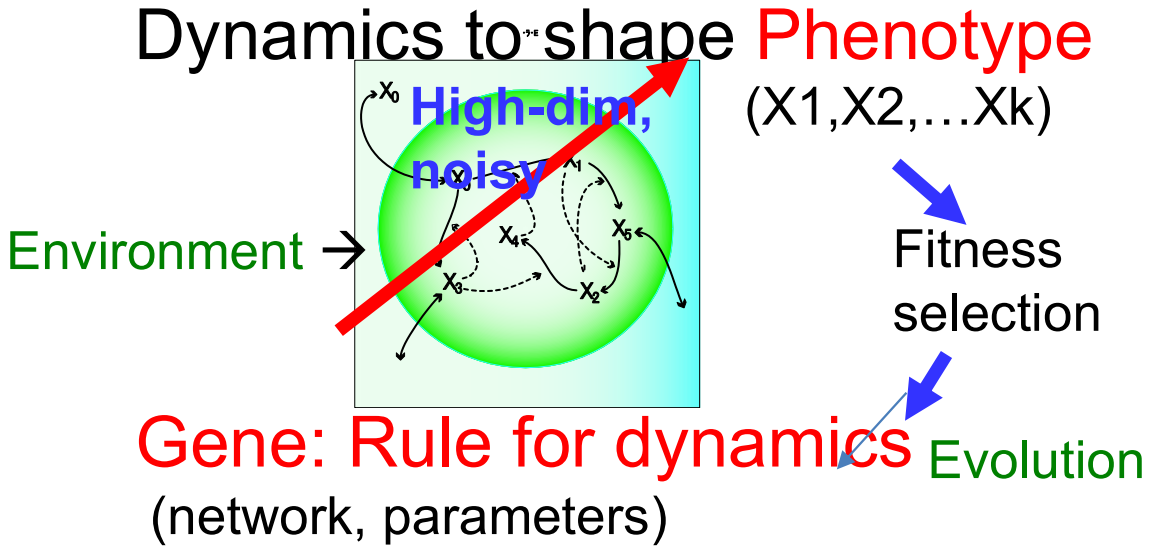
Evolutionary Dimension Reduction:

Why low-dim macroscopic picture a la thermodynamics works?

- Basic Setup (Exp/Theory/Model)
- Phenotype=Abundances of each component (e.g., protein/mRNA) (~5000 dimensions)

Genotype- DNA seq, or rule for dynamics:

Geno-Pheno Mapping?



* **Experiment**: transcription analysis of E Coli
* **Model**: (i)catalytic reaction network for growth

(ii) Gene regulation net: (high-dim dynamics):

* **Theory**: Low-dim constraint in high-dim states

Trivial(?) Law in Adaptation: Focus on steady-growth cells → universal constraint

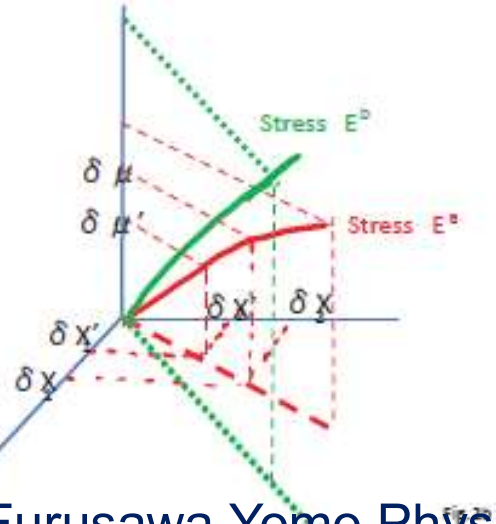
all the components have to be roughly doubled (for cell division) : steady-growth condition

Xi – log(concentration of component i) (i=1,,,M)

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

M large: e.g., # of protein species $\sim (10^3 \sim 10^4)$

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



E: Environment; δE; added Stress

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

Linearization, "small" δE, δX、 δμ

$$\frac{\delta X_j(E)}{\delta X_j(E')} = \frac{\delta \mu(E)}{\delta \mu(E')}$$

= indep't of j

for given type of stress E (changing strength)

KK,Furusawa,Yomo,PhysRevX(2015)

Linearization w.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}. for F({X})

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

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

Trivial
+ linearization

No evolution yet

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

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

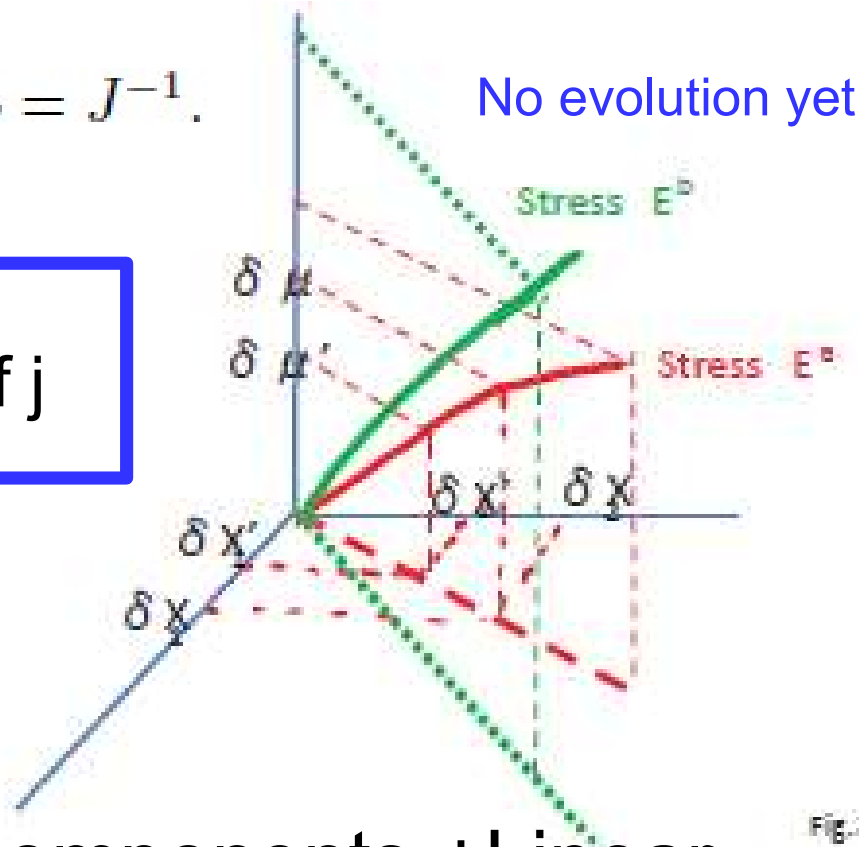


Fig. 2b

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

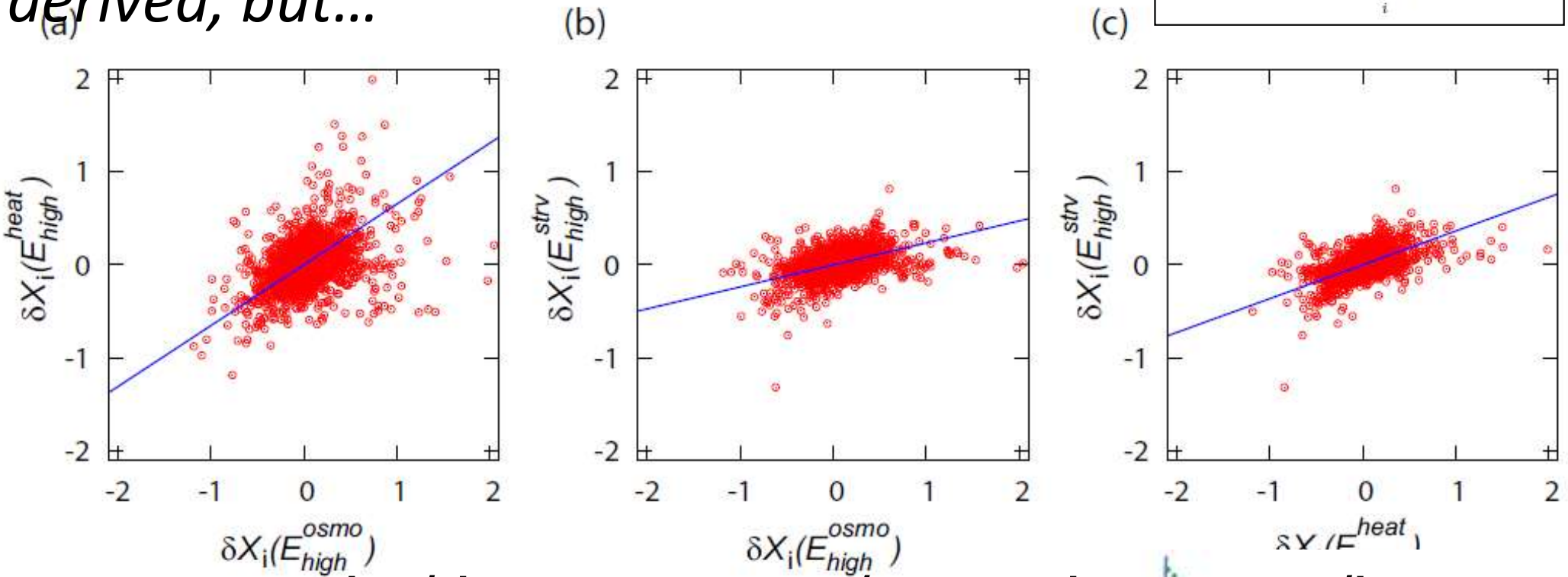
←Steady-growth sustaining all components +Linear

Across Different types of stresses:

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

γi(*a*) depends on stress type *a* *so correlation not derived, but…*

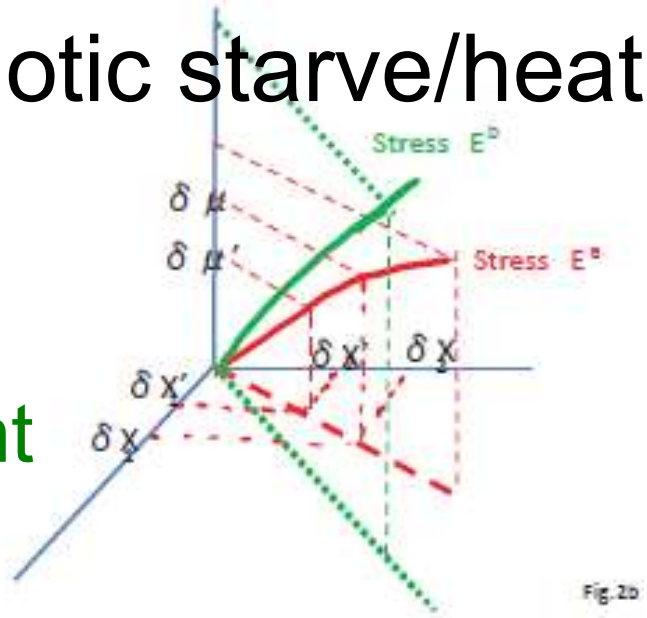
$$\delta X_j(E) = \delta\mu(E) \times \sum_i L_{ji}(1 - \gamma_i/\alpha)$$



osmotic / heat starve/osmotic starve/heat

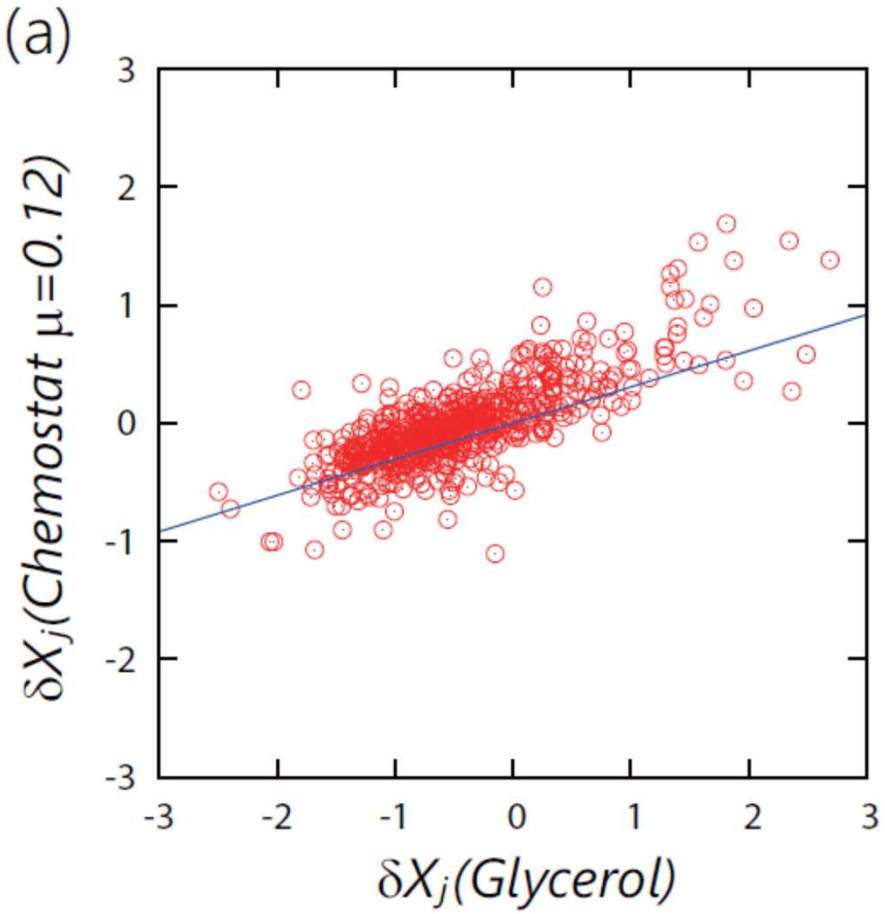
Still highly correlated

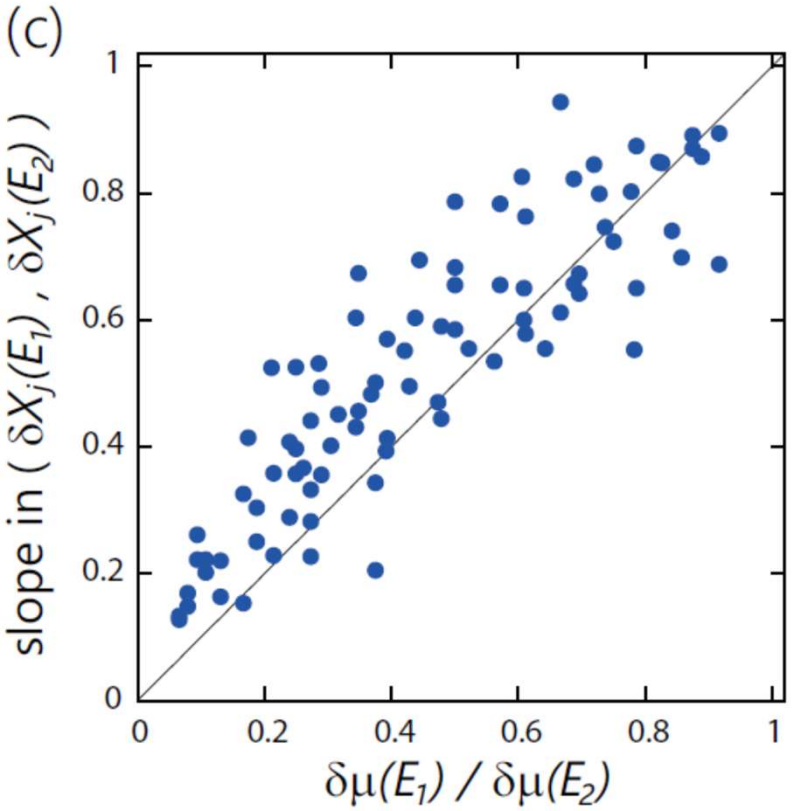
Confirmed also in protein expression changes across different environmental conditions



Better(?) confirmed in protein expression changes across different environmental conditions (based on the data by Heinemann)

20 different conditions on E Coli



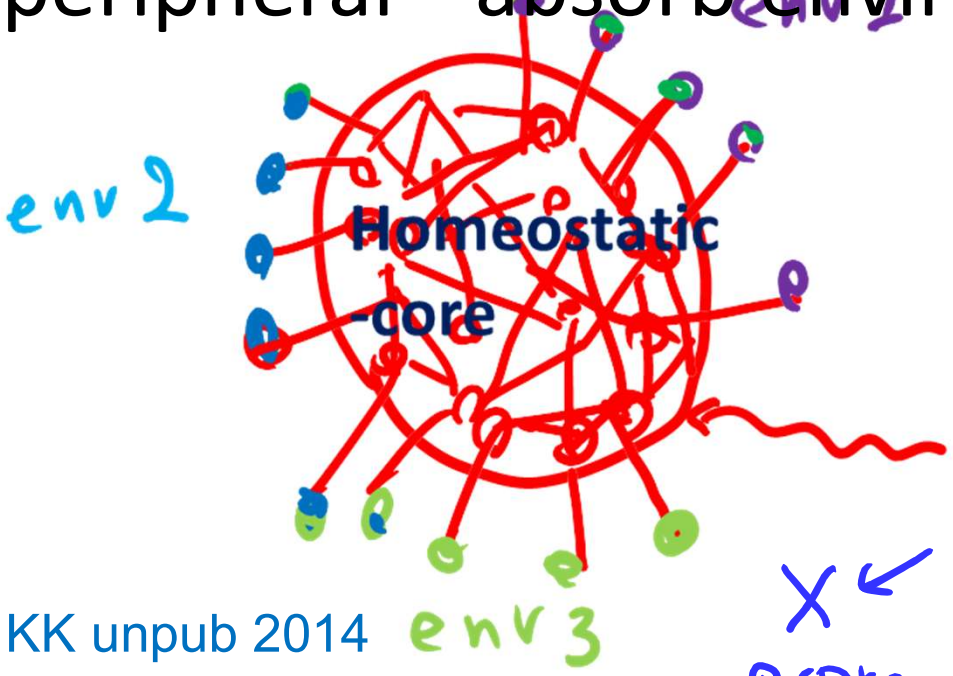


Furusawa, KK Phys.Rev.E 2018

~~Originally lo-dim~~ Originally high-dim and dimensional reduction → essential to deep linearity + adaptation to diverse environments

* emergence of 'collective' slow variable

homeostatic core (major parts) mutually stabilize keep robustness; growth-rate as 'mean-field'; peripheral-- absorb environmental changes (plasticity)



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

KK unpub 2014

Cf Kamei,Wakamoto; Furusawa

Intuitively, macro-micro consistent states must be rare

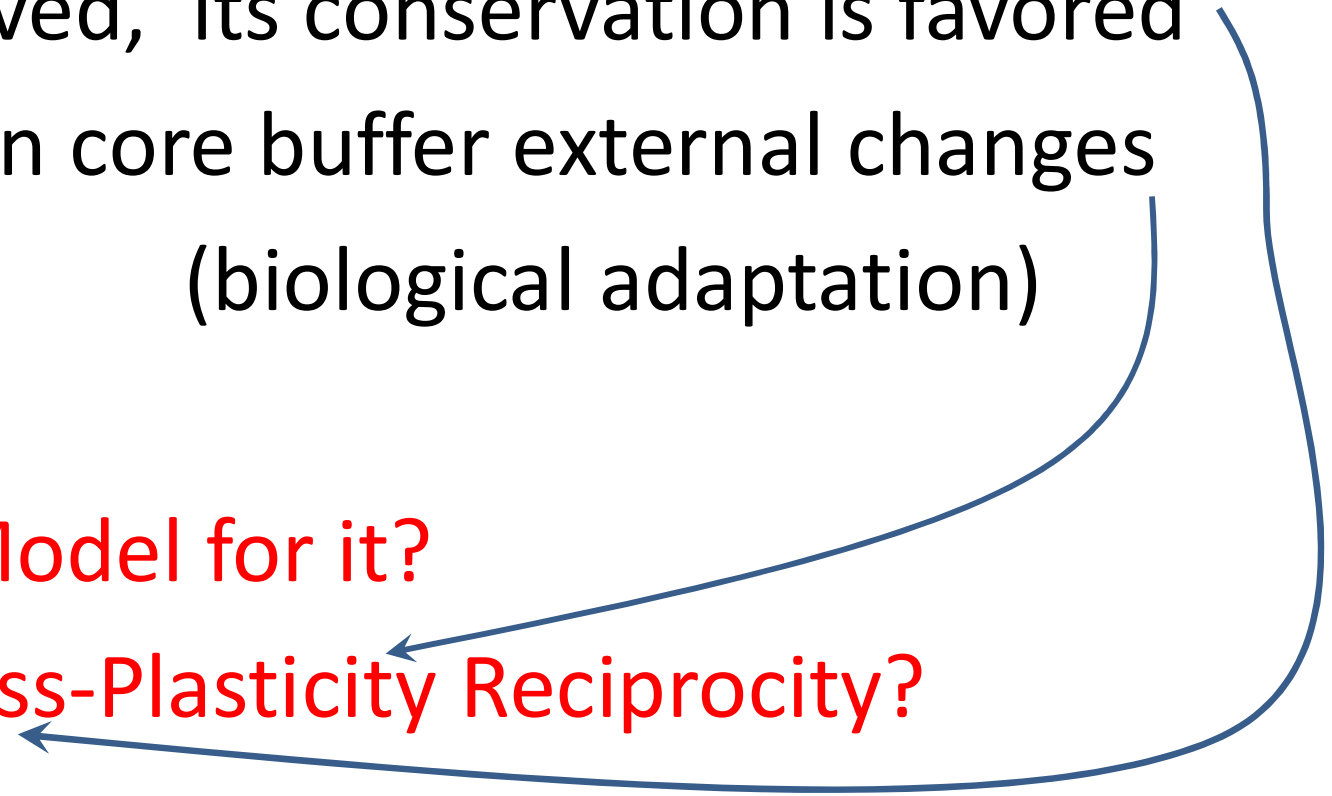
→once it is achieved, its conservation is favored

→other parts than core buffer external changes

(biological adaptation)

Theory/ Simple Model for it?

Law for Robustness-Plasticity Reciprocity?



(Hatakeyama, KK PRL2015;arXiv2020)

Non-trivial point: Emergent "Deep Linearity"

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

--beyond just steady-growth system

achieved in an evolved system ?

