

Use of Multicanonical Monte Carlo Method for Exploring Mutational Robustness of Gene Regulatory Network

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Collaborators

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references

- T. Kaneko and MK "Evolution enhances mutational robustness and suppresses the emergence of a new phenotype: A new computational approach for studying evolution" PLoS Comput Biol **18**, e1009796 (2022)
- S. Nagata and MK "Emergence of cooperative bistability and robustness of gene regulatory networks" PLoS Comput Biol **16** e1007969 (2020)

Introduction 1

Mutational Robustness

- Living systems do not easily lose their viability even when some of the genes are mutated.
- This trait of **mutational robustness** has been developed through the long history of evolution.
- The answer to the question, “**Does mutational robustness increase in evolution?**” remains unclear because experimental investigations are difficult.
- We numerically investigated the evolution of mutational robustness for **gene regulatory network** (GRN) model.

Introduction 2

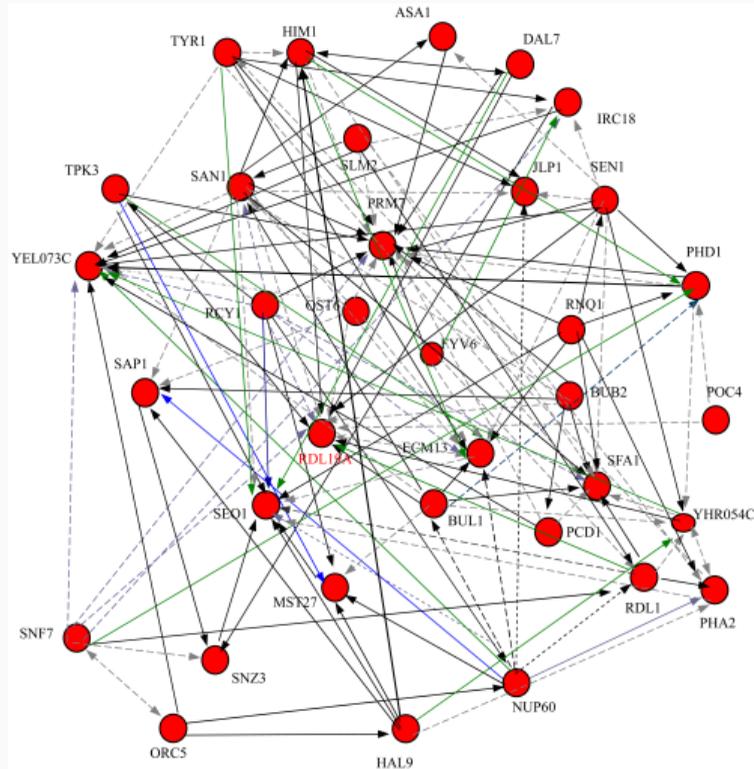
Problem

- Evolutionary simulations only provide evolutionary-path-dependent traits.
- To study **the universality and the characteristics** of evolution, we need a reference system.
- The reference system that we consider appropriate is a set of **randomly sampled** GRNs.
- A simple random sampling is hopeless because highly fit GRNs are **rare**.

Solution

- Rare event sampling using the **multicanonical Monte Carlo** (McMC) method
 - Random sampling over wide range of fitness

Gene Regulatory Network

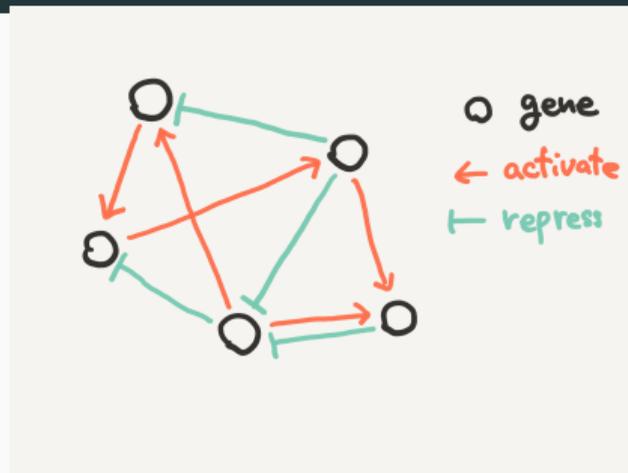


- Genes make complex regulatory networks in a cell to change cell state.
 - Adaptation to environmental change.
 - Cell maturation, cell differentiation

Model 1

Connectionist model

- We ignore details of gene expression and take into account only regulatory interactions.
 - Node: Gene
 - Edge: Regulation



