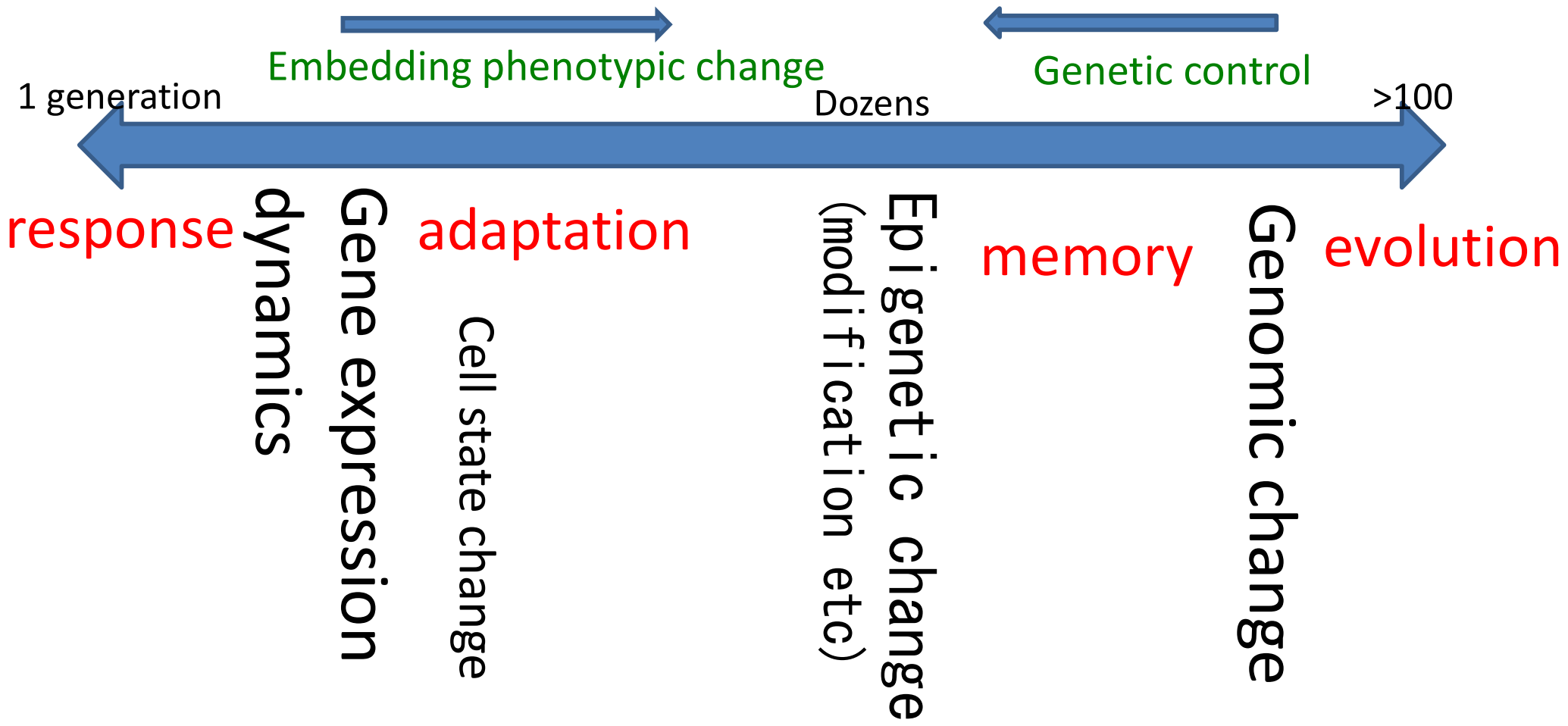
Evolutionary Fluctuation Response Relationship, Evolution of Phenotypic Robustness

(skip some pages ,last part)

Consistency between Developmental Process and Evolution (Evo-Devo Congruence)

Micro-Macro : Multiple-time scale dynamics



∗ **Consistency between dynamics with distinct time scales**

Macroscopic relationship among plasticity, robustness, evolvablity, and phenotypic fluctuations: Waddinton's legacy revisited under the spirit of Einstein

Kunihiko Kaneko Univ of Tokyo+
ERATO complex systems biology

1 **Phenotypic Fluctuation (Plasticity) vs Evolution**

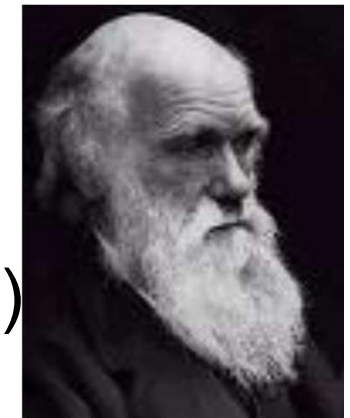
2 Phenotypic Fluctuation vs Genetic Variation

3 **Evolution of Robustness to Developmental Noise and to Mutation**

4 Regaining **Plasticity and Evolvability**

cf selection of dynamical systems
by dynamical systems for dynamical systems

Darwin and Lincoln
(born on the same day、Feb.12 1809)



- Evolution

1)Genotype(rule for developmental dynamical systems)

2) only genotype is transferred to offspring (in most cases,,)

3) Phenotype ← Development dynamics

Gentype-Phenotype mapping

4) Fitness(phenotype) →

selection process in the distribution

Now, genotype → phenotype

→if this mapping is uniquely determined

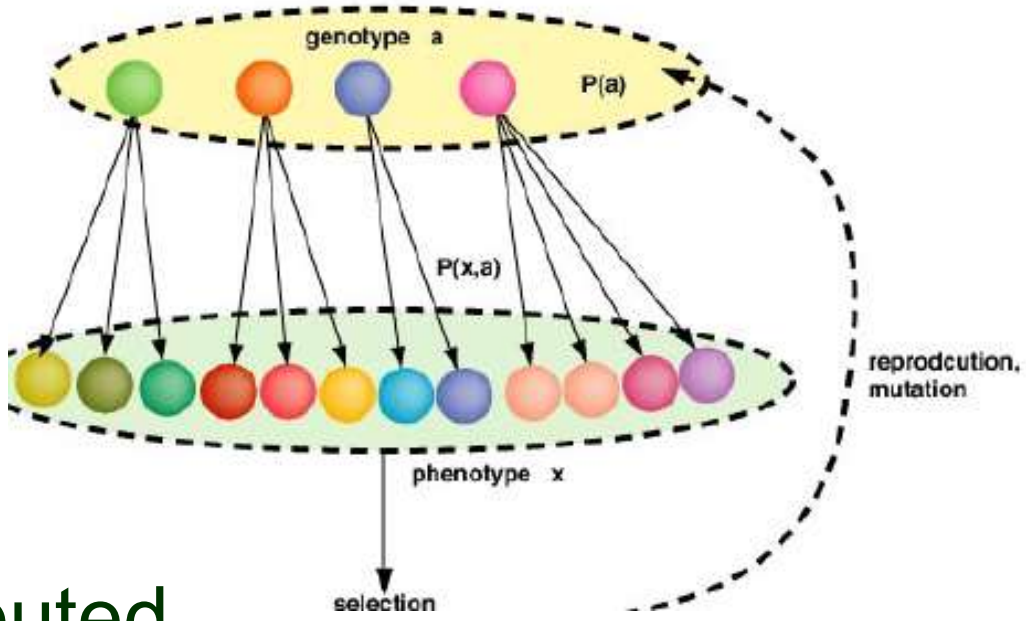
→ Fitness(Genotype) instead

- Cf;

1) Non-genetic inhertanace is possible in principle: (‘eigenetic memory’ typical in unicellular-organism. Protein concentration. Methylation, Histon modification, Membrane..)
2) Just time-scale difference? ~10 generation memory is typical in bacteria?
3) Lamarckism would be possible, but it seems it is avoided (eg., germ-line segregation):

   If one phenotype was successful in one generation, it may not be so for the next generation, especially when all adopt the same phenotypes

Evolution= change in
Population of geneotypes
(''Population genetics'')

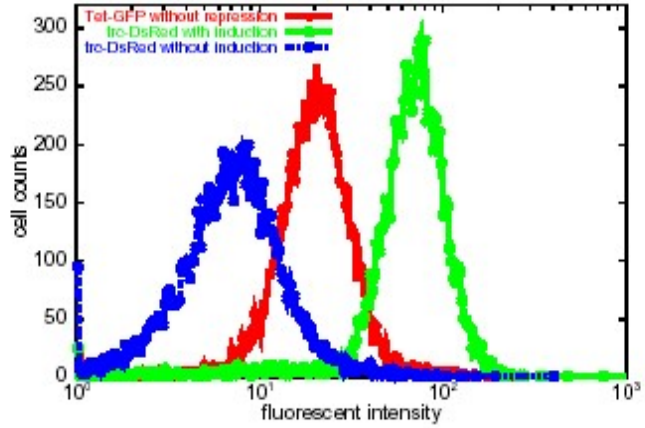


But gene—``development ''
→Phenotype
geno-pheno mapping distributed
Phenotypic fluctuation of isogenic organisms

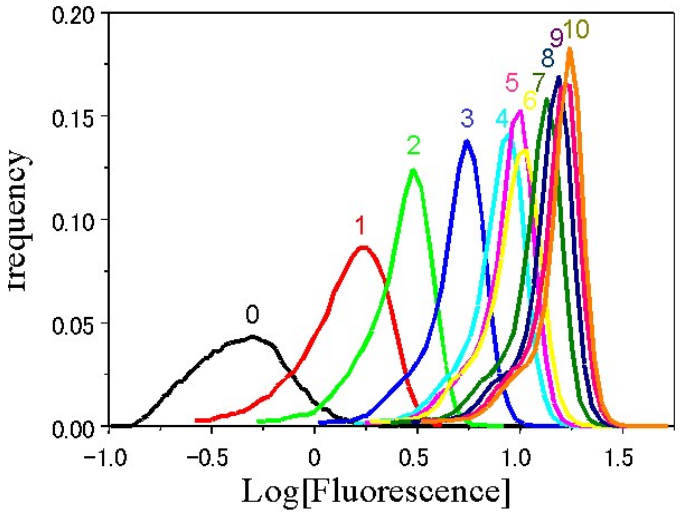
P(x; a) x—phenotype, a – gene

Ensemble of dynamical Systems
Change of distribution of DS according to the
Behavior of DS

- Motivatio1:Evolvability? Some species are faster to evolve? -- ‘Ambiguous question’. Quantitative discussion by simplifying the issue?
- Phenotypic Fluctuation → gives a measure for Evolution?
- Even in isogenic indiviudals large phenotypic fluctuation (theory, experiments)
- Motivation1 Relevance of this fluctuation to evolution? Positive role of noise?



umber distribution of the proteins measured by fluorescent intensity.
hree Escherichia coli cell populations containing different reporter plas



Motivation2:Evolution of Robustness

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

  ← due to environmental change

  ← against noise during 'developmental process

  ← against parameter change by mutation

*Question :

relationship among these robustness

condition for evolution of robustness

Connect Motivation 1 and 2:

Study evolvalibity, robustness, in terms of phenotypic fluctuations

→Insight into Geno-pheno coupling

(Waddington;;;,Ancel-Fontana.Wagner,.,)

- General Viewpoint:

  x: phenotype (variable)

  a: genotype (parameter)

parameter→ variable: condition （1）

central dogma of molecular biology

a： scalar continuous parameter showing gene (say, number of matched sequences etc.)

for given direction of specific function,

x is distributed even if gene (a) is specified

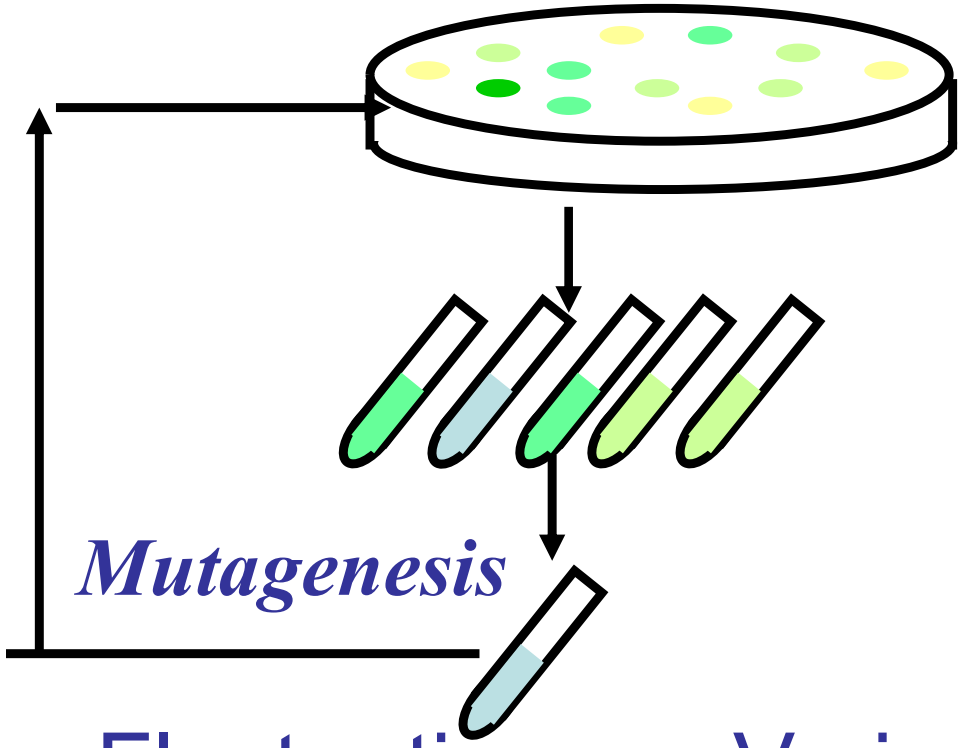
consider P(x;a；h) under given environment h

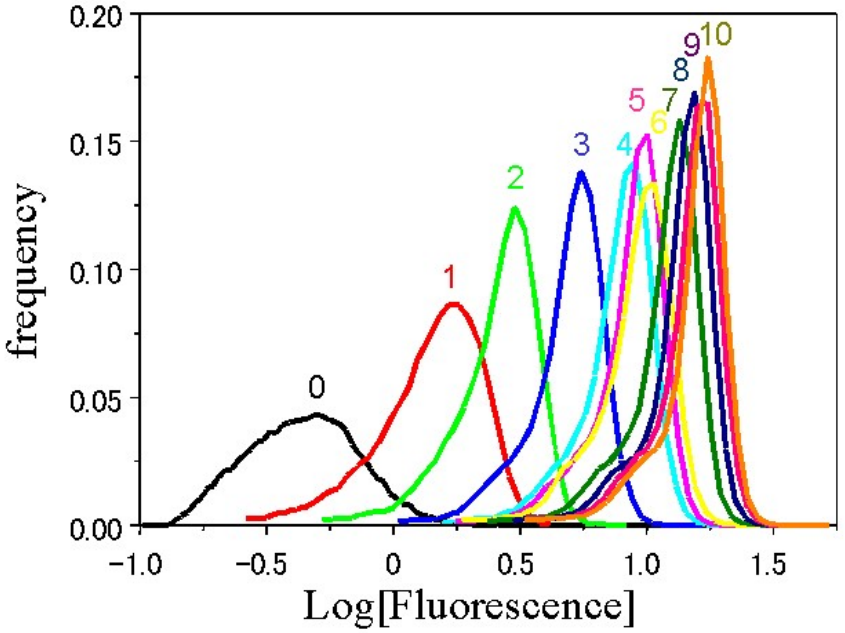
Environment h change to select ‘a’ value

selection : change in distribution with a

Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacter





Fluctuation ---- Variance of phenotype of clone

Larger phenotypic fluctuation

---higher evolution speed？

-

Sato, etal
PNAS(2003)

So-called fluctuation-response relationship 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)

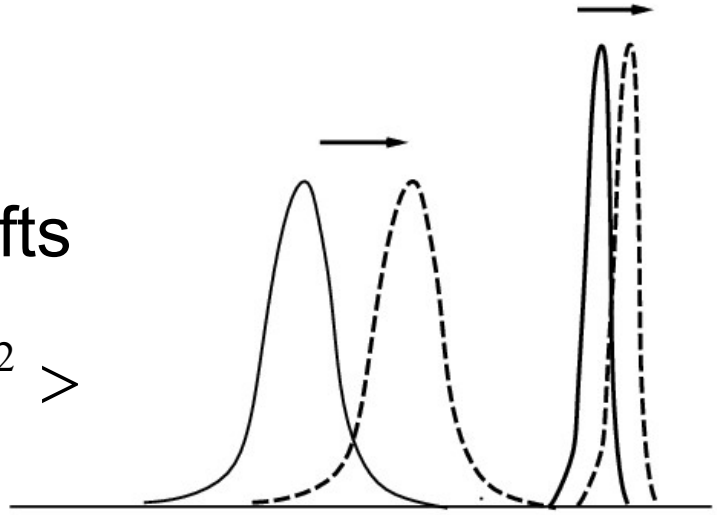
response ratio of some variable x against the change of parameter a versus fluctuation of x

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

change of the parameter a →

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

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



--``Response against mutation+selection'' --Fluctuation

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

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

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

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

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 ;

Non-trivial point

(1) Assumption of representation by P(x;a)

x : phenotype a ; gene (or control parameter)

(2) The coupling form Cxa is also assumption

→Not derivation, but need to check experimentally

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

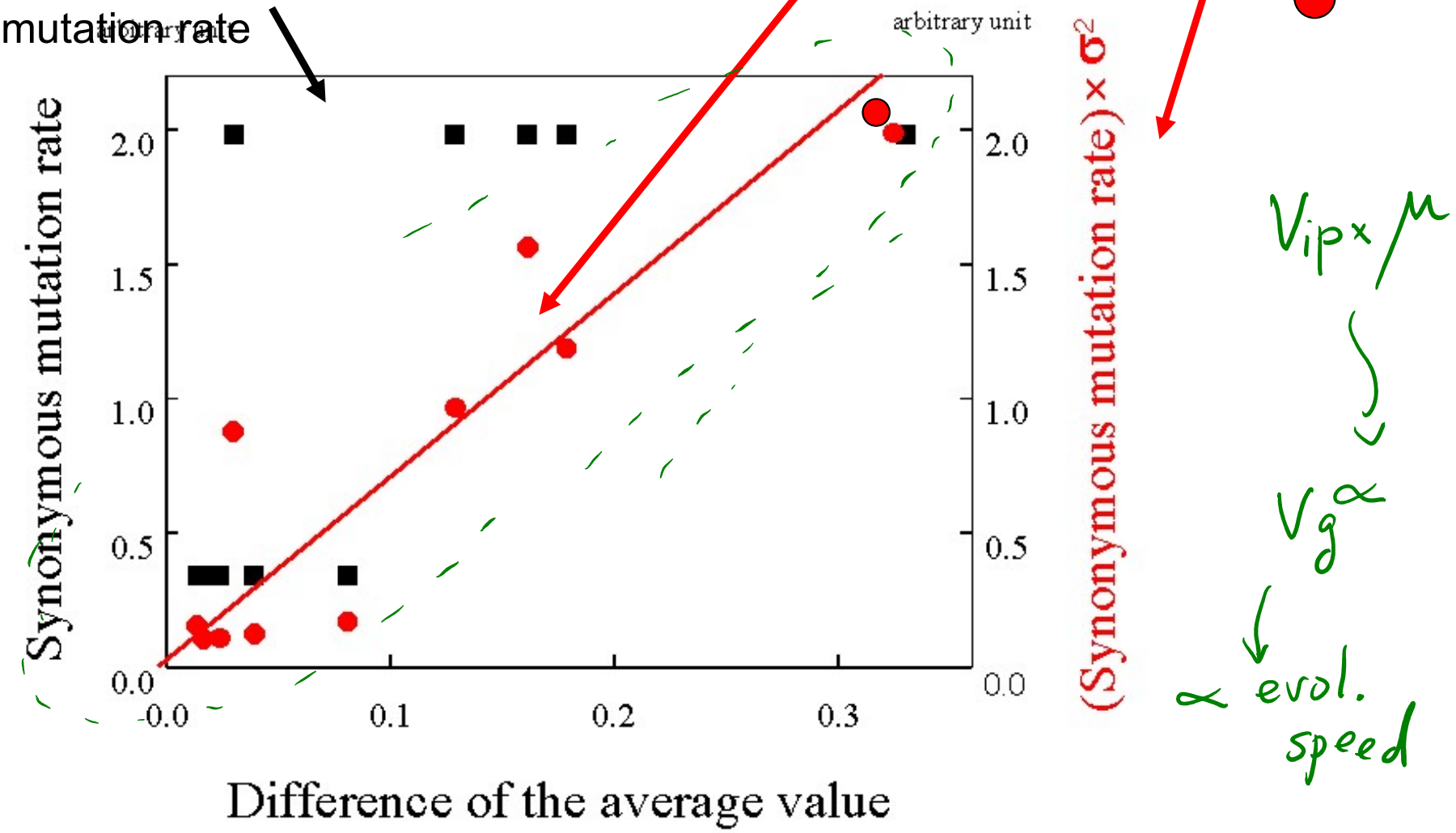
Fluctuation in the phenotype x of clone

⇔ speed of evolution to increase <x>

(proportional or correlated)

Fluctuation-response relation
Phenotype fluct. × mutation rate

Naïve expectation:
Just propt to mutation rate



$V_{ip} \times \mu$

$\propto V_g$

$\propto$ evol. speed

(Evolution Speed per generation)

