Universal Biology in Adaptation and Evolution: Multilevel Consistency, Dimension Reduction, and Fluctuation-Response

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Universal Biology

Life system as a universality class in nature

→

Phenomenological theory (a la thermodynamics)

→ general characteristics, universal laws

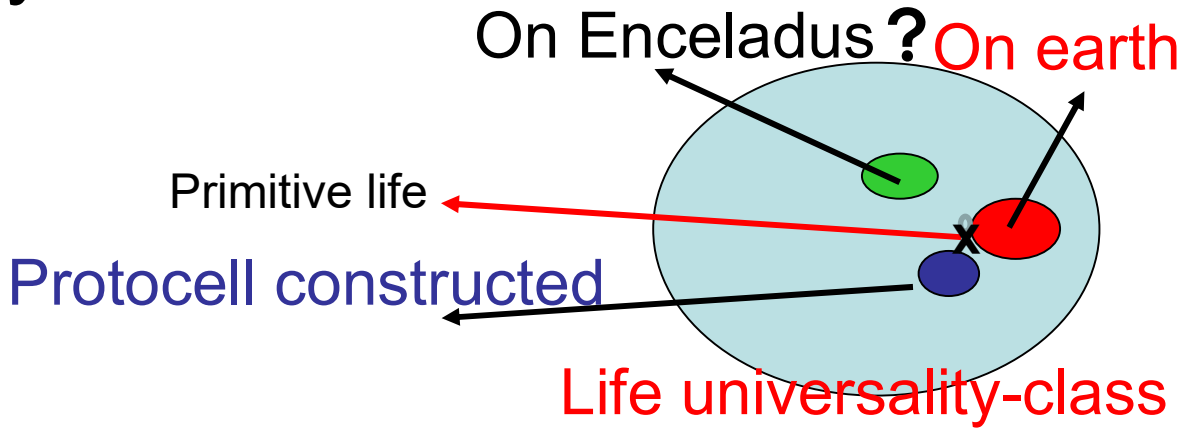
＊Biology not restricted to those that happen to be evolved on earth

(coined originally by SF writer

小松左京

(Komatsu Sakyo）

at 1972



Universal Biology – proposed? 1968 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)

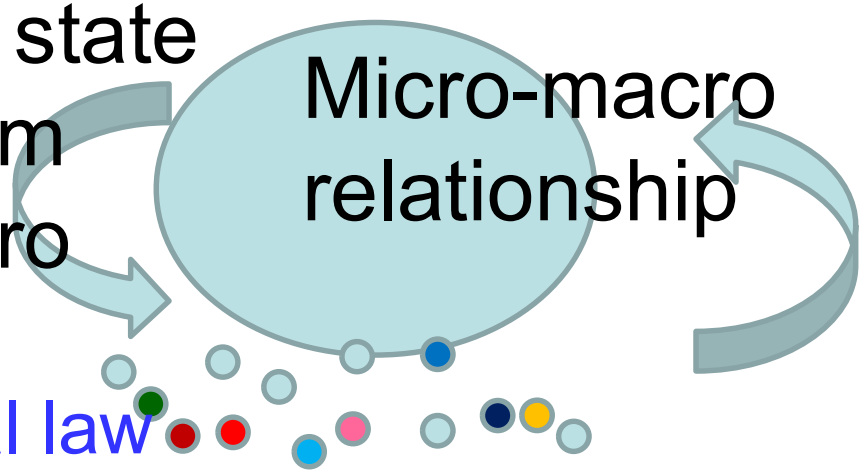
  macro – unit to sustain/ reproduce as a whole

(*low-dimensional description*?)

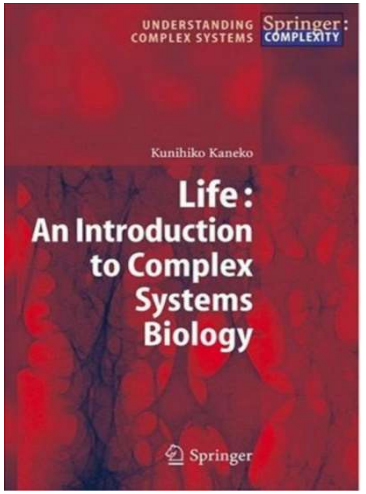
molecule – cell, cell–tissue etc.

Steady (growth) state

Constraint from macro to micro



Universal statistical law



Complex-systems Biology

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,KK etal, PRX2015)

(2)Adaptation → universal adaptation laws (Kashiwagi et al Plos One2005; Furusawa, KK Phys RevE2018)

(3) Differentiation: **Cell 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,Furusawa,KK,Interface2015,PRE 2018)

Part I: Consistency (with robustness) between molecule and cell levels :

→ Dimension Reduction in phenotypic dynamics by adaptation & evolution

→ Law in Adaptation and Evolution

Response Theory

Part II: Evolutionary Fluctuation-Response Relationship

→Pheno Variance by noise ∝that by mutation

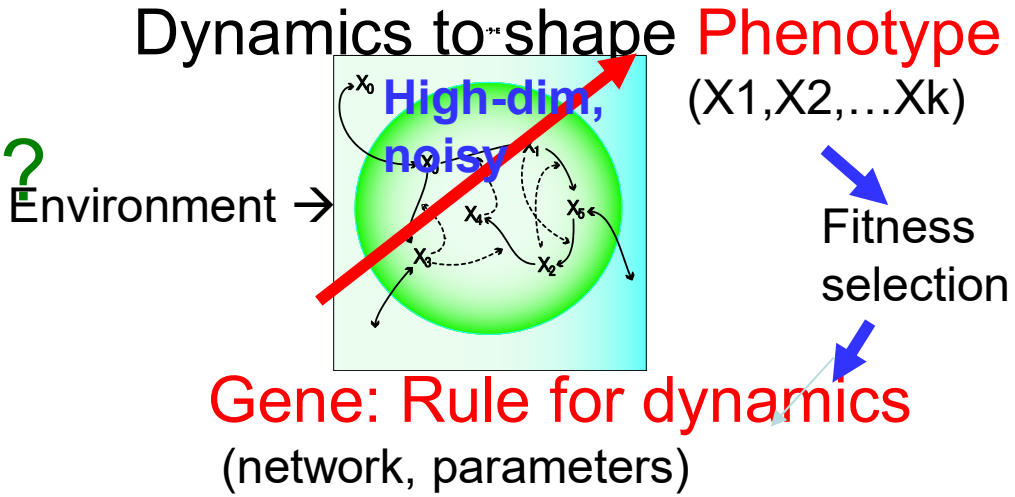
∝ evolution speed

Phenotypic Evolution is directed, constrained even before genetic change

- 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

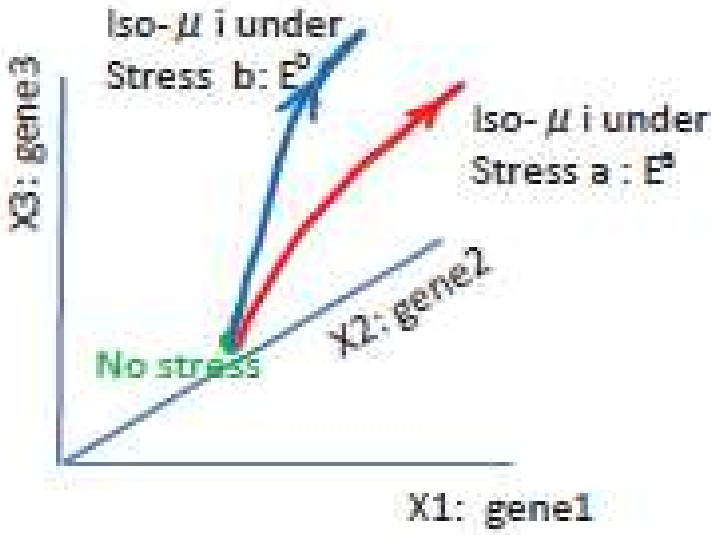
Trivial(?) Law in Adaptation: Focus on steady-growth cells → universal constraint

all the components have to be roughly doubled 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) ~ $(10^3 \sim 10^4)$ measurable by microarray

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

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

Temporal change of concentration x (Any reaction dynamics)

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

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

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

Trivial so far

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}.

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

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

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

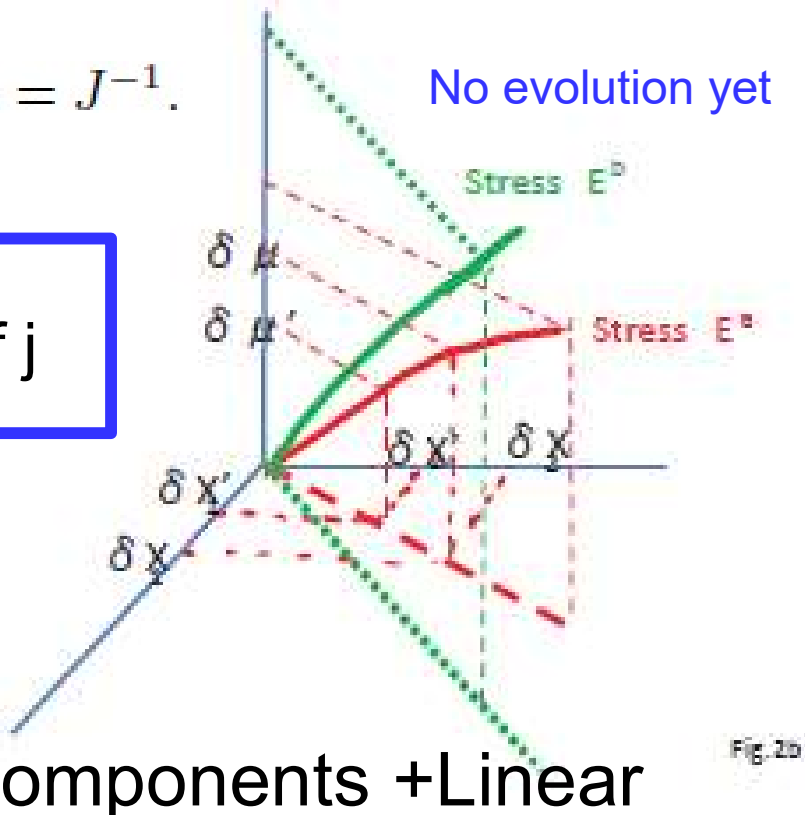


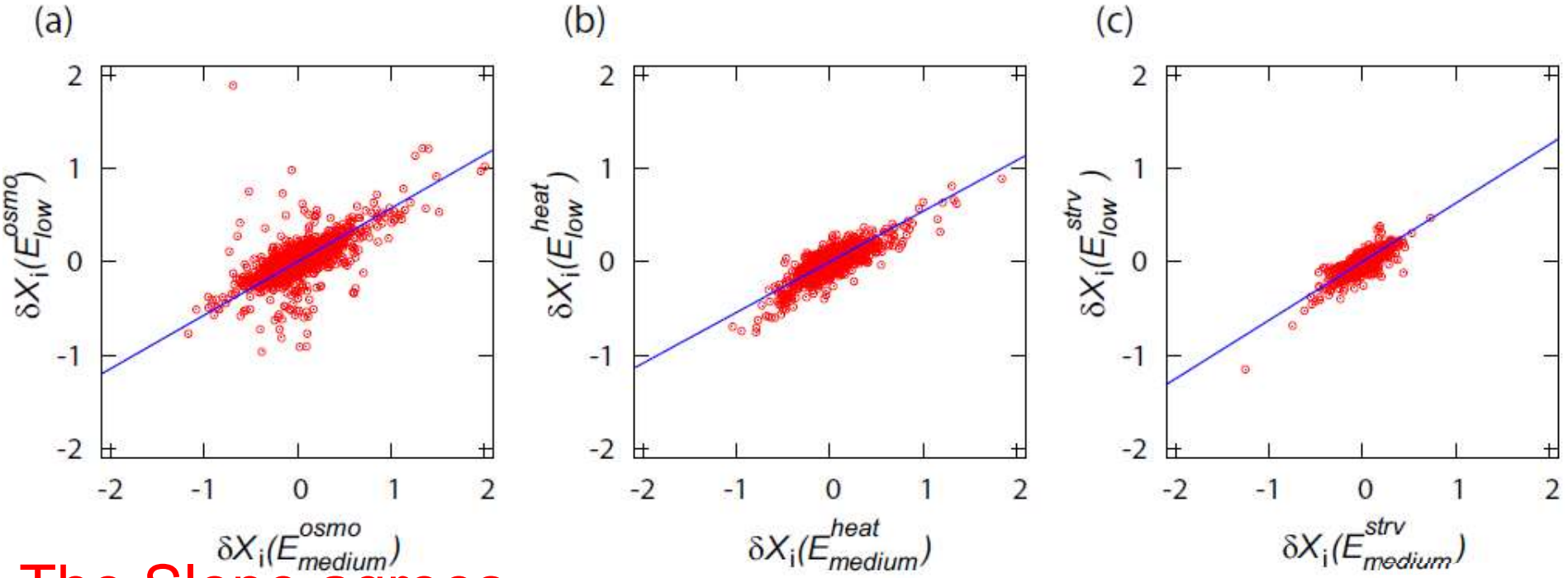
Fig. 2b

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

←Steady-growth sustaining all components +Linear

Put E Coli under different strength of stress conditions; Measure gene expressions

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

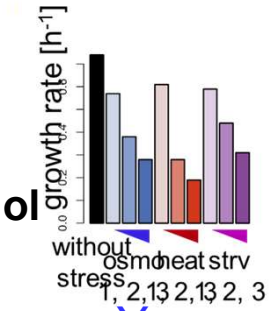


The Slope agrees with the growth rate change δμ'/δμ

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)

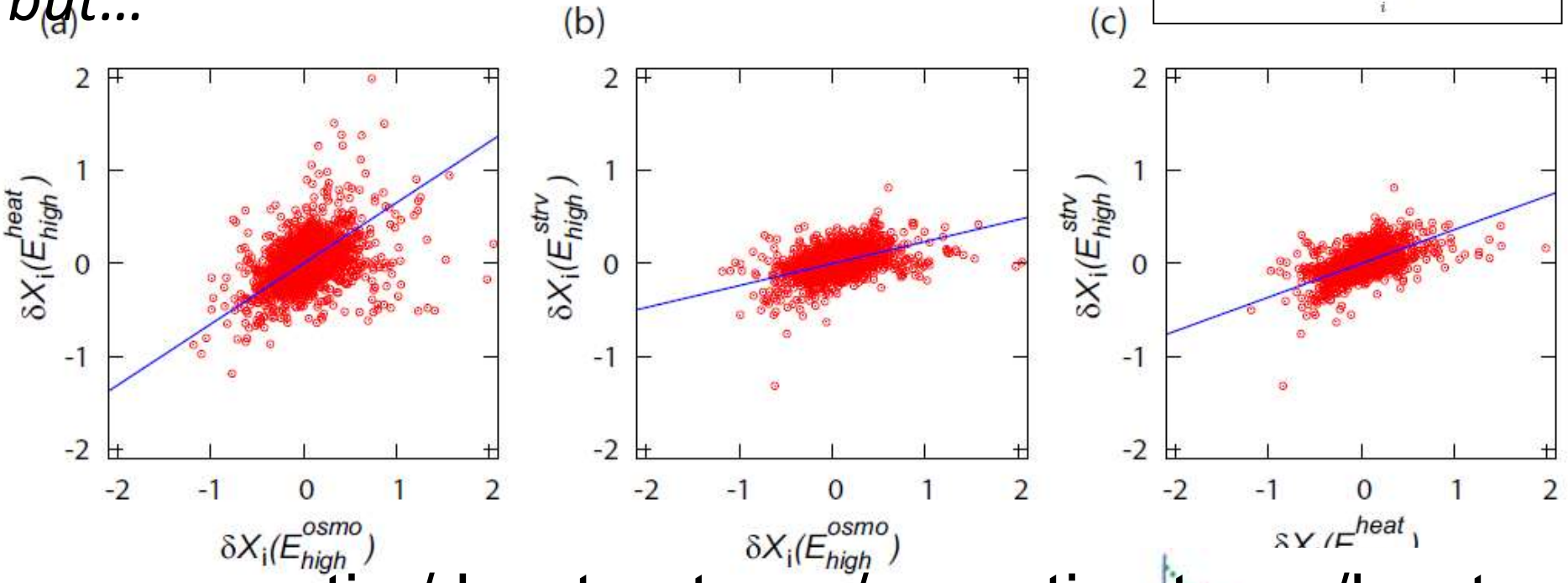
Linearization works for too(?) broad regime

Across Different types of stresses:

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

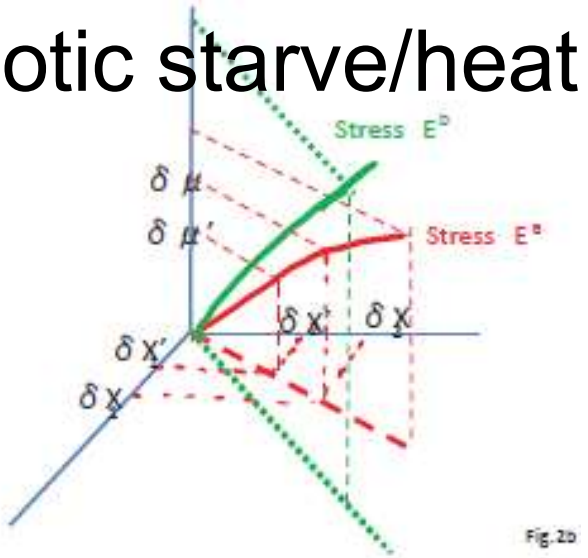
γi(*a*) depends on type *a* *so correlation not expected, but…*

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



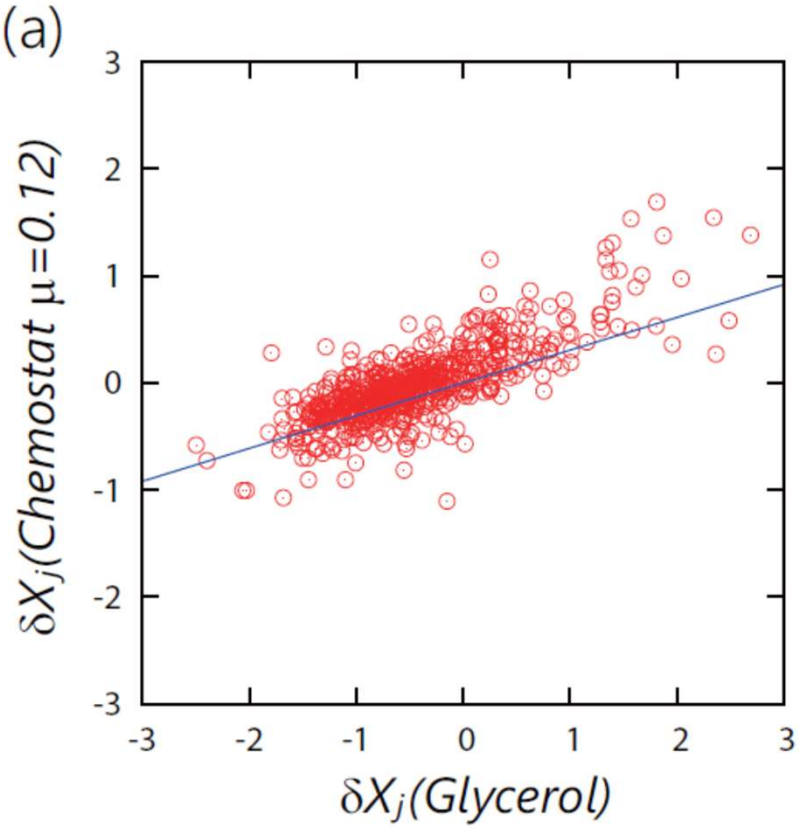
osmotic / heat starve/osmotic starve/heat

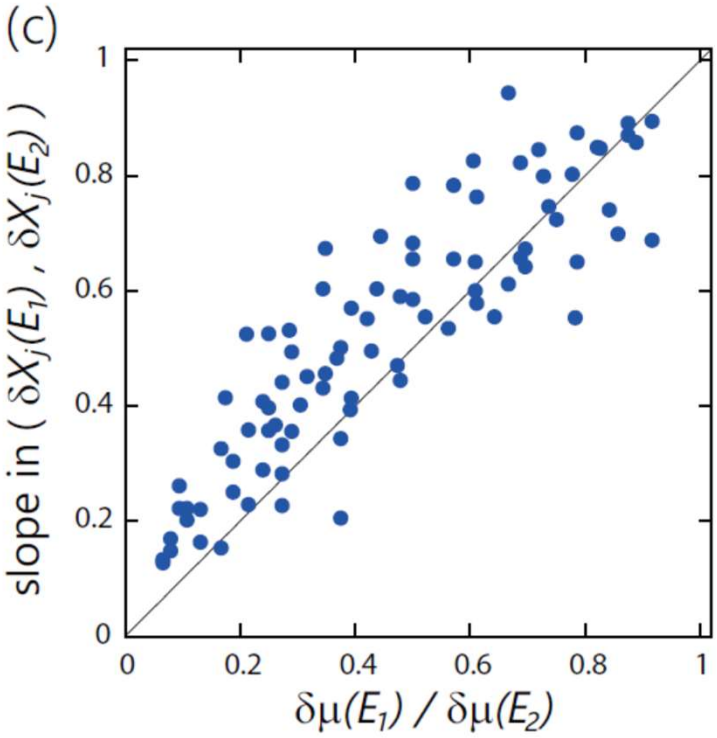
Still highly correlated



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

Non-trivial point: Emergent macroscopic Linearity

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

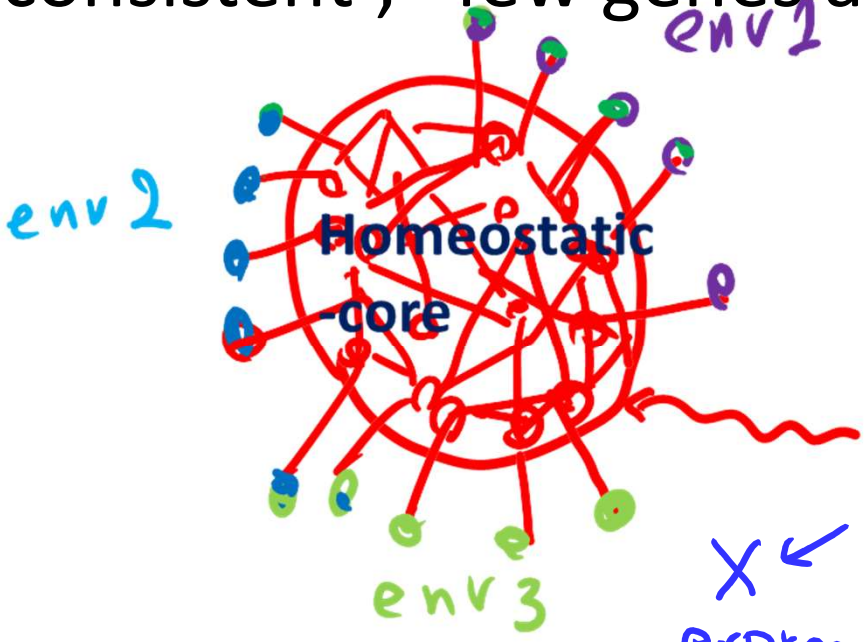
achieved in an evolved system ?

