# Universality in Biology?: Fluctuation-response relationship and Deep Linearity in Adaptation and Evolution

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# Universal Biology

Life system as a universality class in nature

→

Phenomenological theory ( a la thermodynamics)

→ general characteristics, universal laws

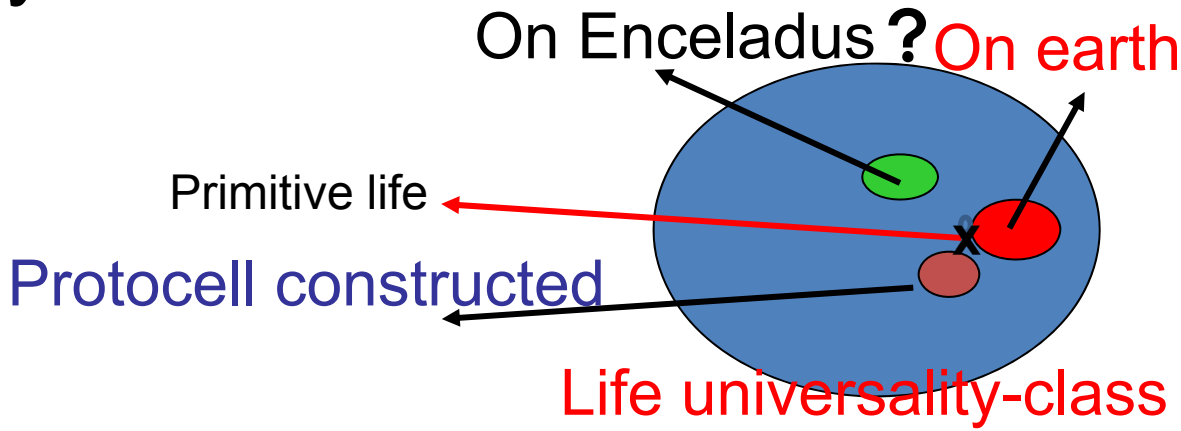
＊Biology not restricted to those that happen to be evolved on earth

(coined originally by SF writer

小松左京

(Komatsu Sakyo）

at 1972



# Universal Biology – proposed? 1972 by Sakyo Komatsu (SF novelist)

- *Universal biology – science to explore universal patterns and possible variations of living organisms in this cosmos. It started to expand the end of last century (* i.e. 20c). Since then, characterization of life in terms of topological geometry (* dynamical systems?) has developed, and now, grand theory comparable to relativity is anticipated… ---*

Universal Biology Institute (in real world) launched 2016, Univ Tokyo

- Life ~ System that consists of diverse components and that maintains itself and can continue to produce itself ––consequence→
- Guiding Principle––Micro-macro Consistency:

micro – many components (high-dimensional)

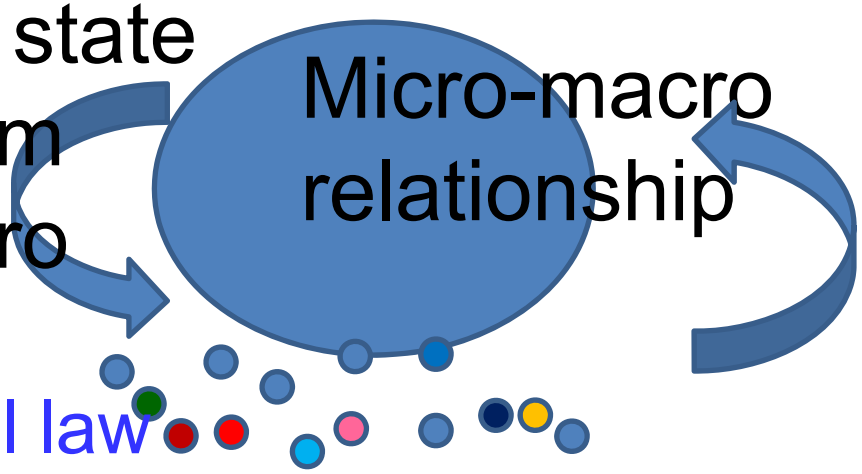
macro – unit to sustain/ reproduce as a whole

(*low-dimensional description*?)

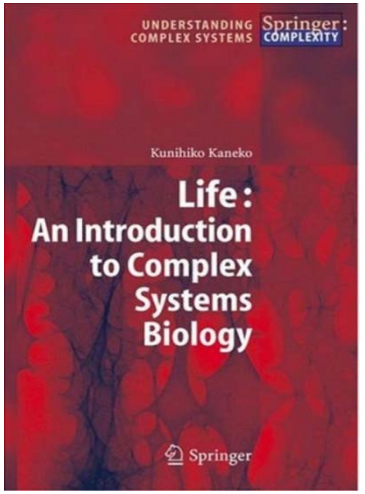
molecule – cell, cell–tissue etc.

Steady (growth) state

Constraint from macro to micro

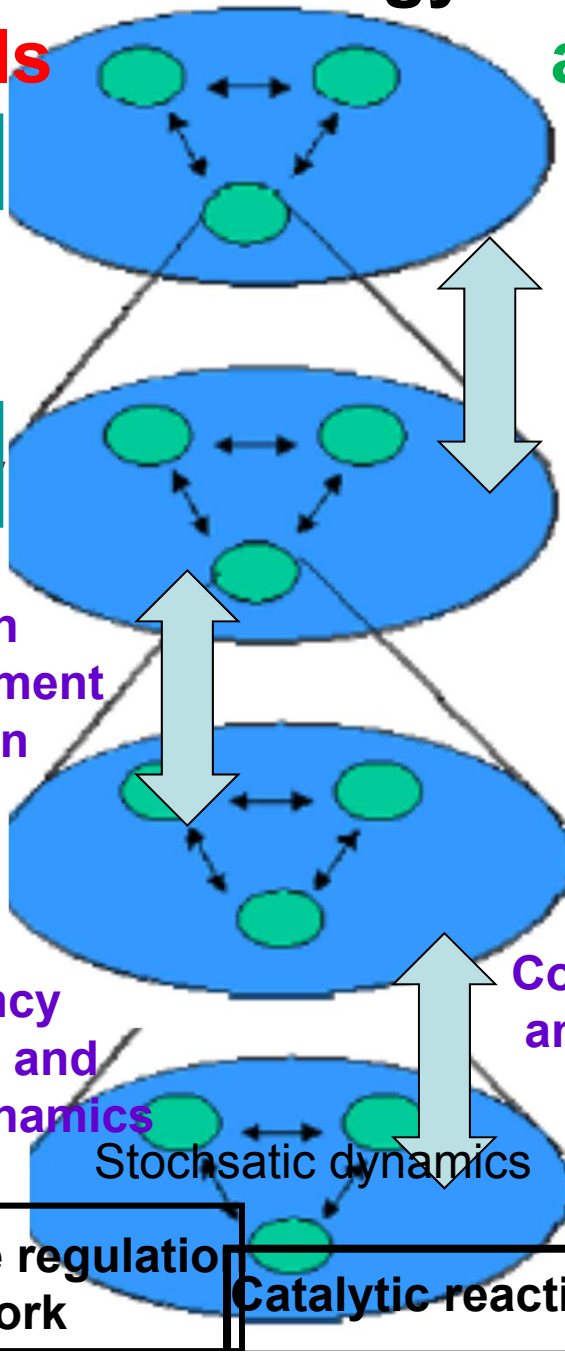



Universal statistical law




Complex-systems Biology

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



Ecosystem

*Consequence of Dynamical Systems rather than fitness*

Phenotypic Plasticity vs Symbiosis
Or Ecological diversification

Multicelluarity

Consistency between
Multicelluar development
and cell reprodcution

Evolutionary relationship on
Robustness and Fluctuation

Genotype ⟷ Phenotype

Cell

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

Consistency between Cell reproduction
and molecule replication

Stochsatic dynamics

Molecule

Gene regulation network

Catalytic reaction network

***Space/Time Hierarchy***

## Consistency between dynamics of different levels

**(1)Cell reproduction vs molecule replication →**
universal statistical laws in gene expression
(Furusawa et al, PRL 2003,2012, Biophysics 2006)

**(2)Cell Growth vs molecule replication →** universal adaptation laws (Kashiwagi et al Plos One2005, KK et al Phys RevX2015)

**(3) Cell reproduction vs multicellularity →**

**oscillatory dynamics => pluripotency + cell-cell interaction → differentiation, loss of pluripotency**

**(KK&Yomo 1997, Furusawa&KK,1998,Science 2012)**

**(4) Genetic vs phenotypic changes→**

Isogneic Phenotypic Variance by noise ∝ variance by genetic change Vg ∝ Evolution Speed (plasticity)

**robustness to noise ～ to robustness to genetic change, (PNAS03,PLosOne07,…)**

- Grand Challenge:

  Cell --- very high-dimensional dynamical systems ( ~5000 proteins for bacteria etc.)

- Can we understand it?
- Recall thermodynamics : huge-dimensional molecular dynamics, but described by few degrees ← restricting to *equilibrium*
- From high-dimensional dynamics of cell, surprisingly low-dimensional structure is extracted, with deep linearity ← restricting to *steady-growth states*: Valid after evolution, not any high-dim dynamical systems

- Basic Setup (Exp/Theory/Model)
- Phenotype=Abundances (State Variables)
- Genotype-DNA seq, or rule for dynamics: Mapping?
- Quantify: Abundances of each component (protein/ mRNA), (~5000 dimensions); their (log) change under adaptation/evolution

* **Experiment**: transcription analysis of E Coli

* **Model**: (i)catalytic reaction network for growth

(ii) Gene regulation net:(high-dim): Micro->Macro

* **Theory**: Low-dim manifold from high-dim

1)Evolutionary Fluctuation-Response Relationship

(Sato et al PNAS 2003, Furusawa,KK 2006)

2)Proportionality between Fluctuation by noise and by mutation (robustness relationships)

(KK, Plos One 2007)

3)Macroscopic universality of steady-growth cells

(*kk et al, PhysRevX2015, Furusawa,kk, Interface 2015*)

**（brief review, partial overlap with Furusawa-san's talk) →deep linearity as a result of evolution**

4)Slow-Manifold hypothesis and its consequence

**→macroscopic theory a la thermodynamics**

(KK, Furusawa, in preparation)

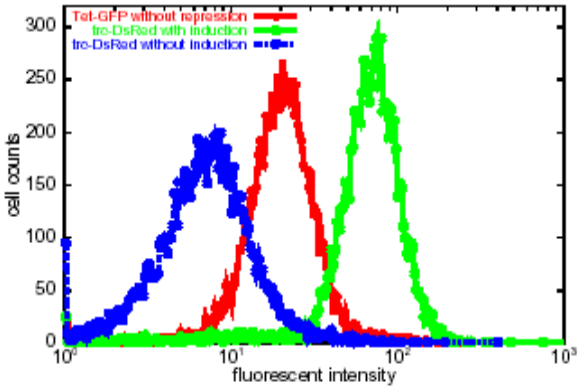
- Evolvability,Robustness,Plasticity: Basic Questions in Biology, but often discussed qualitatively : Idealizing the situation:

→quantitative theory?

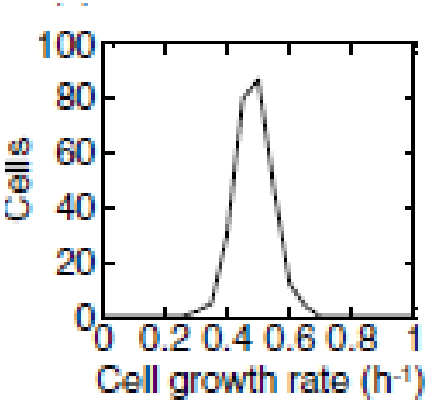
- Phenotypic Fluctuation → gives a measure for Evolution?
- Even in isogenic individuals large phenotypic fluctuation (theory, experiments)
- Motivation Relevance

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



## (i) evolutionary fluctuation-response relationship:

*Vip variance of phenotype ( fitness) over isogenic individuals (Ve, Vnoise)

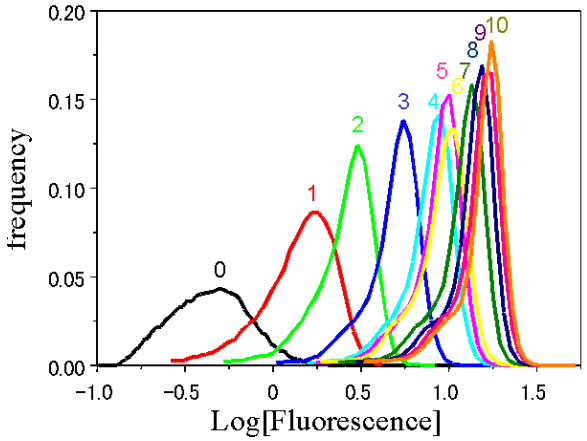
Vip ∝ evolution speed

through evolution course

bacteria evolution experiment

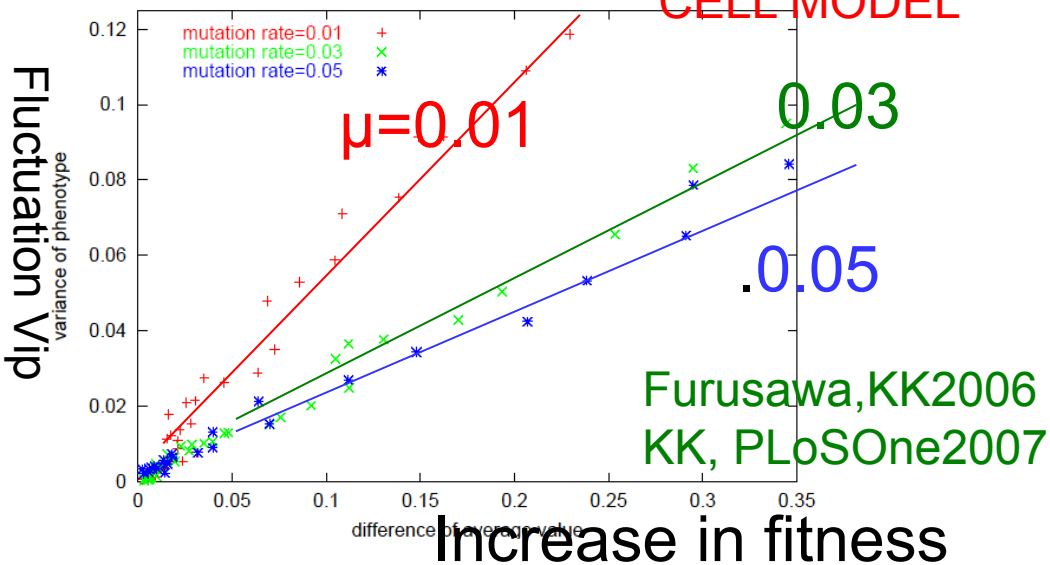
+ models (cell, gene-regulation-net),

+Phenomenological Theory

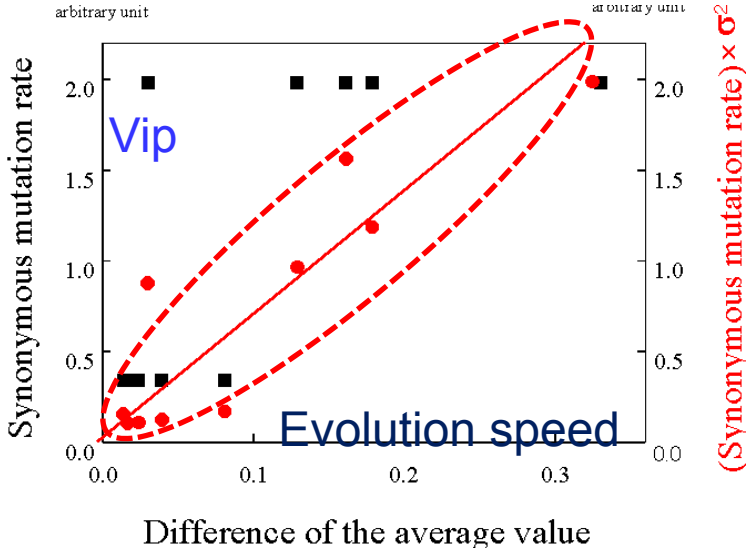



EXPERIMENT

CELL MODEL



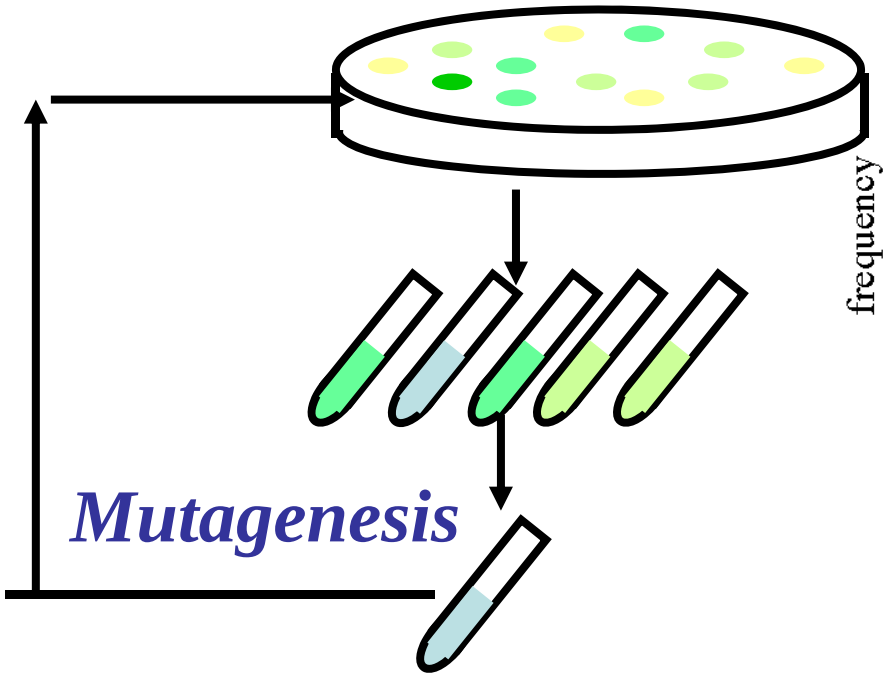

Increase in fitness

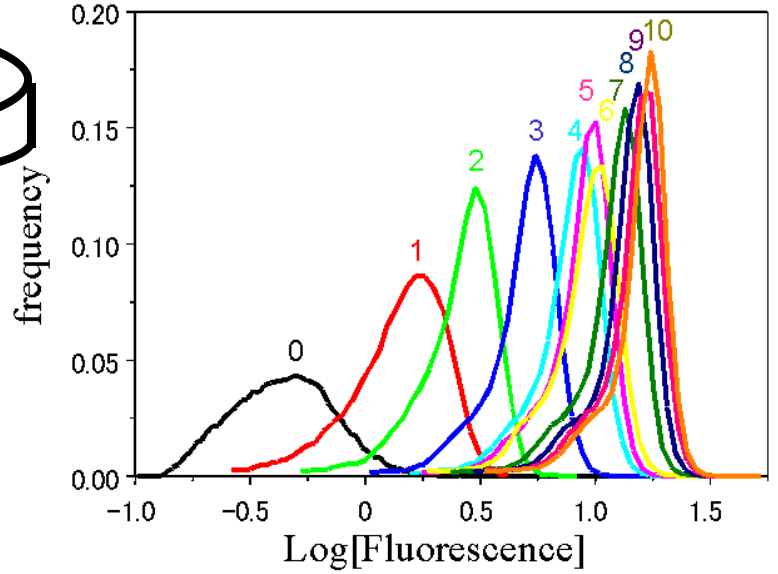



Sato Ito Yomo KK; PNAS 2003,

# Earlier study:Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria



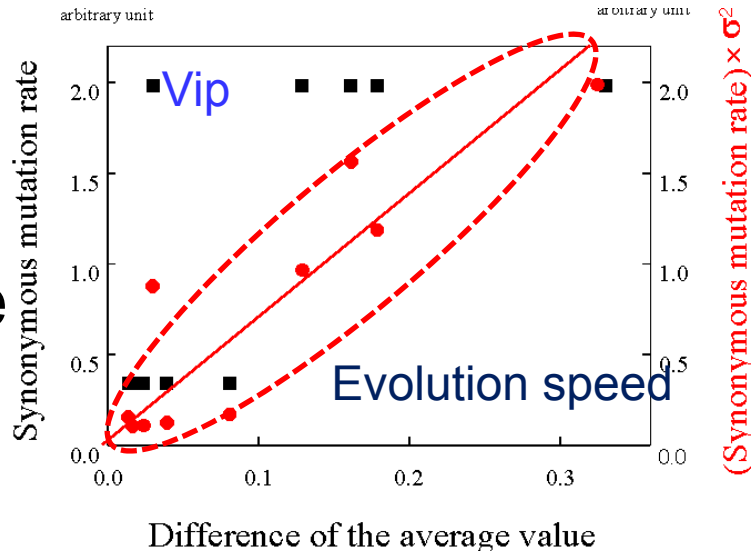

Sato,Ito,
Yomo,KK
PNAS(2003)

Fluctuation ----

Variance of phenotype of clone

Larger phenotypic fluctuation

---higher evolution speed？



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

Generalize by distribution function

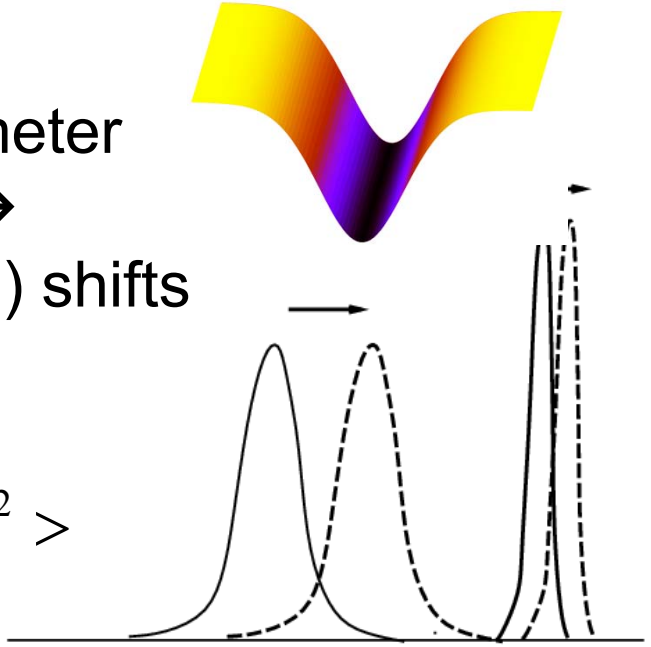
response ratio of some variable x against

change of parameter a versus fluctuation of x

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

change of the parameter a →

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




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

--``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

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

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

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, but need to check experimentally

