• 2nd Talk: Phenotypic Evolution

• Evolutionary Fluctuation-Response Relation
• Evolution of Robustness, Genotype-Phenotype Relation
• Sympatric Speciation as a result of phenotype differentiation
• Evolution of Development
• Spontaneous Adaptation by Noise
• Summary+Discussion
Motivation 1: Phenotypic Fluctuation \( \rightarrow \) evolution?

- Even in isogenic individuals (clones) there is large phenotypic fluctuation

Recognized now extensively

Exp + Model + Theory

- Relevance of this fluctuation to evolution?

Positive role of noise?
• Phenotypic Fluctuation → Relationship to Evolution?

* Standard evolutionary genetics;

(0) selection is based on phenotype
(activity, size, protein abundances, fluorescence,…),
Fitness(phenotype)

(i) gene a → phenotype x
→ if this mapping is uniquely determined
→ Fitness(Genotype) instead

(ii) only genotype is transferred the offspring
Change of distribution P(geneotype) → evolution
But gene—``development “ → Phenotype
Is not necessarily unique

Phenotypic fluctuation of isogenic organisms
→ P(x; a) x—phenotype, a – gene
Motivation 2: Evolution of Robustness

• Robustness ------ Insensitivity of Fitness (Phenotype) to system’s change
  ➔ due to environmental change
  ➔ against noise during ‘developmental process
  ➔ against parameter change by mutation

*Question:

relationship among these robustness
condition for evolution of robustness

Background

(1) relationship between development and evolution,
(2) robustness increases through evolution? ---
  Schmalhausen’s stabilizing selection: Waddington’s canalization
(3) Landscape in Geno-pheno coupling (Ancel-Fontana.Wagner,..)
Motivation 1 and 2, combined:

- (A) Plasticity, Potency, Flexibility, (Robustness), Evolvability … Tradational concepts
  Ambiguous Concepts; Often Explained only Verbally but probably important biologically (as an organism level)
  *(B) Quantitative Biological studies on dynamics and fluctuations: Progresses rapidly recently*

- Still Large Gap between (A) and (B);

- Especially when (A) concerns with macroscopic biological characteristics

Need to fill the gap

(cf: stat mechanics is constructed after establishment of thermodynamics to be consistent)
Plasticity Measure

--- changeability (response against external change)

--- related with degree of fluctuation?
(negatively correlated with) robustness
So-called fluctuation-dissipation theorem in physics:
Force to change a variable $x$;
response ratio $= \frac{\text{shift of } x}{\text{force}}$
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., $\langle x \rangle$ average) shifts

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

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

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

at \( a=a_0 \)

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

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

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

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

*generalized force* \( C(a - a_0)(x - X_0) \) to shift the distribution.
\[ P(x, a_0 + \Delta a) = N' \exp\left(-\frac{(x - X_0 - C\Delta a\alpha(a_0 + \Delta a))^2}{2\alpha(a_0 + \Delta a)}\right) \]

Hence, we get

\[ \frac{<x>_{a=a_0+\Delta a} - <x>_{a=a_0}}{\Delta a} = C\alpha(a_0 + \Delta a), \]

Noting that \( \alpha = <(\delta x)^2> \)

\[ \frac{<x>_{a=a_0+\Delta a} - <x>_{a=a_0}}{\Delta a} = C <(\delta x)^2>, \]

Approximate formula; trivial by itself

Non-trivial point: representation by \( P(x;a) \)

\( x \): phenotype \( a \); environment etc
• General Viewpoint:
  x: phenotype (variable)
  a: genotype (parameter)

parameter $\rightarrow$ variable: condition (1)

  
  \[ a: \text{ scalar continuous parameter showing gene (say, number of matched sequences etc.) for given direction of specific function,} \]

  \[ x \text{ is distributed even if gene (a) is specified} \]

  \[ \text{consider } P(x;a) \text{ under given environment } h \]

  \[ \text{Environment } h \text{ change to select ‘a’ value} \]

  \[ \rightarrow \text{ change in } P(x;a) \]
Artificial selection experiment with bacteria for enzyme with higher catalytic activity for some protein with higher function

