- 2nd Talk: Phenotypic Evolution

- **Evolutionary Fluctuation-Response Relation**
- **Evolution of Robustness, Genotype-Phenotype Relation**
- Sympatric Speciation as a result of phenotype differentiation
- Evolution of Development
- Spontaneous Adaptation by Noise
- Summary+Discussion

Motivation 1:Phenotypic Fluctuation →evolution?

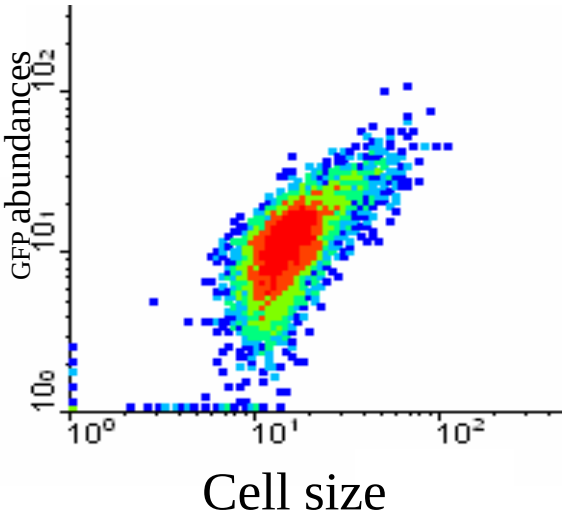
- Even in isogenic indiviudals (clones) there is large phenotypic fluctuation

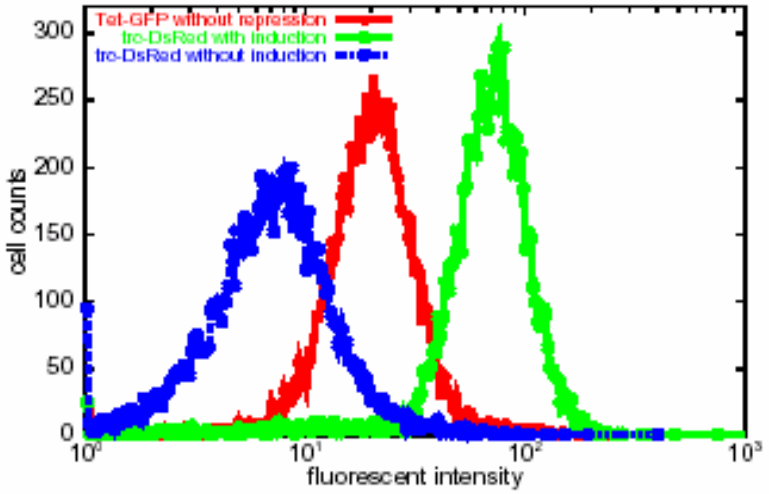
Recognized now extensively

Exp + Model+Theory

- 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

- Phenotypic Fluctuation → Relationship to Evolution?

＊Standard evolutionary genetics;

(0) selection is based on phenotype

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

Fitness(phenotype)

(i)gene a → phenotype x

→if this mapping is uniquely determined

→ Fitness(Genotype) instead

(ii) only genotype is transferred the offspring

Change of distribution P(geneotype) → evolution

But gene—``development ‘’ → Phenotype

Is not necessarily unique

Phenotypic fluctuation of isogenic organisms

→P(x; a) x—phenotype, a – gene

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

Background

(1) relationship between development and evolution,

(2) robustness increases through evolution? ---

Schmalhausen's stabilizing selection: Waddington's canalization

(3)Landscape in Geno-pheno coupling (,Ancel-Fontana.Wagner,.,)

Motivation 1 and2, combined:

- (A)Plasticity, Potency, Flexibility, (Robustness), Evolvability …. Traditional concepts

Ambiguous Concepts; Often Explained only Verbally but probably important biologically (as an organism level)

* (B) Quantitative Biological studies on dynamics and fluctuations: Progresses rapidly recently

- Still Large Gap between (A) and (B);
- Especially when (A) concerns with macroscopic biological characteristics

Need to fill the gap

(cf: stat mechanics is constructed after establish-ment of thermodynamics to be consistent)

Plasticity Measure

--- changeability (response against external change)

--- related with

degree of fluctuation ?

(negatively correlated with) robustness

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)

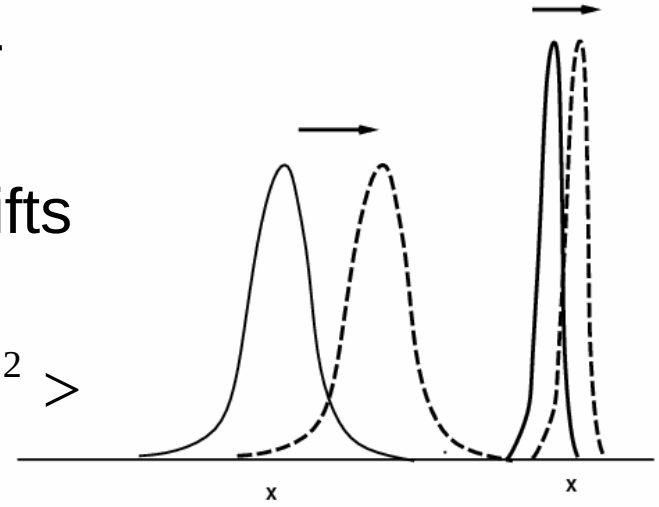
response ratio of some variable x against the change of parameter a versus fluctuation of x

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

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

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

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

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； trivial by itself

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

x：phenotype a；enviroment etc

- General Viewpoint:

  x: phenotype (variable)

  a: genotype (parameter)

parameter→ variable: condition （1）

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) under given environment h

Environment h change to select ‘a’ value

selection → change in P(x;a)

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

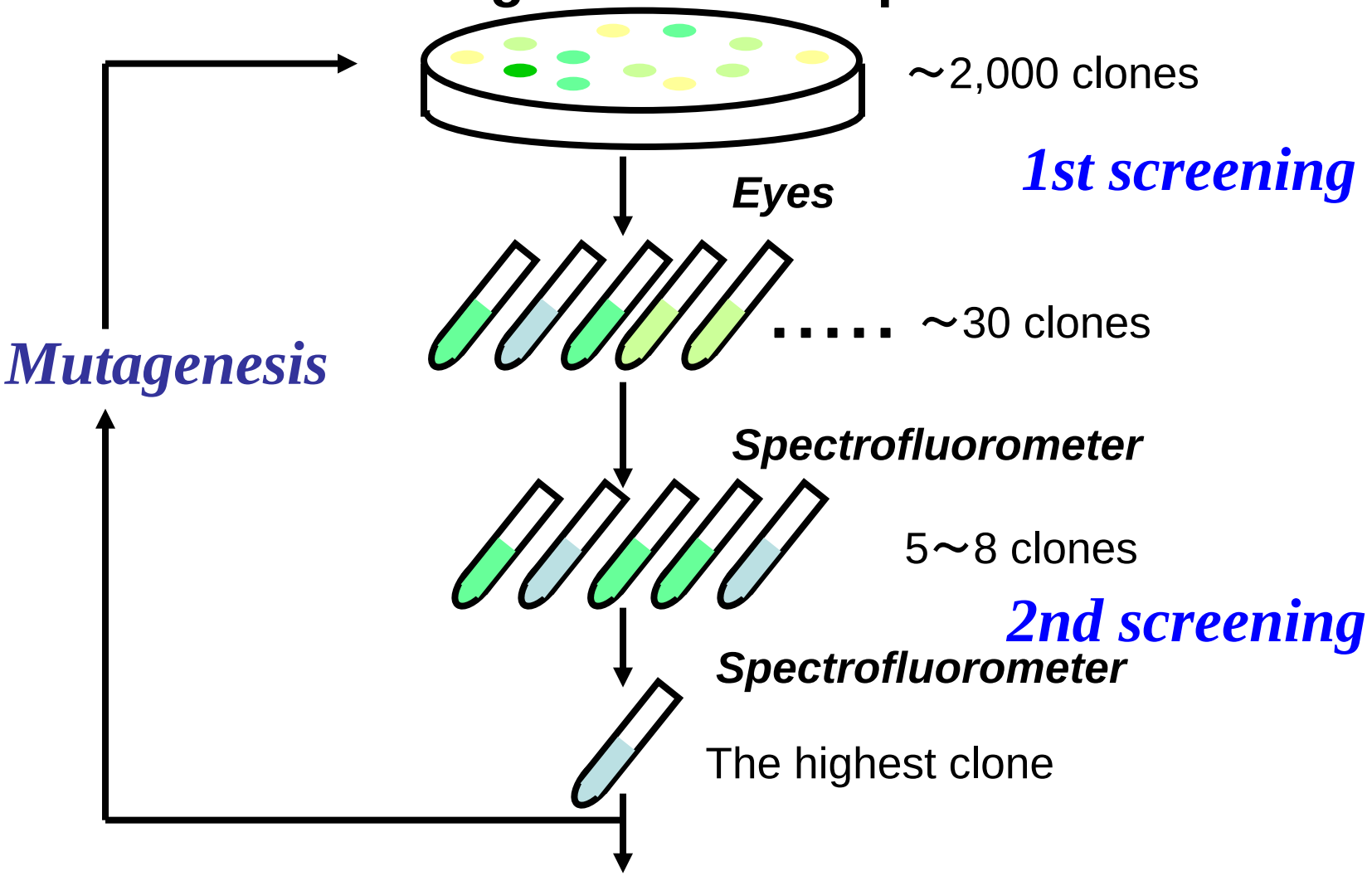
⇔ speed of evolution to increase <x>

(proportional or correlated)

Artificial selection experiment with bacteria

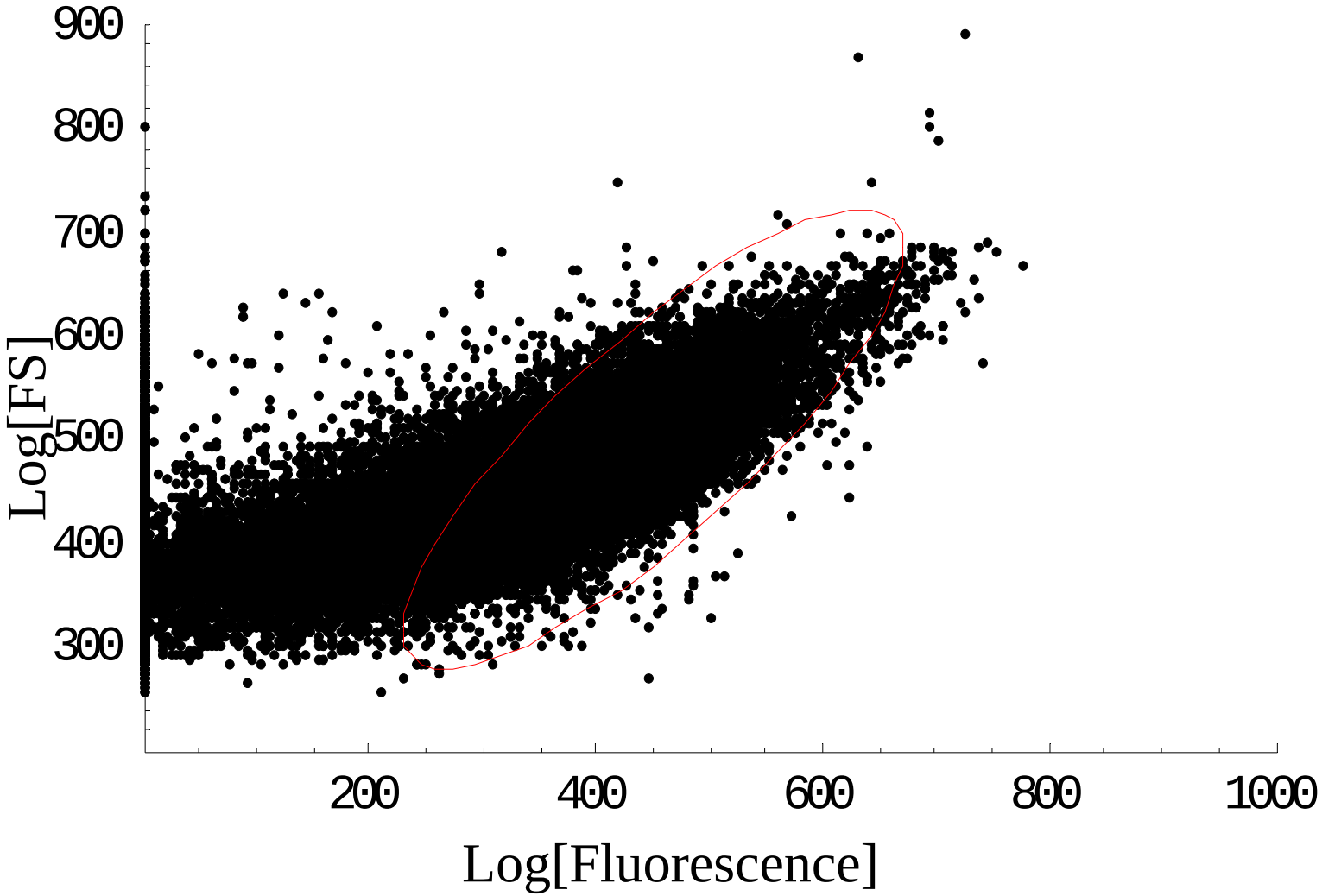
Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process

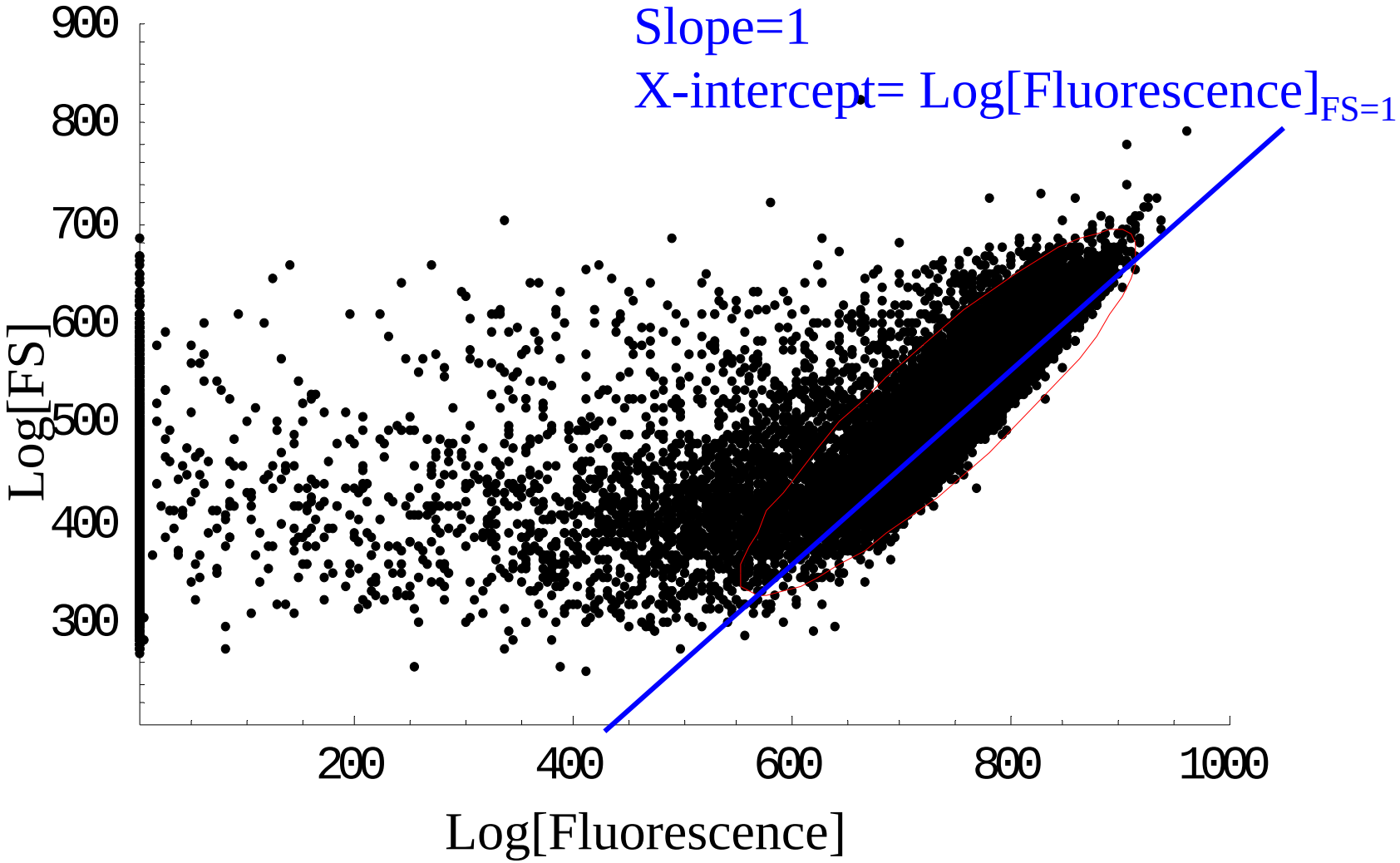


Ito,Yomo,..

RP-334Log.LMD



I10-6Log.LMD


Slope=1
X-intercept= Log[Fluorescence]FS=1
900
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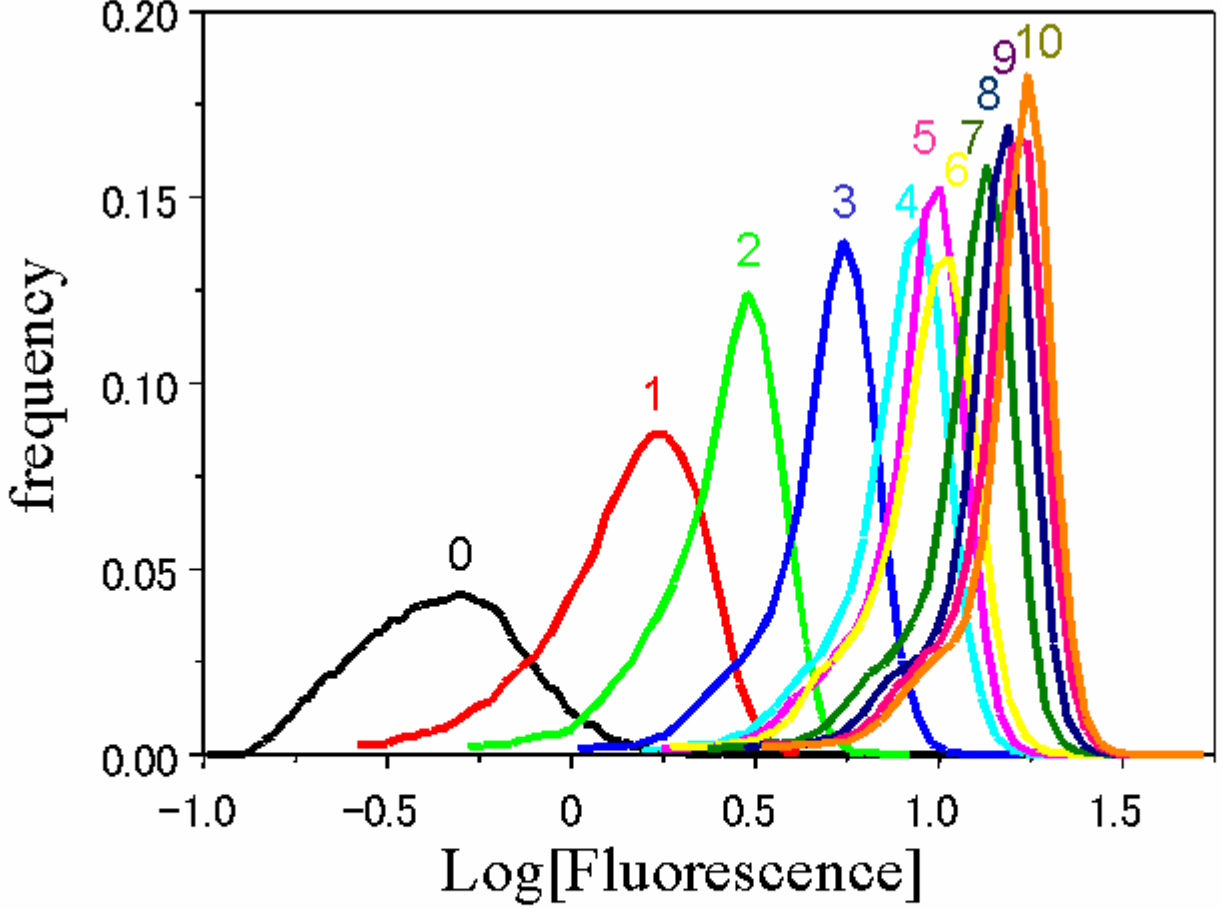


Sato,Ito,
Yomo,KK
PNAS(2003)

Fluctuation ---- Variance of phenotype of clone

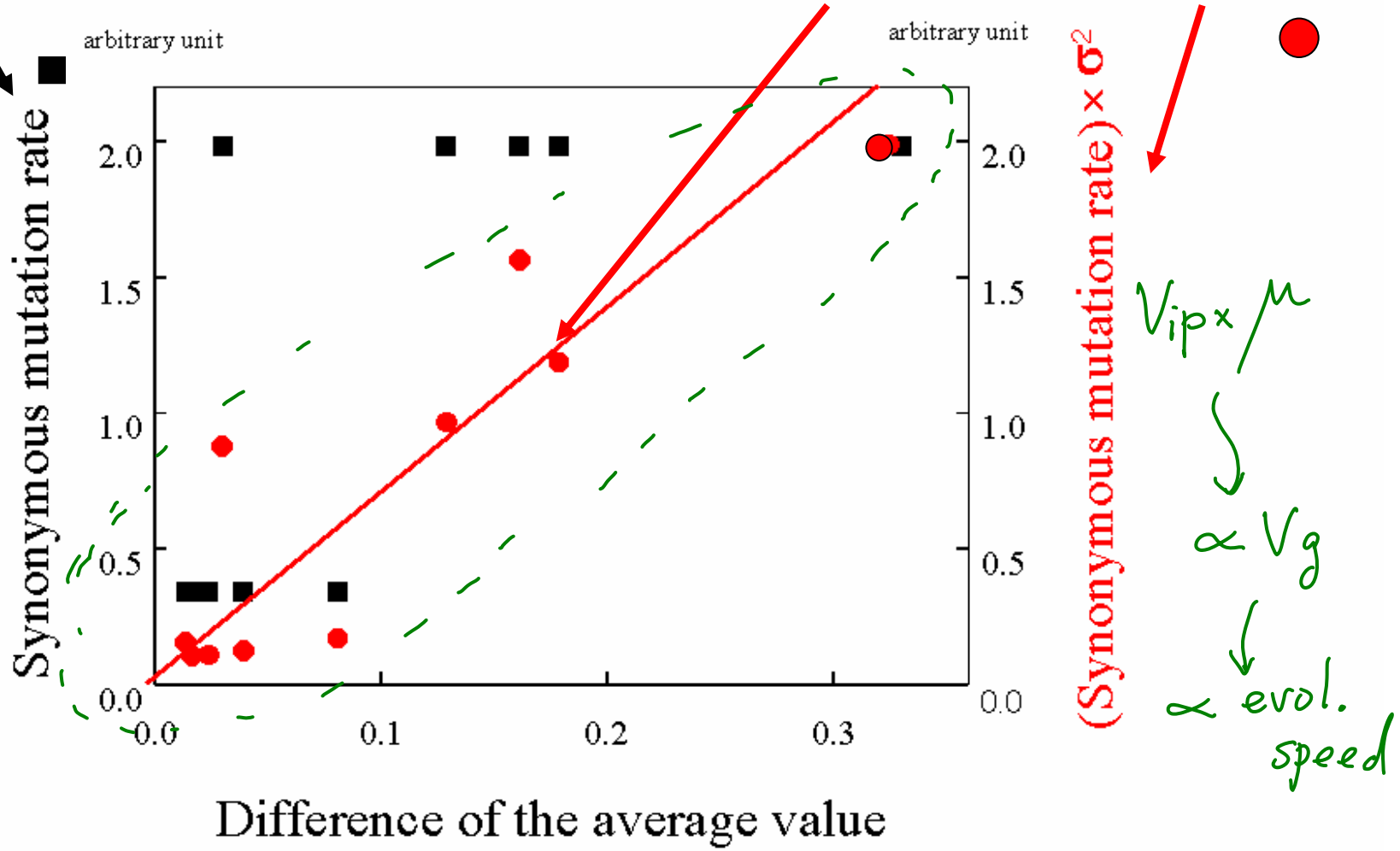
Organisms with larger phenotypic fluctuation higher evolution speed;

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

Response ←→ Fluctuation

Naïve expectation:
Just propt to mutation rate

Fluctuation-response relation
Phenotype fluct. × mutation rate



(Evolution Speed per generation)

