Complex Systems Biology

- cf. Life as Complicated System: (current trend)
  Enumeration of molecules, processes
detailed models describing the life process
But understanding??

Life as Complex System:
Understand Universal features at a System with mutual dependence between parts and whole

Strategy:
1) extension of Dynamical Systems & Statistical Physics
   → Catch consistency between micro-macro levels
2) Constructive Approach: (Exp & Theory)
   `construct simple system to catch universal features' as simple as possible
Consistency between different levels
(1) Cell reproduction vs molecule replication (03-)
(2) Reproduction of multicellular organism vs of cells (97-)
(3) Adaptation vs Reproduction (06-)
(4) Genetic change vs Phenotypic Fluctuation (03-)
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Complex Systems Biology Project (JST, ERATO; KK, Yomo, …)
How is recursive production of a cell sustained? Each cell complex reaction network with diversity of chemicals;
The number of molecules of each species not so large
Cell Model with Catalytic Reaction Network

Crude but whole cell model ♤

\[ \text{model} \]

(Cf. KK&Yomo 94,97)

- \( k \) species of chemicals \( \mathbb{Q}_0 \ldots \mathbb{Q}_{k-1} \)
- random catalytic reaction network
  - with the path rate \( p \)
  - for the reaction \( \mathbb{Q}_0^+ \mathbb{Q}_0^- \rightarrow \mathbb{Q}_0 \mathbb{Q}_0 \)
- 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 \( N = \sum n_i \), when it exceeds \( N_{\text{max}} \)
  - the cell divides into two

\[ \frac{dX_1}{dt} = X_0 X_4; \quad \text{rate equation; Stochastic model here} \]
In continuum description, the following rate eqn., but we mostly use stochastic simulation

\[
\frac{dn_i}{dt} = \sum_{j, \ell} \text{Con}(j, i, \ell) \epsilon n_j n_\ell / N^2 \\
- \sum_{j', \ell'} \text{Con}(i, j', \ell') \epsilon n_i n_{\ell'} / N^2 \\
+ D \sigma_i (\bar{n}_i / V - n_i / N),
\]

where \(\text{Con}(i, j, \ell)\) is 1 if there is a reaction \(i + \ell \rightarrow j + \ell\), and 0 otherwise, whereas \(\sigma_i\) takes 1 if the chemical \(i\) is penetrable, and 0 otherwise. The third term describes the transport of chemicals through the membrane, where \(\bar{n}_i\) is
Growth speed and fidelity in replication are maximum at $D_c$.

Similarity $H$ is defined from inner products of composition vectors between mother and daughter cells.

Growth speed and similarity are maximum at $D_c$.
Zipf’s Law is observed at $D = D_c$

Average number of each chemical $\frac{1}{1/(\text{its rank})}$

(distribution of $x$: $\frac{1}{x}$ for $x \geq 1$)

Furusawa & KK, 2003, PRL
Confirmed by gene expression data

Human Liver

\[ \mathcal{a} = -1 \]

Human Heart

Human Kidney

Human Colorectal Cancer
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

Catalyze chemicals of higher rank mainly
• Remarks:

(0) Universality

(1) Evolution to the critical state (with Zipf law) is confirmed numerically

(2) Evolution to scale-free network appears later as embedding of power-law abundances into network (Furusawa, KK, PRE 2006)

(3) Self-organization to critical state, if transport of ‘nutrition chemicals’ is catalyzed by some chemicals (no need for choice of D) (instead of simple diffusion) (Furusawa, KK, 2007)
Evolution of Network to satisfy Zipf’s law? Yes

Critical D value depends on connectivity in the network; mutation of network + selection \(\rightarrow\) approaches Zipf’s law

![Graph showing rank distribution of chemical concentrations]

\[ y = x^{-1.0} \]

Furusawa

Fig1. rank distribution of chemical concentrations
Zipf’s law holds, irrespective of network structure, but later, the connectivity in the network approaches a 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; $q(x) \rightarrow$ transformation of abundance distrib. to connectivity distrib.

Furusawa, KK, PRE, 2006
So far average quantity of all components;

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

Log normal distribution!

