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Educational, Scientific
and Cultural Organization

International Atomic
Energy Agency

Summer School on

Design and Control of Self-Organization in Physical, Chemical, and Biological Systems

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1668/5

Reproduction, Adaptation, and Evolution as a Universal Feature of Dynamical Systems with Growth

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Complex Systems Biology

cf. Life as Complicated System: (current trend)

Enumeration of molecules, processes

detailed models mimicking the life process

But understanding??

Life as Complex System:

Understand General features at a System Level

Strategy:

1) Search for universal features in cellular processes :
extension of Dynamical Systems & Statistical Physics

2) Constructive Approach: (Exp & Theory)

` construct simple system to catch universal features'

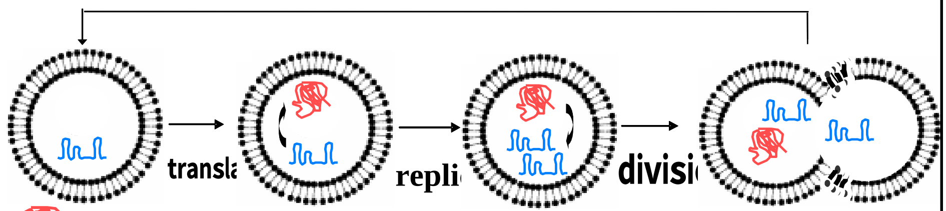
as simple as possible

Constructive Biology Project

theme	experiment	theory	question
replicating system	in vitro replication with enzymatic reaction	minority control	origin of heredity; evolvability
○ cell system	replicating cell with internal reactions	universal statistics in reaction dynamics	condition for recursive growth
cell differentiation. development	differentiation of E Coil by interaction	emergence of differentiation rule from dynamics	irreversibility robustness
○ Spontaneous adaptation	Artificial gene network	Adaptive attractor selection by noise	Robust adaptation without signalling
○ evolution	Relevance of phenotypic fluctuation and dynamics	Genetic assimilation of phenotype fluct.and dynamics	geno-pheno type relationship

ERATO Project Complex Systems Biology (2004 -2010, wiith Tetsuya Yomo (experimentalist)

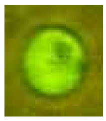
Replicating artificial cell (experiment)
(←→theory; fluctuation, minority control)

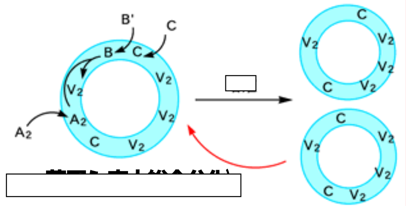


RNA polymerase

RNA polymerase geneRNA

(Yomo's group)





(Sugawara's group)

Tranlation in liposome

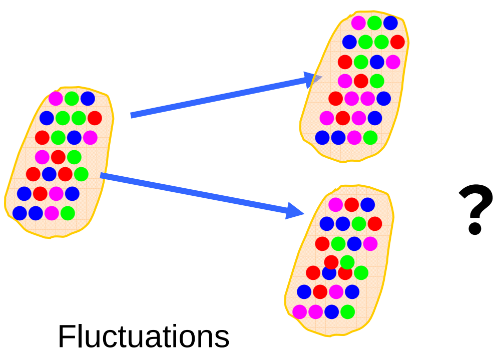
RNAreplication in liposome

Continouos division of liposomes

How recursive production of a cell is sustained ?

each cell complex reaction network with diversity of chemicals;

The number of molecules of each species not so large



Fluctuations

Toy Cell Model with Catalytic Reaction Network
'Crude but whole cell model'

C.Furusawa & KK、PRL2003

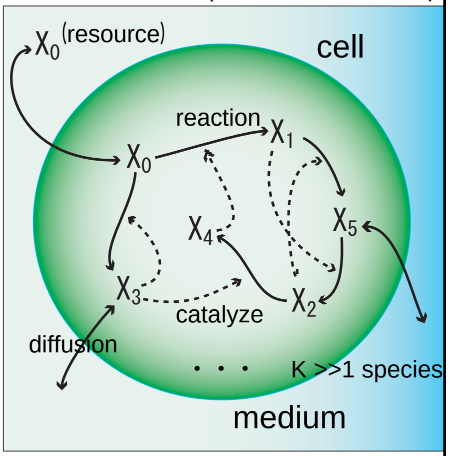
- k species of chemicals、$X_0 \cdots X_{k-1}$
number ---n_0、n_1 … n_{k-1}