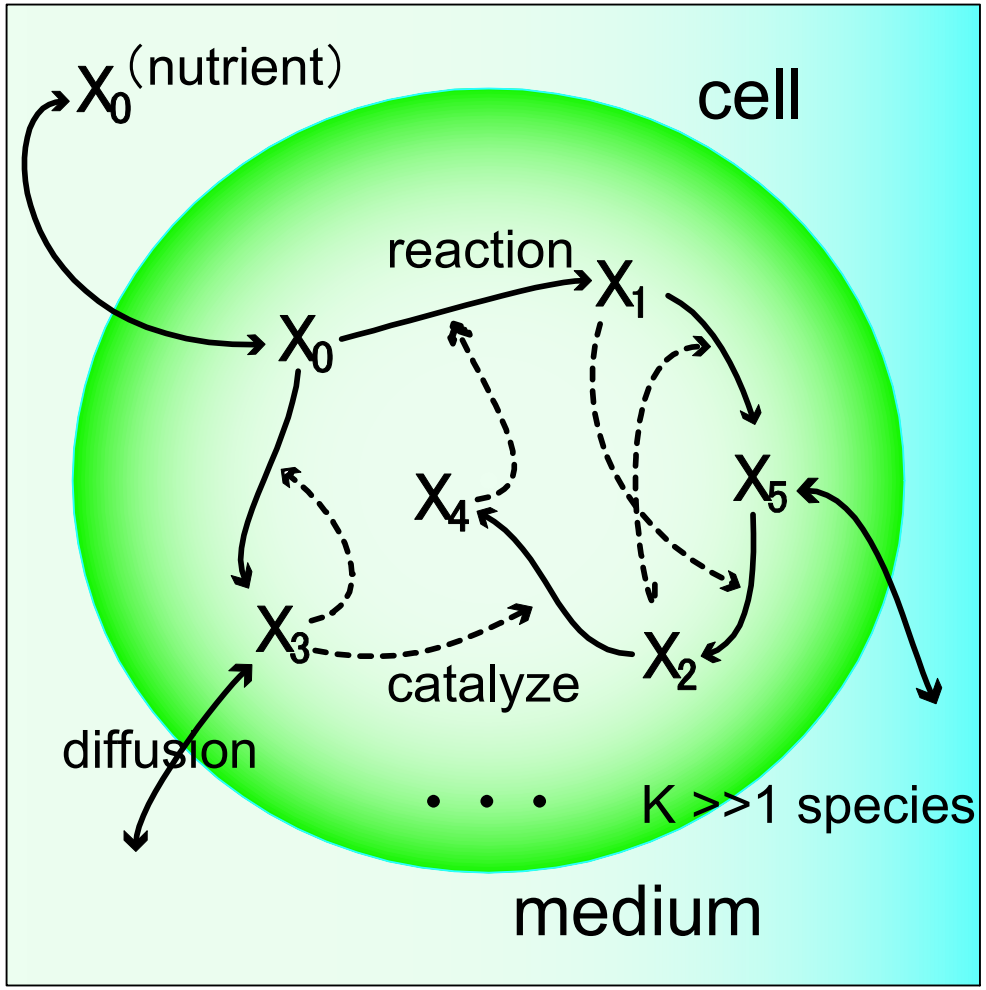
Sato, etal, PNAS 2003

Confirmation by Toy Cell Model with Catalytic Reaction Network

C.Furusawa & KK、PRL2003

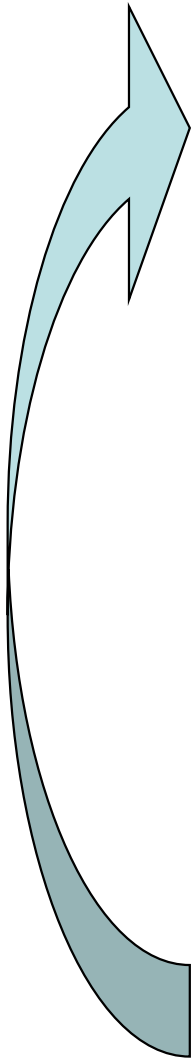
- **k species of chemicals** 、$X_o \cdots X_{k-1}$ number ---n_0 、$n_1 \ldots n_{k-1}$
- random catalytic reaction network with the path rate p for the reaction $X_i + X_j -> X_k + X_j$
- some chemicals are penetrable through the membrane with the diffusion coefficient D
- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth in $N = \Sigma n_i$, when it exceeds N_{max} the cell divides into two

model (Cf. KK&Yomo 94,97)



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

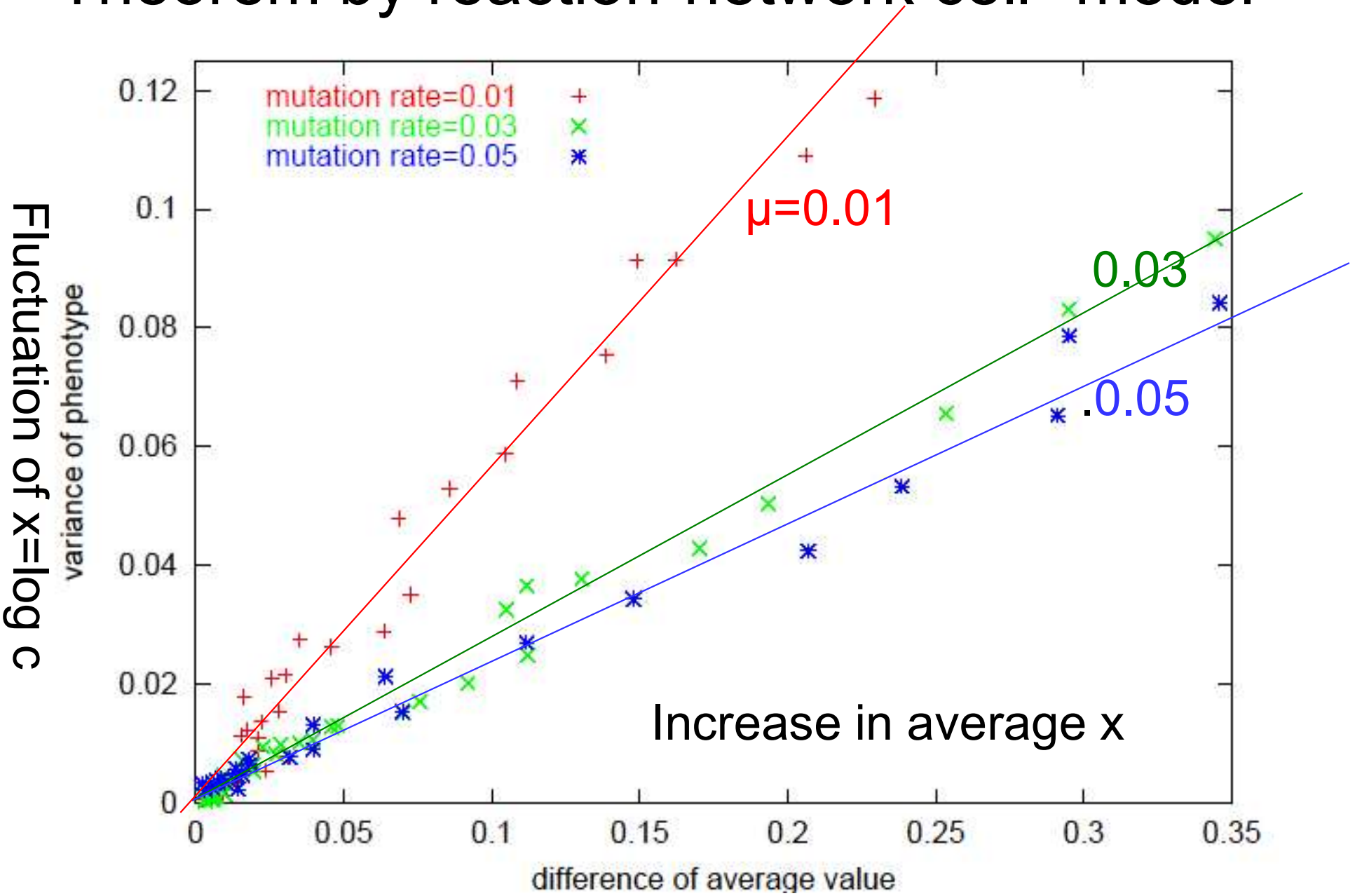
- Confirmation by numerical evolution experiment by the reaction-net cell model



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. Cells with higher x (top 5%) are selected as parent cells of next generation

phenotype x = log (n_s)

Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model



Furusawa,KK 2005

New mystery？

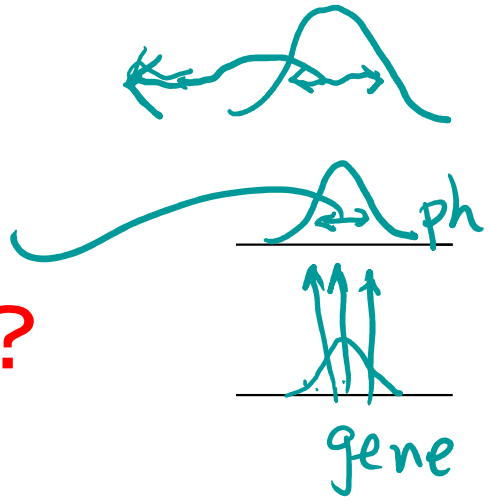
phenotype fluctuation of clone　vs　evolution speed　in contrast to

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

phenotypic fluctuation　of clone　Vip

∝　phenotypic fluctuation

by gene variation　Vg？



（fluct by noise　∝　variation in ‘equation’）

- Remark:

Population Genetics

V_total (Vp): Total phenotypic variance consists of

Vg (additive genetic variance)

Ve (environmental)

or Fluctuaing Assymetry

....

(sexual reproduction case – more complicated)

- Vip here due to 'developmental noise'

(Or could be called as V_noise)

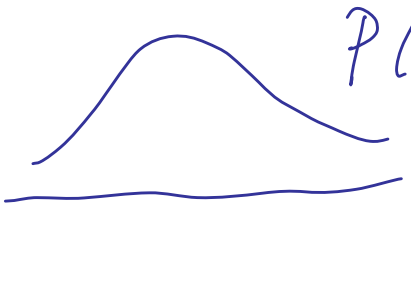
In reality, it may not be easy to distinguish V_noise from Ve

- Anyway, relationship between Vip (V_noise) and Vg, if any, is non-trivial

→ check by cell model

Vip ∝ evolution speed (exp (?), model)

Vg ∝ evolution speed (Fisher) a simple derivation(?)



mutation $P_n(g)$

(growth rate ~fitness)

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

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

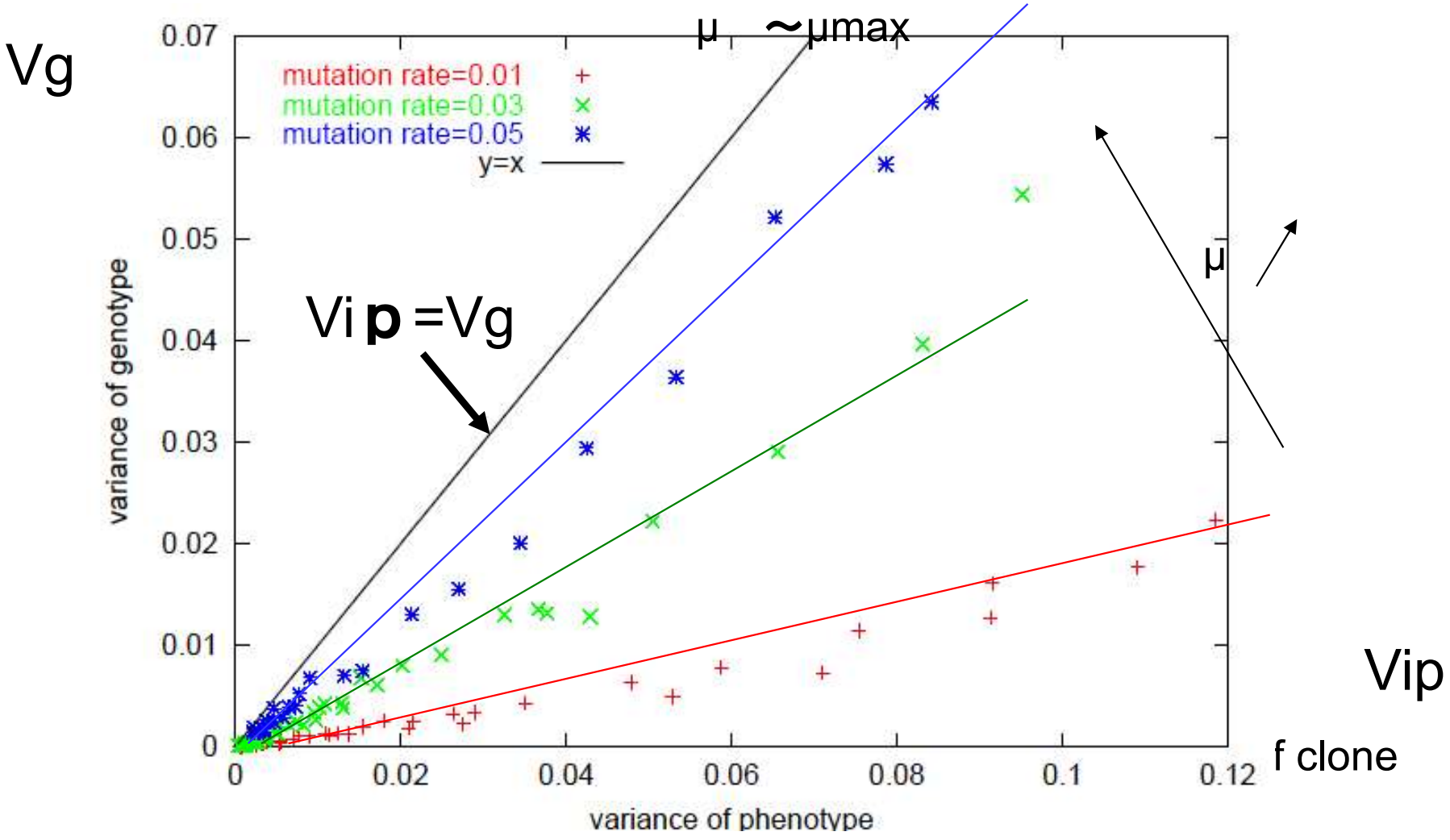
$$\bar{g}_{n+1} - \bar{g}_n = \frac{\int g^2 P_n(g)\, dg}{\bar{g}_n} - \bar{g}_n = \frac{1}{\bar{g}_n}\left(\int g^2 P_n(g)\, dg - \left(\int g P_n(g)\, dg\right)^2\right)$$

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

(Fisher ?)

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

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



variance of log(x), x is the concentration of the molecule

Result of evolution;

first few generations deviated from proportionality

As μ (mutation rate) increases to μ max,

(1) the distribution collapses (error catastrophe)

(2) evolution no longer progresses beyond μ max

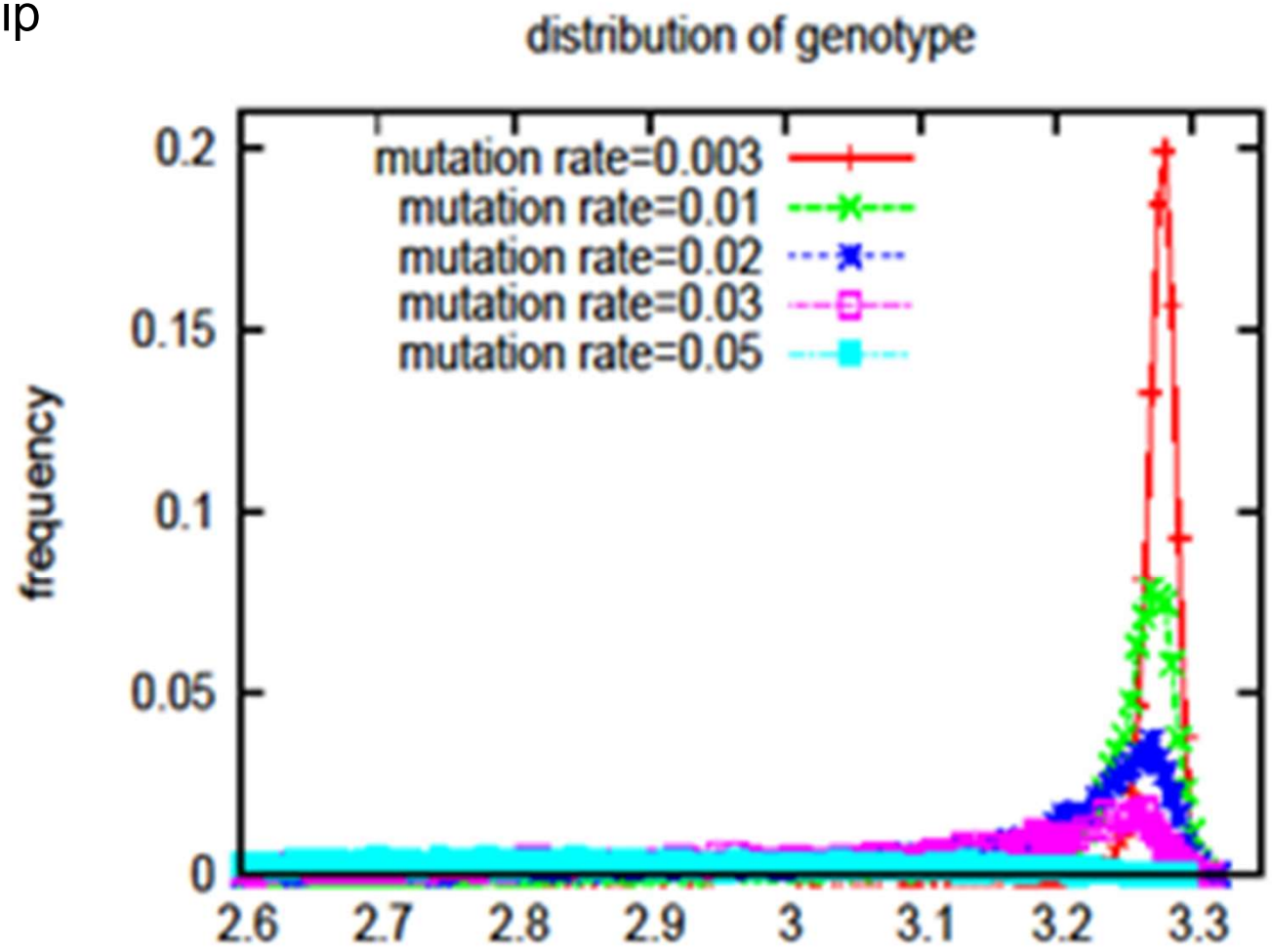
evolution speed is maximal at μ ~ μ max

(3) Vg approaches Vp

Vip

As μ is increased,
The distribution
'collapses'

Error catastrophe



Consider 2-variable distrb

P(x=phenotype,a=genotype) =exp(-V(x,a))

Keep a single-peak (stability condition).

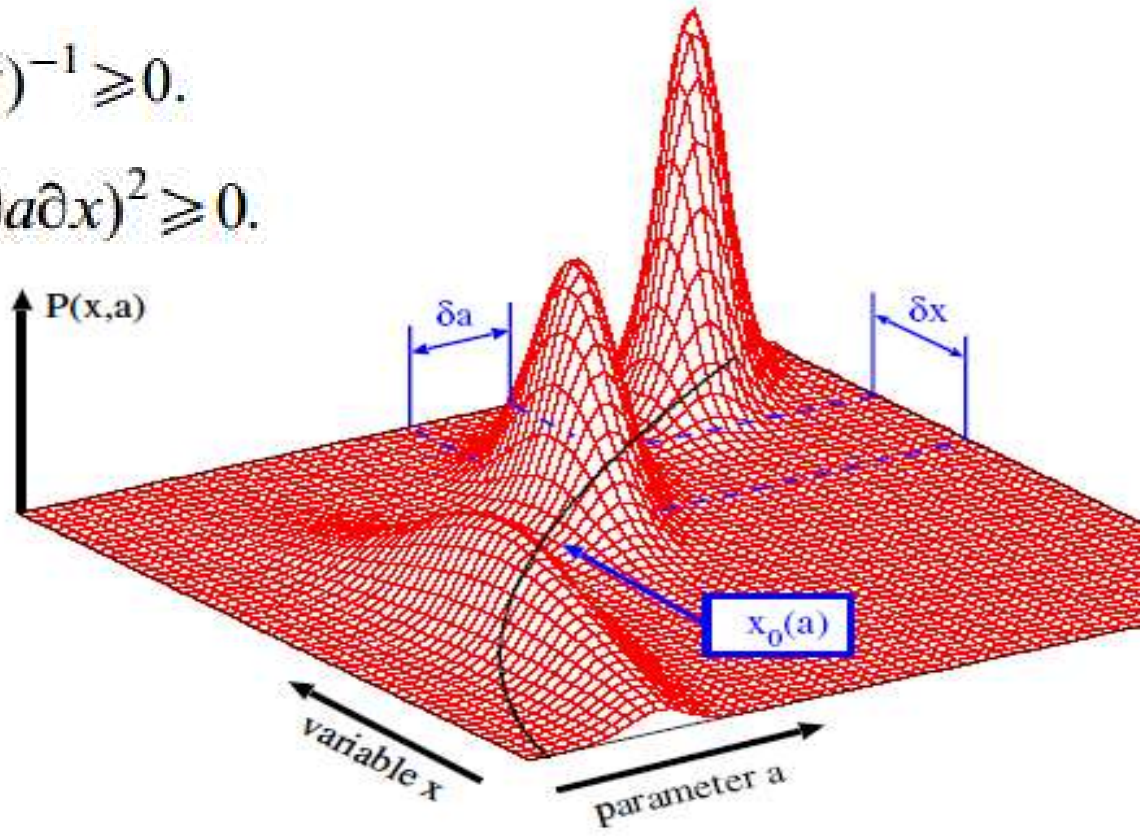
KK,Furusawa, 2006 JTB

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

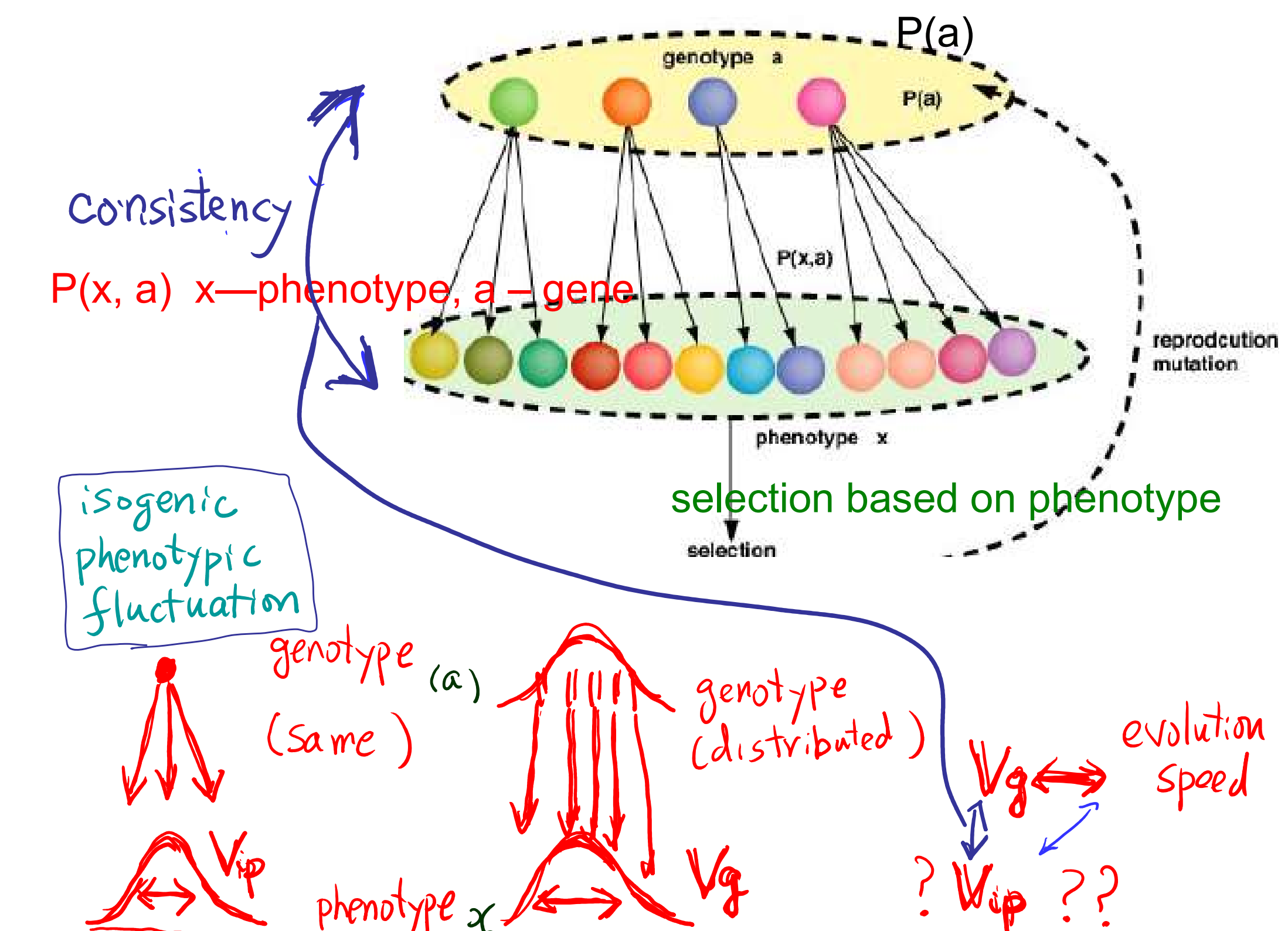
$$(\partial^2 V/\partial x^2)(\partial^2 V/\partial a^2) - (\partial^2 V/\partial a \partial x)^2 \geqslant 0.$$