# Examine by Toy Cell Model with Catalytic Reaction Network

(Cf. Furusawak,KK, PRL 2003, 2012)

- **k species of chemicals 、$X_o \cdots X_{k-1}$**

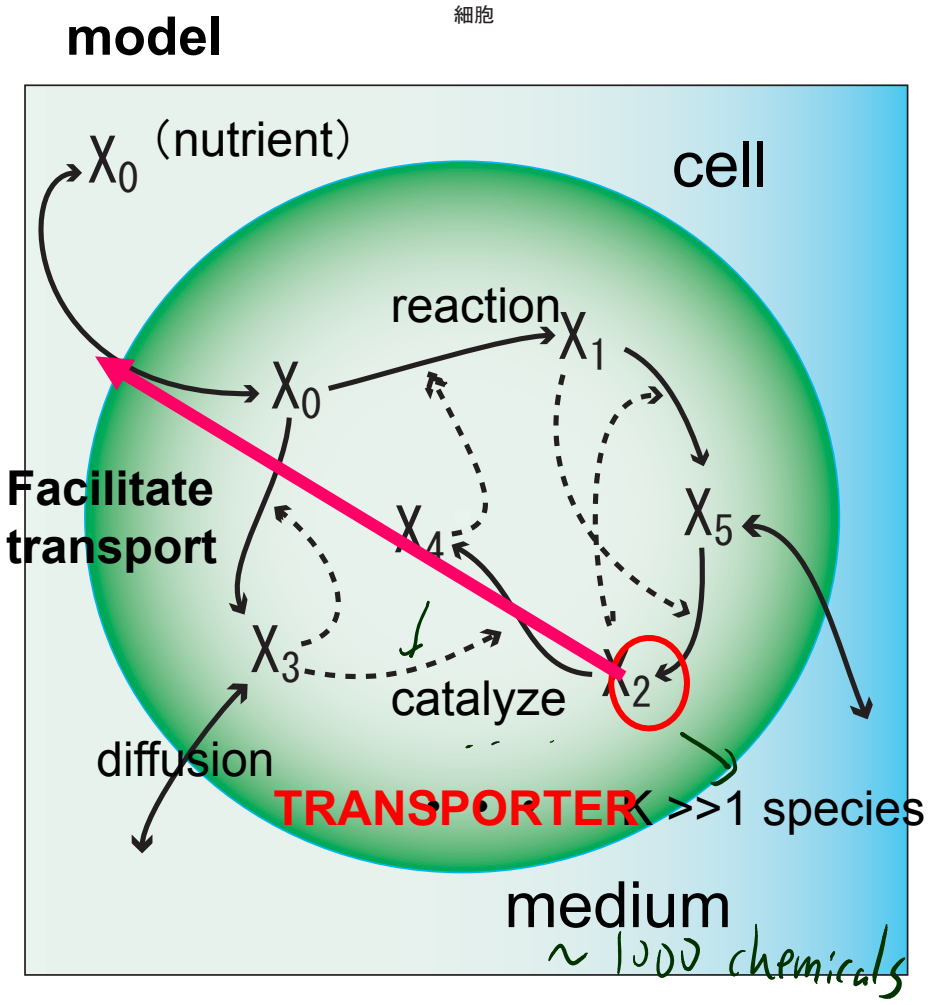
number ---$n_0$ 、$n_1 \ldots n_{k-1}$

- random catalytic reaction network

with the path rate p

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

- **Resource chemicals (<- environment) are transported with the aid of a given catalyst, transporter**
- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth.
- **$N = \Sigma n_i$** exceeds $N_{max}$ (model 1)
- Genotype: Network;
- Fitness: e.g., abundances of given component
- Evolution: Mutate reaction paths, and select those with higher fitness



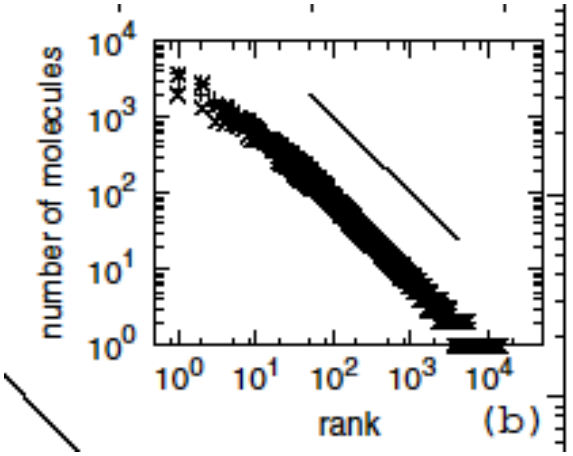

**dX1/dt ∝ X0X4; rate equation; Stochastic model** here

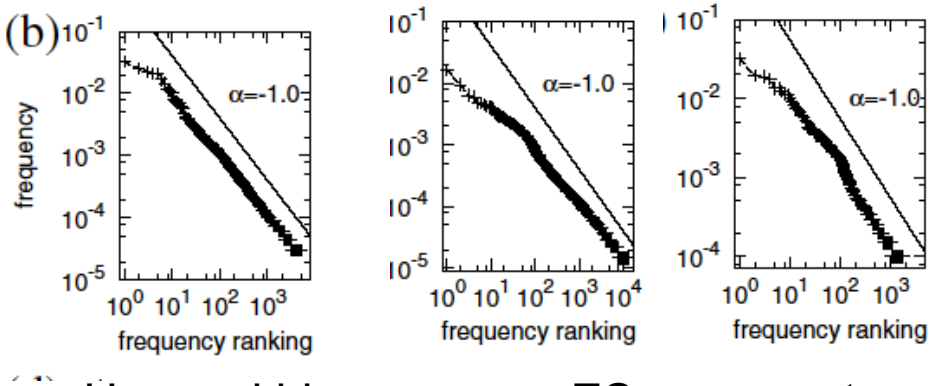
Statistical Laws ( confirmed by experiments and simple toy cell models)

☑ Power Law in abundances across components （inverse proportionality between abundance and its rank)

☑ Log-normal distribution for cell-cell variation+ universal variance –mean square relationship

☑Fold-change detection (Weber-Fechner Law)



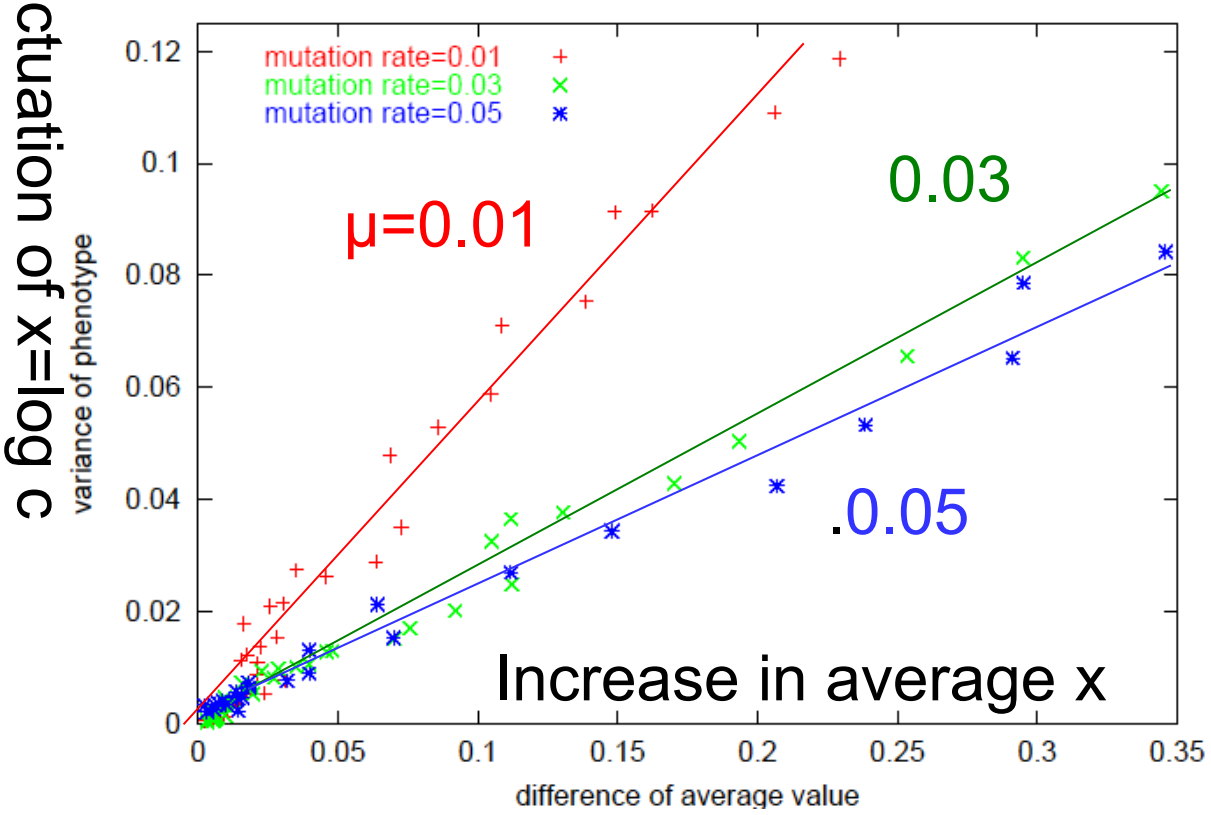



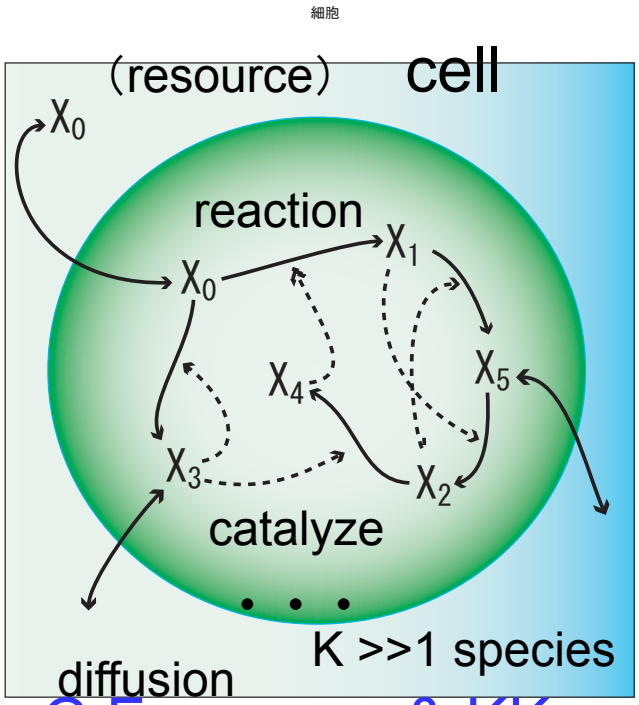

Human kidney, mouse ES yeast

Furusawa, KK, 2003, 2012, Furusawa et al 2005, KK Furusawa 2005,…

# Confirmation by a simulation model (evolve catalytic reaction network to increase a concentration of given protein)

transported resources: successively transformed to catalysts through mutually catalytic reaction network for cell growth




C.Furusawa & KK 2006

## (ii) Geno-Pheno relationship on variances

*but Vg ∝ evolution speed (Fisher)

*Vip variance of fitness over isogenic individuals

*Vg variance of average fitness over heterogenic pop

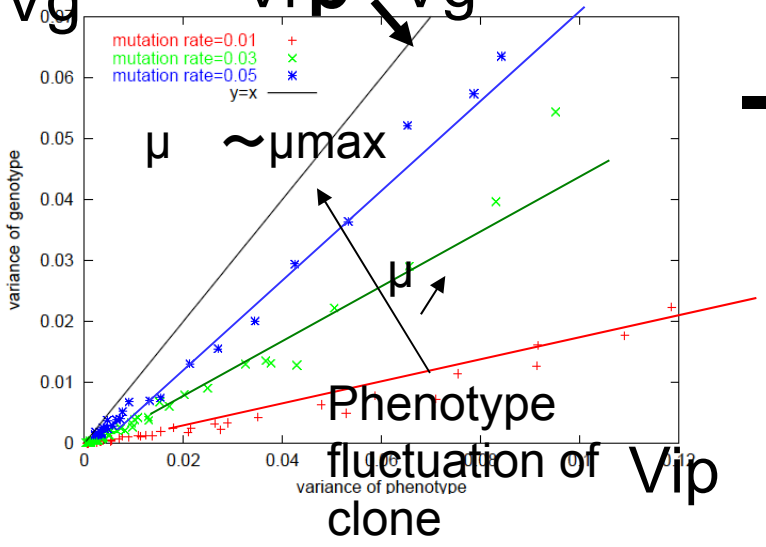
Vip ∝ Vg ∝ evolution speed through evolution course confirmed; experiment, theory, models

WHY??➔ result of robust evolution + distribution theory

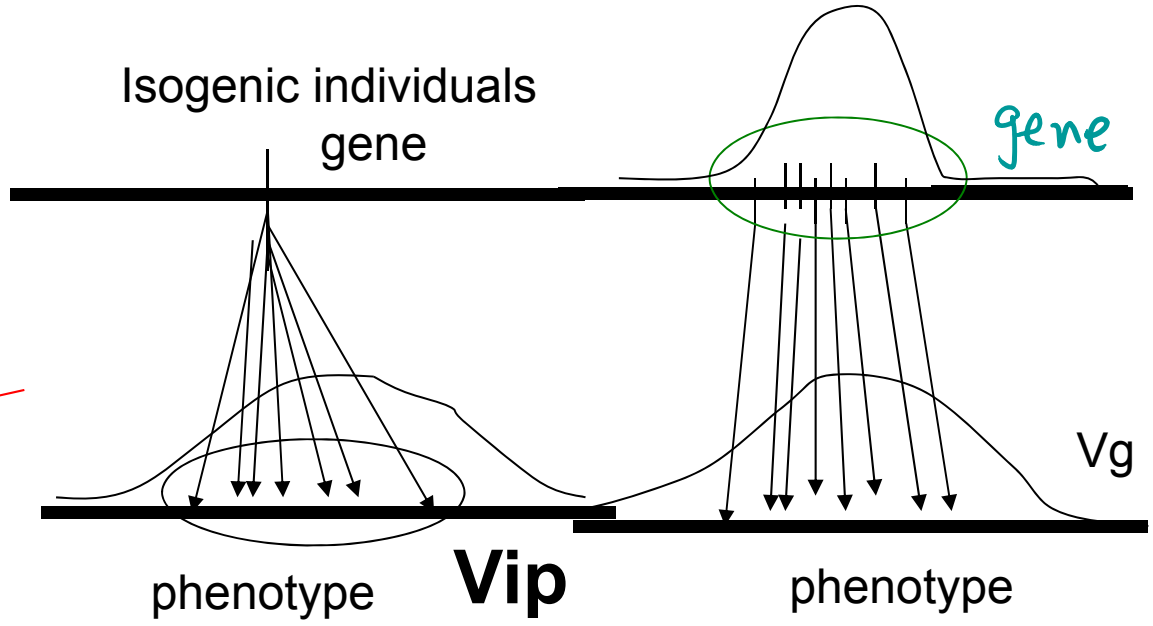
Robustness to noise ↑ → Robustness to Mutation ↑

**Vip ↓ → Vg ↓**

Vg Vi**p**=Vg




Phenotype fluctuation of clone Vip



As μ (mutation rate) increases to μ max,

(1) the distribution collapses (error catastrophe)

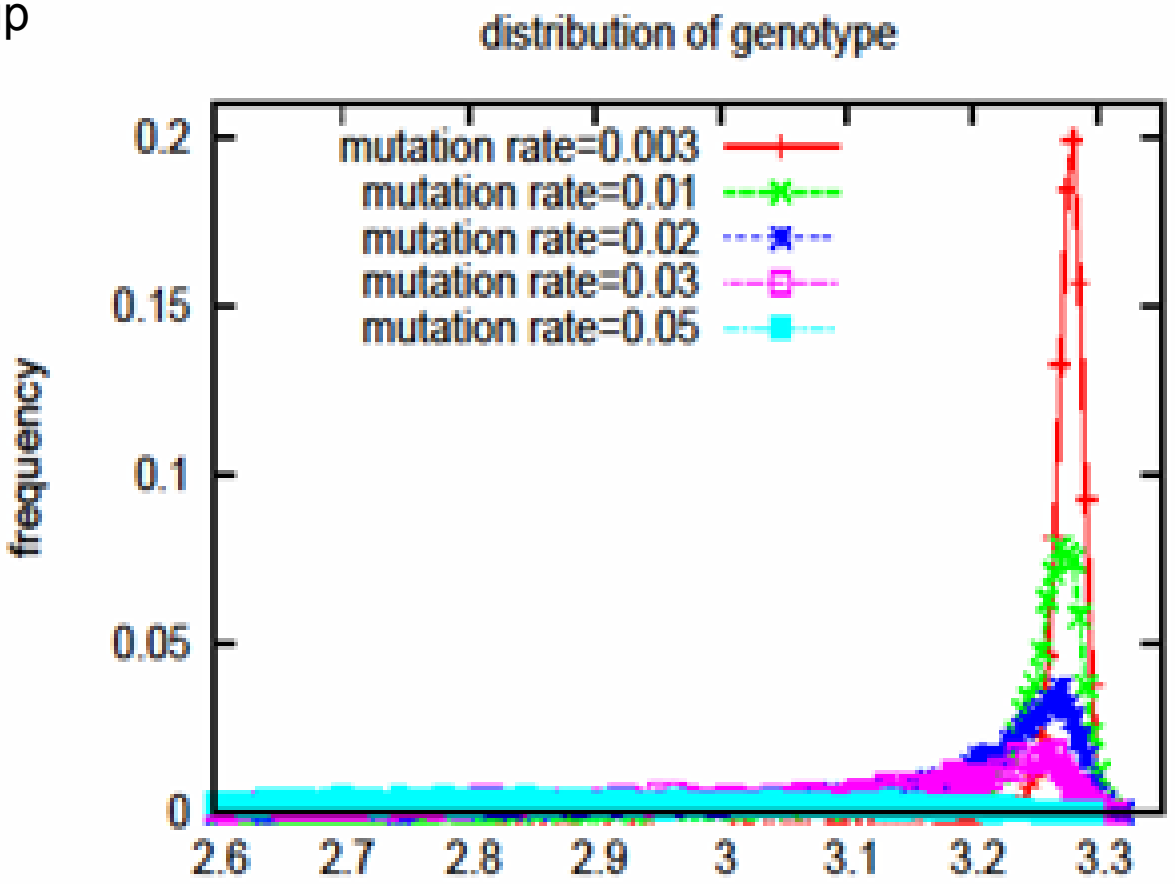
(2) evolution no longer progresses beyond μ max

evolution speed is maximal at μ ~ μ max

(3) Vg approaches Vip

As μ is increased,
The distribution
'collapses'

Error catastrophe



WHY? (Phenomenological theory assuming evolutionary robustness)

Consider 2-variable distrb

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

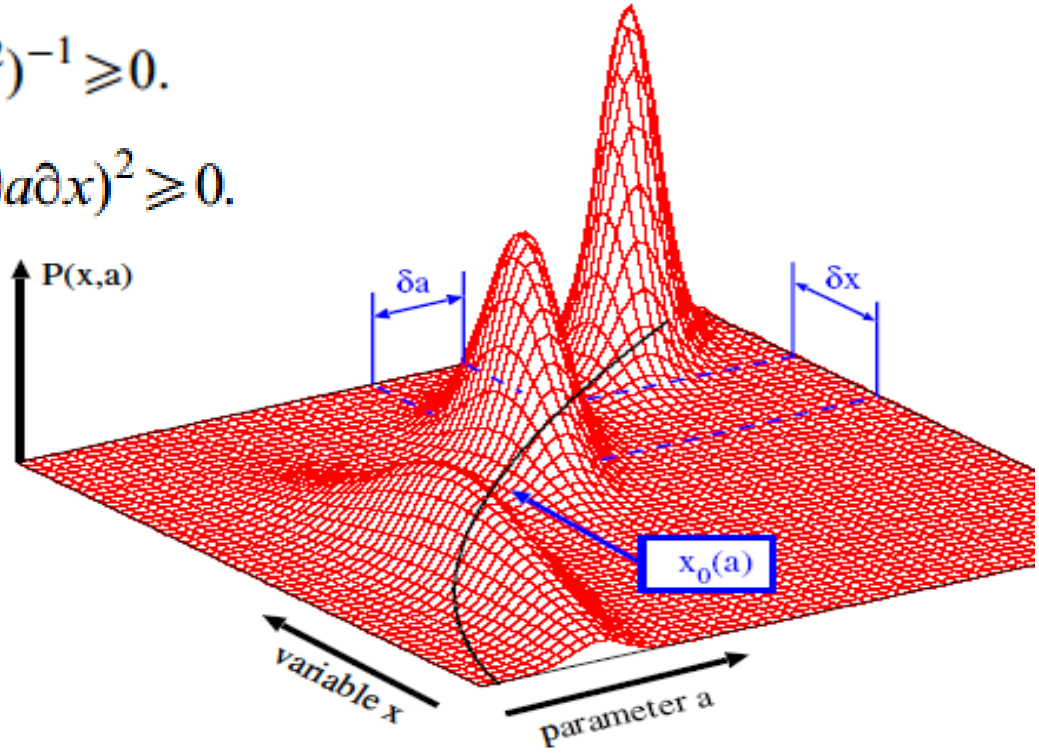
Keep a single-peak (stability condition).

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

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

Hessian condition

Leads to relationship between Vip and Vg




KK,Furusawa, 2006 JTB

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

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

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

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

$$V_g = \frac{\mu C^2}{1-\mu C^2/\alpha}$$ ~Vig= μC$^2$ Vip=α

If mutation rate μ is small, Vg<Vip,

Vg ~ (μ/μmax )Vip ∝ Vip

Consistency between pheno & geno

also in *Evolutionary Systems Biology* 2012, ed. Soyer

- (i) Vip ≧ Vg ?（for stability?) ( **)

(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,,,,,

Assumptions on P(x,a) and Robust Evolution??

Why higher developmental noise leads to robust evolution?

