Robustness against Fluctuations and Mutation in Gene Regulatory Network

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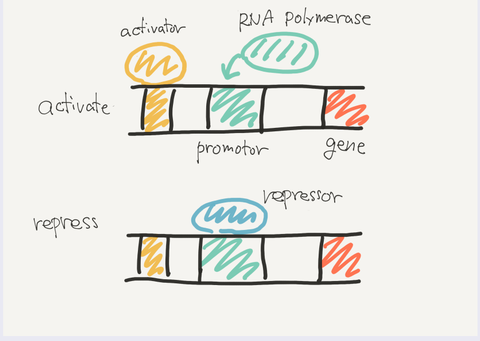
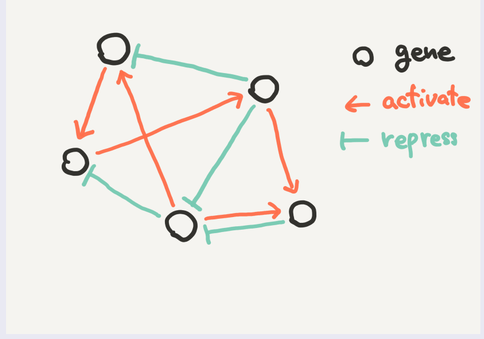
Gene Regulatory Network (GRN)

- 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.
- 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
- Robustness against the internal nose

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

- We apply the multicanonical MC method for sampling GRNs randomly instead of applying GA.

Model

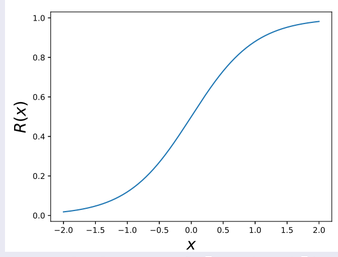
Directed random graph N nodes and K edges

- Node: Gene
- Edge: Regulatory relation
  - Self regulation and mutually-regulating pair are not considered.
- We consider 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 environment
- R: Soft response function of each gene

Definition of the Fitness

- Sensitivity of gene 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 sensitivity is selected as the output gene.
  - r: S of the output gene (response of the network)
- Fitness F: sensitivity of the output gene.

Fitness Landscape

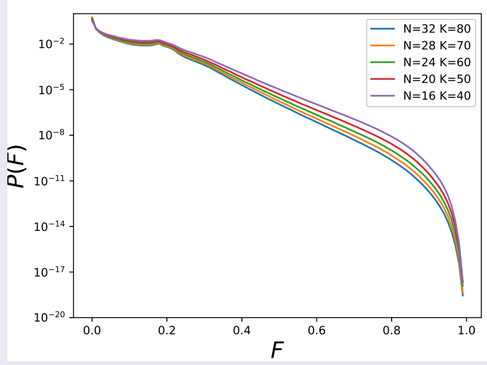


Figure: Appearance probability of fitness

Highly fitted GRNs are very rare!

- We investigate the universal properties of the fittest ensemble ($F = 0.99 \sim 1$)

Steady-State Response to Input

Fittest RGNs respond step-function-like (cooperatively) to input: Emergence of bistability (two fixed points!).