Hessian condition

Leads to relationship between Vip and Vg



KK,Furusawa, 2006 JTB


P(a)
genotype a
P(a)
P(x,a)
reprodcution
mutation
phenotype x
selection
consistency
P(x, a) x—phenotype, a – gene
selection based on phenotype
isogenic
phenotypic
fluctuation
genotype (a)
(same)
genotype
(distributed)
Vg
evolution
speed
Vip
phenotype x
Vg
? Vip ??

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

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

$$\mu \leq \frac{1}{\alpha C^2} \equiv \mu_{max}.$$

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

$$V_g = < (\overline{x(a)} - X_0)^2 > = \frac{\mu C^2\alpha^2}{1-\mu C^2\alpha} = \alpha\frac{\frac{\mu}{\mu_{max}}}{1-\frac{\mu}{\mu_{max}}}.$$

Vip=α

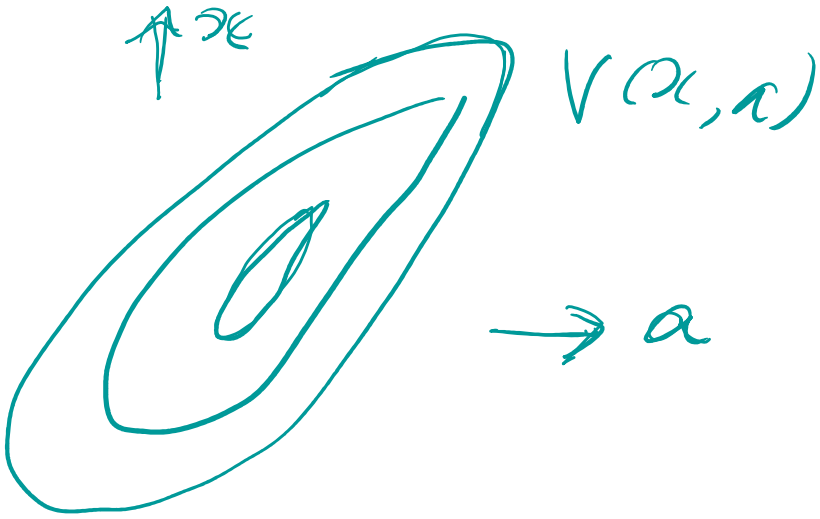
If mutation rate μ is small, Vg<Vip,

Vg ~ (μ/μmax)Vip ∝ Vip

- P(x,a) theoy; assumption --- 2- variable distribution (potential in geno- and phenotype)
- Q:x and a are represented in a single potential?

Consequence of Genetic Variation to phenotype already exists in phenotype fluctuation

e.g.,Variation of chemical abundances Xi
←correspond to→ change in reaction network of Jij by mutation in reaction XiXj* Jij



- (i) Vip ≧ Vg （from stability condition) (**)

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

(where the evolution does not progress)

(iii) Vg~(μ/μmax)Vip∝μVip

（∝evolution speed) at least for small μ

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

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

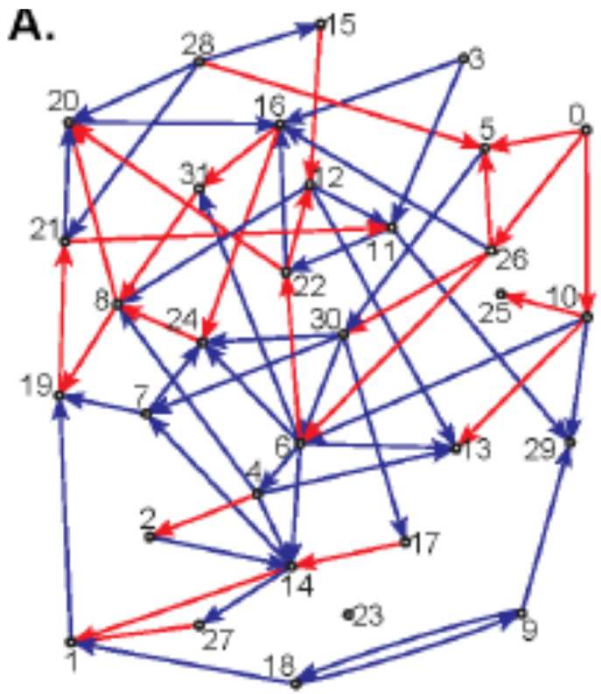
+ Robust Evolution assumption ?? +

Why higher noise 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



Activation
Repression
Jij=1,-1,0

Xi – expression of gene i :

on off

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

$$\langle \eta_i(t) \eta_j(t') \rangle = \delta(t-t') \delta ij$$

Gaussian white

M;total number of genes, k : output genes

Noise strength σ

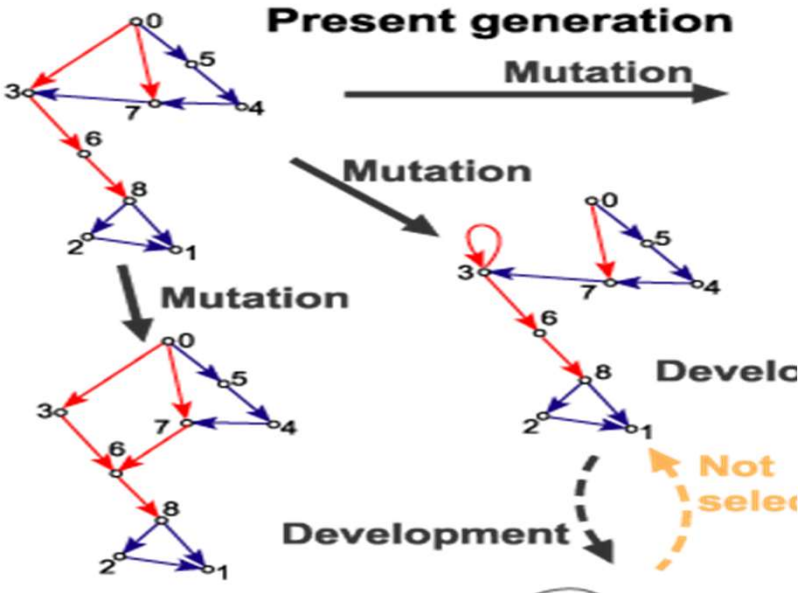
- Fitness: Starting from off of all genes, after development genes xi i=1、2、···、k should be on （Target Gene Pattern)

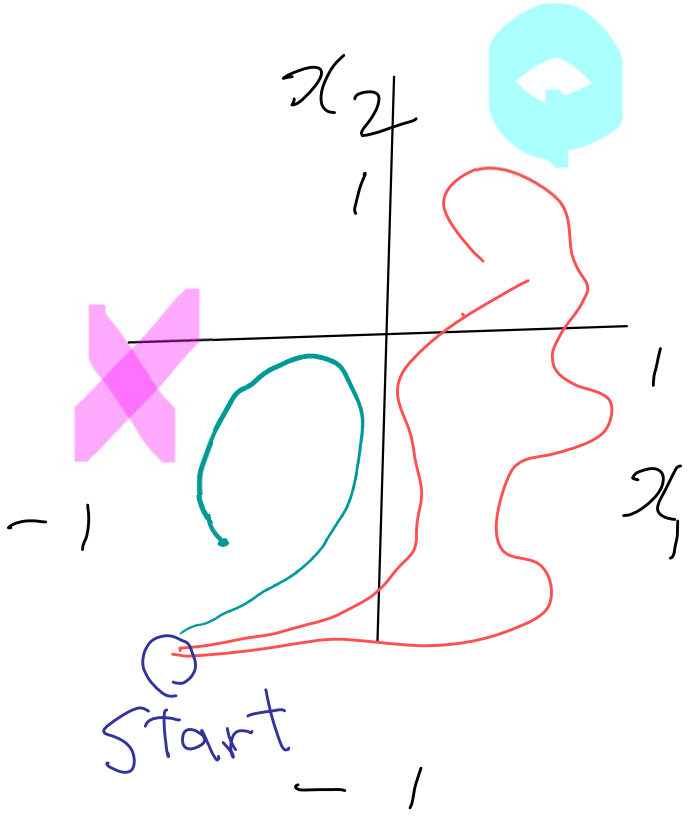
Fitness F= －（Number of off x_i）

Genetic Algorithm

Mutate networks and Select those with higher <F>

Choose top n networks among total N,
and mutate with rate μto keep N networks





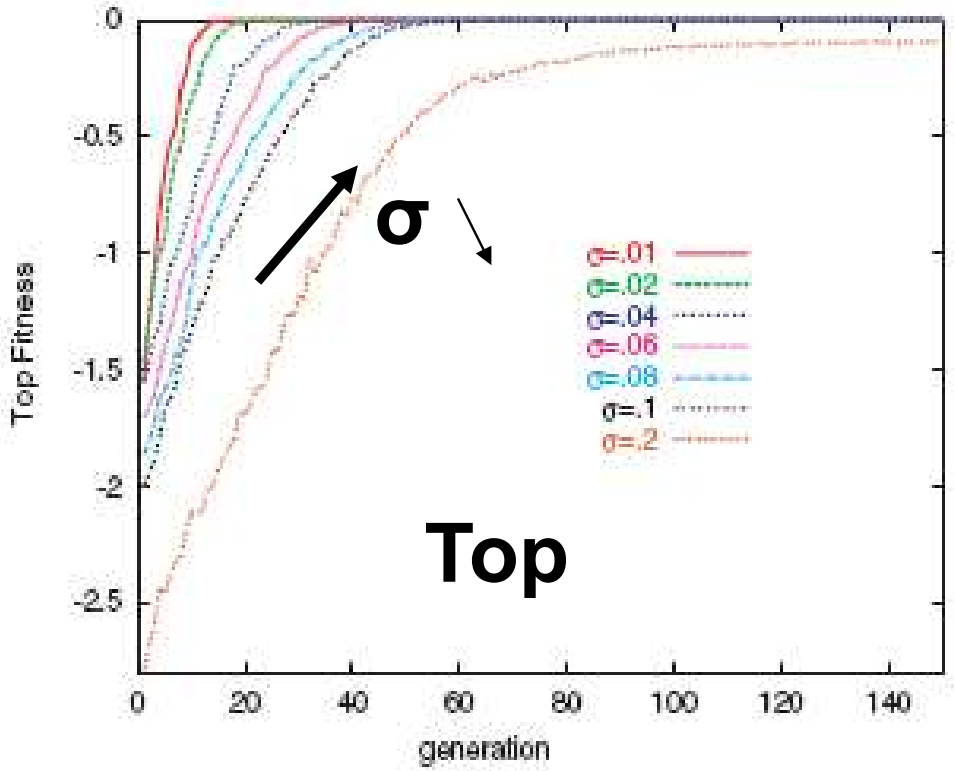
Result of evolution

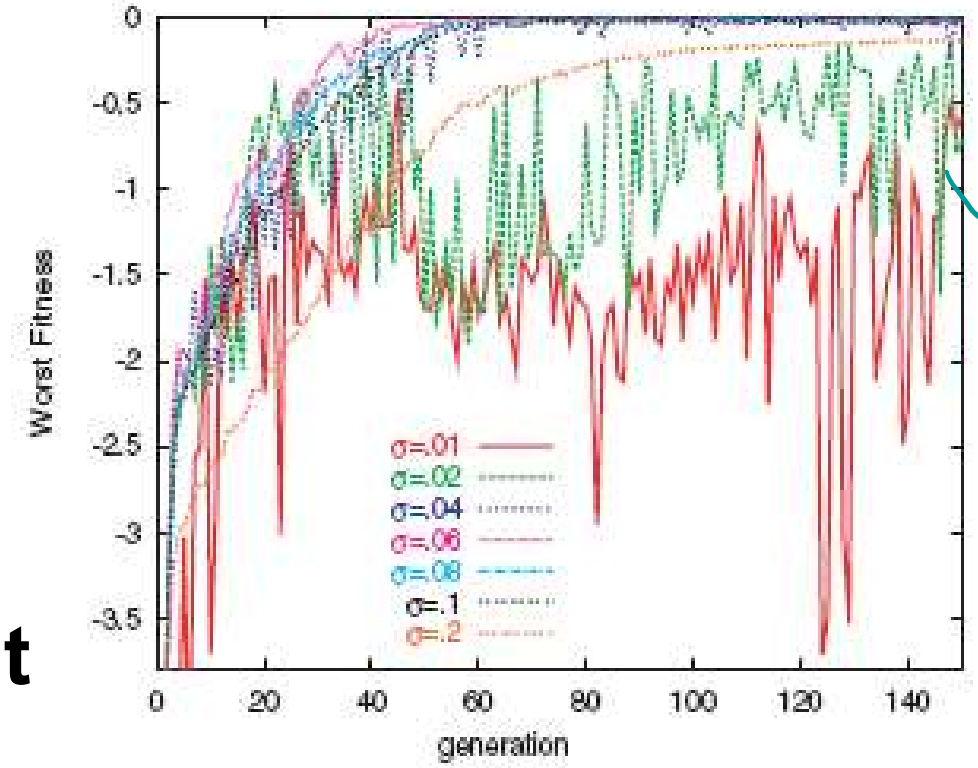
Top:reaches the fittest

faster for lower noise(σ)

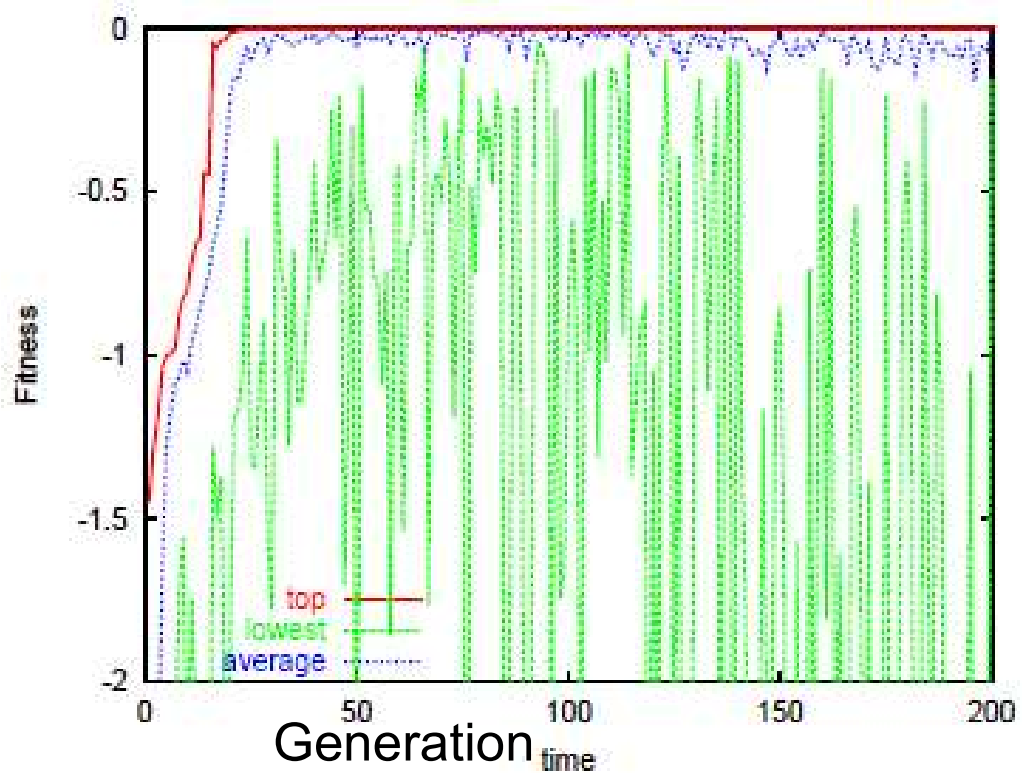
Lowest; cannot evolve

for low noise(σ)

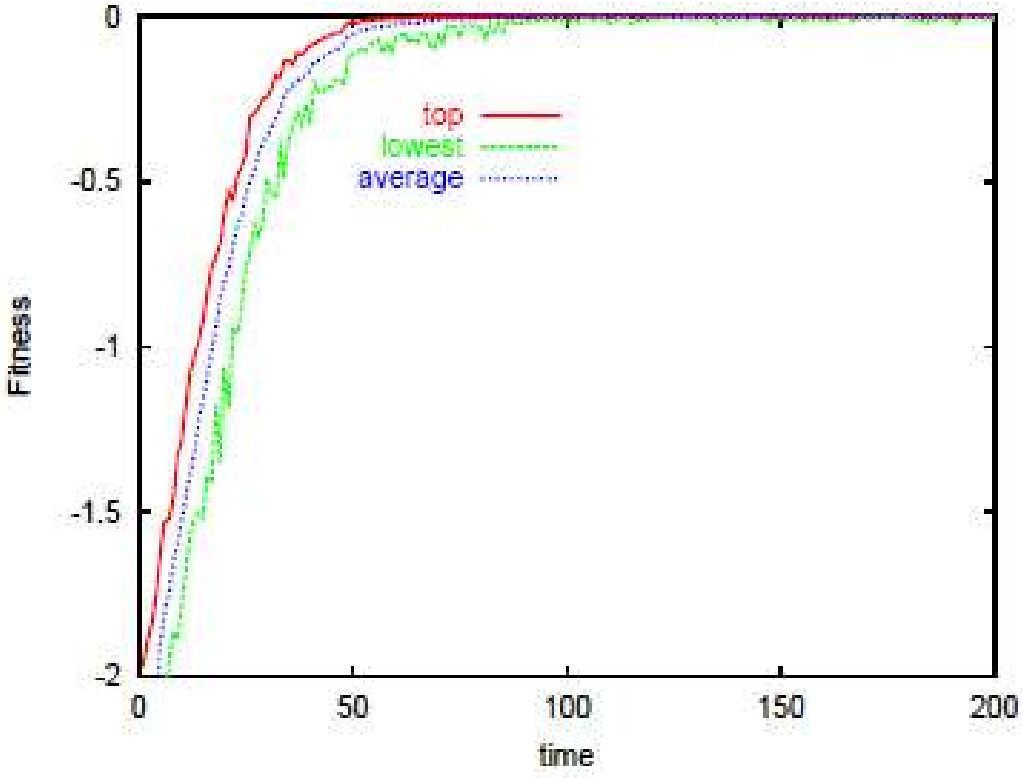




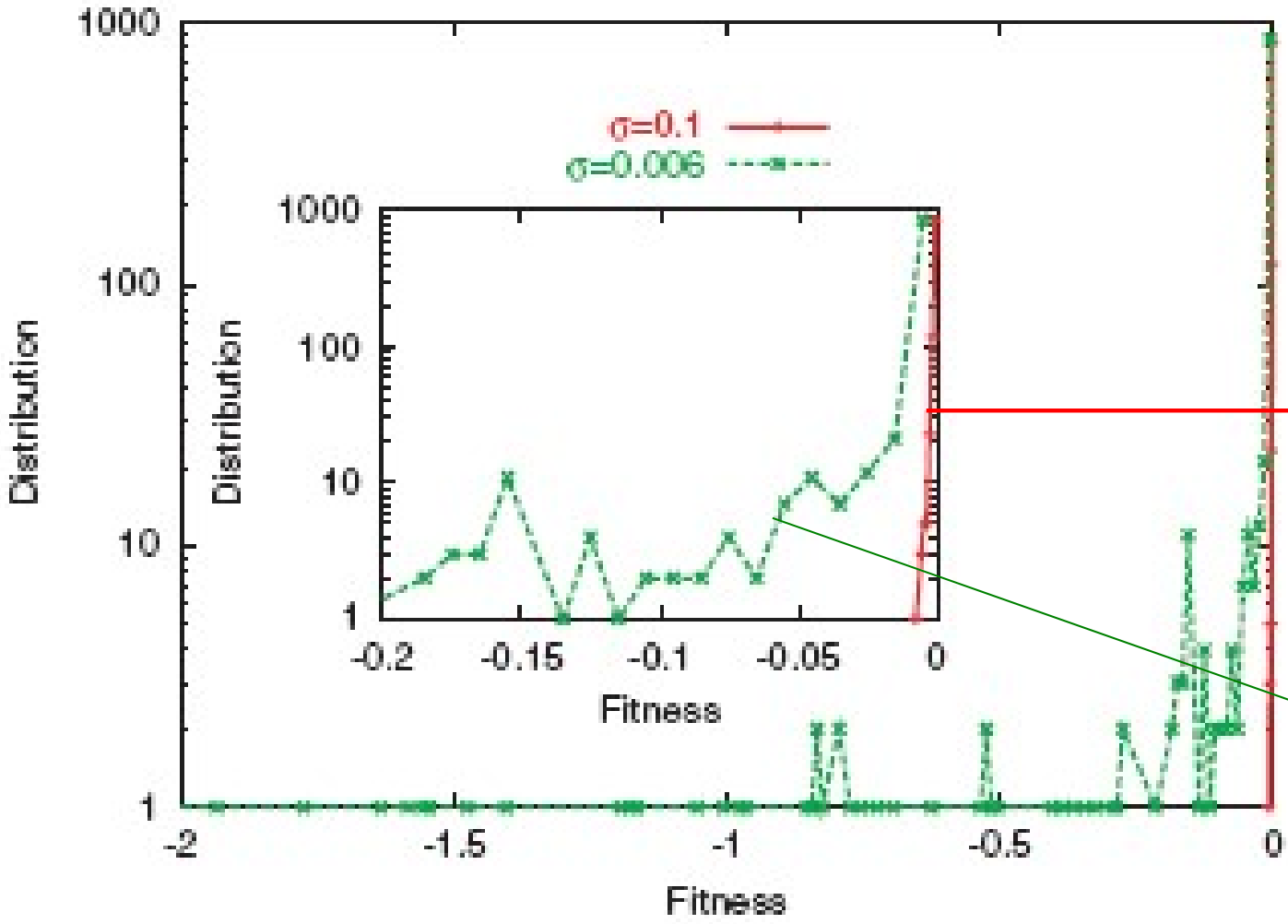
Lowest



Low noise case:
top reaches the fittest
but low-fitness
mutants remain



High Noise case:
top-lowest
All reach the fittest



Result of evolution

Top:reaches the fittest

Lowest;cannot evolve for low noise(σ)

