宇宙での生命?

地球上と同じタイプ？？？？

水がなければいけない？？？　　　(cf　T.　Gold)

ーータイタン、エウロパ、火星、...に生命があるかではなく、どこでも生命があれば満たすべき普遍的性質を探ろうという話ーー

「たまたま地球で現存する生物という形にしばられずに、生命の持つ普遍則を探ろう」

小松左京「普遍生物学」

「生命の基本的普遍性を生命システムを構成することで理解しよう」 (実際の歴史は問わない)

四方・金子「構成的生物学」

生命とは？

複製できる？　　　進化できる？
自己を維持？自律性？自主性？
：
複雑なシステムとしての普遍的性質

内部に多様な自由度を持ち増殖できる系の
普遍的性質

↓

『物理学』

今日の話題
◎同じものをつくる？
◎多様化できる？

Complex Systems Biology

cf. Life as Complicated System:

Enumeration of molecules, processes (Ome)

detailed models mimicking the life process

But understanding??

Life as Complex System:

Understand General features :

➔General Answer as a System Level?

Strategy:

1) Search for universal features in cellular processes :
extension of Dynamical Systems & Statistical Physics

2) Constructive Approach: (Exp & Theory)
` construct simple system to catch universal features'
`not to imitate'

Constructive Biology Project at Komaba-Osaka Clife prjoect 1999-2004

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

Kaneko- Yomo- Asashima- Sugawara; Yasuda,..

Q **複製能 (触媒活性の維持) ー困難 ←複製エラー**

遺伝の起源

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

e.g., differentiation in roles between DNA

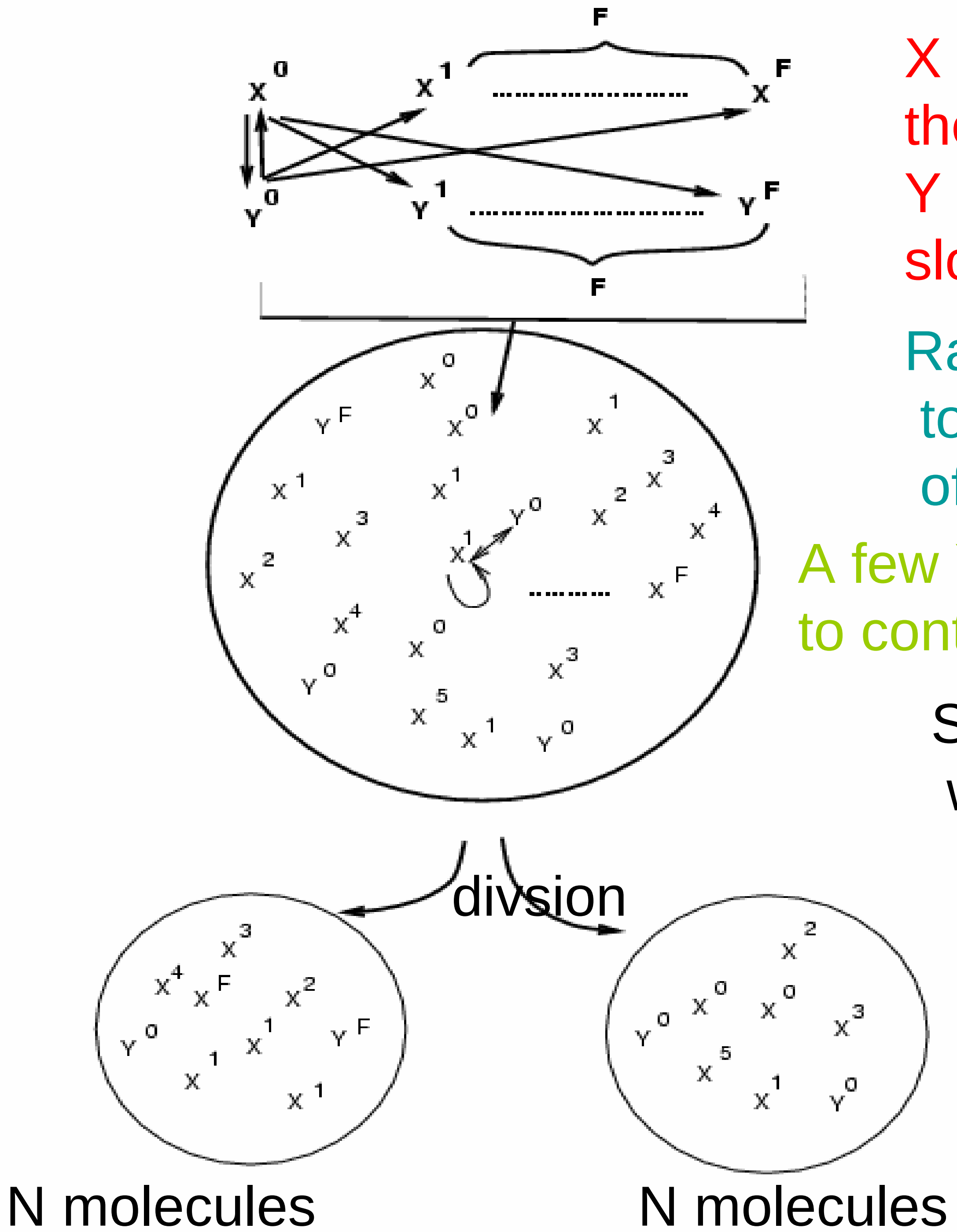
and protein,…

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

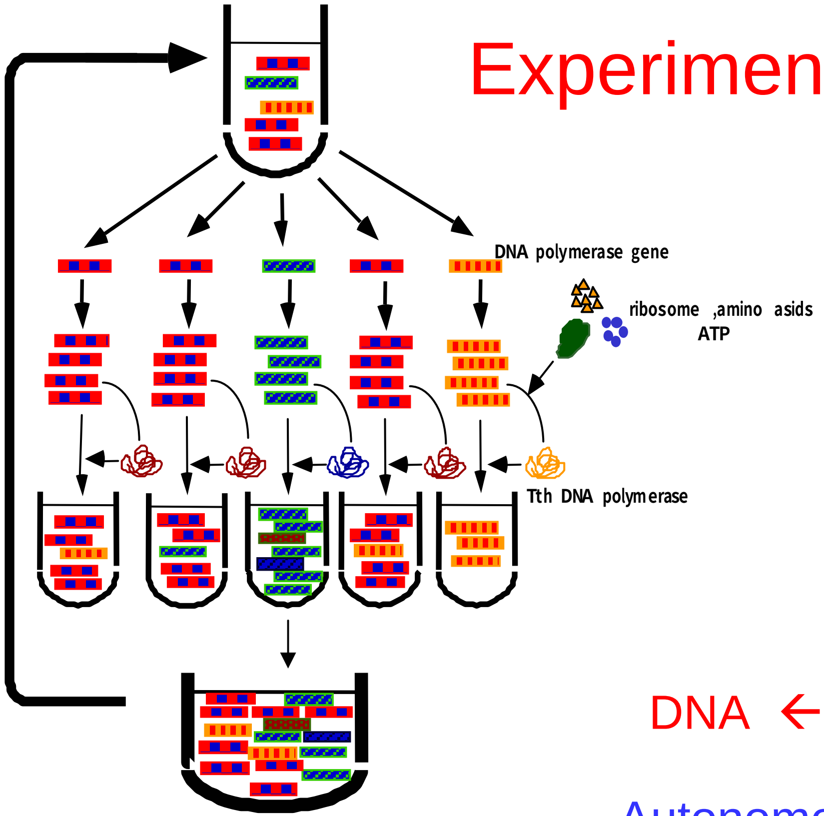
Selected are ‘rare’ states with a few Y molucules

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

Carrier of heredity

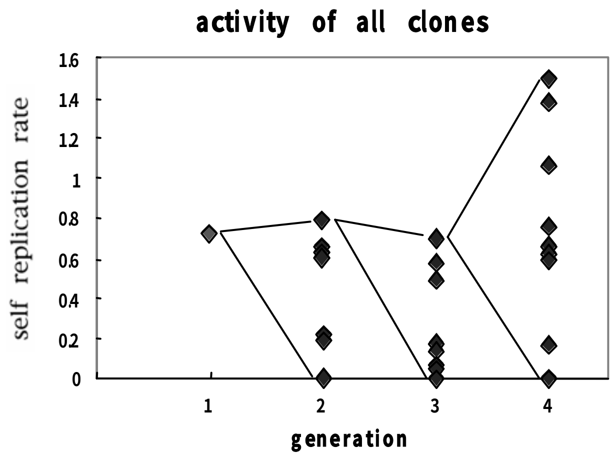
Experimental verification

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

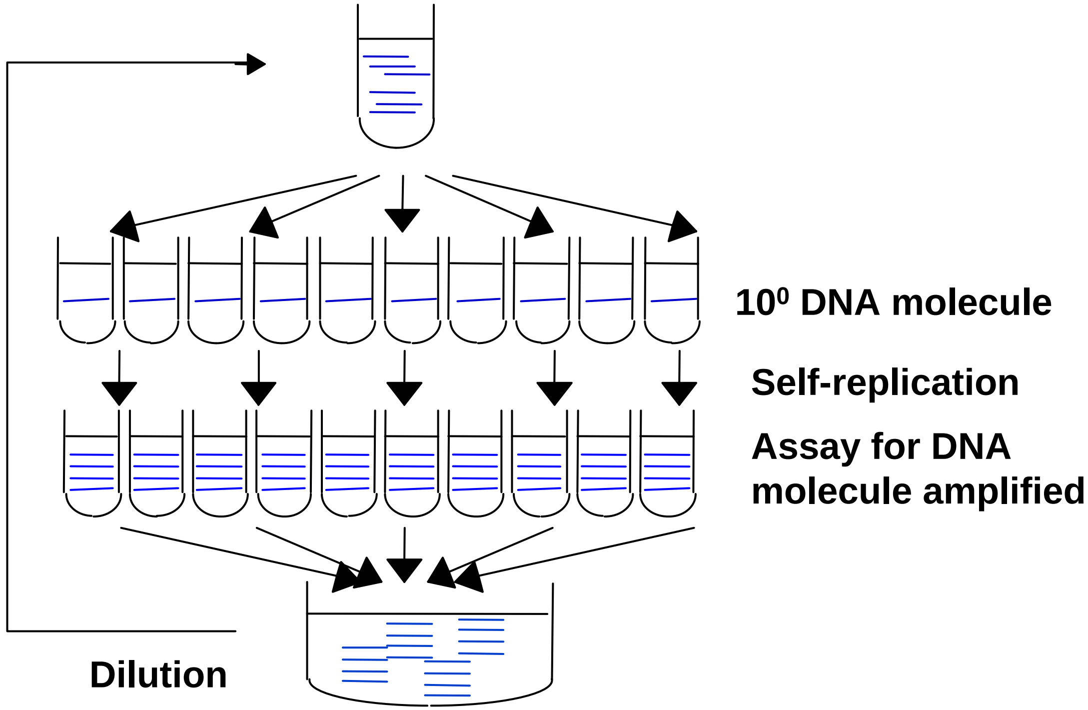


DNA ←→ enzyme

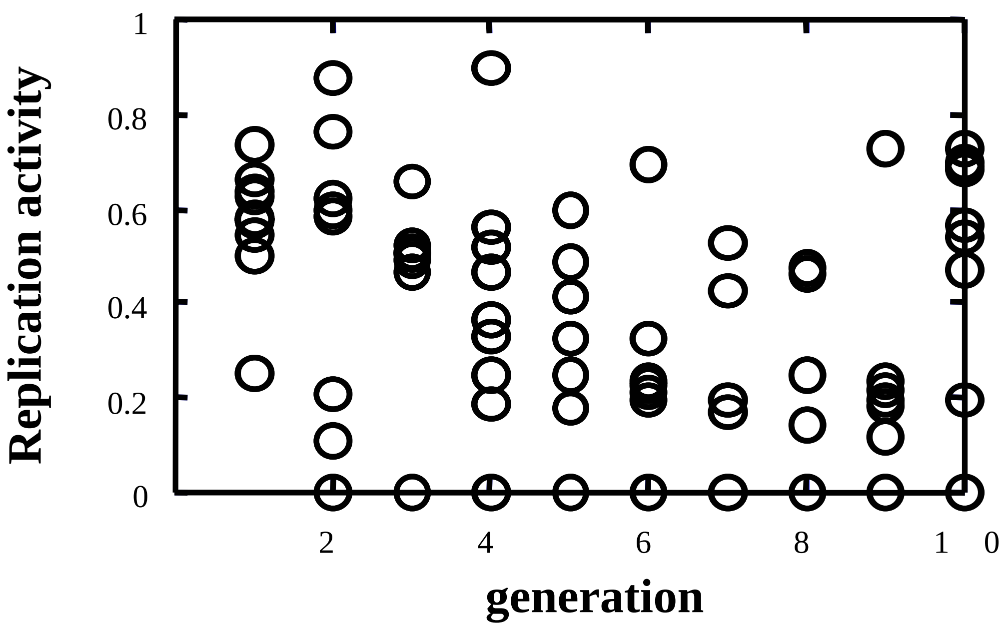
Autonomous Replicating
System (self-contained,
In contrast to PCR)



