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Bridging the Gap between Chemical Reaction Dynamics and Cell Biology

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Bridging the gap between chemical reaction dynamics and cell biology

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	Robust adaptation without signalling
○ evolution	Relevance of phenotypic fluctuation and dynamics	Genetic assimilation of phenotype fluct.and dynamics	geno-pheno type relationship

- Problem

＊1 assumed nonequilibrium reaction process. But,
how can a state out of equilibrium be sustained？.

*2 Universal Log-normal distribution: But,
do all chemicals have such large fluctuations?
Important ones are protected??
Origin of heredity (genetic information)
why is there genotype and phenotype?
in terms of dynamical systems
gene: control parameter, phenotype: variable
→Origin of heredity, genetic information？Evolvability

*3 Multicellularity:
irreversible cell differentiation and development
through cell-cell interaction

Levels of Reaction Network Models

*(0) including all reversible reactions, to check the consistency with thermodynamics

*(1) eliminating some chemical variables & assuming nonequilibrium

Xi+Xj → Xm+Xj (resource→product)

*(2) assuming replicating units

(e.g.. Hypercycle by Eigen&Shcuster)

Xi+Xj → 2Xi+Xj

*(3) more specific models with gene expression,

----

rate-eq.: Continuous (Langevin) description?

Number discreteness? Crowdedness?

Internal dynamics of molecules

- Q1: Reluctance to relaxation to equilibrium??

Macroscopic : Biological system is not in thermal eqb. →'Dissipative Structure(e.g.Turing pattern)

- How is non-equilibrium condition sustained?; reluctant relaxation to equilibrium?
- Cf seed –closed but not approaching eqb.

A first step study;

- reverse question; is non-eqb condition sustained longer once transient dissipative structure is formed? Yes. (A. Awazu & KK,PRL2004)

Example Reaction I) $A + v + 2u \rightleftharpoons^{k_{AB}}_{k_{BA}} B + 3u$, II) $u \rightleftharpoons v$, III) $A + u \rightleftharpoons A + v$, and also diffusion.

A simple chemical reaction model to realize the Turing instability:

Model equations

$$\dot{U} = AU^2V - kBU^3 - (1+A)(U-V) \qquad (k << 1)$$

$$\dot{V} = -AU^2V + kBU^3 + (1+A)(U-V) + D_V\nabla^2 V$$

$$\dot{A} = -AU^2V + kBU^3 + D_A\nabla^2 A$$

$$\dot{B} = AU^2V - kBU^3 + D_B\nabla^2 B$$

(Space :1D space, periodic boundary condition.)

$$S = \frac{1}{2L}\int (U+V)dx$$ is conserved due to the system being closed

In initial：Resource **A**: large → reaction of **U** and **V** by consuming **A**

Time → ∞: a unique equilibrium state with A=kB、U=V=S is realized

If A is set high constant → dissipative structure

The relaxation with consuming A ⇔? The pattern formation of U and V

Space-time evolution of U and A with different initial conditions (S=4)

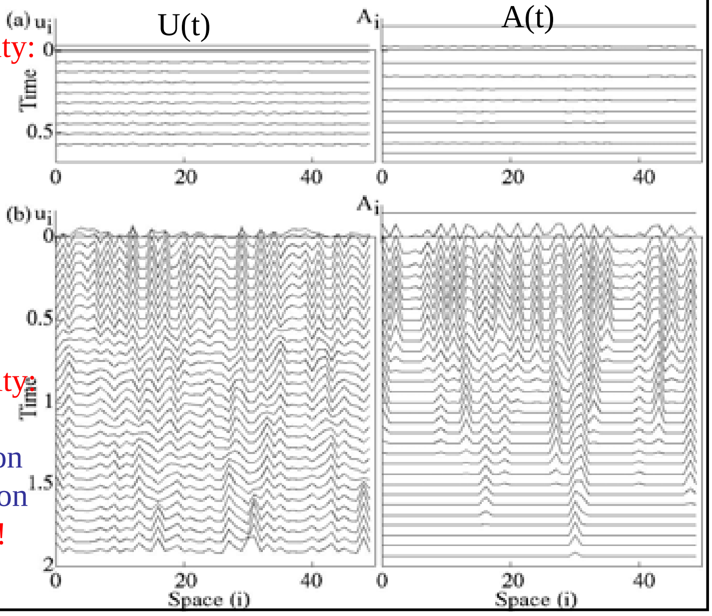
In initial：A=100 V=4、 U: random number in (4−δ)～(4+δ)

Initial inhomegenity: Small (δ=0.1)
→no patterns

Relaxation Fast !

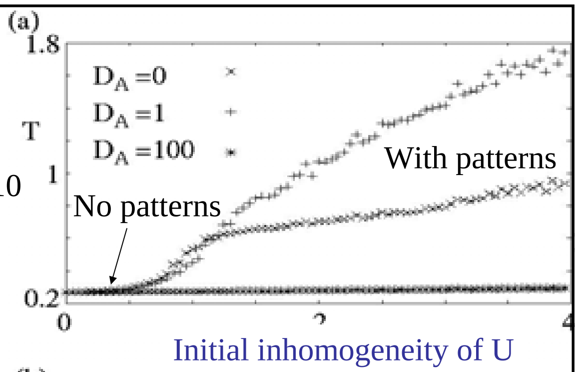
Initial inhomgeneity: Large (δ=4)
→pattern formation
& re-organization

Relaxation Slow !



