Complex Systems Biology

Life as Complicated System:

Enumeration of molecules, processes

detailed numerical models mimicking the life process

But understanding??

Life as Complex System:

Understand General features :

robustness in development

irreversibility in differentiation

origin of heredity, ...

➔General Answer as a System Level?

Strategy:

1) Search for universal features in cellular processes :
extension of Dynamical Systems Theory

2) Constructive Approach: (Exp & Theory)

` construct simple system to catch universal features'

`not to imitate'

Constructive Biology Project at Komaba Clife group

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 differ. development	differentiation of E Coil by interaction	emergence of differentiation rule from dynamics	irreversibility robustness
morphogenesis	controlled construction of tissues	self-consistency between pattern and dynamics	origin of positional Information
evolution	phenotypic diff. by interaction	symbiotic speciation	geno-pheno type Relationship

experiment: Yomo; Asashima; Sugawara; Yasuda,..

- 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,…

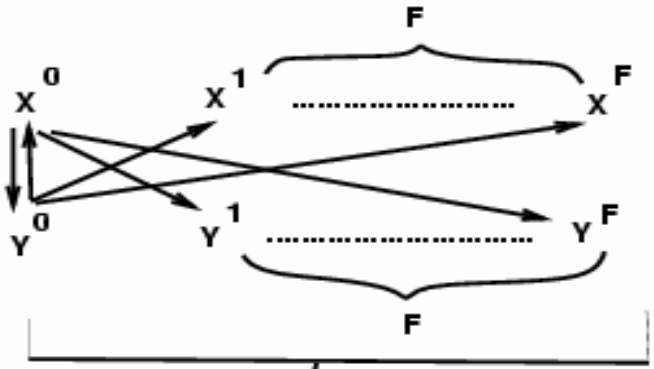
one hypothesis (KK & Yomo, 2002)

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

tochastic
mulation

Selected are ‘rare’ states with a few Y molucules

divsion

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

Carrier of heredity

N molecules

N molecules

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

and

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

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

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

Expected from rate equation

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

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.

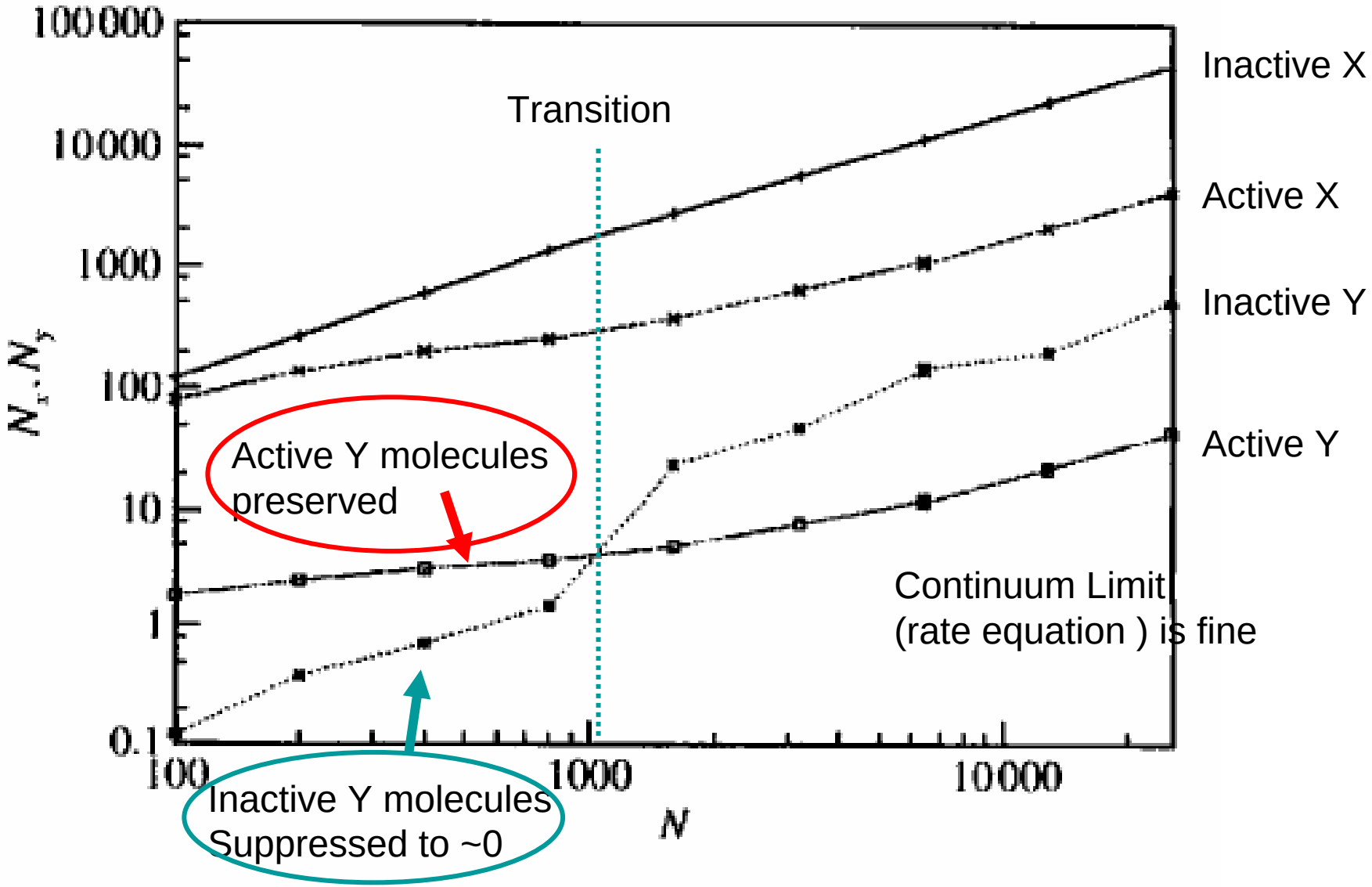


FIG. 2. Dependence of $\langle N_x^A \rangle$ (×), $\langle N_x^I \rangle$ ( ), $\langle N_y^A \rangle$ (□), and $\langle N_y^I \rangle$ (•) on N. The parameters were fixed as $\gamma_x = 1$, $\gamma_y = 0.01$, and $\mu = 0.05$. The averages of N_x^A, N_x^I, N_y^A, and N_y^I at the division event are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

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

Cf. Without selection by growth

As dynamical systems, novel state is realized by discreteness in molecule numbers?

novel --- not expected from continuum description?

(i.e., rate equation + noise (Langevin-type)

i.e., distinct from noise-induced phenomena)

Yes (Togashi & KK 2001PRL, JSPJ 2003)

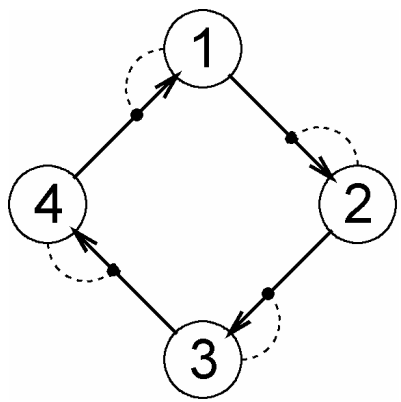
an example: Autocatalytic reaction loop

discreteness-induced symmetry breaking;

4 Chemicals : X_1, X_2, X_3, X_4

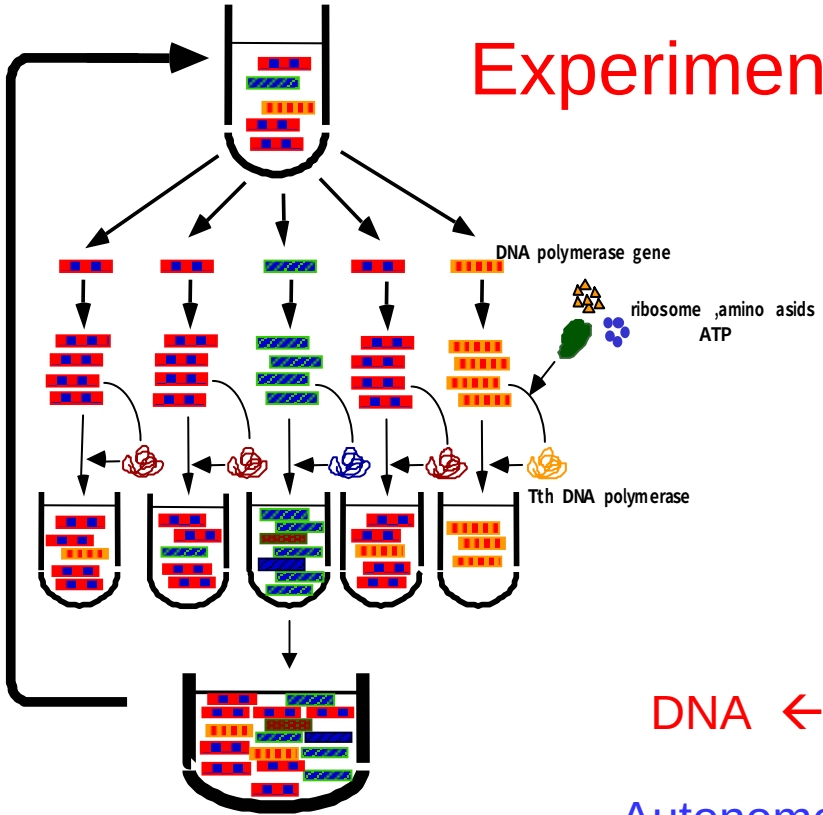
$X_i + X_{i+1} \rightarrow X_{i+1} + X_{i+1}$, $X_5 \equiv X_1$

– Reaction constant r=1 for all reactions.



Experimental verification

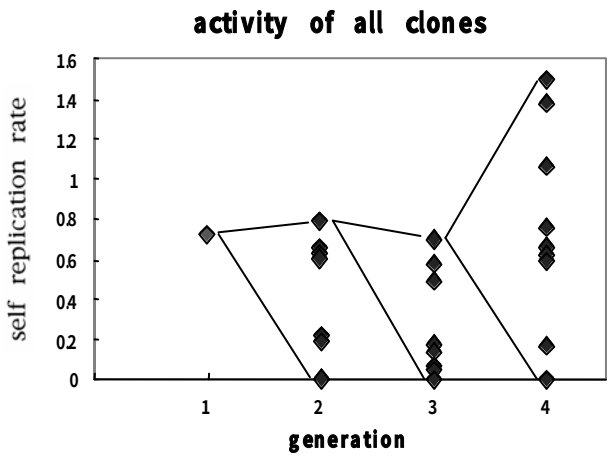
Importance of
Minority molecules
for replication
to continue
is confirmed
experimentally.

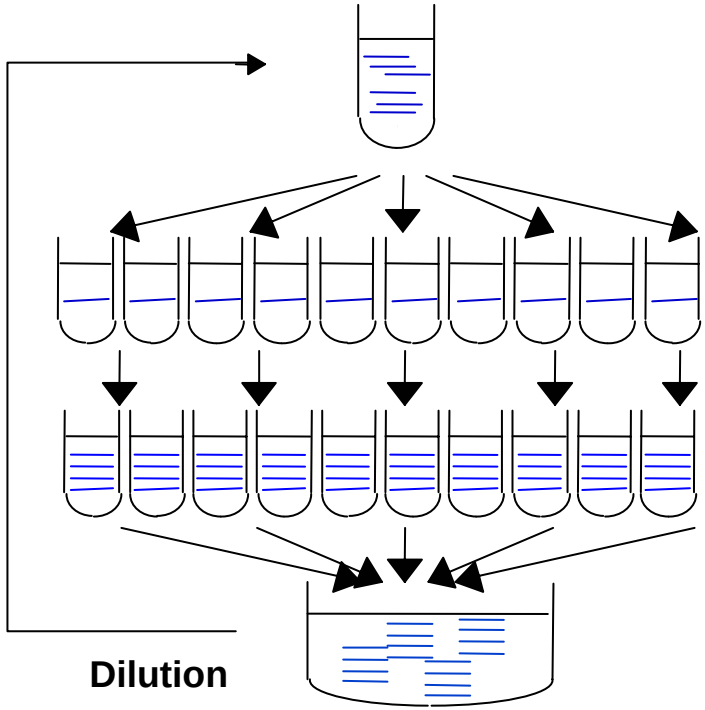


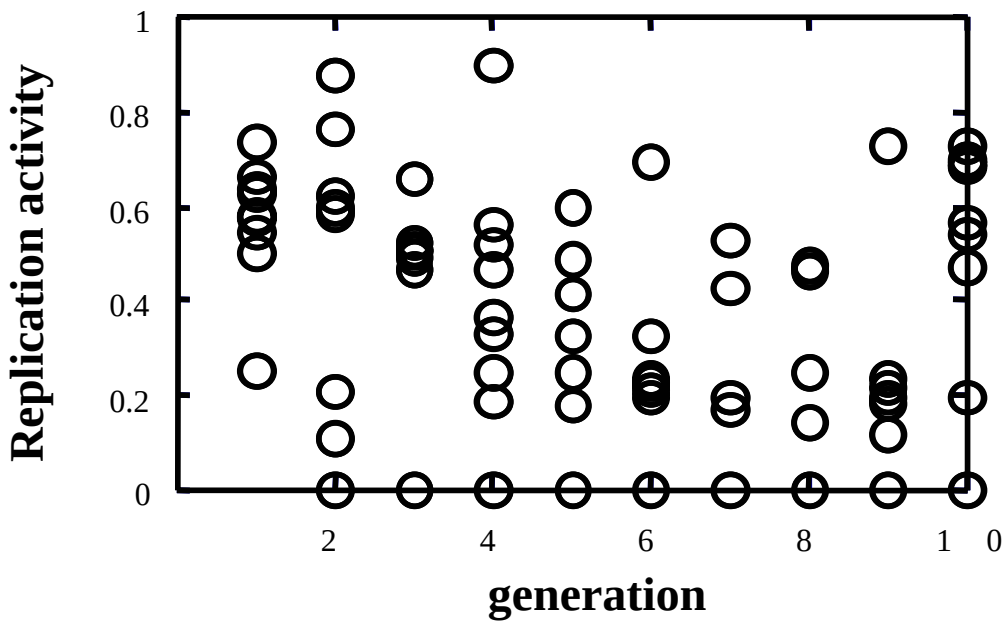
DNA ←→ enzyme

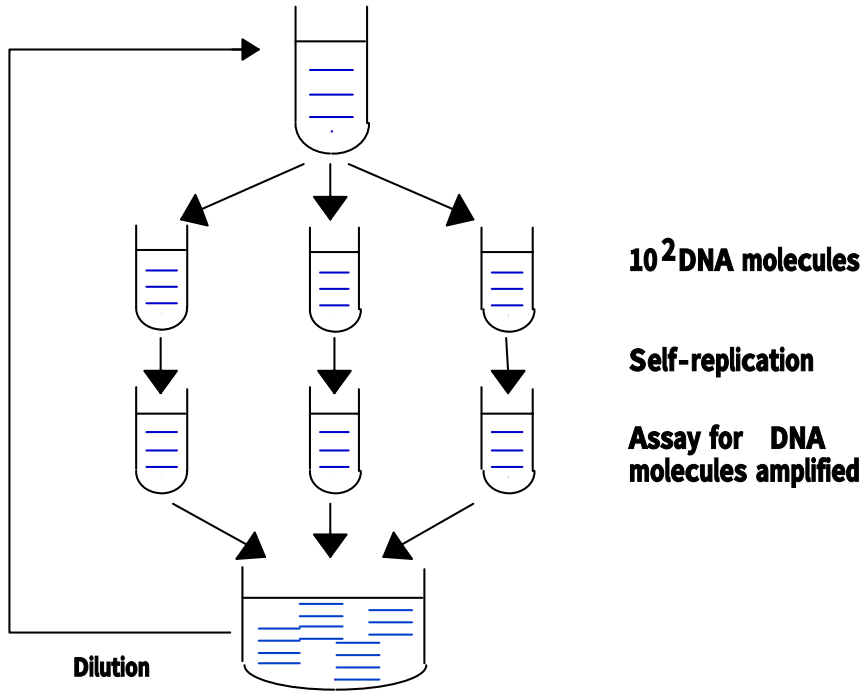
Autonomous Replicating
System (self-contained,
In contrast to PCR)