Furusawa,.. KK, Biophysics 2005

e.g.
cell1 X1 10000
cell2 8000
cell3 15000
cell4 20000

.....

histogram

Each color gives different chemical species
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 --$N_X$, $N_A$

$$\frac{d N_X}{dt} = N_X N_A$$

then

$$\frac{d \log( N_X )}{dt} = N_A$$

If $N_A$ fluctuates around its mean $<N_A>$, with fluct. $(t)$

$$\frac{d \log( N_X )}{dt} = <N_A> + \Box (t)$$

$log( N_X )$ shows Brownian motion $\rightarrow N_X$ 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.
Replicating artificial cell (experiment) (↔ theory; fluctuation, minority control)

RNA polymerase gene RNA replication in liposome

Translation in liposome

RNA replication in liposome

Continuous division of liposomes

(Sugawara’s group)

(Yomo’s group)
Questions
(1) All chemicals have such large fluctuations? Important ones are protected?? Origin of heredity (genetic information) why is there genotype and phenotype Minority control mechanism (discreteness important) (KK,Yomo  JtheorBiol.2002)

(2)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
• Phenotypic Fluctuation → Relationship to Evolution?
  selection is based on phenotype
  (activity, size, protein abundances, fluorescence,…),
  but
  in standard evolutionary genetics;
  gene a → phenotype x uniquely determined

mostly discusses the phenotype distribution
  as a result of genetic variation

Phenotypic fluctuation of isogenic organisms
  → P(x; a) x—phenotype, a – gene
Artificial selection experiment with bacteria
Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process

Mutagenesis

1st screening

Eyes

Spectrofluorometer

2nd screening

Spectrofluorometer

The highest clone

FACS analysis

Ito, Yomo, ..
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 $\leftrightarrow$ Fluctuation
So-called fluctuation-dissipation theorem in physics:
Force to change a variable $x$;
response ratio $= \frac{\text{(shift of } x \text{ )}}{\text{force}}$
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 $a$ $\to$
peak of $P(x; a)$ (i.e., $<x>$ average) shifts

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

Gaussian distribution of \( x \); under the parameter \( a \)

\[
P(x; a_0) = N_0 \exp\left(-\frac{(x - X_0)^2}{2\alpha_0}\right),\quad \text{at } a=a_0
\]

Change the parameter from \( a_0 \) to \( a \)

\[
P(x : a) = N \exp\left(-\frac{(x - X_0)^2}{2\alpha(a)} + v(x, a)\right)
\]

\[
v(a, x) = C(a - a_0)(x - X_0) + \ldots, \text{ with } C \text{ as a constant,}
\]

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

Hence, we get

\[
\frac{\langle x \rangle_{a=a_0+\Delta a} - \langle x \rangle_{a=a_0}}{\Delta a} = C\alpha(a_0 + \Delta a),
\]

Noting that \( \alpha = \langle (\delta x)^2 \rangle \)

\[
\frac{\langle x \rangle_{a=a_0+\Delta a} - \langle x \rangle_{a=a_0}}{\Delta a} = C < (\delta x)^2 >,
\]
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 prop to mutation rate

Difference of the average value

(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 ̶, (rewire the path of the network with the rate) and select such network having highest concentration ̲ of a specific chemical

1. Prepare initial mother cells.

2. From each parent cell, mutant cells are generated by randomly replacing reaction paths, with mutation rate ̶

3. reaction dynamics of all mutants are simulated to determine phenotype x

4. Top 5% cells with regard to phenotype x are selected as parent cells of next generation

phenotype x = \log (n_s)
Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model

Furusawa, KK 2005

\[
\text{Fluctuation of } x = \log c
\]

Increase in average \(x\)

Decrease in variance of phenotype

difference of average value

Furusawa, KK 2005
(1) the use of log(fluorescence), because log \( x \) is close to Gaussian distribution in experiments.

(2) New mystery? phenotype fluctuation of clone vs evolution speed in contrast to evolution speed — phenotypic fluctuation by genetic variation (\( V_g \)): (fundamental theorem of natural selection; established)

- pheno fluct of clone \( V_p \)
- pheno fluct by gene variation \( V_g \) ?

(fluct by noise — variation in ‘equation’)

Follow the spirit of Einstein;
micro-macro consistency → Brownian motion.
Consider 2-variable distrb
$P(x=\text{phenotype}, a=\text{genotype}) = \exp(-V(x,a))$

Keep a single-peak (stability condition).

