Exploring the Fitness Landscape and Emergence of Mutational Robustness in Gene Regulatory Network

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Motivation

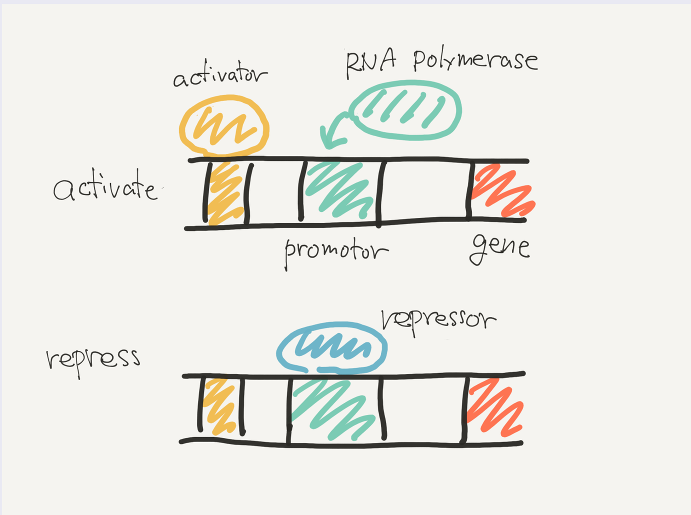
Significant difference of Life phenomena from other physical phenomena is in that the former are rare phenomena made by evolution and exhibit robustness against mutation.

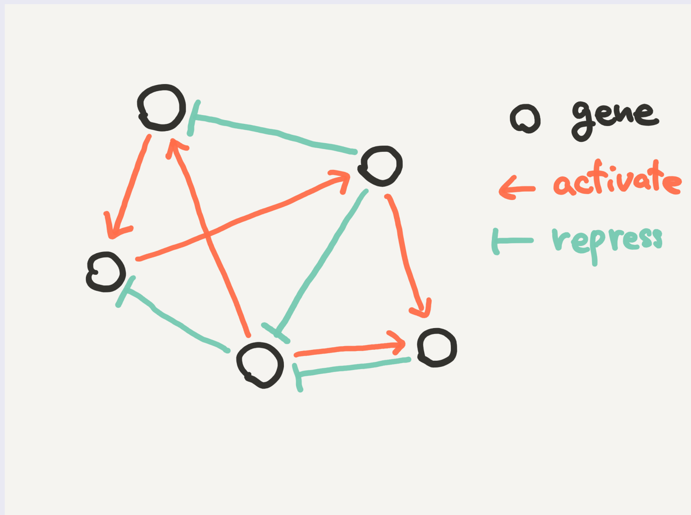
Two Questions

1. What are the characteristics of the fitness landscape?
2. Is mutational robustness aquired in the course of evolution or the high fitness inevitably produces robustness?

Gene Regulatory Network (GRN)

- The state of the cell is regulated by the degree of expression of many genes, namely through quantities and balance of many proteins, adaptively to the environmental conditions.
- Genes are mutually regulated through the transcription factors.
- The mutual regulations of genes form a complex network.





Purpose and Method

We investigate GRNs that respond cooperatively to the input focusing their robustness in particular.

- Robustness against the mutation
- Robustness against the input fluctuation

For that purpose, we produce the ensemble of GRNs with cooperative response.

- We do not apply GA: We would like to explore properties independent of the evolutionaly path.
- We apply the multicanonical MC method instead for sampling GRNs randomly.

Model

Directed random graph N nodes and K edges

- Node: Gene
- Edge: Regulatory relation
  - Self regulation and mutually-regulating pair are not considered (although they exist in real GRNs).
- We deal with GRNs having 1 input gene and 1 output gene.

