

Phenotype selection due to mutational robustness in gene regulatory networks

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Introduction 1: Purpose

- Living systems have been developed through Darwinian evolution.
 - Understanding evolution is necessary to understand [life](#).
- Darwinian evolution consists of two processes: [mutation](#) and [selection](#).
 - This causes selection biases.
 - Best-known bias is bias of mutational robustness.
 - Living systems do not lose their functions easily by a gene mutation.
- We examine this bias [quantitatively](#) for a simple model of [gene regulatory networks](#) (GRN).

Introduction 2: New methodology

- Evolutionary simulation (ES) alone is insufficient for exploring characteristic properties of evolution.
 - ← Biases are involved in outcome of ES.
- We need some reference.
 - Appropriate reference is a set of **randomly** generated GRNs.
- Simple random sampling does not work.
 - ← GRNs with high fitness are **rare**.
 - → We need to conduct **rare-event sampling**.
- → Use of **multicanonical ensemble MC** (McMC).

Introduction 3: McMC

- Original McMC samples entire range of energy evenly.
Berg and Neuhaus (1991,1992)
- It has been realized that McMC can be used also for **non-physical** systems by regarding any function as **energy**.
Review: Y. Iba, N. Saito, and A. Kitajima (2014)
- We have proposed use of McMC for investigating evolution.
N.Saito and MK (2013) New J. Phys. 15, 053037.
S.Nagata and MK (2020) PLoS Comput Biol 16, e1007969.
ST.Kaneko and MK (2022) PLoS Comput Biol 18, e1009796.
- → enables random sampling in the entire range of fitness.

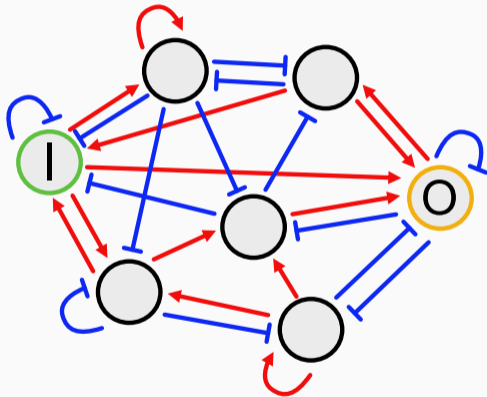
Model 1: Network

Connectionist-type model

- GRNs are expressed by directed graph, ignoring details of gene expression.
- Node: Gene
- Edge: Regulatory relations

Detail

- $N = 40$ nodes, $K = 120$ edges
- One input gene and one output gene



An example of a small network

Model 2: Dynamics

Discrete-time dynamics

$$x_i(t+1) = R \left(I\delta_{i,0} + \sum_j J_{ij}x_j(t) \right)$$

$$R(y) = \frac{1}{1 + e^{-\beta(y-\mu)}}$$

- x_i : Expression level of i -th gene ($[0, 1]$)
- J_{ij} : Regulation from j -th gene to i -th gene ($0, \pm 1$)
 - $+1$: activation, -1 : repression
- I : Input signal ($[0, 1]$)
- $R(y)$: Sigmoidal response function
- $\beta = 2, \mu = 424$ (Spontaneous expression 0.3)

Model 4: Fitness function

Fitness

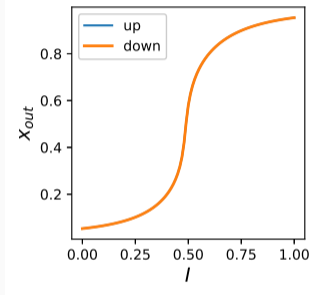
- Obtain the steady state for $l = 0 \rightarrow$ Change to $l = 1$ and obtain the steady state.

$$f = x_{out}(1) - x_{out}(0),$$

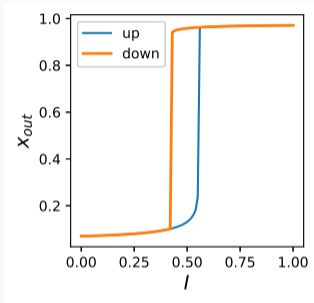
- $x_{out}(l)$: Expression level of the output gene for input l .
- $f < 0$ is regarded as $f = 0$.

Classification of Stability

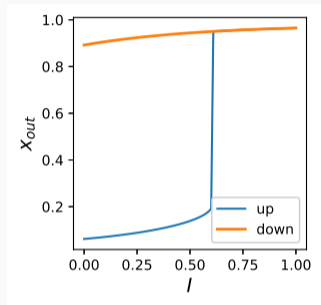
Three stabilities for high fitness.



Monostable



Toggle switch



One-way switch

- One-way switch realizes the irreversible change in the cell state.
- We regard these three stabilities as different **phenotypes**.

Multicanonical MC

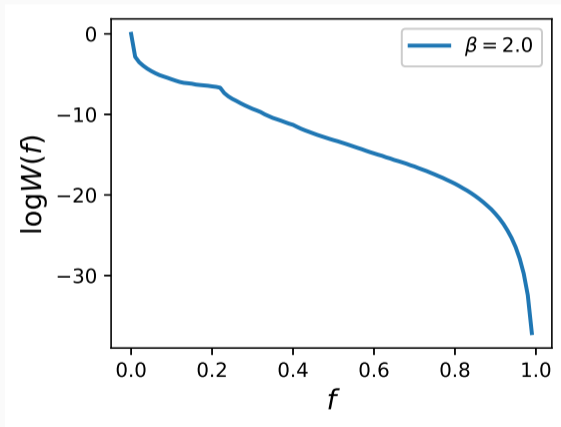
- Fitness $[0, 1]$ are divided into 100 bins.
- McMC weights are determined by Wang-Landau method.
F. Wang and D.P. Landau (2001)