---

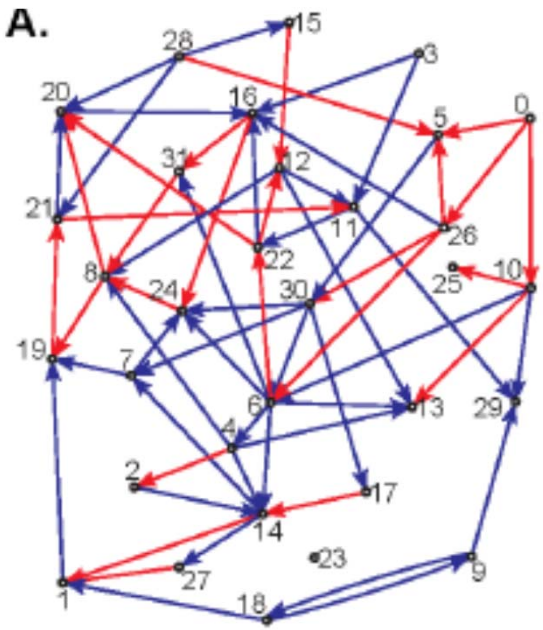
(**) under selection of given trait. if μ is small:

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

Vg/(Vip+Vg) is known as heritability (smaller for important trait)

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

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




**$x_i$ – expression of gene i :on off**

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

(on) x>θi (off) x<θi

off on

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

Activation
Repression
…=1,-1,0

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

**Gaussian white noise**

**M;total number of genes, k : output genes**

**Noise strength σ**

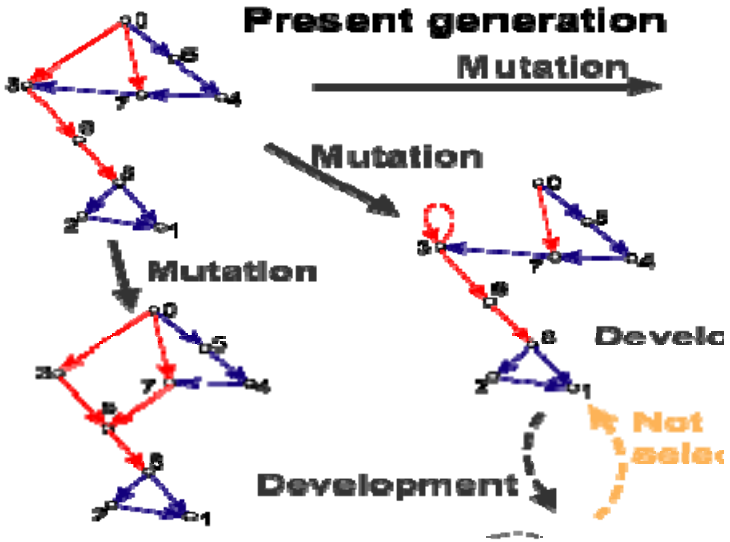
- Fitness: Starting from off of all genes, after development genes $x_i$ i=1、2、···、k should be on (Target Gene Pattern)

**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

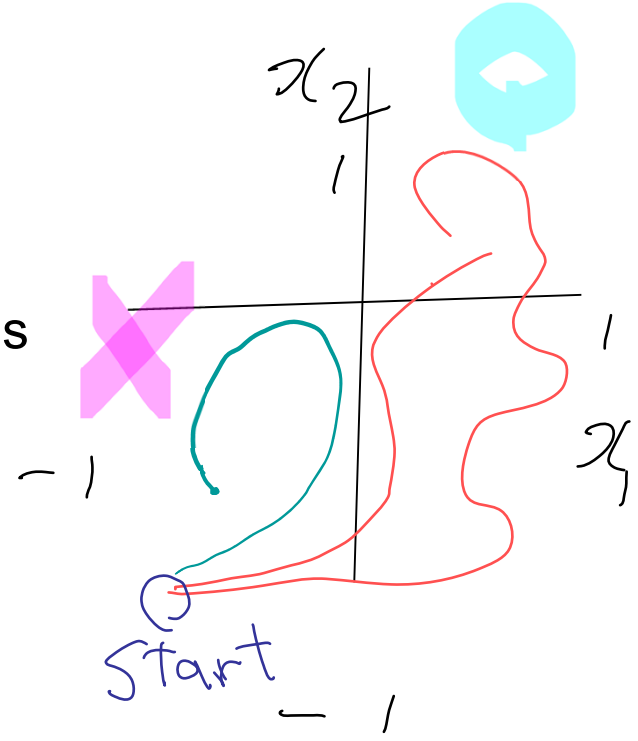



If M=k=2→

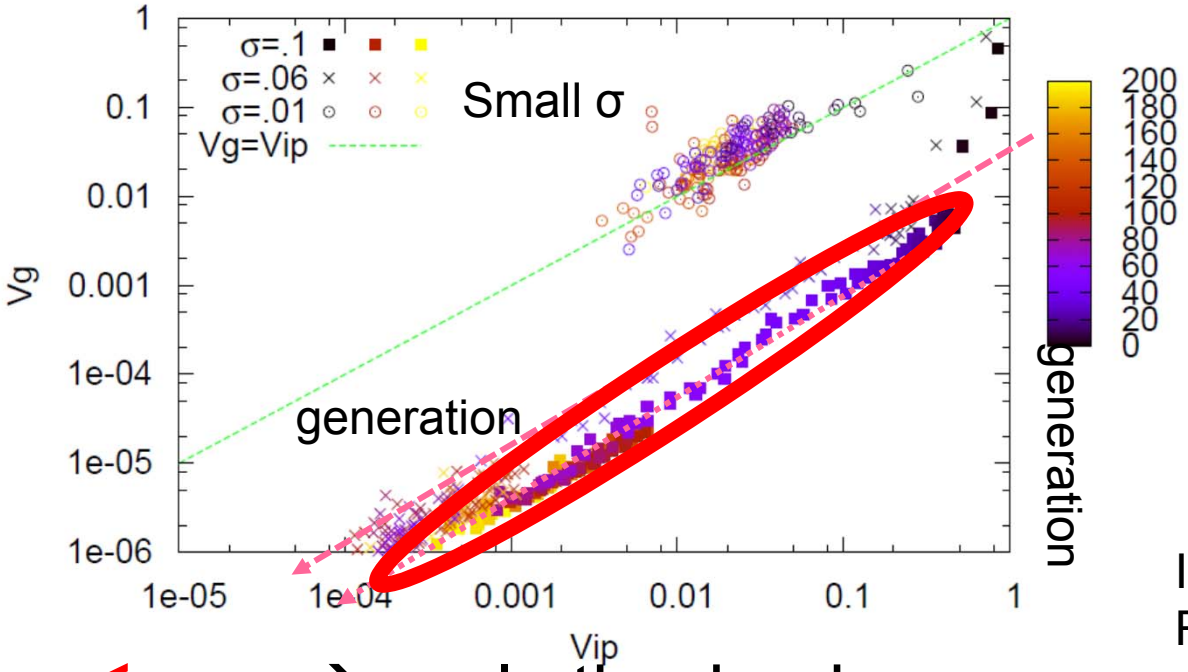
Most simulations

M=64

K=8



# ‘’Robustness transition by increasing noise”




(1)Vip≧Vg forσ≧σc

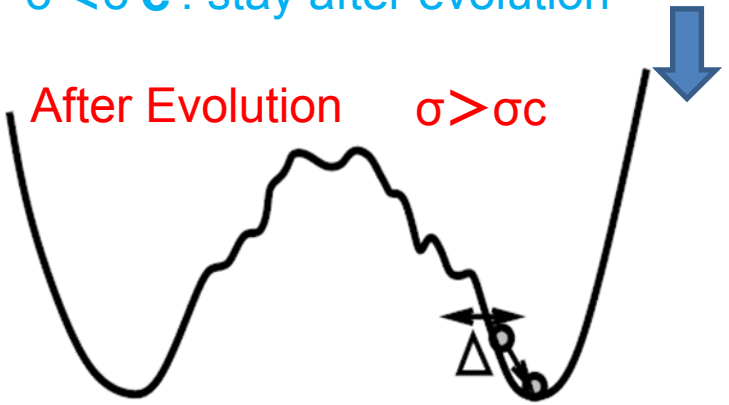
(2) Vg→Vip as σ→σc

(4) Vip∝Vg through evolution course

KK,PLosOne,2007

Initial (most probable networks, Random)

σ＜σ**c** : stay after evolution




σ＜σ**c** → only tiny basin around target orbit

σ＞σc →robustness evolves proportional decrease in Vip &Vg

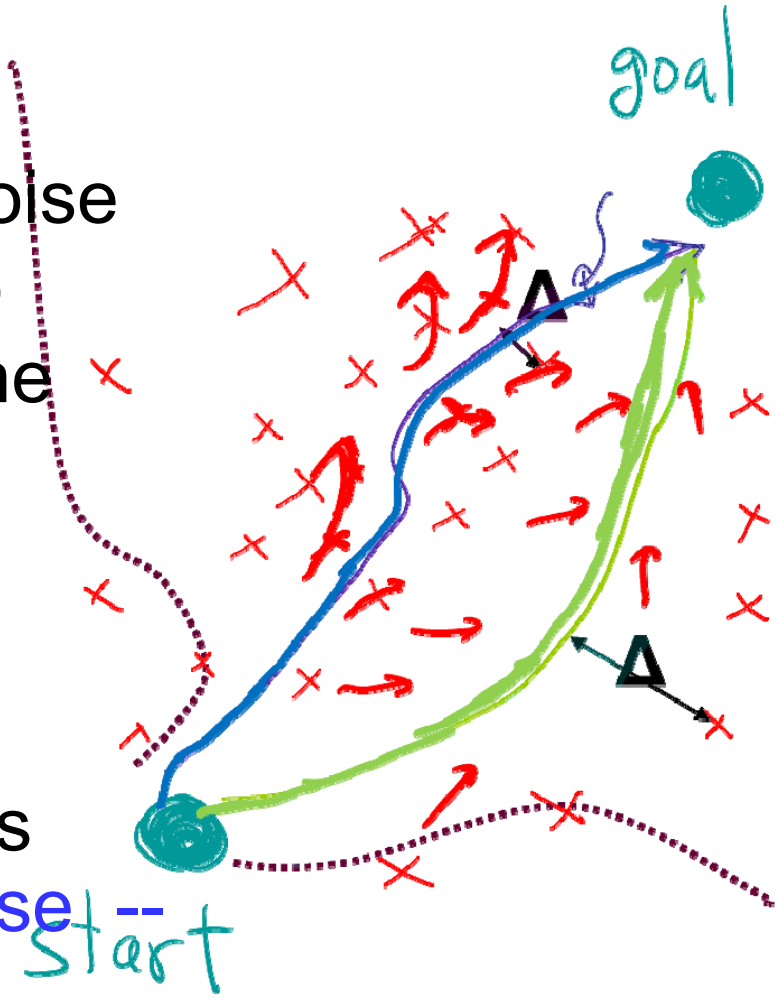
Large basin for target attractor

Smooth developmental landscape

Difference in basin structure

## Evolution of Robustness

If developmental dynamics (gene expression) are under sufficient noise level, robustness to noise leads to robustness to mutation, through the evolution.




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

"Inverse" of phenotypic variances

Developmental Robustness to noise -- -- Vip

Robustness to mutation in evolution -- --Vg

Vip ∝ Vg →Developmental robustness is embedded into genetic (evolutionary) robustness for $\sigma > \sigma c$

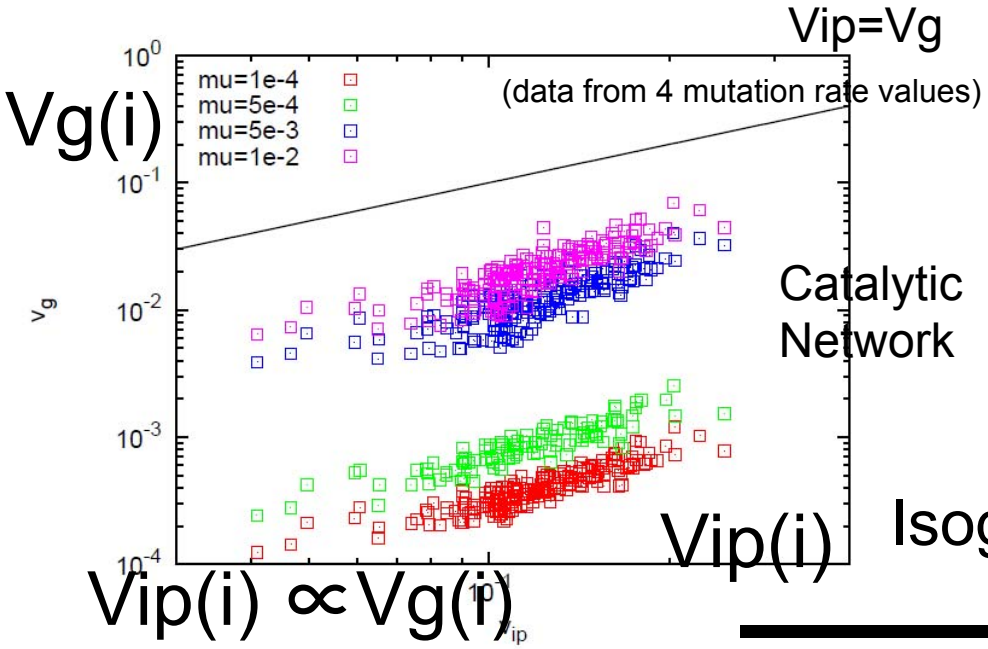
# Further---  Vip-Vg relationship for each component

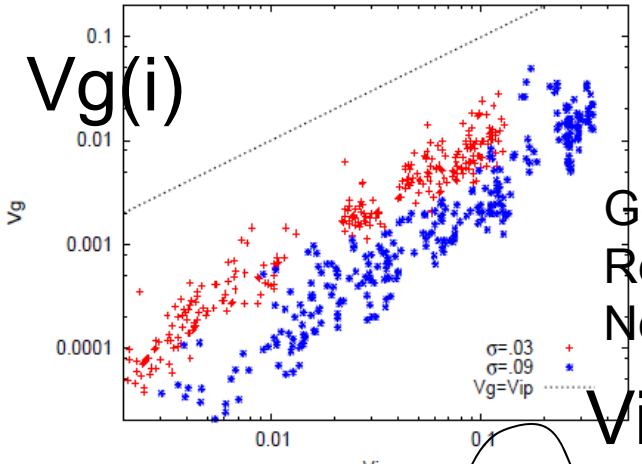
Vg(i) : Variation of i-th expression due to mutation

Vip(i) : Variation due to noise in dynamics

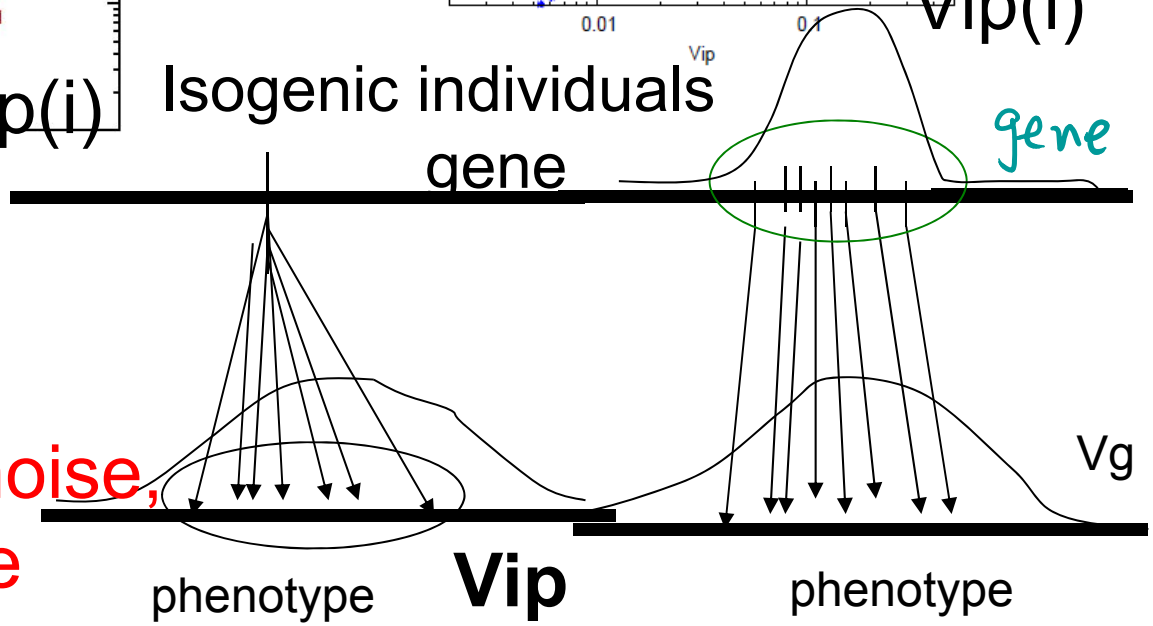
Furusawa, kk Interface 2015

After evolution proportional across all components



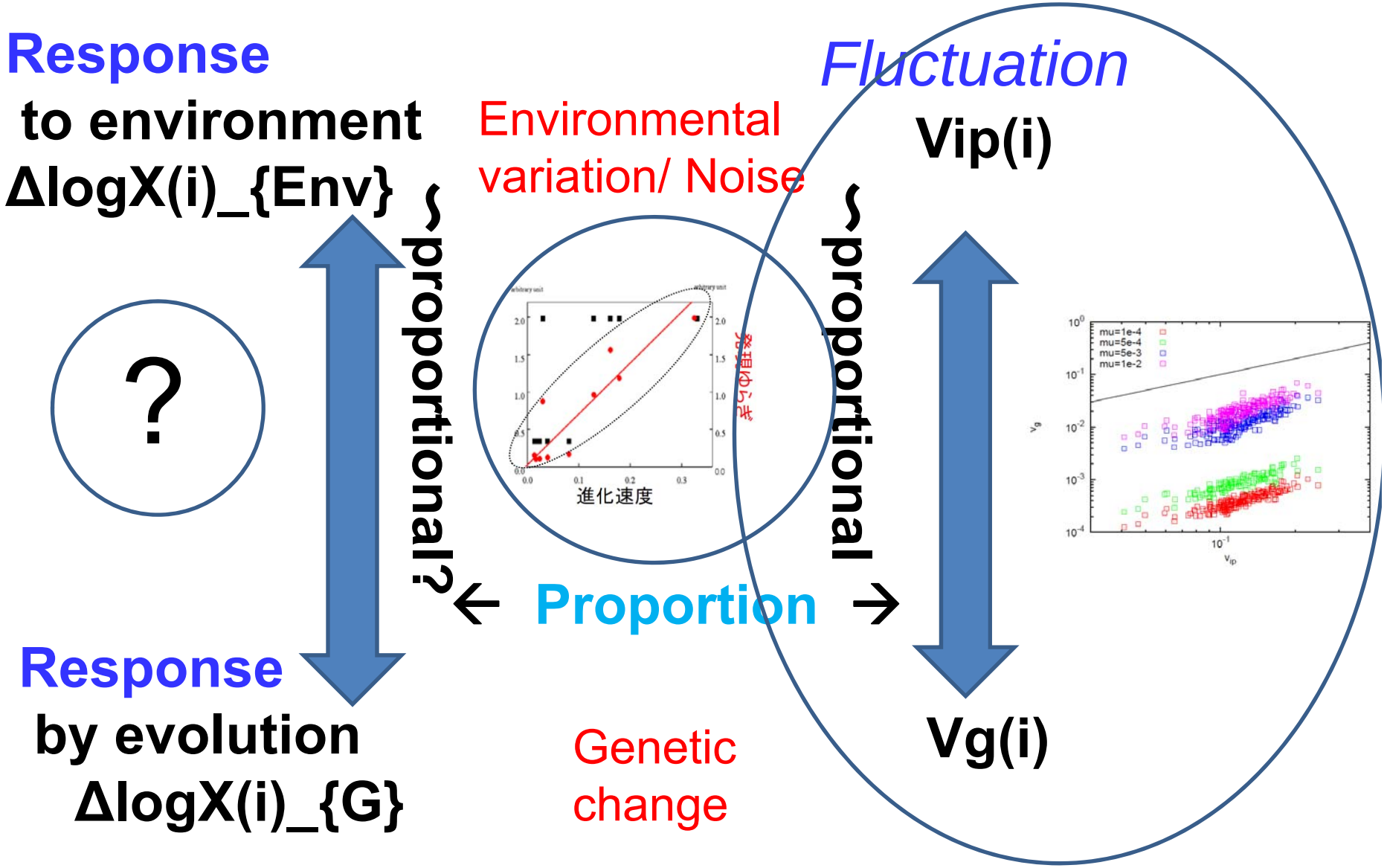




Vip(i) ∝Vg(i) over all components i




If highly variable by noise,
More easily evolvable

# Env-Evo Fluctuation Response Relationship



## Part II

0) Constraint on 1-dim manifold by steady-growth cells (*kk et al, PhysRevX2015*)

1) But linear relationship works “too well”
Universal Law in Phenotypic Evolution *(Furusawa,kk, Interface 2015)*

* macroscopic linear relationship;
low-dimensionality in state/parameter space
← some simulation, experimental results

→ **results of evolution**

2) Slow-manifold hypothesis and its consequence
**macroscopic theory a la thermodynamics**

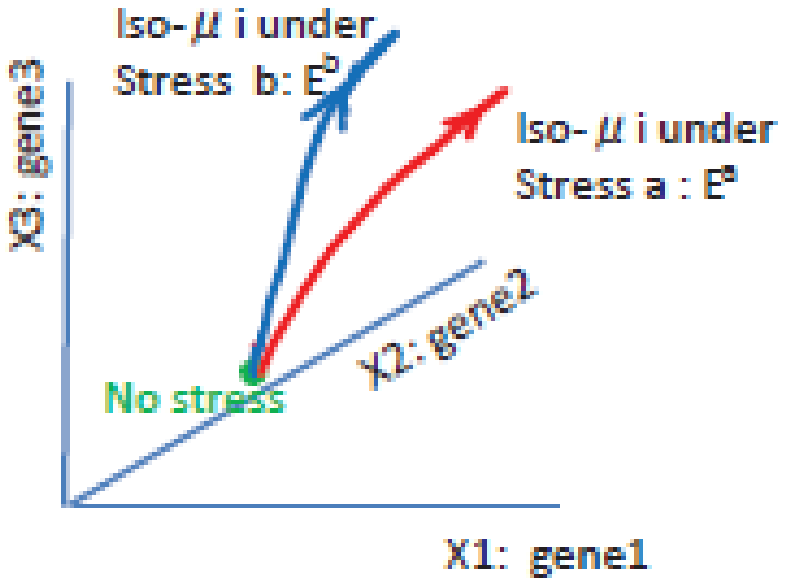
## Focus on steady-growth cells →universal constraint

all the components have to be roughly doubled within a cell division time)