Check by simulations of toy models with high-dim dynamical systems

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

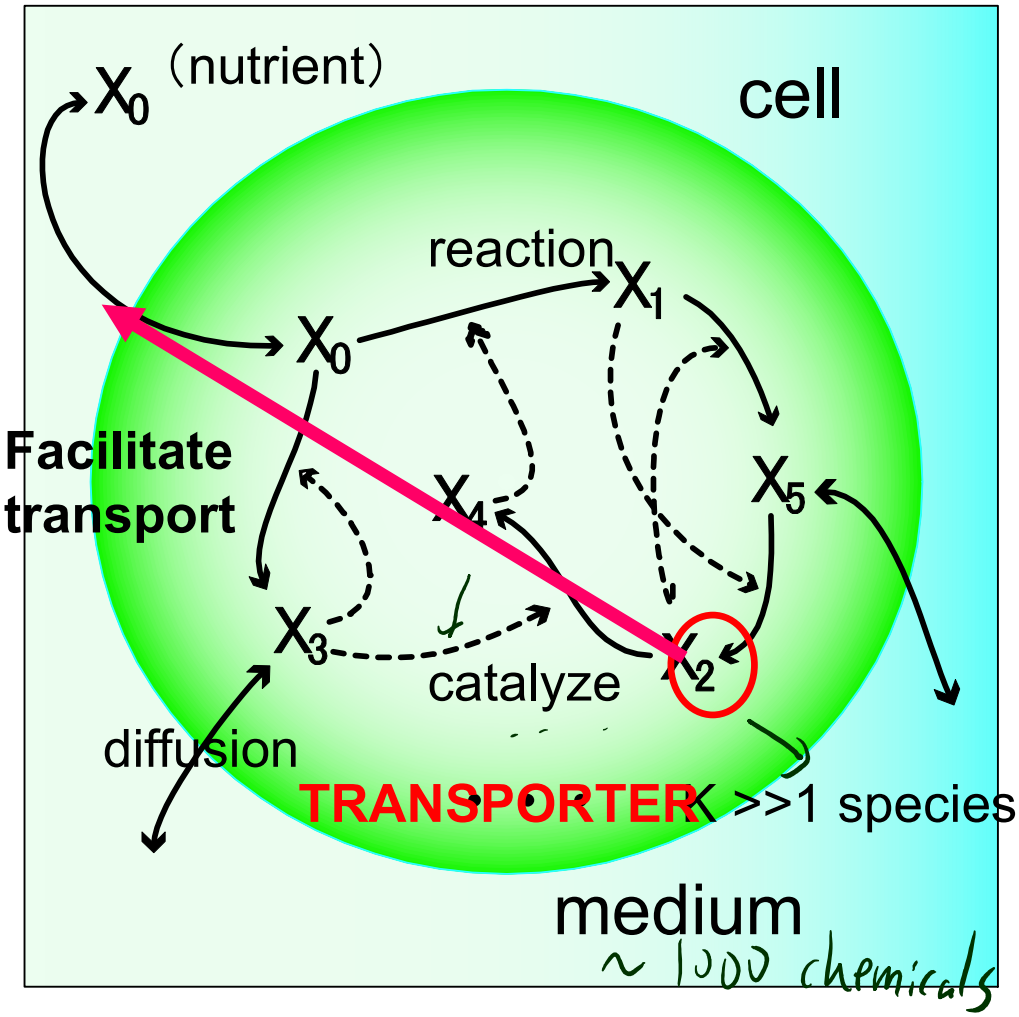
with the path rate p

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

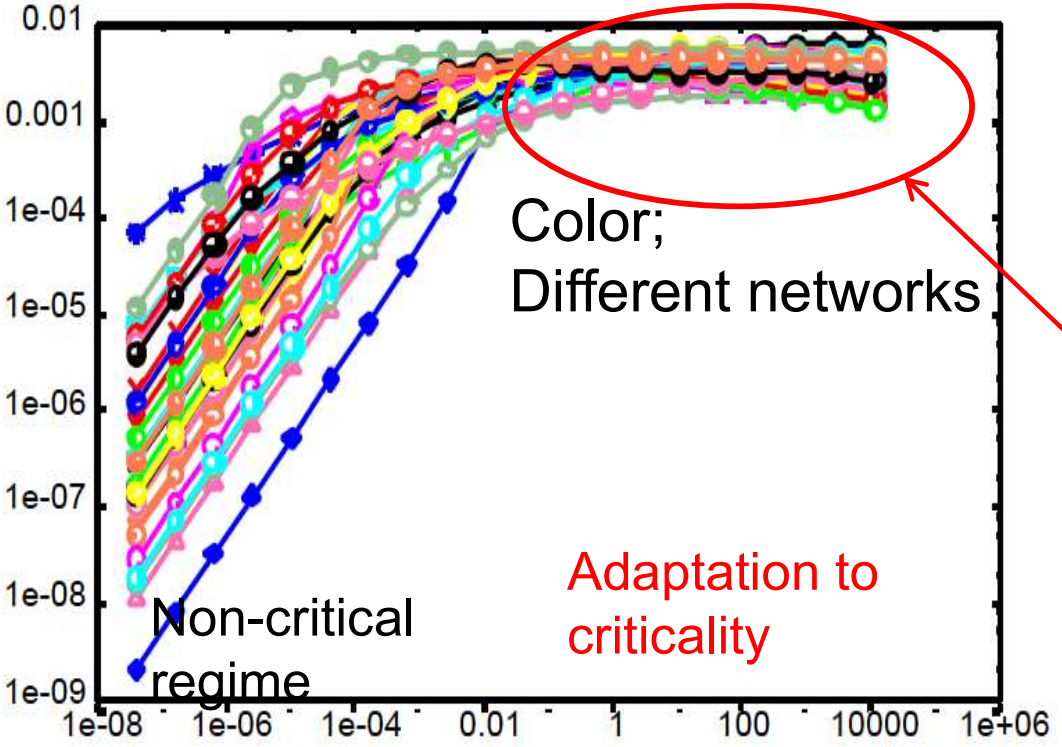
model



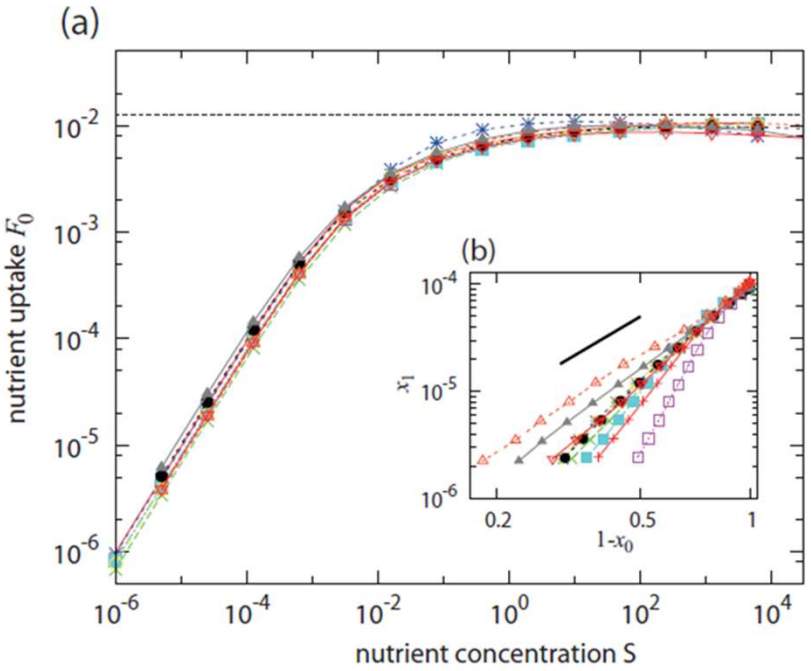
$dX1/dt \propto X0X4$; rate equation;
Stochastic model here

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

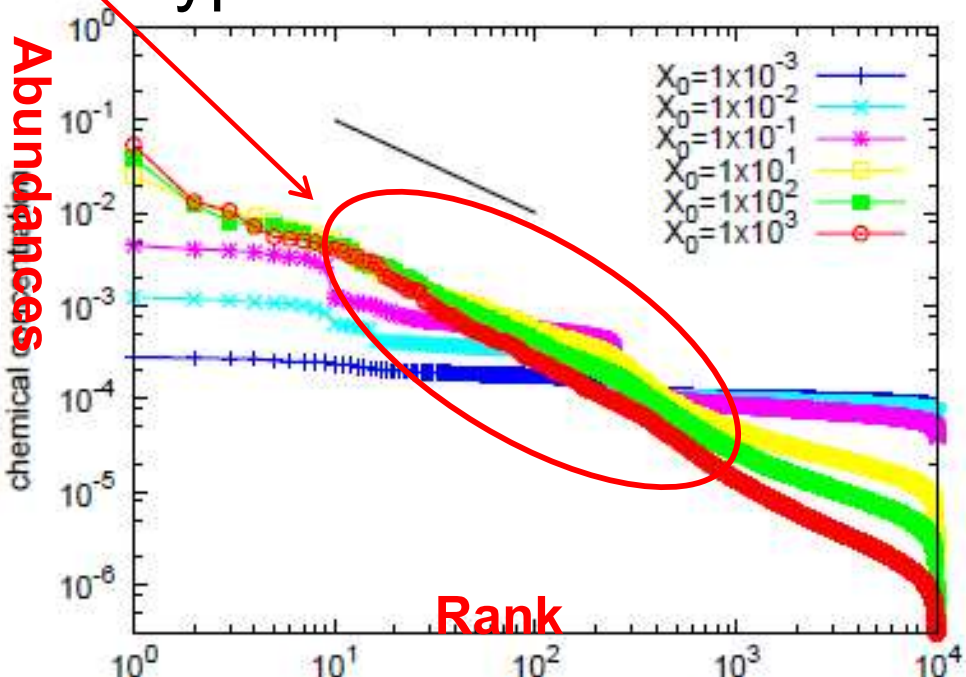
Growth speed (∝resource conc.)



concentration of external resource

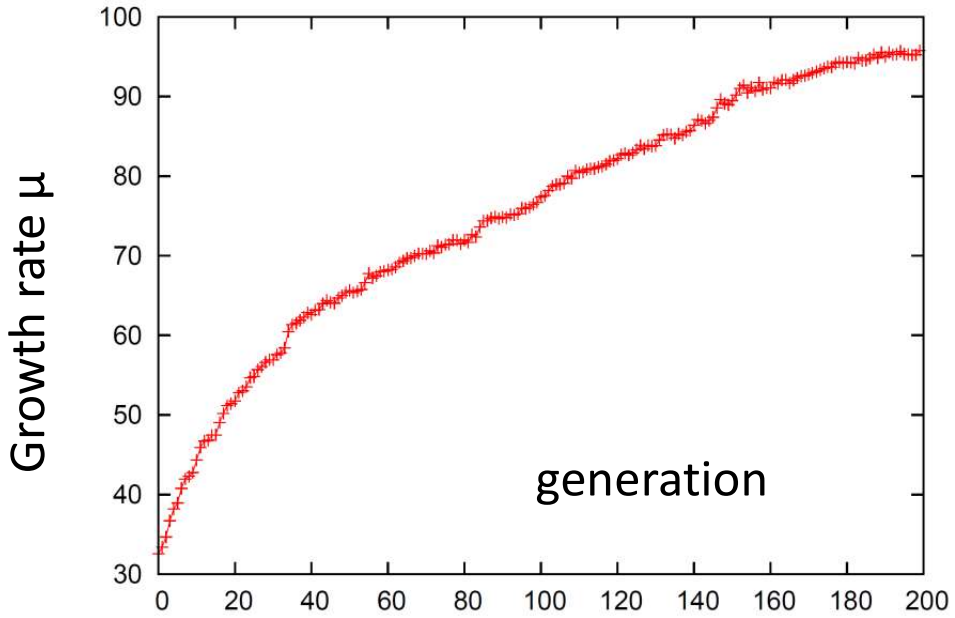


Also, demonstrated by mean-field-type calculations



Power law abundances is (alomost) sustained →

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)

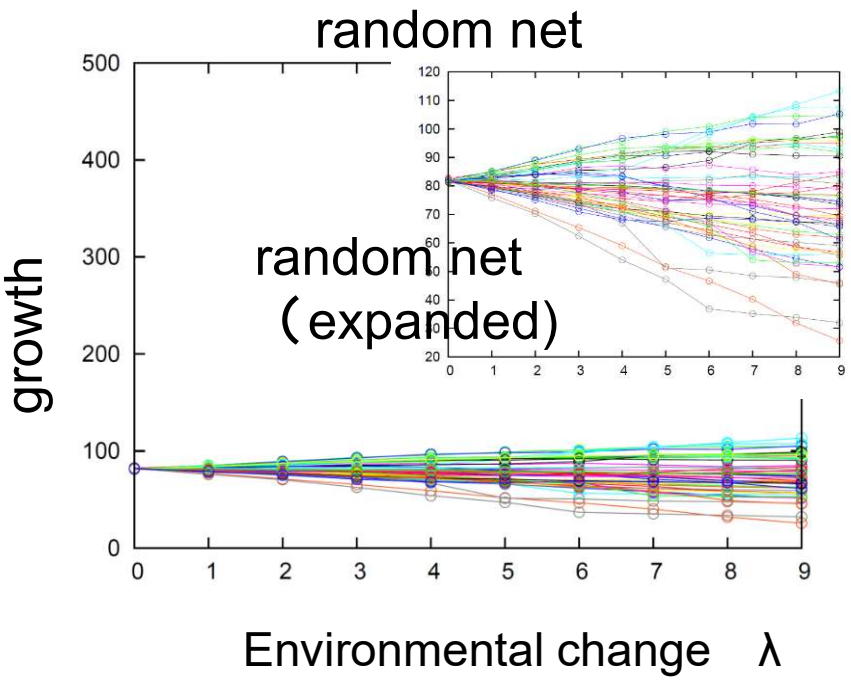
Then put an environment

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

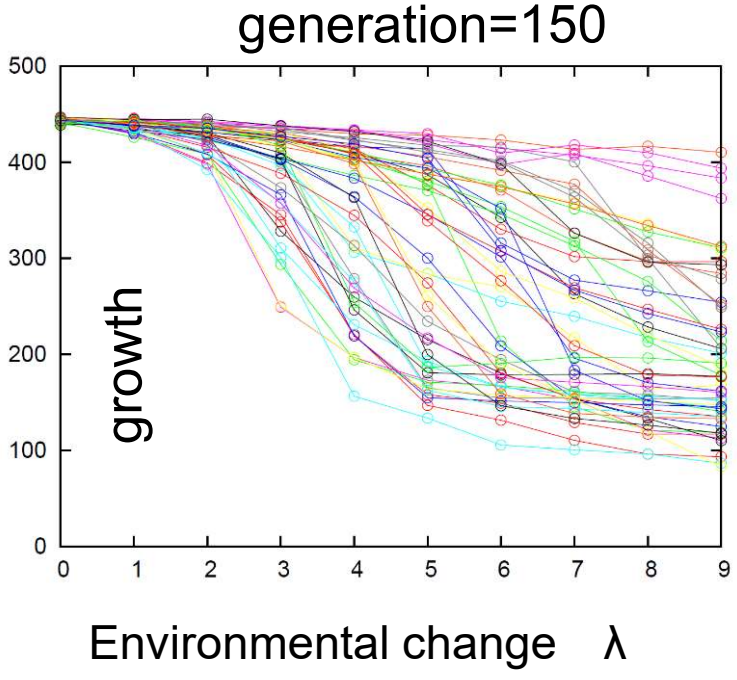
-1< e1,e2,… <1 (randomly chosen)

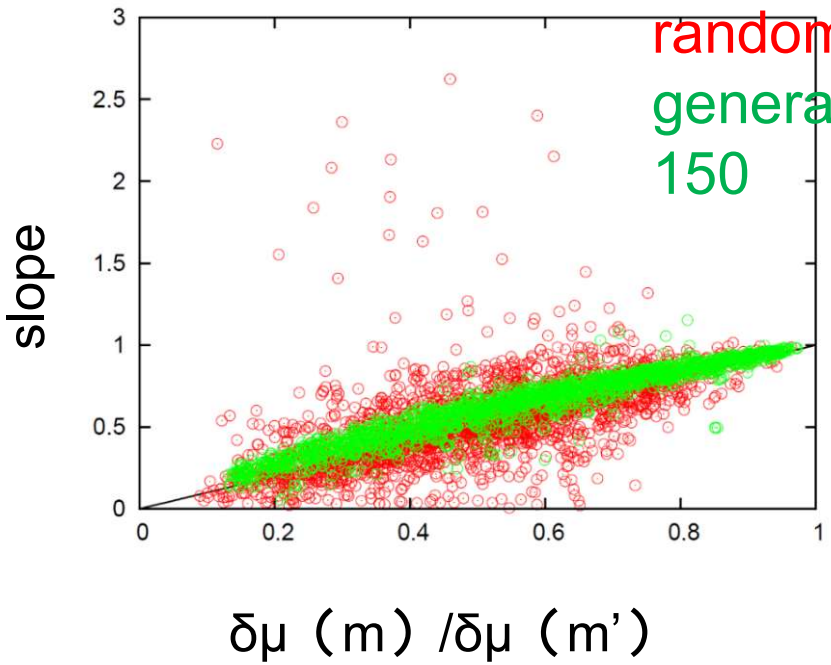
Check the change in concentrations and growth rates against λ

Linear Regime is Expanded after evolution

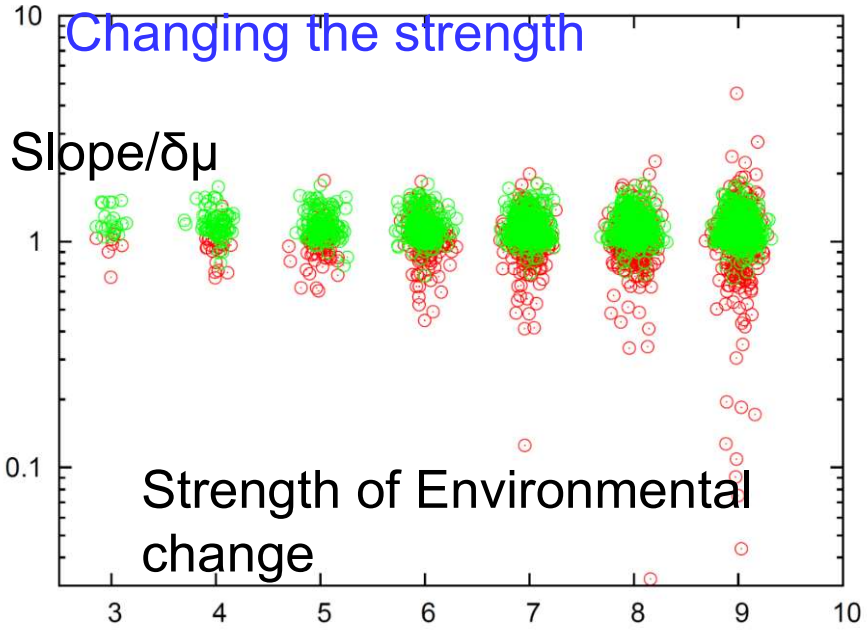


Different lines: Different env types (diff (e_i))

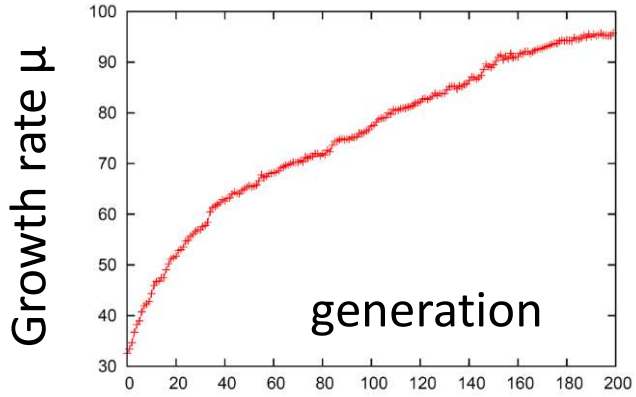


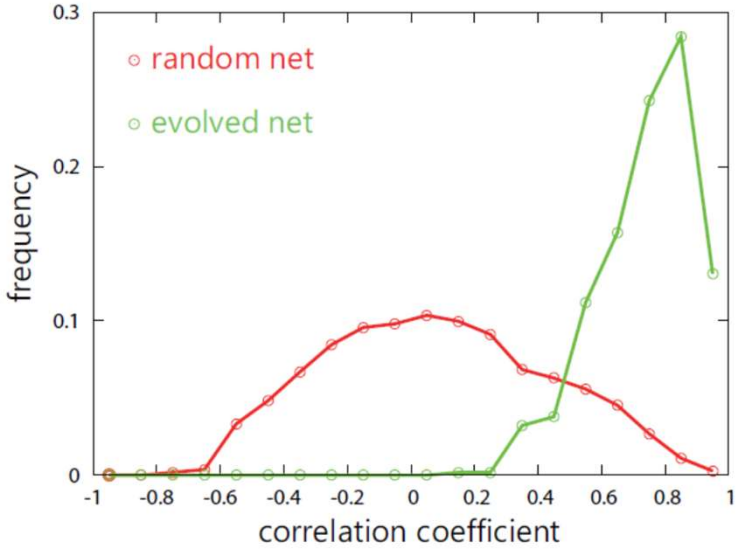


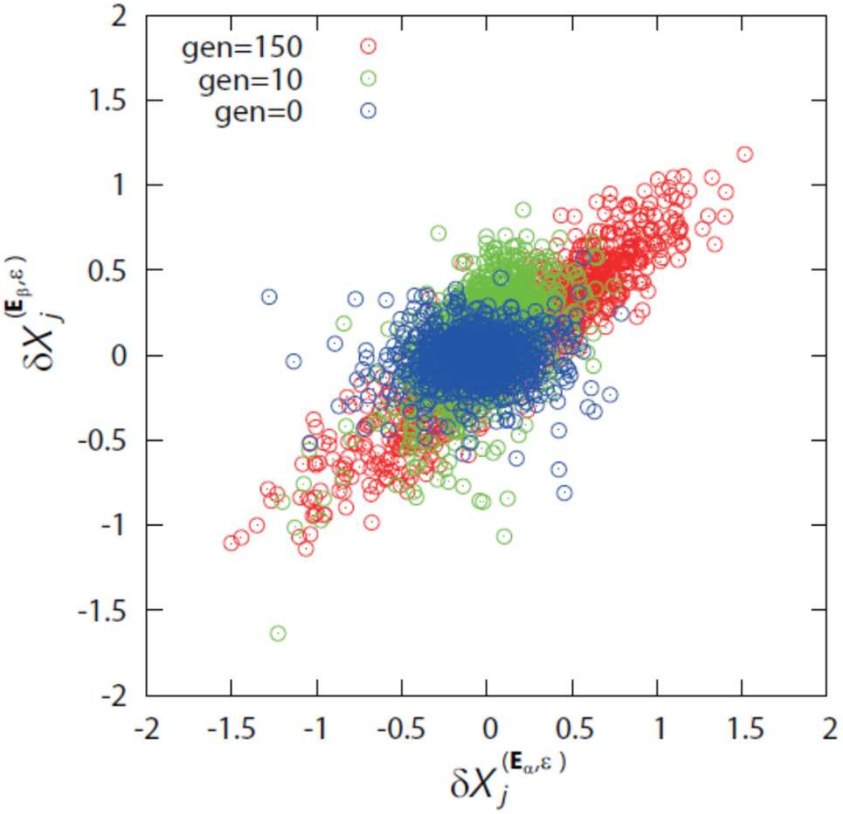
Under same environment
Changing the strength

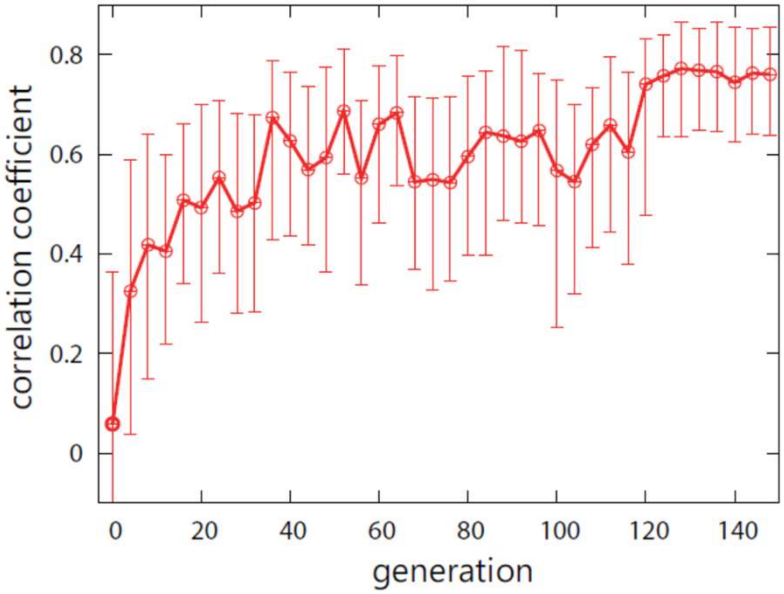


Evolution shapes Global Proportionality across different environmental conditions



