Evolution of Phenotype
as selection of Dynamical Systems

1 Phenotypic Fluctuation (Plasticity) versus Evolution

2 Phenotypic Fluctuation versus Genetic Variation

consistency between Genetic and Phenotypic Levels

3 Evolution of Robustness to Developmental Noise and to Mutation

4 Sympatric speciation:

Fixation of Bifurcation of Phenotype to Genes

- Underlying Motivation as Dynamical Systems
- Dynamical Systems Model in Biology (development/gene expression,,,)

  Study the behavior : OK as mathematics/physics, but
- In biology, choice of such dynamical systems itself is an essential issue
- (+) selection of dynamical systems rule through evolution, which is based on dynamics itself

  → constraint in choice of rule, 'smooth dynamics'
- (*) Selection of 'restricted' low-dimensional dynamical systems from higher-dimensional space through development

- Mathematical Theory for Evolution and Development? (case under fixed environment, without interaction) simplified

- Development = Dynamical Systems
- Gene = Rule (parameter etc) of the DS
- Phenotype = State value at attractor of the DS
- Evolution = Selection of Phenotype

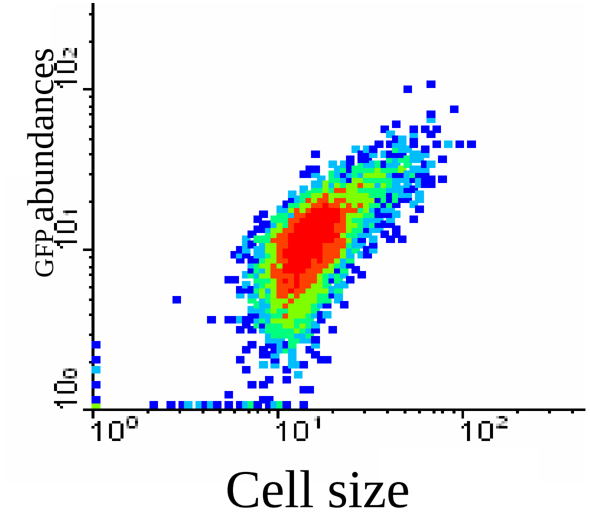
which leads to selection of Gene

(only gene is transferred to the next generation)

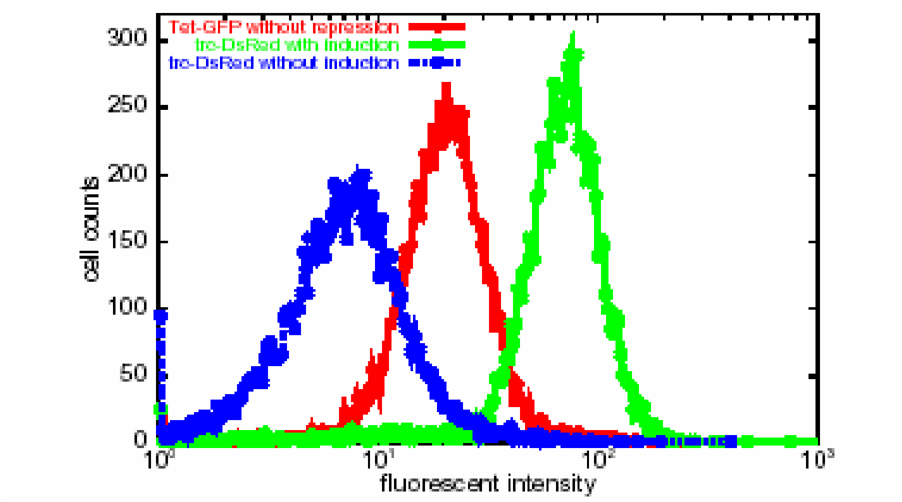
‘Walk in the ‘Model(rule/parameter) space’

Proposal: choice of model assimilates DS

Starting point:
Phenotypic Fluctuation →evolution？



- Even in isogenic indiviudals (clones) there is large phenotypic fluctuation :recognized extensively
  Exp + Model+Theory
- Relevance of this fluctuation to evolution?
  Gene（rule for dynamics)
  ---(gene expression)
  development dynamics ---
  →Phenotype (with fluctuation)
  → selection

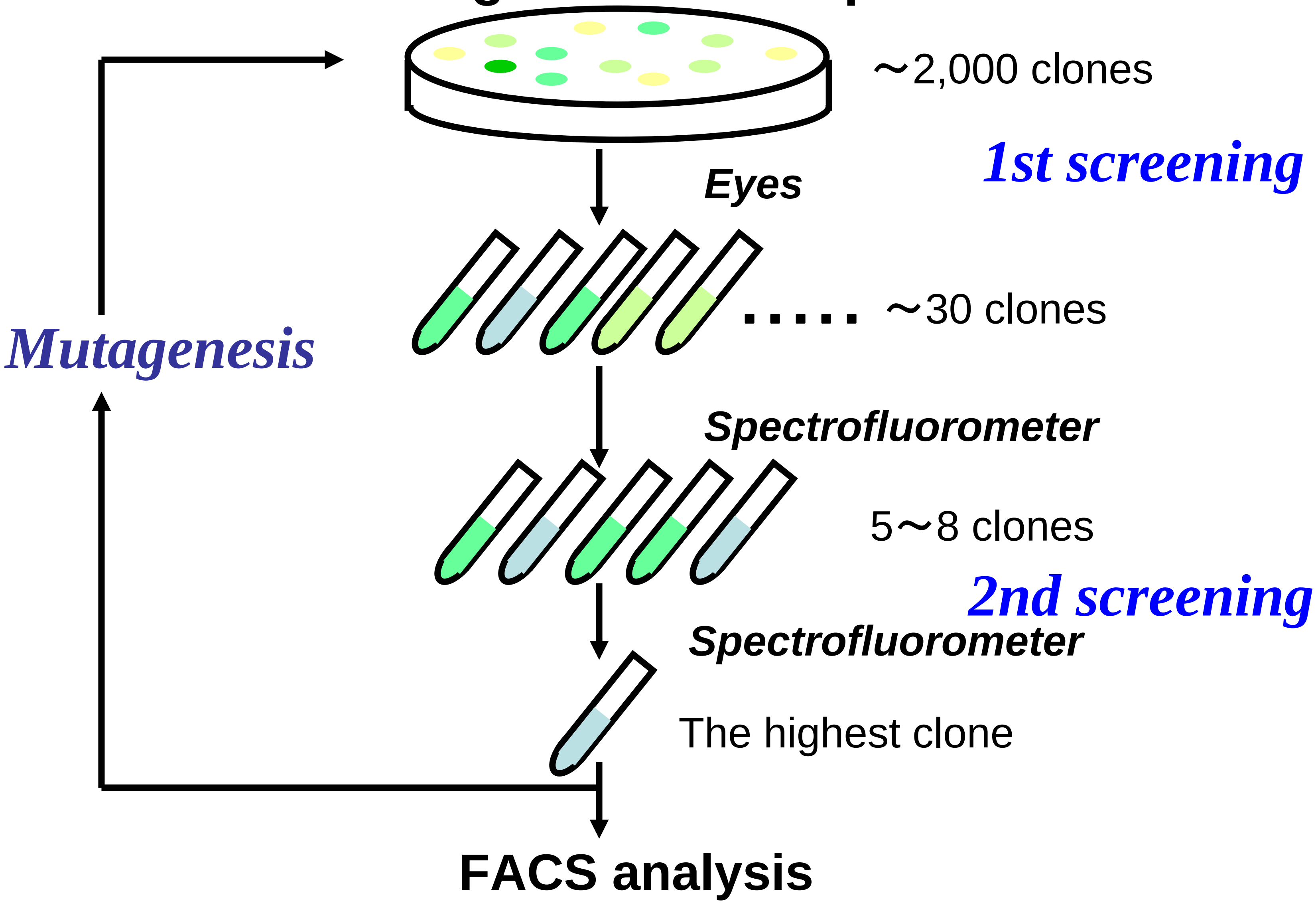


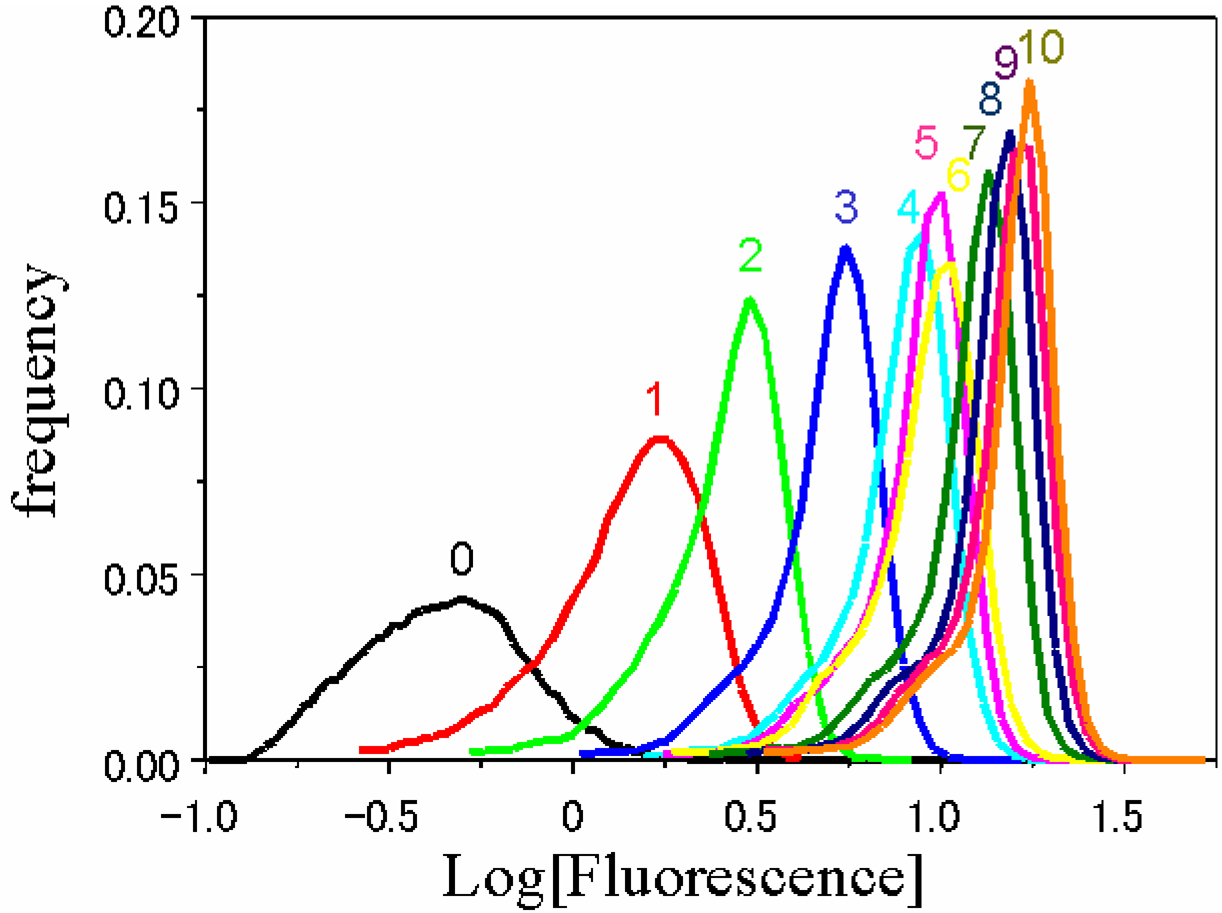
.umber distribution of the proteins measured by fluorescent intensity.

Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process





Sato,Ito,
Yomo,KK
PNAS(2003)

Fluctuation ---- Variance of phenotype of clone

Organisms with larger phenotypic fluctuation have higher evolution speed;

Evolvability ←→ Fluctuation

Remind of fluctuation－response relation 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 …

Generalization::(mathematical formulation)

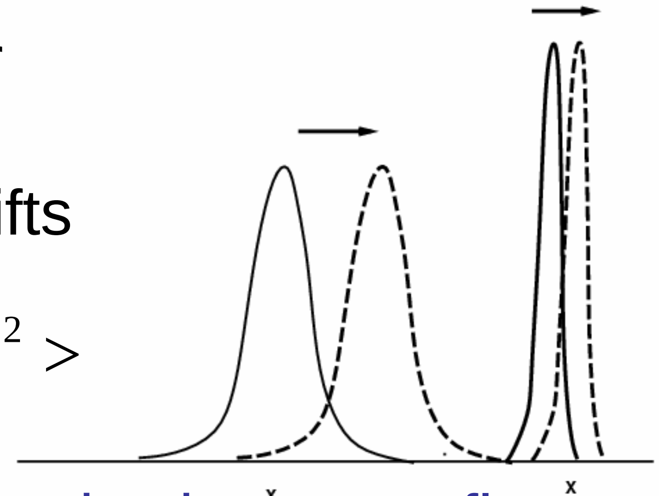
plasticty~response ratio of some variable x against change of parameter a versus fluctuation of x

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 mutation rate ∝ isogenic phenotype fluctuatior

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

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

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

$$P(x:a) = N(\mathrm{a})exp(-\frac{(x-X_0)^2}{2\alpha(a)} + C(a-a_0)(x-X_0)),$$

generalized force $C(a-a_0)(x-X_0)$ to shift the distribution.