(Hessian condition)

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

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

Up to this point, pheno $(x)$ and geno $(a)$ are treated in the same way. Then given $a$, the peak (average) phenotype is $x_0(a)$ -- function of $a$ -- $\partial V/\partial x \mid_{x=x_0} = 0$
Gene a is also regarded as variable: Now, we discuss stability $P(x,a)$ as 2 variables instead of $P(x;a)$. write as $P(x,a) = \exp(-V(x,a))$

Condition if it keeps a single-peak solution (stability problem in thermodynamics).

Hessian condition

$$\frac{\partial^2 V}{\partial a^2} \geq 0$$ (1)

$$\frac{\partial^2 V}{\partial x^2} \geq 0$$ (2)

$$\left(\frac{\partial^2 V}{\partial x^2}\right)\left(\frac{\partial^2 V}{\partial a^2}\right) - \left(\frac{\partial^2 V}{\partial a \partial x}\right)^2 \geq 0$$ (3)

Up to this point pheno (x) and geno (a) are treated in the same way. Then given a, the peak (average) phenotype is $x_0(a)$--function of a --

$$\frac{\partial V}{\partial x}|_{x=x_0} = 0$$
x0(a); the average phenotype x of a clone of genotype a; x is given as a function of a
Hessian $\rightarrow$ $V_g \neq V_i \rho$

$V_g =$ Variance of $x$, due to the distribution of gene $a$

\[
< (x_a - x_0)^2 > = V_g = < (\delta a)^2 > \left(\frac{\partial x_0}{\partial a}\right)^2,
\]

$V_i =$ Variance of $x$, for the isogenic organism
(i.e., $a = a_0$, fixed)

$V_g$ increases with mutation rate $\mu$, thus, there is critical mutation rate $\mu_c$ beyond which the distribution becomes flat (error catastrophe).

As $V_g \neq \mu$ approximately,

$V_g = (\mu / \mu_c) V_i \rho$

Since $V_g \neq$ evolution speed (Fisher theorem)

evolution speed $\neq \mu V_i \rho$ $\rightarrow$ fluct-response relation
We can do the analysis by using Gaussian 2-body distribution function for phenotype \( x \) and gene \( a \); around \( a = a_0 \), and \( x = x_0 \), with coupling between \( x \) and \( a \) (variance of \( a \) is the mutation rate). 

\[
P(x, a) = \text{Nexp} \left[ -\frac{(x - X_0)^2}{2\alpha(a)} + C(a - a_0)(x - X_0) - \frac{1}{2\mu}(a - a_0)^2 \right],
\]

\[
P(x, a) = \text{Nexp} \left[ -\frac{(x - X_0 - C(a - a_0)\alpha)^2}{2\alpha(a)} + \left(\frac{\alpha C^2}{2} - \frac{1}{2\mu}\right)(a - a_0)^2 \right],
\]

**Stability condition**

\[
\frac{\alpha(a_0)C^2}{2} - \frac{1}{2\mu} \leq 0, \quad \text{i.e.,} \quad \mu \leq \frac{1}{(C^2\alpha(a_0))} \equiv \mu_c
\]

For high mutation rate single-peak is not sustained (error catastrophe).
Distribution of phenotype $x$ of a clone $\Rightarrow Vp$

Change of distribution through evolution

Distribution of phenotype $x$ over mutants (genetic variation) $\Rightarrow Vg$
Phenotype fluct. (Vp) vs Gene Fluct. (Vg) in the evolution of toy cell model

Vp: fluct. for given network, Vg: fluct. by network variation

Vp = Vg

\[ \text{variance of \( \log(x) \), } \quad x \text{ is the concentration of the molecule} \]

Beyond Darwin with the spirit of Einstein!
As $\mu$ (mutation rate) increases to $\mu_{\text{max}}$,
(1) the distribution collapses (error catastrophe)
(2) evolution no longer progresses beyond $\mu_{\text{max}}$
evolution speed is maximal at $\mu \sim \mu_{\text{max}}$
(3) $V_g$ approaches $V_p$

As $\mu$ is increased,
The distribution 'collapses'
Error catastrophe
• ??? to the theory
• P(x,a) rather than conditional probability (TRICK)
  “Genetic-Phenotypic correspondence”
  what phenotype can vary ↔ what gene can change
  fluctuation of variable (micro) vs variation of equation (genetic evolution)
  (cf Waddington’s genetic assimilation)