Dependence of Relaxation Time T on initial inhomogeneity δ

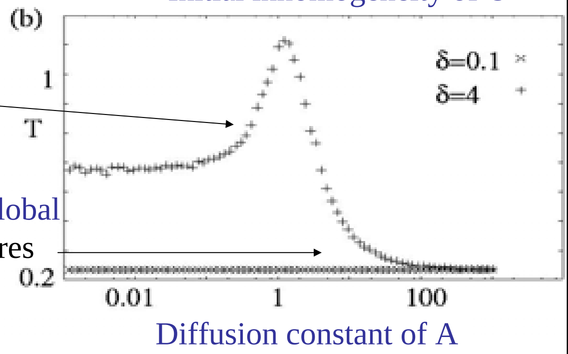
T:Time interval of A=100→10



D_A dependency of T

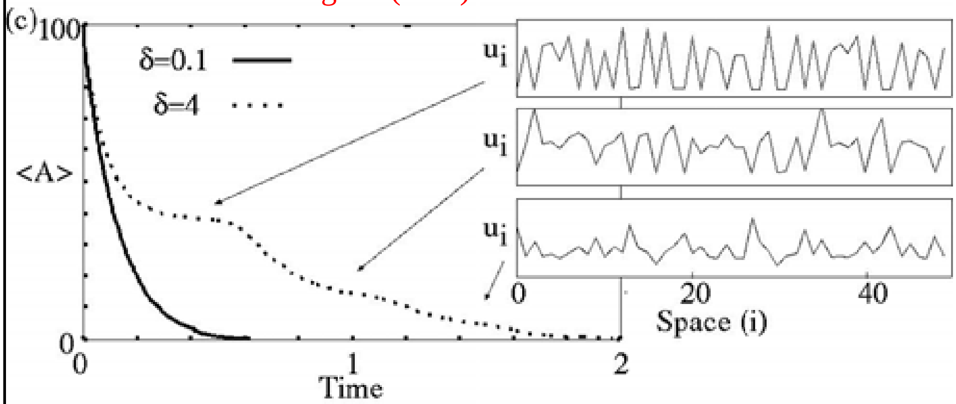
A is consumed locally
→Slow relaxation

Diffusion of A …Large
A consumptions are always global
independent of spatial structures
→Relaxation is fast



Awazu&KK,PRL2004

Time evolution of average A (<A>) ⬄ Pattern formations of U



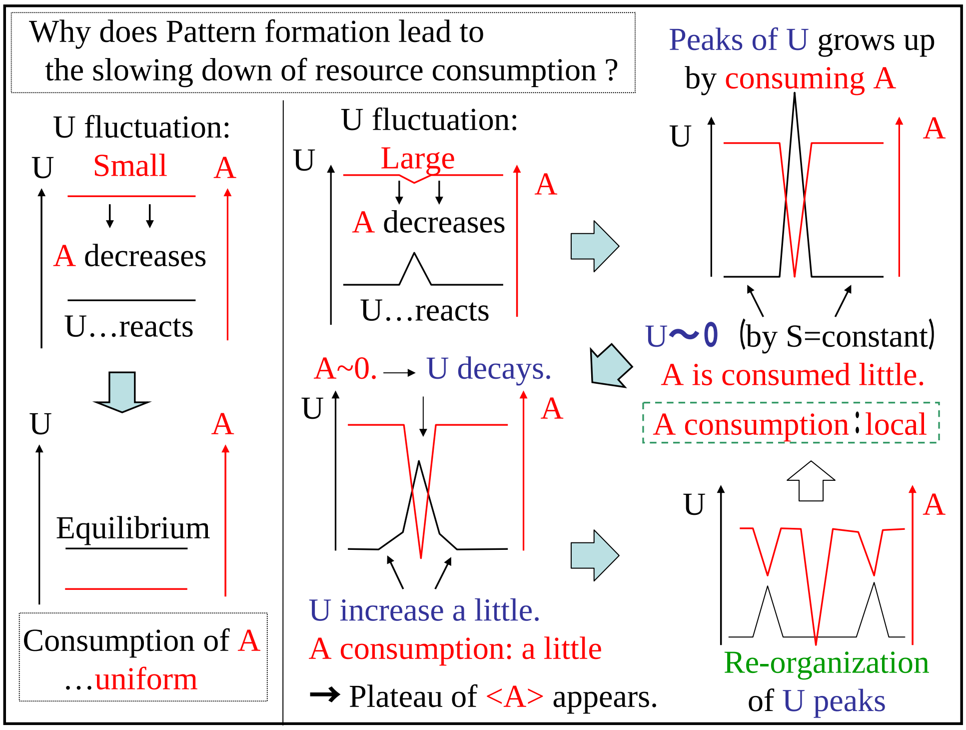
Initial fluctuation

Small： Relaxation… Fast ← A is consumed uniformly.

Large： Relaxation …Slow (with some plateau.).

Pattern formation A is consumed locally → Pattern re-organizations

Non-uniform Structure suppresses consumption of resources → Sustain nonequilibrium condition



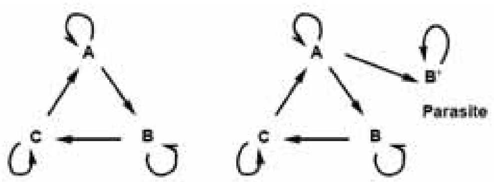
- Q2: Origin of Life:

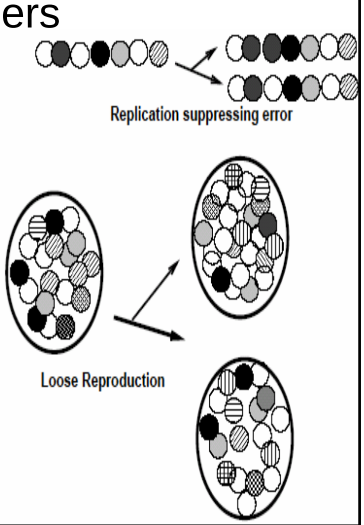
Eigen's error catastrophe

most polymers are not 'good' (as for catalytic activity), then, for long polymers

'bad' mutants dominate

Eigen-Schuster Hypercylce





Dyson's loose reproduction

then Genetic-takeover?