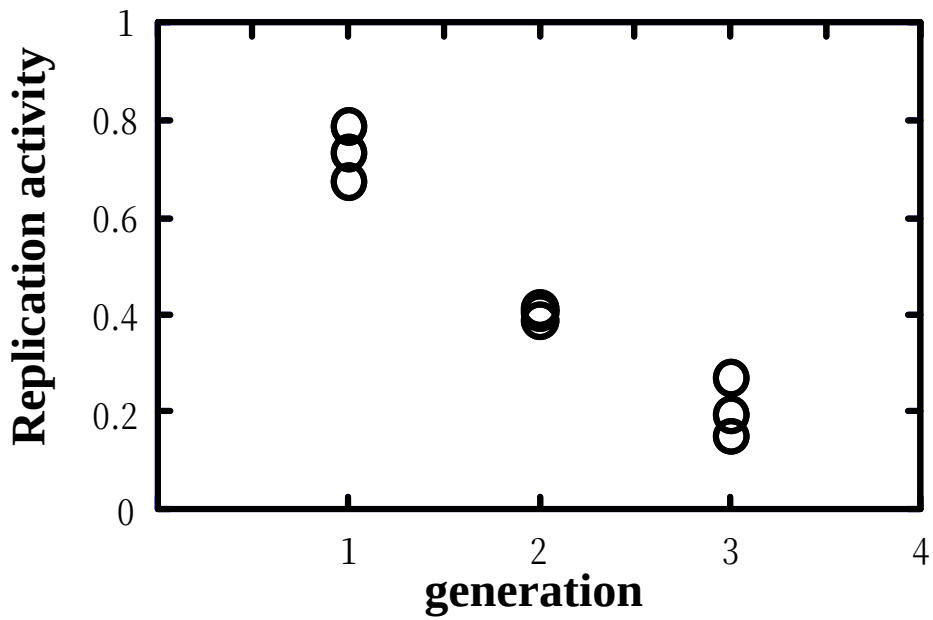
Matsuura,
Yomo.,…
PNAS 2002




10^0 DNA molecule
Self-replication
Assay for DNA molecule amplified
Dilution


Replication activity
1
0.8
0.6
0.4
0.2
0
2
4
6
8
10
generation


10^2DNA molecules
Self-replication
Assay for DNA molecules amplified
Dilution


Replication activity
1
0.8
0.6
0.4
0.2
0
1
2
3
4
generation

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Toy Cell Model with Catalytic Reaction Network

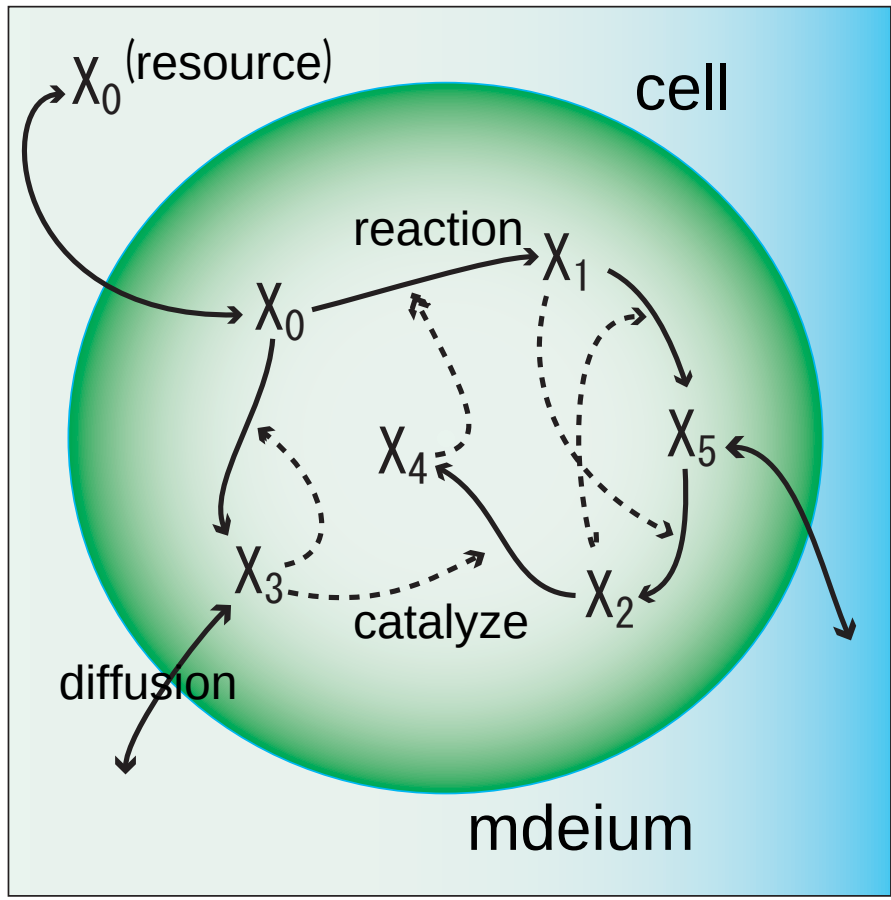
C.Furusawa & KK

- **k species of chemicals、$X_o \cdots X_{k-1}$**
number ---n_0、n_1 … n_{k-1}

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

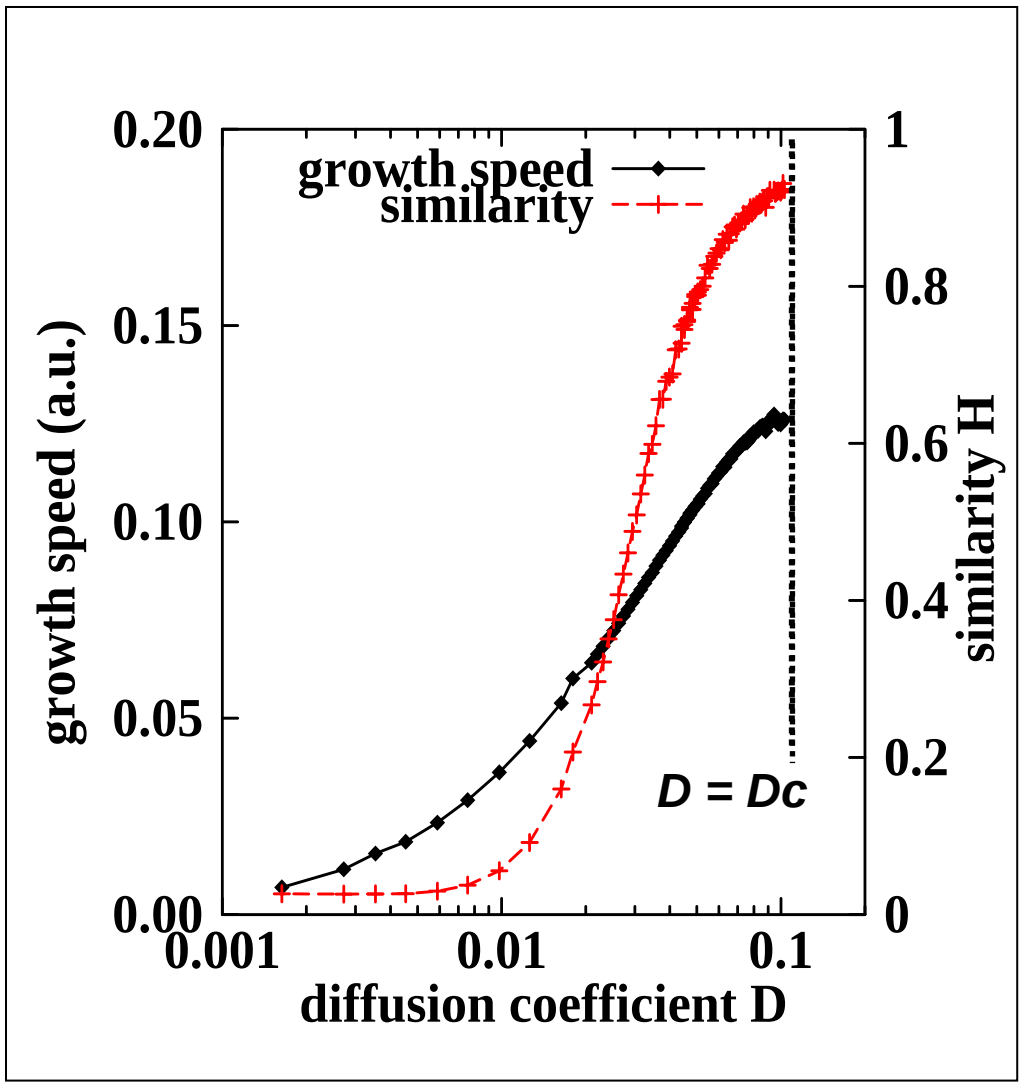
- some chemicals are penetrable
through the membrane with the diffusion coefficient D

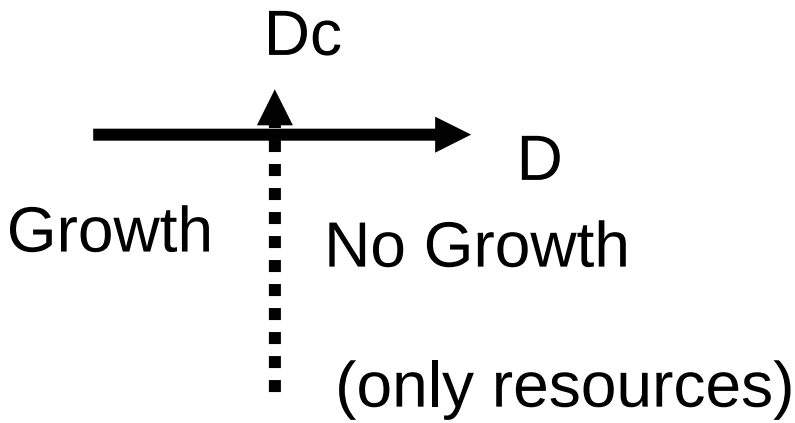
- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth in $N = \Sigma n_i$, when it exceeds N_{max}
the cell divides into two



model

☆Growth speed, and fidelity in replication is Maximum at Dc

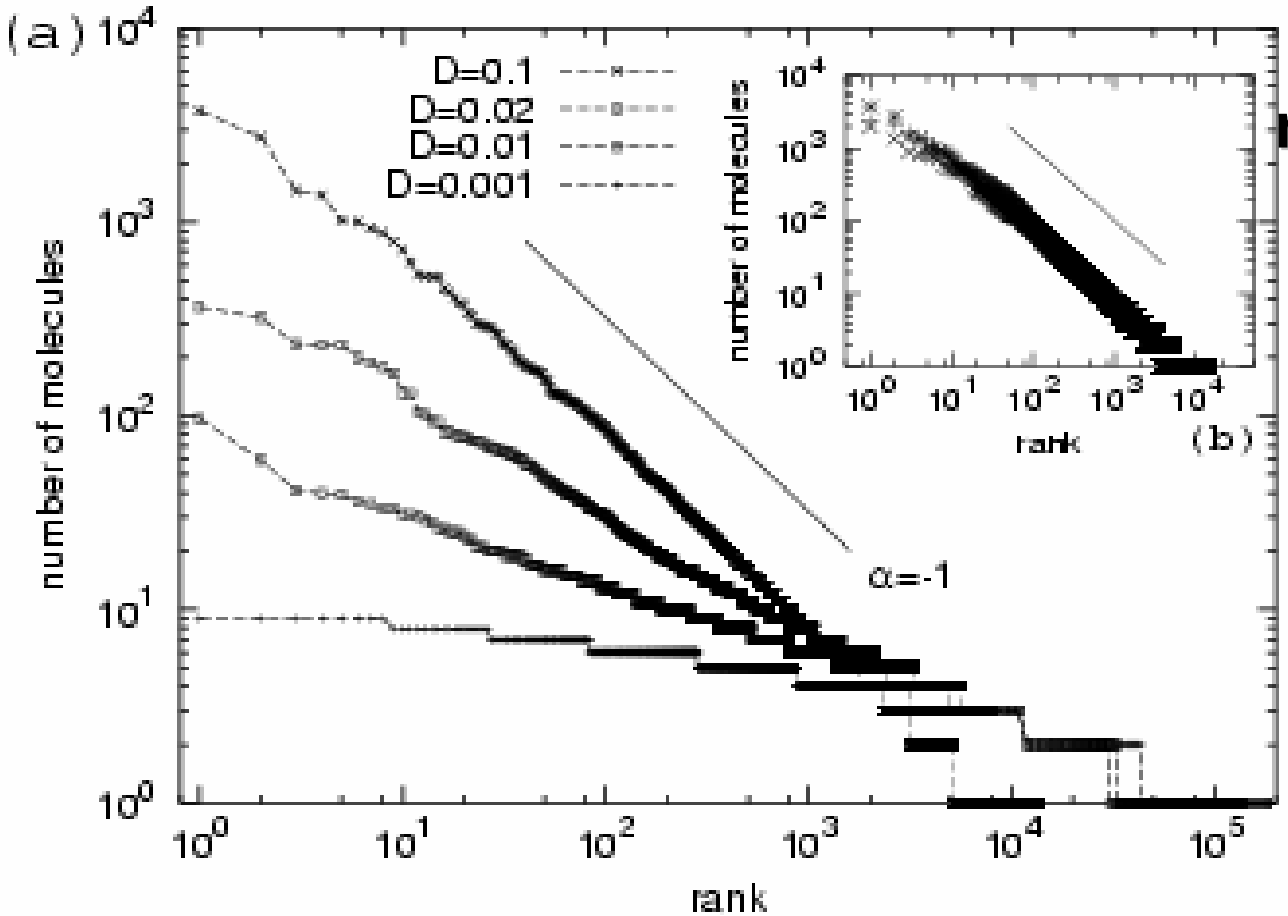


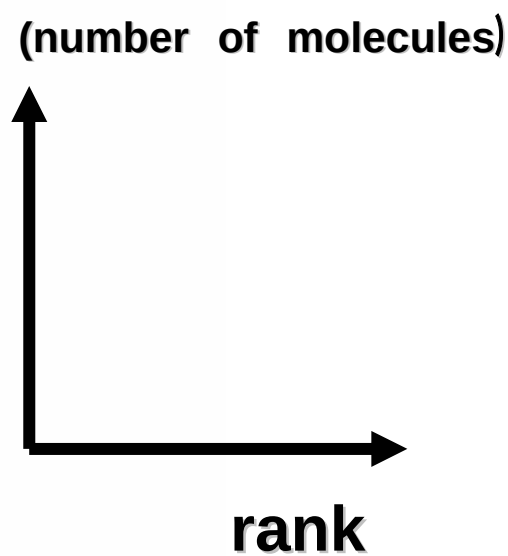


※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

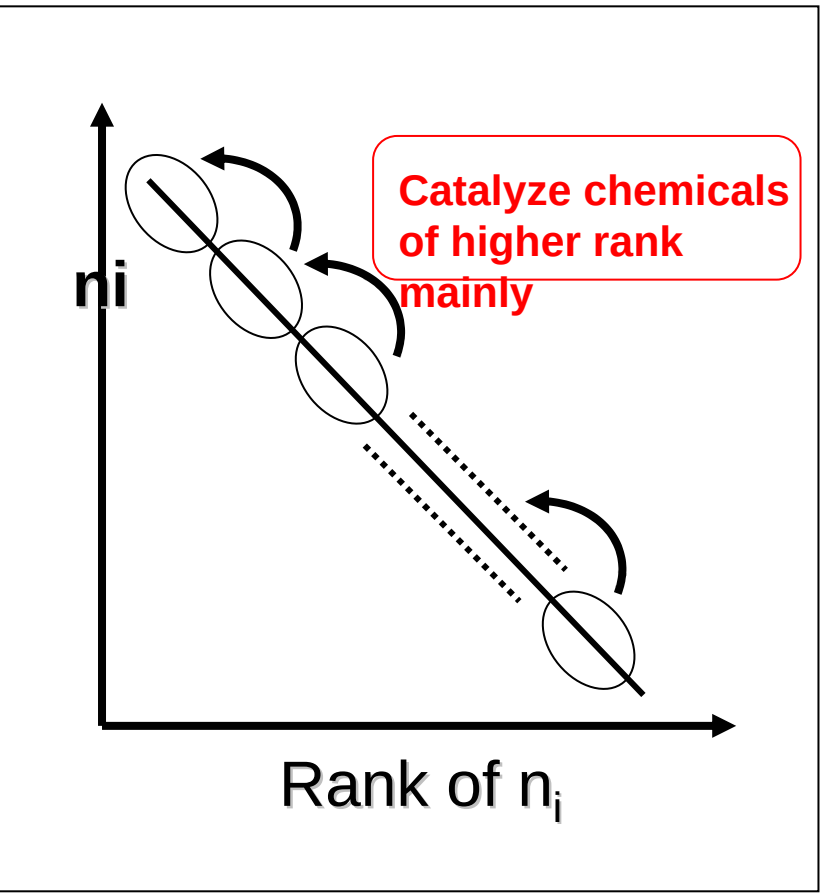
Zipf's Law is oberved at D = Dc

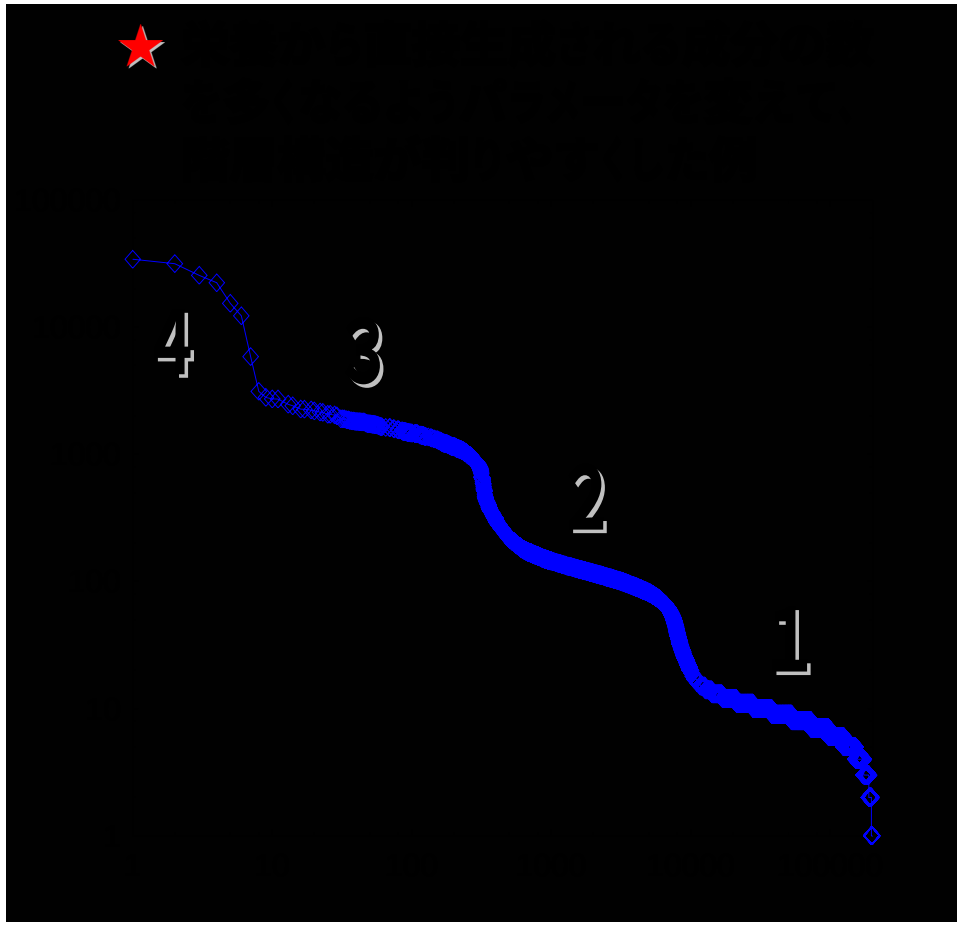




Average number of each chemical ∝ 1/(its rank)