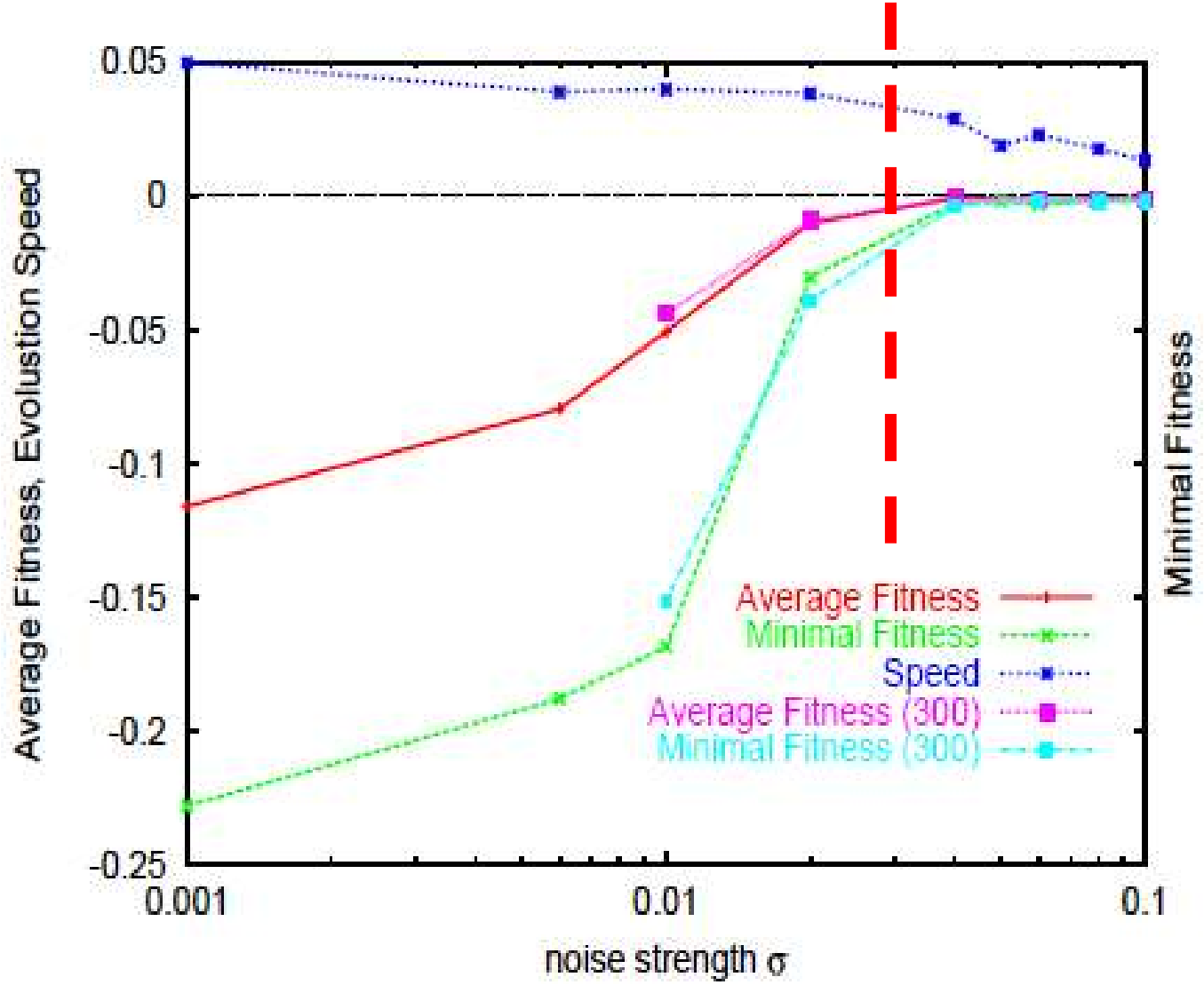
$\sigma > \sigma_c$

$\sigma < \sigma_c$

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)

- Comment on error catastrophe
- Error Catastrophe (Eigen,Schuster)

  --combinatorial explosion of unfit states (static)

  catastrophe w.r.t. mutation rate

*the robustness transition here

  combinatorial explosion of orbits reaching unfit states

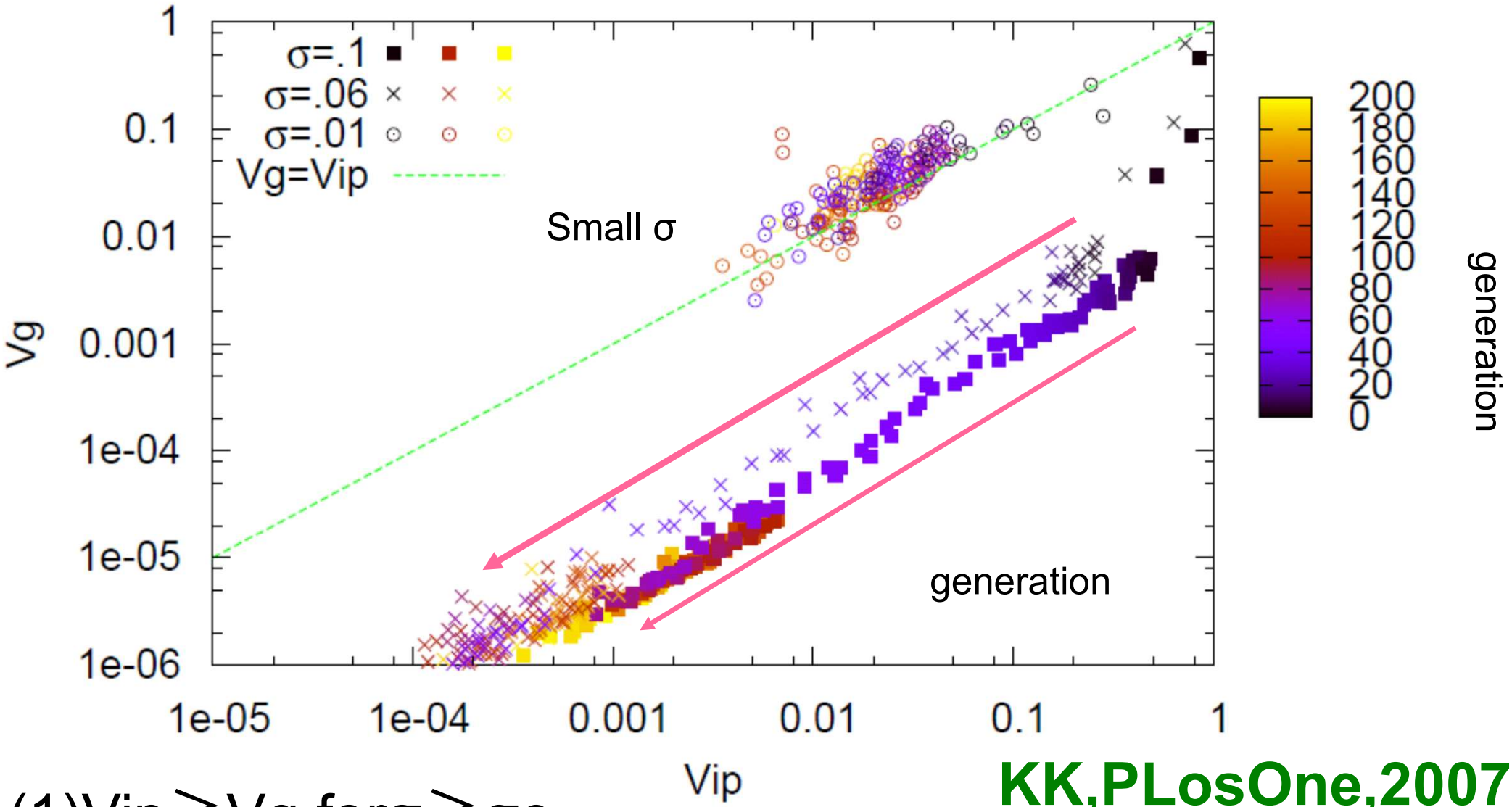
  catastrophe w.r.t. noise and mutation rate

? In EC by Eigen, discontinuous transition

  (even top fitness is not sustained)

Here, continuous transition?

condition for it?



KK,PLosOne,2007

(1)Vip≧Vg forσ≧σc

(2) Vg→Vip as σ→σc

(3) evolution progresses only for Vip ≧Vg

(4) Vip∝Vg through evolution course

Distribution Theory confirmed

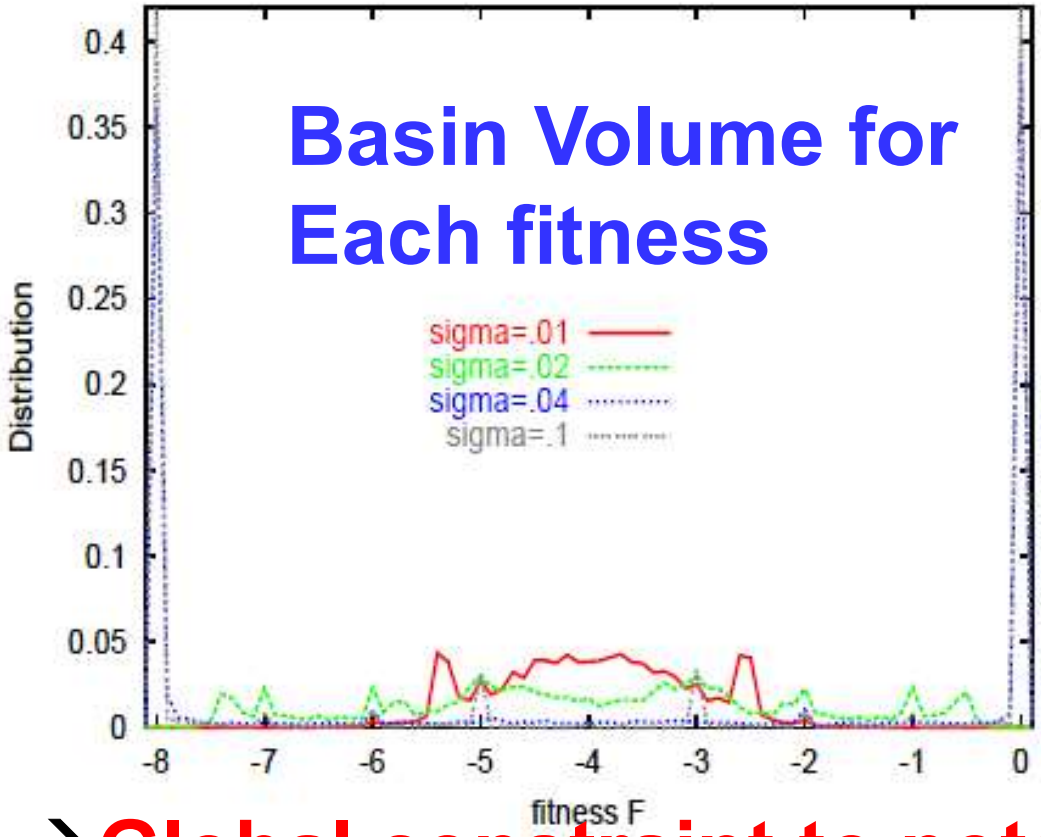
Why?; difference in basin structure

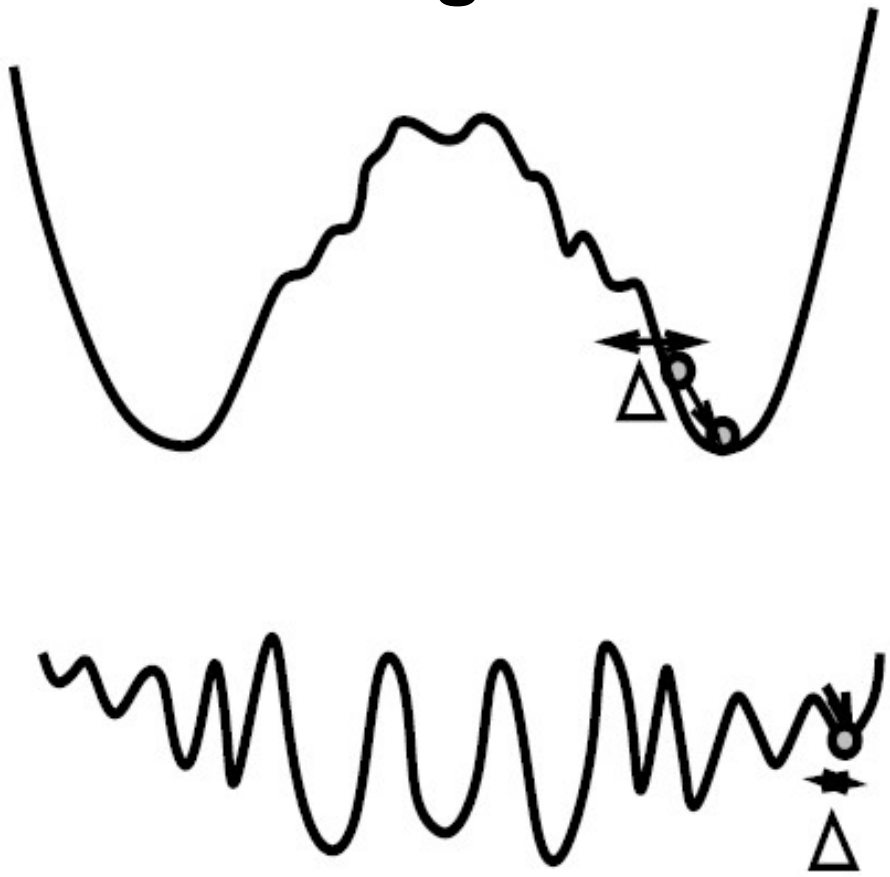
σ＞σc → large basin for target attractor

(robust, Δ（distance to basin boudary) ↑

σ＜σc → only tiny basin around target orbit

Δ remains small





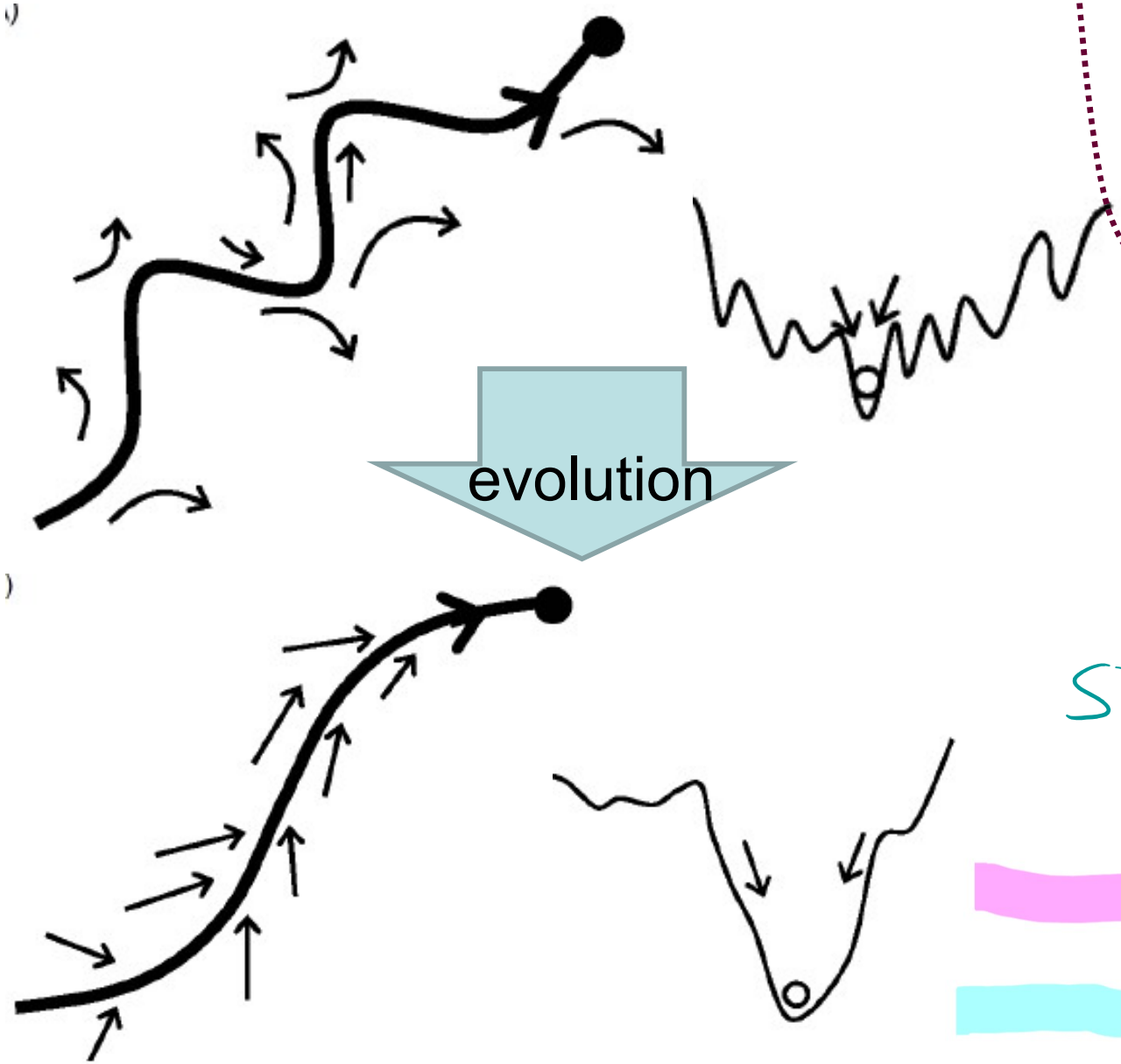
→Global constraint to potential landscape(funnel?)

