Fitness Landscape and Emergence of Robustness in Gene Regulatory Networks

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Motivation

- Living systems exhibit high fitness and robustnesses simultaneously.
  - Robustness against mutation
  - Robustness against noise
- These robustnesses have been aquired through Darwinian evolution.
  - Otherwise, high fitness would have resulted in fragile structures

Question

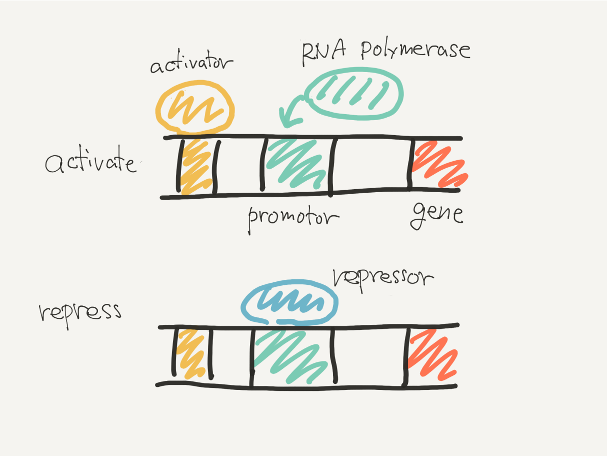
Can these robustnesses be realized only through the evolution?

- We study a simple model of the gene regulatory network
  - without using evolutionary simulations
  - make an ensemble of GRNs with high fitness by Multi-canonical MC
- To explore how rare are the robust GRNs

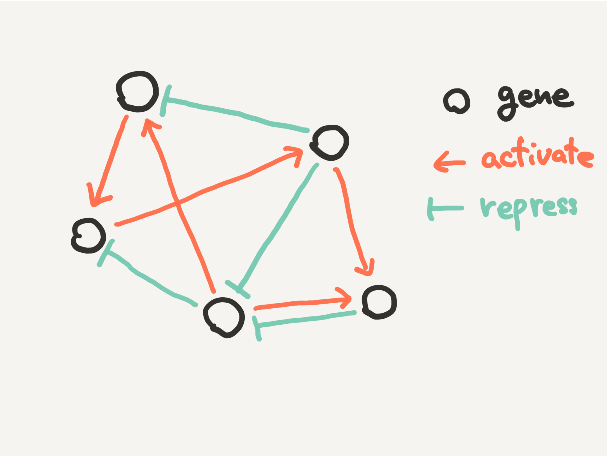
What is the gene regulatory network

- The state of the cell is regulated by the degree of expression of many genes adaptively to the environmental conditions.
- Gene expressions are regulated by the transcription factors (TF), which themselves are proteins produced from genes.
- Genes are mutually regulated through TF

Gene Regulation



Gene Regulatory Network



Model

- Directed random graph N nodes and K edges
  - Node: Gene
  - Edge: Regulatory relation

- Self regulation and mutually-regulating pair are not included (although they exist in real GRNs

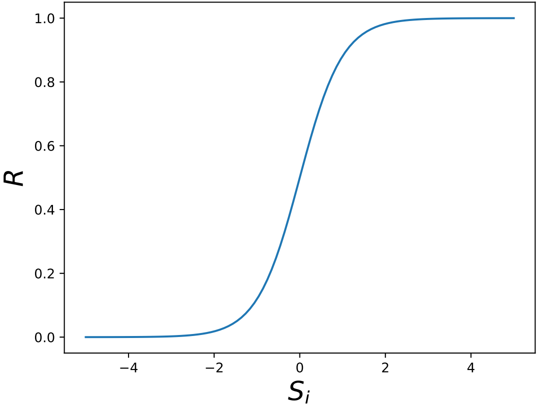
We consider GRNs having 1 input gene and 1 output gene with $2K/N = 5$

- S_i : Expression of ith gene (continuus variable of $[0, 1)$)
- J_{ij} : Interaction from jth to ith gene
  - $J_{ij} = \pm 1$ (activation or repression) or 0 (no regulation)
- σ : Input signal from outside

