Consistency Principle In Biological Dynamical Systems

Kunihiko Kaneko

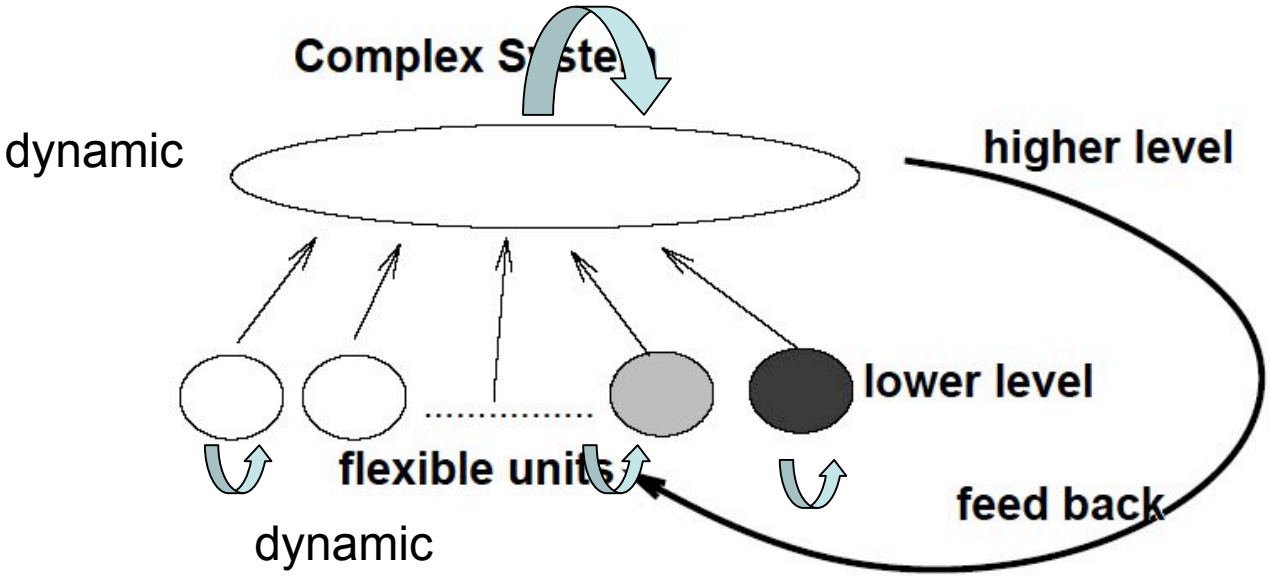
Complex Systems Biology

Understand Universal features of Biological System

--Mutual dependence between parts and whole

Guiding Principle:

Consistency between different levels



- **Cell reproduction vs molecule replication (briefly review)　15%**
- **Genetic change（evolution)vs Phenotypic Fluctuation　75%**

***Gene expression vs Growth –Adaptation 5%**

*** Reproduction of multicellular organism vs of cells (briefly)　(development)5%**

Underlying Biological Motivation;

* Plasticity - Phenotypic Fluctuation- Evolvability

*Link between development and evolution

*Evolution of Robustness;

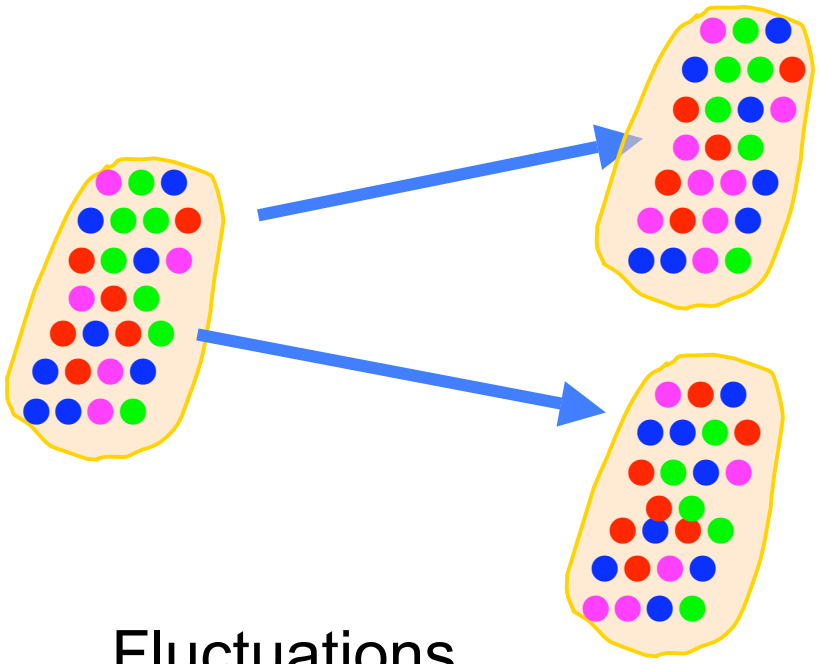
--- which type of systems is selected

How is recursive production of a cell sustained ?

each cell complex reaction network

with diversity of chemicals;

The number of molecules of each species not so large



?

Fluctuations

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

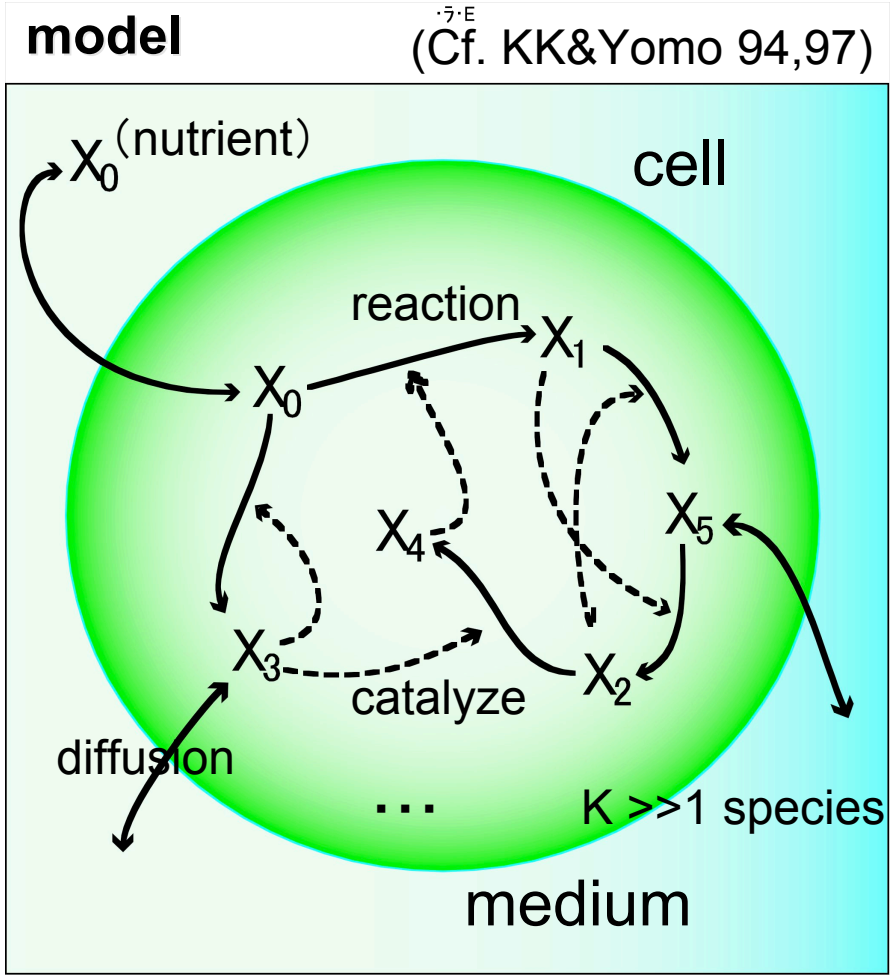
C.Furusawa & KK、PRL2003

- **k species of chemicals 、$X_0 \cdots X_{k-1}$**
number ---n_0 、$n_1 \ldots n_{k-1}$

- 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



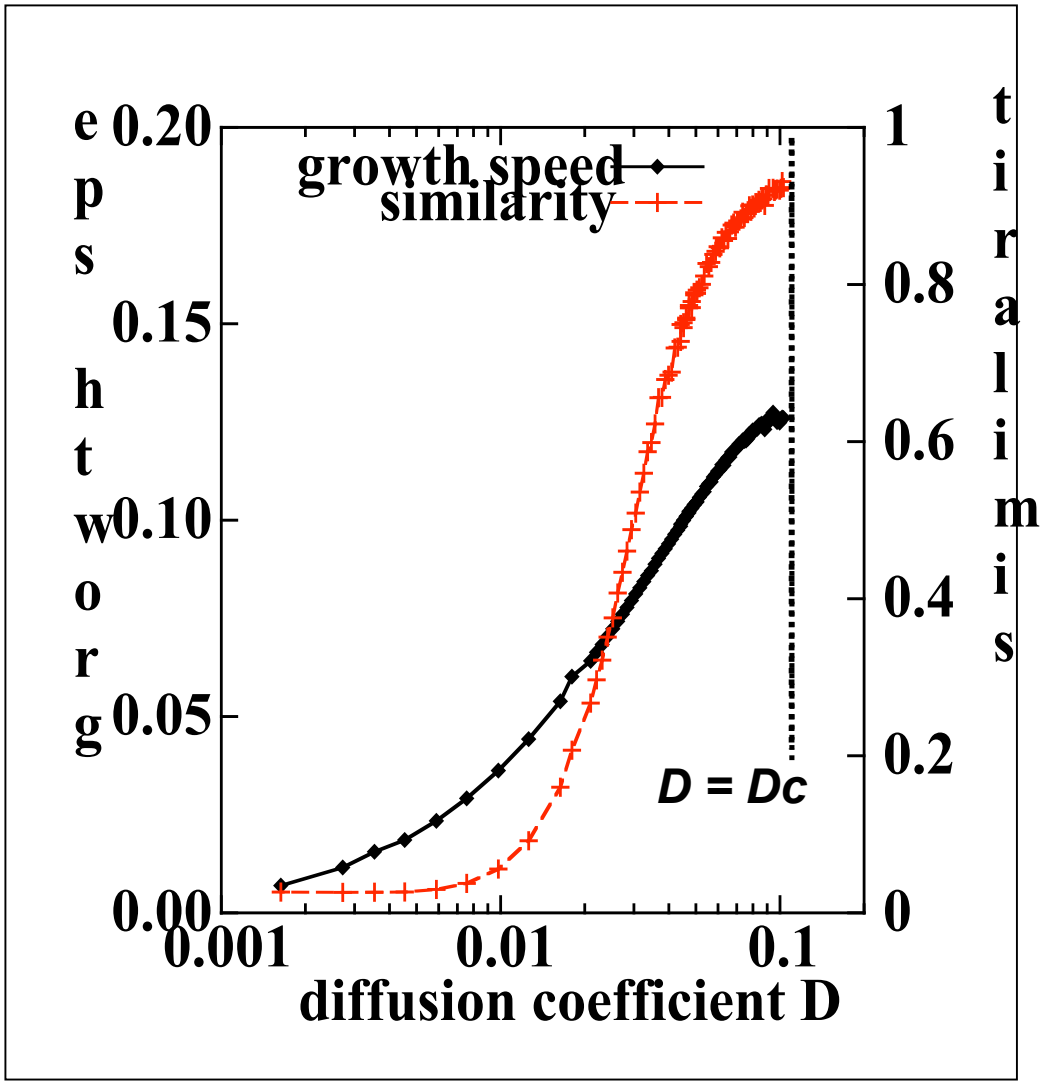
dX1/dt ∝ X0X4; rate equation;
Stochastic model here

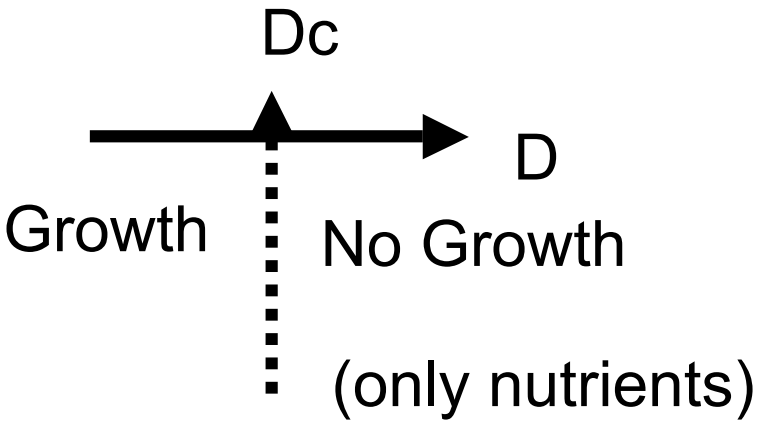
In continuum description, the following rate eqn., but we mostly use stochastic simulation

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

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

☆Growth speed and fidelity in replication are maximum at Dc





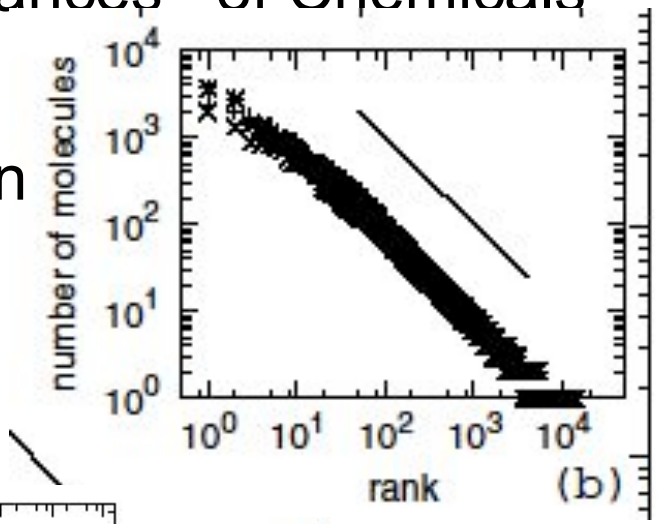
※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

Traces: universal statistics

Power Law in Abundances of Chemicals

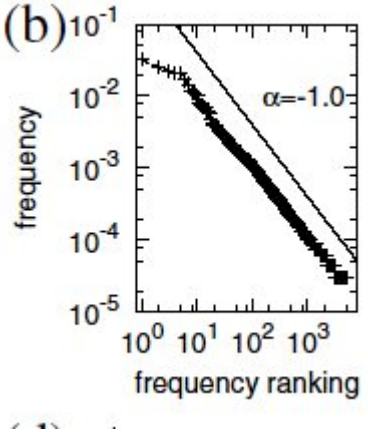
Theory;
To keep reproduction
preserving
compositions→

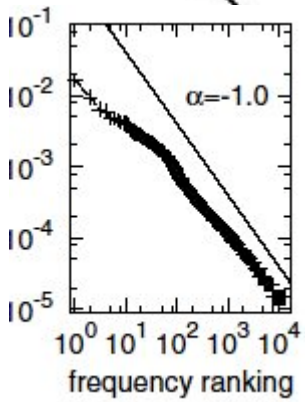


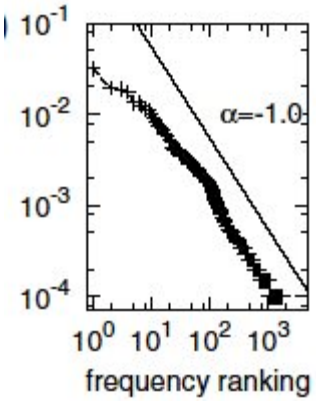
n_i (number of molecules)

rank

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







Human kidney, mouse ES yeast

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

- Remarks:

（0）Universality

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

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

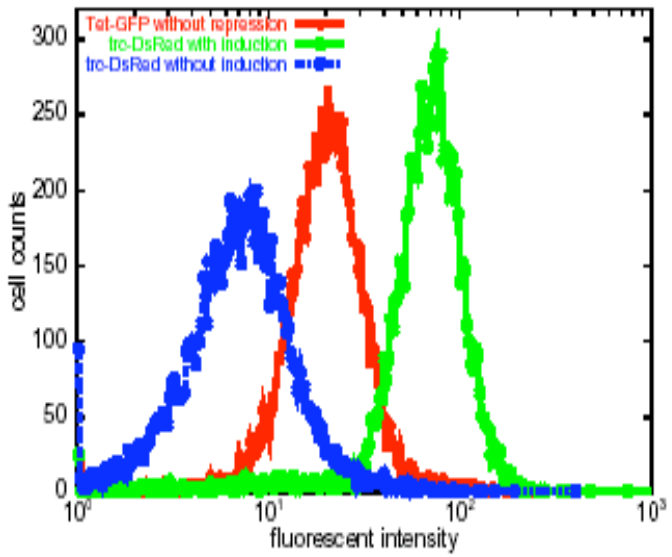
（3） Self-organization to critical state, if transport of ‘nutrition chemicals’ is catalyzed by some chemicals （no need for choice of D) (instead of simple diffusion) (Furusawa,KK,2007)

: fluctuation by cells:
distribution of each Ni by cells

Furusawa,..
KK,
Biophysics2005

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

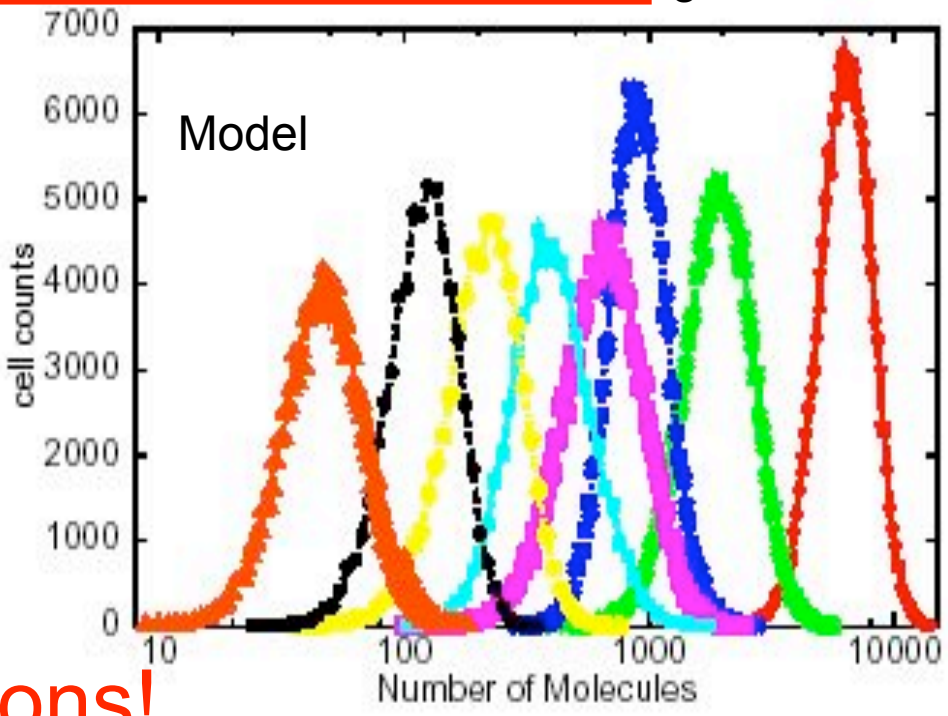
E Coli



umber distribution of the proteins measured by fluorescent intensity.

Log normal distribution !

histogrram



Each color gives different chemical species

QUITE LARGE Fluctuations!

LOG SCALE

ber distribution of the molecules of chemical abundances. Distri

☆Heuristic explanation of log-normal distribution

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

$$d N_X /dt = N_X N_A$$

then

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

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

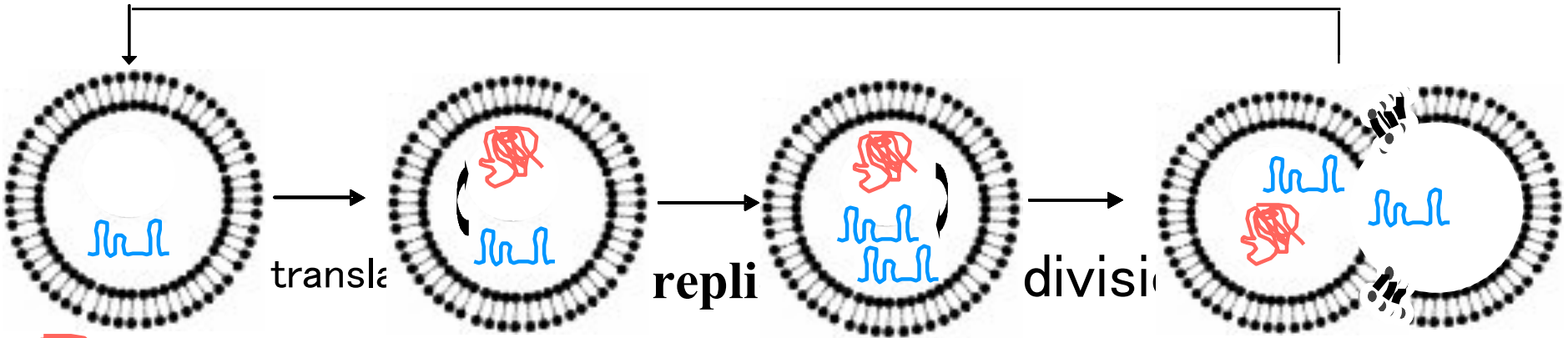
$$d \log(N_X)/dt = <N_A> + \eta (t)$$

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

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

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

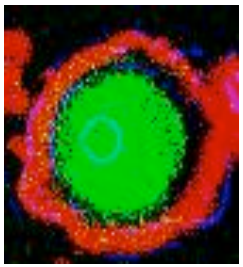
Replicating artificial cell (experiment)
(←→consistency, minority control)



RNA polymerase

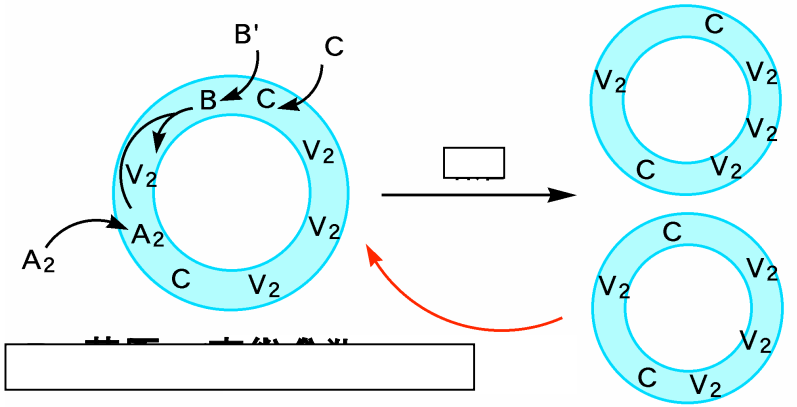
RNA polymerase geneRNA

(Yomo‘s group)



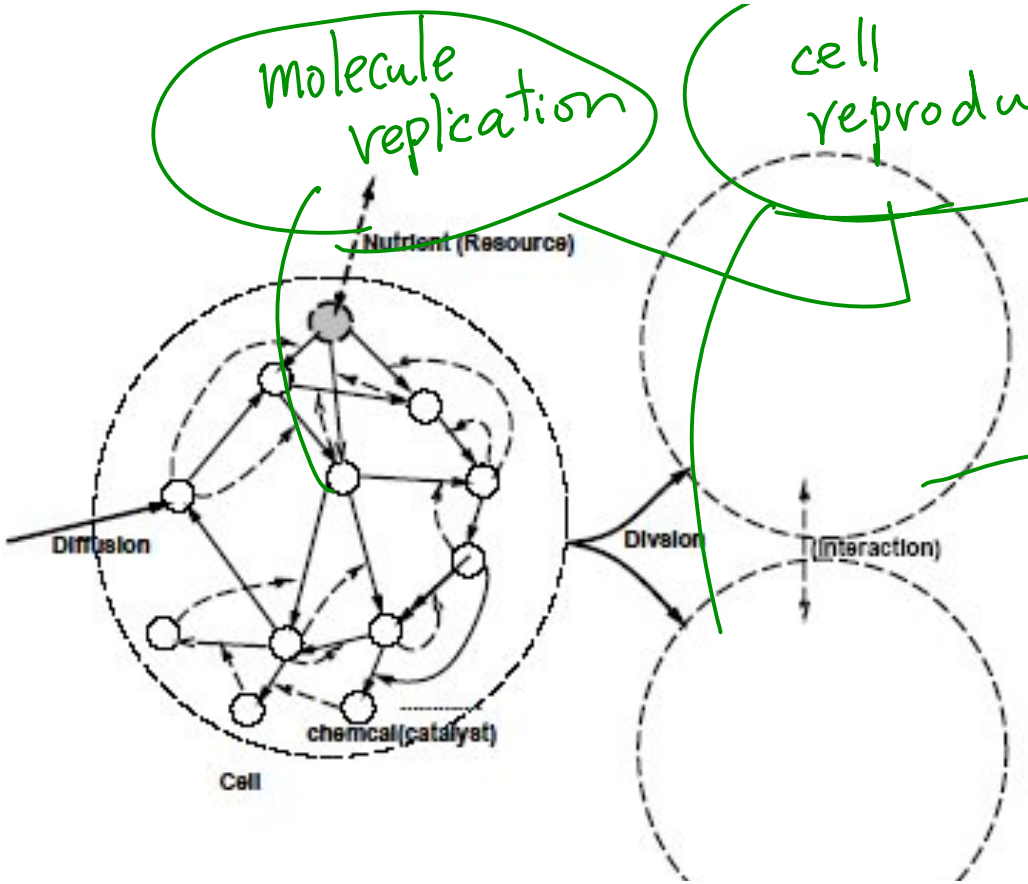
Tranlation in liposome

RNAreplication in liposome



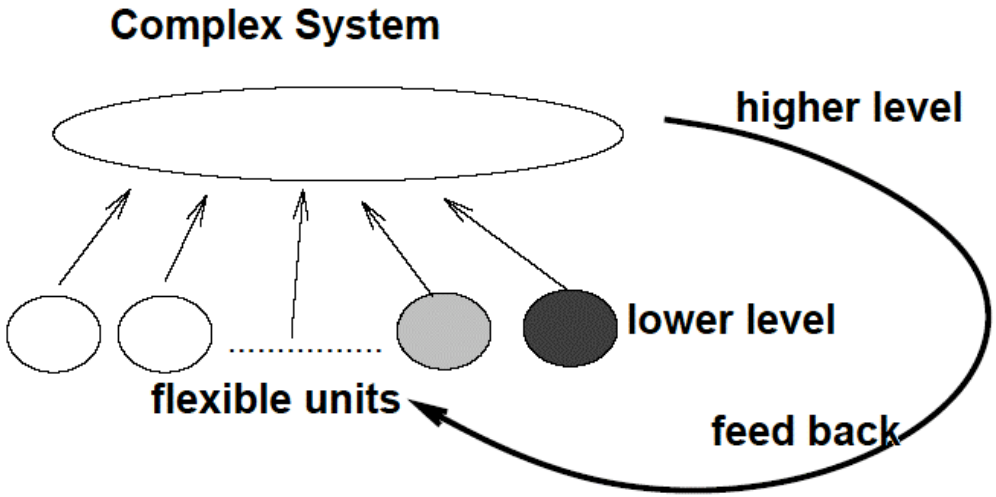
(Sugawara’s group)

Continouos division of liposomes



Consistency between replication of chemicals and reproduction of cell;

keeping composition and activity



Consistency Principle for Biological System → universal characteristics

- **Phenotypic Fluctuation →**

Relationship to Evolution?

selection is based on phenotype

（activity, size, protein abundances, fluorescence,…),

but

in standard evolutionary genetics;

gene a → phenotype x uniquely determined

Mostly discusses the phenotype distribution

as a result of genetic variation

——only the distribution of gene is discussed,

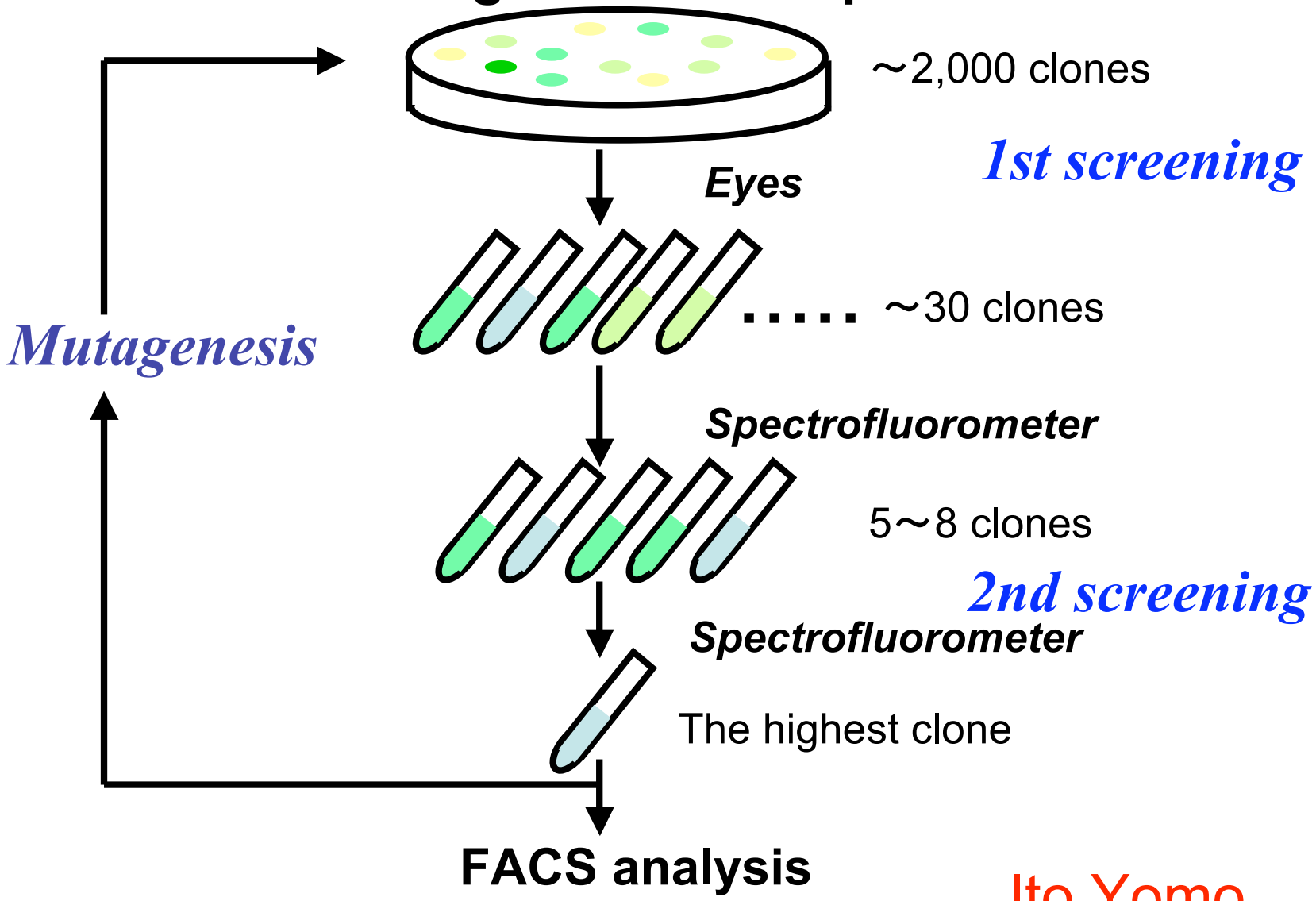
Phenotypic fluctuation of isogenic organisms