Ni(i=1,…,M)

dNi/dt= μi Ni → exp(μi t); all μi are equal;

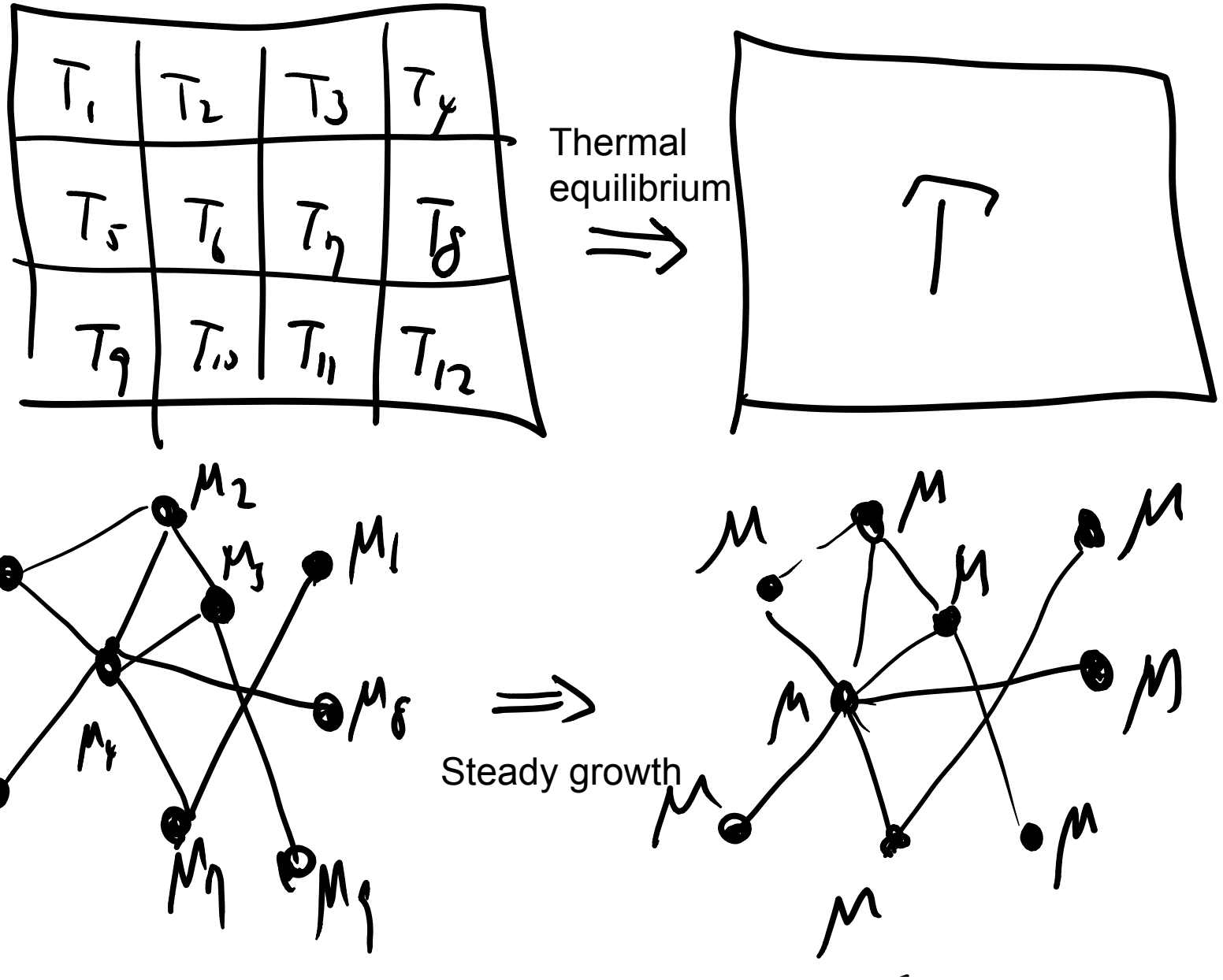
→(M-1) conditions → 1-dimensional line




**M(e.g. proteins) ~ ($10^3$~$10^4$) measurable by microarray**

**Adaptation/evolution progresses on an iso-μi-line ('quasi-static process') in an M-dimensional state space**

Restriction to steady growth (here) vs to equilibrium (in thermodynamics): Transient state can involve many degrees



# Theory for steady growth: a constraint

Concentration xi=Ni/V: (dV/dt)/V= μ （volume V)

Temporal change of concentration x

$$dx_i/dt = f_i(\{x_j\}) - \mu x_i$$ dilution

fi includes all reactions,
Synthesis, degradation,..

Now, the stationary state is given by a fixed point condition

$$x_i^* = f_i(\{x_j^*\})/\mu$$

for all $i$.

As a convenience, denote $X = logx$, and $f_i = x_i F_i$. Then,

$$dX_i/dt = F_i(\{X_j\}) - \mu$$

Response under different stress strength E

$$F_i(\{X_i^*(E)\}, E) = \mu(E).$$

# Linearization around original statew.r.t X(=log x)

KK, Furusawa Yomo. Phys Rev X(2015)

$$\sum_j J_{ij}\delta X_j(E) + \gamma_i \delta E = \delta\mu(E)$$

Jacobi matrix $J_{ij}$.

with $\gamma_i \equiv \frac{\partial F_i}{\partial E}$. ← Susceptibility to stress

In the linear regime $\delta\mu = \alpha\delta E.$

$$\delta X_j(E) = \delta\mu(E) \times \sum_i L_{ji}(1 - \gamma_i/\alpha) \qquad L = J^{-1}.$$

$$\frac{\delta X_j(E)}{\delta X_j(E')} = \frac{\delta\mu(E)}{\delta\mu(E')} = \text{indep't of j}$$

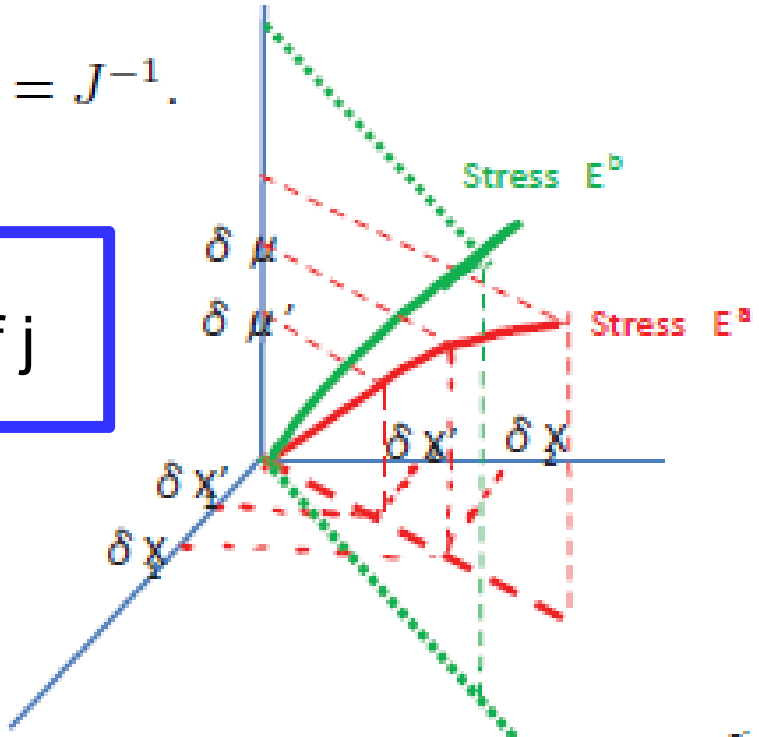



Fig. 2b

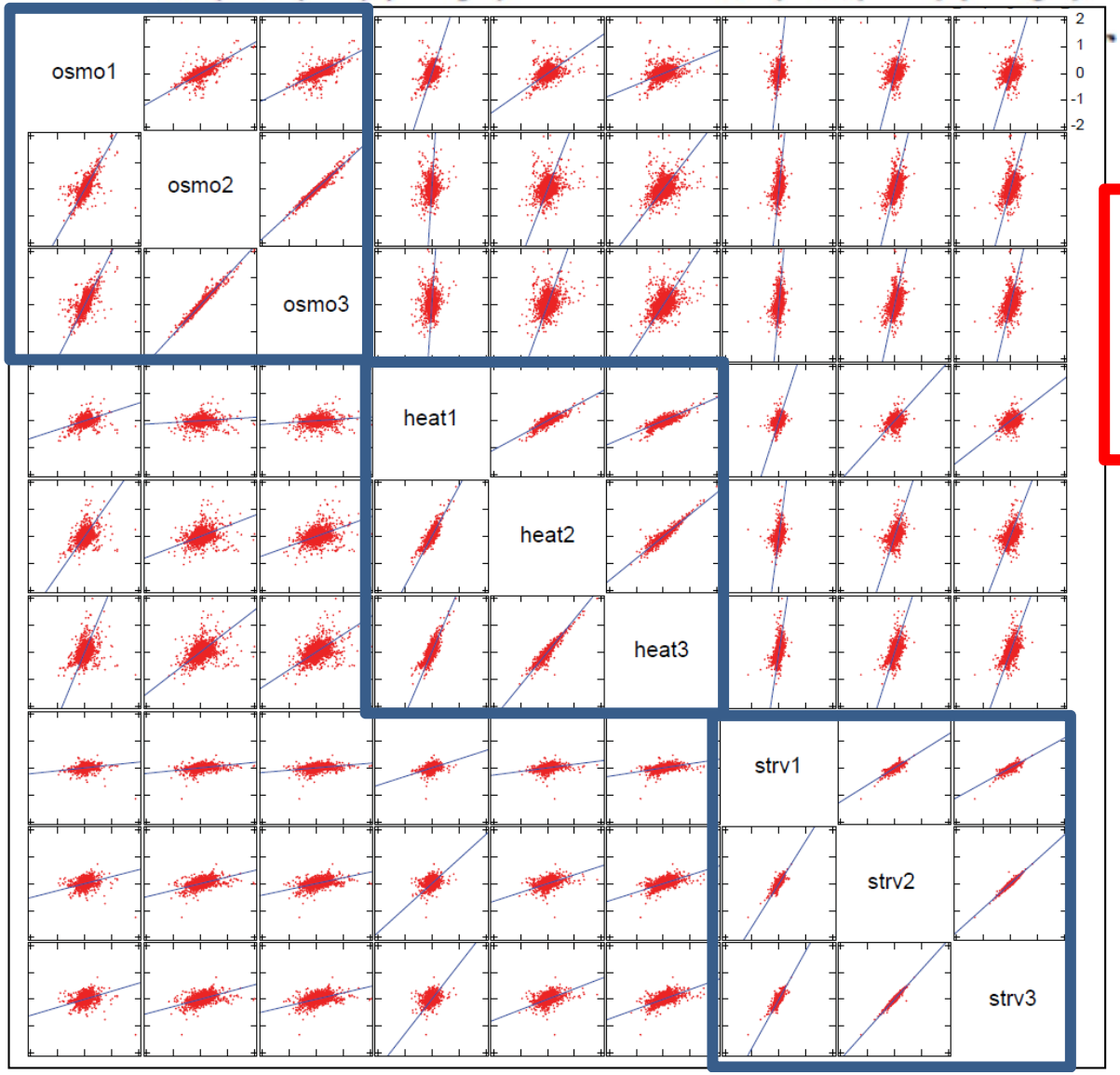
Common proportionality for log-expression change δXj for all components j

←Steady-growth sustaining all components +Linear

**Transcriptome expreiment**

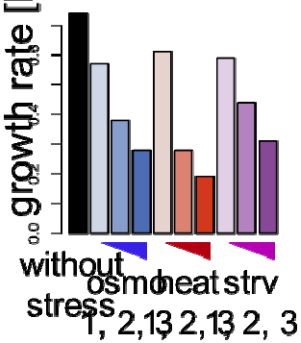
**Put E Coli under different stress conditions; Measure gene expressions**

$log(x_i(E)/x_i^O)$ and $log(x_i(E')/x_i^O)$



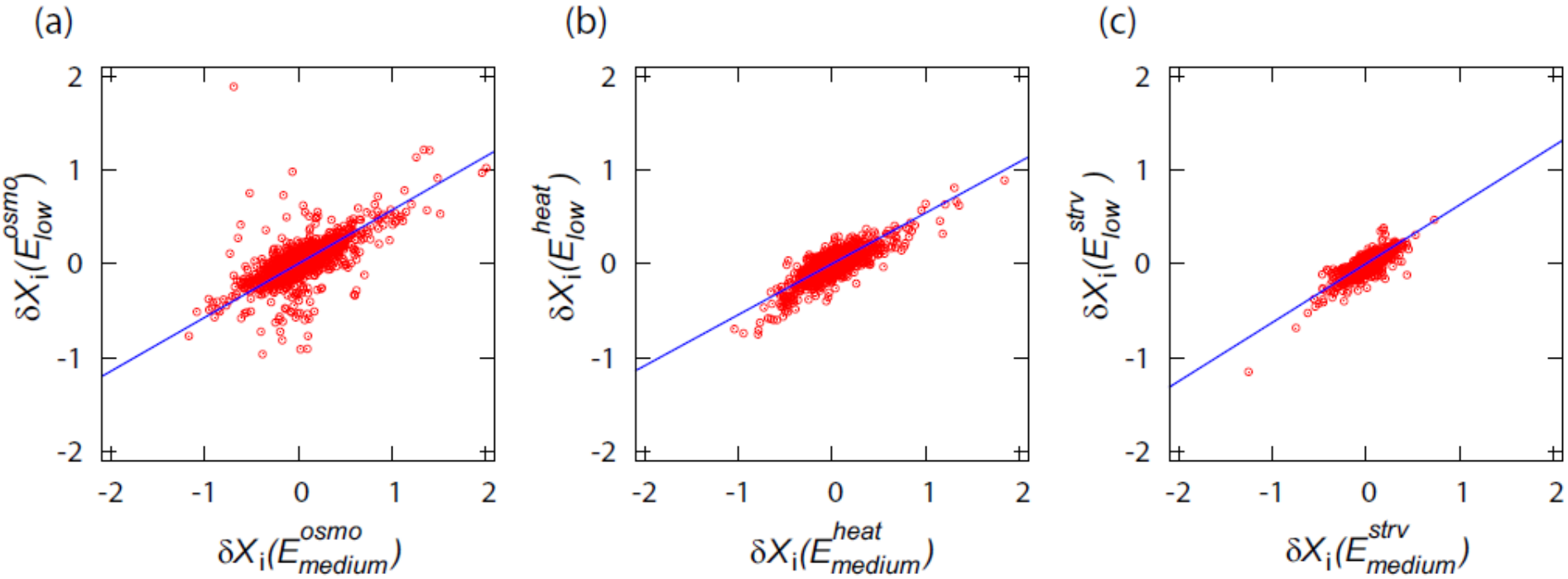

**O: no stress**
**E,E' : osmotic pressure, heat, starvation**
**Low, medium high**

Matsumoto,Yomo
NatCellBiol2013



# Expression changes under same stress with different strengths

$$log(x_i(E)/x_i^O) \text{ and } log(x_i(E')/x_i^O)$$




The Slope agrees with
The growth rate change
δμ'/δμ

A: low vs medium osmo
B low vs medium heat
C low vs medium starvation

δX^E、δX^E'
over few thousand genes

**Data from**
**Matsumoto**
**etal**
**BMC Evol Biol**
**l2013**

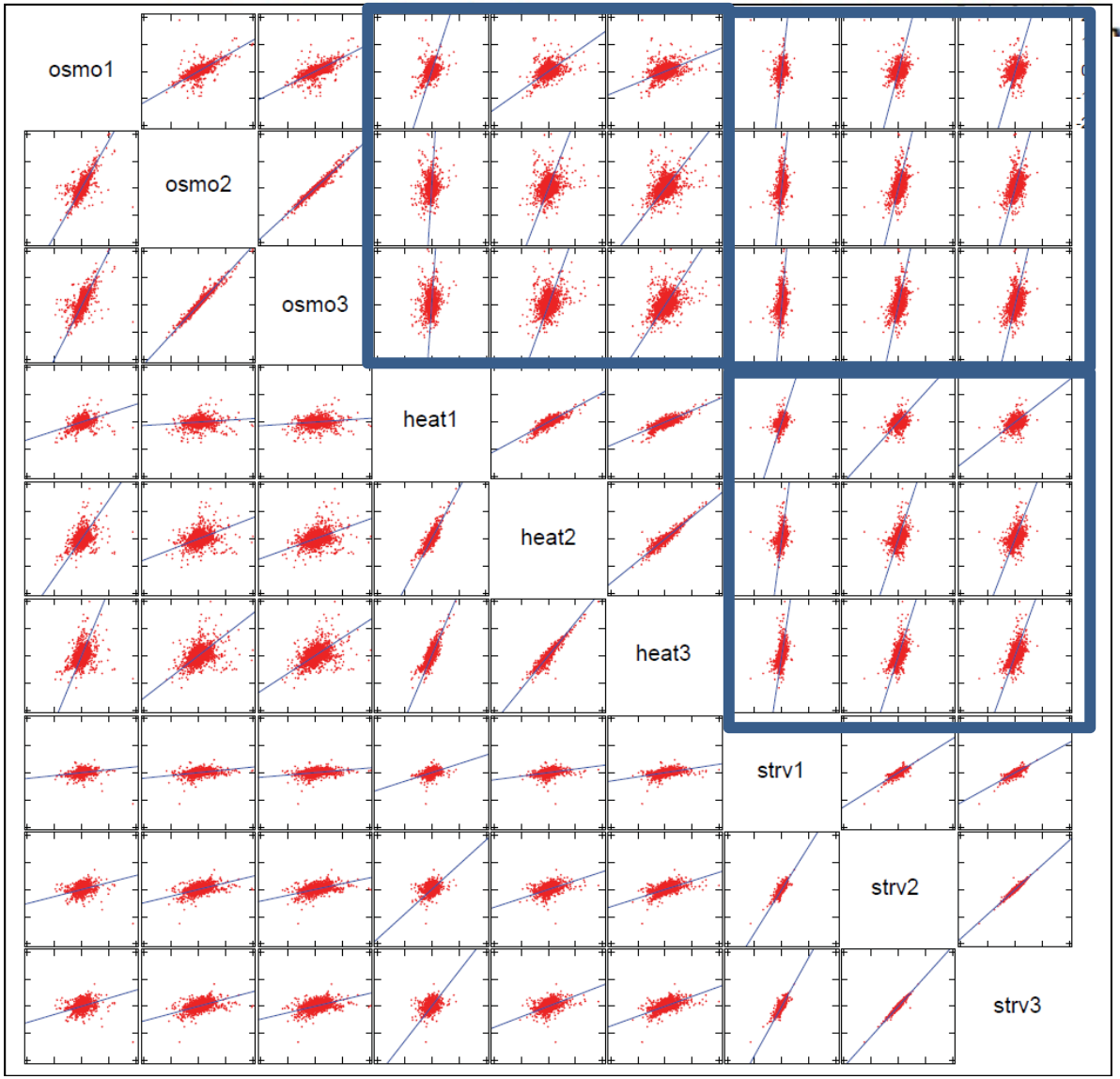
KK,Furusawa,Yomo,
Phys Rev X (2015)

# Transcriptome expreiment

# Comparison across different stress conditions;

$log(x_i(E)/x_i^O)$ and $log(x_i(E')/x_i^O)$

# expressions




**O: no stress**
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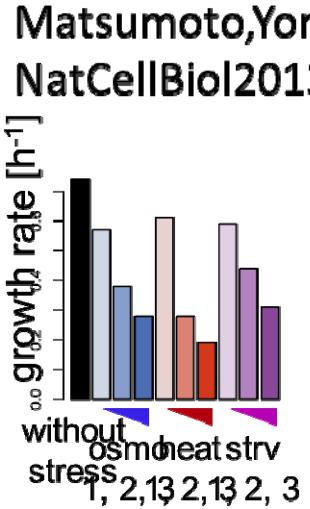
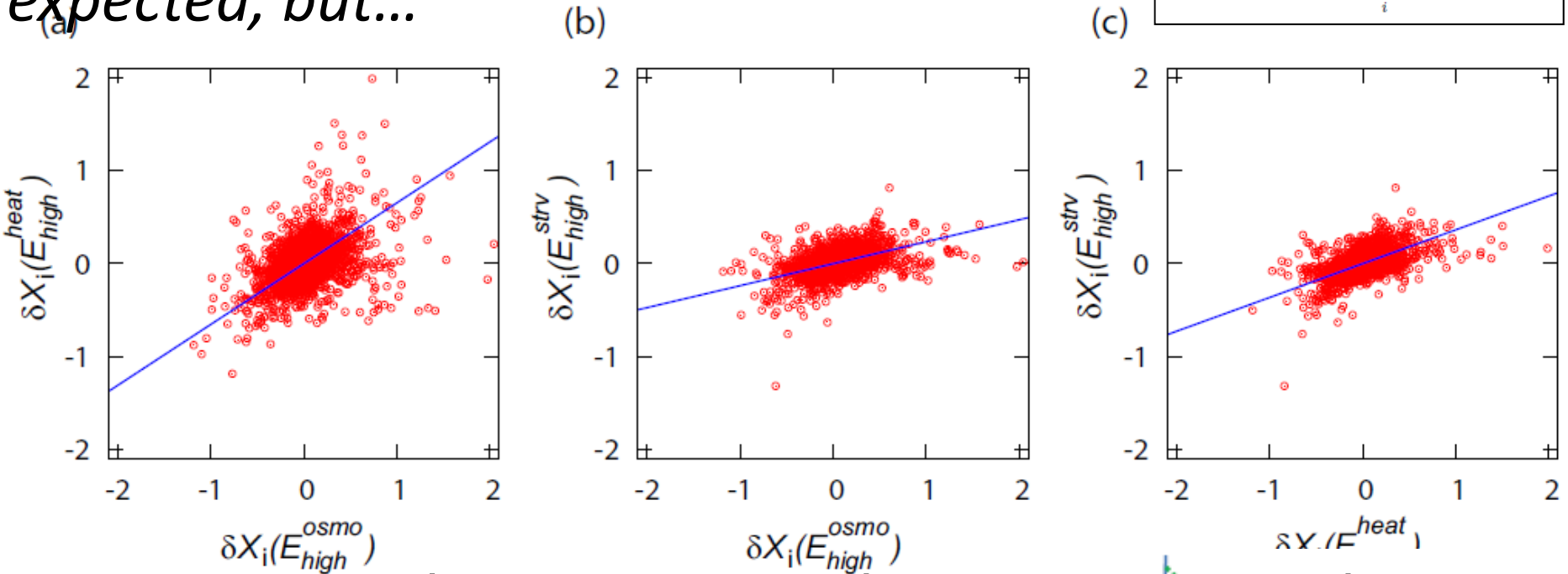


