Plasticity and Robustness in Evolution: Macroscopic Theory, Model Simulations, and Laboratory Experiments

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1 Phenotypic Fluctuation (Plasticity) vs Evolution

2 Phenotypic Fluctuation vs Genetic Variation

3 Evolution of Robustness to Noise and to Mutation

4 Plasticity of each phenotype

5 Restoration of Plasticity

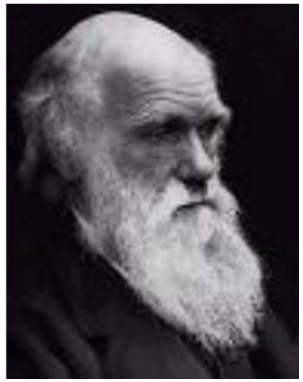
6 LeChatlier Principle?

7 Symbiotic Sympatric Speciation

8 Evolution of Morphogenesis

selection of dynamical systems
by dynamical systems for dynamical systems

Darwin and Lincoln (born on the same day)



Complex-Systems Biology : Consistency between different levels as guiding principle

Ecosystem

Multicelluarity

Consistency between Multicelluar development and cell reprodcution

Cell

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

Molecule

Gene regulation network

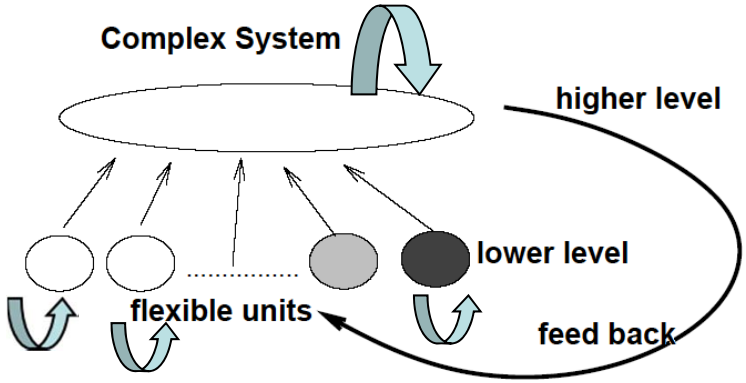
Stochsatic dynamics

Catalytic reaction network

Consistency between Cell reproduction and molecule replication

Evolutionary relationship on Robustness and Fluctuation

Genotype ⟷ Phenotype



Consistency between dynamics of different levels

(1)Cell reproduction vs molecule replication → adapt to critical state with optimal growth (Furusawa,kk PRL 03,12)

(2) Cell Growth vs Protein Expression →
generic adaptation (without signal network) as a result of cell growth + noise (Kashiwagi etal,PLosOne 06)

(3) Cell reproduction vs multicellularity →

(unstable) oscillatory dynamics = stem cell + cell interaction → differentiation, loss of pluripotency
(KK&Yomo 1997, Furusawa&KK,Science 2012)

+ minimal model (Goto, kk, arXiv)

(4) Genetic vs phenotypic changes→ Today's talk

Other Recent Related topics (to be discussed informally)

(1) Cooperative Adaptation Dynamics by high-dimensional gene regulation dynamics (Inoue,kk,PLosCB2013)

(2) Adaptive Dynamics by Epigenetic Feedback Regulation (Furusawa,kk,PLoSOne2013)

(3) Temperature Compensation in Circadian Rhythm by enzyme limited competition (Hatakeyama,kk,PNAS2012)

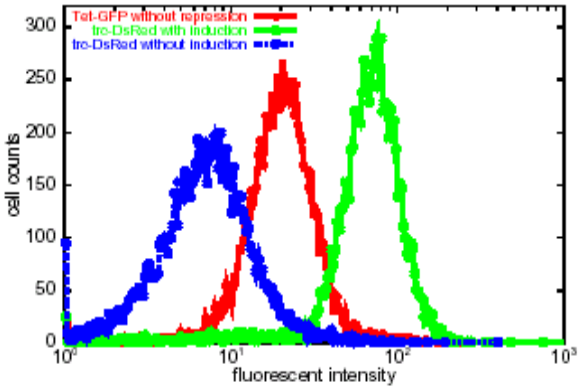
(4) Kinetic memory due to enzyme-limited competition: basis for epigenetic memory(Hatakeyama,kk, in prep)

- Evolvability,Robustness,Plasticity: Basic Questions in Biology, but often discussed qualitatively : Idealizing the situation:

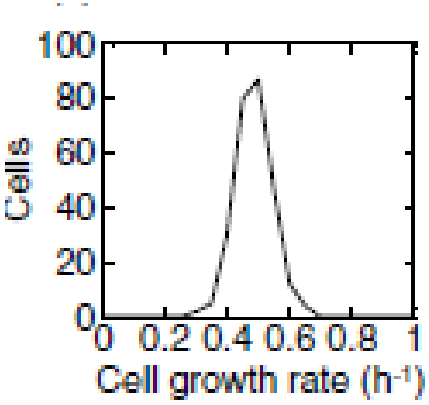
→quantitative theory?

- Phenotypic Fluctuation ←→ Phenotypic Evolution?
- Even in isogenic individuals 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



Phenotypic fluctuation in EvoDevo

genotype —``development '' → Phenotype

Selection by f(Phenotype)（given environment)

If this genotype→phenotype mapping is uniquely determined → selection by f(Genotype). Then

Change in distribution P(genotype)

But gene—``development '' → Phenotype distributed

Phenotypic fluctuation of isogenic organisms

→P(x; a) x—phenotype, a – gene

*Even if fluctuated phenotype is not heritable, degree of fluctuation depends on gene and is heritable

Correspondence between Devo and Evo

congruence between dev dynamics &evolution

Motivation2:Evolution of Robustness

- Robustness ----- Insensitivity of Phenotype to system's change

  ← due to environmental change

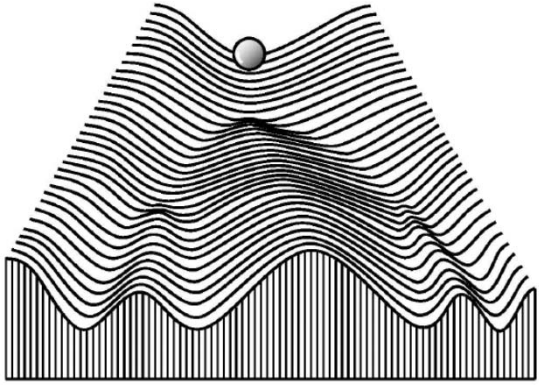
  ← against 'developmental noise'

  ← against change by mutation

*Question :

relationship among these robustness

condition for evolution of robustness



Waddington's image For robustness (canalization)

Connect Motivation 1 and 2:

Study evolvalibity, robustness, in terms of phenotypic fluctuations

→Insight into Geno-pheno coupling

Waddington– Genetic Assimilation

(Ancel-Fontana.Wagner,.,)

- Note;

phenomenological theory for relation between stochasticity in geno—pheno mappings and genetic variances, based on Lab+Numerical experiments+ phenomenological argument;

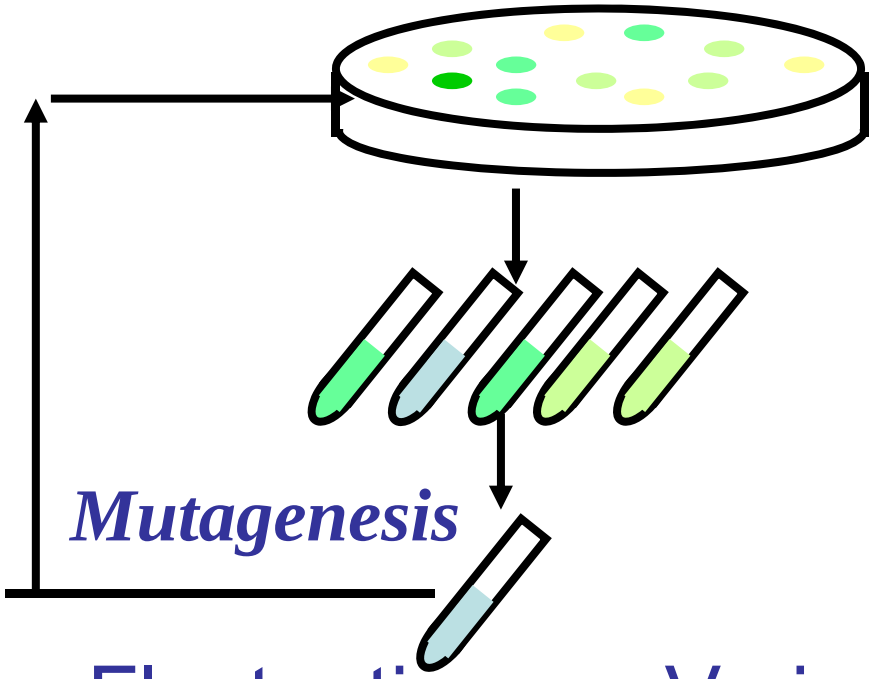
No sophisticated framework as in population genetics

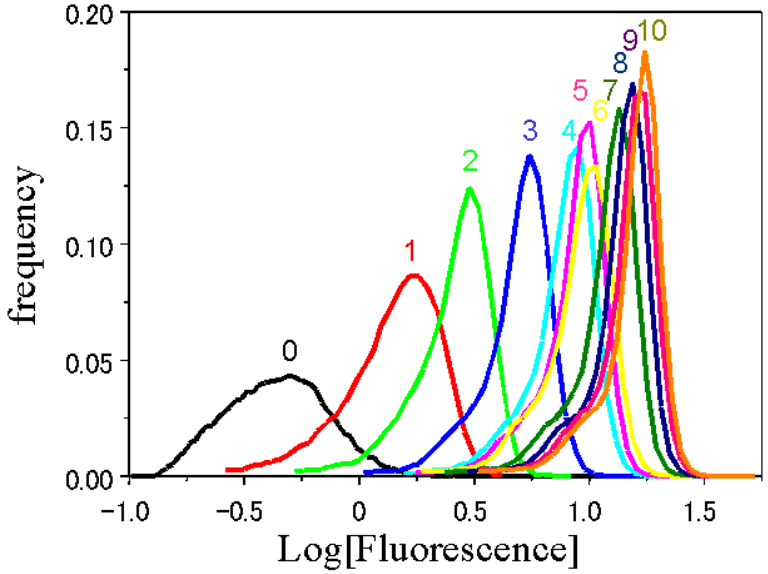
(cf: consequence of covariances is established in Price, Lande,…..)

Here, consequence of evo-devo (plasticity, robustness)

Earlier study:Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria





Fluctuation ---- Variance of phenotype of clone

Larger phenotypic fluctuation

---higher evolution speed？

Sato,Ito,
Yomo,KK
PNAS(2003)

Analogy with fluctuation-response relationship

Force to change a variable x;

response ratio = (shift of x) / force

fluctuation of x (without force)

response ratio proportional to fluctuation

Generalization::(mathematical formulation)

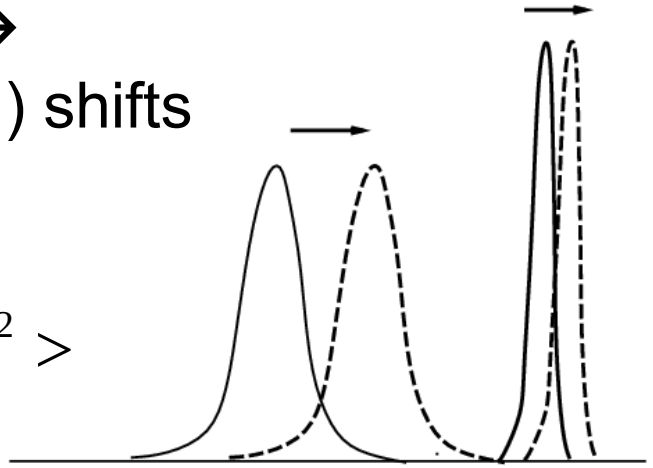
response ratio of some variable x against the change of parameter a versus fluctuation of x

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

change of the parameter a →

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

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



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

Phenomenological Distribution argument

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

$$P(x:a) = Nexp(-\frac{(x-X_0)^2}{2\alpha(a)} + v(x,a)) \quad v(a,x) = C(a-a_0)(x-X_0) + ..., \text{ with } C \text{ as a constant,}$$

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

Hence, we get

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

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

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

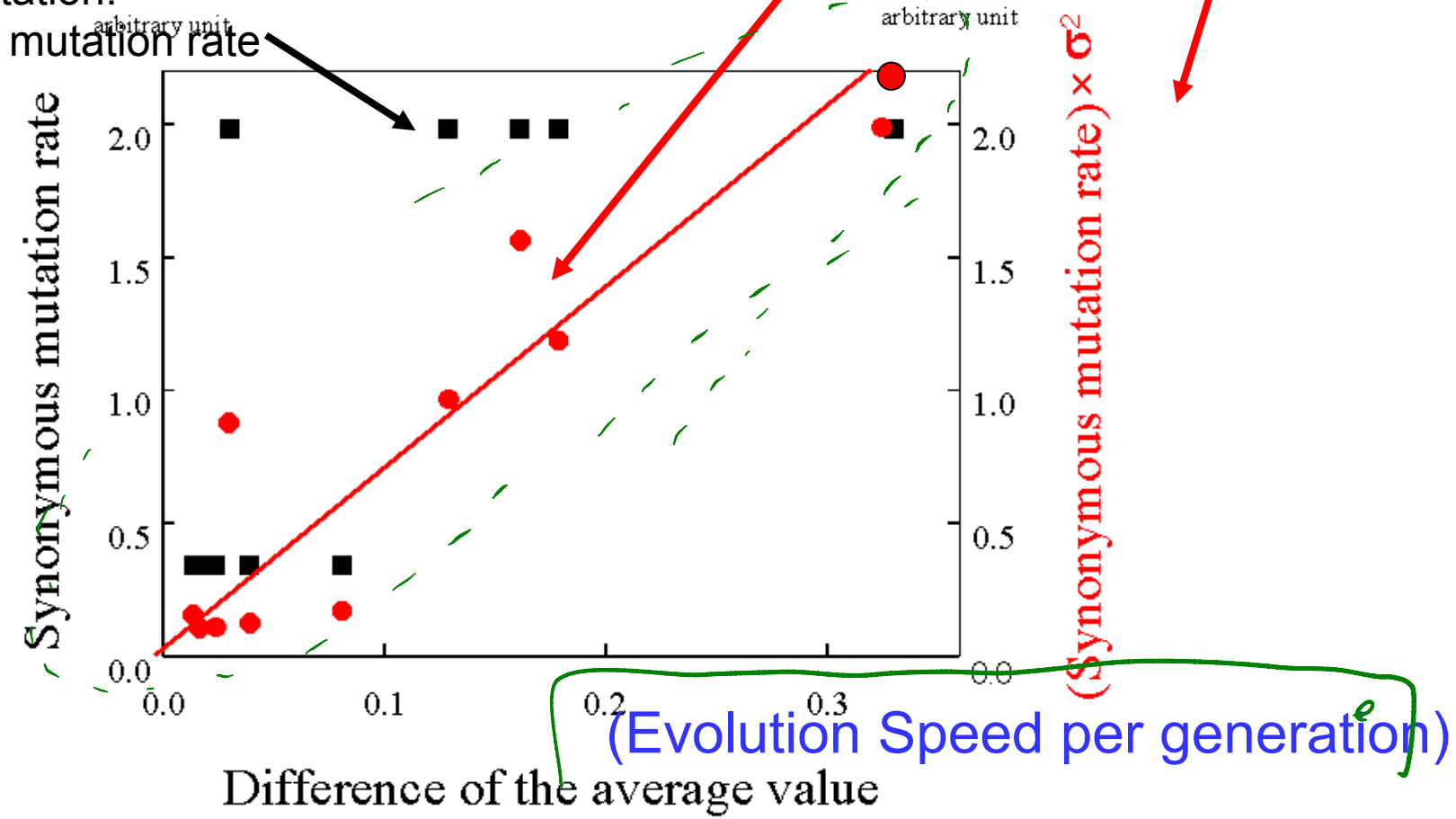
(1) Assumption of representation by P(x;a) **x** : phenotype a ; gene
(2) The coupling form Cxa is also assumption

→Not derivation; need to check experimentally

Evolution Speed／ mutation rate
∝ phenotype variance ?

Fluctuation-response relation
Phenotype fluct. × mutation rate

Naïve expectation:
Just propt to mutation rate



(Evolution Speed per generation)

Sato,Ito,Yomo,KK, PNAS 2003

- Confirmation by models

Requirement for models

Genotype – rule for dynamics (networks + parameters)

Dynamics – high-dimensional (many degrees, e.g., expressions of proteins) + noise

Phenotypes are shaped by attractor of the dynamical system

Fitness (Phenotype) (high-fitness state is rare)

Mutation+Selection process

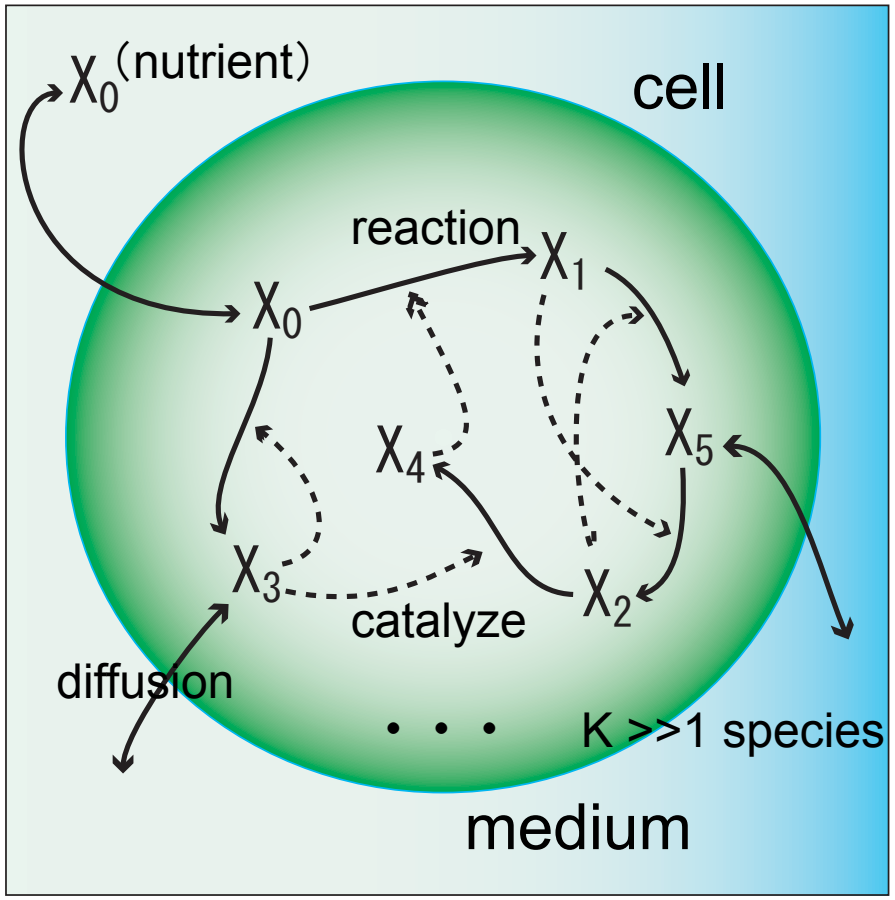
Previous Study on Recursive Production? :

Toy (Ideal) 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 細胞 (Cf. KK&Yomo 94,97)



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

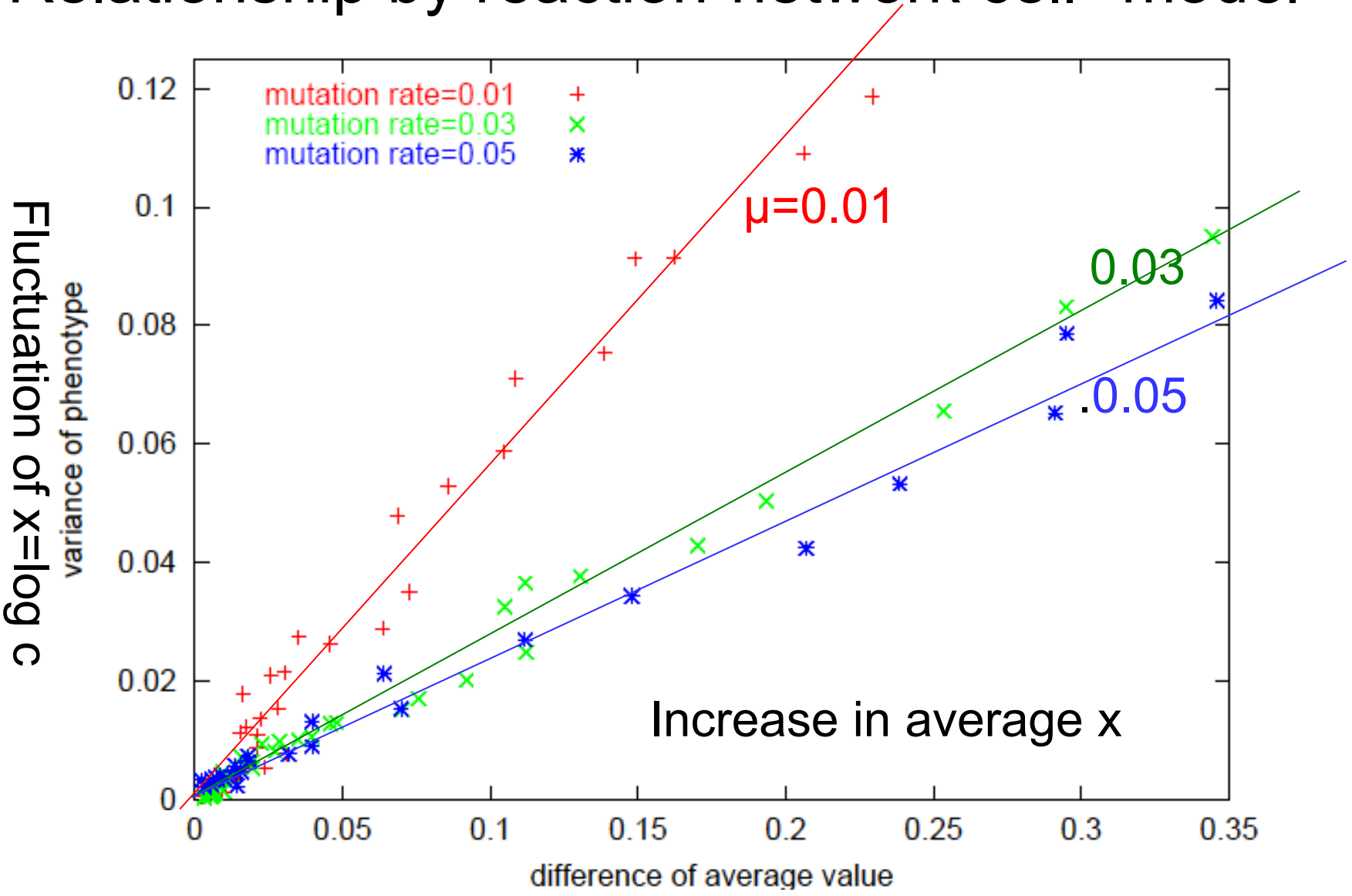
- Confirmation by numerical evolution experiment by the reaction-net cell model