Matsuura,
Yomo.,…
PNAS 2002

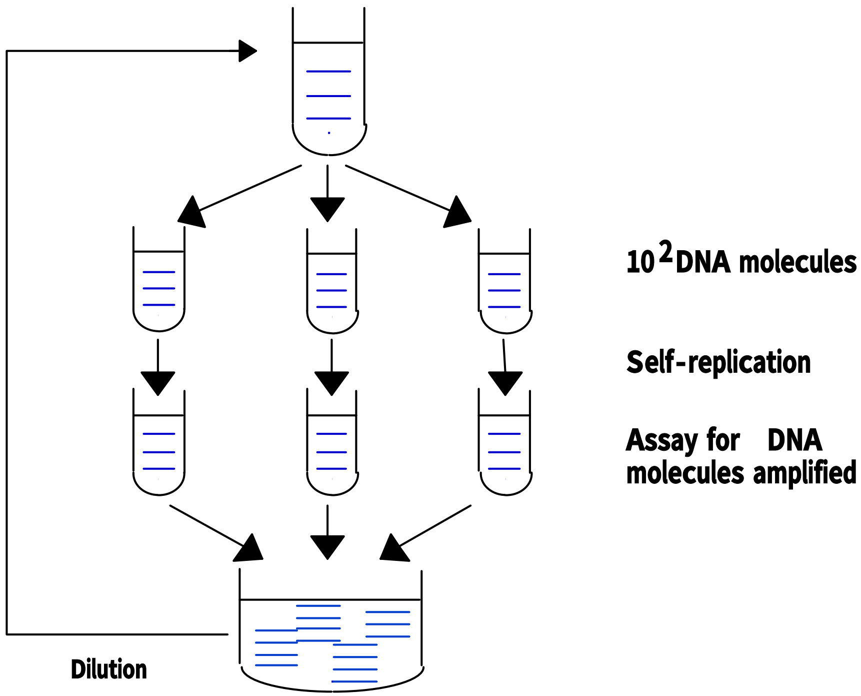


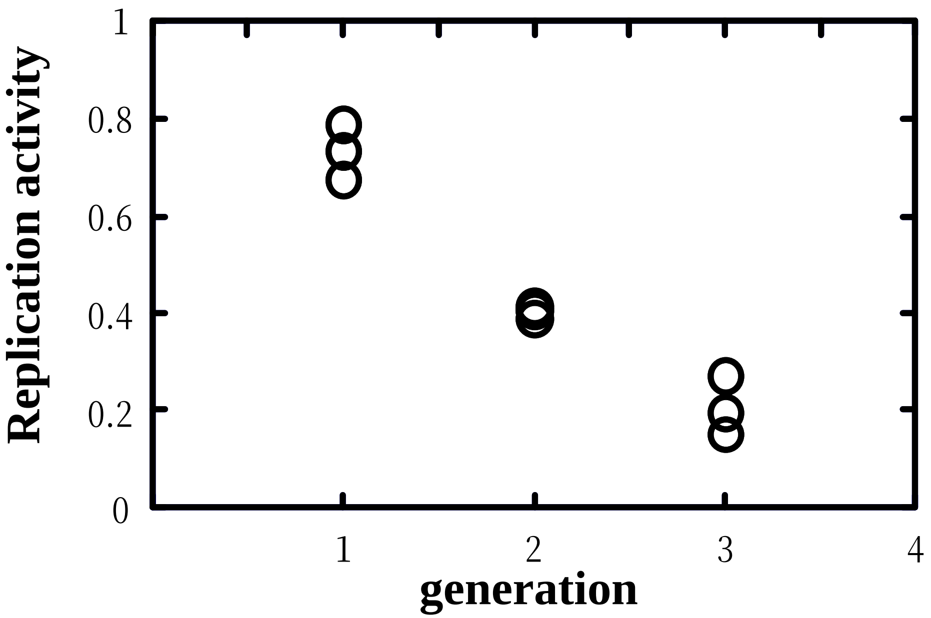
10^0 DNA molecule
Self-replication
Assay for DNA molecule amplified
Dilution



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

１００DNA分子
では
複製能を失う



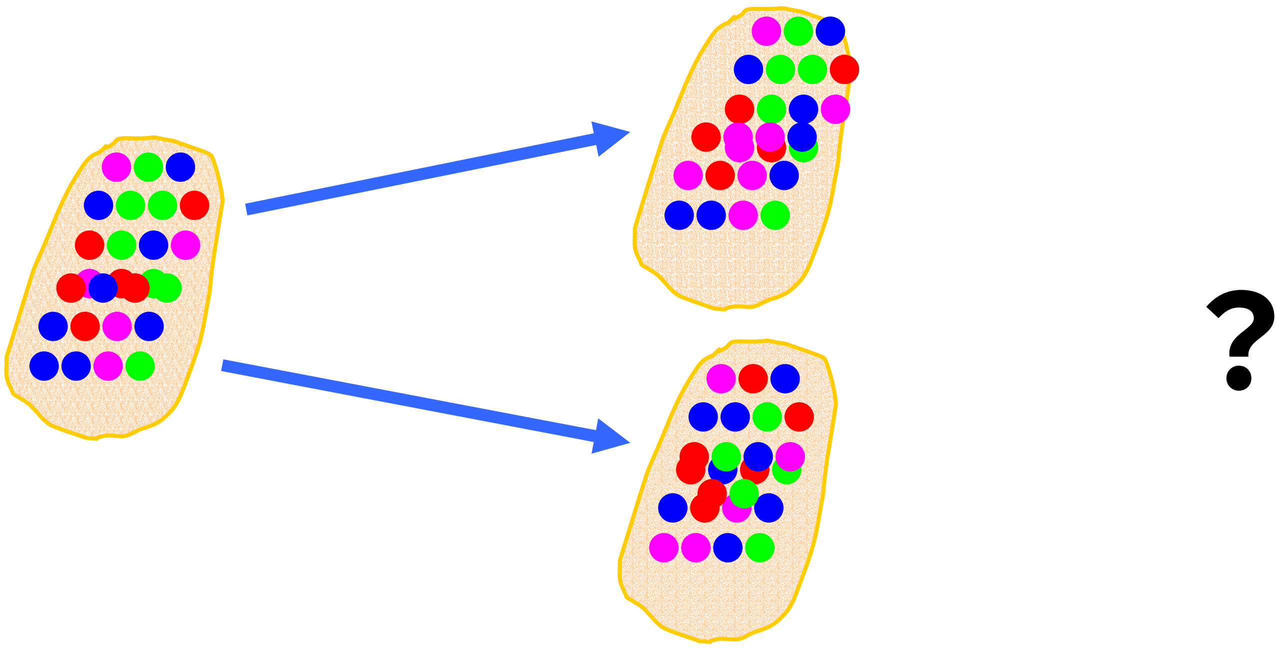


Constructive Biology Project at Komaba Clife group

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,..

複雑な反応ネットワーク
しかし、状態を維持
ほぼ同じものを複製していく。



Toy Cell Model with Catalytic Reaction Network

C.Furusawa & KK

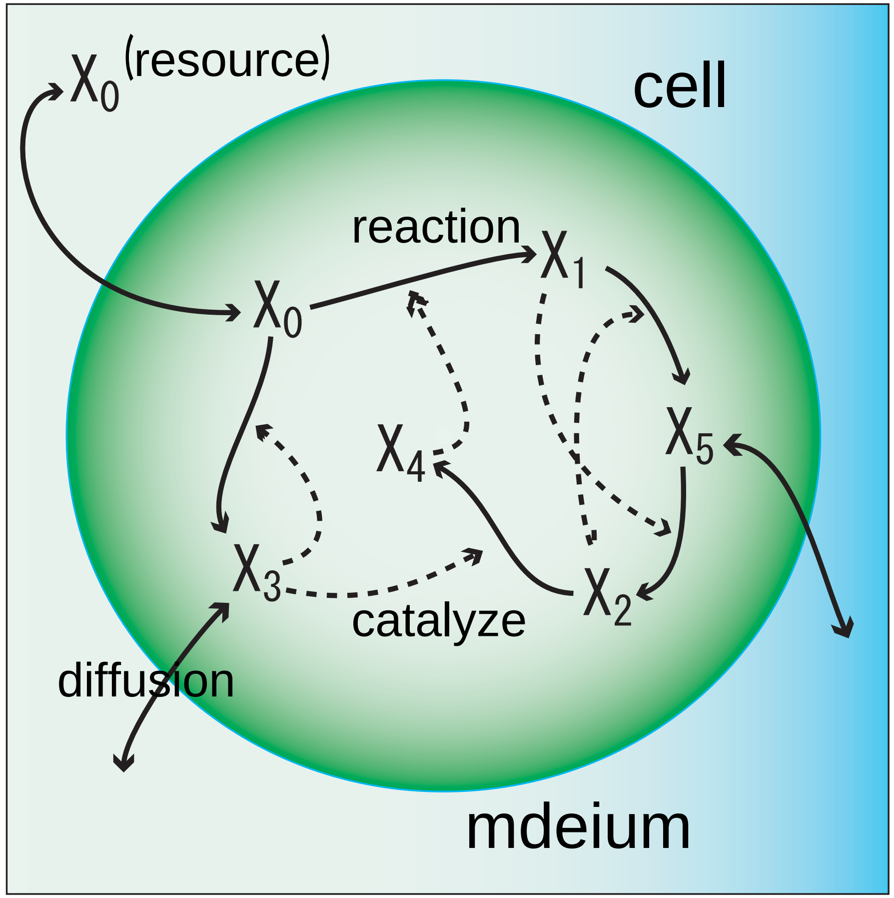
- k species of chemicals、$X_o \cdots X_{k-1}$
number ---n_0、n_1 … n_{k-1}

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

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

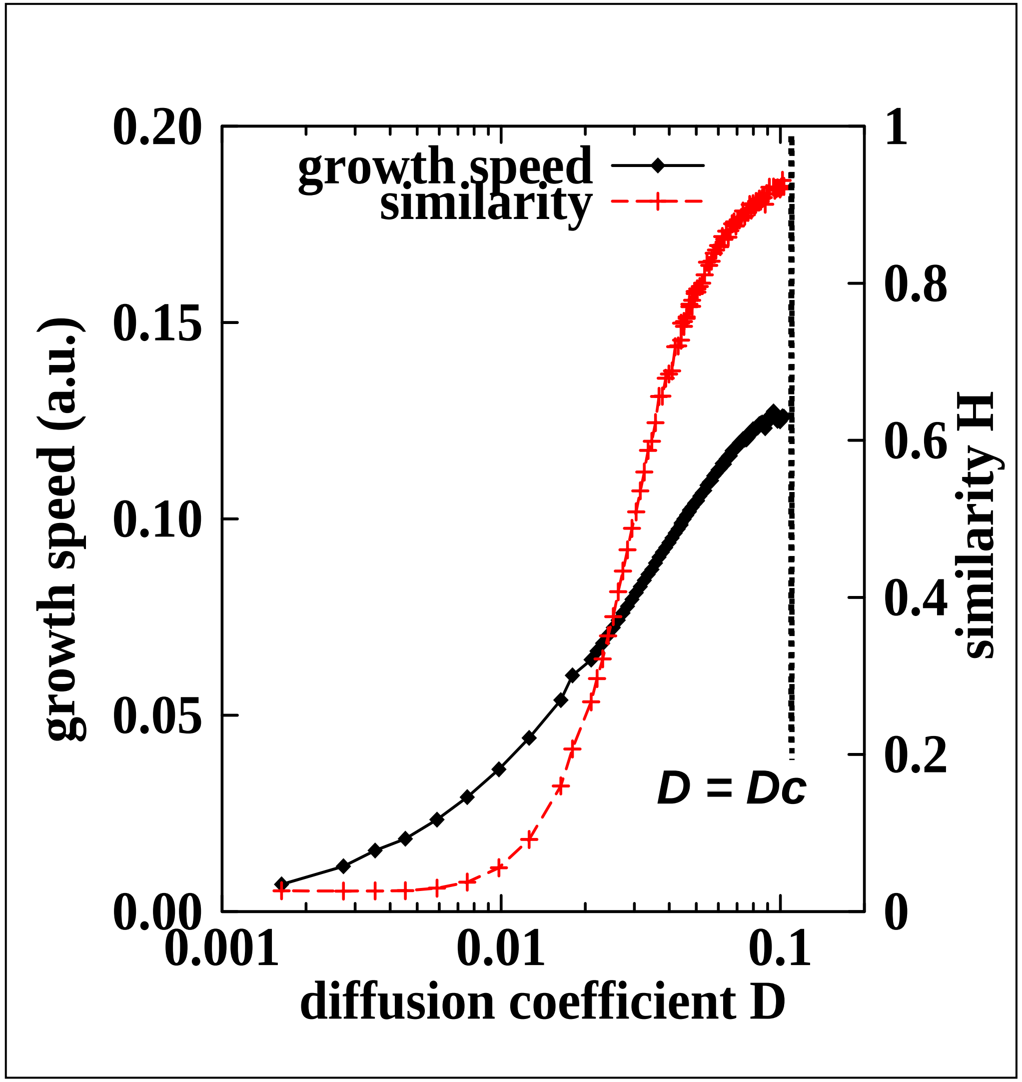
- resource chemicals are thus
transformed into impenetrable
chemicals, leading to the growth in
$N = \Sigma n_i$, when it exceeds N_{max}
 the cell divides into two