Formation of cascade catalytic reaction



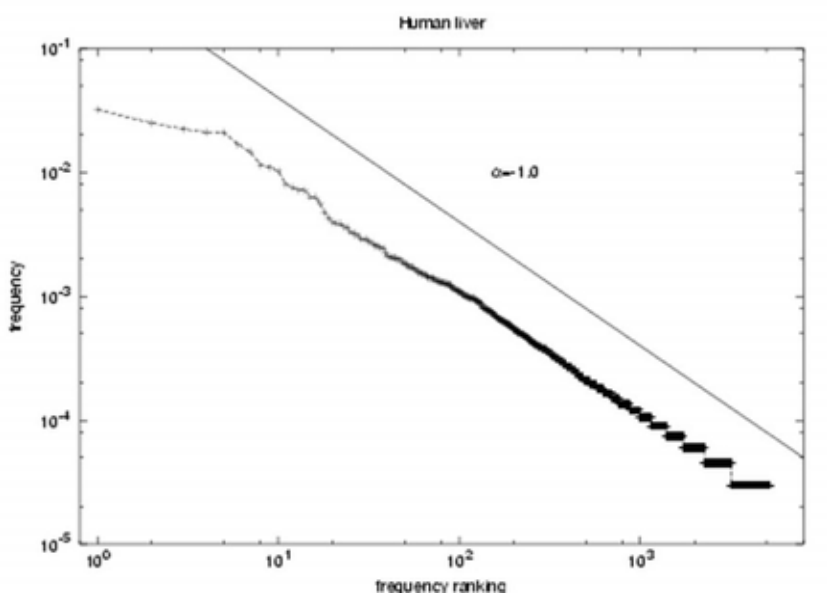


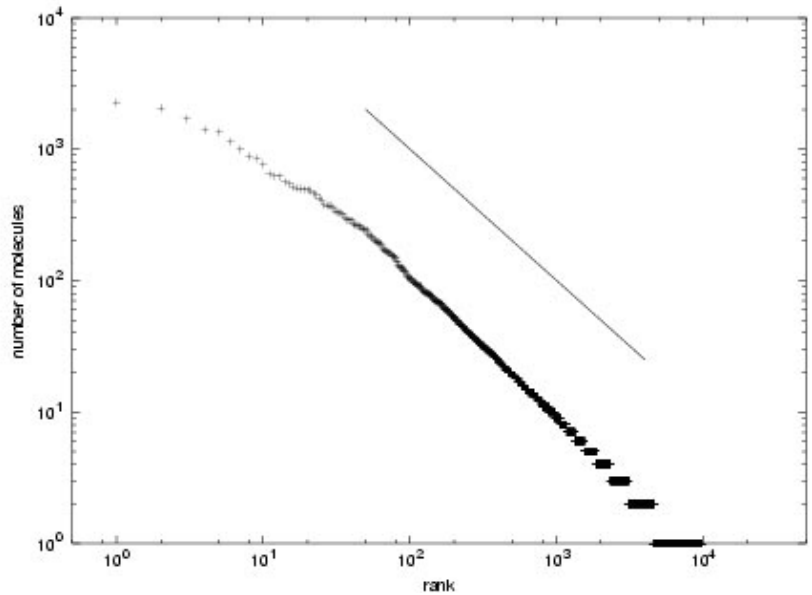
1：minority molecules

2：catalyzed by 1, synthesized by resource

3：catalyzed by 2

：

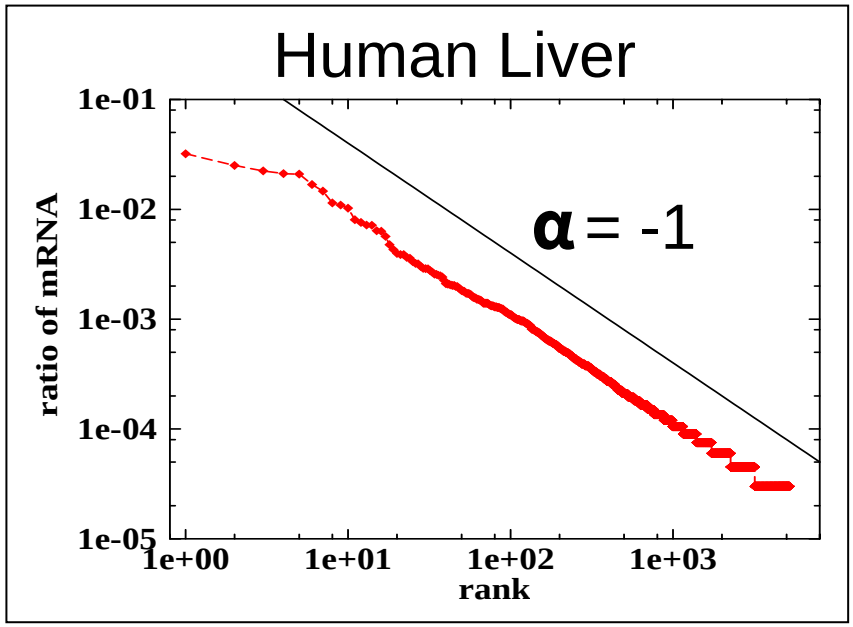


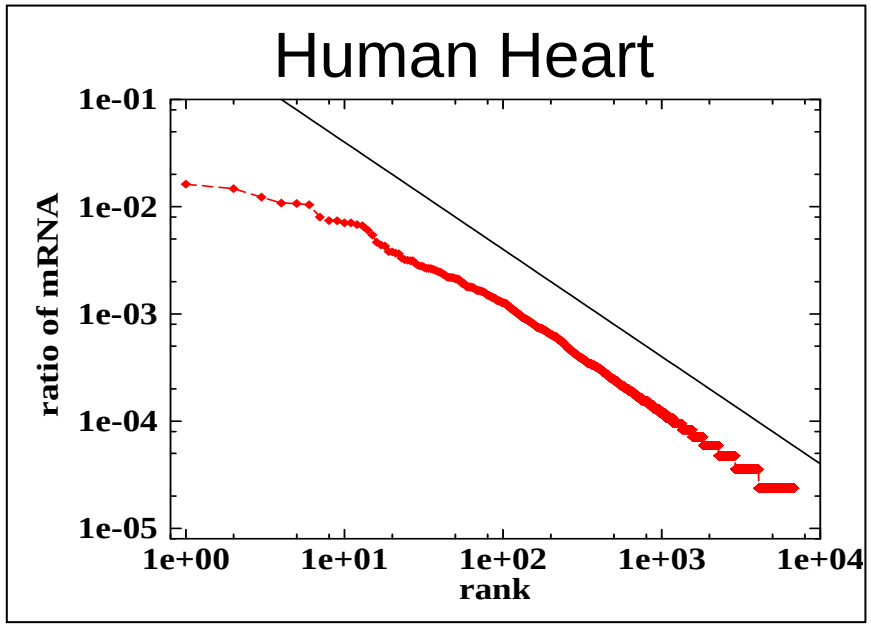


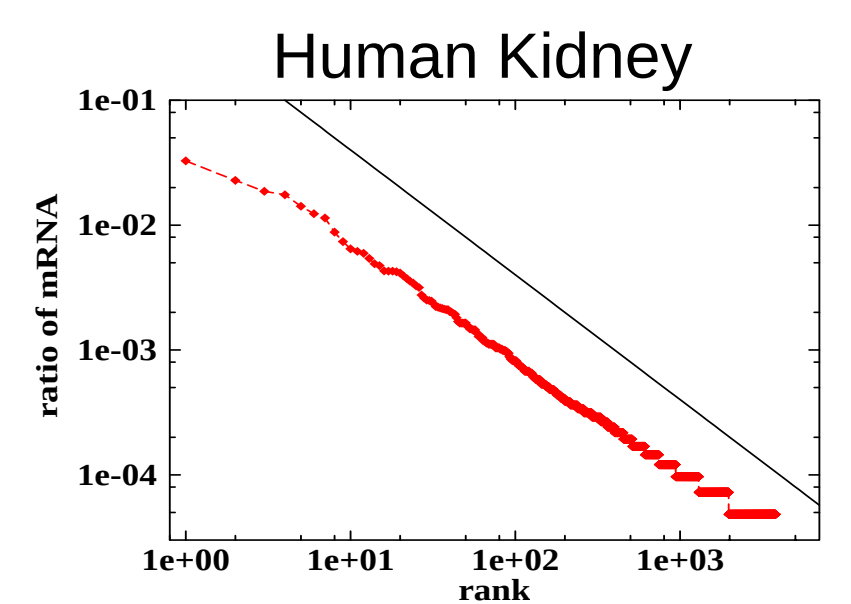
Theory

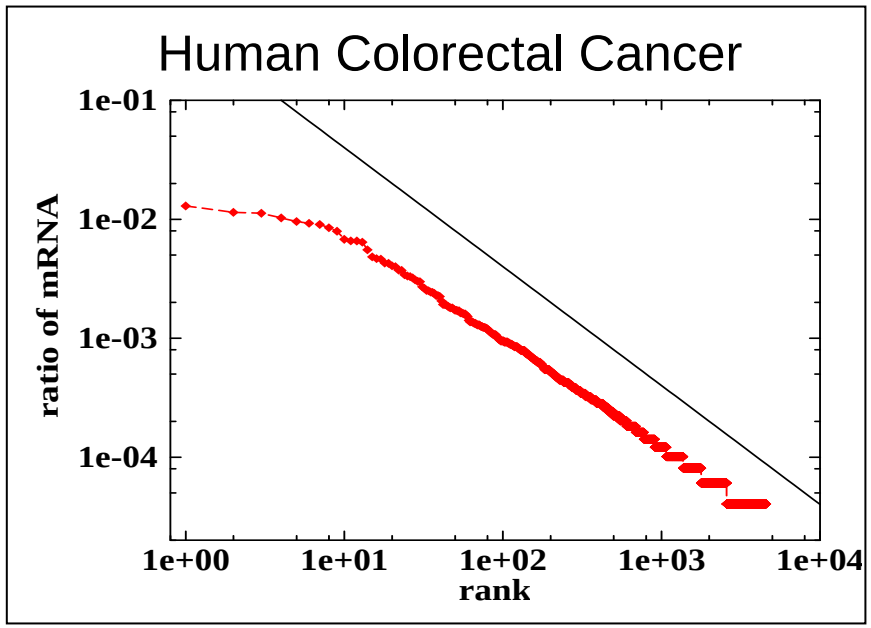
Experiment

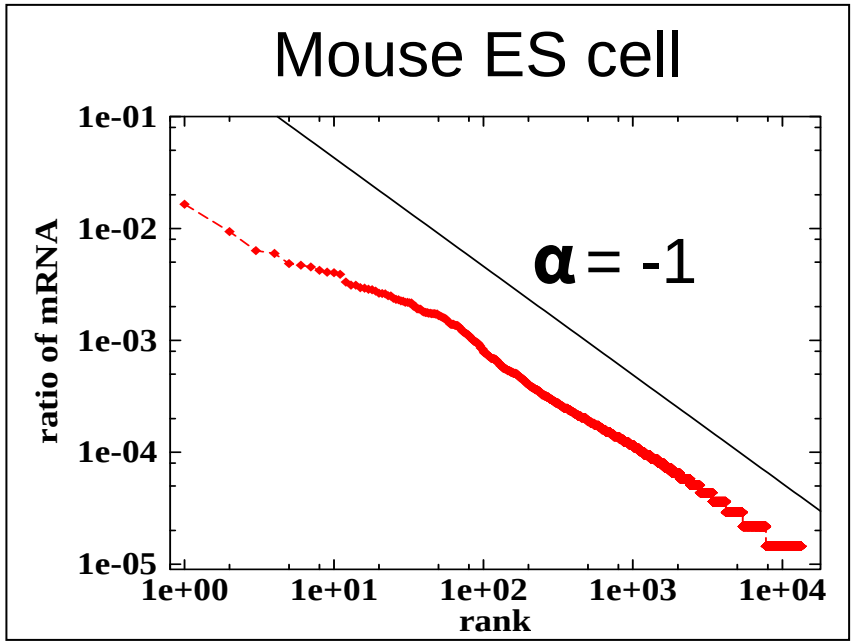
Confirmed by gene expression data

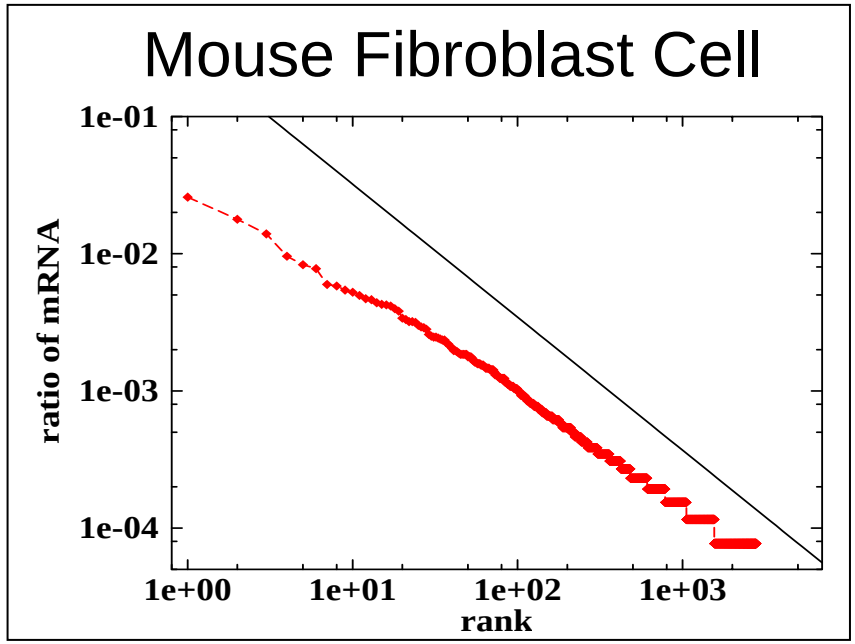


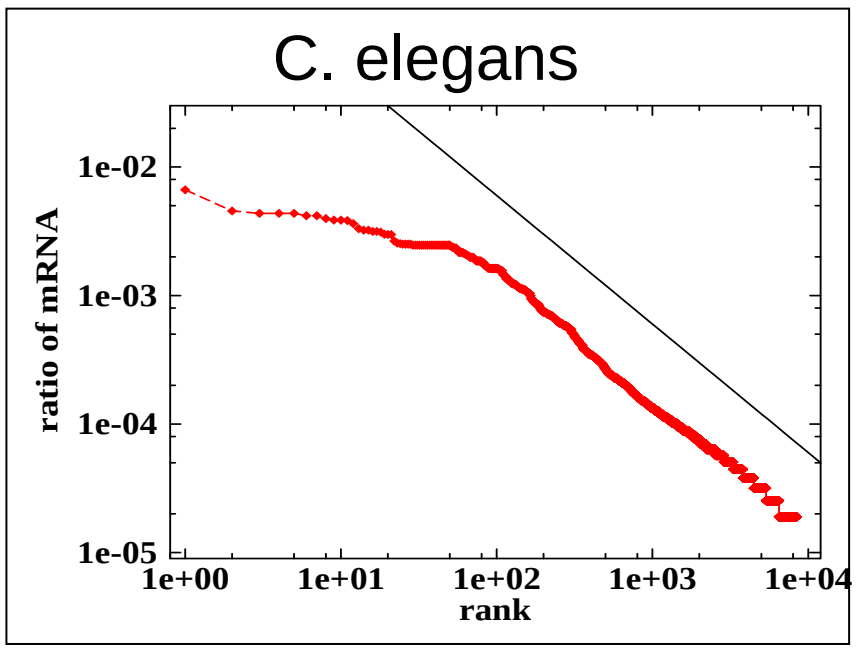


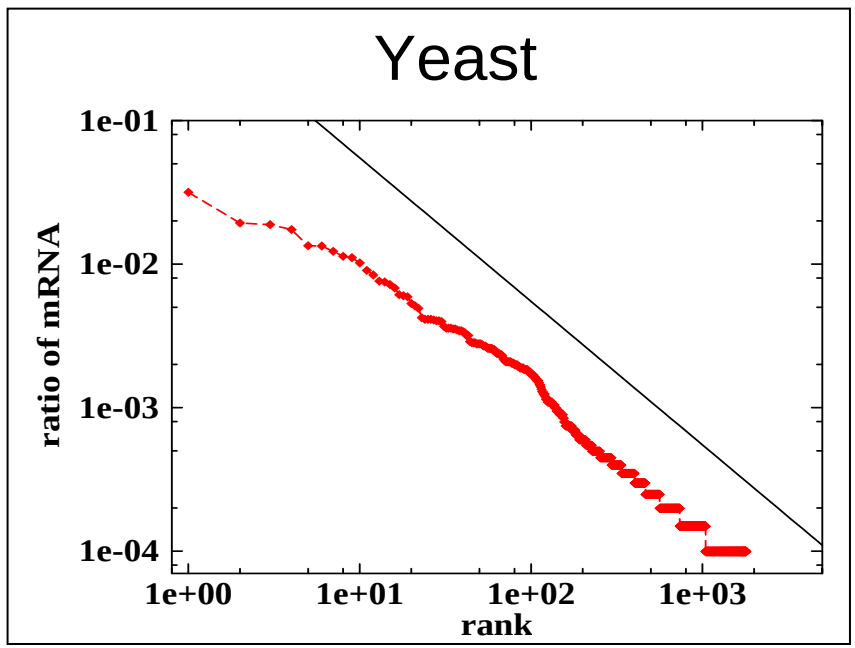





Mouse ES cell
α = -1
ratio of mRNA
rank
1e-01
1e-02
1e-03
1e-04
1e-05
1e+00
1e+01
1e+02
1e+03
1e+04


Mouse Fibroblast Cell
ratio of mRNA
rank
1e-01
1e-02
1e-03
1e-04
1e+00
1e+01
1e+02
1e+03


C. elegans
ratio of mRNA
rank
1e-02
1e-03
1e-04
1e-05
1e+00
1e+01
1e+02
1e+03
1e+04

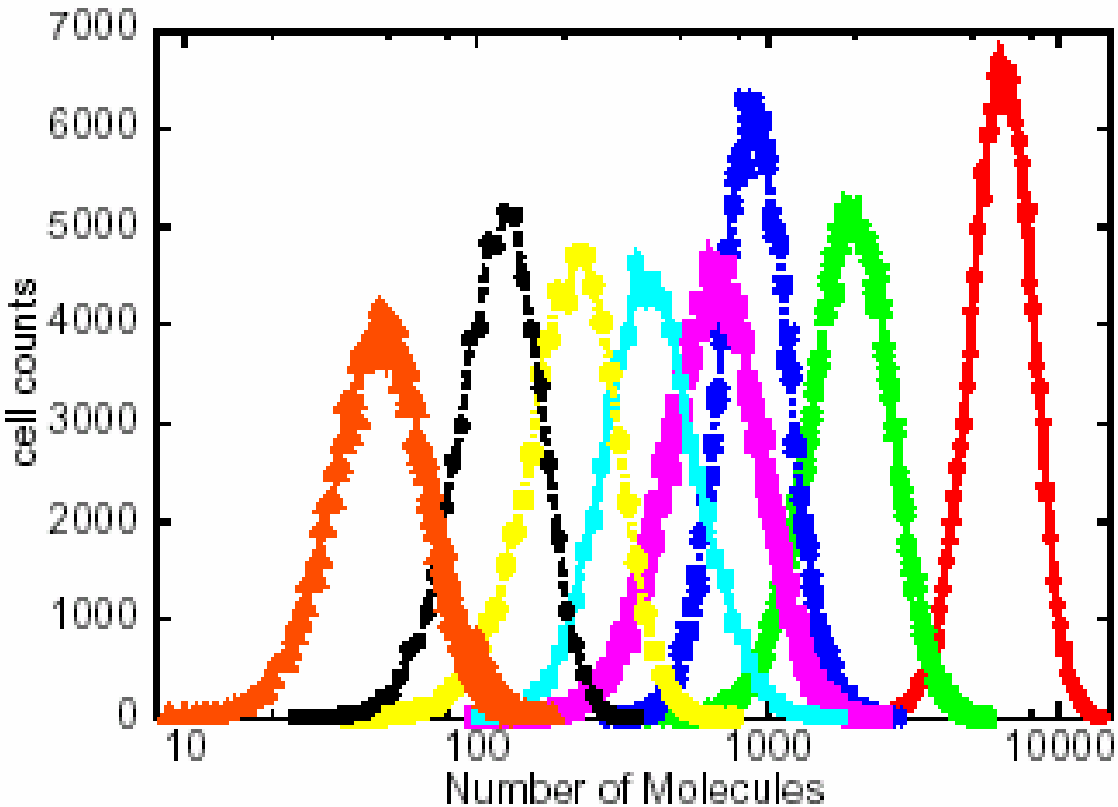

Yeast
ratio of mRNA
rank
1e-01
1e-02
1e-03
1e-04
1e+00
1e+01
1e+02
1e+03

So far average quantity of all components;