Across Different types of stresses:

$$\gamma_i \equiv \frac{\partial F_i}{\partial E}$$

γi(*a*) depends on type *a so correlation might not be expected, but…*

$$\delta X_j(E) = \delta\mu(E) \times \sum_i L_{ji}(1 - \gamma_i/\alpha)$$




osmotic / heat starve/osmotic starve/heat

Still highly correlated

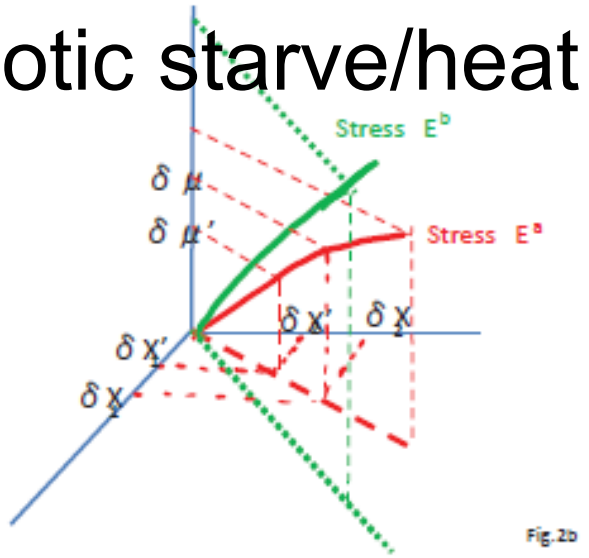
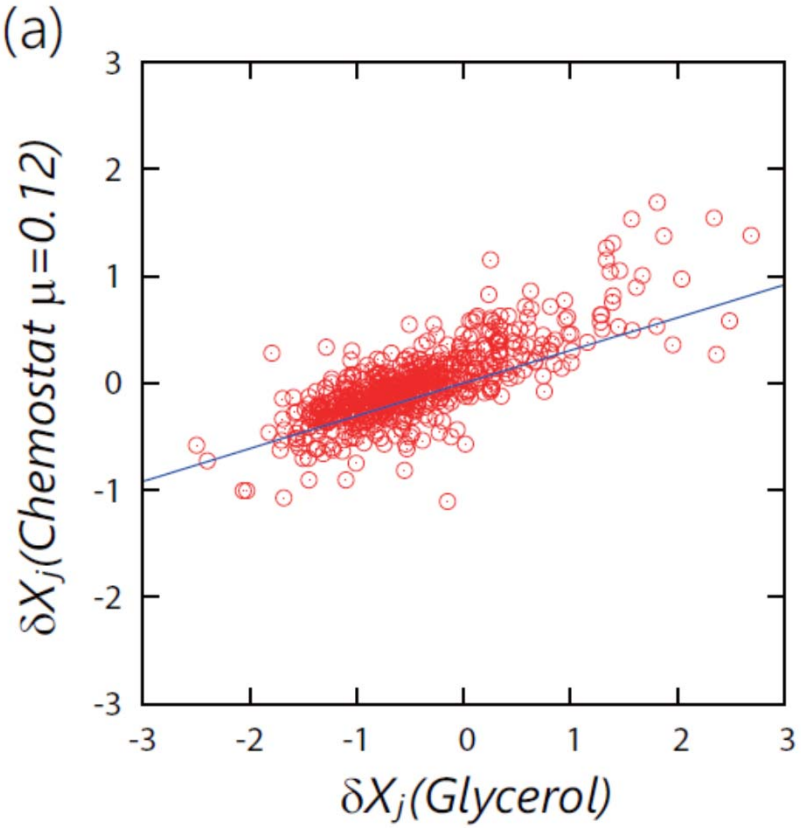
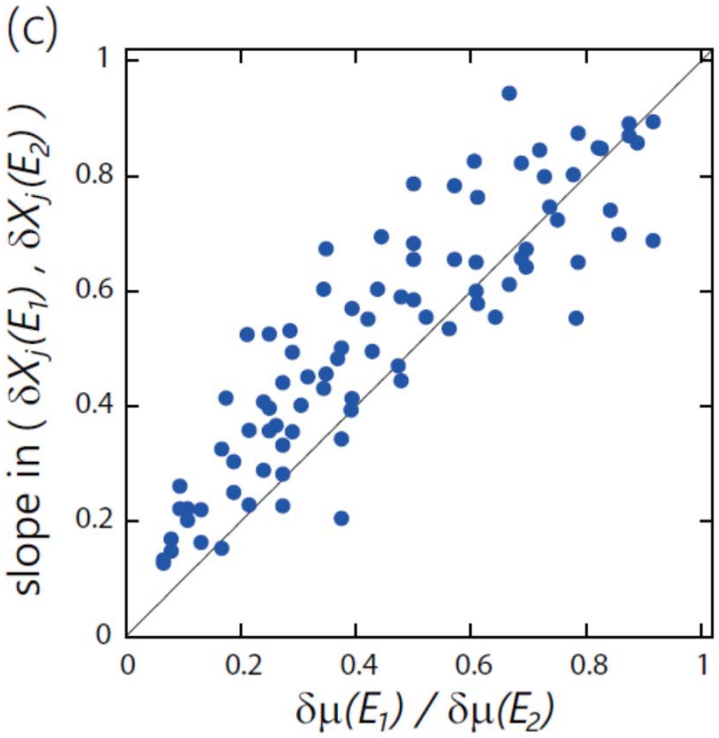



Fig.2b

# Confirmed also protein expression changes across different environmental conditions (based on the data by Heinemann) 20 different conditions on E Coli




Furusawa, KK bioRxiv 2017

# Non-trivial point: Emergent macroscopic Linearity

- (1) Large Linear Regime?
- (2) Validity across different environmental condition?

Q : achieved in an evolved system(to macro regime)?

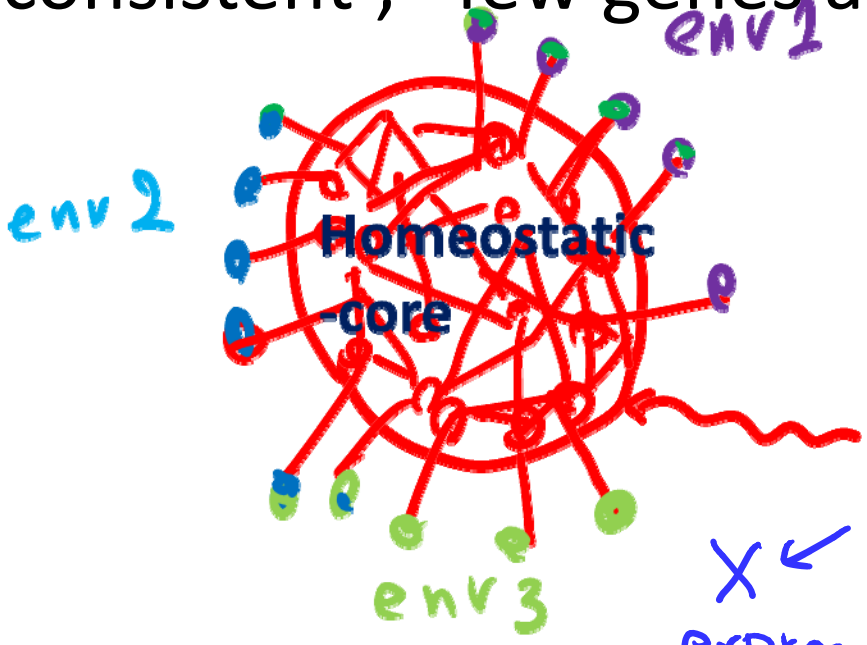
before addressing it..

**Is this universal relationship extended to evolution-environmental relationship? ←**

- High-dimensional adaptation system (diversity) is important for expanded liner regime and applicability for diverse environmental changes

  * emergence of 'collective' slow variable (Image)

homeostatic core (major parts) mutually stabilize; growth-rate as 'mean-field'; self-consistent ; few genes absorb environmental stresses




**Relevant for robustness of a high-dimensional state**

core part (no direct X ← expression)

$$d\mu = C\,dX + \sum_{\alpha} \gamma^{\alpha} dE^{\alpha}$$

α : Environment

# Examine by Toy Cell Model with Catalytic Reaction Network

(Cf. Furusawak,KK, PRL 2003, 2012)

- **k species of chemicals 、$X_o \cdots X_{k-1}$**

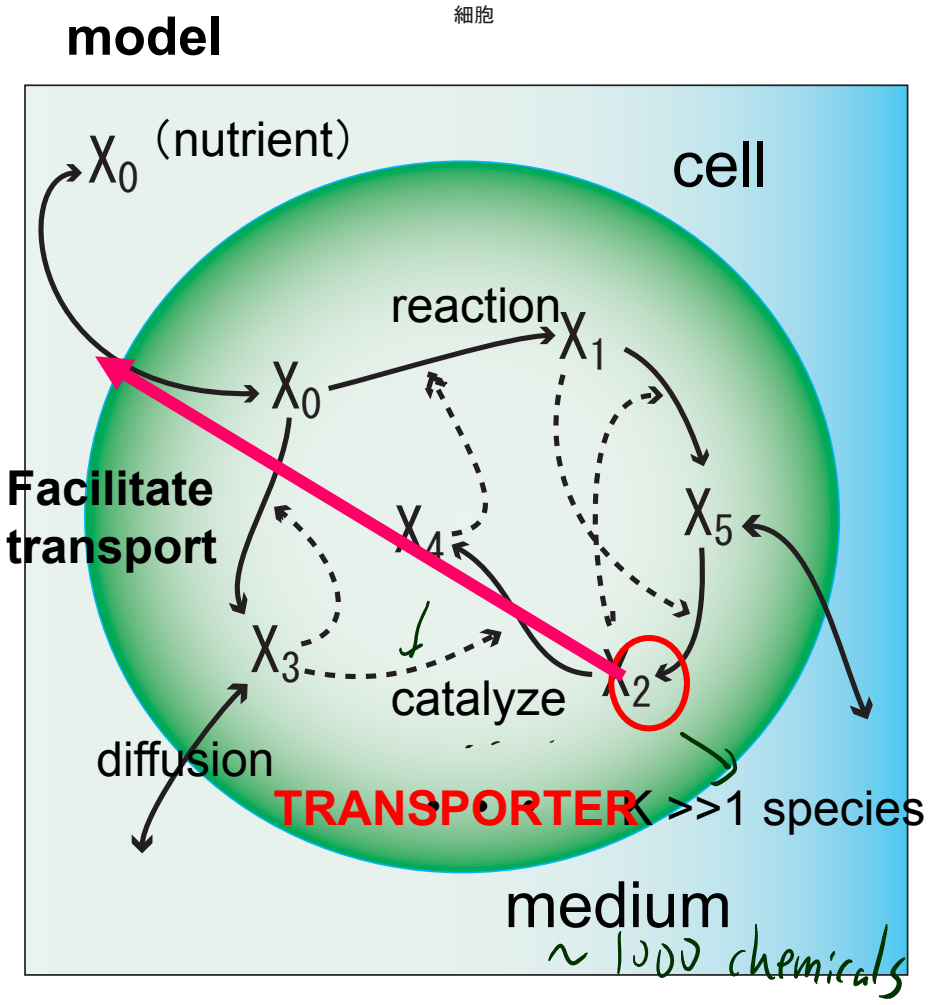
number ---$n_0$ 、$n_1 \ldots n_{k-1}$

- random catalytic reaction network

with the path rate p

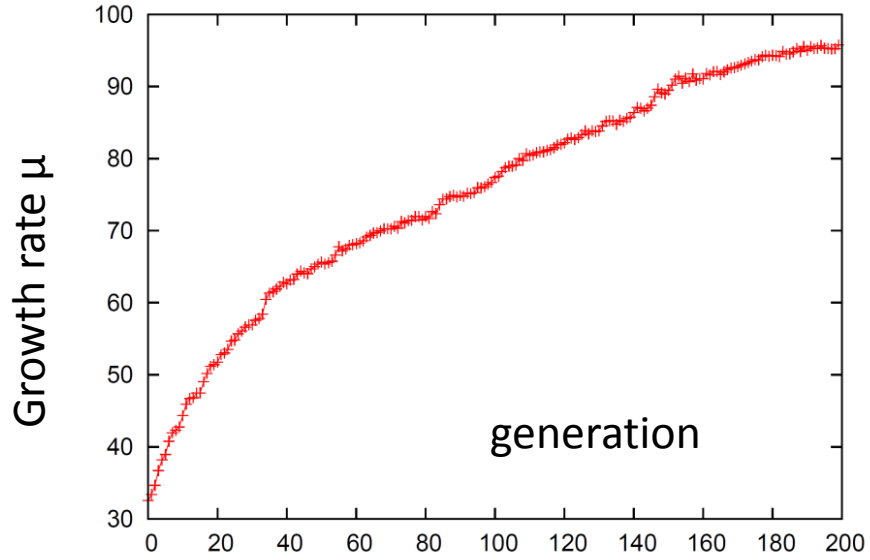
for the reaction $X_i + X_j -> X_k + X_j$

- **Resource chemicals (<- environment) are transported with the aid of a given catalyst, transporter**
- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth.
- **$N = \Sigma n_i$** exceeds $N_{max}$ (model 1)
- Genotype: Network;
- Fitness: e.g., abundances of given component
- Evolution: Mutate reaction paths, and select those with higher fitness




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

# Evolve Network to increase the growth rate under given resource condition




evolution under the resource environment

with concentrations i=1,2,..,10 (e0,e0,,,e0)

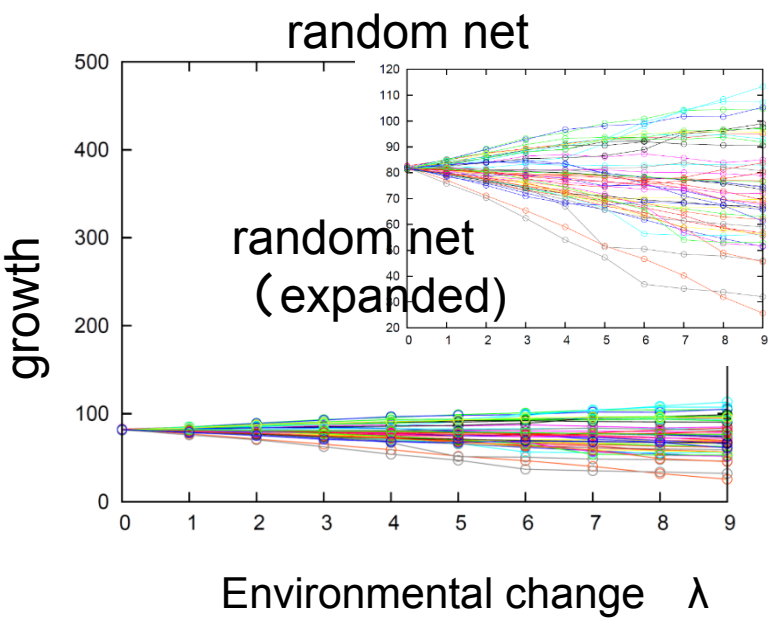
Then put an environment

Env = λ (e1,e2,e3,..e10) + (1-λ) (e0,e0,…, e0)

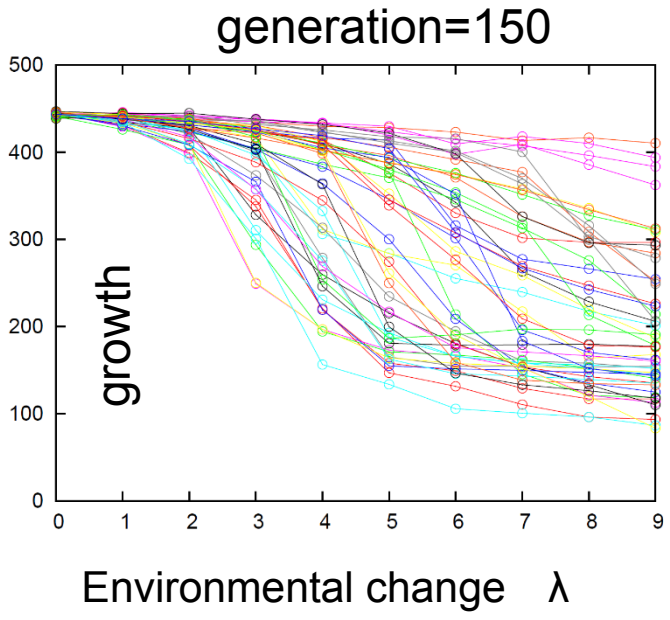
-1< e1,e2,… <1 (randomly chosen)

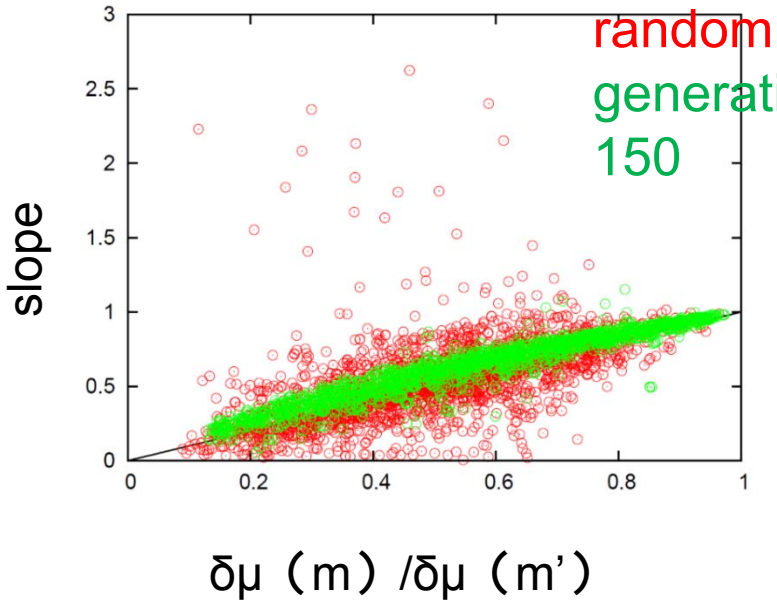
Check the change in concentrations and growth rates against λ

# Linear Regime is Expanded after evolution

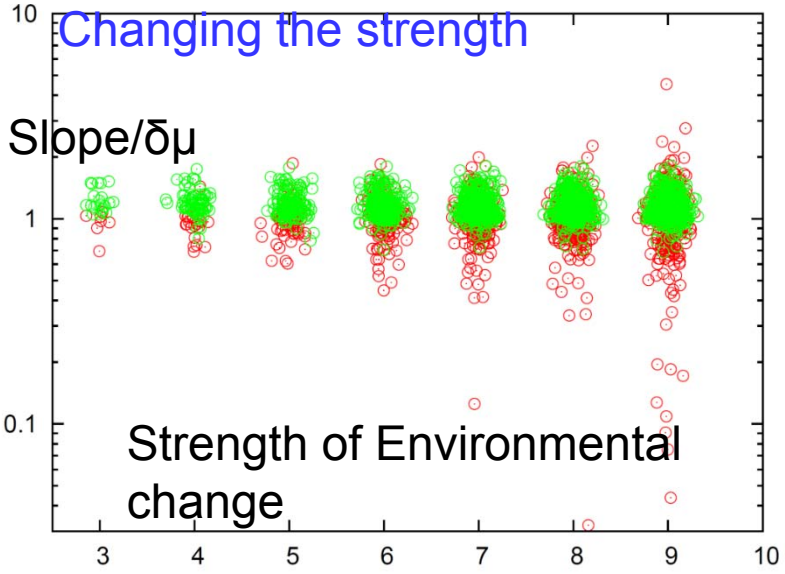



Different lines: Different env types ( diff (e_i))