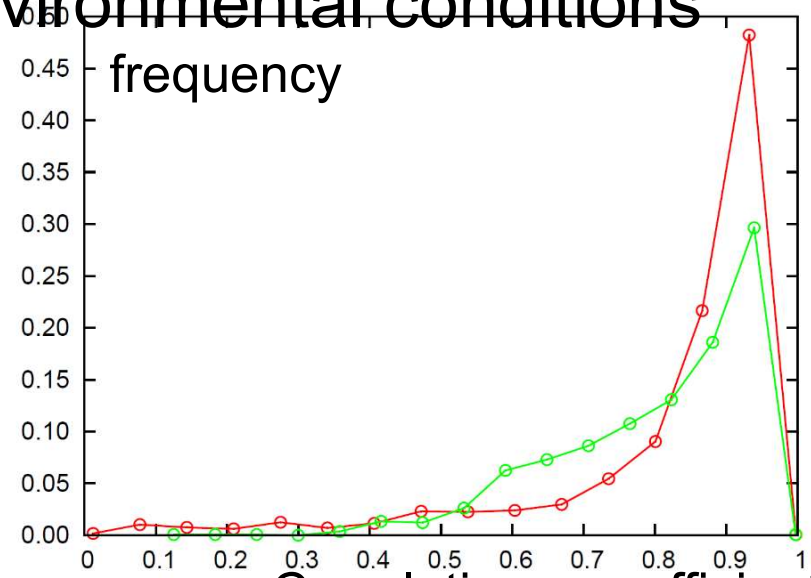






After evolution, correlation across different env cond. is increased, and slope-growth-rate linearity is enhanced

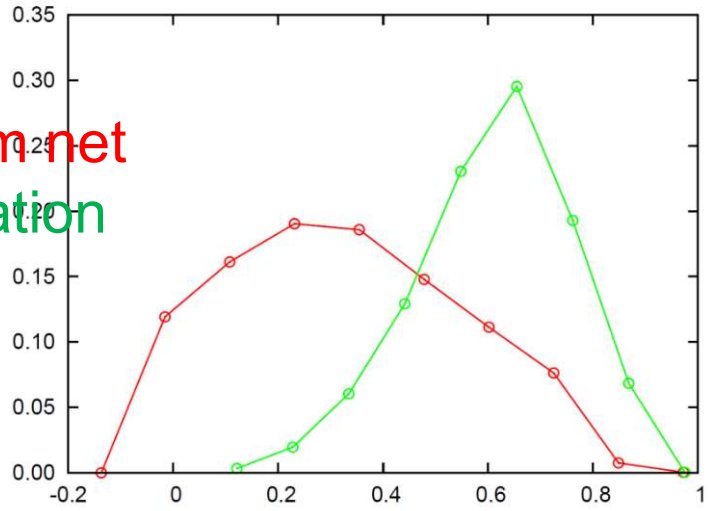
Between same environmental conditions



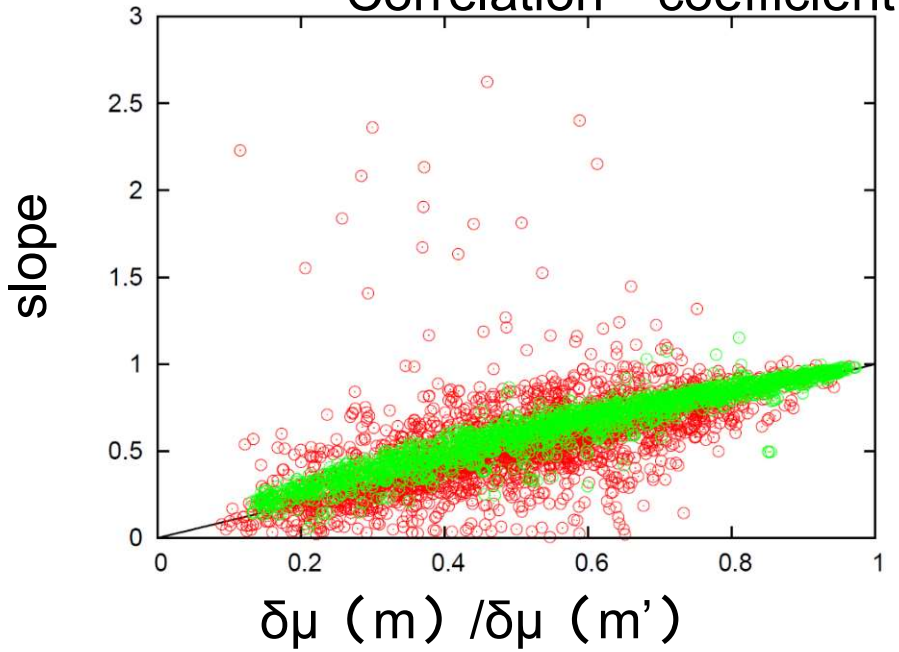
Across different env conditions

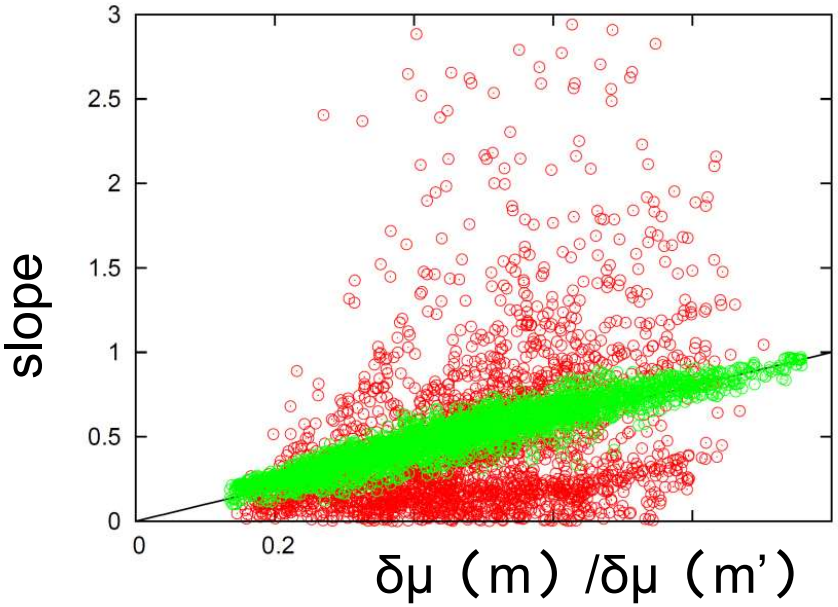
random-net

generation =150



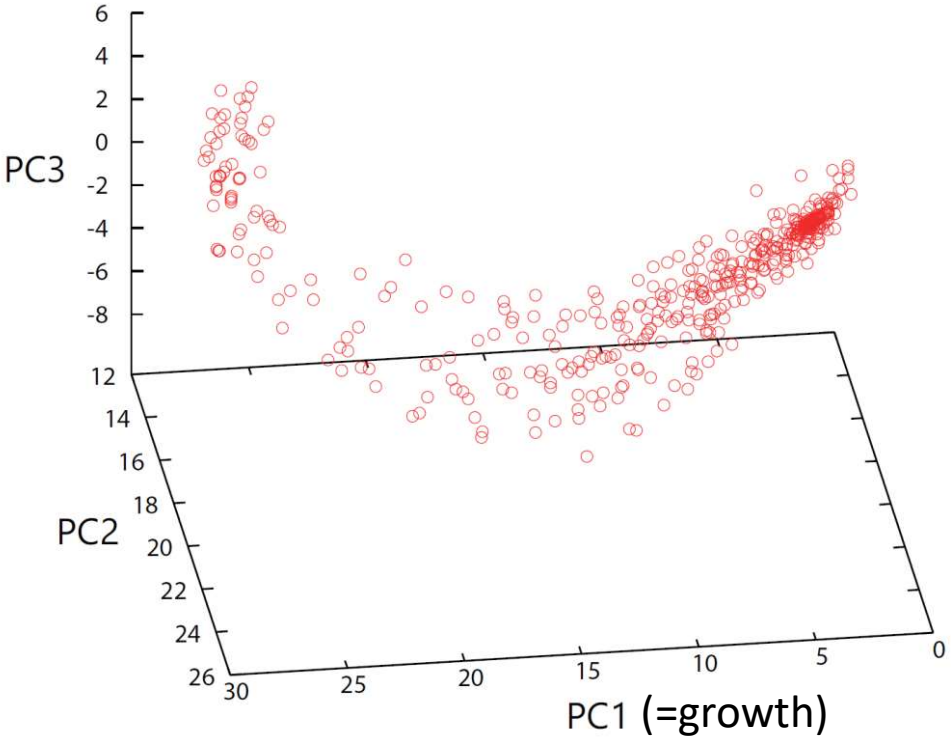
Correlation coefficient across component concentrations



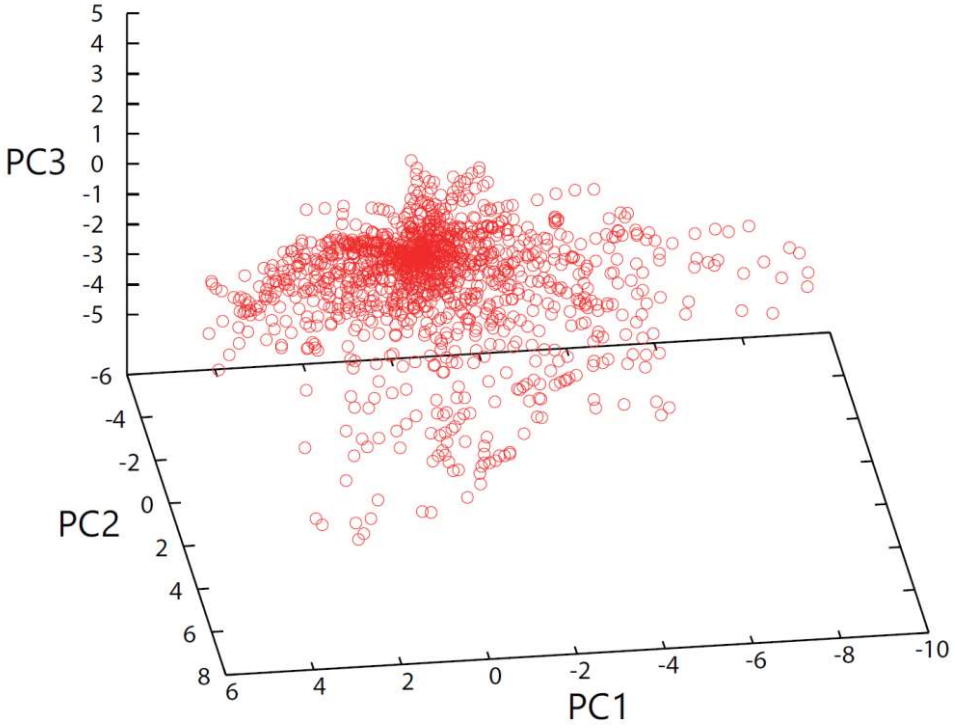


Phenotypic constraint on a low-dimensional space

After evolution

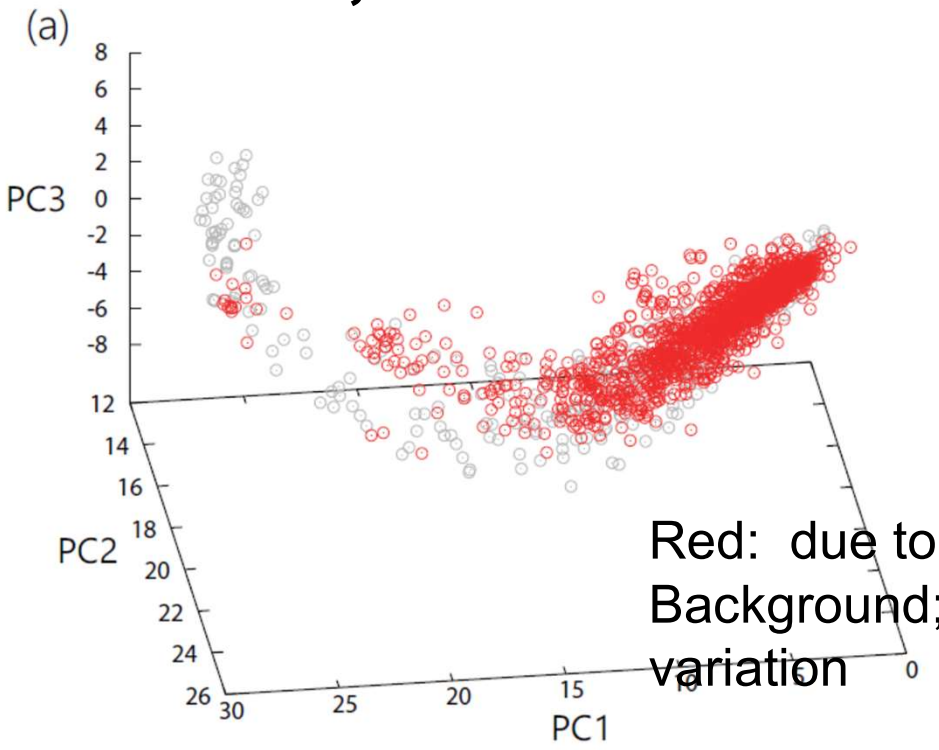


Random network

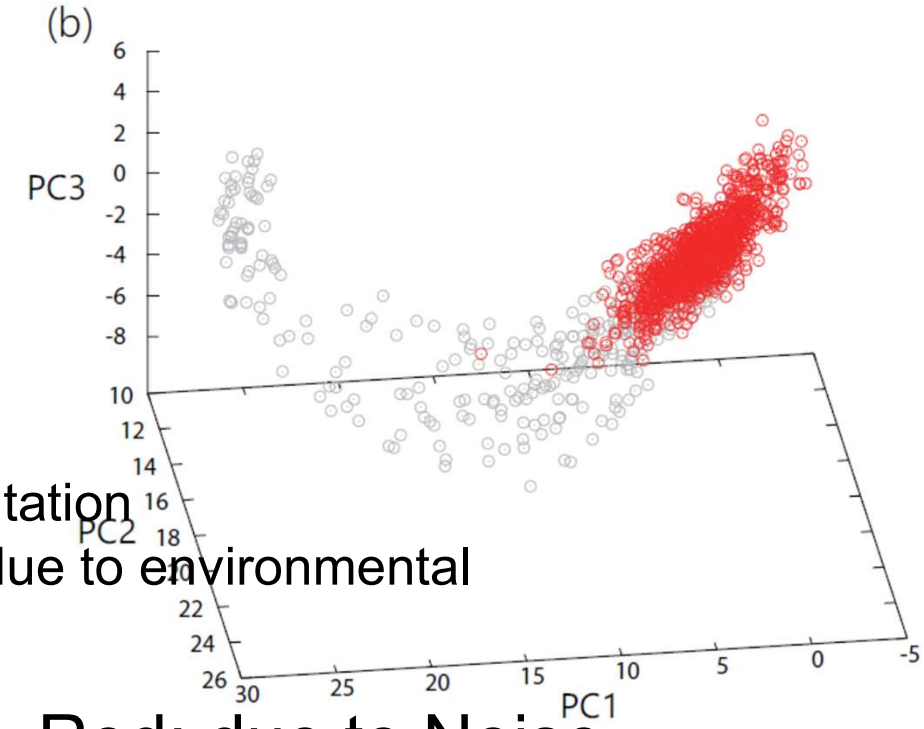


After evolution, the environmental response is constrained on a low-dimensional phenotype space.

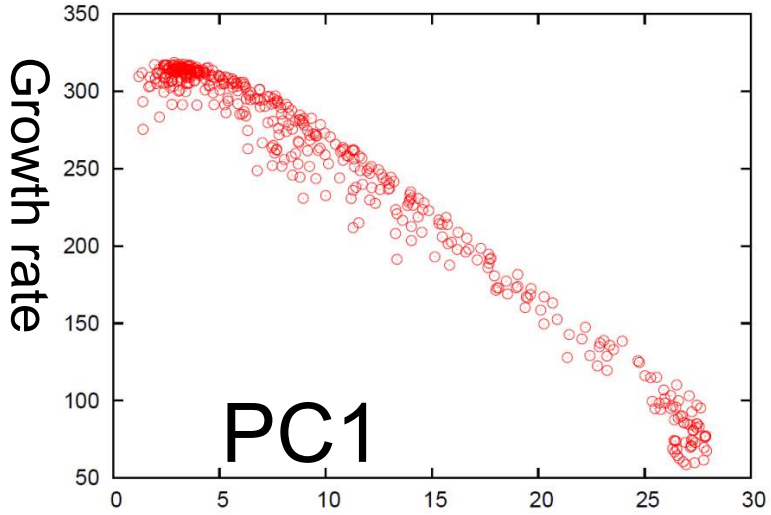
Phenotypic change due to environmental variation, mutation, noise are constrained along a major axis



Red: due to Mutation
Background; due to environmental variation



Red: due to Noise
Background; due to environmental variation



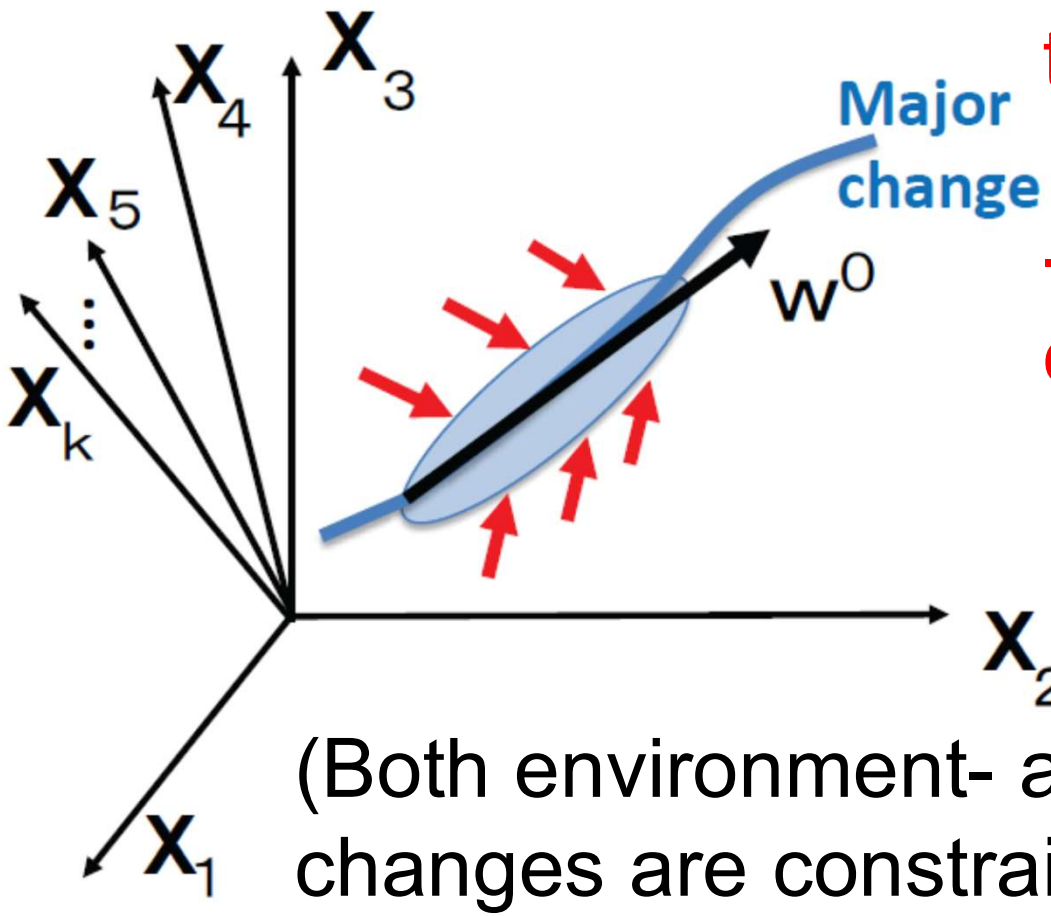
?Phenotypic change occurs along a common slow-manifold

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 direction –- -along which evolutionary progresses

(Both environment- and evolution- induced) changes are constrained along one-dimensional manifold

1）One mode significantly separated

2）The mode is along with the evolutionary direction

Furusawa, KK, Phys.Rev E 2018; KK, Furusawa, Ann Rev Biophys 2018

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

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

Formulation and Consequence of Hypthesis

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

with $\gamma_i \equiv \frac{\partial F_i}{\partial E}$. $$\delta \mathbf{X} = \mathbf{L}(\delta\mu \mathbf{I} - \gamma\delta E)$$

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

Only the smallest eigenvalue in J (or largest in L=1/J) contributes $|\lambda^i| >> |\lambda^0| \sim 0$

Most changes occur along such slow manifold

$$\delta \mathbf{X} = \lambda^0 \mathbf{w_0}(\delta\mu(\mathbf{v_0}\cdot\mathbf{I}) - (\mathbf{v_0}\cdot\gamma)\delta E).$$

Projection to this manifold w_0

w^0 (v^0) right(left) eigenvector for the smallest eigenvalue, i.e., Projection to this slow manifold

$$\frac{\delta \mathbf{X}(\mathbf{E})}{\delta \mathbf{X}(\mathbf{E}')} = \frac{\delta\mu(E) - (\mathbf{v_0}\cdot\gamma(\mathbf{E}))\delta E/(\mathbf{v_0}\cdot\mathbf{I})}{\delta\mu(E') - (\mathbf{v_0}\cdot\gamma(\mathbf{E}')\delta E'/(\mathbf{v_0}\cdot\mathbf{I})}$$

$\gamma \cdot v_0$ small

Consequence of Slow-Manifold Hypothesis (cont'd)

→Slow manifold is roughly orthogonal to **γ**

$$\gamma \cdot v_0 \sim 0$$

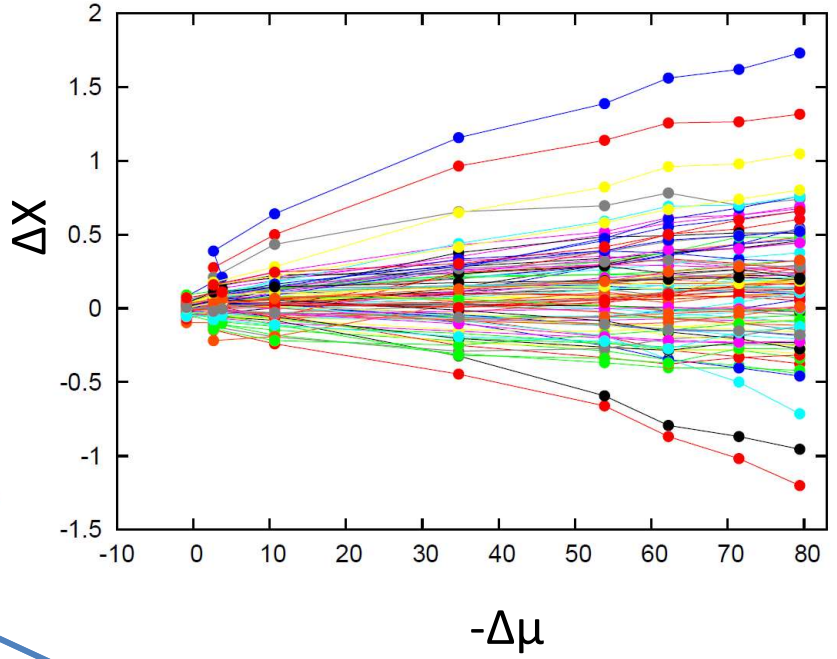
→ $$\delta\hat{\mathbf{X}} = \lambda^0 \delta\mu \mathbf{w}^0$$