Change in gene \( \text{(parameter; } a) \) \implies \``\text{Response}'' \quad \text{------ change of phenotype } \langle x \rangle \\
\quad \quad \quad \quad \quad \quad \quad \quad \text{(e.g., fluorescence intensity)}

per generation per (synonymous) mutation rate

\text{Fluctuation} \quad \text{---- } \text{Variance of phenotype } x \text{ of clone}

\text{Fluctuation in the phenotype } x \text{ of clone} \quad \Leftrightarrow \quad \text{speed of evolution to increase } \langle x \rangle \\
\quad \quad \quad \quad \quad \quad \quad \quad \text{(proportional or correlated)}
Artificial selection experiment with bacteria
Selection to increase the fluorescence of protein in bacteria

Schematic drawing of selection process

Mutagenesis

1st screening

2nd screening

FACS analysis

Ito, Yomo, ..
I10-6Log.LMD

Slope = 1
X-intercept = Log[Fluorescence]_{FS=1}
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
Naïve expectation: Just proportional to mutation rate

Fluctuation-response relation
Phenotype fluct. $\times$ mutation rate

Difference of the average value
(Evolution Speed per generation)

Sato, Ito, Yomo, KK, PNAS 2003
Cofirmation by model:
Toy Cell Model with Catalytic Reaction Network

- **k species of chemicals** \( X_0 \cdots X_{k-1} \)
  number \( n_0, n_1 \cdots n_{k-1} \)

- **random catalytic reaction network**
  with the path rate \( p \)
  for the reaction \( X_i + X_j \rightarrow X_k + X_j \)

- **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

\[
N = \sum n_i, \quad \text{when it exceeds } N_{\text{max}}
\]

the cell divides into two

---

C.Furusawa & KK

---

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

Mutate the network (‘gene’) with mutation rate $\mu$, (rewire the path of the network with the rate) and select such network having highest concentration $c$ 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 $\mu$.
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.

$\text{phenotype } x = \log (n_s)$
Fluctuation of Phenotype x

Change of distribution of phenotype x through evolution

Prepare $10^5$ clonal cells (having an identical network)

Distributions of phenotype $x$ are plotted.
Confirmation of Fluctuation Dissipation Theorem by reaction-network cell model

\[ \mu = 0.01 \]

Fluctuation of \( x = \log c \)

Increase in average \( x \)

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 \( \propto \) phenotypic fluctuation by genetic variation (\( V_g \)): (fundamental theorem of natural selection; established)

  \[
  \text{pheno fluct of clone } V_p \propto \text{pheno fluct by gene variation } V_g
  \]

(fluct by noise \( \propto \) variation in ‘equation’)

Follow the spirit of Einstein;

micro-macro consistency \( \rightarrow \) Brownian motion
Vip \propto \text{evolution speed (exp (?), model)}
Vg \propto \text{evolution speed (Fisher) \ a simple derivation(?)}

\[ P(g) \]

\[ g \]

\text{(growth rate \sim \text{fitness})}

\[ \bar{g}_n = \int g \, P_n(g) \, dg \]

\[ P_{n+1}(g) = \frac{g P_n(g)}{\int g P_n(g) \, dg} = \frac{g P_n(g)}{\bar{g}_n} \]

\[ \bar{g}_{n+1} - \bar{g}_n = \frac{\int g^2 P_n(g) \, dg}{\bar{g}_n} - \bar{g}_n = \frac{1}{\bar{g}_n} \left( \int g^2 P_n(g) \, dg - (\bar{g}_n)^2 \right) \]

\[ = \frac{1}{\bar{g}_n} \left( \overline{(g\bar{g}_n)^2} \right) \]

\text{(Fisher ?)
consistent

isogenic phenotypic fluct.

genotype \( a \)

(same)

genoype \( \text{distributed} \)

phenotype \( x \)

\( V_{ip} \)

\( V_g \)

\( V_{ip} \)
Change of distribution through evolution

Distribution of phenotype $x$ of a clone $\rightarrow V_p$

Log(concentration)

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

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

Beyond Darwin with the spirit of Einstein!

\[ \mu \sim \mu_{\text{max}} \]

\[ V_p = V_g \]

variance of log(x),

x is the concentration of the molecule

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

As $\mu$ is increased,
The distribution 'collapses'
Error catastrophe
Consider 2-variable distrb
\[ P(x=\text{phenotype}, a=\text{genotype}) = \exp(-V(x,a)) \]
Keep a single-peak (stability condition).