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

- 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

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

α : Environment

Examine by Toy Cell Model with Catalytic Reaction Network

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

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

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

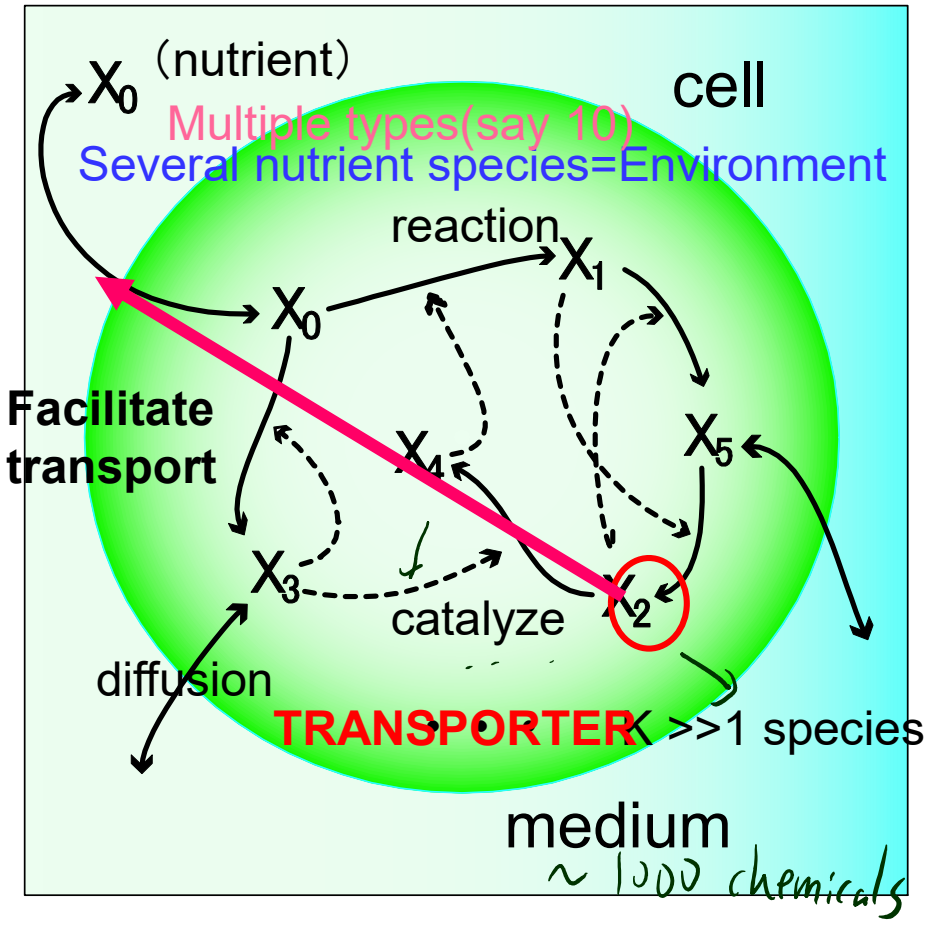
- random catalytic reaction network

with the path rate p

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

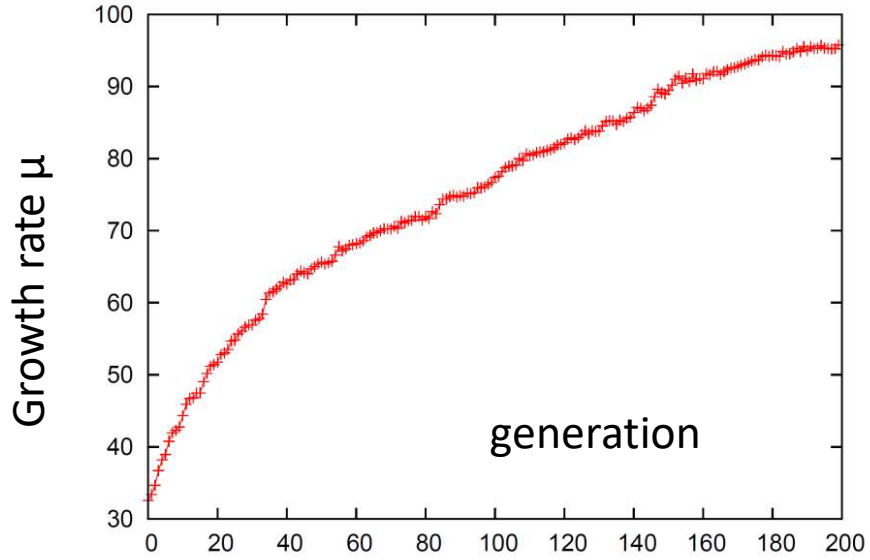
- **Resource chemicals (<- environment) are transported with the aid of a given catalyst, transporter**
- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth.
- $N = \Sigma n_i$ exceeds N_{max} (model 1)
- Genotype: Network;
- Fitness: e.g., abundances of given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

model



dX1/dt ∝ 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 e.g., (e0,e0,,,e0)

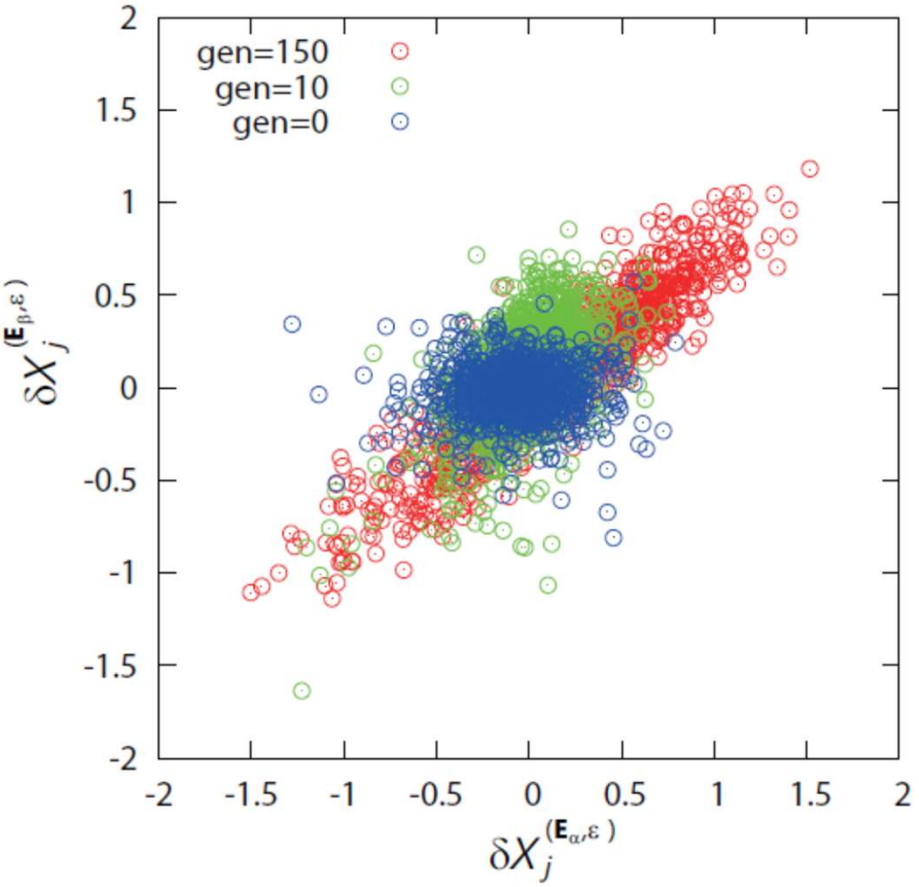
Then put an environment

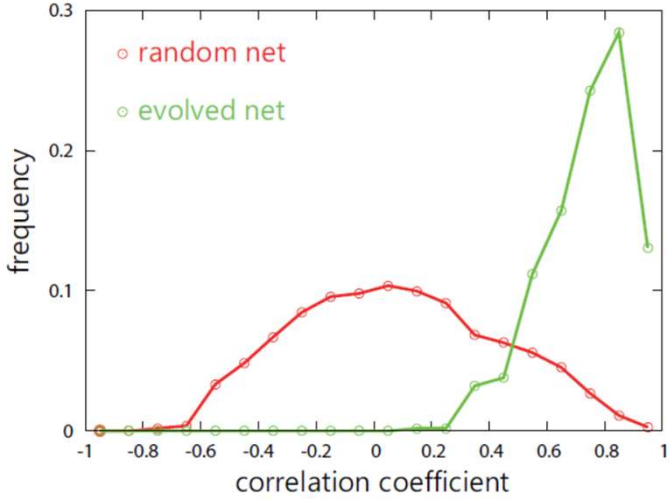
Env = λ (e1,e2,e3,..e10) + (1-λ) (e0,e0,…, e0)

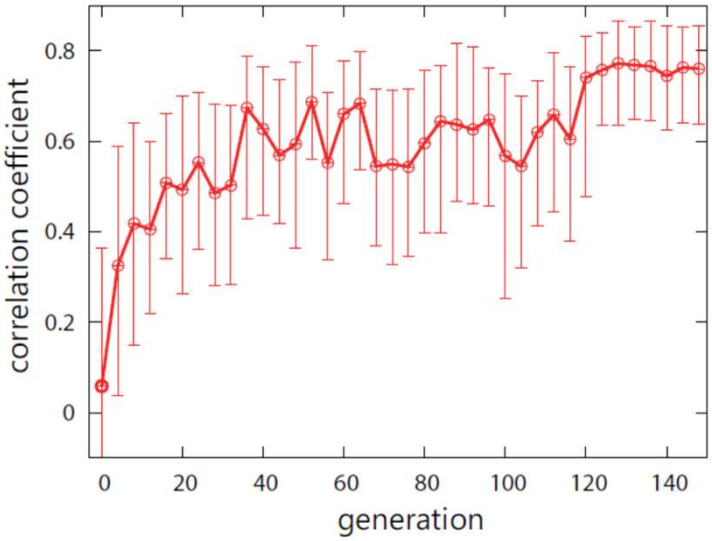
-1< e1,e2,… <1 (randomly chosen)

Check the change in concentrations and growth rates against λ

Evolution shapes Global Proportionality across different environmental conditions



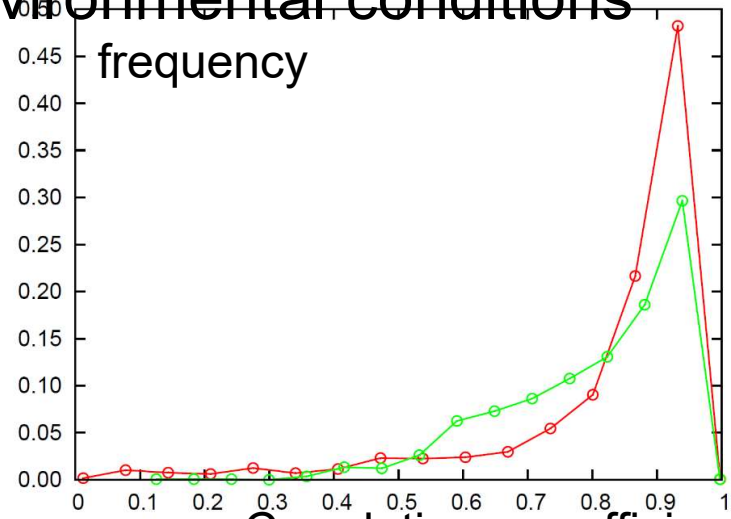




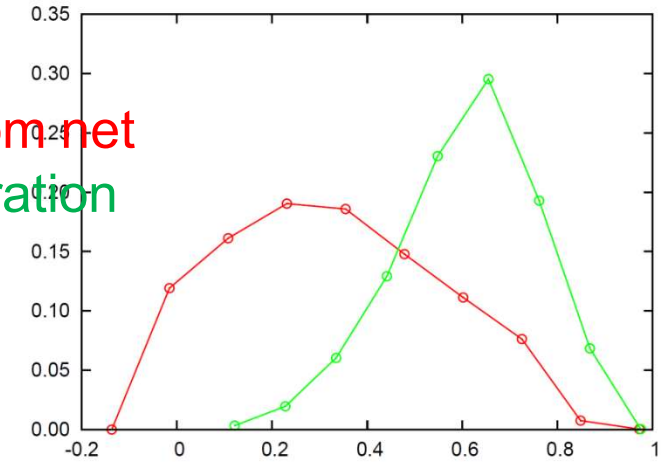
Furusawa, KK, Phys.Rev E 2018
KK, Furusawa, Ann Rev Biophys 2018

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

Between same environmental conditions

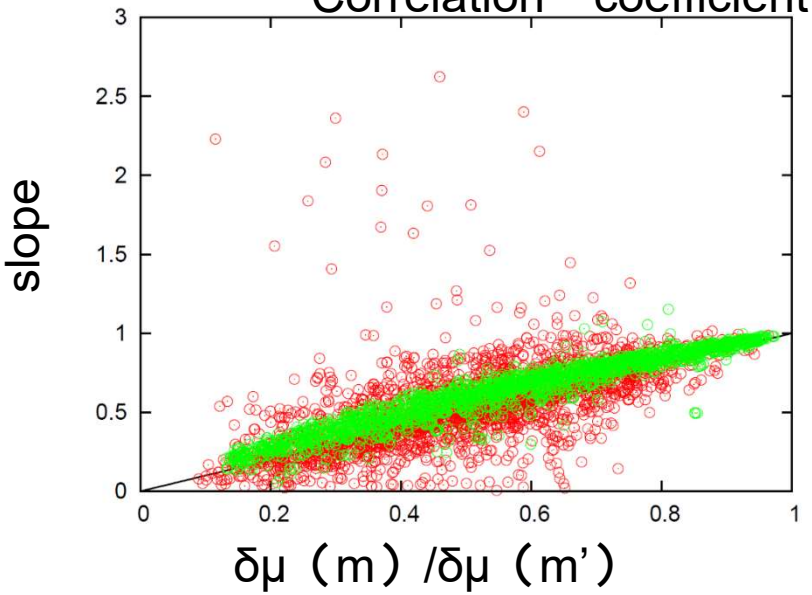


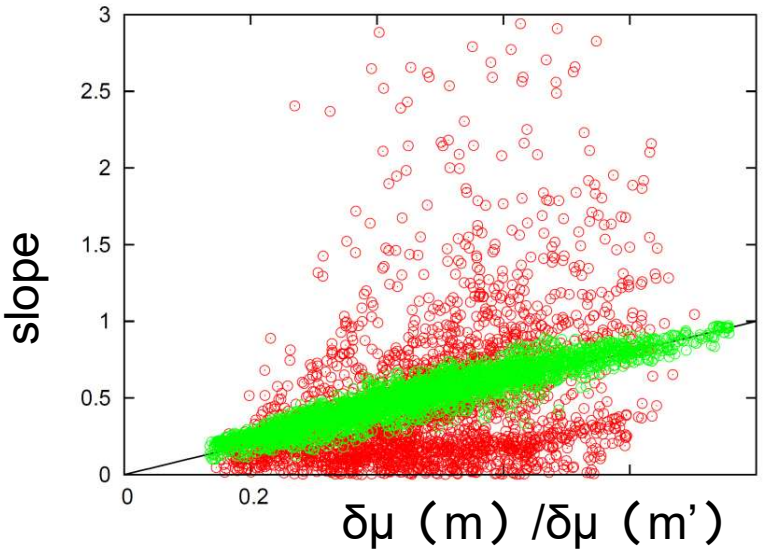
Across different env conditions



random-net generation =150

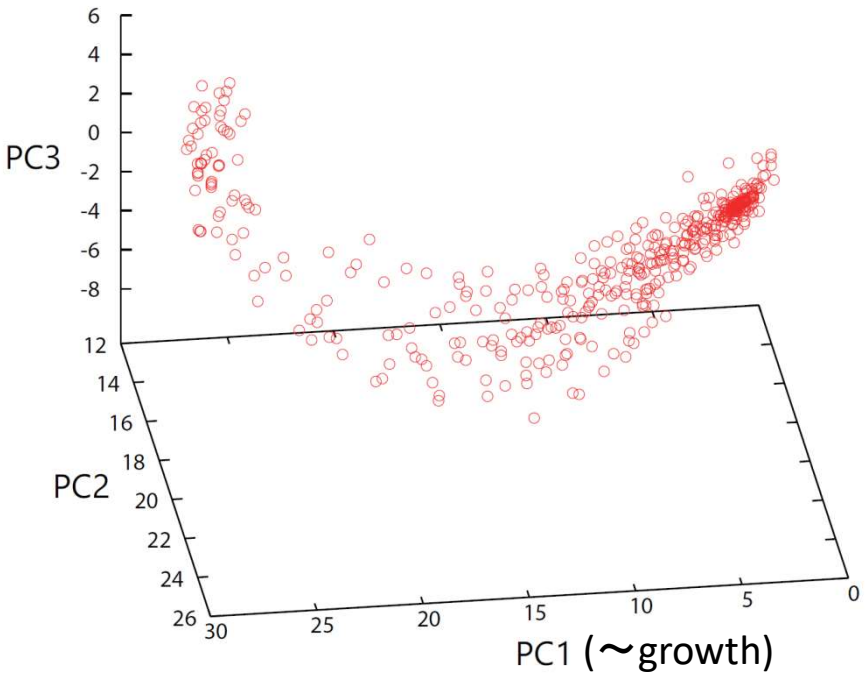
Correlation coefficient across component concentrations