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

Furusawa
KK,2003

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)

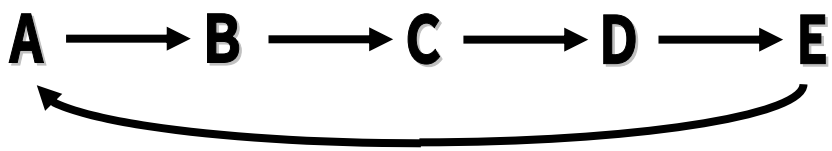
$$d \log(N_X)/dt = <N_A> + \eta (t)$$

log(N_X) shows Brownian motion → N_X log-normal dist.

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. Is applied

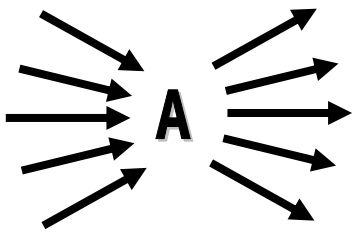
☆Cascade leads to multiplicative propagation of noise (at critical region)



Propagation of fluctuation, feedback to itsel

Leading to tail of log-normal type

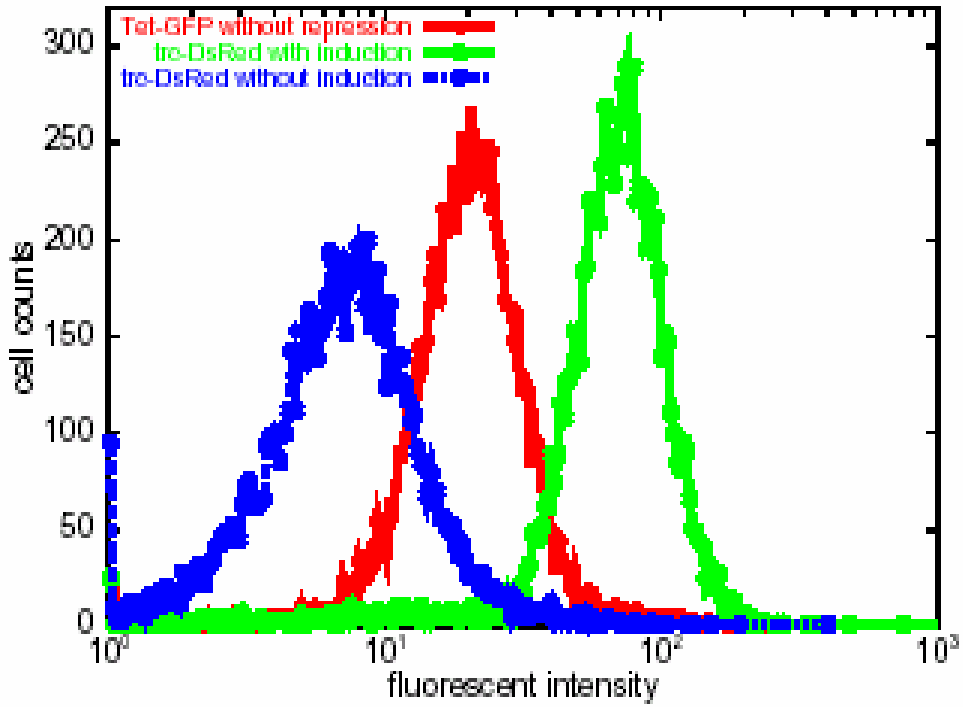
Cf. off-critical region



Fluctuations come in parallel:

Usual central limit theorem is valid

Experiment; protein abundances measured by fluorescence



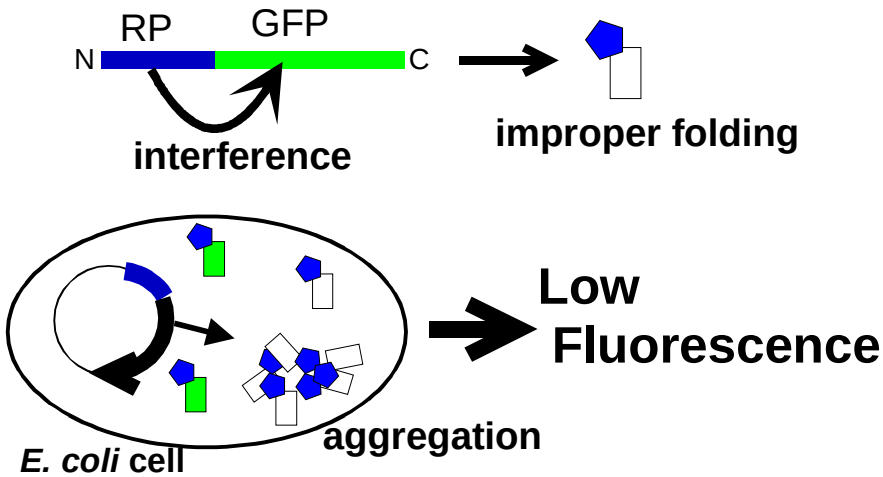
Log-normal Distribution Confirmed experimentally

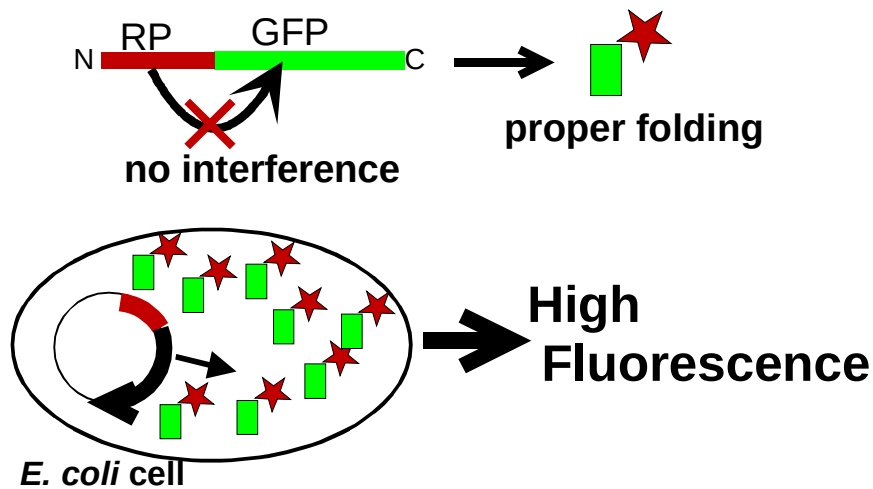
Kashiwagi,Suzuki,Yomo

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.

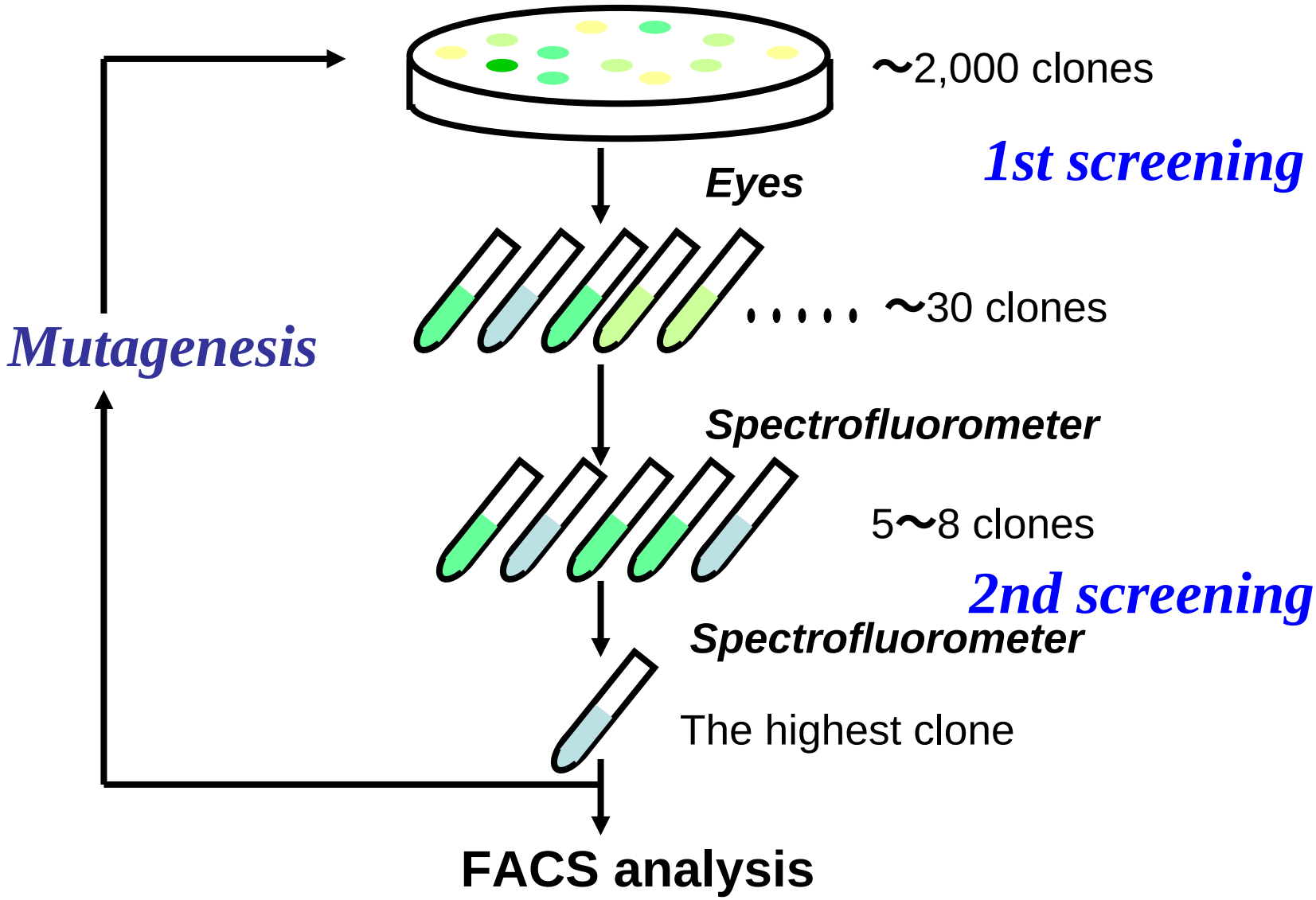
Large phenotypic fluctuation → relevance to evolution (Sato et al., PNAS,2003)

