Evolutionary Shaping of Low-Dimensional Path Facilitates Robust and Plastic Switching Between Phenotypes

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Research question

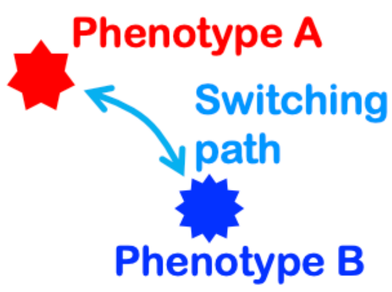
Background

- Biological systems must be robust against perturbations for stable function, but robustness alone is not sufficient.
- Switching between appropriate phenotypes in response to different conditions is essential for biological functions.
  - Allosteric enzymes, motor proteins, etc.

How are robustness and plasticity simultaneously acquired through evolution?

We need to understand

- Evolution of stability of multiple phenotypes
- Evolution of switching pathways



- **Allosteric regulation**

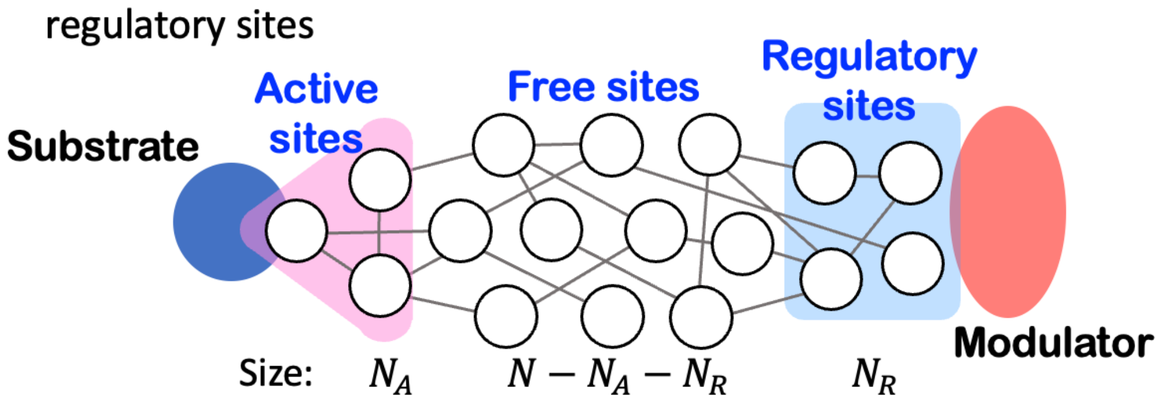
- Regulatory sites distant from active sites
- Binding of modulator to regulatory sites changes the conformation of active sites

Two patterns appear in the active sites

- When the regulatory site is turned "on", then pattern A appears in the active site.
- When the regulatory site is turned "off", then pattern B appears in the active site

Model for conformational switching

- Spin model for conformational switching that has active and regulatory sites



- Setting of genotype and phenotype
  - We set spin configuration and interaction matrix as phenotype and genotype, respectively.
- Setting of desirable configuration depending on regulation
  - Active site and regulatory site have no direct interaction.
  - When a modulator binds to a regulatory site, the regulatory site takes on one of the specific configurations.
  - Then, if the active site can have one of the specific configurations, the substrate can bind to the active site.

Mathematical expressions

- Spin variables (phenotype): $\boldsymbol{S} \in \{-1, +1\}^N$
- Interaction matrix (genotype): $J_{ij} \in \{-1/\sqrt{N}, 0, 1/\sqrt{N}\}$
- Configuration of regulatory site under regulation: $\boldsymbol{S}_R^+$
- Configuration of regulatory site without regulation: $\boldsymbol{S}_R^-$
- Desirable configuration of active site under regulation: $\boldsymbol{S}_A^+$
- Desirable configuration of active site without regulation: $\boldsymbol{S}_A^-$
- Distribution of phenotype $\boldsymbol{S}$ under genotype $\boldsymbol{J}$:

$$P(\boldsymbol{S}) \propto \exp\left\{\beta \sum_{i<j} J_{ij} S_i S_j\right\}$$

- Fitness function for evolution of genotype

$$\phi(\boldsymbol{J}) = \frac{1}{2}\left\{\left\langle |m_t^+| \prod_{i\in\mathcal{R}} \delta_{S_i,1} \right\rangle + \left\langle |m_t^-| \left(1 - \prod_{i\in\mathcal{R}} \delta_{S_i,1}\right) \right\rangle\right\}$$

$$m_t^+ = \frac{1}{N_A} \sum_{i\in\mathcal{A}} S_i S_{Ai}^+, \quad m_t^- = \frac{1}{N_A} \sum_{i\in\mathcal{A}} S_i S_{Ai}^-$$

Summary of results

i. Fitness increases at $T = \beta^{-1} < T_0$, namely, two desirable phenotypes can appear with a high probability.