Hessian condition

\[
(\frac{\partial^2 V}{\partial a^2})^{-1} \geq 0; \quad (\frac{\partial^2 V}{\partial x^2})^{-1} \geq 0.
\]
\[
(\frac{\partial^2 V}{\partial x^2})(\frac{\partial^2 V}{\partial a^2}) - (\frac{\partial^2 V}{\partial a \partial x})^2 \geq 0.
\]

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 \(a\)--
Phenomenological Theory for these experimental observations? Consider $P(\text{phenotype, genotype})$ distribution $P(x,a)$ or $P(x,a) = \exp(-V(x,a))$

Condition to keep single peak (evolutionary stability).

$V_{ip} : (\delta x)^2$ of isogenic individuals

$V_{ig} :$ variance of $x$ due to genetic variation for the identical phenotype

$\langle (x_a - x_0)^2 \rangle = V_{ig} = \langle (\delta a)^2 \rangle \left( \frac{\partial x_0}{\partial a} \right)^2$.
\[ P(x, a) = \hat{N} \exp\left[ -\frac{(x - X_0)^2}{2\alpha(a)} + \frac{C(a - a_0)(x - X_0)}{\alpha} - \frac{1}{2\mu}(a - a_0)^2 \right] \]

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

\[ \mu \leq \frac{\alpha}{C^2} \equiv \mu_{\text{max}}. \]

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

\[ V_g = \frac{\mu C^2}{1 - \mu C^2/\alpha}, \quad \overline{V}_{ip} = \frac{\alpha}{1 - \mu C^2/\alpha}, \quad \frac{\overline{V}_{ip}}{V_g} = \frac{\alpha}{\mu C^2} \]

\[ V_g \leq \overline{V}_{ip}. \]

\[ V_{ig} = \frac{\mu}{\mu_{\text{max}}} \overline{V}_{ip} \]

= Ave over all populations
From Stability condition $\rightarrow$ \( V_{ip} \geq V_{ig} \) is derived.

\( V_{ig} \) increases with the mutation rate \( \mu \).
If the increase continues, there is a critical mutation rate \( \mu_c \) at which \( V_{ip} \sim V_{ig} \).

Error catastrophe $\rightarrow$ evolution stops.

Here, \( V_{ig} \neq V_{g} \) for distribution for a given phenotype, \( V_{g} \) for all population.

But for small \( \mu \),

\[ V_{g} \approx V_{ig} \approx \frac{\mu}{\mu_c} V_{ip} \]

\[ \mu V_{ip} \propto V_{g} \propto \text{evolution speed} \]

consistent
• (i) $V_{ip} \geq V_g$ (from stability condition) (**)

(ii) error catastrophe at $V_{ip} \sim V_g$ (**) (where the evolution does not progress)

(iii) $V_g \sim (\mu / \mu_{max}) V_{ip} \propto \mu V_{ip}$ ($\propto$ evolution speed) at least for small $\mu$

* * * Consistent with the experiments, but,,,,,, Existence of $P(x,a)$ assumption ??;; + Robust Evolution assumption ?? +

Why isogenetic phenotypic fluctuation leads to robust evolution?