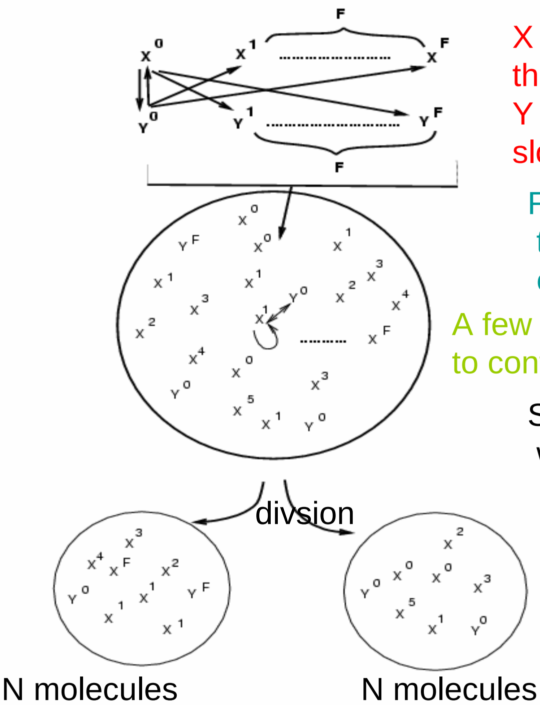
- Q2’: if … then,…---type ‘’switching-like behavior’’ from reaction dynamics??

  * some molecules in a cell are regarded as ‘’important’’, and control the behavior of cell

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

one hypothesis (KK & Yomo, JtheorBiol2002)

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



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 concentration < 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

$$X^J + Y^A \to 2X^J + Y^A \quad (\text{for } J = A \text{ or } I)$$

Continuum Limit

and

$$Y^J + X^A \to 2Y^J + X^A \quad (\text{for } J = A \text{ or } I).$$

$$X^I \to X^A \quad \text{and} \quad Y^I \to Y^A \quad (\text{with rate } \mu),$$

$$X^A \to X^I \quad \text{and} \quad Y^A \to Y^I \quad (\text{with rate } \mu F),$$

Expected from rate equation

$$dN_x^J/dt = \gamma_x N_x^J N_y^A, \quad dN_y^J/dt = \gamma_y N_y^J N_x^A. \quad (1)$$

From these equations, under repeated divisions, it is expected that the relations $N_x^A/N_y^A = \gamma_x/\gamma_y$, $N_x^A/N_x^I = 1/F$, and $N_y^A/N_y^I = 1/F$ are eventually satisfied. Indeed, even with our stochastic simulation, this number distribution is approached as N is increased.

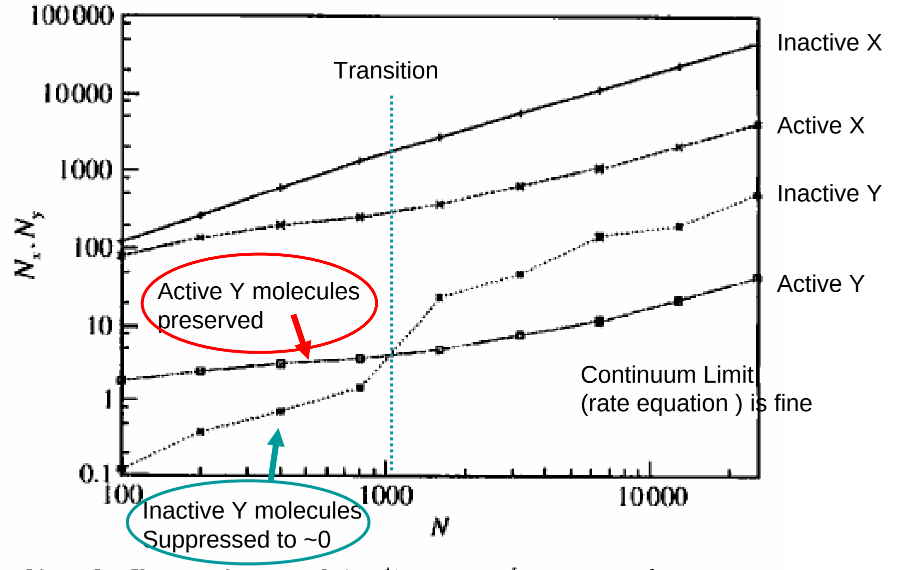
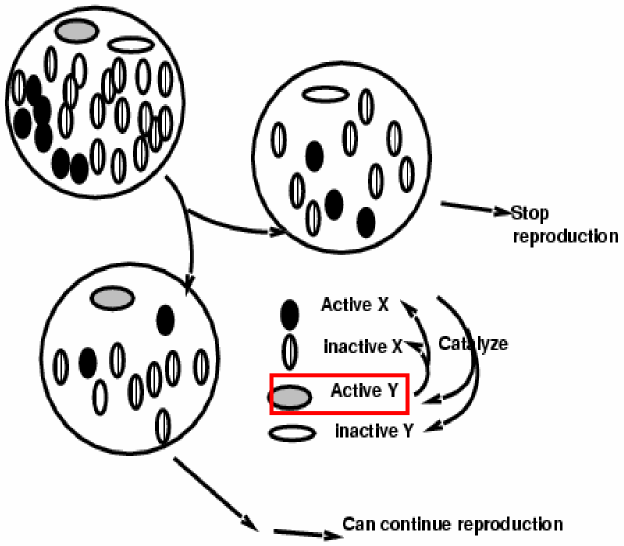


FIG. 2. Dependence of $\langle N_x^A \rangle$ (×), $\langle N_x^I \rangle$ (+), $\langle N_y^A \rangle$ (□), and $\langle N_y^I \rangle$ (·) on N. The parameters were fixed as $\gamma_x = 1$, $\gamma_y = 0.01$, and $\mu = 0.05$. The averages of N_x^A, N_x^I, N_y^A, and N_y^I at the division event are plotted, and thus their sum is $2N$. In all