→P(x; a) x—phenotype, a – gene

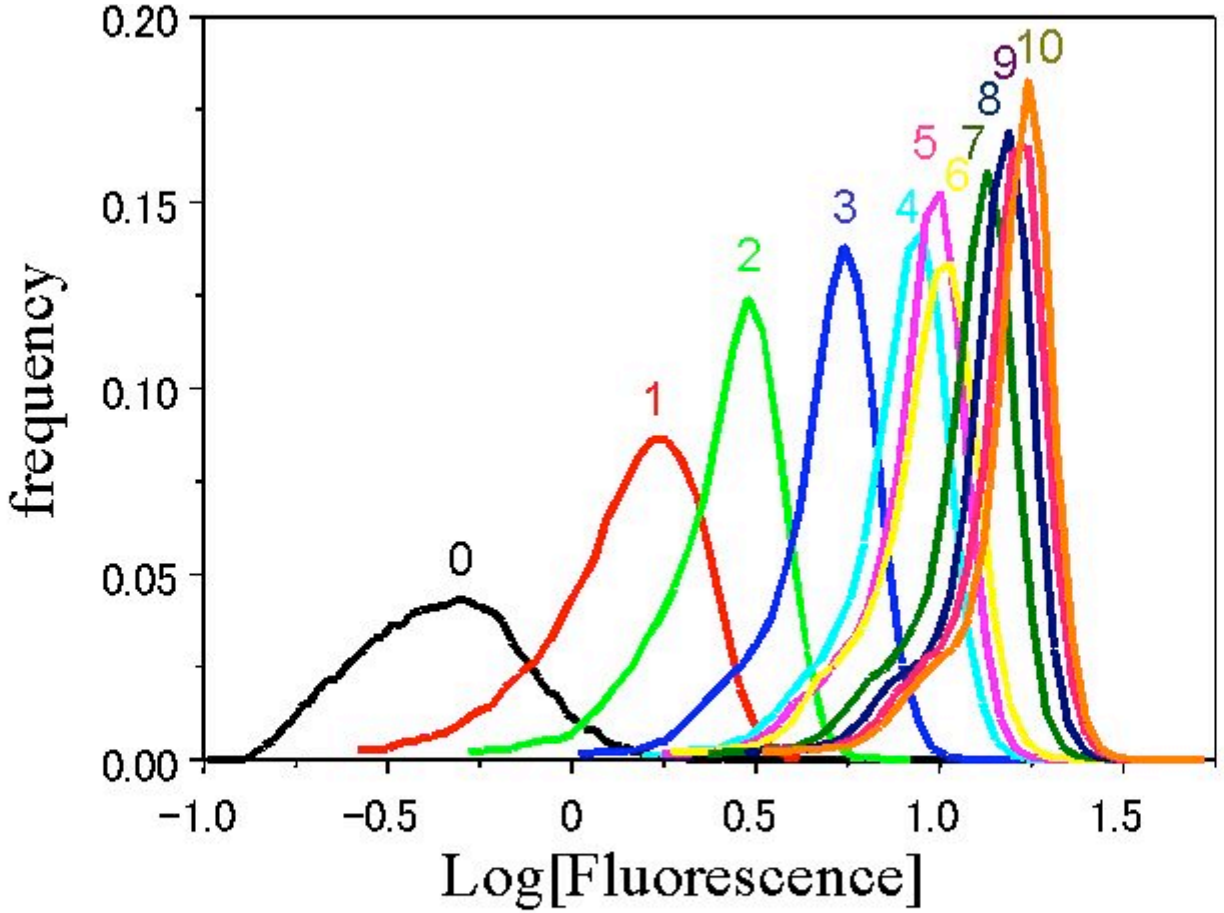
Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process



Ito,Yomo,..



Sato,Ito,
Yomo,KK
PNAS(2003)

Fluctuation ---- Variance of phenotype of clone

Organisms with larger phenotypic fluctuation higher evolution speed;

- change of phenotype per generation per mutation -- ``Response against mutation+selection''

Response ←→ Fluctuation

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

originated by Einstein's paper a century ago…

Generalization::(mathematical formulation)

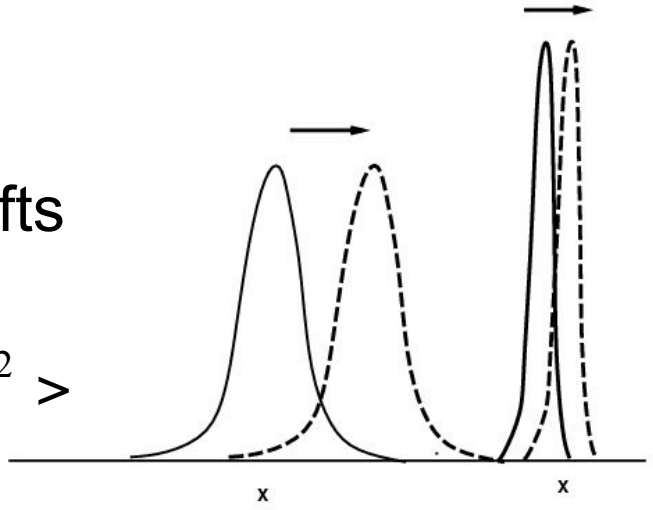
response ratio of some variable x against the change of parameter a versus fluctuation of x

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

change of the parameter a →

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

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



Fluctuation-response relationship (generalized form)

Gaussian distribution of x; under the parameter a

$$P(x;a_0) = N_0 exp(-\frac{(x-X_0)^2}{2\alpha_0}),$$ at a=a0

Change the parameter from a0 to a

$$P(x:a) = N exp(-\frac{(x-X_0)^2}{2\alpha(a)} + v(x,a))$$

$v(a,x) = C(a-a_0)(x-X_0) + ...$, with C as a constant,

$$\longrightarrow \quad P(x, a_0+\Delta a) = N' exp(-\frac{(x - X_0 - C\Delta a\alpha(a_0+\Delta a))^2}{2\alpha(a_0+\Delta a)})$$

Hence, we get

$$\frac{< x >_{a=a_0+\Delta a} - < x >_{a=a_0}}{\Delta a} = C\alpha(a_0+\Delta a),$$

Noting that $\alpha =< (\delta x)^2 >$

$$\frac{< x >_{a=a_0+\Delta a} - < x >_{a=a_0}}{\Delta a} = C < (\delta x)^2 >,$$

Artificial selection experiment with bacteria

for enzyme with higher catalytic activity

for some protein with higher function

Change in gene (parameter; a) ⇒

``Response'' ------ change of phenotype <x>

(e.g.,fluorescence intensity)

per generation per (synonymous) mutation rate

Fluctuation ---- Variance of phenotype x of clone

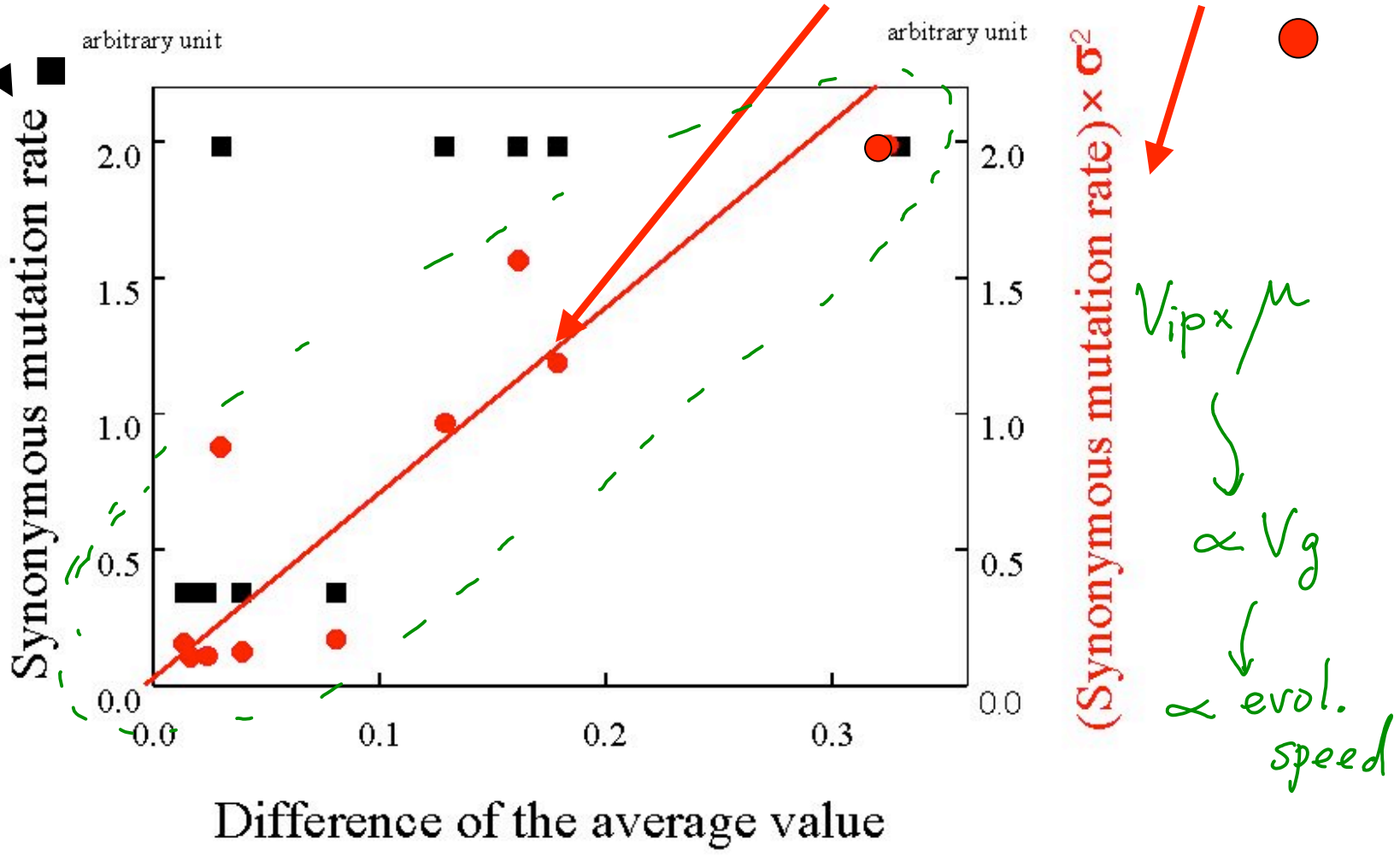
Fluctuation in the phenotype x of clone

⇔ speed of evolution to increase <x>

(proportional or correlated)

Naïve expectation:
Just propt to mutation rate

Fluctuation-response relation
Phenotype fluct. × mutation rate

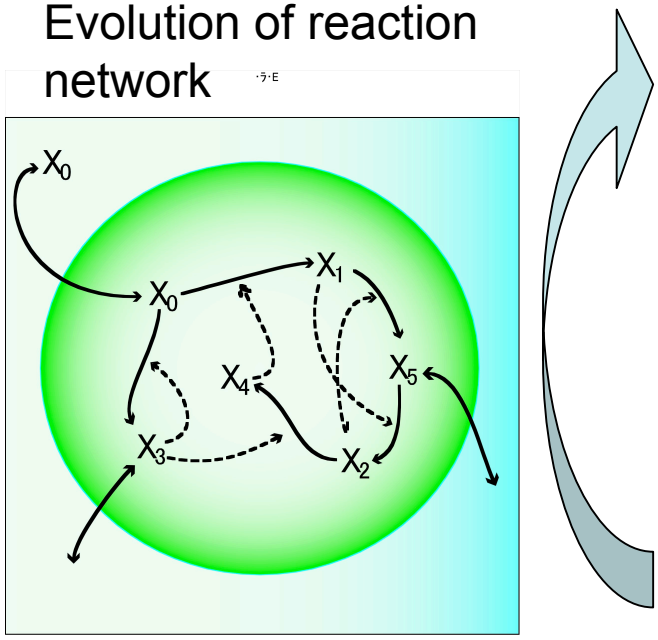


(Evolution Speed per generation)

Sato,Ito,Yomo,KK, PNAS 2003

- # Confirmation by numerical evolution experiment by the reaction-net cell model

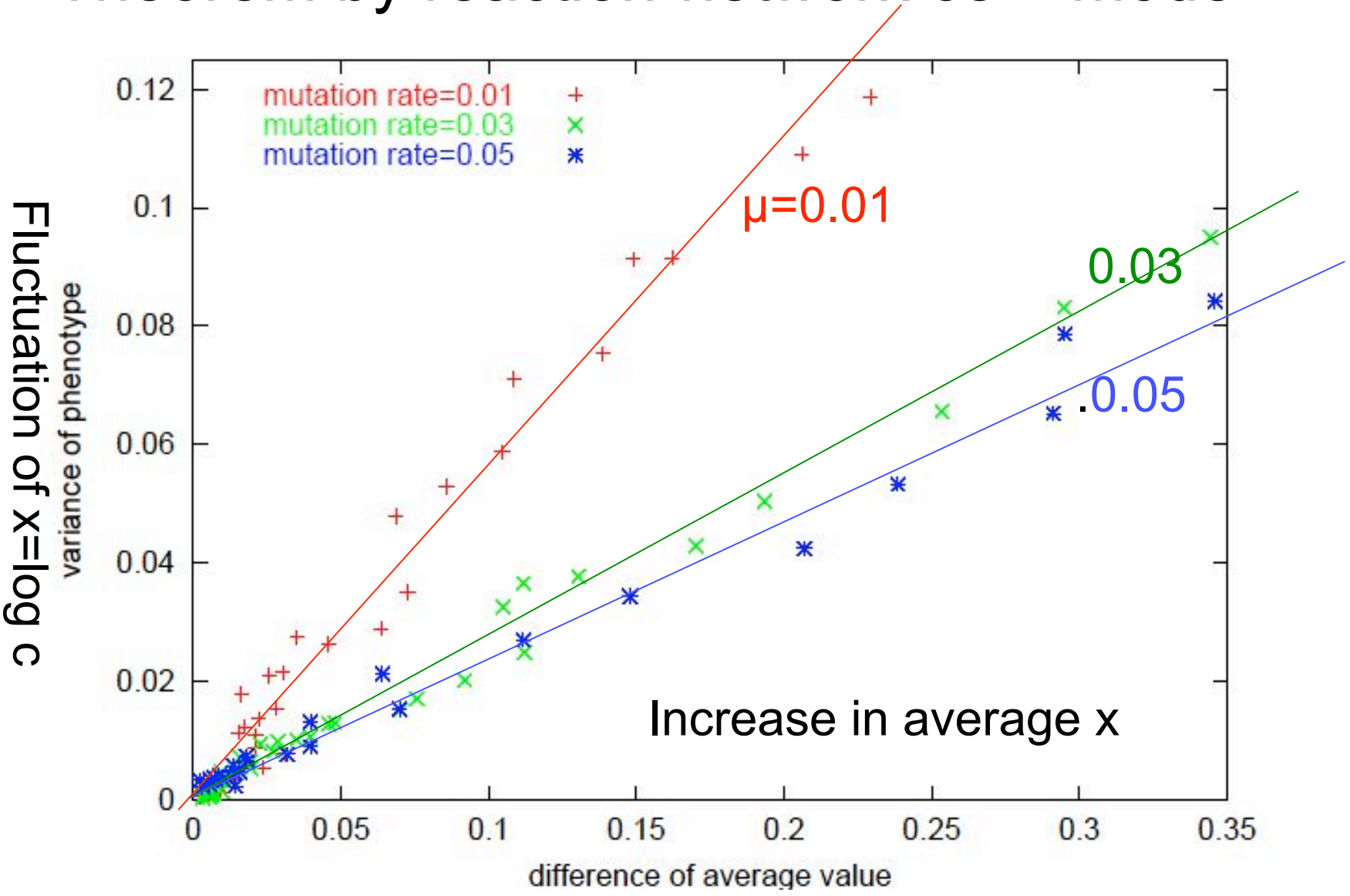
Mutate the network (‘gene’) with mutation rate μ, (rewire the path of the network with the rate) and select such network having highest concentration c of a specific chemical



phenotype x = log (n_s)