(**) to be precisely $V_{ig}$, variance those from a given phenotype $x$: but $V_{ig} \sim V_g$ if $\mu$ is small
• ??? to the theory
• $P(x,a)$ rather than conditional probability (TRICK)
  "Genetic-Phenotypic correspondence"

  what phenotype can vary $\leftrightarrow$ what gene can change
  fluctuation of variable (micro) vs variation of equation (genetic evolution)
  (cf Waddington’s genetic assimilation)

**Q:** Why error catastrophe when $V_g>V_{ip}$?

Robust evolution is possible only under noise
- counterintuitive; it says phenotype noise is important
→ gene-net model
Gene expression dynamics model::
Relevance of Noise to evolution?
Simple Model:Gene-net(dynamics of stochastic gene expression ) → on/off state

\[ X_i \text{ – expression of gene } i \text{ : on off} \]

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

\[
< \eta(t) \eta(t') > = \delta(t - t') \delta_{ij},
\]

\[ M; \text{total number of genes, } k : \text{output genes} \]

\[ \text{Noise strength } \sigma \]
• Fitness: Starting from off of all genes, after development genes $x_i$ $i=1,2,\cdots,k$ should be on (Target Gene Pattern)

Fitness $F = -(\text{Number of off } x_i)$

Genetic Algorithm
Mutate networks and Select those with higher $<F>$
Choose top $n$ networks among total $N$, and mutate with rate $\mu$ to keep $N$ networks
Low noise case: top reaches the fittest but low-fitness mutants remain

High Noise case: top-lowest All reach the fittest
Fitness Distribution

- $\sigma < \sigma_c$ -- low fitness mutants distributed
- $\sigma > \sigma_c$ -- eliminated through evolution

Result of evolution
Top: reaches the fittest
Lowest: cannot evolve for low noise ($\sigma$)
Existence of critical noise level $\sigma_c$ below which low-fitness mutants accumulate (error catastrophe)
(1) $V_{ip} \geq V_g$ for $\sigma \geq \sigma_c$

(2) $V_g \rightarrow V_{ip}$ as $\sigma \rightarrow \sigma_c$

(3) evolution progresses only for $V_{ip} \geq V_g$

(4) $V_{ip} \propto V_g$ through evolution course

Theory confirmed

Why?; difference in basin structure

$\sigma > \sigma_c \rightarrow$ large basin for target attractor

(robust, $\Delta$ (distance to basin boundary) $\uparrow$

$\sigma < \sigma_c \rightarrow$ only tiny basin around target orbit

$\Delta$ remains small

$\rightarrow$ Global constraint to potential landscape (funnel?)
why threshold?

choose paths to avoid turning points within $\sigma$ (noise)

Mutation $\rightarrow$ touches turning points within range of $\mu$

small $\sigma \rightarrow$
an orbit with small $\Delta$
can reach the target
Deviation of basin boundary (turning points) by Noise $\rightarrow \delta p$
by Mutation $\rightarrow \delta g$

$V_g \sim (\delta g / \Delta)^2$
$V_{ip} \sim (\delta p / \Delta)^2$

$\Delta$ increases $\rightarrow$ robustness increases
if $\delta g > \delta p$,
mutation destroys the history

$\rightarrow V_{ip} > V_g$ necessary for evolution of robustness
- Genetic robustness is increased for network evolved under higher noise.
- Increase in genetic robustness to mutation fraction of fitted state for n-mutants.

\[ F = -c(\sigma) m \]
\[ C(\sigma) > 0 \text{ if } \sigma < \sigma_c \]
\[ C(\sigma_c) = 0 \]
Discussion: Evolution of Robustness

- Robustness ---- Insensitivity of Fitness (Phenotype) to system’s change
  - against noise during ‘developmental process
  - against parameter change by mutation
- Developmental Robustness to noise ---- Vip
- Robustness to mutation in evolution ---- Vg

For $\sigma > \sigma_c$, both decrease, i.e., robustness
Noise is necessary for evolution of robustness

$Vip \propto Vg \implies$ Developmental robustness and genetic (evolutionary) robustness are linked (or embedded)

WADDINGTON genetic assimilation

Formation of smooth dynamics; how?

Consolidation of non-target gene expressions

Expression of many non-target gene expressions are fixed successively:
-- variance of many gene expressions $i$ - genetic $Vg(i)$ & epigenetic $Vip(i)$ decrease successively;
Further Surprise; Universal relationship over all genes?