Or, from the linear approximation

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

$$\frac{\delta \mathbf{X}(\mathbf{E})}{\delta \mathbf{X}(\mathbf{E}')} = \frac{\delta\mu(E)}{\delta\mu(E')} \frac{(1 - (\mathbf{v_0} \cdot \gamma(\mathbf{E})/(\alpha \mathbf{v_0} \cdot \mathbf{I}))}{(1 - (\mathbf{v_0} \cdot \gamma(\mathbf{E}')/(\alpha \mathbf{v_0} \cdot \mathbf{I}))}$$

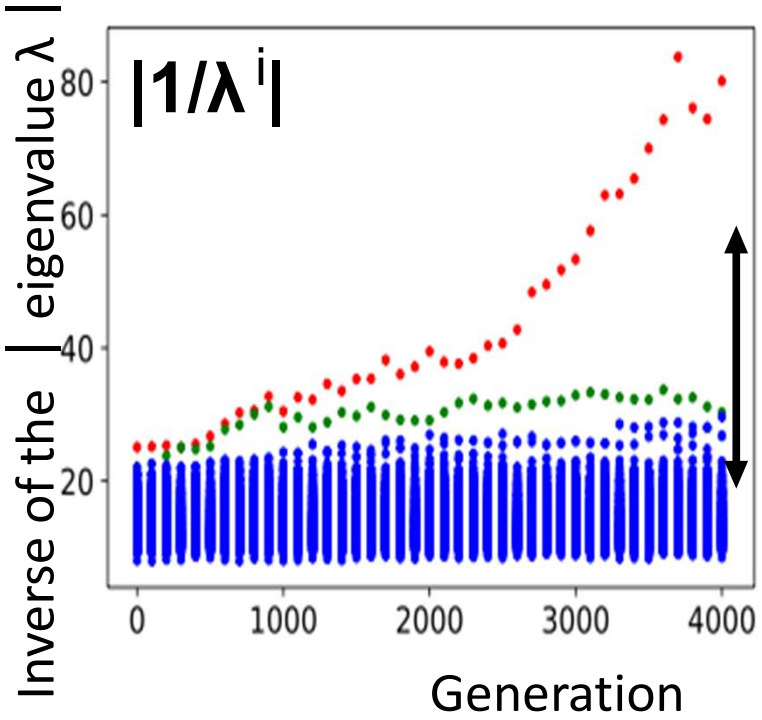
Correction in proportion coefficient

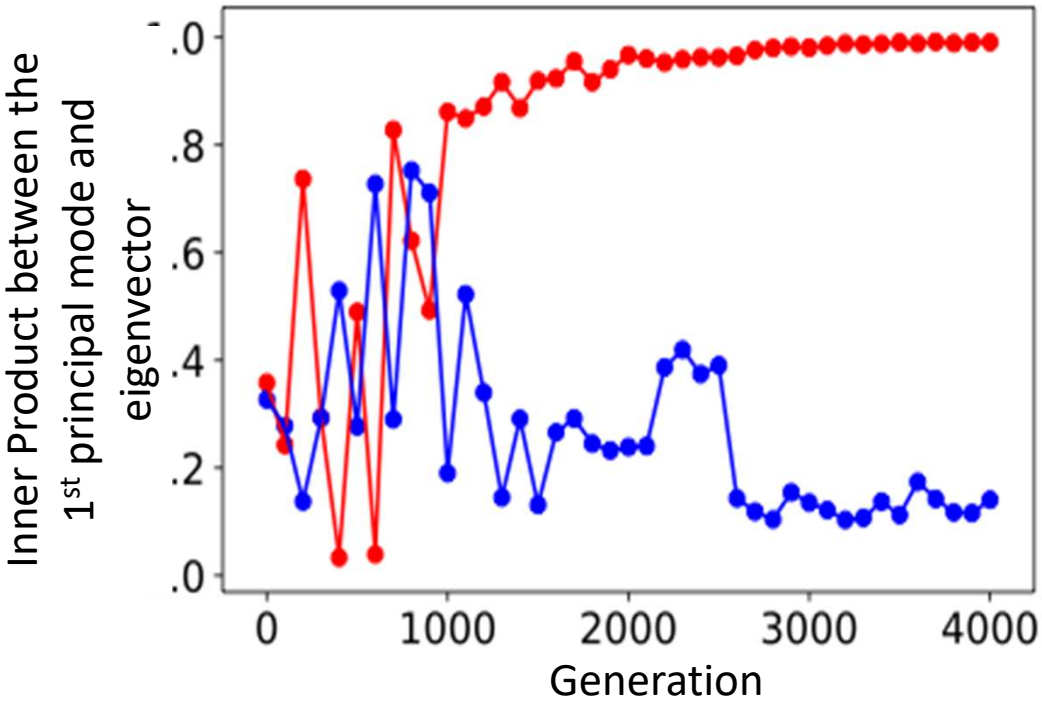


Separation of slowest mode in catalytic reaction net model

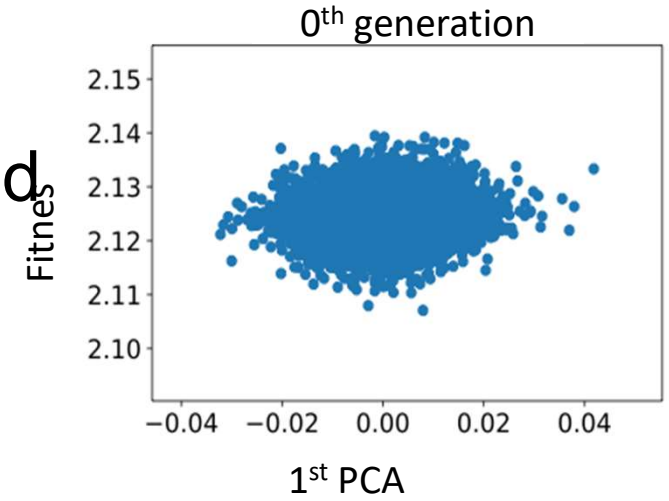
Eigenvalues of $J_{ij} = (\partial \dot{X}_i / \partial X_j)_{\boldsymbol{X}_i = \boldsymbol{X}_i^*}$

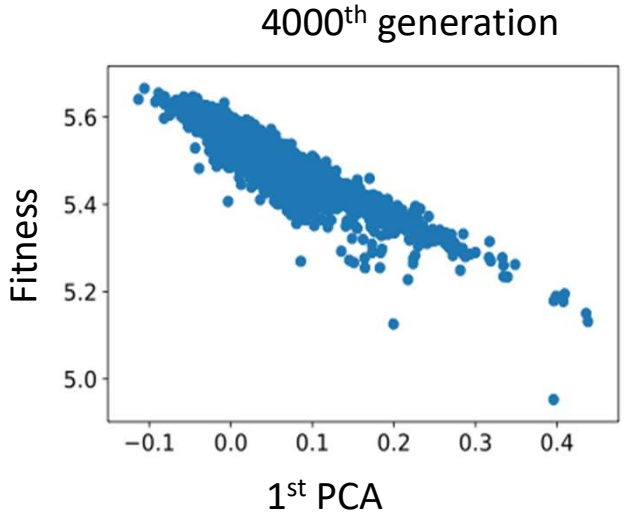
Sato,KK PhysRevR 2020





The directions of slowest mode and the fitness are aligned after evolution



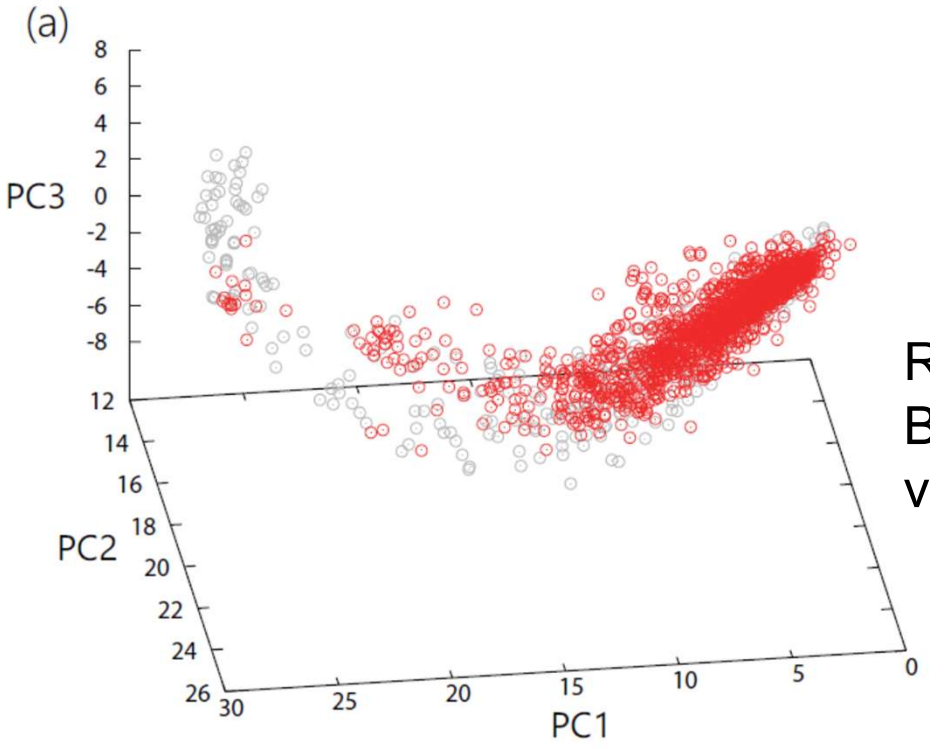


Now apply this idea to evolution G:

General Relationship between

- change in (log) expression by environment
- change in (log) expression by evolution

→ Evolution -- Recall: Phenotypic change due to environmental variation, mutation, noise are constrained along the same major axis



Red: due to Mutation
Background; due to environmental variation

Phenotypic changes by evolution and environmental changes are along a common dominant mode

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 $\gamma \cdot v_0 \sim 0$

(Genetic) evolution under the environmental condition

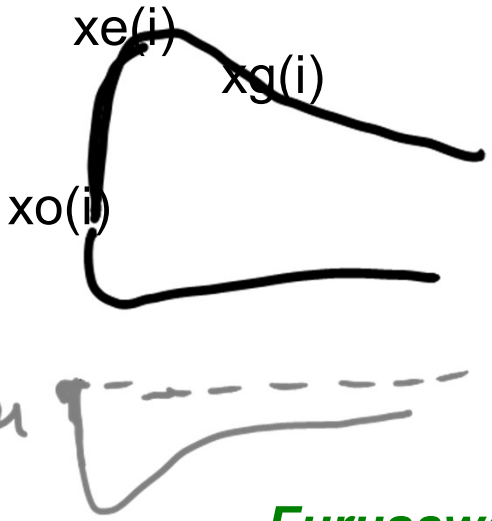
→recover growth-- $|\delta\mu(E)| < |\delta\mu(G)|$

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

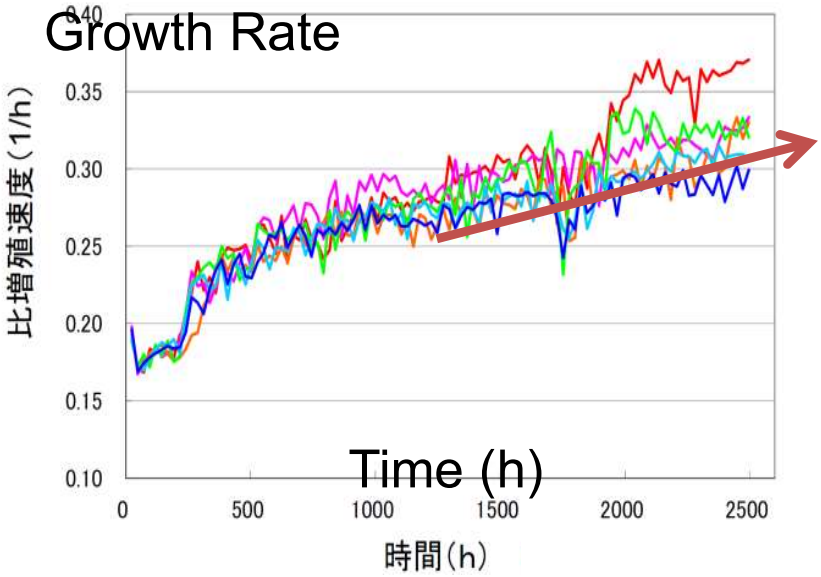
→ All the expression levels tend to return the original level by evolution **Le Chatelier Principle?**

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

Furusawa'sGroup

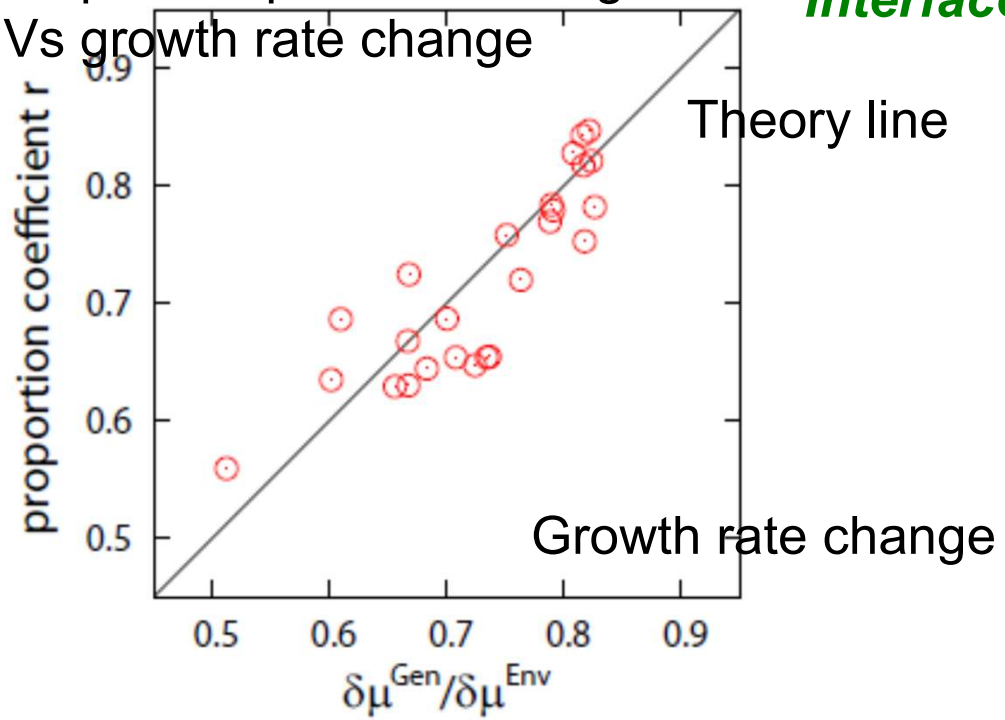


Furusawa,KK Interface,2015

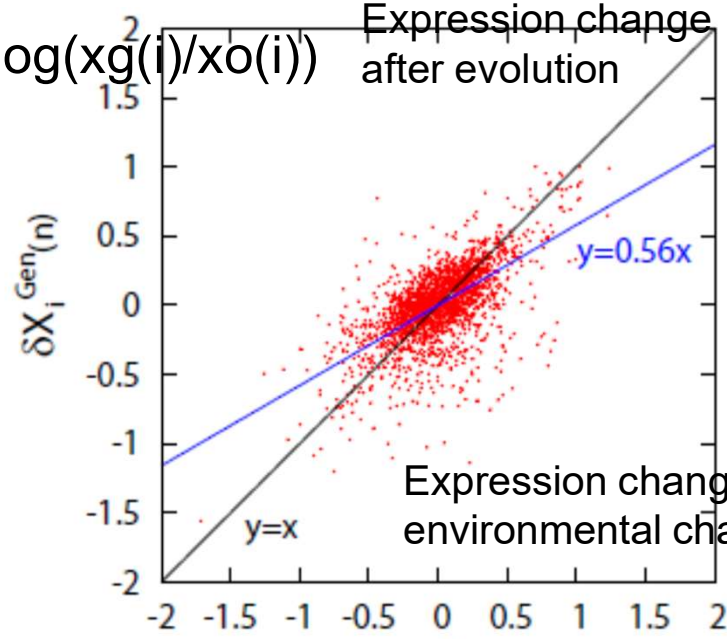


～1000 generations

Slope in expression change
Vs growth rate change



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



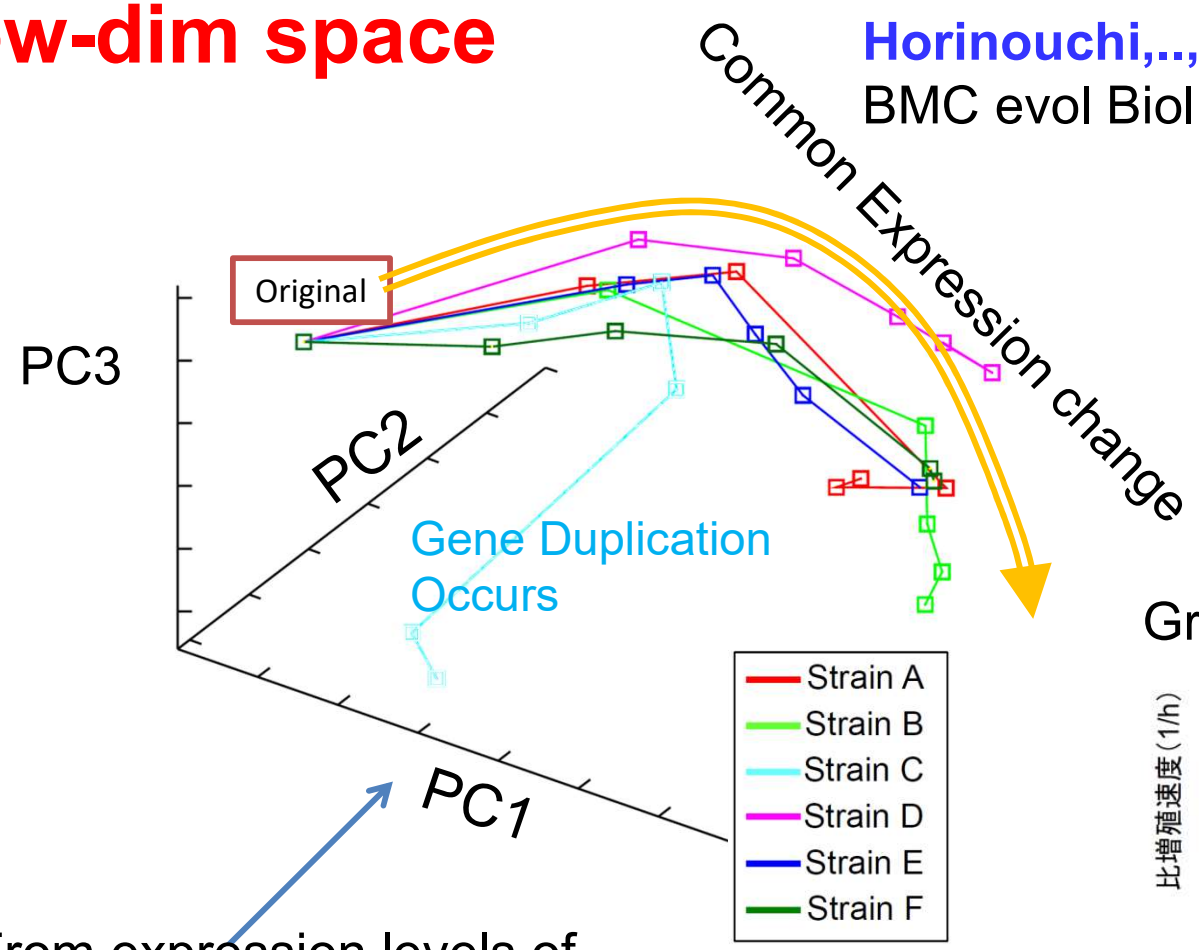
0＜δXi（E,G）/δXi（E）＜1

return to original expression pattern

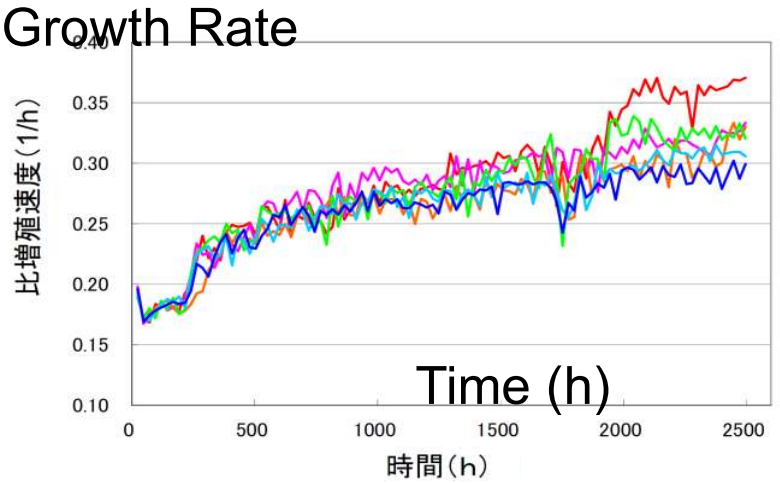
（Le Chatelier principle)

Deterministic phenotypic evolution constrained in low-dim space

Horinouchi,..,Furusawa,
BMC evol Biol 2015



Replaying the tape of evolution, same phenotypic path (not genetic) arises!