$\langle N_y^A \rangle \approx 2 - 10,$

$\langle N_y^I \rangle \approx 0.$

Cf; importance of compartment; noted by Hogeweg, Eigen, Szathmary, McCaskill,,,

Here, the issue is minority

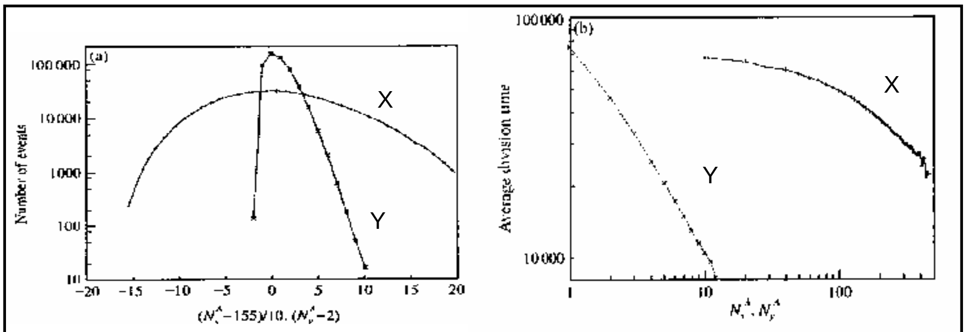


FIG. 6. (a) Histograms of the number of division events with given N_x (·) and with given N_y (·), plotted vs. $(N_x^A - 155)/10$ and $N_y^A - 2$, respectively. The histogram representing the averages for N_x was computed with a bin size of 10 as discussed in the text. These histograms were found with a sampling of divisions occurring between the 6×10^5 and 10^6 time steps. (b) Average number of time steps $\bar{T}_d$ required for the division of protocells for given N_x (·) and

Even after Normalizaed by $\sqrt{}$N
Y 's variance is suppressed

Growth-speed versus the number of Y or X,
Drastically influenced by Y

Essence of the mechanism;

1) discreteness in the molecule number 0,1,..
2) Preservation of rare states realized by fluctuations
3) Selection of such states according to growth condition
4) Suppression of Fluctuation, Minority control

NB: importance of compartment is pre-assumed

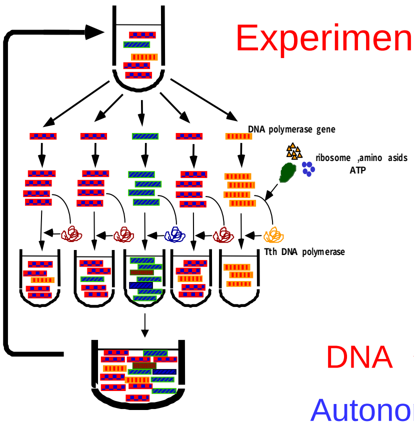
Novel 'attractor'
under discreteness + evolution (selection)

Cf. dynamilcal systems without selection by growth

discreteness-induced novel state (not represented by rate equation+ noise) is found and formulated (Togashi & KK 2001PRL,PRE2004,PhysicaD 2005)

Importance of Minority molecules for replication to continue is confirmed experimentally.