- random catalytic reaction network
 with the path rate p
 for the reaction $X_i + X_j -> X_k + X_j$

- some chemicals are penetrable through the membrane with the diffusion coefficient D

- resource chemicals are thus transformed into impenetrable chemicals, leading to the growth in
$N = \Sigma n_i$, when it exceeds N_{max}
the cell divides into two

model 細胞 (Cf. KK&Yomo 94,97)



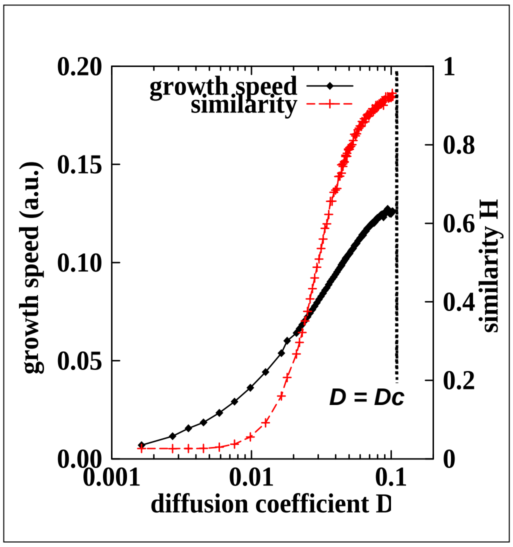
dX1/dt ∝ X0X4; rate equation;
Stochastic model here

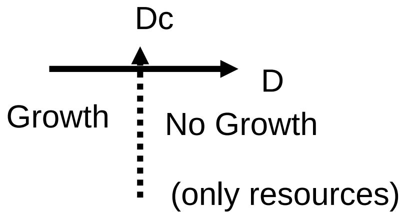
In continuum description, the following rate eqn., but we mostly use stochastic simulation

$$dn_i/dt = \sum_{j,\ell} \mathrm{Con}(j,i,\ell)\epsilon n_j n_\ell / N^2 - \sum_{j',\ell'} \mathrm{Con}(i,j',\ell')\epsilon n_i n_{\ell'} / N^2 + D\sigma_i(\overline{n}_i/V - n_i/N),$$

where $\mathrm{Con}(i,j,\ell)$ is 1 if there is a reaction $i + \ell \rightarrow j + \ell$, and 0 otherwise, whereas σ_i takes 1 if the chemical i is penetrable, and 0 otherwise. The third term describes the transport of chemicals through the membrane, where $\overline{n}_i$ is

☆Growth speed and fidelity in replication are maximum at Dc

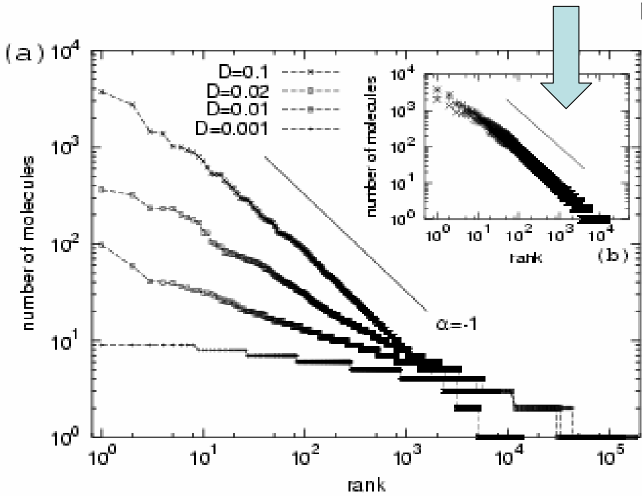


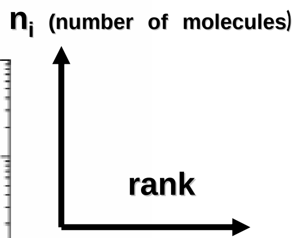


※similarity is defined from inner products of composition vectors between mother and daughter cells