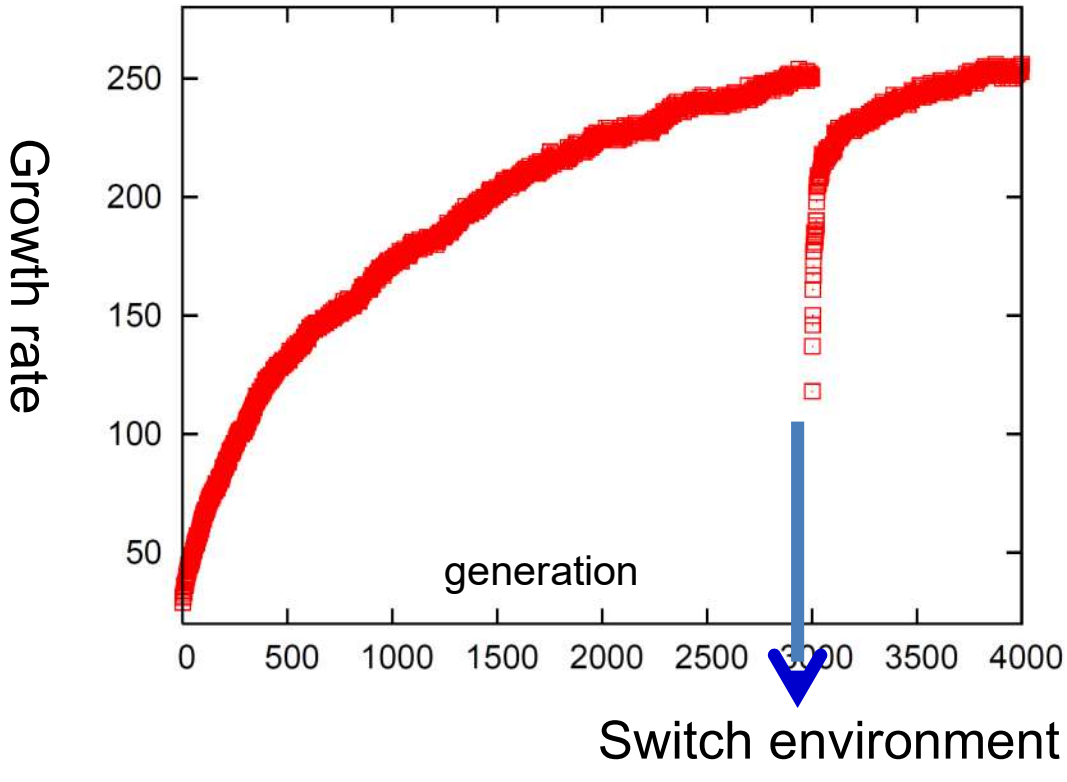
Mutation sites are different by strains. But..
Common trends in phenotypic space (low-dim structure)
PC1 is highly correlated with the growth rate


FilterMax F

Let's check evolution law in this catalytic reaction net model

Switch environment(composition of nutrient) and check response (--env)

Mutate network and select those with higher growth –evo



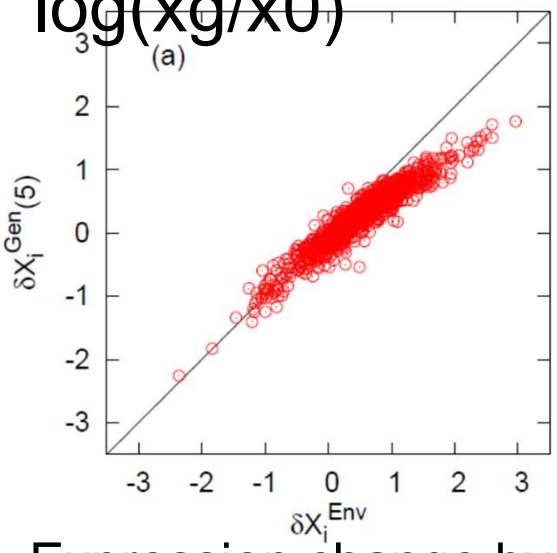
Recovery of growth rate by adaptive evolution to new environment

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

Expression Change by evolution

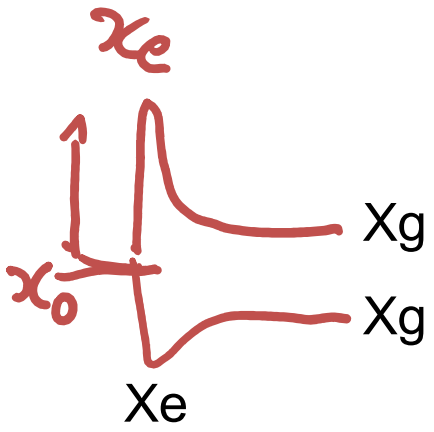
5-th generation

log(xg/x0)



Expression change by env

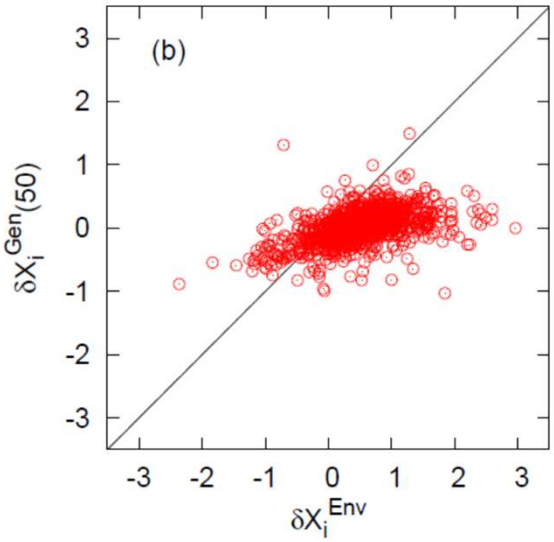
log(xe/x0)



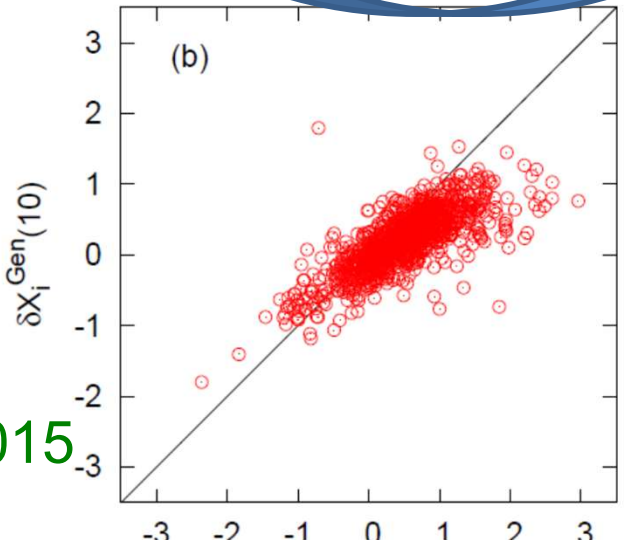
（1）Response by genetic change tends to cancel the change by environment

（2）The two responses are proportional over all components

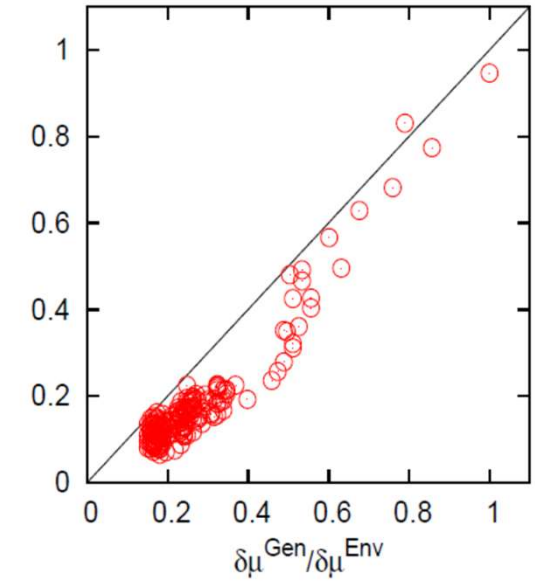
100 th generation



2oth generation



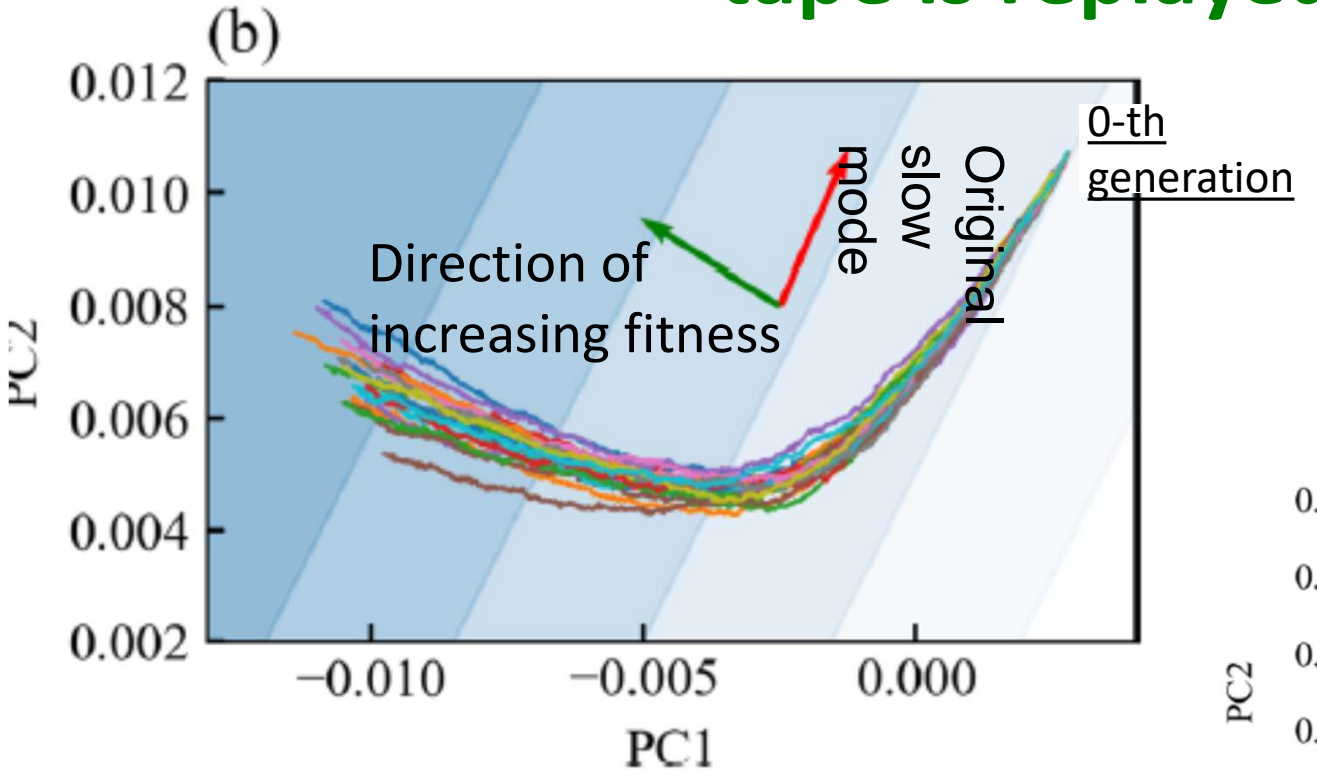
Slope in δX



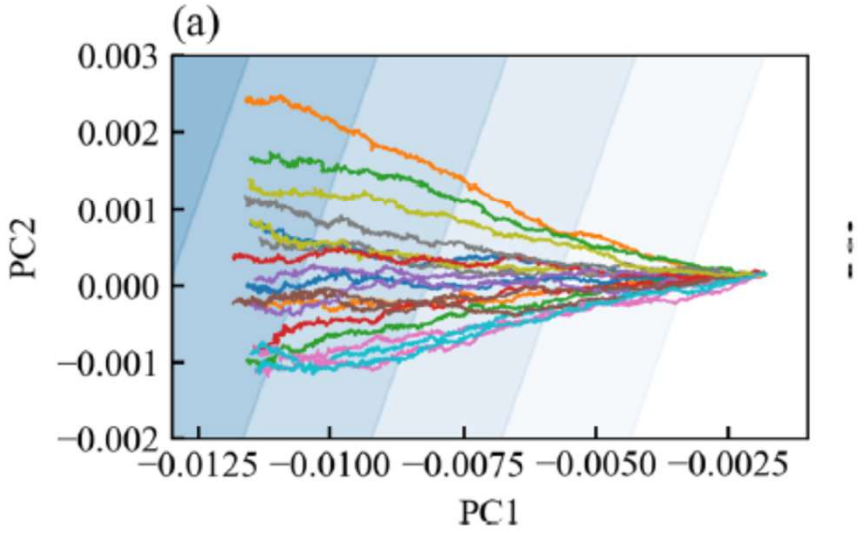
Furusawa,KK, Interface 2015

—Δμ bo by env to by evol

Evolution to novel environment -- the already evolved dominant mode is adopted to adapt to new environment→ **Same phenotypic path when the tape is replayed**.



Cf. When started from non-adapted case (same random network)



Different color : different strains with different genetic change

Sato, KK, PhysRevRes2020

So far response relationship: fluctuation & response are two sides of the same coin (←Einstein)

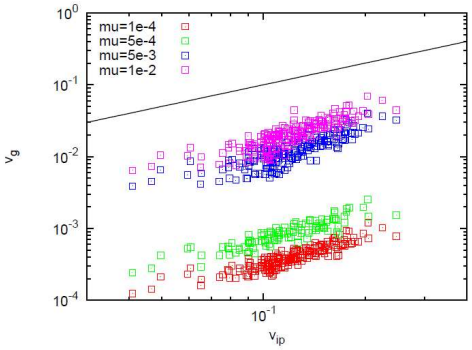
Fluctuation

Variance by gene change Vg

←classic Fisher Theorem→

Response by evolution

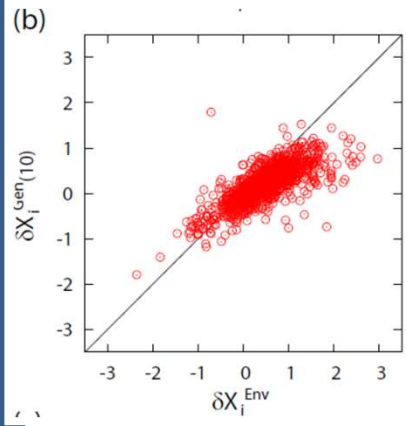
Genetic change



∽proportional

Evolutionary Fluctuation-Response (2003)

∽proportional



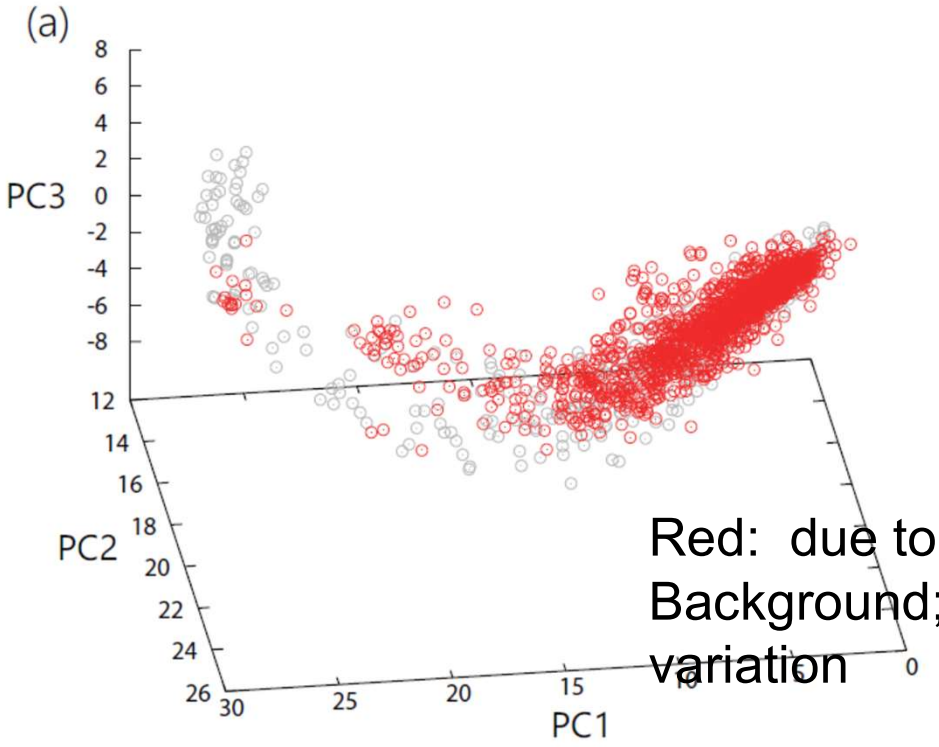
Variance by noise Vip

← **Proportion** →

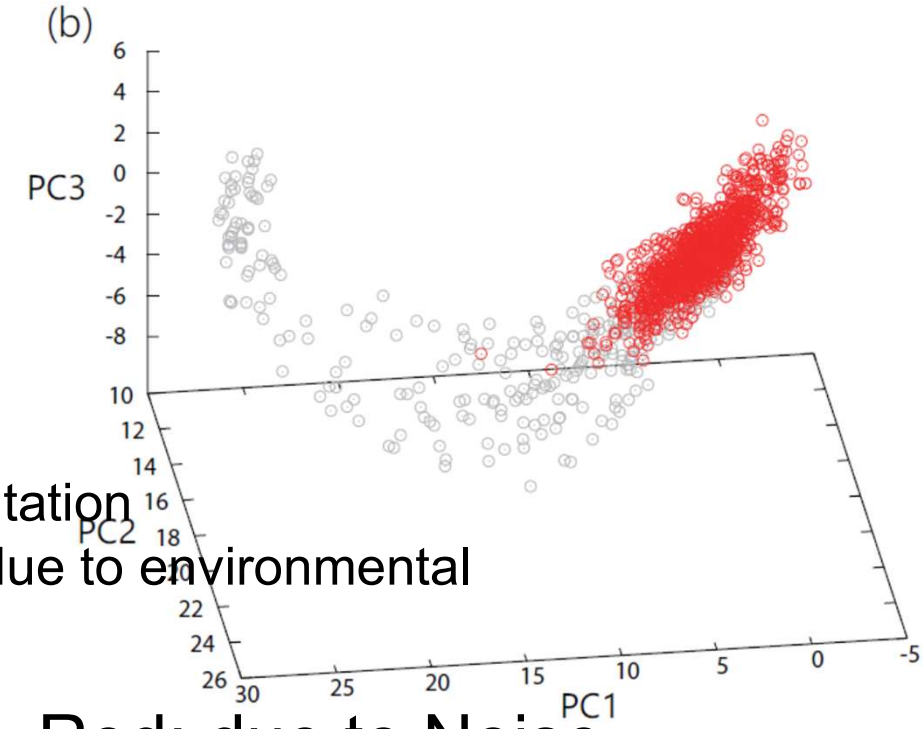
Response by environ-ment

Non-genetic change (noise, environ-ment)

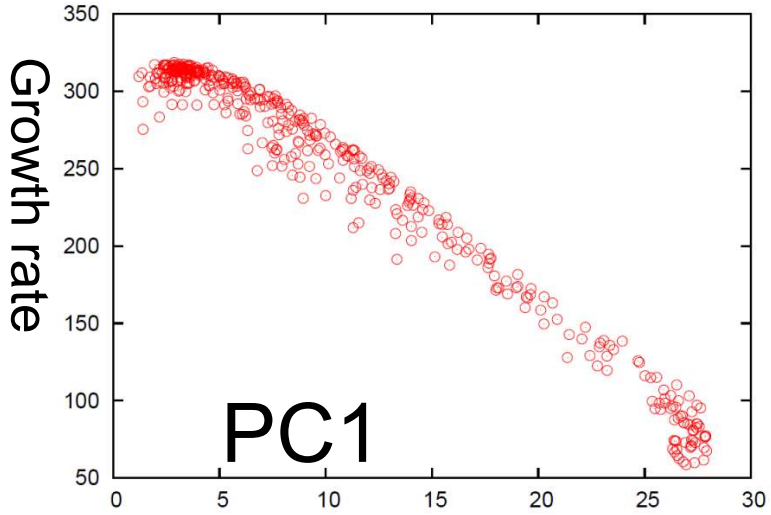
Recall…



Red: due to Mutation
Background; due to environmental variation



Red: due to Noise
Background; due to environmental variation

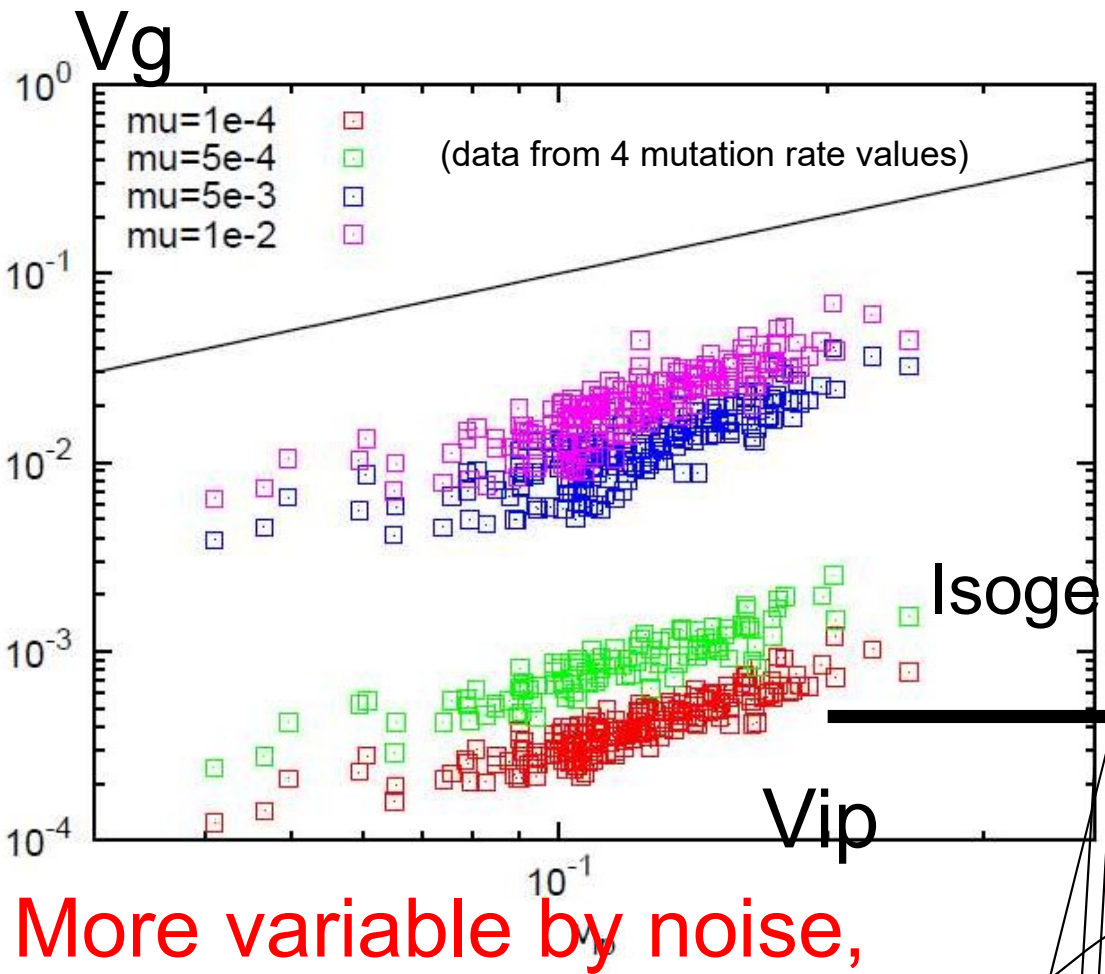


?Phenotypic change occurs along a common slow-manifold

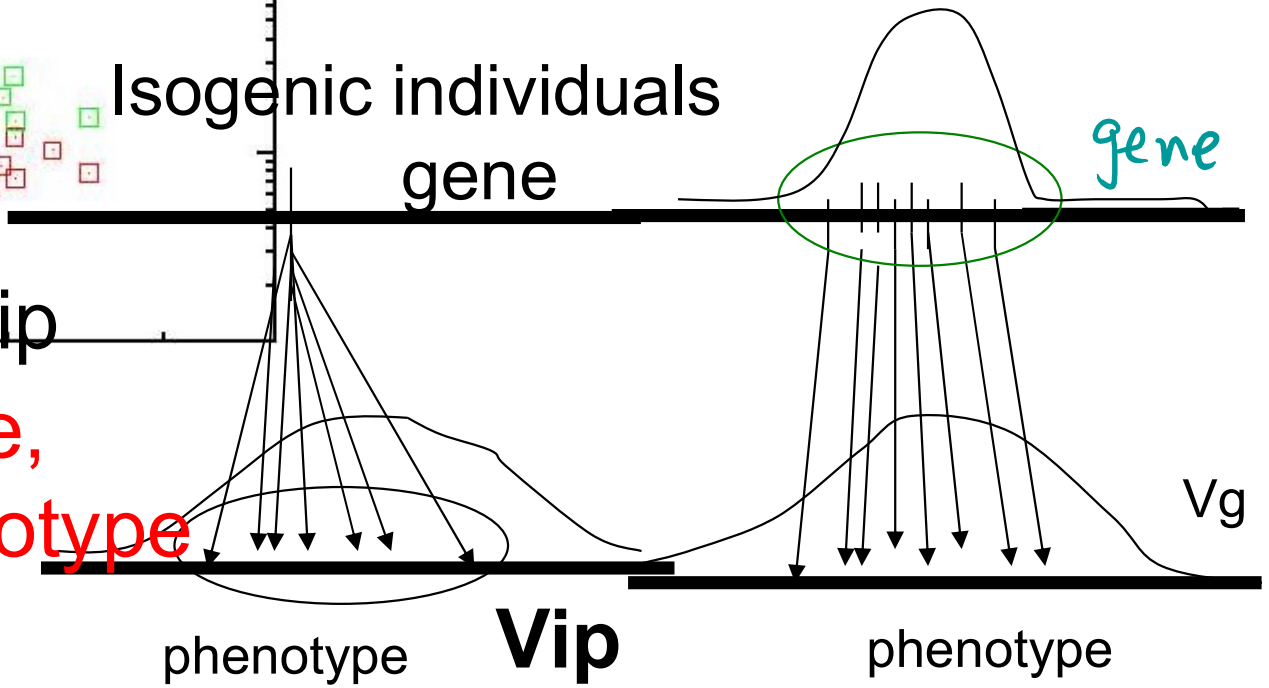
Vip-Vg relationship across traits (phenotypes)