Discrete-time dinamics

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

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



Response function: same for all the genes

Input and output nodes

- Input: Randomly chosen
- Output: The most sensitive gene

Effective response

- Consider the steady state
- Effective response of ith node against the input σ

$$\bar{S}_i[\sigma] \equiv \frac{1}{T} \sum_{t=\tau}^{\tau+T} S_i(t)$$

Fitness

- Sensitivity of gene *i*

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

- Fitness

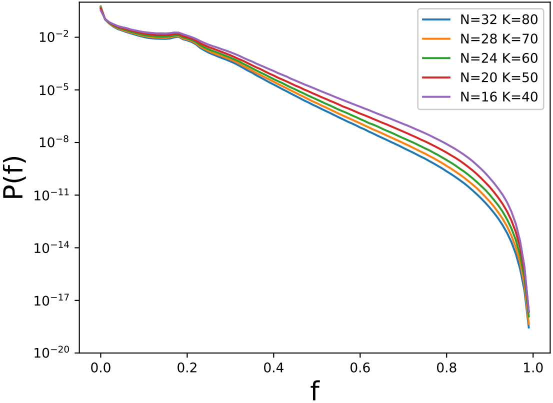
$$f \equiv max\{\Delta_i\}$$

Method

Rare event sampling by the multicanonical Monte Carlo method regarding the fitness f as energy

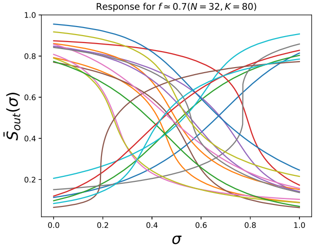
- Uniform sampling (in principle) with respect to f
- Wang-Landau method for determining the weight

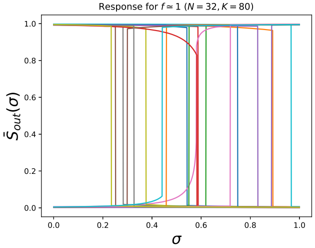
Fitness Landscape



Probability distribution of the fitness

Steady-State Response





$f \simeq 0.7$

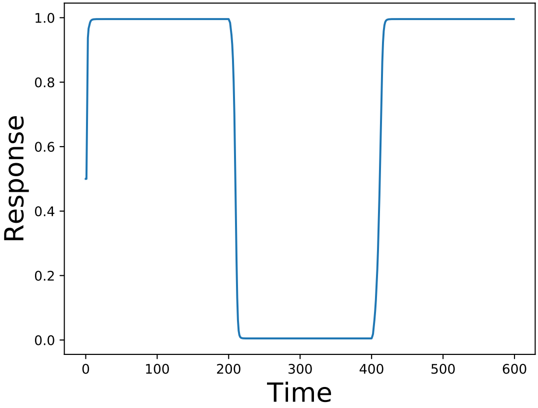
$f \simeq 1$

Fixed-point switching

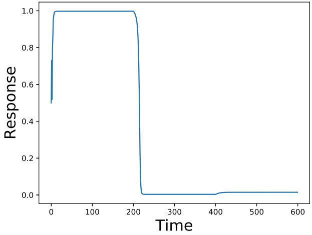
- For $f \simeq 1$, all the networks have two fixed points
- Emergence of the cooperative response to the input using the fixed point switching mechanism

- Then, can they respond quickly to the input change?

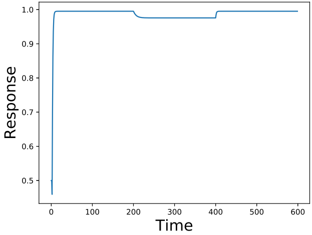
Dynamical Response



Response to abruptly changing input (Success case)



(Fail case)

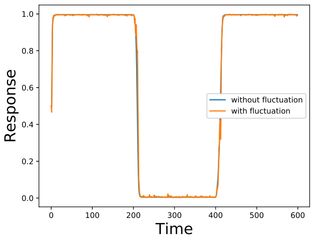


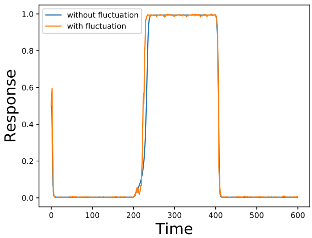
(Fail case)