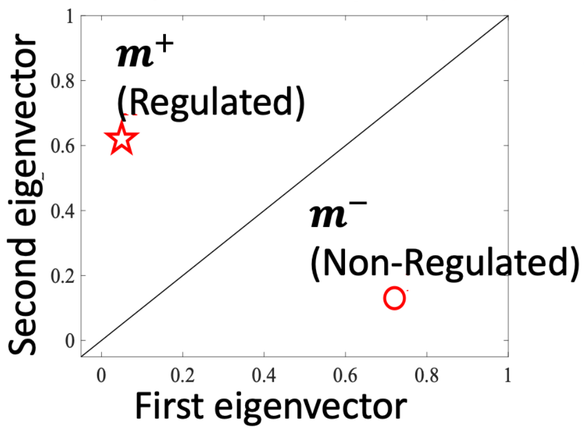
ii. Rugged landscapes evolve at $T < T_2$ ($\simeq$ replica symmetry breaking), and dependency on the initial condition appears.

iii. Characteristic genotypes evolve for $T_2 < T < T_1$, which we refer to as the replica symmetric type 2 (RS2) phase.

- Two phenotypes are assigned to two eigenmodes
  $\simeq$ Large conformational change
- A one-dimensional path between the two phenotypes exists → Quick switching

Phenotype expression in RS2 phase

An example at $T = 1/1.6$ **(RS2)**



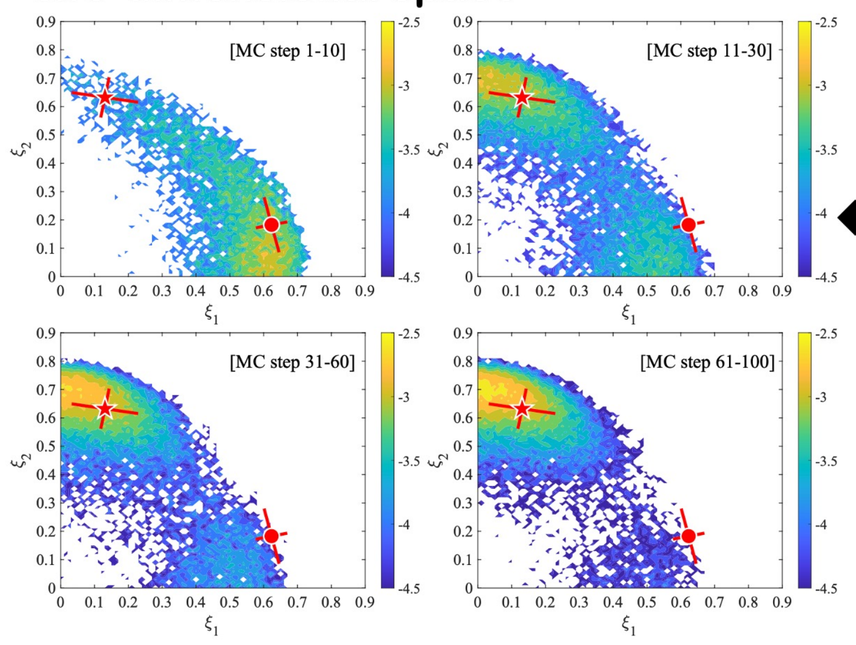
◆Phenotype without regulation ∝ 1st eigenvector

◆Phenotype with regulation ∝ 2nd eigenvector

- Contributions from higher order terms are negligible

- In addition, switching trajectories are concentrated on a one-dimensional path.

Switching trajectory in two-dimensional space



◆We found that this constraint is caused by the random pattern embedded in free sites.

◆Although the free sites do not contribute to fitness explicitly, they are important for stable expression and switching.