1. Prepare initial mother cells.
2. From each parent cell, mutant cells are generated by randomly replacing reaction paths, with mutation rate μ
3. reaction dynamics of all mutants are simulated to determine phenotype x
4. Top 5% cells with regard to phenotype x are selected as parent cells of next generation

Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model



Furusawa,KK 2005

（1）the use of log(fluorescence), because

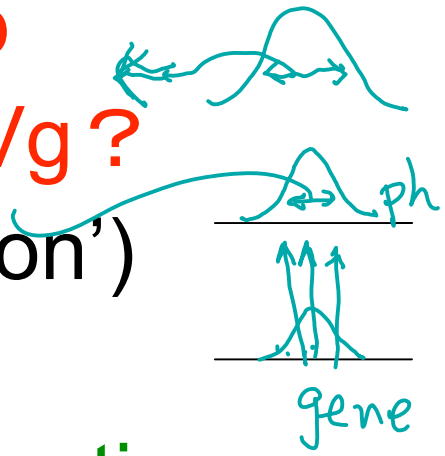
log x　is close to Gaussian distribution in experiments

(2)　New mystery？　phenotype fluctuation of clone　vs　evolution speed　in contrast to

evolution speed　∝　phenotypic fluctuation by genetic variation（Vg): (fundamental theorem of natural selection; established)

isogenic phenotypic　fluct　Vip

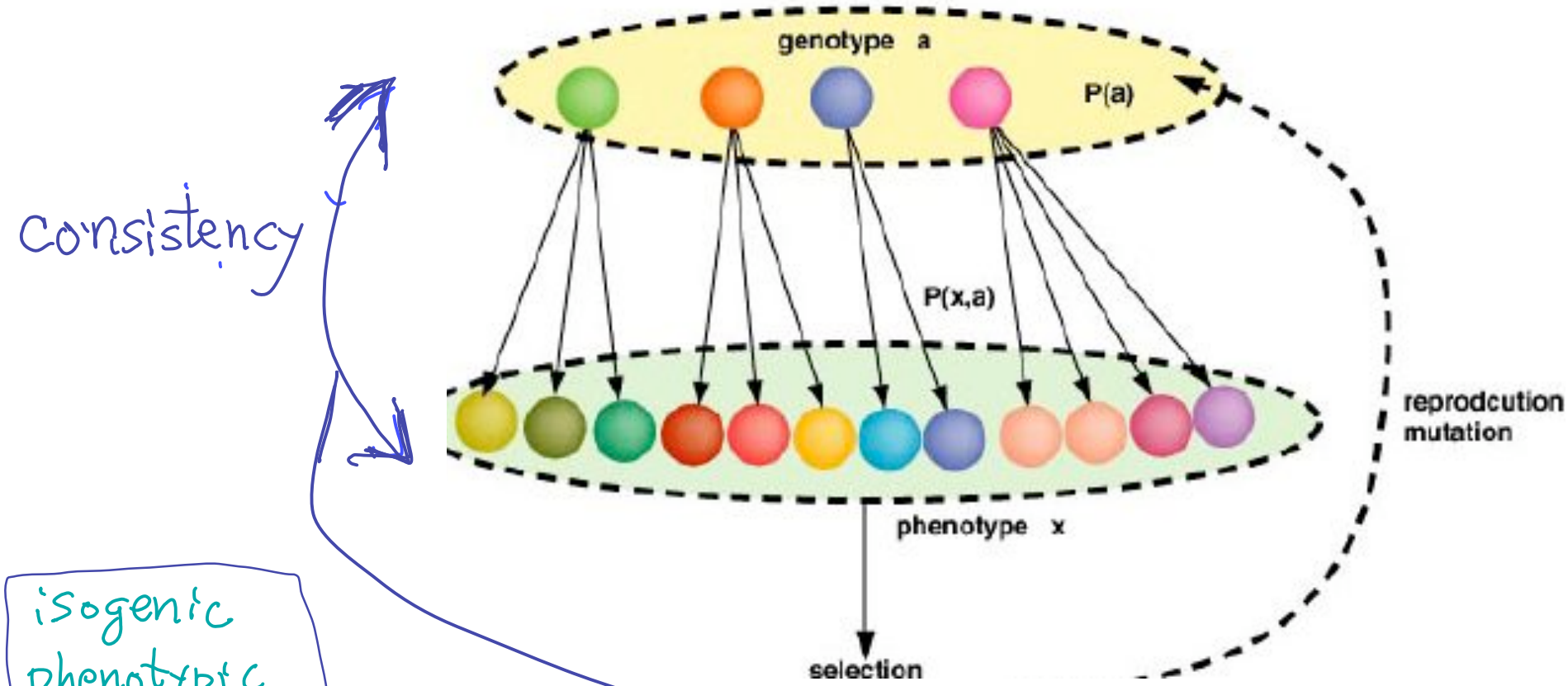
∝　pheno fluct by gene variation　Vg？



（fluct by noise　∝　variation in ‘equation’）

Follow the spirit of Einstein；

micro-macro consistency→Brownian motion



consistency

isogenic phenotypic fluctuation

genotype (a) (same)

V_{ip}

genotype (distributed)

V_g

phenotype x

V_g ⟷ evolution speed

? V_{ip} ??

We can do the analysis by using Gaussian 2-body distribution function for phenotype x and gene a; around a=a0, and x=X0;, with coupling between x and a (variance of a is the mutation rate μ

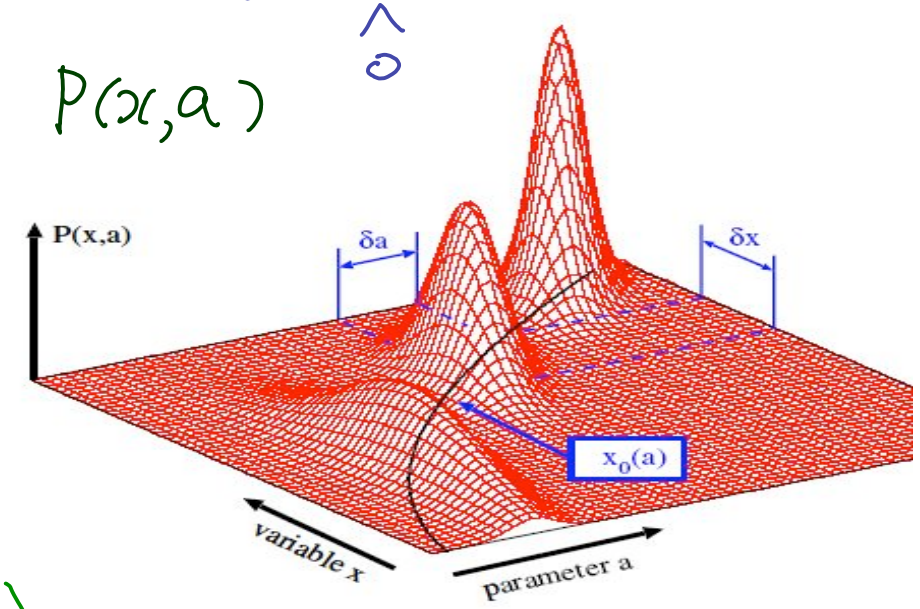
$$P(x,a) = Nexp[-\frac{(x-X_0)^2}{2\alpha(a)} + C(a-a_0)(x-X_0) - \frac{1}{2\mu}(a-a_0)^2],$$

$$P(x,a) = Nexp[-\frac{(x-X_0-C(a-a_0)\alpha)^2}{2\alpha(a)} + (\frac{\alpha C^2}{2} - \frac{1}{2\mu})(a-a_0)^2],$$

Stability condition

$$\frac{\alpha(a_0)C^2}{2} - \frac{1}{2\mu} \lesssim 0, \text{ i.e.,}$$

$$\mu \leq \frac{1}{(C^2\alpha(a_0)} \equiv \mu_c$$



For high mutation rate single-peak is not sustained (:error catastrophe)

Now consider the phenotypic variance due to genetic variation
Recalling the definition

$$V_g =< (\overline{x}_a - \overline{x}_{a_0})^2 >$$

$$\overline{x}_a \equiv \int x exp(-V(x,a))dx = X_0 + C(a - a_0)$$

we obtain

$$V_g =< (\overline{x}_a - \overline{x}_{a_0})^2 > = C^2 < (\delta a)^2 >= C^2 \mu \alpha^2$$

Now the inequality $\mu < 1/(C^2\alpha(a_0) \equiv \mu_c$ is rewritten as

$$V_g \leq \alpha(a_0) \qquad V_g \leq V_{ip}. \quad \textbf{(1)}$$

Note, in the above formulation, $< (\delta a)^2 >= \mu$ and $V_g \propto \mu$. Recalling that V_g at μ_c equals V_{ip}, we get

$$V_g = \frac{\mu}{\mu_c} V_{ip}. \quad \rightarrow \quad V_g \propto V_{ip} \quad \textbf{(3)}$$

Error Catastrophe As Vg >= Vip (2)

(16)

Fisher's theorem : evolution speed ∝ Vg,
EFR : evolution speed ∝ μVip <← Experment

- Three general laws

  (i) Vip ≧ Vg

  (ii)error catastrophe at Vip ~ Vg

  (where the evolution does not progress)

  (iii)Vip ∝ μVg （∝ evolution speed)

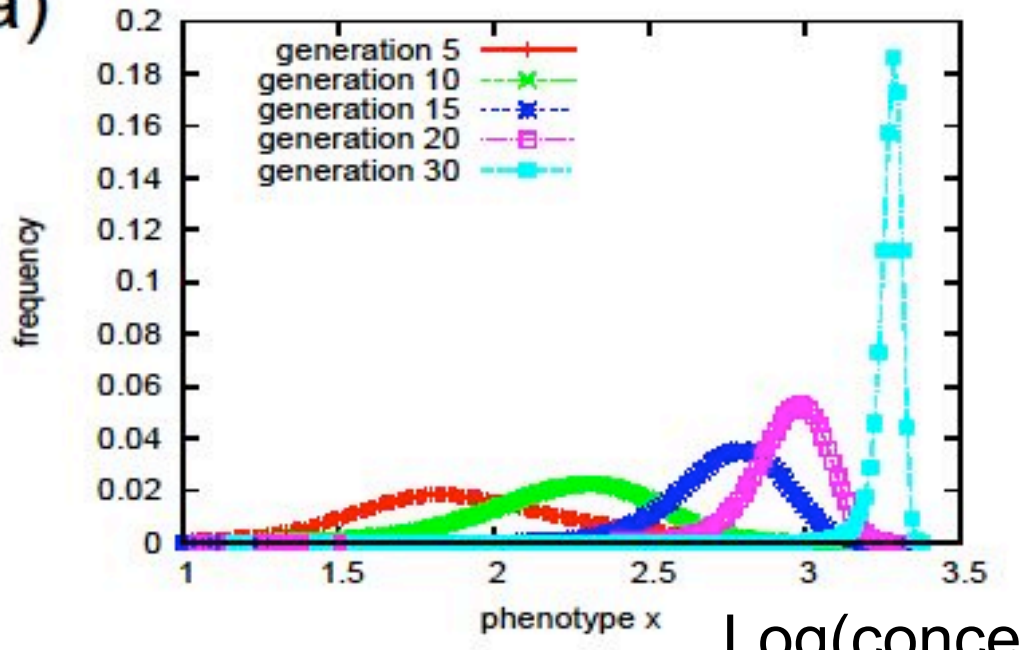
Relation (iii) seems to be fine … but …

relations (i) (ii) are rather surprising

----need confirmation

→ previous reaction-net cell model

(a)

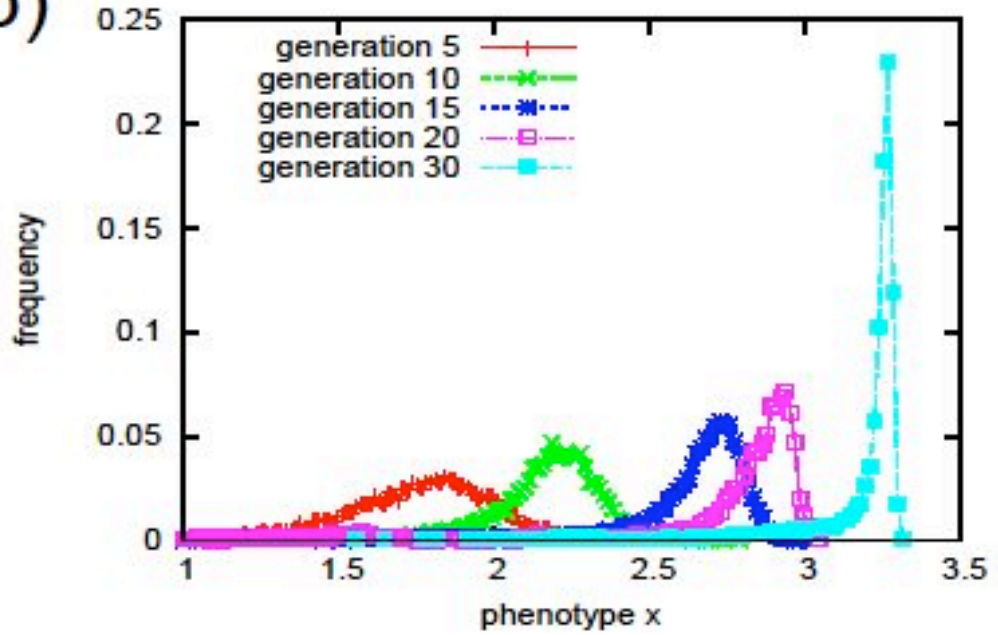


Change in distribution through evolution

Distribution of phenotype x of a clone
→ Vp

Log(concentration)