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

Hence, we get

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

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

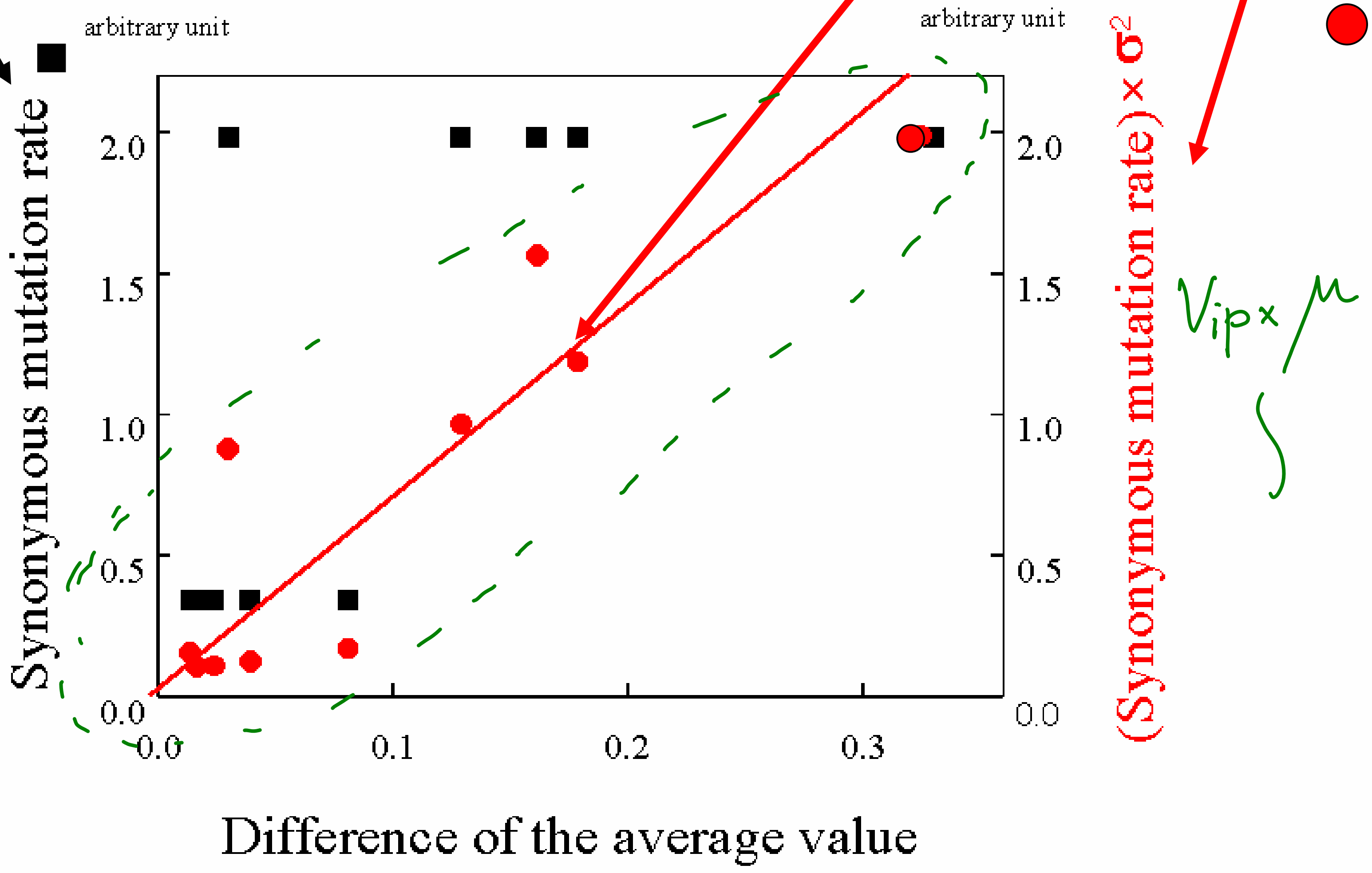
$$\frac{< x >_{a=a_0+\Delta a} - < x >_{a=a_0}}{\Delta a} = C < (\delta x)^2 >,$$

Approximate formula； trivial by itself

Non-trivial point： representation by P(x;a)
x ：phenotype a；enviroment etc

Naïve expectation:
Just propt to mutation rate

Fluctuation-response relation
Phenotype fluct. ✕ mutation rate



(Evolution Speed per generation)

Sato,Ito,Yomo,KK, PNAS 2003

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

C.Furusawa & KK、PRL2003

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

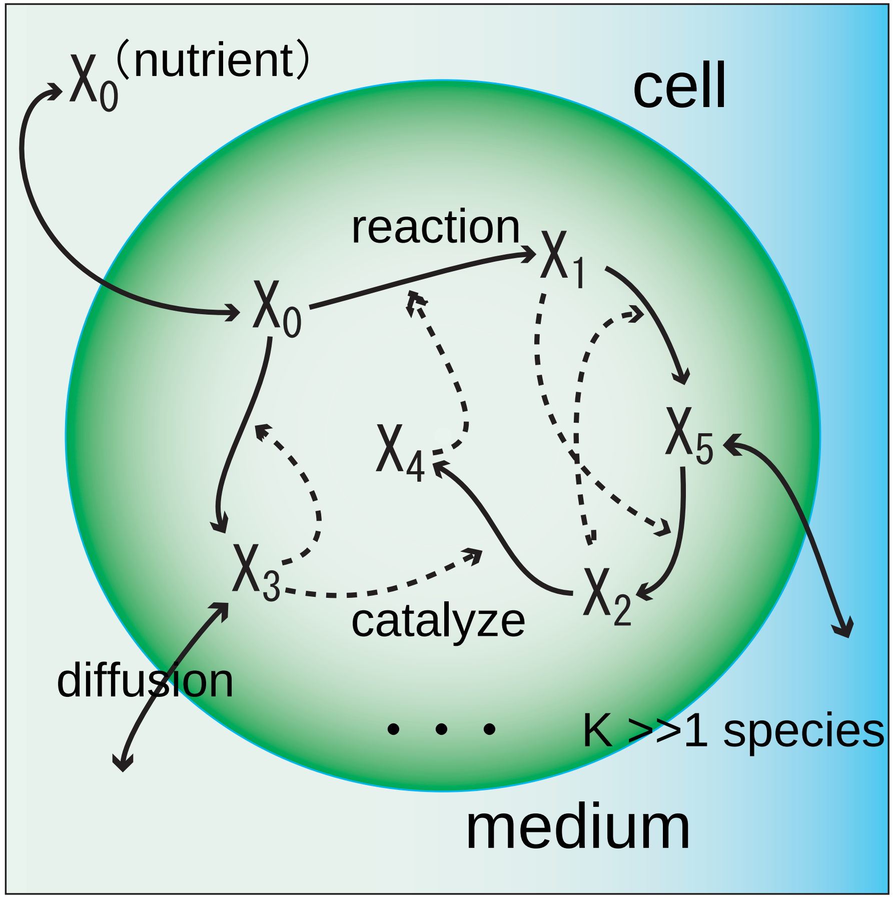
- random catalytic reaction network
with the path rate p
for the reaction $X_i + X_j \rightarrow X_k + X_j$

- 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

model

細胞
(Cf. KK&Yomo 94,97)



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

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

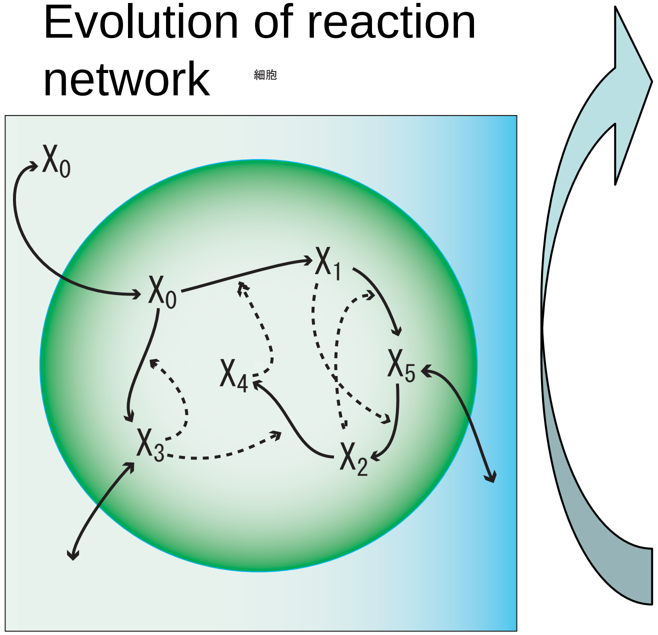
$$dn_i/dt = \sum_{j,\ell} \mathrm{Con}(j, i, \ell)\epsilon n_j n_\ell / N^2 - \sum_{j',\ell'} \mathrm{Con}(i, j', \ell')\epsilon n_i n_{\ell'} / N^2 + D\sigma_i(\overline{n}_i / V - n_i / N),$$

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

- 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

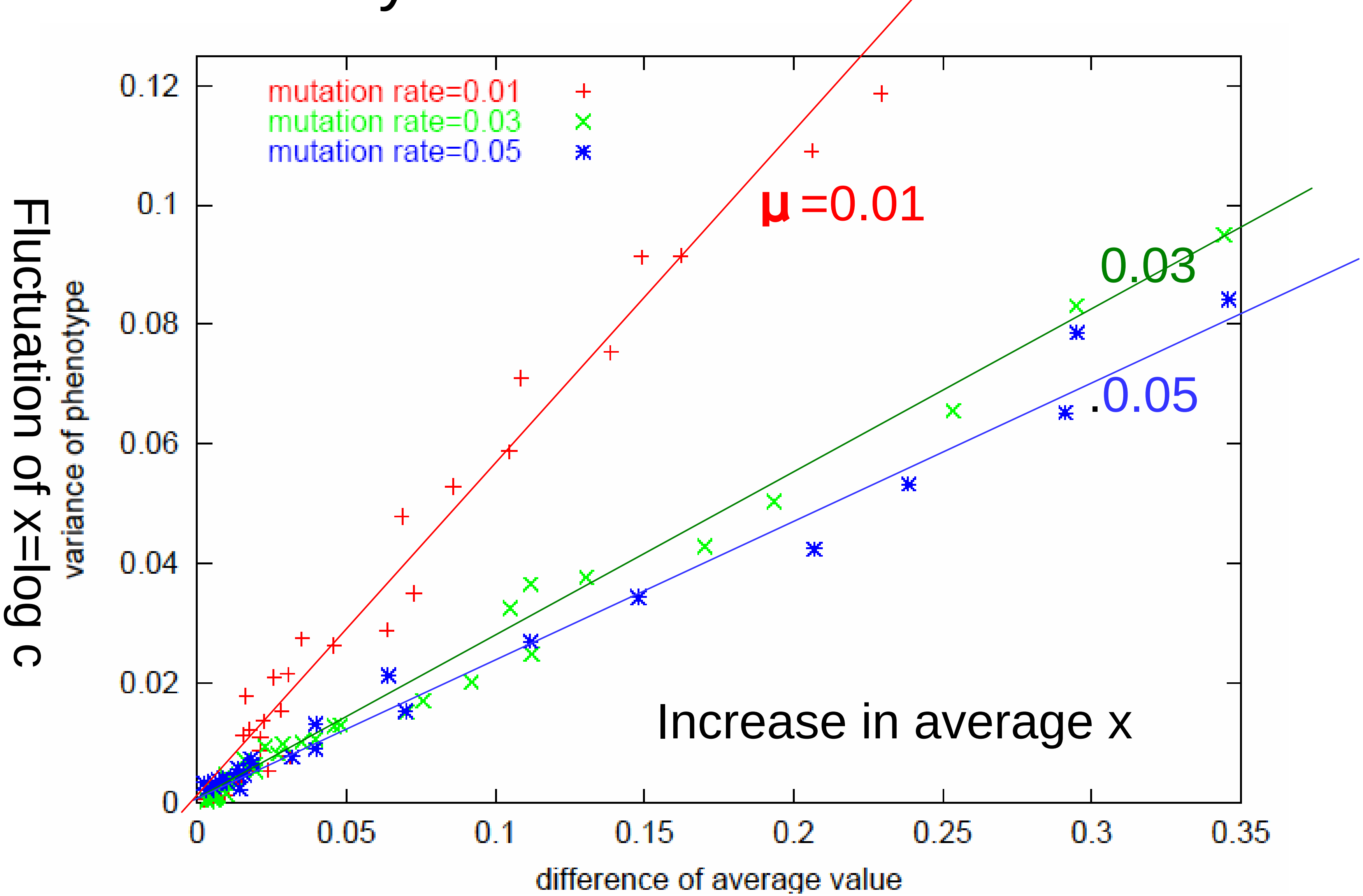
Evolution of reaction network 細胞



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



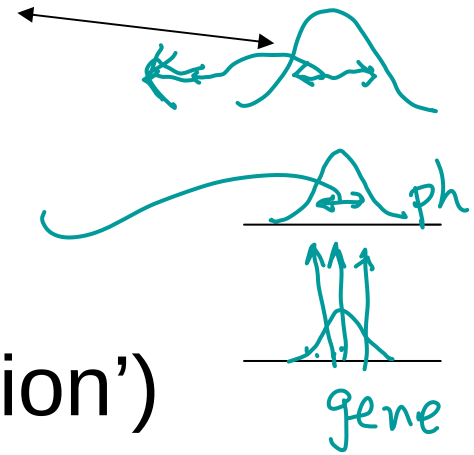
Furusawa,KK 2005

….. Not yet over ….