Q: Why error catastrophe when Vg>Vip?
  Robust evolution is possible only under noise
  -counterintuitive ; it says phenotype noise is important
  → gene-net model
A simple model for Geno-Pheno relationship;
Model: Gene-net (dynamics of stochastic gene expression) \(\rightarrow\) on/off state

\[ x_i \rightarrow \text{expression of gene } i \quad : \quad + (\text{on}) - (\text{off}) \]

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

\[ <\eta(t)\eta(t')> = \delta(t-t'). \]

\[ J_{ij} = -1, 1, 0, \]

Gaussian white noise

\( M; \) total number of genes, \( k \): output genes

Noise strength \( \sigma \)
• Task
  
  Starting from -1,-1,-1,,,-1(all off)
  \[ x_i \quad i=1, 2, \ldots, k \] are +1(on)  (Target Gene Pattern)

  Fitness  \[ F = - \left( \text{Average number of off } x_i \right) \]

  Genetic Algorithm
  
  Select networks with higher \(<F>\)
  top--\(<F>=0\)
  Choose top \( n \) networks
  among total \( N \), and mutate
  with rate \( \rho \) to produce \( N \) networks
  (\( \rho \):fixed mutation rate)
Result of evolution

Top: reaches the fittest faster for lower noise (\( \sigma \))

Lowest: cannot evolve for low noise (\( \sigma \))
Fitness Distribution

\[ \mu < \sigma_c \] -- low fitness mutants distributed

\[ \mu > \sigma c \] - eliminated through evolution
Existence of critical noise level $\mathcal{c}$ below which low-fitness mutants accumulate (error catastrophe)
(1) $V_{ip} \supseteq V_{g}$ for $c$

(2) $V_{g} \supseteq V_{ip}$ as $c$

(3) Evolution progresses only for $V_{ip} \supseteq V_{g}$

(4) $V_{ip} \supseteq V_{g}$ through evolution course

Theory confirmed

Why?; difference in basin structure

\[ \square > \square c \rightarrow \text{large basin for target attractor} \]

(robust, \( \square \) (distance to basin boundary) \( \square \))

\[ \square < \square c \rightarrow \text{only tiny basin around target orbit} \]

\[ \square \text{remains small} \]

\[ \rightarrow \text{Global constraint to potential landscape (funnel?)} \]
why threshold?

choose paths to avoid turning pts within $\mathbb{M}$ (noise)

Mutation $\mathbb{V}$ touches turning points within range of $\mathbb{M}$

small $\mathbb{V}$ - $\mathbb{M}$ - > an orbit with small $\mathbb{V}$
can reach the target

- low ($\leq \sigma_c$)
- high ($\geq \sigma_c$)
Deviation of basin boundary (turning points) by Noise $\rightarrow \Delta p$
by Mutation $\rightarrow \Delta g$

\[ V_g \sim \left( \frac{\Delta g}{\Delta p} \right)^2 \]
\[ V_{ip} \sim \left( \frac{\Delta p}{\Delta p} \right)^2 \]

$\Delta$ increases
$\rightarrow \text{robustness increases}$
if $\Delta g > \Delta p$,
mutation destroys the history
$\rightarrow V_{ip}>V_g$ necessary for evolution of robustness

$\Delta \sim \text{distance to turning points (basin boundary)}$
Discussion
• Developmental Robustness to noise ---- Vip
• Robustness to mutation in evolution ---- Vg
When Vip > Vg, both decrease, i.e., robustness
Noise is necessary for evolution of robustness
Vip > Vg → Developmental robustness and genetic (evolutionary) robustness are linked

• Generality of our result; For a system satisfying:
(1) fitness is determined after developmental dynamics
(2) developmental dynamics is complex
(eg., with distributed catastrophic pt leading to error
(3) effective equivalence between mutations and noise with regards to the consequence to fitness
(→ genetic assimilation by Waddington)
Spontaneous Adaptation

• For all possible changes in environment, signal transduction network is already provided?
• Or, is there any general (primitive) mechanism to make spontaneous adaptation?
• → Constructive Experiment with artificial Gene and theory assuming only growth condition and stochasticity
(ex) Adaptive response without signal transduction