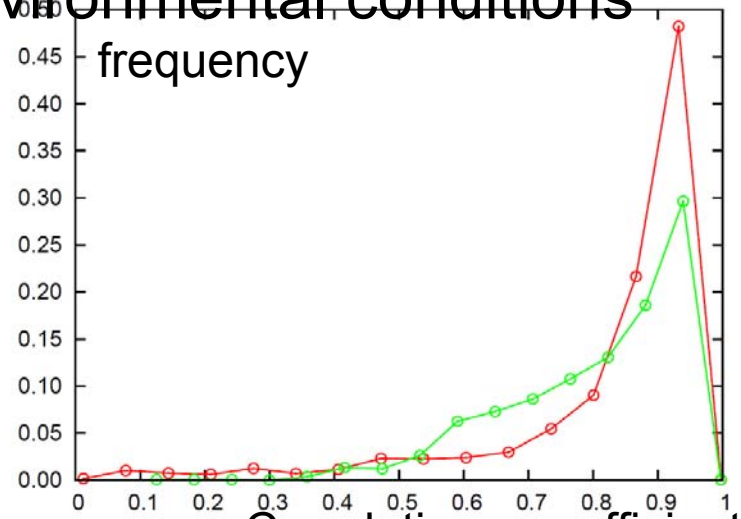




Under same environment
Changing the strength

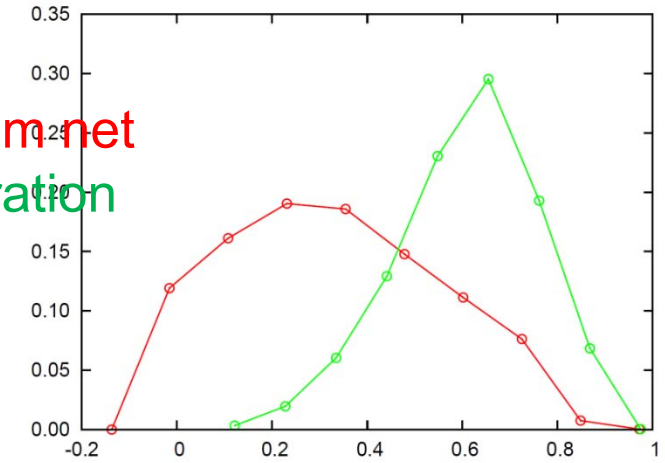


# After evolution, correlation across different env cond. is increased, and slope-growth-rate linearity is enhanced

Between same environmental conditions

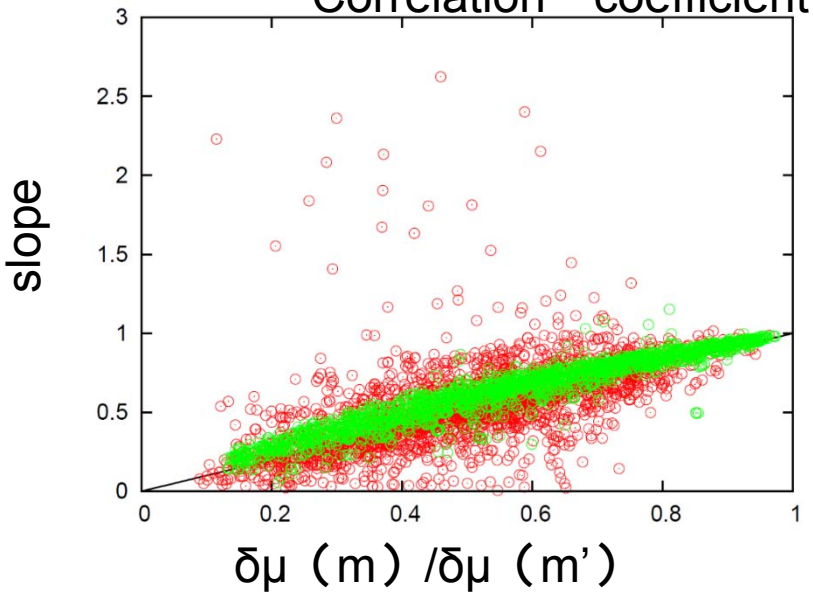


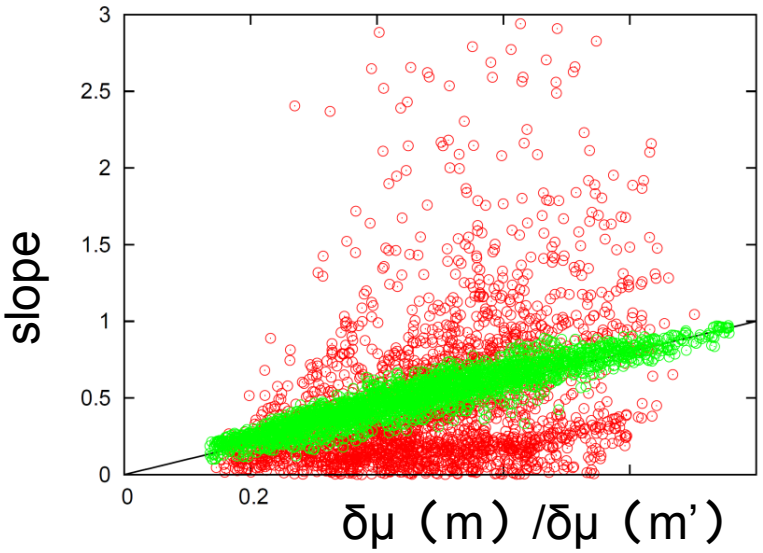

Across different env conditions




random-net generation =150

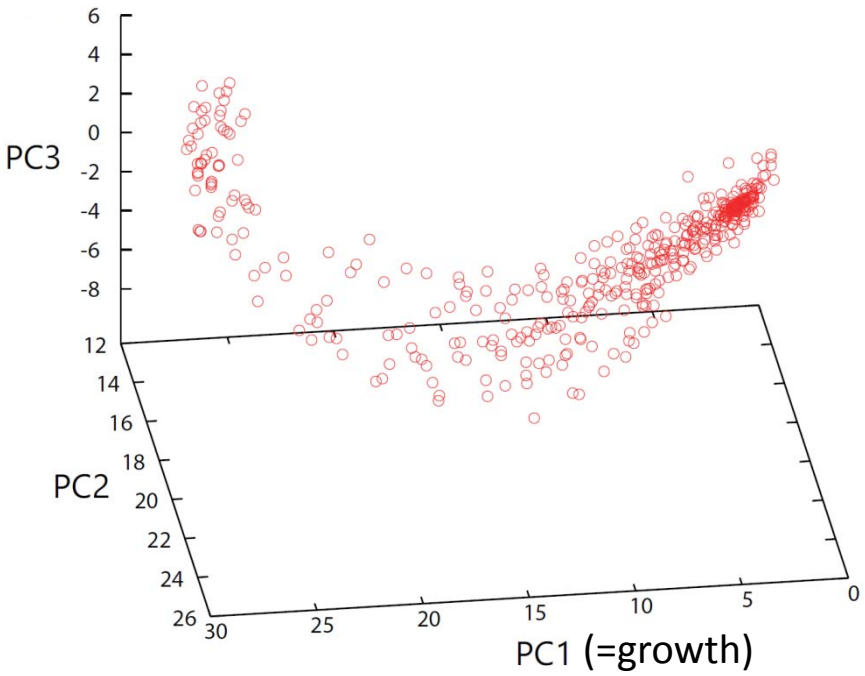
Correlation coefficient across component concentrations



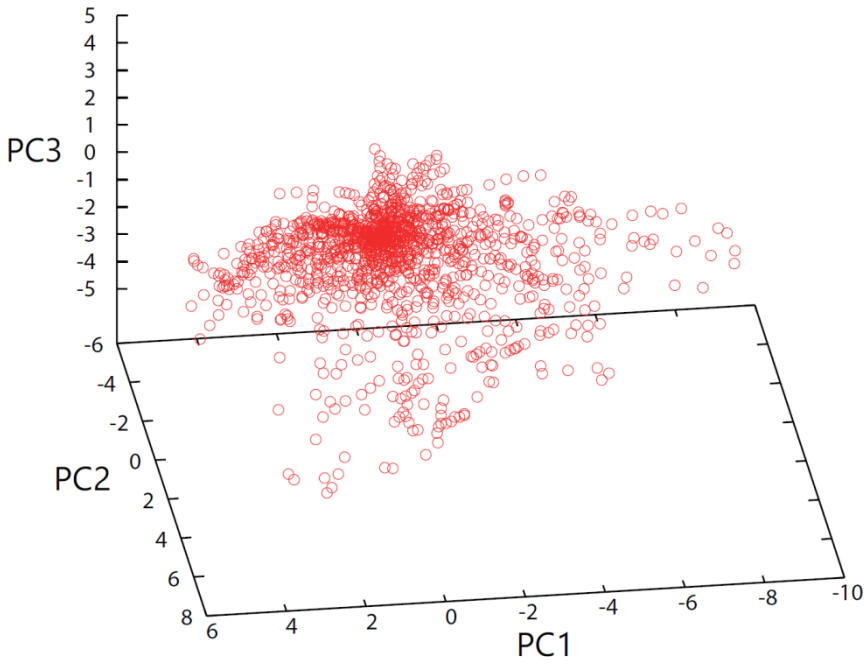



# Phenotypic constraint on a low-dimensional space

After evolution

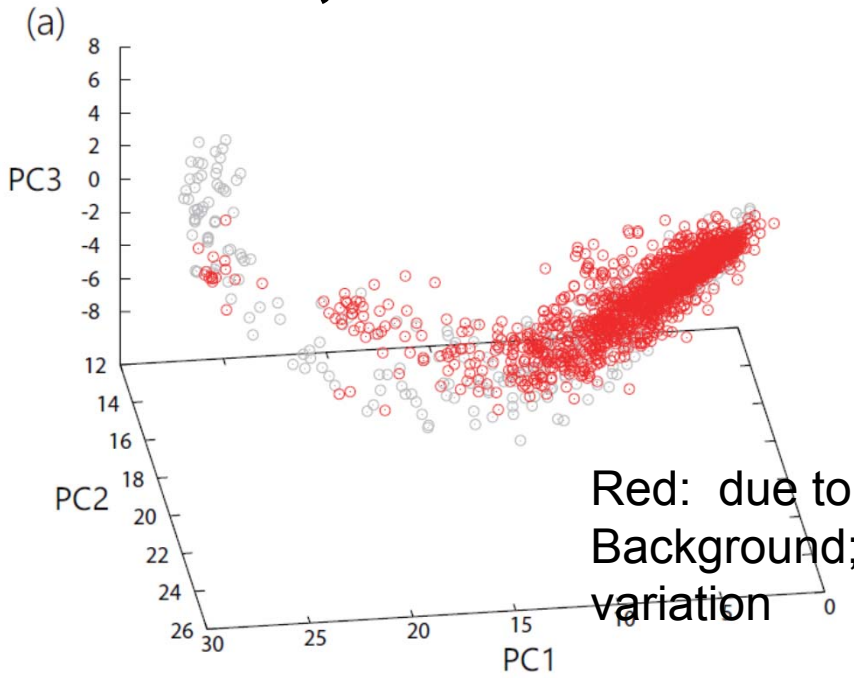



Random network

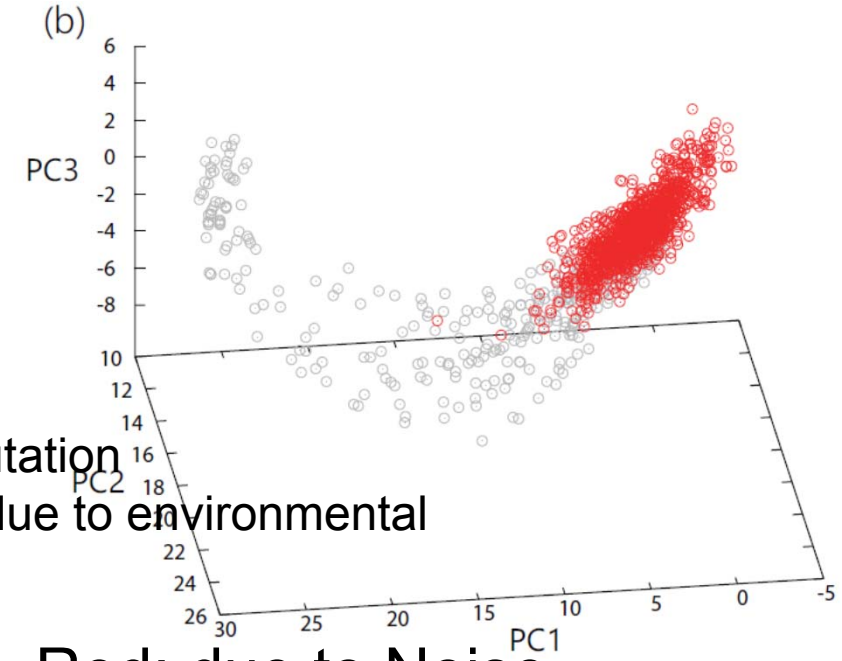



After evolution, the environmental response is constrained on a low-dimensional phenotype space.

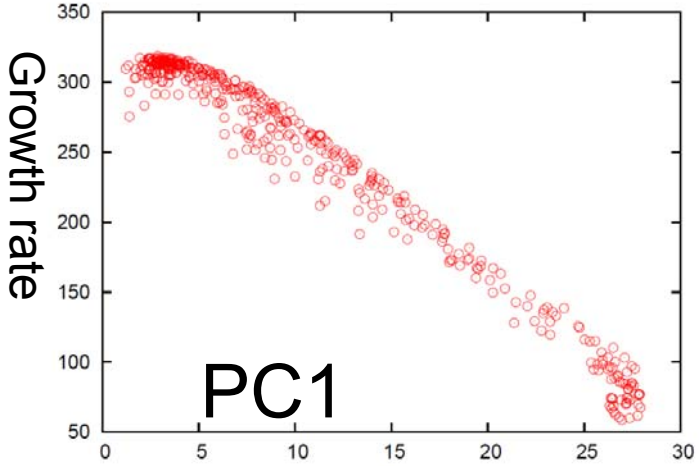
# Phenotypic change due to environmental variation, mutation, noise are constrained along a major axis




Red: due to Mutation
Background; due to environmental variation




Red: due to Noise
Background; due to environmental variation



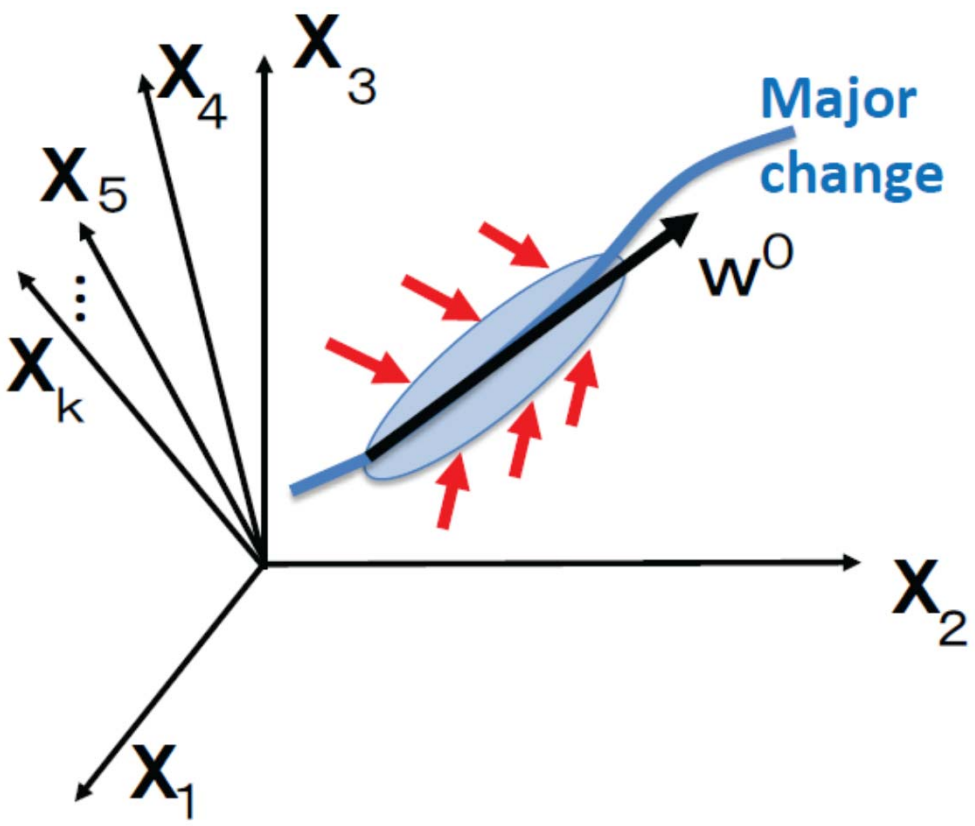

**?Phenotypic change occurs along a common slow-manifold**

Emergent Deep Linearity beyond trivial linearity for tiny change

- After evolution, linearity region is extended to macro level
- Correlation across different environment is increased
- Changes in high-dim phenotype space occur along a low-dim manifold

→ Evolved structure ?

# Formation of Dominant Mode Along Major Axis




Robustness – attraction to most directions except one changeable direction –along which evolutionary progresses

(Both environment- and evolution- induced) changes in high-dimensional phenotype space are constrained along low-dimensional slow-manifold

# Formulation and Consequence of Hypthesis

Recall $$\sum_j J_{ij}\delta X_j(E) + \gamma_i \delta E = \delta\mu(E)$$

$$\delta\mathbf{X} = \mathbf{L}(\delta\mu - \gamma\delta E).$$

with $\gamma_i \equiv \frac{\partial F_i}{\partial E}$.

- **γ(E): susceptibility to environment change**

Slow manifold Hypothesis – Only the smallest eigenvalue in J (or largest in L=1/J) contributes

Most changes occur along such slow manifold

$$\delta\hat{\mathbf{X}} = \lambda^0 \mathbf{w}^0 (\delta\mu - \mathbf{w}^0 \cdot \gamma\delta E).$$

**$\mathbf{w}^0$ eigenvector for the smallest eigenvalue, i.e.,**

Projection to this slow manifold

$$\frac{\delta\hat{\mathbf{X}}(\mathbf{E})}{\delta\hat{\mathbf{X}}(\mathbf{E}')} = \frac{\delta\mu(E) - \mathbf{w}^0 \cdot \gamma(\mathbf{E})\delta E}{\delta\mu(E') - \mathbf{w}^0 \cdot \gamma(\mathbf{E}')\delta E'}.$$

**γ·w small**

# Consequence of Slow-Manifold Hypothesis (cont'd)

→Manifold $\mathbf{w}^0$ is roughly orthogonal to $\gamma$

$$\mathbf{w^0}\cdot\gamma \sim 0,$$

→

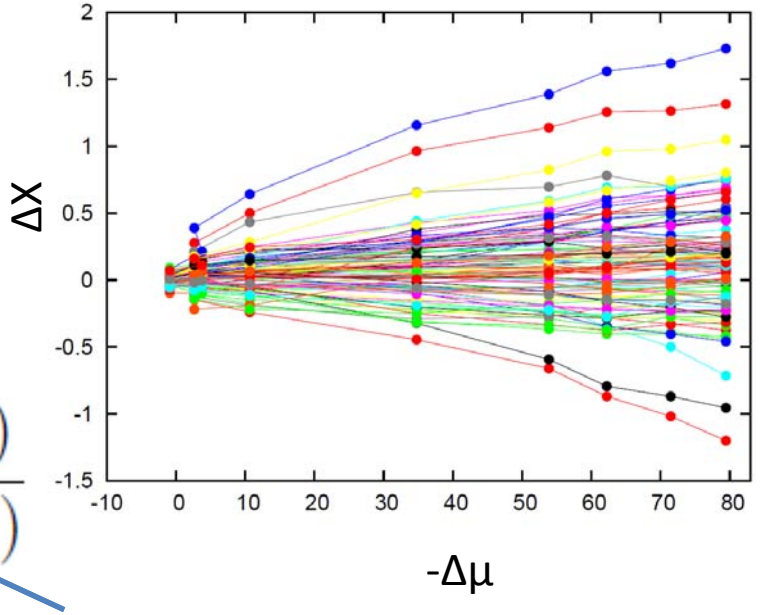
$$\delta\hat{\mathbf{X}} = \lambda^0 \delta\mu \mathbf{w^0}$$

Or, from the linear approximation

$$\delta E = \delta\mu/\alpha(E)$$

$$\frac{\delta\hat{\mathbf{X}}(\mathbf{E})}{\delta\hat{\mathbf{X}}(\mathbf{E}')} = \frac{\delta\mu(E)}{\delta\mu(E')} \frac{(1-\mathbf{w^0}\cdot\gamma(\mathbf{E})/\alpha)}{(1-\mathbf{w^0}\cdot\gamma(\mathbf{E}')/\alpha)}$$

Correction in proportion coefficient



# Consequence of Hypothesis → Correlation between Environment vs Evolutionary Changes

Evolution : $$\mathbf{J}\delta\mathbf{X} + \gamma(\mathbf{E})\delta E + \gamma(\mathbf{G})\delta G = \delta\mu(E).$$

Again, assume that

most changes occur along such slow manifold

Project to this slow manifold →

$$\frac{\delta\hat{\mathbf{X}}(\mathbf{E})}{\delta\hat{\mathbf{X}}(\mathbf{G})} = \frac{\delta\mu(E)}{\delta\mu(G)}$$ using $\mathbf{w}^{\mathbf{0}}\cdot\gamma \sim 0,$

(Genetic) evolution under the environmental condition

→recover growth-- $|\delta\mu(E)| < |\delta\mu(G)|$

$\delta Xi(G)/\delta Xi(E)=\delta\mu(G)/\delta\mu(E) < 1$

→ All the expression levels tend to return the original level by evolution **Le Chatelier Principle?**

# Possible extension to adaptive evolution

E: new environmental condition

— change in (log) expression δX(E,0) δμ(E,0) <0

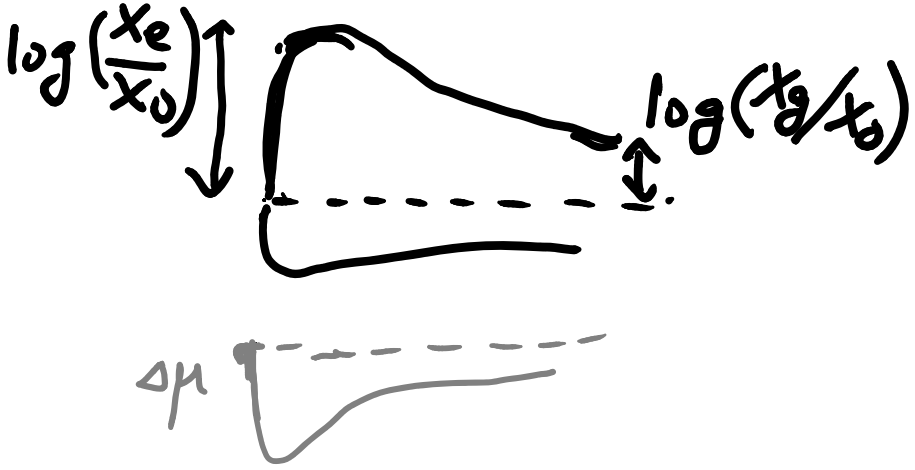
G: (Genetic) evolution under the environmental condition

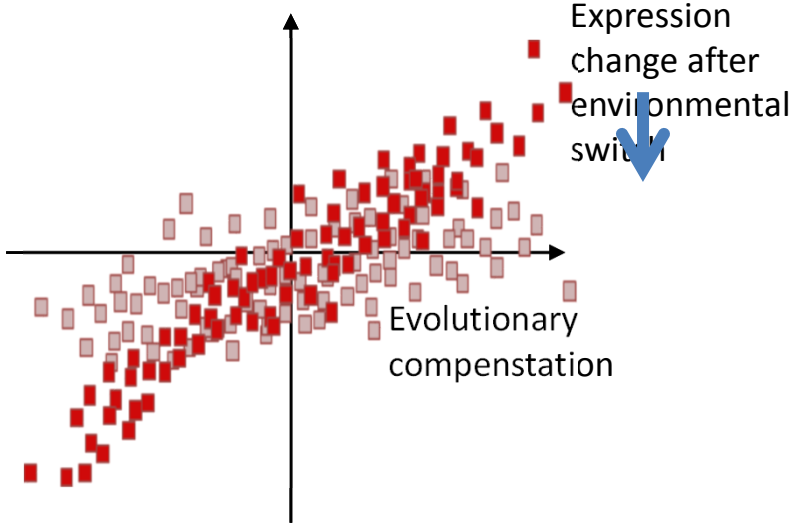
***Assume represented a singe variable (projection)

— change in (log) expression δX(E,G)