Effect of Internal Noise

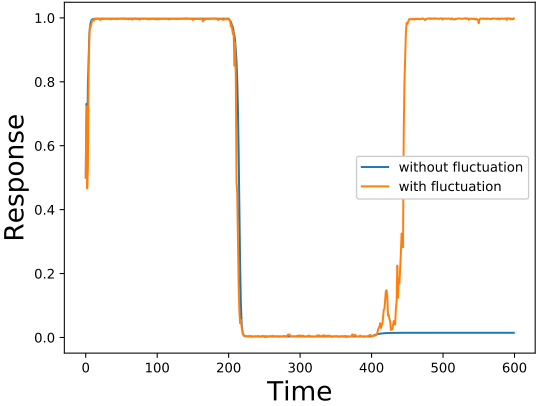
- Consider the number flucturations of TFs as the internal noise.
- $$S_i(t) \to S_i(t) + r_i$$
  r_i: uniform random number in $[-0.1, 0.1]$

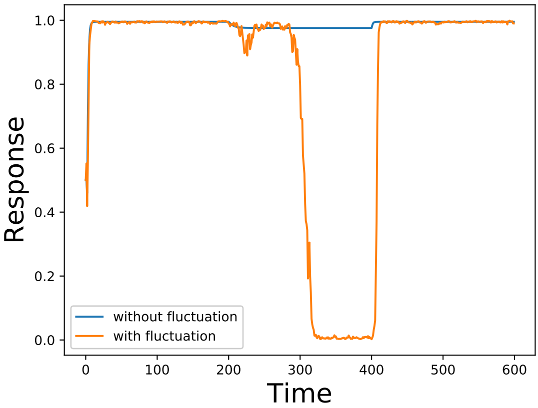
Robustness against noise





Noise-induced sensitive response

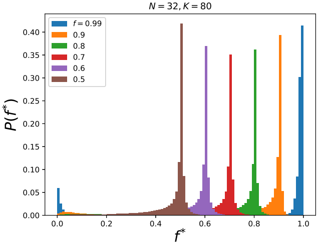




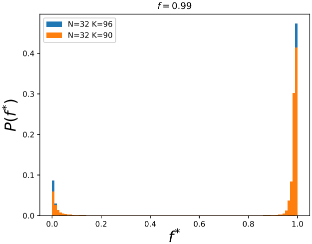
1.0
0.8
0.6
0.4
0.2
0.0
Response
without fluctuation
with fluctuation
0
100
200
300
400
500
600
Time

- w/o noise: $\sim 60\%$ of GRNs can respond sensitively
  - They are robust against internal noise
- w noise: $\sim 74\%$ of GRNs can respond sensitively
  - Noise-Induced sensitive response

Robustness against mutation

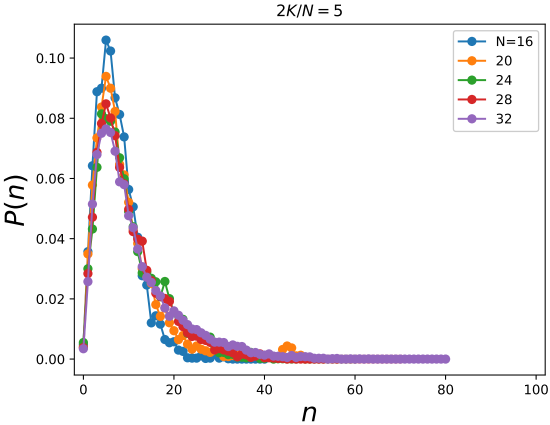


Fitness after single-edge deletion



For $f \simeq 1$

Number distribution of lethal edges



Size dependence

- Small number of lethal edges
  - For $N = 32, K = 80$、86% edges are $n \leq 20$
- The peak of the number distribution of the lethal edges is independent of N
  - Larger GRNs are relatively robust

Summary

Result

- For the GRNs with high fitness, we found that the majority of the networks own the following robustnesses
  1. Mutational Robustness
  2. Robustness against input noise (not shown)
  3. Robustness against internal noise

Proposal

- These robustnesses are characteristic properties accompanying to the high fitness and realize irrespective to the pathway of evolution
  - Similar phenotype from different genotype: pararell evolution?