Vg(i) : Vatiance of X(i) due to genetic mutation

Vip(i) : Variance of X(i) due to noise in dynamics



Vip(i)∝Vg(i)∝evol.speed over all traites i



More variable by noise, more evolvable: Phenotype evolution predictable

Vg-Vip proportionality is explained by the slow manifold Hypothesis

Evolution occurs along this dominamt 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

Theory for Fluctuation

Linearization $$\sum_j J_{ij}\delta X_j(E,G) + \gamma_i^E \delta E + \gamma_i^G \delta_G = \delta\mu(E,G)$$

$$\gamma_i^{(E,G)} \equiv \frac{\partial F_i}{\partial E(G)}.$$

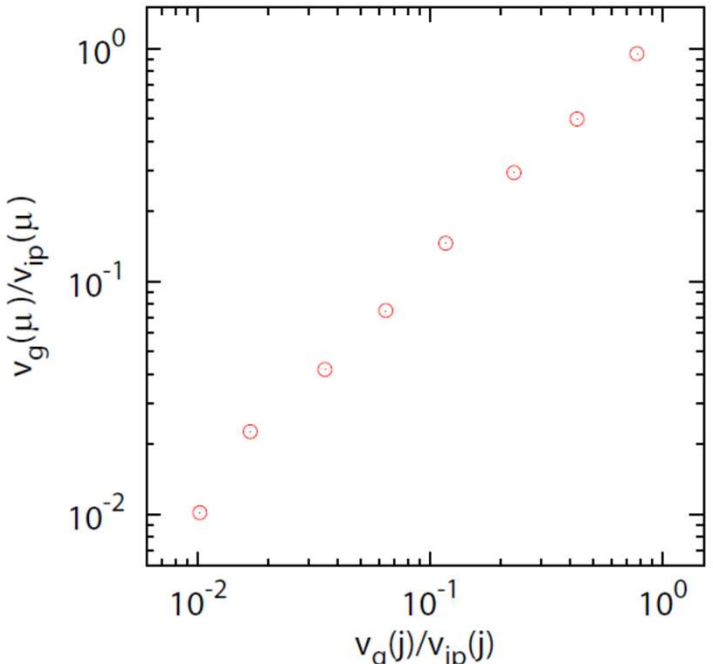
Assumption $$\gamma_i^E = \gamma_i^G$$

Genetic Assimilation(?)

$$\langle(\delta X_j(\delta\Upsilon)^2\rangle = \langle\delta\mu(\delta\Upsilon)^2\rangle(\sum_i L_{ji}(1-\gamma_i/\alpha))^2$$

where Υ is either E or G,

$$\frac{V_{ip}(j)}{V_g(j)} = \frac{\langle\delta\mu(\delta E)^2\rangle}{\langle\delta\mu(\delta G)^2\rangle} = \frac{V_{ip}(\mu)}{V_g(\mu)}$$

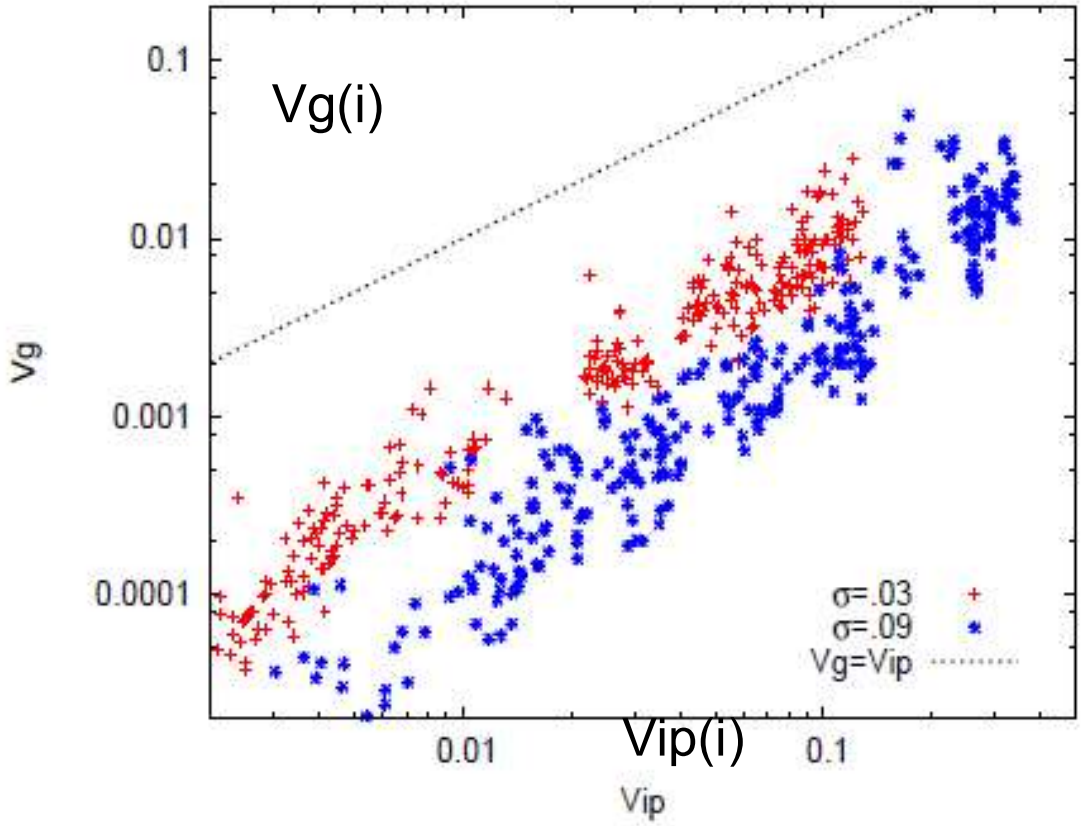


Vg(i),Vip(i) across different protein expression levels also show proportionality

Measure variance of gene expression for each gene i

→ genetic Vg(i) & epigenetic Vip(i)

Vip(i)-Vg(i) proportionally across genes



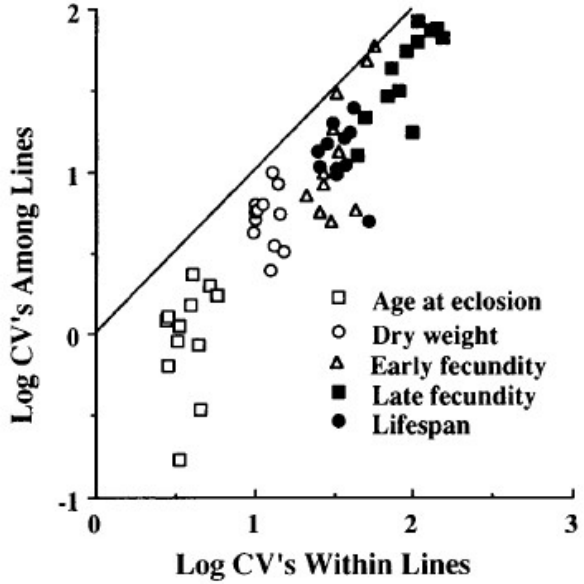


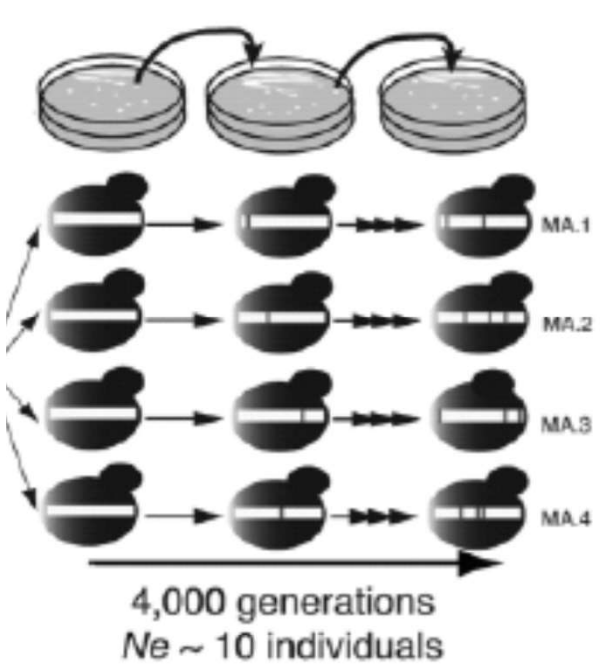
Fig. 2. The genetic (variation among lines) and environmental (variation within lines) coefficients of variation were very similar for each trait but not precisely the same. The line shown is where $CV_{within\ lines} = CV_{among\ lines}$.

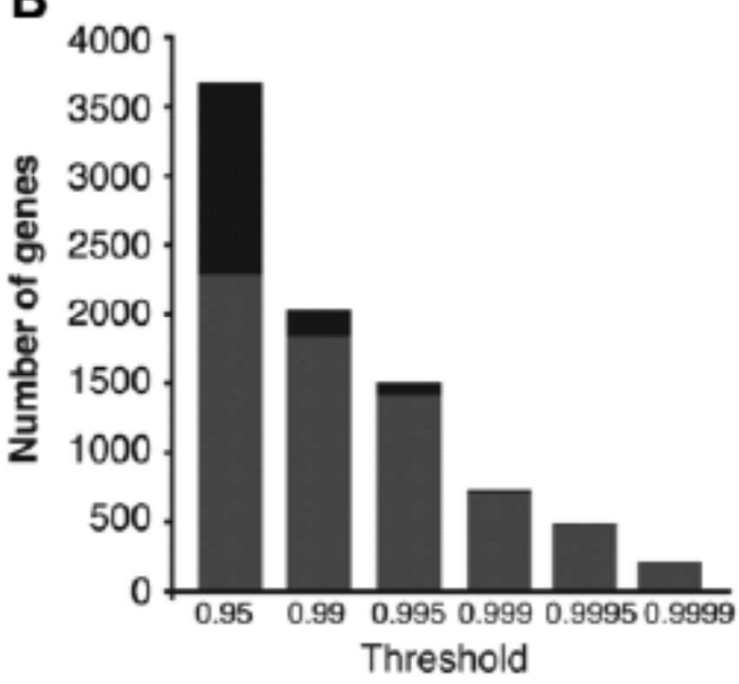
Drosophila selection experiment Vip vs Vg across different phenotypes

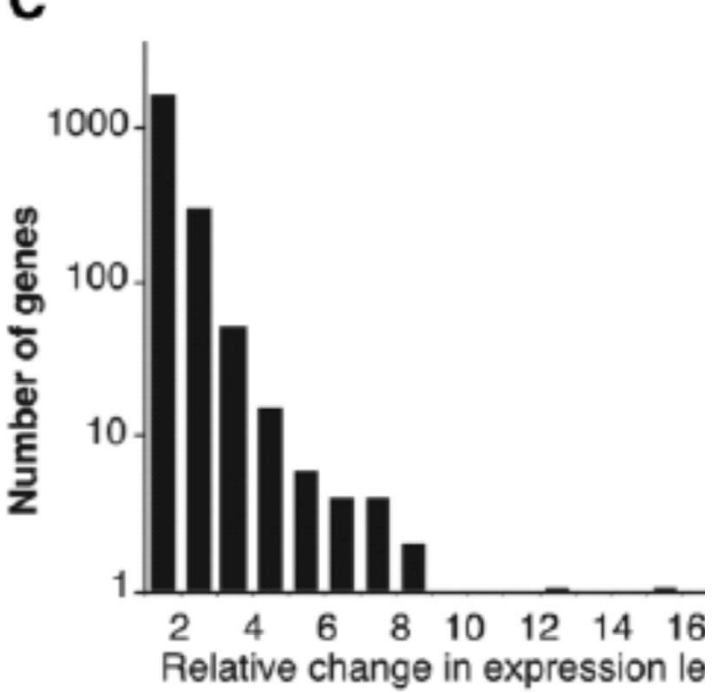
Genetic Properties Influencing the Evolvability of Gene Expression

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

Identifying the properties of gene networks that influence their evolution is a fundamental research goal. However, modes of evolution cannot be inferred solely from the distribution of natural variation, because selection interacts with demography and mutation rates to shape polymorphism and divergence. We estimated the effects of naturally occurring mutations on gene expression while minimizing the effect of natural selection. We demonstrate that sensitivity of gene expression to mutations increases with both increasing trans-mutational target size and the presence of a TATA box. Genes with greater sensitivity to mutations are also more sensitive to systematic environmental perturbations and stochastic noise. These results provide a mechanistic basis for gene expression evolvability that can serve as a foundation for realistic models of regulatory evolution.

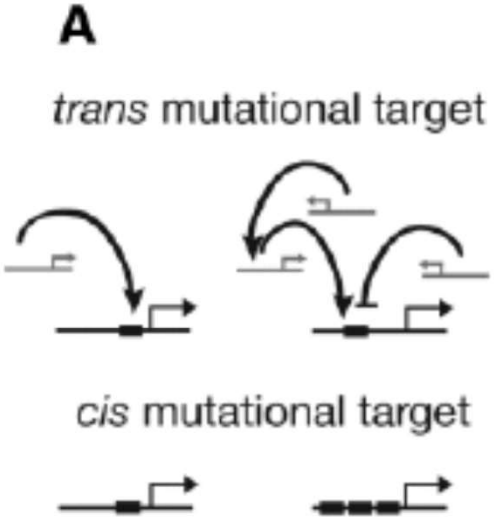


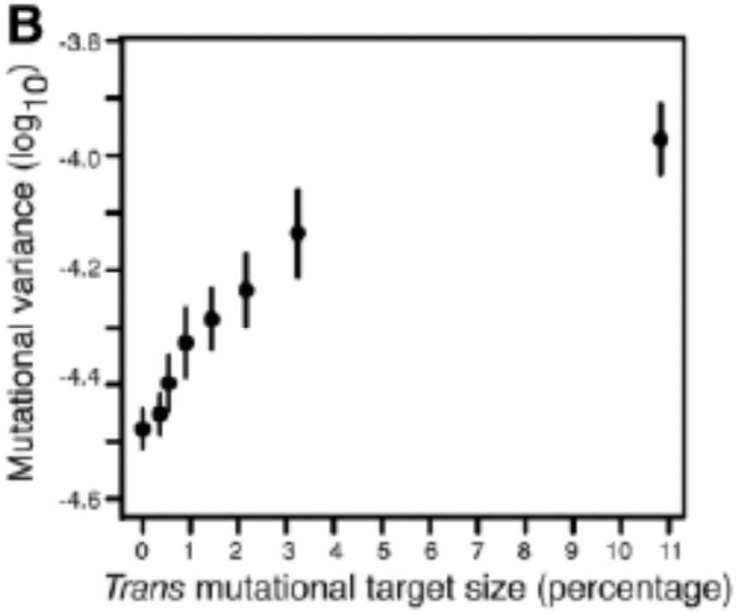


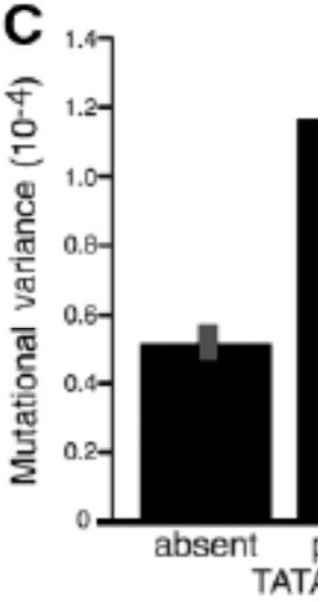


A) MA experimental design. (B) Number of genes differentially
d among the four MA lines as a function of the Bayesian pos-
obability of differential expression. Black bars indicate the es-
timated fraction of genes expected by chance. (C) Relative-fold
in expression level for genes with significant differences among
MA lines.

(A) Schematic of trans- and
ional target sizes. On the left
image are cases of smaller
target sizes, and on the right
r mutational target sizes. The
tational target size does not
lude transcription factors but
acting upstream of the focal
) Positive relationship be-
ans-mutational target size
The averages of 10 bins are
with error bars denoting two
errors. (C) Mean V_m of genes
without a TATA box in their







Genetic Properties Influencing the Evolvability of Gene Expression

Science 08

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

yeast

Vm versus plasticity ~~~ Vg –R relationship

Vm versus expression noise ~~~~ Vg-Vip relationship

Vm

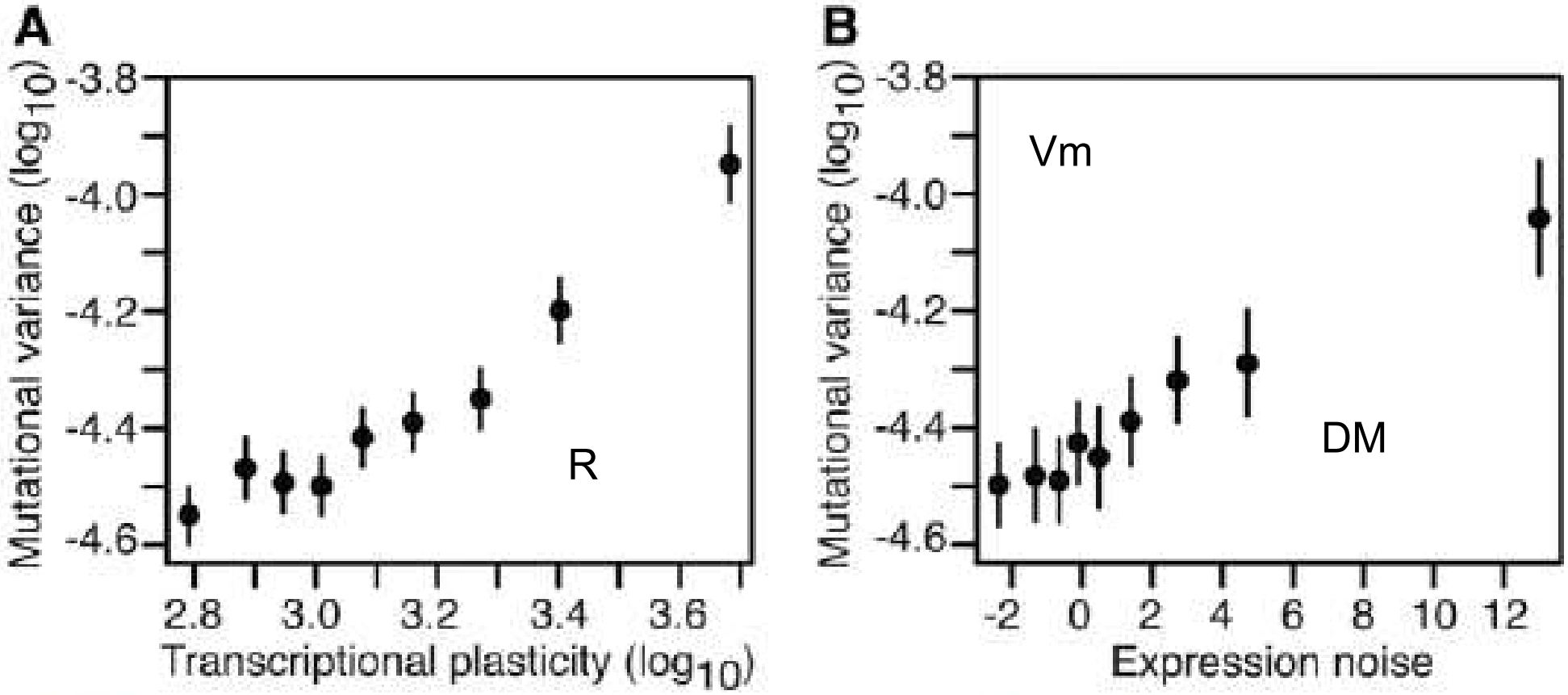


Fig. 3. Mutational variance of gene expression correlates with plasticity of transcriptional response (**A**) and stochastic noise in protein abundance (**B**). In each case, the averages of 10 bins of equal sizes are plotted, with error bars denoting two standard errors.