Furusawa &KK,2003,PRL

Zipf's Law is oberved at D = Dc





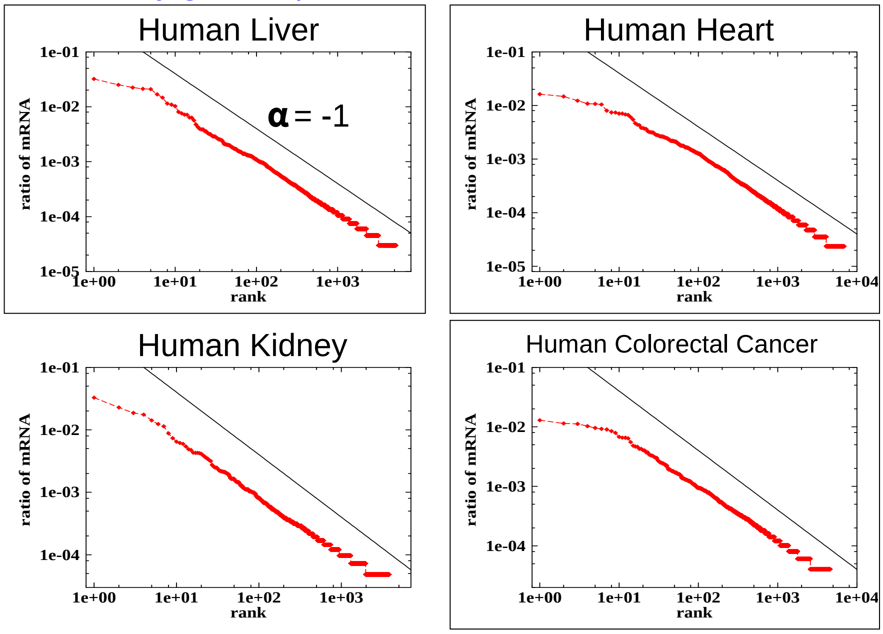
	number	rank
X1	300	5
X2	8000	1
X3	5000	2
X4	700	4
X5	2000	3

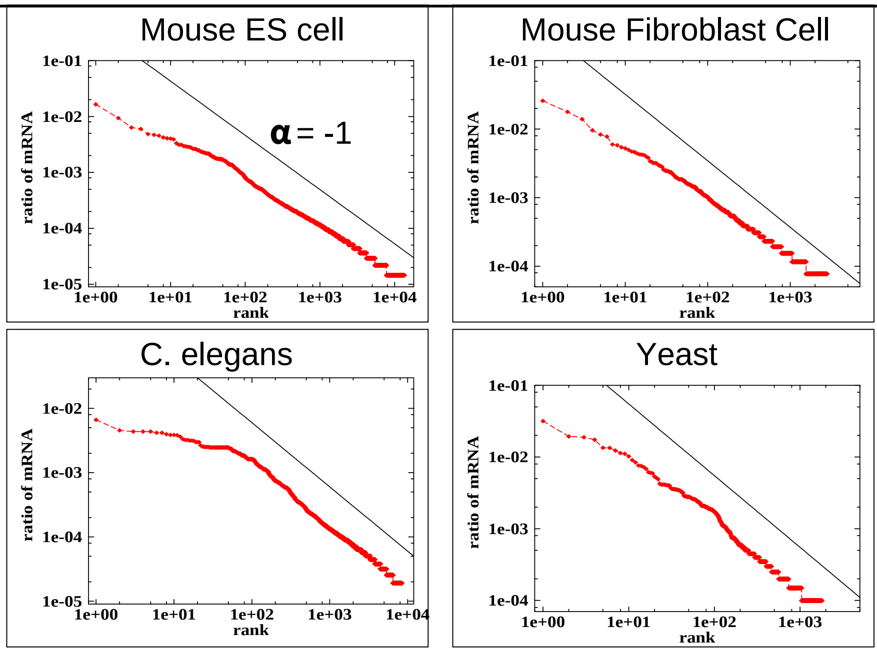
…….. (for example)

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

(distribution of x : $\rho(x) \propto x^{-2}$)