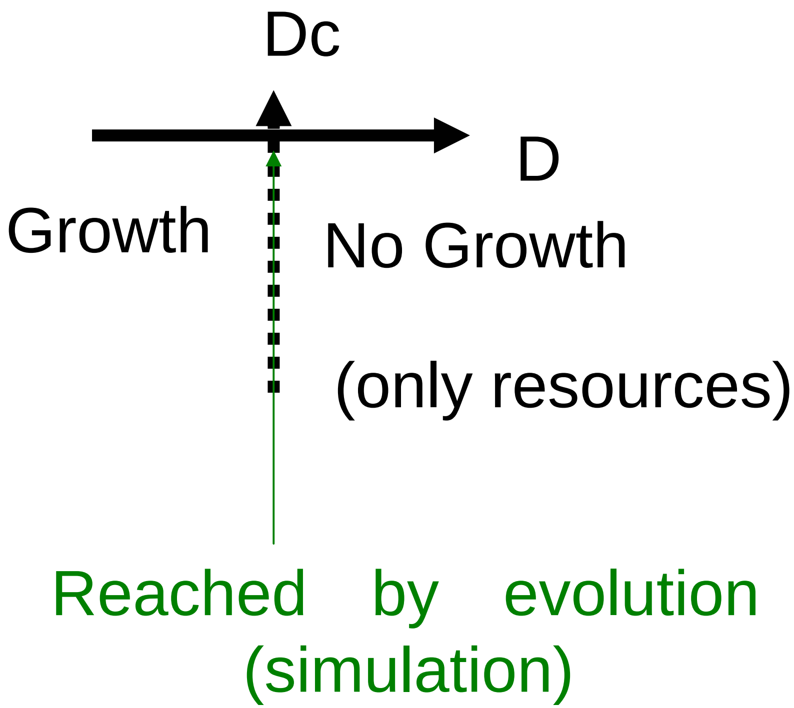
細胞



model

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



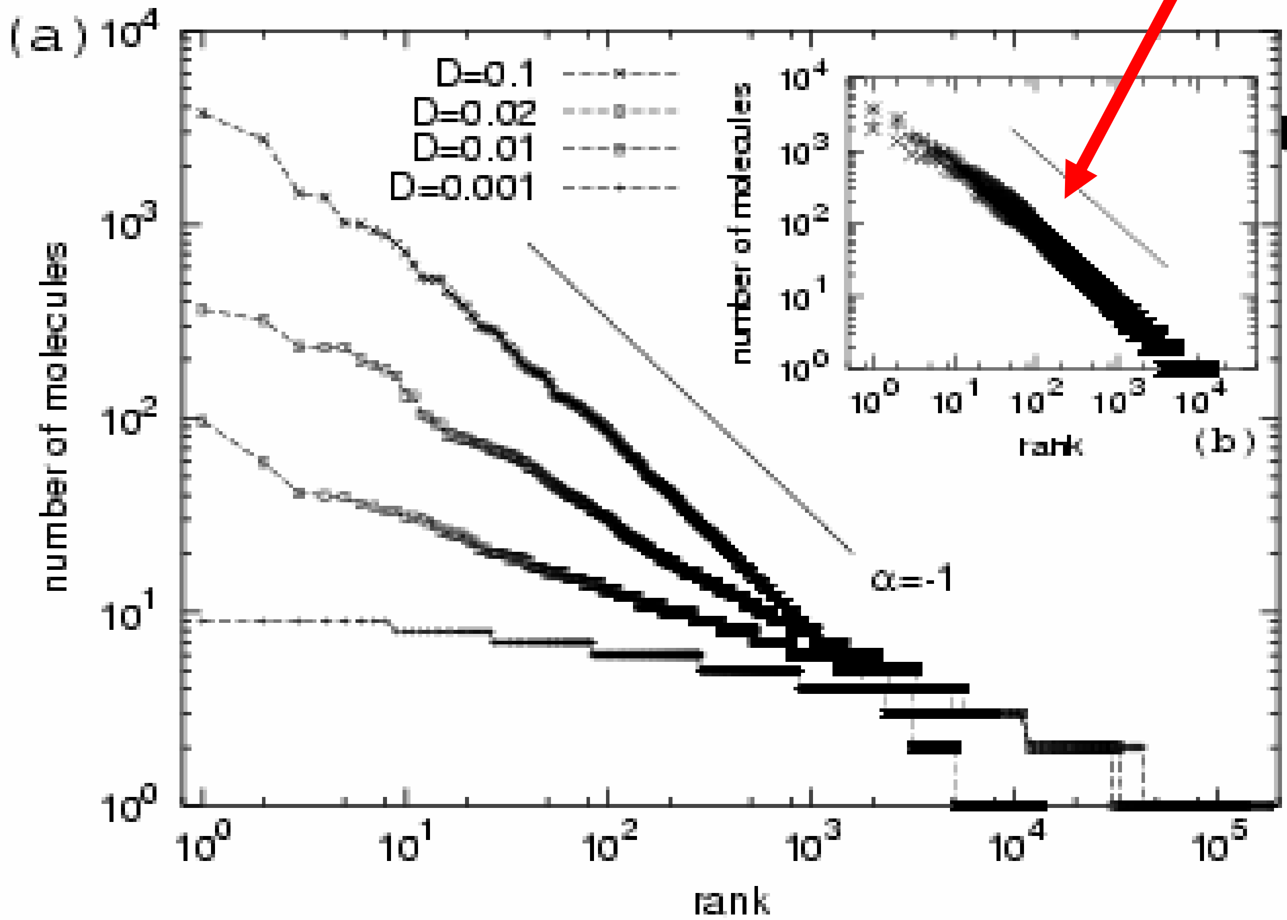


※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

Zipf's Law is observed at D = Dc

Recursive production

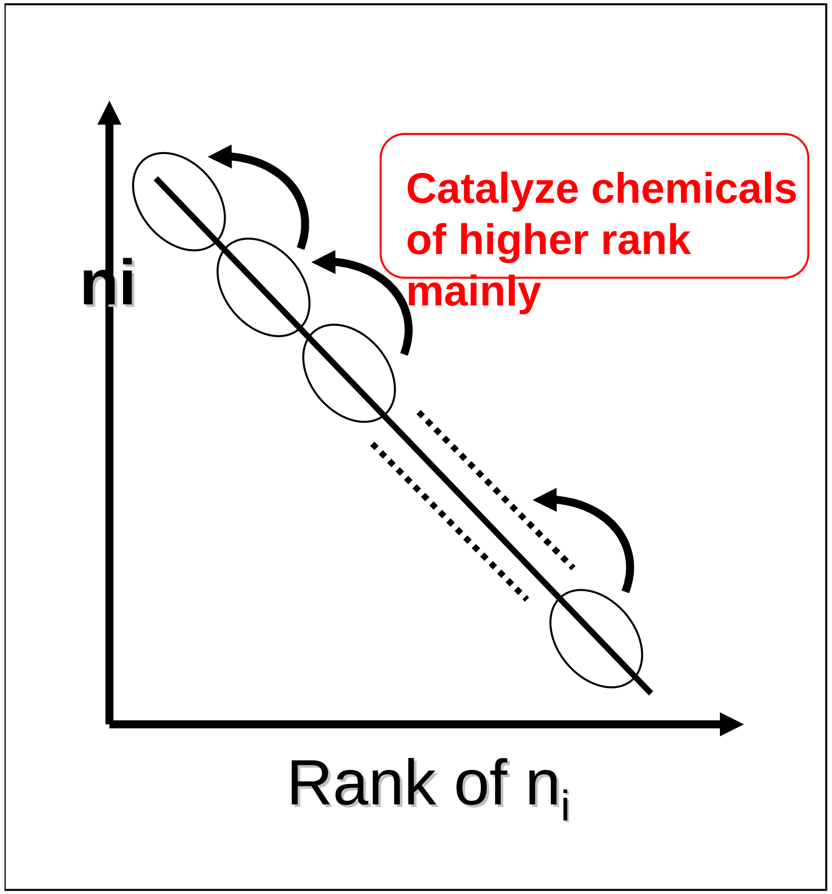


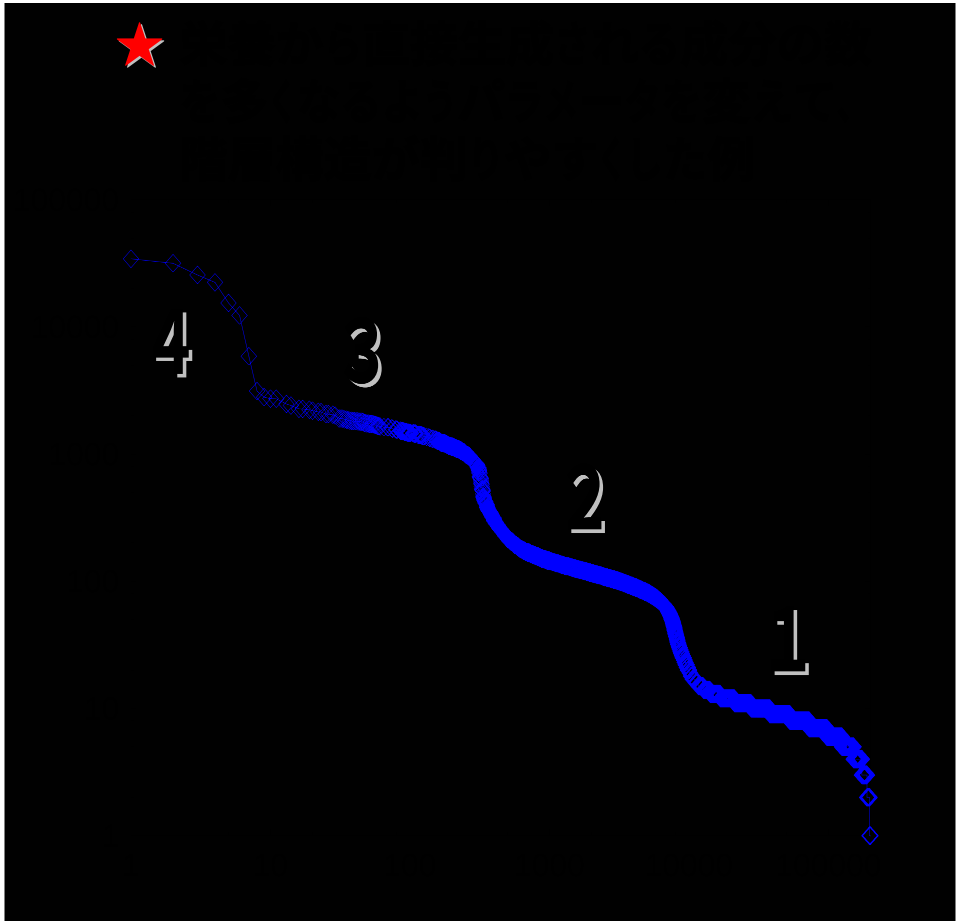
n_i (number of molecules)