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

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

isogenic phenotypic fluctuation Vip

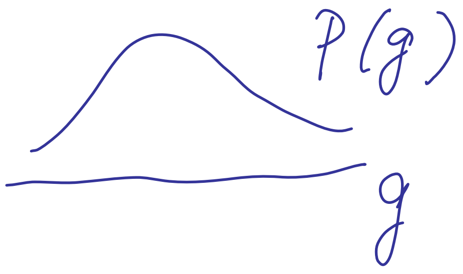


$\propto$

pheno fluct by gene variation Vg？

（fluct by noise $\propto$ variation in ‘equation’)

Vip ∝ evolution speed (exp (?), model)
Vg ∝ evolution speed (Fisher) a simple derivation(?)



(growth rate ~fitness)

distribution

$P_n(g)$

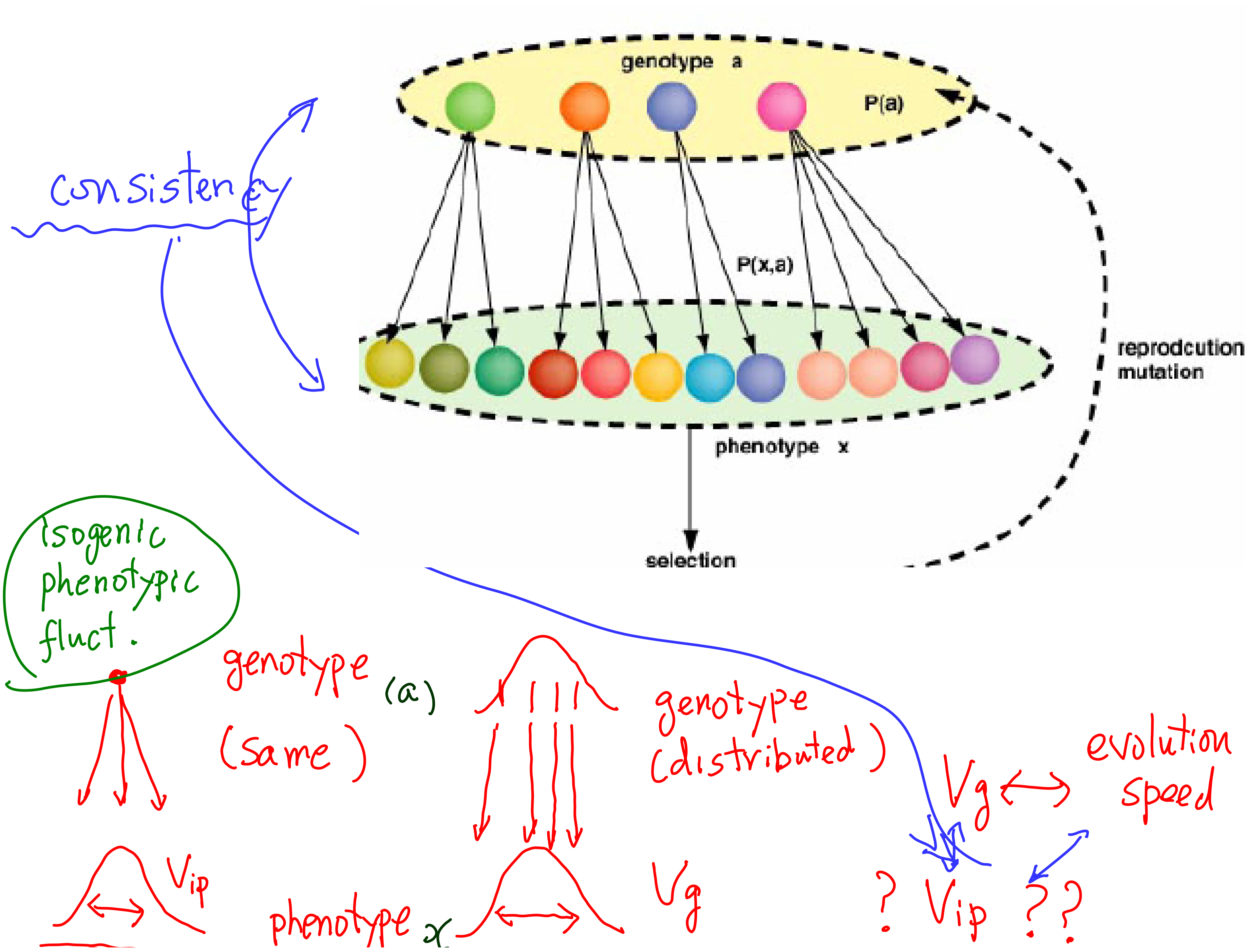
$$\bar{g}_n = \int g P_n(g)\, dg$$

$$P_{n+1}(g) = \frac{g P_n(g)}{\int g P_n(g)\, dg} = \frac{g P_n(g)}{\bar{g}_n}$$

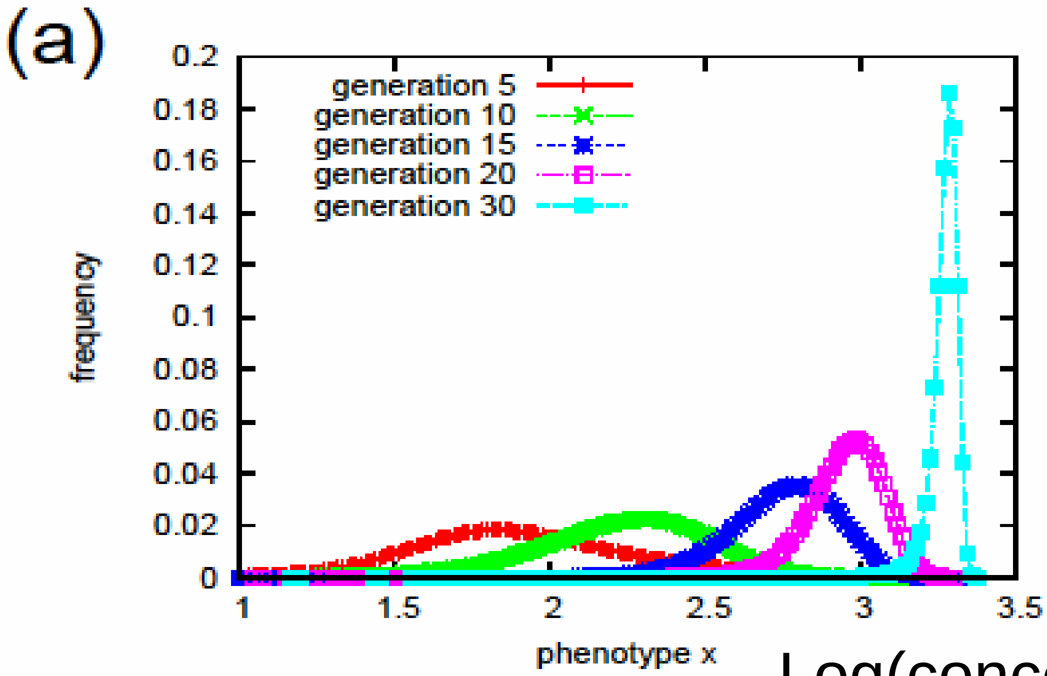
$$\bar{g}_{n+1} - \bar{g}_n = \frac{\int g^2 P_n(g)\, dg}{\bar{g}_n} - \bar{g}_n = \frac{1}{\bar{g}_n}\left(\int g^2 P_n(g)\, dg - \left(\int g P_n(g)\, dg\right)^2\right)$$

$$= \frac{1}{\bar{g}_n} \overline{(\delta g_n)^2}$$

(Fisher ?)

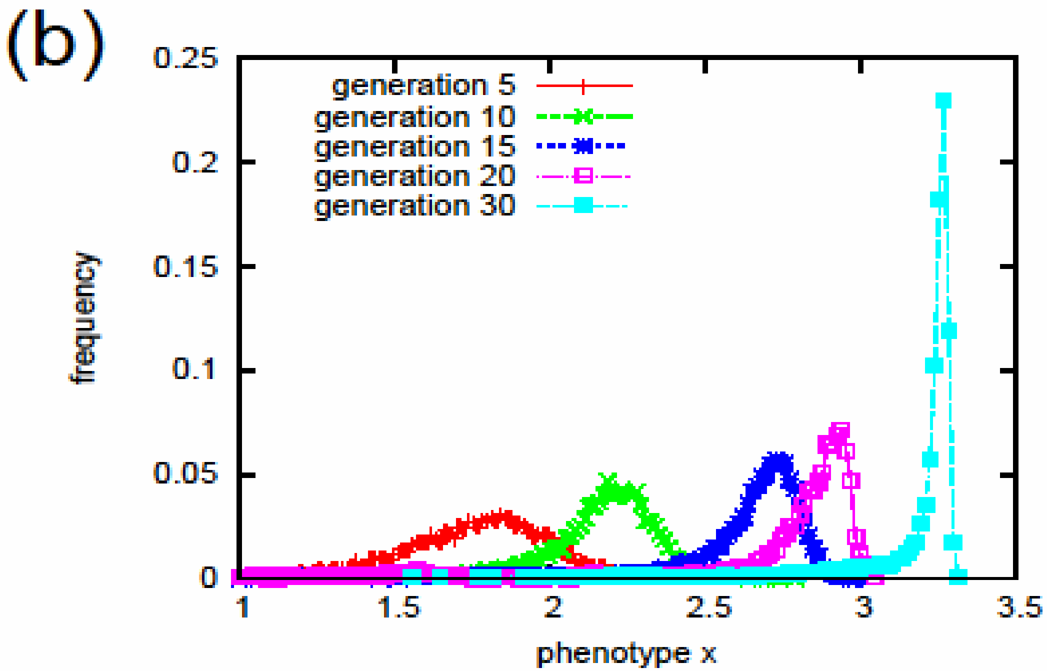

genotype a
P(a)
P(x,a)
reprodcution
mutation
phenotype x
selection
consistency
isogenic
phenotypic
fluct.
genotype (a)
(same)
Vip
phenotype x
genotype
(distributed)
Vg
Vg
evolution
speed
? Vip ??

Change of distribution through evolution



Distribution of phenotype x of a clone
→ Vp

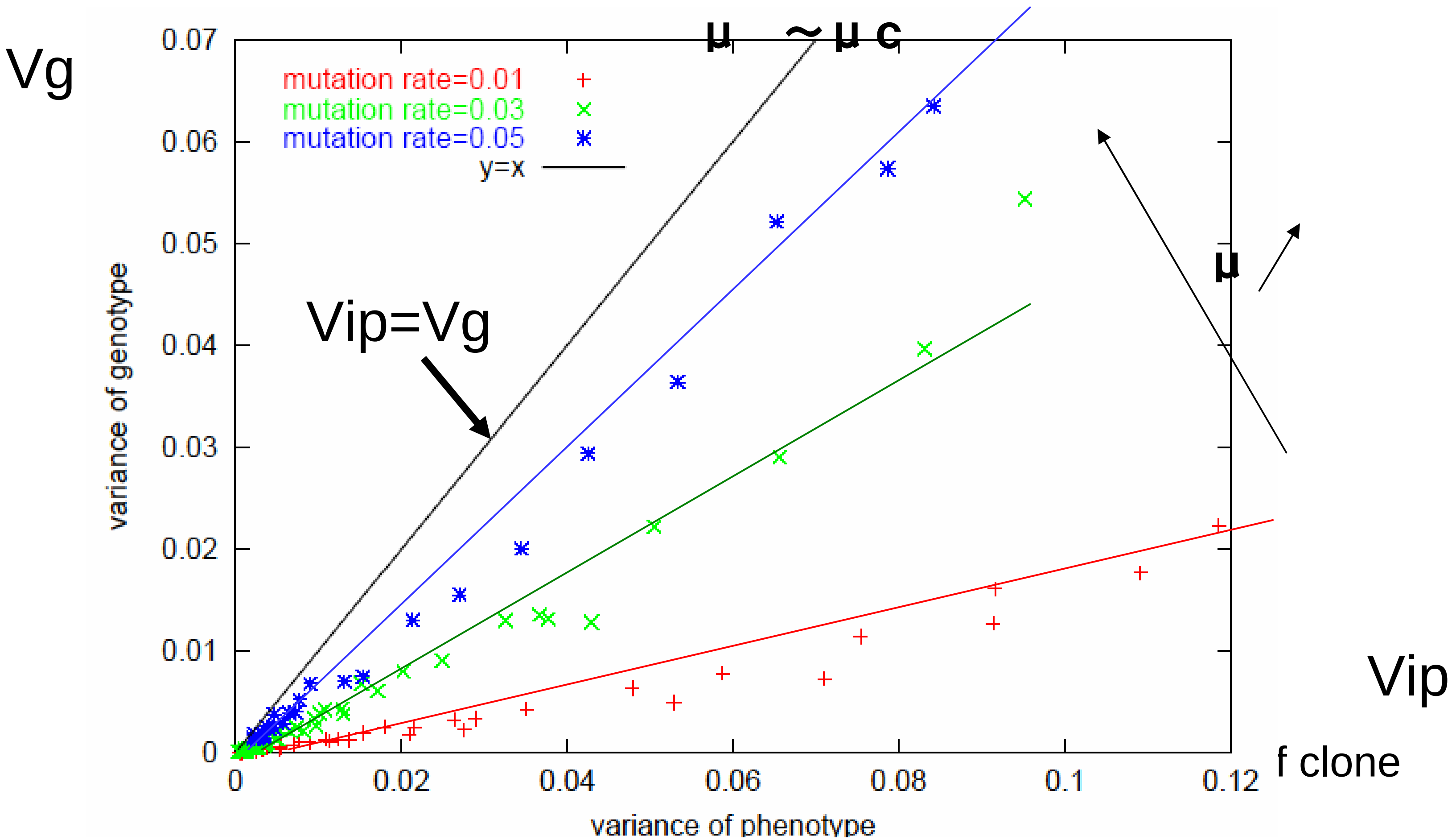
Log(concentration)



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

cf. also true for each molecules species (common proportional coefficient, (Furusawa, private comm.)