Change by G and E follow the same manifold? →

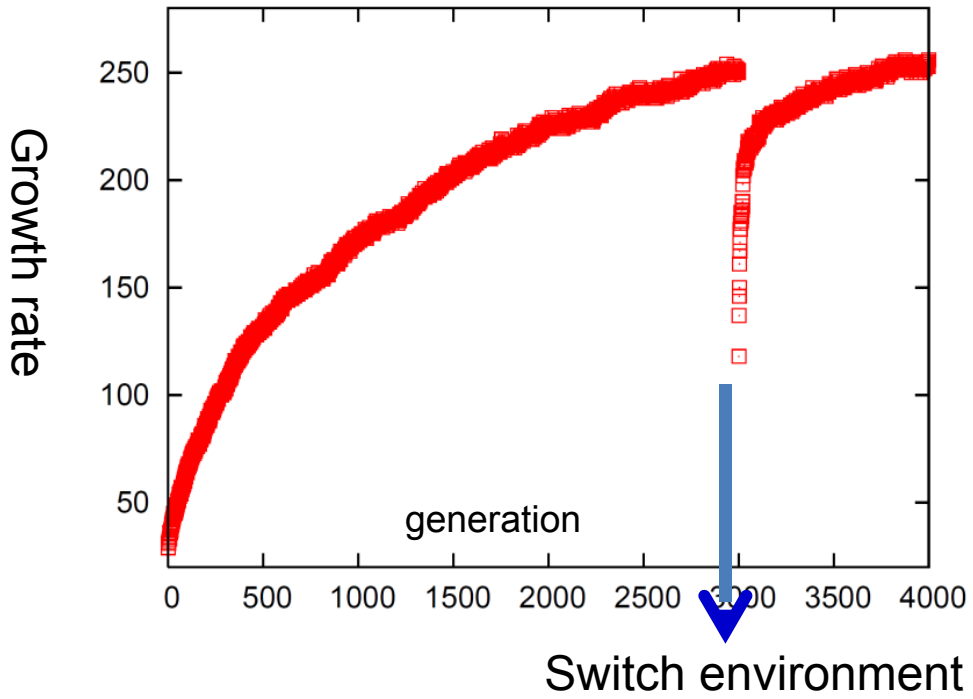
$$\frac{\delta Xj(E,0)}{\delta Xj(E,G)} = \frac{\delta\mu(E,0)}{\delta\mu(E,G)} \; ?$$



Evolution of Catalytic reaction net model by switching environment (nutrient concentratyion) and check evol-env response

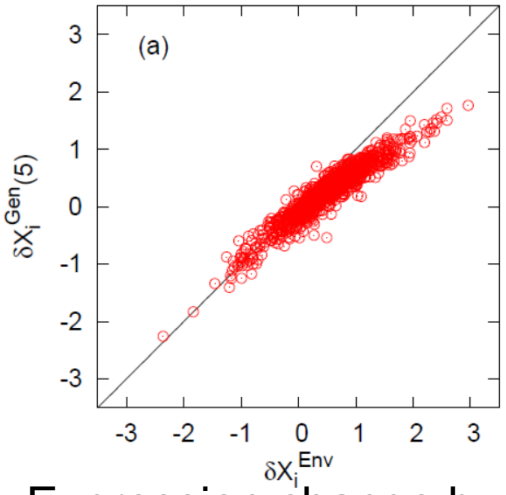
Mutate network and select those with higher growth –evo




Recovery of growth rate by adaptive evolution to new environment

# LeChatelier-type response common to all proteins

5-th generation



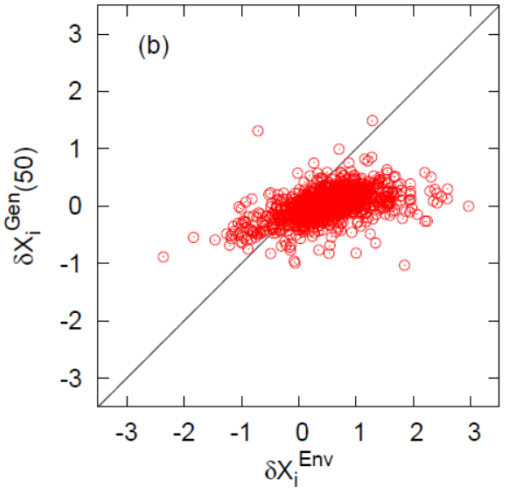

Expression change by env

Expression Change by evolution

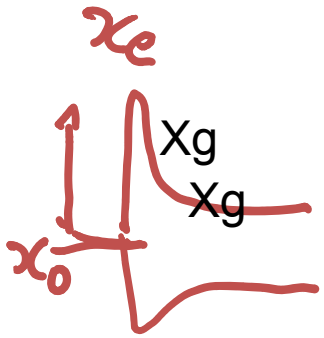
（１）Response by genetic change tends to cancel the change by environment

（２）The two responses are proportional over all components

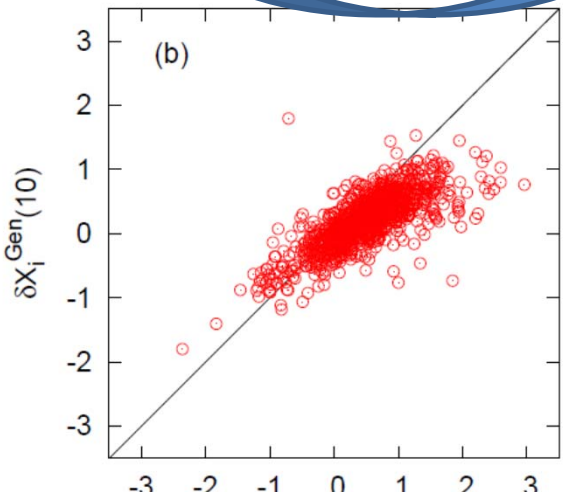
100 th generation

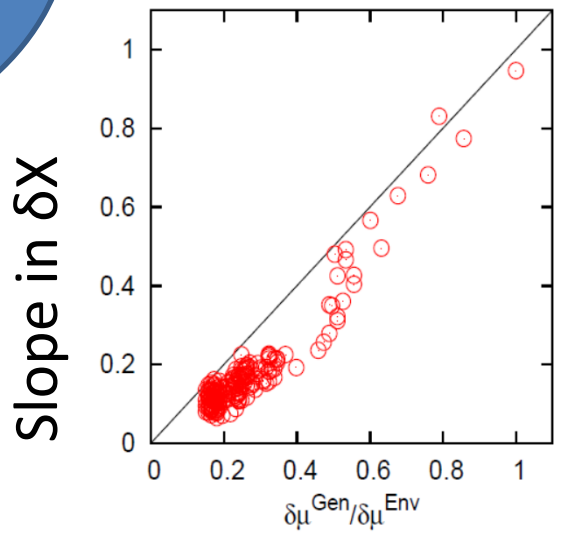



log(xe/x0)
log(xg/x0)




2oth generation

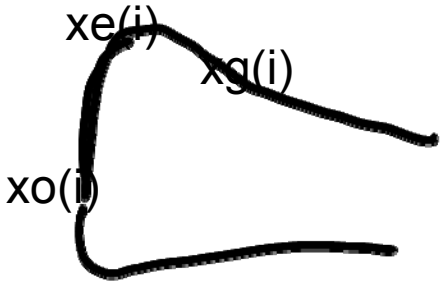


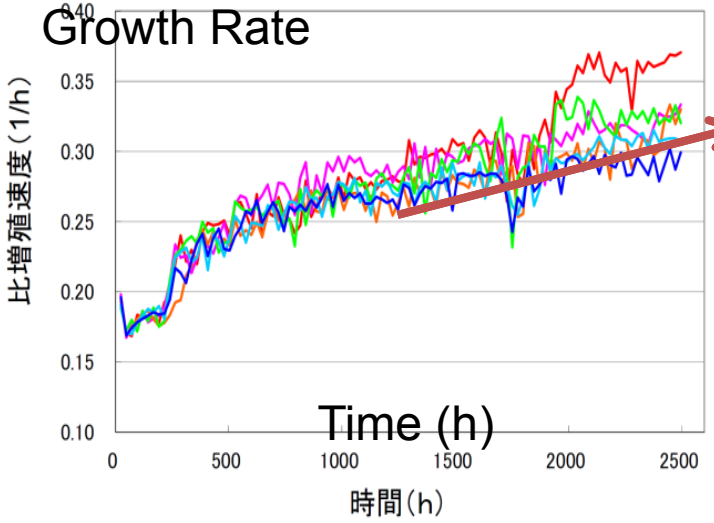




−Δμ bo by env to by evol

# Evolution Experiment of E Coli to adapt in stressed (ethanol) condition

Furusawa'sGroup

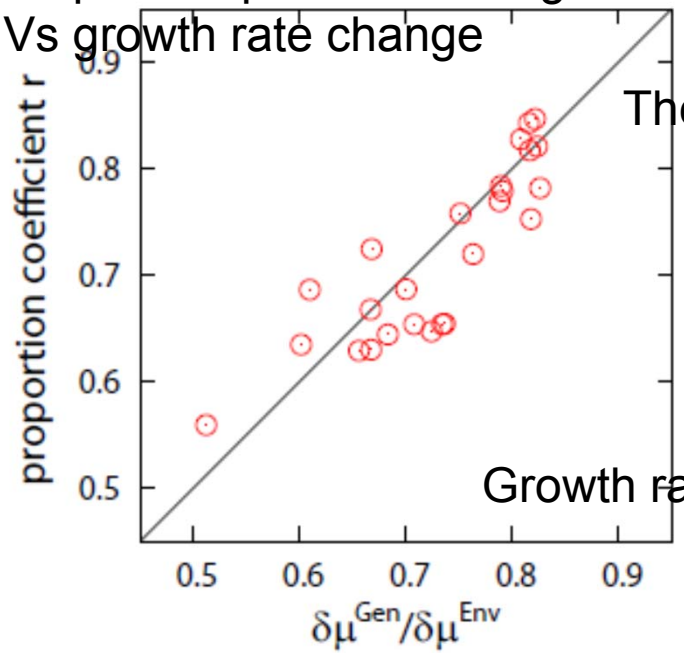



～1000 generations

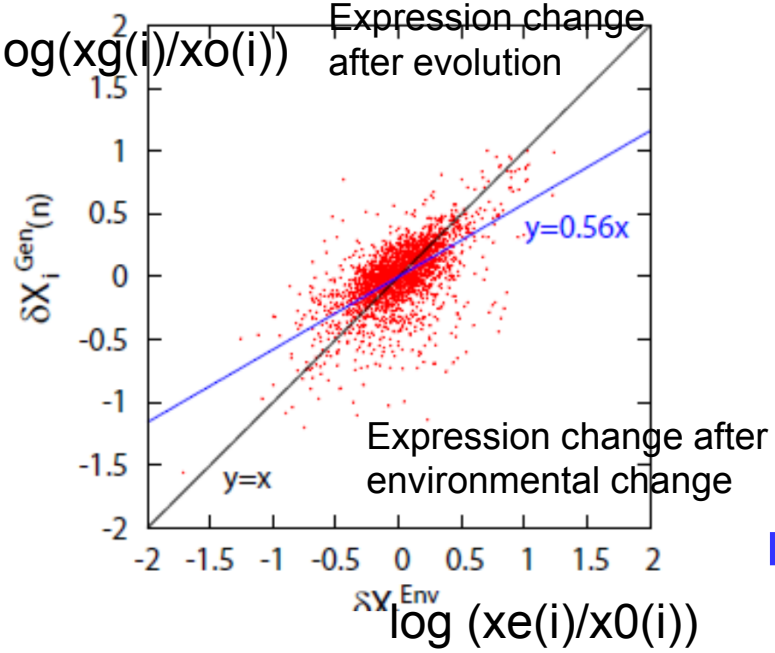

*Furusawa,KK Interface,2015*

Slope in expression change
Vs growth rate change




log(xg(i)/xo(i))

Expression change after evolution



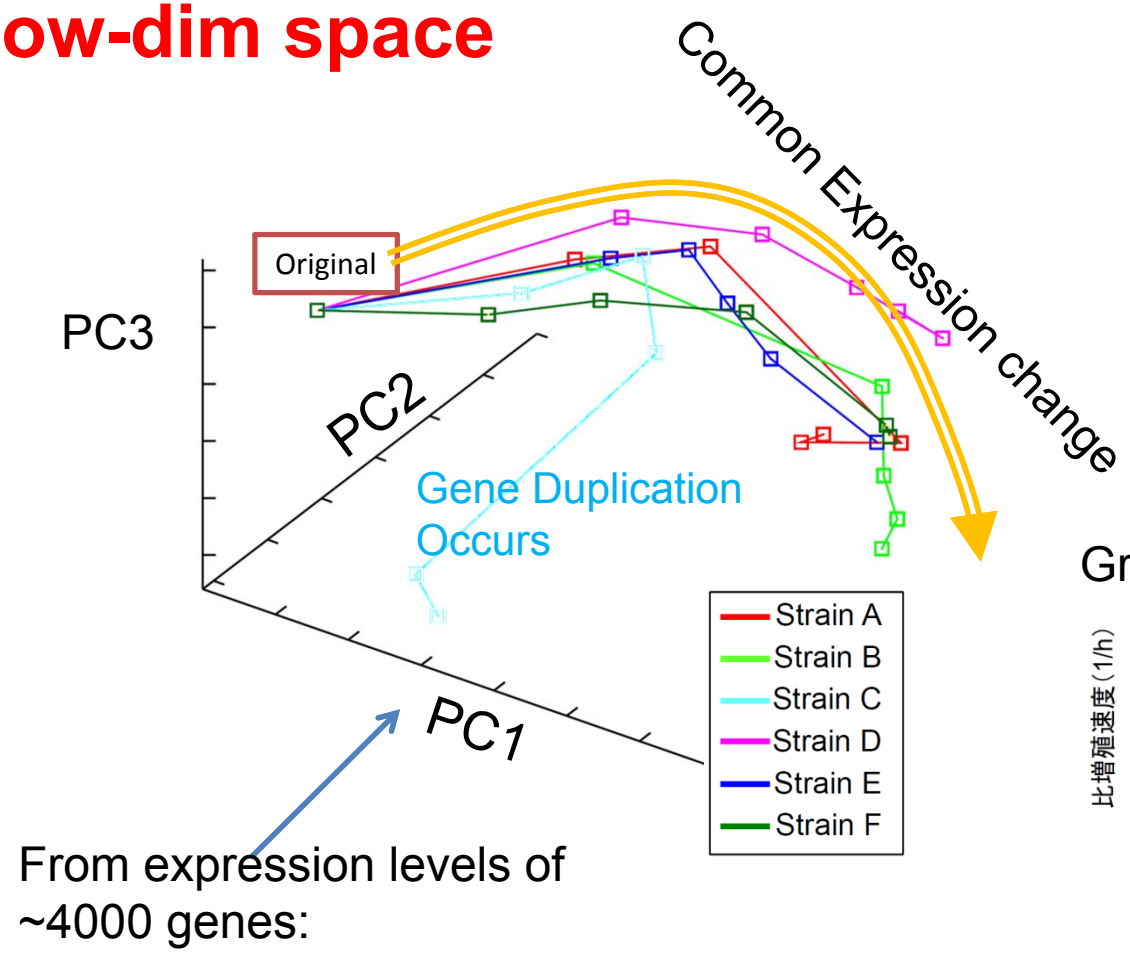

**0＜δXi（E,G）/δXi（E,0）＜1**

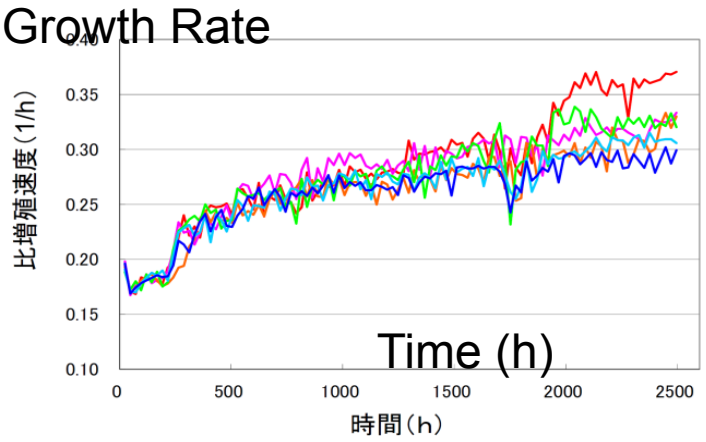
return to original expression pattern

（Le Chatelier principle)

# Deterministic phenotypic evolution constrained in low-dim space

**Horinouchi,..,Furusawa,**
BMC evol Biol 2015



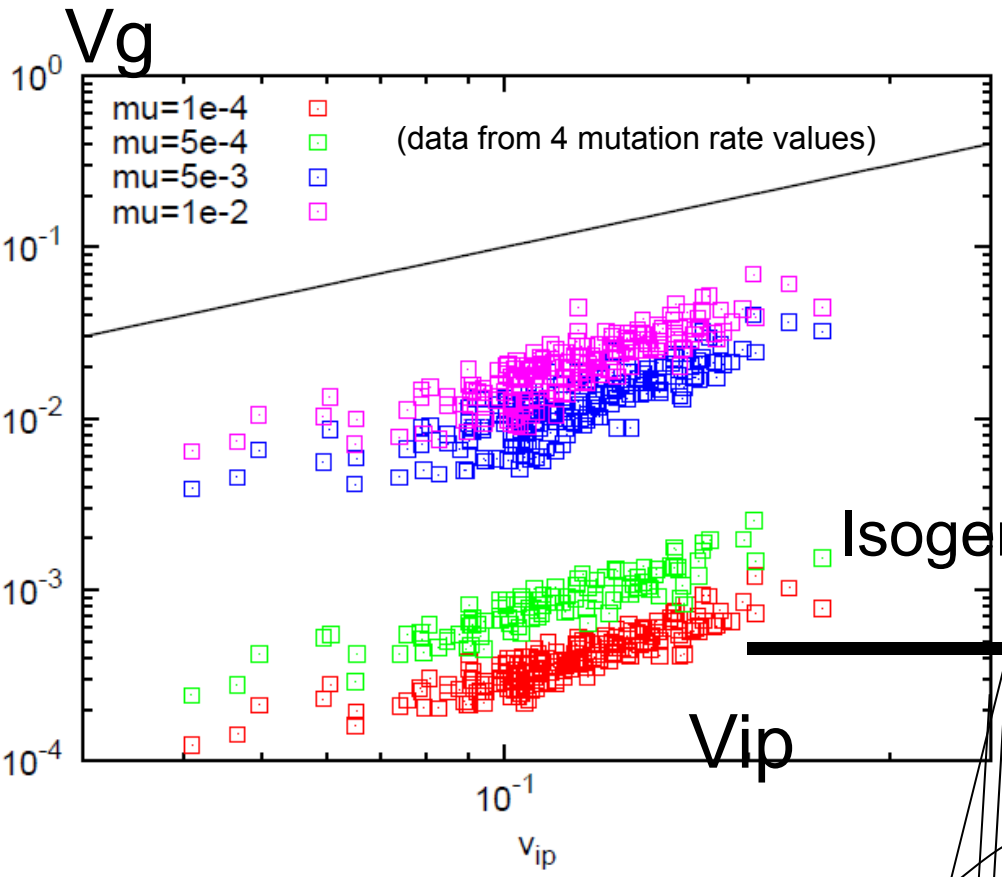




Mutation sites are different by strains. But..
Common trends in phenotypic space (low-dim structure)
PC1 is highly correlated with the growth rate

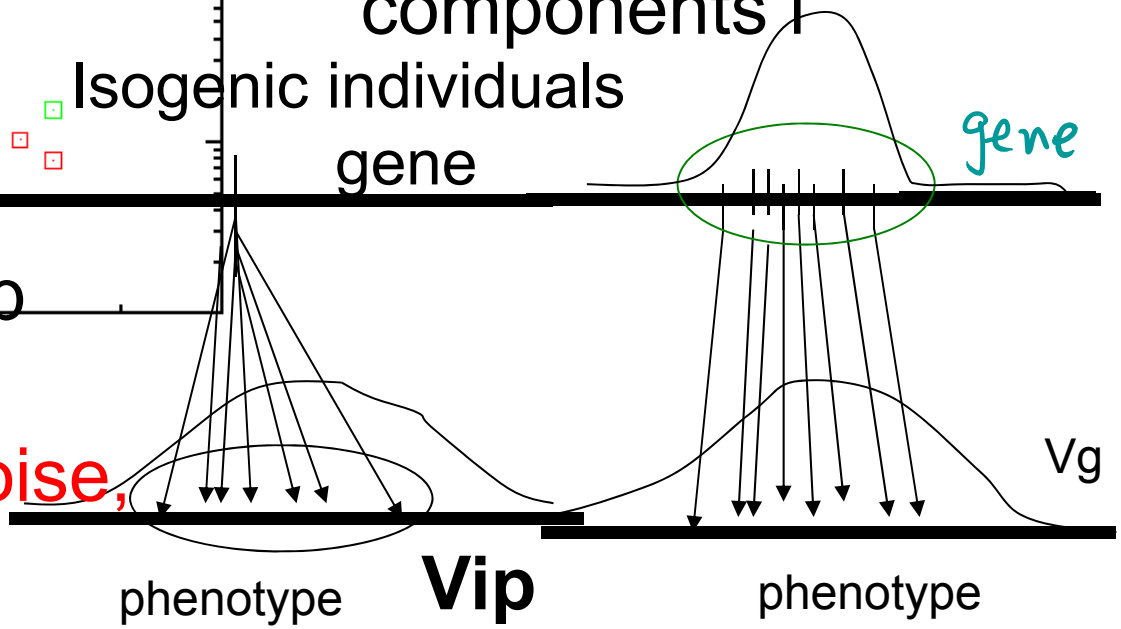
# *Recall Fluctuation:* Vip-Vg relationship

Vg(i) : Variation of i-th expression due to mutation

Vip(i) : Variation due to noise in dynamics




Vip(i) ∝ Vg(i) over all components i




If highly variable by noise,
More easily evolvable

Vg-Vip proportionality is explained by the slow manifold Hypothesis

Evolution occurs along this slow manifold $\mathbf{w}^0$

$$V_{ip}(i) = (\mathbf{w}_i^0)^2 < \delta X^2 >_{noise}$$
$$V_g(i) = (\mathbf{w}_i^0)^2 < \delta X^2 >_{mutation}.$$

→ Vg(i)/Vip(i) = independent of i

(here we do not need the growth-rate constraint, only slow-manifold constraint is needed)

Vg-Vip relationship ← Changes both by (environmental) noise and (genetic) mutations are constrained along the direction