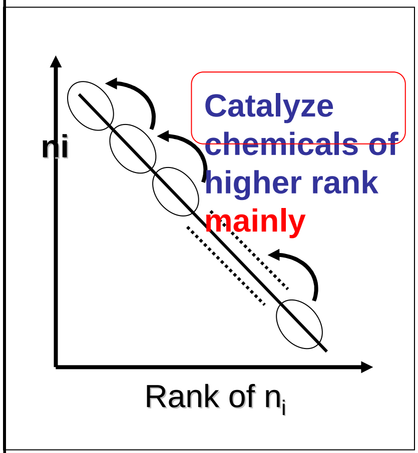
Confirmed by gene expression data

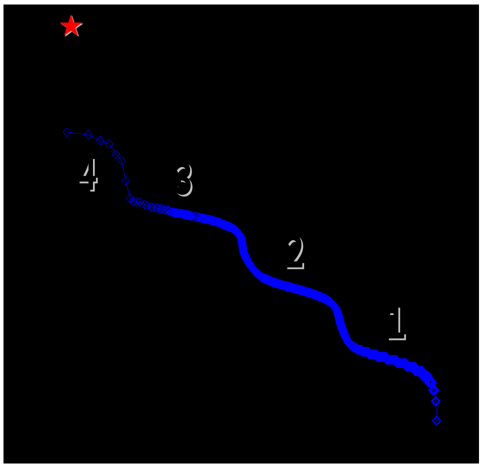




Later confirmed by several other groups

Formation of cascade catalytic reaction





With conservation law,
The exponent -1 is explained

Mean-field type (self-consistent) calc.)

1：minority molecules

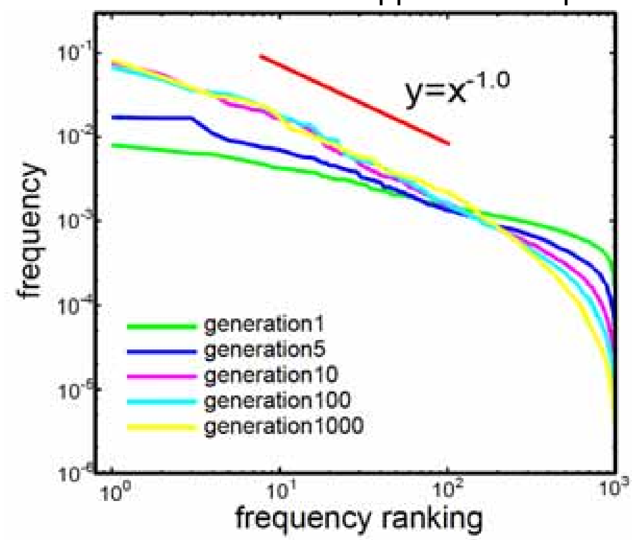
2：catalyzed by 1, synthesized by resource

3：catalyzed by 2

:

Evolution of Network to satisfy Zipf's law? Yes

Critical D value depends on connectivity in the network;
mutation of network + selection → approaches Zipf's law



Furusawa

Fig1. rank distribution of chemical concentrations

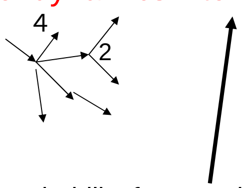
Zipf's law holds, irrespective of network structure, but

Later, the connectivity in the network approaches
" scale-free " network through evolution.

statistical properties; embedded into network structure

Dynamics (abundance) first, structure (equation for dynamics) later

evolutionary embedding of dynamics into network



probability for a path to chemical with abundances x is selected; q(x) → transformation of abundance distrb. to connectivity distrib.

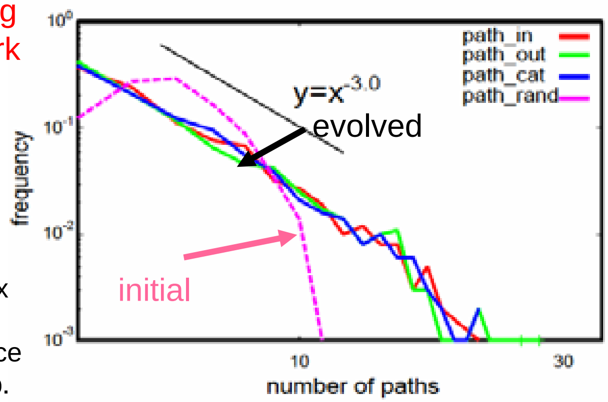


Fig2. connectivity distributions

Furusawa、KK, submitted

Furusawa,.. KK, Biophysics2005

So far average quantity of all components;