Details

- GRNs are represented by directed random graphs
 - $N = 32$ nodes, $K = 80$ edges
- One input gene and one output gene

Model 2

Discrete-time dynamics

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

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

- x_i : Expression of i th gene ($[0, 1]$)
- J_{ij} : Regulation of i th gene by j th gene($0, \pm 1$)
 - $+1$: activation, -1 : repression
- I : Input from exterior world ($[0, 1]$)
- $\mu = 0, \beta = 2$

Model 3

Fitness

- We require that the expression of the output node for $l = 0$ and 1 differ as large as possible.
- Fitness is defined as follows:

$$f = |\bar{x}_{out}(0) - \bar{x}_{out}(1)|$$

- $\bar{x}_{out}(l)$: the fixed-point value (or the long-time average if no fixed point is reached) of the output node for input l .
- $f \in [0, 1]$ by definition

Method 1

Multicanonical Monte Carlo

- Originally developed in statistical physics to sample **energies** evenly.
 - Berg and Neuhaus 1991,1992
- Later, it was realized that McMC can be used also for **non-physical** systems.
 - Review: Y. Iba, N. Saito, and A. Kitajima: Ann Inst Stat Math 66 (2014) 611.

Application to GRN

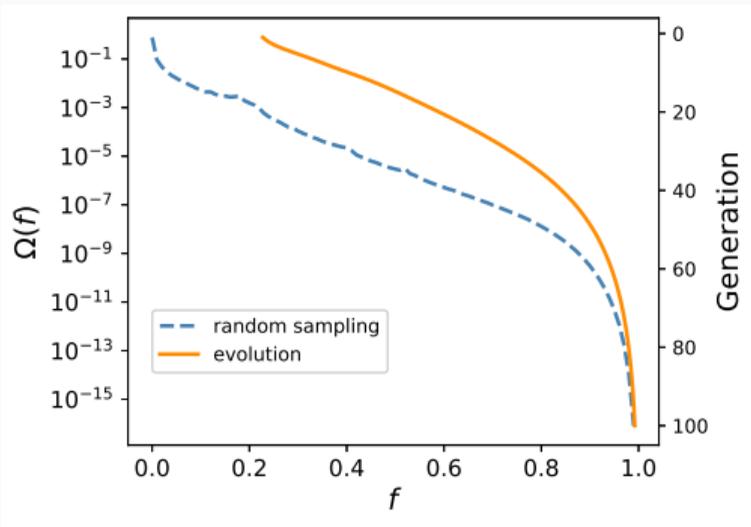
- It enables us to sample GRNs in wide range of fitness **randomly** (in principle).
- Fitness are divided into 100 bins.
- The weight for each bin is determined by **Wang-Landau** method.

Evolutionary simulation

- Mutation
 1. Delete a randomly selected edge
 2. Add a new edge to a randomly selected node pair
- Initial population: 1000 random GRNs.
- 500 GRNs are selected at each generation based on fitness.

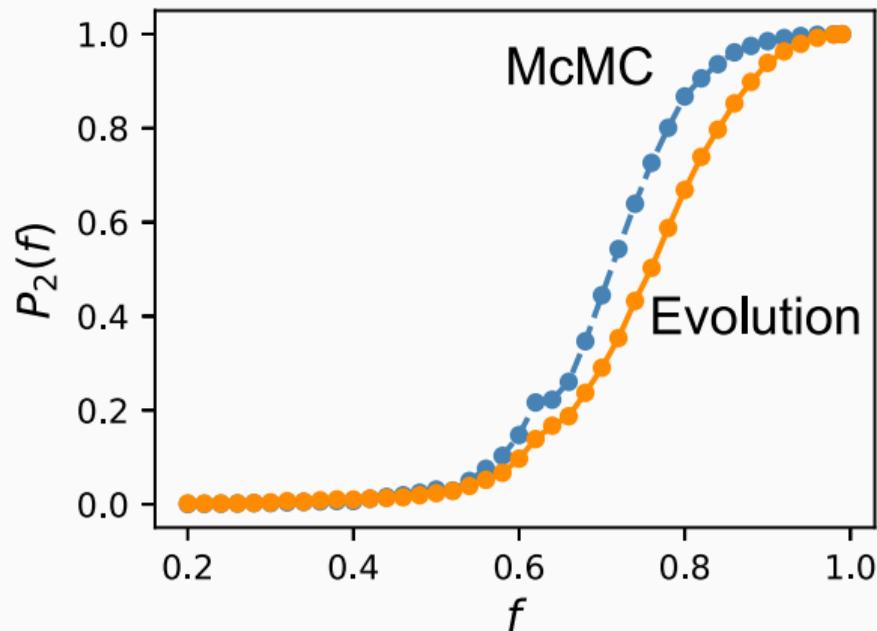
Genotypic entropy and evolutionary speed 1

Probability of fitness and fitness vs. generation



1. Most GRNs have low fitness ($f < 0.1$).
2. GRNs become exponentially rare as fitness increases.
3. For very high fitness ($f > f^*$), GRNs become **faster-than-exponentially** rare.
4. Evolution slows down substantially at $f \simeq f^*$.
 - The evolutionary speed is determined mainly by **genotypic entropy**.