Sato,Ito,Yomo,KK, PNAS 2003

Cofirmation by model:
Toy Cell Model with Catalytic Reaction Network

C.Furusawa & KK

- **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

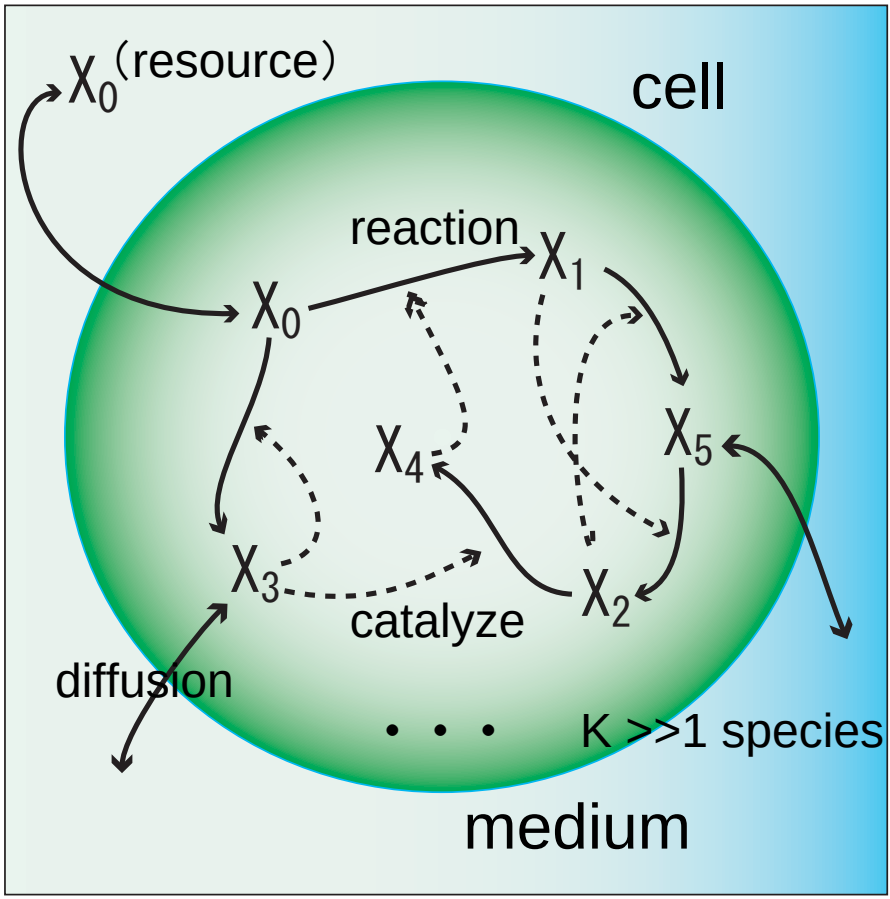
for the reaction $X_i + X_j -> X_k + X_j$

- 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

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

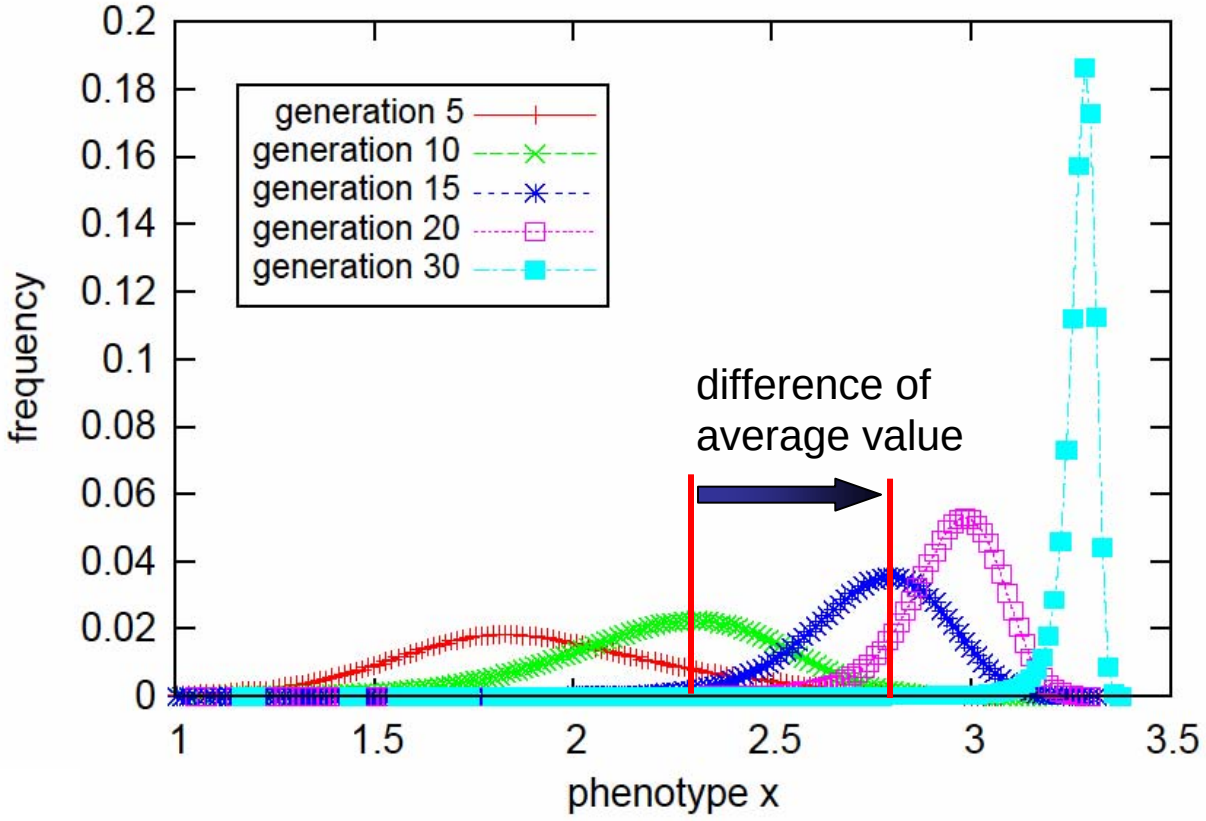
Mutate the network (‘gene’) with mutation rate μ , (rewire the path of the network with the rate) and select such network having highest concentration c of a specific chemical

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

phenotype x = log (n_s)

Fluctuation of Phenotype x

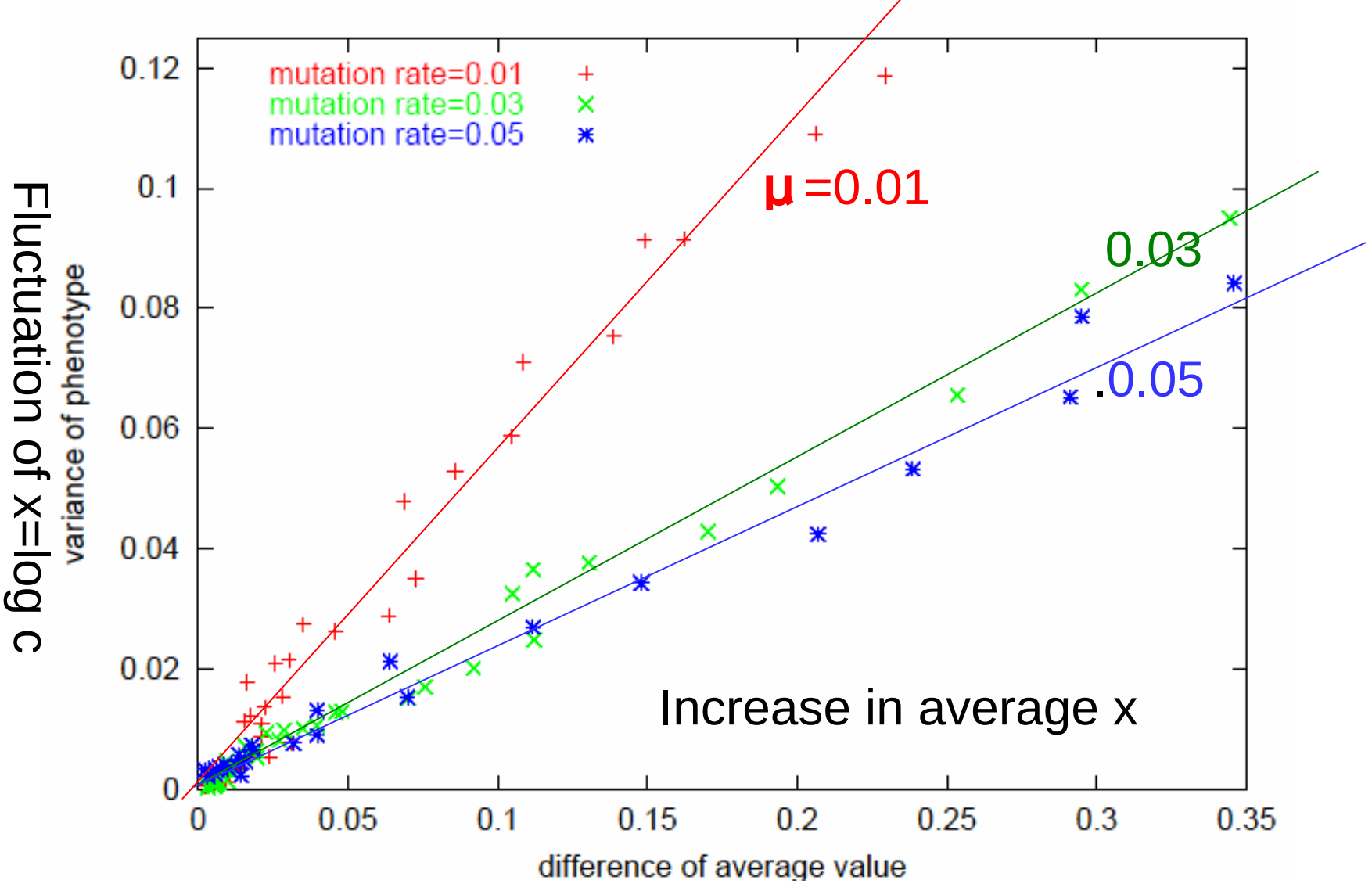
Change of distribution of phenotype x through evolution



Prepare 10^5 clonal cells (having an identical network)

Distributions of phenotype x are plotted.

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

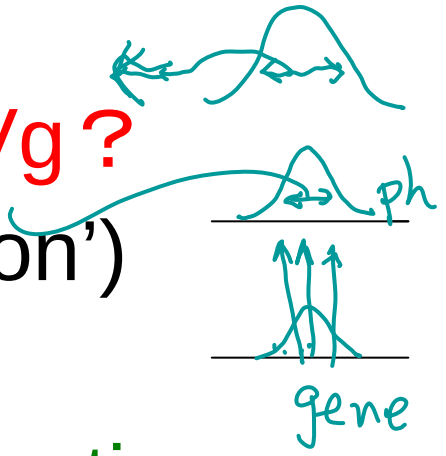
(2)　New mystery？ phenotype fluctuation of clone　vs　evolution speed in contrast to

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

pheno fluct of clone Vp

∝ pheno fluct by gene variation Vg？

（fluct by noise ∝ variation in ‘equation’)

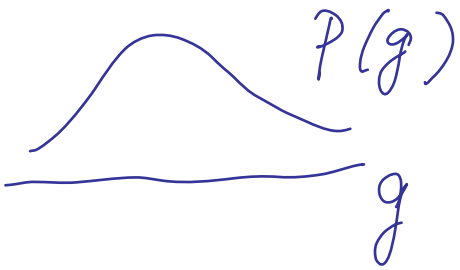


Follow the spirit of Einstein；

micro-macro consistency→Brownian motion

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

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



distribution $P_n(g)$

(growth rate ~fitness)

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

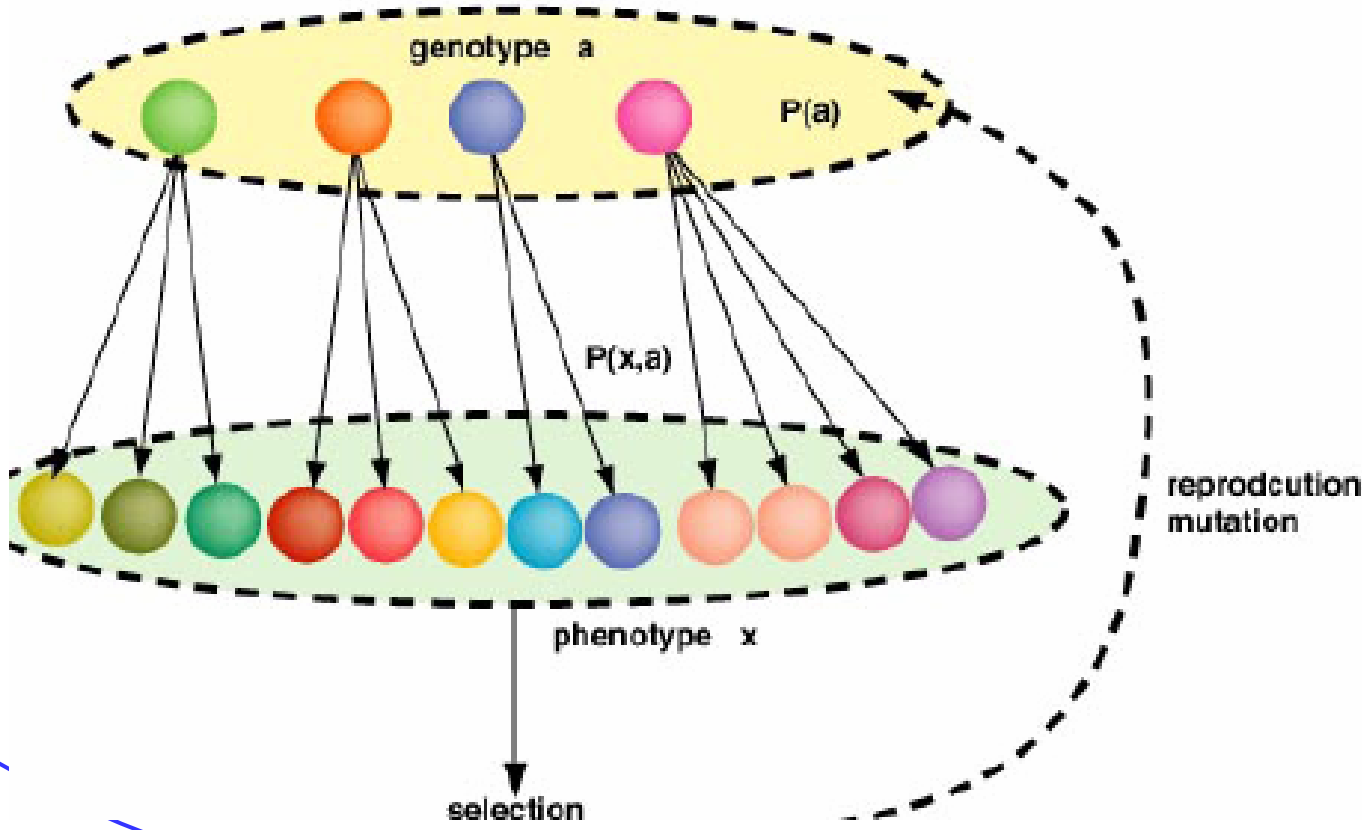
$$P_{n+1}(g) = \frac{g P_n(g)}{\int g P_n(g)\, dg} = \frac{g P_n(g)}{\bar{g}_n}$$

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

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

(Fisher ?)

consistency



isogenic phenotypic fluct.

genotype (same)

(a)

genotype (distributed)

V_{ip}

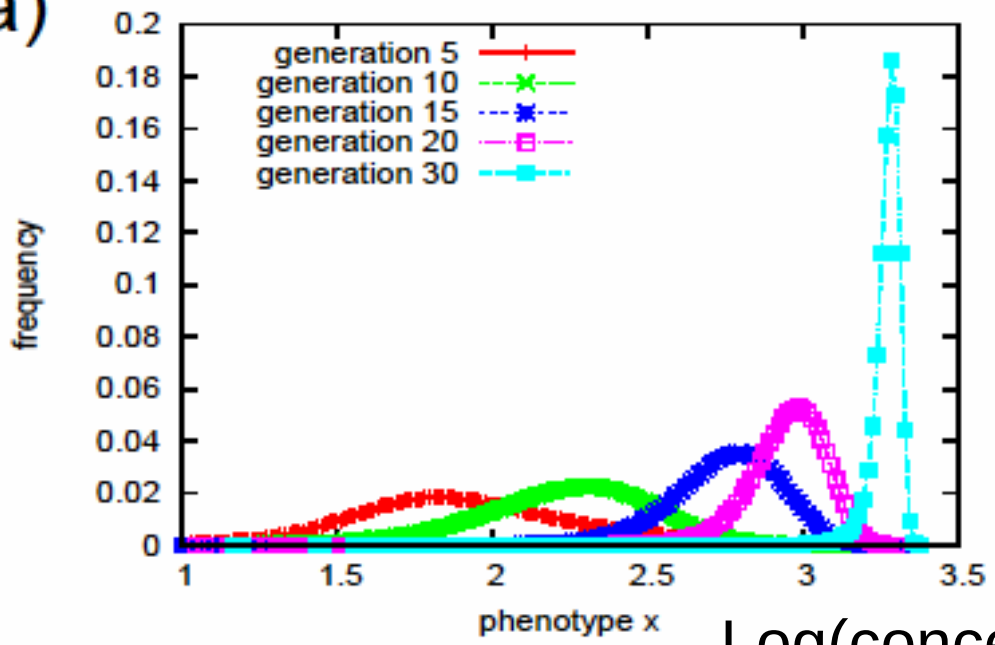
phenotype x

V_g

$V_g \leftrightarrow$ evolution speed

? V_{ip} ??

(a)



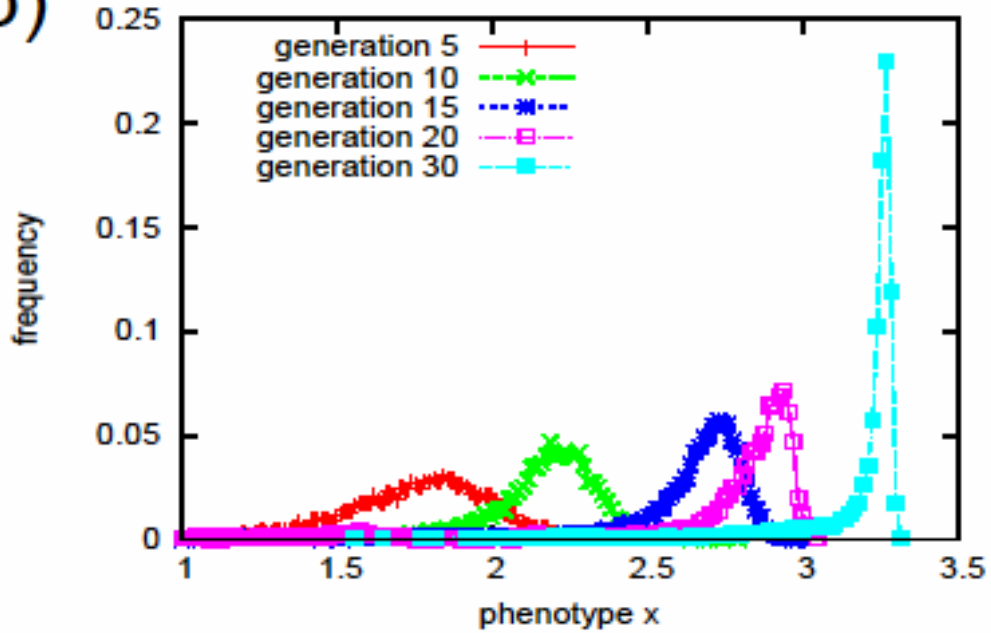
Change of distribution through evolution

Distribution of phenotype x of a clone

→ Vp

Log(concentration)

(b)

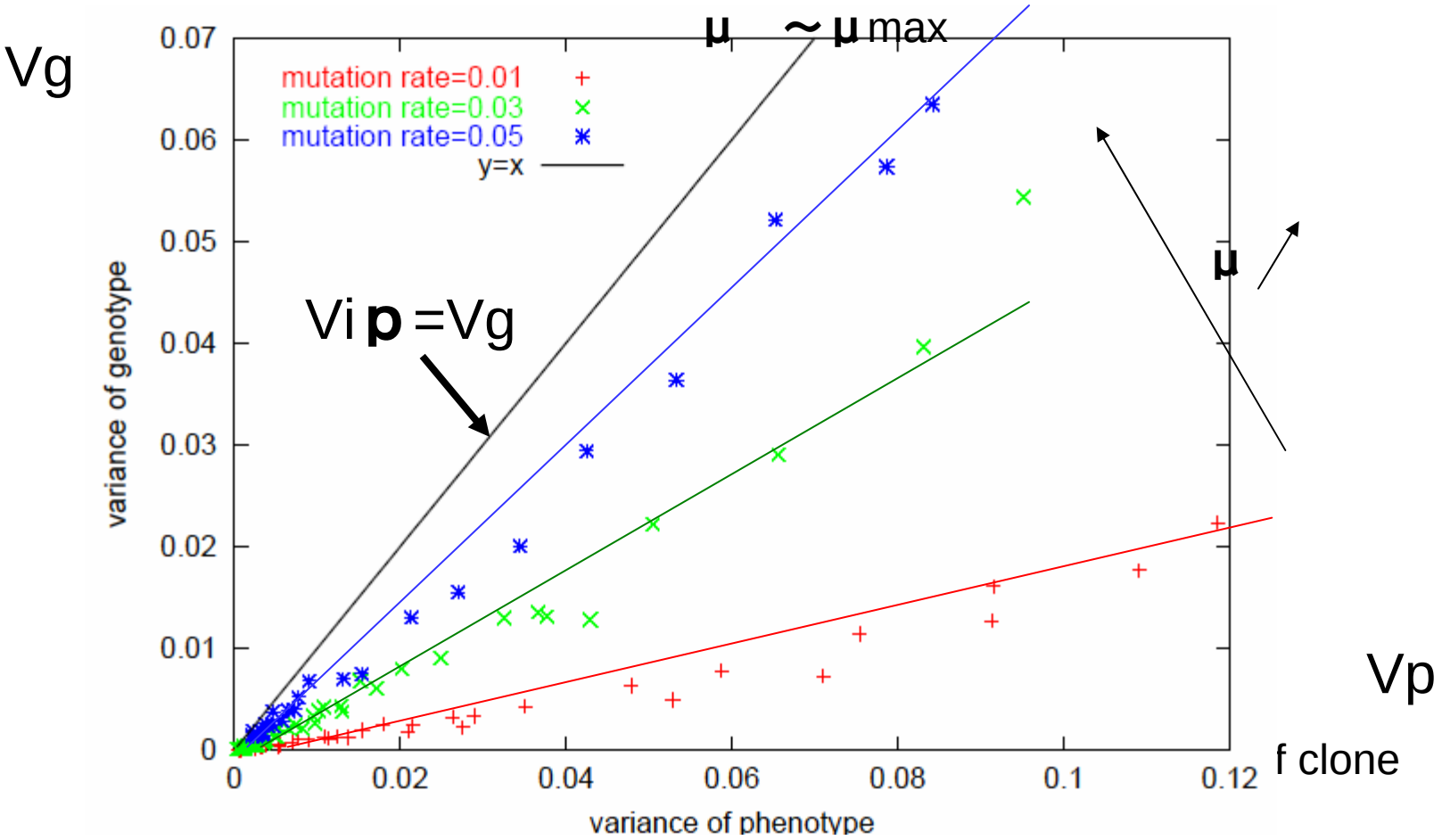


Distribution of phenotype x over mutants (genetic variation)

→ 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)