rank

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

Formation of cascade catalytic reaction





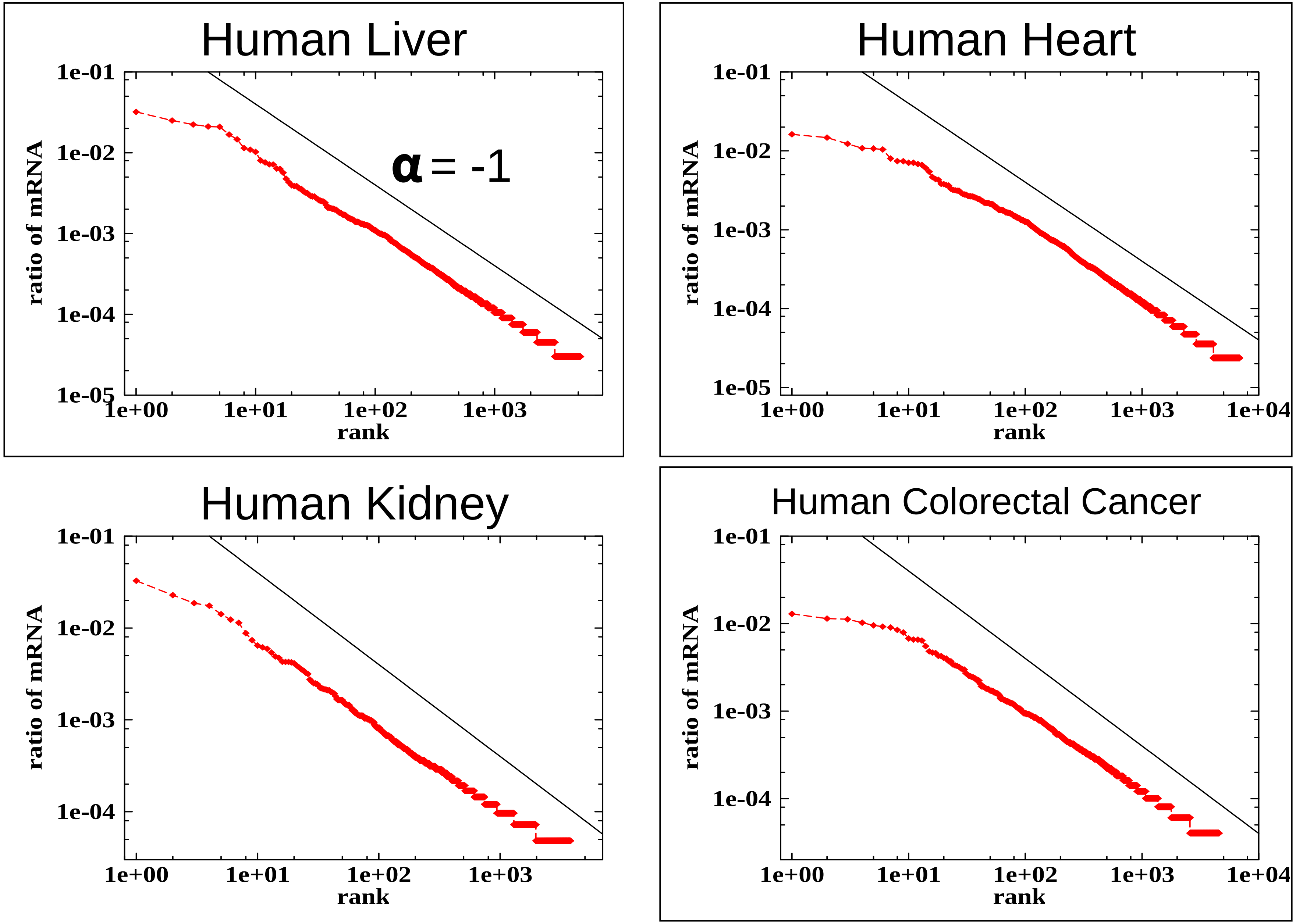
1：minority molecules

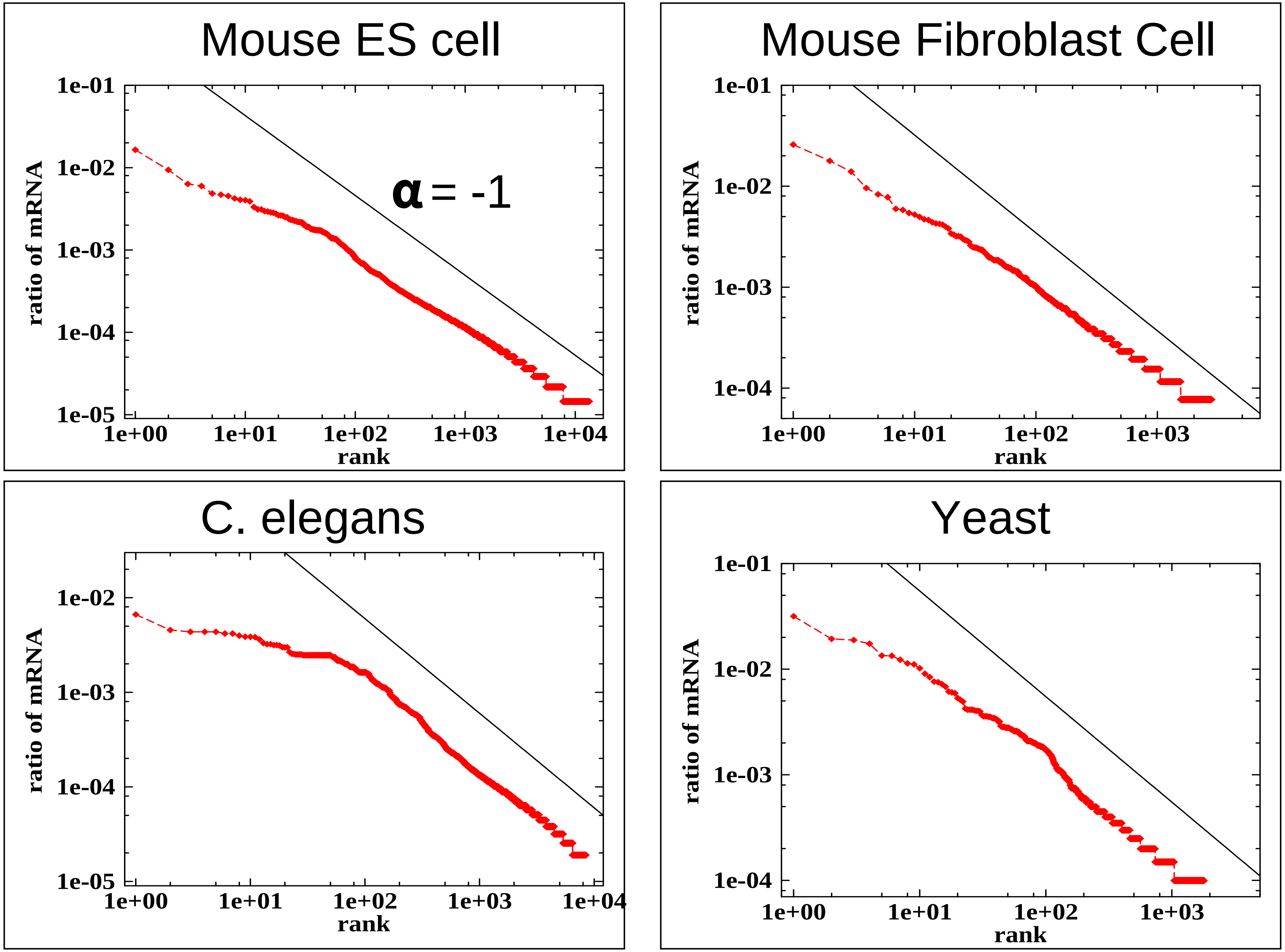
2：catalyzed by 1, synthesized by resource

3：catalyzed by 2

：

Confirmed by gene expression data



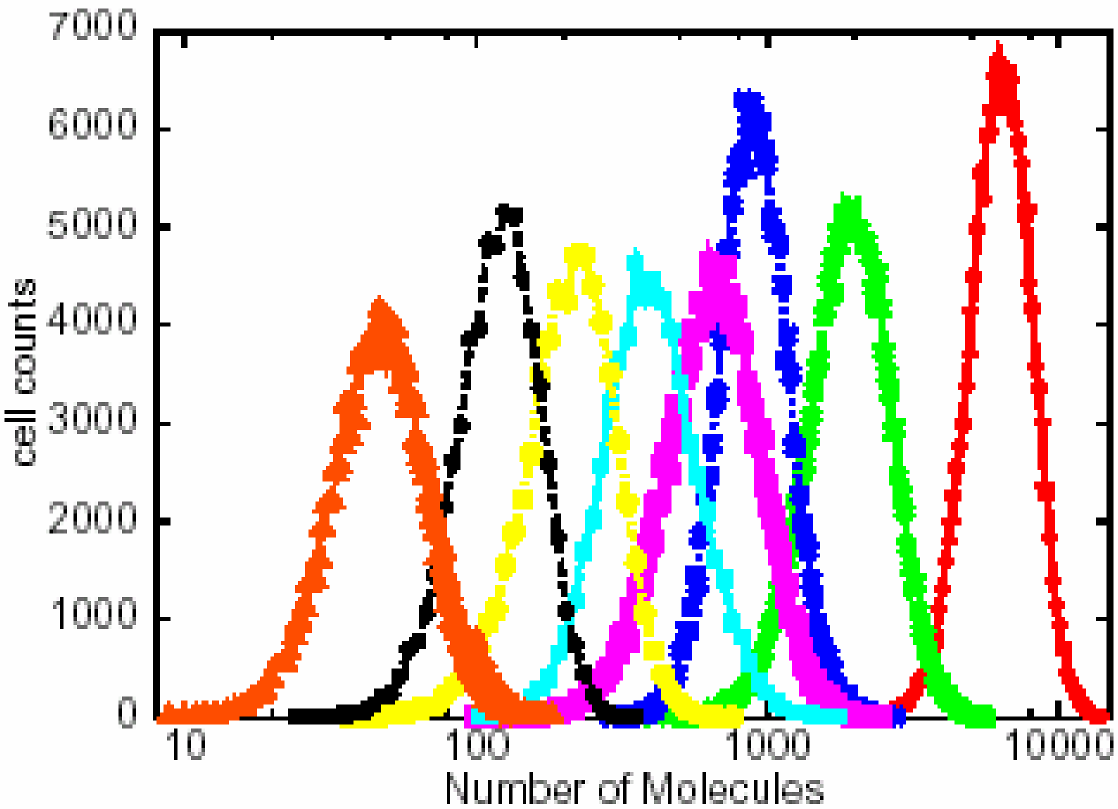

Mouse ES cell
α = -1
ratio of mRNA
rank
1e-01
1e-02
1e-03
1e-04
1e-05
1e+00
1e+01
1e+02
1e+03
1e+04
Mouse Fibroblast Cell
C. elegans
Yeast

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. $\eta(t)$**

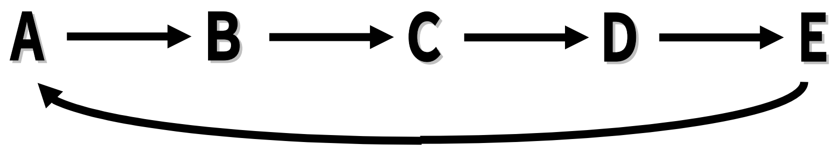
$$d \log(N_X)/dt = < N_A > + \eta(t)$$

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. applied

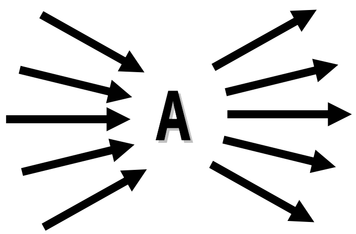
☆Cascade leads to multiplicative propagation of noise (at critical region)