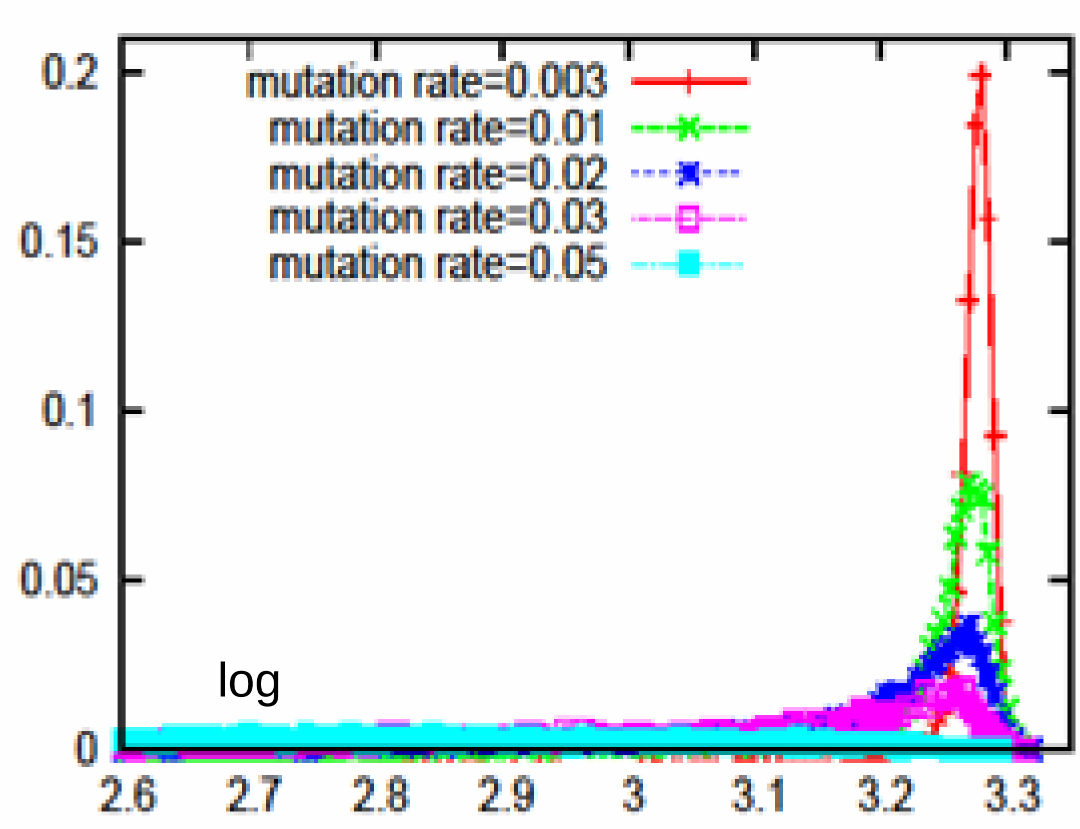
As mutation rate μ is increased beyond some value μ_c,

the peaked distribution collapses → error catastrophe

low-fitness mutants dominate →

evolution does not progress

at μ_c Vip ~Vg



Phenotype；concentration of selected (target) chemical

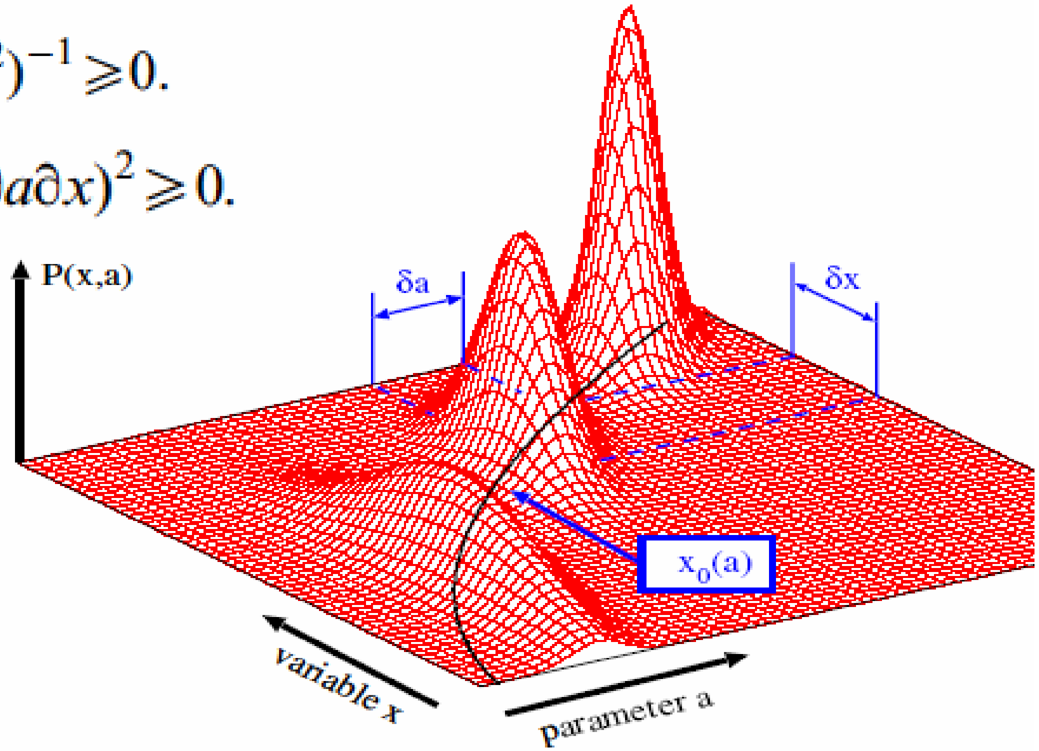
Consider 2-variable distrb
P(x=phenotype,a=genotype) =exp(-V(x,a))
Keep a single-peak (stability condition).

KK,Furusawa, 2006 JTB

$$(\partial^2 V/\partial a^2)^{-1} \geqslant 0; \quad (\partial^2 V/\partial x^2)^{-1} \geqslant 0.$$

$$(\partial^2 V/\partial x^2)(\partial^2 V/\partial a^2) - (\partial^2 V/\partial a \partial x)^2 \geqslant 0.$$

Hessian condition



Up to this point pheno (x) and geno (a) are treated in the same way.
Then given a, the peak (average) phenotype is x0(a)--function of a --

$$\partial V/\partial x|_{x=x0} = 0$$

Phenomenological Theory for these experimental observations?

Consider P(phenotype,genotype) distribution P(x,a)

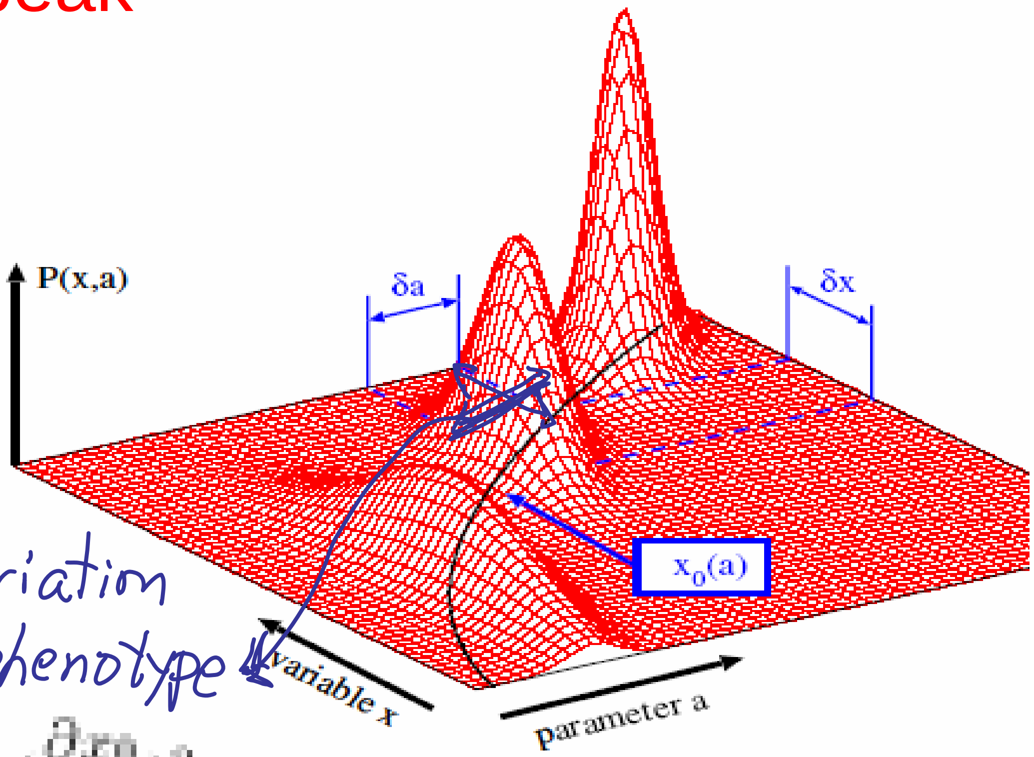
or P(x,a)=exp(-V(x,a))

Condition to keep single peak

(evolutionary stability) .

V_{ip} : $(\delta x)^2$ of isogenic individuals

V_{ig} : variance of x due to genetic variation for the identical phenotype



$$< (\overline{x}_a - \overline{x}_0)^2 >= V_{ig} =< (\delta a)^2 > (\frac{\partial x_0}{\partial a})^2,$$

KK,Furusawa, 2006 JTB

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

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

$$\mu \leq \frac{\alpha}{C^2} \equiv \mu_{max}.$$

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

$$V_g = \frac{\mu C^2}{1-\mu C^2/\alpha}$$

$$\overline{V_{ip}} = \frac{\alpha}{1-\mu C^2/\alpha}$$

$$\overline{V_{ip}}/V_g = \alpha/(\mu C^2)$$

$\overline{}$ = Ave over all populations

$$V_g \leq \overline{V_{ip}}.$$

$$V_{ig} = \frac{\mu}{\mu_{max}} \overline{V_{ip}}$$

From Stability condition → $V_{ip} \gtrapprox V_{ig}$ is derived

Vg increases with the mutation rate

if the increase continues, there is critical mutation rate

μ c at which Vip ~Vig

Error catastrophe → evolution stops

Here, Vig ≠ Vg

Vig for distribution for a given phenotype

Vg for all population

but for small μ

OR def Vp as average of Vip,

Then Vp ≧ Vg

$$V_g \approx V_{ig} \approx \frac{\mu}{\mu_c} V_{ip}$$

⇒ $\mu V_{ip} \propto V_g \propto$ evolution speed

consistent

- (i) Vip $\geqq$ Vg （from stability condition) (**)

(ii)error catastrophe at Vip ~ Vg (**)

(where the evolution does not progress)

(iii) Vg~(μ / μ max)Vip$\propto\mu$ Vip

（$\propto$evolution speed) at least for small μ

＊＊Consistent with the experiments, but,,,,,

Existence of P(x,a) assumption ??;;

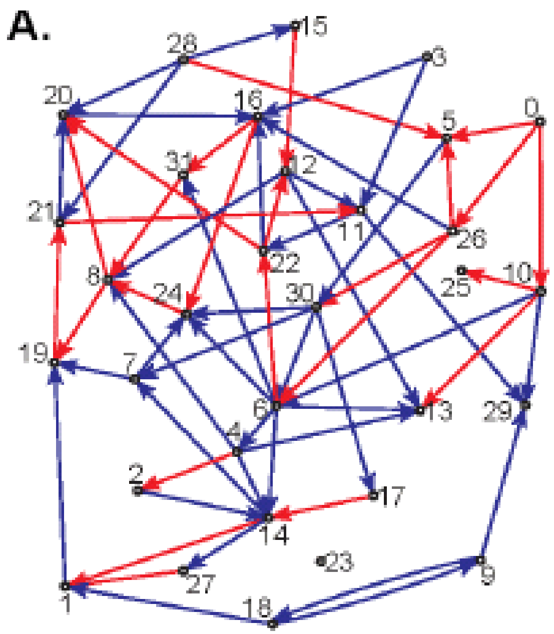
+ Robust Evolution assumption ?? +

Why isogenetic phenotypic fluctuation leads to robust evolution?

(**) to be precisely Vig, variance those from a given phentype x: but Vig ~Vg if μ is small

Gene expression dynamics model::
Relevance of Noise to evolution?