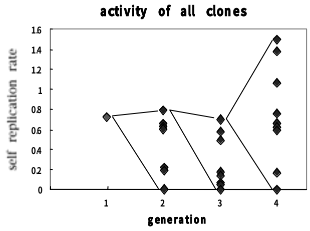
Experimental verification

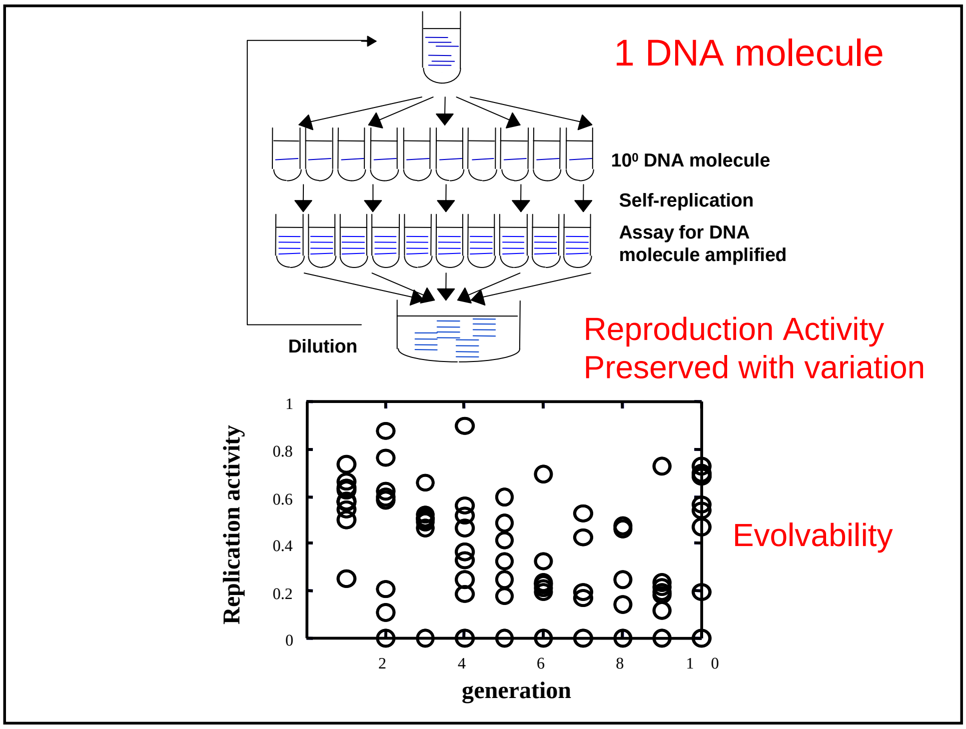


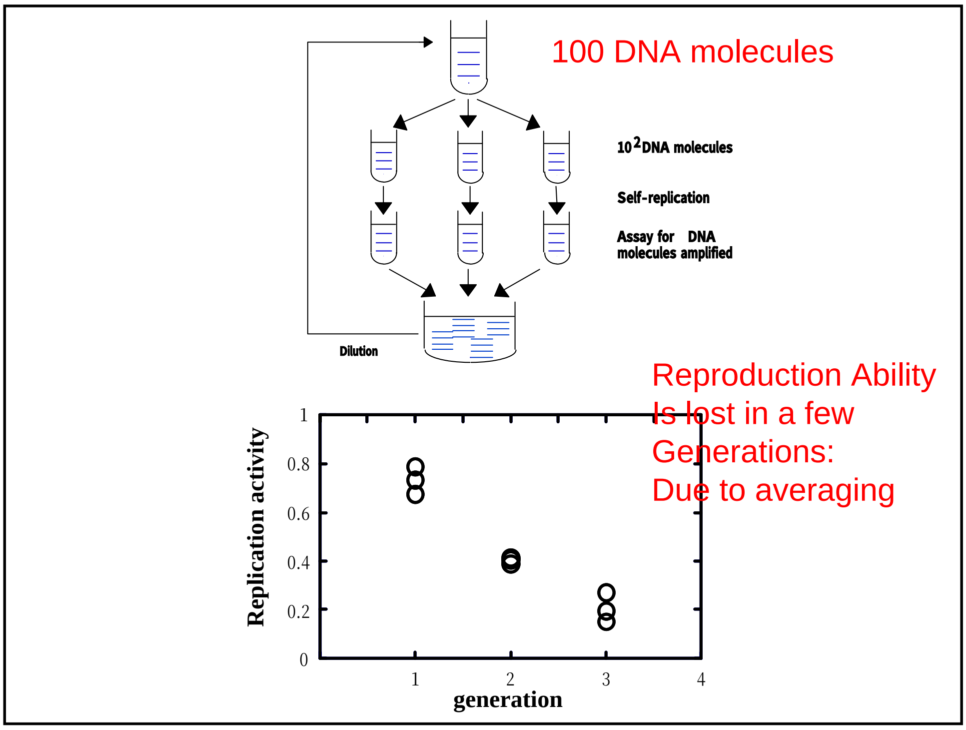
DNA ←→ enzyme

Autonomous Replicating System (self-contained, In contrast to PCR)

Matsuura, Yomo.,… PNAS 2002




1 DNA molecule
10⁰ DNA molecule
Self-replication
Assay for DNA molecule amplified
Dilution
Reproduction Activity Preserved with variation
Evolvability
Replication activity
generation


100 DNA molecules
10²DNA molecules
Self-replication
Assay for DNA molecules amplified
Dilution
Reproduction Ability Is lost in a few Generations: Due to averaging
Replication activity
generation

- Dominance of bad mutants (parasites) are get rid of compartment and minority:

- A hypothesis based on Minority Control

minority (preservation+ control) →

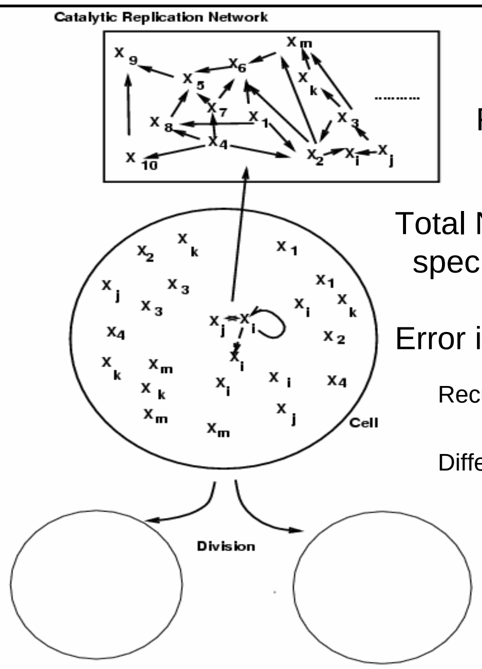
evolution of machinery of faithful transmission of minority molecule.

more chemicals are synthesized with it

package life-critical info. Into minority molecule.

→ Genetic Takeover?

Network?



Random net
path rate p

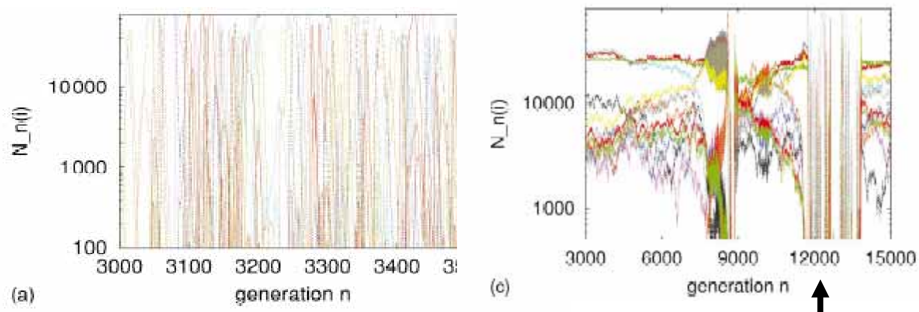
Total No of molecules N
species k

Error in replication rate μ

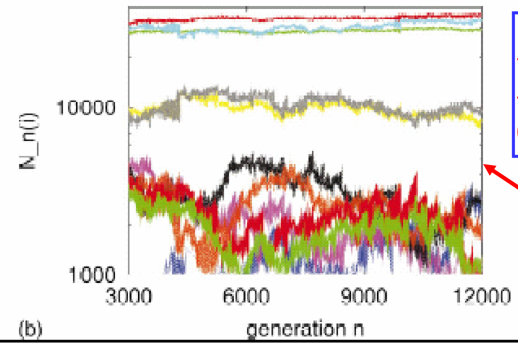
Recursive production?

Differentiation?