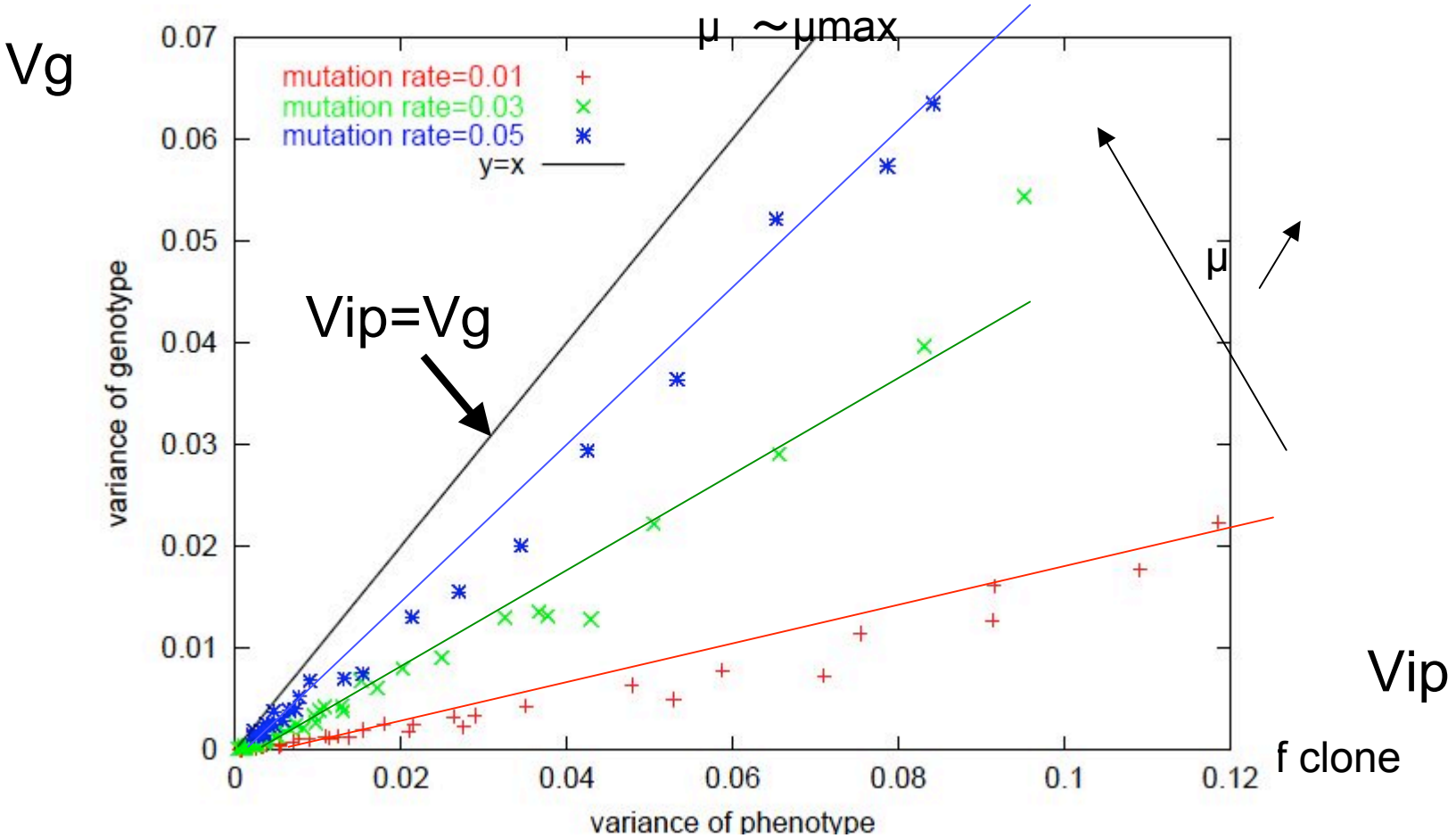
(b)



Distribution of phenotype x over mutants (genetic variation)
→ Vg

Phenotype fluct. (Vp) vs Gene Fluct. (Vg) in the evolution of toy cell model

Vp: fluct. for given network, Vg: fluct. by network variation



variance of log(x),

x is the concentration of the molecule

Beyond Darwin with the spirit of Einstein!

As μ (mutation rate) increases to μ max,

(1) the distribution collapses (error catastrophe)

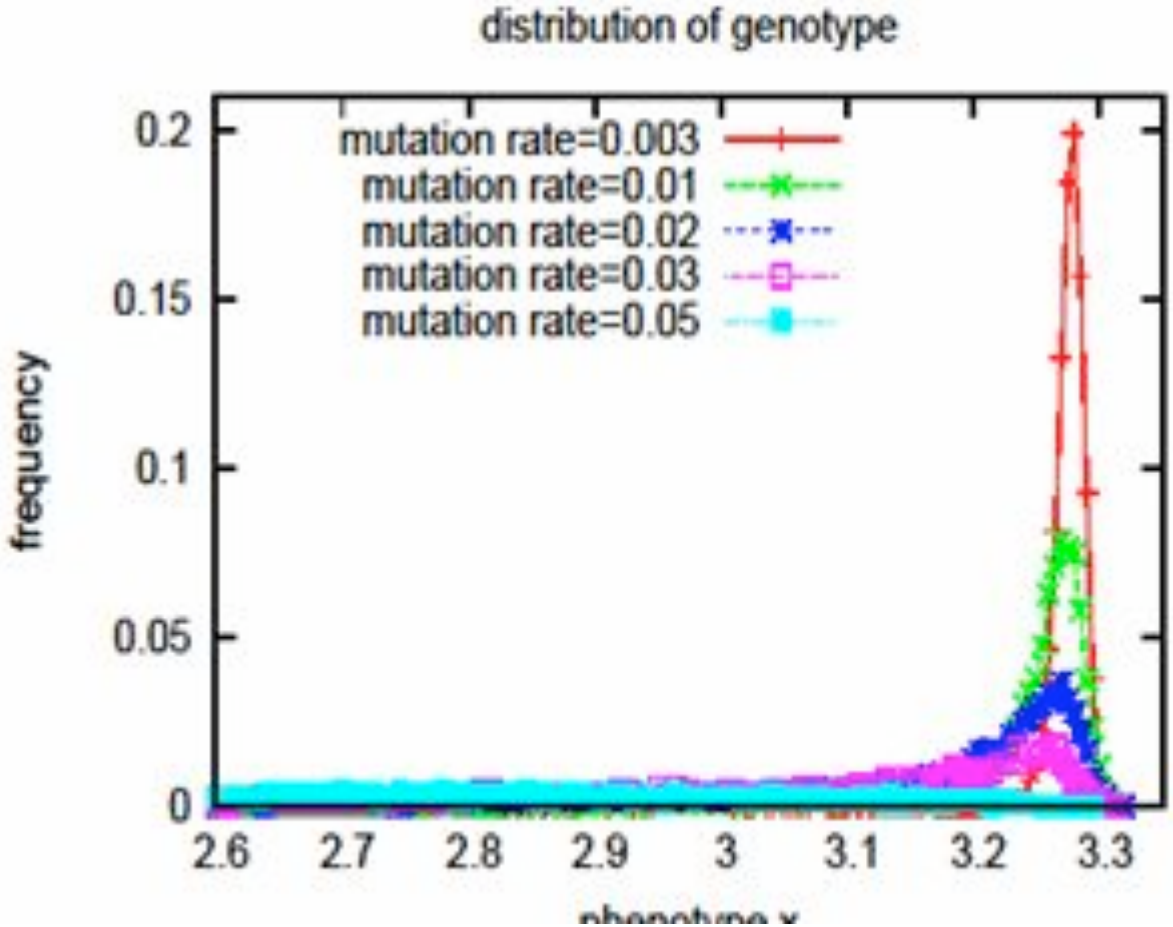
(2) evolution no longer progresses beyond μ max

evolution speed is maximal at μ ~ μ max

(3) Vg approaches Vp

As μ is increased,
The distribution
'collapses'

Error catastrophe



- **Still,,??? to the theory**
- P(x,a) rather than conditional probability (TRICK)

''Genetic-Phenotyic correpondence''

what phenotype can vary ←→

what gene can change

fluctuation of variable (micro) vs

variation of equation (genetic evolution)

(cf Waddington's genetic assimilation)

Q: Why error catastrophe when Vg>Vip?

Robust evolution is possible only under noise

-**counterintuitive ;it says phenotype noise is important**

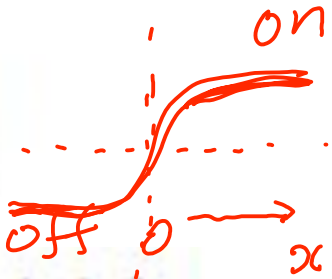
→ gene-net model

A simple model for Geno-Pheno relationship;

Model:Gene-net(dynamics of stochastic gene expression) → on/off state

Xi – expression of gene i : + (on) – (off)

$$dx_i/dt = \tanh[\beta \sum_{j>k}^{M} J_{ij} x_j] - x_i + \sigma\eta(t),$$



$$J_{ij} = -1, 1, 0,$$

$$<\eta(t)\eta(t')> = \delta(t-t').$$ **Gaussian white**

M;total number of genes, k: output genes

Noise strength σ

- Task

  Starting from -1,-1,-1,,-1(all off)

  xi i=1、2、・・・・、k are +1(on) （Target Gene Pattern)

Fitness **F= －（Average number of off x_i）**

$\overline{\cdots}$ is temporal average between $t = T_{ini}$ and $t = T_f$

Genetic Algorithm

Select networks with higher <F>

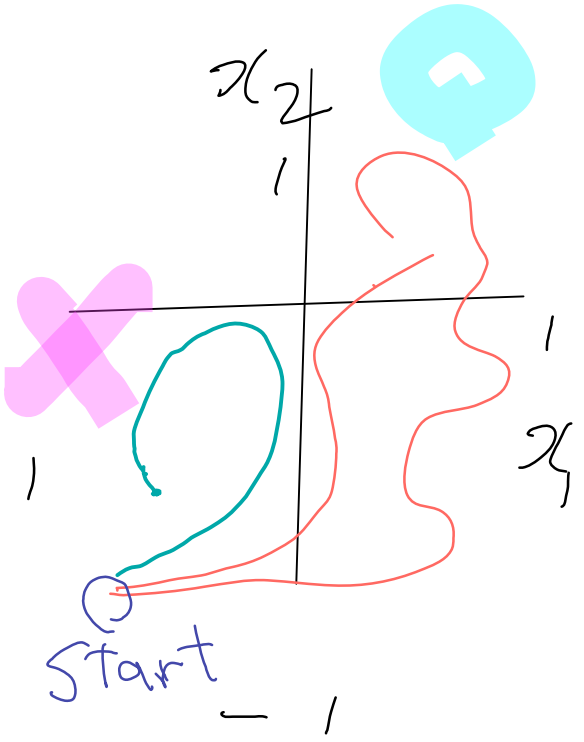
top--<F>=0

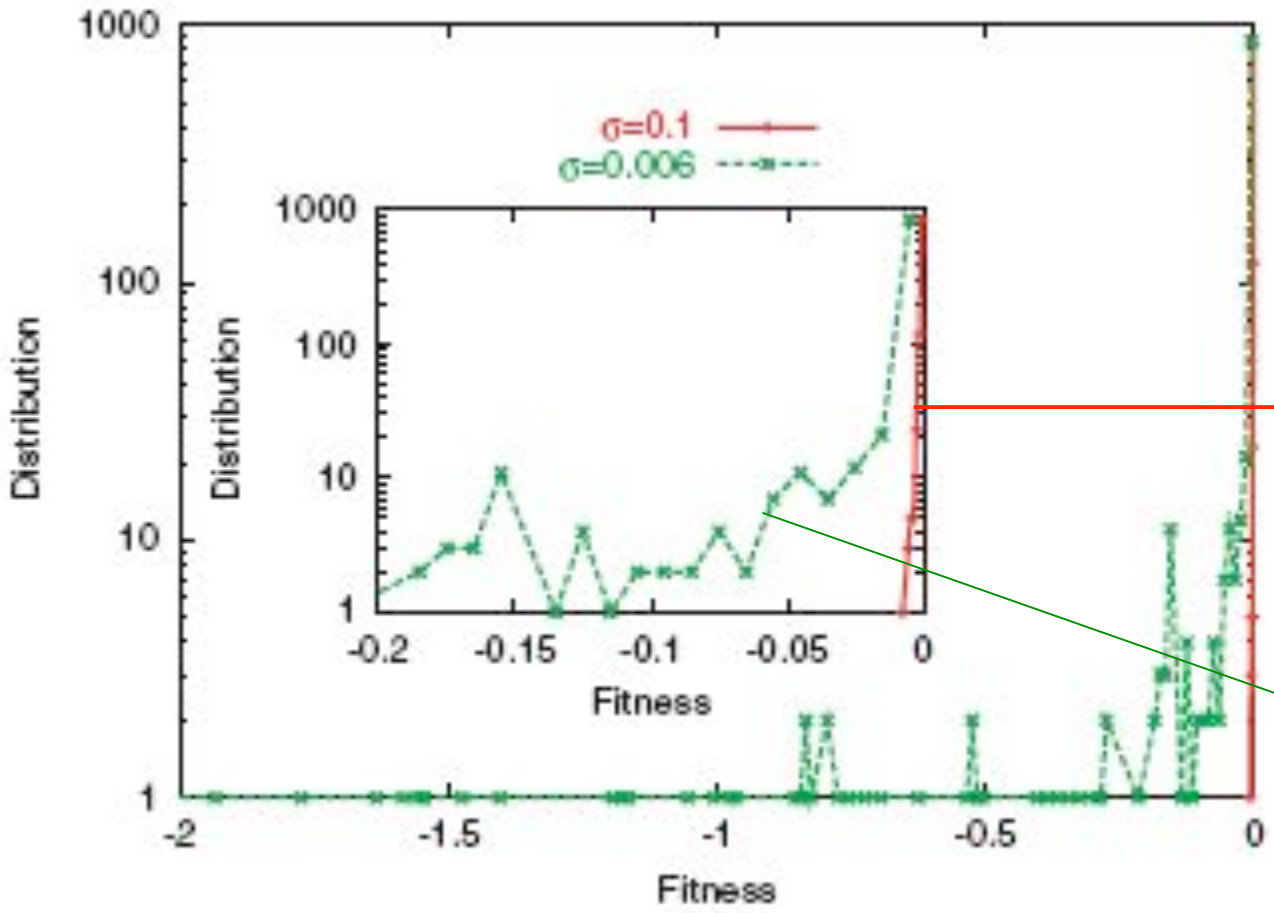
Choose top n networks

among total N,and mutate

with rate μto produce N networks

（μ:fixed mutation rate)





Result of evolution

Top:reaches the fittest

Lowest;cannot evolve for low noise(σ)