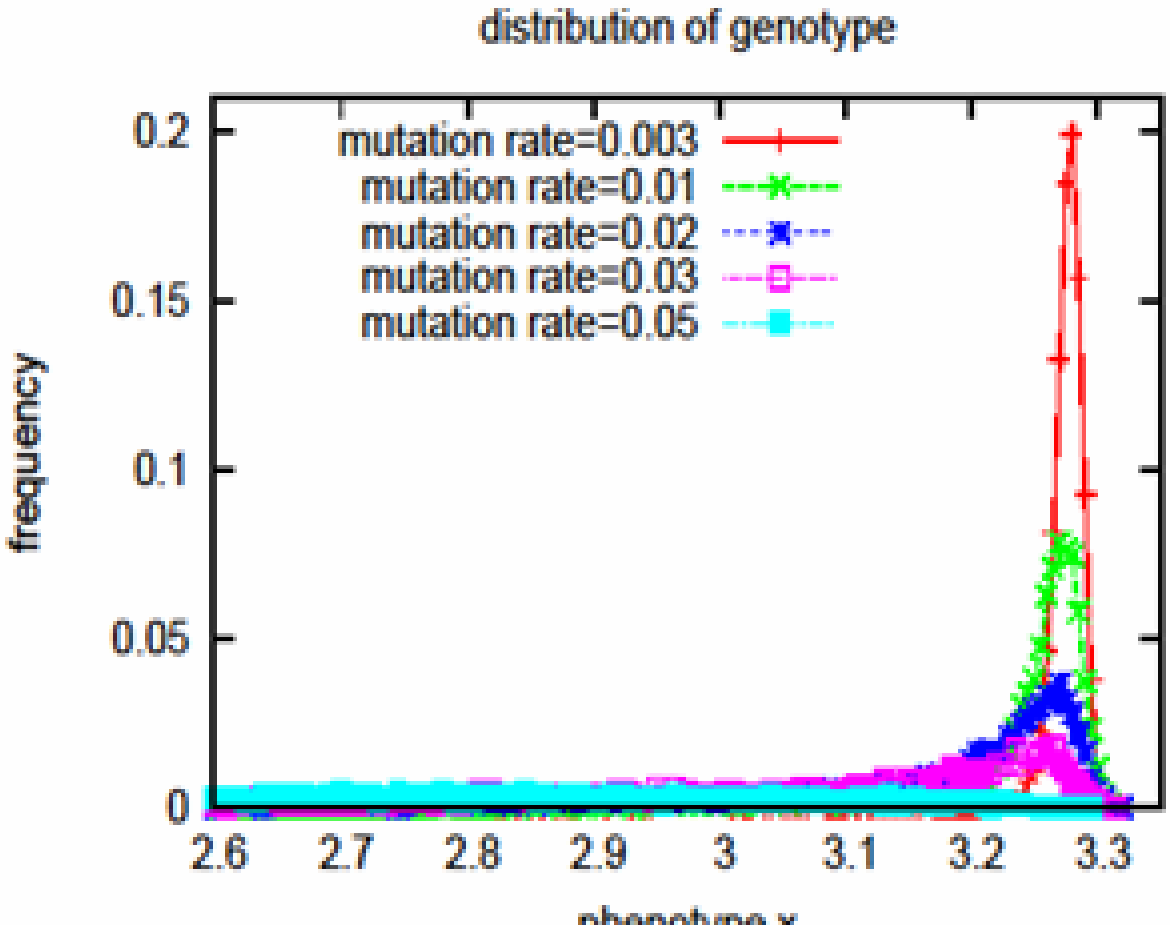
(2) evolution no longer progresses beyond μ max

evolution speed is maximal at μ ~ μ max

(3) Vg approaches Vp

As μ is increased,
The distribution
'collapses'

Error catastrophe



Consider 2-variable distrb

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

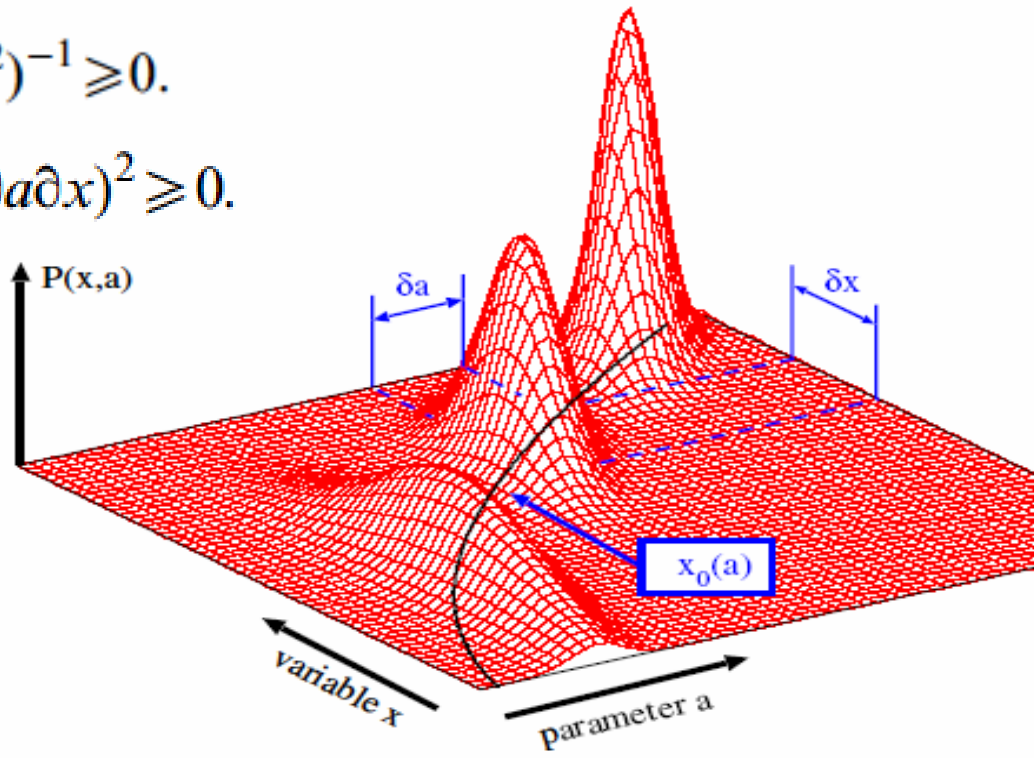
Keep a single-peak (stability condition).

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?

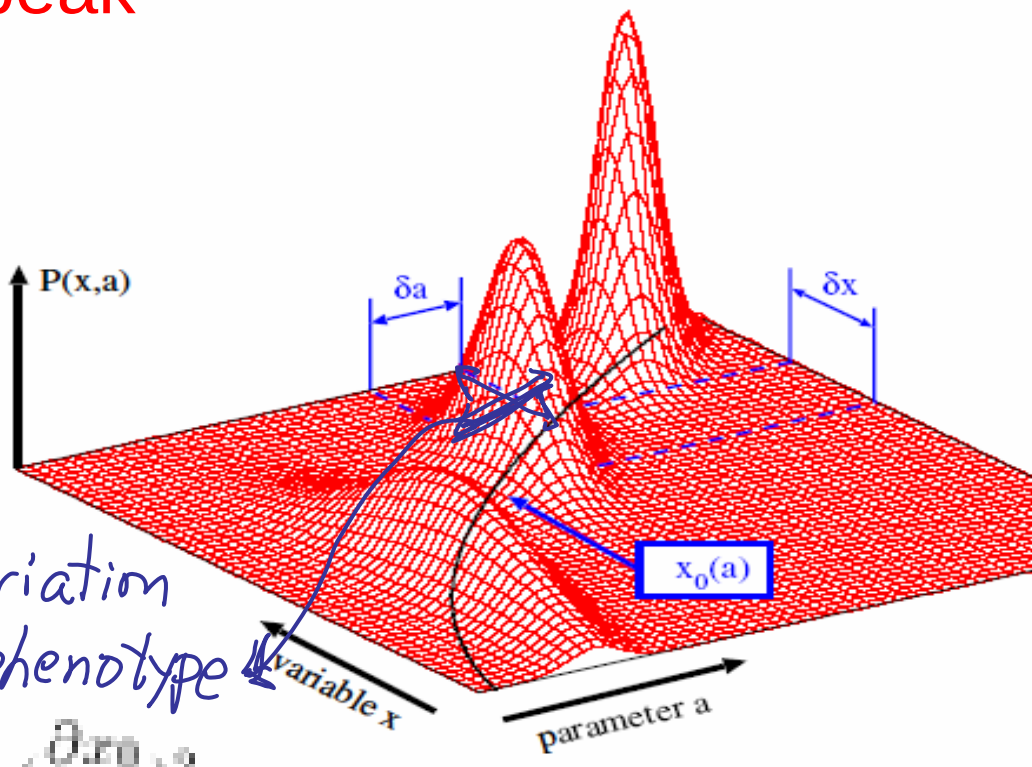
Consider P(phenotype,genotype) distribution P(x,a)

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

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

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

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

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

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

= Ave over all populations

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

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

From Stability condition -→ Vip $\gtrsim$ Vig 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

$$Vg \approx Vig \approx \frac{\mu}{\mu_c} Vip$$

$$\Rightarrow \quad \mu Vip \propto Vg \propto \text{evolution speed}$$

consistent

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

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

(where the evolution does not progress)

(iii) $Vg \sim (\mu / \mu max) Vip \propto \mu Vip$

（∝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

- **??? 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?

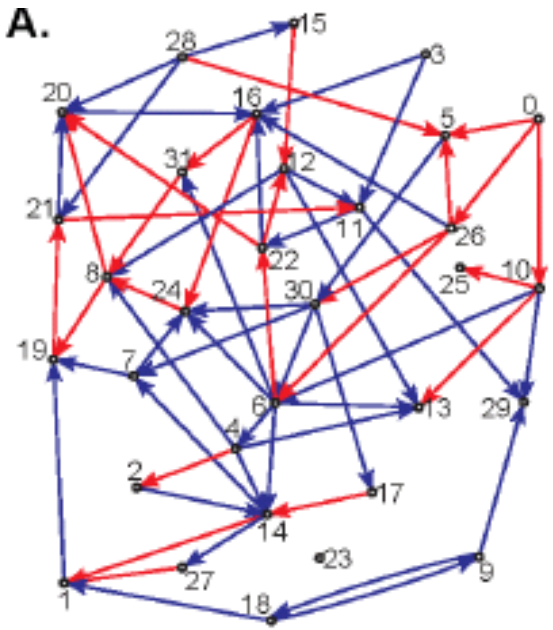
Robust evolution is possible only under noise

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

→ gene-net model

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

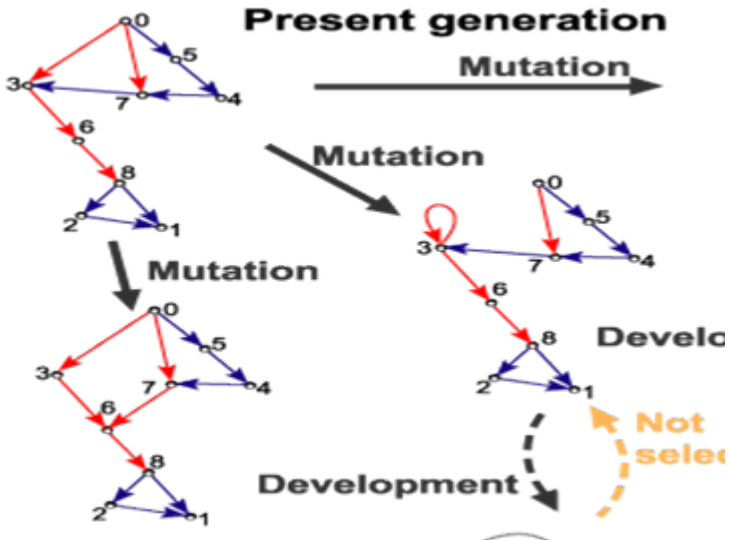
- Fitness: Starting from off of all genes, after development genes xi i=1、2、・・・、k should be on （Target Gene Pattern)

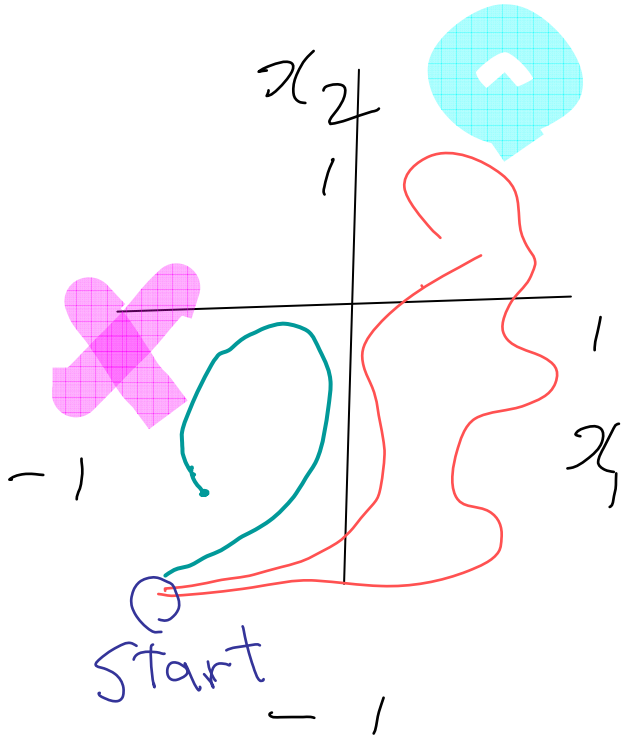
Fitness F= －（Number of off x_i）

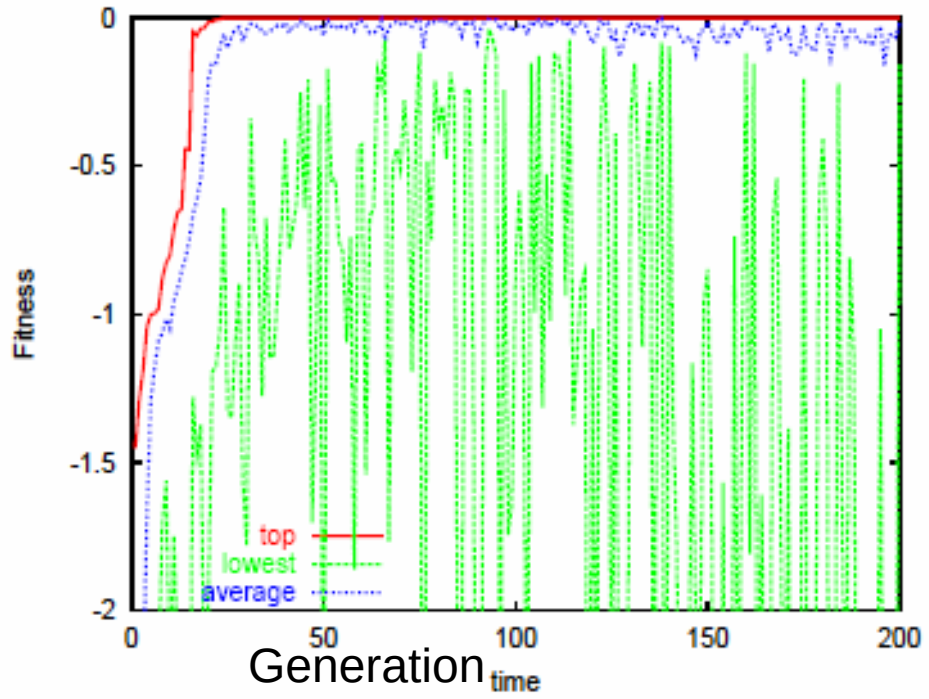
Genetic Algorithm

Mutate networks and Select those with higher <F>

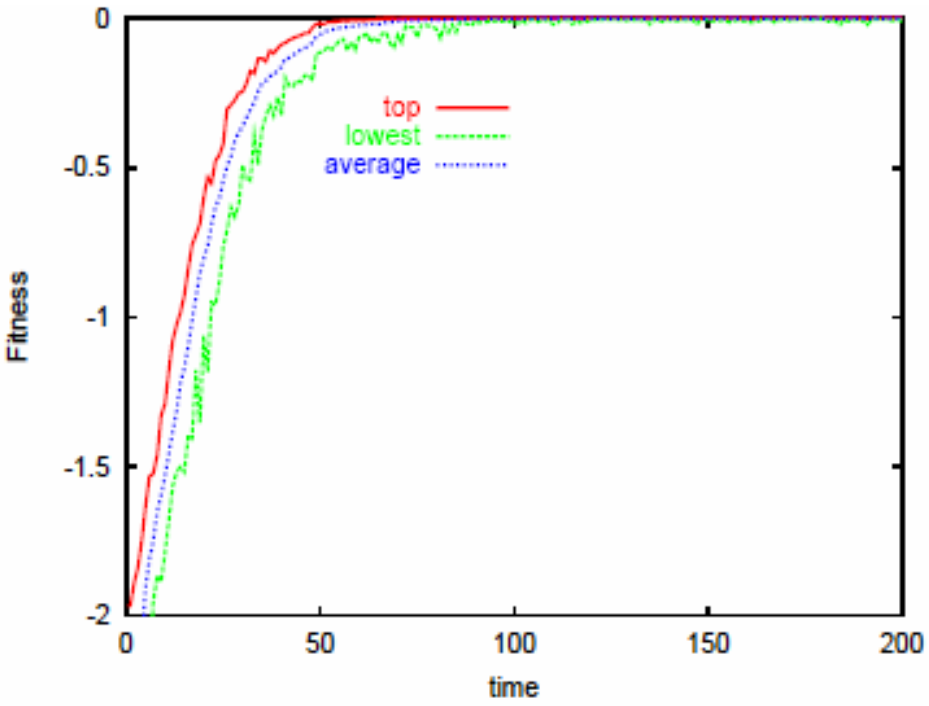
Choose top n networks among total N,
and mutate with rate μ to keep N networks





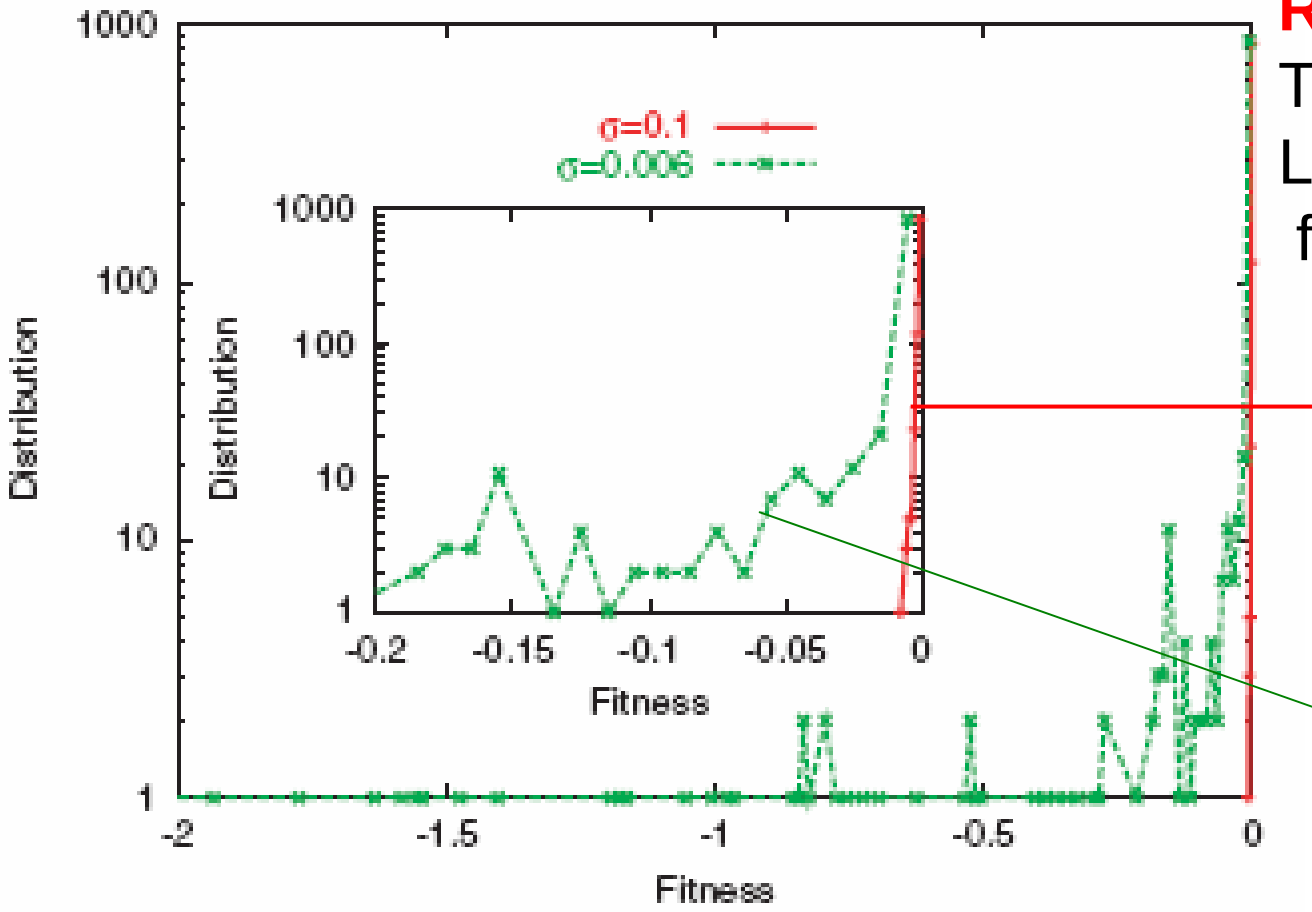


Generation



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**)

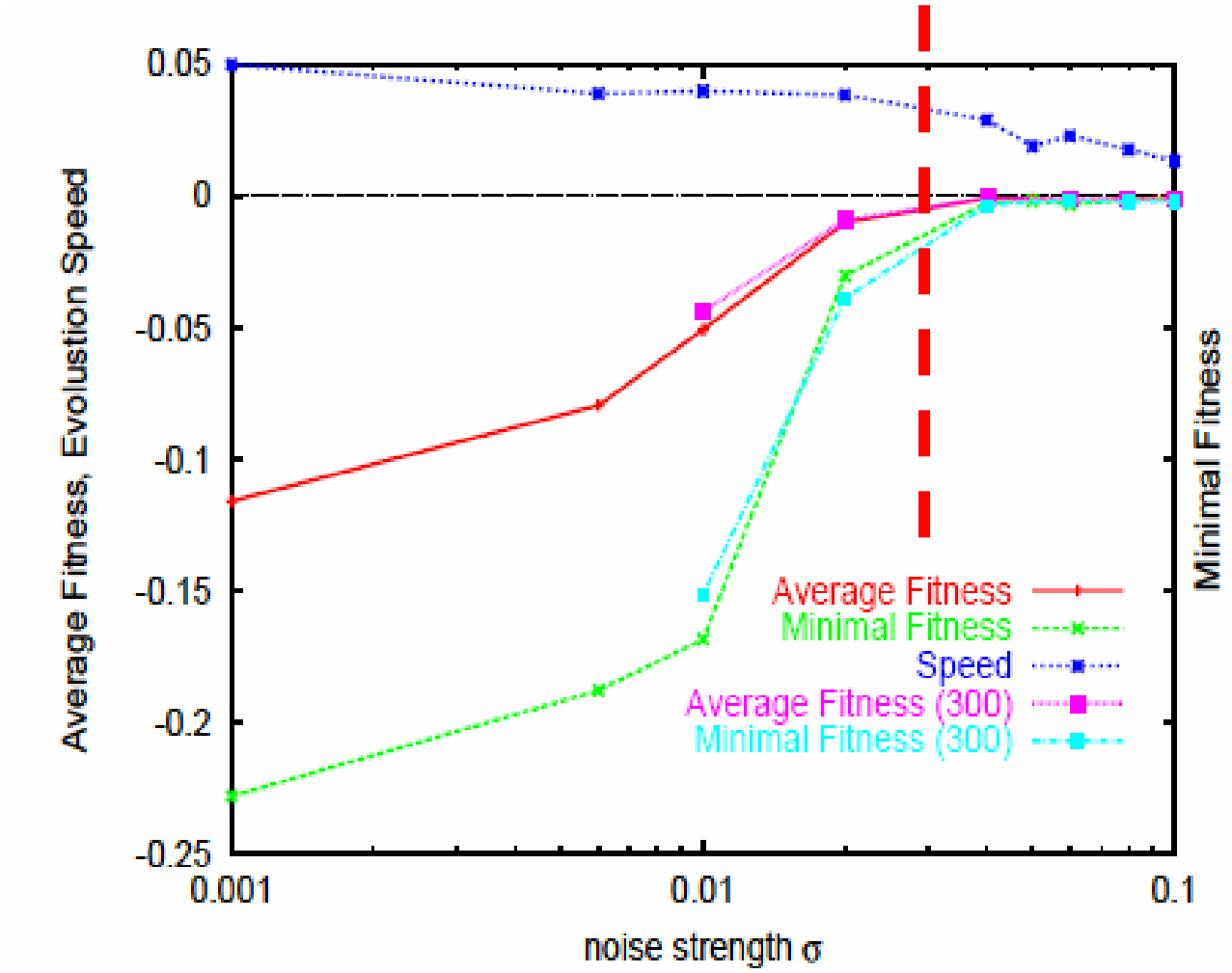
$\sigma > \sigma_c$

σ＜σ c

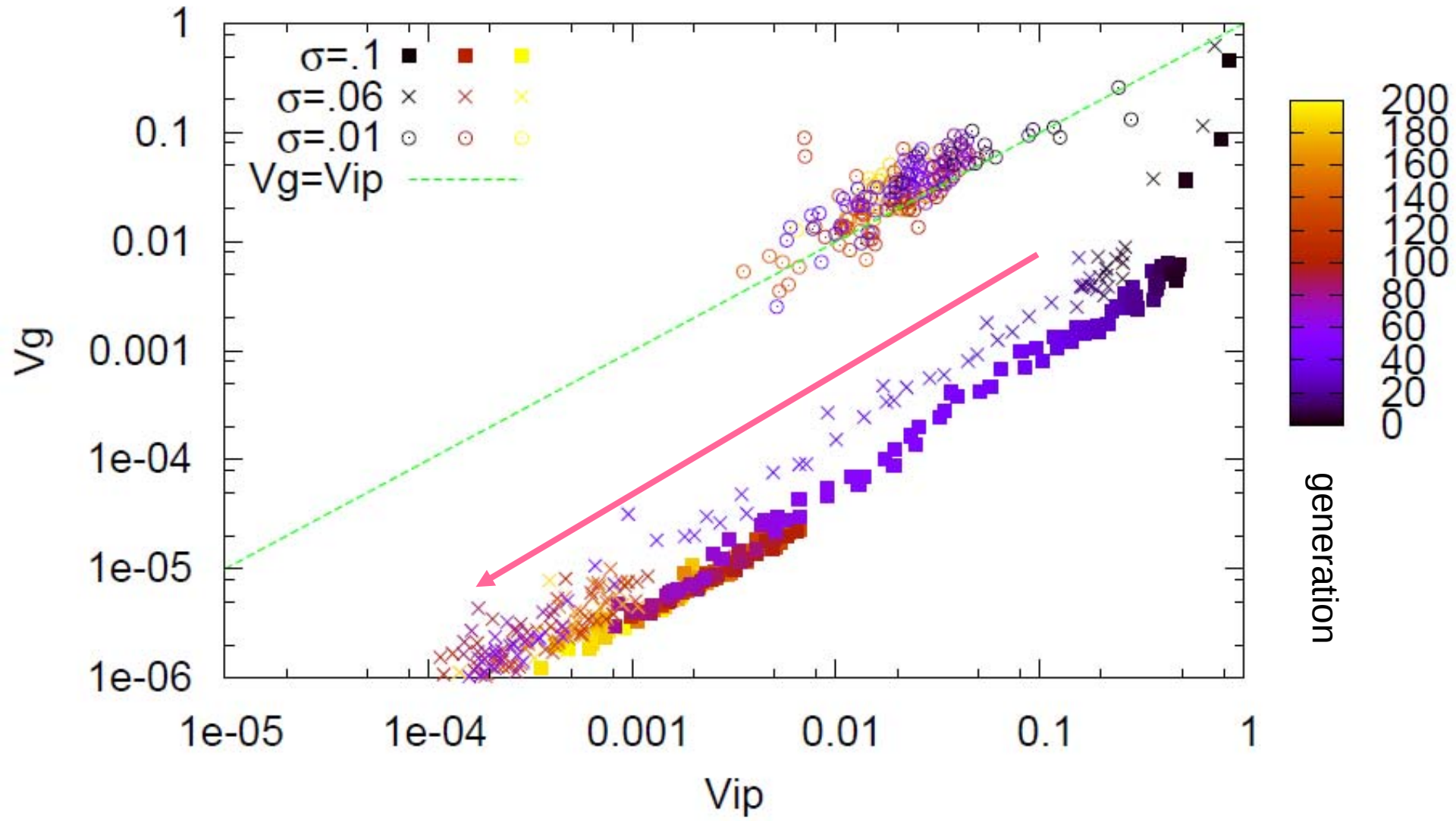
Fitness Distribution

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)