Emergence of bistability 1



Universality of evolution

- All GRNs become bistable as $f \rightarrow 1$.

Particularity of evolution

- Evolution delays the appearance and growth of the fraction of bistable GRNs

The fraction of the bistable GRNs

Enhancement of Mutational robustness 1

Robustness measure

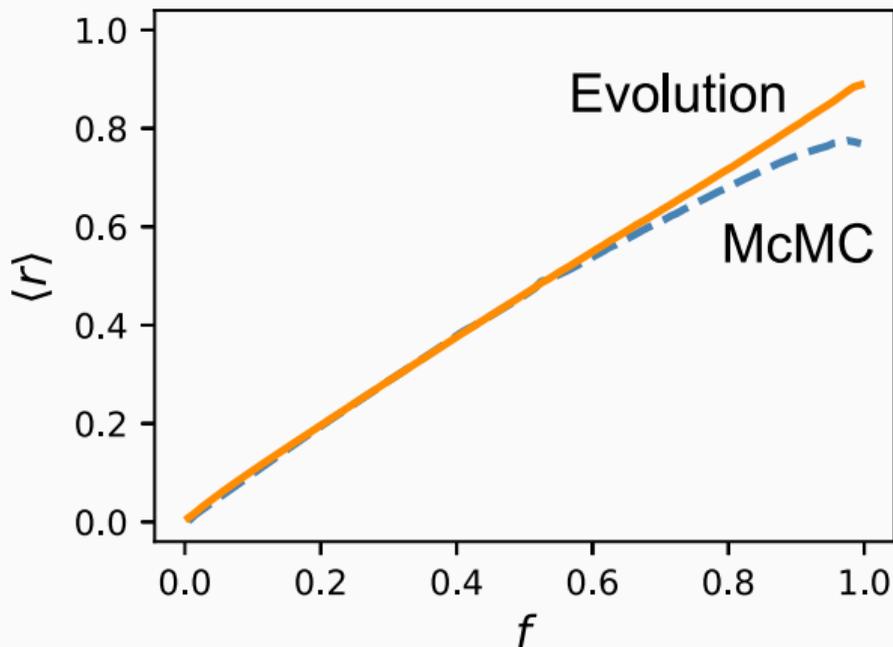
- We consider the single-edge deletion as mutation.
- Delete a single edge from GRN and compute fitness f' after the mutation.
- Robustness measure for a given GRN is the average of f' for all the possible single-edge deletion.

$$r \equiv \frac{1}{K} \sum_i f'_i$$

- f'_i is f' for GRN that i th edge is deleted.