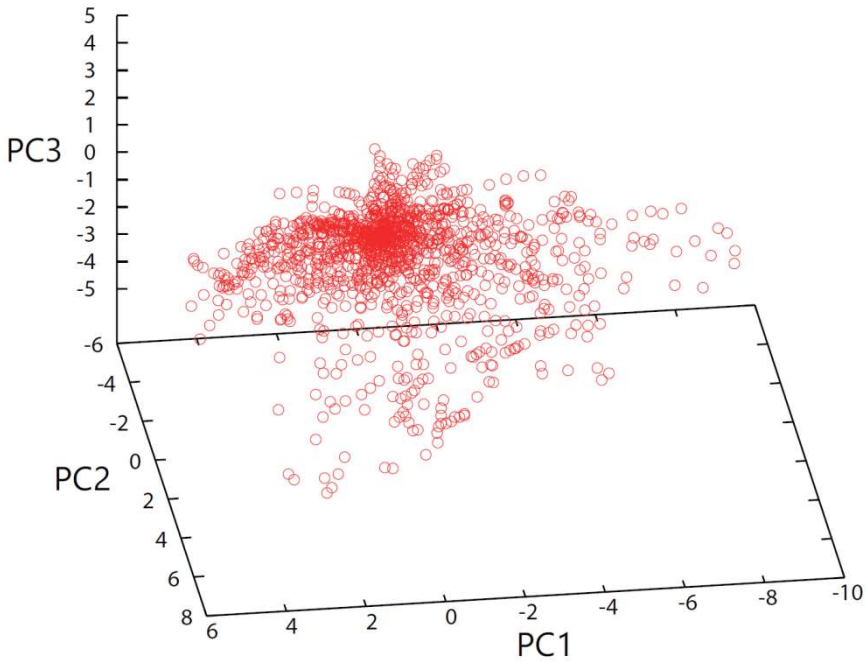


Phenotypic constraint on a low-dimensional space

After evolution

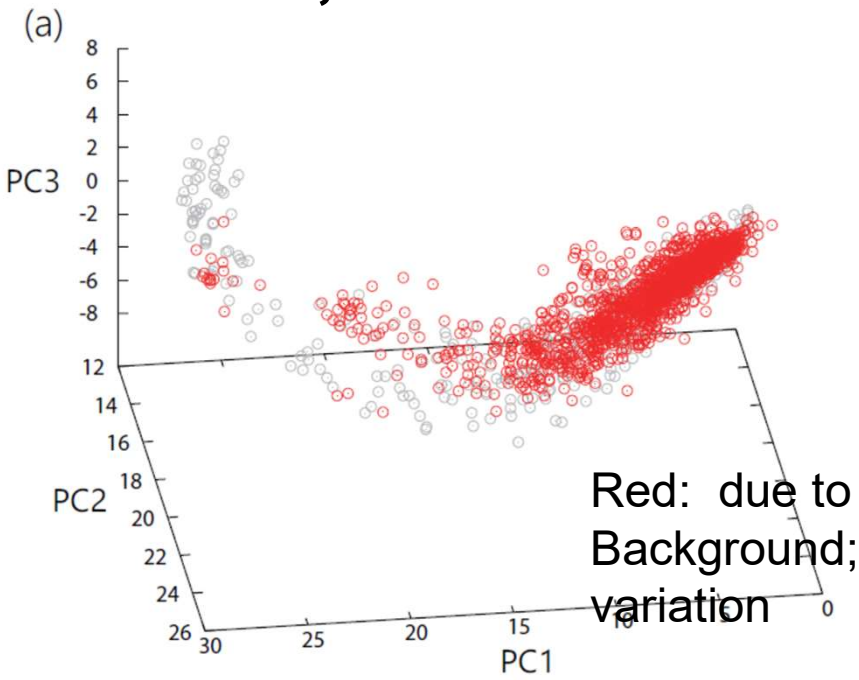


Random network

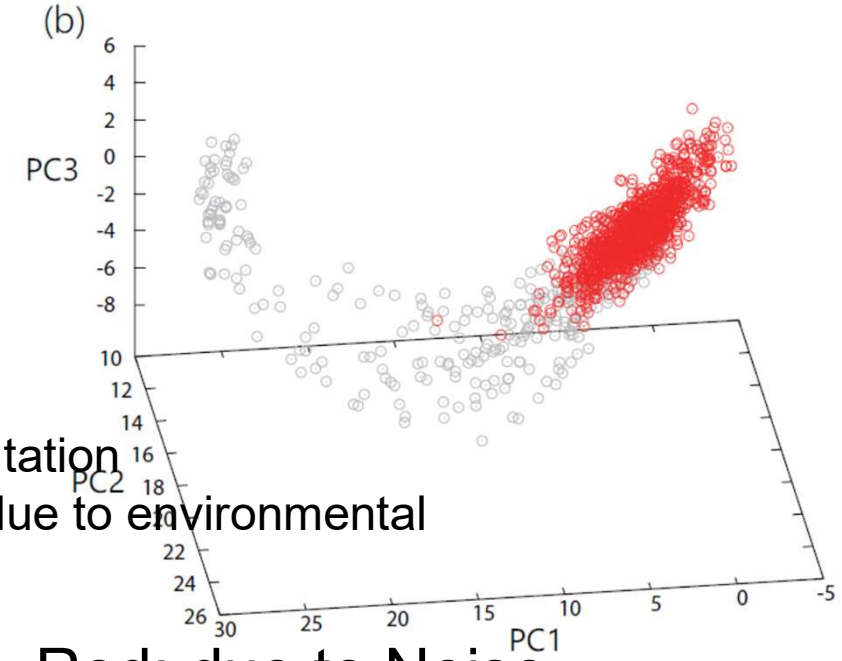


After evolution, the environmental response is constrained on a low-dimensional phenotype space.

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



Red: due to Mutation
Background; due to environmental variation



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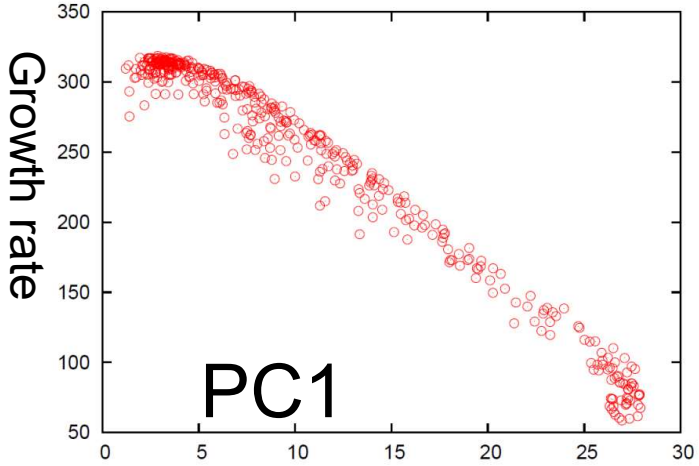
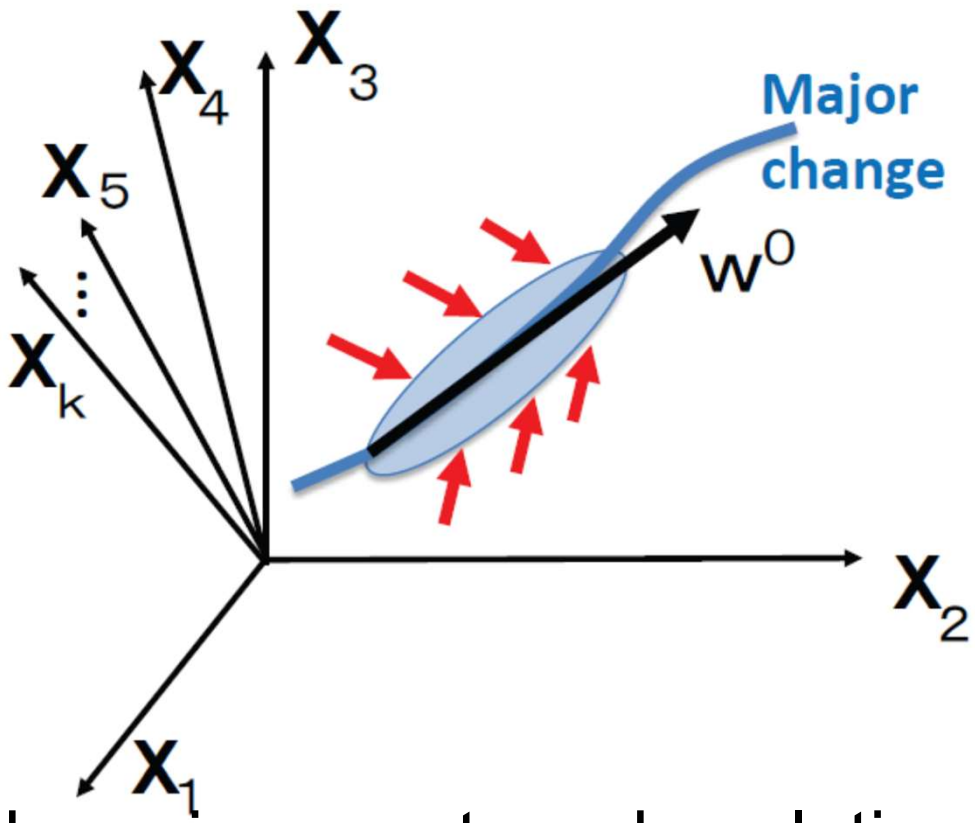


?Phenotypic change occurs along a common slow-manifold

Formation of Dominant Mode Along Major Axis



Robust to perturbations – strong attraction from most directions ……

except one direction along which evolution progresses

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

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

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**

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

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 (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**

$\gamma \cdot v_0 \sim 0$

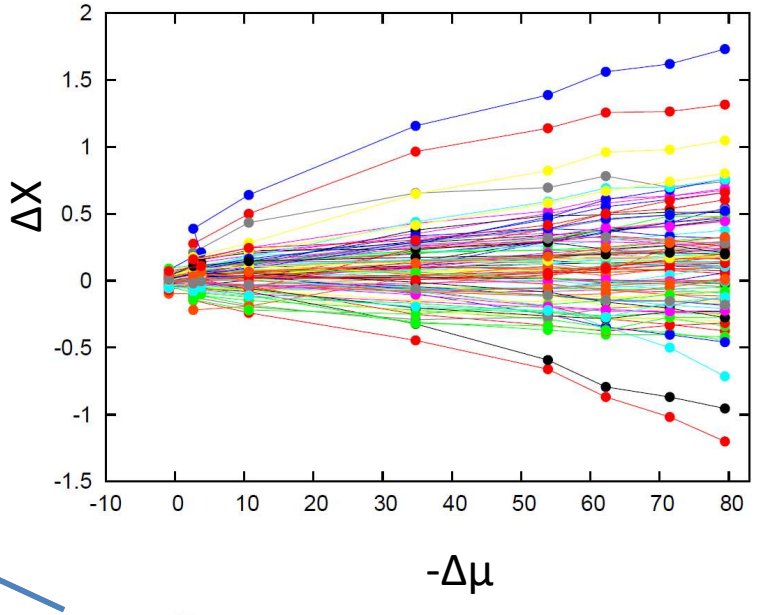
→ $\delta\hat{\mathbf{X}} = \lambda^0 \delta\mu \mathbf{w}^0$

Or, from the linear approximation

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

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

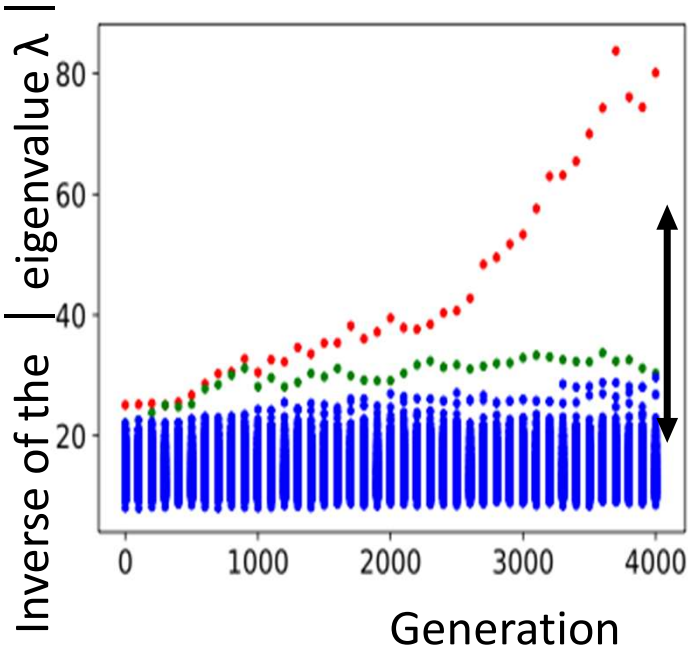
Correction in proportion coefficient

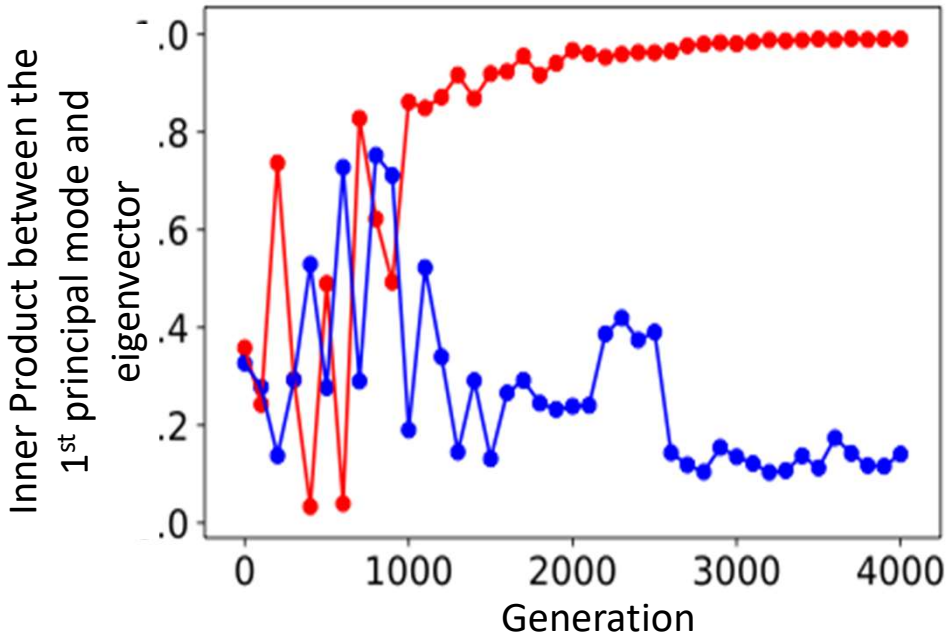


Separation of slowest mode in catalytic reaction net model

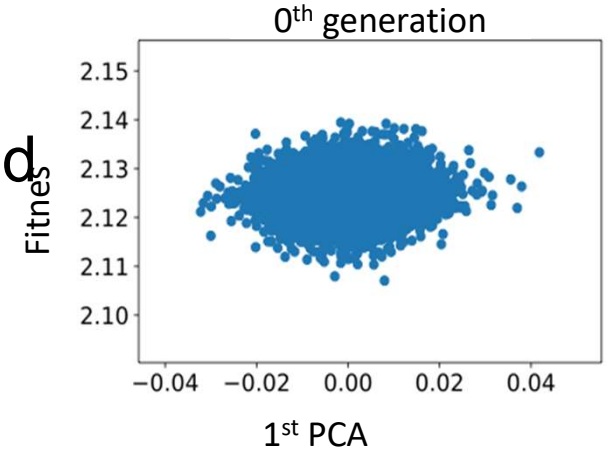
Eigenvalues of $J_{ij} = (\partial \dot{X}_i / \partial X_j)_{\mathbf{X}_i = \mathbf{X}_i^*}$

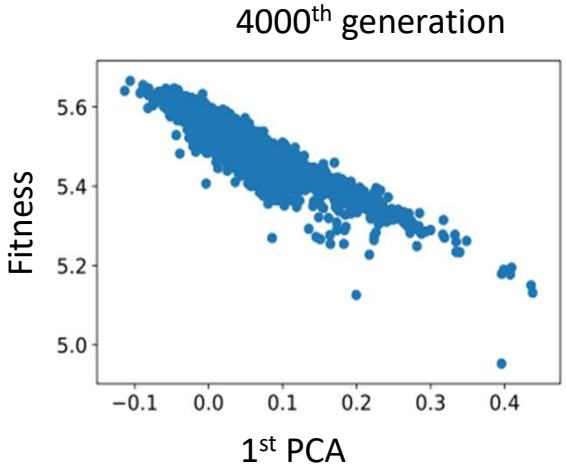
Sato,KK PhysRevR 2020



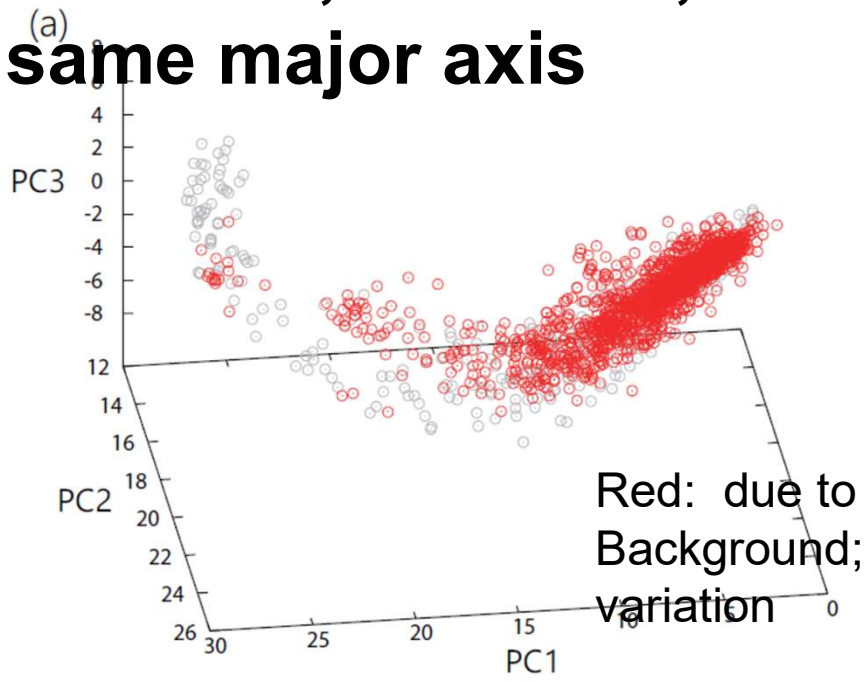


The directions of slowest mode and the fitness are aligned after evolution





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



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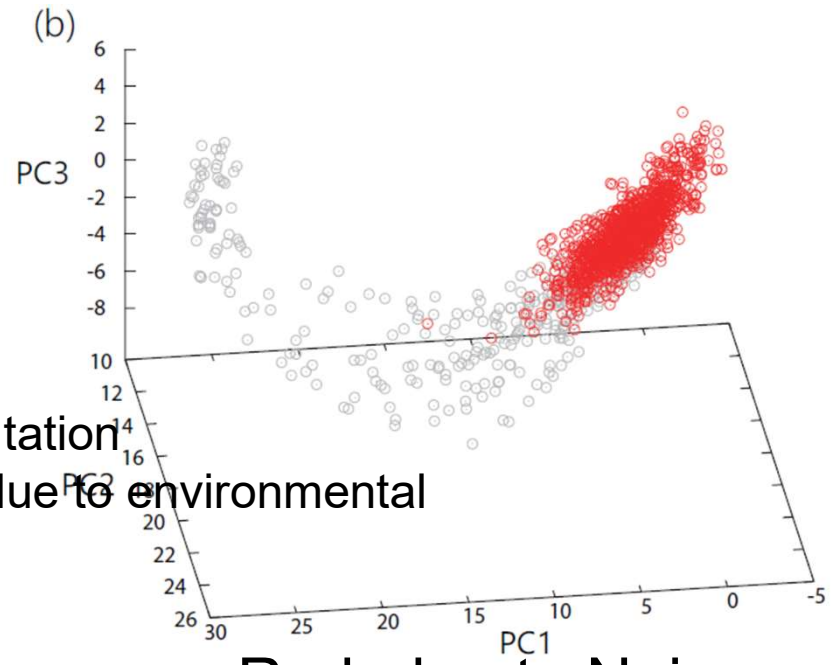
Background; due to environmental variation



Red: due to Noise
Background; due to environmental variation

?Phenotypic changes by evolution and environmental changes are along a common slow-manifold