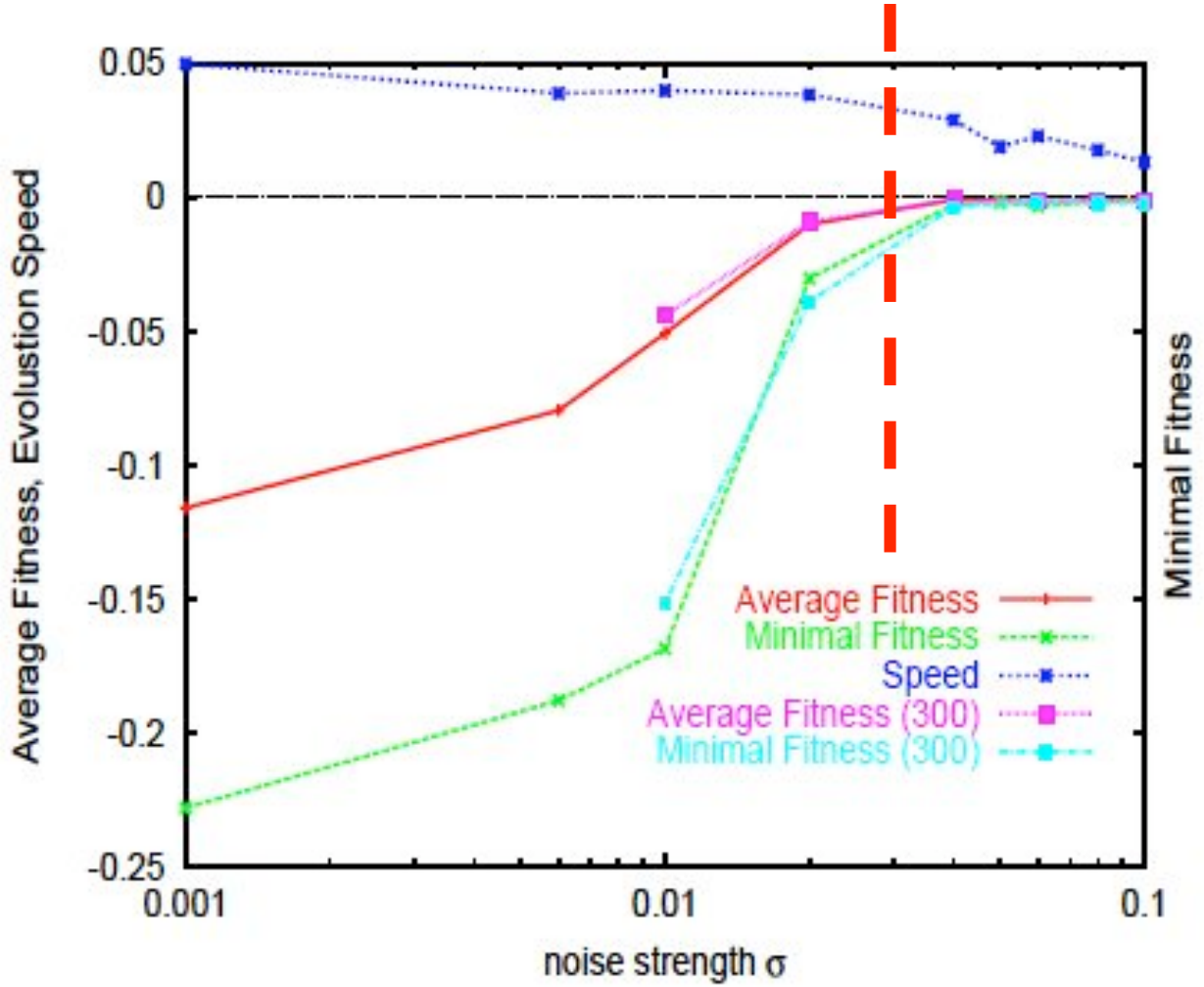
$\sigma > \sigma_c$

$\sigma < \sigma_c$

Fitness Distribution

$\sigma < \sigma_c$ --low fitness mutants distributed

$\sigma > \sigma_c$ — eliminated through evolution



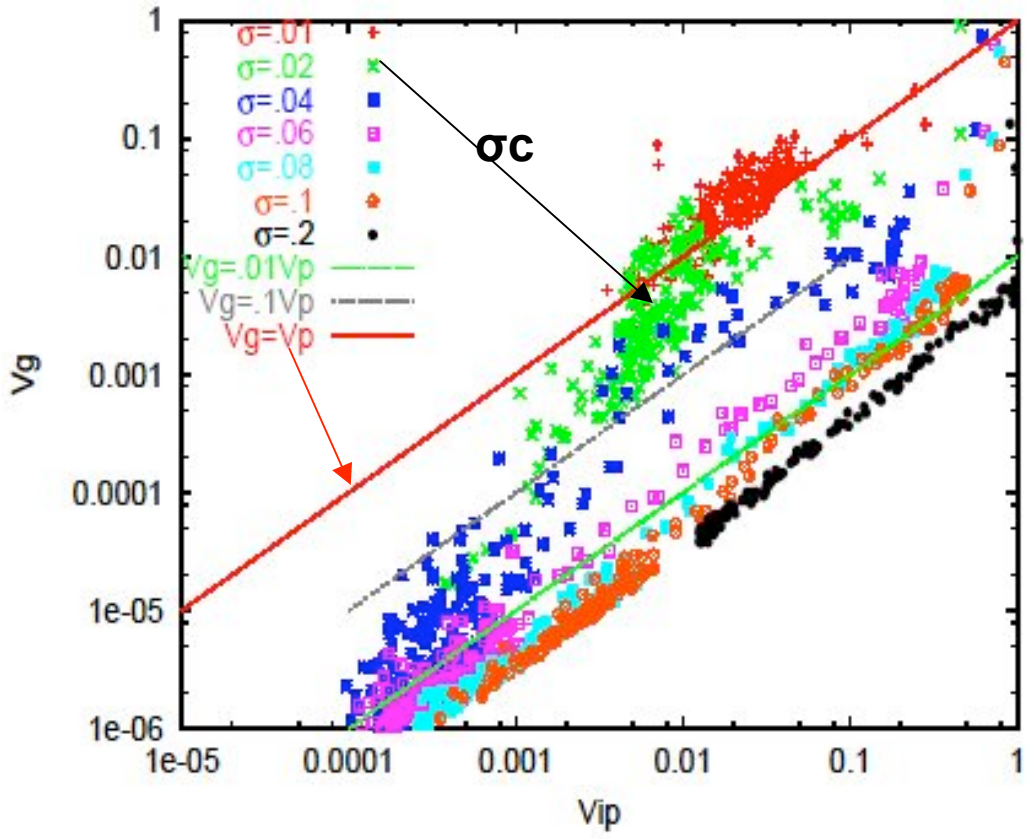
Existence of critical noise level σc below which low-fitness mutants accumulate (error catastrophe)

(1) Vip≧Vg forσ≧σc

(2) Vg→Vip
as σ→σc

(3) evolution progresse
only for Vip ≧Vg

(4) Vip∝Vg
through evolution
course



Theory confirmed

KK,PLosOne,2007

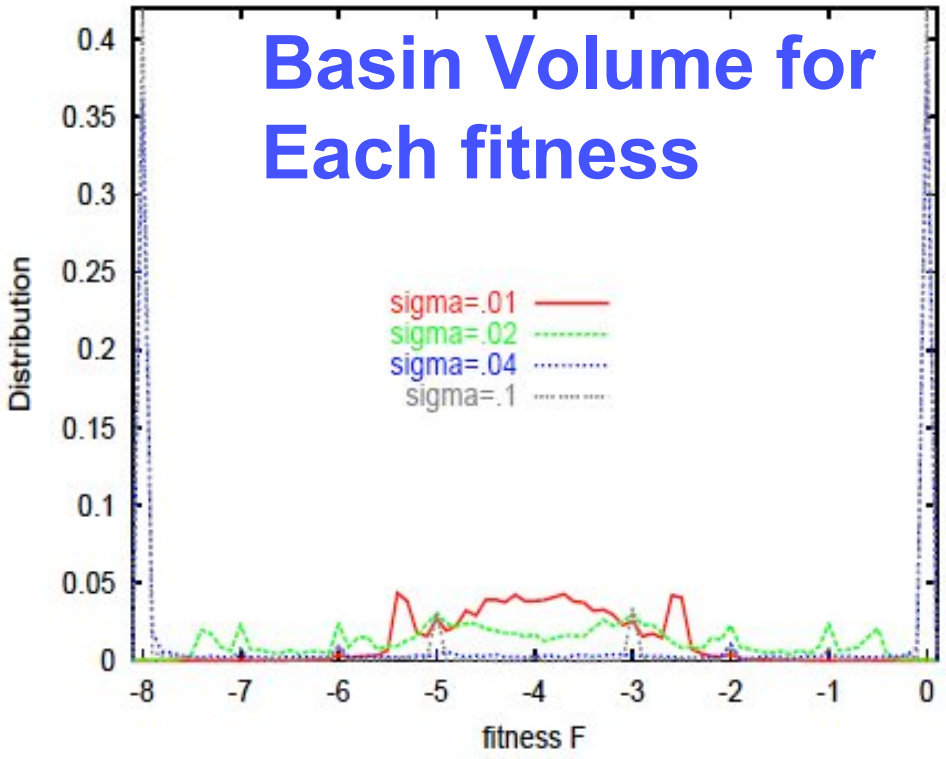
Why?; difference in basin structure

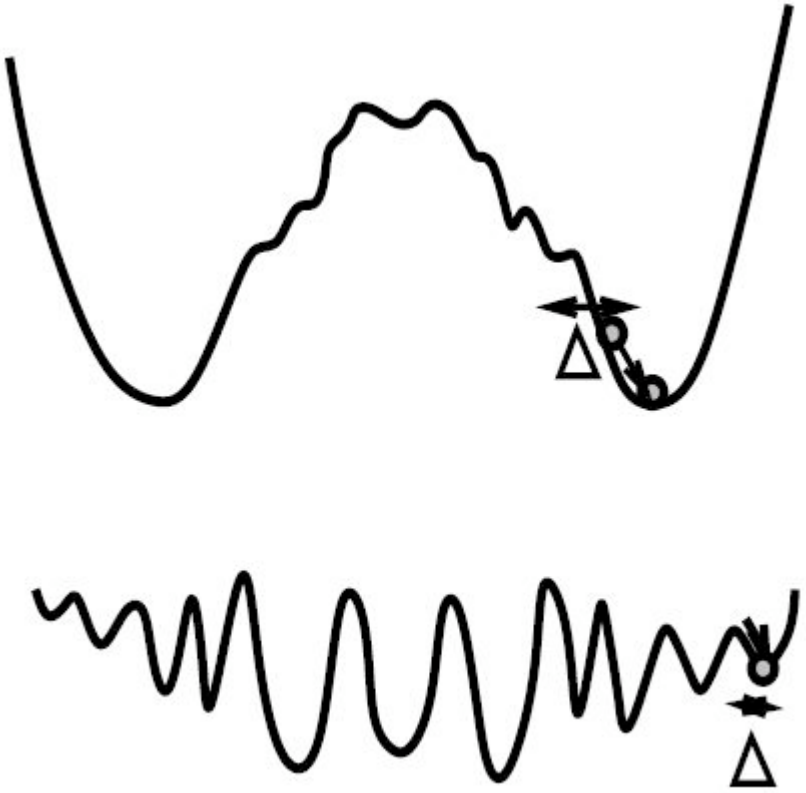
σ＞σc → large basin for target attractor

(robust, Δ（distance to basin boudary) ↑

σ＜σc → only tiny basin around target orbit

Δ remains small





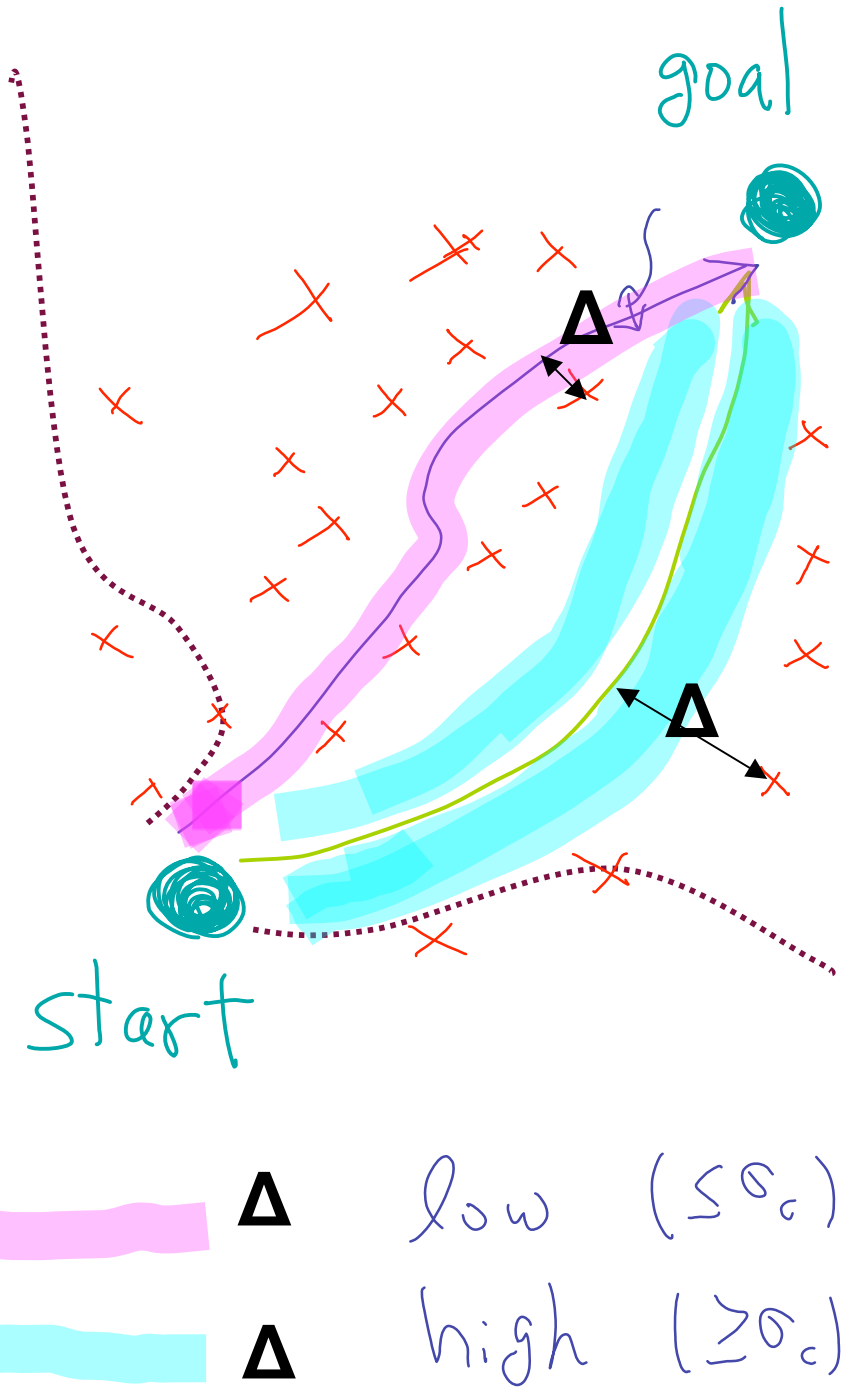
→Global constraint to potential landscape(funnel?)

why threshold?

choose paths to avoid turning pts within σ (noise)