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)

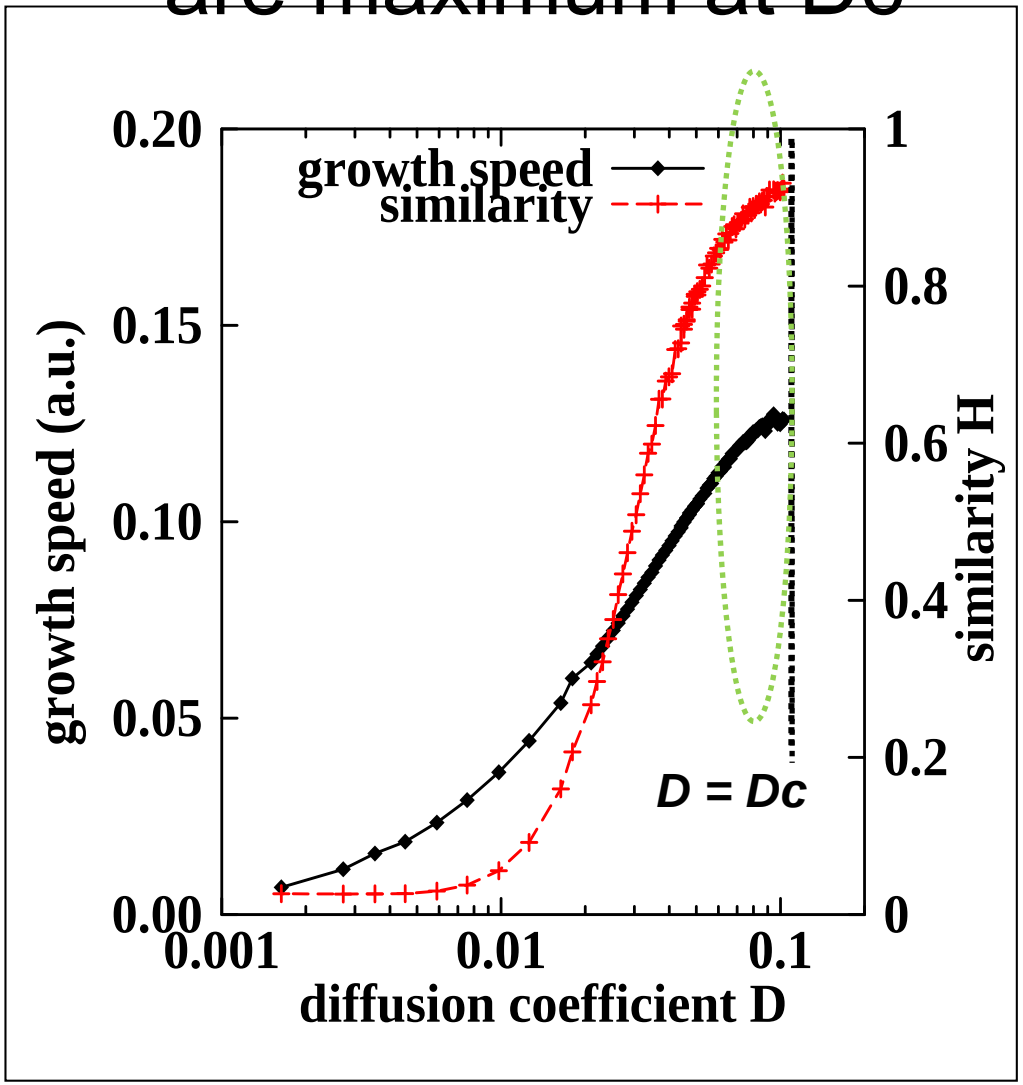
Confirmation of Fluctuation Response Relationship by reaction-network cell model

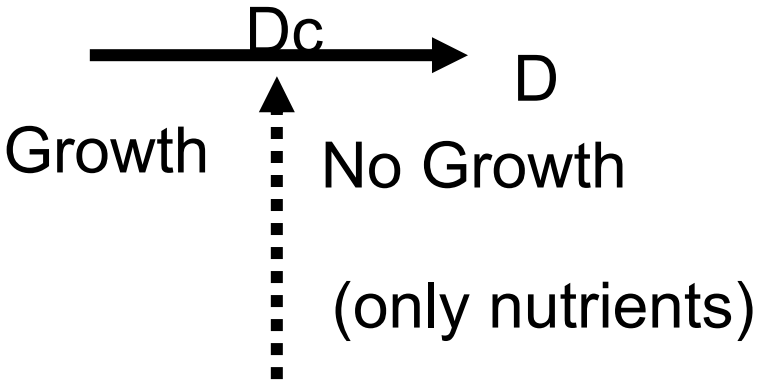


Furusawa,KK 2005

Remarks on the Catalytic Reaction Network Model

☆Growth speed and fidelity in replication are maximum at Dc





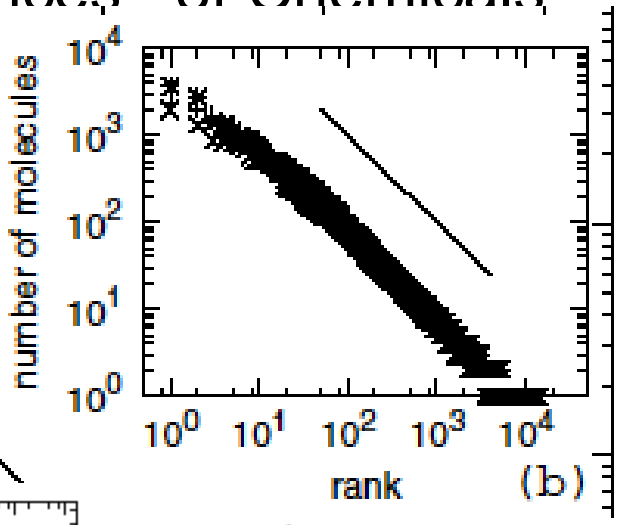
※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

By tuning the flow rate to stay an optimal growth Universal statistical law is observed

Power Law in Abundances of Chemicals

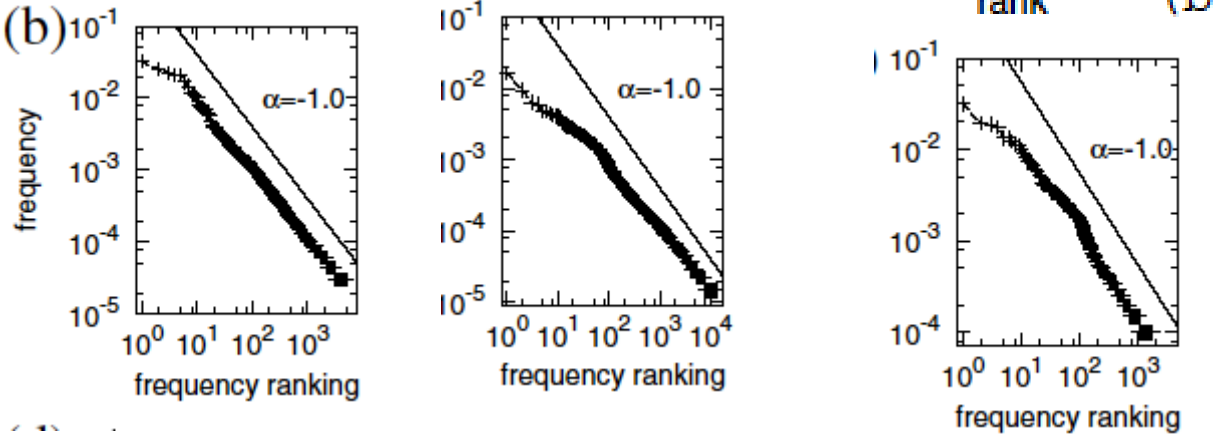
Theory;
To keep reproduction preserving compositions→



n_i (number of molecules

rank

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



Human kidney, mouse ES yeast

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

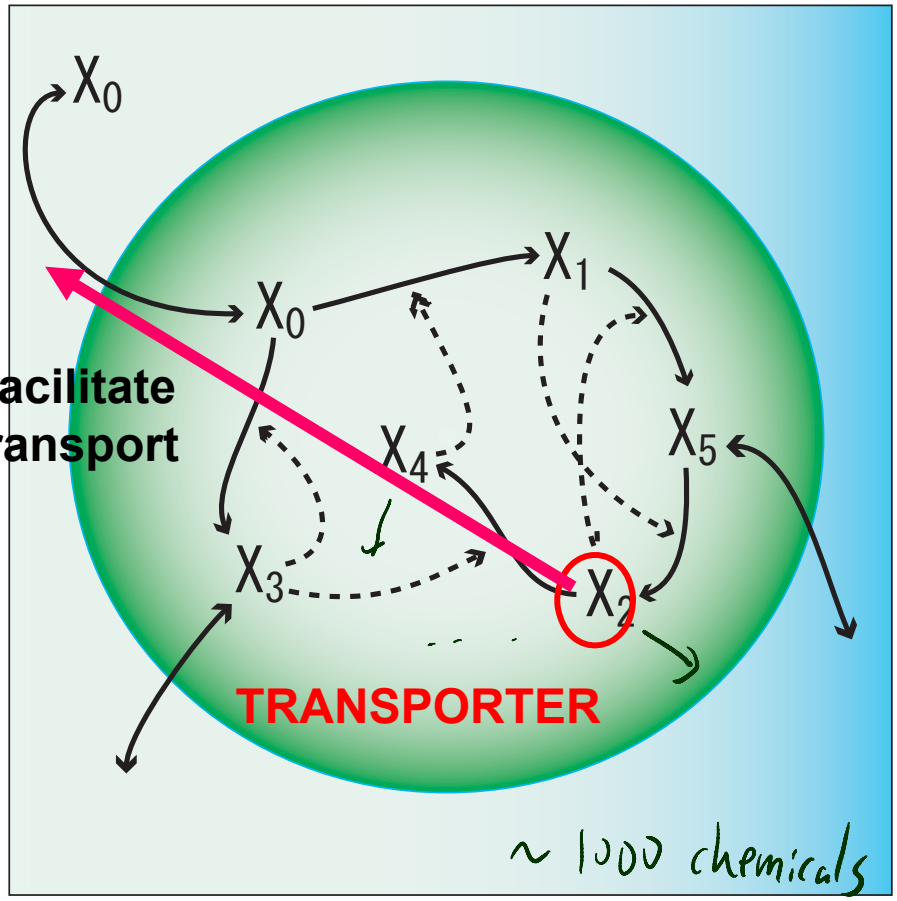
Generic Adaptation of a cellular state consisting of catalytic reaction network → Adaptation to Criticality just by introduction of transporter molecule that catalyzes the transport of resources

→ **self-tune the balance of concentrations of nutrient and catalytic chemicals**

adaptive to environment

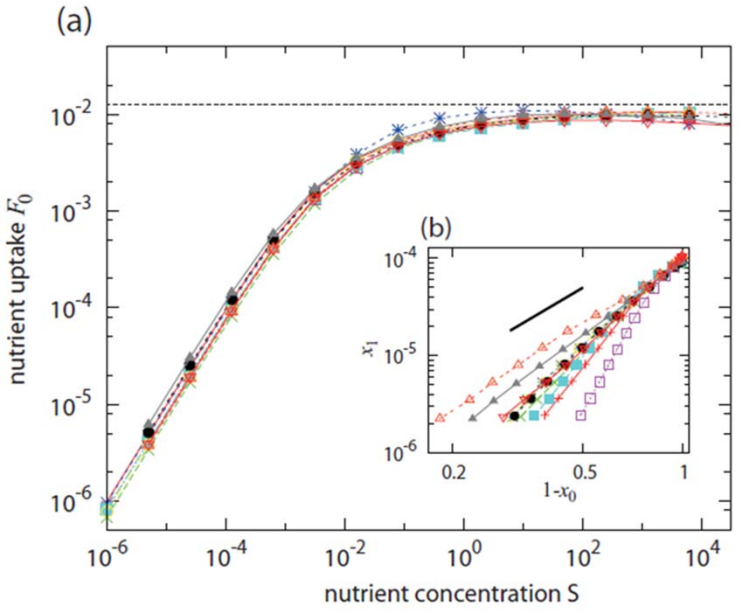
(Furusawa,KK, PRL, 2012)

Autonomous regulation by enzyme abundance

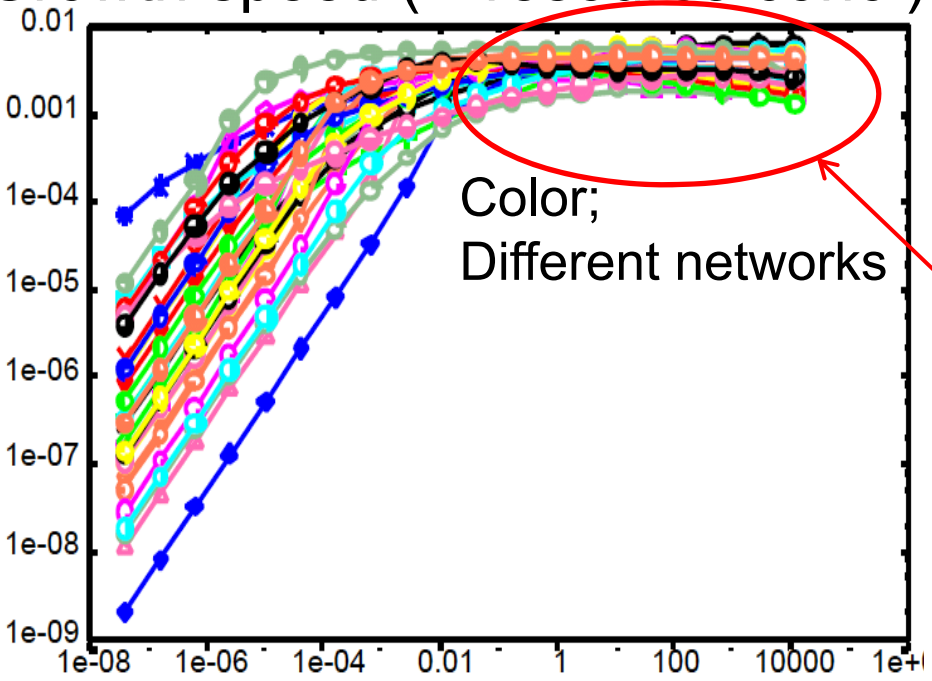


Mutual Dependency leads to maintenance of reproductior

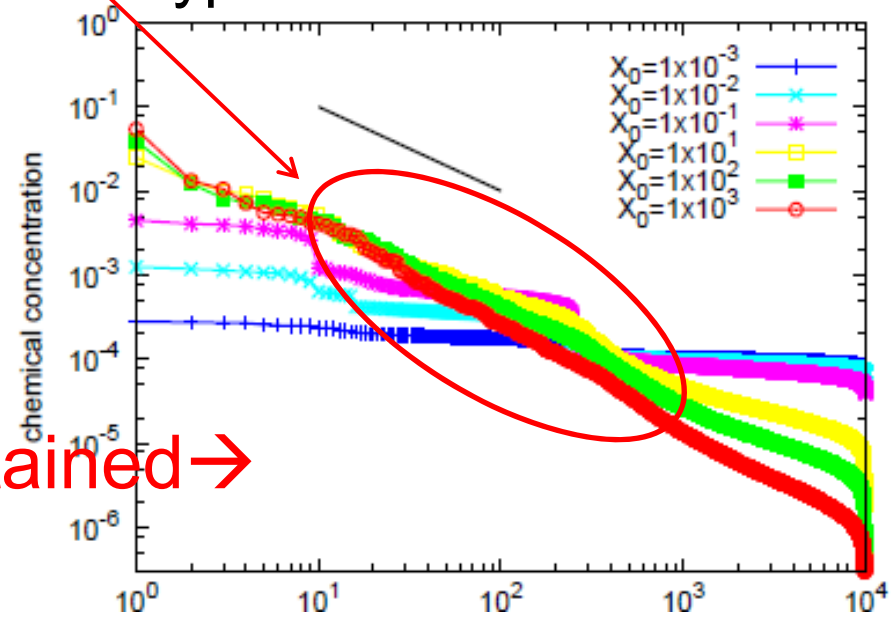
As long as external resource concentration is not too low, a cell adapts to a ‘critical’ state



Growth speed (∝resource conc.)



Also, demonstrated by mean-field-type calculations

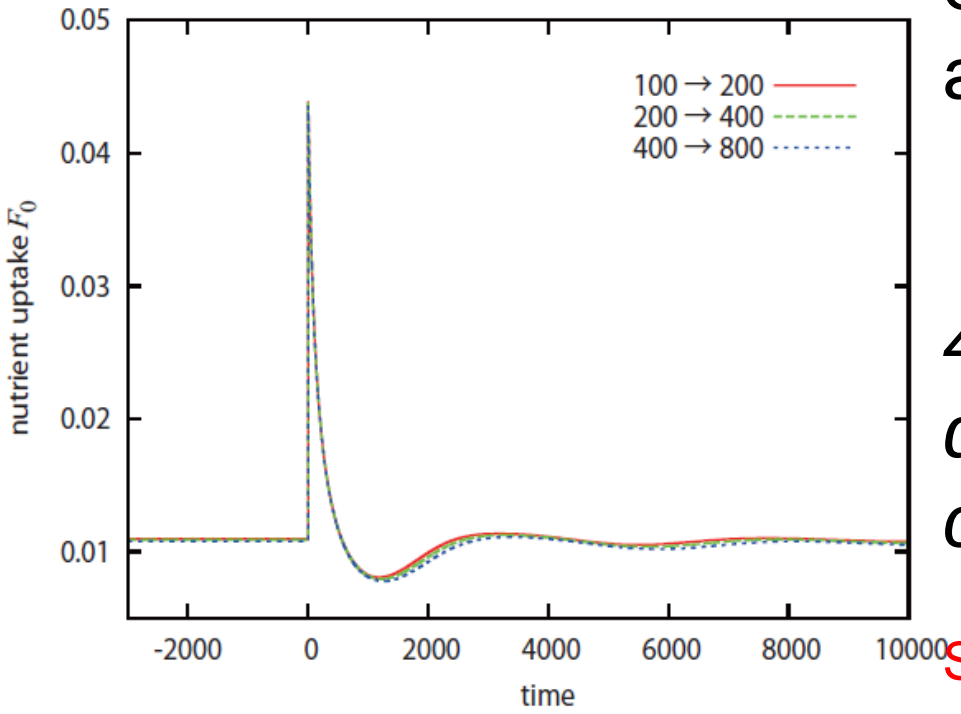


Power law abundances is sustained→

Adaptation dynamics (Fold Change Detection)

Change in environment (Resource)

Adaptive dynamics (growth speed first changes and returns to the original



Fold-change detection:

The adaptive dynamics depends only on the ratio of resources before and after. *e.g., after change of external resources*

100 → 200, 200 → 400, 400 → 800 , identical dynamics

common in present cells

(Goentro-Kirschner, Alon et al, Shimizu, Kamino-Sawai,…2009--),

Layer-mean-field

M paths, N components

Layer 0 (resource) → L1 →L2→ …→Lk

catalyst : mean field

$$dm_0/dt = Sm_k^\alpha - (M/N)(1-m_0)m_0 - Sm_k^\alpha m_0$$

$$dm_j/dt = (M/N)((1-m_0)m_{j-1} - (1-m_0)m_j) - Sm_k^\alpha m_j,$$

$j = 1, \cdots, k$, and $M = \rho N$ indicates the mean number of reaction paths

By setting $dm_0/dt = 0$, we obtain $F_0 = Sm_k^\alpha = \rho m_0$, Growth rate

$dm_j/dt = 0$, we get $m_j = m_{j-1}(1-m_0)$. Thus, we get $m_k = m_0(1-m_0)^k$.