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 →

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

using $\gamma \cdot v_0 \sim 0$

(Genetic) evolution under the environmental condition

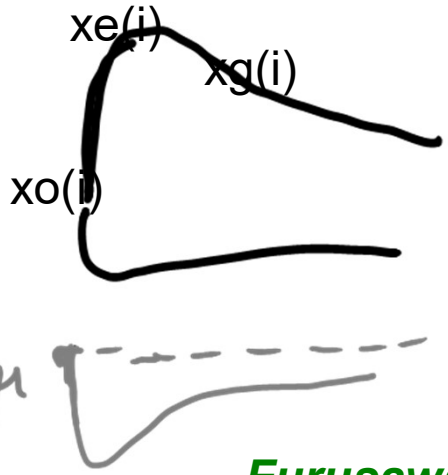
→recover growth-- $|\delta\mu(E)| < |\delta\mu(G)|$

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

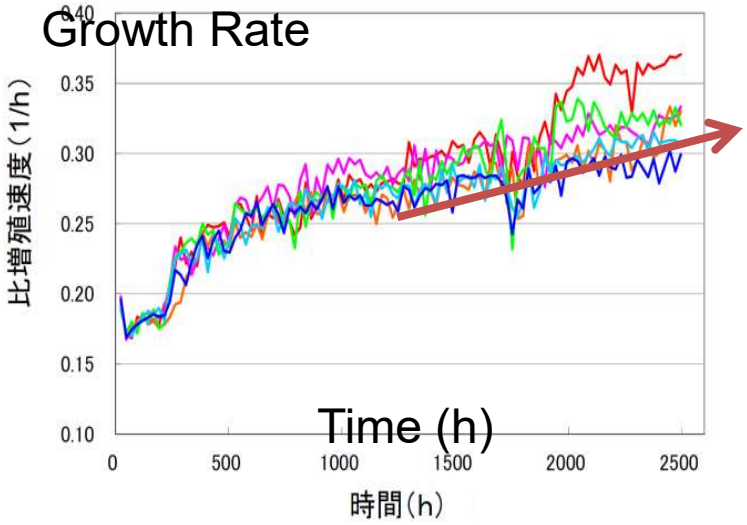
→ All the expression levels tend to return the original level by evolution **Le Chatelier Principle?**

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

Furusawa'sGroup

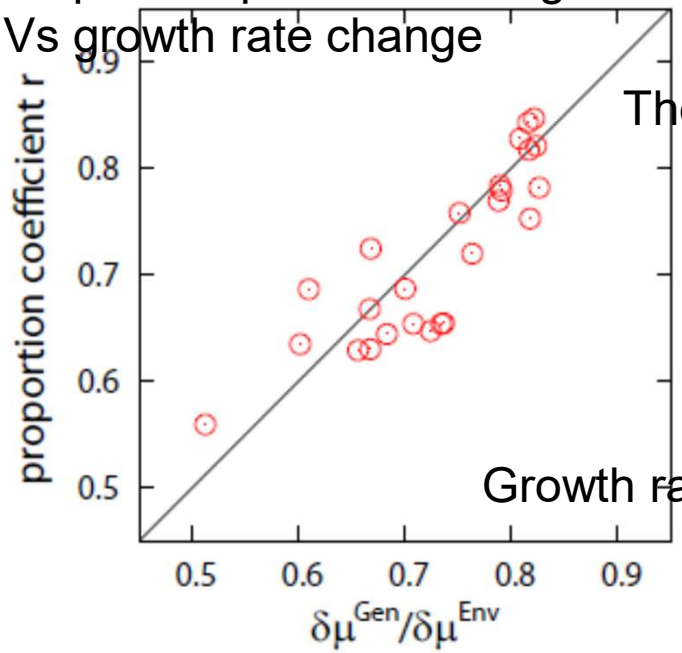


Furusawa,KK Interface,2015



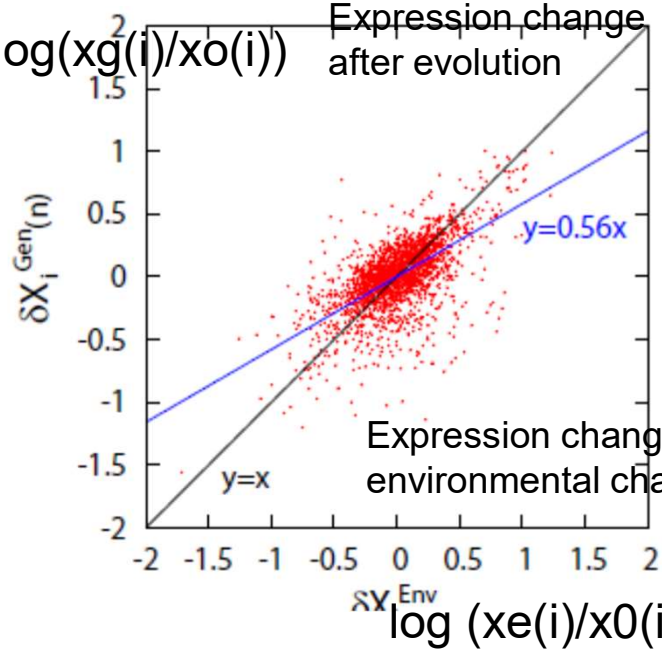
～1000 generations

Slope in expression change
Vs growth rate change



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

Expression change after evolution



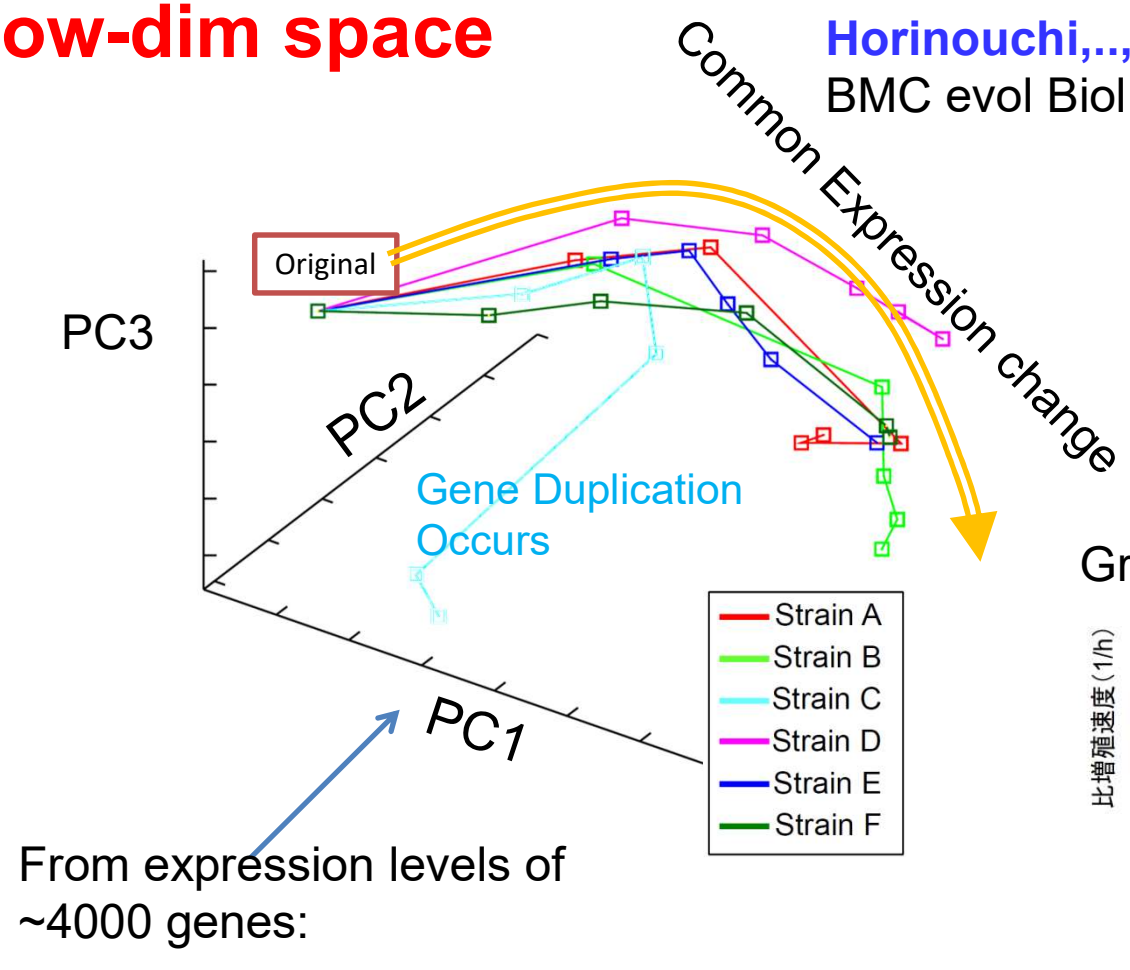
0＜δXi（E,G）/δXi（E）＜1

return to original expression pattern

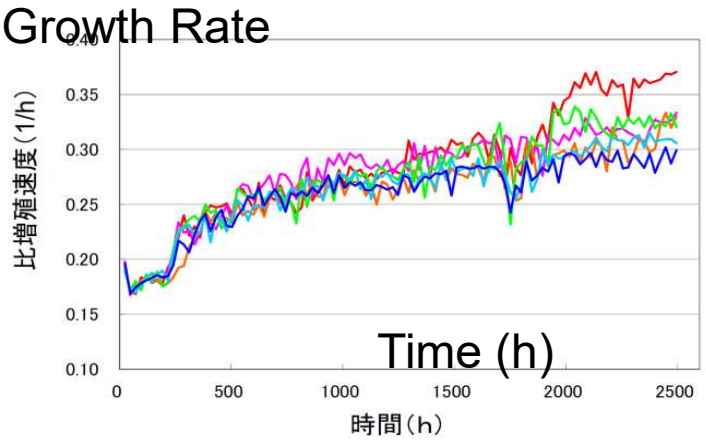
（Le Chatelier principle)

Deterministic phenotypic evolution constrained in low-dim space

Horinouchi,..,Furusawa,
BMC evol Biol 2015



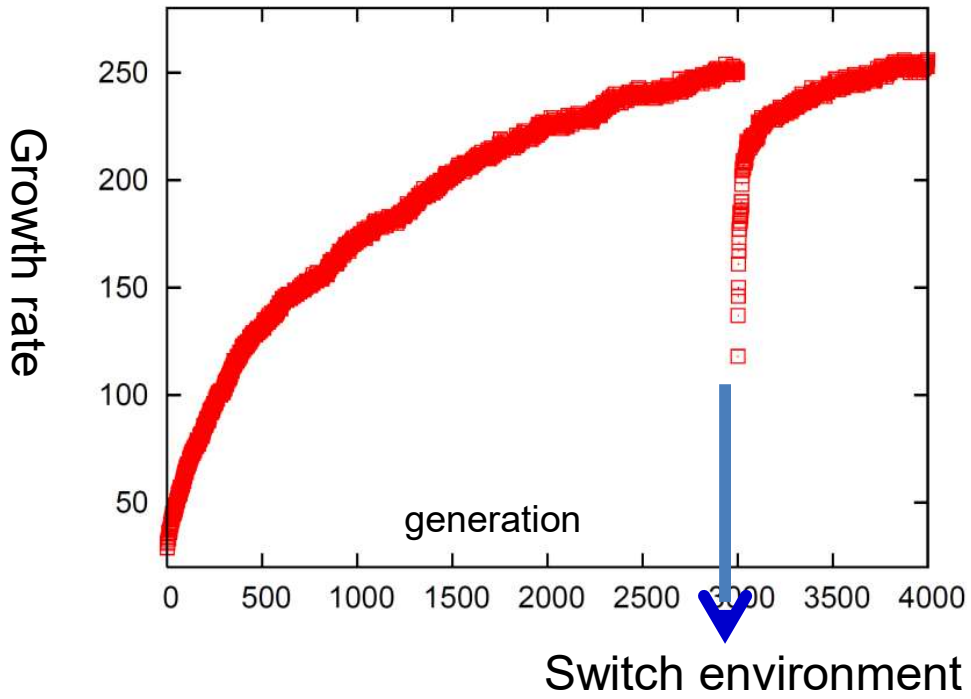
Replaying the tape of evolution, same phenotypic path (not genetic) arises!



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

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

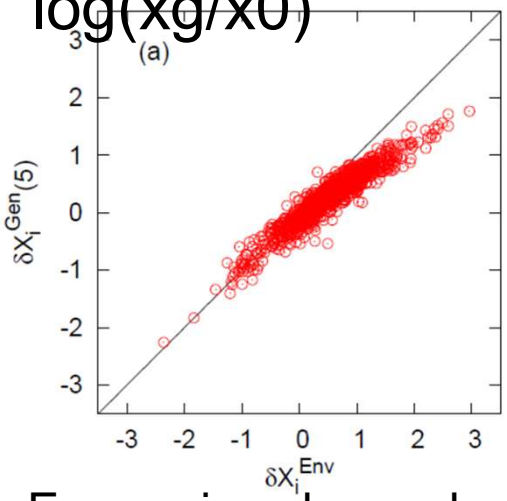


Recovery of growth rate by adaptive evolution to new environment

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

5-th generation

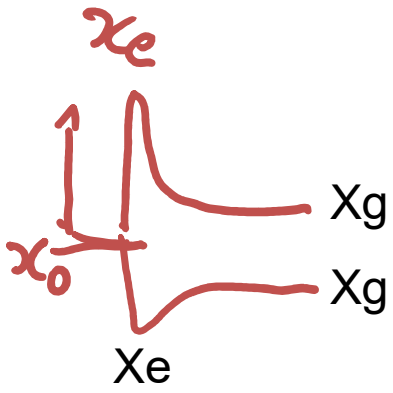
log(xg/x0)



Expression Change by evolution

Expression change by env

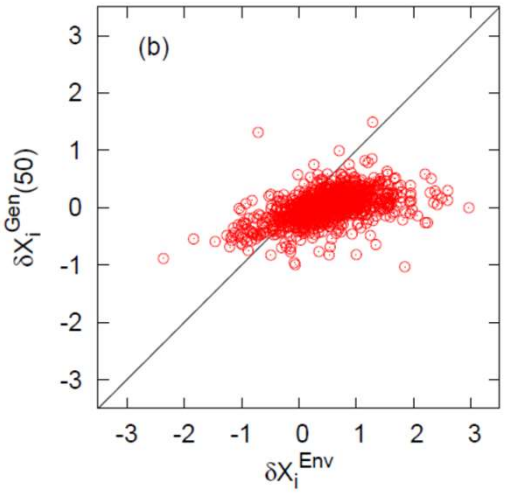
log(xe/x0)



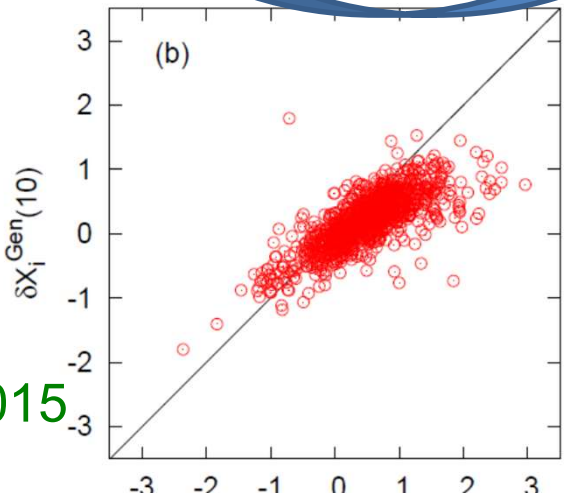
（1）Response by genetic change tends to cancel the change by environment

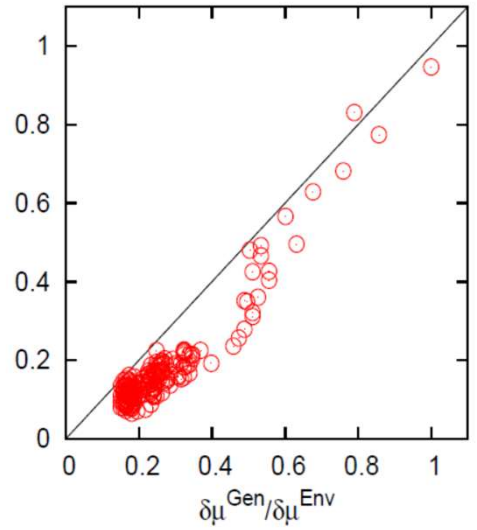
（2）The two responses are proportional over all components

100 th generation



2oth generation



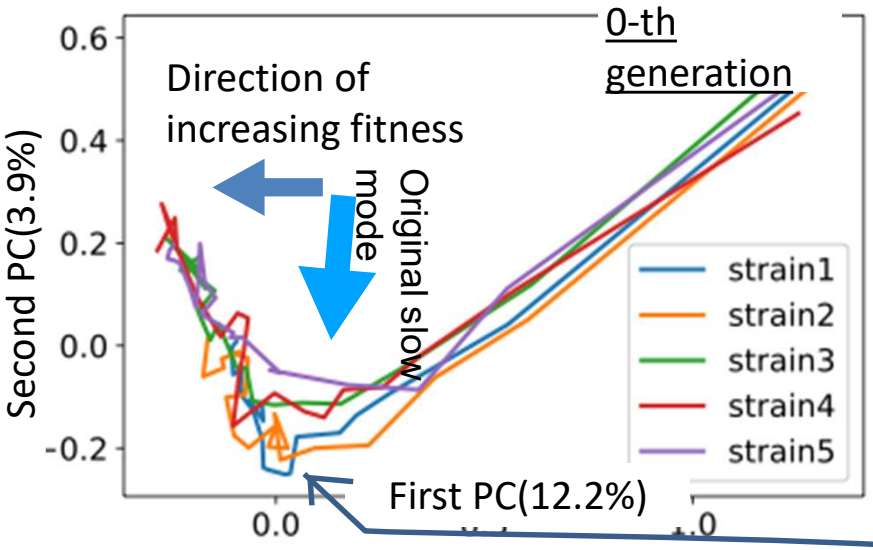


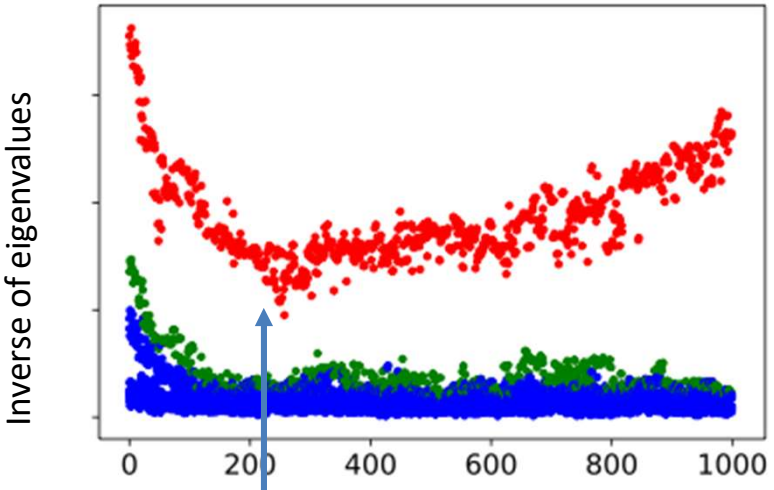
Furusawa,KK, Interface 2015

−Δμ bo by env to by evol

- In evolution to novel environment after adaptation to previous environment, the already evolved slow mode is adopted to adapt to new environment

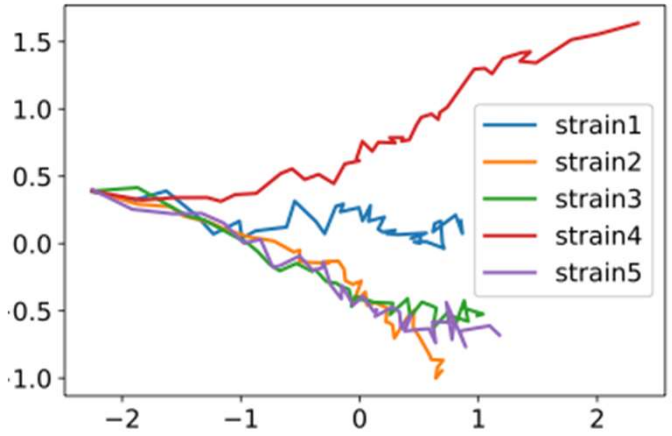
→ **Same phenotypic path when replayed the tape**.