Mutation→ touches turning points within range of μ

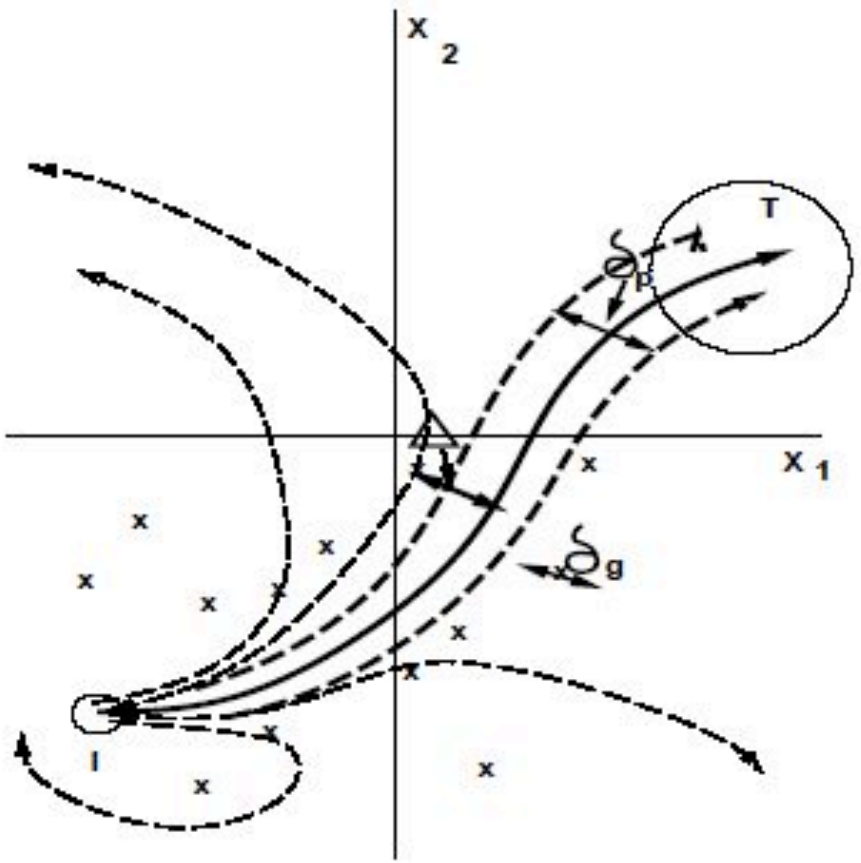
small σ —>
an orbit with small Δ
can reach the target



Deviation of basin
boundary (turning points)
by Noise －＞δp
by Mutation -> δg

Vg ~ (δg/ Δ)^2
Vip ~(δp/Δ)^2

Δ increases
——＞robustness
increases
if δg＞δp,
mutation destroys
the history
→Vip>Vg necessary
for evolution of robustness



Δ~distance to turning points
(basin boundary)

- Generality of our result; For a system satisfying:

(1) fitness is determined after developmental dynamics

（2）developmental dynamics is complex

(catastrophic pts leading to error are distributed)

(3) effective equivalence between mutations and noise with regards to the consequence to fitness

(→ genetic assimilation by Waddington)

Discussion:Evolution of Robustness

- Robustness ----- Insensitivity of Fitness (Phenotype) to system's change

← against noise during 'developmental process

← against parameter change by mutation

- Developmental Robustness to noise ---- Vip
- Robustness to mutation in evolution ----Vg

When Vip>Vg, both decrease, i.e., robustness↗

Noise is necessary for evolution of robustness

Vip ∝ Vg →Developmental robustness and genetic (evolutionary) robustness are linked (WADDINGTON)

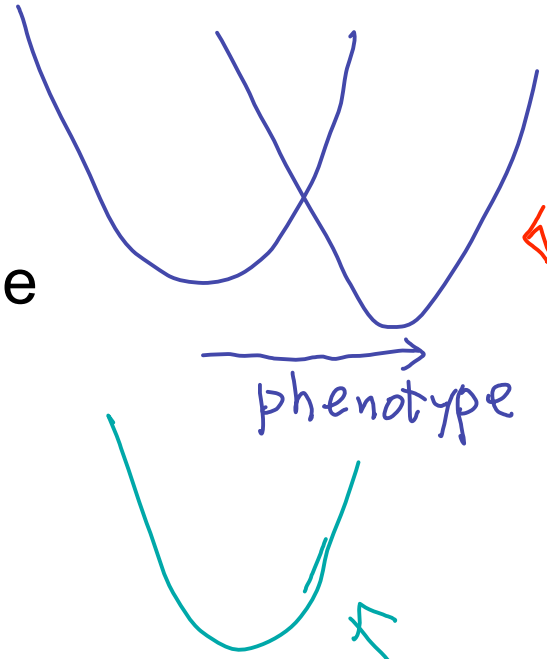
LeChatlier-Braun principle, Waddington's 1957?,

and Vg-Vip relationship

External change → Response to suppress the influence

←stability condition from thermodynamic potential

Ours
Vip ∝
phenotype
response



Vg ∝
genetic response

phenotype change by environmental change (without genetic)

⇓evolution (genetic change)

after environmental change is cut off, change remains (buffered to gene)

- Nature vs Nurture?
- Standard population genetics:

  non-genetic variations are regarded to be due to environmental variation instead of fluctuation
- The ratio of genetic variation to total variation is called ‘’heritability’’ . This value, for most cases is less than .5（cf：data in Drosophilla 0.2-0.5)
- Our argument shows heritabiity <1/2, as heritability= Vg/(Vip+Vg) (if Vip, Vg are added independently) by regarding Vip as origin of non-genetic variation

  →(?Nature < Nurture?) for phenotype relevant to fitness

Through directed evolution; fluctuations decrease

(**Model, experiments, theory, i.e.,

increase of robustness through evolution.)

Then, evolution slows down..

←→

How Evolution continues?

Why Large Fluctuations exist?

?? Is there regain of fluctuations????

- Observed: Appearance of mutants with large fluctuations (due to different source) at further evolution. (← interaction with other genes?)
- → Restoration of Plasticity

Spontaneous Adaptation

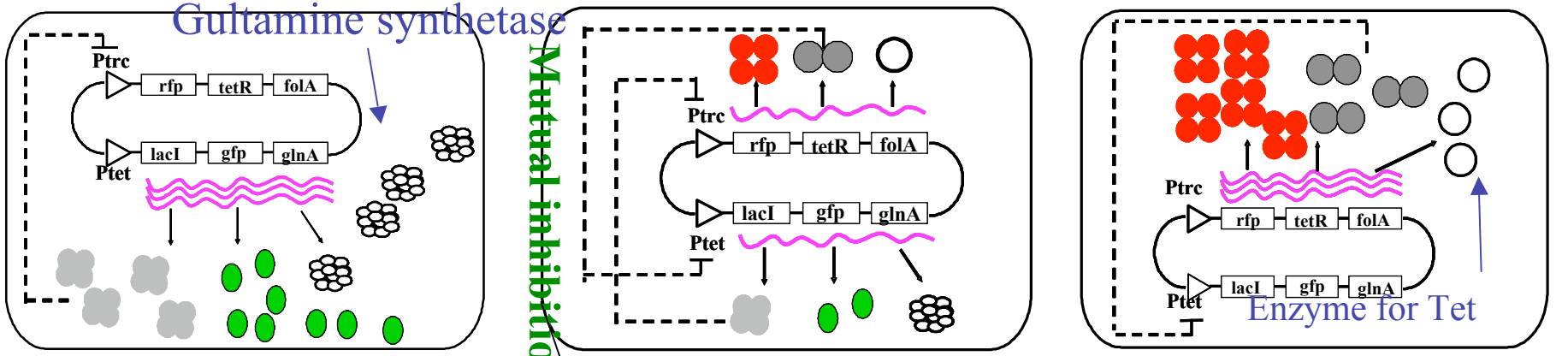
- For all possible changes in environment, signal transduction network is already provided?
- Or, is there any general (primitive) mechanism to make spontaneous adaptation?
- → Constructive Experiment with artificial Gene and theory assuming only growth condition and stochsticity
- From consistency between cellular growth and stochasitic gene expression dynamics, adaptive attractors are generally selected (theory)

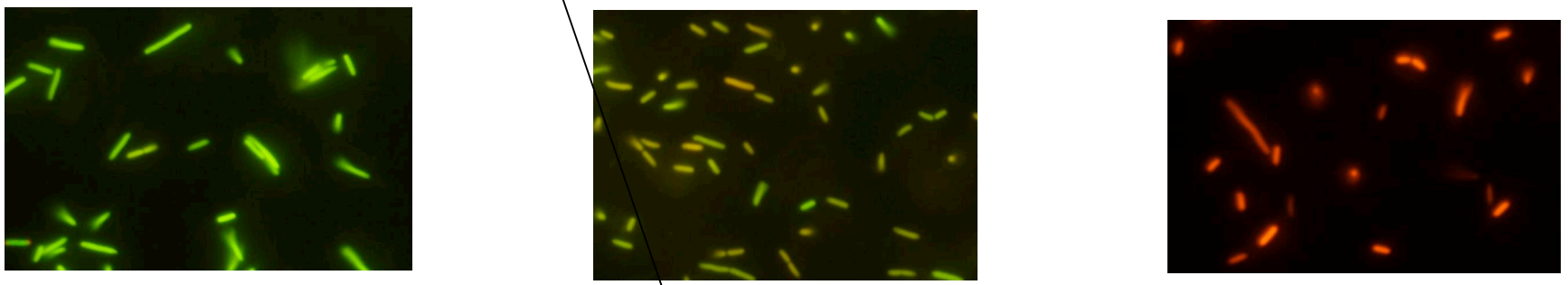
(ex) Adaptive response without signal transduction

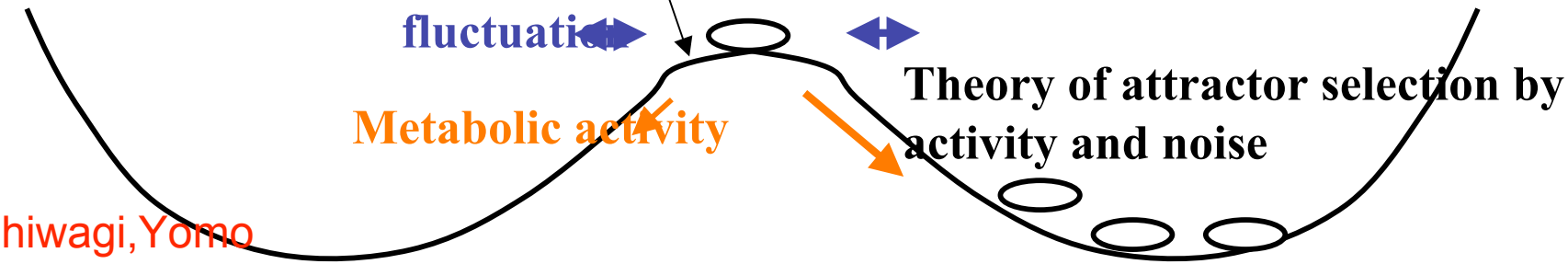
Embedded gene network

Unexpected; beyond designed
Selection of preferable state

Phenomenological theory of attractor selection







Kashiwagi,Yomo

- Growth-Induced-Attractor-Selection (Furusawa kk)
- Basic Logic

$dx_i/dt=f(x_i)-S(\{x_j\})x_i+\eta(t)$

f→ Synthesis S→ dilution due to cell growth

η → noise

Active state：both f and S are large

deterministic part >> noise

Poor state： both f and S are small

deterministic part ~ noise

Switch from Poor state to Active state by noise

Selection before reproduction

General logic in a system with growth and fluctuation

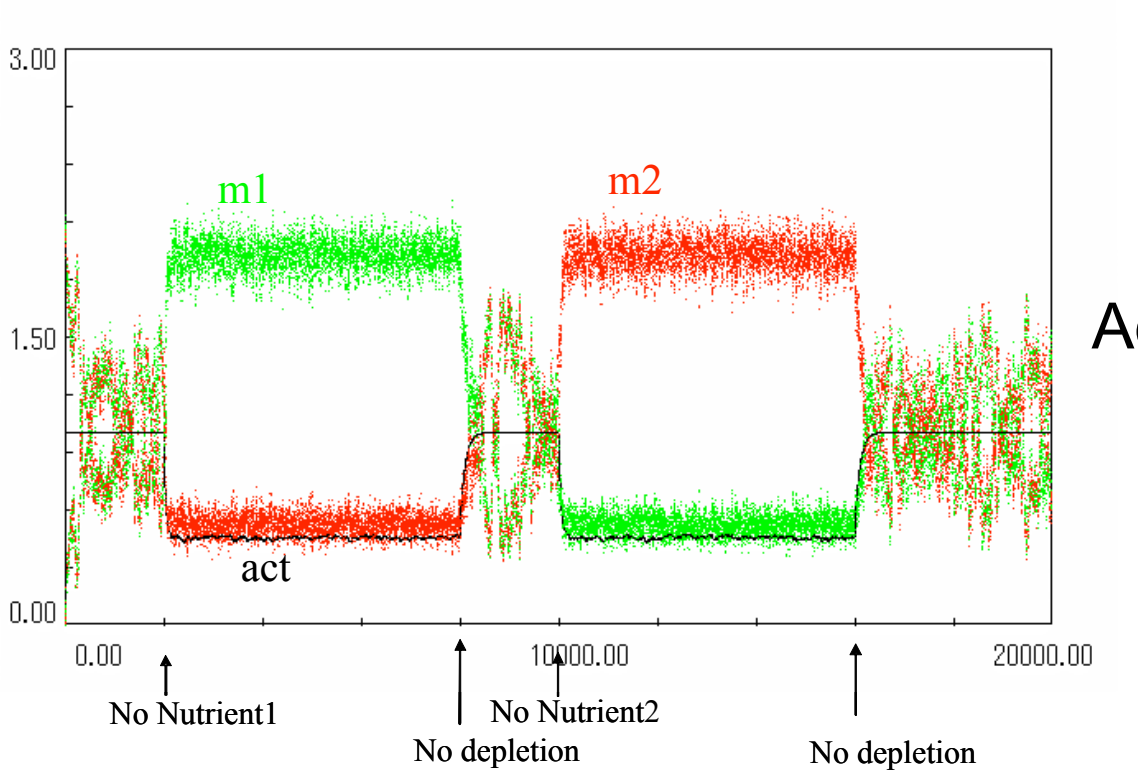
The mechanism for adaptive response by attractor selection

$$\frac{d}{dt}m1 = \frac{syn(act)}{1+m2^2} - \deg(act)\times m1 + \eta_1$$

$$\frac{d}{dt}m2 = \frac{syn(act)}{1+m1^2} - \deg(act)\times m2 + \eta_2$$

$$syn(act) = \frac{6act}{2+act}; \deg(act) = act;$$

$$\frac{d}{dt}act = \frac{pro}{((\frac{Nut\_thread_1}{m1+Nutrient1})^{n_1}+1)\times((\frac{Nut\_thread_2}{m2+Nutrient2})^{n_2}+1)} - cons\times act$$



Adaptive Response of the genetic network to a environmental change

Topic4; Cell differentiation:
Isologous Diversification:
(KK,Yomo1997)