Chemical composition changes by generations:



Switching over recursive States is commonly observed (switch by minority molecule)



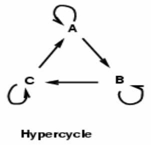
Low connection, and Sufficient # of molecule numbers -→ Recursive State

- Recursive Production for a range in (N,k,path)

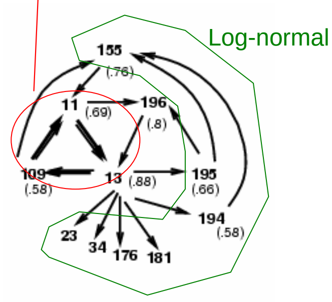
Stability by intermingled hypercycle network against parasites ← parallel paths, relatively stable dynamics

- suppression of fluctuations
- Fluctuations; Components in a small autocatalytic loop (hypercycle) deviate to 'Gaussian'; deviation possible either by small feedback loop or parallel paths (i.e., addition instead of multiplication!)

(KK,PRE 2003)



Hypercycle



*Within the core, (relatively) minority molecules control the behavior of the cell: Many other molecules are connected with this minority molecule:

This formation of hypercycle network follows the ‘’package scenario’’

*Switching over recursive states

switching to other states occur by the extinction of this minority molecule: → controller

* Number fluctuation of this minority molecule is suppressed

Log-normal distribution for catalyzed molecules cf. ubiquity in cascade network, experiment

So far, single cell property

as cells replicate, they should interact.

Multicellularity?

Including simple cell-cell interaction (by diffusion of chemicals) into intra-cellular reaction dynamics

Instability of homogeneous states →

(irreversible) cell differentiation from stem cell,

robust development, pattern formation

(KK,Yomo,Furusawa, 1997-)

← study of coupled dynamical systems

Question on Development and Differentiation

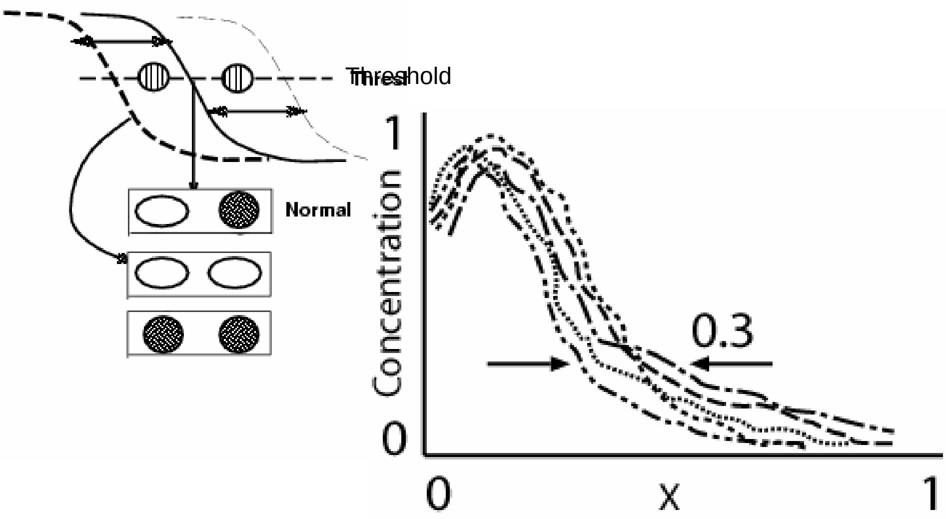
***Robustness in development under large fluctuation**

(signal) molecules of few number -- relevant;
Still robust process (e.g., development)

threshold mechanism only cannot explain?

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

irreversible in normal development in general
how to characterize?
(need some operation to reverse; e.g., somatic clone)



Evidence of fluctuations in Drosophillla egg
(Leibler's group, Nature)

Isologous Diversification:
KK,Yomo; PhysicaD94,BMB97,JtB99
internal dynamics and interaction :
development phenotype

instability
distinct phenotypes
interaction-induced

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

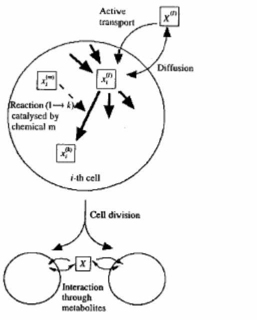


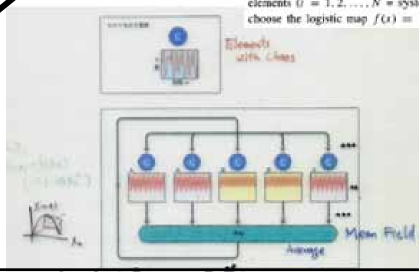
FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

Ex: chemical reaction network
specialize in the use
of some path

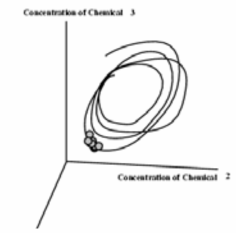
$$x_{n+1}(i) = (1-\epsilon) f(x_n(i)) + \frac{\epsilon}{N}\sum_{j=1}^{N} f(x_n(j)), \quad (1)$$

where n is a discrete time step and i is the index for elements ($i = 1, 2, \ldots, N$ = system size). Here we choose the logistic map $f(x) = 1 - ax^2$ as the lo-

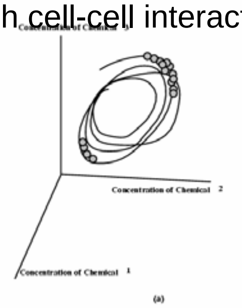
Study of coupled dynamical systems (globally coupled map) etc., (KK89,90--)→ differentiation??