Discrete-Time Dynamics

$$S_j(t+1) = R\left(\sigma\delta_{j,1} + \Sigma_i J_{ij} S_i(t)\right)$$

$$R(x) = \frac{\tanh x + 1}{2}$$

- S_i : Expression of ith gene (continuus variable of $[-1, 1]$)
- J_{ij} : Interaction between ith and jth gene(± 1)
- σ : Input signal from outside

Definition of the Fitness

- Sensitivity of gene i

$$d_i = \bar{S}_i[1] - \bar{S}_i[0]$$

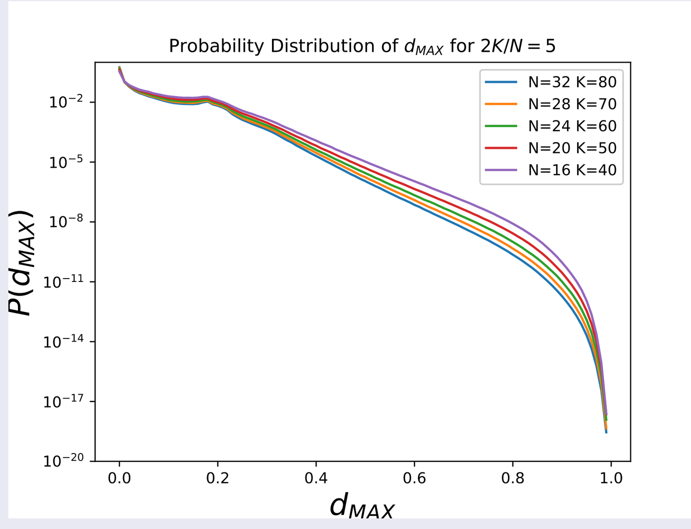
$\bar{S}_i[\sigma]$: time average of the response of ith gene to the input σ

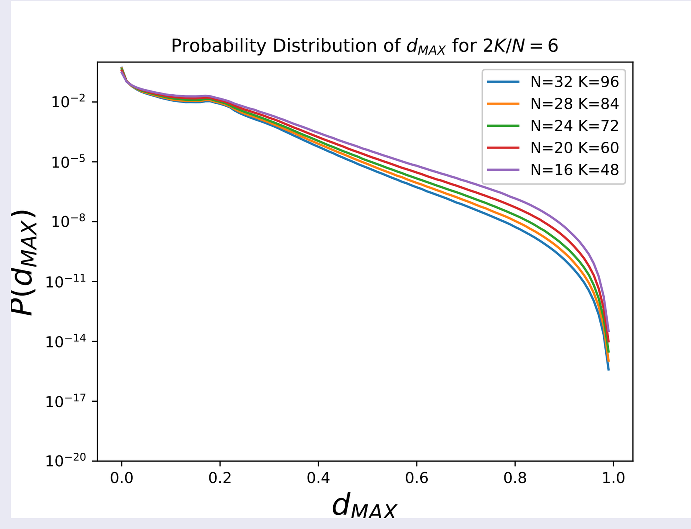
- The node having the largest d_i is selected as the output gene.
- Fitness (Response of the network)

$$d_{MAX} \equiv max\{d_i\}$$

Fitness Landscape

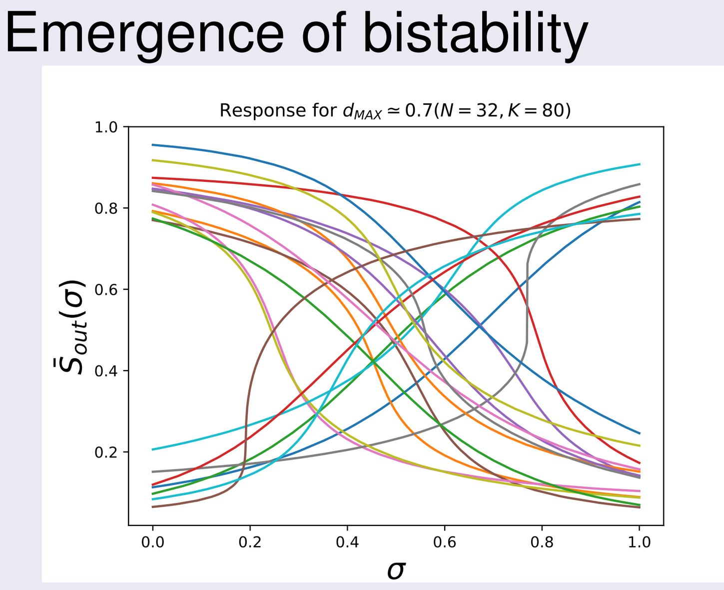
Highly fitted GRNs are very rare!