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



Xi – expression of gene i :

on off

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

Activation
Repression
Jij=1,-1,0

$$< \eta_i(t) \eta_j(t') > = \delta(t-t') . \delta_{ij}$$

Gaussian white

M;total number of genes, k : output genes

Noise strength σ

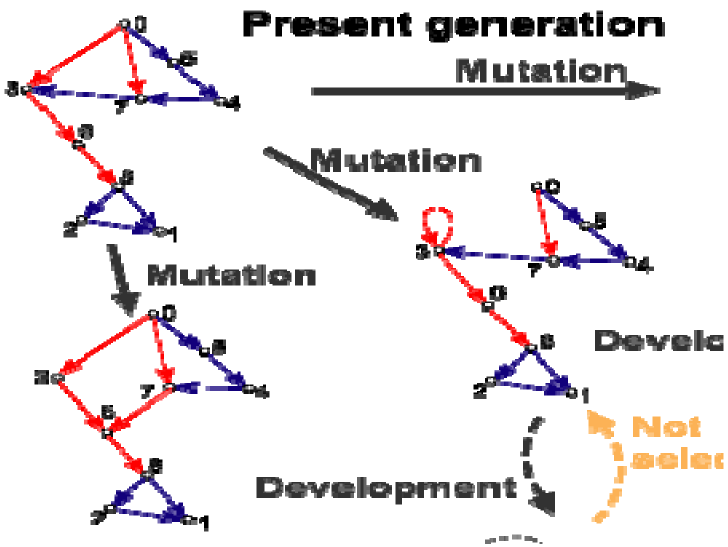
- Fitness: Starting from off of all genes, after development genes xi i=1、2、・・・・、k should be on （Target Gene Pattern)

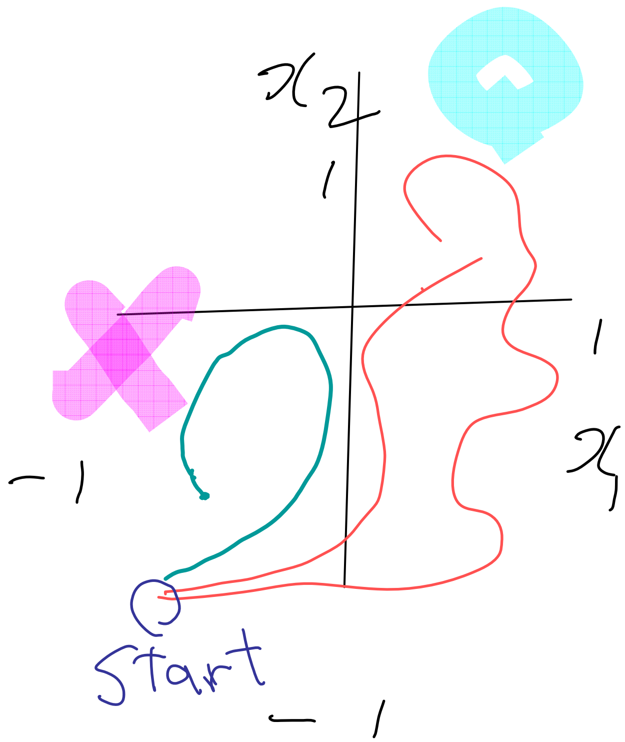
Fitness F= ー（Number of off x_i）

Genetic Algorithm

Mutate networks and Select those with higher <F>

Choose top n networks among total N,
and mutate with rate **μ** to keep N networks



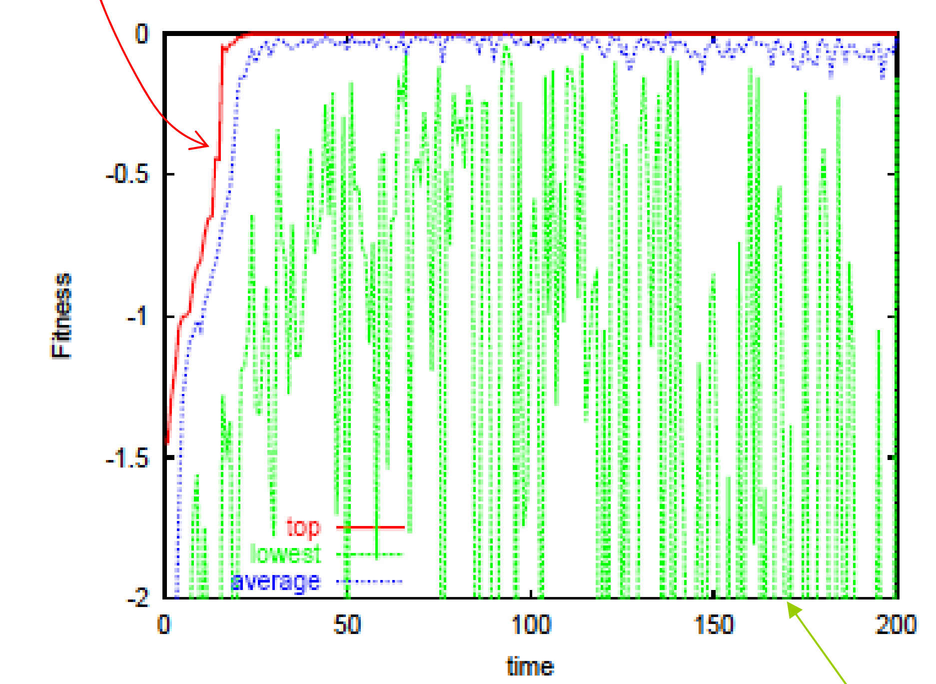


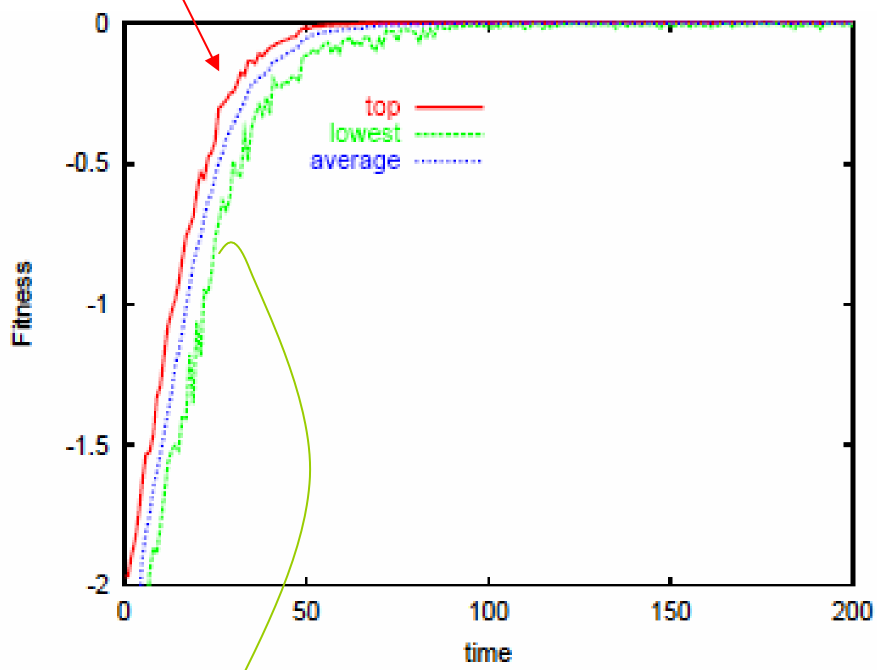
Result of evolution

Top:reaches the fittest faster for lower noise(σ)

Lowest; cannot evolve for low noise(σ)

Top among existing networks (genotypes)

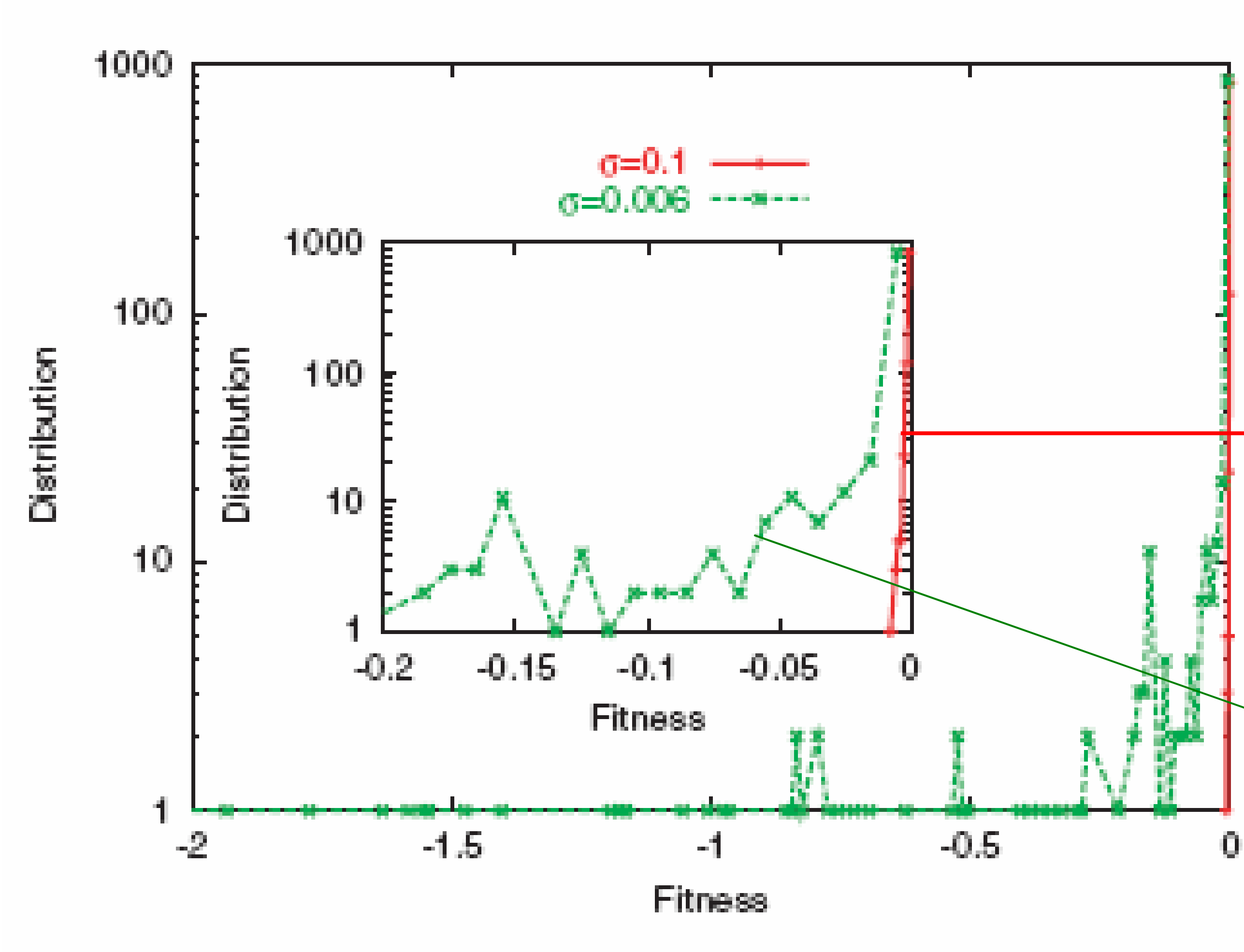




Lowest among genotypes

Low Noise case

High Noise case



Result of evolution

Top:reaches
the fittest

Lowest;cannot evolve
for low noise(**σ**)