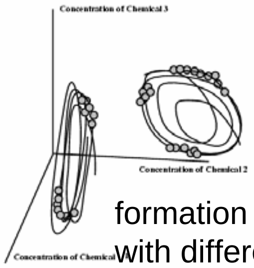


synchronous division:
no differentiation



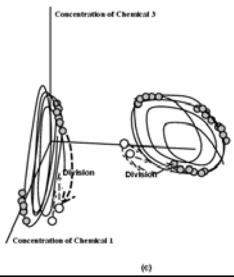
Instability of homogeneous state through cell-cell interaction





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

recursive production



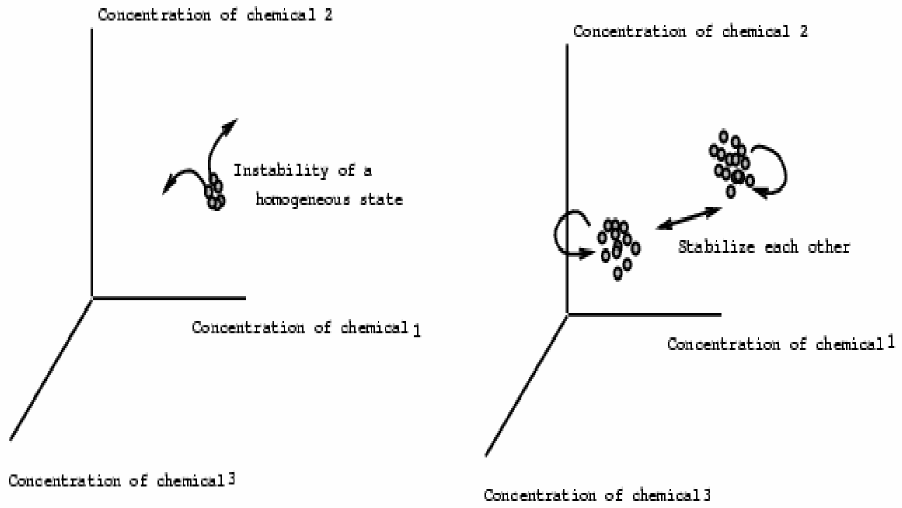
- (1) Synchronous oscillations of identical units
  Up to some threshold number of units,

- (2) Differentiation of the phases of oscillations of internal states. When the number of units exceeds the threshold, they lose identical and coherent dynamics. Still, averaged behaviors over periods are essentially the same. Only the phase of oscillations differs.

- (3) Differentiation of the amplitudes of internal states. States (e.g., composition of chemicals, cycles of oscillations, etc) are differentiated.

- (4) Transfer of the differentiated state to the offspring by reproduction. fixed differentiation

→With the increase of the number



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

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))

(confirmed by stochastic models)

(2) against macroscopic damage;

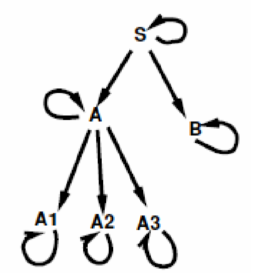
i.e., type A and type B, determined

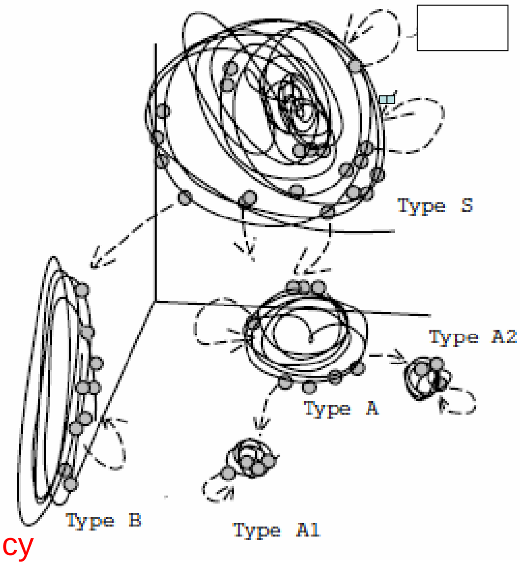
but if type A is eliminated, then B de-differentiates

and initial A-B cell ensemble is recovered

(since A,B is stabilized each other)

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

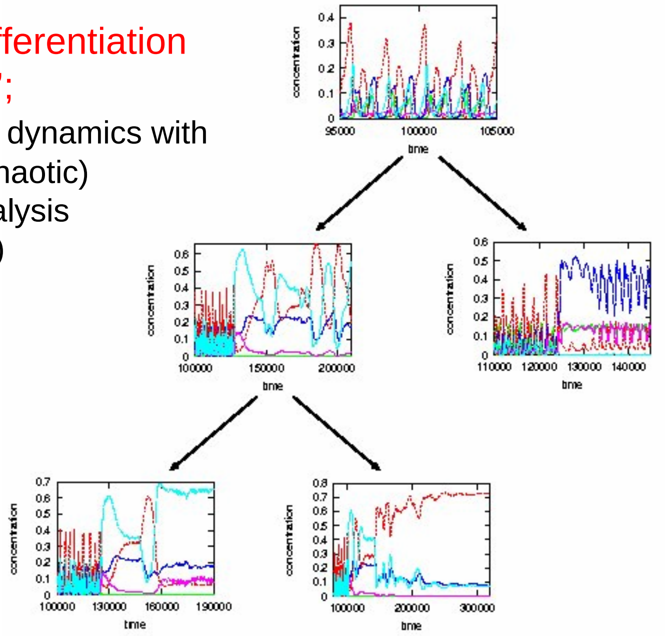




Irreversible loss of omnipotency characterized by the decrease in chemical diversity and phenotype variation