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

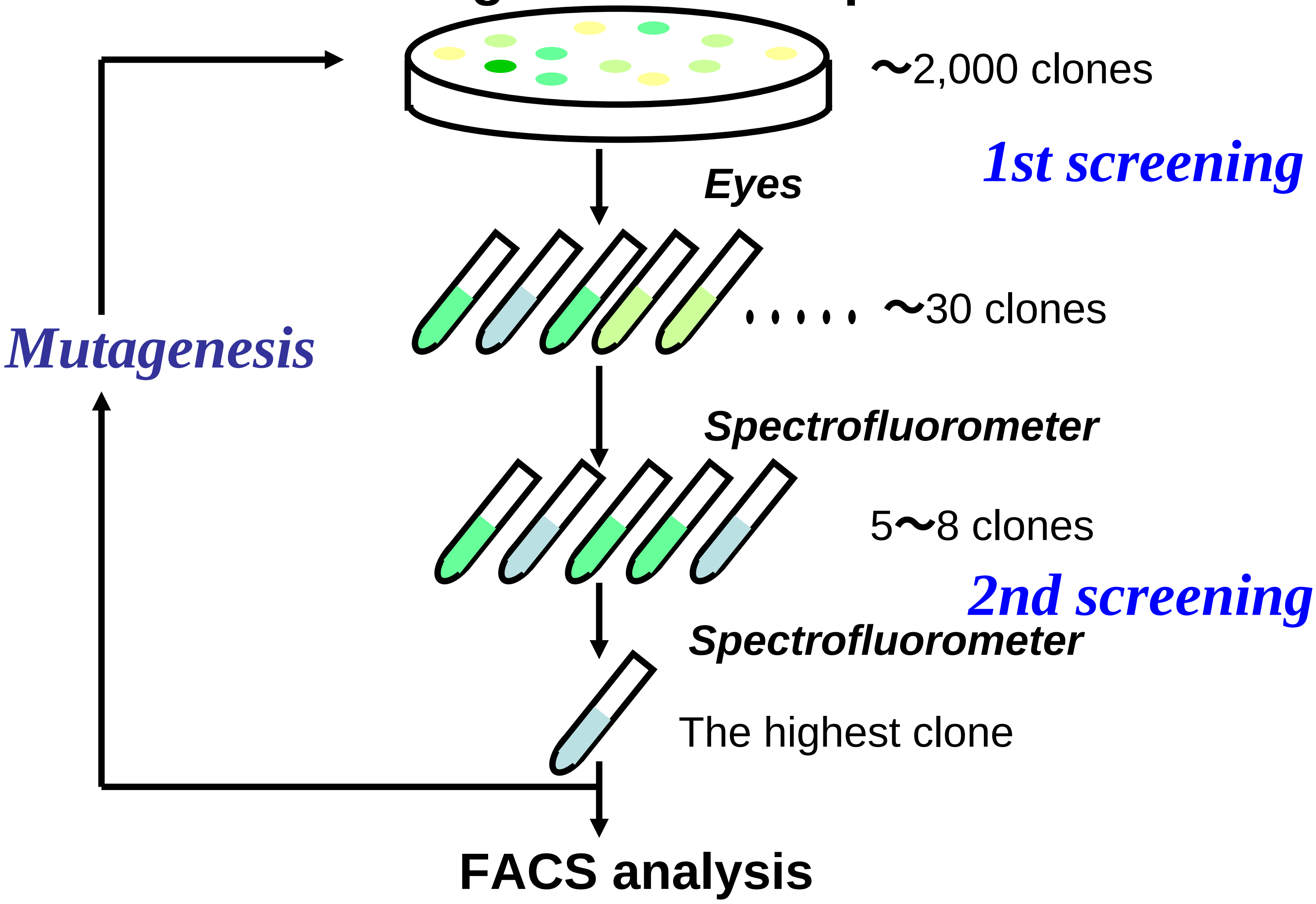
Furusawa. Kashiwagi,Suzuki,Yomo, Kaneko
(submitted) ----- figure is not available at the moment***

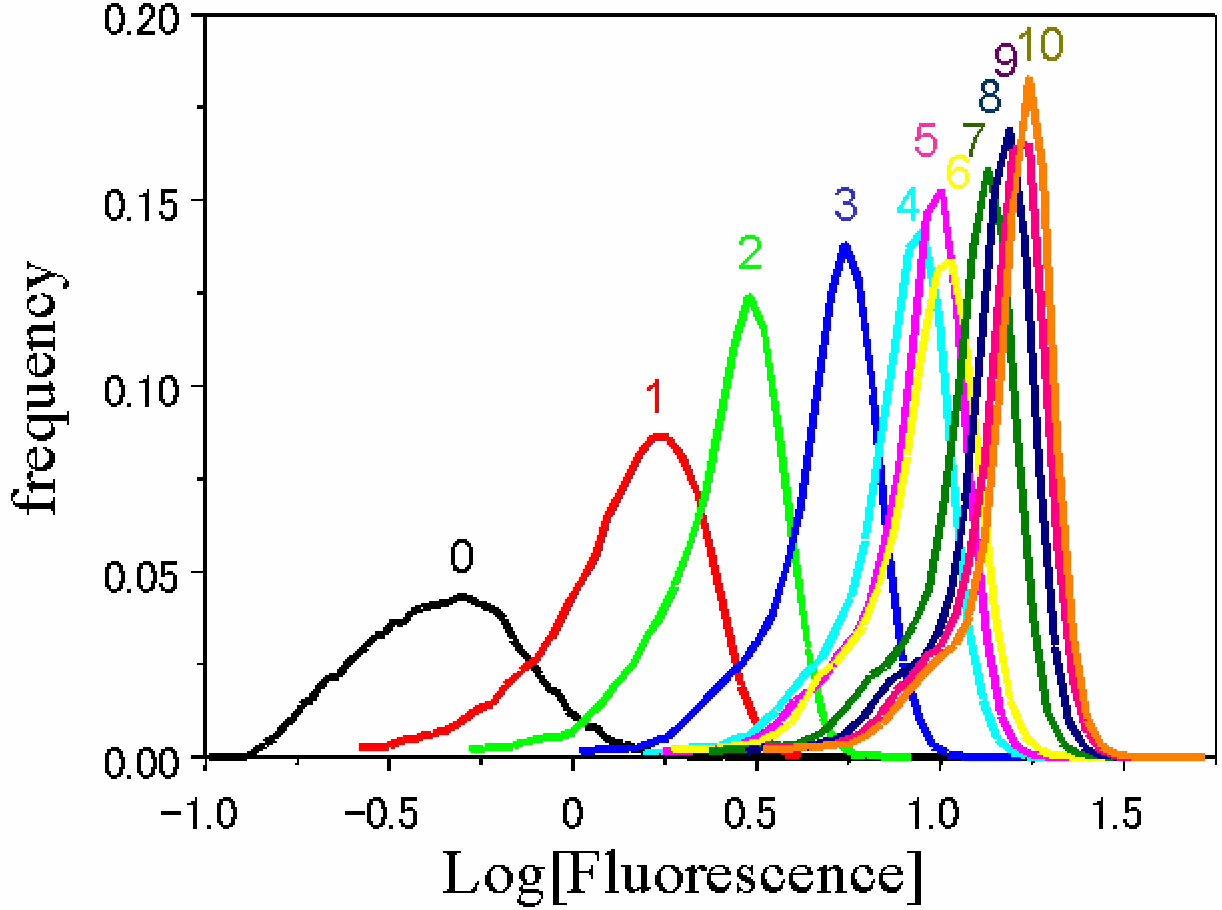
Large phenotypic fluctuation → relevance to evolution (Sato et al., PNAS,2003)

Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria

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)

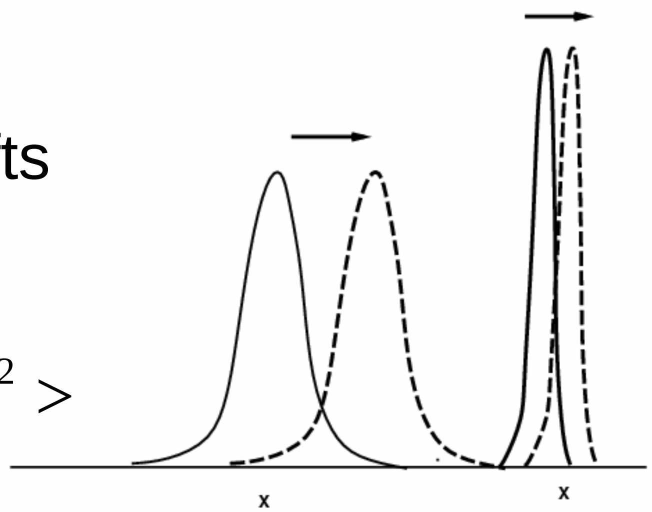
response ratio of some variable x against the change of parameter a versus   fluctuation of x

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

change of the parameter a →

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

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



``Response” ------ change of phenotype

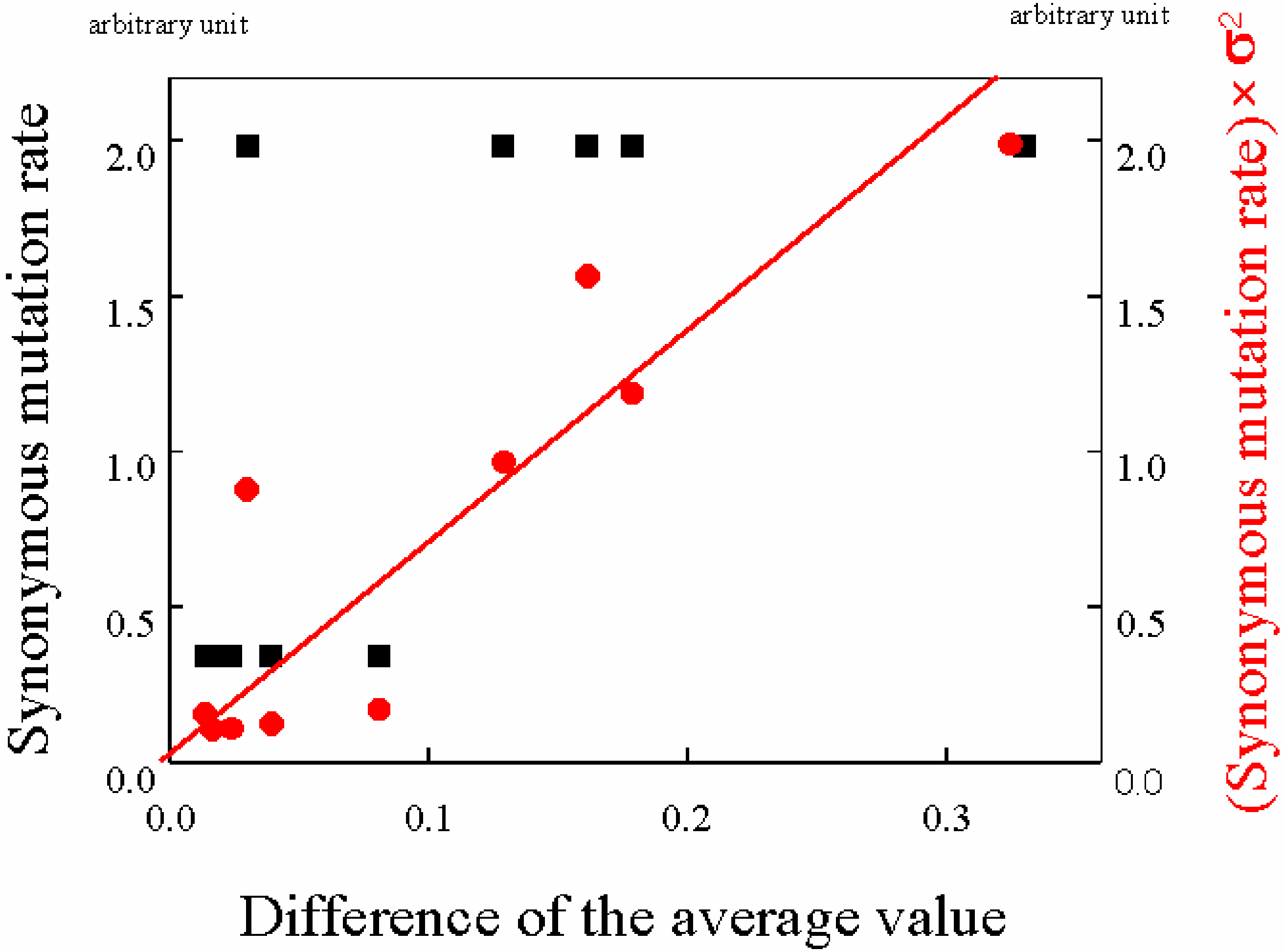
(fluorescence intensity)

per generation per (synonymous) mutation rate

Fluctuation ---- Variance of phenotype of clone

Response proportional to Fluctuation ?

For variables close to Gaussian distribution → for log x



(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?

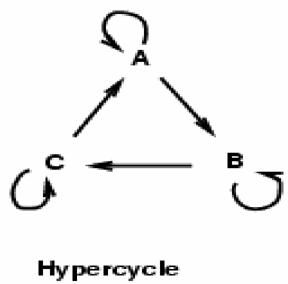
Minority molecules?

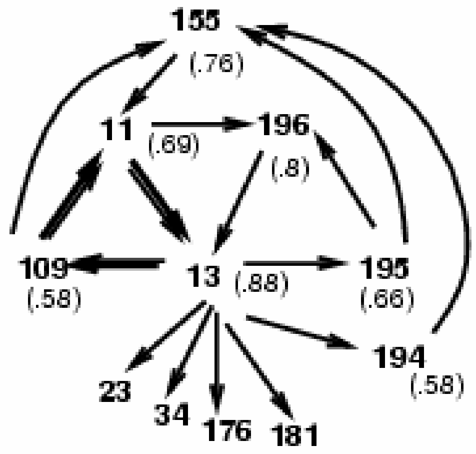
Model including a loop of mutually catalytic reactions, → components in a small autocatalytic loop (hypercylce) deviate to 'Gaussian'; deviation possible either by small feedback loop or parallel paths (i.e., addition instead of multiplication!)

(KK,PRE 2003)

'

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





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

My guess: statistical physicists like power law or log-normal distribution, since they are uncommon.