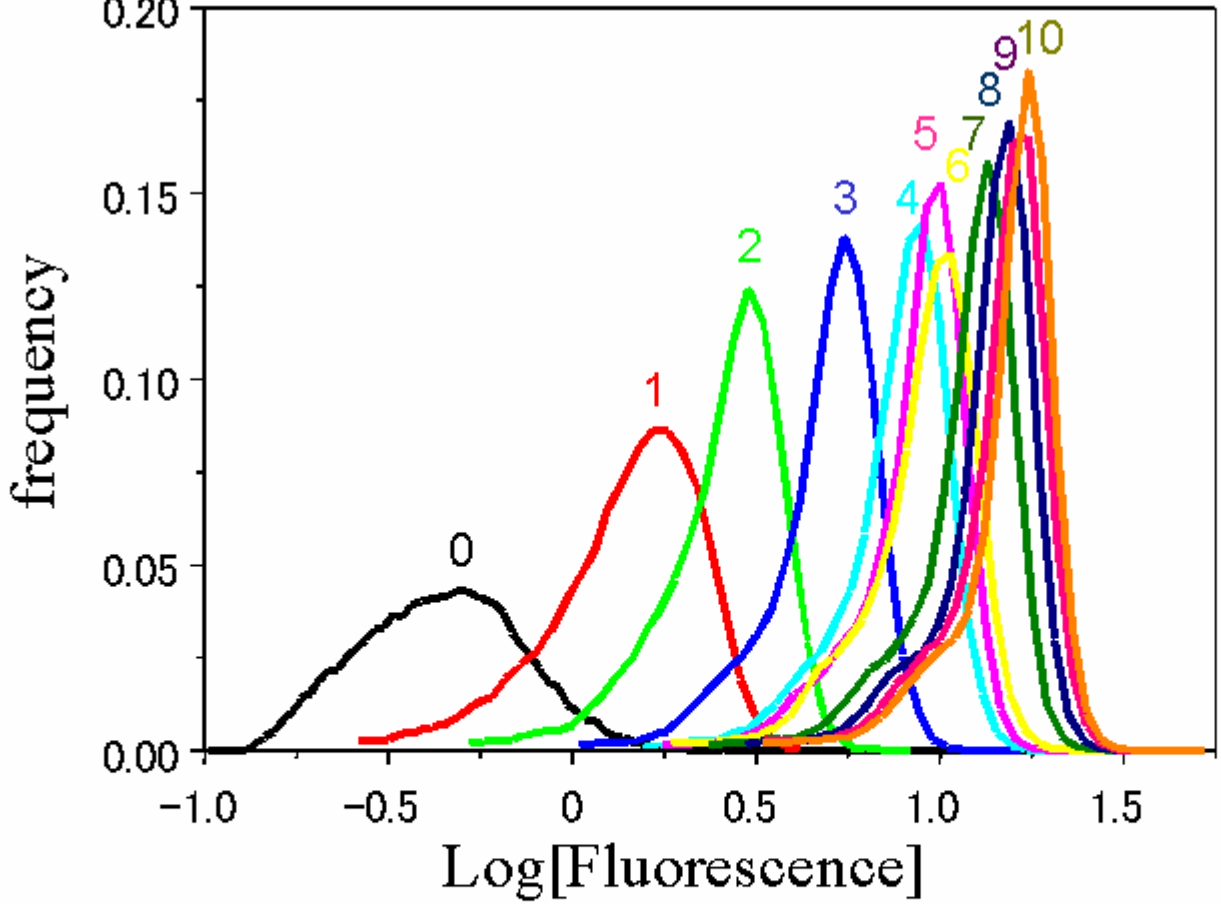
System for detecting the proper folding of a protein





Schematic drawing of selection process





``Response'' --change of phenotype per generation per mutation

Fluctuation ---- Variance of phenotype of clone

Response proportional to Fluctuation

Organisms with larger phenotypic fluctuation

- higher evolution speed; phenotypic plasticity also

So-called fluctuation-dissipation theorem in physics:

Force to change a variable x;

response ratio = (shift of x) / force

fluctuation of x (without force)

response ratio proportional to fluctuation

Generalization::(mathematical formulation)

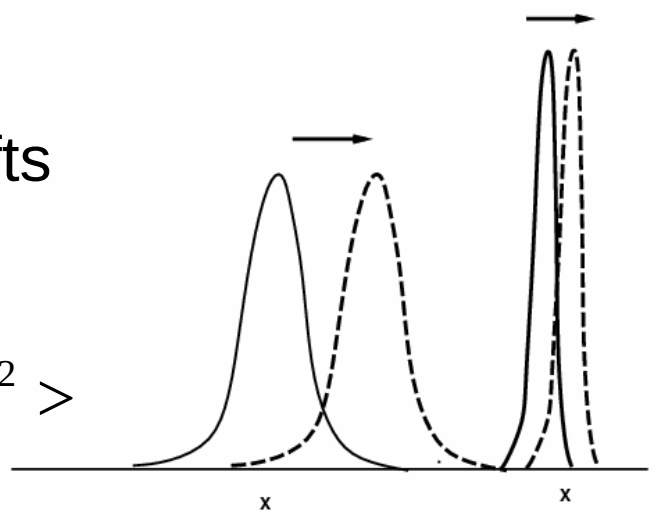
response ratio of some variable x against the change of parameter a versus fluctuation of x

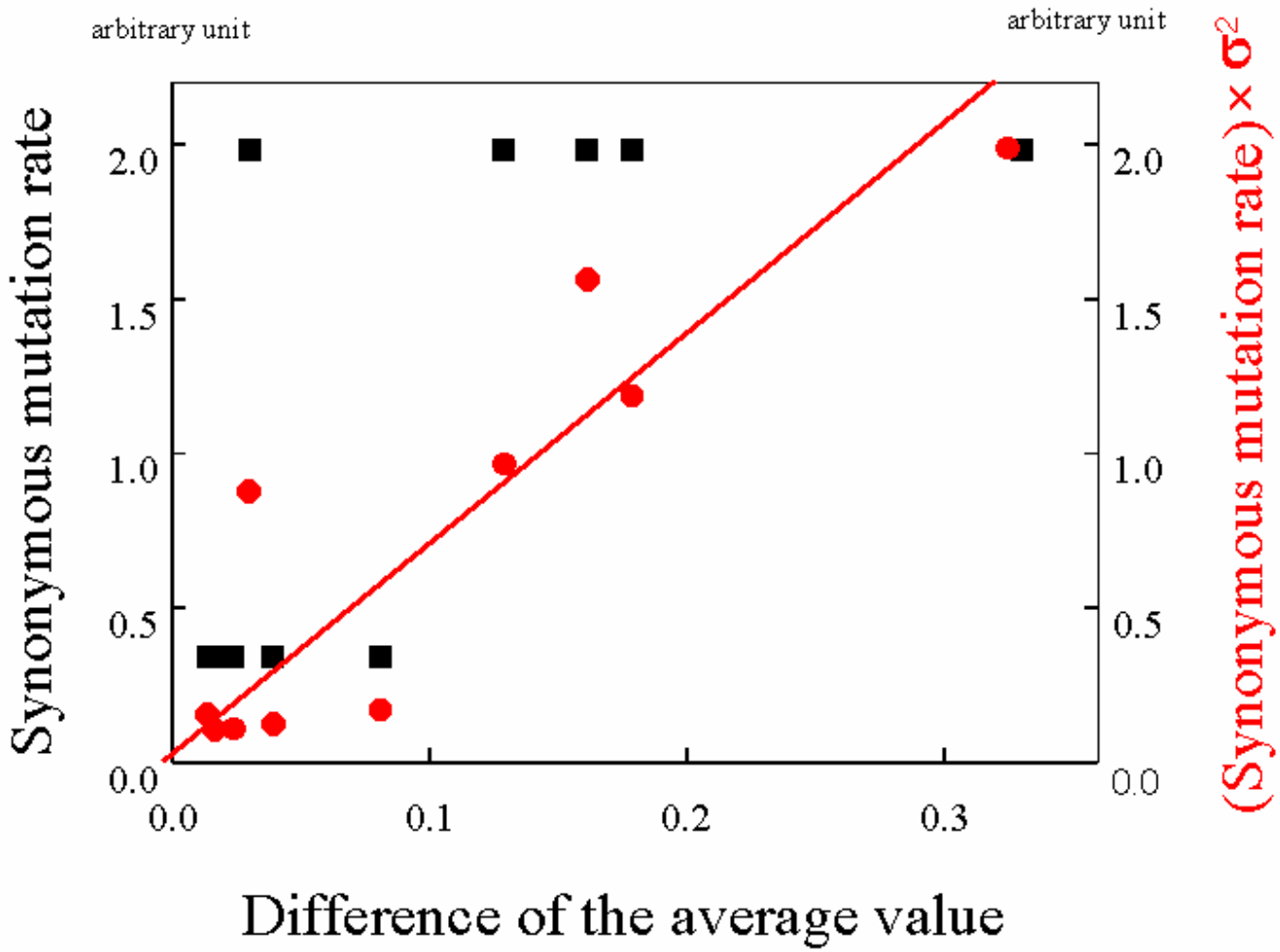
P(x;a) x variable, a: control parameter

change of the parameter a →

peak of P(x;a) (i.e.,<x>average) shifts

$$\frac{< x >_{a+\Delta a} - < x >_a}{\Delta a} \propto < (\delta x)^2 >_a = < (x - < x >)^2 >$$





(Evolution Speed per generation)

- Log-normal:: Is this the end of the story??
  too universal as a theory of biology?
  no need for high control?

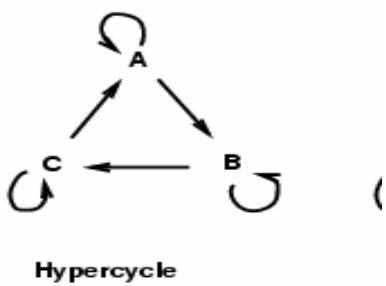
Minority molecules?

Model including a loop of mutually catalytic reactions, → components in a small autocatalytic loop (hypercylce) deviate to ‘Gaussian’; deviation possible either by small feedback loop or parallel paths (i.e., addition instead of multiplication!)

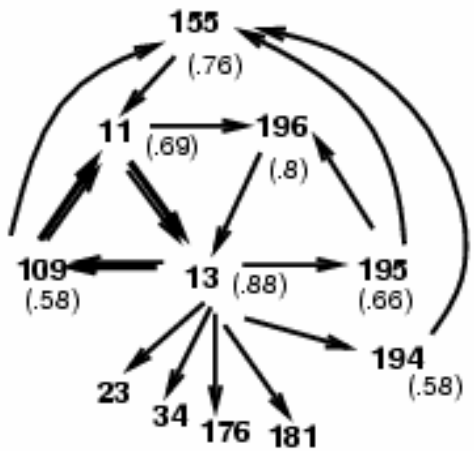
(KK,PRE 2003)

‘

important (control) part may deviate??
(eg.,DNA)



Hypercycle



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cell differ. development	differentiation of E Coil by interaction	emergence of differentiation rule from dynamics	irreversibility robustness
morphogenesis	controlled construction of tissues	self-consistency between pattern and dynamics	origin of positional Information
evolution	phenotypic diff. by interaction	symbiotic speciation	geno-pheno type Relationship

experiment: Yomo; Asashima; Sugawara; Yasuda,..

Development and Differentiation

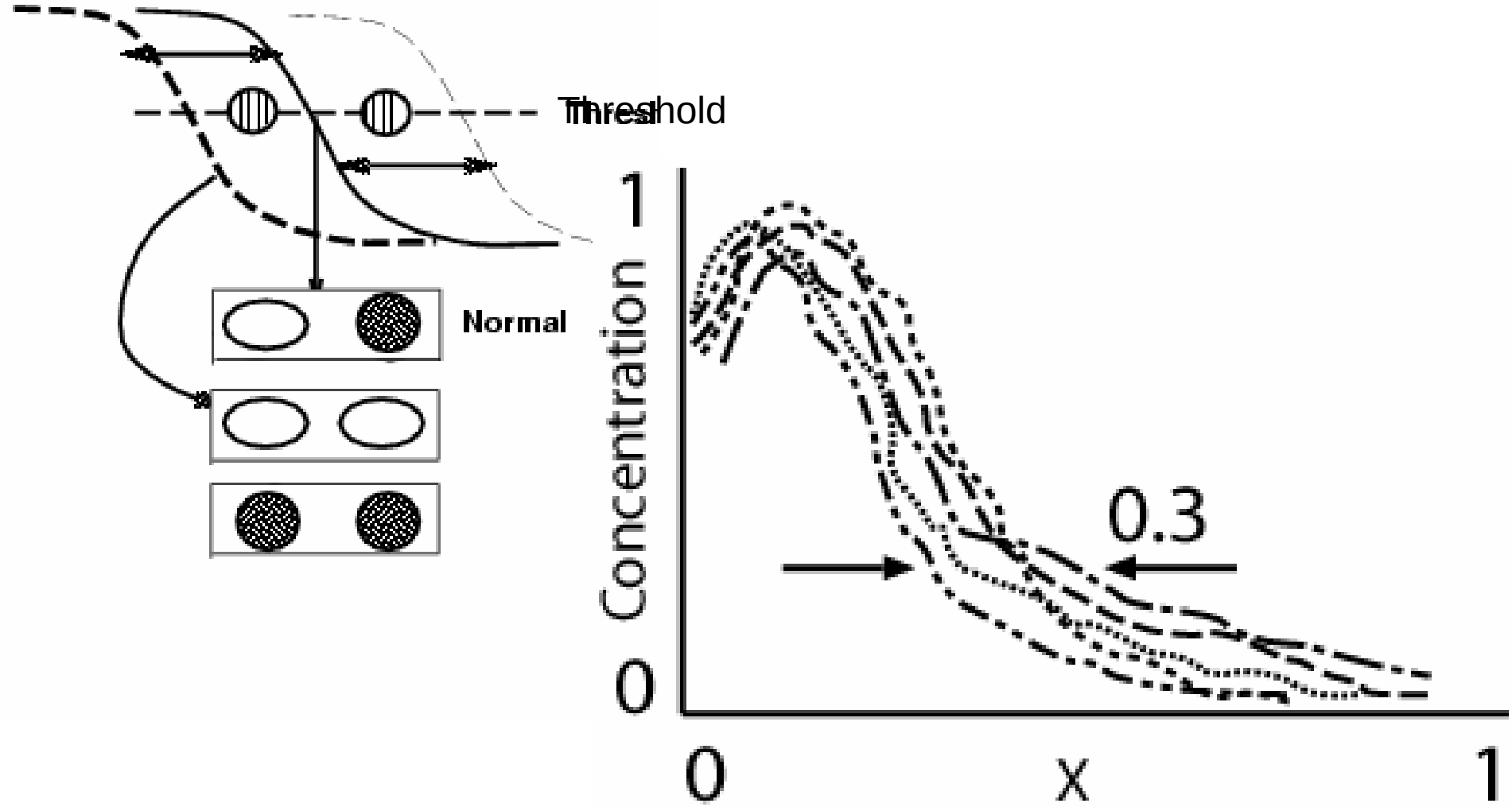
Question
Robustness in development under large fluctuation}

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

threshold mechanism only cannot explain robustness through interaction?

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

irreversible in normal development
reverse the time's arrow (Gurdon)
how to characterize?