S is large, $m_k \propto (1-m_0)^k$ follows;

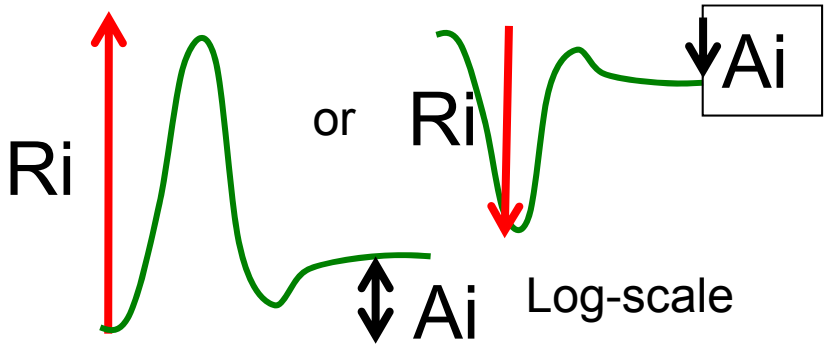
$F_0 \sim \rho$, i

at k-th layer obeys $m_k = m_0(1-m_0)^k$. On the other hand, at each k-th layer, there are $\sim (\rho N)^k$ chemical species. Hence, the ranking of the chemical at k-th layer, denoted by r_k, in the order of abundances increases as $r_k \sim (\rho N)^k$ when ρN is enough large, and thus $k = \log(r_k)/\log(\rho N)$. From these equations, we obtain $m(r_k) = m_0(1-m_0)^{\log(r_k)/\log(\rho N)}$, where $m(r_k)$ represents the chemical concentration of r_k-th ranked chemical. Thus,

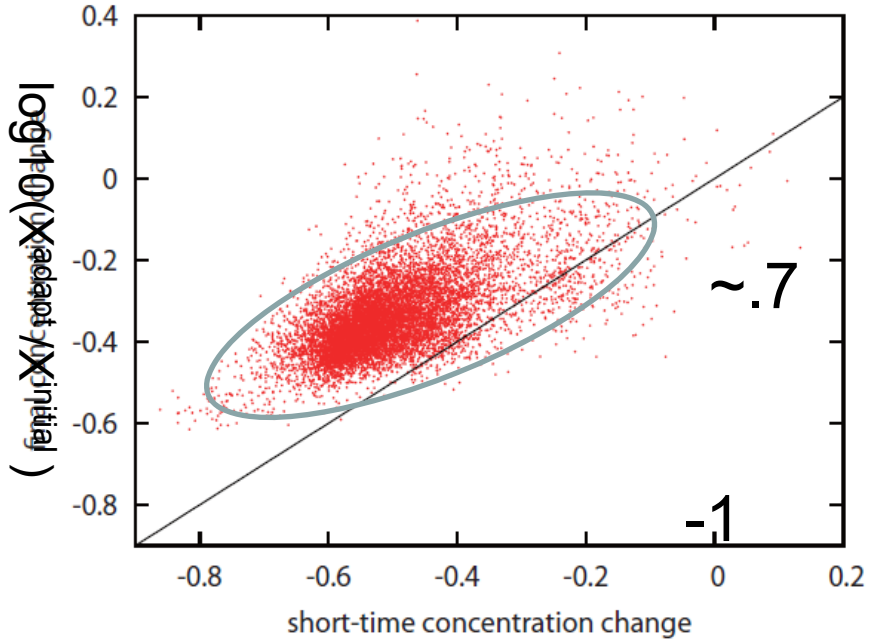
$$\log m_k = \log m_0 - \alpha \log(r_k) \qquad \text{(S1)}$$

Common High-dimensional Adaptation dynamics

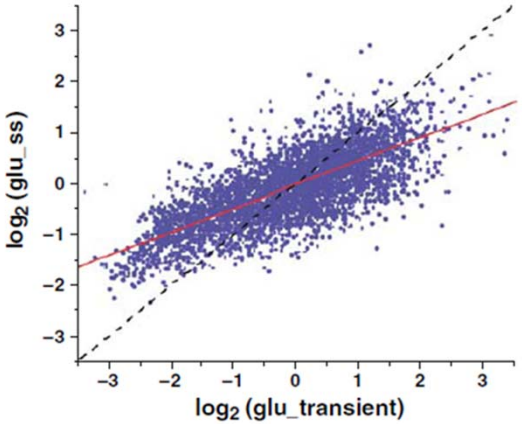
all chemicals show 'partial' adaptation



All of 10000 chemicals i show imperfect adaptation.
Response/Adapt
Ri= C * Ai with 1> C>0



$\log_{10}(X^{response} / X^{initial})$



Yeast, change in expression level of each gene by environmental change

Molecular Systems Biology 3; Article number 106; doi:10.1038/msb4100147
Citation: *Molecular Systems Biology* 3:106

www.molecularsystemsbiology.com

Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge

Shay Stern[1], Tali Dror[1], Elad Stolovicki[2], Naama Brenner[1] and Erez Braun[2,*]

- Ideal-Cell-Model of this version

(1)Optimal growth is achieved

(2)Power Law in abundances (Zipf's law)

(3)Adaptation dynamics of growth rate with FCD

(4)General trend of partial adaptation

just by catalytic reaction network +feedback from transporter(=enzyme).

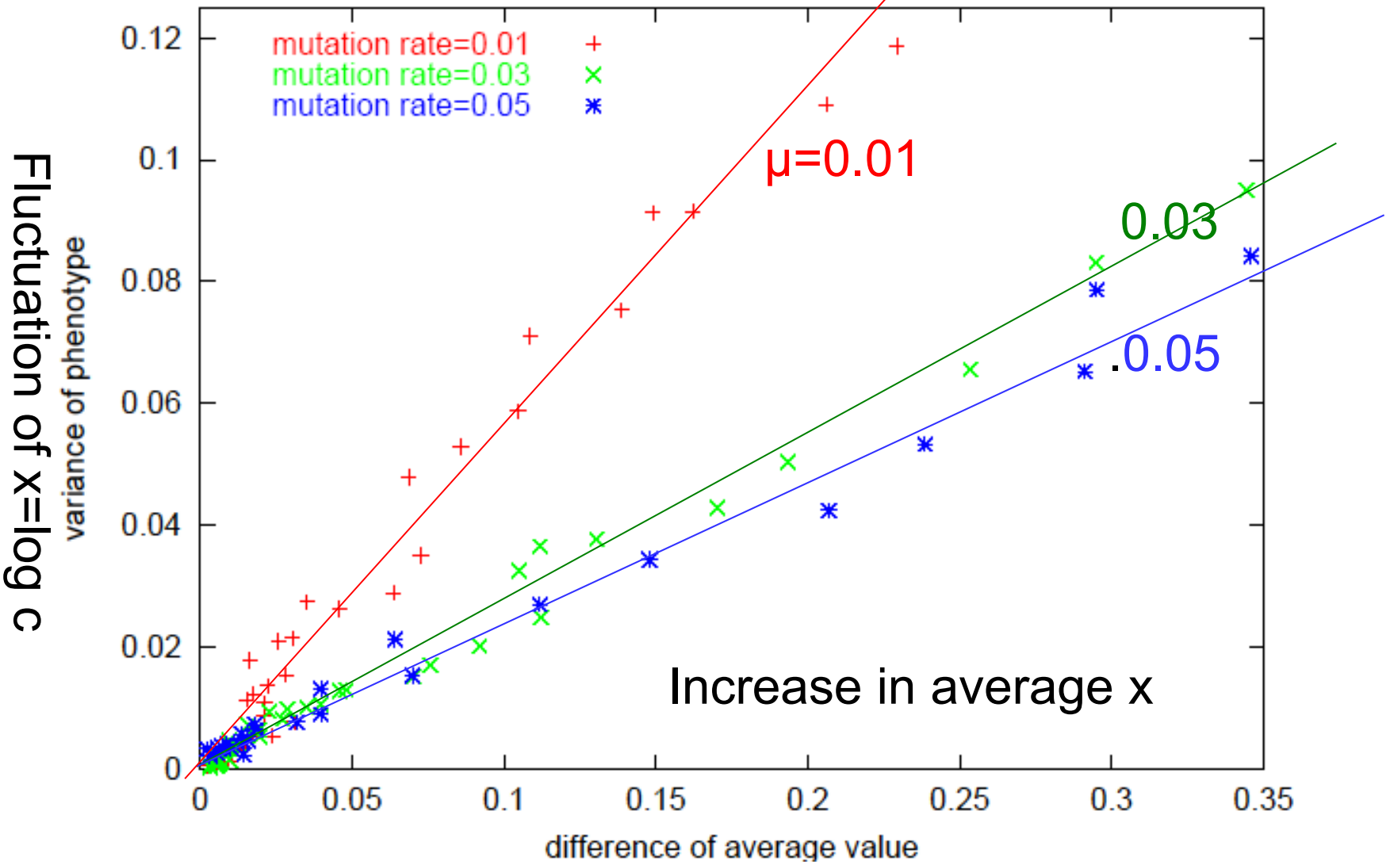
Interestingly, (1)-(4) agree well with the observations in the present cells

(1)-(3) is explained by layer-mean-field theory

Autonomous Regulation by enzyme abundances

(cf. Temperature Compensation in Circadian rhythm by autonomous regulation in time scale?)

Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model



Furusawa,KK 2005

NB: the use of log(fluorescence), or log(abundances), because

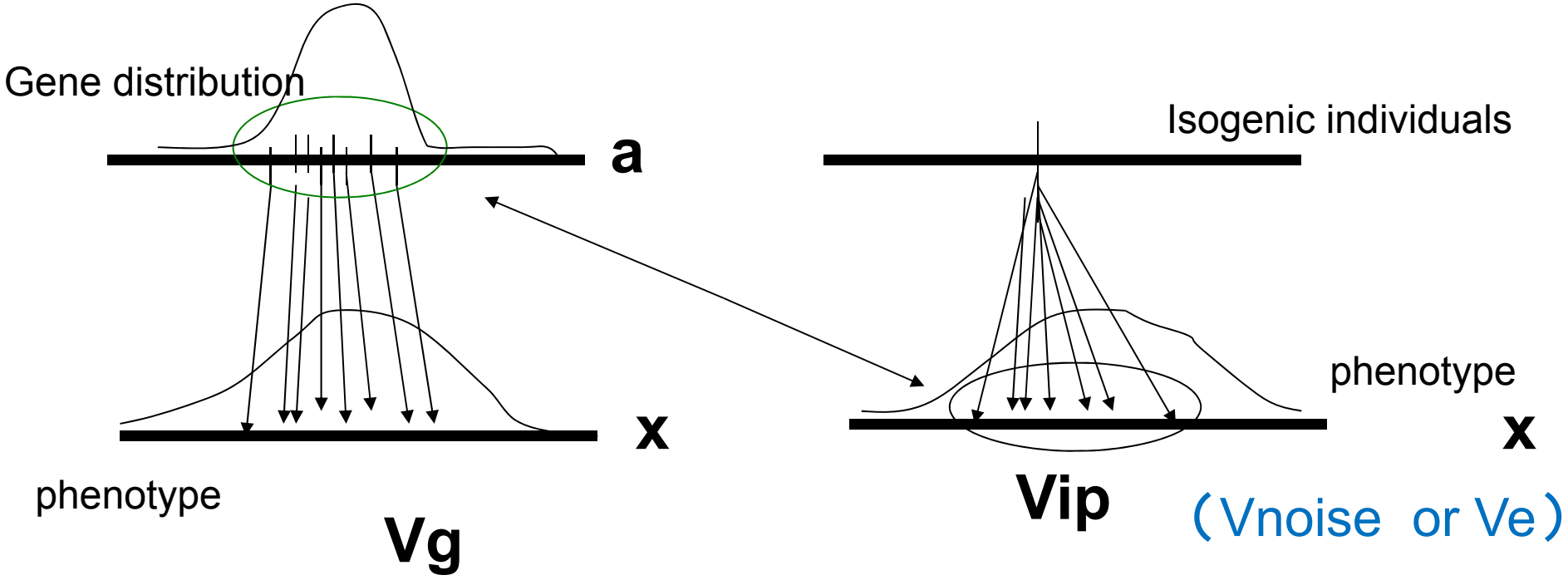
log x is close to Gaussian distribution in experiments

So far: Variance of Phenotype over Isogenic Individuals

Vip ∝ Evolution Speed

Harder to evolve as development is rigid

- ？Further Mystery？ Fundamental Theorem of Natural Selection
- Evolution speed∝ Variance of Average Phenotype over heterogenic distribution Vg
- （Fisher,established）: Then → Vip ∝Vg？？



- 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 I should call V_noise)

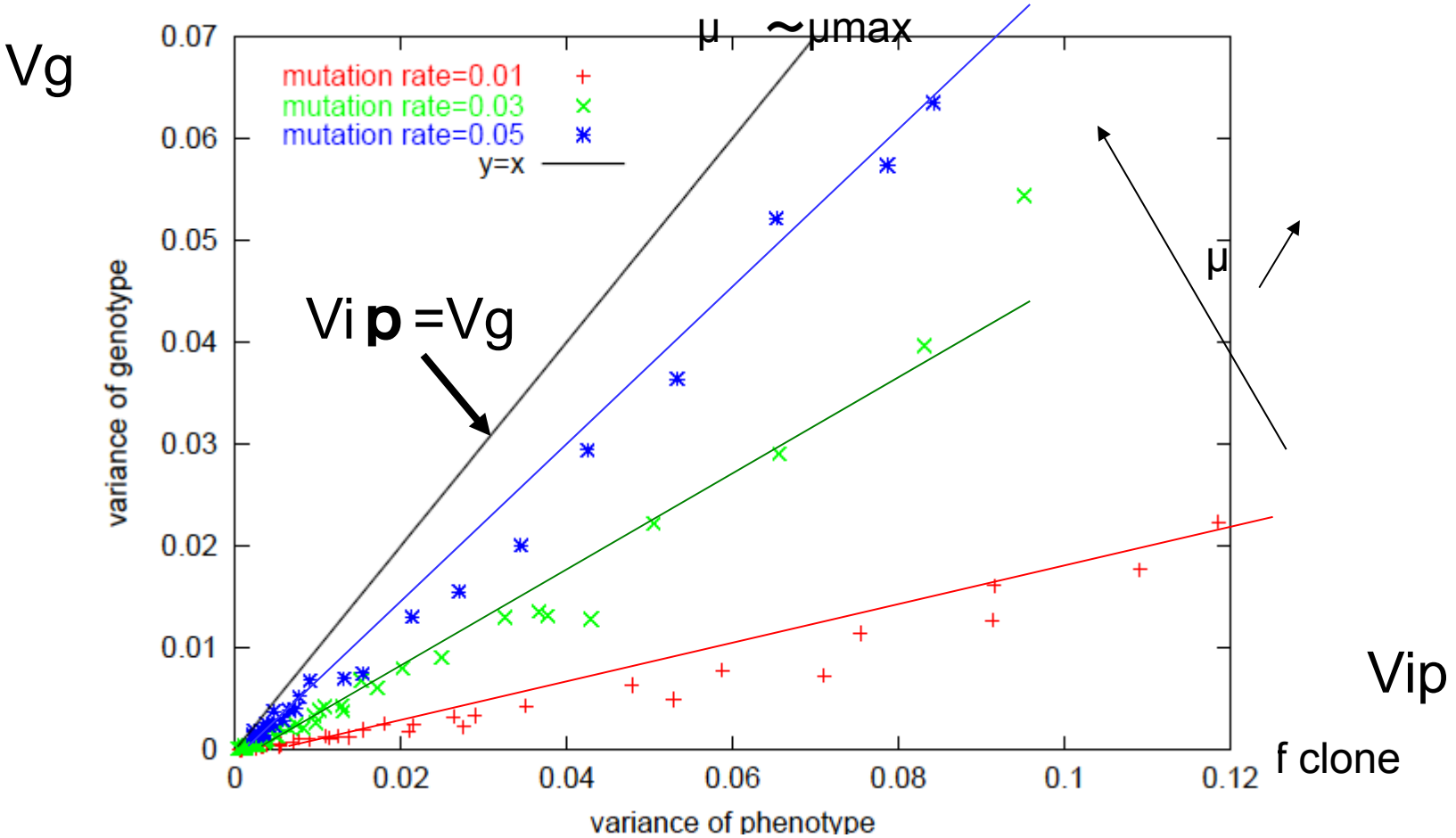
(It may not be easy to distinguish V_noise from Ve..)

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

→ check by cell model

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

Proportionality -- Result of evolution;

first few generations -- deviated

As μ (mutation rate) increases to μ max,

(1) the distribution collapses (error catastrophe)

(2) evolution no longer progresses beyond μ max

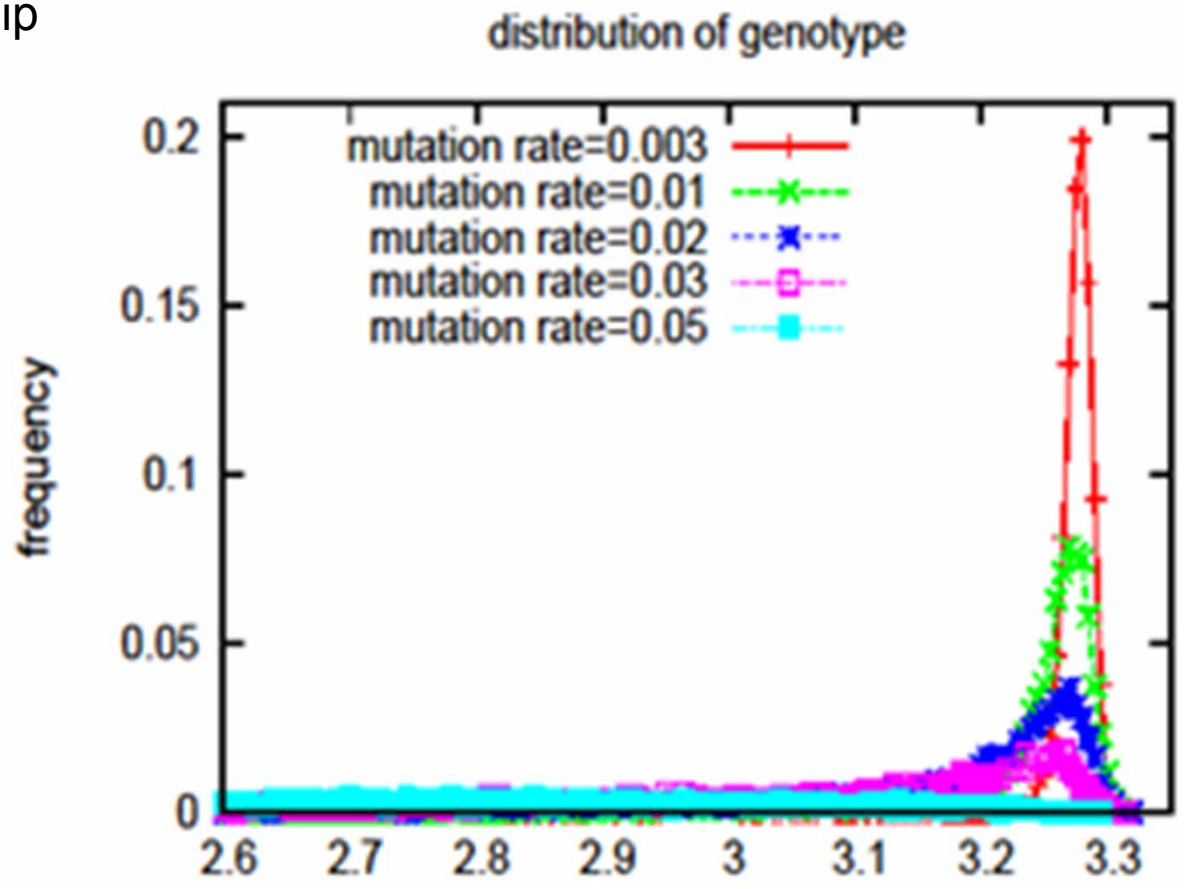
evolution speed is maximal at μ ~ μ max

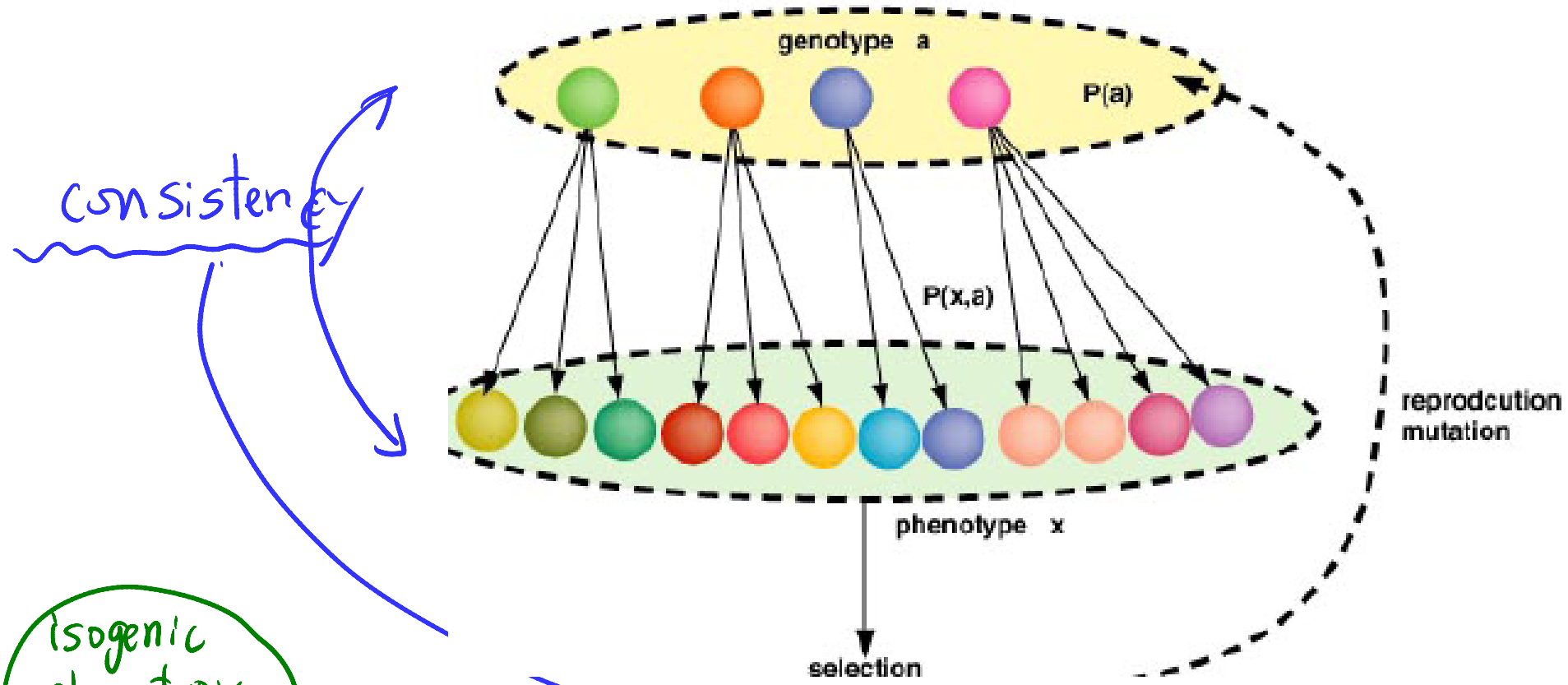
(3) Vg approaches Vp

Vip

As μ is increased,
The distribution
'collapses'

Error catastrophe





consistency

isogenic phenotypic fluct.

genotype (a) (same)

V_{ip}

genotype (distributed)

phenotype x

V_g

$V_g \leftrightarrow$ evolution speed

? V_{ip} ??