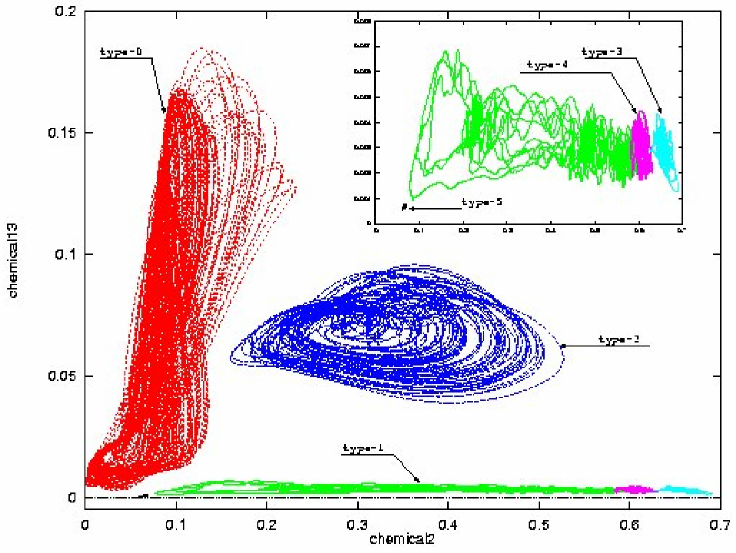
Hierarchical differentiation from ‘stem cell’;

by taking initially dynamics with instability (e.g., chaotic) (higher order catalysis or gene-network)

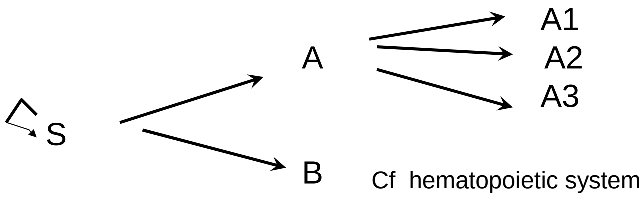


Furusawa & KK

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



Generated Rule of Differentiation (example)

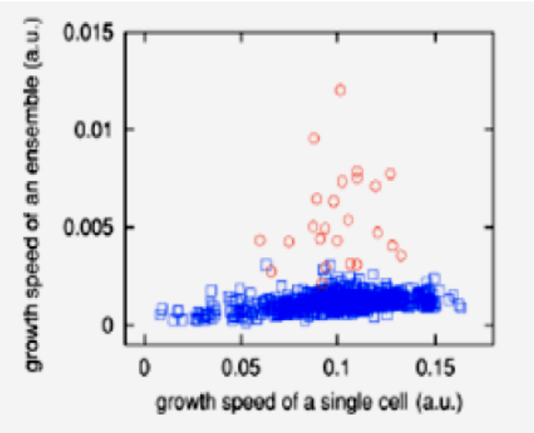


(1)hierarchical differentiation: stem cell system
(2) Stochastic Branching:
stochastic model proposed in hematopoietic system
(3) probability depends on # distrib. of cell types
with prob. *pA* for *S* → *A*
if #(A) ↘ then *pA* ↗
—— global info. is embedded into internal cell states
→STABILITY

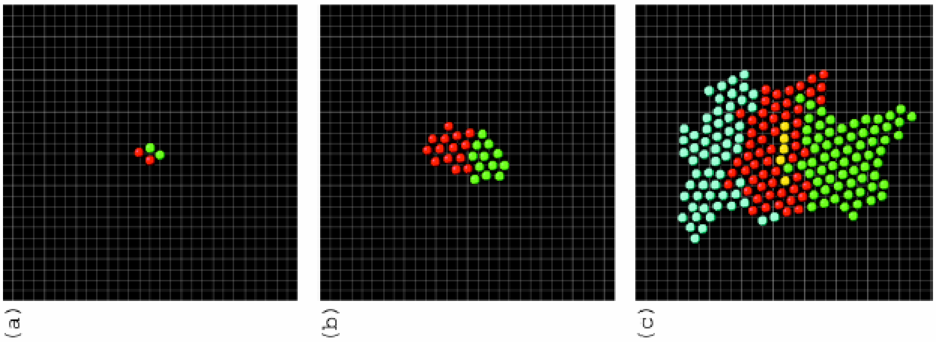
Stem cell dynamics are marginally stable attractors
(Milnor attractors)

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



Chemical Gradient for Positional Information is generated

cell differentiation ←→ graidient for pattern

図9. 5

Consolidation to Patterns

Explained:

Robustness in development under large fluctuation in molecule numbers

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

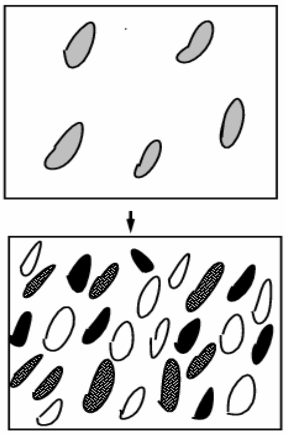
Loss of potency from totipotent cell (ES), to multipotent stem cell, and to determination

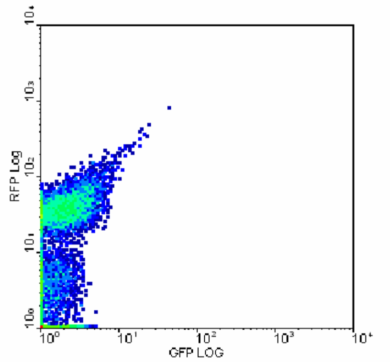
Irreversibility in cell differentiation process characterized by the loss of phenotypic variation

+stochasticity;; use of threshold dynamics (gene-net) OK

Present multicellular organism (eg., Drosophilla, fruit-fly) highly controlled by genes (Dynamics vs gene control)

ALSO; construction of ‘multicellular organism by E coli with embedded gene network is in progress





Measurement by fluoresecent proteins

Character of bacteria differentiate in a crowded condition

Summary

- Pattern can suppress the relaxation process to equilibrium; (further by discreteness, crowdedness) → general tendency? (even in biomolecules?)
- minority control mechanism → origin of genetic information

separation of slow control part→ gene=parameter

suppression of fluctuation : deviation from Log-normal

- Cell differentiation and robust development

as a result of phenotypic differentiation due to instability of homogeneous states and cell-cell interaction

- →Theory of speciation (diversity) (KK,Yomo2000.KK2002)

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A.Awazu(relaxation) Chikara Furusawa (development)

What is Life?
a complex systems approach
Springer 2006?

K. Kaneko, (translation, in progress….)