σ=.1
σ=.06
σ=.01
Vg=Vip
Vg
Vip
1
0.1
0.01
0.001
1e-04
1e-05
1e-06
1e-05
1e-04
0.001
0.01
0.1
1
generation
200
180
160
140
120
100
80
60
40
20
0

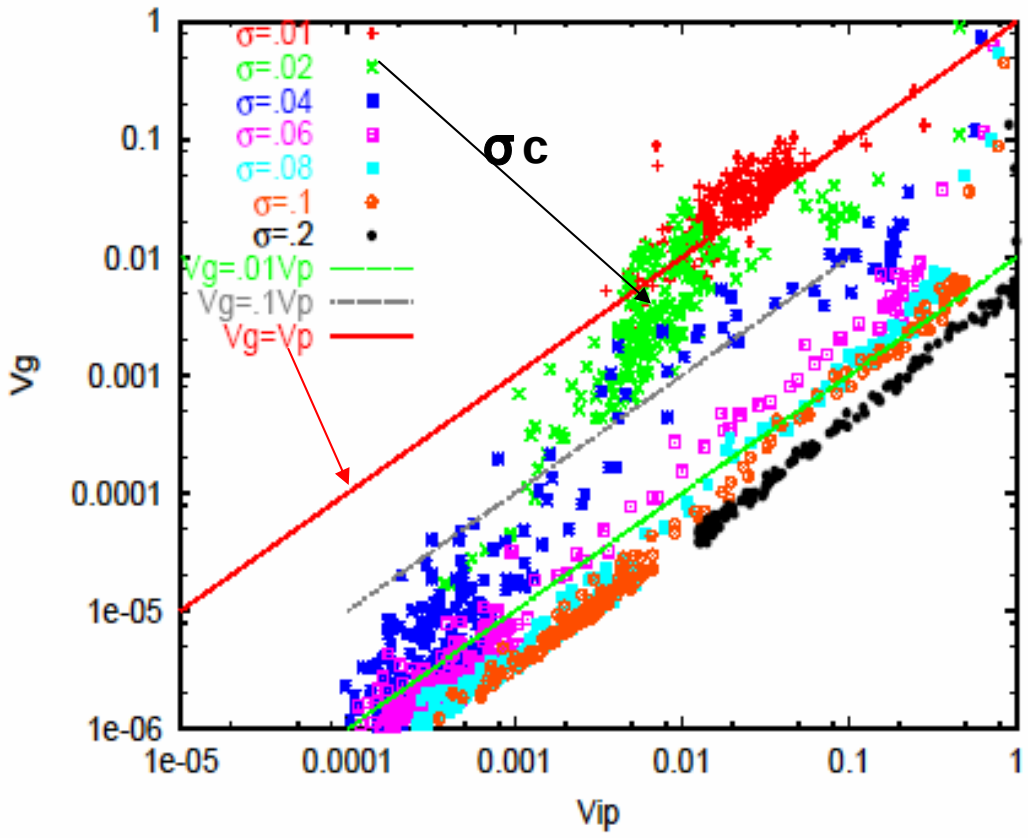
(1) $Vip \geqq Vg$ for $\sigma \geqq \sigma c$

(2) $Vg \rightarrow Vip$ as $\sigma \rightarrow \sigma c$

(3) evolution progresse only for $Vip \geqq Vg$

(4) $Vip \propto Vg$ through evolution course

Theory confirmed



KK,PLosOne,2007

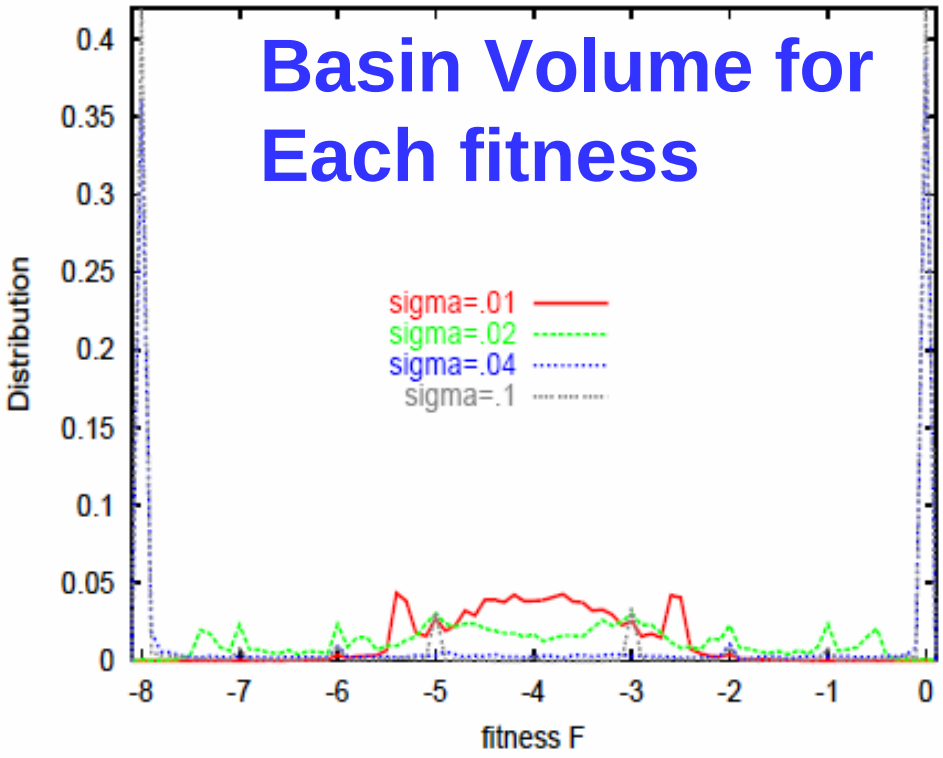
Why?; difference in basin structure

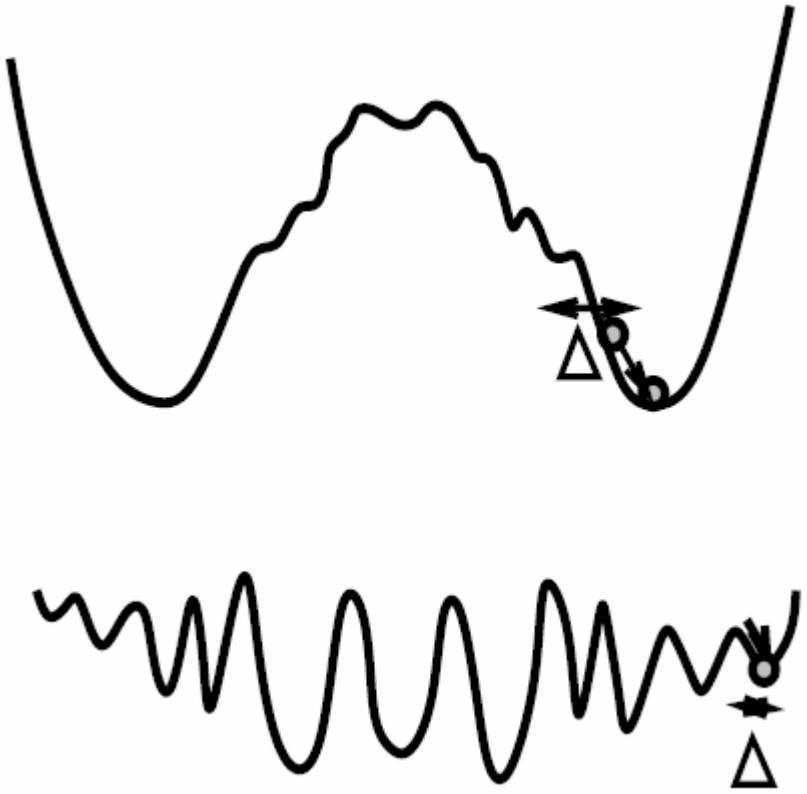
σ＞σc → large basin for target attractor

(robust, Δ（distance to basin boudary) ↑

σ＜σc → only tiny basin around target orbit

Δ remains small





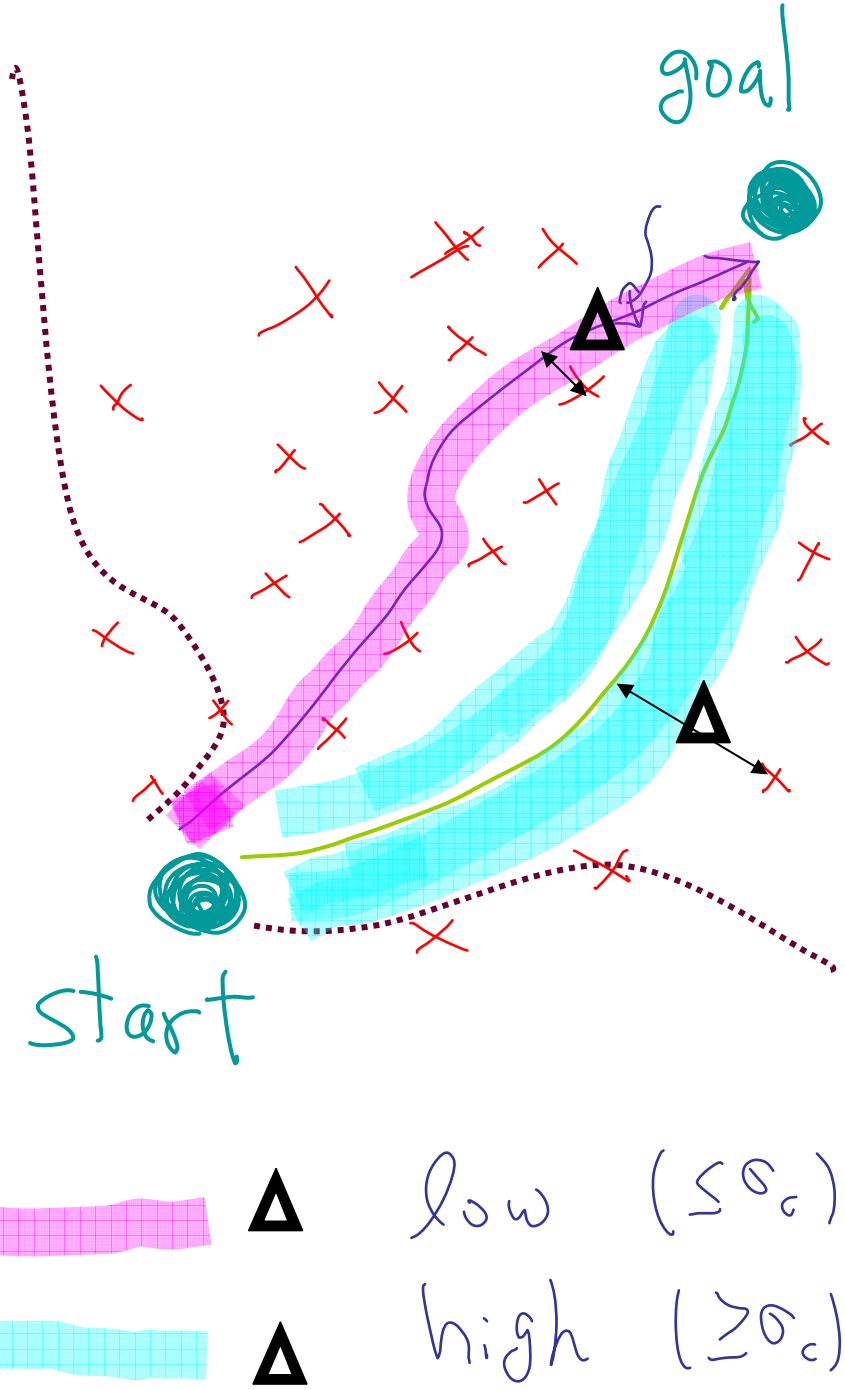
→Global constraint to potential landscape(funnel?)

why threshold?

choose paths to avoid turning pts within σ (noise)

Mutation→ touches turning points within range of μ

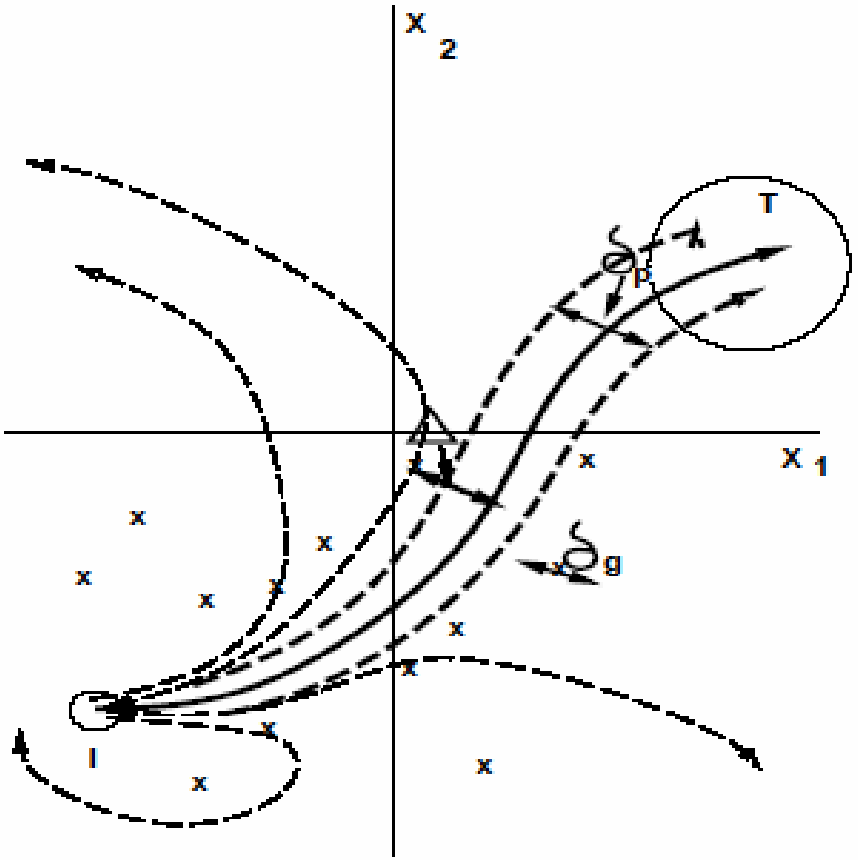
small σ −>
an orbit with small Δ
can reach the target



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

Vg ~ （δg/Δ）^2
Vip ~（δp/Δ)^2

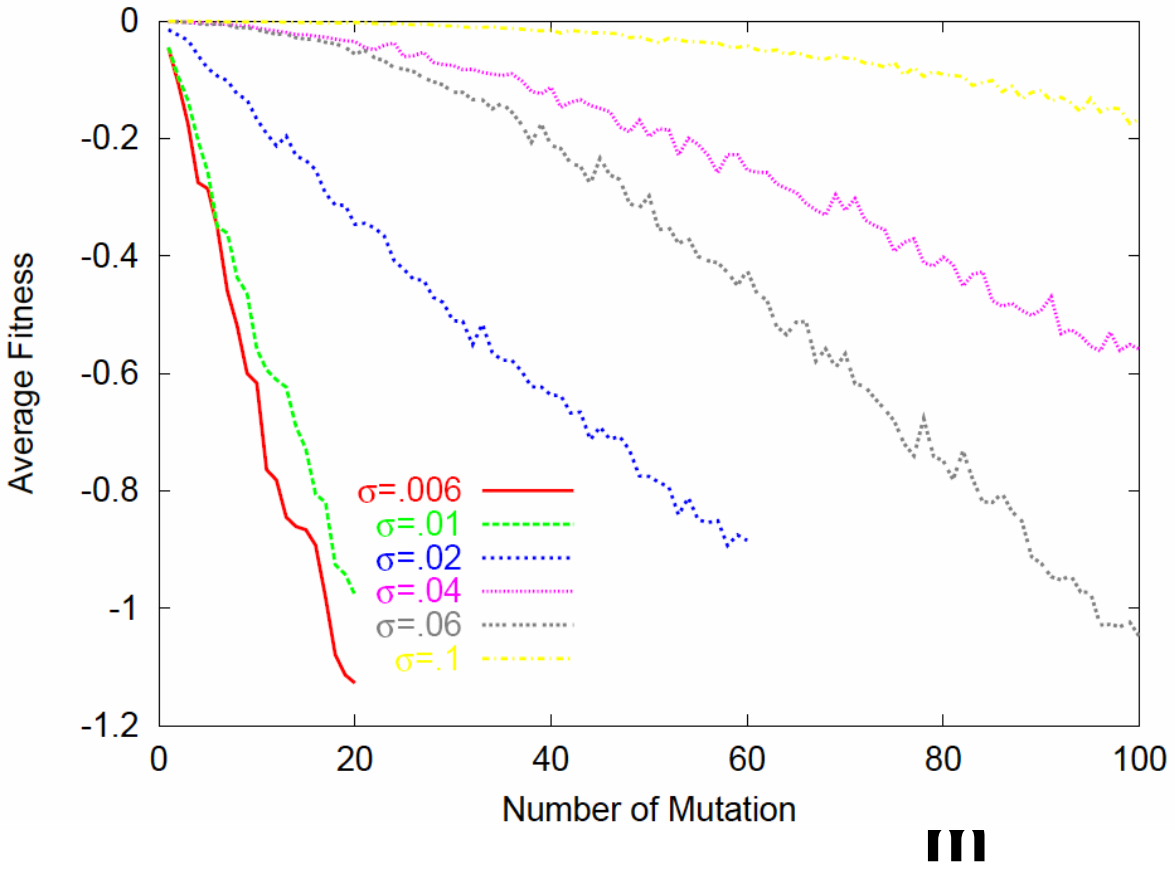
Δ increases
－－＞robustness
increases
if δg＞δp,
mutation destroys
the history
→Vip>Vg necessary
for evolution of robustness



Δ~distance to turning points
(basin boundary)

- Genetic robustness is increased for network evolved under higher noise
- Increase in genetic robustness to mutation

fraction of fitted state for n-mutants



F=-c(σ) m ;
C(σ)>0 if σ<σc
C(σc) =0

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

Noise is necessary for evolution of robustness

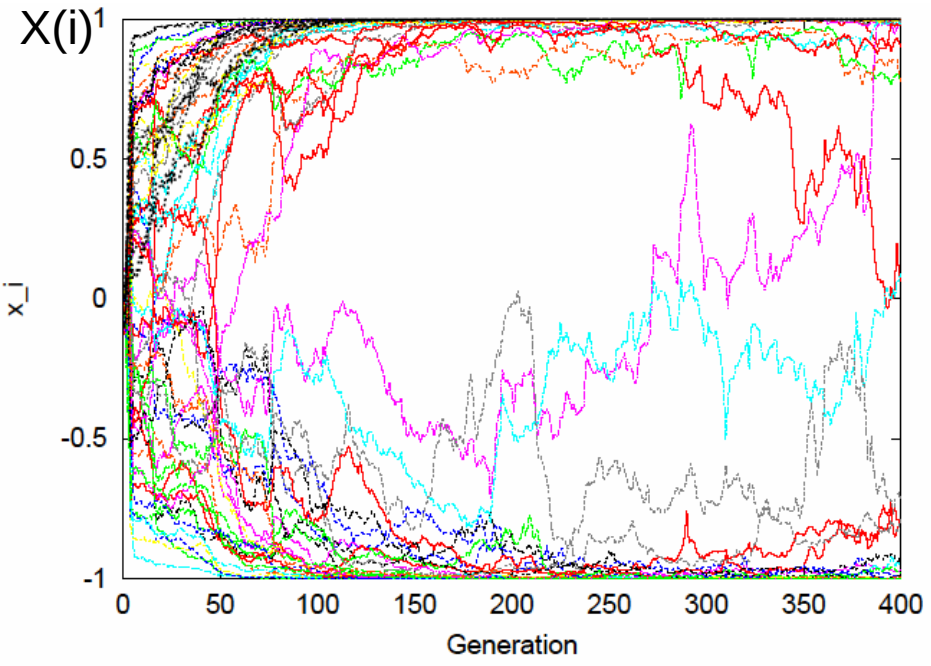
Vip $\propto$ Vg →Developmental robustness and genetic (evolutionary) robustness are linked (or embedded)
WADDINGTON genetic assimilation

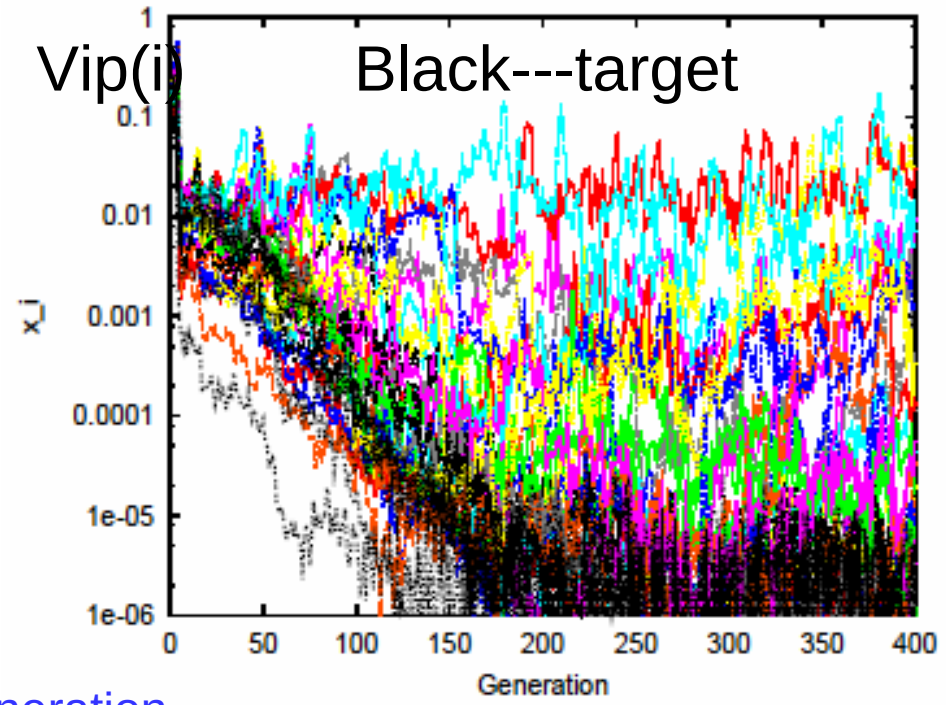
(cf. Ancel-Fontana J ExpZoolB 2000

A Wagner et al, PLoS Comp Biol 2007)