Phenomeonological explanation?

Consider 2-variable distrb

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

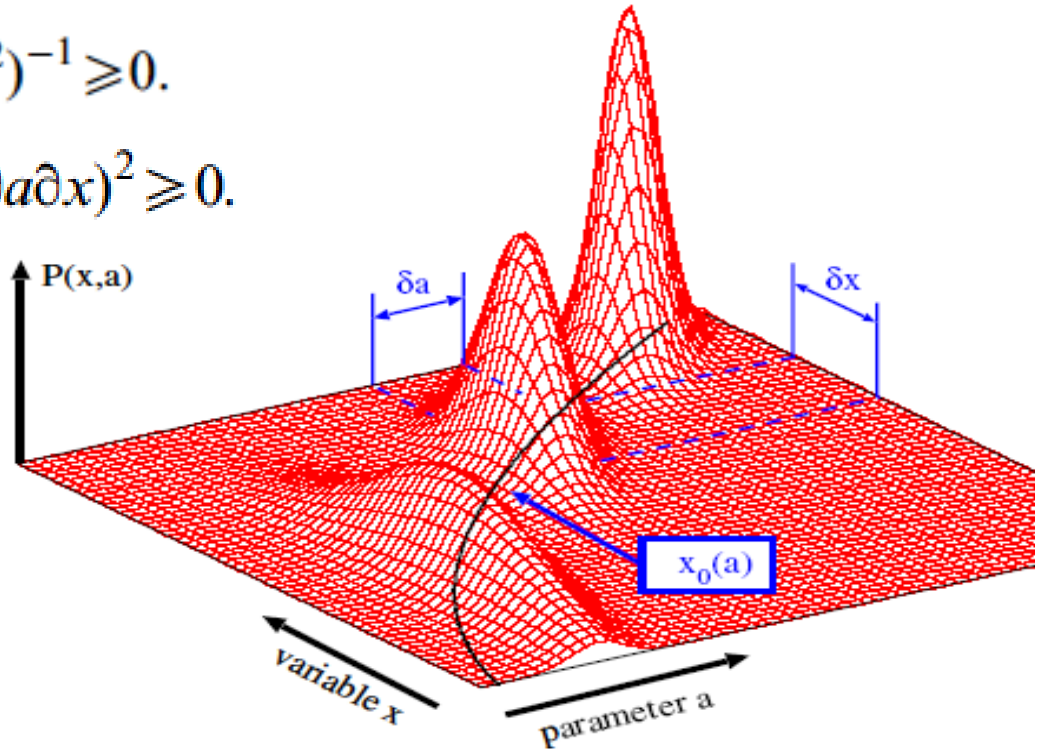
Keep a single-peak (stability condition).

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

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

Hessian condition

Leads to relationship between Vip and Vg



KK,Furusawa, 2006 JTB

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

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

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

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

$$V_g = \frac{\mu C^2}{1-\mu C^2/\alpha} \quad \sim \text{Vig} = \mu C^2 \qquad \text{Vip} = \alpha$$

If mutation rate μ is small, Vg<Vip,

Vg ~ (μ/μmax)Vip ∝ Vip

(i) Vip ≧ Vg （from stability condition)

(under strong selection pressure) (**)

(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,,,,,

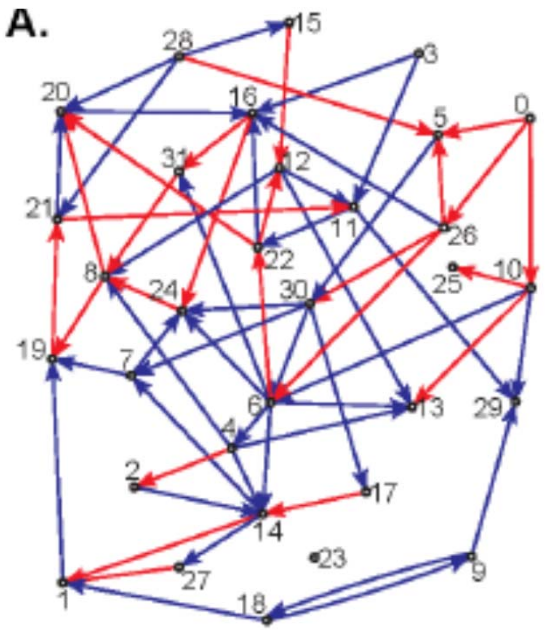
Existence of P(x,a)?;+ Robust Evolution? +

Why isogenetic phenotypic fluctuation leads to robust evolution?

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

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

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



Activation
Repression
Jij=1,-1,0

Xi – expression of gene i :

on off

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

$$<\eta_i(t)\eta_j(t')> = \delta(t-t')\delta ij$$

Gaussian white

M;total number of genes, k : output genes

Noise strength σ

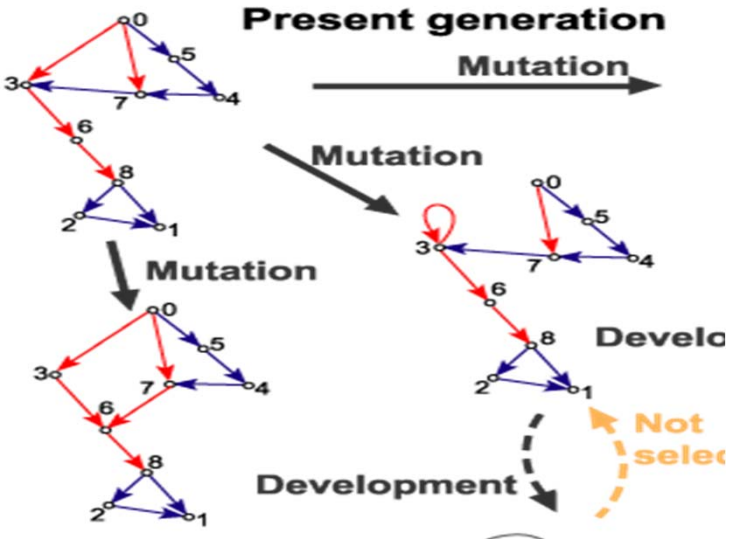
- Fitness: Starting from off of all genes, after development genes xi i=1、2、···、k should be on (Target Gene Pattern)

Fitness F= －（Number of off x_i）

Genetic Algorithm

Population of N different genotypes(networks). Select those with higher <F> and mutate with rate μ

Keep N networks

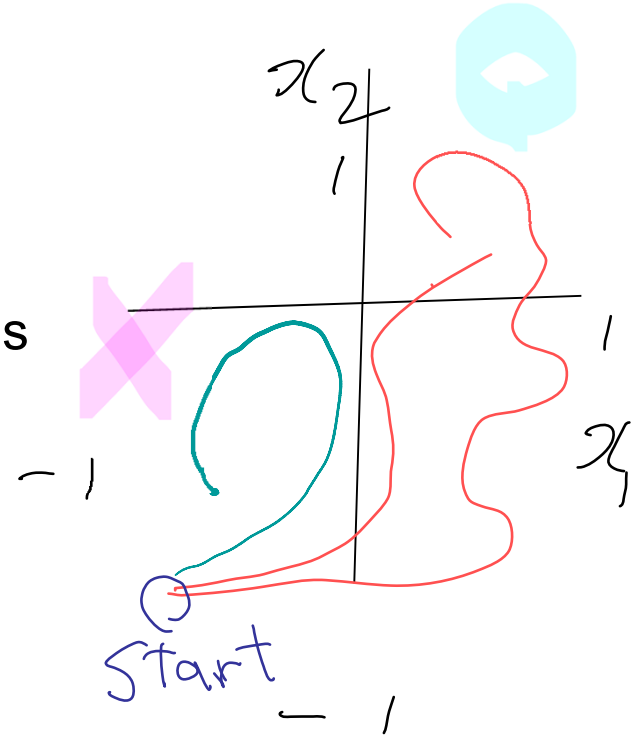


If M=k=2→

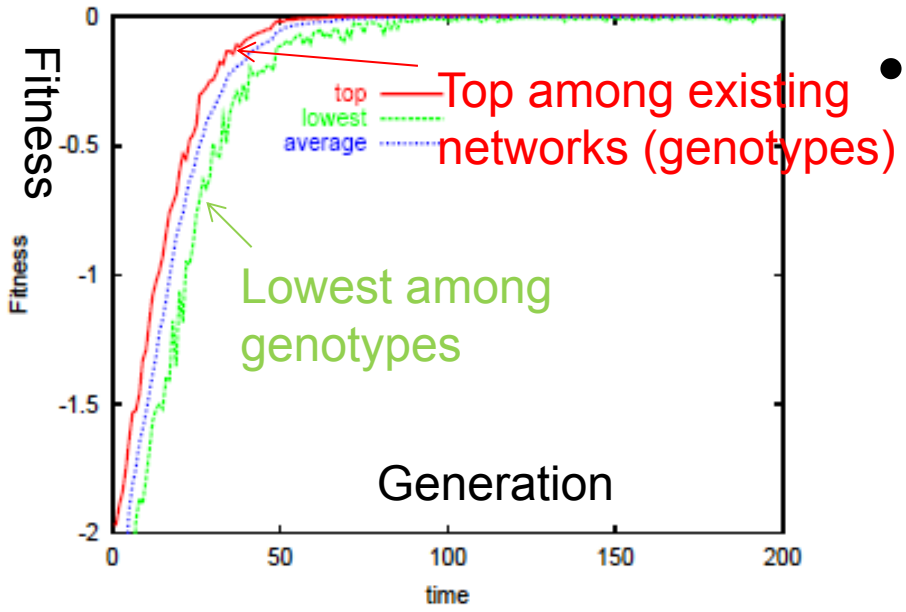
Most simulations

M=64

K=8

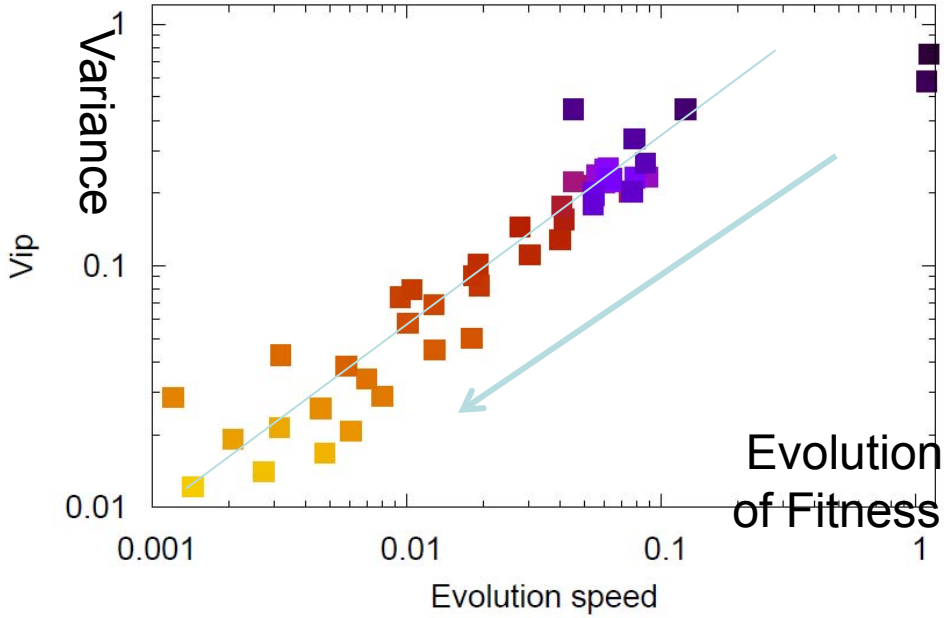


Results of Evolution Simulation （noise　σ=.08)