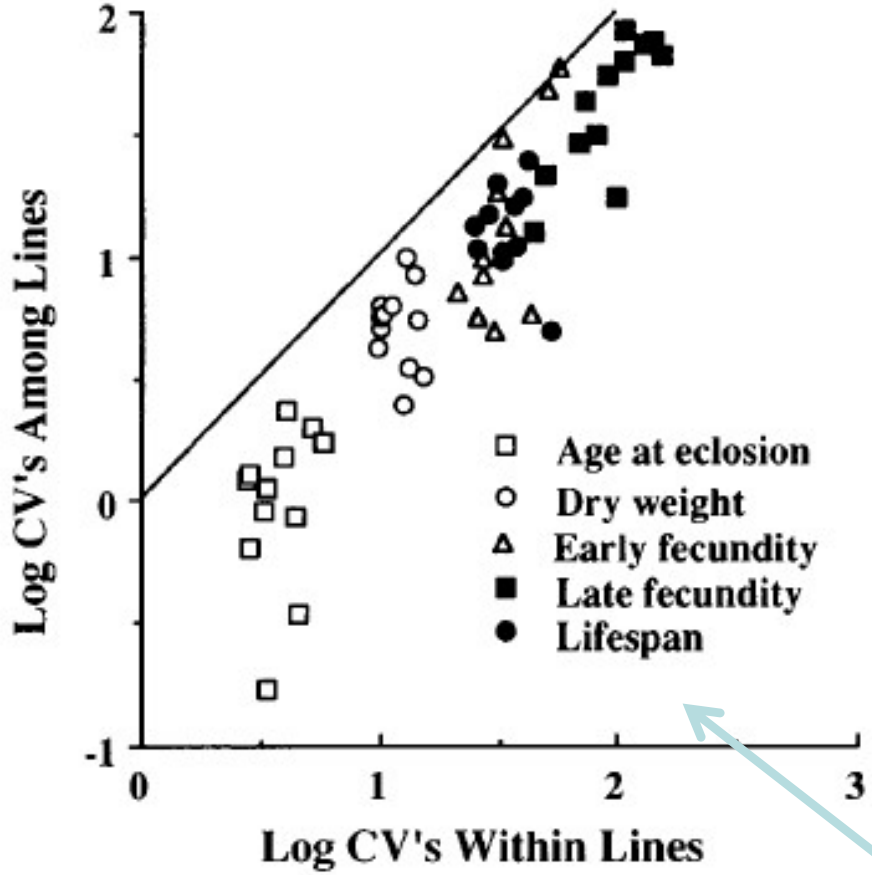
Averaged over bins

Experimental evidences
yeast gene expression
fruitfly phenotypic trait

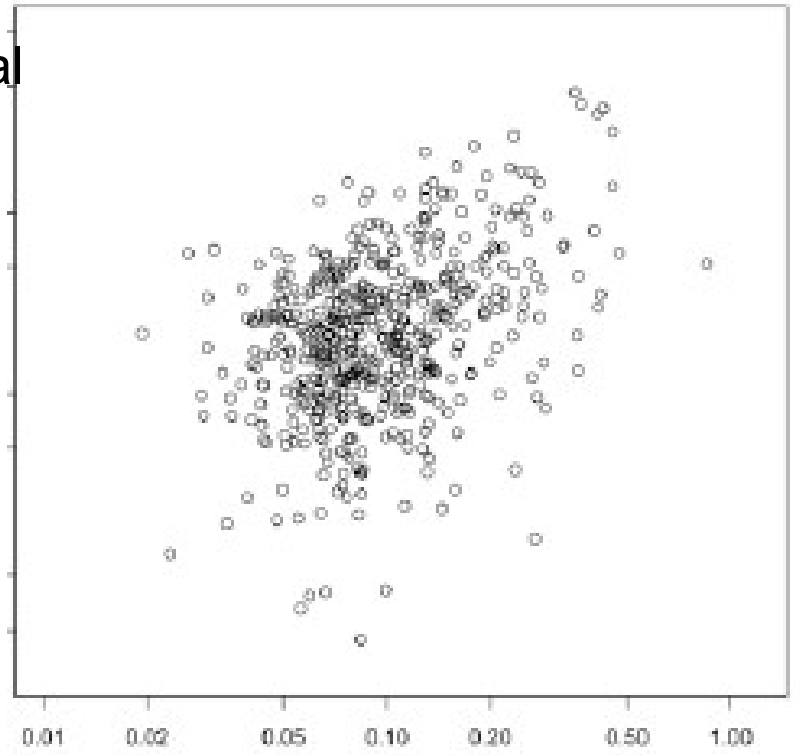
Genetic Properties Influencing the Evolvability of Gene Expression

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

Science 08



Mutational variance ~ Vg



Fluctuation

Expression Noise ~ Vip

Ben Lehner & KK 2011

e genetic (variation among lines) and environmental (variation within lines) coefficients of were very similar for each trait but not precisely the same. The line shown is where $_s = CV_{among}$

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

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

Env-Evo Fluctuation Response Relationship

Response

to environment

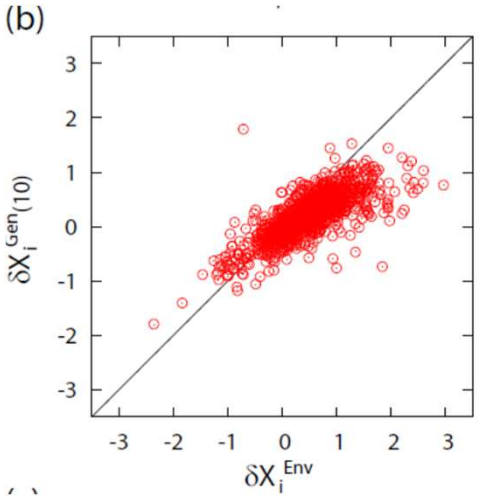
ΔlogX(i)_{Env}

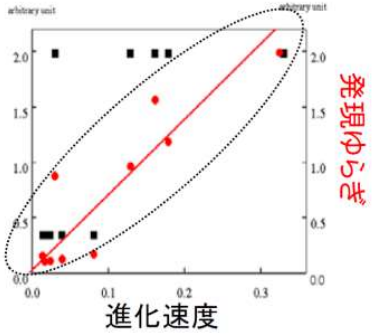
Fluctuation

Vip(i)

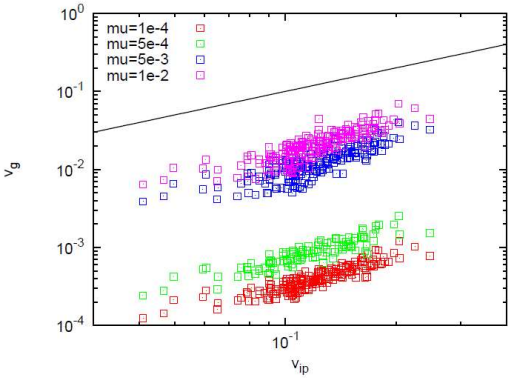
Environmental variation/ Noise

~proportional





~proportional



← **Proportion** →

Response

by evolution

ΔlogX(i)_{G}

Genetic change

Vg(i)

Why control by slow modes？

How to tame complex systems?

Few, Separated slow modes

→ control others

→ change of the modes collectively/effectively

cellular states

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

(If many degrees of the similar time scale interfere, they mutually cancel out, to hinder directional change)

Result of evolution but fosters evolvability

too many cocks spoil the broth

∗slow modes – result of evolution and fascilitate evolution → dimension reduction

Theory for such slow-mode separation?

Some support

3(space-dim) slow control modes separated??

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

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

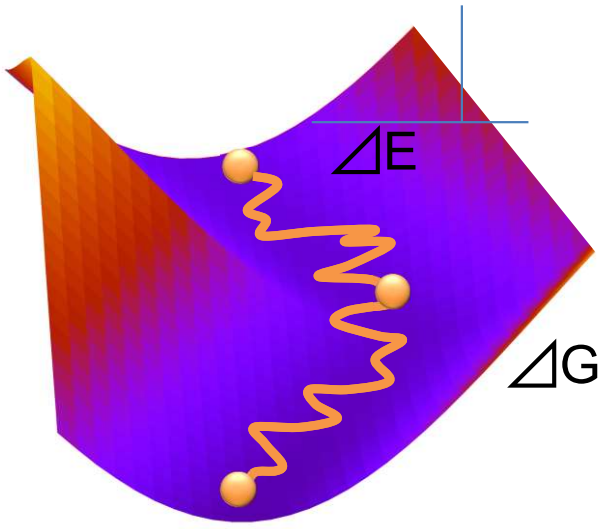
E=environment, G=Genetic (evolutionary) change

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

Macro: Potential Theory for phenotypic evolution a la thermodynamics ? → Le Chatelier Principle

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

E=environment, G=Genetic (evolutionary) change

μ determined by the low-dim mode X→μ (X(E,G))

Original state: maximum in E,G

→ Formulation a la thermodynamics

$$\frac{\Delta X_G}{\Delta X_E} = \frac{\frac{\partial X}{\partial G}\Delta G}{\frac{\partial X}{\partial E}\Delta E} = \frac{z}{z_{max}} = c \quad < 1$$

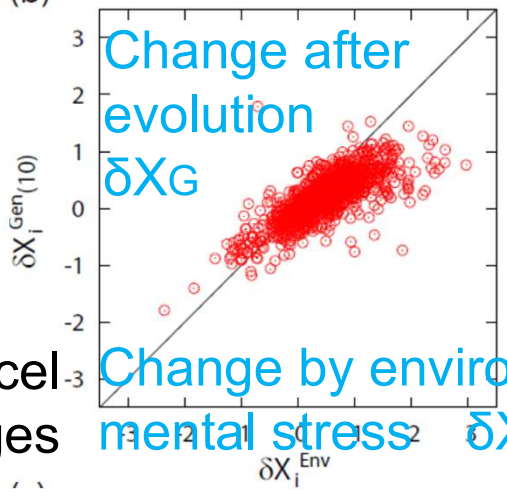
$$\frac{\partial \mu}{\partial X} = 0$$

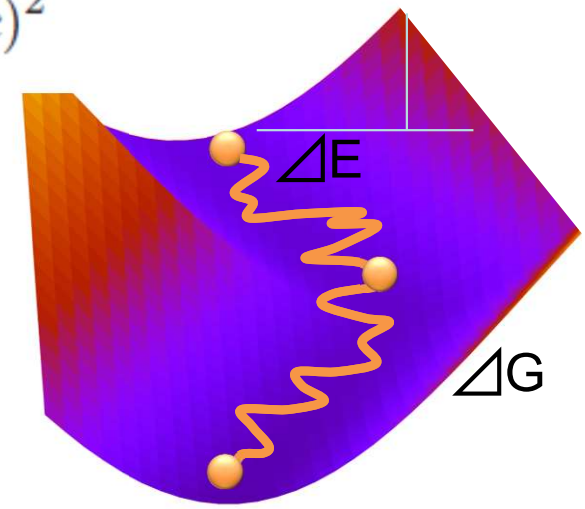
$$\Delta\mu_{EG}/\Delta\mu_E = (1-c)^2$$

$\delta X_G / \delta X_E$ < 1

→ LeChatelier Principle

Evolution occurs to the direction to cancel out the environmentally induced changes





Component Change (Model),
Gene Expression Change(Exp by Furusawa)

Need further studies to establish the present theory

(i) Further Confirmation by Experiments

(ii) Confirmation by Models/Data : Universality?

Catalytic Reaction Net-Cell Model ☑

Gene regulation Net Model (Sato, KK, submitted) ☑

Protein Model/Data (Tang KK., PRL2021) ☑

+Tang,Hatakeyama,KK 2020 Tang,KK 2021

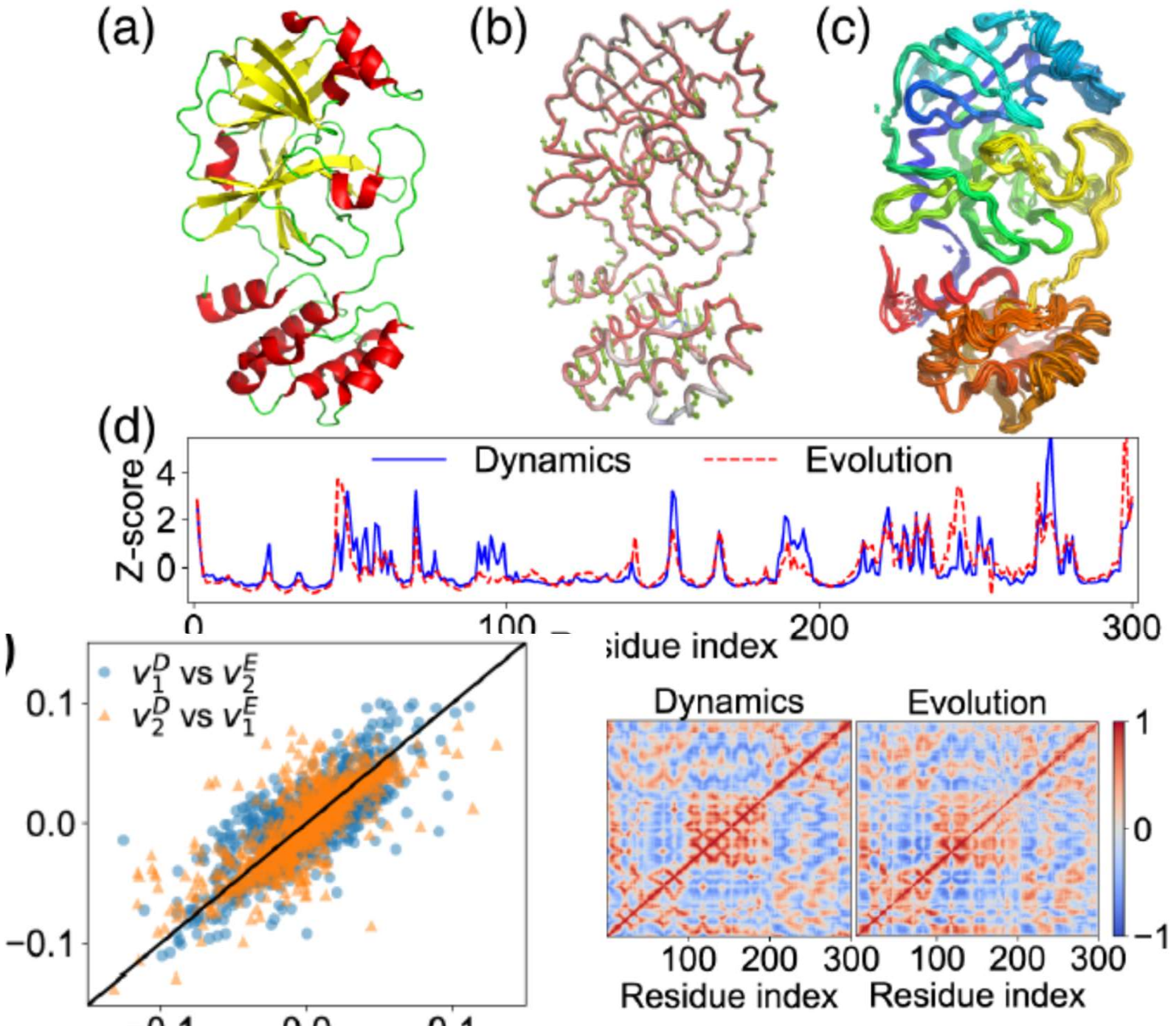
correlation in structure dynamics & evolutionary dim reduction

Spin-glass Models (Sakata KK., PRL 2020) ☑

evolve spin Hamiltonian JijSiSj to achieve certain configuration

dimensional reduction at replica symmetric phase

Protein; Change in Native structure by noise & by evolution — highly correlated in common low-(~10) dimensional structure



fluctuation according to structural data+ elastic net model vs

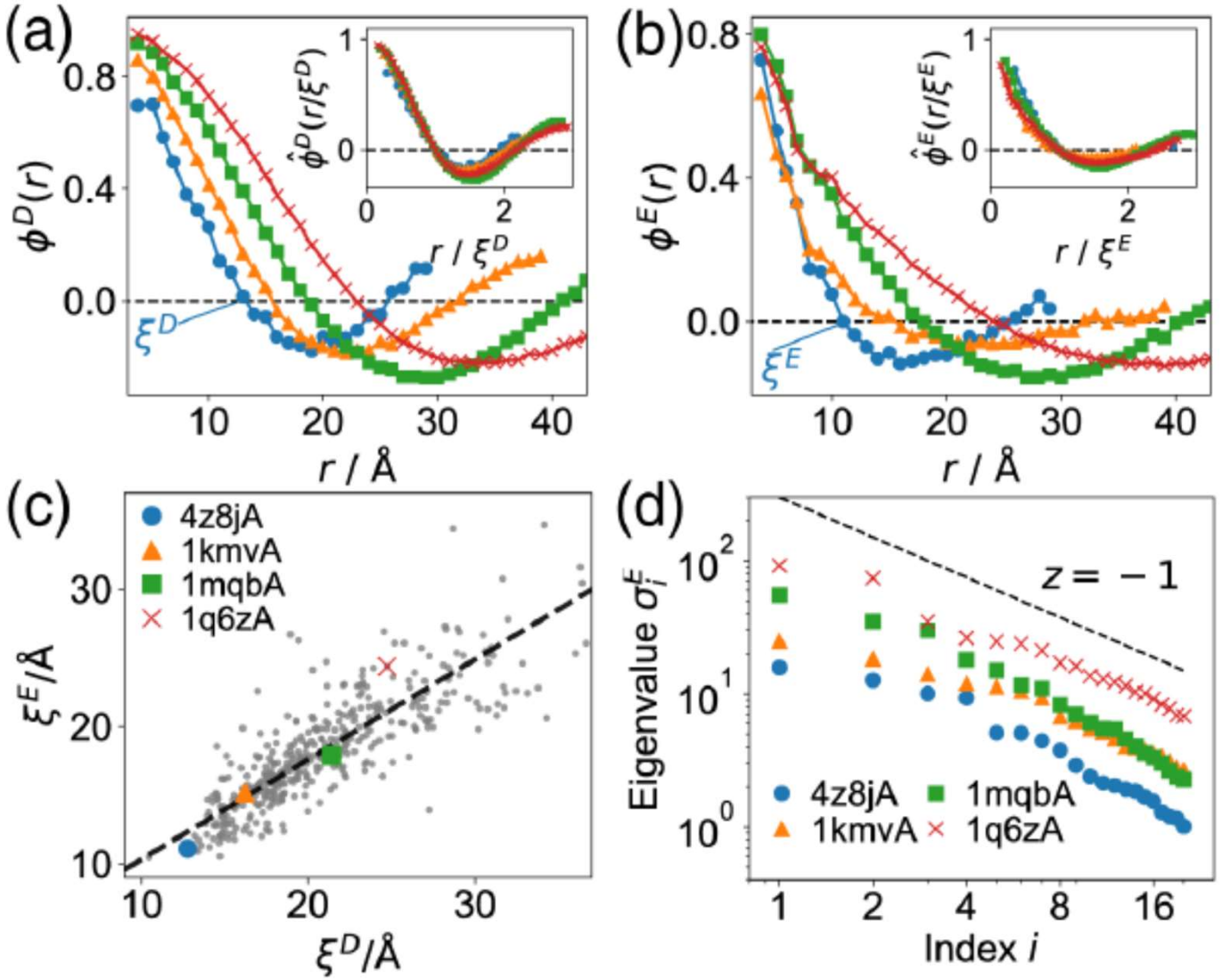
Difference within family (mutational change)

Changes are lo-dim, and correlated

Tang,KK
PRL2021

Correlation function

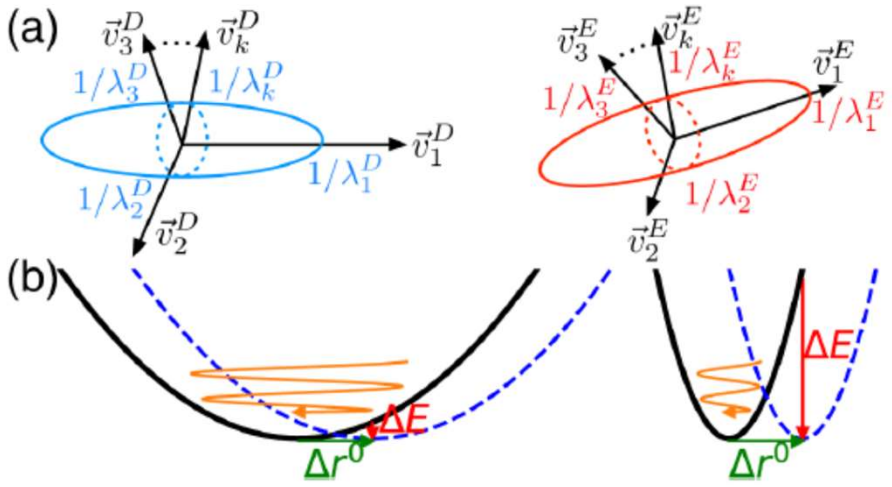
Dynamics, Evolution Similar correlation functiorn, correlation length ξEvo ξDyn correlated



Tang,KK
PRL
2021

$$E(\vec{x};\vec{\theta}) = \frac{\gamma}{2}\left[\vec{r}(\vec{x}) - \vec{r^0}(\vec{\theta})\right]^\intercal \cdot H \cdot \left[\vec{r}(\vec{x}) - \vec{r^0}(\vec{\theta})\right],$$

$$H_{ij} = \frac{\partial^2 E}{\partial r_i \partial r_j} \qquad F_{ij} = \frac{\partial^2 E}{\partial r_i^0 \partial r_j^0}$$



tries $J_{ij} = \partial r_i^0 / \partial \theta_j$, according to the chai

$$F_{ij}^{\vec{\theta}} = \frac{\partial^2 E}{\partial \theta_i \partial \theta_j} = \frac{\partial r_j^0}{\partial \theta_i} \frac{\partial^2 E}{\partial r_i^0 \partial r_j^0} \frac{\partial r_i^0}{\partial \theta_j} = (J^\intercal F J)_{ij}.$$

$$F^{\vec{\theta}} = J^\intercal F J = J^\intercal H J.$$

Spin-Statistical Model

Sakata,KK,PRL 2020

Phenotype=Spin config.Si Genotype－Interaction Jij

Hamiltonian H=-ΣJijSiSj

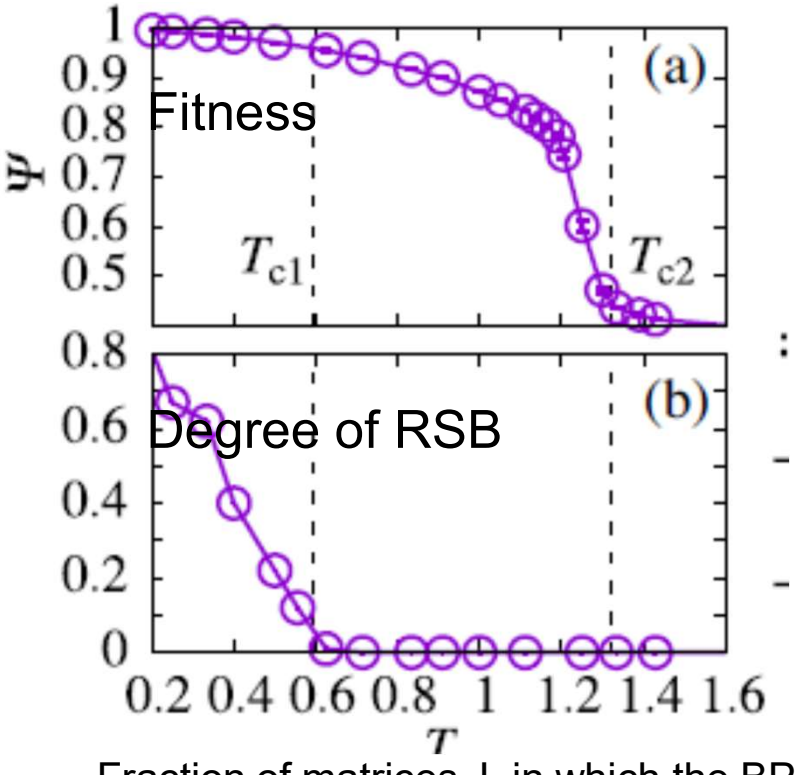
Fitness align target spins; environment– external field

$$\psi(\boldsymbol{J}) = \overline{|m_{\mathcal{T}}|}, \qquad m_{\mathcal{T}} = \frac{1}{N_T}\sum_{i\in\mathcal{T}} S_i,$$