Next question: fluctuation by cells: distribution of each Ni by cells

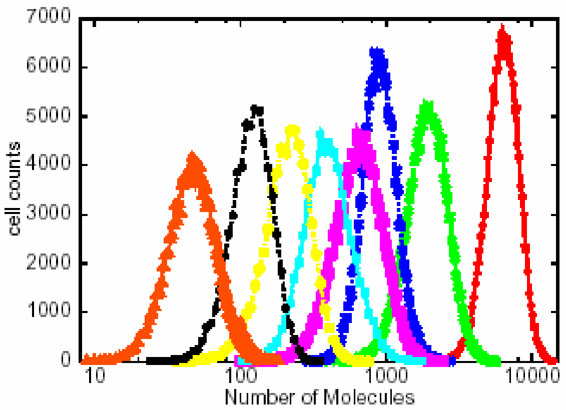
e.g.

cell1	X1	10000
cell2		8000
cell3		15000
cell4		20000

.....

histograrm

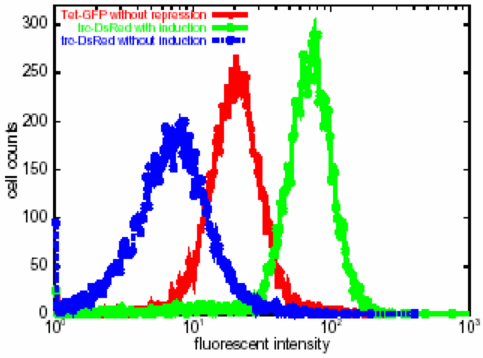
Log normal distribution !



Each color gives different chemical species

LOG SCALE

Experiment; protein abundances measured by fluorescence



+flow-cytometry

Log-normal Distribution Confirmed experimentally

Furusawa,Kashiwagi,,Yomo,KK

Figure 3: The number distribution of the proteins measured by fluorescent intensity. Distributions are obtained from three *Escherichia coli* cell populations containing different reporter plasmids, i.e., EGFP (enhanced green fluorescent protein) under the control of the tetA promoter, DsRed (red fluorescent protein) under the control of the trc promoter with and without IPTG induction. Note that, although the IPTG induction changes the average fluorescent intensity, both the distributions (with and without the induction) can be fitted by log-normal distributions well.

Also studied in GFP synthesis in liposome

☆Heuristic explanation of log-normal distribution

Consider the case that a component X is catalyzed by other component A, and replicate; the number --N_X、N_A

$$d N_X /dt = N_X N_A$$

then

$$d \log(N_X)/dt = N_A$$

If、 N_A fluctuates around its mean $\langle N_A \rangle$, with fluct. $\eta(t)$

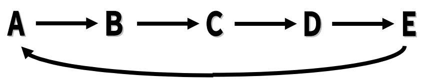
$$d \log(N_X)/dt = \langle N_A \rangle + \eta(t)$$

log(N_X) shows Brownian motion → N_X log-normal distribution

too, simplified, since no direct self-replication exists here

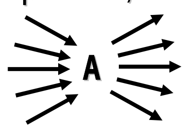
But with cascade catalytic reactions, fluctuations are successively multiplied, (cf addition in central limit theorem.);Hence after logarithm, central limit th. applied

☆Cascade leads to multiplicative propagation of noise (at critical region)



Propagation of fluctuation, feedback to itself, leading to log-normal distribution tail.

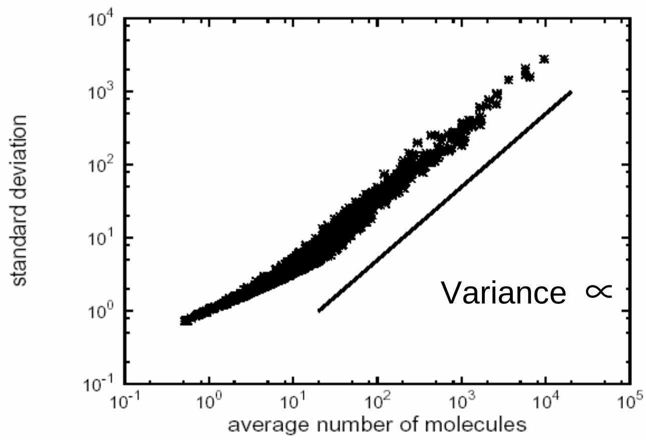
Cf. If parallel,



Fluctuations come in parallel:

Usual central limit theorem is valid;

normal distribution.