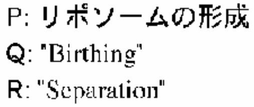
But, they are so common in a biological system with reproduction.

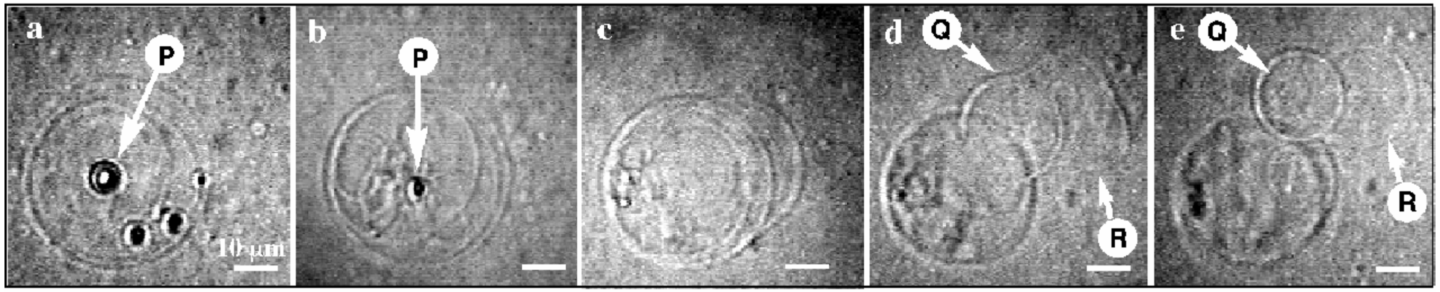
Important is deviation from them

Including instability in intra-cellular dynamics & internal reaction dynamics -→ (irreversible) cell differentiation from stem cell, robust development, pattern formation

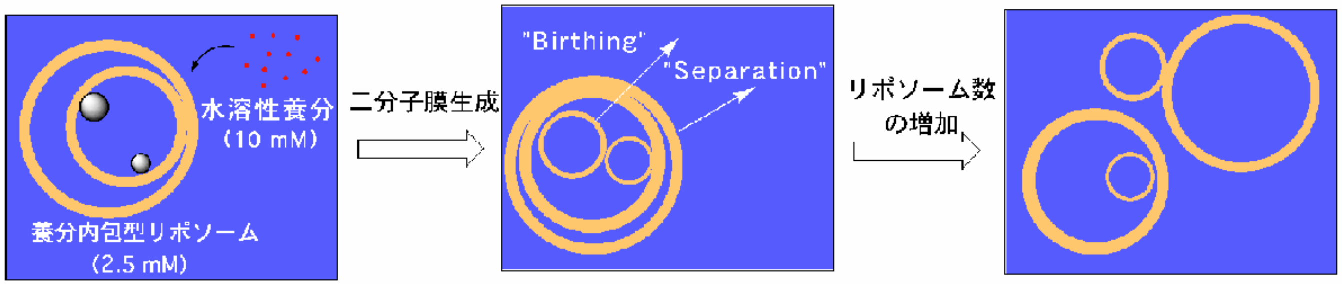
(KK,Yomo,Furusawa, 1997-2003)

• 養分をとりこみ複製するベシクル (油の膜) の系の構築:

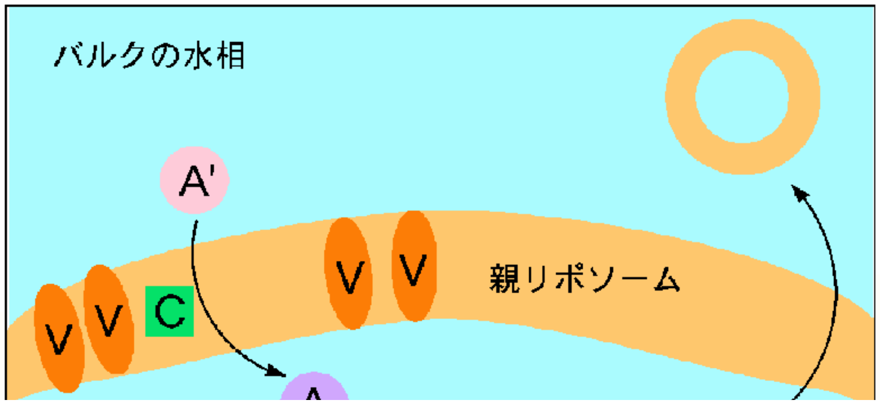


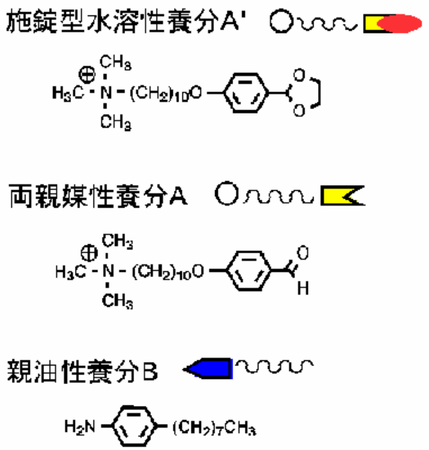


10分後　20分後　23分後　26分後



内部の油脂養分がリポソームに変化し、さらに生成したリポソームがバルクの水相に放出された。

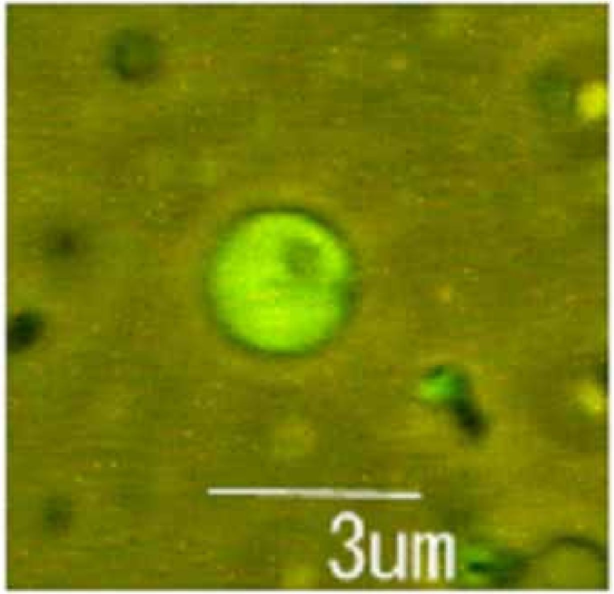


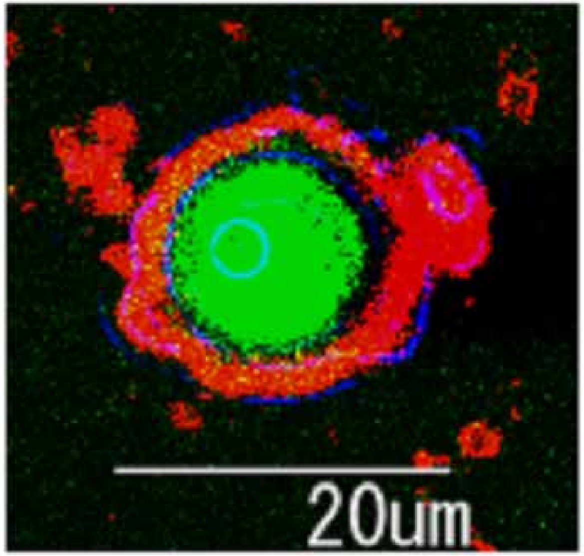


Sugawara Group

Pioneer: Luisi

ベシクル内での転写翻訳(RNA複製) および
タンパク質合成ーーそれぞれは成功



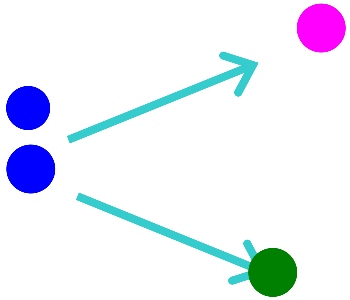


Yomo

膜複製と組み合わせれば自律複製細胞系の完成？
まだ：：：プロセスの干渉が邪魔？

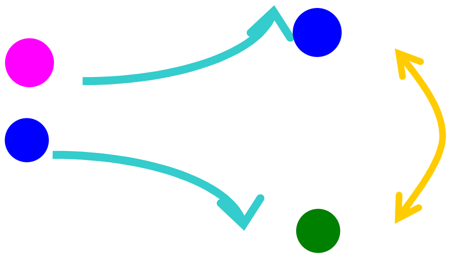
minorityのbottleneck効果必要？
環境のスイッチ的変動？
外部環境の上で？　（Cairns-Smith,　Szostak)

多様化　細胞分化、種の分化、………
同じものが異なるには ————
[通常の考え]



←異なるための
「原因」を探れ！

「原因」がゆらぐとエラー
[別な見方]　——力学系･カオス



小さなゆらぎ

ゆらぎを増巾して
異なる

互いに影響しあって安定化

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,..

Development and Differentiation

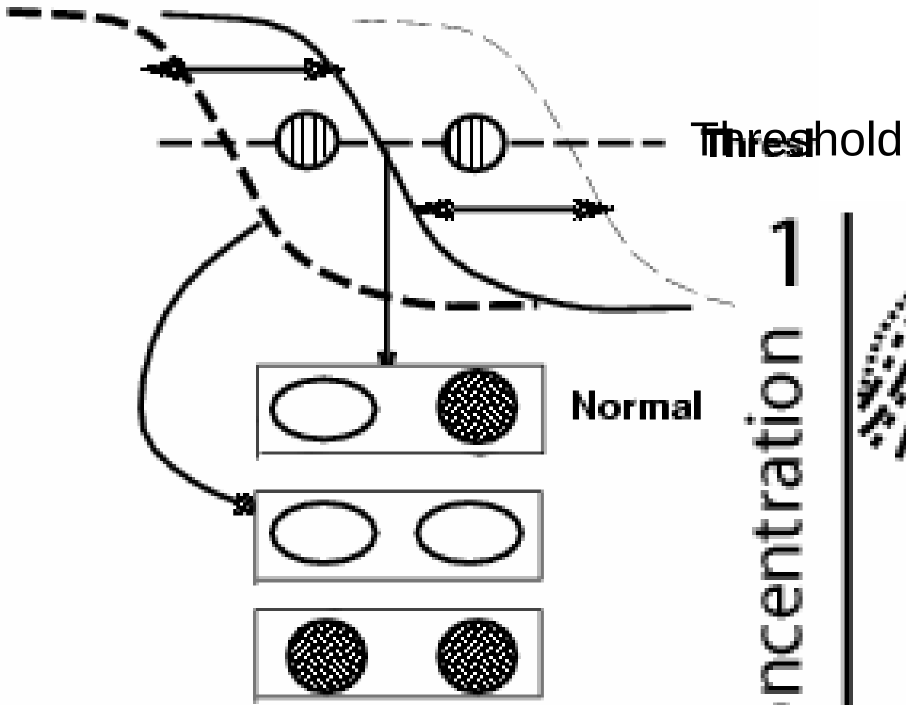
Question
Robustness in development under large fluctuation}

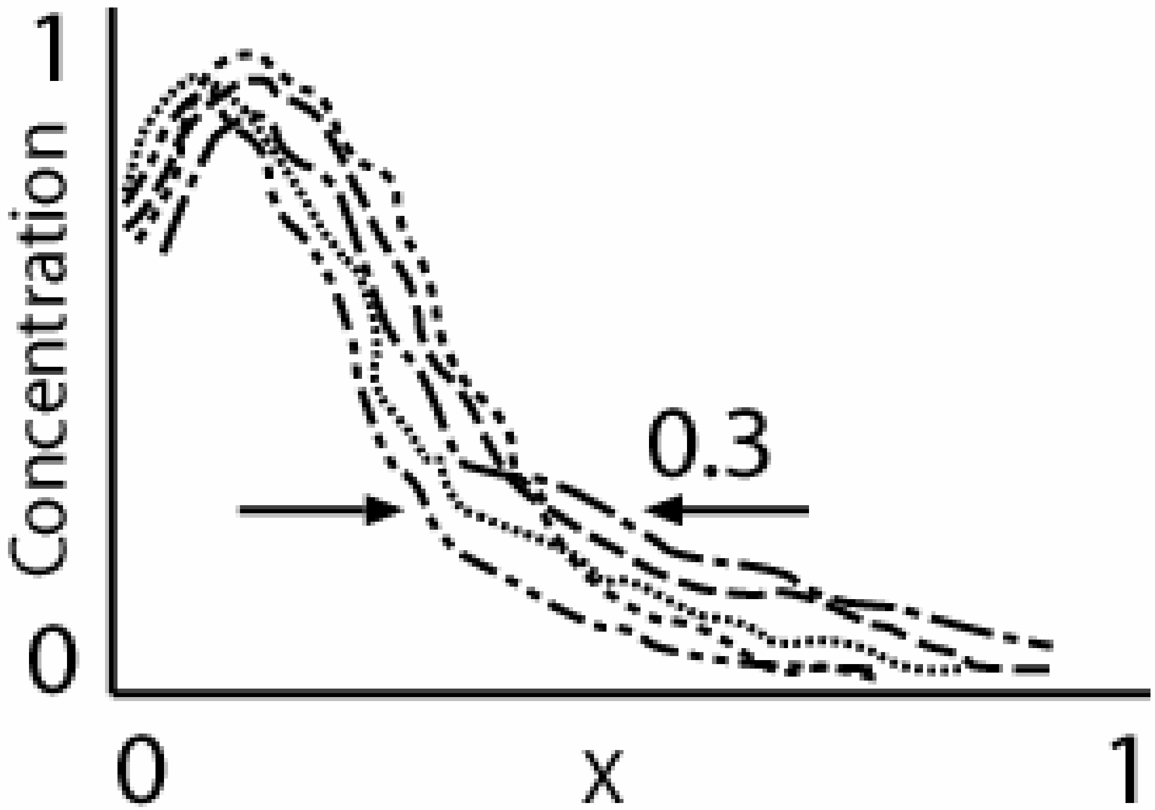
(signal) molecules of few number -- relevant;
Still robust process (e.g., development)