Slow mode is adjusted to novel fitness

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



Sato, KK, PhysRevRes2020

Messages

- (Cellular) Phenotypes are high-dimensional, but their adaptive changes are drastically restricted in a low-dimensional space

←Result of steady-growth and evolutionary robustness (to noise and to genetic changes)

- Phenotypic evolution is rather deterministic even though genetic changes can be stochastic

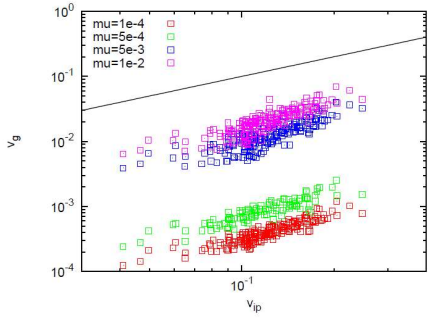
(replaying the tape, phenotypically same path)

← Phenotypic evolvability correlated by fluctuations

So far response relationship: but earlier we showed evolutionary fluctuation response

Fluctuation

Variance by gene change Vg



proportional

Variance by noise Vip

← **Proportion** →

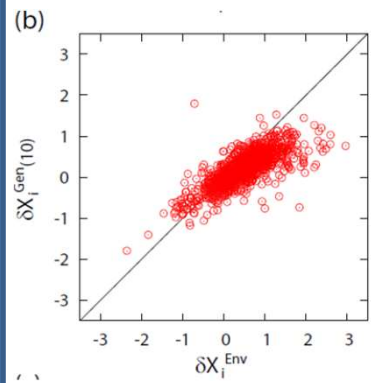
Evolutionary Fluctuation-Response (2003)

←classic Fisher Theorem→

Response by evolution

Genetic change

proportional



Response by environ-ment

Non-genetic change (noise, environ-ment)

Part II

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, Furusawa,KK Inerface 2015)

(i) evolutionary fluctuation-response relationship:

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

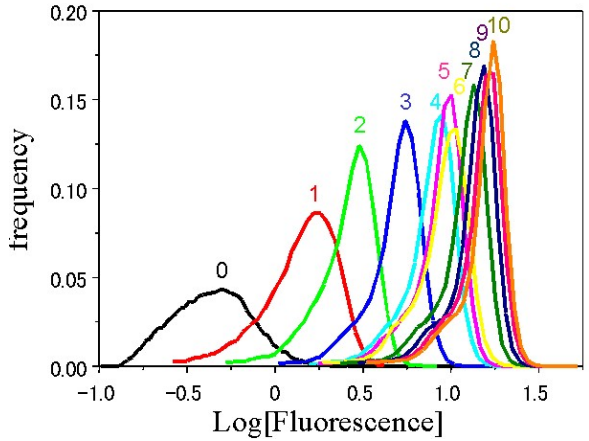
Vip ∝ evolution speed

through evolution course

bacteria evolution experiment

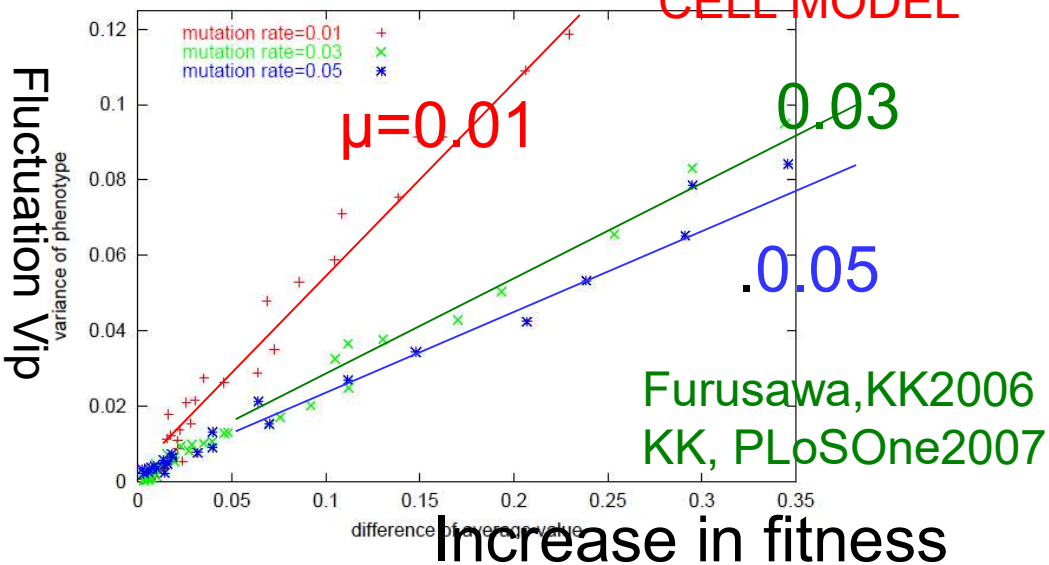
+ models (cell, gene-regulation-net),

+Phenomenological Theory



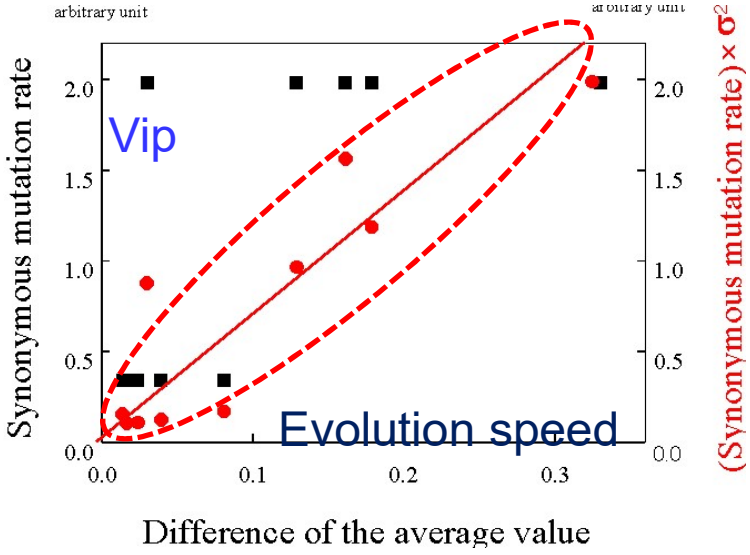
EXPERIMENT

CELL MODEL



Furusawa,KK2006

KK, PLoSOne2007



Sato Ito Yomo KK; PNAS 2003,

Analogy with fluctuation-response relationship

Force to change a variable x;

response ratio = (shift of x) / force

fluctuation of x (without force)

response ratio proportional to fluctuation

Generalize by distribution function

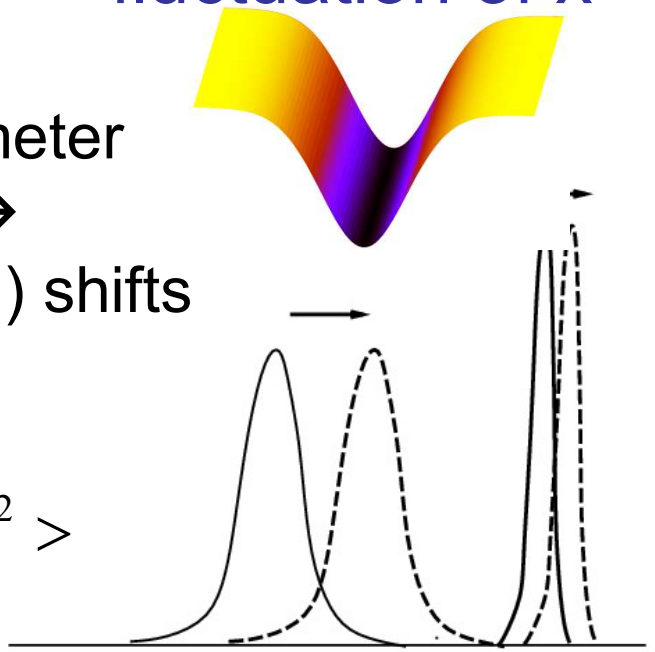
response ratio of some variable x against

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

(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

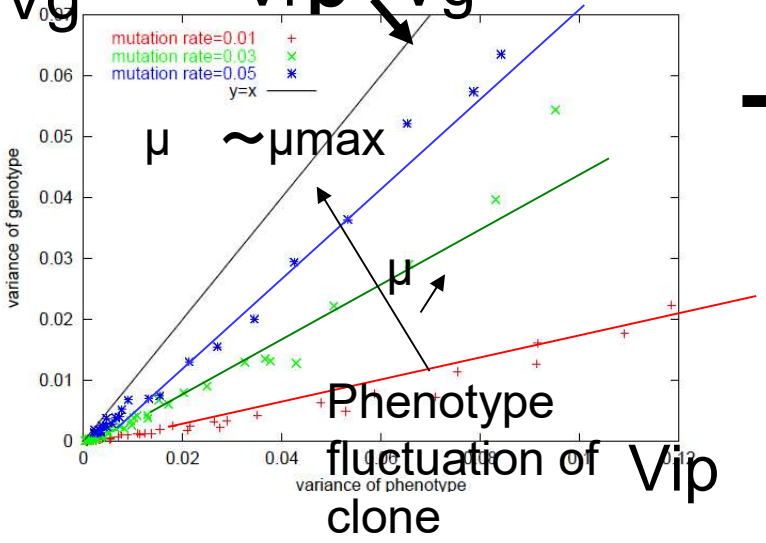
Vip ∝ Vg ∝ evolution speed through evolution course confirmed; experiment, theory, models

WHY??➔ result of robust evolution + distribution theory

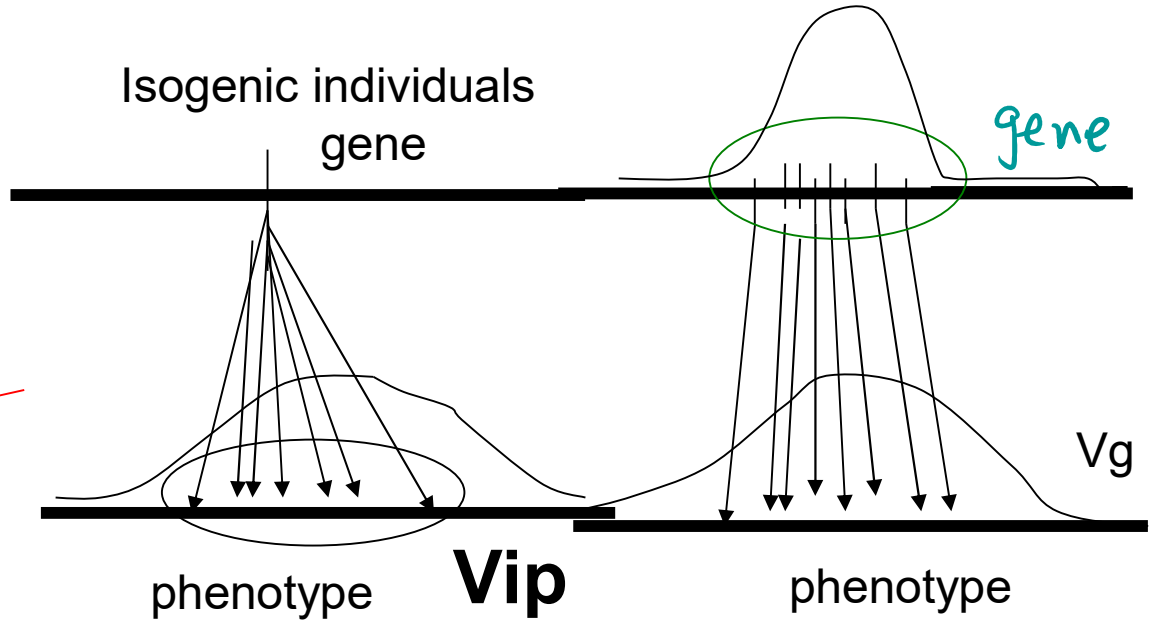
Robustness to noise ↑ → Robustness to Mutation ↑

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

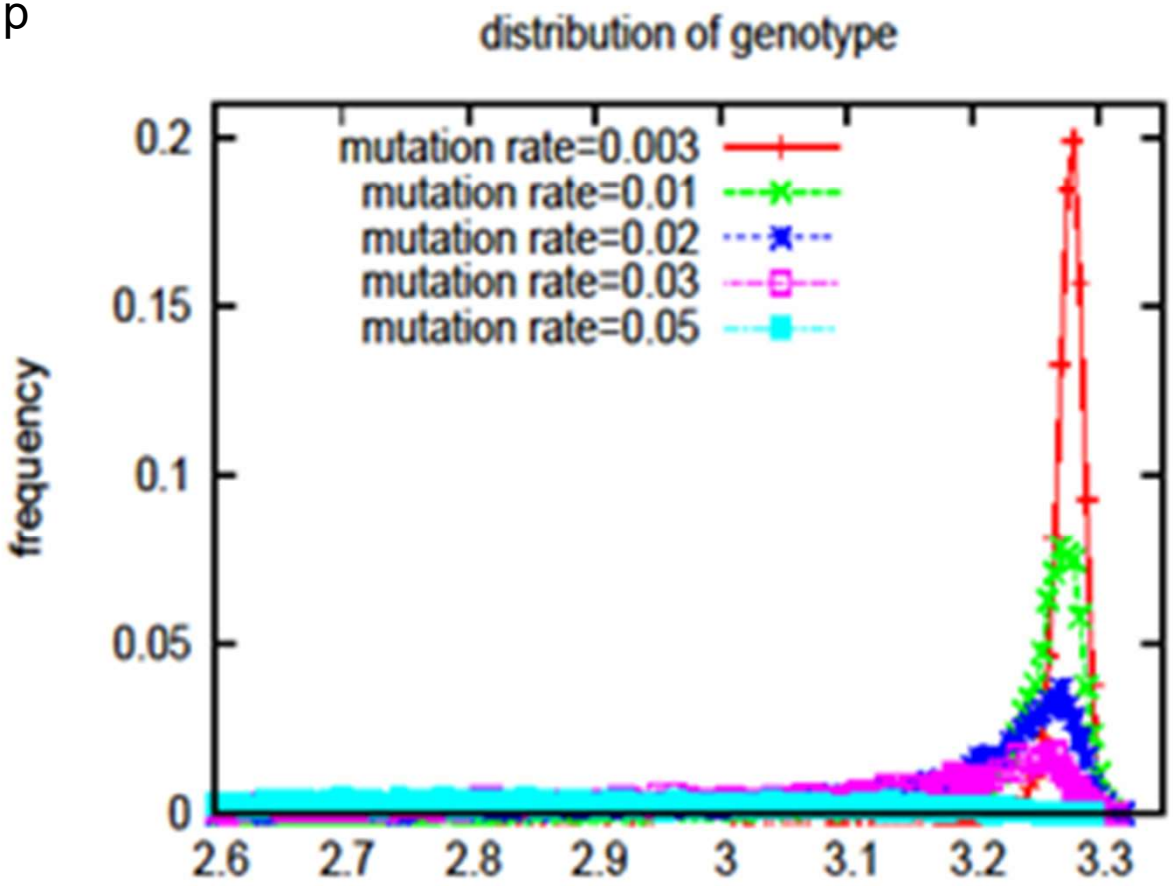
evolution speed is maximal at μ ~ μ max

(3) Vg approaches Vip

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))

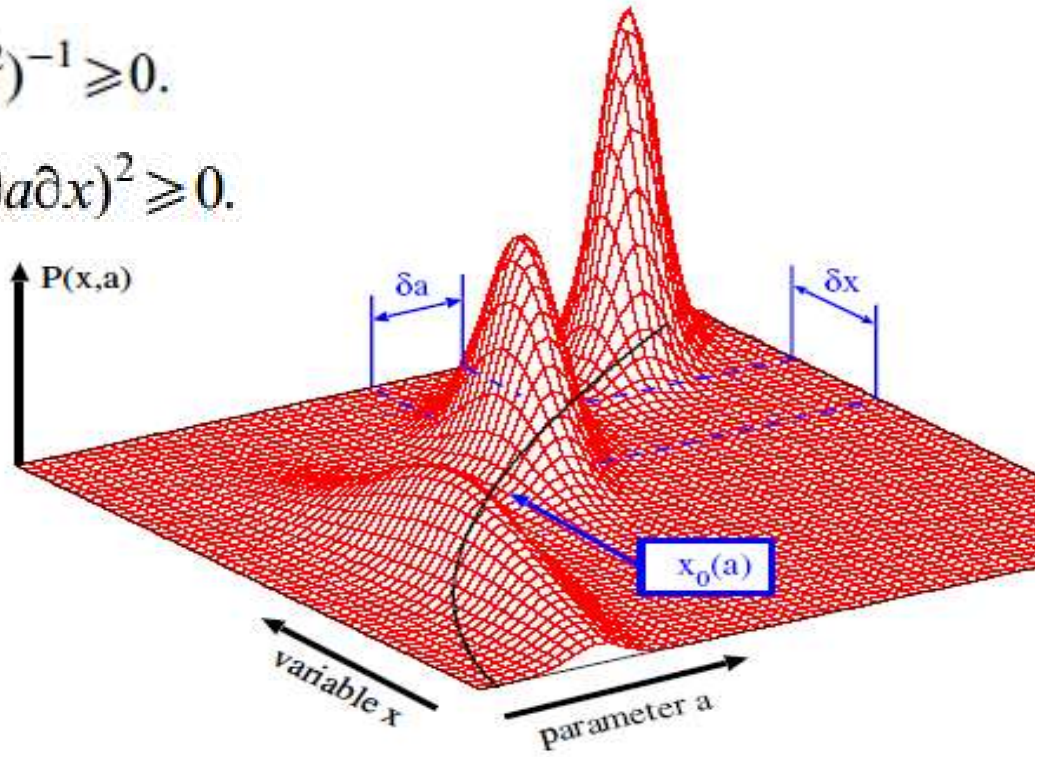
Keep a single-peak (stability condition).

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

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

Hessian condition

Leads to relationship between Vip and Vg



KK,Furusawa, 2006 JTB

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

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

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

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

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

If mutation rate μ is small, Vg<Vip,

Vg ~ (μ/μmax)Vip ∝ Vip

Consistency between pheno & geno

KK, PLoS One 2007, &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?