1) Robust fitted state at Replica Symmetric phase

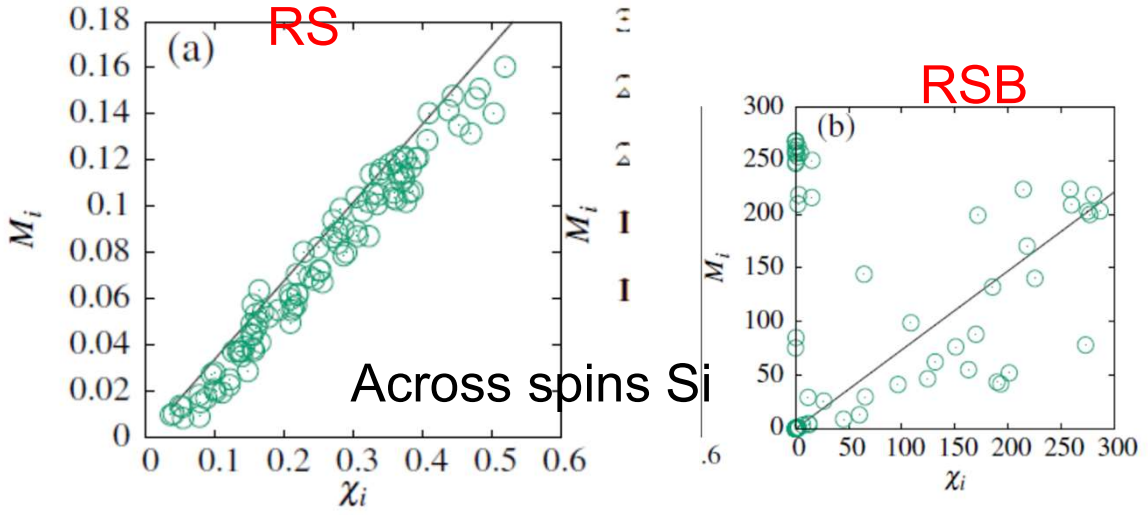
2) RSB → loss of robustness

(cf Sakata,Hukushima,KK PRL 2009)



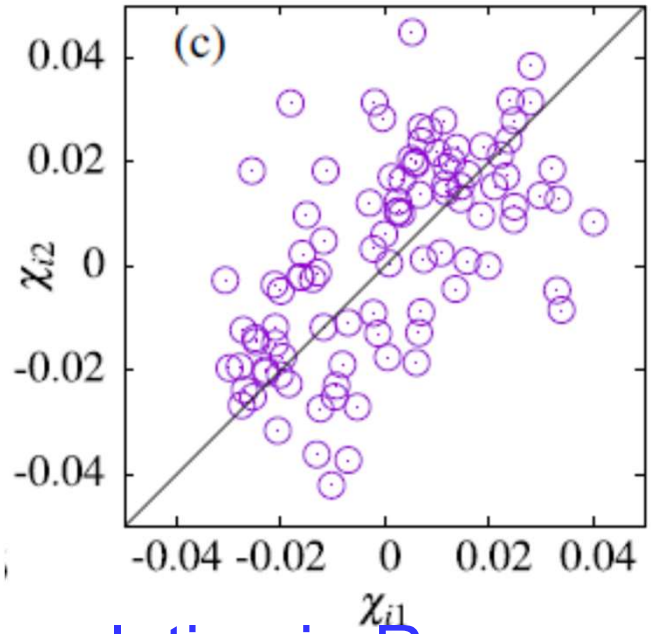
Fraction of matrices J in which the RS

Correlation in Responses to ext field and to mutation to Jij

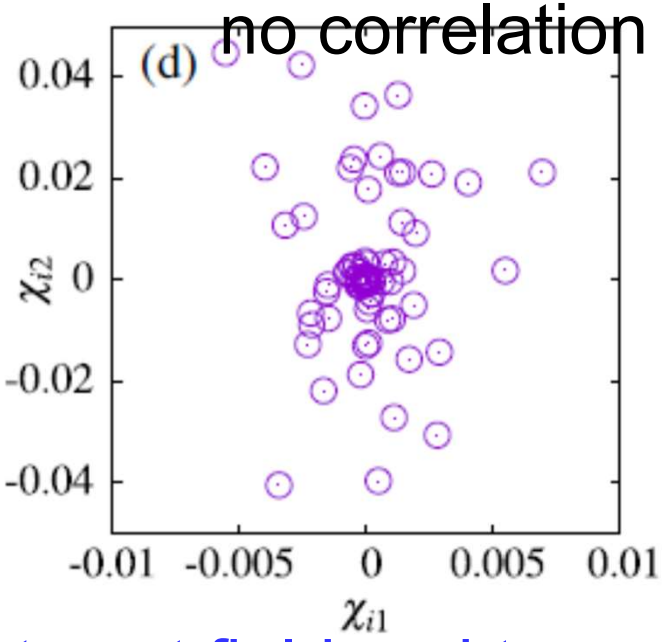


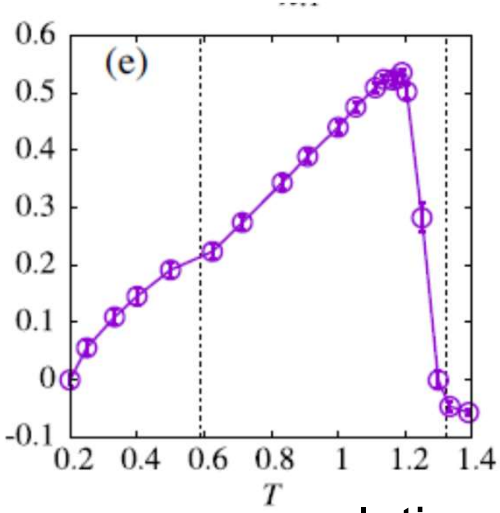
Correlation in Responses to different external fields (environment)

Mid temp (RS) high :



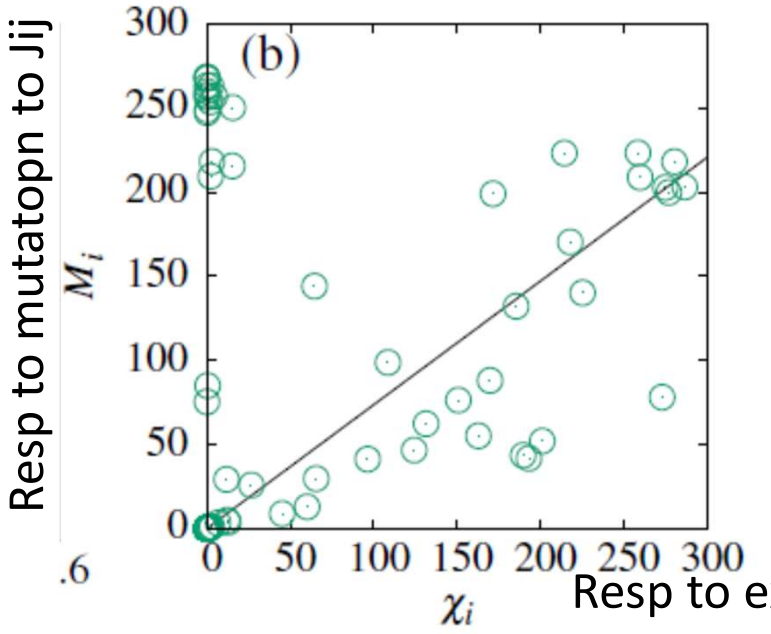
Low temp (RSB)
no correlation



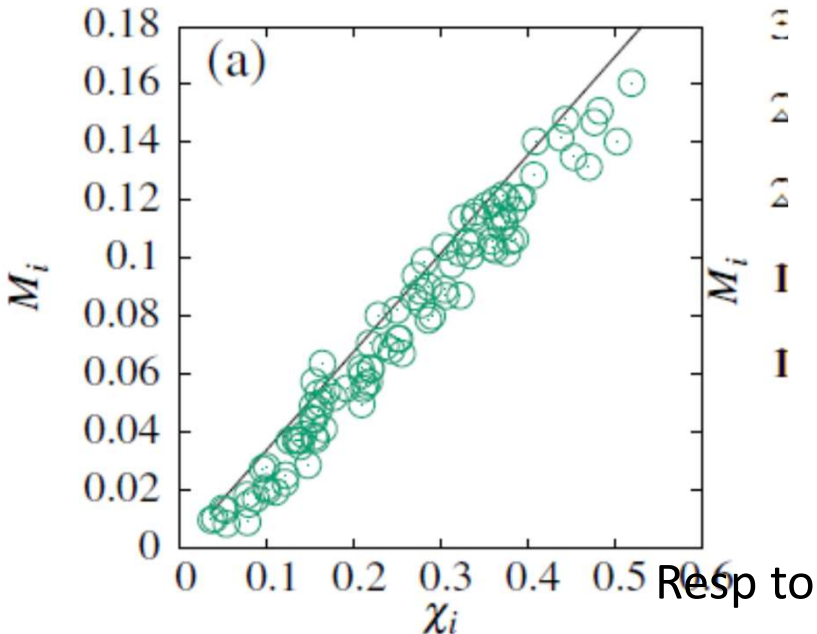


average correlation coefficients between χ_{ij} χ_{ik} .

Correlation in Responses to ext field and to mutation to Jij



Resp to ext field



Resp to ext field

dimensional reduction: rank reduction

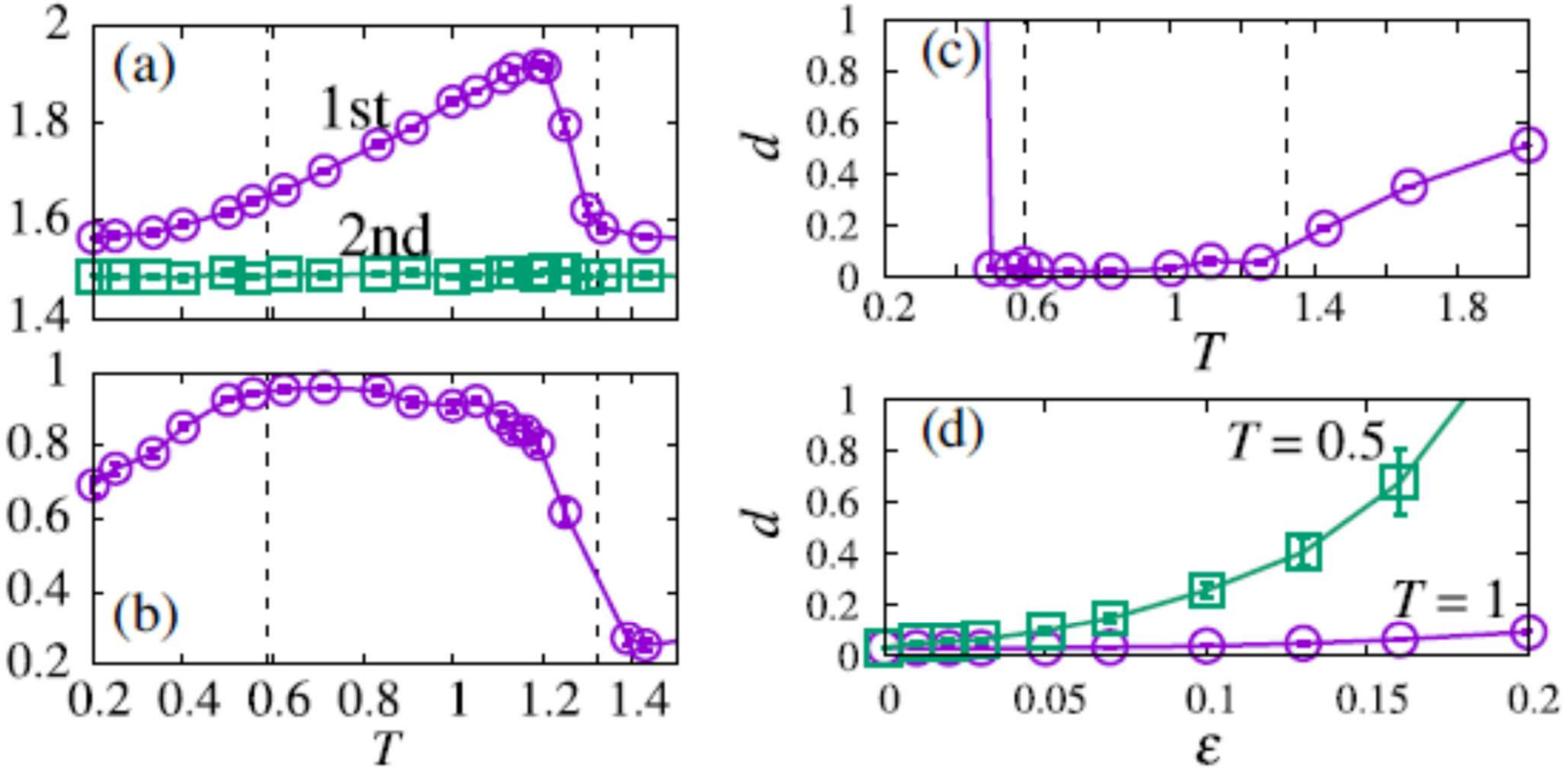


FIG. 3. T dependence of (a) averaged first and second eigenvalues of $\boldsymbol{J}$, (b) correlation coefficient between $\operatorname{arc\,tanh}(\mu_i)$ and ξ_i^{I}, and (c) averaged d. Vertical dashed line denotes transition temperatures. (d) ϵ dependence of d for $T = 1$ (RS) and $T = 0.5$ (RSB).

(iii) Theory for dimensional reduction? –1 or few dim?

(a)Eigenvalue Spectra ; few outliers (close to zero) from others ← evolution Sato,KK 2020

Slow collective modes as 'Epi-gene'

random matrix+ outliers(low-rank)? Cf Terrence Tao

'Control by Slow Variables' (Kohsokabe,KK, JEZB2022

Reasonable to tame complex systems (robustness+plasticity)

But so far hand-waiving argument

(b) RS vs RSB transition (Sakata,Hukushima, KK 2009,2020)

dual replica theory, Pham, KK 2022

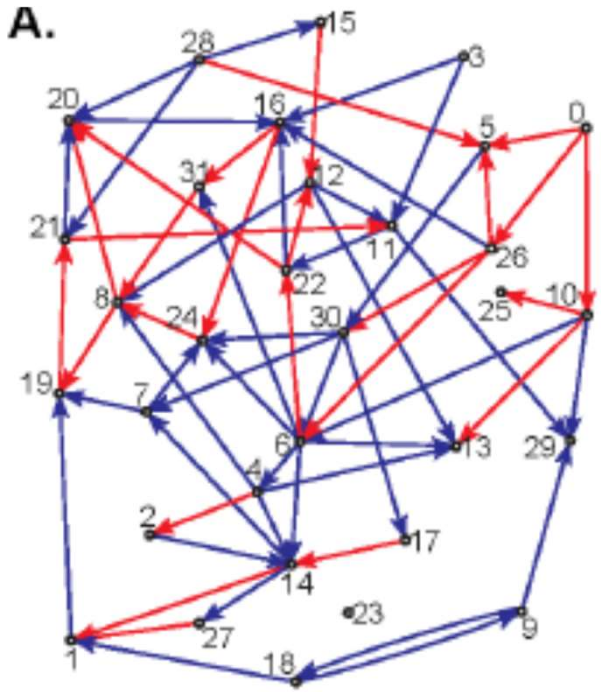
Need theory to explain universality??

Renormalization Group?

Deep Learning (Neural Tangent Kernel)?

Standard Stat Mech (Projection)? …. ???

Gene expression dynamics model::



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

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

Activation
Repression
…=1,-1,0

Gaussian white Noise σ δij $<\eta_i(t)\eta_j(t')> = \delta(t-t')$.

I: Input (environment) Jij ← gene
M;total number of genes, k : output genes→fitness

1)Evolutionary Dimensional Reduction ☑
2)Under different conditions → prediction of cross fitness

Extension: (i)two types of stresses (antibiotics)

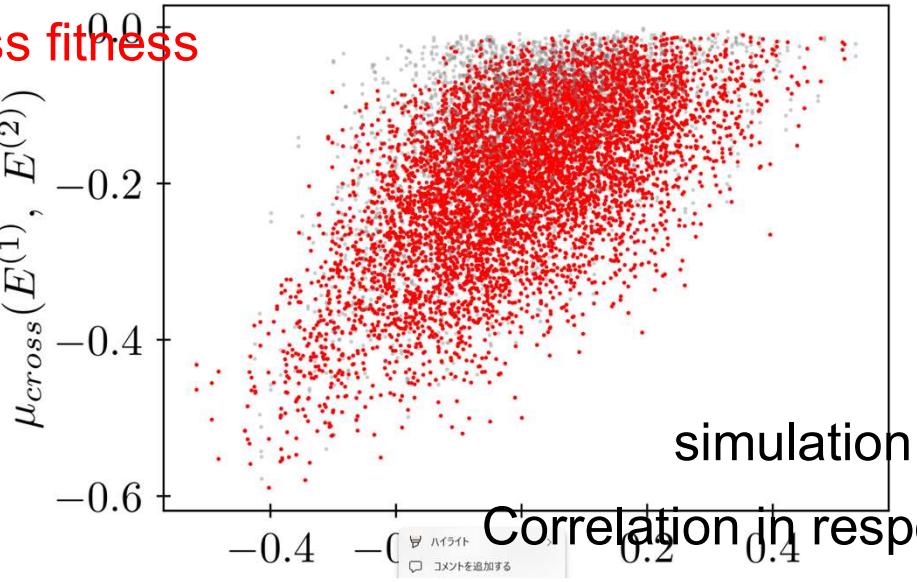
→ Prediction of Cross Fitness： Sato,Furusawa KK, submitted

→ fitness change under the stress E2,

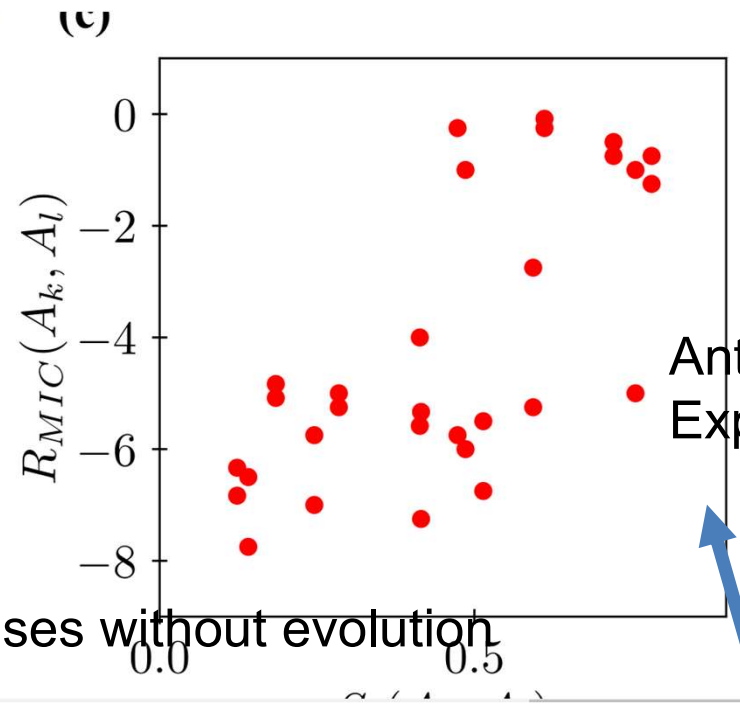
for those evolved under stress E1 are correlation in responses against E1 and E2 in prior to evolution

←With dimensional reduction, environmental response evolution across different environmental stresses are predicted only by the environmental respor

Cross fitness



simulation



Antibiotics Experiments

Correlation in responses without evolution

Bacteria evolved against one antibiotics E1: strong/weak against other AB E2?
Predictable before evolution (from the correlation in the transcriptome response to each)?

(ii)Diploid, sexual reproduction

Okubo,KK;2022PNAS Nexus

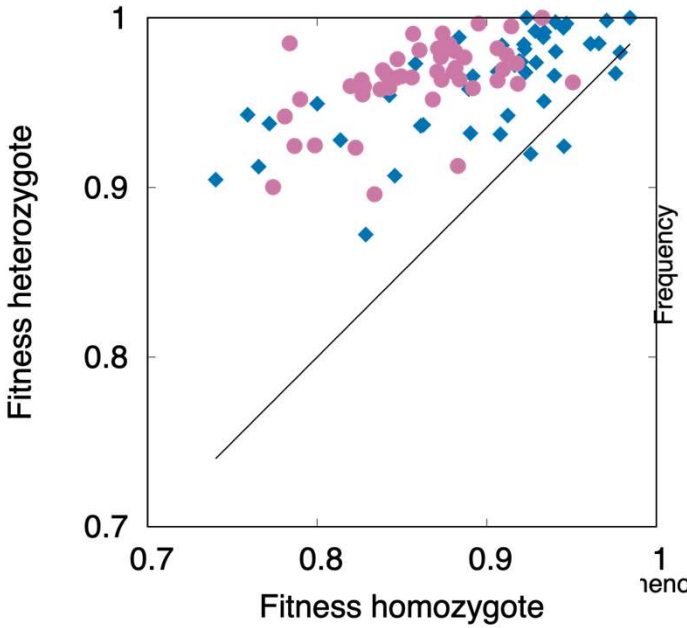
2-Gene-regulation network model

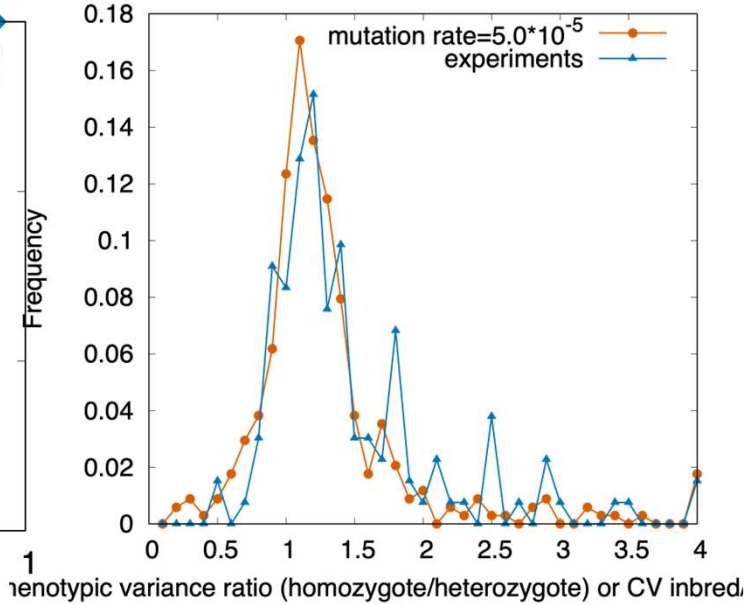
$$x_i(t+1) = f[\sum_{j=1}^{N} J_{ij}^{1}(x_j(t)-\theta)/2] + f[\sum_{j=1}^{N} J_{ij}^{2}(x_j(t)-\theta)/2] - x$$

1)Collective Mendelian Dominance for gene set

2) Heterosis – hybrid vigor + lower phenotypic variance for hybrid

Due to Evolution of Robustness + Dimensional Reduction?





Variance(homo)/Variance(hetero

Summary; Deep Linearity is a result of evolutionary robustness, description by few marcoscopic variables a la thermodynamics

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!Surprising Description of Universal Biology in the Novel by Sakyo Komatsu (1968)

……..In an organism, extracted basic elements (such as metabolism or genetin information) shape a system that balance each other in an organism. Each element can vary to some degree, but due to this balance, the variation is restricted. Then with rough approximation, the variation of these elements (such as cell-density, mass, cell-differentiation) are given depending on the environment. By further analysis, the basic model of evolved life is approximately given by a linear model.