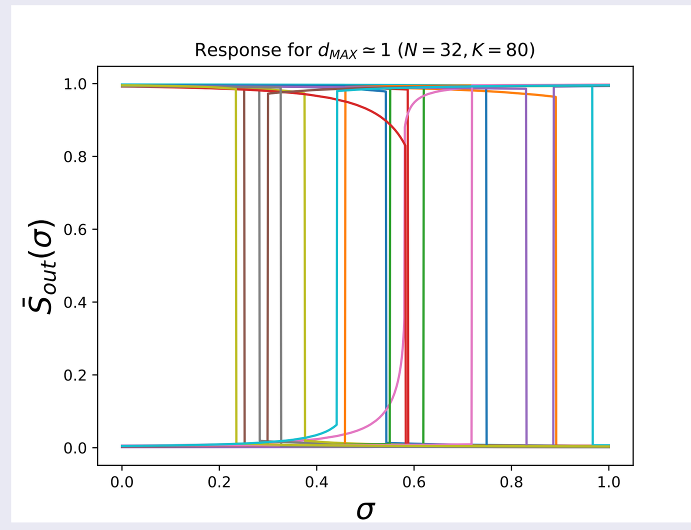




Response to Input

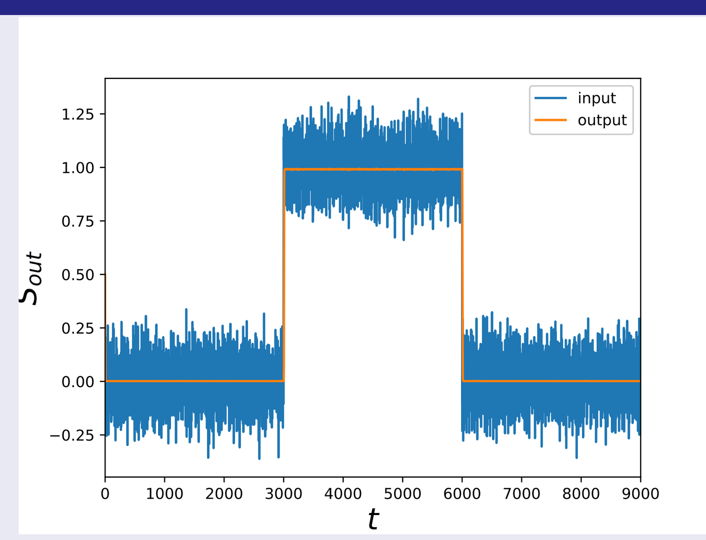
Fittest RGNs respond step-function-like (cooperatively) to input: Emergence of bistability





Dynamical Response to Noisy Input

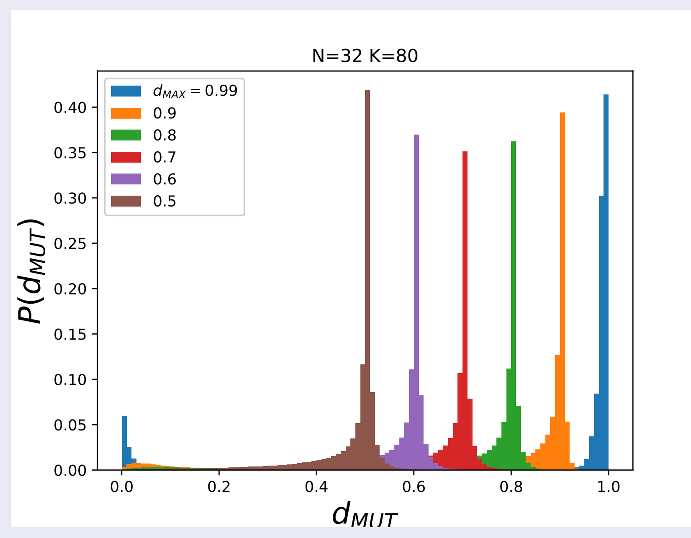
$\sim$ 60% of GRNs in the fittest ensemble can respond quickly to the noisy input
: Robustness against the input noise



