Phenotype Selection Due To Mutational Robustness: A Computational Study

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Abstract

The mutation-selection mechanism of evolution induces the enhancement of mutational robustness. Suppose that more than one phenotypes have the same fitness. We expect that some phenotypes are more likely to be selected while some are less likely to be selected as a result of the difference in mutational robustness, even if they have the same fitness. We studied this phenotype selection for a model of gene regulatory networks (GRNs). We generated a random reference ensemble using the multicanonical Monte Carlo (McMC) method and compared it with evolutionary simulations (Evo) for investigating particular properties of evolution. By comparing the ratio of the toggle switches and the one-way switches between McMC and Evo for one-in-one-out GRNs, we demonstrate that the one-way switches are suppressed in evolution due to mutational robustness.

Introduction

1. **Background: Selection by mutational robustness**
   Because of the mutation-selection mechanism of evolution, there is a selection bias towards mutationally robust genotypes. Since this bias is not directly related to function, the selection due to the mutational robustness is called ”second order”
2. **Proposal: Phenotype selection due to the second-order selection**
   Suppose more than one phenotypes have the same fitness. Since the distribution of mutational robustness should differ for different phenotypes, we expect that some phenotypes are suppressed because of the selection due to the mutational robustness.
3. **Aim of the research**
   We investigate the above phenotype selection for a model of gene regulatory networks (GRNs).
4. **Methodology: Use of multicanonical MC**
   To investigate characteristic properties of evolution, we need a reference system to compare with evolutionary simulation (Evo). The appropriate reference is a set of randomly generated GRNs. For that purpose, we use the multicanonical MC (McMC).

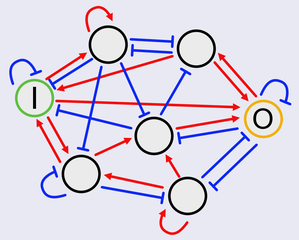
Method

1. **Evolutionary simulation (Evo)**
   - Mutation: single-edge rewiring.
   - Initial population: 1000 random GRNs.
   - 500 GRNs are selected at each generation based on fitness.
   - The lineage of the highest fitness at final generation is sampled.
   - Distribution over many lineages.
2. **Multicanonical MC (McMC)**
   - A set of random GRNs are generated by McMC.
     Random GRNs in the whole range of fitness are obtained.
   - Fitness is divided into 100 bins.
   - Weight for McMC is determined by Wang-Landau method

Model

Connectionist-type model GRNs are expressed by directed graph, ignoring details of gene expression.

- Node→Gene, Edge→Regulatory relations.
- 40 nodes, 120 edges
- One input and one output



Example of a small GRN

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 ($[0,1]$)
- $\beta = 2$, $\mu = 0.424$: Spontaneous expression is 0.3

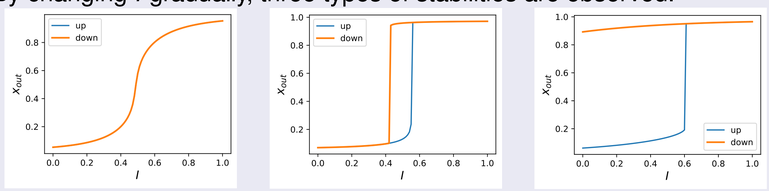
Fitness Obtain the steady state for $I = 0 \rightarrow$ Change suddenly to $I = 1$ and obtain the steady state.

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

where $x_{out}(I)$: Expression level of the output gene for input I.

Classification of stability

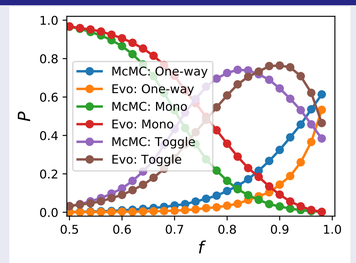
By changing I gradually, three types of stabilities are observed.



Monostable | Toggle switch | One-way switch

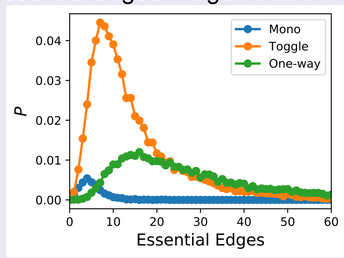
Stability vs. fitness

1. Bistable GRNs (toggle switches and one-way switches) appear for high fitness.
2. Emergence of bistable GRNs ”delays” in Evo compared with McMC.

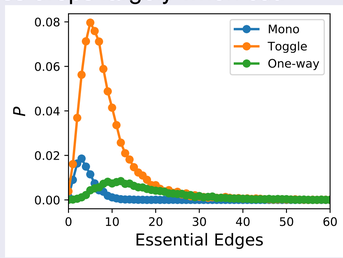


Essential edge distribution for $f = 0.9$

Essential edges: Edges that the fitness drops largely when cut.



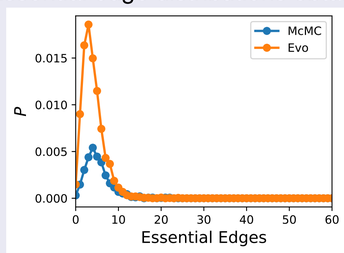
McMC (random reference set)



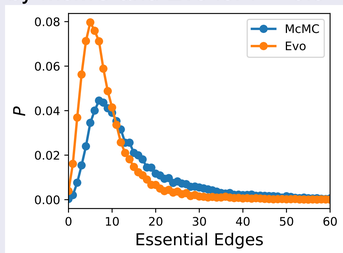
Evolution

Essential edge distribution for each stability

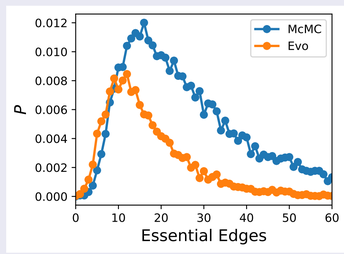
Essential edge distributions obtained by McMC and Evo for $f = 0.9$



Monostable



Toggle switch



One-way switch

In case of one-way switches, GRNs with large number of essential edges, namely, mutationally less robust GRNs, are largely suppressed.

Conclusion

1. One-way switches are mutationally less robust and are suppressed in evolution.
2. This is an example of phenotype selection due to mutational robustness.
3. McMC is useful to reveal characteristic properties of evolution.

references

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