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

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

Example: chemical reaction network

specialize in the use of some path

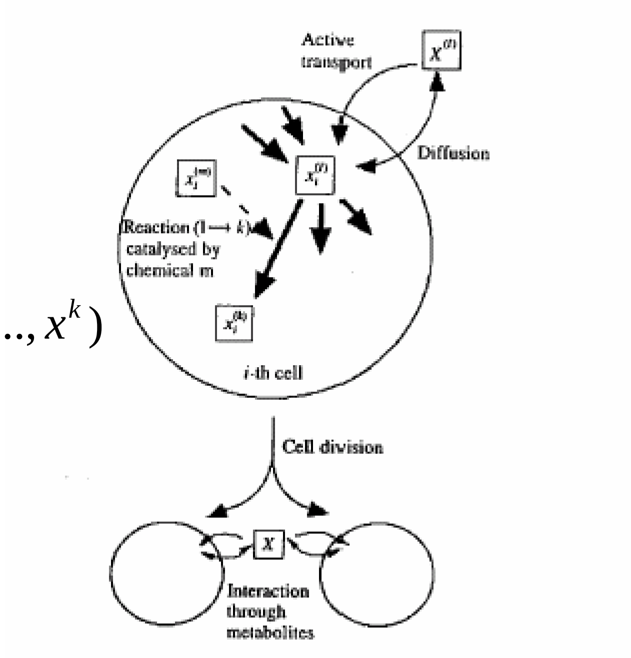
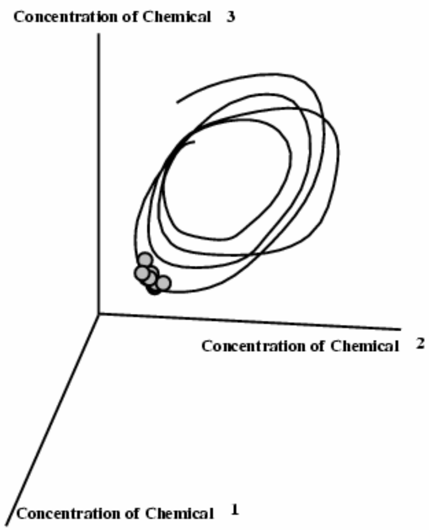


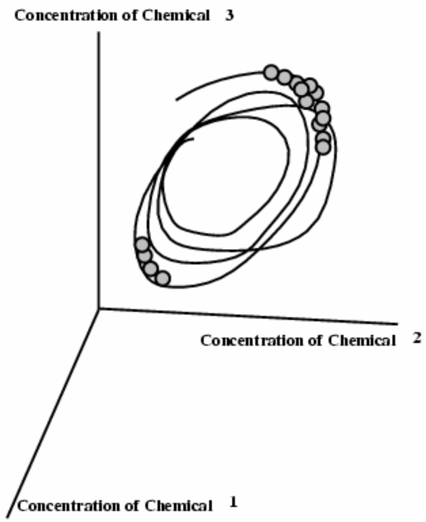
FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

synchronous division:
no differentiation



(a)

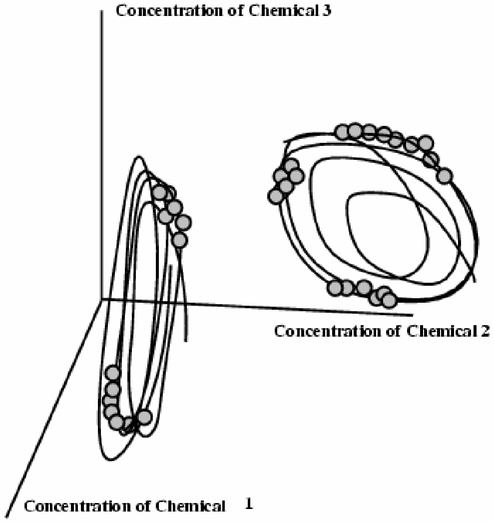
Instability of homogeneous state
through cell-cell interaction



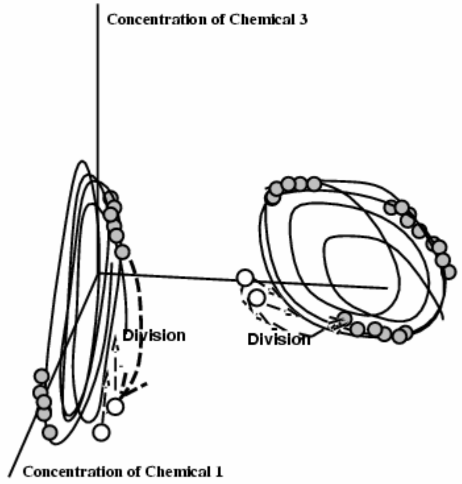
(a)

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

recursive production



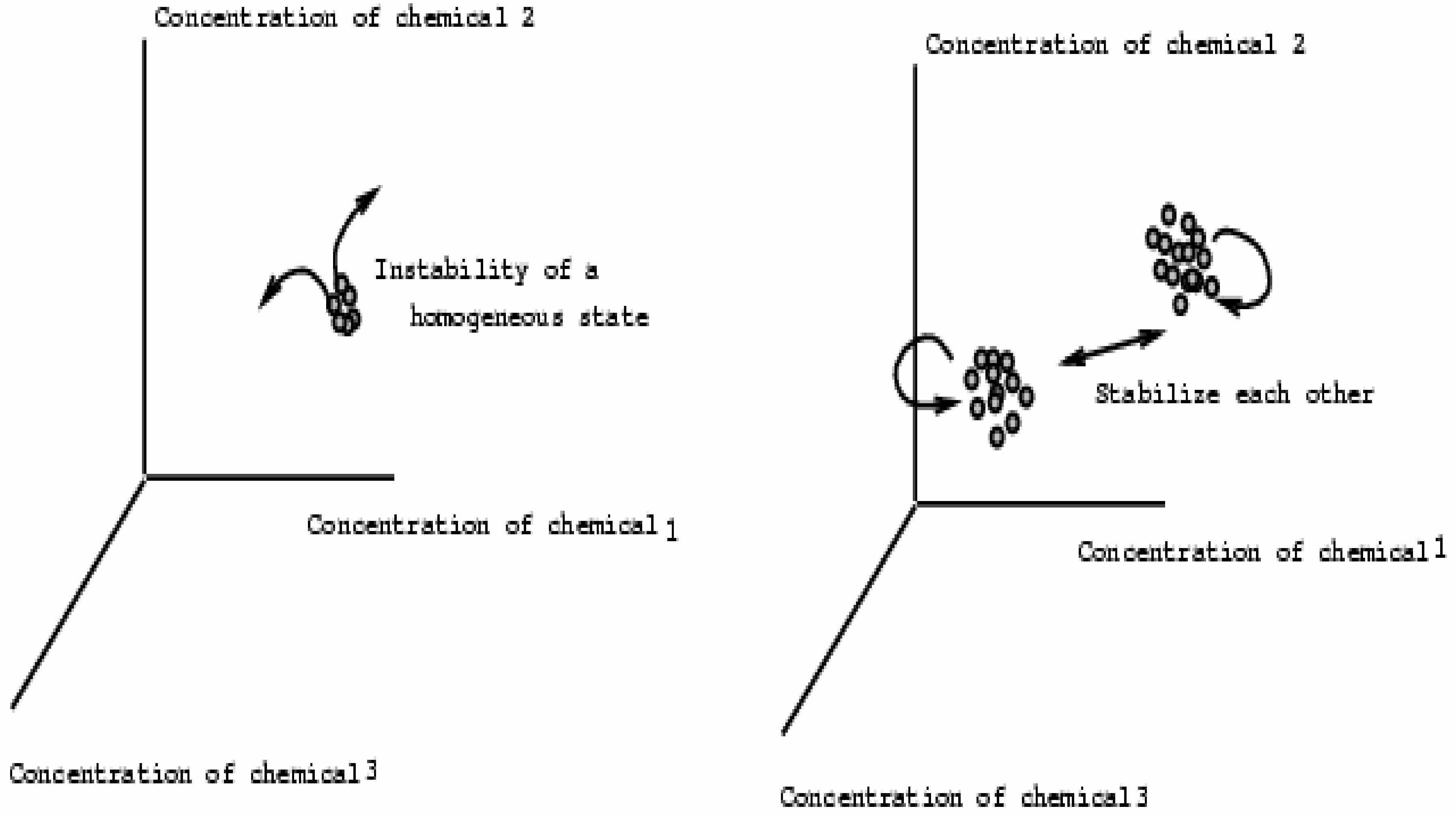
(b)



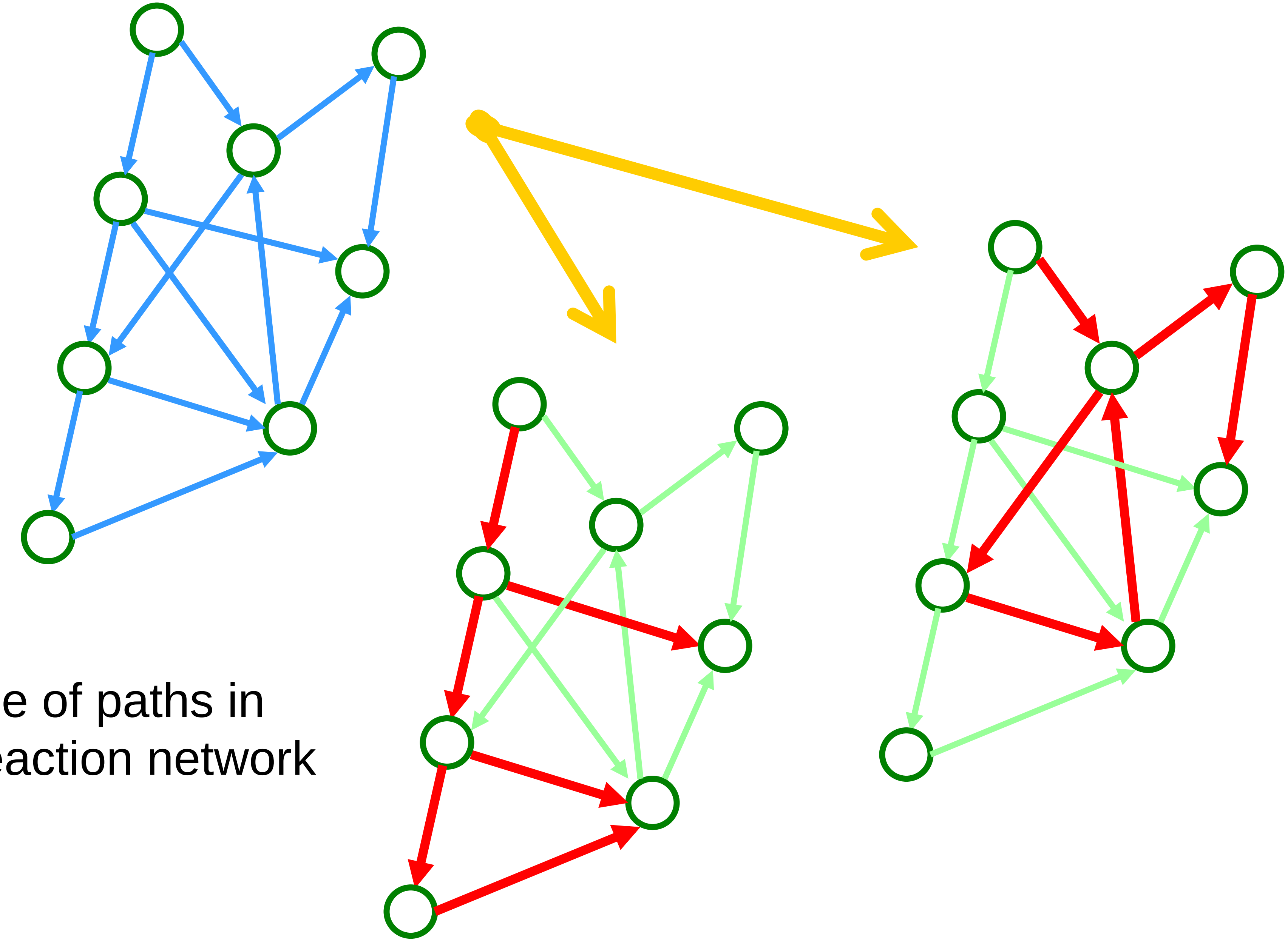
(c)