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

Isologous Diversification:

internal dynamics and interaction : development phenotype

instability

distinct phenotypes

interaction-induced

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

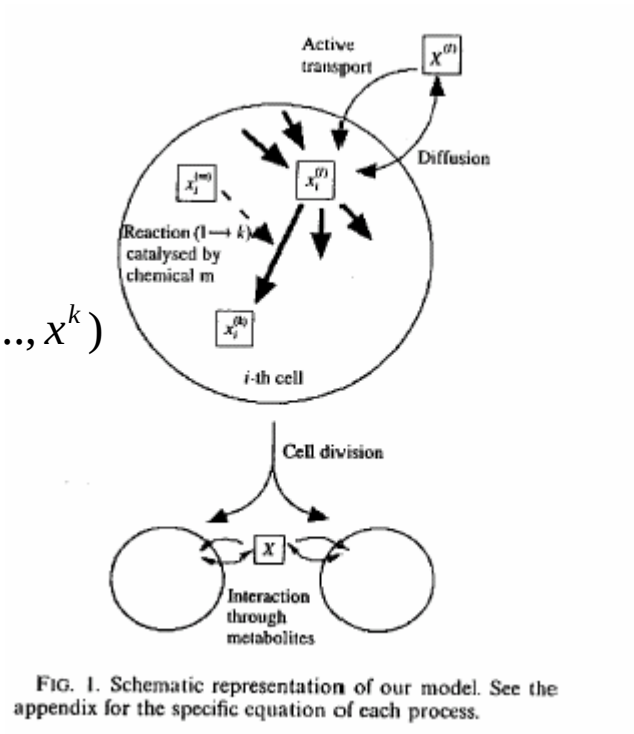
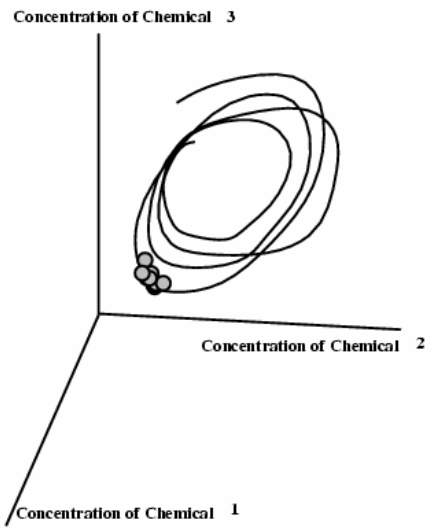


FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

Example: chemical reaction network

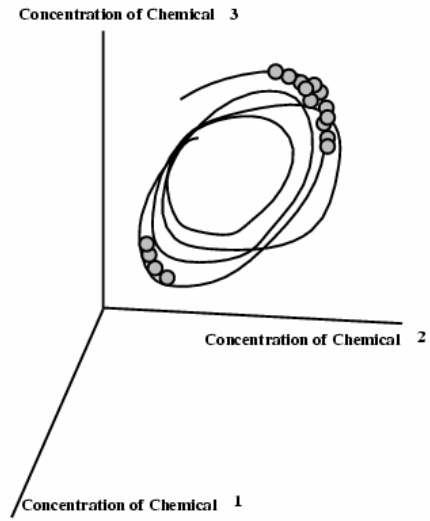
specialize in the use of some path

synchronous division:
no differentiation



(a)

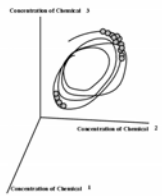
Instability of homogeneous state
through cell-cell interaction



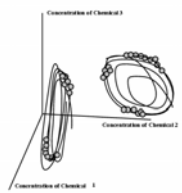
(a)


Concentration of Chemical 3
Concentration of Chemical 2
Concentration of Chemical 1

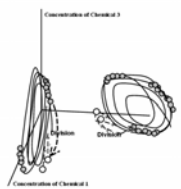
(a)


Concentration of Chemical 3
Concentration of Chemical 2
Concentration of Chemical 1

(a)


Concentration of Chemical 3
Concentration of Chemical 2
Concentration of Chemical 1

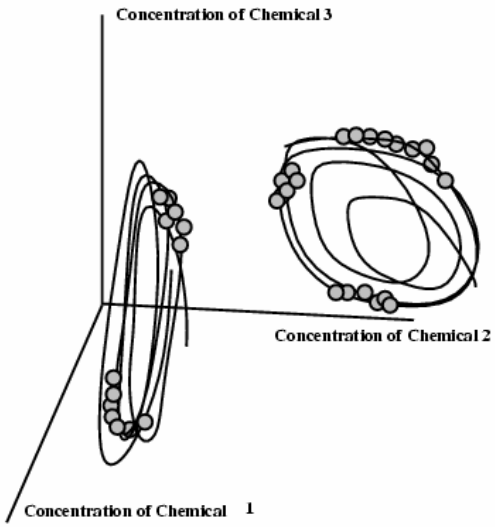
(b)


Concentration of Chemical 3
Depletion
Division
Concentration of Chemical 1

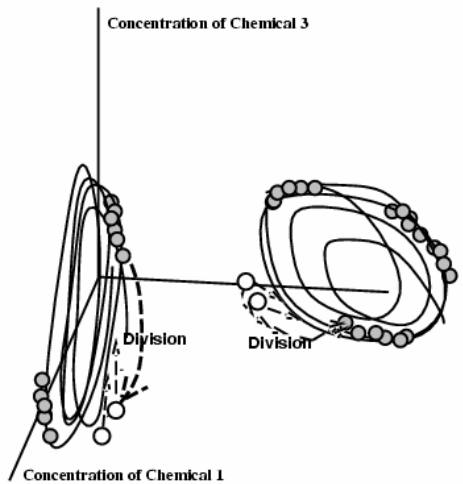
(c)

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

recursive production



(b)

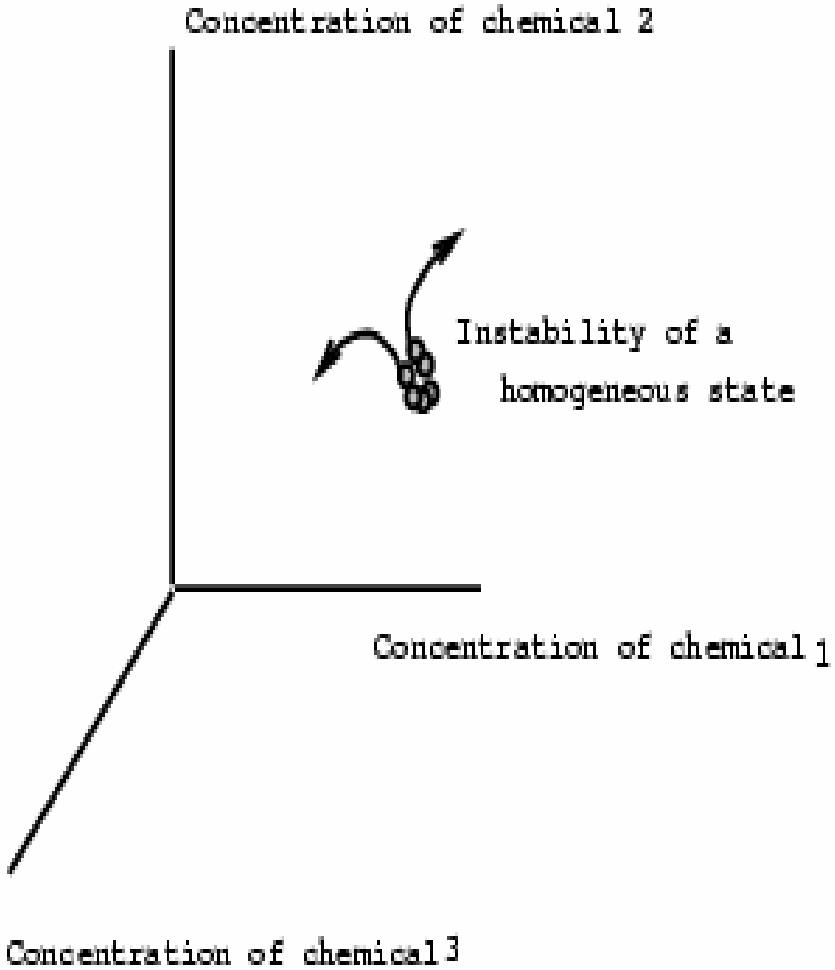


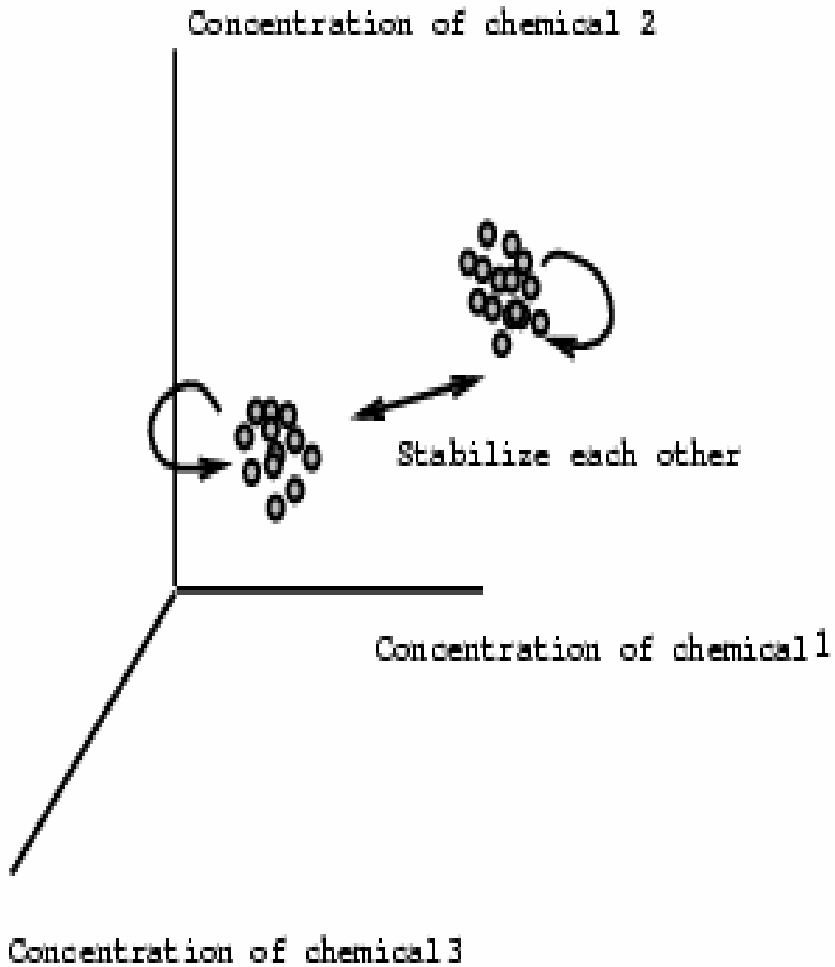
(c)

- (1) Synchronous oscillations of identical units

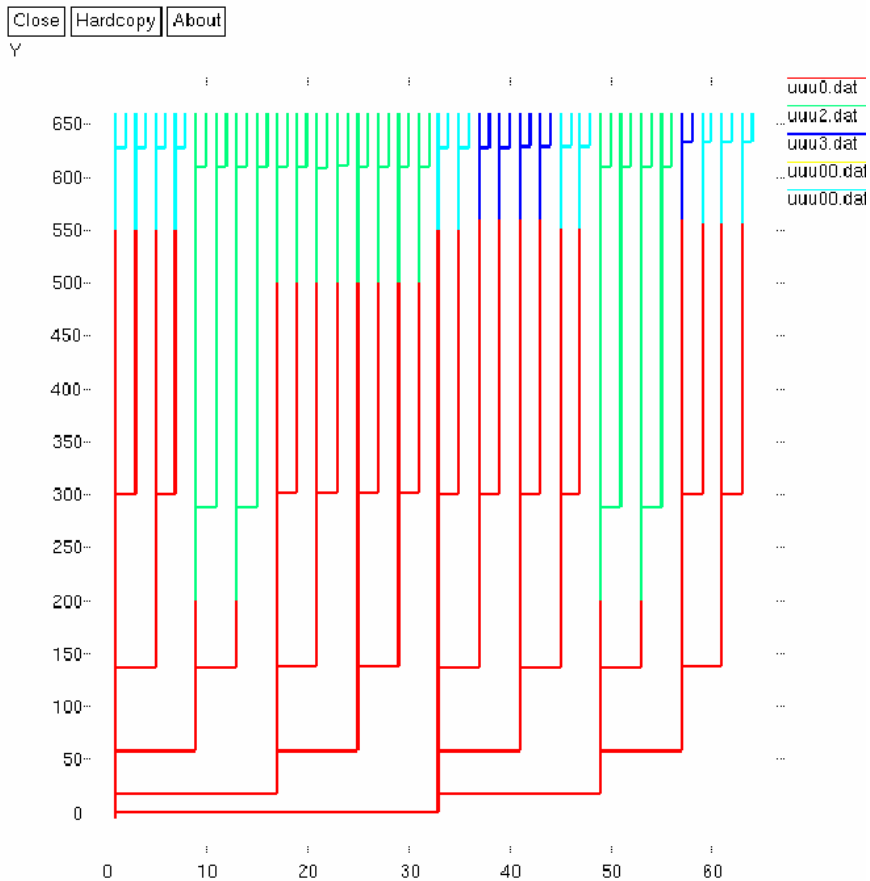
  Up to some threshold number of units, all of them oscillate synchronously, and their states are identical.}
- (2) Differentiation of the phases of oscillations of internal states. When the number of units exceeds the threshold, they lose identical and coherent dynamics. Although the state of units are 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)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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;

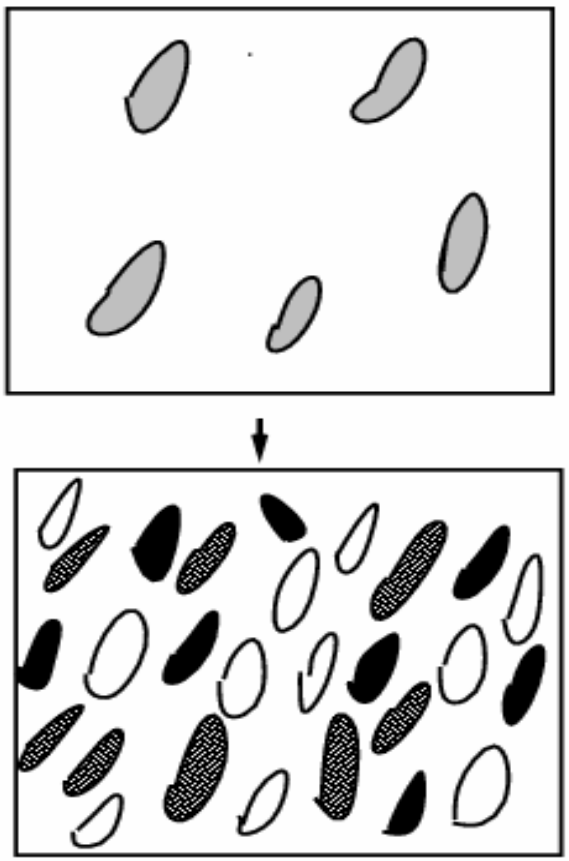
i.e., type A and type B, determined

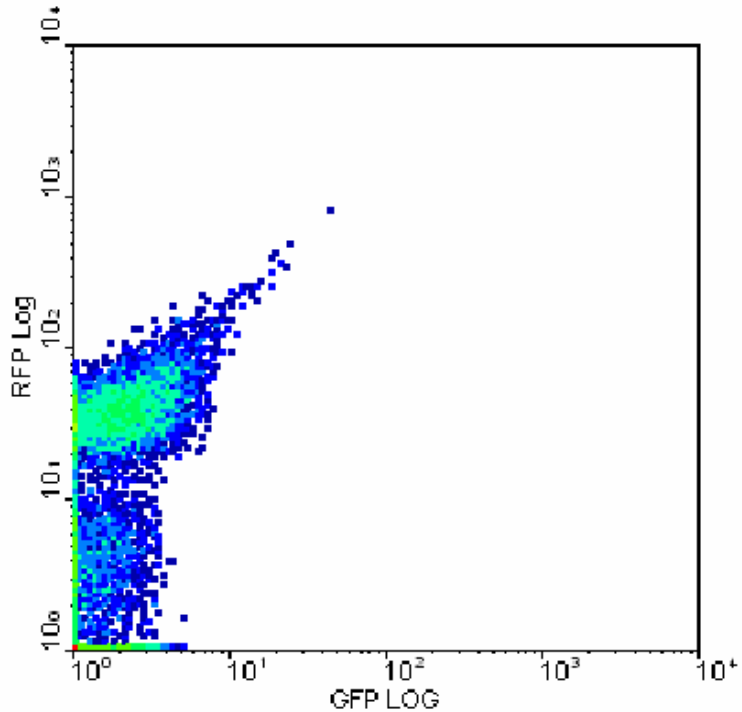
but if type A is eliminated, then B de-differentiates

and initial A-B cell ensemble is recovered

(since A,B is stabilized each other)