# (Common) Slow-manifold for Phenotypic change
# →Env-Evo Fluctuation Response Relationship

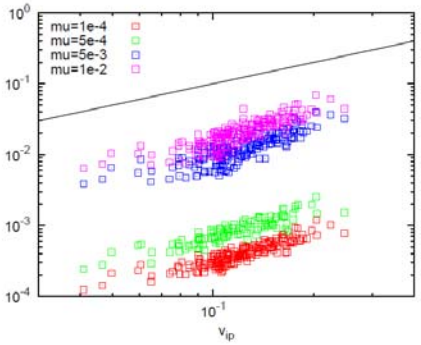
***Fluctuation***

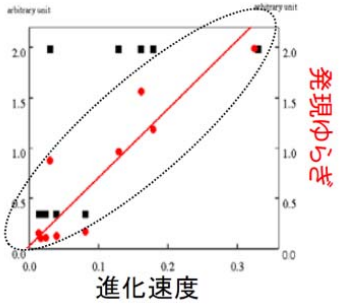
**Vg(i)**

Genetic change

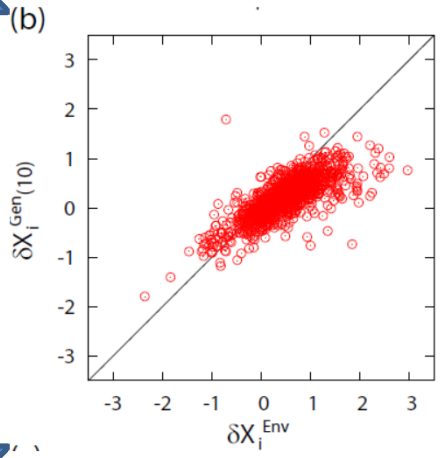
**Response by evolution ΔlogX(i)_{G}**

~proportional




~proportional




← **Proportion** →

**Vip(i)**

Environmental variation/ Noise

**Response to environment ΔlogX(i)_{Env}**

# Why Slow Dominant Mode Evolved????

## Time-scale difference

→ Separation of control/controlled is possible which allows for evolvability

(If many degrees of the similar time scale interfere, not easy to directional change)

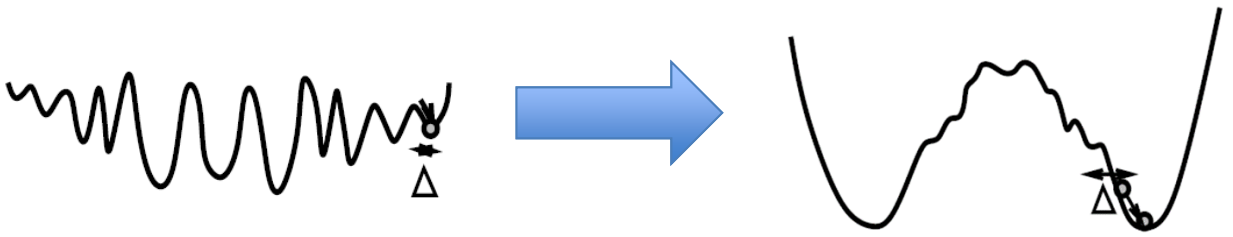
Result of evolution but fosters evolvability

*Cf Kohsokabe, kk, JEZB 2016*

Expanded Linearity in terms Potential picture:

robustness evolved ( get out of error catastrophe)

*Cf, kk Plos One 2007*



# Macro Theory of Phenotype Evolution a la thermo-dynamic potential: derivation of LeChatelier relation

Macro Quantity = growth rate **μ (E,G)** :

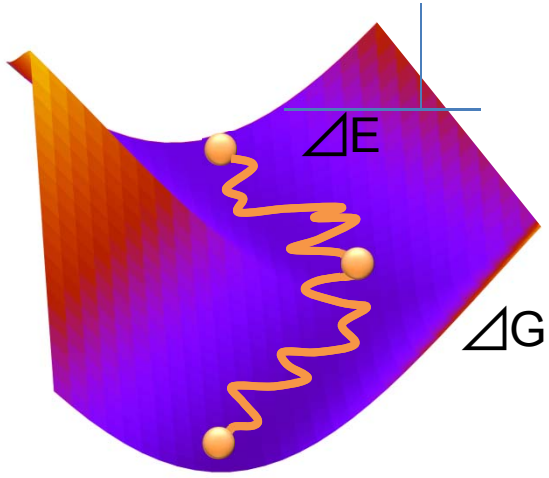
E=environment, G=Genetic (evolutionary) change

but μ is determined by gene expression (phenotype)

→μ (X(E,G))

Original state: maximum in E,G

$$\frac{\partial \mu}{\partial X} = 0$$




→ Formulation a la thermodynamics

$\delta X_G / \delta X_E < 1$

→ LeChatelier Principle

# Explanation of Universal Biology in the novel by Sakyo Komatsul

The fundamental elements of life extracted here-- metabolic system, genetic information, ,,, - are well-balanced well under certain conditions and create a single organism. Each of these elements can have an infinite range in variation, but by balance with each other, it falls within a certain width. .. ..

Well, roughly speaking, by changing many extrapolation conditions such as environment, cell assembly density, total mass, possibility of specialization of each cell, unit of genetic information, their levels that can achieve balance gradually change. If these are appropriately formulated, the model of fundamental evolution of life can be approximated by a linear model. (translation by Google+KK)

Future Issues

(1) Validity of the present theory

(i) Further Confirmation by Experiments

(ii) Confirmation by Models (Universality)/Condition?

Catalytic Reaction Cell Model – somehow good

GRN? Spin Models??(cf Sakata et al., PRL 2009)

(iii) Phenomenology a la 'Thermodynamic Potential'?

Projection to slow modes: Other degrees like 'heat'

(2) **Beyond Steady-Growth state, cf stationary state**

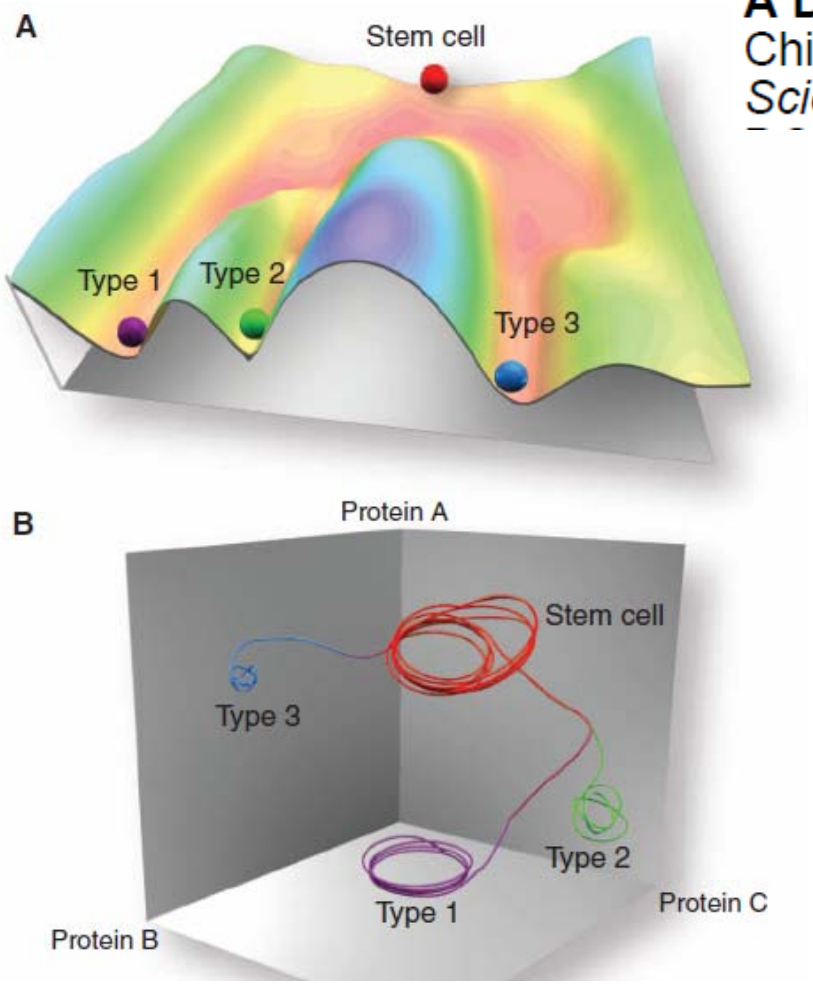
Transition from exponential growth to non-growth?

(cf, Himeoka,KK, Phys Rev X in press (next wek))

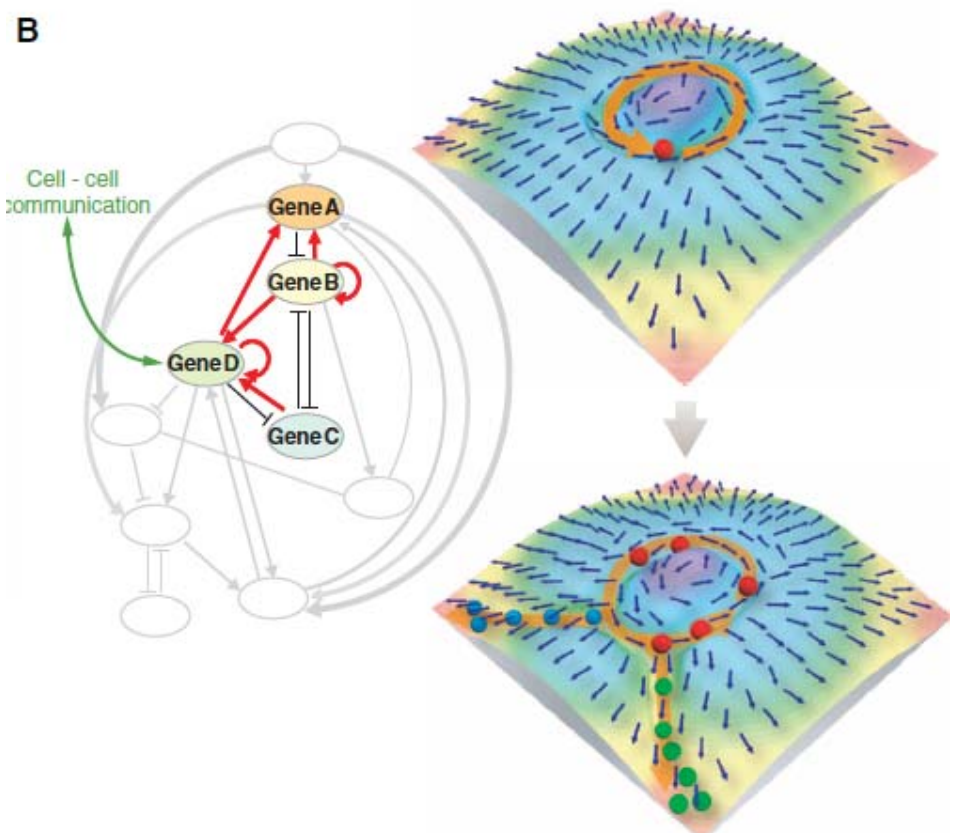
No longer low-dim?

*cf. Happy families are all alike; every unhappy family is unhappy in its own way. (Anna Karenina)*

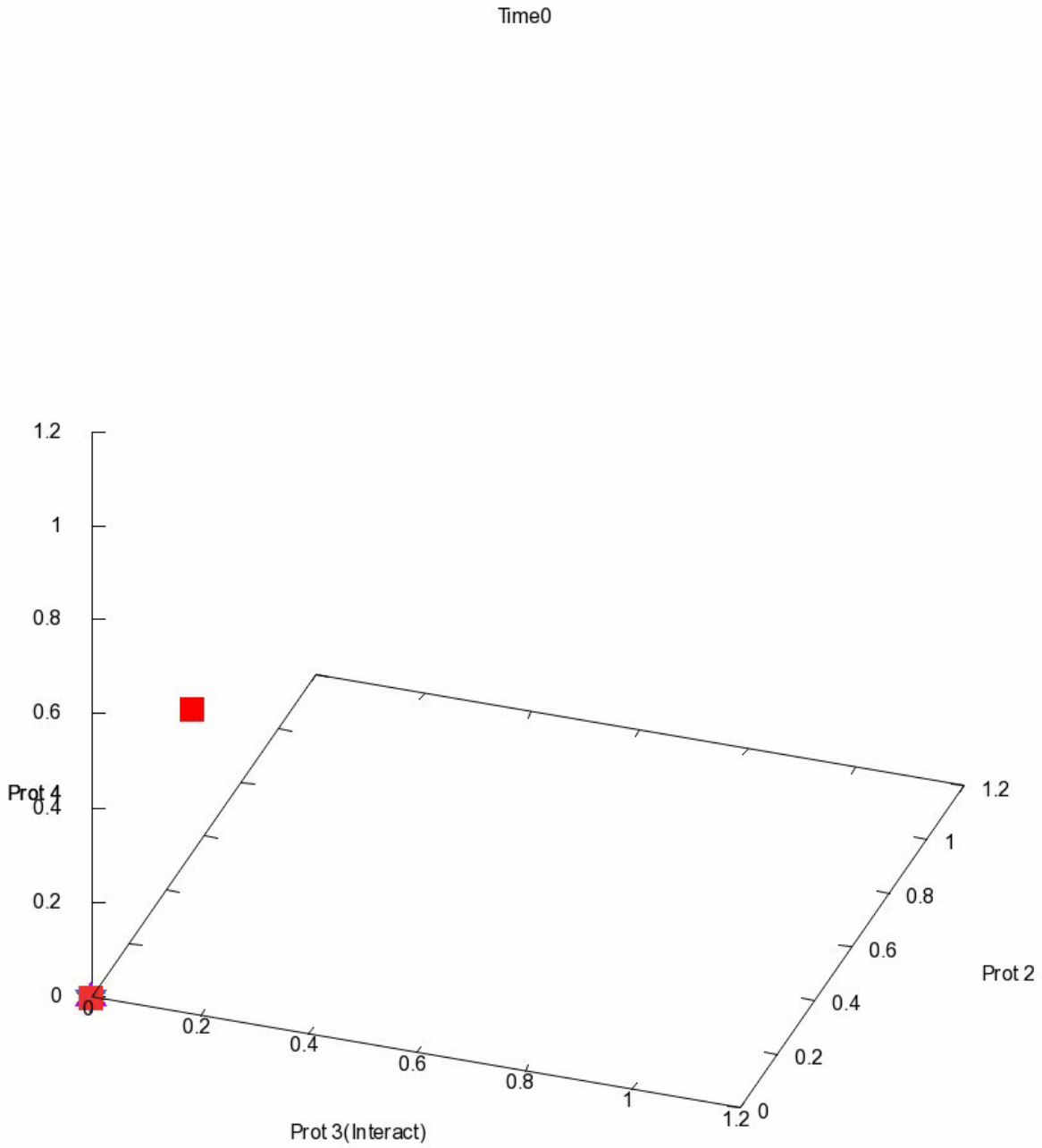
Stem-Cell(pluriopotency） ＝Champion of Plasticity
spontaneous generation of fluctuation (oscillation, chaos) its irreversible loss － loss of pluripotency
（cf: Furusawa,Kaneko1998）



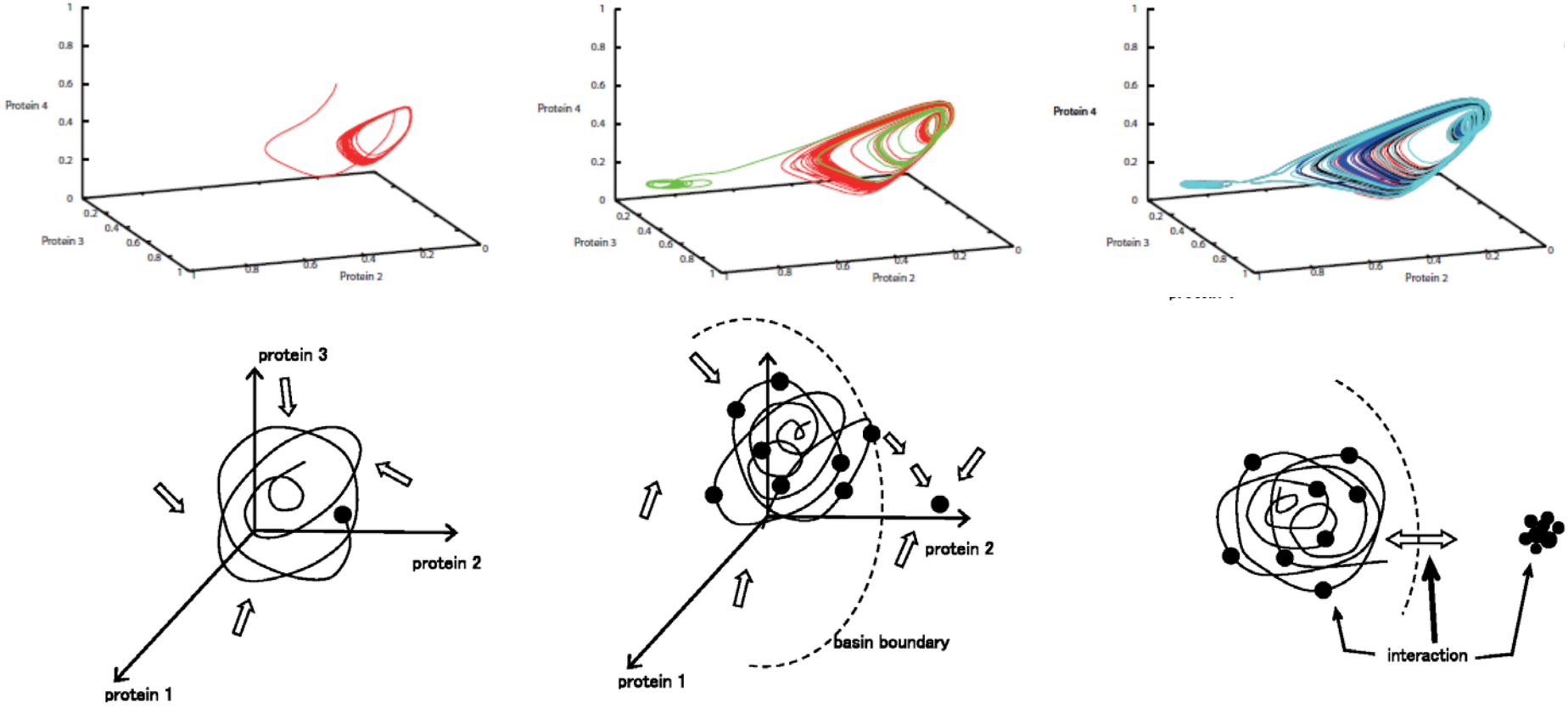

**A Dynamical-Systems View of Stem Cell Biology**
Chikara Furusawa and Kunihiko Kaneko
*Science* **338**, 215 (2012);



ou can find this movie in Youtube. Check by Suzuki,Furusawa,Kaneko



# Differentiation from stem cell; in terms of dynamical systems




oscillation

with the increase in cell number→ cell-cell synchrony is lost, then with cell-cell interaction, bifurcation to different states

（Furusawa,kk 2001）

To recover Stemness → increase in degrees of freedom (Furusawa,KK 2001) ←?→ Yamanaka's iPS (2006)by expressing 4 genes

*J. theor. Biol.* (2001) **209**, 395–416

# Theory of Robustness of Irreversible Differentiation in a Stem Cell System: Chaos Hypothesis

CHIKARA FURUSAWA* AND KUNIHIKO KANEKO

## 8. Predictions

We believe that our results are universal in a class of dynamical systems satisfying minimal requirements of the developmental process. Although some of these universal features are not yet examined experimentally, we make some predictions here as general features commonly satisfied in real stem–cell systems. To conclude our paper, we summarize the predictions we can make using our model, and discuss the possibility of experimental verification.

### 8.4. IRREVERSIBLE LOSS OF MULTIPOTENCY CHARACTERIZED BY DECREASE OF COMPLEXITY IN CELLULAR DYNAMICS

While during the normal course of development, this loss of multipotency is irreversible, it is possible to recover the multipotency of a differentiated cell through perturbation, by changing the diversity of chemicals or the complexity of the dynamics. For example, by expressing a variety of genes compulsively in differentiated cells, the original multipotency may be regained. Note that, according to our model simulations, the basin of attraction of the stem cell is much larger than that of differentiated cells. This implies that by adding a large perturbation that results in the presence of a variety of chemicals in a cell, the cell de-differentiates back into a stem cell.

- Macroscopic Phenomenology in Biology?

0)Restrict to steady--growth states and the transition between them → each molecule's replication rate exp($\mu_i$ t) : all $\mu_i$ equal as if temperatures are equal everywhere in eqb

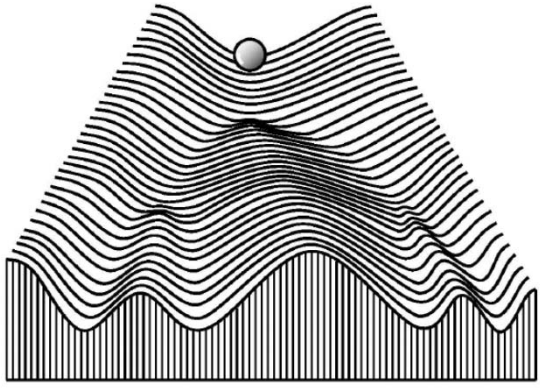
→ Description by few degrees of freedom

1)Irreversibility: ES->Committed->Death, etc

→ characterization to quantify ordering ←→

2) Stability (robustness):
Waddignton's potential

3) Activity distinguishable from Growth



4) Equation of states?:  characterizing log, stationary dormant phases

5) Le Chatelier's principle? ( change by environment is compensated by evolution)

6) Fluctuation-Response relationship ( plasticity (changeability) proportional to fluctuations)

7) Ideal Cell Model?

---- Difficulty ----

- Many kinds instead of a large numbers?
- Hierarchy not well separated? (instead of micro/macro) but consistency is achived
- Inherently Dynamic – oscillation,,,

# Summary

## Evolutionary Fluctuation-Response Relationship

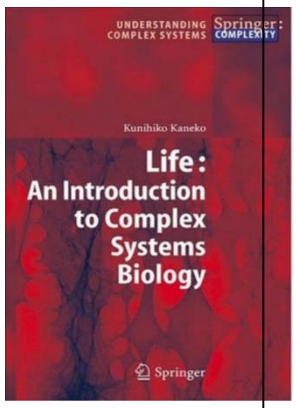
(KK, in Evol Syst Biol 2012, PLoSOne 2007　Sato et al PNAS 2003)

## Universal law for adaptation

(KK　FurusawaYomo　PRX2015)

## Evolutionary LeChatelier Principle

（Furusawa KK　Interface 2015)




Expansion of linear regime, correlation across different environment　by evolution:

　low-dimensional structure formed from high-dimensional phenotypic space

Dominant Mode is shaped → 　explains macro-universality and all that　(Furusawa, KK, bioRxiv,2017)

**Main collaborator**

**Chikara　Furusawa**

Most papers available　at

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