Formation of smooth dynamics；how？

Consolidation of non-target gene expressions



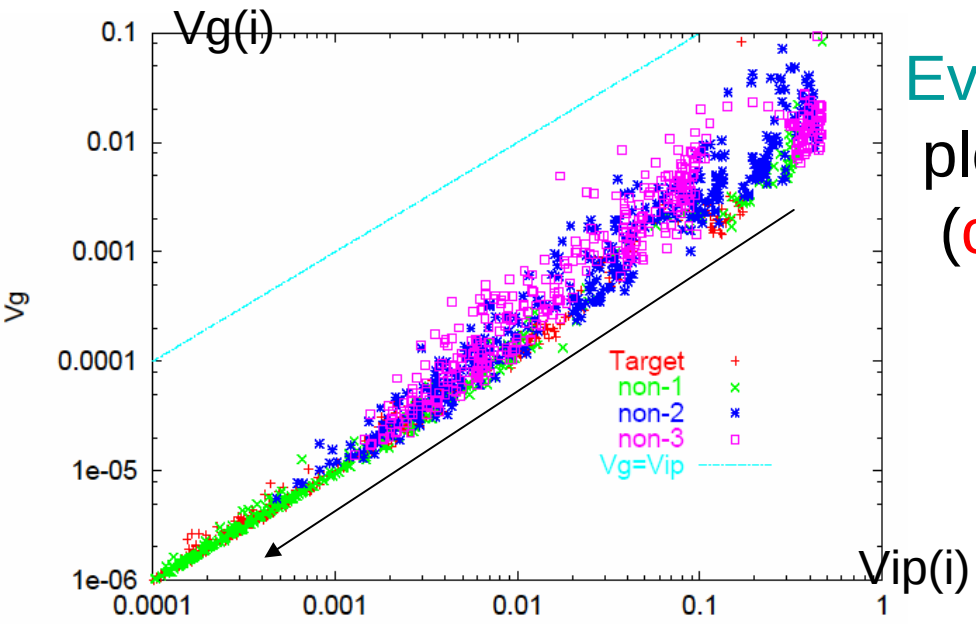


Generation

Expression of many non-target gene expressions are fixed successively:

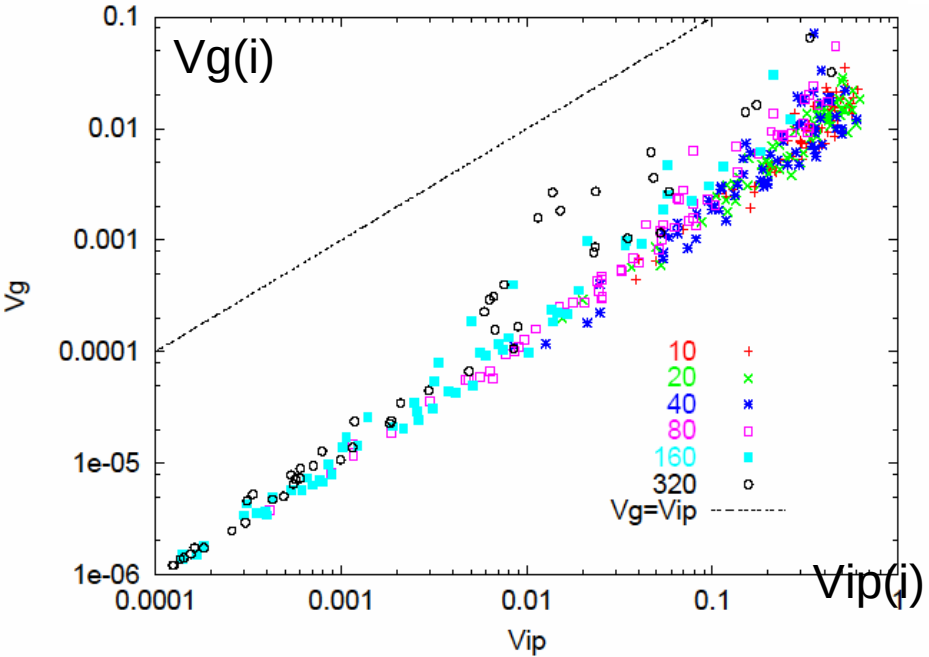
-- variance of many gene expressions i - genetic Vg(i) & epigenetic Vip(i) decrease successively ;

Further Surprise; Universal relationship over all genes?



Evolutionary course of (Vip(i),Vg(i)) plot for several genes I (color –different gene i)

Approaches proportionality relationship

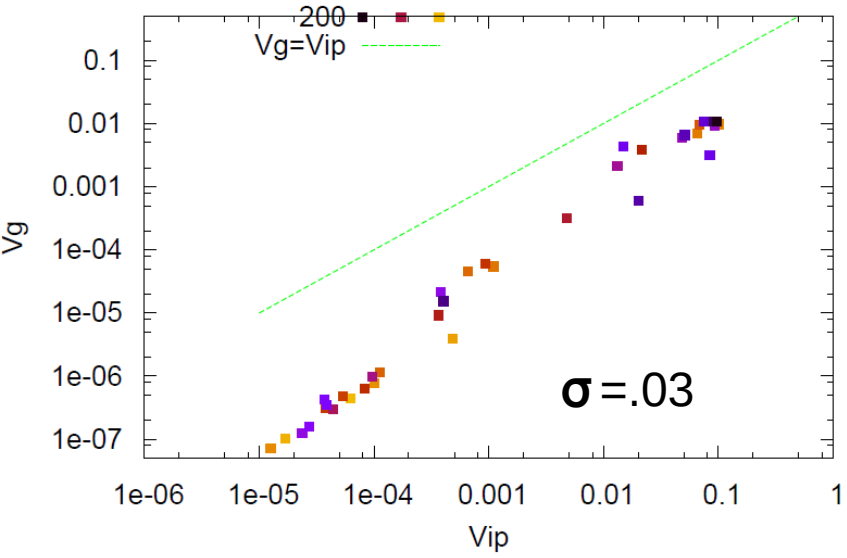


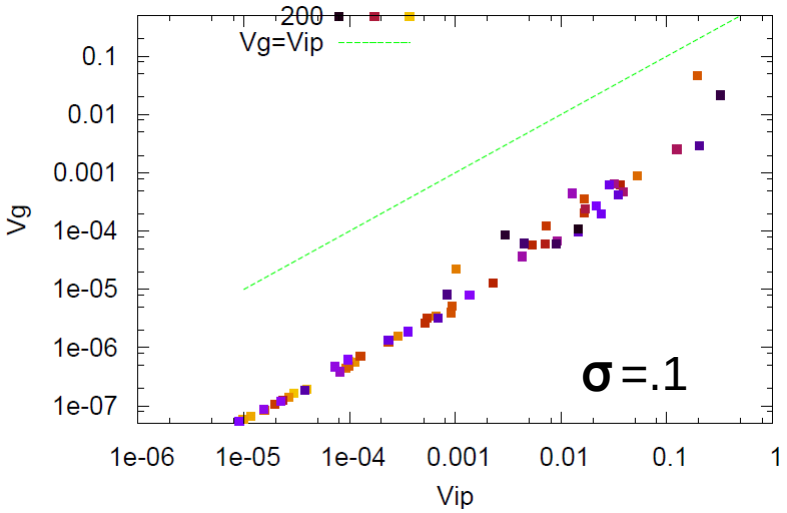
Snapshot plot of all gene expression variances ; (color different generation)

Approach a unique line for all genes(?!)

KK,Chaos 2008

Vip(i)-Vg(i) relationship over genes; snapshot at 200th generation

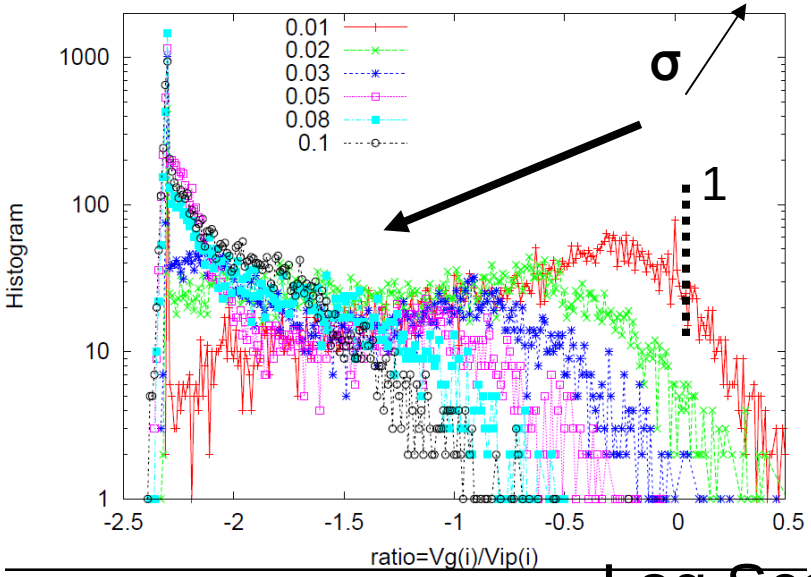




As noise increases, evolved dynamics are more robust, to lose plasticity

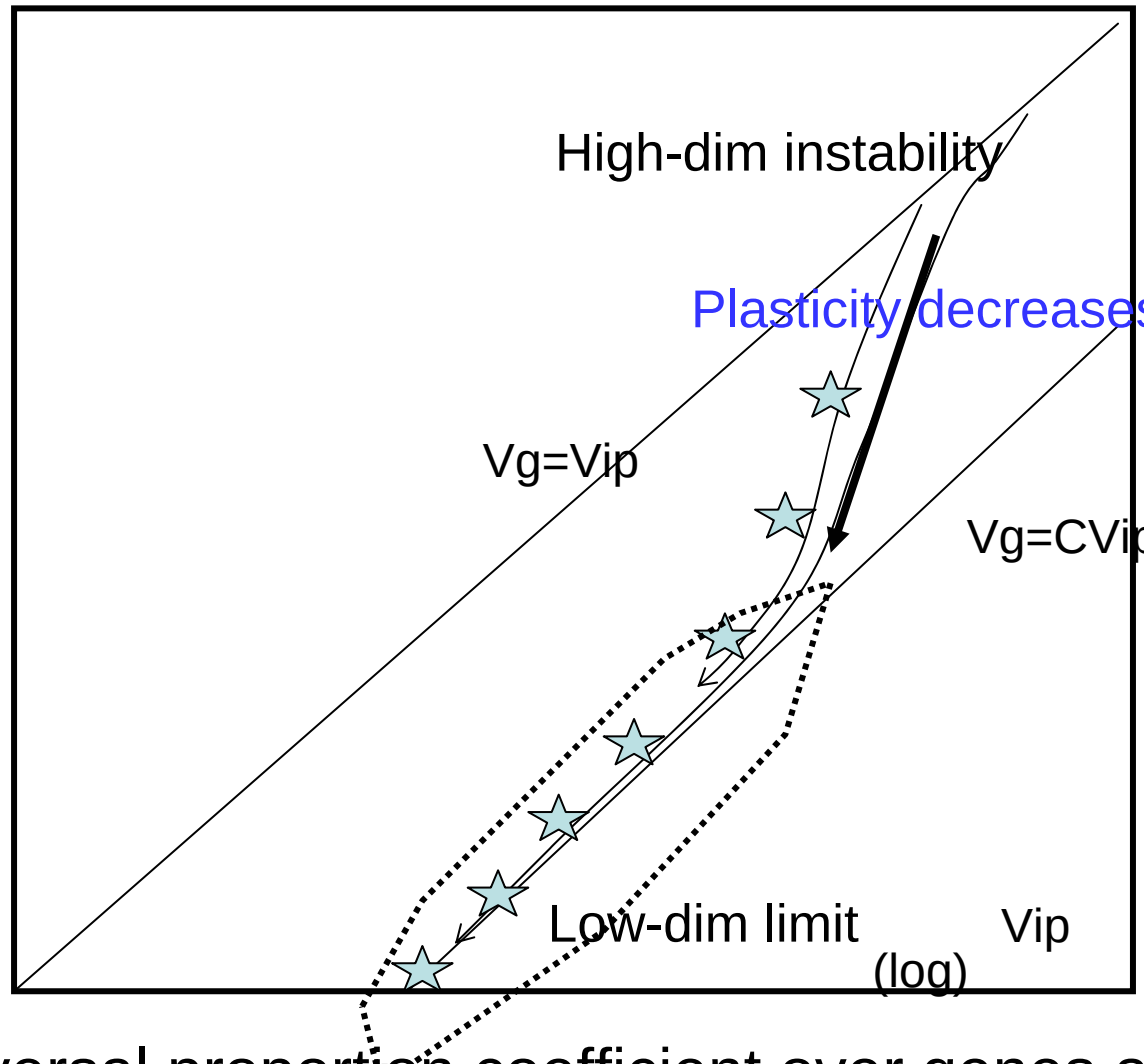
Plasticity ~ Vg(i)/Vip(i)
Fraction of plastic gene expression decreases as σ ↗

Histogram of Vg(i)/Vip(i)



Log Scale

‘universal line is approached ‘over genes’ and ‘over generations’



Recent experiment (Landry etal, Science07) suggests such correlation over genes (KK.Lehner, in prep)

-but scattered

Universal proportion coefficient over genes akin to fluctuation-dissipation relation ----- result of consistency of each gene expression dynamics and fitness as collective state (cf Einstein)

Through directed evolution; fluctuations decrease

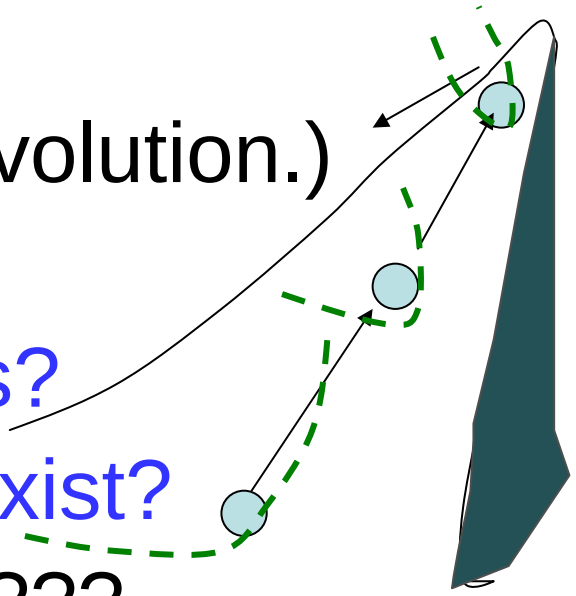
(**Model, experiments, theory, i.e., increase of robustness through evolution.)

Then, evolution slows down..

←→ How Evolution continues?

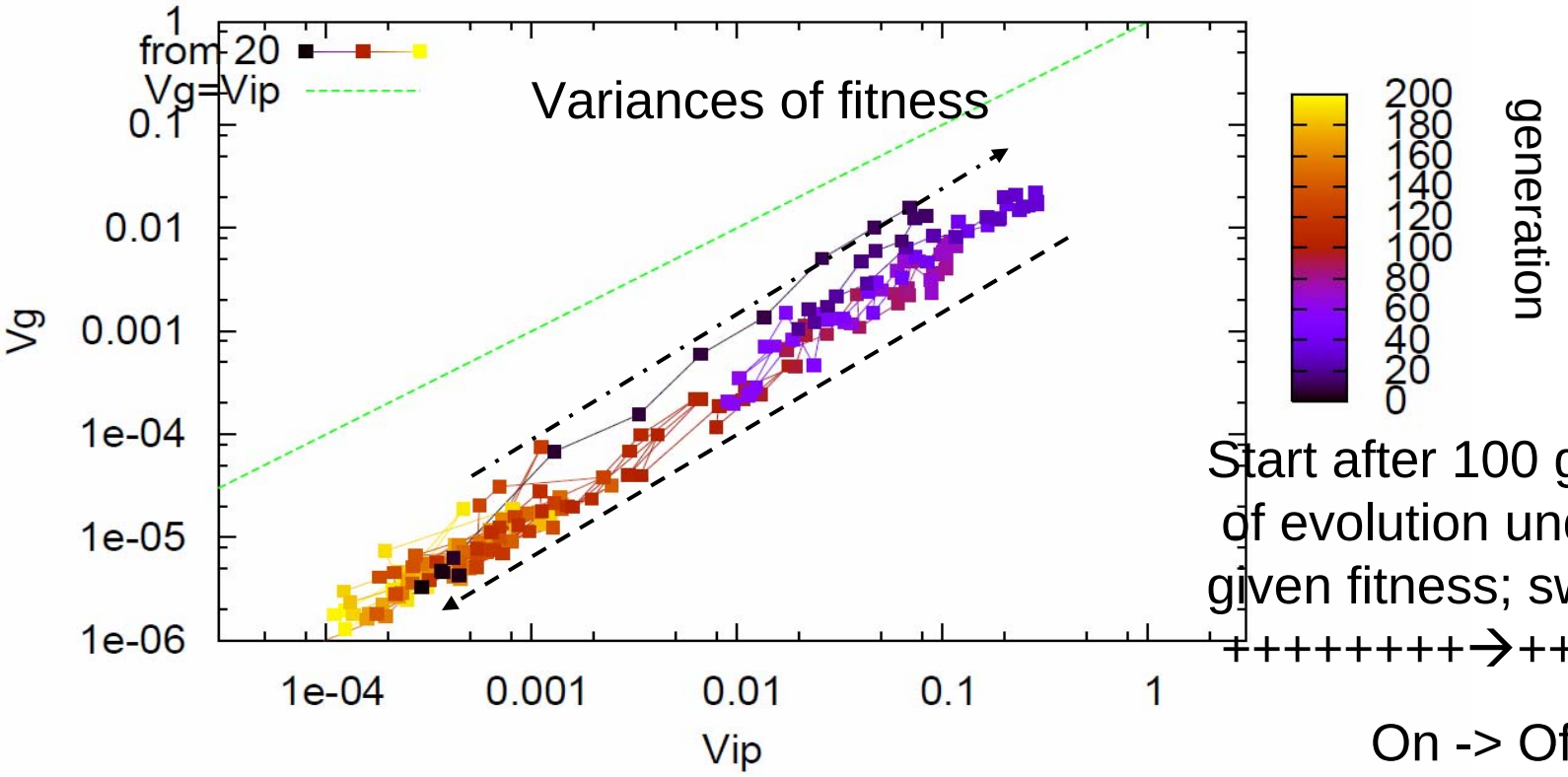
Why Large Fluctuations exist?

?? Is there regain of fluctuations????



- Experimentally Observed: Appearance of mutants with large fluctuations at further evolution. (← interference with other processes) (Ito,Toyota,KK,Yomo, submitted)
- → Restoration of Plasticity

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

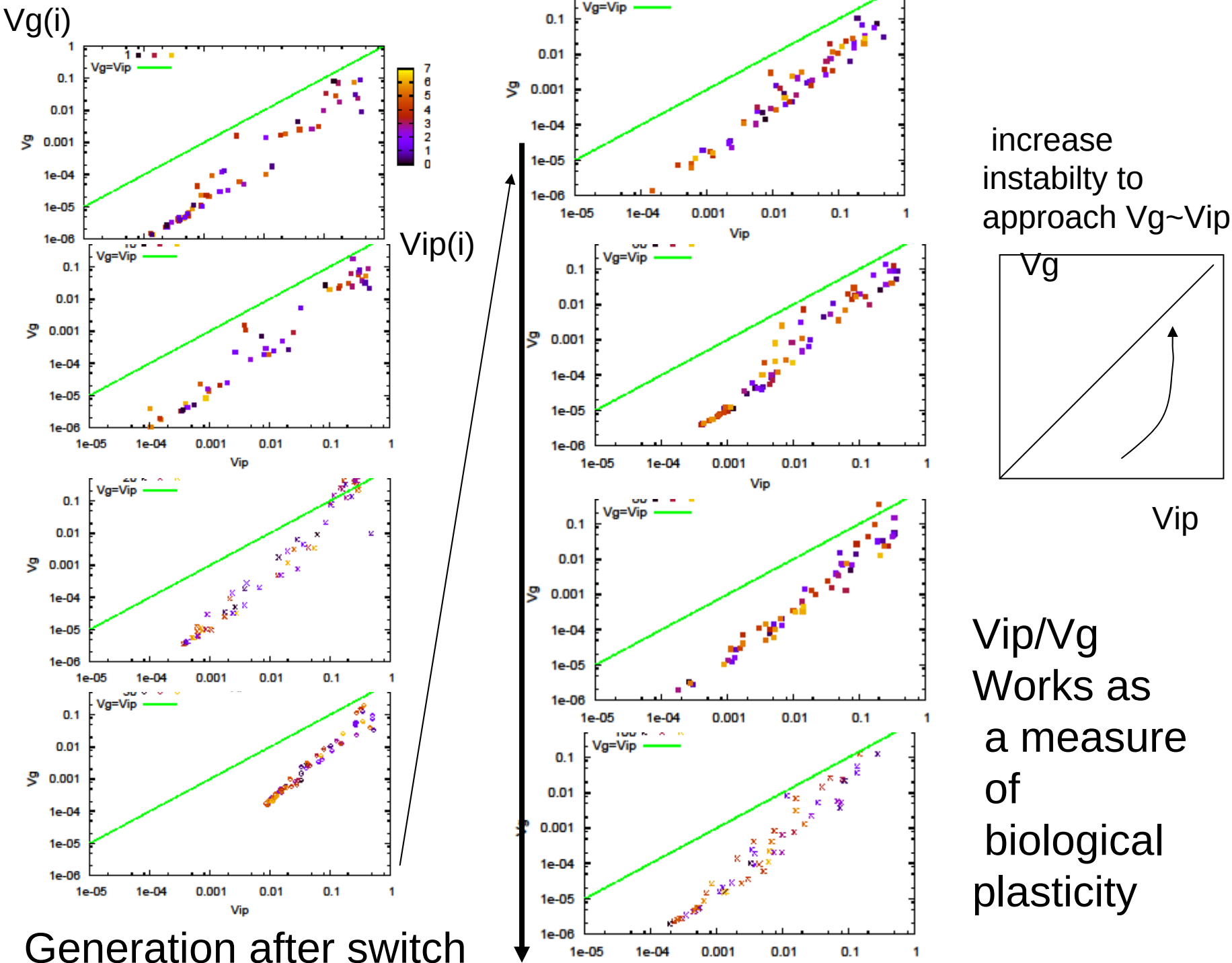


Start after 100 generation of evolution under given fitness; switch
++++++++→++++----

On -> Off for some Target genes

In a fluctuating environment, fluctuation (plasticity) Is sustained

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


Vg(i)
Vip(i)
Vg=Vip
Vg
Vip
Generation after switch
increase instabilty to approach Vg~Vip
Vip/Vg Works as a measure of biological plasticity

- 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)

Symbiotic Sympatric Speciation

Kk,Yomo2000 ProcRoySoc

- So far, 'fluctuation' – 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

Isologous Diversification:

internal dynamics and interaction : development phenotype

instability

distinct phenotypes

interaction-induced

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

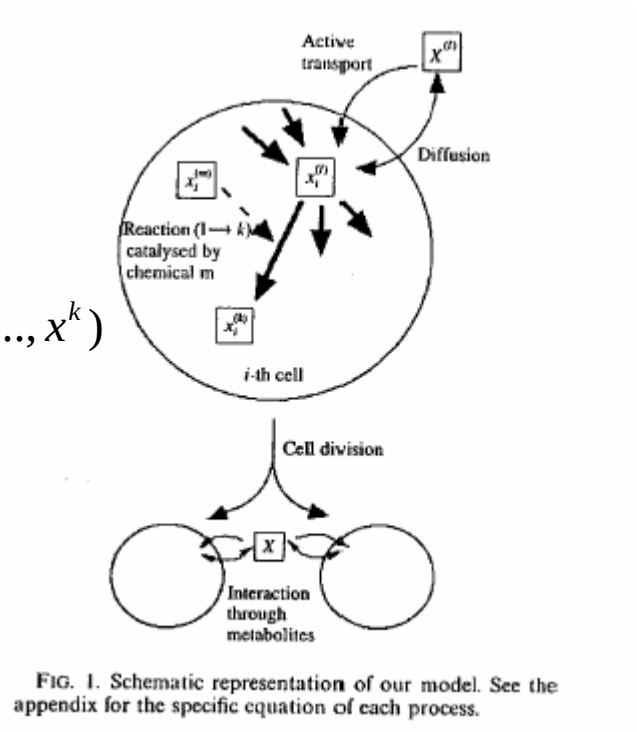


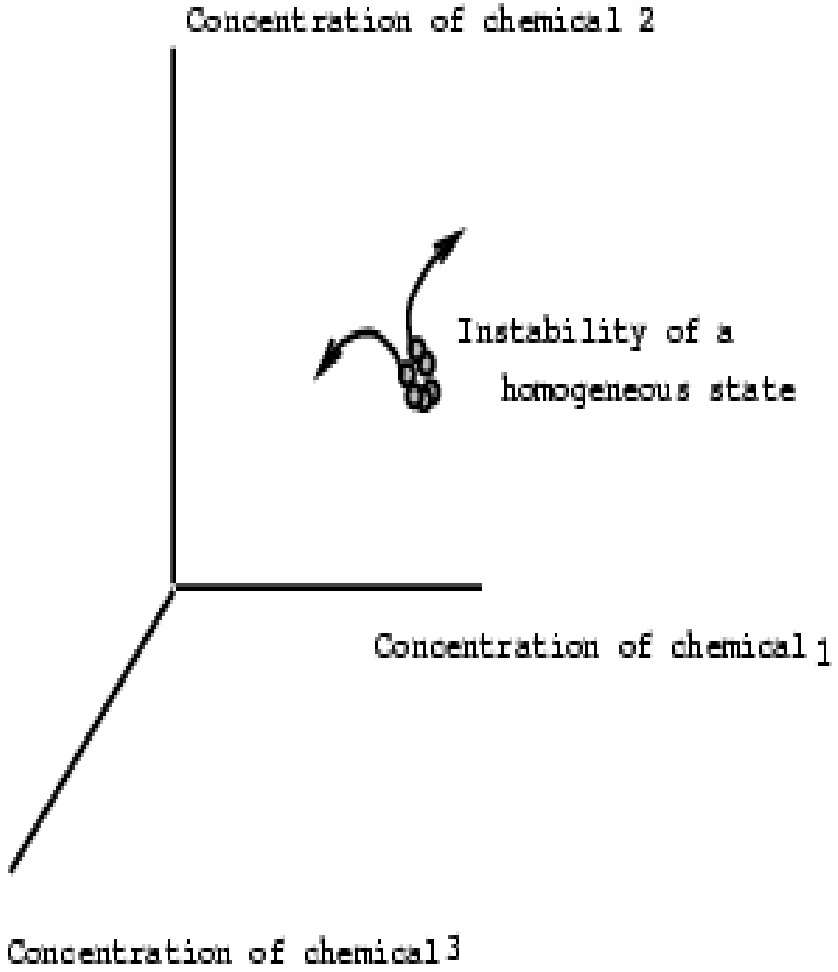
FIG. 1. Schematic representation of our model. See the appendix for the specific equation of each process.