Variance $\propto$ (average)^2

Also confirmed experimentally (indirectly)

2. Standard deviation versus average number of molecules. Using the same data set arameters as for Fig.1, the relationship between the average and standard deviation tted for all chemical species. The solid line is for reference.

Questions
(1)Large phenotypic fluctuation →
relevance to biology ?
ans. evolution (Sato et al., PNAS, 2003) adaptation,….
--- recall in standard evolutionary genetics,
only the distribution of gene is discussed, by assuming unique phenotype from a given genotype

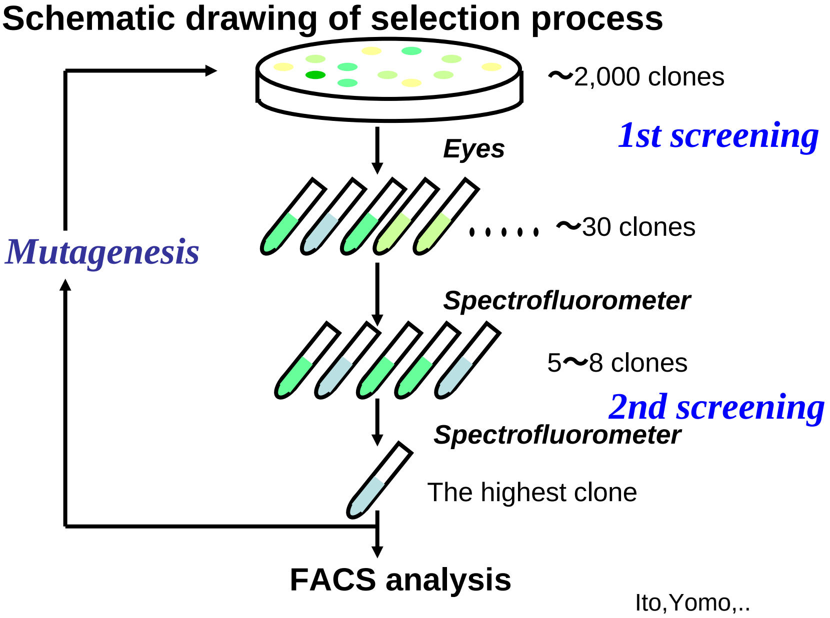
(2) All chemicals have such large fluctuations?
Important ones are protected??
Origin of heredity (genetic information)
why is there genotype and phenotype

--in terms of dynamical systems
gene: equation of dynamical systems, parameter,
Phenotype: variable according to the dynamical systems (with fluctuations)

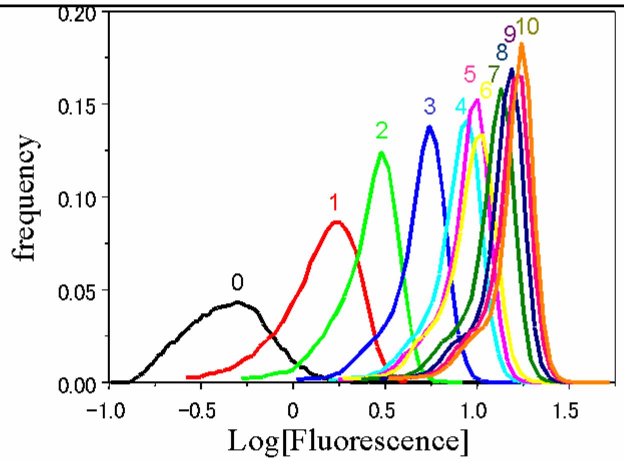
Artificial selection experiment with bacteria

Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process



Ito,Yomo,..



