Simultaneous Emergence of Cooperative Response and Mutational 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 evolution.
  - The evolution is considered as something special

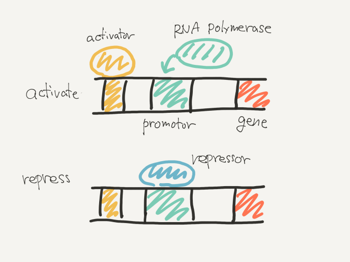
Problem

Relationship between evolution and robustnesses

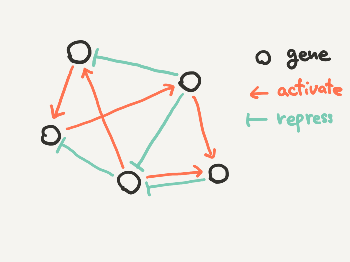
- We study a simple model of the gene regulatory network
  - without using evolutionary simulations
  - make an ensemble of GRNs with high fitness by Multi-canonical MC
- To explore the universal properties of highly fitted GRNs. The robustnesses in particular.

The gene regulatory network

- The cell state is regulated by the expression levels 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



GRN

Model

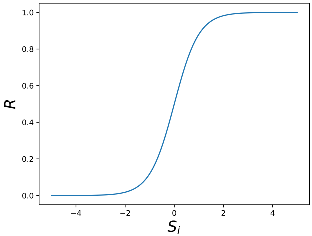
- Directed random graph with N nodes and K edges
  - Node: Gene
  - Edge: Regulatory relation
- 1 input gene and 1 output gene
- Average number of edges connected to a node is $2K/N = 5$

Discrete-time dinamics

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

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

- 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



- Response function
  - each gene respond moderately

Effective response

- Consider the steady state
- Effective response of ith gene 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

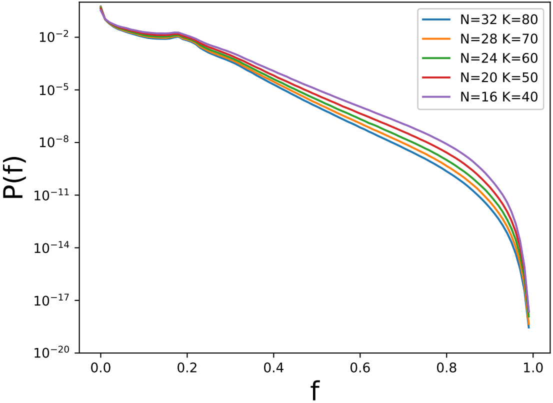
$$f \equiv max\{\Delta_i\}$$

Method

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

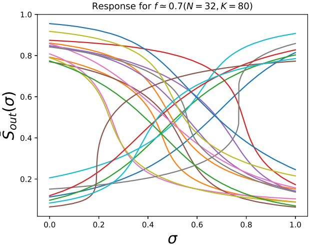
- It ebables us to sample GRNs in a wide range of fitness randomly (in principle).
- Wang-Landau method for determining the Monte Carlo weight

Fitness Landscape

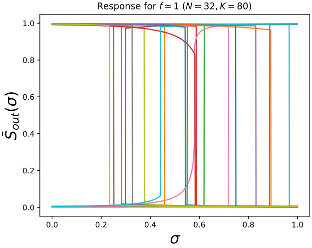


Probability distribution of the fitness

Steady-State Response



$f \simeq 0.7$



$f \simeq 1$

Emergence of fixed-point switching

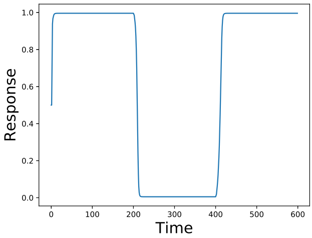
- For $f \simeq 1$, all the networks have two fixed points
- Emergence of the cooperative response to the input using the fixed point switching mechanism
  - A kind of inovation takes place inevitably for highly fitted GRNs.

Question

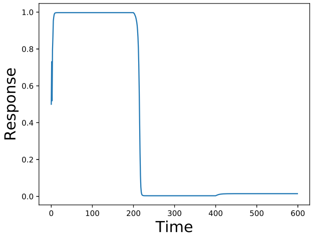
- Then, can they respond properly to the rapid change of input?