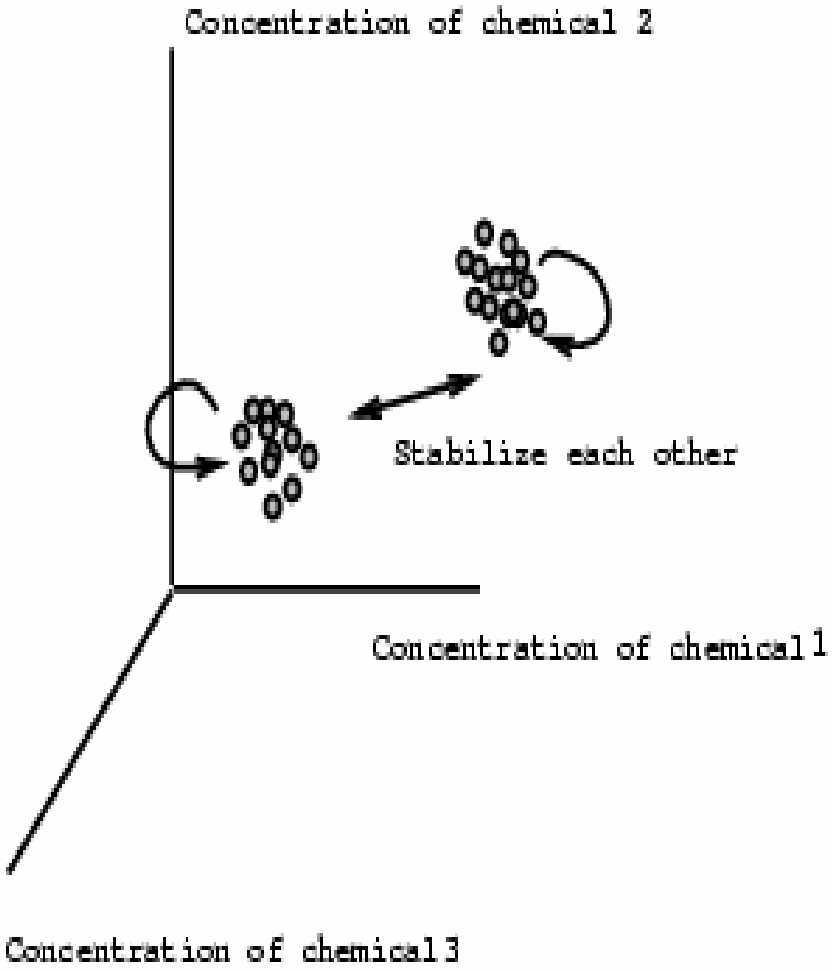
Example: chemical reaction network

specialize in the use of some path

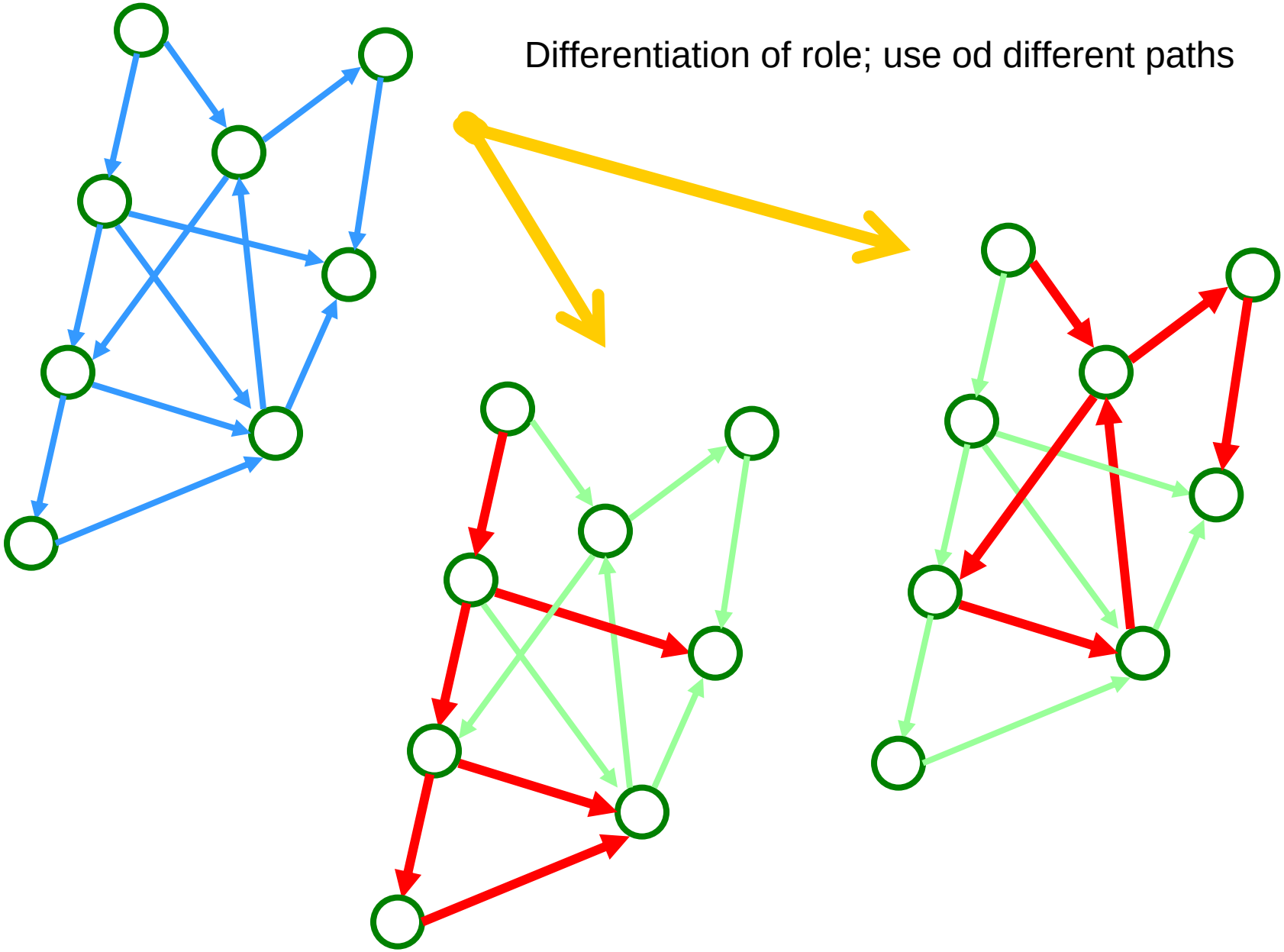
Study of coupled dynamical systems (globally coupled map) etc., differentiation??

→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 od different paths

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)

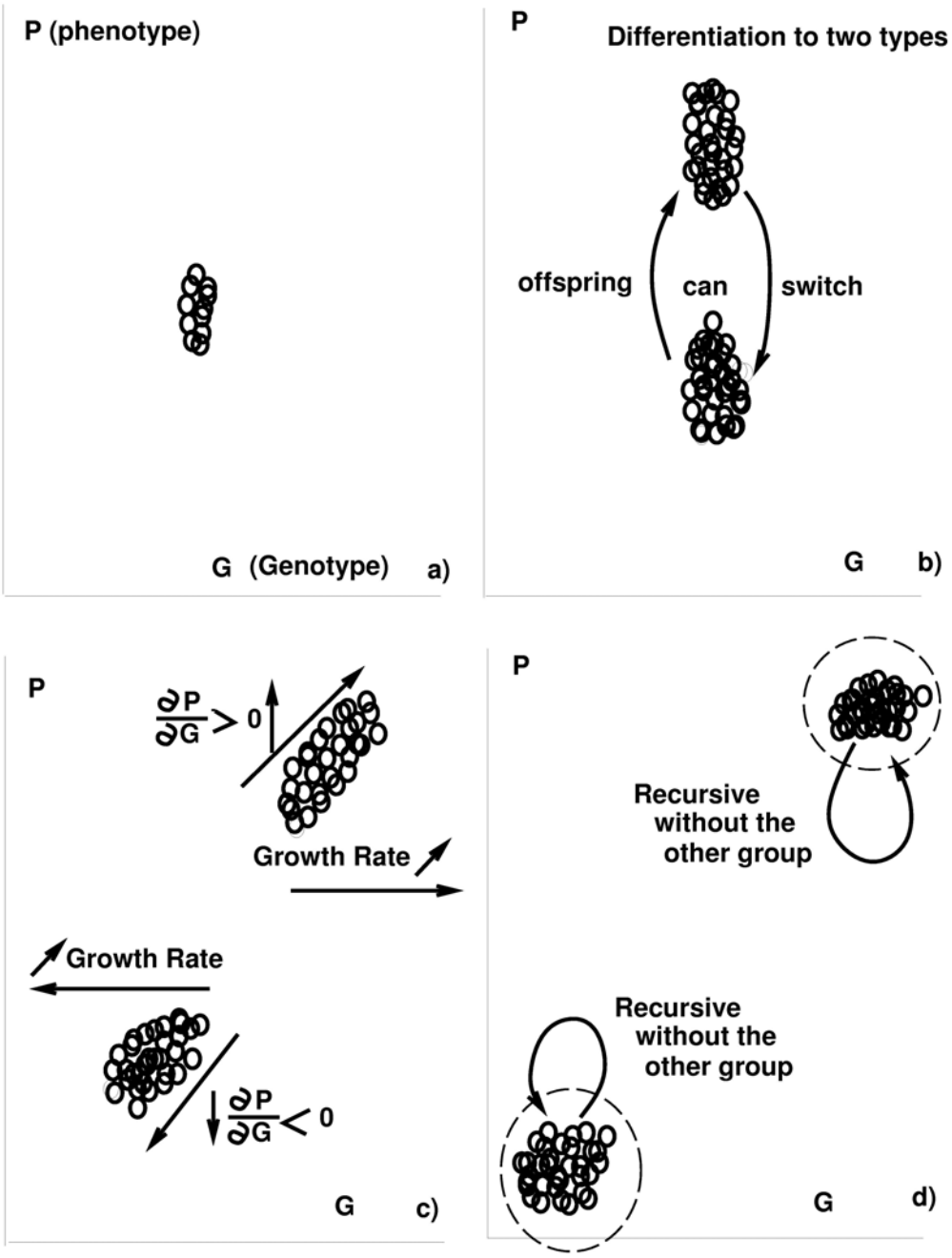
X(t=0)→X(t)

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))


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

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
(Baldwin effect or genetic assimilation→ speciation)

Plasticity in phenotype from loose dynamics → interaction-induced phenotypic differentiation

Consolidated to Genes → Mating → Allele-correlation, Space..

Prove the above scenario?? From observation-- often remains a guess…

Real experiment wanted:

E Coli ; interaction-induced phenotypic differentiation observed

Evolution (Yomo's group)

genetic fixation --- not yet; but

coexistence of diverse types by 'crowded' condition is confirmed

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

Questions

(1) All chemicals have such large fluctuations?

Important ones are protected??

Origin of heredity (genetic information)

Minority control mechanism

(KK,Yomo JtheorBiol.2002)

(2)Large phenotypic fluctuation →

relevance to biology ?

ans. evolution (Sato et al., PNAS, 2003)

adaptation,

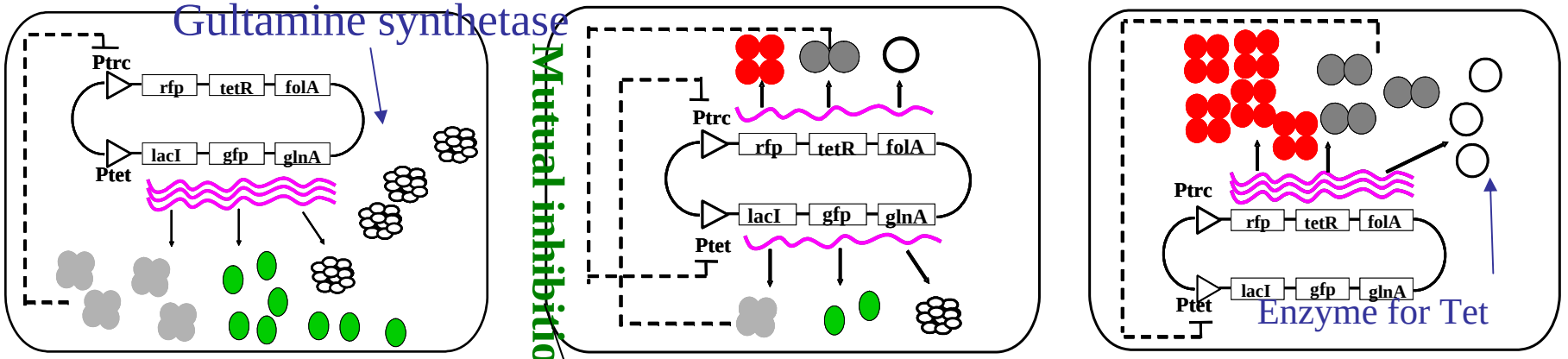
differentiation….

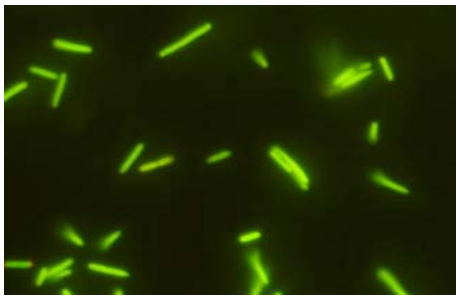
(ex) Adaptive response without signal transduction

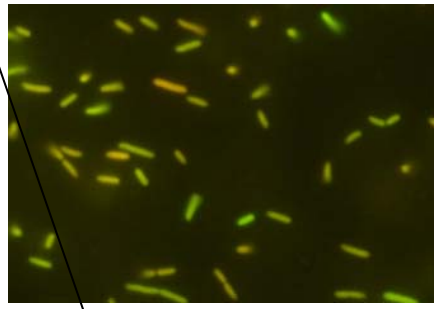
Embedded gene network

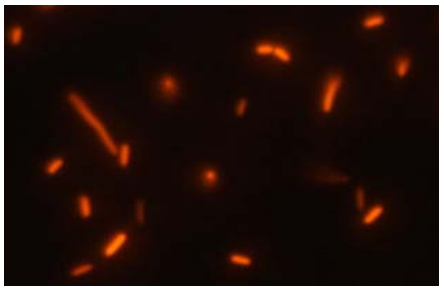
Unexpected; beyond designed
Selection of preferable state

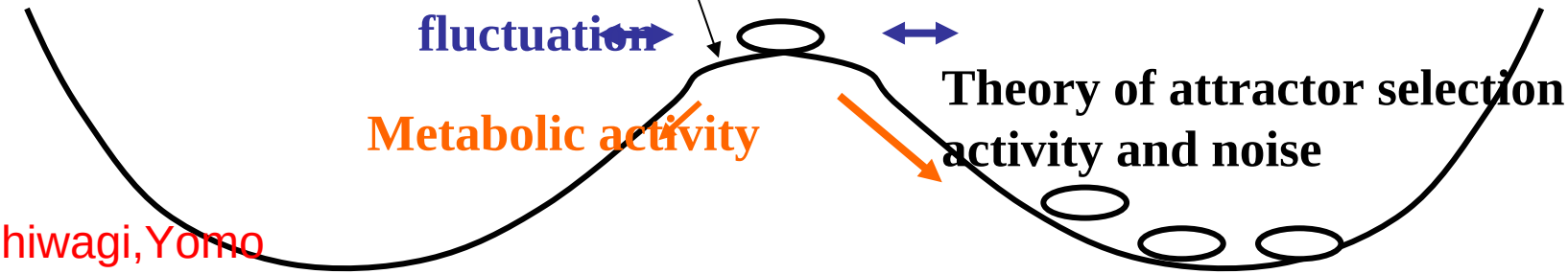
Phenomenological theory of attractor selection











Kashiwagi,Yomo

- Embedded network: each of the two can be selected equally. However, ‘good’ attractor in each environment is selected. Why?
- Due to hidden signal network?

  NO!: verified by exchanging the promoter
- After each state is attracted with 50%,

cells in a ‘bad’ attractor cannot grow,

cells in a good attractor can grow, so that

good attractors are selected?

NO!; the process occurs without (or before) the cell division process

Novel Mechanism of Spontaneous Adaptation (without the use of signal transduction) should exist!

- 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

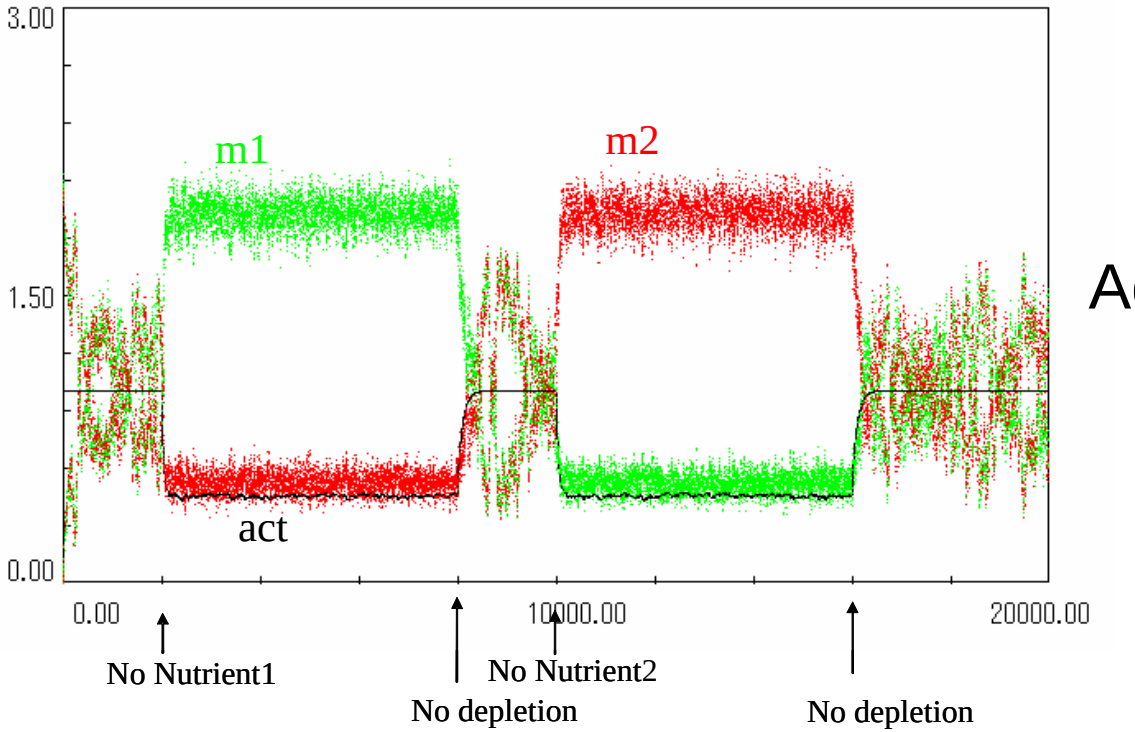
The mechanism for adaptive response by attractor selection

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

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

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

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



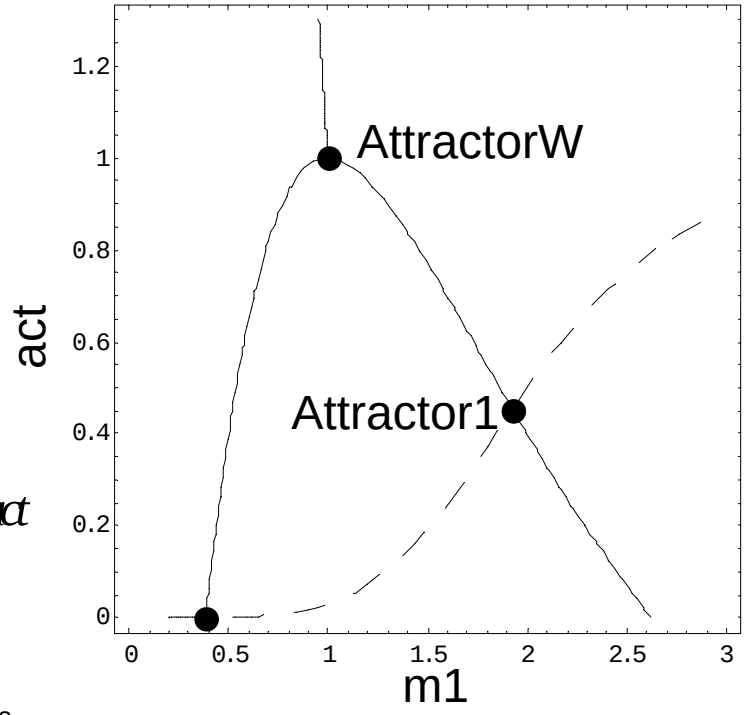
Adaptive Response of the genetic network to a environmental change

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

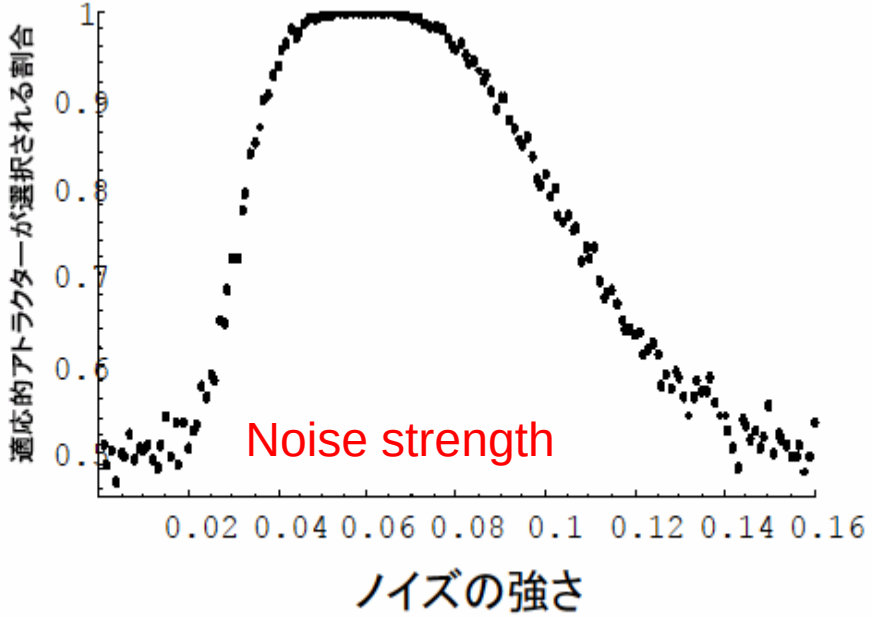
$$\frac{d}{dt}m2 = \frac{syn(act)}{1+m1^2} - \deg(act)\times m2 + \eta_2$$