- (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)



Use of paths in
Reaction network

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;

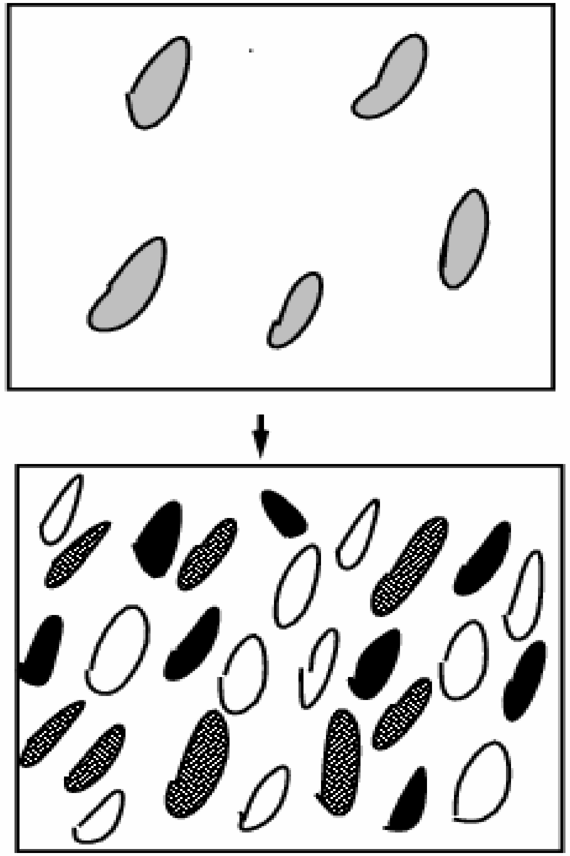
i.e., type A and type B, determined

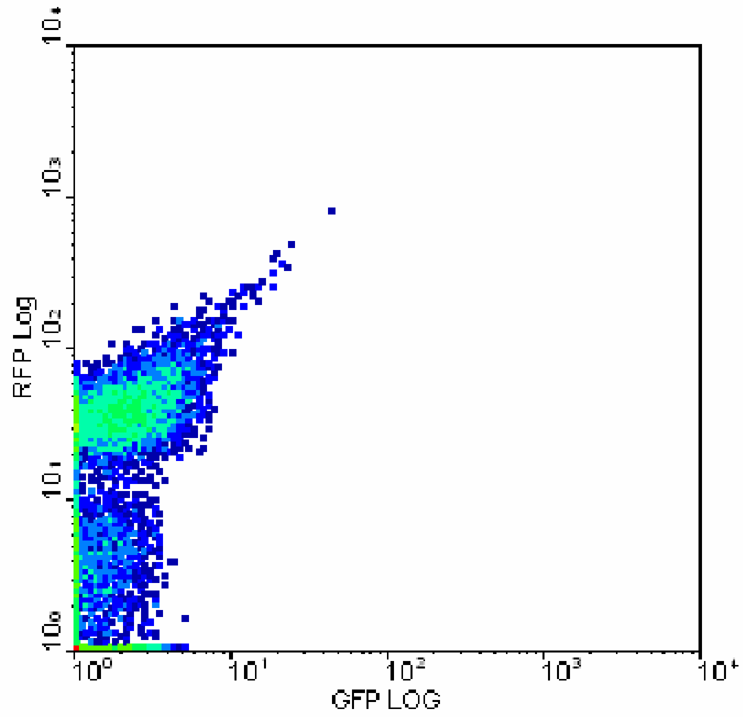
but if type A is eliminated, then B de-differentiates

and initial A-B cell ensemble is recovered

(since A,B is stabilized each other)

Differentiation of E Coli



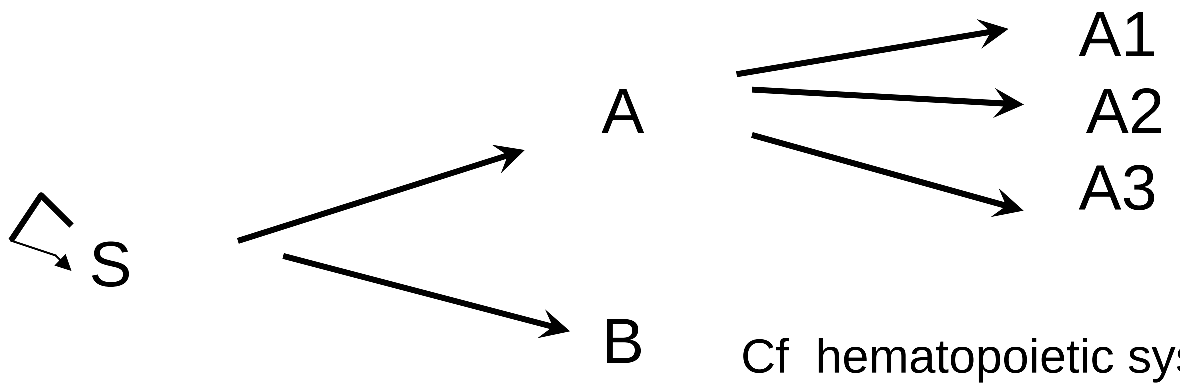


Measurement by fluoresecent proteins

Character of bacteria differentiate in a crowded condition

(Kashiwagi, Yomo,…)

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*

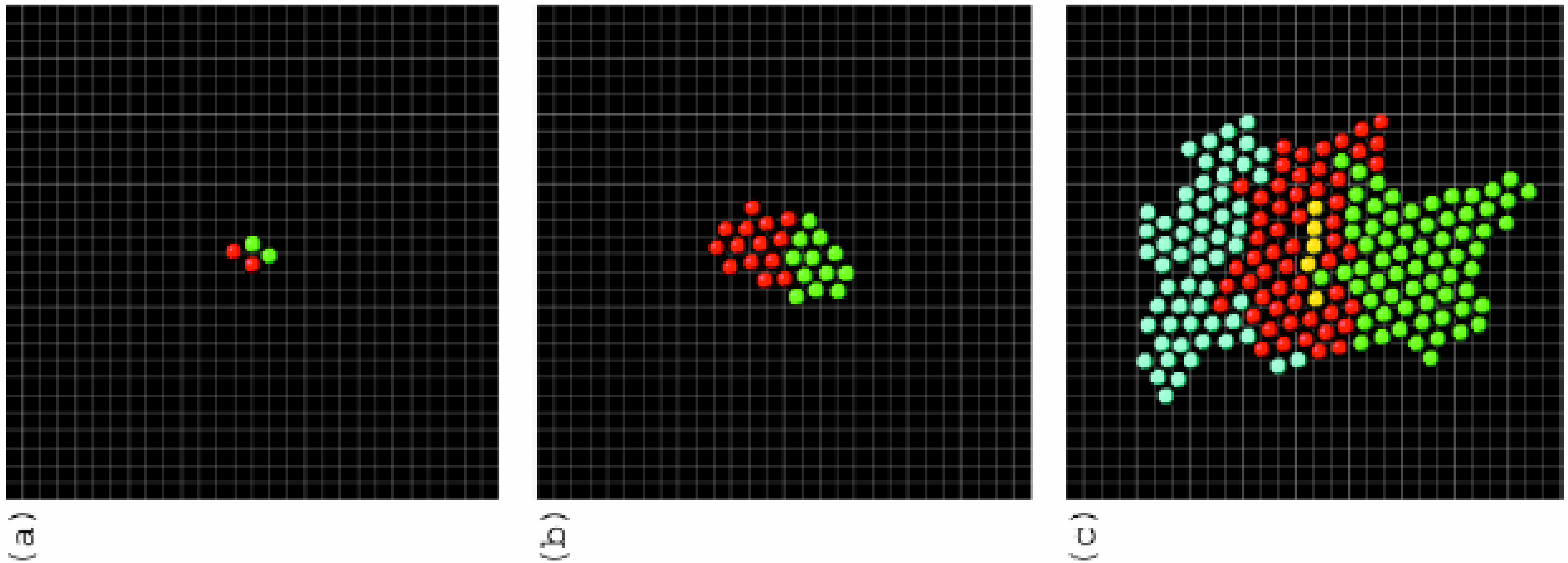
if #(A) ↘ then *pA* ↗

—— global info. is embedded into internal cell states

→STABILITY

(4) Differentiation of cell ensemble (tissue)

——multiple stable distrib. { N_i }



Chemical Gradient for Positional Information is generated

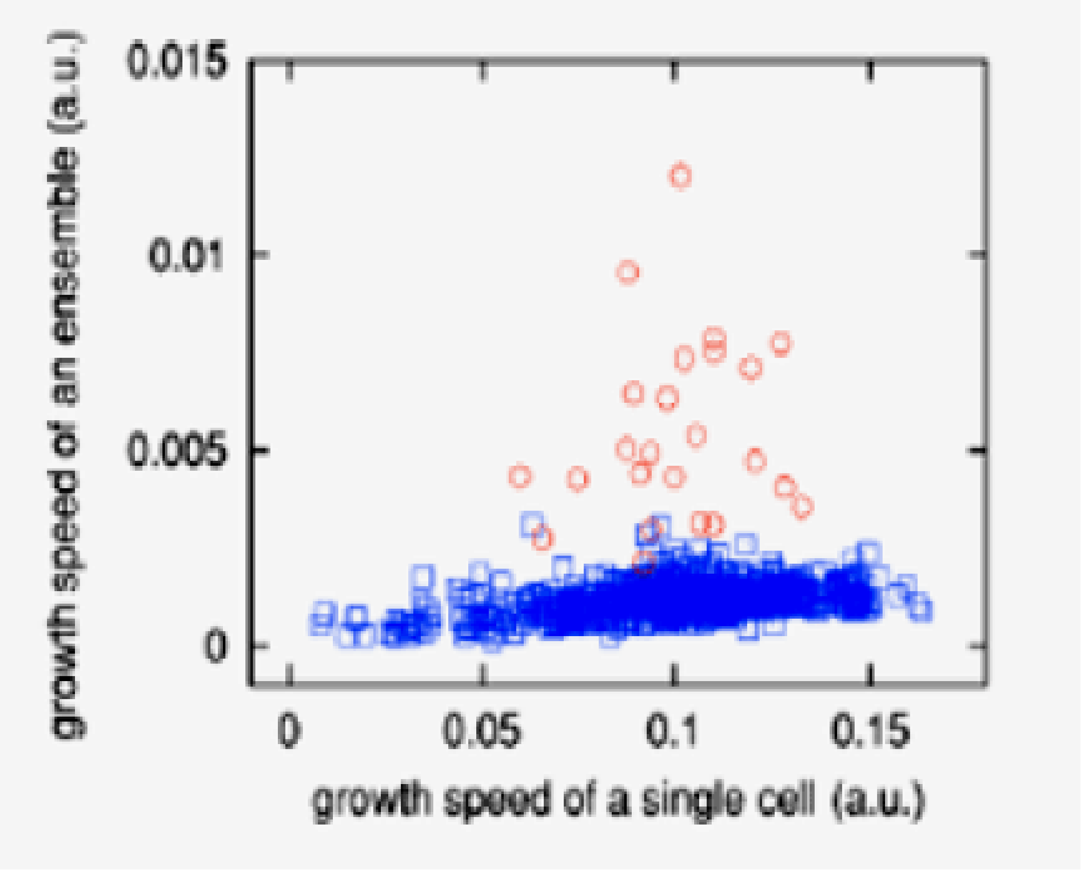
cell differentiation ←→ graidient for pattern

図9.5

Consolidation to Patterns

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

- 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

- 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

9784130623032
1923040032000
ISBN4-13-062303-6
C3040 ¥3200E
定価(本体価格3200円＋税)

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 すべての読者に贈る

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初の入門書，ついに刊行