- Fitness　increases

Isogenic Phenotypic Variance　of decreases by generations through evolution

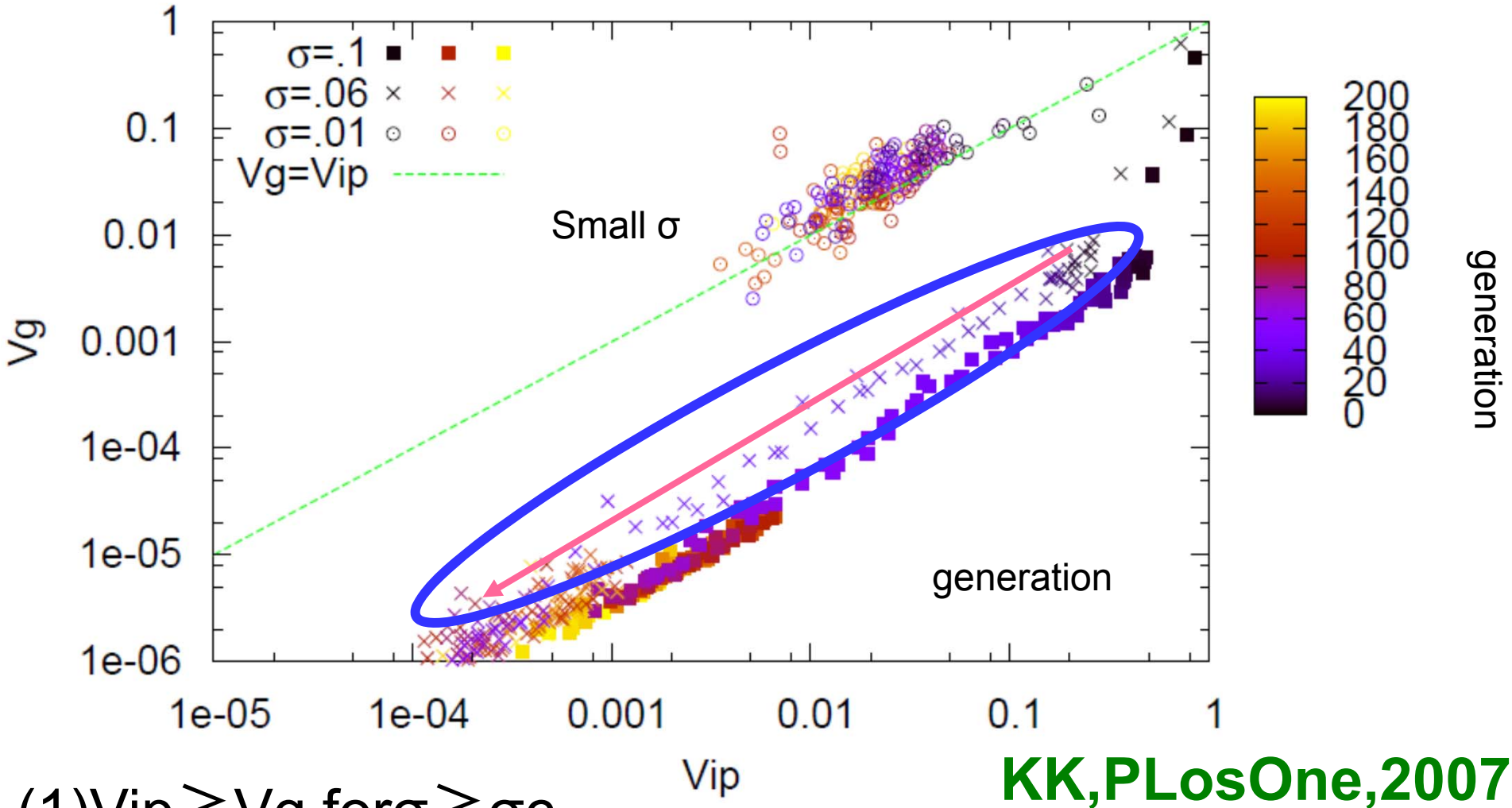


Variance

∝　evolution speed

through generations

Evolution speed= Increment of Fitness per generations



KK,PLosOne,2007

(1)Vip≧Vg forσ≧σc

(2) Vg→Vip as σ→σc

(3) evolution progresses only for Vip ≧Vg

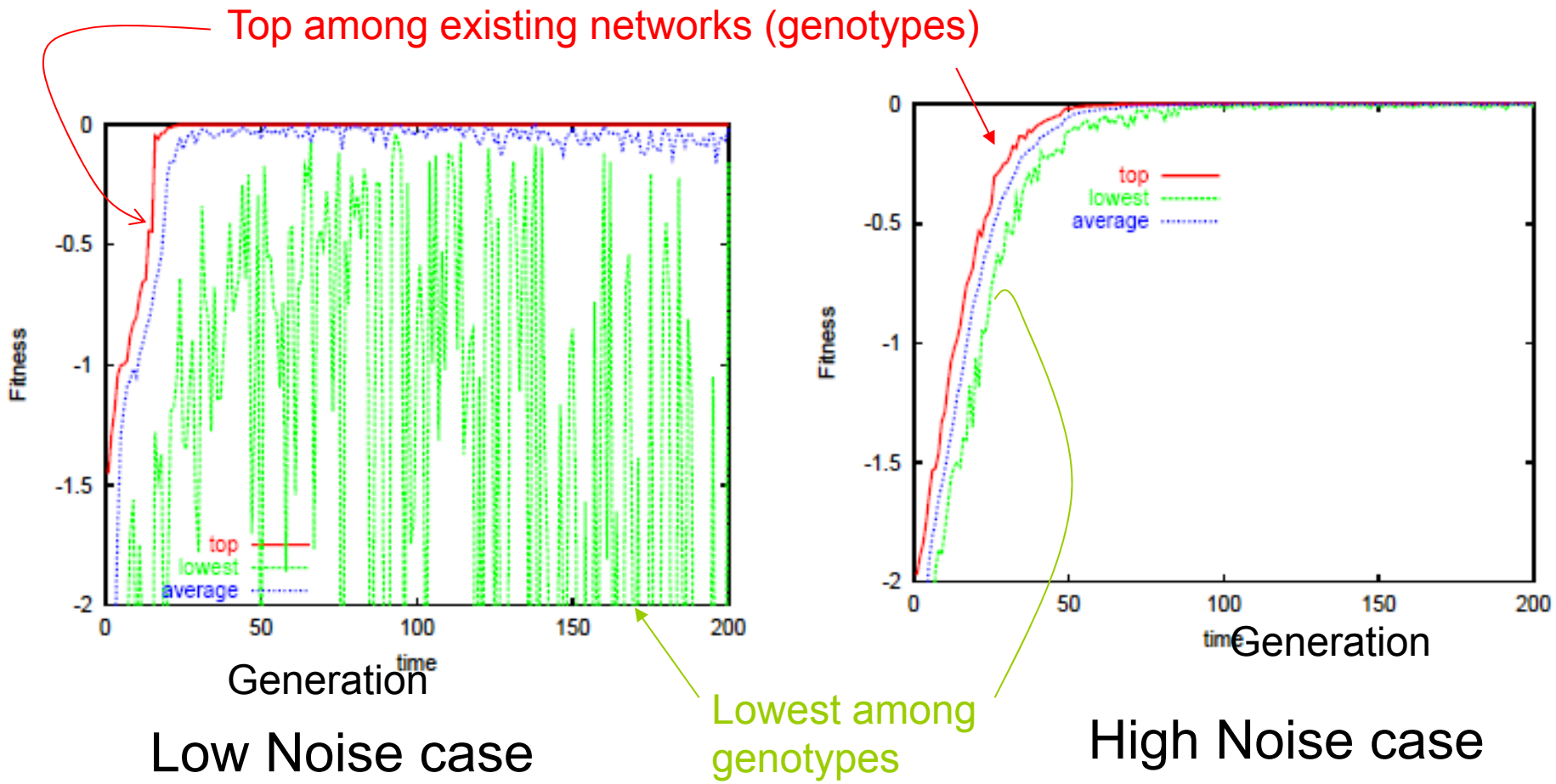
(4) Vip∝Vg through evolution course

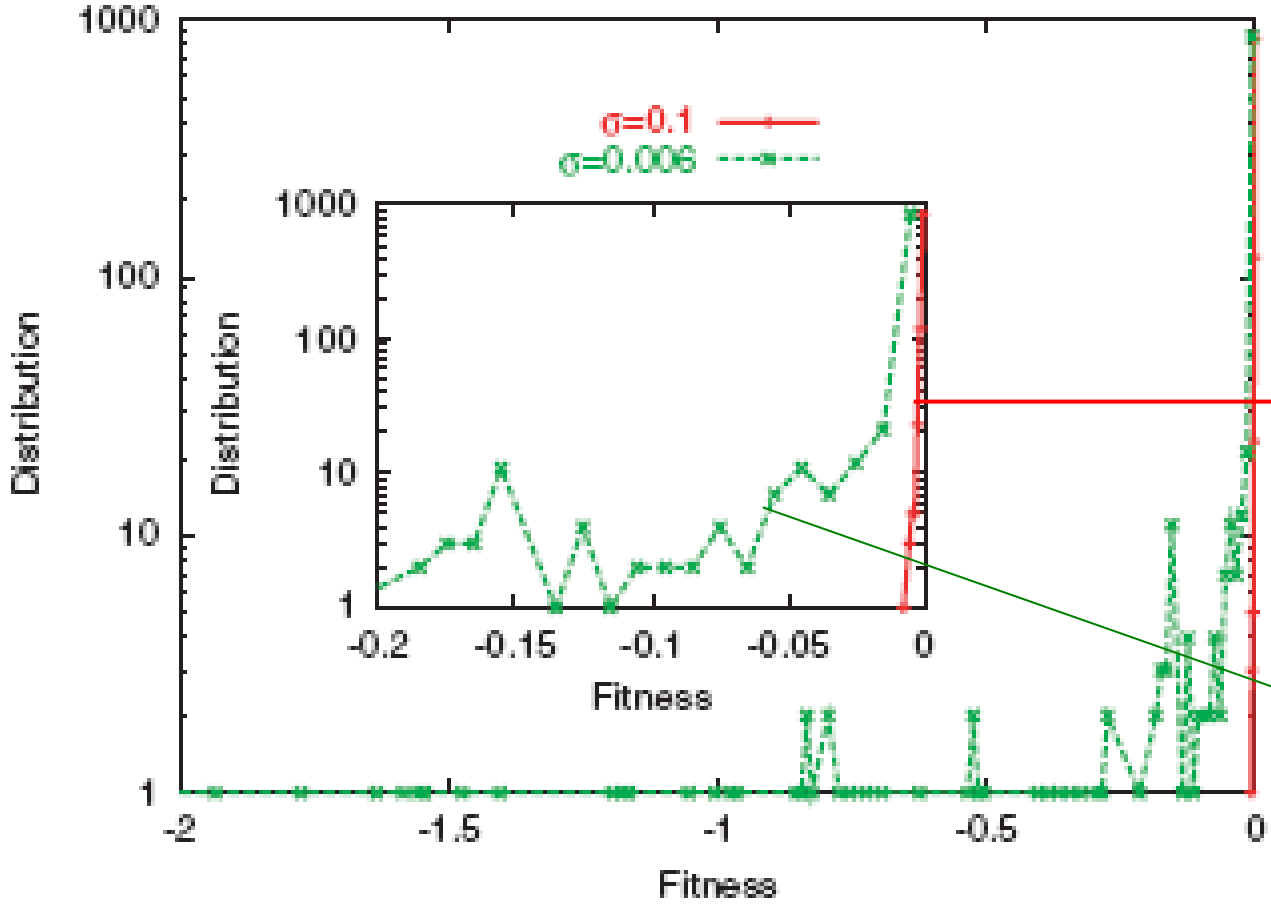
Distribution Theory confirmed

This Vg-Vip relation is valid in the evolution under noise

high noise(σ) → all (including mutants) reach the fittest

lower noise(σ) → non-fit mutants remain





Result of evolution

Top:reaches the fittest

Lowest;cannot evolve for low noise(σ)

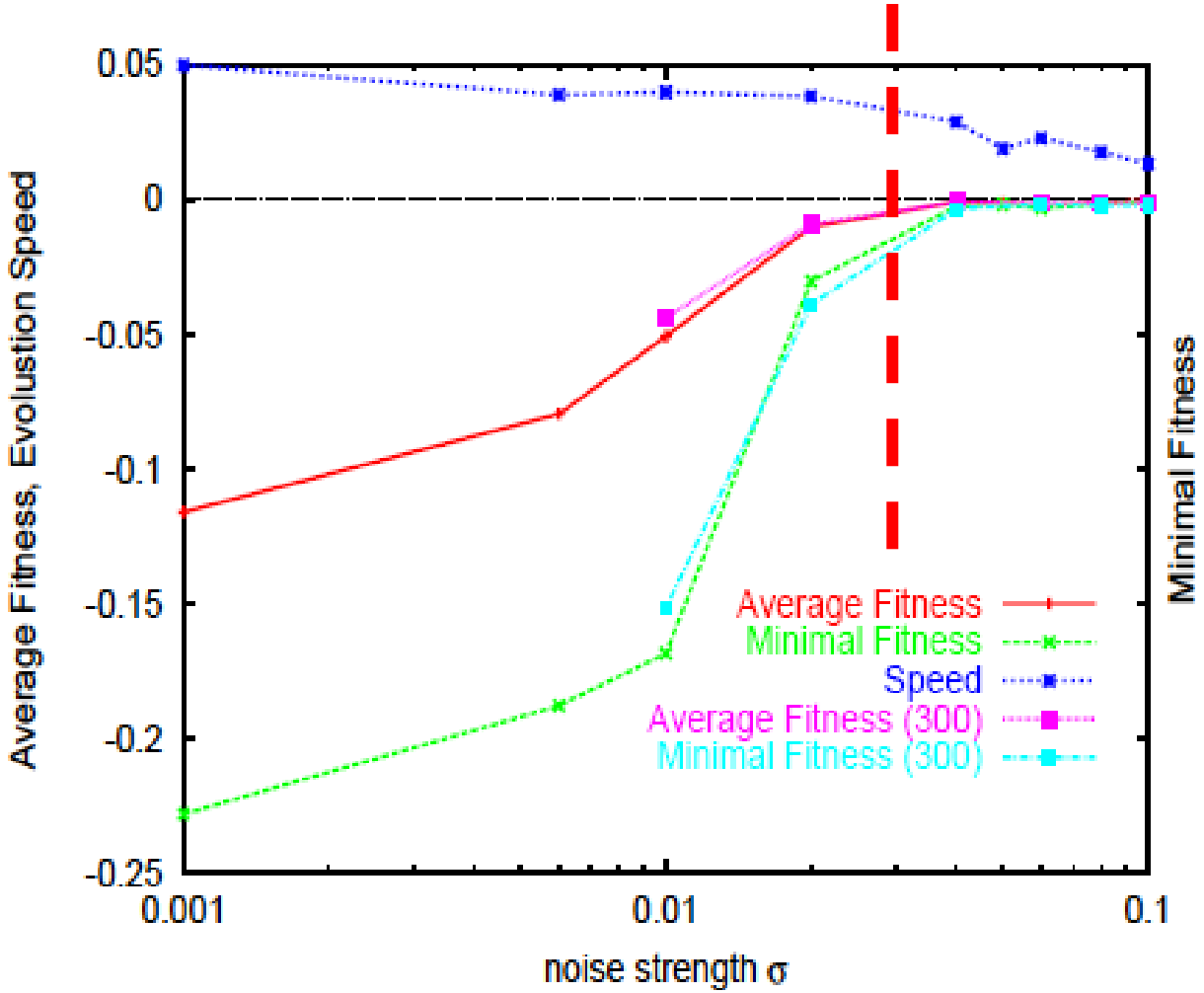
$\sigma > \sigma_c$

$\sigma < \sigma_c$

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)

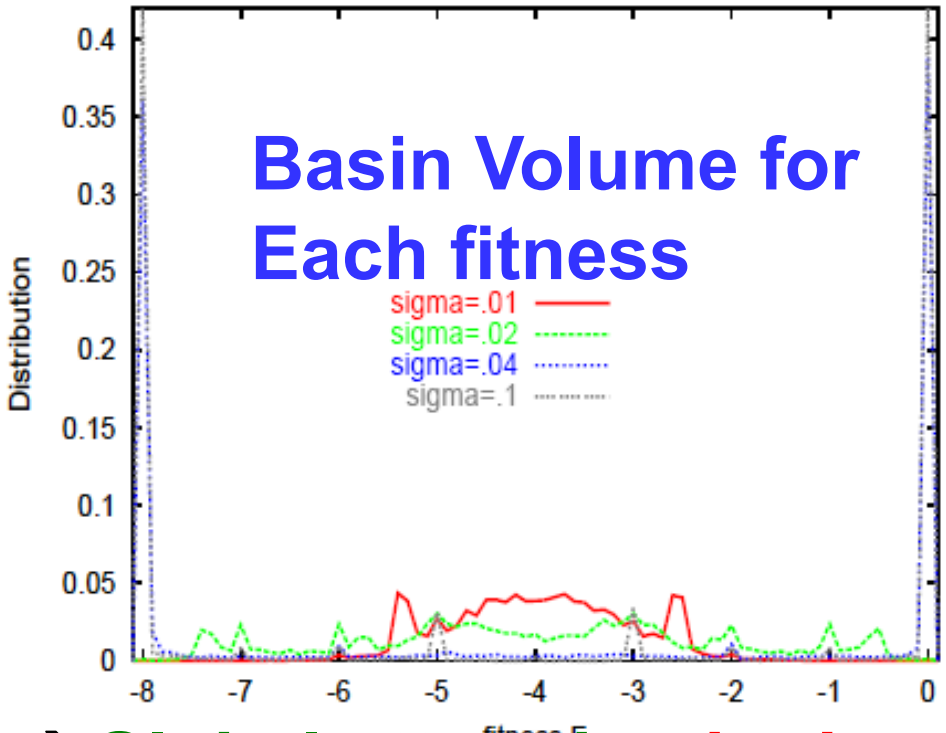
Why?; difference in basin structure

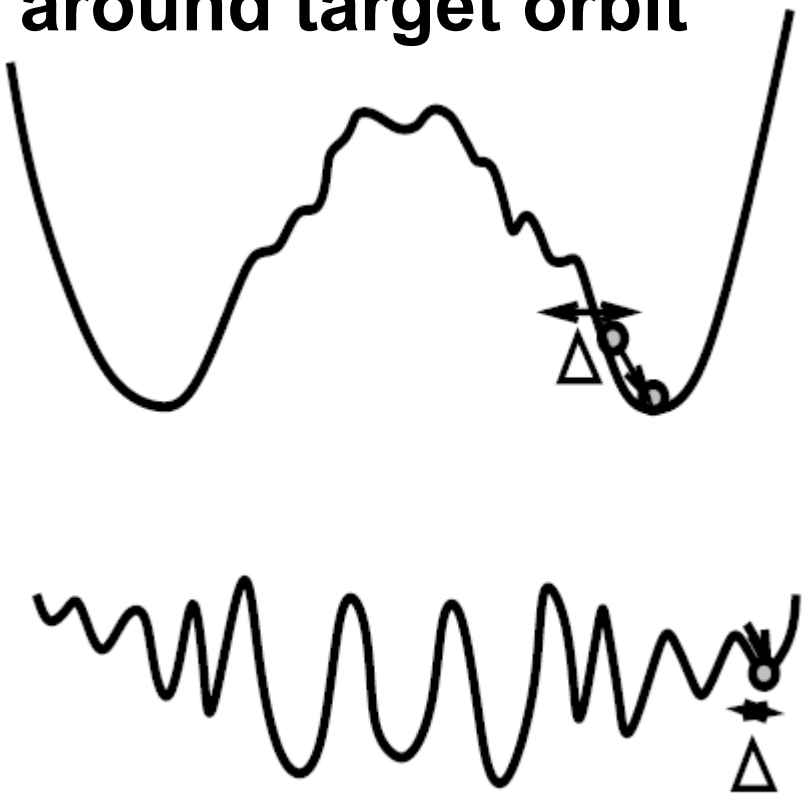
σ＞σc → large basin for target attractor

(robust, Δ（distance to basin boudary) ↑

σ＜σc → only tiny basin around target orbit

Δ remains small





→Global attraction in developmental landscape

←→ evolutionary landscape (neutral)

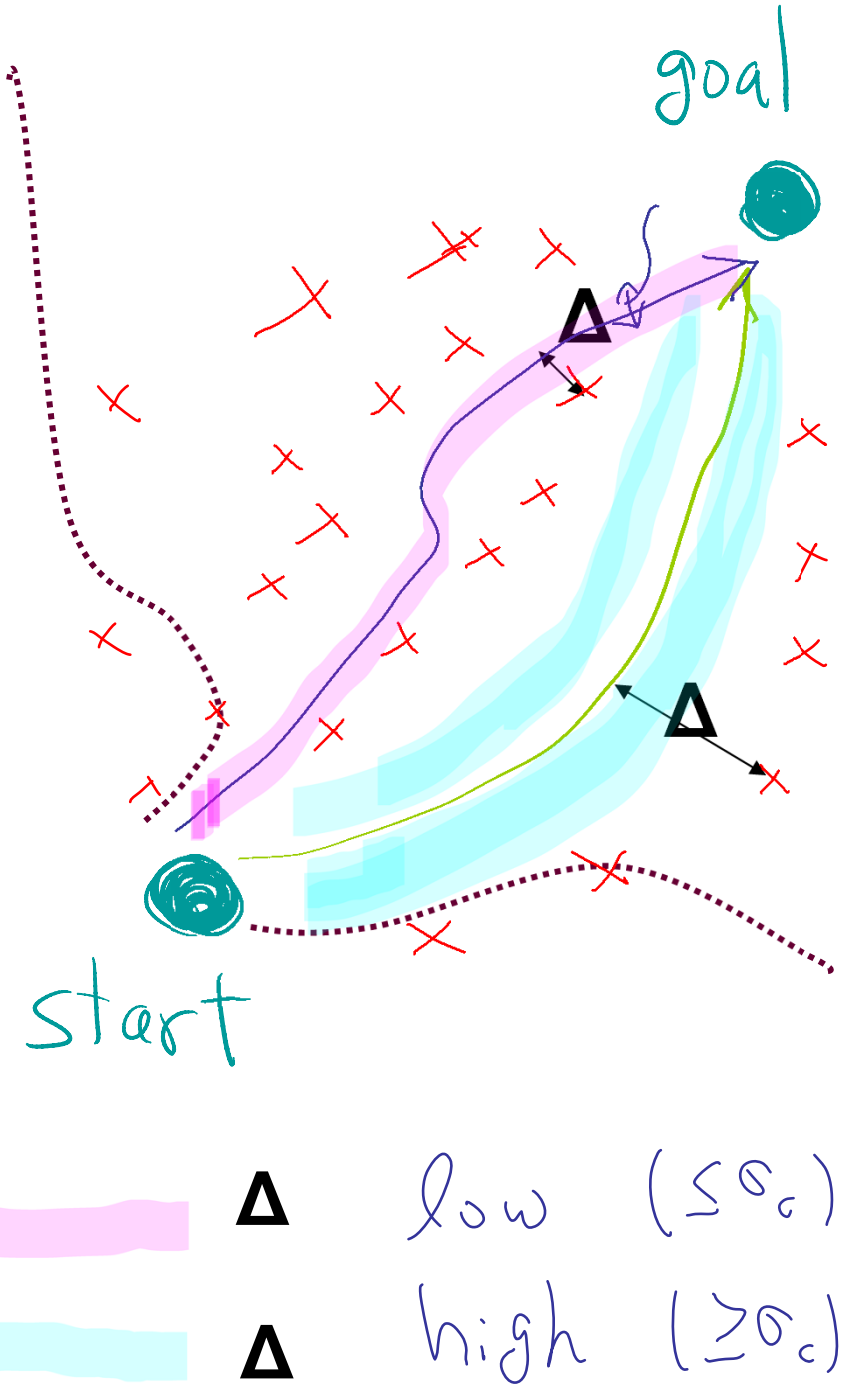
cf. funnel in gene-expression (Li,Long,Lu,Ouyang,Tang)

why threshold?

choose paths to avoid turning pts within σ (noise)

Mutation→ touches turning points within range of μ

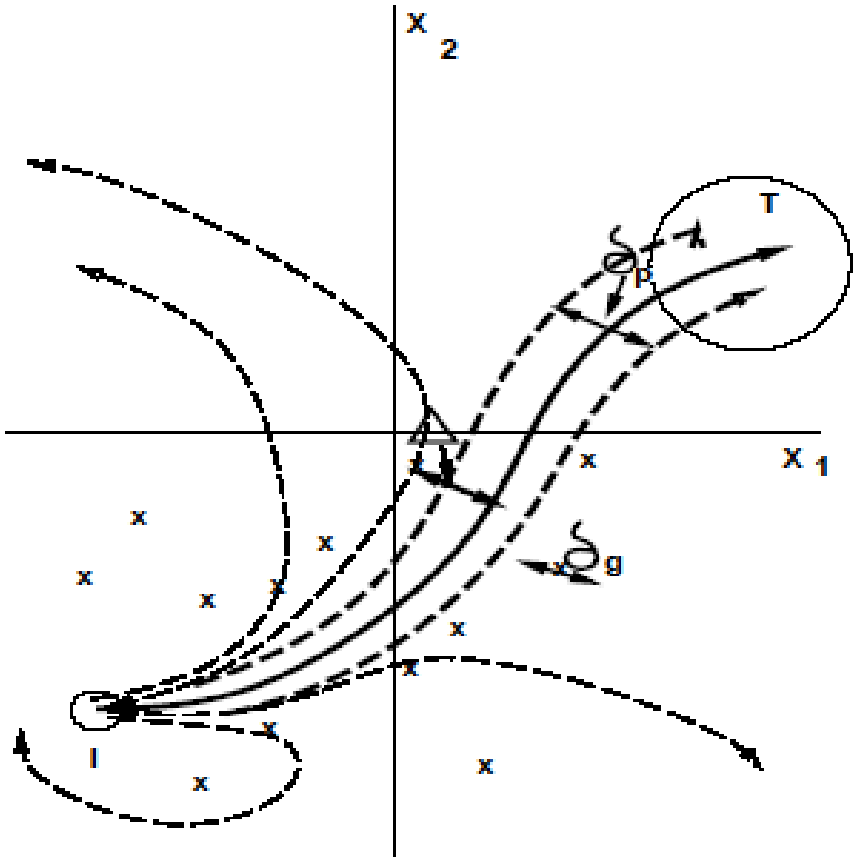
small σ −>
an orbit with small Δ
can reach the target



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

Vip ~（δp/Δ)^2
Vig ~ (δg/Δ）^2

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



Δ~distance to turning points
(basin boundary)

3: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 ∝ Vg →Developmental robustness and genetic (evolutionary) robustness are linked (or embedded)
WADDINGTON genetic assimilation

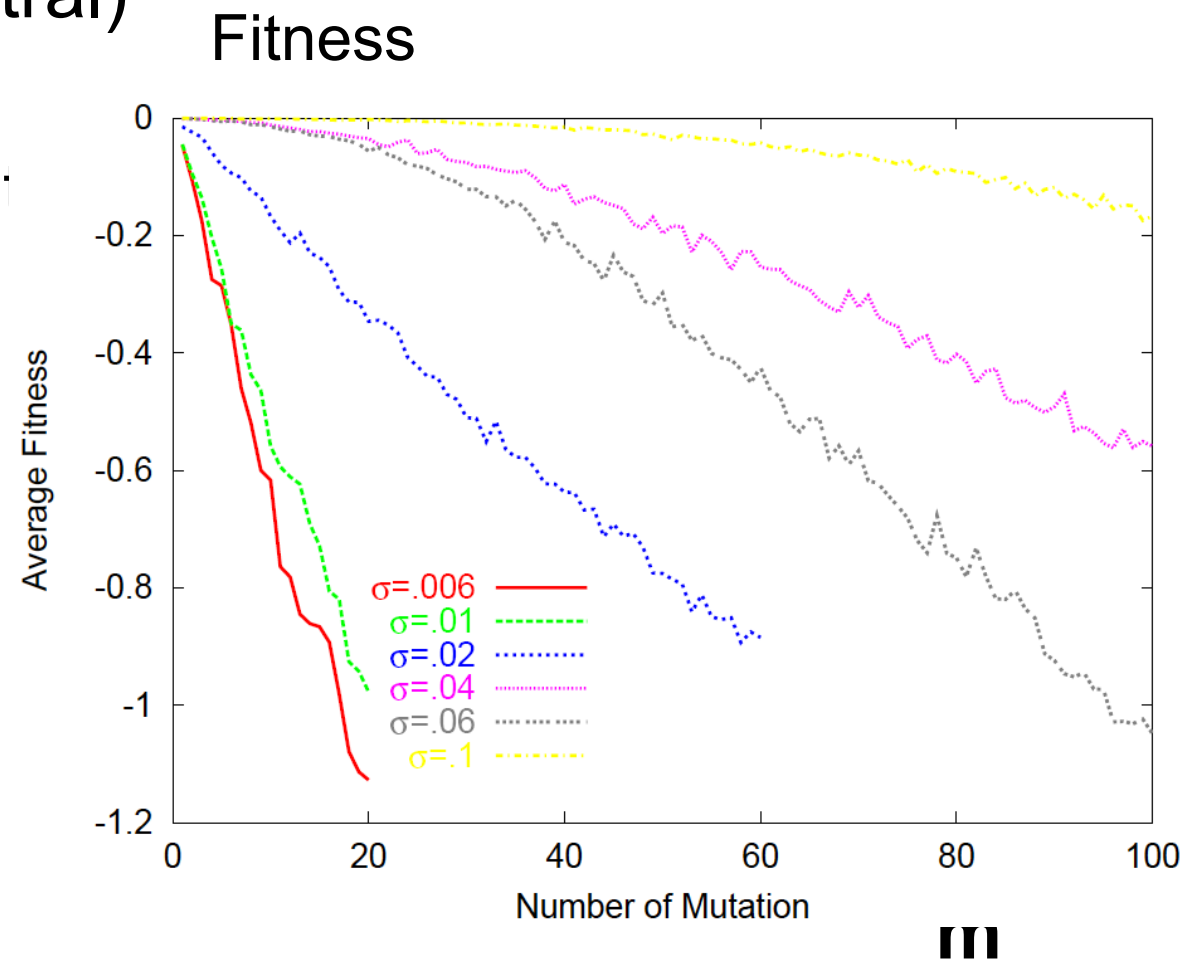
(cf. Ancel-Fontana J ExpZoolB 2000)