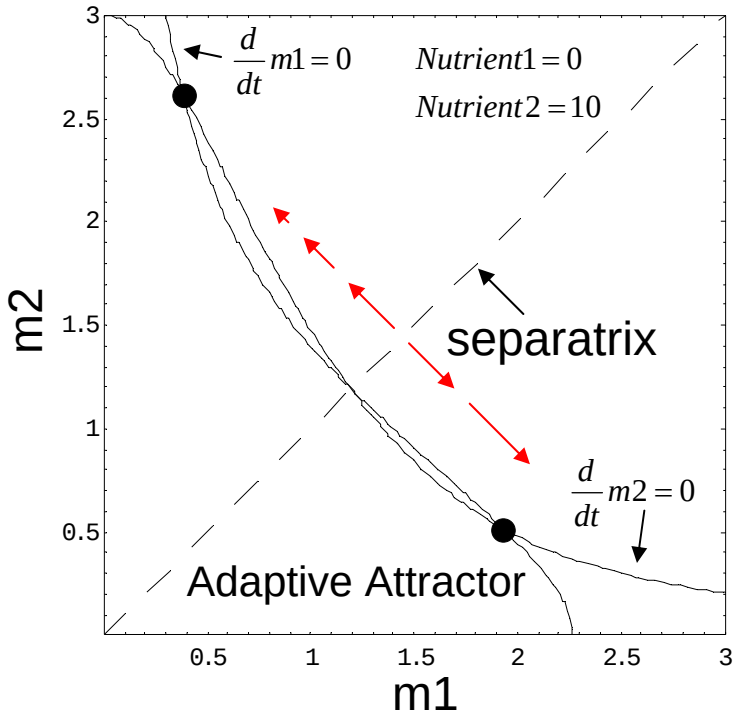
$$syn(act) = \frac{6act}{2+act}; \deg(act) = act;$$

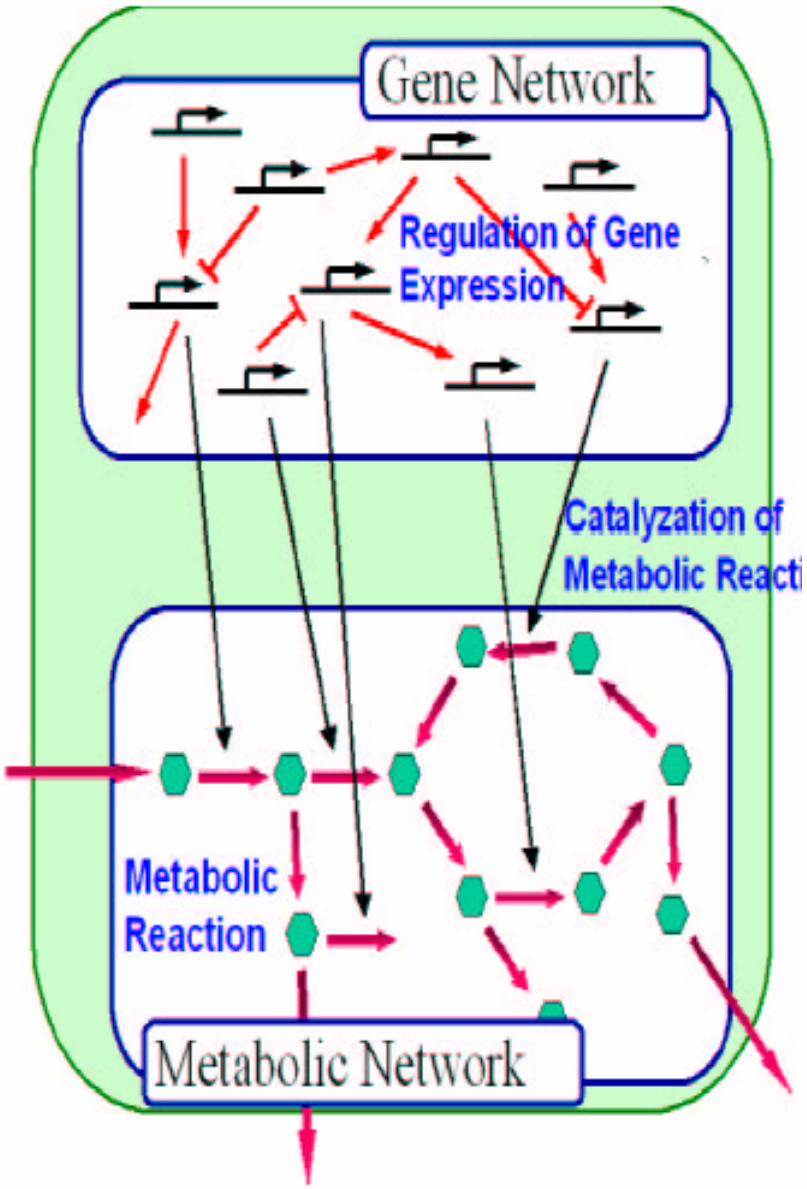
$$\frac{d}{dt}act = \frac{pro}{((\frac{Nut\_thread_1}{m1+Nutrient1})^{n_1}+1)\times((\frac{Nut\_thread_2}{m2+Nutrient2})^{n_2}+1)} - cons\times act$$

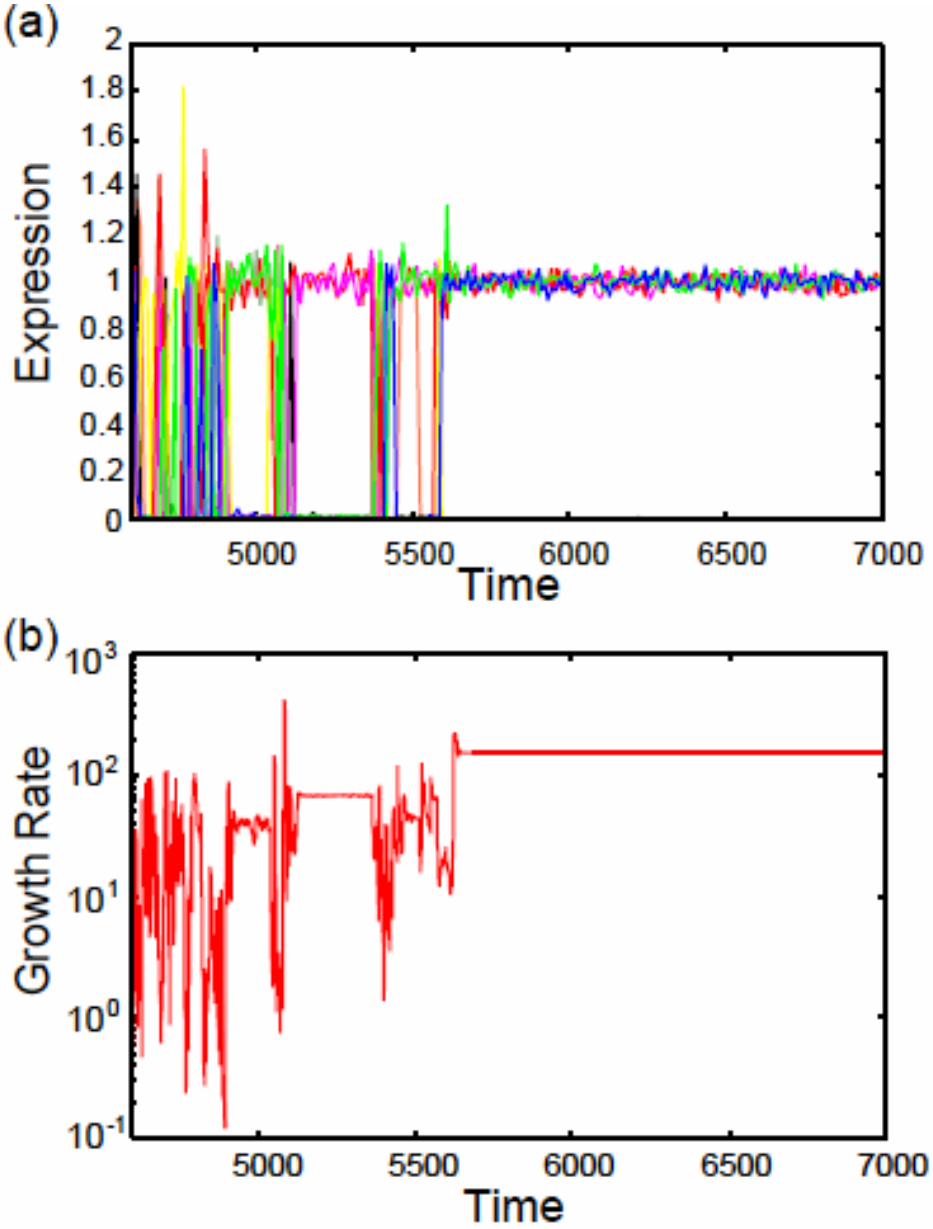


Fraction that adaptive attractor is selected

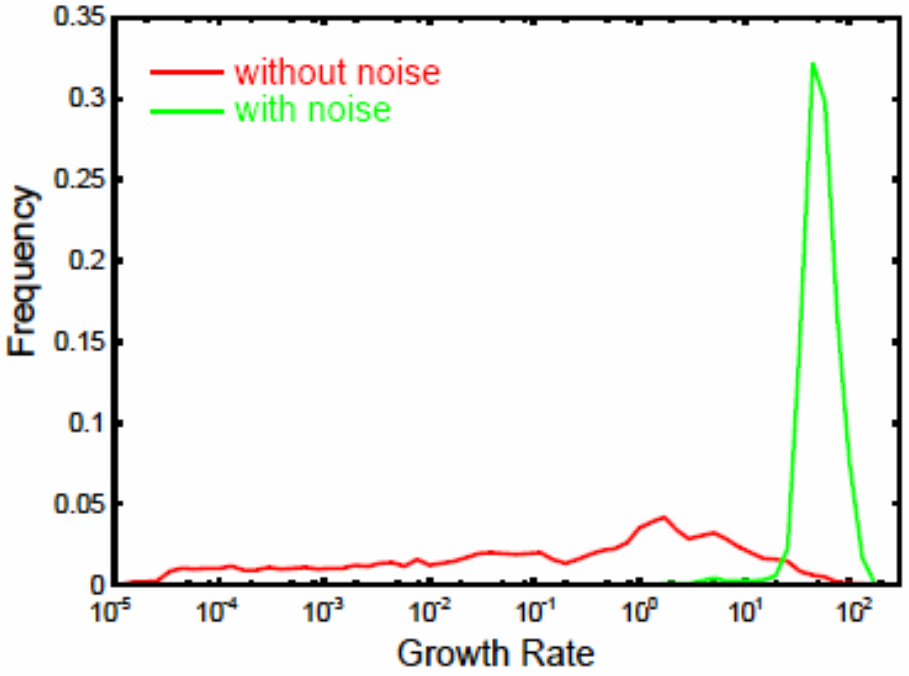


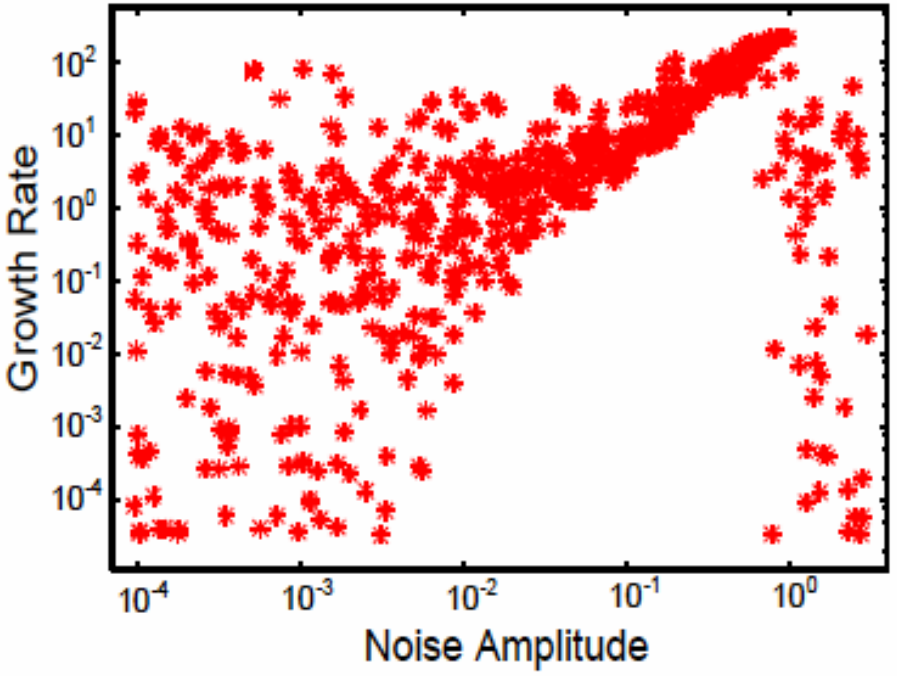






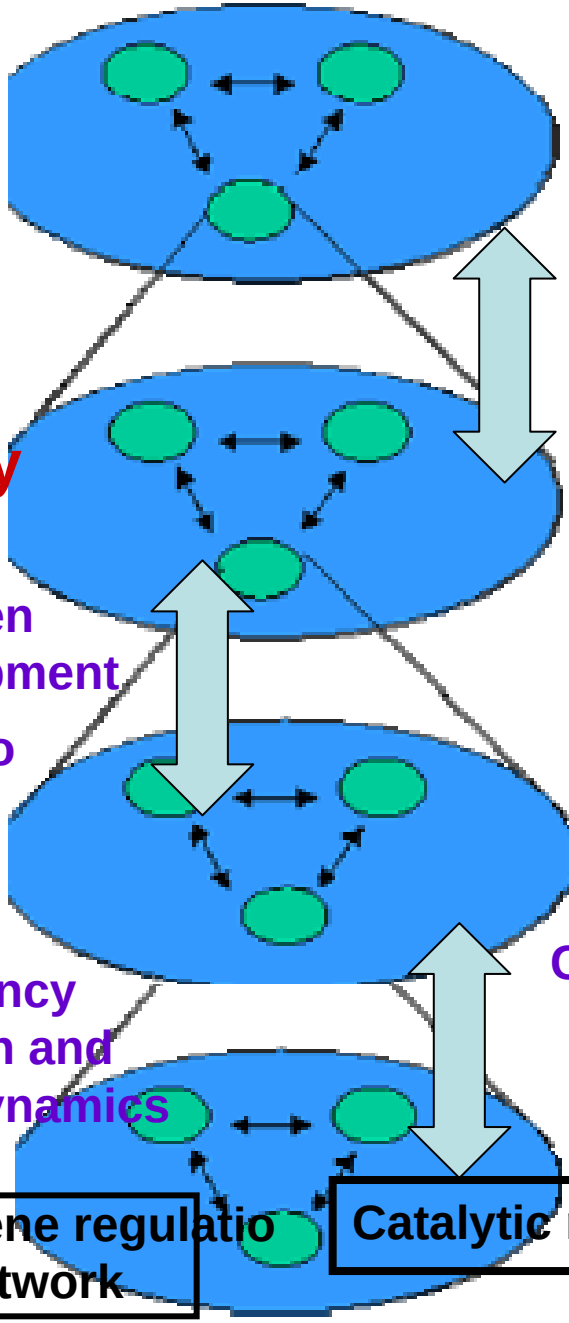
Gene network -> a huge number of attractors coexist with different growth speeds





Spontaneous selection of optimal growth states

General in a system with noise and growth



Ecosystem

Phenotypic Plasticity vs Symbiosis
Or Ecological diversification

Multicelluarity

Consistency between
Multicelluar development
and cell repdorcutio

Evolutionary relationship on
Robustness and Fluctuation

Genotype ⟷ Phenotype

Cell

Adaptation as
a result of consistency
between cell growth and
gene expression dynamics

Consisteny between Cell reproduction
nd molecule replication

Molecule

Gene regulatio
network

Catalytic reaction network

Summary

Consistency Principle for Biology

-- replication of molecules and cells :Universal Laws

(-- replication of cells and cell ensembles)

--- adaptation of internal cellular state and growth

--- genetic and phenotypic changes

(+speciation)

- Biological relevance of phenotype fluctuations?

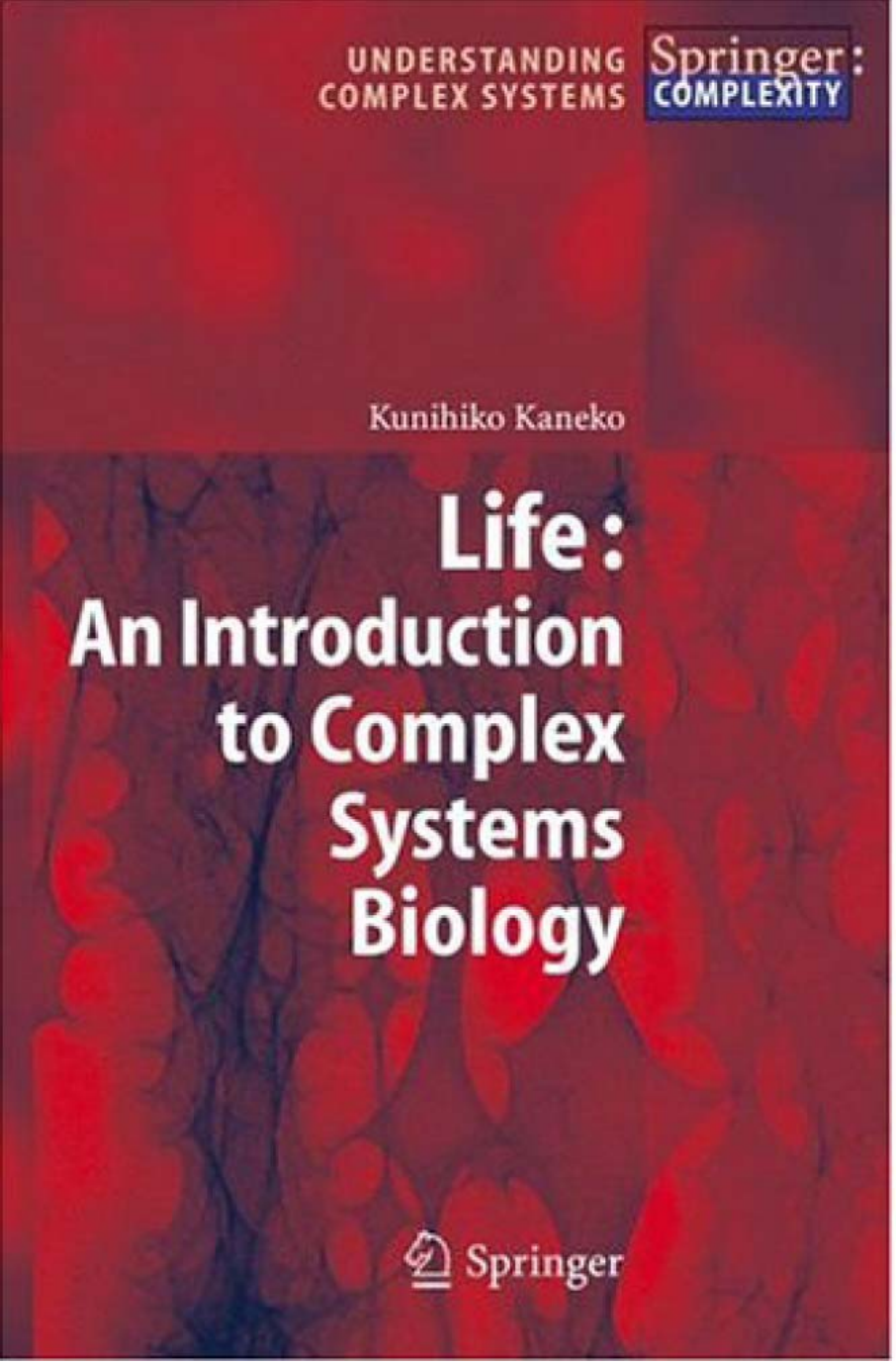
→Phenotypic Fluctuation ∝ Evolution Speed

→ Relation between

(isogenic)phenotype fluctuation vs

phenotype variation by mutation

- Robustness to mutation and to developmental noise are linked
- Growth system → general adaptation by noise
- consequence of steady growth system



Collaborators

Chikara Furusawa

Katsuhiko Sato

experiment

Tetsuya Yomo

Yochiro Ito

Akiko Kashiwagi

Most papers (biology, Dynamical systems) Available at

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

ERATO Complex Systems Biology Project

(**2006,August**)

Evolution of gene regulation network for more complex function:

Choice of complex dynamical systems to give gene expression pattern for segmentation

Found Two basic strategies to generate stripes

→ use of generic dynamics such as oscillation

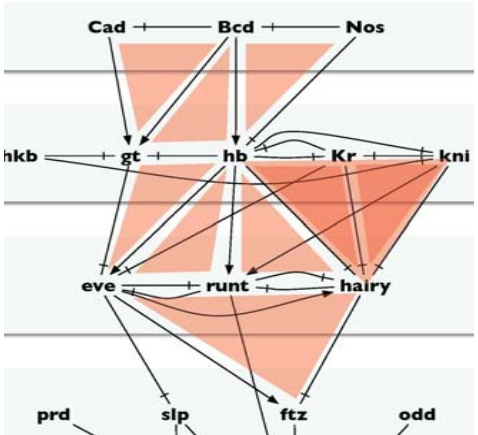
→ genetic control by logical (on/off) operations

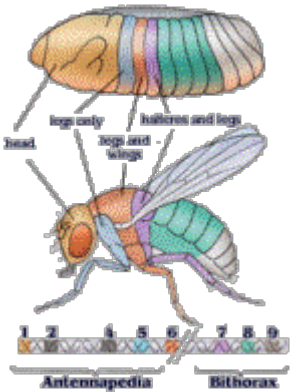
(pioneered ; Salzar-Ciudad, Newman, Sole, EvoDev2001)

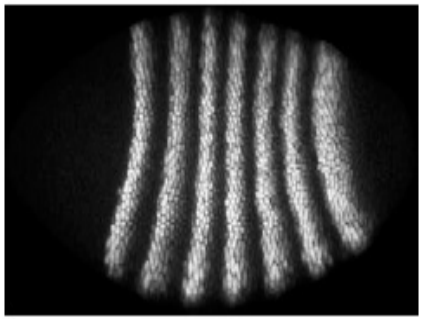
Network evolution of body plans

Fujimoto,Ishihara,KK (PLoS One 2008)

Also talk tomorrow by Fujimoto(>>4.4C1)







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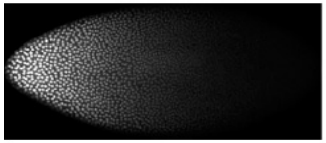
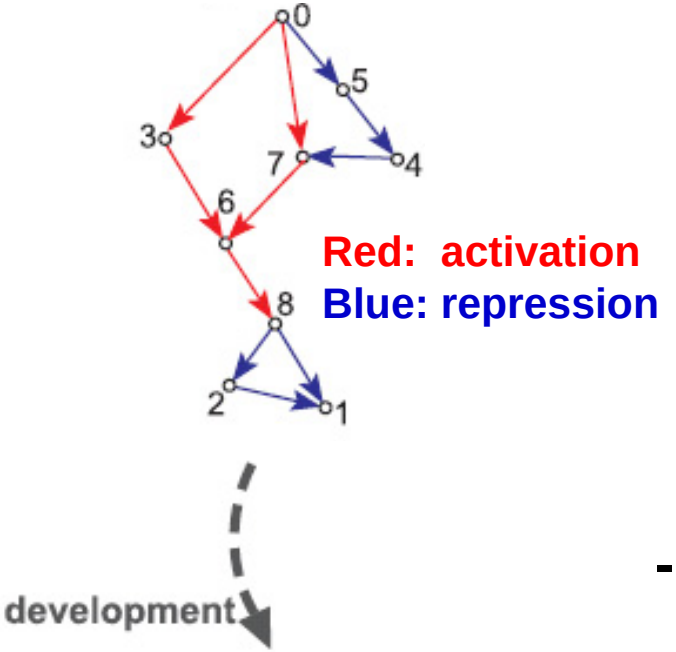
Current Opinion in Genetics & Development

Method: Calculating development

- Take Gene regulation networks with activation and repression
- These genes are located spatially and chemicals diffuse (reaction+diffusion)