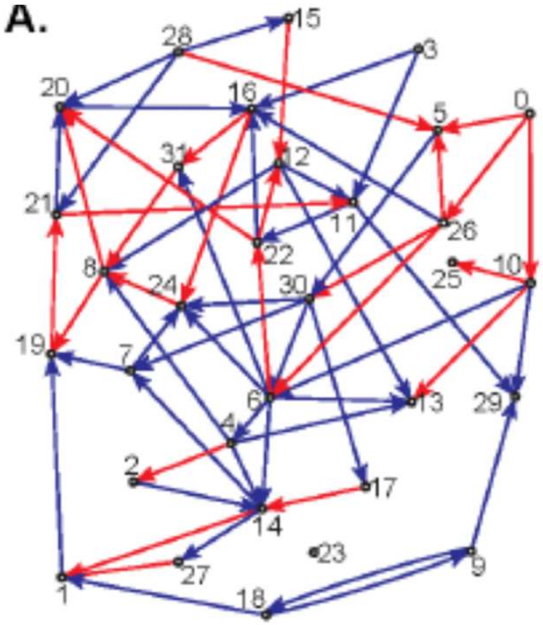
(**) under selection of given trait. if μ is small:

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



Activation
Repression
…=1,-1,0

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

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

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

Gaussian white noise

M;total number of genes, k : output genes

Noise strength σ

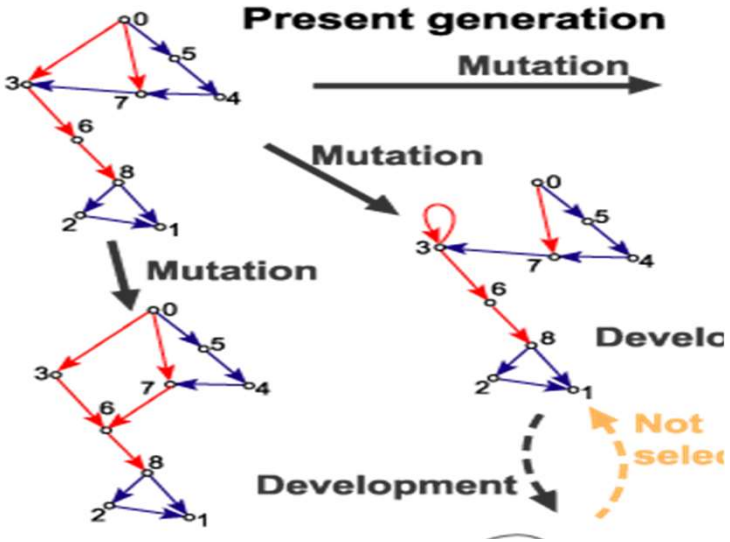
- Fitness: Starting from off of all genes, after development genes x_i i=1、2、···、k should be on （Target Gene Pattern)

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

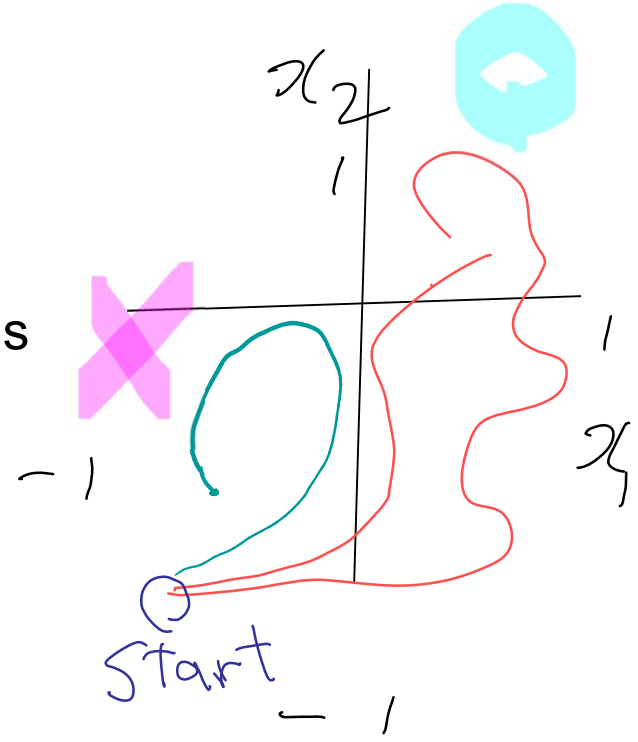


If M=k=2→

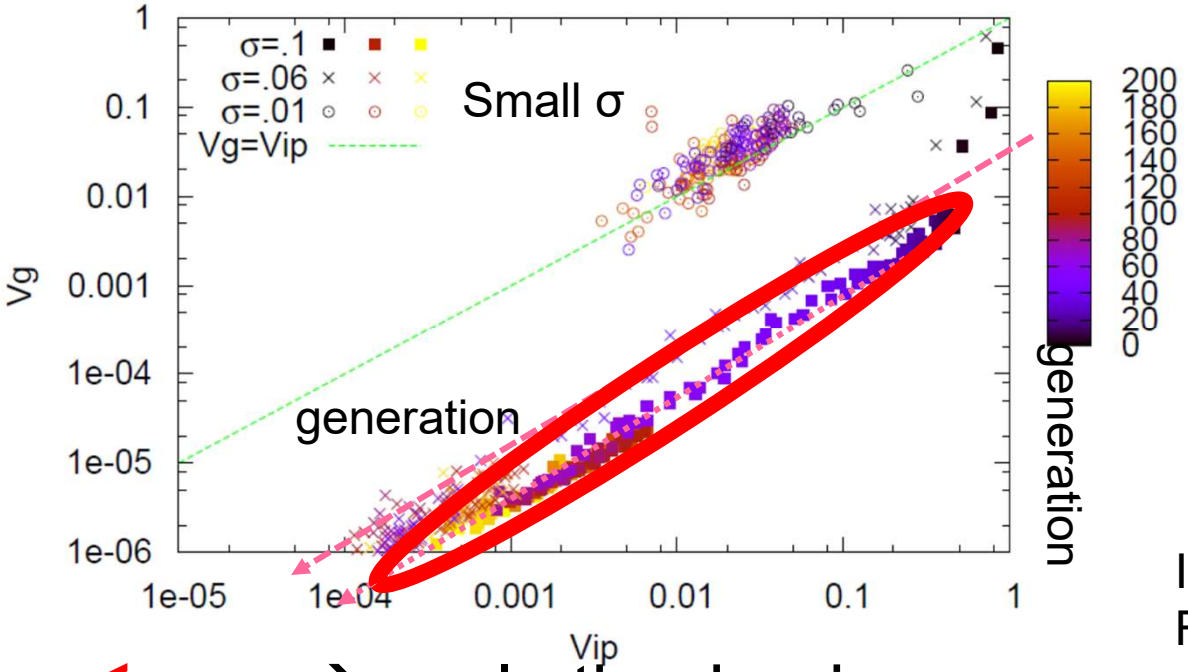
Most simulations

M=64

K=8



''Robustness transition by increasing noise''



(1)Vip≧Vg forσ≧σc

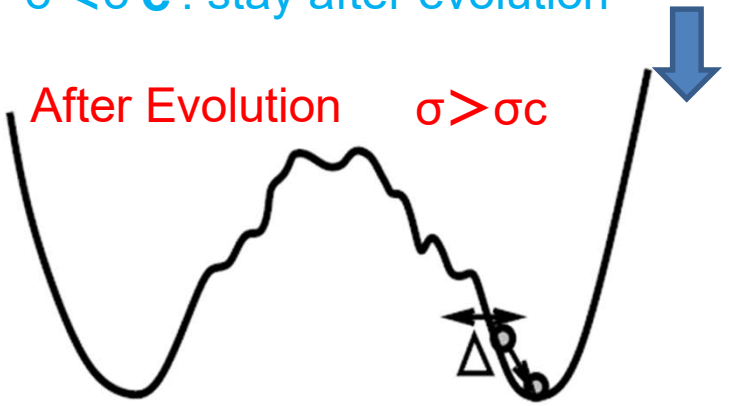
(2) Vg→Vip as σ→σc

(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

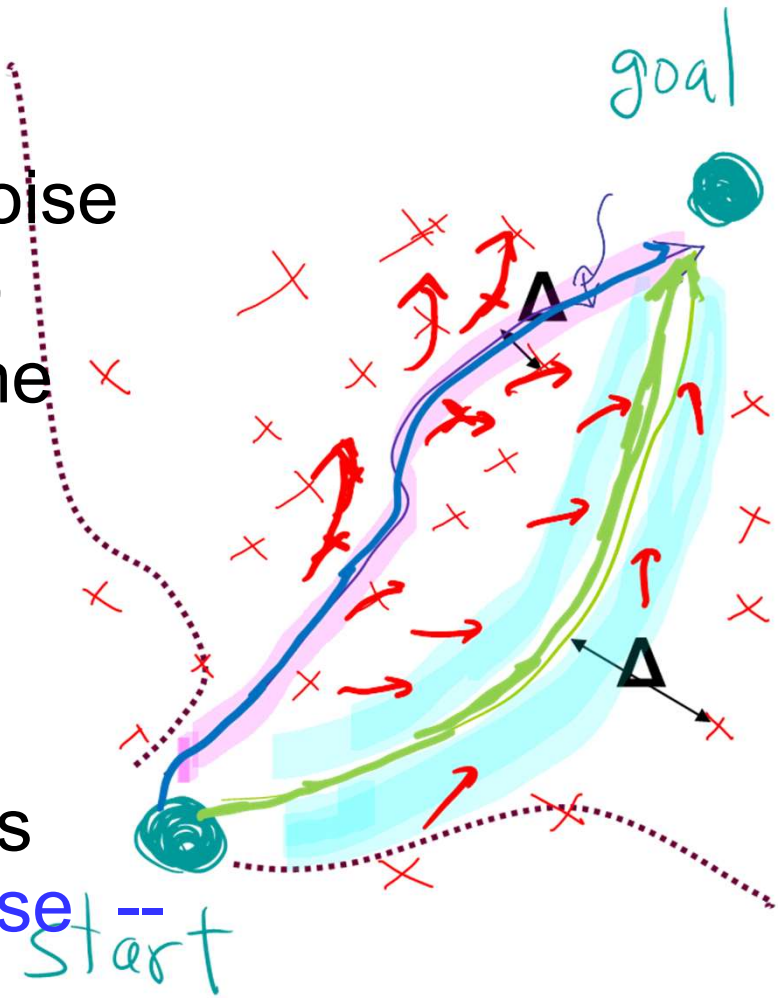
Difference in basin structure

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

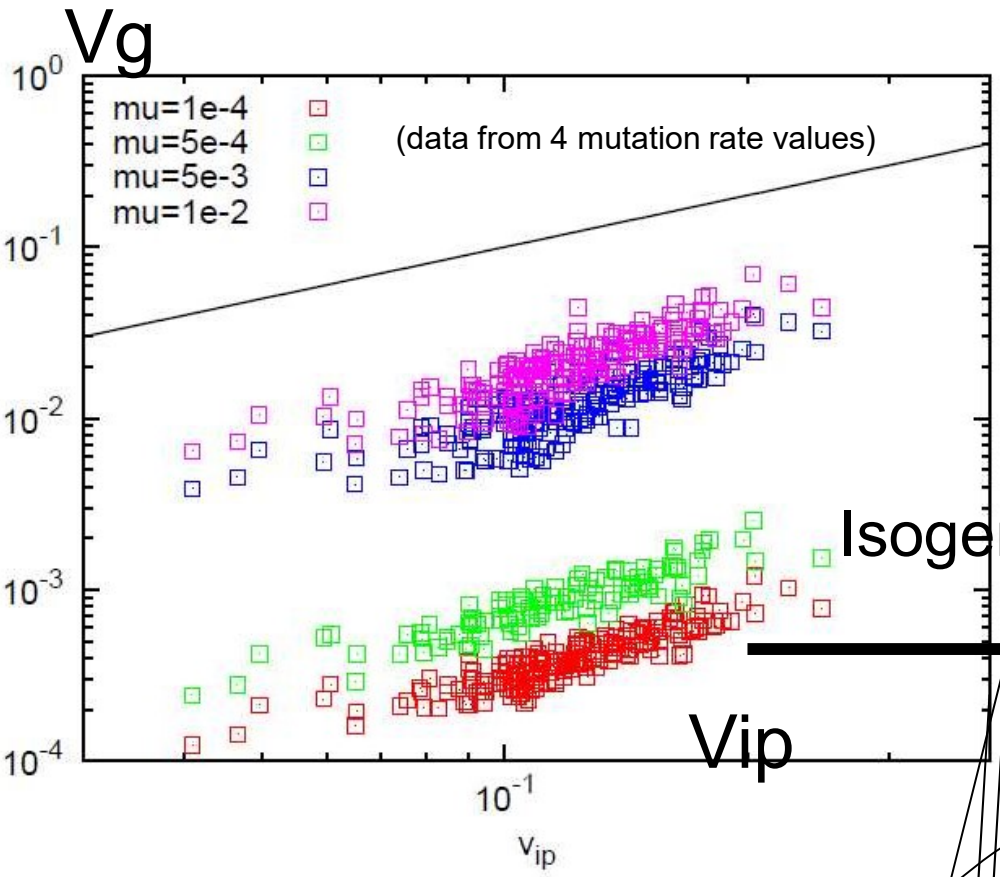
Vip ∝ Vg →Developmental robustness is embedded into genetic (evolutionary) robustness for $\sigma > \sigma c$

Furusawa, kk Interface 2015

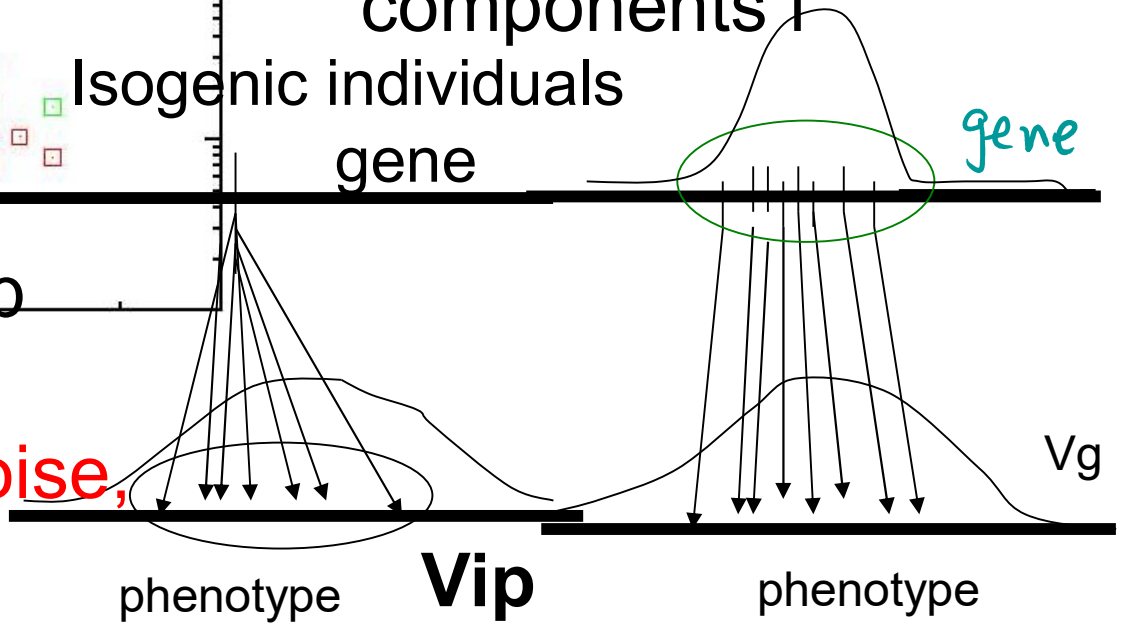
Vip-Vg relationship across traits (phenotypes)

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

Vip(i) : Variation due to noise in dynamics

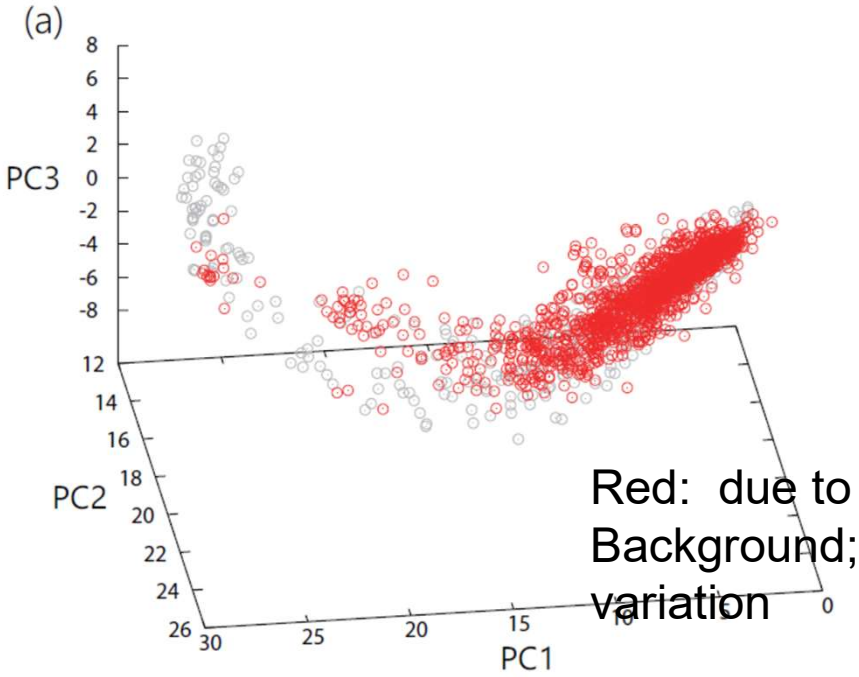


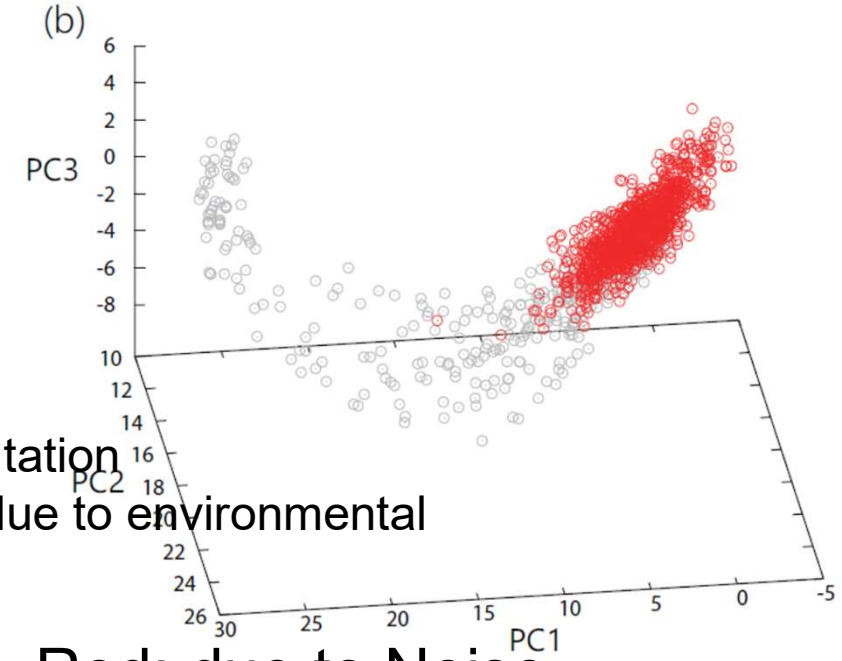
Vip(i) ∝ Vg(i)
over all
components i



If highly variable by noise,
More easily evolvable

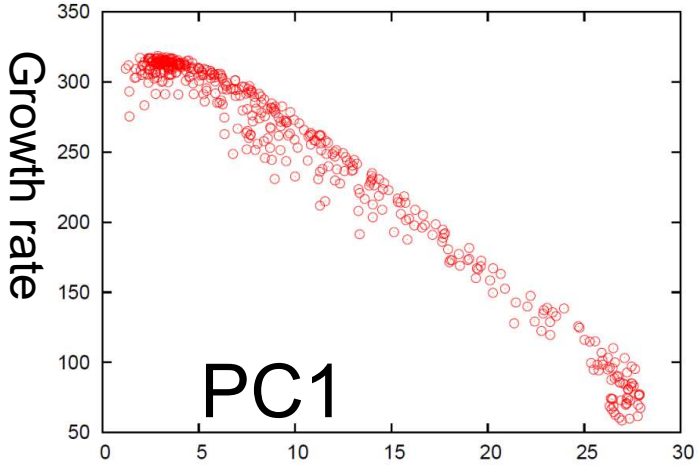
Recall…





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

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

Need further studies to establish the present theory

(i) Further Confirmation by Experiments

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

Catalytic Reaction Cell Model ☑

Gene regulation network Model (Inoue,KK arXiv) ☑

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

evolve spin Hamiltonian JijSiSj to achieve certain configuration

dimensional reduction at replica symmetric phase

Protein Model/Data? (Tang et al., PLoSCB,PRR2020) ☑

critical state to satisfy robustness and plasticity

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

outliers in eigenvalues – separation of slow modes,

Renormalization Group???

Projection to Collective Modes?

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) *too many cocks spoil the broth*

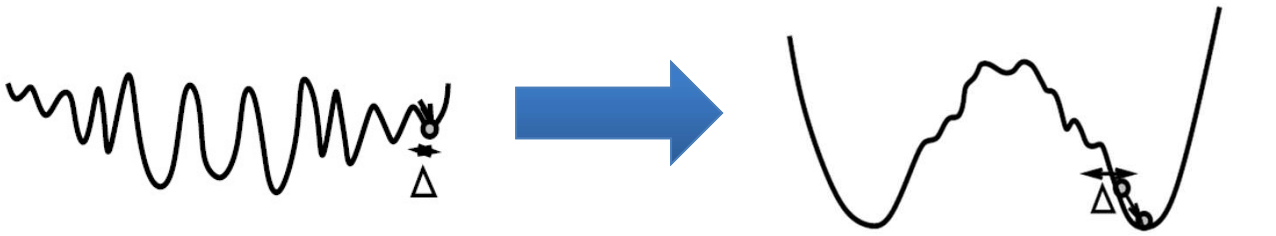
Result of evolution but fosters evolvability

Cf Kohsokabe, KK, JExpZoologyB 2016

Expanded Linearity in terms Potential picture:

robustness evolved (get out of error catastrophe)

Cf, KK PLoS One 2007



Related Issues

(1)Why Genotype/ Phenotype are separated

i.e., origin of central dogma as symmetry breaking (information/function) (Takeuchi,Hoegeg,KK, Nat.Comm 2018; Takeuchi,KK Proc Roy Soc B 2019)

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

State with μ=0? Extension to no-exponential growth?

Transition from exponential growth to non-growth?

(cf, Himeoka,KK, Phys Rev X 2017)

No longer low-dim?