Mutational Robustness

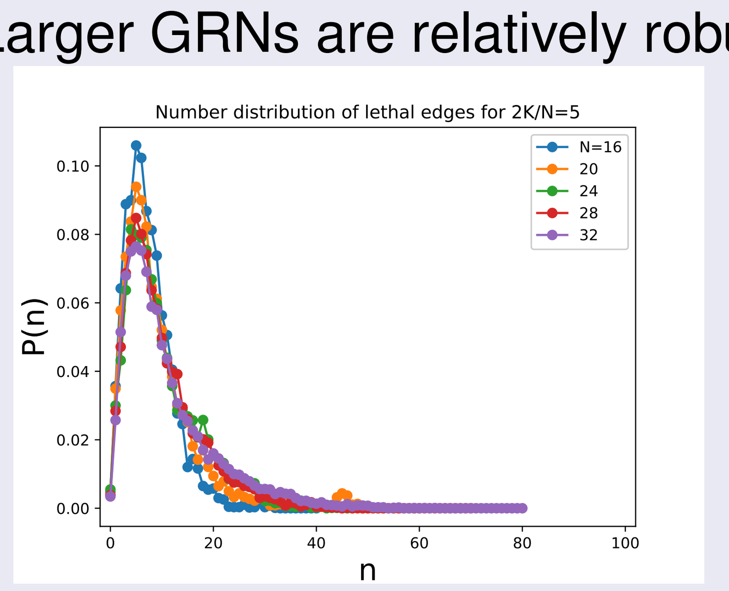
Consider the single-edge deletion.

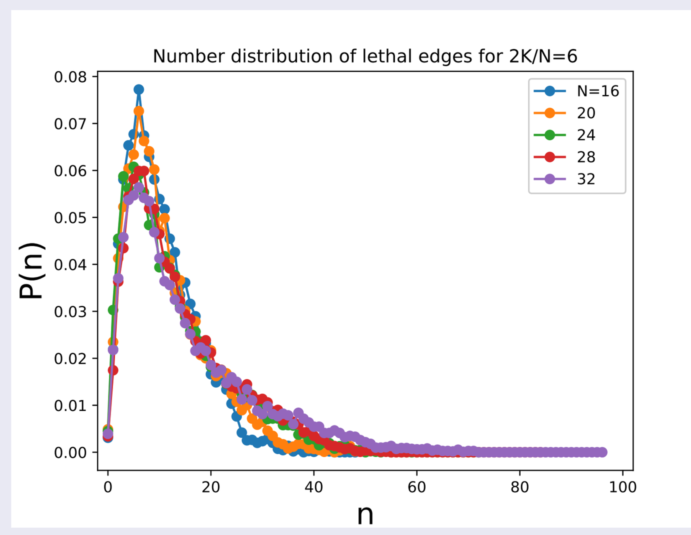
- Distribution of fitness after the mutation splits into two peaks for large fitness (> 0.8).
  - Majority of edges are neutral against mutation.
  - Only a small number of edges are lethal.



Probability Distribution of the Lethal Edges

The peak of the number distribution of the lethal edges is independent of N:
Larger GRNs are relatively robust.





Summary

GRNs in the fittest ensemble exhibit the following properties:

1. Cooperative response using the bistability.
2. Majority of GRNs respond stably to the noisy input.
3. Robust against mutation.

Proposal

Two robustnesses are characteristic properties accompanying to the high fitness and realize irrespective to the pathway of evolution.