$\sigma > \sigma_c$

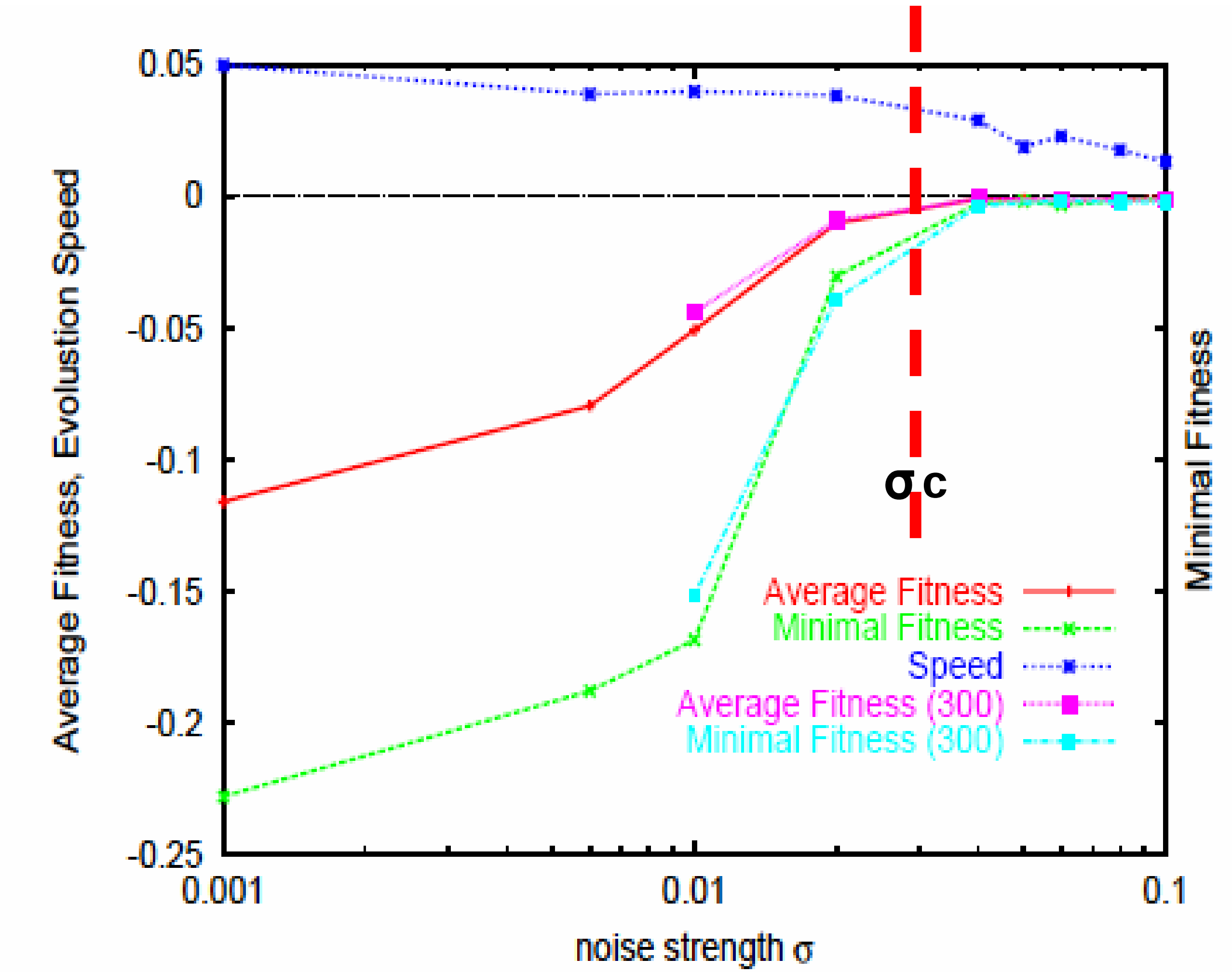
σ＜σ c

Fitness Distribution

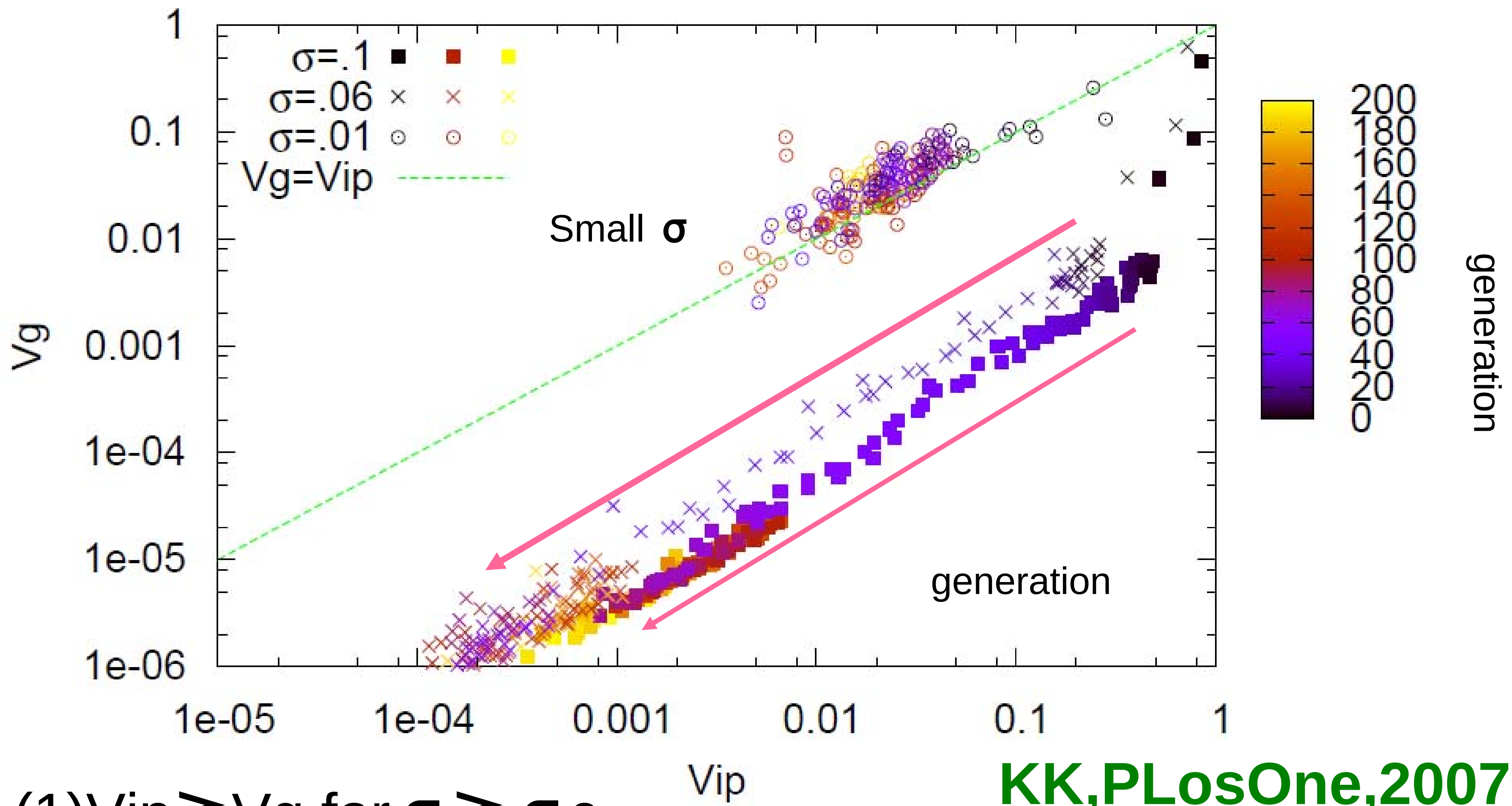
σ＜σ c --low fitness mutants distributed

σ＞σ c – eliminated

through evolution



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



KK,PLosOne,2007

(1) Vip≧Vg for **σ** ≧ **σ** c

(2) Vg→Vip as **σ** → **σ** c

(3) evolution progresses only for Vip ≧Vg

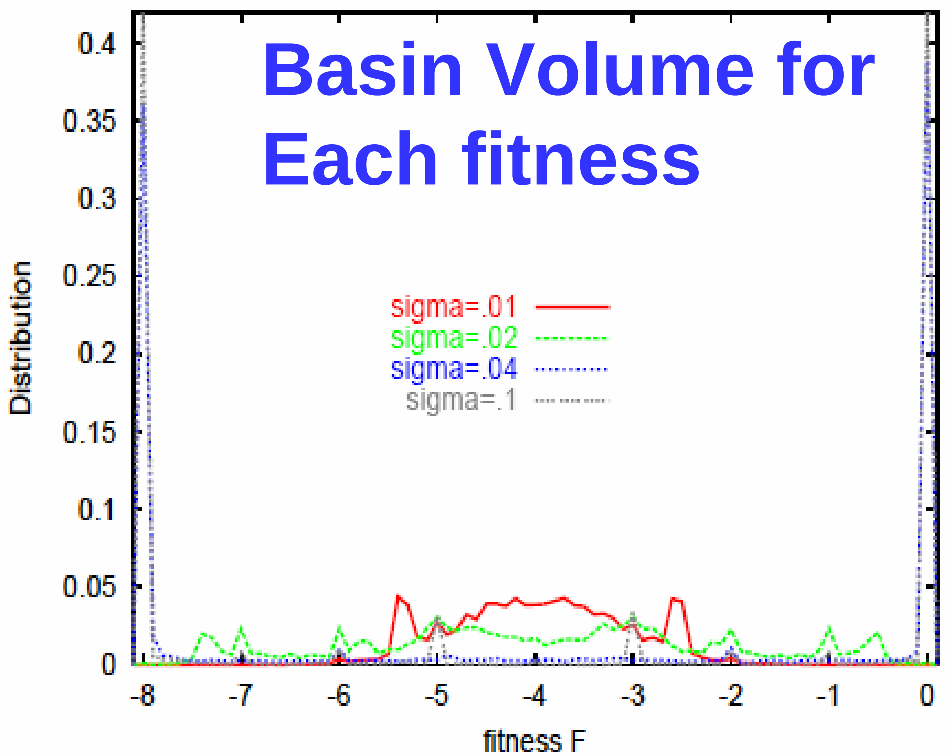
(4) Vip∝Vg through evolution course

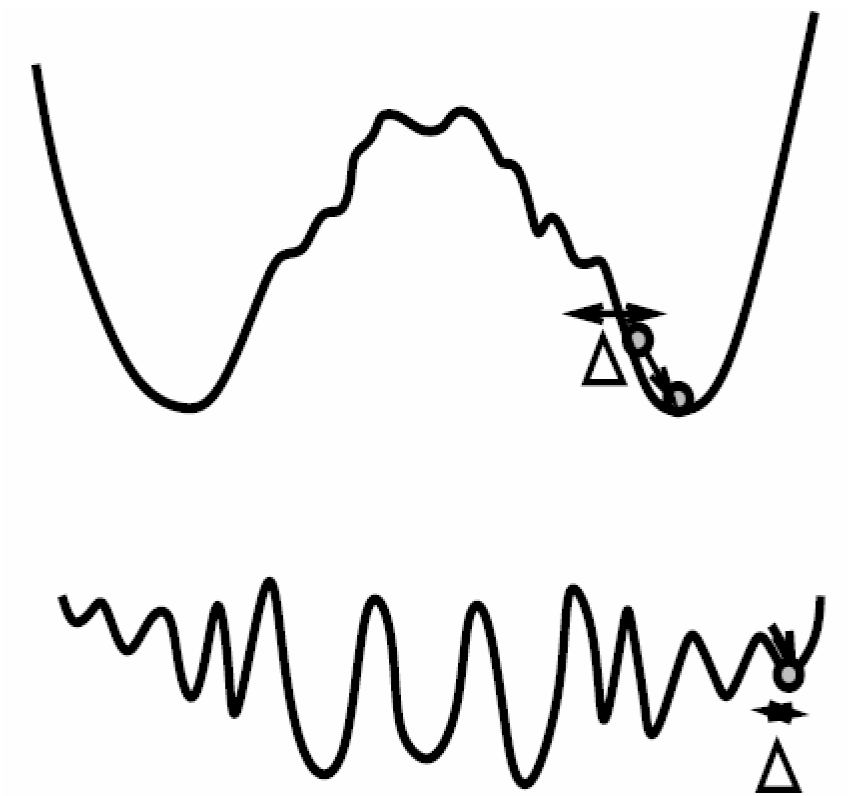
Distribution Theory confirmed

Why?; difference in basin structure

σ＞σc → large basin for target attractor (robust, Δ（distance to basin boudary) ↑

σ＜σ c → only tiny basin around target orbit Δ remains small





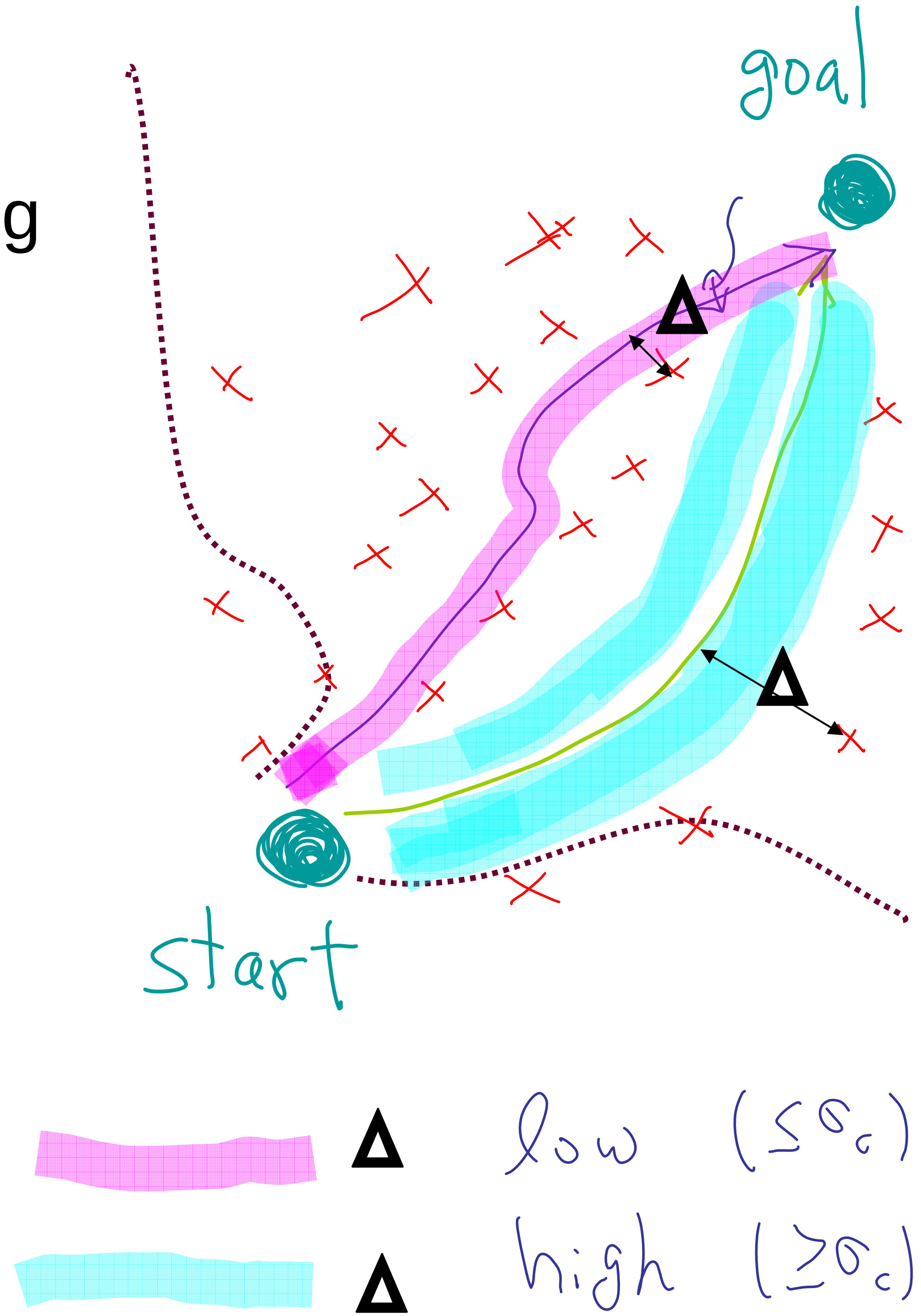
→Global constraint to potential landscape(funnel?)