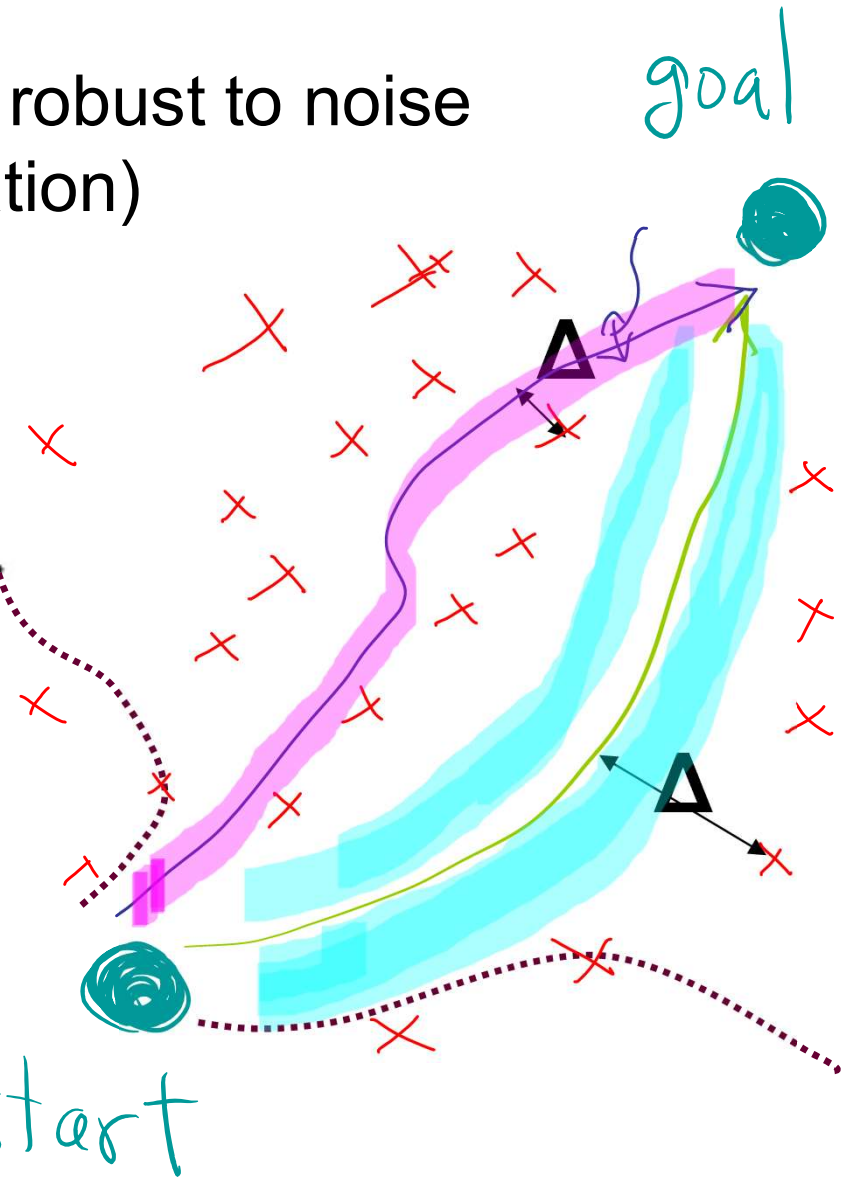
cf. protein; gene-expression (Li,Long,Lu,Ouyang,Tang)

Evolution of dynamical systems

dynamical systems whose attractor is robust to noise

→ robust to parameter changes (mutation)





Δ low ($\leq \sigma_c$)

Δ high ($\geq \sigma_c$)

Deviation of basin boundary (turning points)

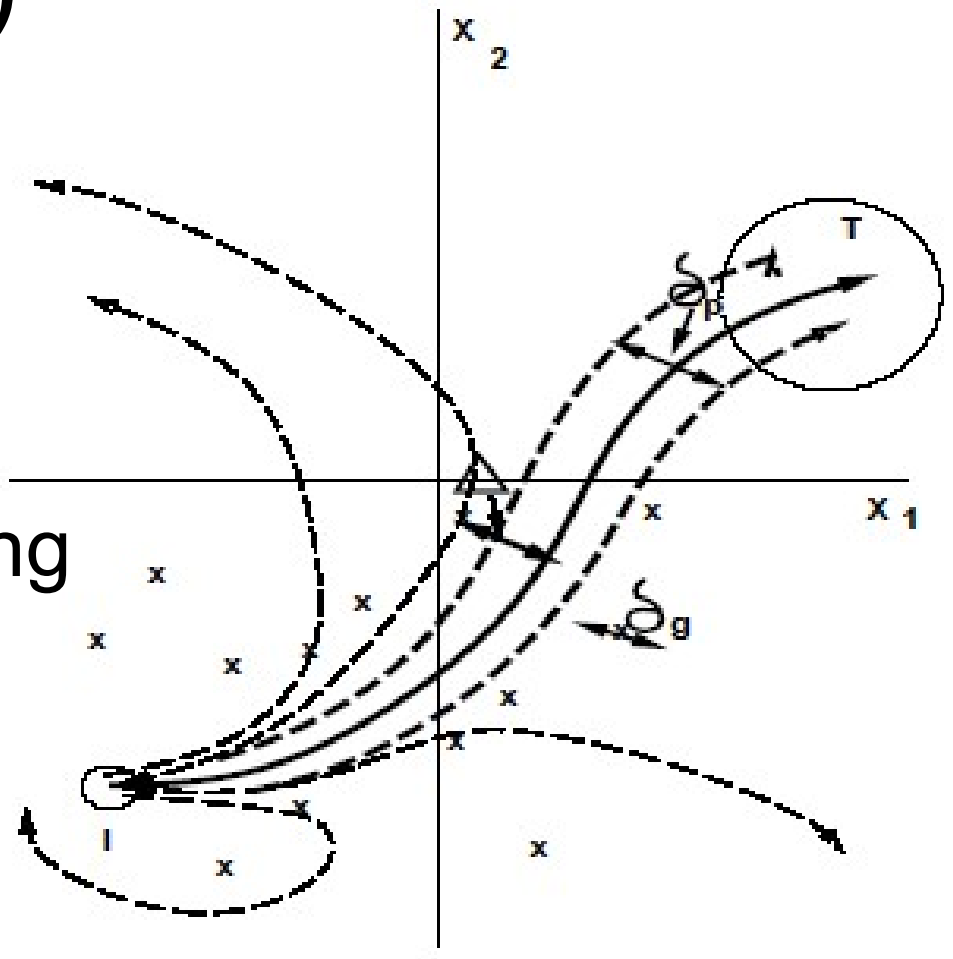
Δ increases

→robustness increases

why threshold?

choose paths to avoid turning pts within σ (noise)

Mutation→ touches turning points within range of μ



Δ~distance to turning points (basin boundary)

small σ −>

an orbit with small Δ

can reach the target

- Robustness to mutation is increased for network evolved under higher noise

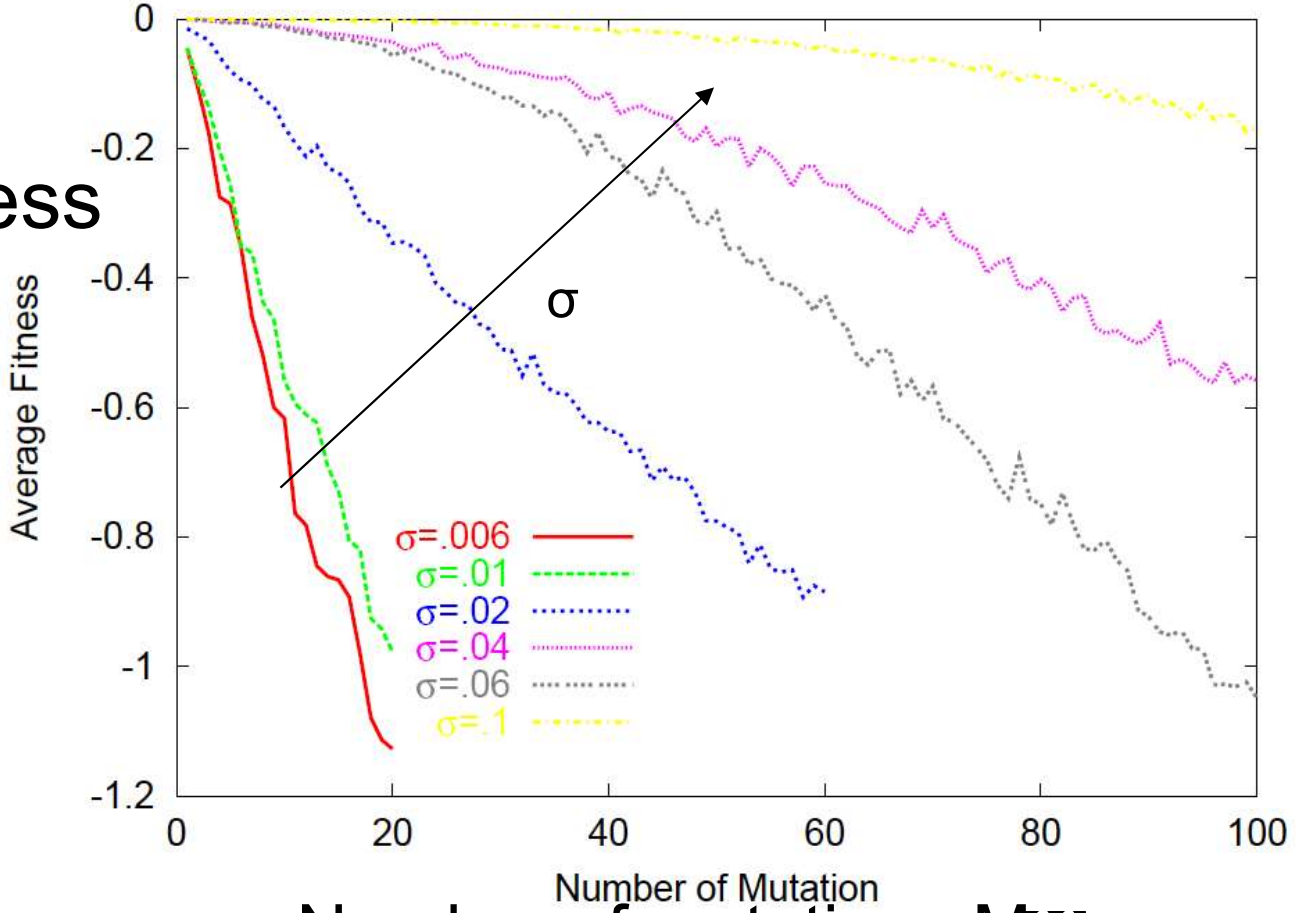
F=-c(σ) m ;
C(σ)>0 if σ<σc
C(σc) =0

Almost Neutral of fitness over mutations

accordingly robust case (high σ) allow for higher genetic diversity

Cf Tomoko Ohta

Average fitness over mutants with M mutations



Number of mutations M

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 increases

Noise is necessary for evolution of robustness

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

(cf. Ancel-Fontana J ExpZoolB 2000

A Wagner et al, PLoS Comp Biol 2007)

Waddington's and Einstein's Legacy

Robustness is Essential

- Canalization
- Genetic Assimilation

→These are linked through potential picture

Environmental change -→ potential change

how it is buffered in genetic change

We represented by P(x,a) and in terms of fluctuations based on consistency between geno and pheno fluctuation

Einstein's Brownian motion theory (consistency between micro fluct vs macro motion)

Ours: that between geno and pheno fluctuation

- Q again:Why phenotypic fluctuation is favored for evolutionary stability?

(1) ‘fatal’ states around highly optimized state

(2) Small noise case

Trapped at ‘metastable’ state in ‘model’ space

(3) simple structure both in ‘gene’ direction and ‘phenotype’ direction is favored

(Funnel-like structure is preferred (even though complex dynamics may be hidden somewhere)

Protein (Go), Gene expression dynamics (Tang-Ouyang), Developmental process

- 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? But the precise formula is Vip>Vig: but if selection is strong -? <.5)

- Generality? For a system satisfying:

(1) fitness is determined after developmental dynamics

(2) developmental dynamics is complex

(eg.,with distributed catastrophic pts.

(⇒ deleterious mutants, error catastrophe)

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

---

*Vip variance of phenotype over isogenic individuals

*Vg variance of average phenotype over heterogenic population

Plasticity ∝ **Vip** ∝ **Vg** ∝ evolution speed

through evolution course

and over genes at given snapshot

Spin Model for evolution Sakata.Hukushima. KK, PRL 2009

eg. Protein folding dynamics

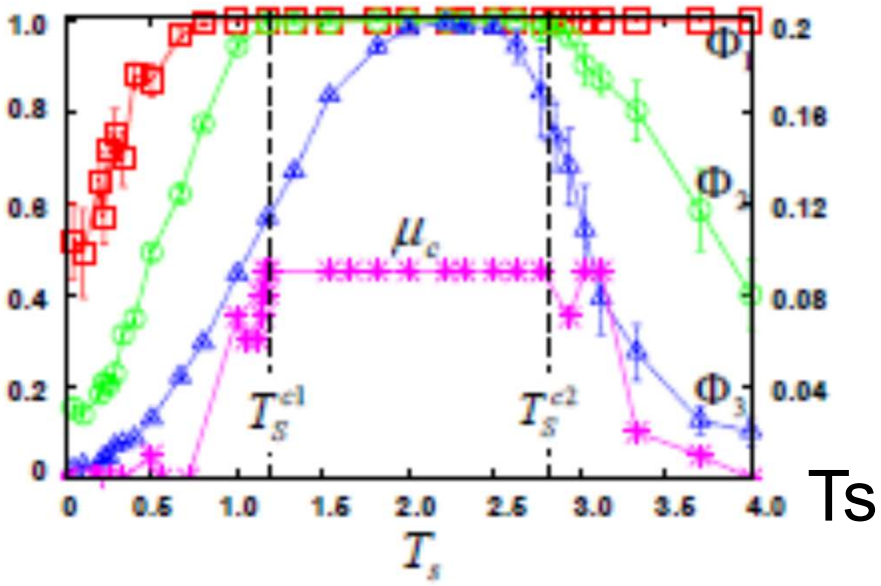
spin configuration --- configuration in protein

H folding dynamics

$$H(\boldsymbol{S}|\boldsymbol{J}) = -\frac{1}{\sqrt{N}}\sum_{i<j} J_{ij}S_iS_j$$

Fitness; to allign target spins

evolve Jij



Ts

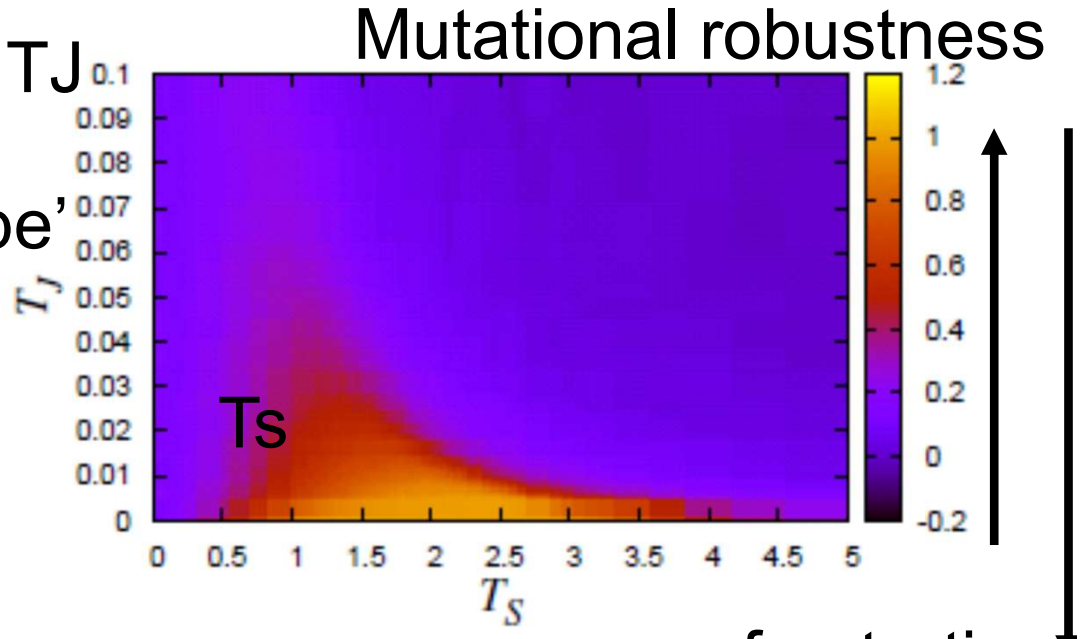
Again transition;

As noise is increased

high fitness with robustness

to mutation is achieved

Form Jij to have 'funnel landscape'



Ts noise during 'developmental' dynamics

TJ selection pressure

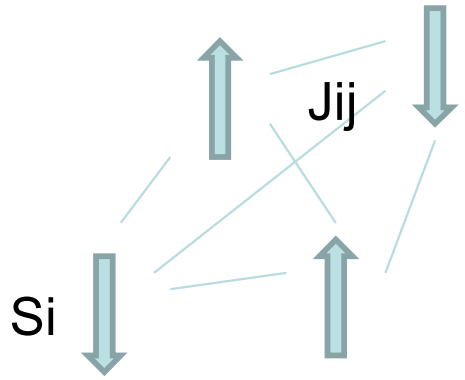
(high as TJ → 0)

Spin Model for evolution (Sakata.Hukushima,KK, PRL 2009)

eg. Protein folding dynamics

spin configuration --- configuration in protein

H folding dynamics



$$H(\boldsymbol{S}|\boldsymbol{J}) = -\frac{1}{\sqrt{N}}\sum_{i<j} J_{ij}S_iS_j$$

librium distribution for a given $\boldsymbol{J}$, $P(\boldsymbol{S}|\boldsymbol{J},T_S) = e^{-\beta_S H(\boldsymbol{S}|\boldsymbol{J})}/Z_S(T_S)$, where $\beta_S = 1/T_S$ and $Z_S(T_S) = \mathrm{Tr}_{\boldsymbol{S}} \exp[-\beta_S H(\boldsymbol{S}|\boldsymbol{J})]$. In the steady state of the dynamics, the phenotype $\boldsymbol{S}$

$$Fit(\boldsymbol{J}|T_S) = \left\langle \prod_{i<j\in \boldsymbol{t}} \delta(S_i - S_j) \right\rangle$$

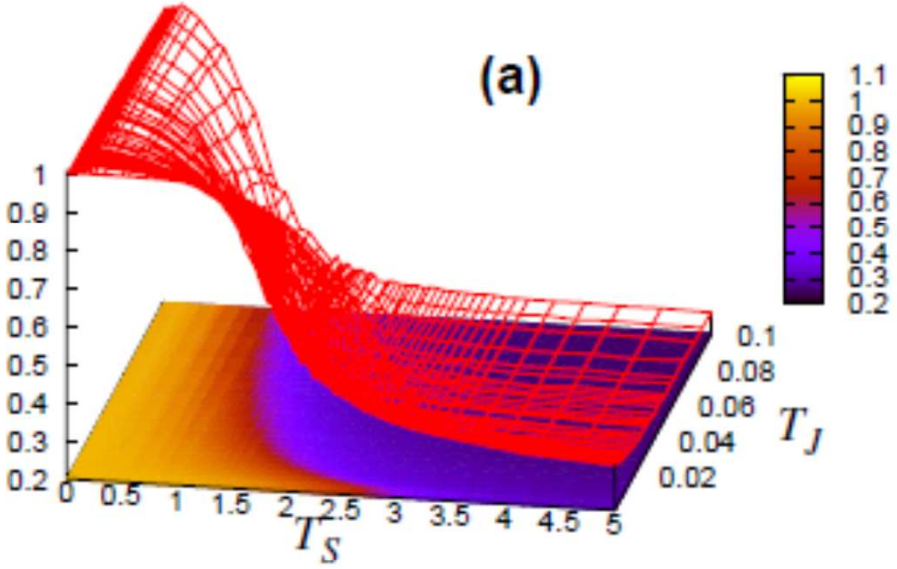
t :target spin; fitted if alligned

tionary distribution, $P(\boldsymbol{J},T_S,T_J) = e^{\beta_J Fit(\boldsymbol{J},T_S)}/Z_J(T_S,T_J)$, where $\beta_J = 1/T_J$ and $Z_J(T_S,T_J) = \mathrm{Tr}_{\boldsymbol{J}} \exp[\beta_J Fit(\boldsymbol{J},T_S)]$.