Becoid, Drosophila



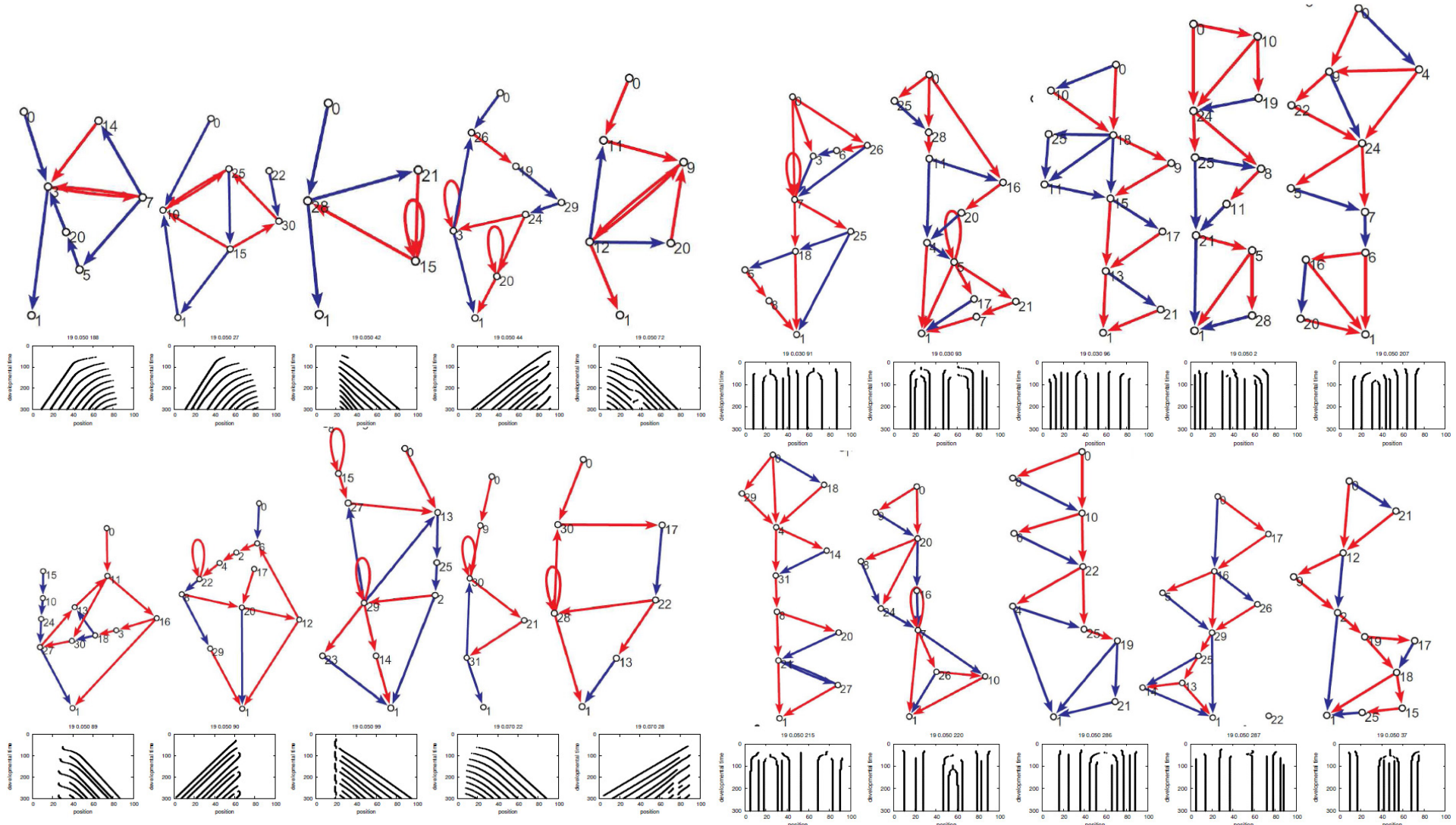
•Development under external environment as input (spatial gradientent imposed)

$$\frac{\partial Y}{\partial t} = -Y + f_Y(X, K_{xy}) + D_y \frac{\partial^2 Y}{\partial l^2}$$

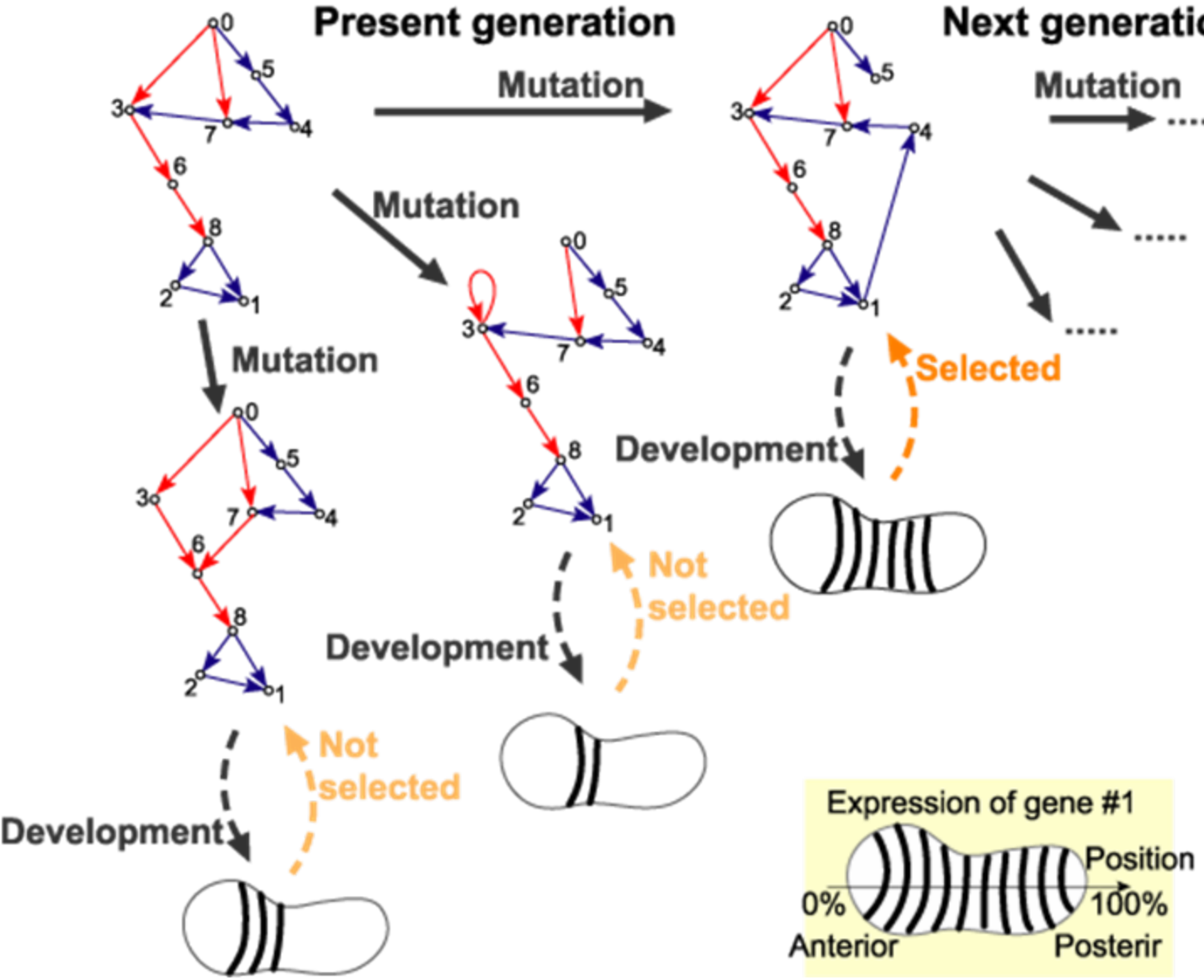
- Gene #0 is distributed with spatial gradient.

- Reaction-diffusion equation for each gene expression.

Strategy: <u>Numerical</u> evolution of gene regulatory networks to form stripe pattern.



Method: Numerical evolution



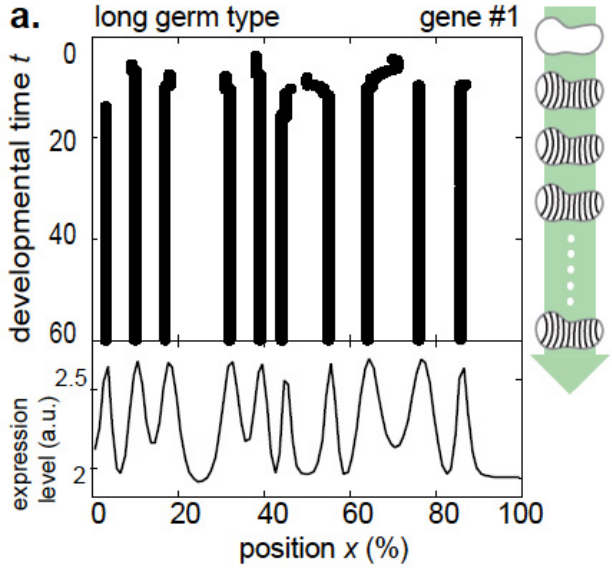
Cf. Salzar-Ciudad, Newman, Sole EvoDevo 2001

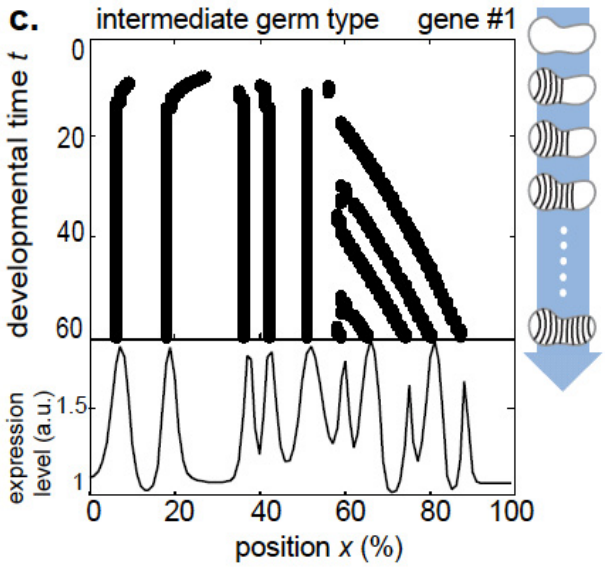
Development dynamics over >1000 evolved networks are classified just into 3 modes

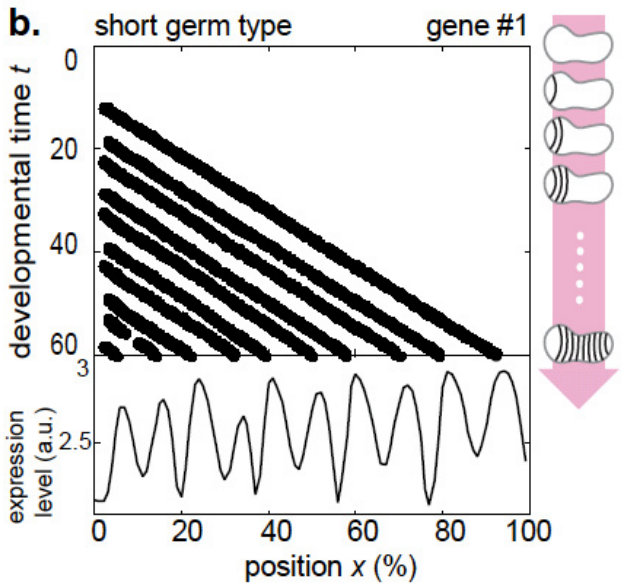
Long germ mode: simultaneous

Intermediate germ mode: combinatorial

Short germ mode: sequential





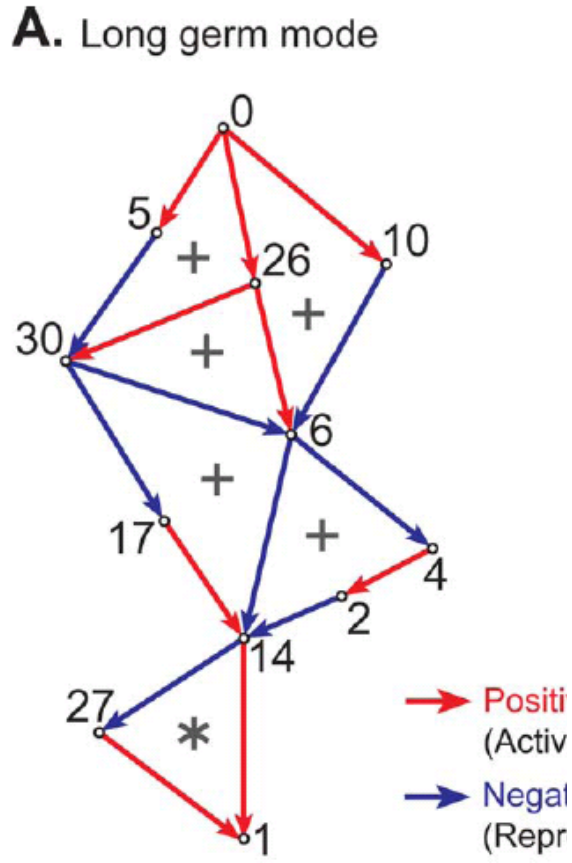


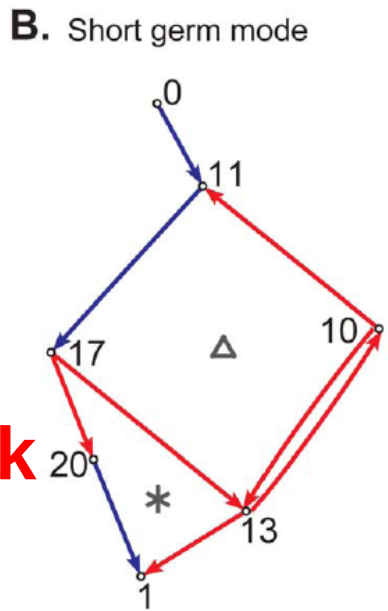
*Simultaneous generation
Combination of on/off regulations by fixed expression dynamics

Sequential Generation
Use of oscillatory gene expression

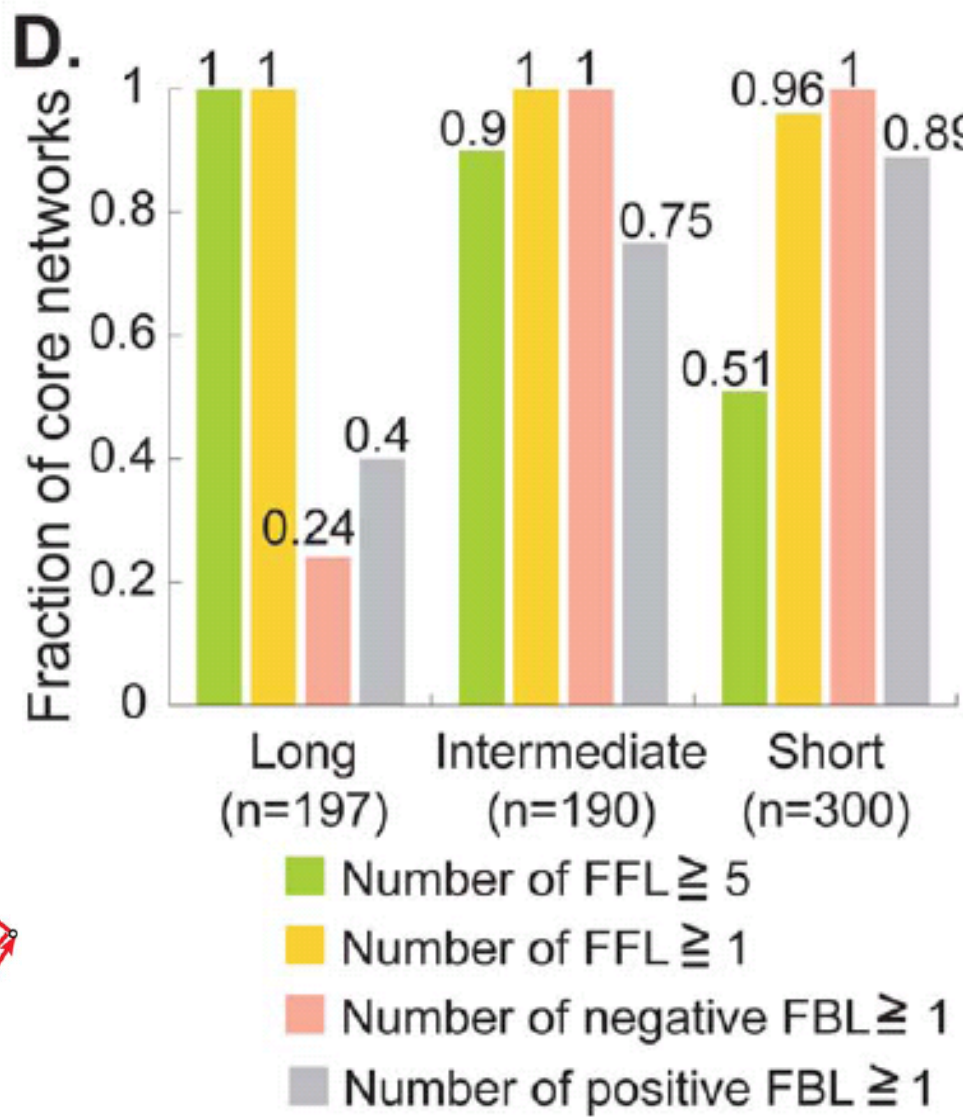
Difference in (core) network structure

Long-germ uses feed forward loop (FFL) dominantly



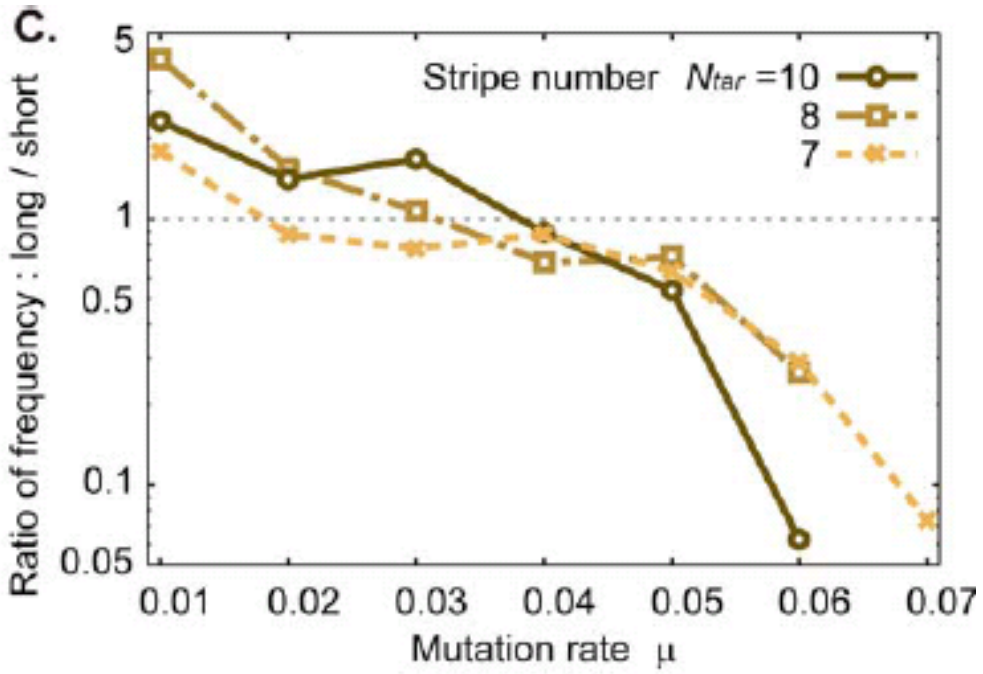


Short-germ uses mainly feed-back loop (FBL)



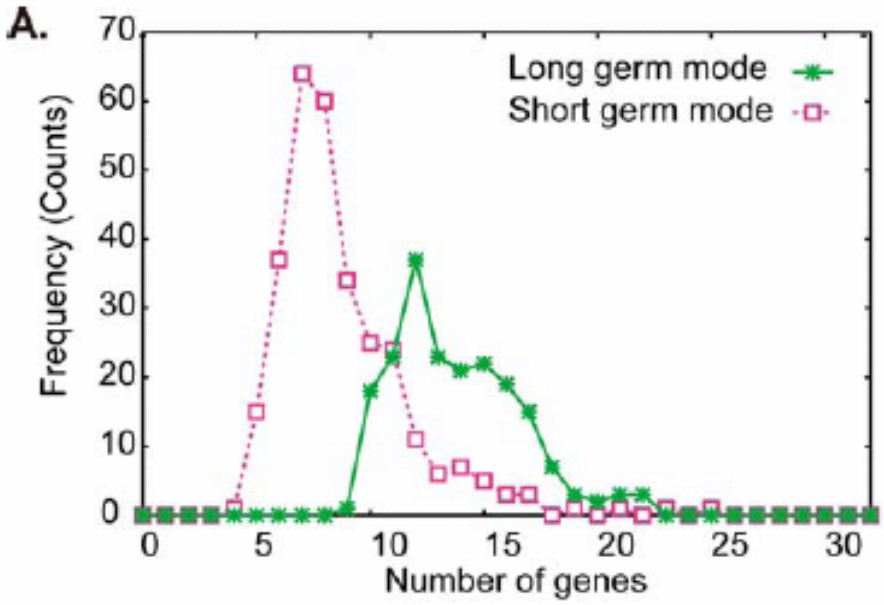
Short-germ mode has higher robustness to mutation to network, as the number of involved genes is fewer

Ratio of Long to Short



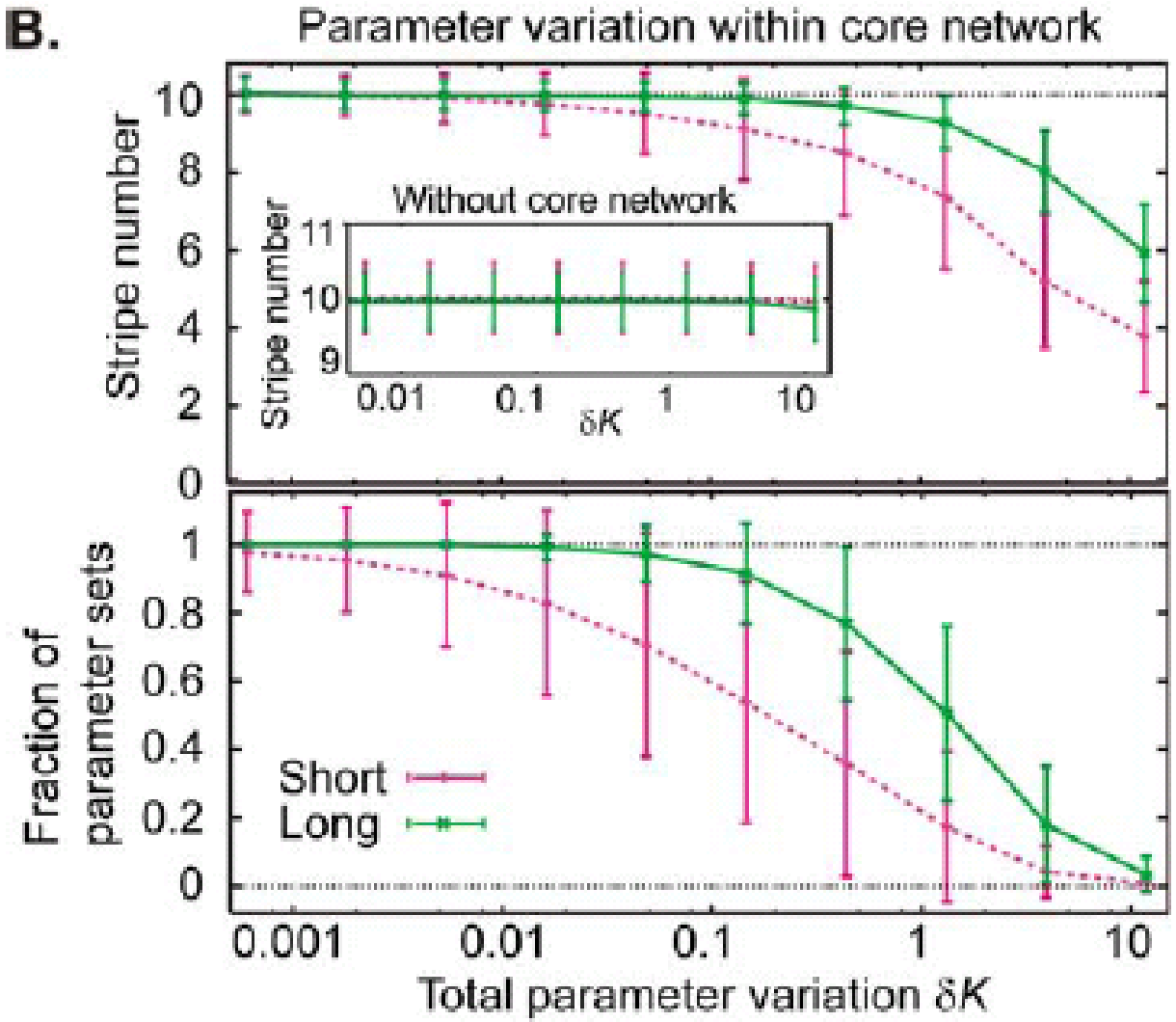
Mutation rate

Distribution of the number of required genes



Number of required genes

Remarkably, however, Long Germ Mode development has high robustness against changes in the parameters in the gene expression dynamics



Summary

1. ***We classified networks according to sequential or simultaneous stripe formation.***
2. ***They are characterized by network modules, FBL and FFL.***
3. ***Compared them with observed short and long germ segmentation in arthropod.***
4. ***Correspondences between numerical and real evolution suggest that the diverse segmentation is an inevitable property of evolving networks.***

Segmentation mode	Pattern formation	Network module	Spatial Hierarchy	Knockout response	Development	Mutation rate
Short	**sequential**	**FBL**	No need	simple	Slower	Higher
Intermediate	**combinatorial**	**FBL +FFL**	?	variety		
Long	**simultaneous**	**FFLs**	necessary	variety	Faster	Lower