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



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

For $\sigma > \sigma c$, both decrease, i.e., robustness↗

Noise is necessary for evolution of robustness

Vip $\propto$ Vg →Developmental robustness and genetic (evolutionary) robustness are linked (or embedded) WADDINGTON genetic assimilation

? Extension of Structural Stability Needed?

- Generality of our result; For a system satisfying:

(1) fitness is determined after developmental dynamics

(2) developmental dynamics is complex

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

-- under noise smooth dynamic landscape is formed (‘Funnel’)

Symbiotic Sympatric Speciation

Kk,Yomo2000 ProcRoySoc

- So far, no interaction, evolution under fixed environment -- – single-peaked distribution
- Speciation → change to double peaked distribution

** Allopatric vs Sympatric (S fundamental? Difficult?)

- Our scenario for sympatric speciation (confirmed by several models):

(1) Isologous divesification (interaction-induced phenotype differentiation);

homogeneous state is destabilized by the interaction

e.g., by the increase in resources

(2) Amplification of the difference through geno-pheno relation

Two groups form symbiotic relationship, and coevolve

(3) Genetic Fixation and Isolation of Differentiated Group consolidated to genotypes

Model with Evolution :

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

Gene :: Parameter in the model e.g., reaction rate

$(g_1, g_2, ..., g_k)$

Parameter → Variable (dynamical systems)

X(t=0)→X(t)

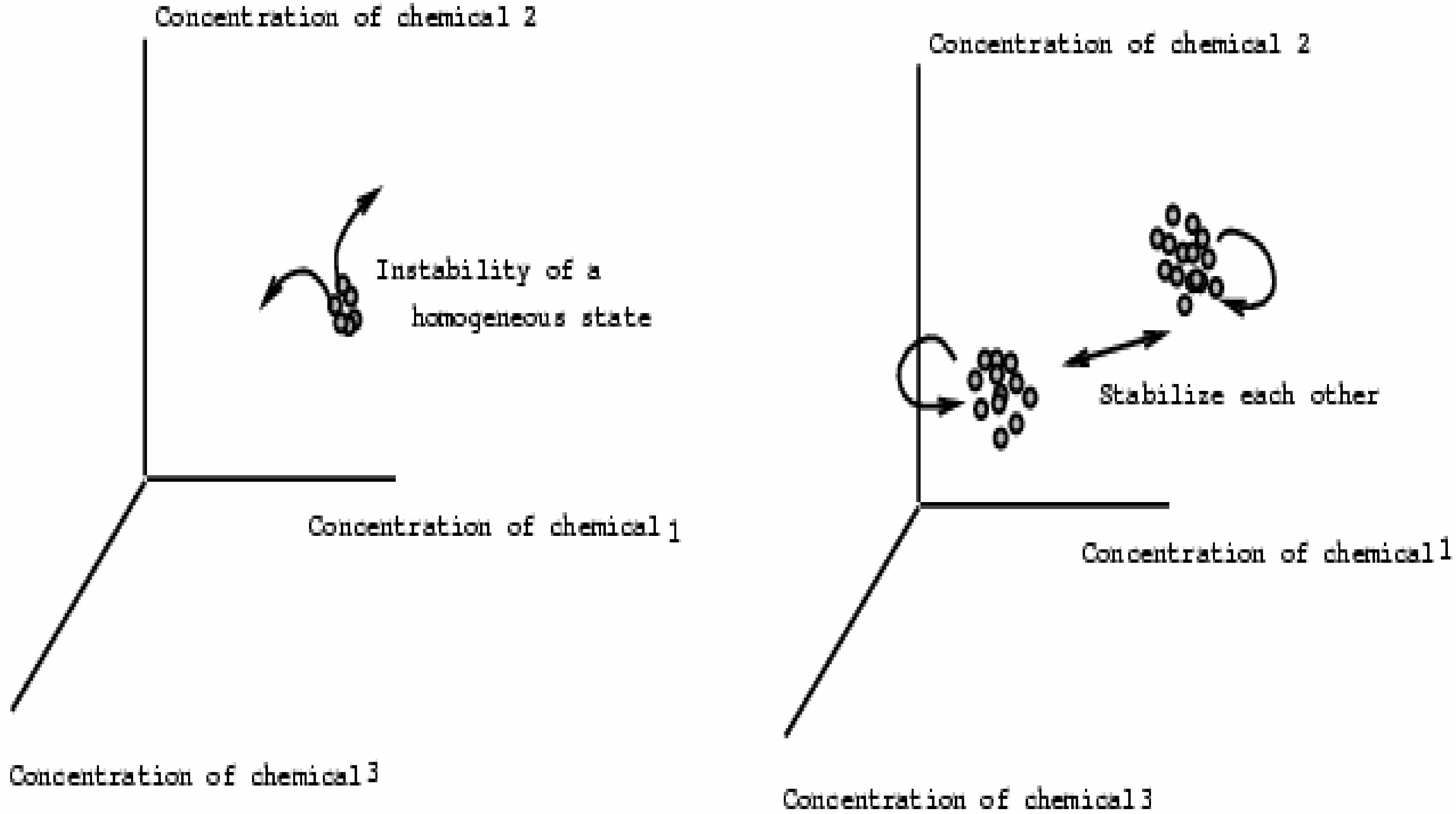
Reproduction when maturity threshold condition (given by X) is satisfied

Mutation ---- small change in parameter in reproduction

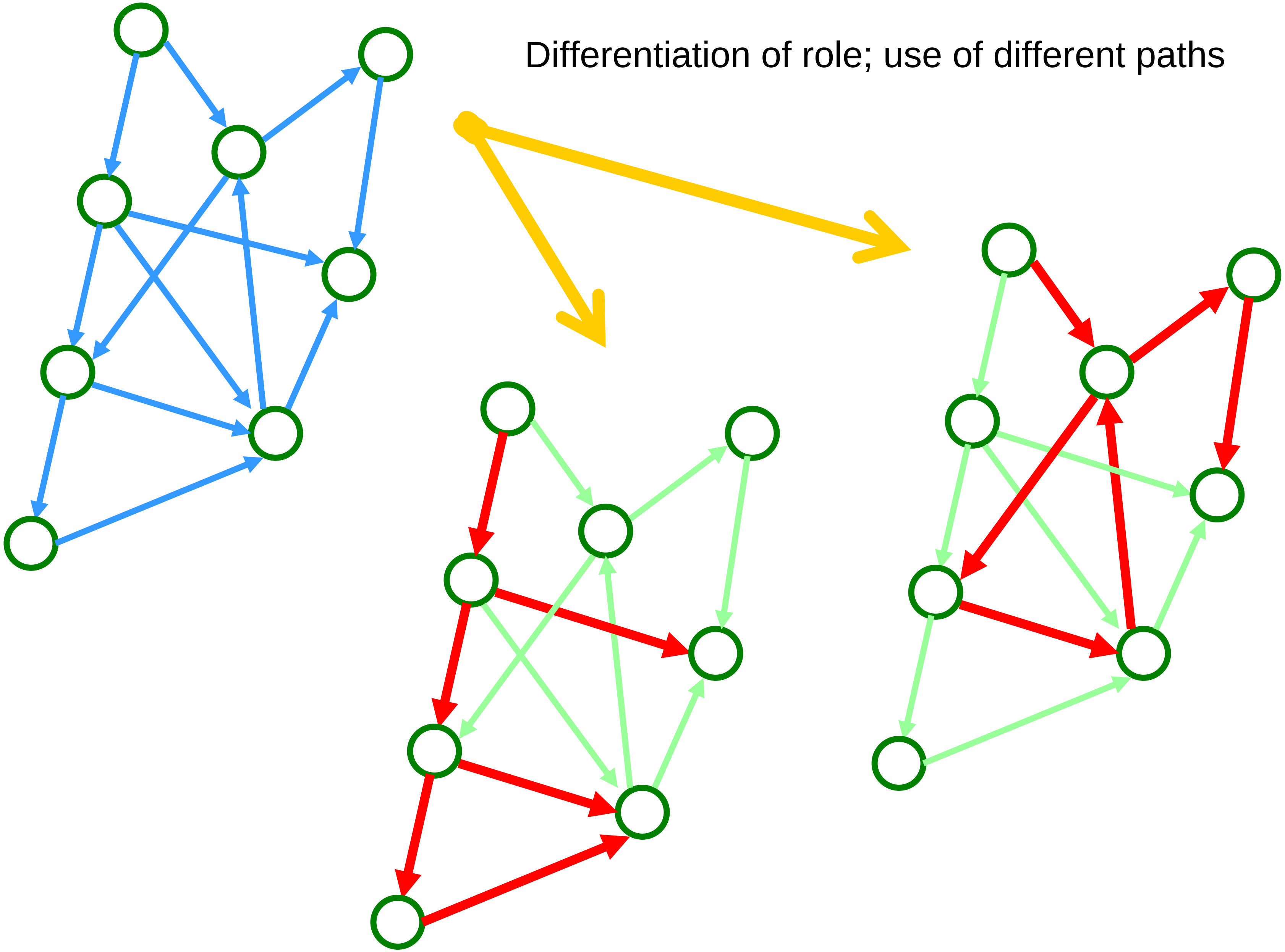
Competition for survival:

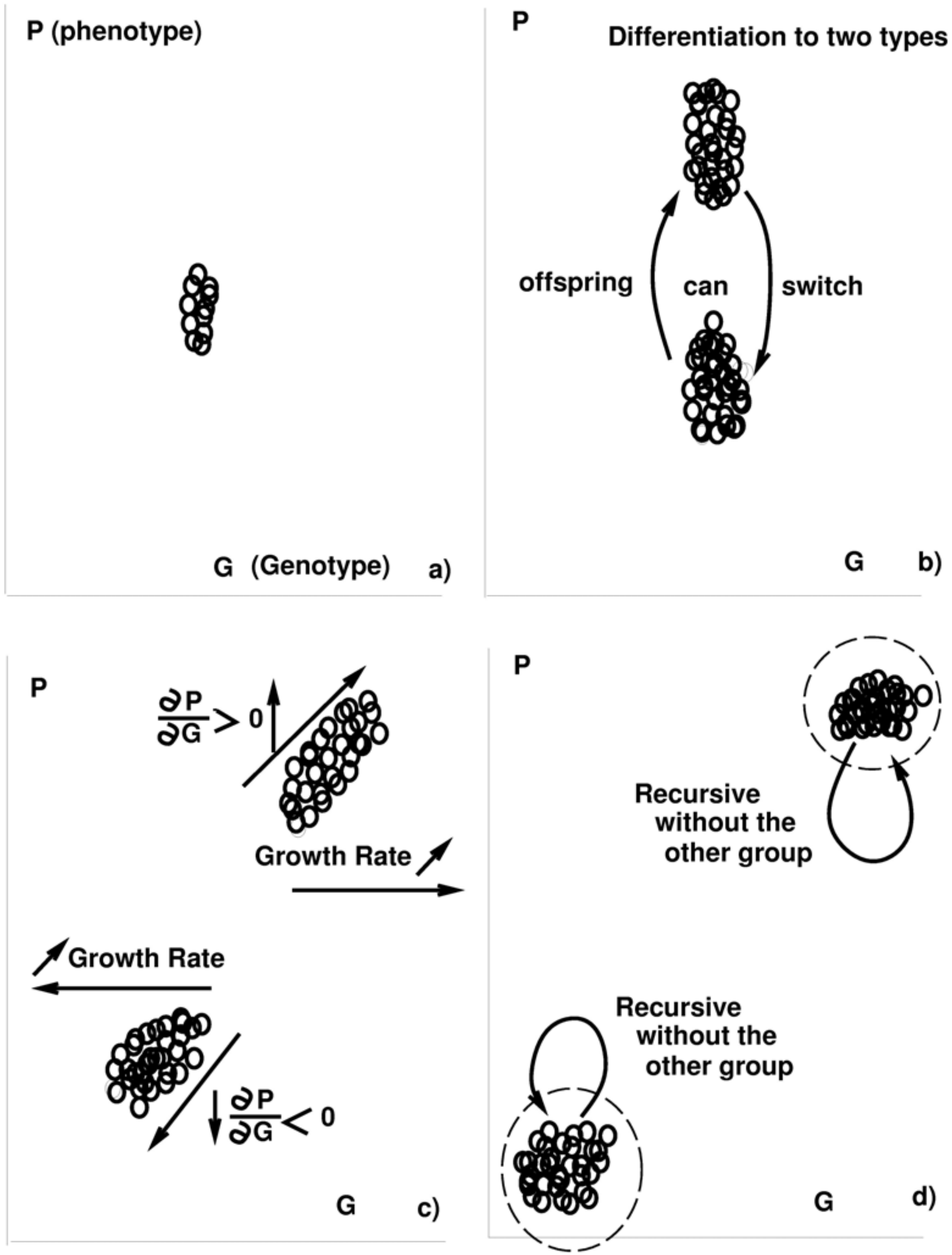
(remove some units (either randomly or under some condition))