Dynamical Response

Response to abruptly changing input



Some GRNs can follow,

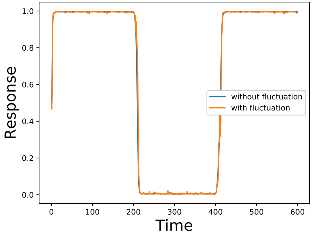


Some cannot

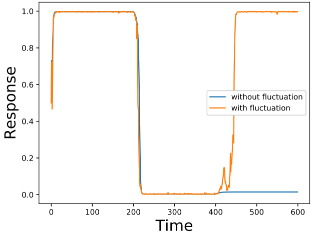
Effect of Internal Noise

- Consider the number flucturations of TFs as the internal noise.
- $$S_i(t) \rightarrow S_i(t) + r_i$$

  r_i: uniform random number in $[-0.1, 0.1]$



Robust against internal noise

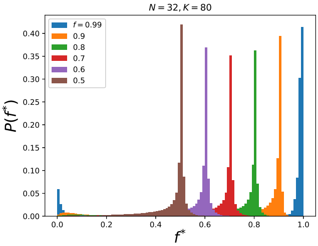


Noise-induced response

- 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

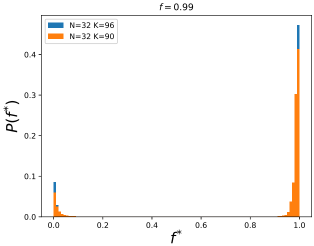
Internal noise makes GRNs to respond properly

Robustness against mutation



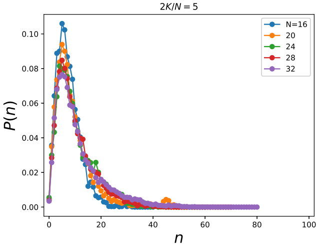
Fitness after mutation

- Consider single-edge deletion
  - A moderate mutation
- All the possible cuts are tried



For $f \simeq 1$

- Majority of edges are neutral
- Small number of edges are lethal
- No intermediate edge



Number distribution of lethal edges

- Small number of lethal edges
- The peak is independent of N
  - Larger GRNs are relatively robust

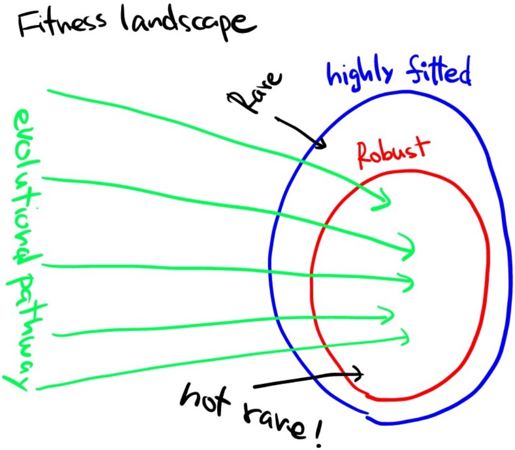
Summary

Result

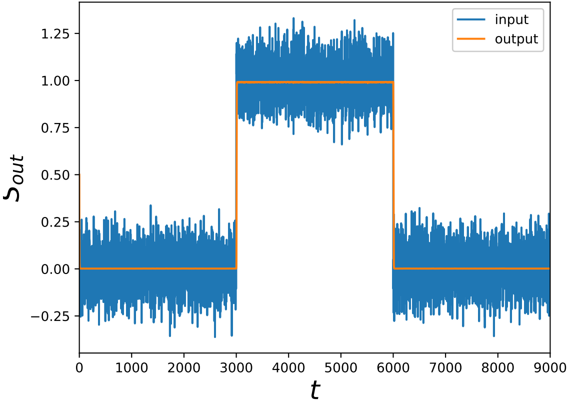
- For the GRNs with high fitness, we found that the majority of the networks own the following robustnesses
  1. Mutational Robustness
  2. Robustness against internal noise
  3. Robustness against input noise (not shown)

Proposal

- These robustnesses are not the consequence of the evolution, but the characteristic properties accompanying to the high fitness irrespective to the pathway of evolution


Fitness landscape
highly fitted
Rare
Robust
evolutional pathway
not rare!

Rubustness ageinst input noise



Response to a noisy input