Evolutionary course of \((V_{ip}(i), V_{g}(i))\) plot for several genes (color – different gene \(i\))

Approaches proportionality relationship

Snapshot plot of all gene expression variances; (color different generation)

Approach a unique line for all genes(?!)

KK, Chaos 2008
Vip(i)-Vg(i) relationship over genes; snapshot at 200th generation

As noise increases, evolved dynamics are more robust, to lose plasticity

Plasticity \sim Vg(i)/Vip(i)

Fraction of plastic gene expression decreases as \sigma
‘universal line is approached ‘over genes’ and ‘over generations’

Recent experiment (Landry et al, Science07) suggests such correlation over genes (KK. Lehner, in prep) - but scattered

Universal proportion coefficient over genes akin to fluctuation-dissipation relation ----- result of consistency of each gene expression dynamics and fitness as collective state (cf Einstein)
Through directed evolution; fluctuations decrease

(**Model, experiments, theory, i.e., increase of robustness through evolution.)

Then, evolution slows down..

\[ \longleftrightarrow \text{How Evolution continues?} \]

\[ \text{Why Large Fluctuations exist?} \]

?? Is there regain of fluctuations????

• Experimentally Observed: Appearance of mutants with large fluctuations at further evolution. (\[ \leftrightarrow \] interference with other processes) (Ito, Toyota, KK, Yomo, submitted)

• \[ \rightarrow \text{Restoration of Plasticity} \]
In fixed environment/fitness, plasticity decreases. When environmental condition is switched in the model → fluctuation once increases to regain plasticity (evolvability) and then decreases

In a fluctuating environment, fluctuation (plasticity) is sustained

(Decrease of fluctuation in bacterial evolution; Ito-Toyota-KK-Yomo)
Vip(i) and Vg(i) show Generation after switch. Vip/Vg Works as a measure of biological plasticity. Increase instability to approach Vg~Vip.

Vip/Vg

Works as a measure of biological plasticity.
• Generality of our result; For a system satisfying:

(1) **fitness is determined after developmental dynamics**

(2) **developmental dynamics is complex**
   (catastrophic pts leading to error are distributed)

(3) **effective equivalence between mutations and noise with regards to the consequence to fitness**

   (→ genetic assimilation by Waddington)
Symbiotic Sympatric Speciation

- So far, ‘fluctuation’ – single-peaked distribution
- Speciation → change to double peaked distribution

** Allopatric vs Sympatric (S fundamental? Difficult?)

- Our scenario for sympatric speciation (confirmed by several models):
  1. **Isologous diversification** (interaction-induced phenotype differentiation);
     homogeneous state is destabilized by the interaction e.g., by the increase in resources
  2. **Amplification of the difference through geno-pheno relation**
     Two groups form symbiotic relationship, and coevolve
  3. **Genetic Fixation and Isolation of Differentiated Group**
     consolidated to genotypes
Isologous Diversification:

internal dynamics and interaction: development phenotype

instability

distinct phenotypes

interaction-induced

Example: chemical reaction network

specialize in the use of some path

Study of coupled dynamical systems (globally coupled map) etc., differentiation??
With the increase of the number

Distinct types are formed through instability in ‘developmental dynamics’ and interaction  (both types are necessary)
Differentiation of role; use od different paths
Model with Evolution:

Each unit Phenotype :: Variable $X = (X_1, X_2, \ldots, X_k)$

Gene :: Parameter in the model e.g., reaction rate $(g_1, g_2, \ldots, g_k)$

Parameter $\rightarrow$ Variable (dynamical systems) $X(t=0) \rightarrow X(t)$

Reproduction when maturity threshold condition (given by $X$) is satisfied

Mutation ---- small change in parameter in reproduction

Competition for survival:

( remove some units (either randomly or under some condition))
Characteristics of the Symbiotic Sympatric Speciation

*Valid (possible) in the presence of strong interaction

*Robust speciation; two groups coevolve; works under sexual and asexual cases as well (indeed, hybrid sterility is resulted)

*Genetic separation always follows if there appears interaction-induced phenotypic differentiation

*Relevance of the phenotypic differentiation, rather than genetic change, to genetic diversification (Baldwin effect or genetic assimilation → speciation)
Plasticity in phenotype from loose dynamics $\rightarrow$ interaction-induced phenotypic differentiation

Consolidated to Genes $\rightarrow$ Mating $\rightarrow$ Allele-correlation, Space..