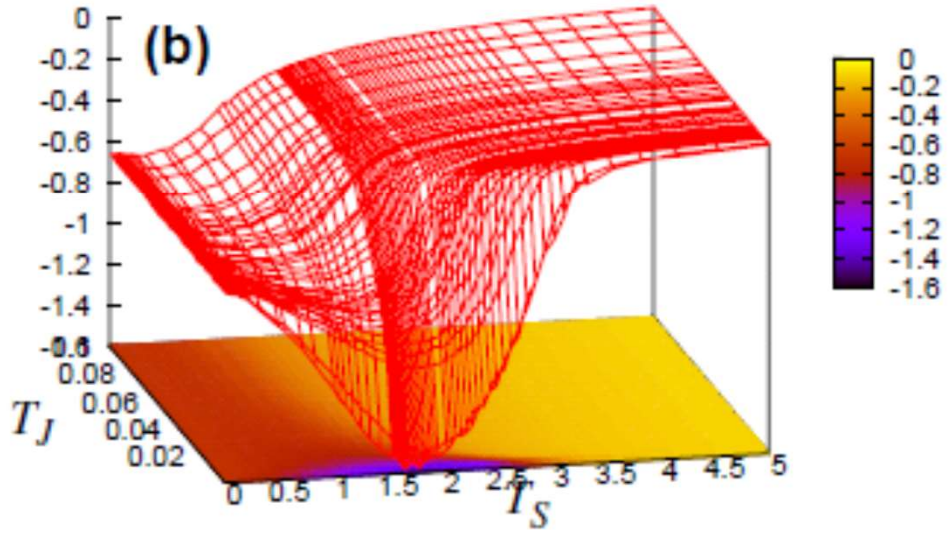
T **S** noise during 'developmental' dynamics

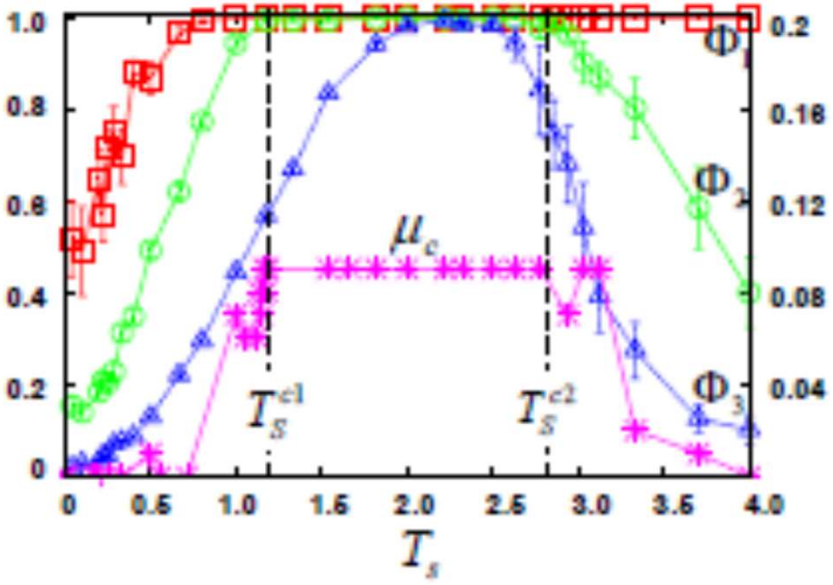
TJ mutation-selection process (selection pressure

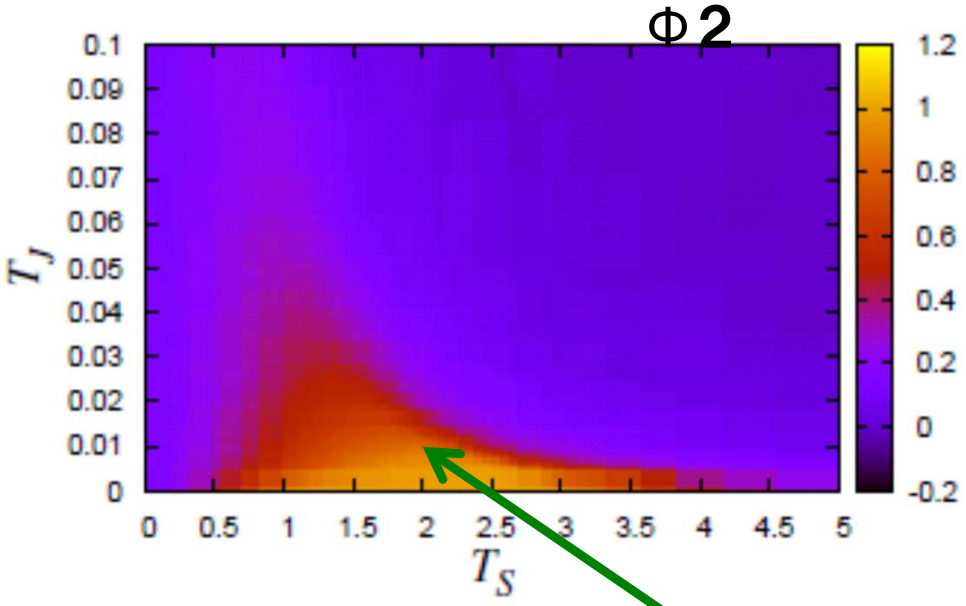
Fitness



Energy







Funnel Phase

1-Φ**2**: Frustration in spins around the target

μc: mutation in network necessary to destroy the target config

- Phase transition

Ts<Tc1 – high fitness state is achieved, but not robust to mutation: Spin-glass phase

Tc1<Ts<Tc2 -- high fitness state. Robust to mutation. No frustration around the target spins, but frustration remains elsewhere: 'local Mattis' state; ~

funnel developmental landscape

the target equilibrium reached globally and fast

Ts>Tc2, -- high fitness is not achieved. 'paramagnetic' phase

*Ubiquity of **funnel developmental landscape--**result of evolution under noise, which also leads to robustness to mutation

***Evolutionary Meaning of RSB! ***

Double-replica theory for evolution of genotype-phenotype interrelationship

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[1] *The Niels Bohr Institute, University of Copenhagen, Blegdamsvej 17, Copenhagen, 2100-DK, Denmark*
[2] *Center for Complex Systems Biology, Universal Biology Institute, University of Tokyo, Komaba, Tokyo 153-8902, Japan*

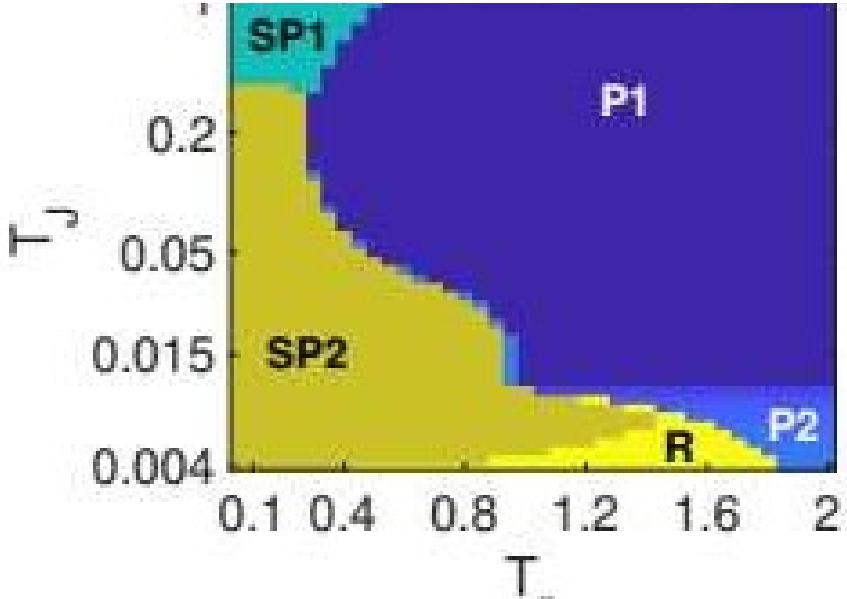
(Dated: November 29, 2022)

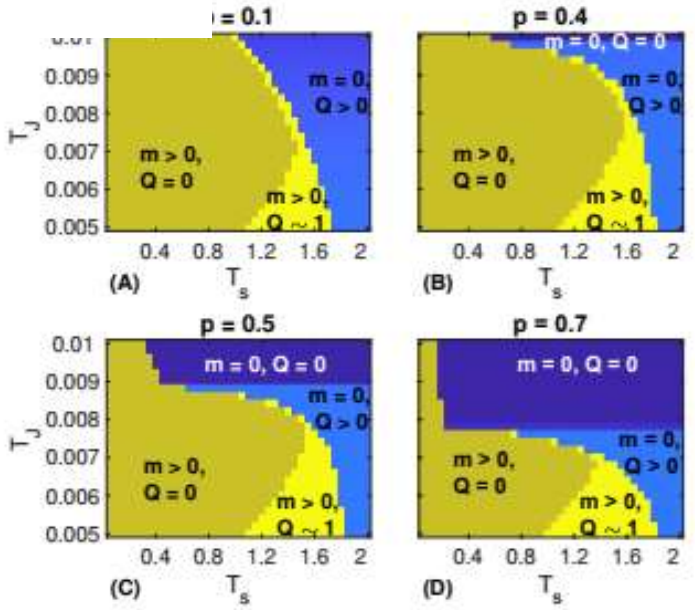
The relationship between genotype and phenotype plays a crucial role in determining the function and robustness of biological systems. Here the evolution progresses through the change in genotype, whereas the selection is based on the phenotype, and genotype-phenotype relation also evolves. Theory for such phenotypic evolution remains poorly-developed, in contrast to evolution under the fitness landscape determined by genotypes. Here we provide statistical-physics formulation of this problem by introducing replicas for genotype and phenotype. We apply it to an evolution model, in which phenotypes are given by spin configurations; genotypes are interaction matrix for spins to give the Hamiltonian, and the fitness depends only on the configuration of a subset of spins called target. We describe the interplay between the genetic variations and phenotypic variances by noise in this model by our new approach that extends the replica theory for spin-glasses to include spin-replica for phenotypes and coupling-replica for genotypes. Within this framework we obtain a phase diagram of the evolved phenotypes against the noise and selection pressure, where each phase is distinguished by the fitness and overlaps for genotypes and phenotypes. Among the phases, robust fitted phase, relevant to biological evolution, is achieved under the intermediate level of noise (temperature), where robustness to noise and to genetic mutation are correlated, as a result of replica symmetry. We also find a trade-off between maintaining a high fitness level of phenotype and acquiring a robust pattern of genes as well as the dependence of this trade-off on the ratio between the size of the functional (target) part to that of the remaining non-functional (non-target) one. The selection pressure needed to achieve high fitness increases with the fraction of target spins.

arXiv

Dual Replicas for
Spin(phenotype)
Jij-interaction (genotype)

Replica Symmetric Phase
-robust to noise and mutation





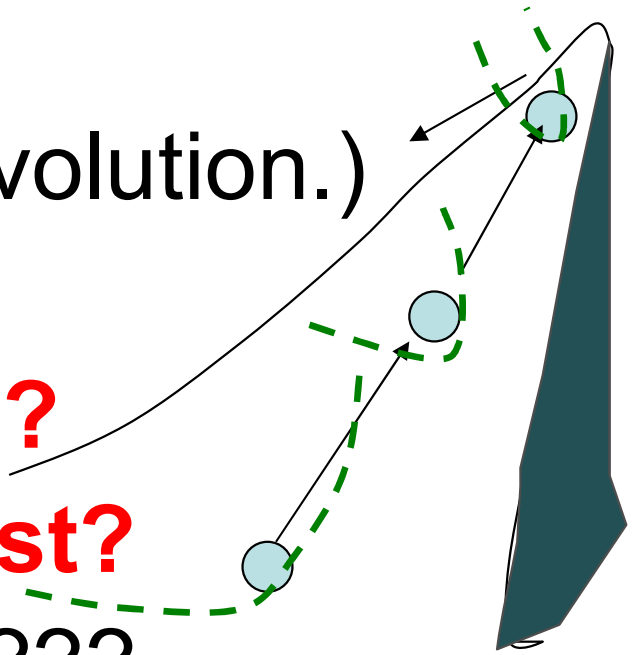
Through directed evolution; fluctuations decrease

(**Model, experiments, theory, i.e., increase of robustness through evolution.)

Then, evolution slows down..

←→ **How Evolution continues?**

Why Large Fluctuations exist?



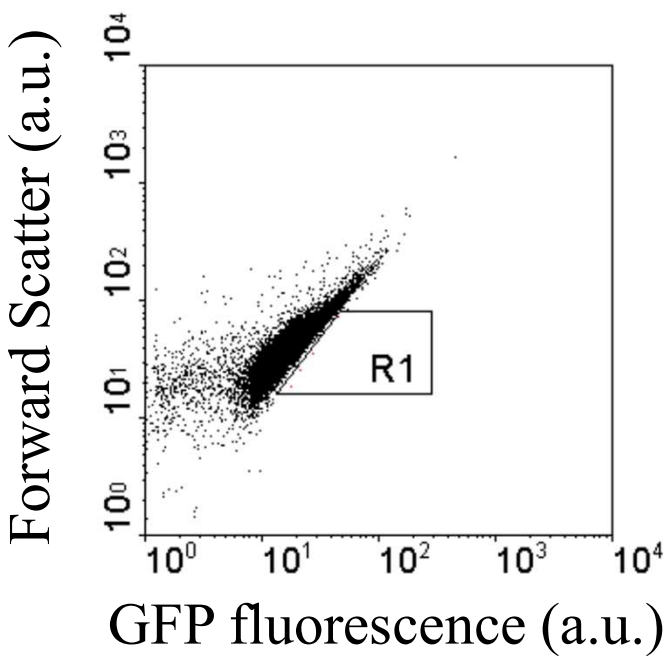
?? Is there regain of fluctuations????

- Experimentally Observed: Appearance of mutants with large fluctuations at further evolution. (← interference with other processes) (Ito, etal, MSB 2009)
- → Restoration of Plasticity

Strategy for survival with the increase of fluctuation

Fig.1

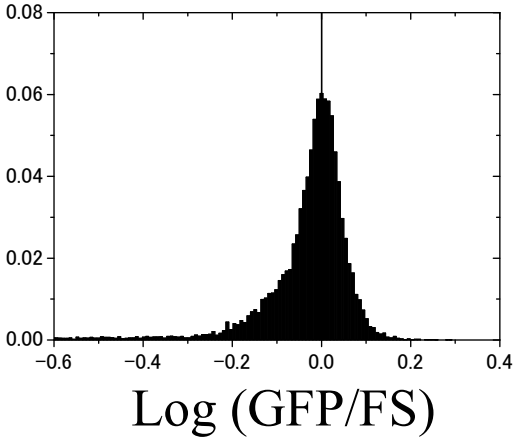
A



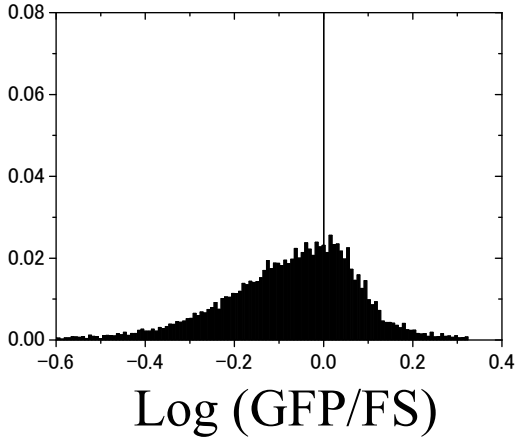
Selection experiment at individual level (strong selective pressure) (Ito etal, Molecular Systems Biology 2009)

Appearance of 'broad mutants'