- Genetic robustness is increased for network evolved under higher noise (almost neutral)
- Increase in genetic robustness to muta

fraction of fitted

state for n-mutants

F=-c(σ）m；
c(σ)>0 if σ<σc
c(σc）=0
neutrality



m

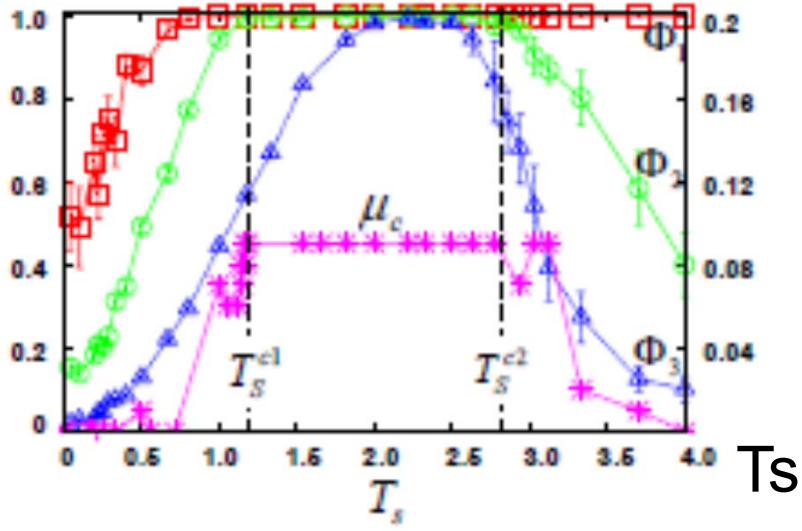
Generailty;Spin Stat-Mech Model for abstract protein evolution

Sakata,Hukushima, KK, PRL 2009

spin configuration --- configuration in protein

H folding dynamics

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



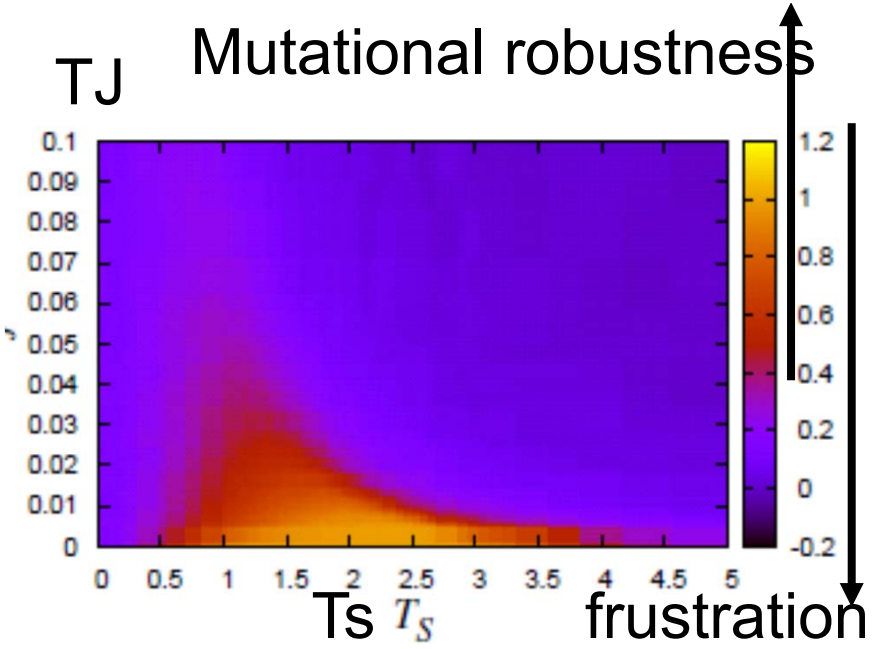
Ts: noise during 'developmental' dynamics

Monte Carlo with exp(-H/Ts)

Fitness; to alligne target spins

→ evolve Jij

Selection pressure by exp(-Fitness/TJ) ;higher selection as TJ→0



- Phase transition

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

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 (RS)

the target equilibrium reached globally and fast

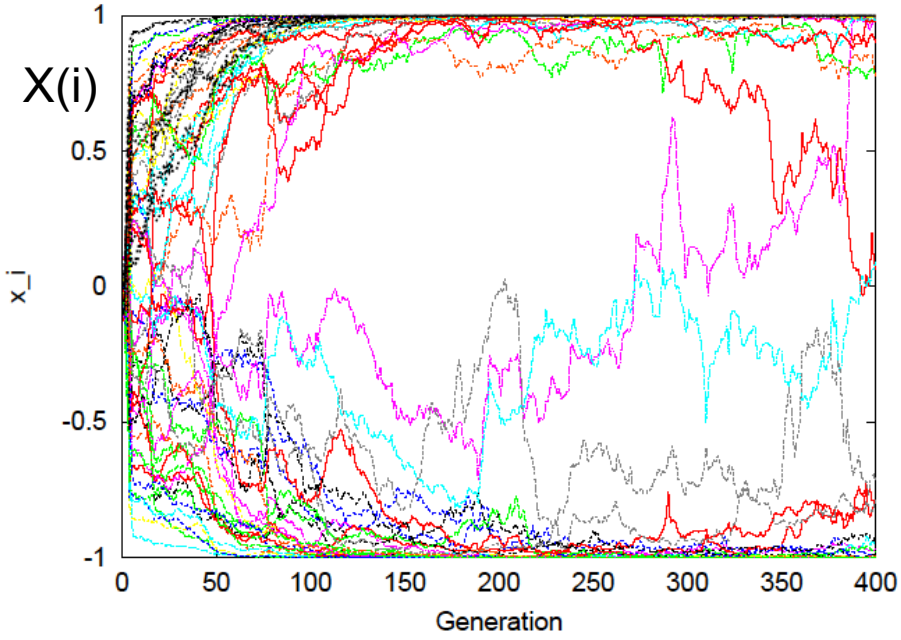
Ts>Tc2, -- high fitness is not achieved. 'paramagnetic' phase

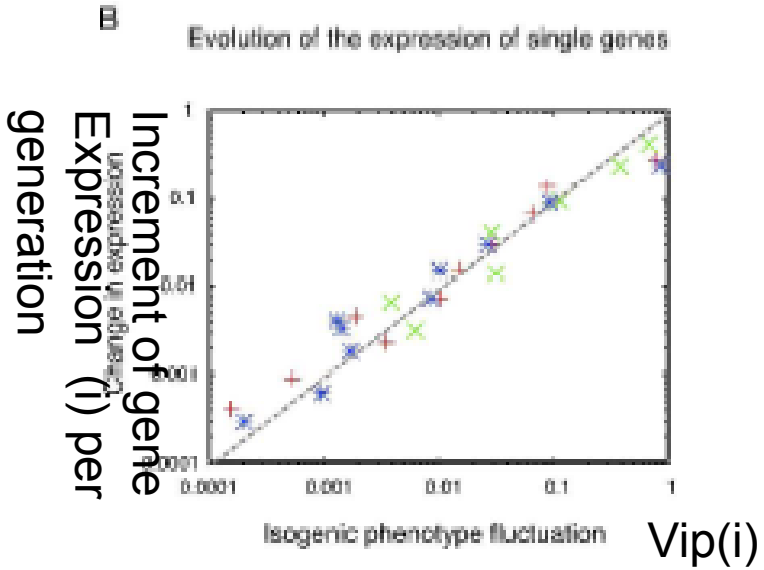
*Ubiquity of **funnel developmental landscape--**result of evolution under noise, which also leads to robustness to mutation

***Evolutionary Meaning of RSB! ***

4: Plastcity in each component (gene expression)

Consolidation of non-target gene expressions





For robust network
Many non-target gene expressions are fixed successively:

Still,some gene expressions are more variable than others:

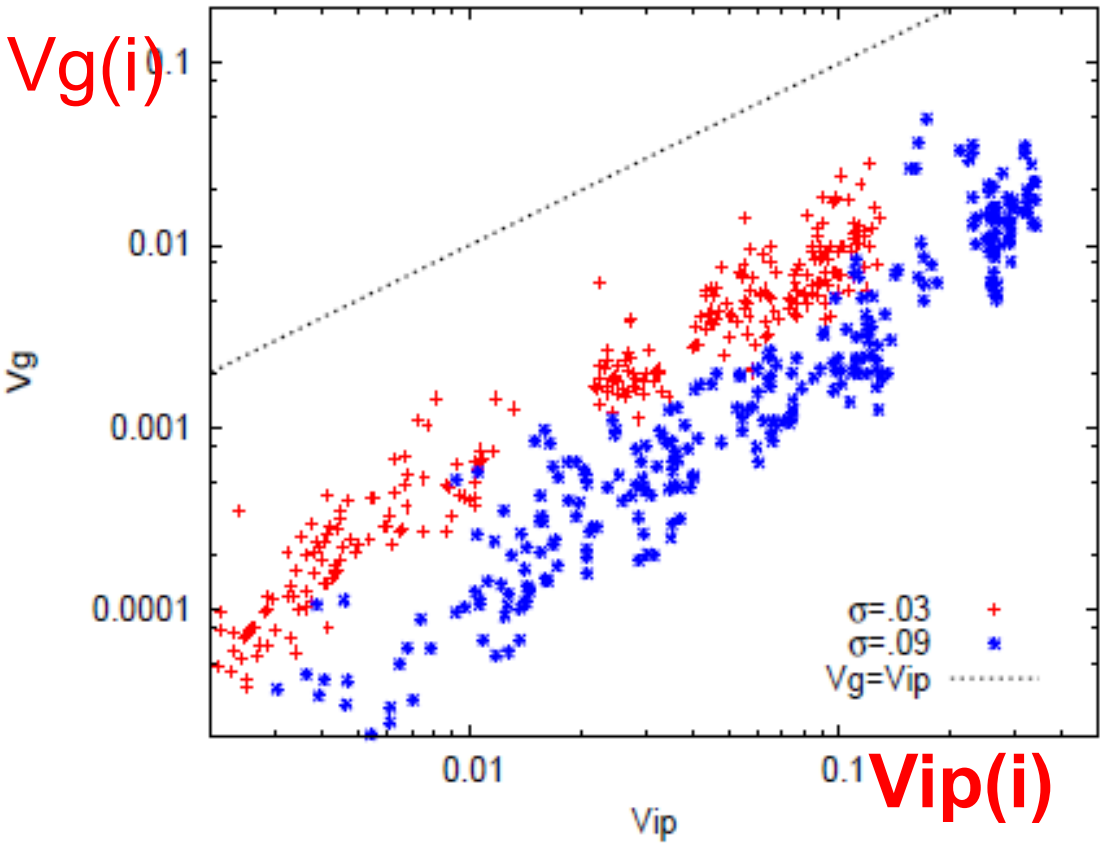
→ Define variance for each gene expression level i
Vip(i) and Vg (i)

Vg(i),Vip(i) across different genes (proteins) also show proportionality

Measure variance of gene expression for each gene i

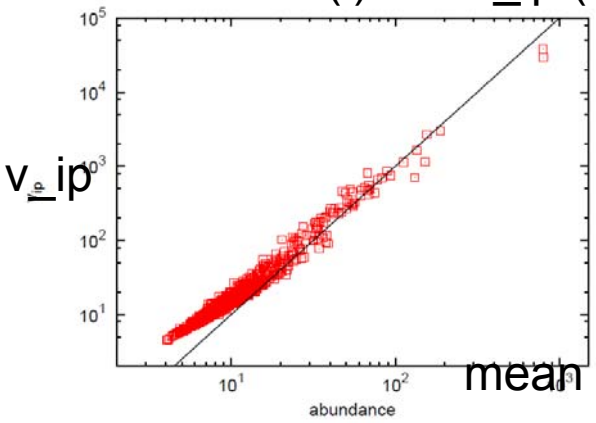
→ genetic variance Vg(i) ∝ isogenic variance Vip(i)

over different genes i, for given generation



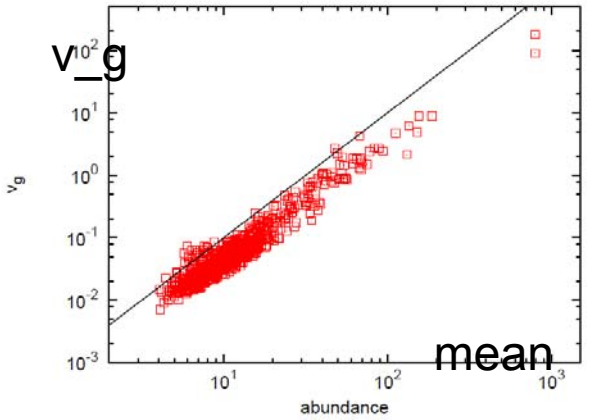
Vip-Vg relationship in catalytic reaction network model

Mean abundance (i) vs v_ip (i)



slope＝2

Mean abundance (i) vs v_g (i)

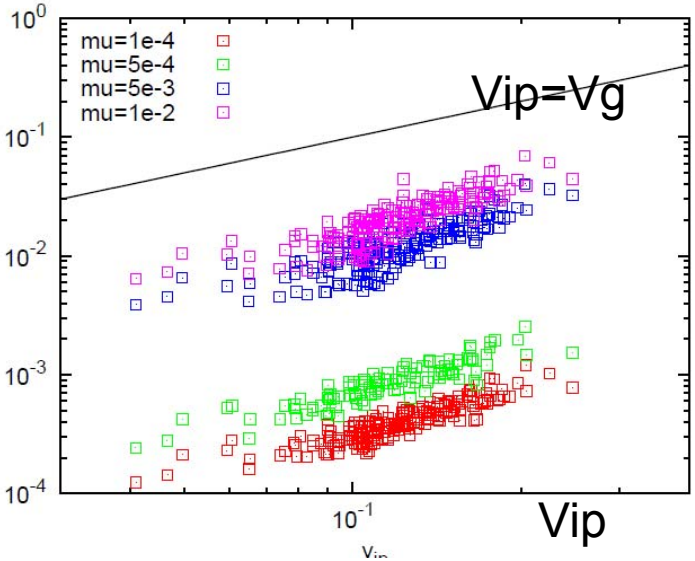


黒線は傾き＝2
変異率mu=1e-4
（10000本の反応パスのうち1本を入れ替え）

v_ip, v_g ∝ square of mean
(← lognormal)

⇒ normalize by divided by mean square

Vg V_ip vs V_g



(data from 4 mutation rate values)

Vip(i) ∝ Vg(i) over all components i

At around V_g=V_ip, growth is not sustained (error catastrophe)

Experimental evidences

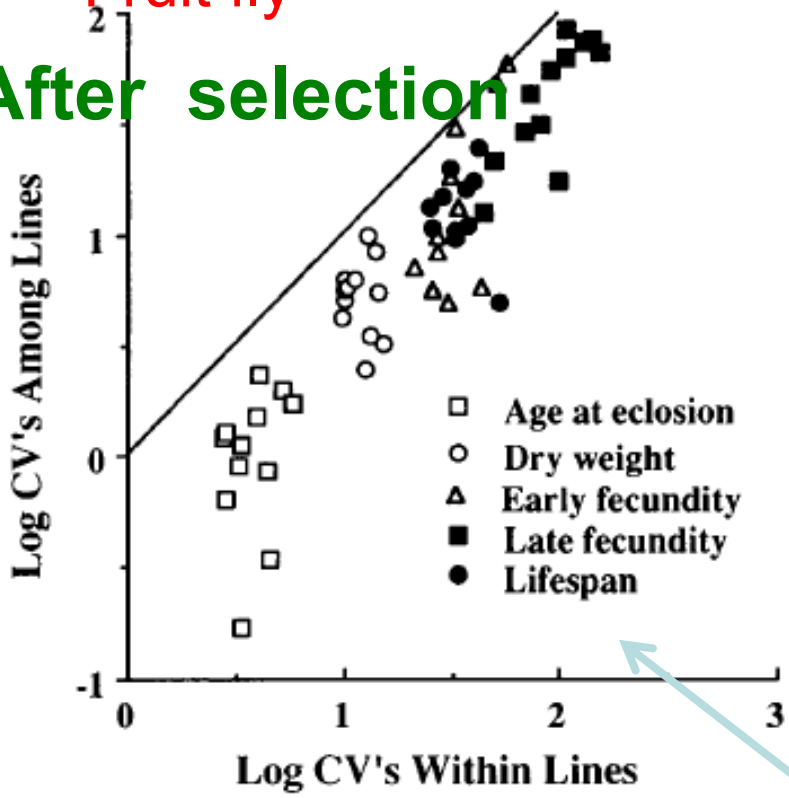
Genetic Properties Influencing the Evolvability of Gene Expression

Christian R. Landry,[1]*† Bernardo Lemos,[1]* Scott A. Rifkin,[1]‡ W. J. Dickinson,[2] Daniel L. Hartl[1]

Science 08

Fruit fly

After selection



e genetic (variation among lines) and environmental (variation within lines) coefficients of were ve $_s = CV_s$

The differential genetic and environmental canalization of fitness components in *Drosophila melanogaster*

Stephen C. Stearns,[1] Marcel Kaiser[1] and Tadeusz J. Kawecki[2]

yeast Without selection

Mutational variance ~ Vg

Fluctuation

Expression Noise ~ Vip

Courtesy of Ben Lehner

Why existence of universal proportionality relationship? Existence of 'developmental temperature' to support 'fluctuation-dissipation-type relationship?

No answer yet; just only primitive argument

Note this relationship appears only after evolution under single fitness condition;

Selection under a given single fitness condition → Projection of high-dimensional gene expression dynamics to low-dimension under the fitness condition

(Projection allows for 1-dimensional collective dynamics + noise (cf Mori formalism in Stat. Mech)).

Why proportionality over genes?: Sketchy argument

(i) Heuristic argument based on phenomenological distribution theory on expression x_i of gene i

$$P(\{x_i\}, a) = N_0 exp(-\frac{x_i^2}{2\alpha_i} + C_i x_i a - \frac{a^2}{2\mu}).$$

$$P(x_i, a) = exp(-\frac{(x_i - C_i a \alpha_i)^2}{2\alpha_i} - \frac{1}{2}(\frac{1}{\mu} - C_i^2 \alpha_i) a^2)$$

Stability → $\mu < \mu_{max}^i \equiv \frac{1}{C_i^2 \alpha_i}$,

For higher robustness →'postpone' error catastrophe.

Then it occurs simultaneously→ common error threshold

$$\mu_{max}^i = (C_i^2 \alpha_i)^{-1} =$$ Indep't of (most) genes i

$$V_g(i)/V_{ip}(i) = C_i^2 \alpha_i < (\delta a)^2 >,$$ ~ constant

NB: Vg-Vip proportionality law is a result of evolution

Most gene expressions are dominated by such ‘collective modes’ in developmental landscape that is correlated with evolutionary landscape

Recall Vg/Vip=μ/μ_max. This could be applied to any genes. In general, the mutation for the ‘error catastrophe’ can differ by genes. But assuming that genes are mutually correlated through the above low-dimensional collective dynamics, at such error threshold, the collective dynamics collapse. Then fixation of most genes (i.e., single-peaked-ness in each gene expression distribution) collapses simultaneously at the same μ. Then one may expect universal μmax, which may imply universal Vip-Vg relationship

(ii)A heuristic argument on Vip-Vg law: Self-consistent fluctuation --

Assume collective variable F and its fluctuation

$$P(x;F) = N_0 exp(-\frac{x_i^2}{2\alpha_i} + C_i x_i F - \frac{F^2}{2\beta}). = exp(-\frac{(x_i - C_i F\alpha_i)^2}{2\alpha_i} - (1/2\beta - C_i^2\alpha_i)F^2)$$

The variance of x_i due to this 'mean fleid', is given by

$$< (\delta x_i)^2 >= C_i^2 \alpha_i^2 < (\delta F)^2 >$$

Now if the variance of x_i is mostly due to this 'mean fleid', then but this equals to α_i.
Hence, $C_i^2\alpha_i = 1/ < (\delta F)^2 >$ which is independent of the gene i.
Now, we replace F by gene a, then, as already discussed before,

$$V_g(i) = C_i^2 \alpha_i^2 < (\delta a)^2 > \quad (4)$$

where $< (\delta a)^2 >$ is the mutation rate. $V_{ip}(i) = \alpha_i$
Hence,

$$V_g(i)/V_{ip}(i) = C_i^2\alpha_i < (\delta a)^2 >=< (\delta a)^2 > / < (\delta F)^2 >$$

but this value is indepenendent of gene i

- Generality of our result; (probably..) If

fitness is determined after developmental dynamics, sufficiently ‘’complex’’ (nonlinear)

(errors are often generated, fitted ones are rare)

---

*Vip variance of phenotype over isogenic individuals

*Vg variance of average phenotype over heterogenic population

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

through evolution course & over different phenotypes

Property as a result of evolution under fixed fitness cond.