Prove the above scenario?? From observation-- often remains a guess…

Real experiment wanted:

E Coli; interaction-induced phenotypic differentiation observed

Evolution (Yomo’s group)

genetic fixation --- not yet; but

coexistence of diverse types by ‘crowded’ condition is confirmed
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
Questions

(1) All chemicals have such large fluctuations? Important ones are protected??
   Origin of heredity (genetic information)
   Minority control mechanism
   (KK, Yomo, JtheorBiol. 2002)

(2) Large phenotypic fluctuation → relevance to biology?
   ans. evolution (Sato et al., PNAS, 2003)
   adaptation,
   differentiation....
Embedded gene network

Phenomenological theory of attractor selection

Unexpected; beyond designed
Selection of preferable state

Metabolic activity

fluctuation

Theory of attractor selection by activity and noise

Env. Without glutamine

Gluatamine synthetase

Mutual inhibition

Env. Without Tetrahydro..
• 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!
• Growth-Induced-Attractor-Selection (Furusawa kk)

• Basic Logic

\[ \frac{dx_i}{dt} = f(x_i) - S(\{x_j\})x_i + \eta(t) \]

- \( f \to \) Synthesis
- \( S \to \) dilution due to cell growth
- \( \eta \to \) noise

**Active state**: both \( f \) and \( S \) are large

- deterministic part >> noise

**Poor state**: both \( f \) and \( S \) are small

- deterministic part ~ noise

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

Selection before reproduction

**General logic in a system with growth and fluctuation**
The mechanism for adaptive response by attractor selection

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

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

\[
\frac{d}{dt} \text{act} = \frac{\text{pro}}{((\frac{\text{Nut} \_ \text{thread}_1}{m_1 + \text{Nutrient1}})^{n_1} + 1) \times ((\frac{\text{Nut} \_ \text{thread}_2}{m_2 + \text{Nutrient2}})^{n_2} + 1)} - \text{cons} \times \text{act}
\]

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

Adaptive Response of the genetic network to a environmental change
\[
\frac{d}{dt} m_l = \frac{\text{syn}(act)}{1 + m_2^2} - \text{deg}(act) \times m_l + \eta_1
\]
\[
\frac{d}{dt} m_2 = \frac{\text{syn}(act)}{1 + m_1^2} - \text{deg}(act) \times m_2 + \eta_2
\]
\[
\text{syn}(act) = \frac{6act}{2 + act}; \quad \text{deg}(act) = act;
\]
\[
\frac{d}{dt} act = \frac{\text{pro}}{\left(\left(\frac{\text{Nut\_thread}_1}{m_1 + \text{Nutrient}_1}\right)^m + 1\right) \times \left(\left(\frac{\text{Nut\_thread}_2}{m_2 + \text{Nutrient}_2}\right)^n + 1\right)} - \text{cons} \times \text{act}
\]

\text{Fraction that adaptive attractor is selected}

\text{Noise strength}
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
Consistency between cell reproduction and molecule replication

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

Consistency between multicellular development and cell reproduction

Evolutionary relationship on robustness and fluctuation

Phenotypic plasticity vs symbiosis or ecological diversification

Gene regulation network

Ecosystem

Multicellularity

Cell

Molecule

Phenotype

Genotype

Catalytic reaction network
Summary
Consistency Principle for Biology
-- replication of molecules and cells: Universal Laws
(-- replication of cells and cell ensembles)
--- adaptation of internal cellular state and growth
--- genetic and phenotypic changes
(+speciation)
• 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
Evolution of gene regulation network for more complex function:
Choice of complex dynamical systems to give gene expression pattern for segmentation
Found Two basic strategies to generate stripes
  → use of generic dynamics such as oscillation
  → genetic control by logical (on/off) operations
    (pioneered; Salzar-Ciudad, Newman, Sole, EvoDev2001)
Network evolution of body plans
  Also talk tomorrow by Fujimoto (>>4.4C1)
Method: Calculating development