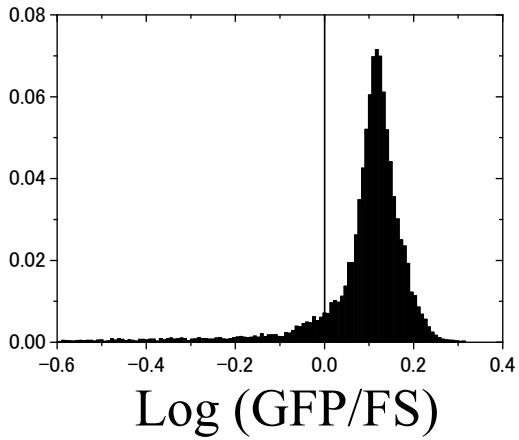
B

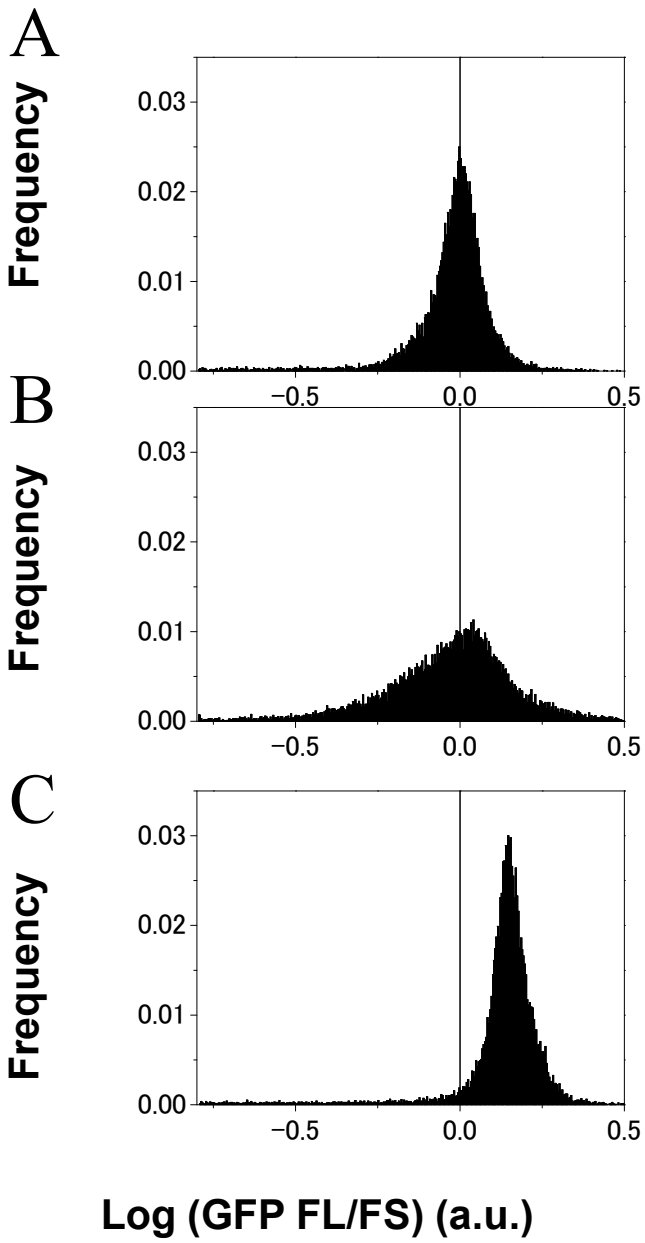


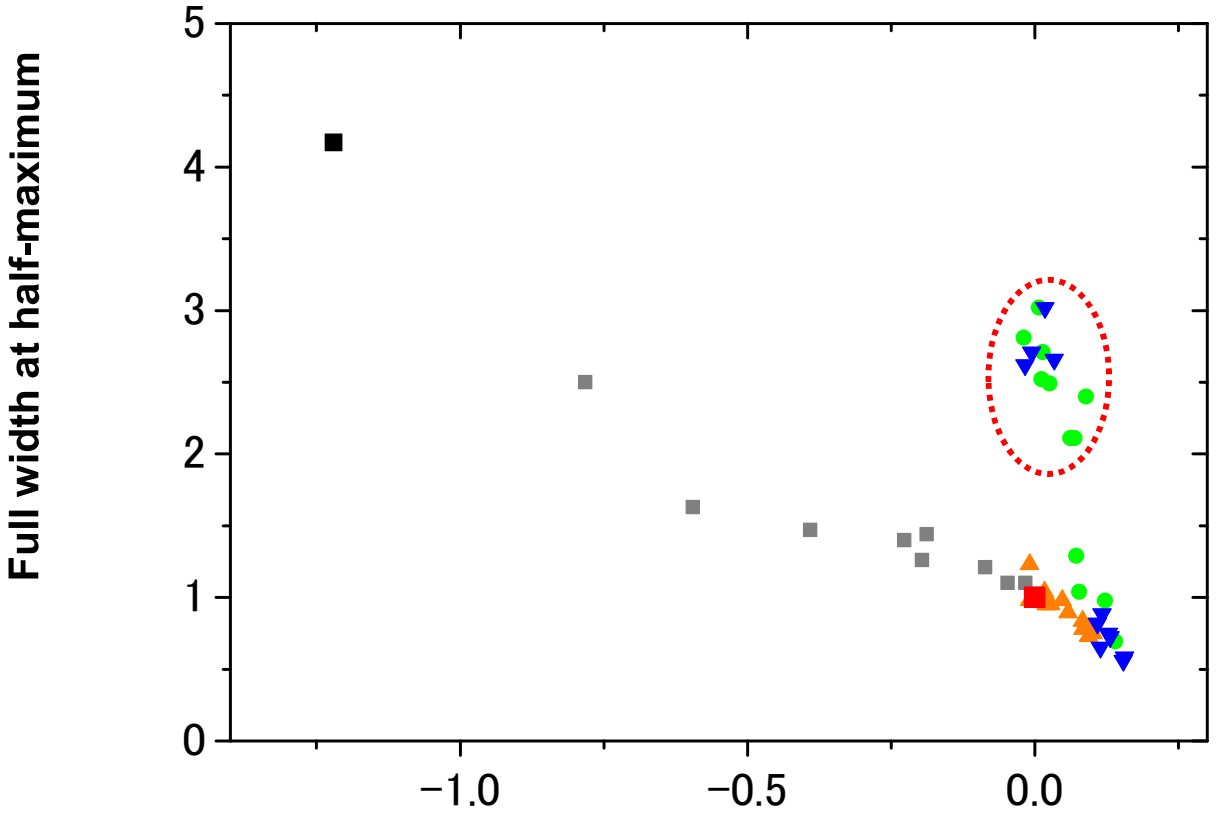
C



D







Here Fluctuation in mRNA conc. Is increased
→Use of 'new' degrees of freedom

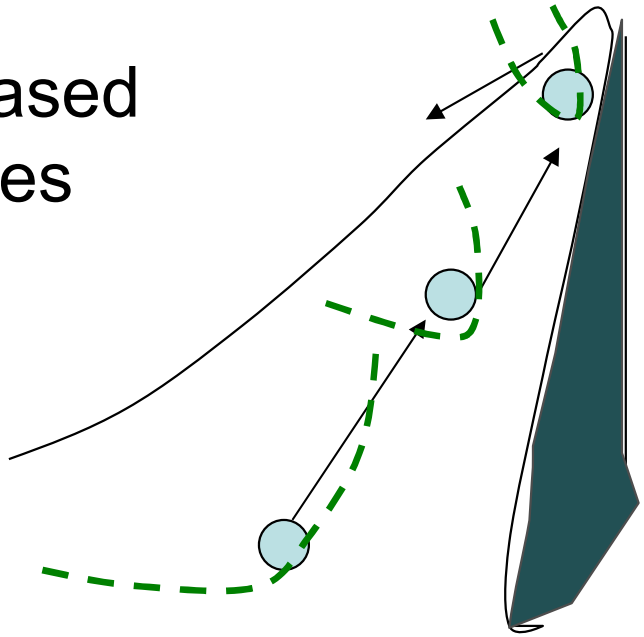


Figure S1 C

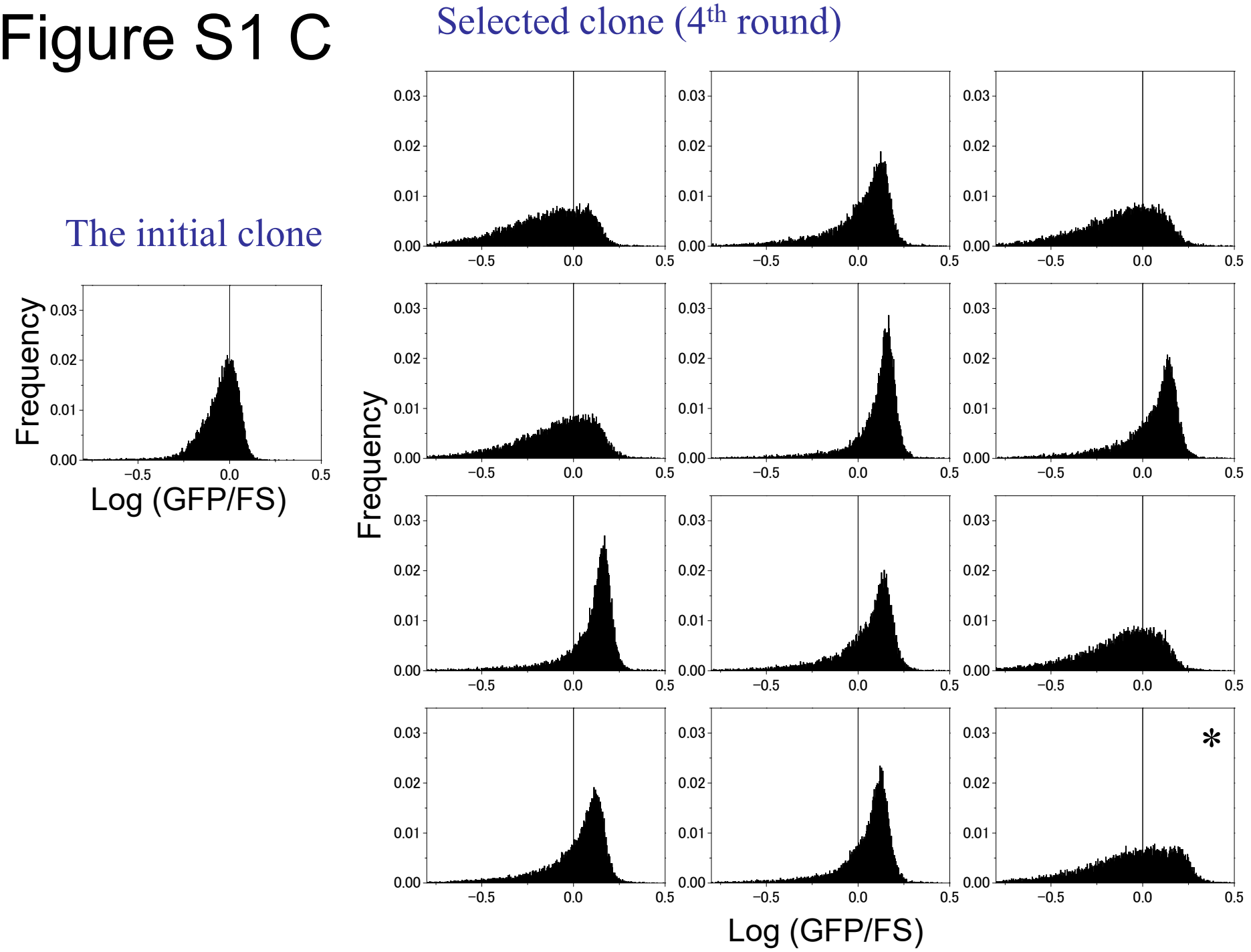

Selected clone (4th round)
The initial clone
Frequency
Log (GFP/FS)
*

Figure 1

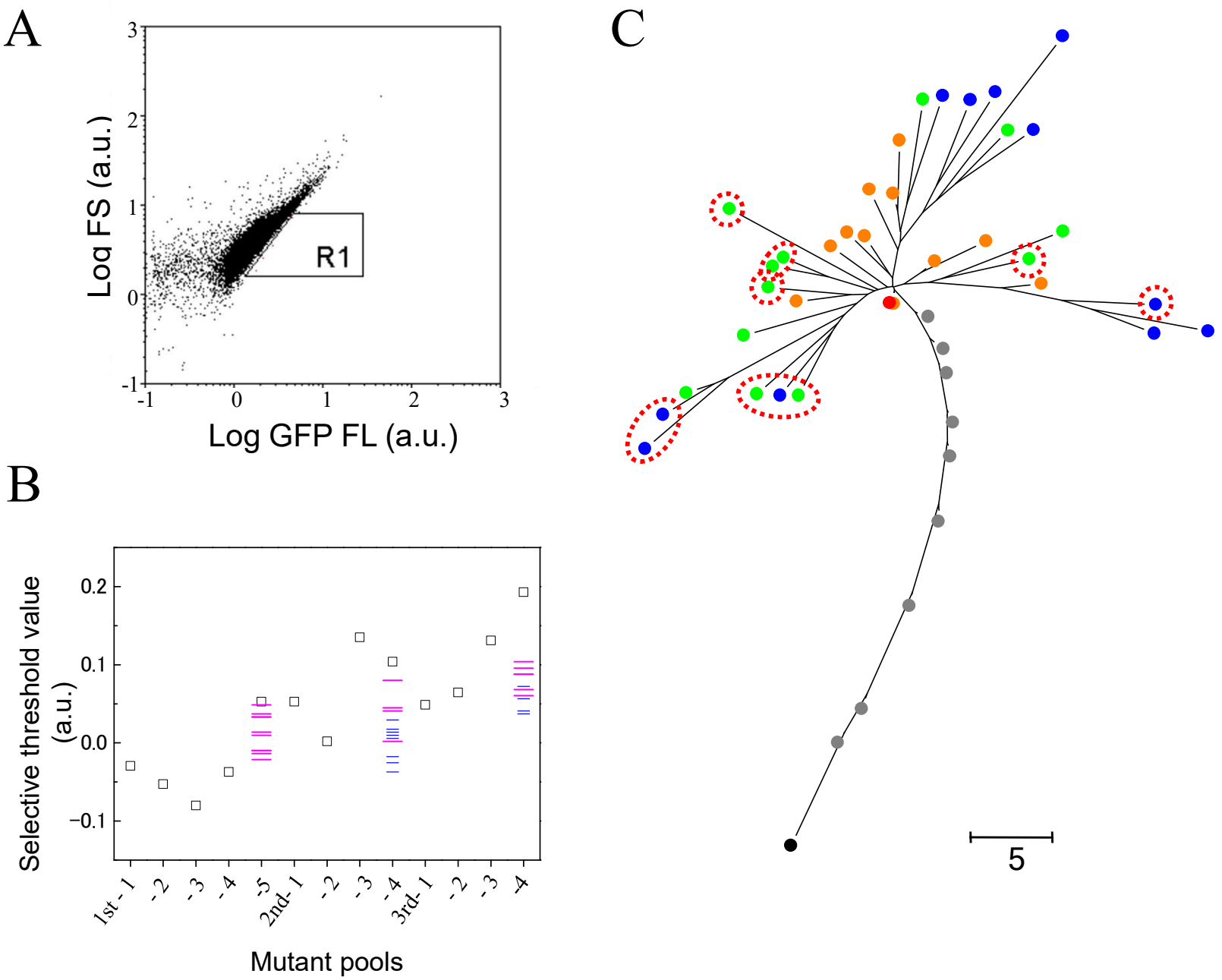
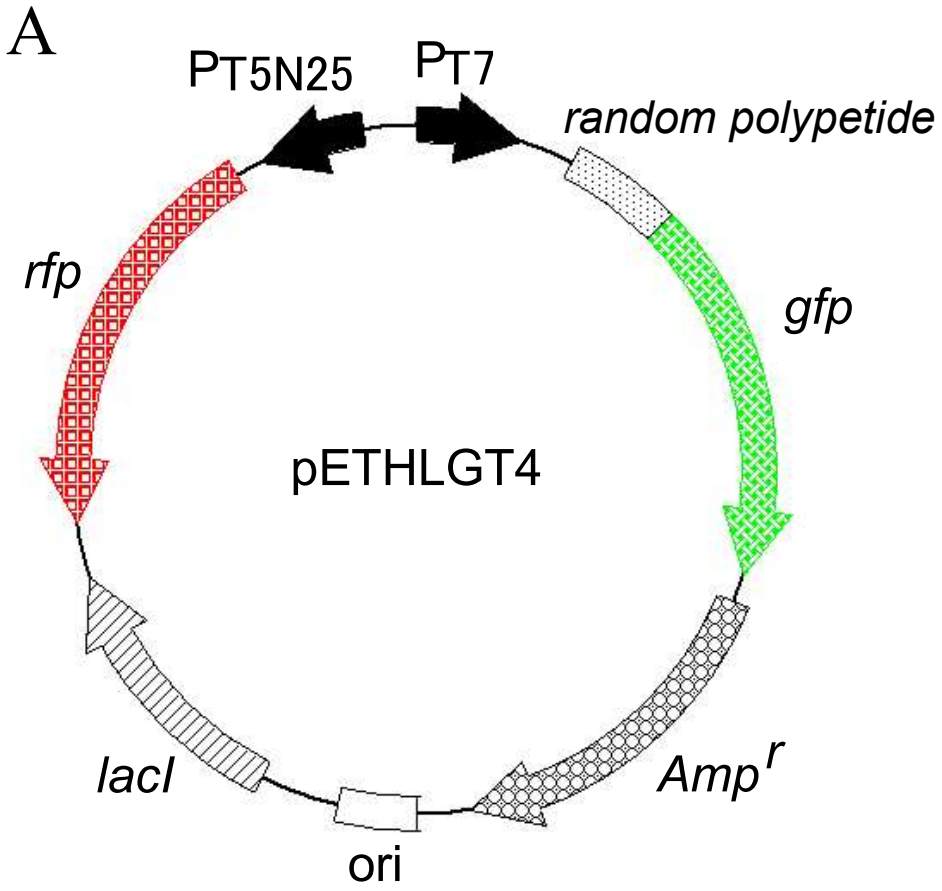
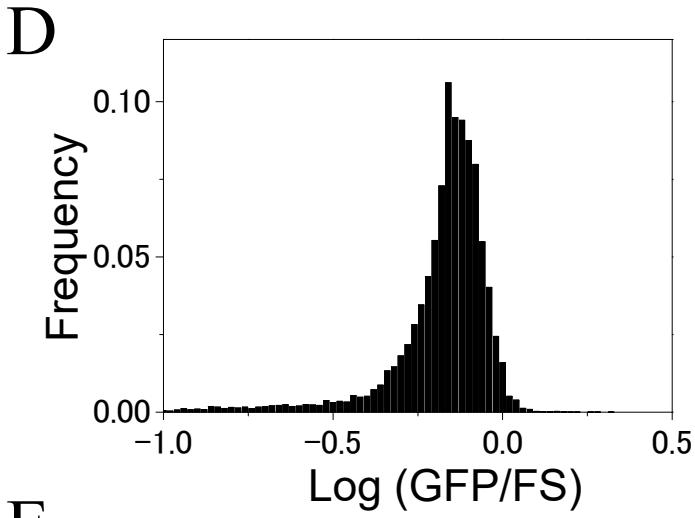
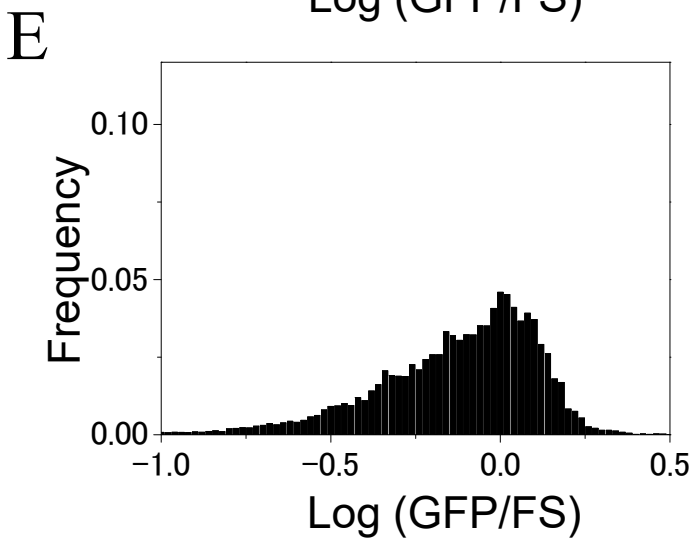

A
Log FS (a.u.)
Log GFP FL (a.u.)
R1
B
Selective threshold value (a.u.)
Mutant pools
1st- 1
-2
-3
-4
-5
2nd- 1
-2
-3
-4
3rd- 1
-2
-3
-4
C
5

Figure S3


A
PT5N25
PT7
random polypetide
rfp
gfp
pETHLGT4
lacI
Amp^r
ori


D
Frequency
0.10
0.05
0.00
−1.0
−0.5
0.0
0.5
Log (GFP/FS)


E
Frequency
0.10
0.05
0.00
−1.0
−0.5
0.0
0.5
Log (GFP/FS)

A possible scenario:

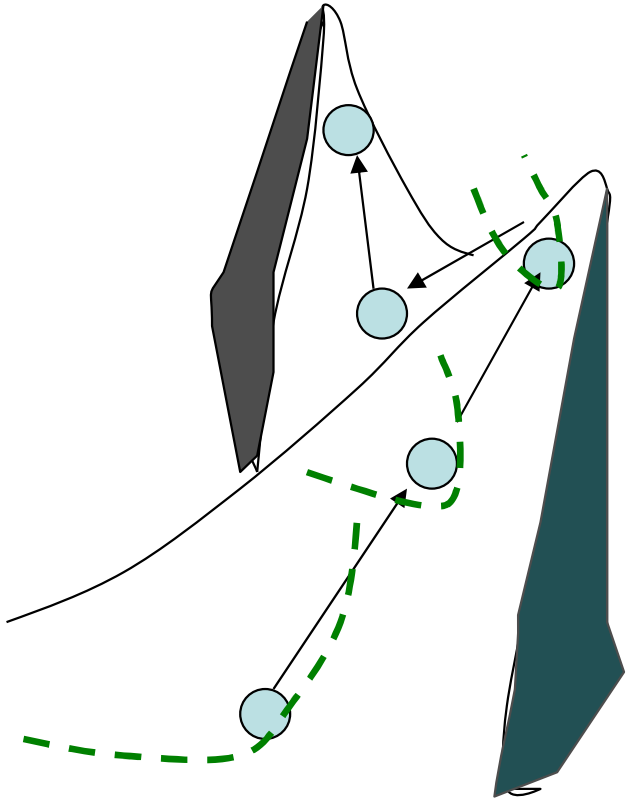
directed evolution → decrease in fluctuation and plasticity,

loss of evolvability

Cliff Landscape (fall down to some other directions than the original 1-dimensional direction)

Re-increase of fluctuation → Recovery of evolvability

Evolve to some other direction → (Gain of novel function)



Modularity?

- Flourescence Intensity

combination of several factors

(1) Solubility ← indeed major source for the initial stage

(2) Flourescence in single molecule

(3) Expression level

(3.1) plasmind copy number

(3.2) mRNA level

← also related with cell growth

Change in broad mutants

neither (1) nor (2) (average, variance)

(3) –

avergae decreased, variance is increased

not (3.1), but (3.2)

- Toxicity in GFP?
- influences cell growth
- Broad; GFP synthesis/growth are suppressed for many cells, but some continue

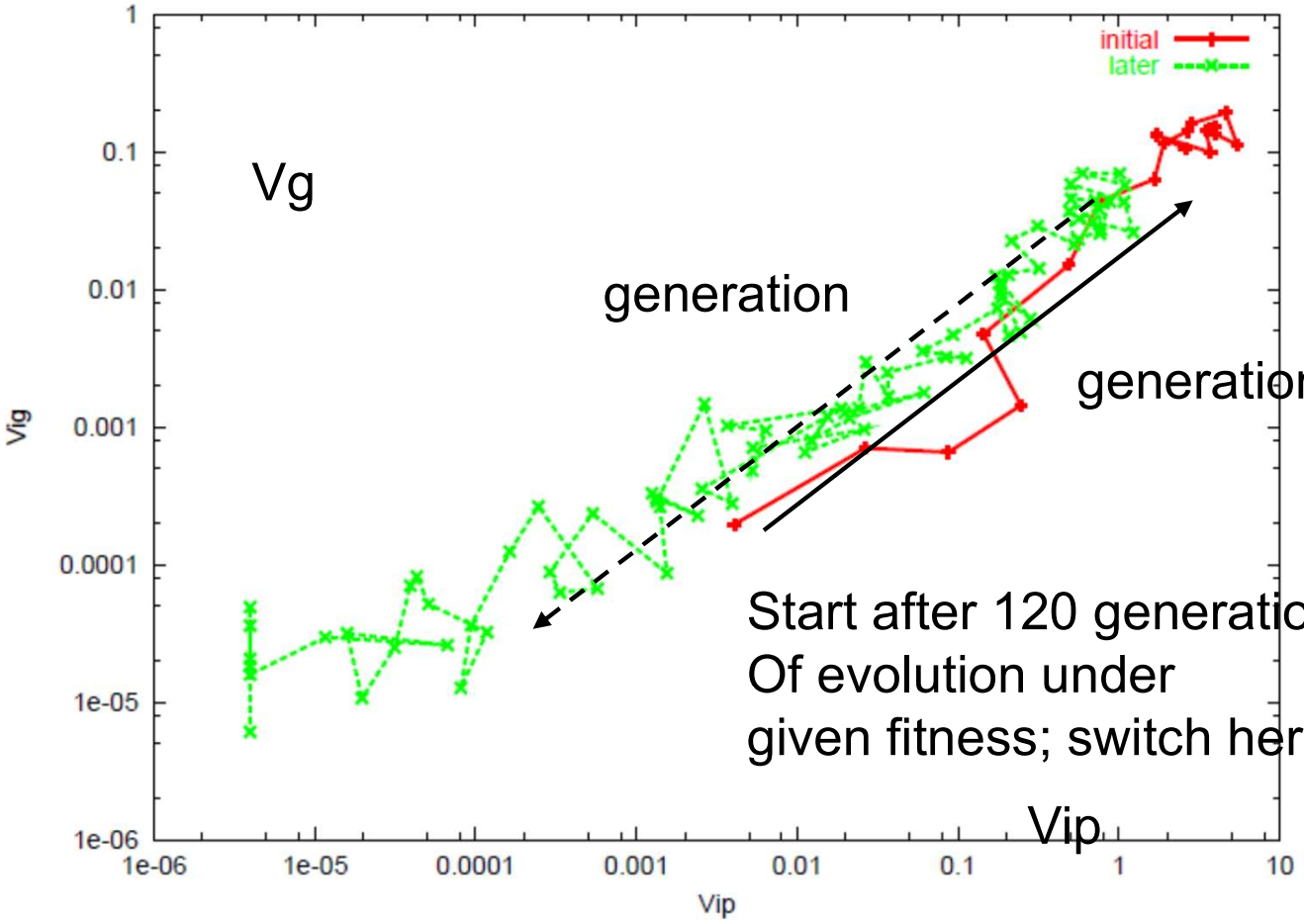
→ difference in timing in suppression

→source of increase in fluctuation?

('heterochrony' in Gould?)

When environmental condition is switched in the model

→ fluctuation once increases to regain evolvability and then decreases



++++----

→

----++++

?? Increase in fluctuation also proportionally??