If more variable by developmental or environmental noise, also variable by mutation

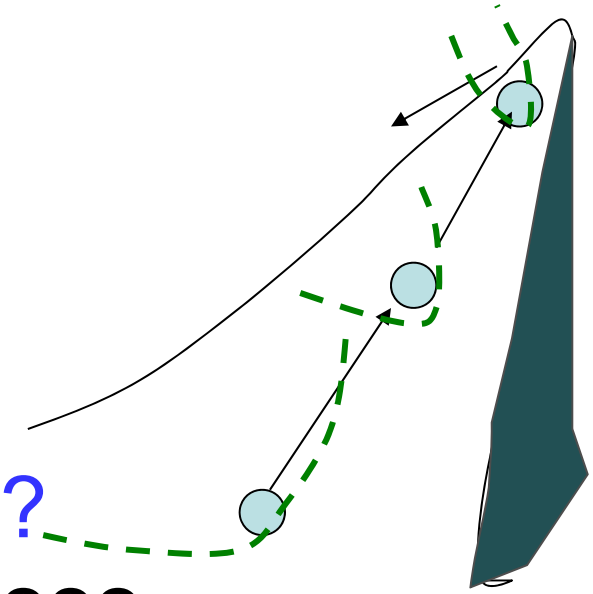
(→ qunatitative representation of genetic assimilation by Waddington)

5. Restoration of Plasticity

Through directed evolution; under single fitness, robustness increases, fluctuations and evolution speed decrease (theory, experiments)

←→ How Evolution continues?

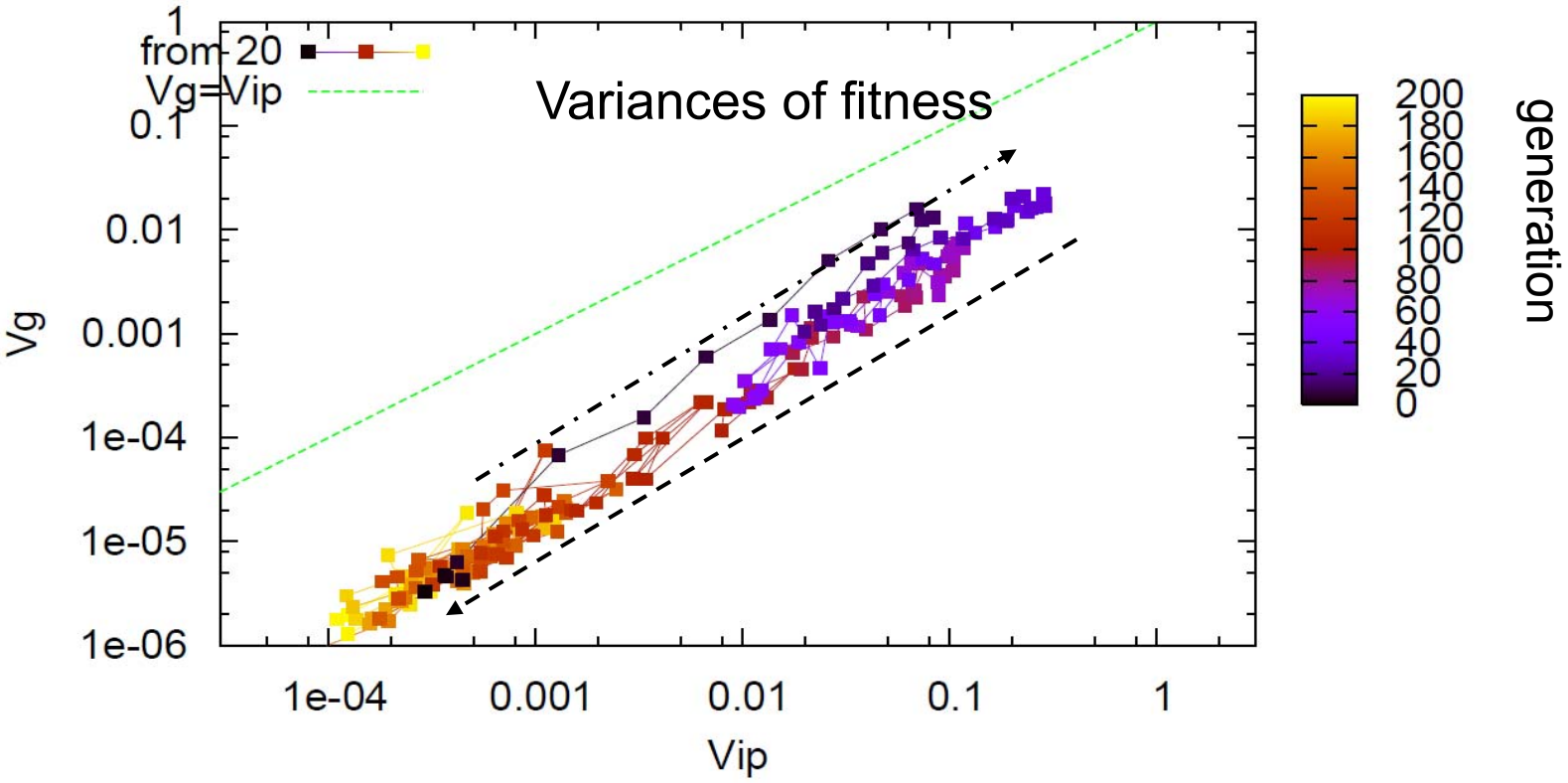
Why Large Fluctuations exist?



?? Is there regain of fluctuations????

- Experimentally: Appearance of mutants with large fluctuations (← interference with other processes) (Ito,Toyota,KK,Yomo, MSB 2009)
- Model: environmental change→ Restoration

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; then switch
++++++++→++++----

On -> Off for some target genes

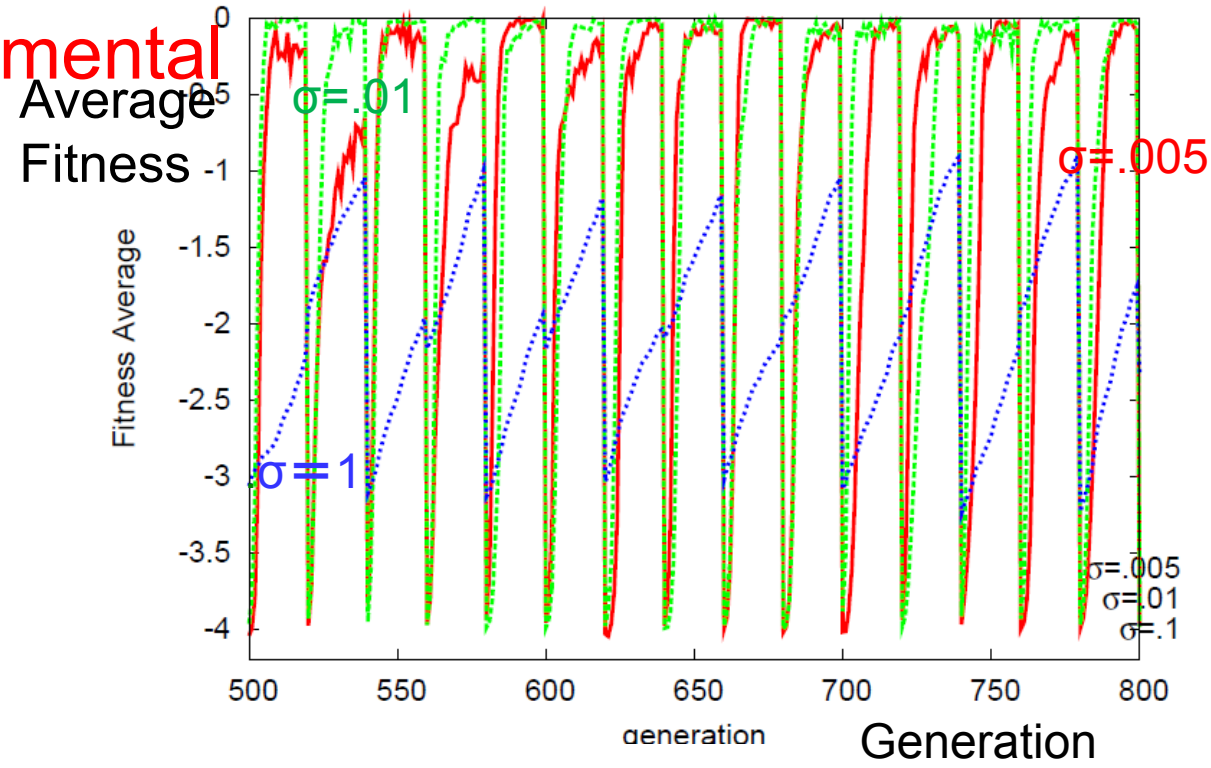
Contunuous environmental change

Switch the Fitness Condition per 20 generations

＋＋＋＋＋＋＋＋＋＋

← →

＋＋＋＋－－－－－－



Large σ (low Vg/Vip) -- too robust

cannot follow the environmental change

Small σ（high Vg/Vip) – non-robust;

non-fit mutants remain

Near σ ~ σ**c** --cope with environmental change

satisfy both adaptation to new environment and robustness

Contunuous environmental change

Switch the Fitness Condition per (10) generations

＋＋＋＋＋＋＋＋＋＋

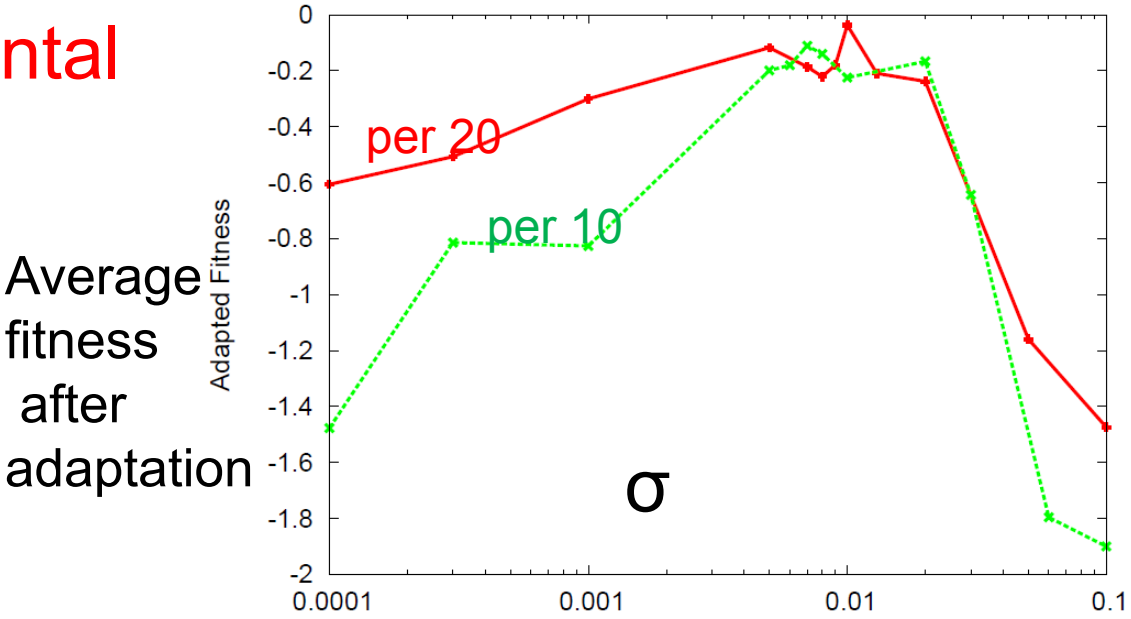
←　→

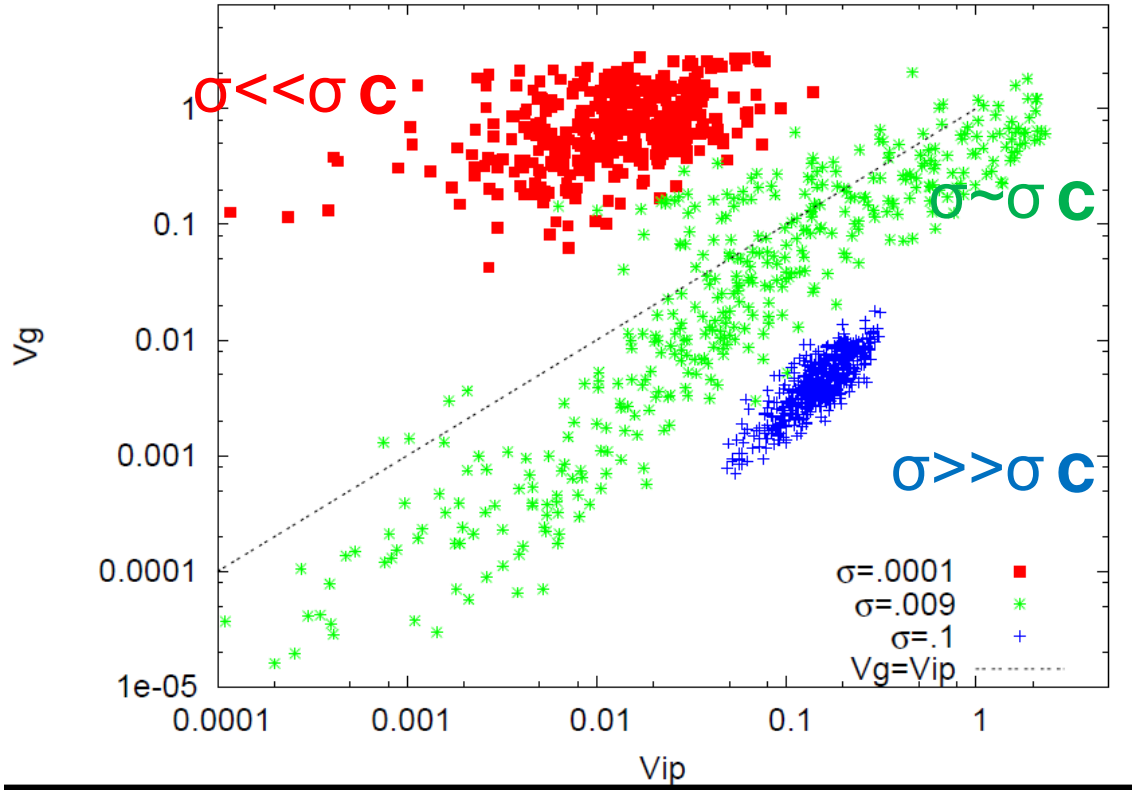
＋＋＋＋－－－－－－

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

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

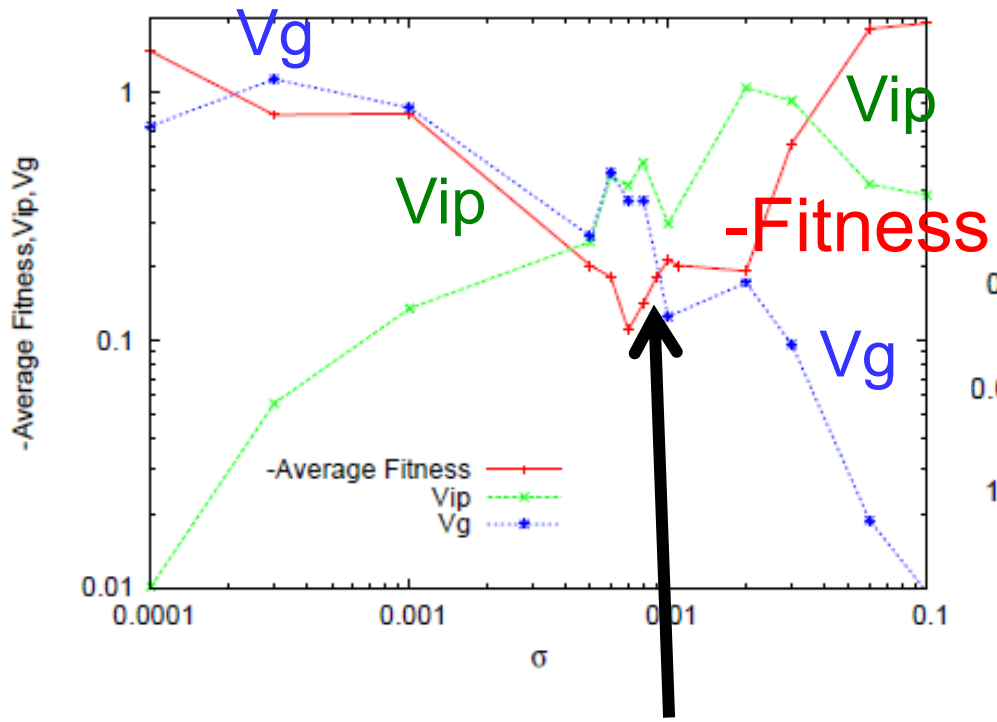
Near σ ~ σ **c** satisfy both adaptation to new environment, and robustness



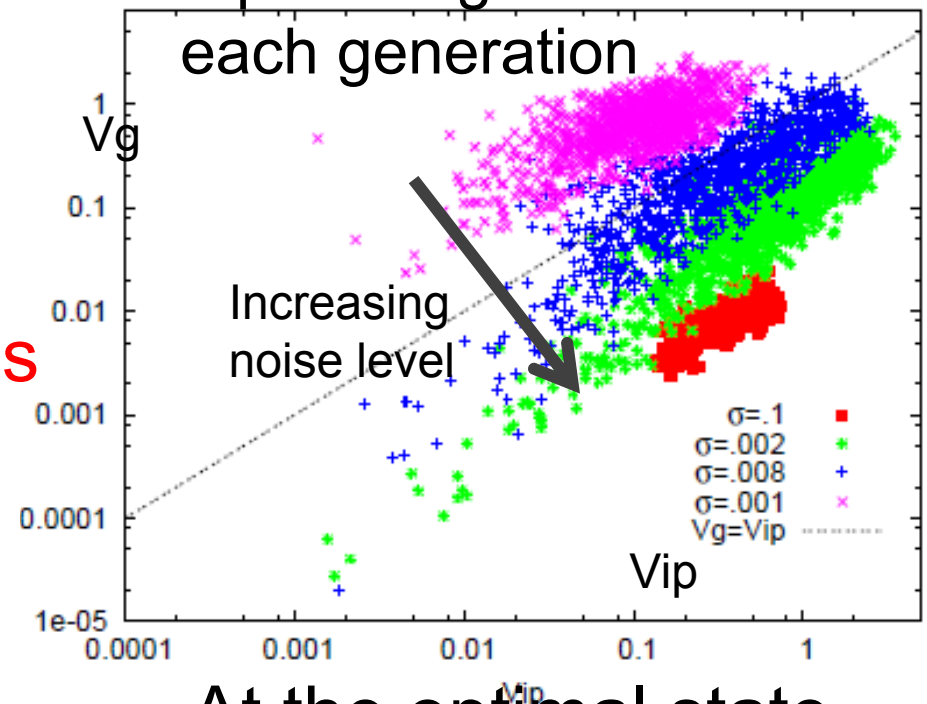


Under random environmental changes

Average Fitness, Vip, Vg over generations



Vip and Vg at each generation



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

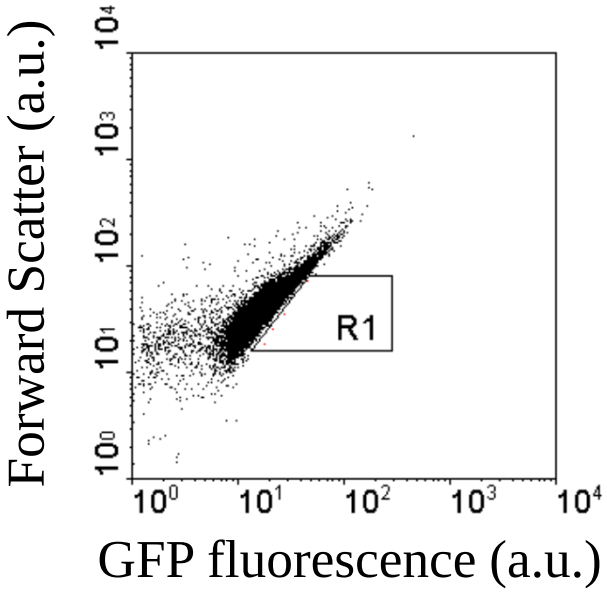
At the optimal state Vip and Vg goes up and down over generations, following proportionality

K.K, J. Stat. Phys. 2012

Strategy for survival with the increase in fluctuation

Fig.1

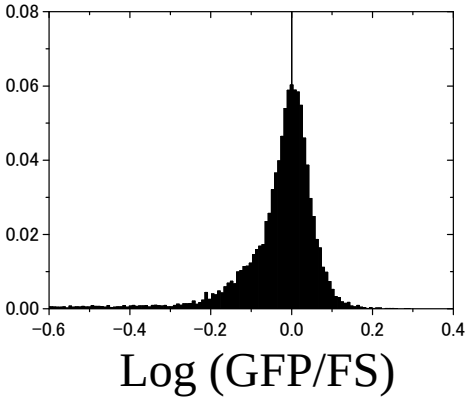
A



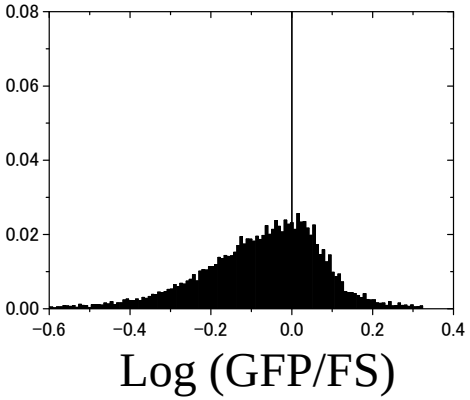
Selection experiment
at individual level
(strong selective pressure)
(Ito,Toyota,KK,Yomo
Molecular Systems Biology
2009)