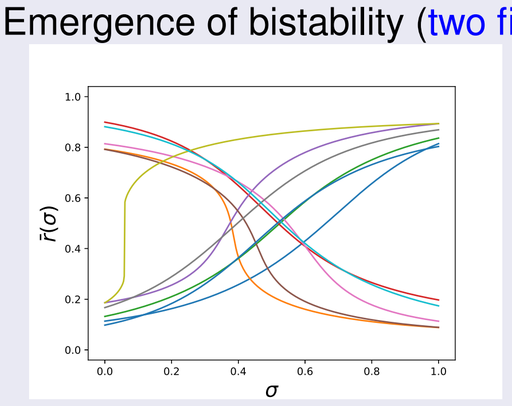


Figure: $F = 0.7 \sim 0.71$

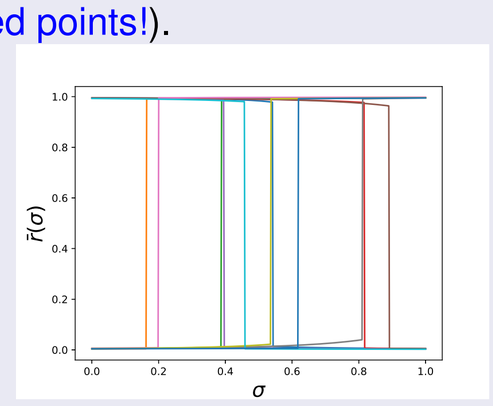


Figure: The fittest ensemble

Dynamical Response using the Fixed-Point Switching

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

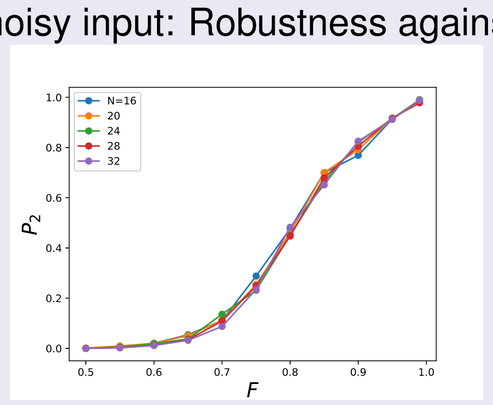


Figure: Ratio of the GRNs having two fixed points

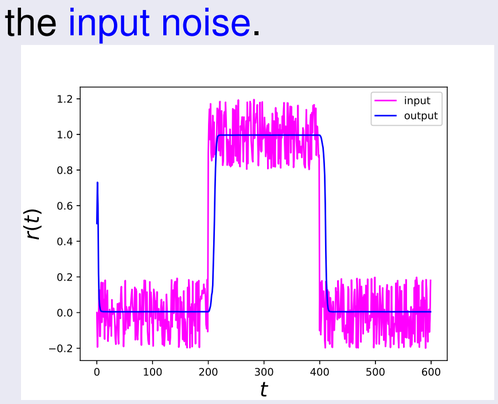


Figure: Stable response to the noisy input due to the fixed-point switching

Noise-Induced Sensitive Response (Effect of Internal Noise)

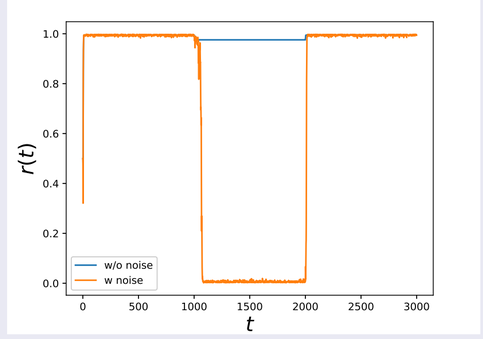


Figure: Response to input with and without internal noise

In some cases that the GRNs cannot follow the rapid change of input, the internal noise helps them follow the input:
$\sim$ 70% of GRNs can follow the change of the input in total

Mutational Robustness

Single-edge deletion.

- Distribution of fitness after the mutation splits into two peaks for large fitness.
  - Majority of edges are neutral against mutation.
  - Only a small number of edges are lethal.
  - Larger GRNs are relatively more rubust against mutation.

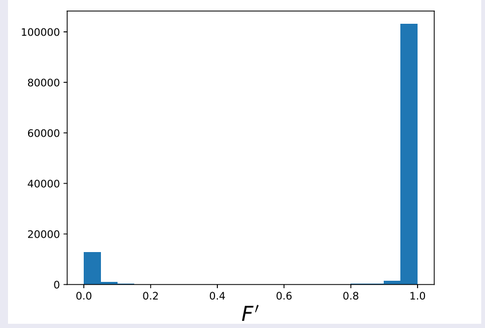
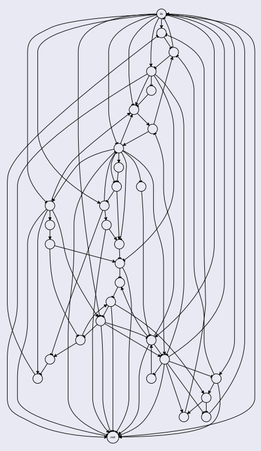


Figure: Fitness distribution after the mutation

Example of Robust GRN



This GRN has no lethal edge and robust against both the input noise and the internal noise.

Proposal

Three robustnesses are characteristic properties accompanying to the high fitness and realize (almost) irrespective to the pathway of evolution.