Embedded gene network

Phenomenological theory of attractor selection

Unexpected ; beyond designed
Selection of preferable state

Kashiwagi, Yomo
• Embedded network: each of the two can be selected equally. However, ‘good’ attractor in each environment is selected. Why?
• Due to hidden signal network? NO!: verified by exchanging the promoter
• After each state is attracted with 50%, cells in a ‘bad’ attractor cannot grow, cells in a good attractor can grow, so that good attractors are selected? NO!; the process occurs without (or before) the cell division process

**Novel Mechanism of Spontaneous Adaptation (without the use of signal transduction) should exist!**
• Basic Logic
  \[
  \frac{dx_i}{dt} = F(\text{Activity}) f(x_i) - G(\text{Activity}) x_i + \mathcal{N}(t)
  \]
  
  $F, G$: increase with activity.
  
  active: synthesis, degradation both are fast
  
  $\mathcal{N} \rightarrow$ noise

*Active state*: both $F f$ and $G x$ are large
  
  deterministic part $>>$ noise

*Poor state*: both $F f$ and $G x$ are small
  
  deterministic part $\sim$ noise

**Switch from Poor state to Active state by noise**

(Kashiwagi, Urabe, kk, Yomo; submitted)
The mechanism for adaptive response by attractor selection

\[
\frac{d}{dt} m_1 = \frac{\text{syn}(act)}{1 + m_2^2} - \text{deg}(act) \times m_1 + \eta_1
\]

\[
\frac{d}{dt} m_2 = \frac{\text{syn}(act)}{1 + m_1^2} - \text{deg}(act) \times m_2 + \eta_2
\]

\[
\frac{d}{dt} act = \frac{\text{pro}}{((\frac{\text{Nut}_1}{m_1 + \text{Nutrient}_1})^{n_1} + 1) \times ((\frac{\text{Nut}_2}{m_2 + \text{Nutrient}_2})^{n_2} + 1)} - \text{cons} \times act
\]

\[
\text{syn}(act) = \frac{6act}{2 + act}; \text{deg}(act) = act;
\]

Adaptive Response of the genetic network to a environmental change.
\[
\frac{d}{dt} m_1 = \frac{\text{syn}(act)}{1 + m_2^2} - \text{deg}(act) \times m_1 + \eta_1
\]

\[
\frac{d}{dt} m_2 = \frac{\text{syn}(act)}{1 + m_1^2} - \text{deg}(act) \times m_2 + \eta_2
\]

\[
\text{syn}(act) = \frac{6act}{2 + act}; \text{deg}(act) = act;
\]

\[
\frac{d}{dt} act = \frac{\text{pro} \times \text{cons} \times act}{(\frac{\text{Nut\_thread}_1}{m_1+\text{Nutrient1}})^n + 1) \times (\frac{\text{Nut\_thread}_2}{m_2+\text{Nutrient2}})^n + 1)
\]

**Fraction that adaptive attractor is selected**

---

Noise strength

---

Adaptive Attractor
• Growth-Induced-Attractor-Selection (Furusawa kk)

• Basic Logic
\[\frac{dx_i}{dt} = f(x_i) - S(x_j) x_i + \theta(t)\]
  \[S \rightarrow \text{dilution effect}\]
  \[\theta \rightarrow \text{noise}\]

**Active state**: both \( f \) and \( S \) are large
  deterministic part \( >> \) noise

**Poor state**: both \( f \) and \( S \) are small
  deterministic part \( \sim \) noise

Switch from Poor state to Active state by noise

Selection before reproduction

General logic in a system with growth and fluctuation
Gene network -> a huge number of attractors coexist with different growth speeds
Spontaneous selection of optimal growth states
General in a system with noise and growth
Summary

Consistency Principle for Biology
-- replication of molecules and cells: Universal Laws
(--- replication of cells and cell ensembles)
--- genetic and phenotypic changes
  (+speciation)
--- adaptation of internal cellular state and growth

Biological relevance of phenotype fluctuations?
  ➔ Phenotypic Fluctuation △ Evolution Speed
  ➔ Relation between
    (isogenic)phenotype fluctuation vs phenotype variation by mutation

• Robustness to mutation and to developmental noise are linked
• Growth system ➔ general adaptation by noise
• consequence of steady growth system
Collaborators
Chikara Furusawa
Katsuhiko Sato

experiment

Tetsuya Yomo
Yochiro Ito
Akiko Kashiwagi

Most papers (biology, Dynamical systems)
Available at
http://chaos.c.u-tokyo.ac.jp

(2006, August)

ERATO Complex Systems Biology Project