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

(3) Evolution-Development Congruence?

correspondence in process; (Kohsokabe, KK, JEZ B 2016)

(4) Cell-cell interaction → Coexistence of Diverse species by leaked chemicals *(Yamagishi et al. bioRxiv)*

origin of reproduction

Replication of catalytic molecules catalyzed by others

Evolution of catalytic activity k (through replication error):

While working as catalyst, the molecule is not replicated

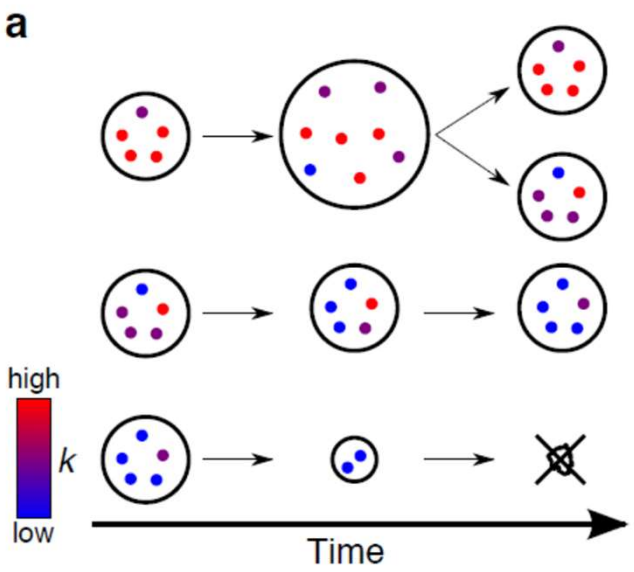
→Selfishness preferable k↘ --- molecular level

→…..Extinct →remedy Put molecules into a protocell

Protocell divides when the total # of molecules reaches N

those with smaller <k> are selected out

Cell level <k>↗ Conflicting Mutilevel Evolution



b

$R + R' \xrightarrow{k} R\text{-}R'$

$R' + R \xrightarrow{k'} R'\text{-}R$

Formation of complex

each molecule needs catalysts for replication

$R\text{-}R' + S \xrightarrow{1} R + R' + R'$

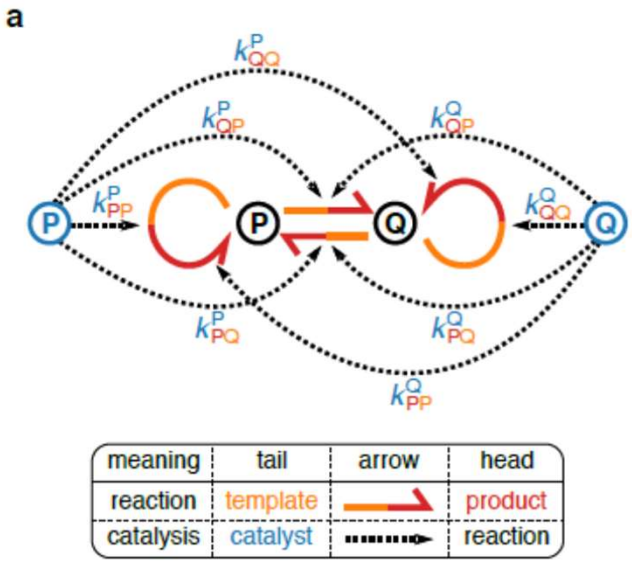
$R'\text{-}R + S \xrightarrow{1} R' + R + R$

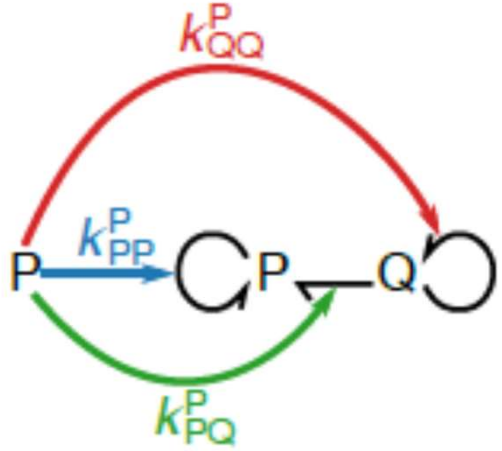
$R \xrightarrow{d} S$

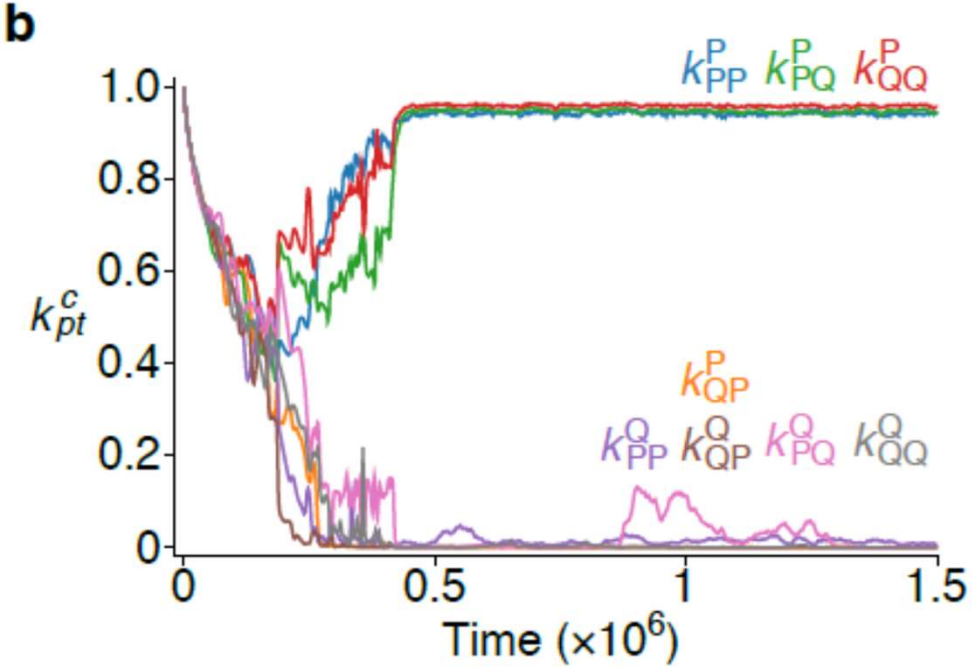
Takeuchi,KK,Hogeweg ProcRoy.Soc.2016

Origin of 'Central Dogma' -- allow for cells with larger N

Two-species (P,Q) →Symmetry breaking to Functional (catalytic) vs information (template)molecules





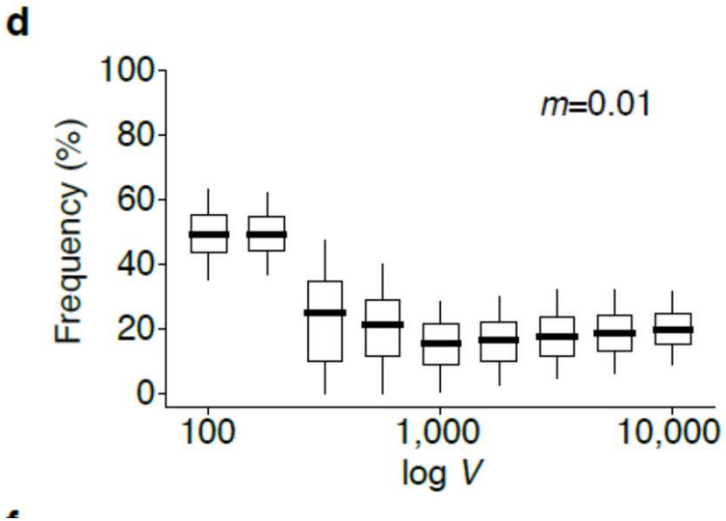


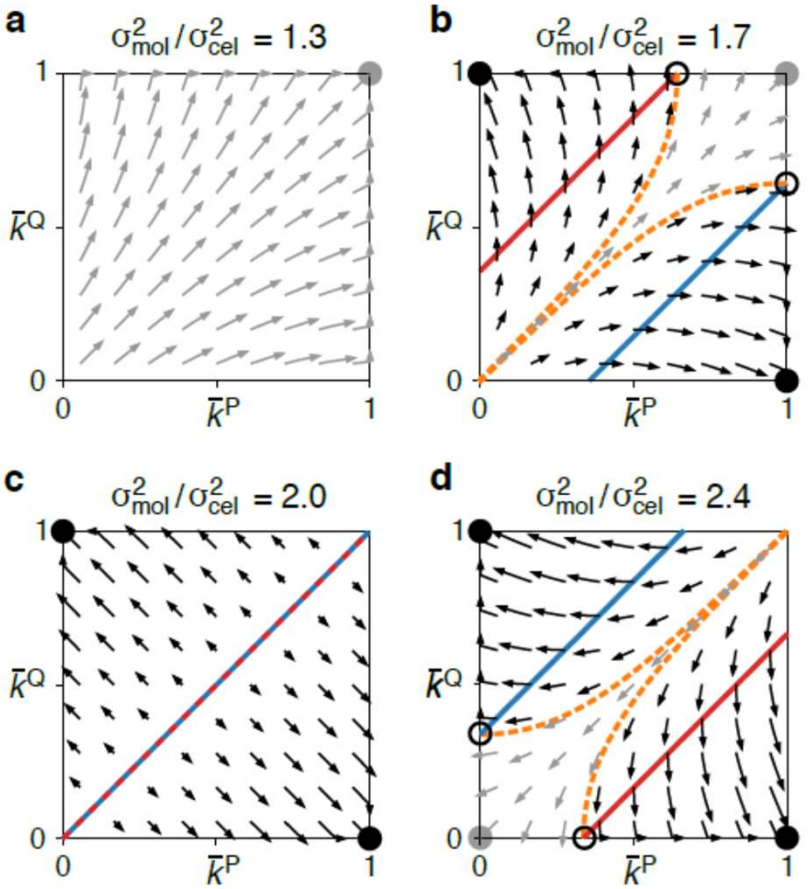
Takeuchi, KK, BioRxiv 2019

Theoretical Explanation by Price equation (with multilevel)

$$\Delta \bar{k}^{\mathrm{P}} \approx \bar{\omega}^{\mathrm{P}} \left(\beta_{\mathrm{P}}^{\mathrm{P}} \sigma_{\mathrm{cel}}^2 - \gamma_{\mathrm{P}}^{\mathrm{P}} \sigma_{\mathrm{mol}}^2 \right) + \bar{\omega}^{\mathrm{Q}} \beta_{\mathrm{P}}^{\mathrm{Q}} \sigma_{\mathrm{cel}}^2$$

$$\Delta \bar{k}^{\mathrm{Q}} \approx \bar{\omega}^{\mathrm{P}} \beta_{\mathrm{Q}}^{\mathrm{P}} \sigma_{\mathrm{cel}}^2 + \bar{\omega}^{\mathrm{Q}} \left(\beta_{\mathrm{Q}}^{\mathrm{Q}} \sigma_{\mathrm{cel}}^2 - \gamma_{\mathrm{Q}}^{\mathrm{Q}} \sigma_{\mathrm{mol}}^2 \right)$$





Intuitively: loss of template information
→ Not as a unit for selection
→ No longer evolution to lose catalysis

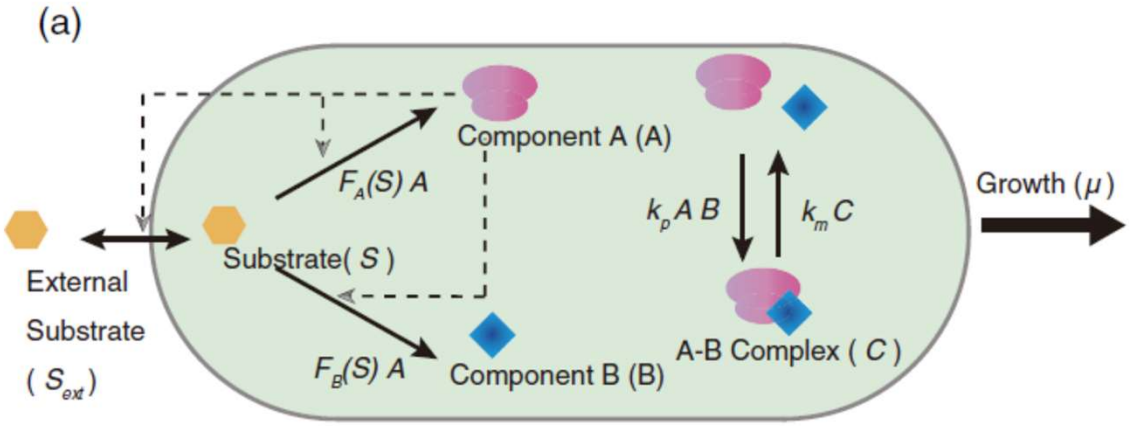
Takeuchi, KK, BioRxiv 2019

Transition to Stationary Phase ("Sleeping") State

Minimal(?) Model

Himeoka,KK 2017 Phys Rev X

Autocatalytic growth by Active (eg Ribosomal) protein + Waste Molecules by replication error etc



Waste+Active Form a Complex C

$$\frac{dS}{dt} = -F_A(S)A - F_B(S)A + A(S_{\text{ext}} - S) - \mu S,$$

$$\frac{dA}{dt} = F_A(S)A - G(A,B,C) - d_A A - \mu A,$$

$$\frac{dB}{dt} = F_B(S)A - G(A,B,C) - d_B B - \mu B,$$

$$\frac{dC}{dt} = G(A,B,C) - d_C C - \mu C,$$

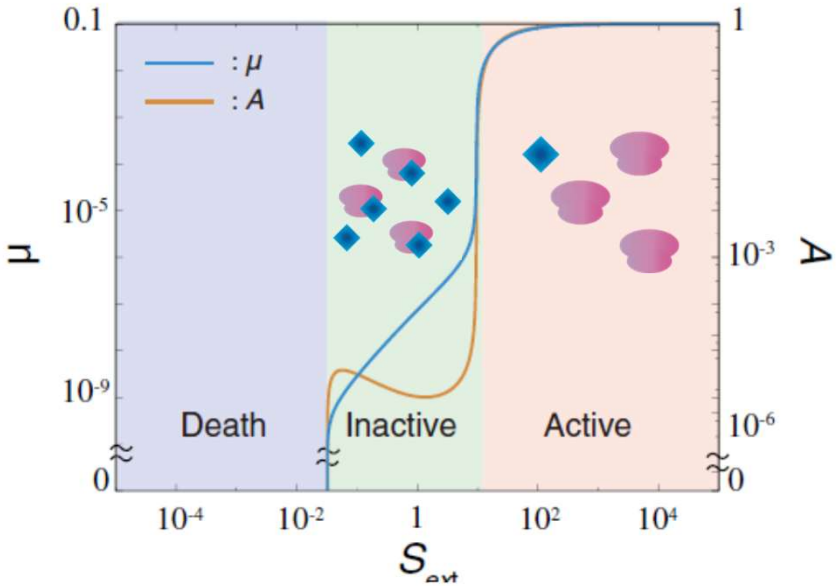
$$G(A,B,C) = k_p AB - k_m C.$$

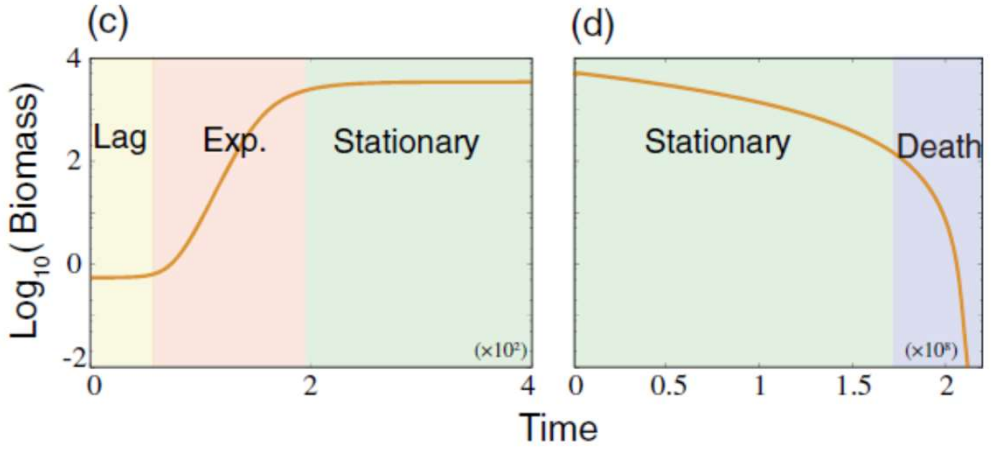
Low Nutrient → Slow Accumulation of Waste

$$[d/(dS)]\{[F_A(S)]/F_B(S)\} > 0.$$

we assume that this ratio increas

Activator for Growth +Inhibition by Waste → Transition to Sleeping state with μ∼0 upon nutrient depletion



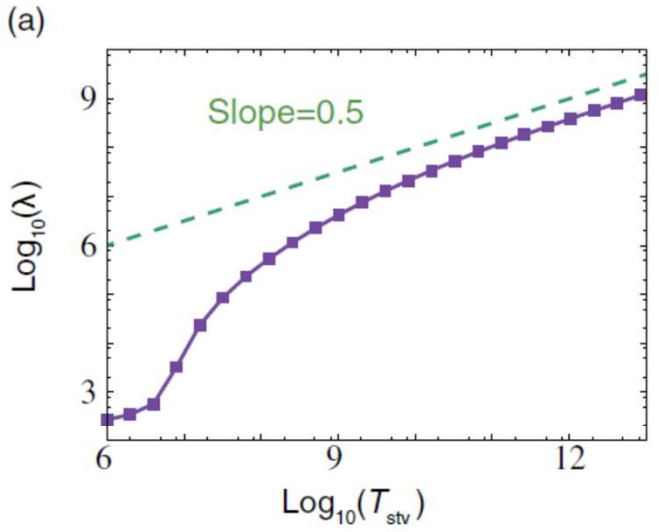


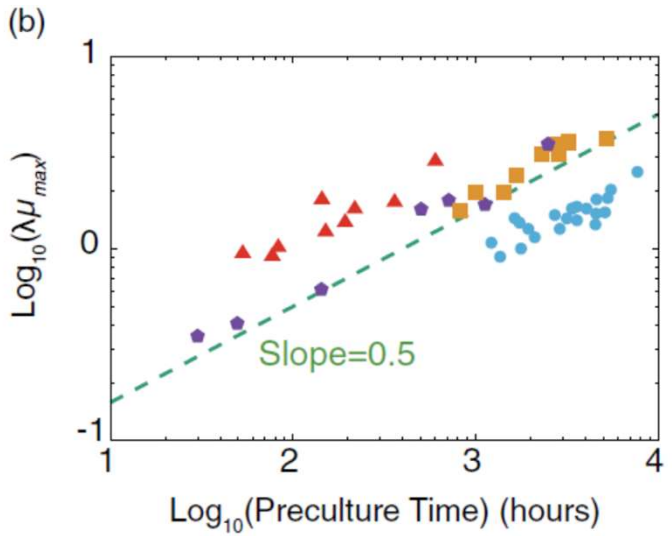
Most Active Proteins are trapped in Complex

Active Proteins are protected

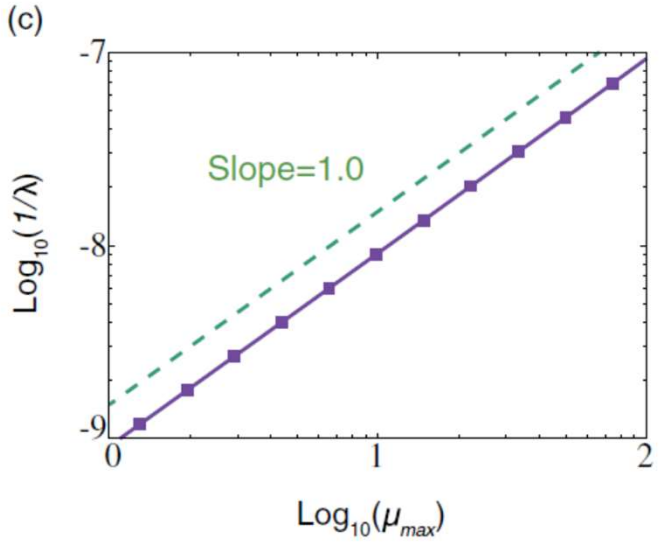
Transition from exponentially growing state to suppressed growth state (growth rate reduced to 5-6 digits)

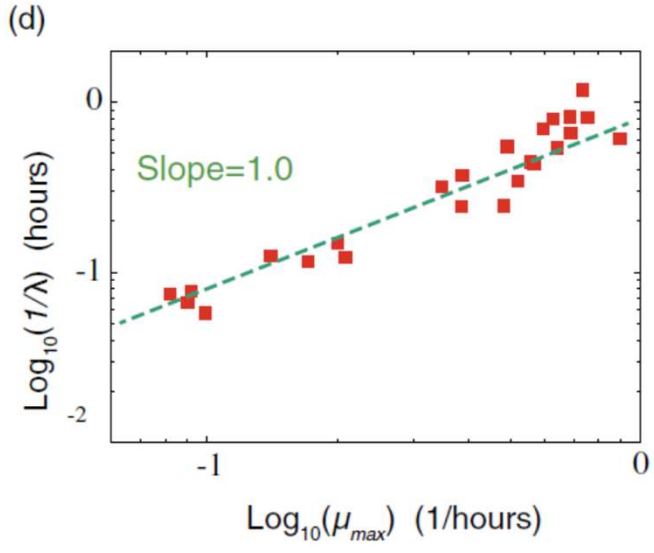
→ Waste Inhibits the growth (and degradation) by forming a Complex





$\lambda \propto \sqrt{T_{\mathrm{stv}}}$.