Differentiation of E Coli



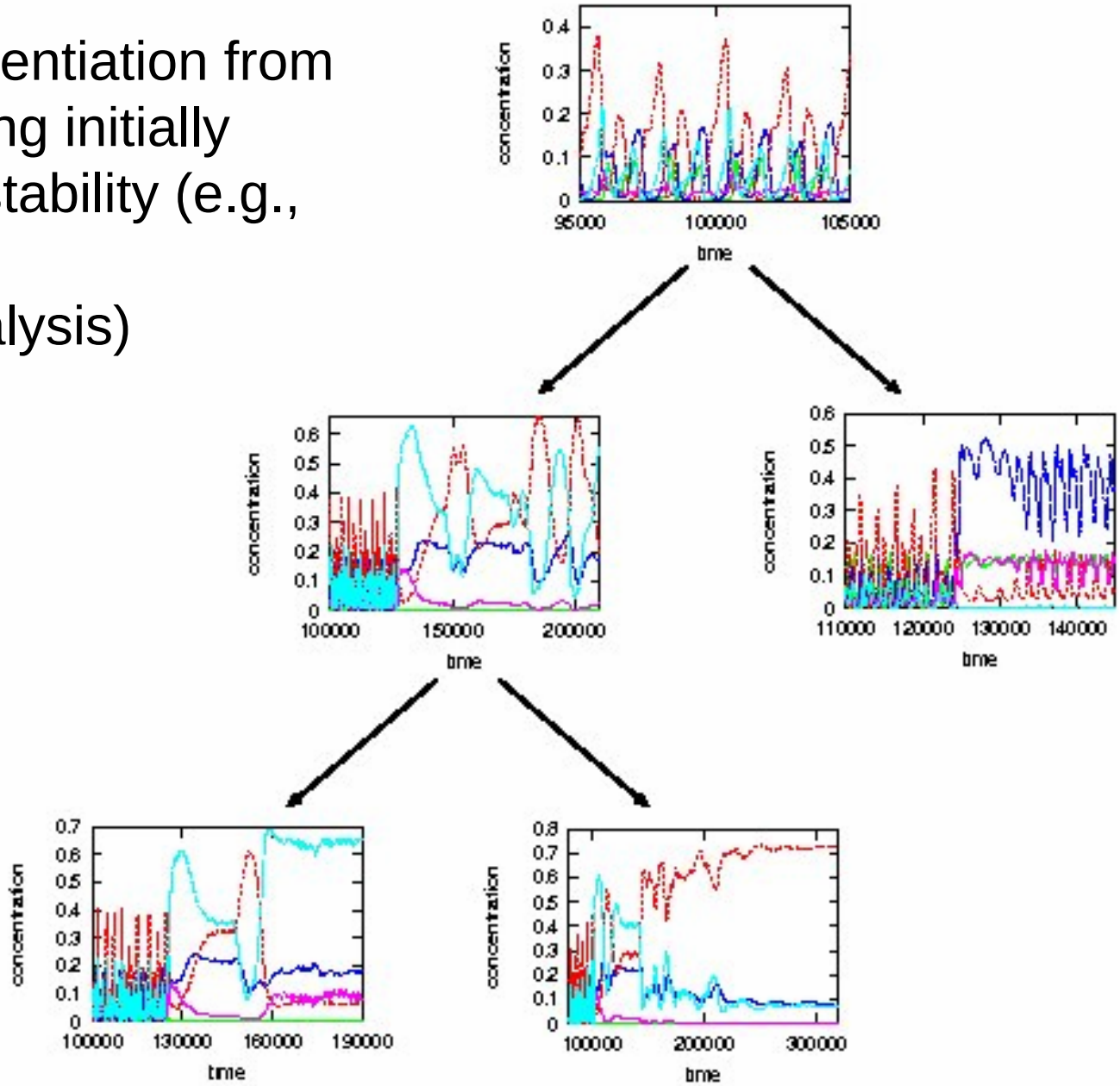


Measurement by fluoresecent proteins

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)



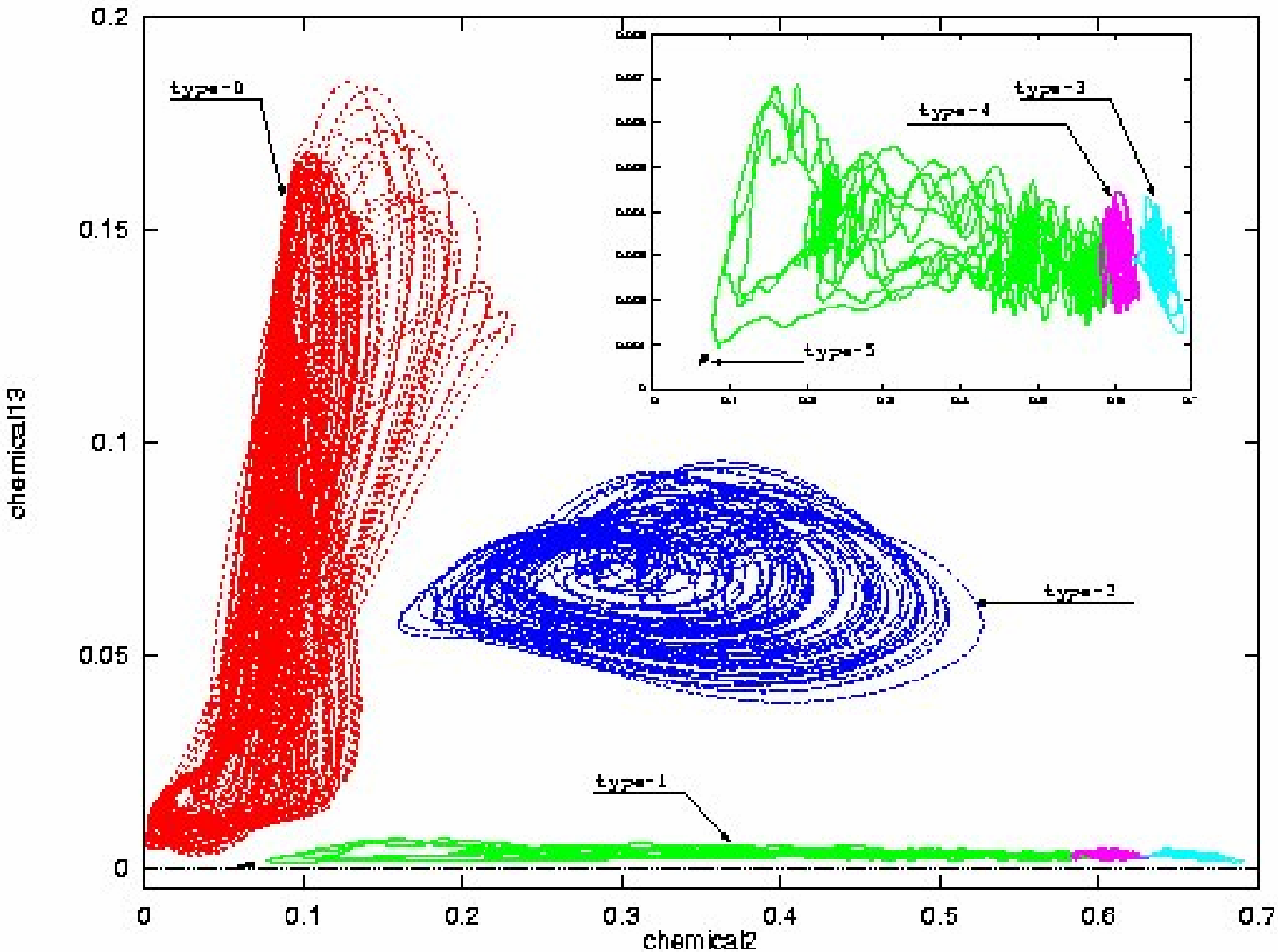
Furusawa & KK

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

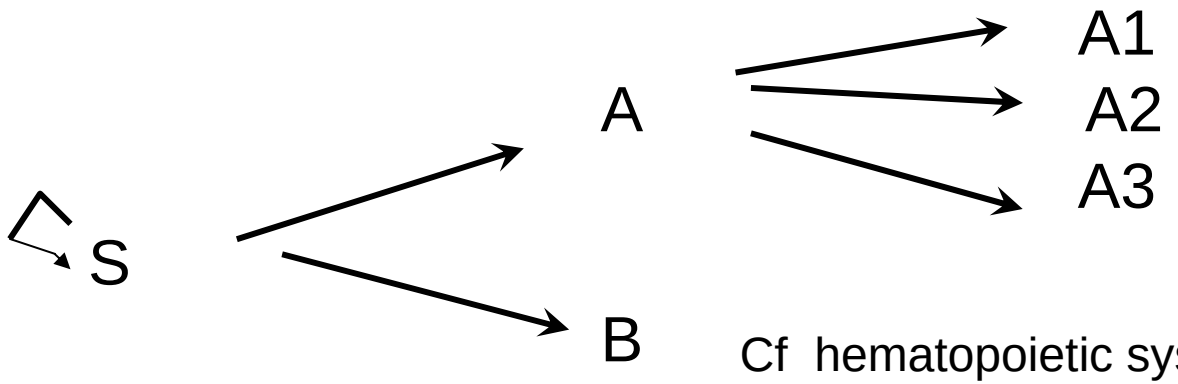
with

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

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



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* }

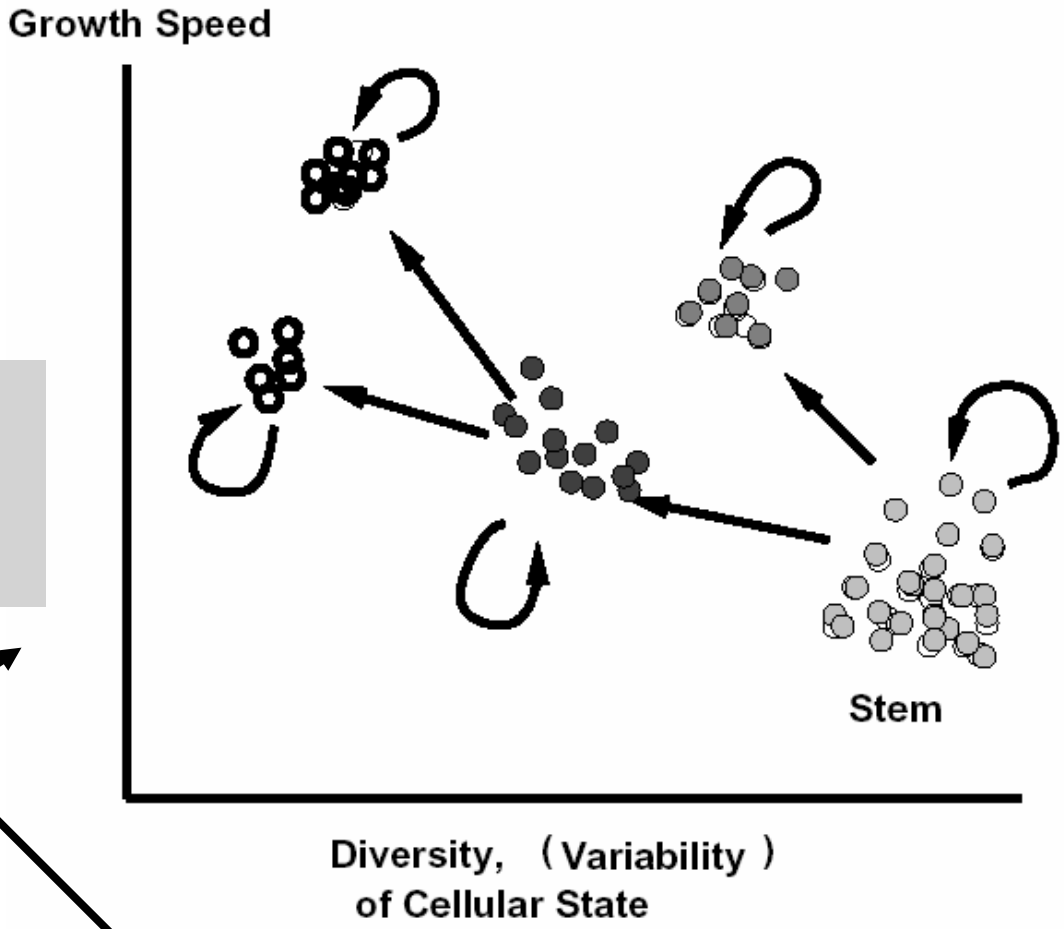
- **Irreversibility: Loss of multipotency**
- **diversity in chemicals**

$$S_i = -\sum_{j=1} p_i(j) \log p_i(j) \qquad (4)$$

with

$$p_i(j) = \left\langle \frac{x_i^{(j)}}{\sum_{m=1}^{k} x_i^{(m)}} \right\rangle, \qquad (5)$$

- **stability of the cellular state**
- **growth speed**



Prediction:

gene expression of stem cells diverse, weak

rate of proliferation/differentiation dep. on cell distribution

If #(stem) proliferation is decreased externally

then proliferation increases

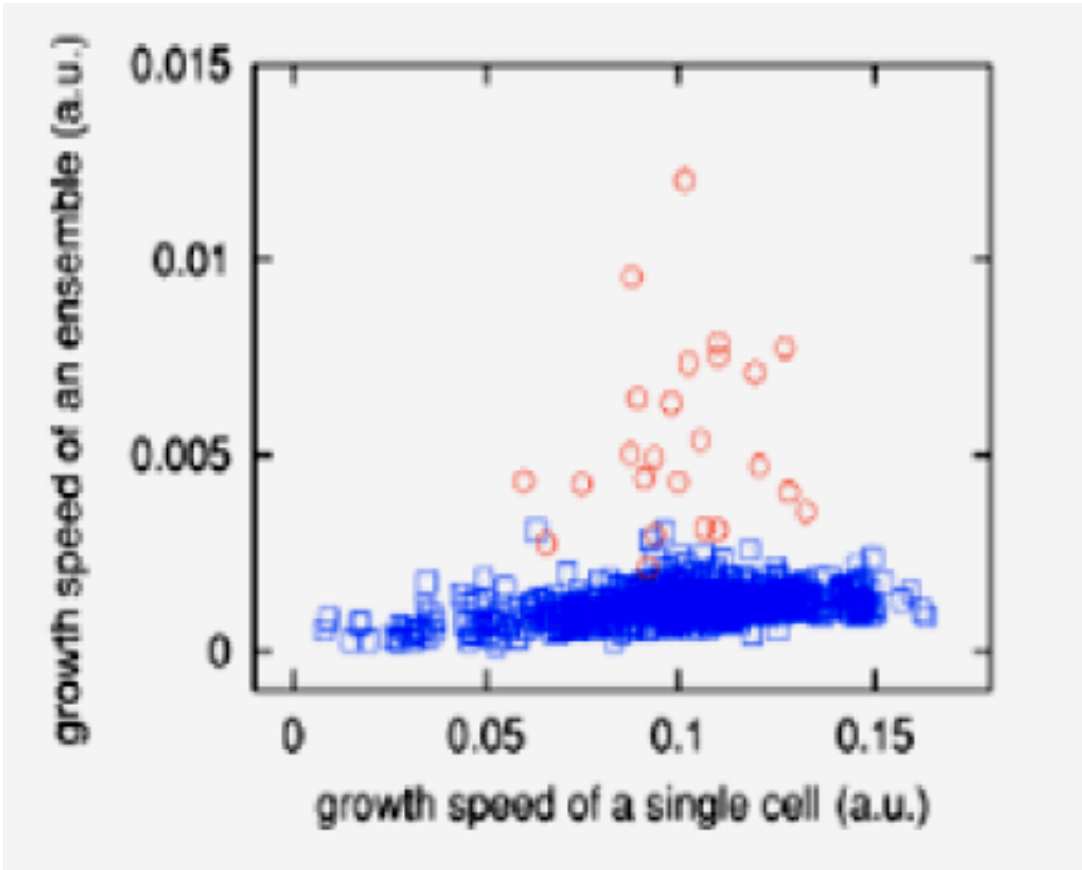
How to recover plasticity (clone, regeneration)

Universality?

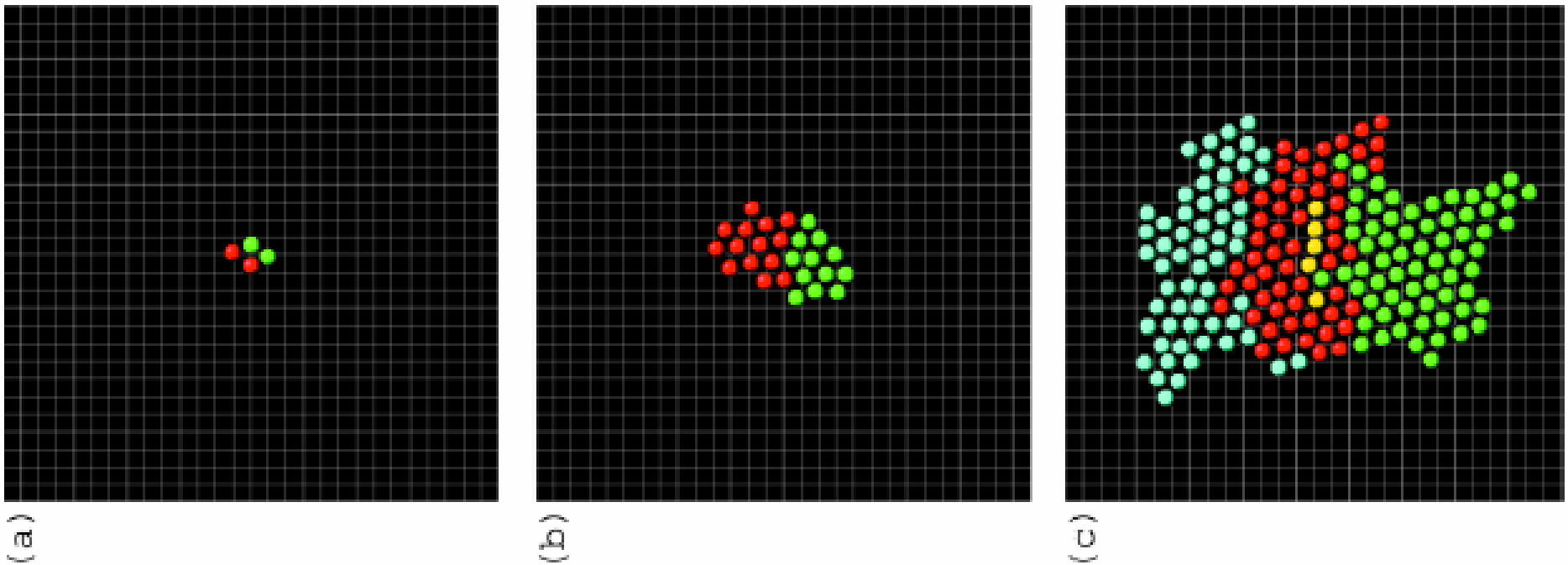
checked a huge number of networks; only some fraction of them show chaotic dynamics & differentiation

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

Constructive Biology Project at Komaba Clife group

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 differ. development	differentiation of E Coil by interaction	emergence of differentiation rule from dynamics	irreversibility robustness
morphogenesis	controlled construction of tissues	self-consistency between pattern and dynamics	origin of positional Information
evolution	phenotypic diff. by interaction	symbiotic speciation	geno-pheno type Relationship

experiment: Yomo; Asashima; Sugawara; Yasuda,..