Sato,Ito,Yomo,KK
PNAS(2003)

Fluctuation ---- Variance of phenotype of clone

Organisms with larger phenotypic fluctuation higher evolution speed;

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

Response ←→ Fluctuation

So-called fluctuation-dissipation theorem in physics:

Force to change a variable x;

response ratio = (shift of x) / force

fluctuation of x (without force)

response ratio proportional to fluctuation

originated by Einstein's paper a century ago…

Generalization::(mathematical formulation)

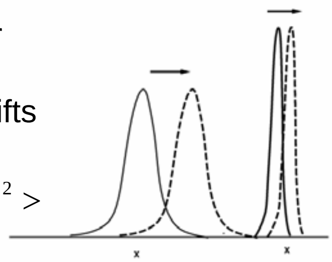
response ratio of some variable x against the change of parameter a versus fluctuation of x

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

change of the parameter a →

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

$$\frac{\langle x \rangle_{a+\Delta a} - \langle x \rangle_a}{\Delta a} \propto \langle (\delta x)^2 \rangle_a = \langle (x - \langle x \rangle)^2 \rangle$$



Gaussian Distribution

$$P(x;a) = Ne^{-\frac{(x-\beta(a))^2}{2\alpha(a)}}$$

Change of distribution by the change of parameter a→a+△a

$$P(x;a+\Delta a) = N'e^{-\frac{(x-\beta(a+\Delta a))^2}{2\alpha(a+\Delta a)}}$$

$$= N'e^{-\frac{(x-\beta(a))^2}{2\alpha(a)}+\varepsilon^{(1)}(a,\Delta a)(x-\beta(a))+\frac{1}{2}\varepsilon^{(2)}(a,\Delta a)(x-\beta(a))^2}$$

where

$$\varepsilon^{(1)}(a,\Delta a) = \frac{\beta(a+\Delta a)-\beta(a)}{\alpha(a)}$$

$$\varepsilon^{(2)}(a,\Delta a) = \frac{\alpha(a+\Delta a)-\alpha(a)}{\alpha(a)^2}$$

then

$$\langle x\rangle_{a+\Delta a} - \langle x\rangle_a = \varepsilon^{(1)}(a,\Delta a)\sigma_a^2$$

$$\sigma_{a+\Delta a}^2 - \sigma_a^2 = \varepsilon^{(2)}(a,\Delta a)(\sigma_a^2)^2$$

If change of a is not large

$$\varepsilon^{(1)}(a,\Delta a) = b\,\Delta a$$

b; constant

$$\langle x\rangle_{a+\Delta a} - \langle x\rangle_a = b\,\Delta a\,\sigma_a^2$$

Response ratio is proportional to fluctuation

Artificial selection experiment with bacteria

for enzyme with higher catalytic activity

for some protein with higher function

Change in gene (parameter; a) ⇒

``Response'' ------ change of phenotype <x>

(e.g.,fluorescence intensity)

per generation per (synonymous) mutation rate

Fluctuation ---- Variance of phenotype x of clone

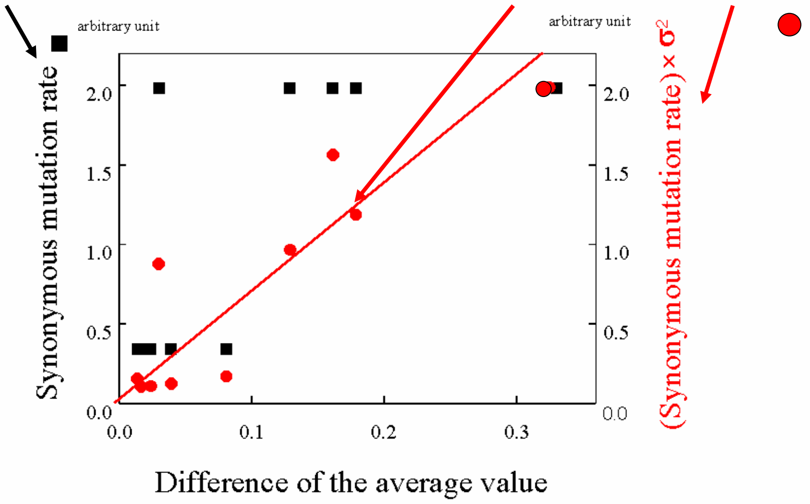
Fluctuation in the phenotype x of clone

⇔ speed of evolution to increase <x>

(proportional or correlated)