Enhancement of Mutational robustness 2

Robustness measure

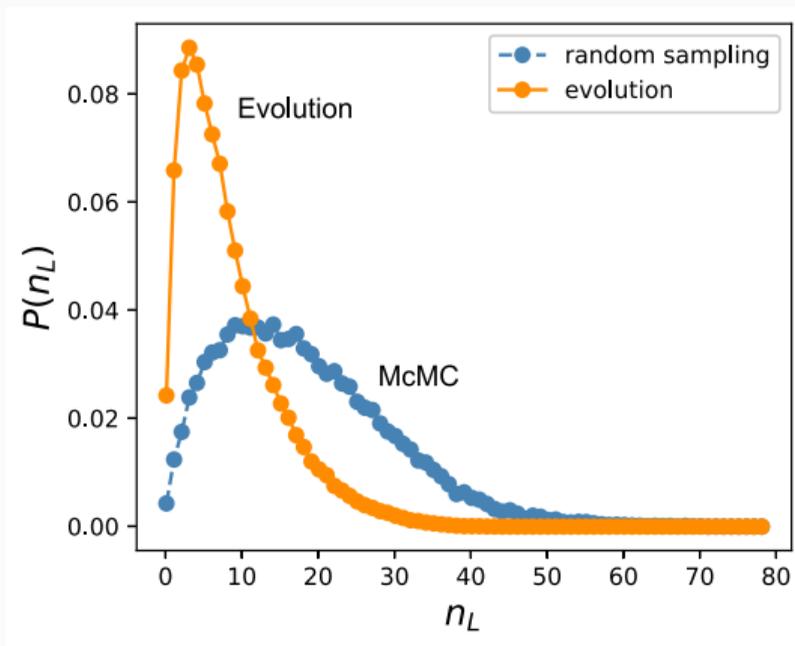


Two-step evolution

1. Early: $\langle r \rangle$ coincides with McMC.
2. Late: $\langle r \rangle$ exceeds McMC.

Enhancement of Mutational robustness 3

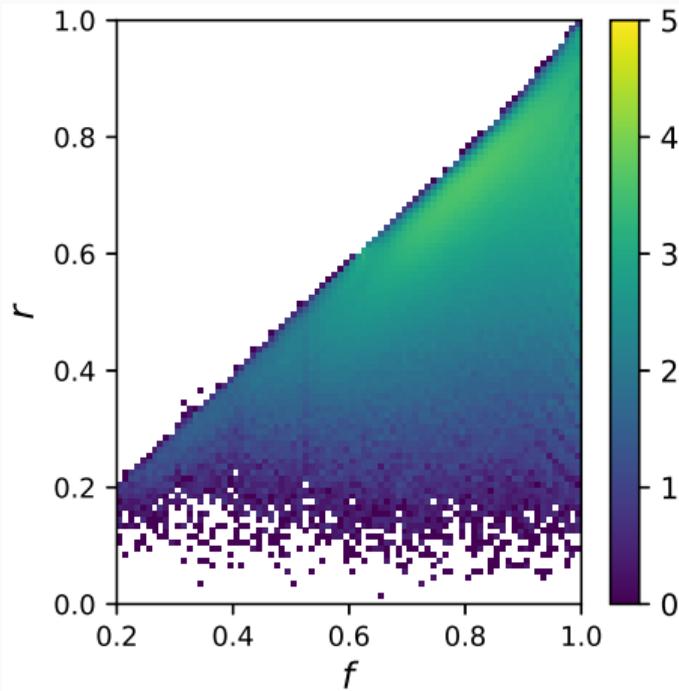
Distribution of essential edges (deletion of such edges is lethal)



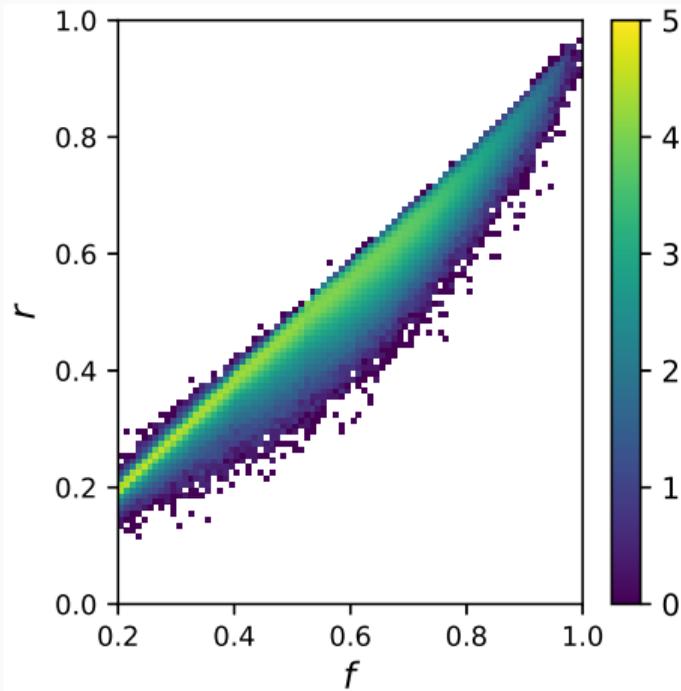
- Essential edges are significantly scarce in evolutionally obtained GRNs.
 - The origin of the difference in the mutational robustness is the difference in the number of essential edges.

Robustness and bistability 1

Results of McMC



Bistable GRNs



Monostable GRNs

Robustness and bistability 2

- The ensemble of the bistable GRNs contains many mutationally fragile GRNs.
- Mutationally robust GRNs are favored by evolution
- As a result, bistable GRNs are selected less likely by evolution.
- An example of phenotype selection due to robustness.
 - A particularity of evolution

New method

- We compared the evolution of GRNs with a randomly sampled set generated by the multicanonical Monte Carlo.

Main Results

- We quantitatively showed that the mutational robustness is enhanced during evolution.
- Emergence of bistability is delayed in evolution because mutationally robust GRNs are selected in evolution.