Evolutionary simulation

- Population 1000
- Mutation: Single-edge move
- Deterministic evolution (zero temperature)
 - 48000 independent runs
- Finite-temperature stochastic evolution (Steady state)
 - 1000000 generation, 5 runs

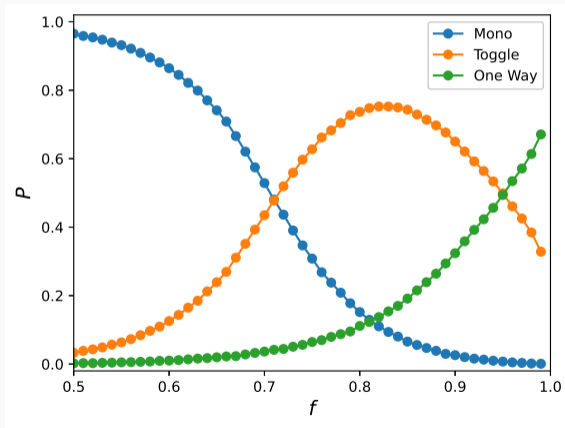
Result 1: Entropy

Genotypic entropy vs. fitness obtained by McMC



Result 2: Phenotypes

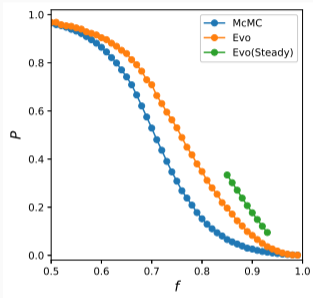
Probability of phenotypes (Stabilities) by MCMC



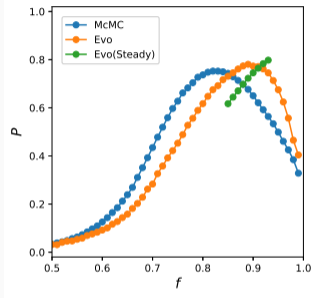
Equilibrium distribution in a sense that "The law of equal probability" holds.

Result 3: Bias on phenotypes

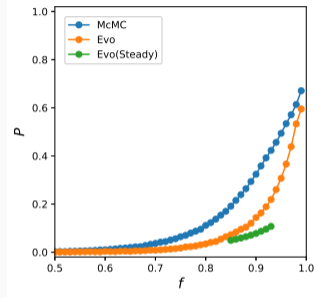
Probability of phenotypes vs. fitness by three methods



Monostable



Toggle switch



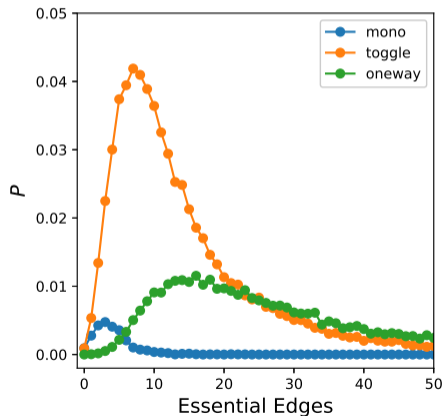
One-way switch

- Monostable GRNs remains high and One-Way switch is suppressed largely in evolution.
- "The law of equal probability" does not hold for evolution: phenotype bias

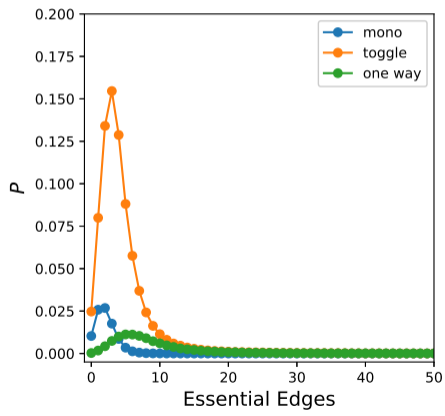
Result 4: Essential edges

Essential edge: An edge that fitness drops close to zero when cut

Number distribution of essential edges ($f = 0.9$)



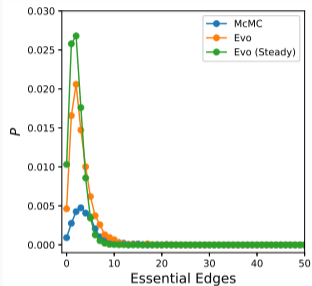
McMC



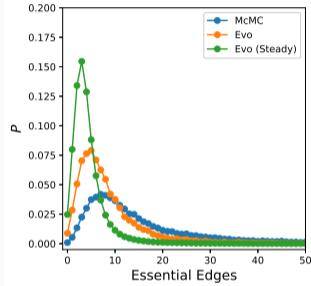
Steady-state evolution

Result 5: Essential edges (cont.)

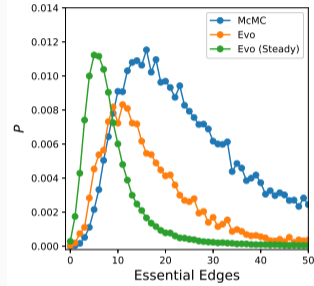
Number distribution of essential edges ($f = 0.9$)



Monostable



Toggle switch



One-way switch

- Mutationally non-robust GRNs are largely suppressed by evolution.
 - → Non-robust phenotype is not selected.

Summary

1. Evolutionary bias: Mutational robustness is enhanced by evolution.
 - We showed it **quantitatively**.
2. Some phenotype is suppressed in evolution due to **mutational robustness**.
 - → New mechanism of phenotype selection.
 - This mechanism is considered to be universal for **any** phenotype.
3. Multicanonical ensemble is effective for constructing a reference set for understanding characteristic properties of evolution.

Acknowledgement

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