Naïve expectation:
Just propt to mutation rate

Fluctuation-response relation
Phenotype fluct. × mutation rate



(Evolution Speed per generation)

Sato,Ito,Yomo,KK, PNAS 2003

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

Mutate the network ('gene') with mutation rate μ, (rewire the path of the network with the rate) and select such network

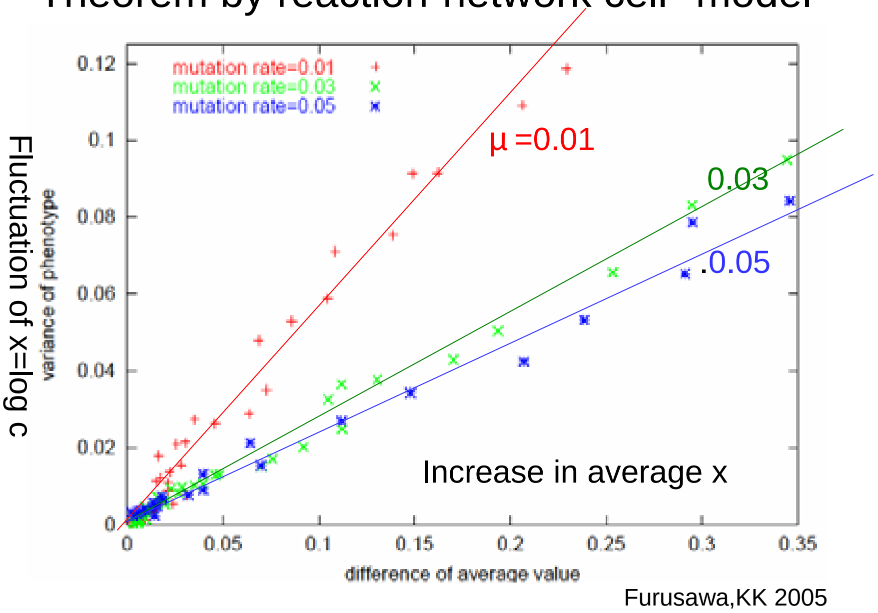
having highest concentration c of

a given specific chemical

Measure the phenotypic fluctuations of clone

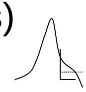
concentration distribution is log-normal, so we choose log c as a variable

Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model



Furusawa,KK 2005

(1) the use of log(fluorescence), because
log x is close to Gaussian distribution in experiments
(2): relationship between
phenotype fluctuation of clone vs evolution speed
in contrast to
phenotype fluctuation by gene variation (mutation) vs. evolution speed (standard population genetics)
relationship??



what phenotype can vary ←→what gene can change
fluctuation of variable (micro) vs
variation of equation (genetic evolution)
Indeed, by assuming also gene a variable, and P(x,a) as 2 variable distrib., a general relation between geno- and pheno-type fluctuations is obtained
(KK,Furusawa submitted) →theory of genetic assimilation
self-consistency between micro & genetic levels

- In the talk I derived general relationship between the phenotypic fluctuation of clone vs phenotypic fluctuation by genetic change.
- This leads to a theory of geno-pheno relationship at fluctuation level
- Since the contents are not ye published

(under review), they ar omitted here. Please ask me if you are interested in

In the talk, we have proposed

novel Mechanism of Spontaneous Adaptation (without the use of signal transduction)

based on stochastic fluctuation.

Here I omit this part since the results are not yet published (I can tell you privately if you are interested)

Summary

- How is recursive production of cells possible in the amidst of diversity and fluctuations?

  → Universal Statistics: amplification and regulation of fluctuations. (Zipf's law and log-normal distribution)

- Biological relevance of such large fluctuations?

  → Phenotypic Fluctuation ∝ Evolution Speed

- Spontaneous adaptation with noise to select a state with higher growth in advance

All are 'universal features' in steady growth system!

- Collaborators:

  Chikara Furusawa （Reaction network of cell(Zipf's law,Log-normal), Cell-differentiation)

  Katsuhiko Sato (fluctuation-response relationship)

  experiments：

  Tetsuya Yomo

  Akiko Kashiwagi, Takao Suzuki, Yoichiro Ito (Yomo's group)

・Most papers mentioned here are available at

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

(PNAS,2003;PRL2003;…)