Contunuous environmental change

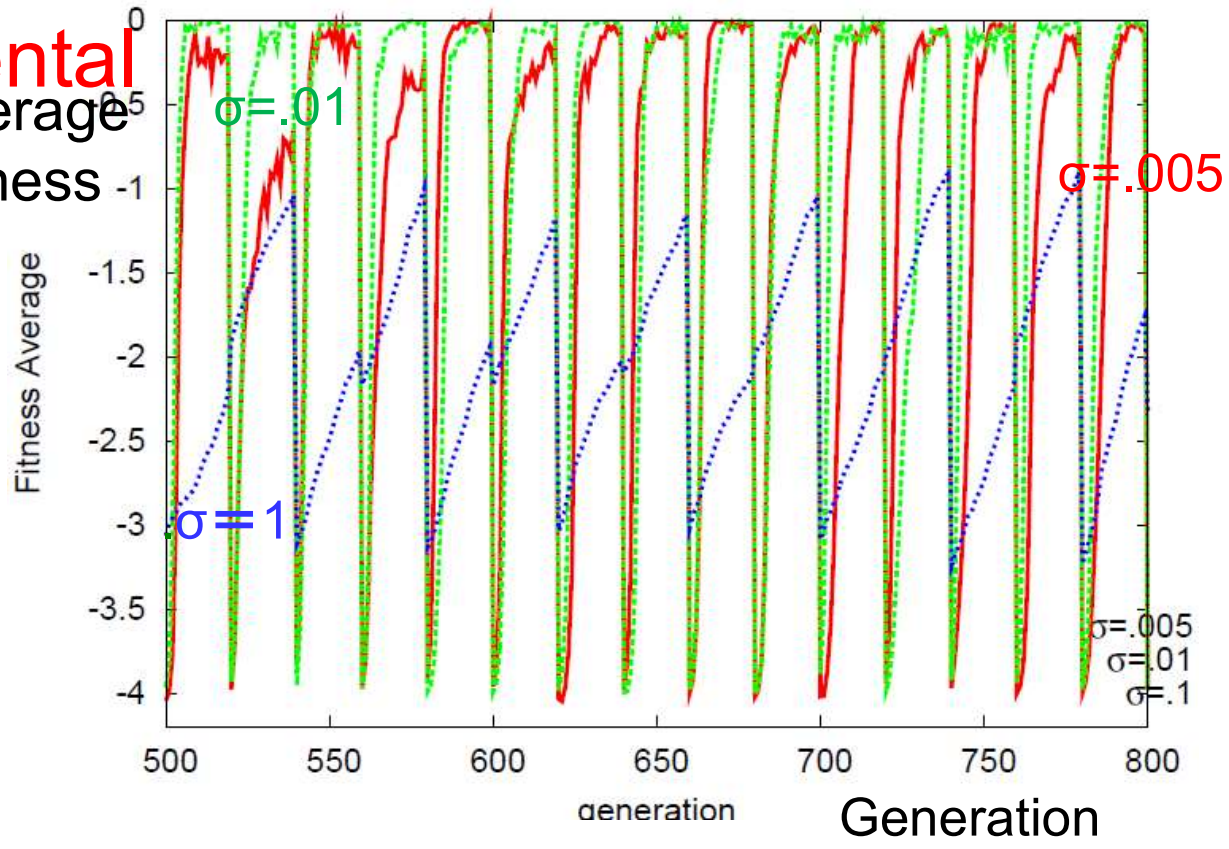
Switch the Fitness Condition per

2 0 generations

＋＋＋＋＋＋＋＋＋＋

← →

＋＋＋＋－－－－－

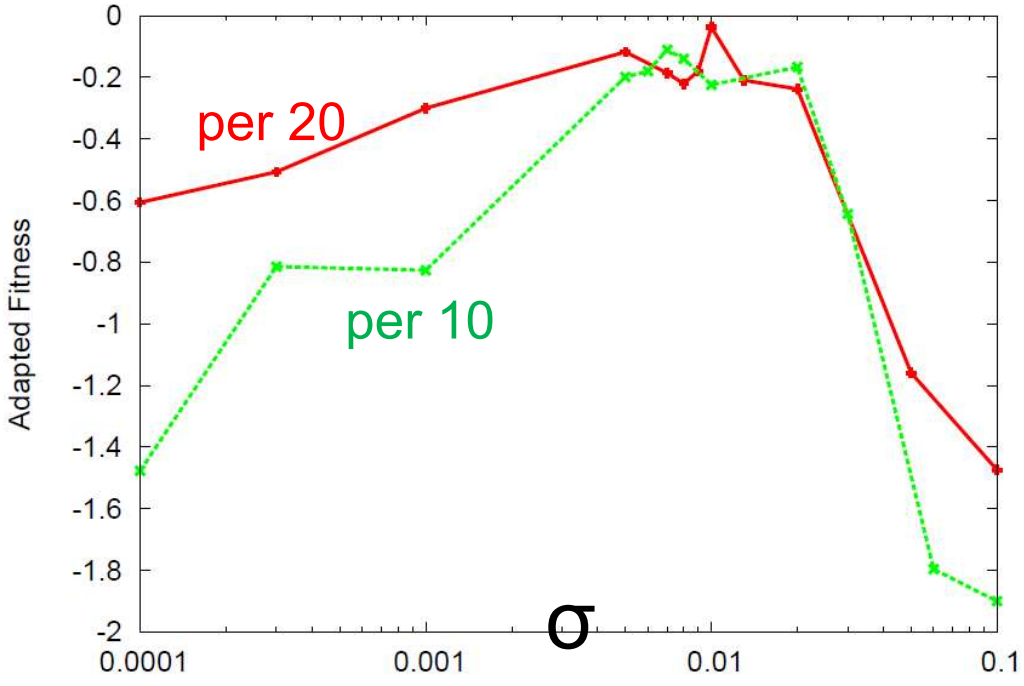


Large σ (low Vg/Vip)
cannot follow the environmental change

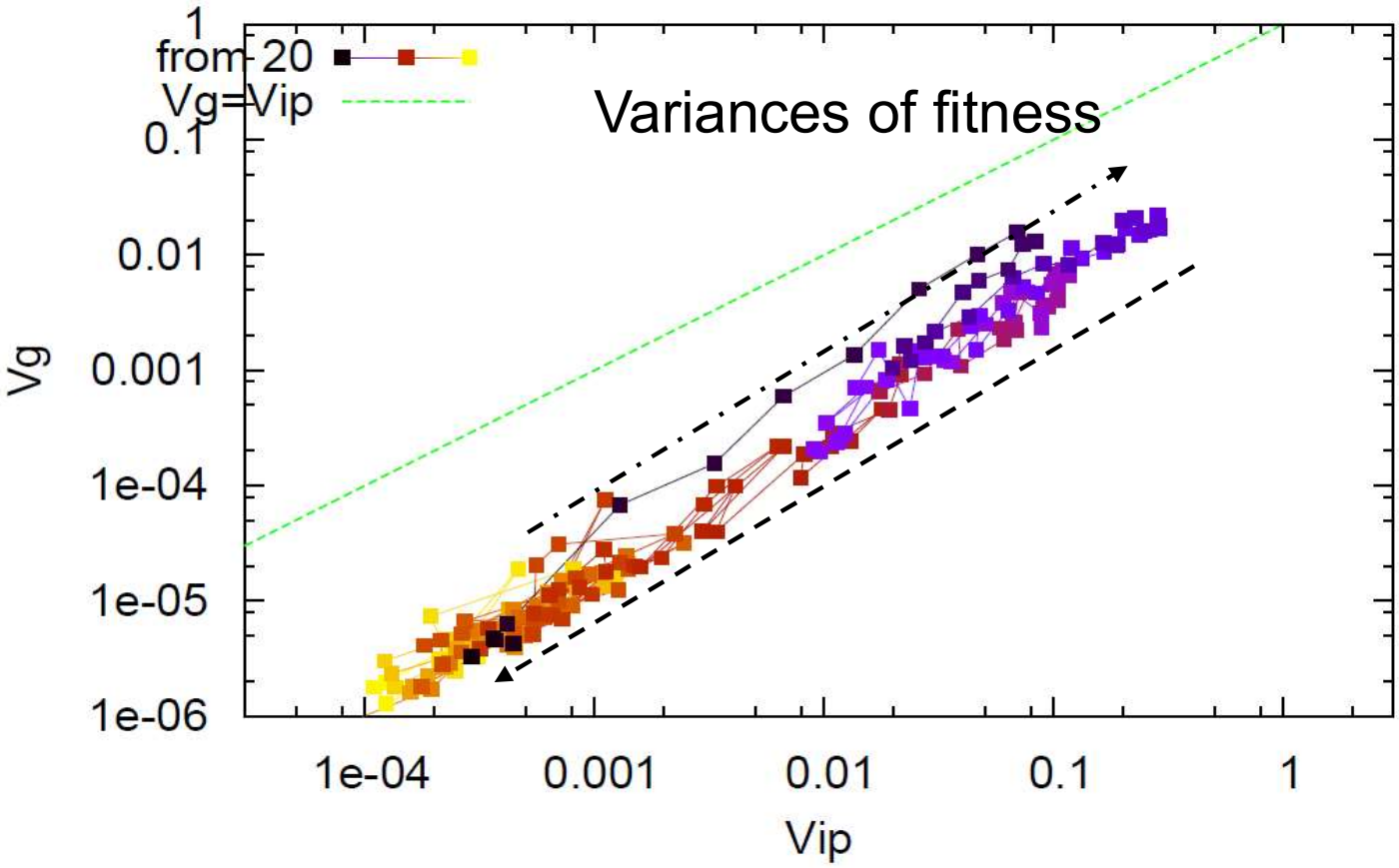
Small σ（high Vg/Vip)
non-fit mutants remain

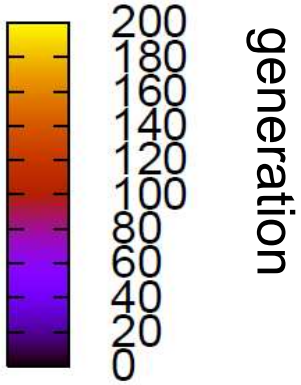
Near σ ~ σ**c**
cope with environmental change
satisfy both adaptation to new environment and robustness

Average fitness after adaptatio



In fixed environment/fitness, plasticity decreases.
When environmental condition is switched in the model
→ fluctuation once increases to regain plasticity
(evolvability) and then decreases





Start after 100 generation of evolution under given fitness; switch
++++++++→++++----

On -> Off for some Target genes

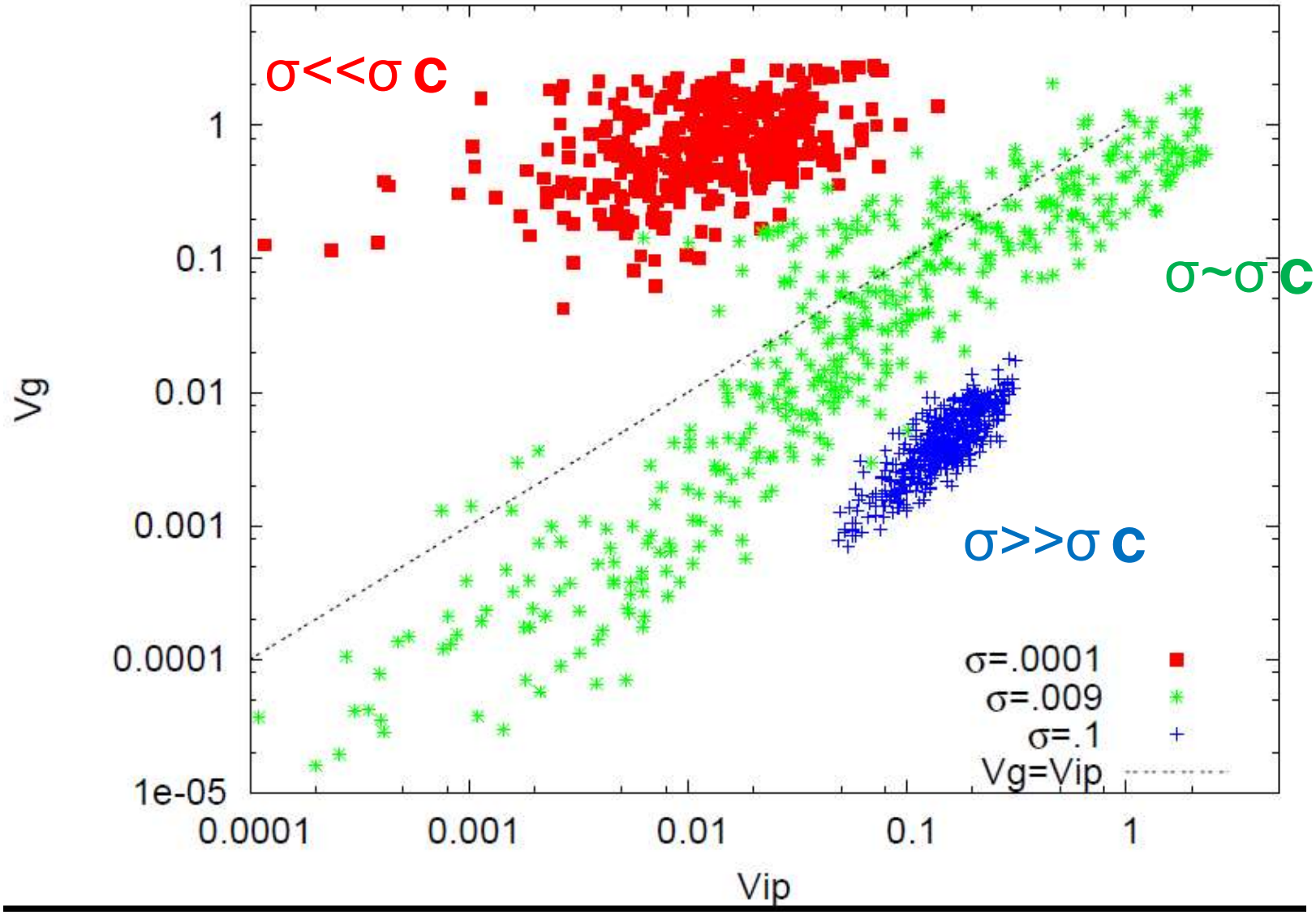
In a fluctuating environment, fluctuation (plasticity) Is sustained

(Increase of fluctuation in bacterial evolution; Ito-Toyota-KK-Yomo)

Critical State can adapt most efficiently

to environmental change

Vip-Vg of fitness temporally varies to a large degree



(B)Environmental variation?

Noise level σ＞σc→robustness increases and

Vg,Vip decreases (loss of evolvability)

In wildtype fluctuation and plasticity are maintained

How？(←environmental fluctuation, interactions)

(a) individual environmental variation within each generation

(b) environmental change over generations (n)

$$dx_i/dt = F[\sum_j^M J_{ij}x_j - \theta_i] - x_i + I_i(n) + (\sigma\eta_i(t))$$

$$F(X) = 1/(exp(-\beta X)+1)$$

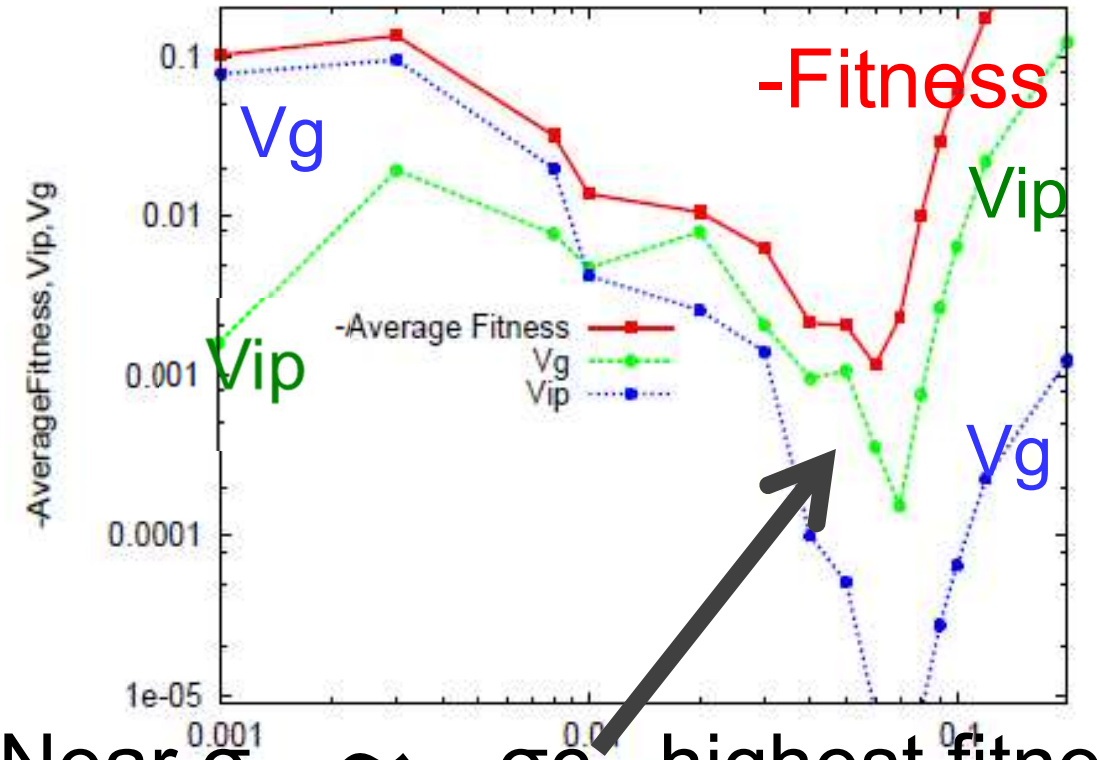
:he Model

Ii=0 except for few input genes

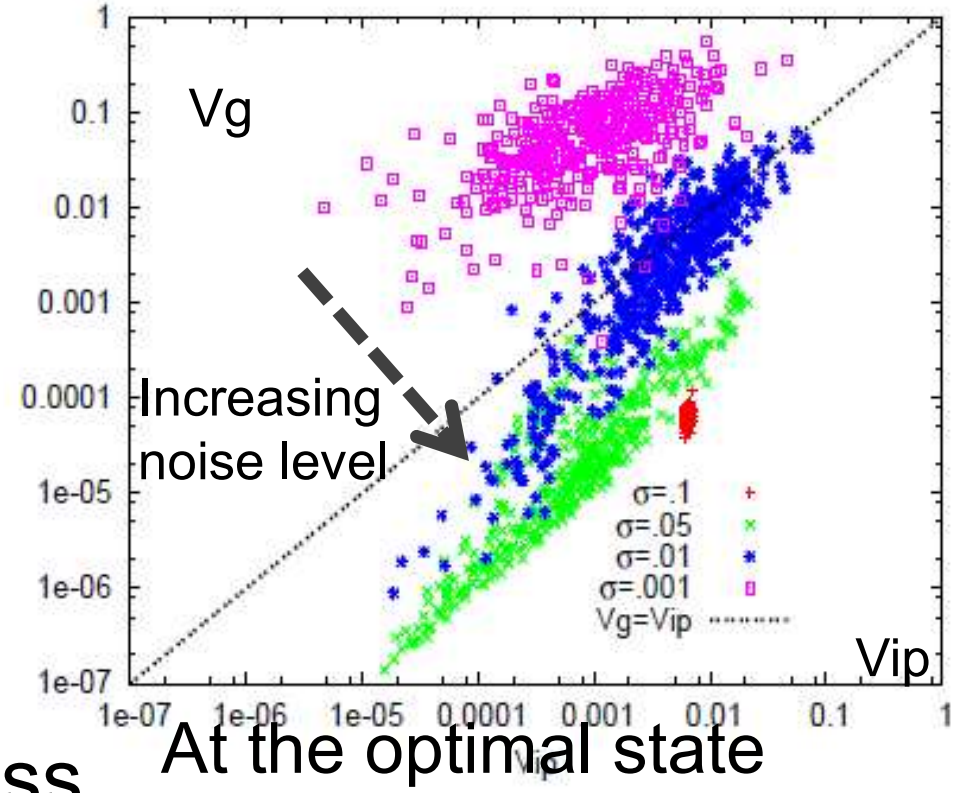
(a) Ii= ξi (n) (b) Ii= ξ(n) (not dep on t but varies by generation n)

Similar behaviors are observed by the input-change model

Average Fitness, Vip, Vg over generations



- Generation-to generation
- change of Vip and Vg



Near σ ~ σc, highest fitness where average Vip and average Vg crossovers

At the optimal state Vip and Vg goes up and down over generations, following proportionality

Symbiotic Sympatric Speciation

KK etal 2000
ProcRoySoc

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

** Sympatric Speciation -- fundamental but difficult?

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

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

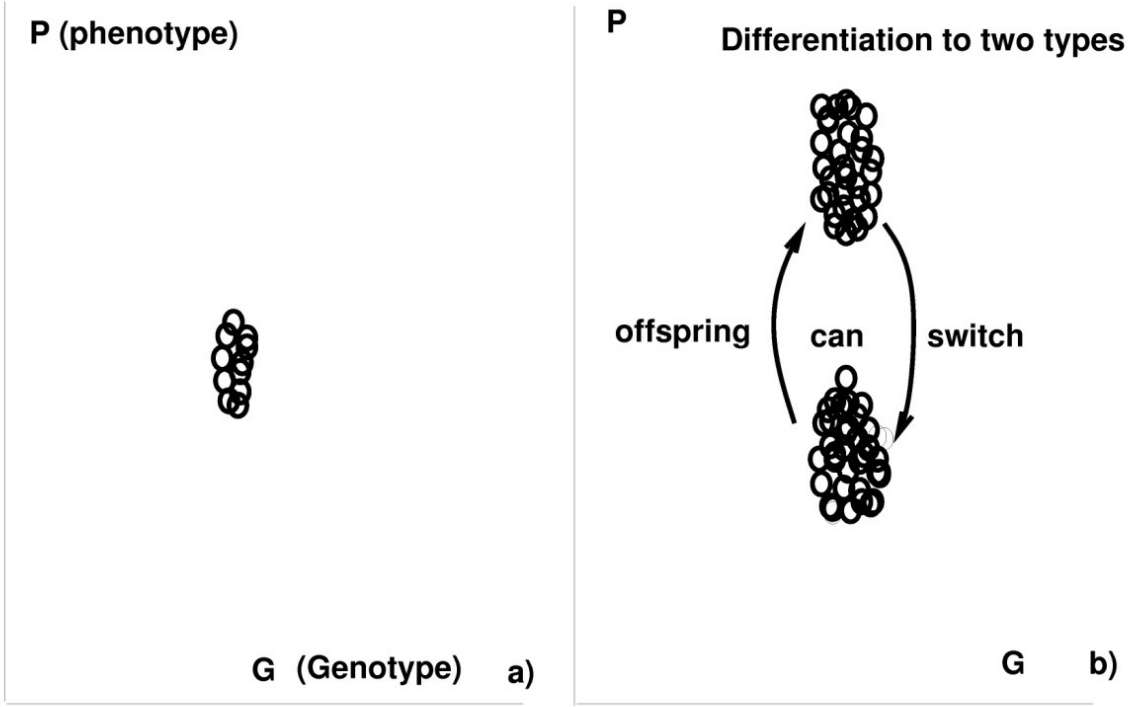
homogeneous state is destabilized by the interaction

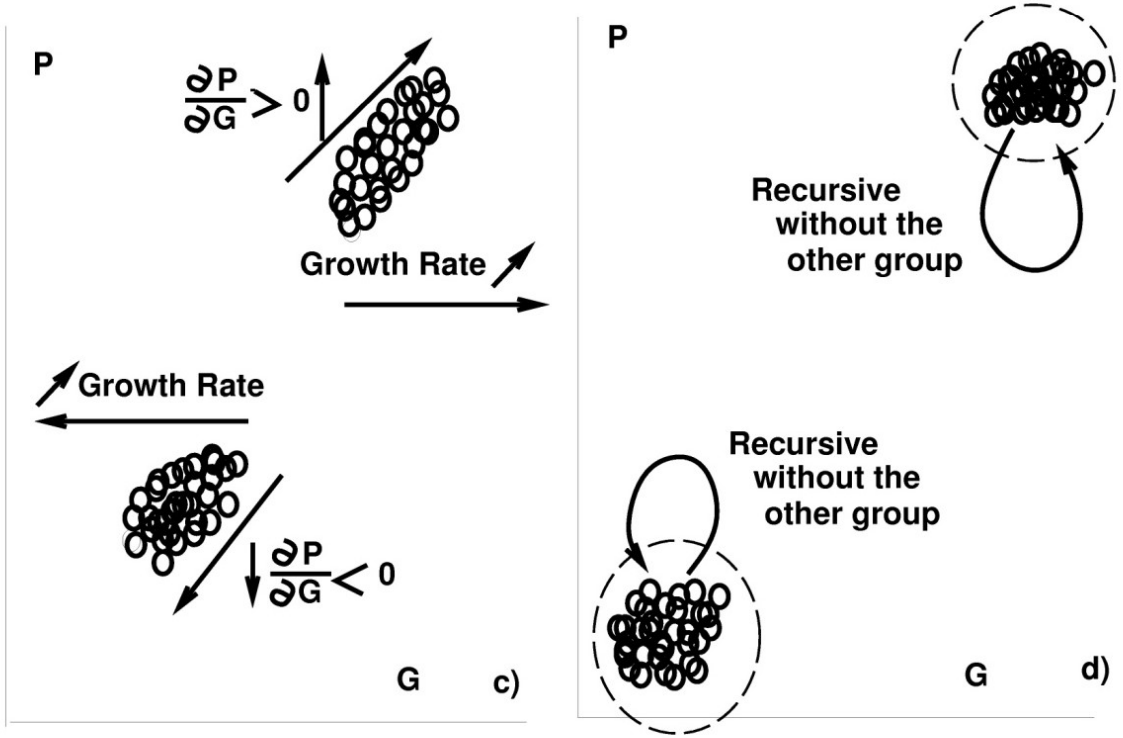
e.g., by the increase in resources

(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





Cf: pithcfork possible

$dXi/dt = aXi - Xi^3 - (\Sigma j\ Xj)^2\ Xi$

a increases with # of units