Appearance of 'broad
mutants'

B



C



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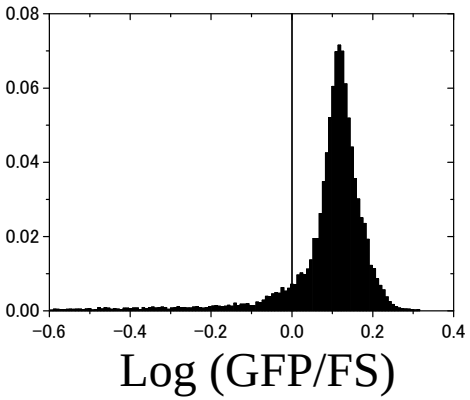
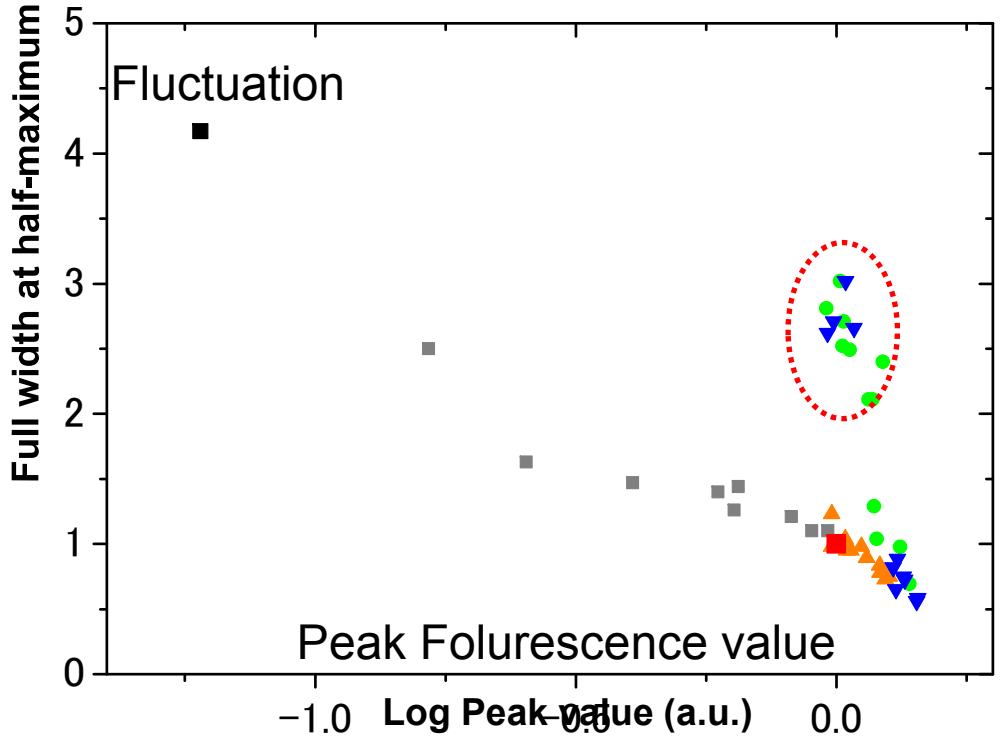
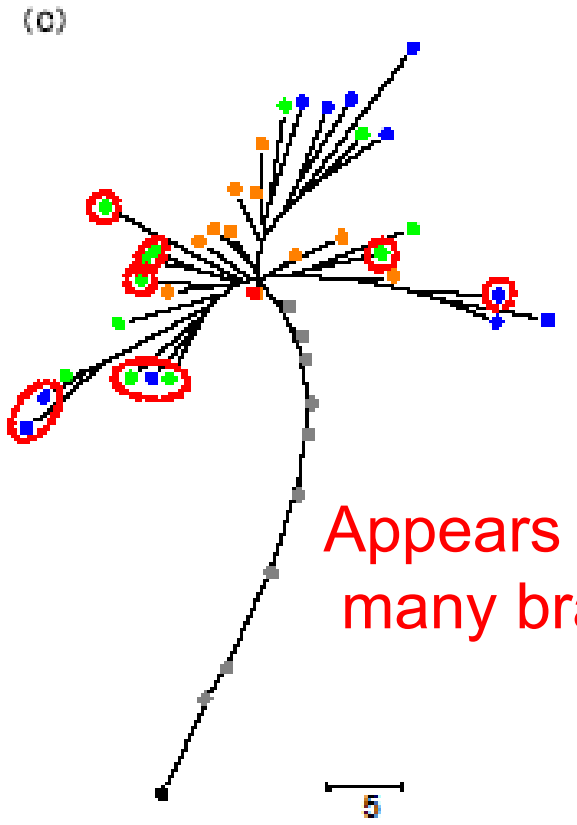
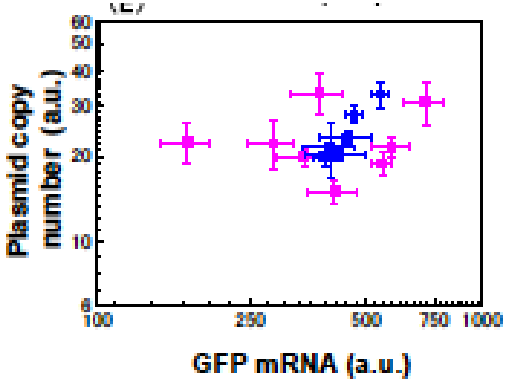


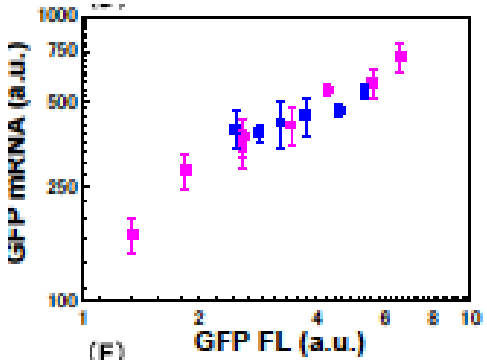
Emergence of Broad Mutants





Appears from many branches





Not due to Plasmid number Variance

Correlated with concentration of mRNA (through cell growth dynamics) →

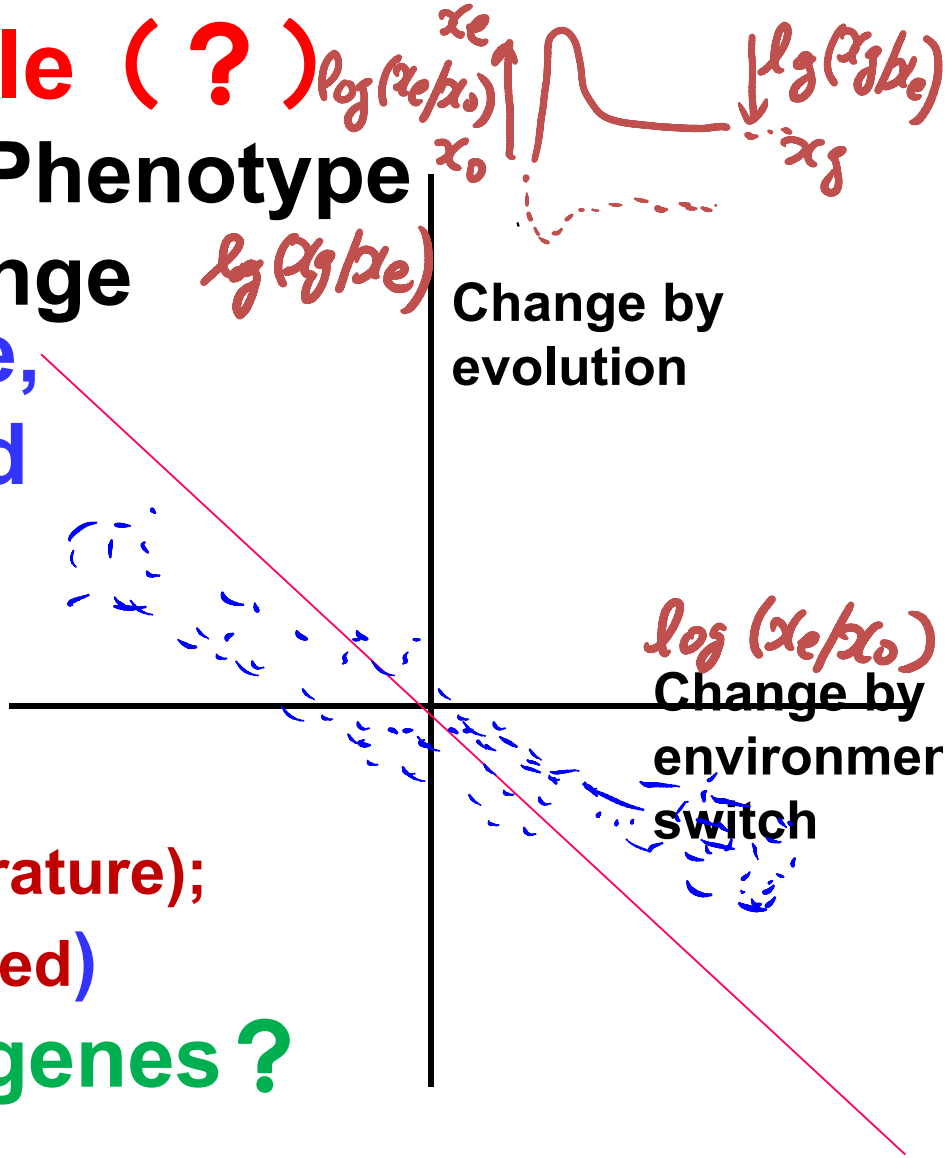
Use of ‘new’ degrees of freedom

6. Le Chatlier Principle（？）

Environment switch -> Phenotype Change-> ‘Genetic’ change

With the genetic change, growth rate is recovered (partially), while most gene expressions tend to return to the original level(Yomo (temperature); Furusawa(chemical): unpublished)

common trend over all genes？



Check by using catalytic reaction-net model

- **Macro phenomenological theory**

---this part is omitted here---

- Probably.....

Existence of

macroscopic phenomenological theory a la thermodynamics (for universal biology)

Waiting for Carnot and Clausius of 21th century??

Short History: Macro-state theory('Systems Physics')

~1860 Thermodynamics (Clausius,…)

~1910 Relativity, Brownian motion (Einstein)

~1960 Chaos (Lorenz,…)

~2010 ????? ←

7 Symbiotic Sympatric Speciation

Kk,Yomo2000
ProcRoySoc

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

** Scenario for Sympatric Speciation

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

differentiation by the interaction (‘bifurcation’)

e.g., by the limit in resources (KK,Yomo1997)

(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

1 Isogenic Phenotypic Fluctuation (Plasticity) ∝ Evolution

2 Isogenic Phenotypic Fluctuation ∝ Genetic Variance

3 Evolution of Robustness to Noise∝to Mutation

4 Plasticity of each phenotype： Vg(i)/Vip(i)～const

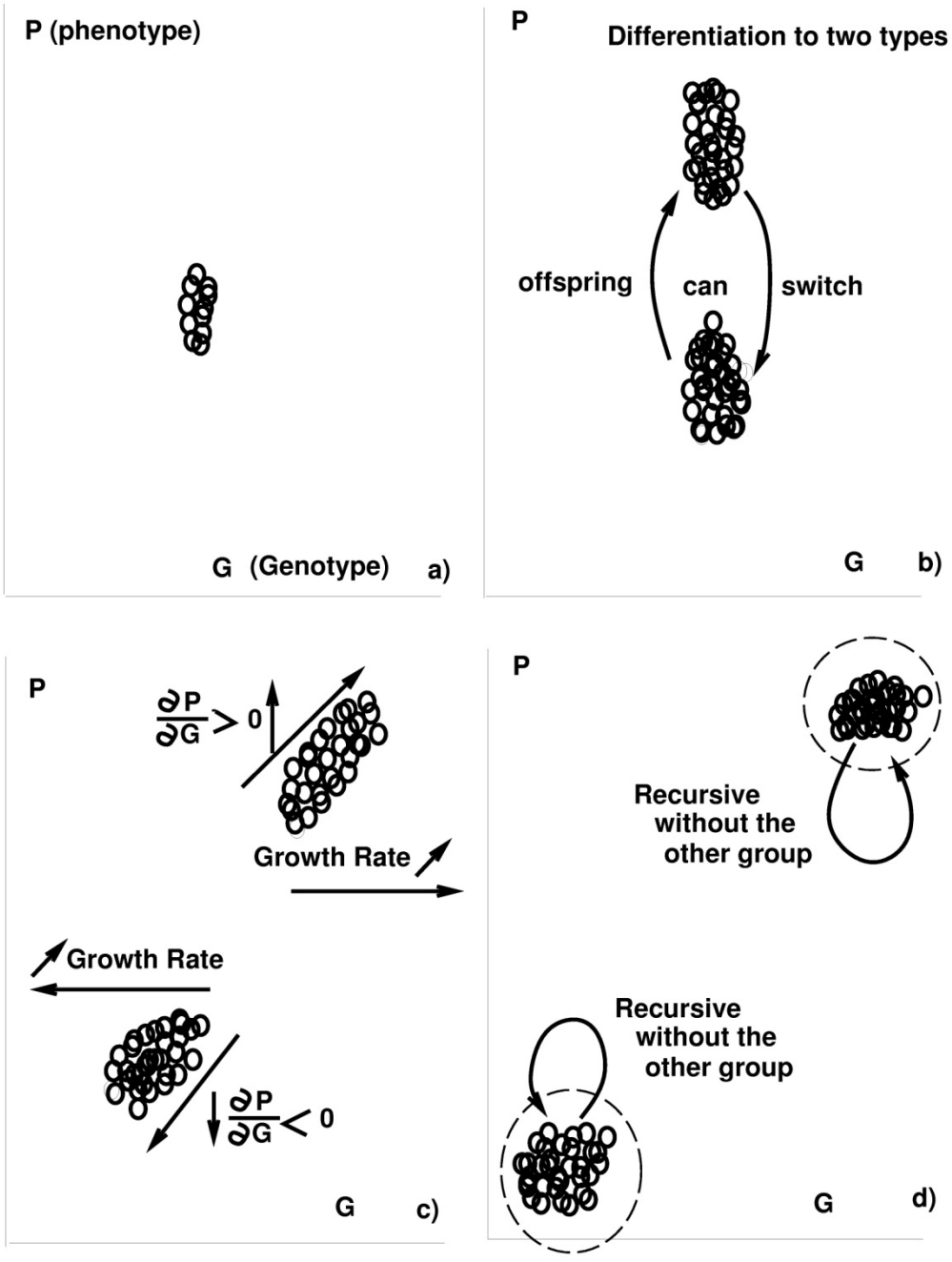
5 Restoration of Plasticity to increase variances

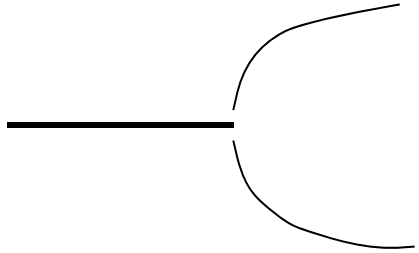
6 LeChatlier Principle? Macro Phenomenology?

7 Symbiotic Sympatric Speciation

8 Evolution of Morphogenesis

Evolution –shaping dynamical systems
by dynamical systems





Cf: pithcfork possible
eg dXi/dt= aXi-Xi^3
-(Σj Xj)^2 Xi

a increases with # of units

8. Development of morphogenesis

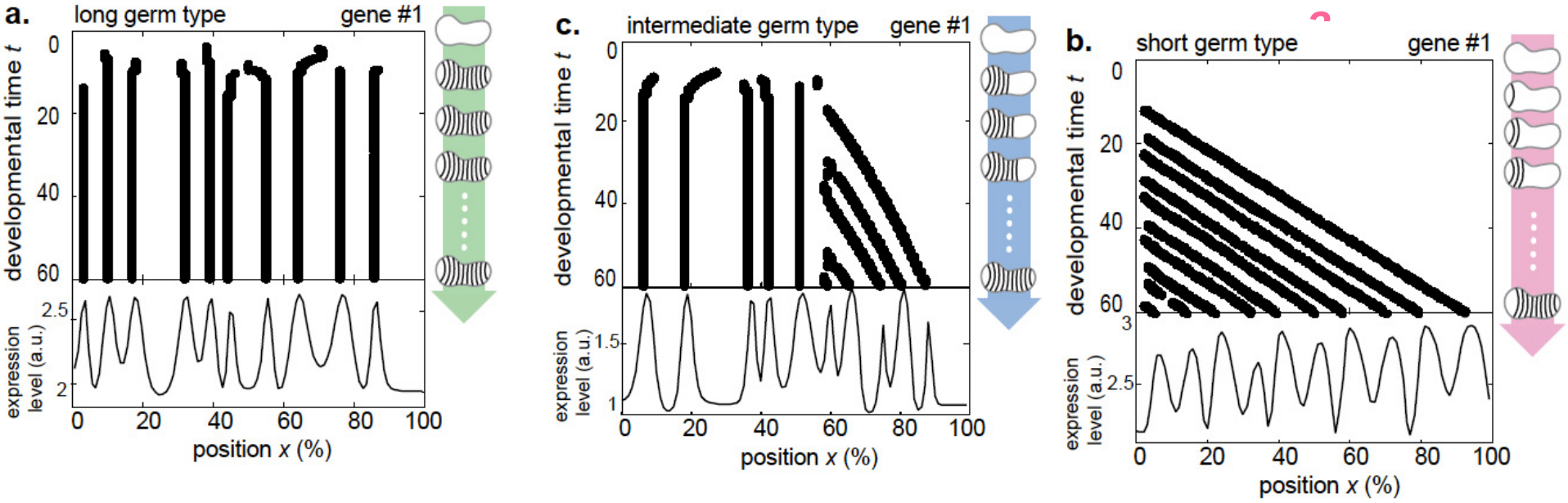
(Fujimoto,Ishihara,kk,PLoSOne2009)

Evolve GRN dynamics (+diffusion) to form stripes

Long germ mode: simultaneous

Intermediate germ mode: combinatorial

Short germ mode: sequential



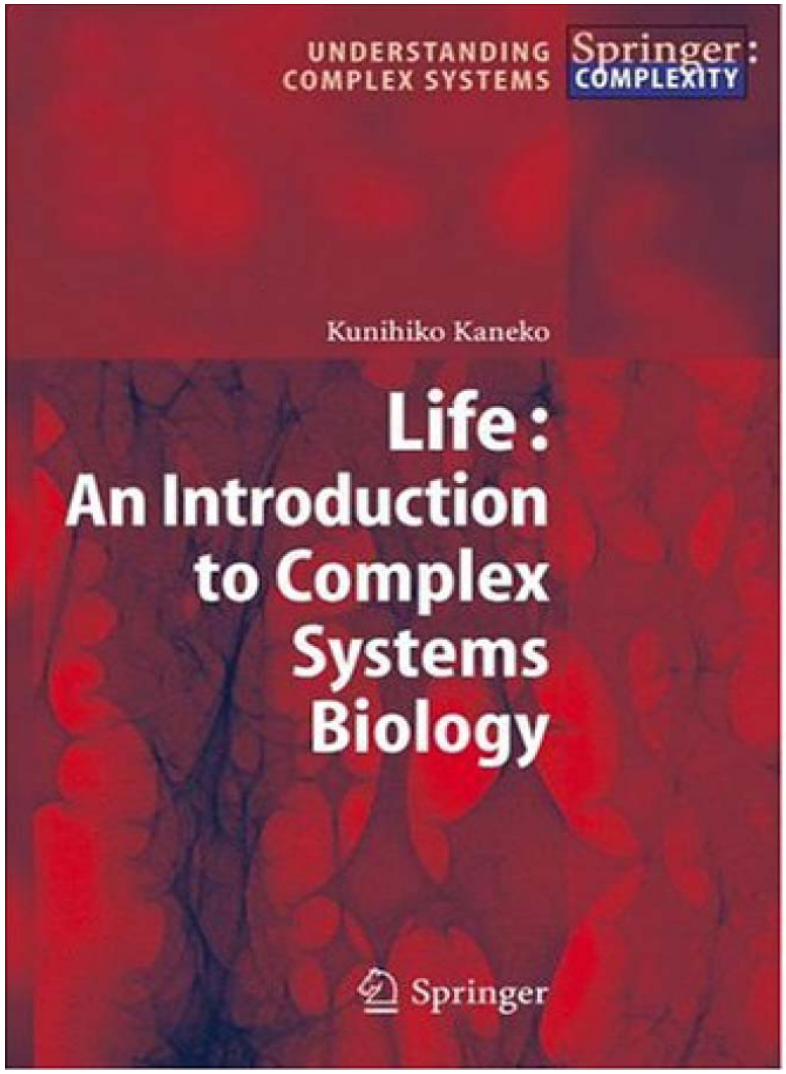
*Simultaneous generation
Combination of on/off regulations
by fixed expression dynamics

Sequential Generation
Use of oscillatory
gene expression

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



Collaborators

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experiment

Tetsuya Yomo

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KK, PLoS One 2007

2012 In Evolutionary Systems Biology

KK & Furusawa, JTB 2006 + in prep

Sato etal PNAS 2003

Ito et al MSB 2009

Also Sakata,Hukushima,kk,PRL2009

Cf. KK,Yomo, ProcRoySoc 2000,

Fujimoto,Ishihara,KK,2009)

Most papers available at

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