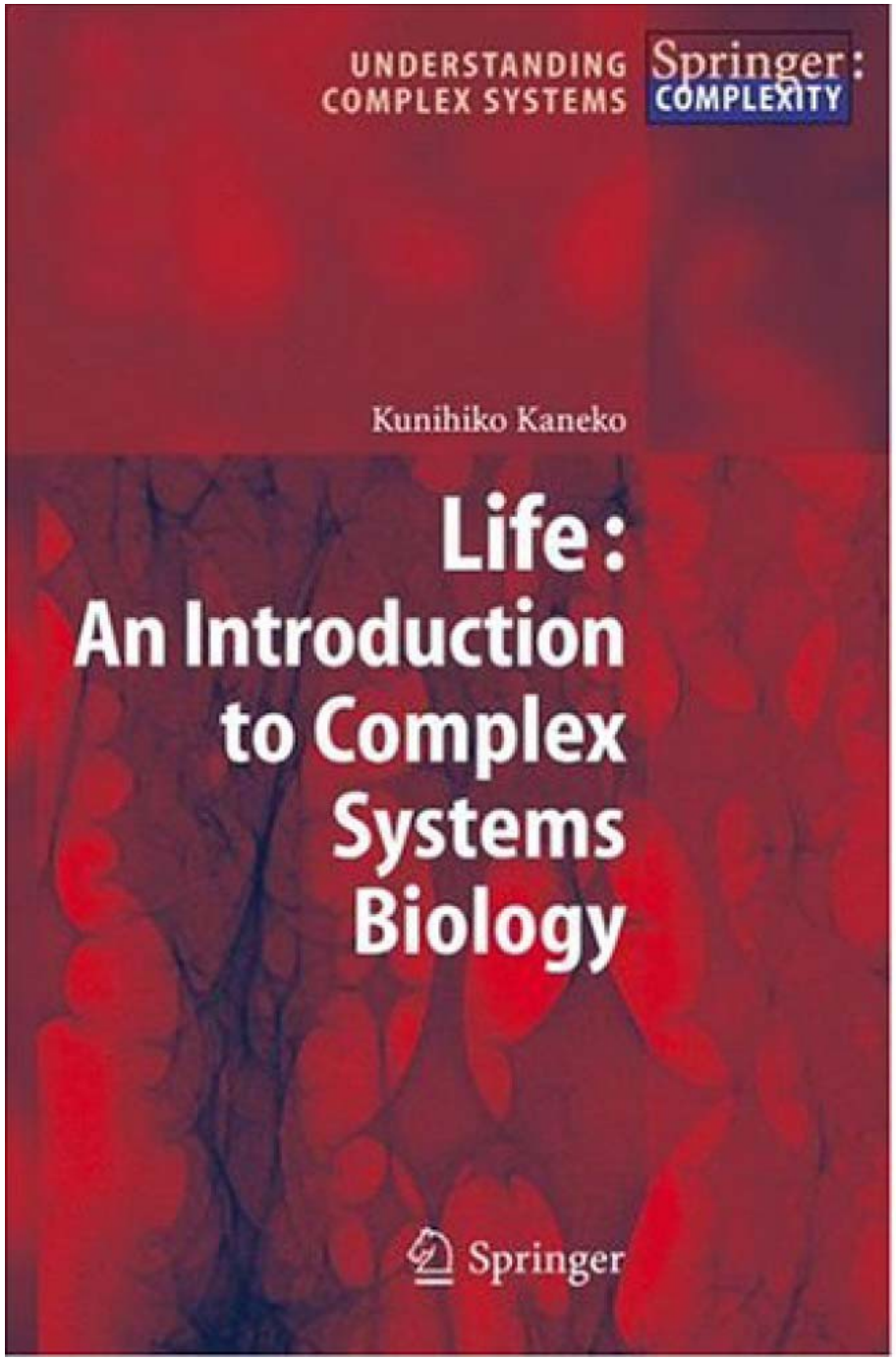


図 14: カオス的遍歴の模式

In such case, dynamics called ‘Chaotic Itinerancy’ is often observed

Cf Itinerant dynamics of cellular state reported recently By Sui Huang’s group (Nature 2008)



(2006,August)

Collaborators

Chikara Furusawa

experiment

Tetsuya Yomo

Akiko Kashiwagi

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

ERATO Complex Systems Biology Project