- Take Gene regulation networks with activation and repression
- These genes are located spatially and chemicals diffuse (reaction+diffusion)

- Development under external environment as input (spatial gradientent imposed)

\[
\frac{\partial Y}{\partial t} = -Y + f_y(X, K_{xy}) + D_y \frac{\partial^2 Y}{\partial l^2}
\]

- Gene #0 is distributed with spatial gradient.
- Reaction-diffusion equation for each gene expression.
Strategy: **Numerical** evolution of gene regulatory networks to form stripe pattern.
Method: Numerical evolution

Cf. Salzar-Ciudad, Newman, Sole EvoDevo 2001
Development dynamics over >1000 evolved networks are classified just into 3 modes

Long germ mode: simultaneous
Intermediate germ mode: combinatorial
Short germ mode: sequential

*Simultaneous generation
Combination of on/off regulations by fixed expression dynamics

Sequential Generation
Use of oscillatory gene expression
Difference in (core) network structure

Long-germ uses feed forward loop (FFL) dominantly

Short-germ uses mainly feed-back loop (FBL)

A. Long germ mode

B. Short germ mode

D. Fraction of core networks

<table>
<thead>
<tr>
<th></th>
<th>Long (n=197)</th>
<th>Intermediate (n=190)</th>
<th>Short (n=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of FFL $\geq 5$</td>
<td>1.1</td>
<td>0.9</td>
<td>0.96</td>
</tr>
<tr>
<td>Number of FFL $\geq 1$</td>
<td>1.1</td>
<td>1.1</td>
<td>0.8$\dagger$</td>
</tr>
<tr>
<td>Number of FBL $\geq 1$</td>
<td>0.24</td>
<td>0.4</td>
<td>0.75</td>
</tr>
<tr>
<td>Number of negative FBL $\geq 1$</td>
<td>0.4</td>
<td>0.75</td>
<td>0.6$\ddagger$</td>
</tr>
<tr>
<td>Number of positive FBL $\geq 1$</td>
<td>1.1</td>
<td>1.1</td>
<td>0.8$\dagger$</td>
</tr>
</tbody>
</table>
Short-germ mode has higher robustness to mutation to network, as the number of involved genes is fewer.

**Ratio of Long to Short**

**Distribution of the number of required genes**

![Graph showing the ratio of long to short genes](image1)

![Graph showing the distribution of required genes](image2)

**Mutation rate**

**Number of required genes**
Remarkably, however, Long Germ Mode development has high robustness against changes in the parameters in the gene expression dynamics.
Summary

1. We classified networks according to *sequential* or *simultaneous* stripe formation.

2. They are characterized by network modules, **FBL** and **FFL**.

3. Compared them with observed *short* and *long* germ segmentation in arthropod.

4. Correspondences between numerical and real evolution suggest that the diverse segmentation is an inevitable property of evolving networks.

<table>
<thead>
<tr>
<th>Segmentation mode</th>
<th>Pattern formation</th>
<th>Network module</th>
<th>Spatial Hierarchy</th>
<th>Knockout response</th>
<th>Development</th>
<th>Mutation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>sequential</td>
<td>FBL</td>
<td>No need</td>
<td>simple</td>
<td>Slower</td>
<td>Higher</td>
</tr>
<tr>
<td>Intermediate</td>
<td>combinatorial</td>
<td>FBL + FFL</td>
<td>?</td>
<td>variety</td>
<td>Faster</td>
<td>Lower</td>
</tr>
<tr>
<td>Long</td>
<td>simultaneous</td>
<td>FFLs</td>
<td>necessary</td>
<td>variety</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table**: Segmentation modes and corresponding characteristics.