•Evolution (speciation)

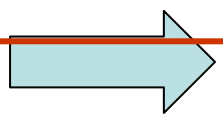
Recall underlying assumption in population genetics:

Selection by fitness=Function(Phenotype, environment)

but

assumption; Genotype ----> Phenotype: Single-Valued determined uniquely

then Fitness=function(Genotype,environment)



individuals with little change in gene should compete under the same niche

???

Reconsider Genotype-Phenotype mapping

Consider seriously G -------[Development] → P;

** G-P relationship can be one to many

(1) Isologous diversification (---theory so far)

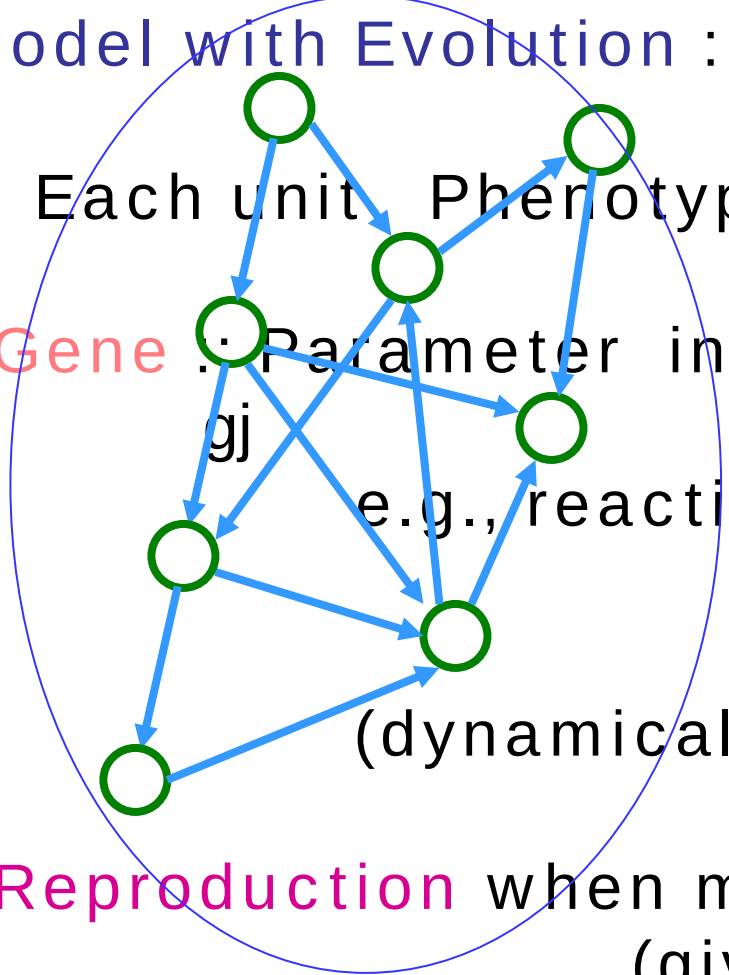
(2) Interaction-induced differentiation in experiments

bacteria (E.coli) Shapiro, Yomo, …..

(3) Low penetrance (often in mutants?)
(---observation)

non-unique phenotypes (often in mutants)

Model with Evolution :



Each unit Phenotype :: Variable X = $(X_1, X_2, .., X_k)$

Gene :: Parameter in the model $(g_1, g_2, ..., g_k)$

gj

e.g., reaction rate

Parameter ⇒ Variable

(dynamical systems)

X(t=0)→X(t)

Reproduction when maturity threshold condition (given by X) is satisfied

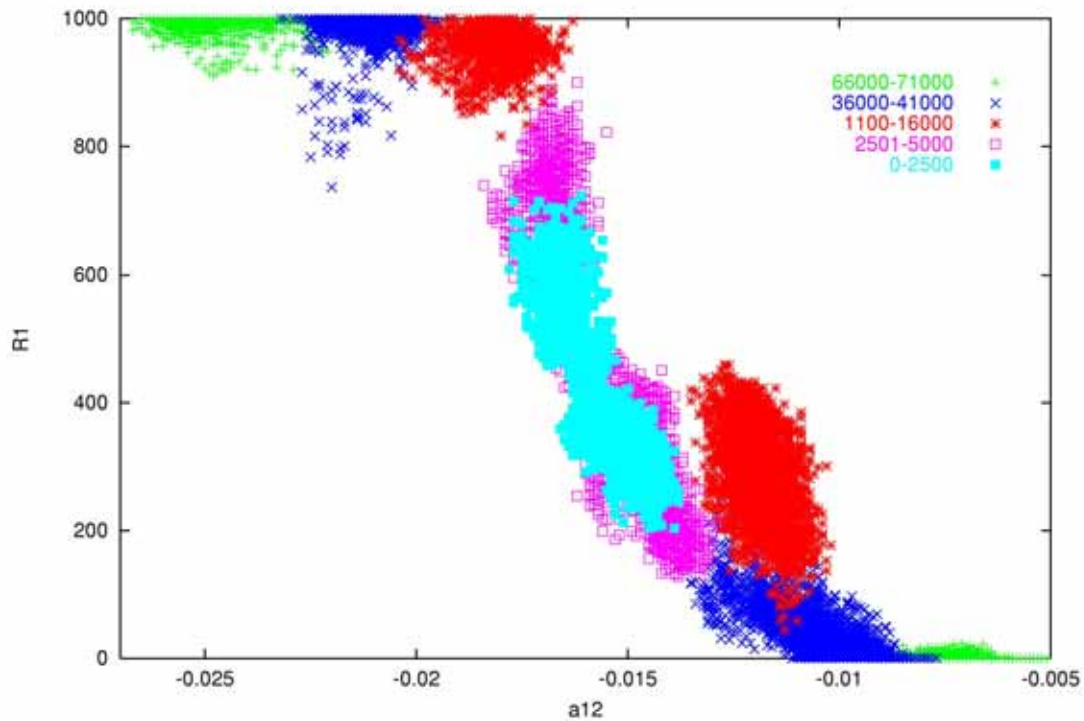
Mutation --- change in parameter in reproduction

Competition for survival:

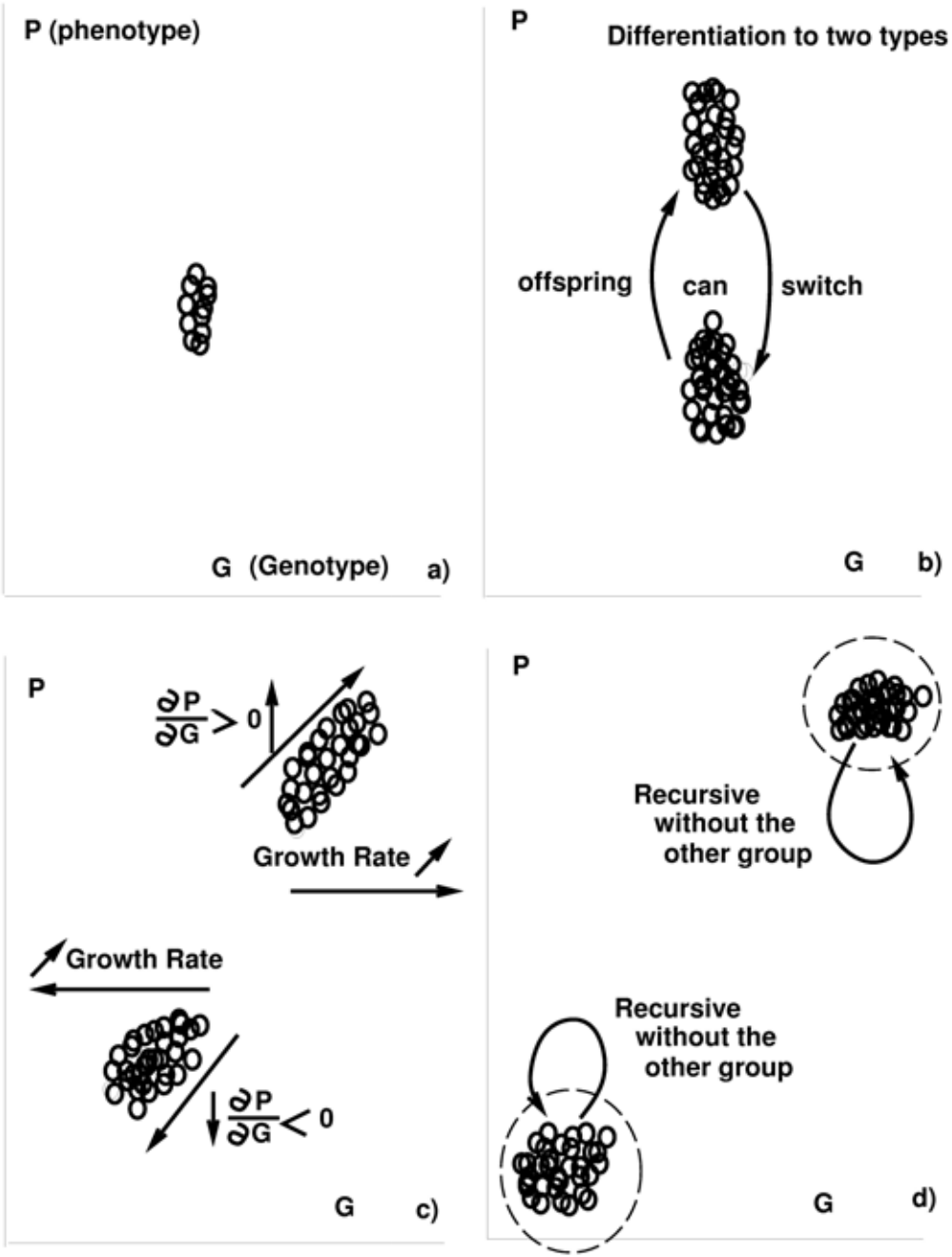
(remove a unit (randomly or with some condition)

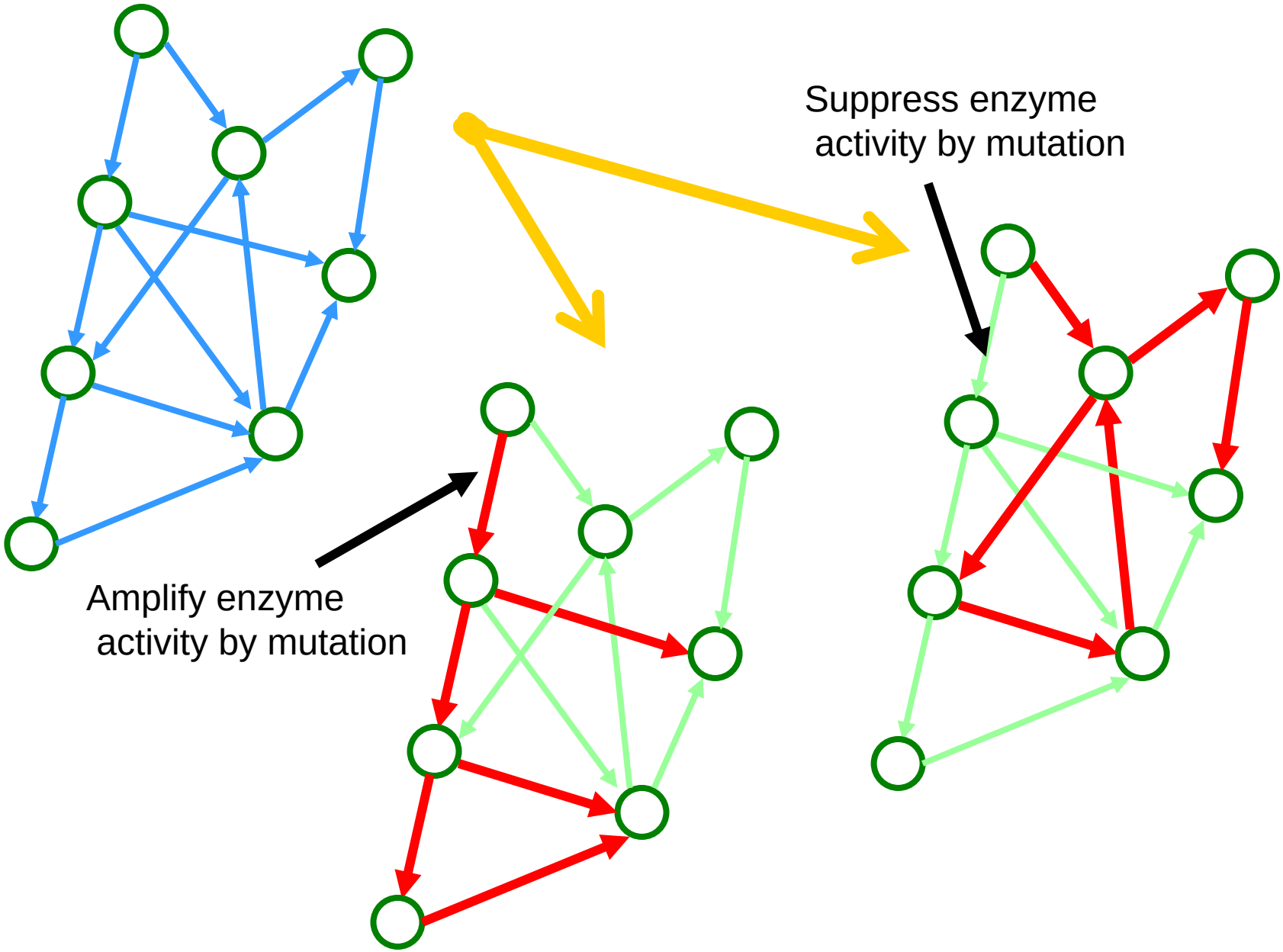
Example of numerical simulation

Phenoptype(variable)



Gene (parameter)


P (phenotype)
G (Genotype)
a)
P
Differentiation to two types
offspring
can
switch
G
b)
P
∂P/∂G > 0
Growth Rate
Growth Rate
∂P/∂G < 0
G
c)
P
Recursive
without the
other group
Recursive
without the
other group
G
d)



Phenotypic change embedded into genetic change (cf Waddington)

Sympatric Speciation observed

(1) First interaction-induced phenotype differentiation;
homogeneous state is destabilized by the interaction

(2) Amplification of the difference through geno-pheno relation
Two groups form symbiotic relationship, and coevolve

(3) Genetic Fixation and Isolation of Differentiated Groups
consolidation to genes
(Example) chemical secreted out by one group are used as resources for the other, and vice versa
create a niche each other and specialized in this created niche

(4) Works for sexual reproduction case without assuming mating preference
hybrid sterility as a result.
as its consequence mating preference evolves

**Experimental Verification by Using E Coli in progress

- Origin of heredity?

  →Minority Control: use of rare fluctuations

- How is recursive production of cells possible in the amidst of diversity and fluctuations?

  → hierarchy of catalytic reactions formed:

  Universal Statistics: amplification and regulation of fluctuations. (Zipf's law and log-normal distribution)

  - Biological relevance of such large fluctuations?

    →Phenotypic Fluctuation ∝ Evolution Speed

- Robustness of development under fluctuations? Irreversibility of cell differentiation?

  → phenotypic differentiation due to instability of homogeneous states, and formation of discrete attracting states by cell-cell interaction. Loss of plasticity in dynamics by the increase of cell number

- How is speciation to discrete pheno-and geno-types possible under interaction among organisms?

→Dynamic consolidation; fixation to slower time scale change

(phenotype →genotype)

Flexibility of Unit and System

Regulation of Fluctuations
Loss of Plastic Dynamics

Universal Features: Theory and Experiment

- Collaborators:

  Chikara Furusawa (Reaction network of cell(Zipf's law,Log-normal), Cell-differentiation)

  Tetsuya Yomo (all the experiments; sharing idea for all topics)

  Katsuhiko Sato (fluctuation-response relationship)

  Akiko Kashiwagi, Takao Suzuki, Yoichiro Ito (experiments by Yomo's group)

- Most papers mentioned here are available at

http://chaos.c.u-tokyo.ac.jp

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生命とは何か

［複雑系生命論序説］

金子邦彦

［主要目次］

この問いに興味を抱く
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生命科学を複雑系の科学として再構築し，
理論・モデル・実験から，「生命」現象の本質へと迫る
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