$\lambda \propto 1/\mu_{\mathrm{max}}$

Starvation $A + B \leftrightarrow C$

$k_p AB \sim k_m C$

$\dot{B}(t) \propto F_B(S)/B \quad dB^2/dt \sim \text{const.} \qquad B(t) \propto \sqrt{t}.$

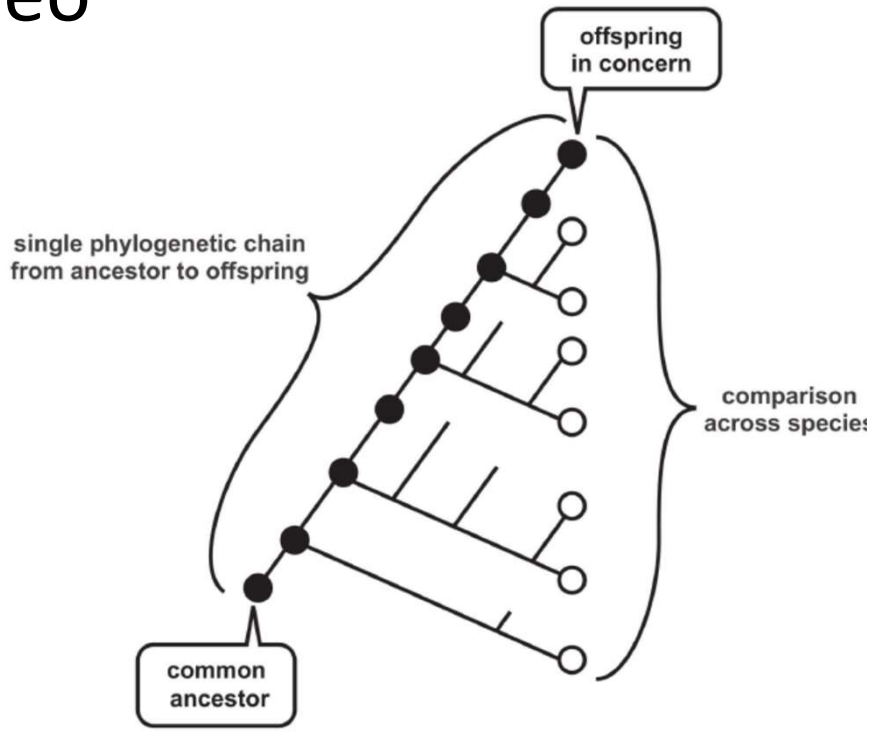
Lag time (recovery) $\mu B = F_A AB \propto B/B = \text{const}$

$\mu = F_A A$ and $A \propto 1/B.$ $\dot{B}(t) \propto -\text{const}$ $B(t) \sim$ (0) $-$ const $\times$

(3) Evolution-Development Congruence?

- Discussed by Haeckel as ontogeny recapitulates phylogeny but too inaccurate, and dismissed
- ?But maybe some relationship between the two
- Merit in numerical evo-deveo

Consistency between
Processes of
different-scale (not states)



Numerical Evolution of development

Cells in 1-dim line

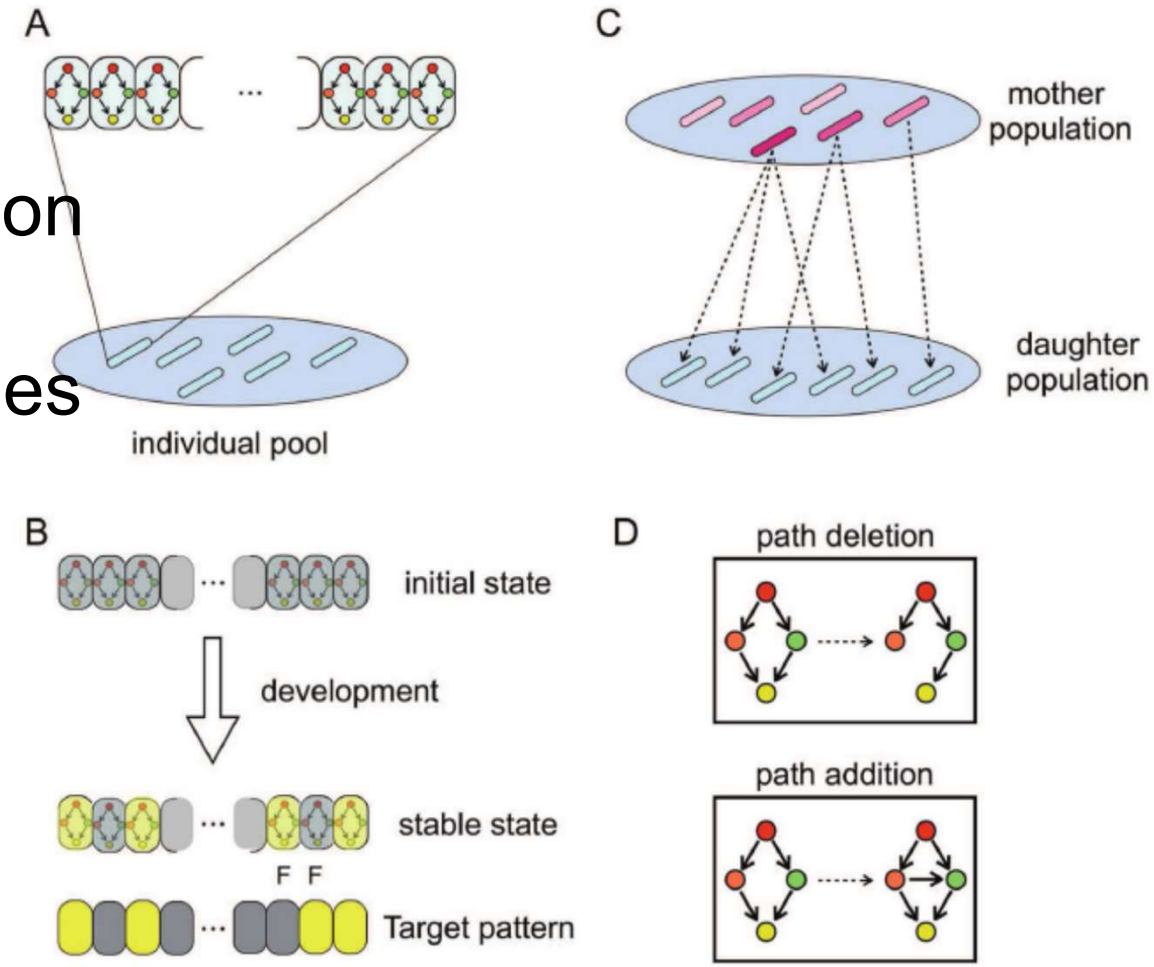
Each cell has protein expression dynamics by GRN

External morphogen gradient for input genes

diffusion of proteins

Evolve GRN by mutation

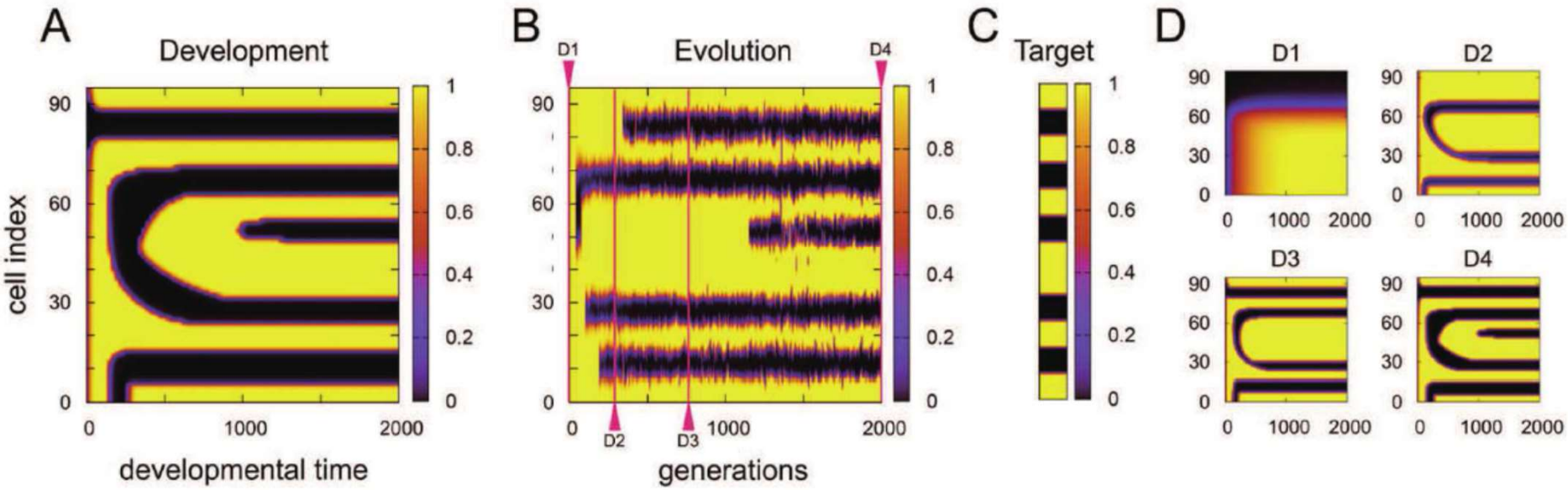
Fitness: Given target pattern for output genes



Kohsokabe & KK
J Exp Zoology B
(2016)

Evo-devo congruence

topology (+ ordering) of stripe pattern formation agrees,

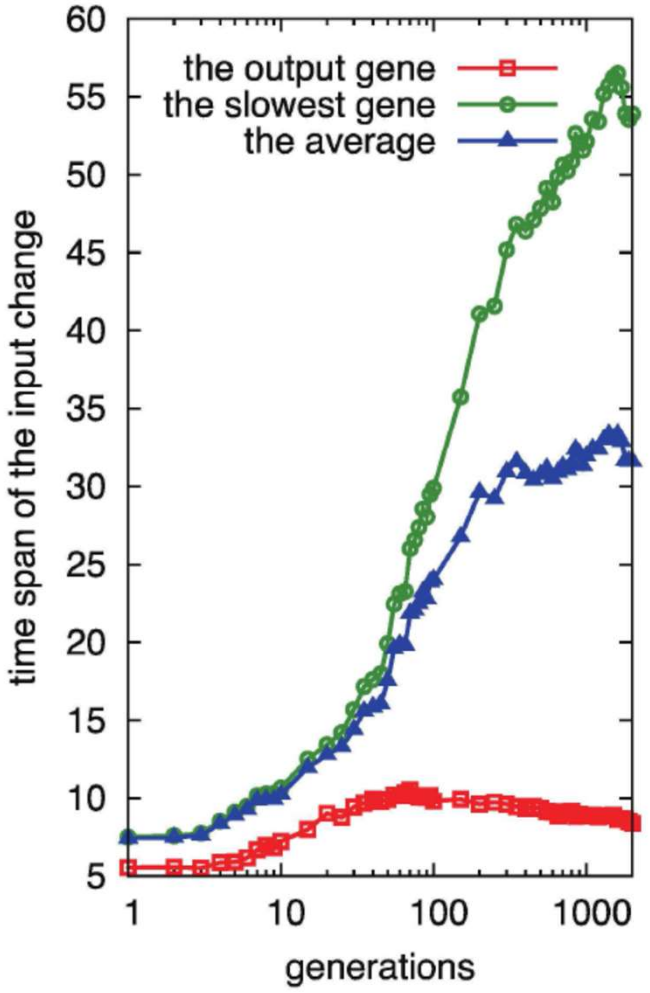


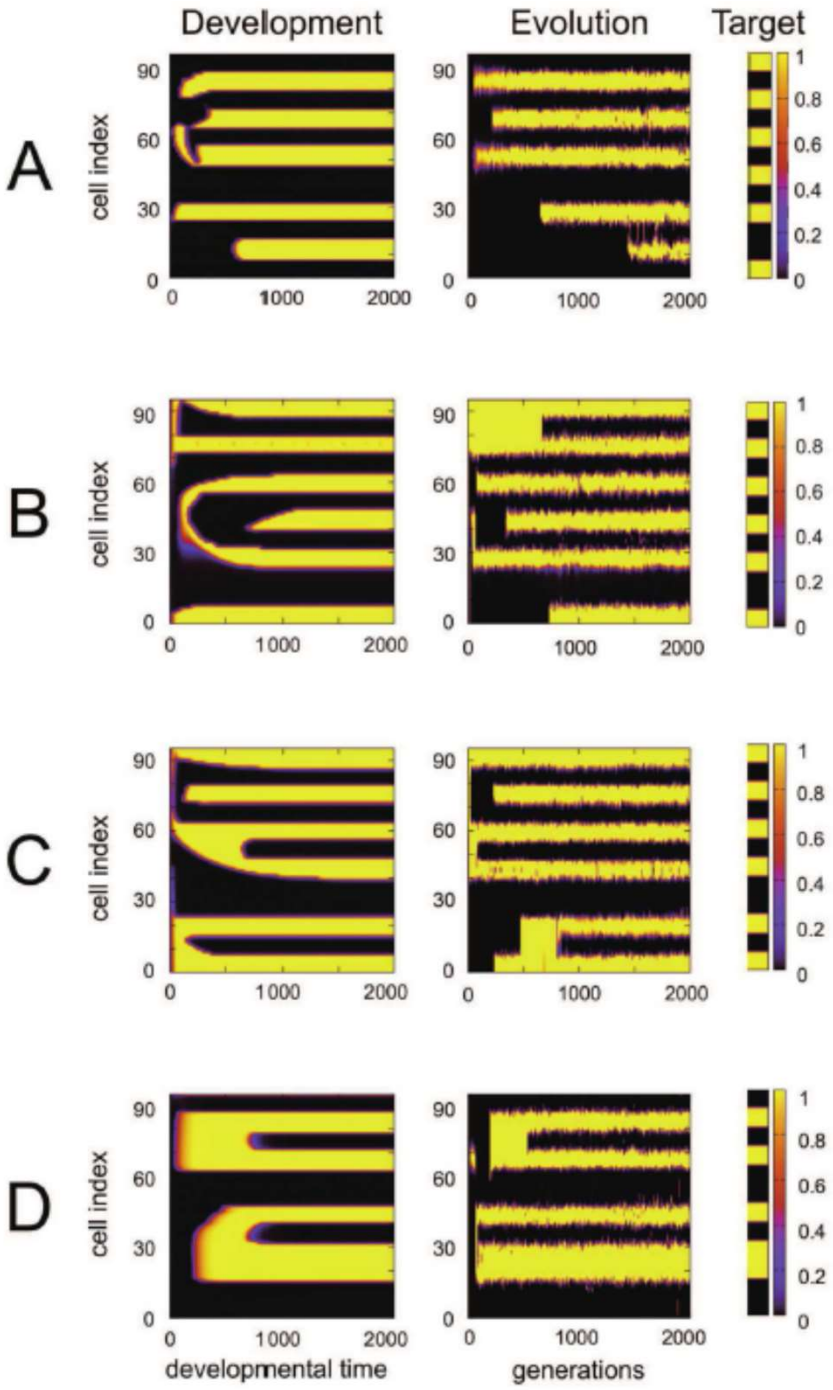
Why congruence?

both evo and devo consist of quasistationary regime + epoch for rapid stripe formation

Evolution –- punctuated equilibrium (need time for relevant mutation)

Development – emergence of genes whose expression change slowly and control the output expression → works as a " bifurcation parameter"

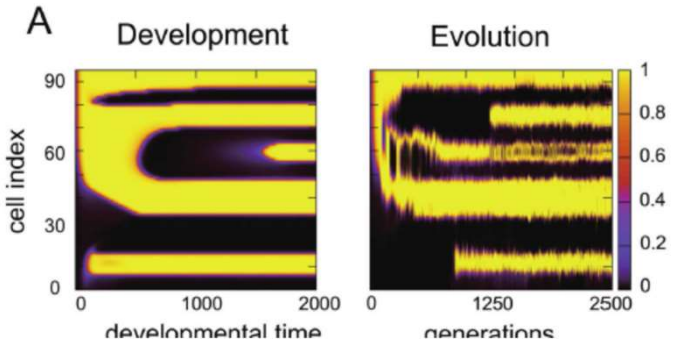




Comparison between evo and devo

For most (95%) examples, good evo-devo congruence

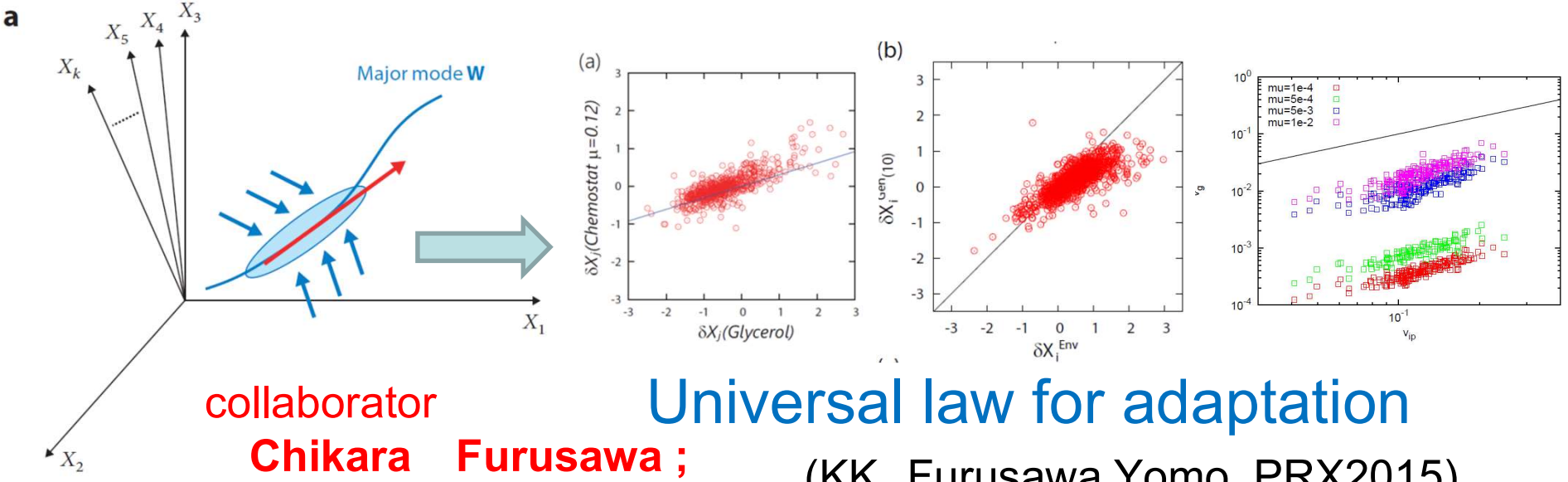
Rare exception



Summary

Low-dimensional structure formed from high-dimensional phenotypic space ← robustness

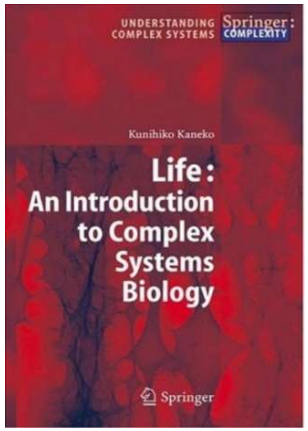
(Furusawa, KK, Phys Rev E, 2018; KK, Furusawa, Ann Rev Biophys 2018; Sato, KK, PRR 2020; Sakata, KK, PRL 2020)



collaborator

Chikara Furusawa ;

Takuya Sato



Universal law for adaptation

(KK Furusawa Yomo PRX2015)

Evolutionary LeChatelier Principle

(Furusawa KK Interface 2015)

Vg-Vip Law (→ direction in phenotypic evolution)