→With the increase of the number



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

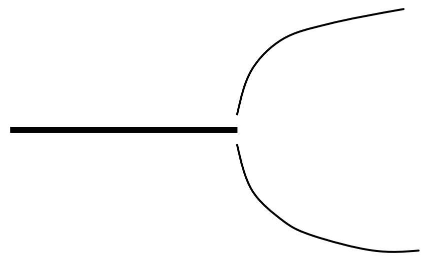

Differentiation of role; use of different paths

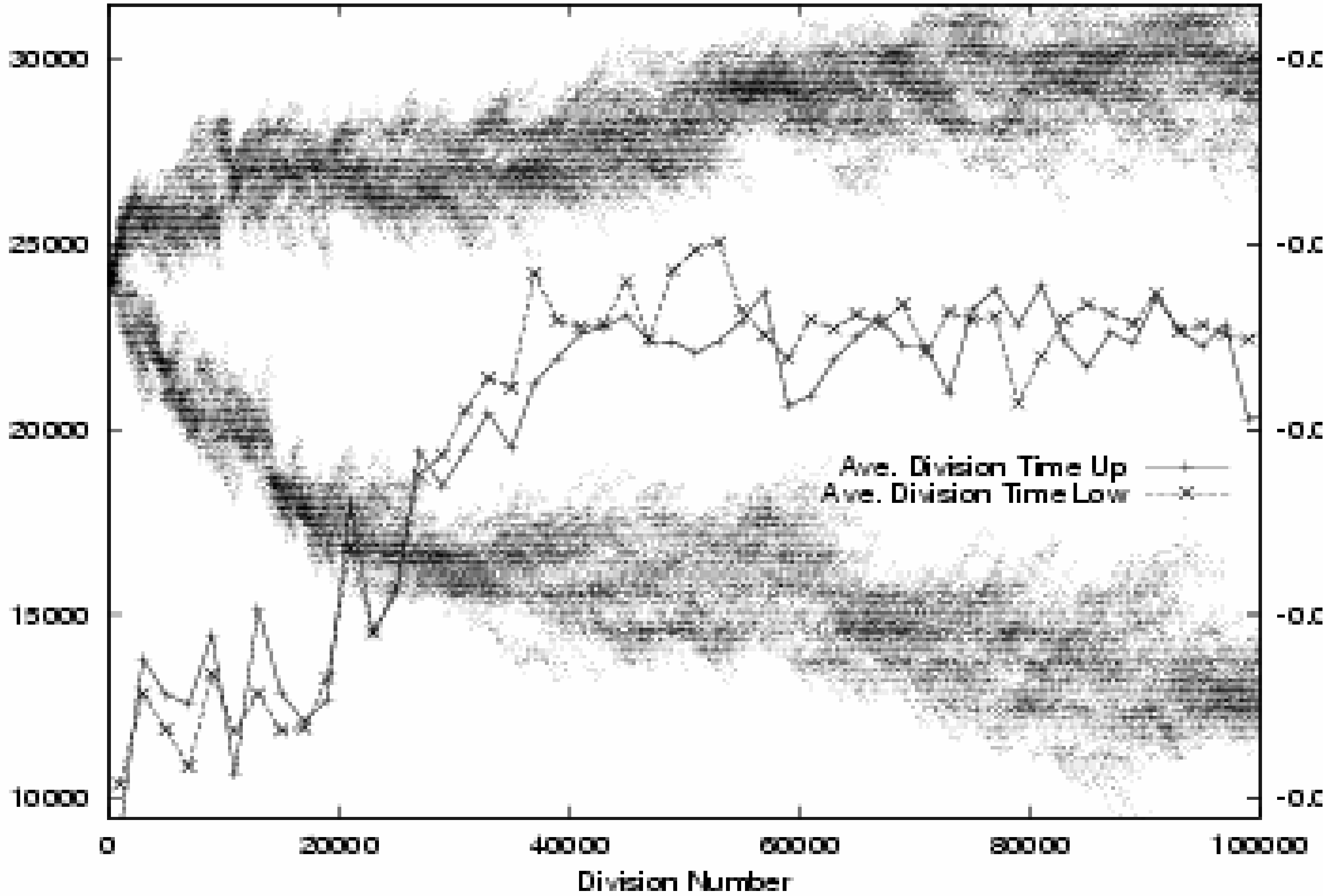


Cf: pithcfork possible

$$dX_i/dt = aX_i - X_i^3 - \left(\Sigma_j X_j\right)^2 X_i$$

a increases with # of units

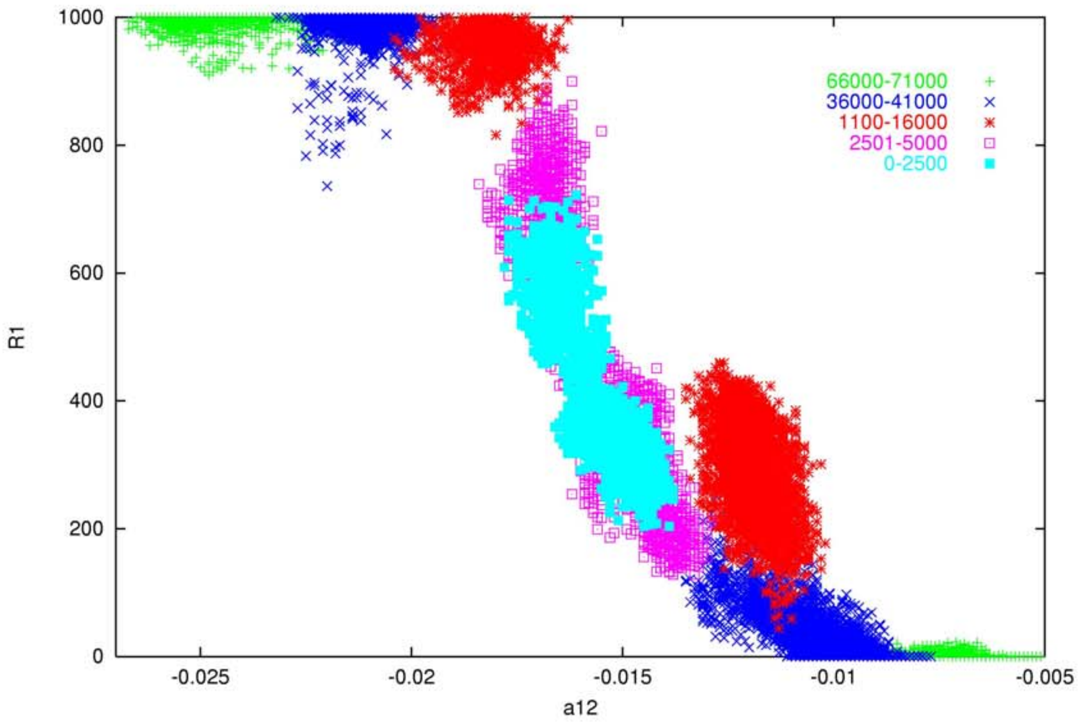




30000
25000
20000
15000
10000
0
20000
40000
60000
80000
100000
Division Number
Ave. Division Time Up
Ave. Division Time Low

Example of numerical simulation

Phenoptype(variable)



Gene （parameter）

Characteristics of the Symbiotic Sympatric Speciation

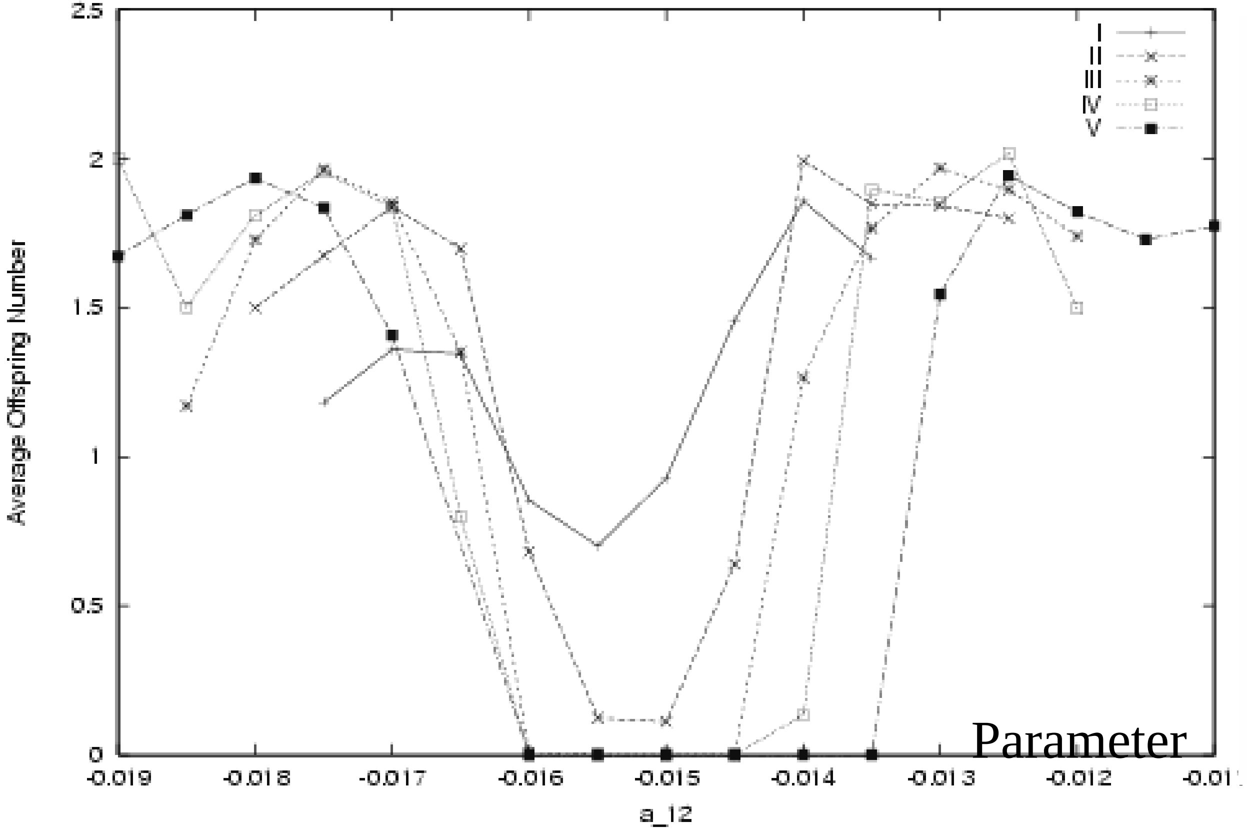
*Valid (possible) in the presence of strong interaction

*Robust speciation; two groups coevolve; works under sexual and asexual cases as well
(indeed, hybrid sterility is resulted)

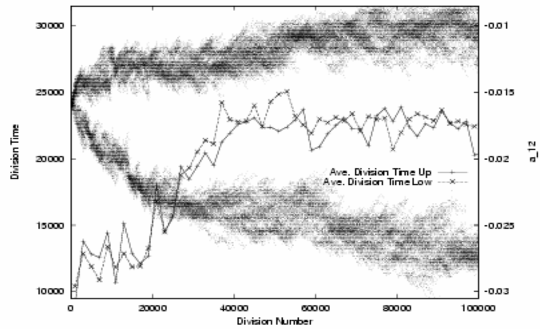
*Genetic separation always follows if there appears interaction-induced phenotypic differentiation

*Relevance of the phenotypic differentiation, rather than genetic change, to genetic diversification (cf Baldwin effect or genetic assimilation)

Stage
I→II→III→IV→V



Parameter

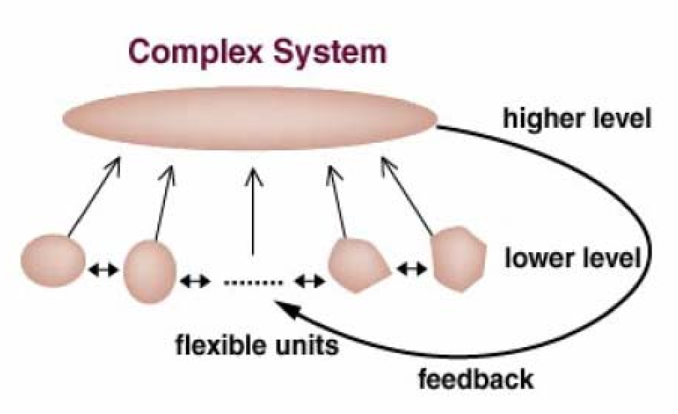


Complex Systems Biology

Understand Universal features of Biological System with

--Mutual dependence between parts and whole (dynamic, flexible, and reproducible)

Consistency between different levels



dynamic