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

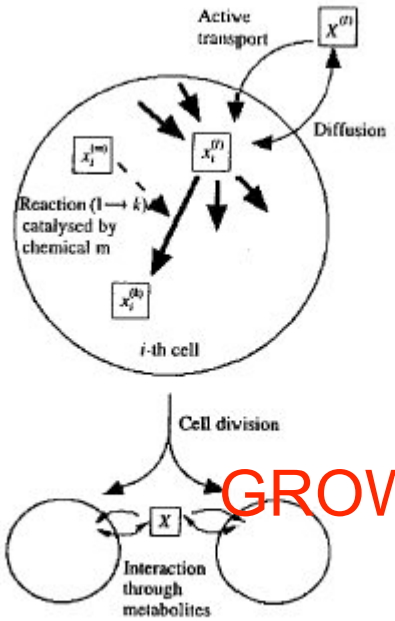


FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

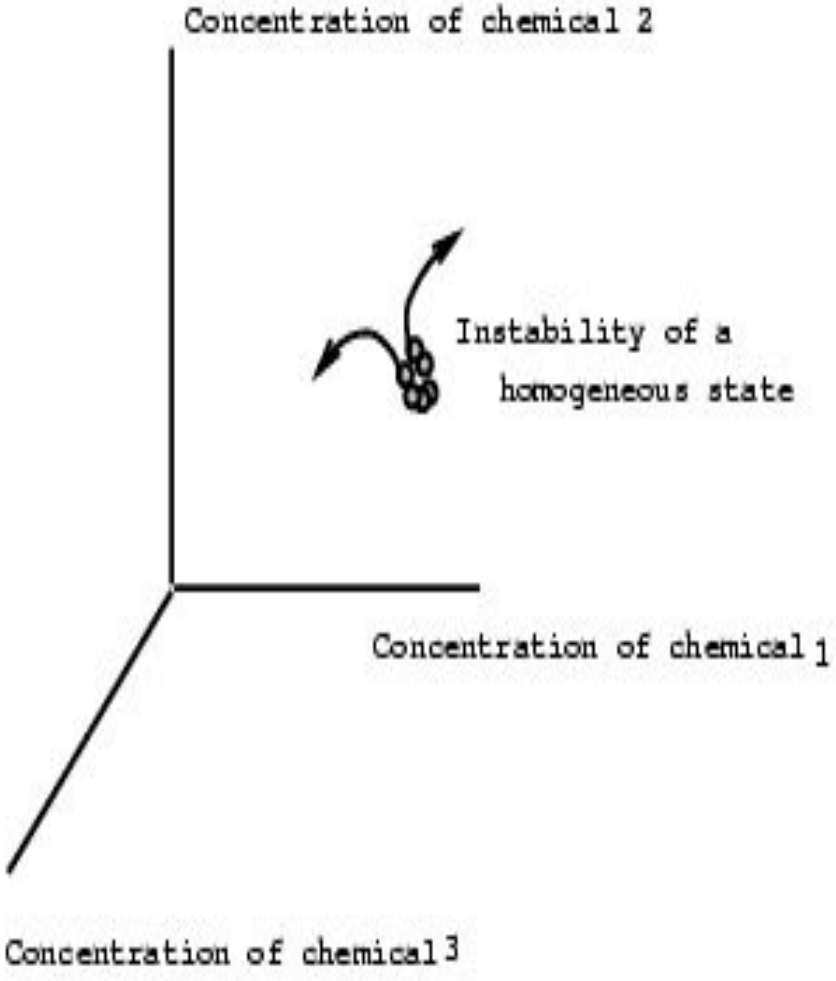
Reproduction of a cell
vs growth as a multicellular organism
→ development

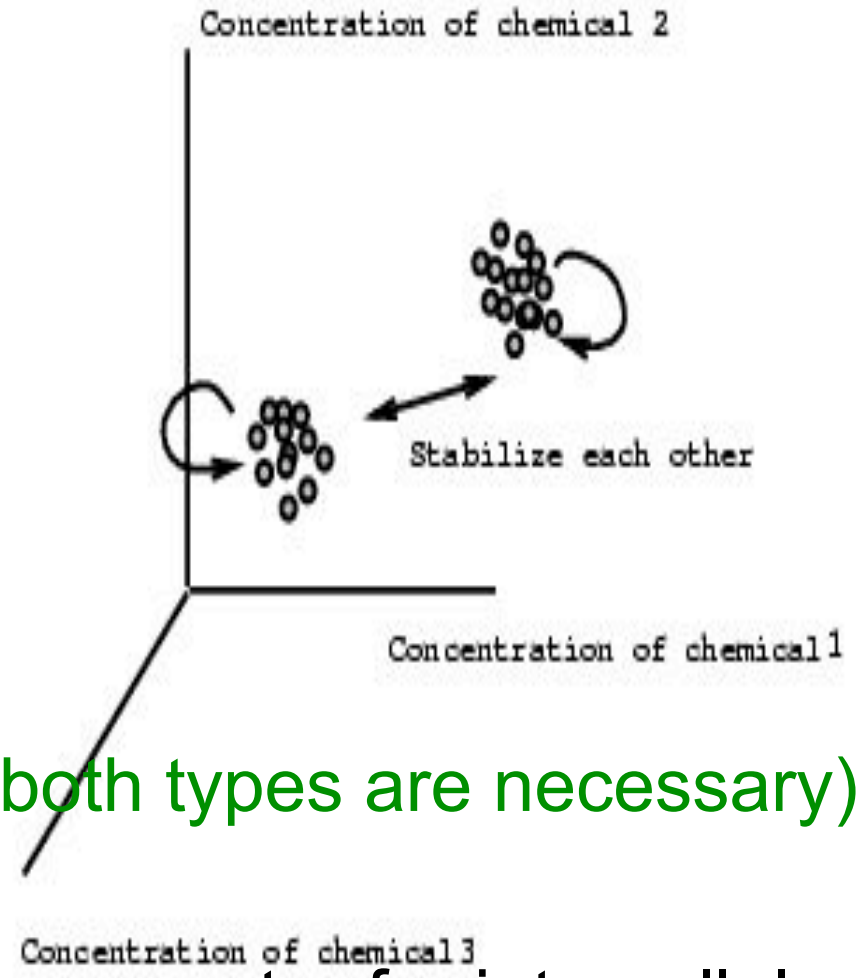
GROWTH

Internal chemical reaction dynamics
and interaction and cell division

Assuming oscillatory reaction dynamics.,
+GROWTH (→ change phase space dimension)
Cell number increases→ interaction change
→Bifurcation of intra-cellular dynamics→ differentiation
Stem Cell (chaotic dynamics) → stochastic differentiation with spontaneous regulation of probability to keep the consistency between cell and population

→With the increase of the number

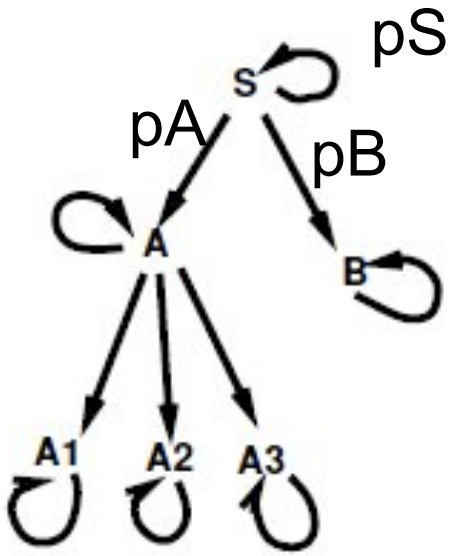


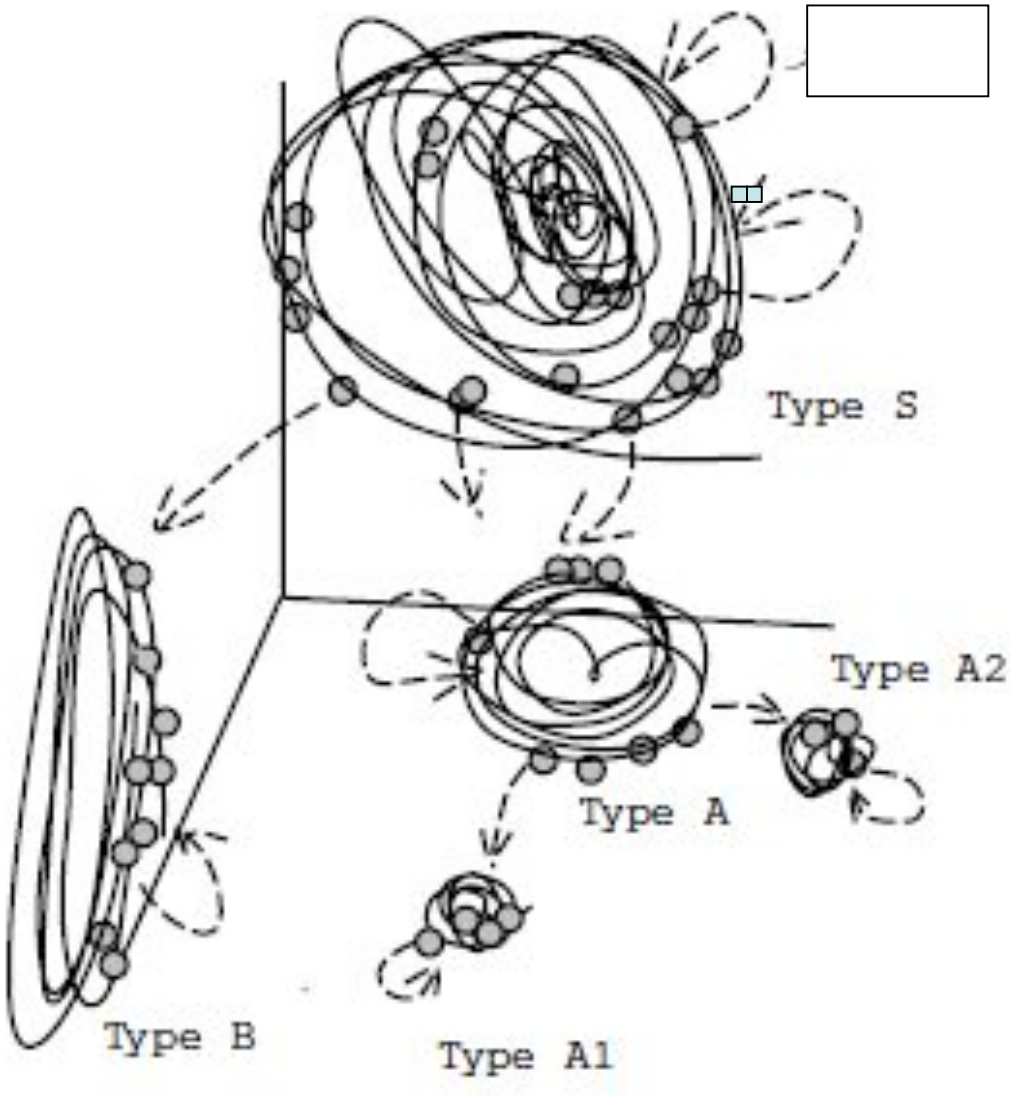


(both types are necessary)

Interaction works as bifurcation parameter for intracellular dynamics: self-consistency between intracellular dynamics and distribution of each cell type (Nakajima,kk2007)

Hierarchical differentiation from ‘stem cell’;by taking initially dynamics with instability
(e.g., chaotic)
stem cell as Milnor attractor?





probability depends on # distrib. of cell types
with prob. *pA* for *S* → *A*
if #(A) decreases then *pA* increases: **STABILITY**

Summary: **Consistency Principle for Biology**

(1)replication of molecules and cells :Universal Laws

(2)genetic and phenotypic changes

→Phenotypic Fluctuation ∝ Evolution Speed

→ Relation between

(isogenic)phenotype fluctuation vs

phenotype variation by mutation

Robustness to mutation and to developmental noise are linked

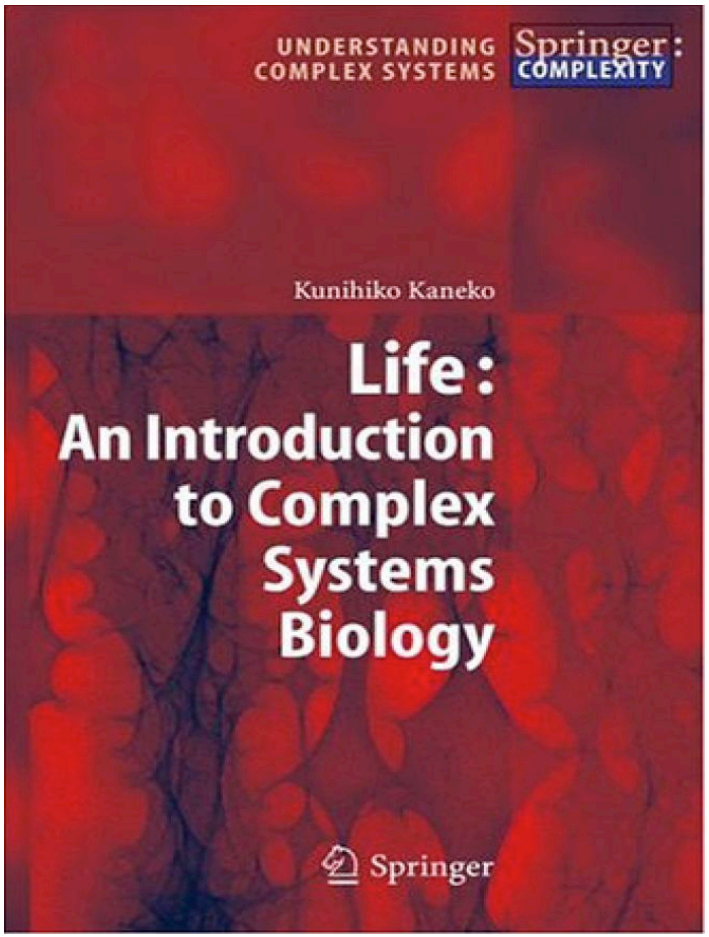
(3)adaptation of internal cellular state and growth

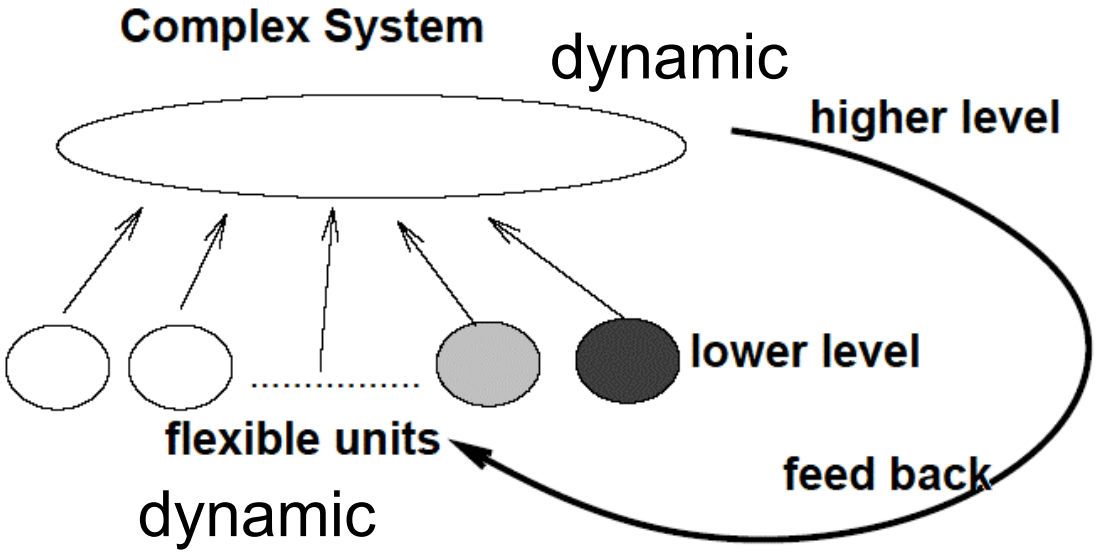
Growth system → general adaptation by noise

(4) replication of cells and cell ensembles

*differentiation from stem cell, developmental robustness

Consistency Principle
for stable state but
for innovation,
breakdown
of consistency
→ Chaotic Itinerancy





Collaborators

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Most papers available at
http://chaos.c.u-tokyo.ac.jp