Model gene regulatory networks under mutation-selection balance

Marcin Zagórski

Institute of Physics, Jagiellonian University, Kraków, Poland

in collaboration with

Zdzislaw Burda, Andre Krzywicki and Olivier C. Martin

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Outline

- What are gene regulatory networks (GRNs)?
- Biological aspects of GRNs
- GRN model
- Main results
- Conclusions and outlook

Genomes

Number of protein-coding genes

E. coli	$\sim$	4000
Yeast	$\sim$	6000
Fruit fly	$\sim$	14000
Human	$\sim$	22000

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It seems, we are not even an order of magnitude better than bacteria...

Gene regulation

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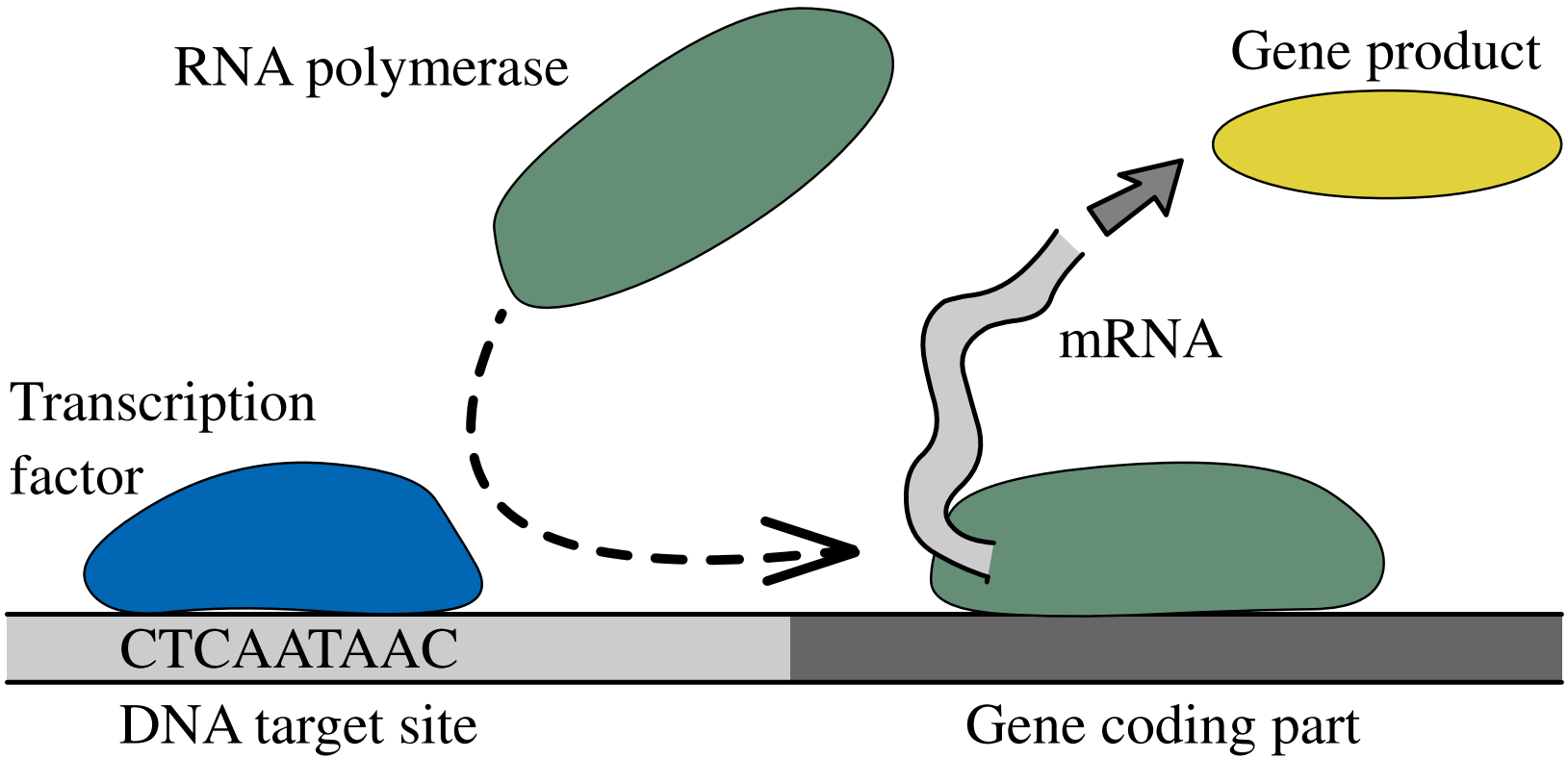
Gene regulatory network

GRN consists of interactions mediated by TFs (edges) which are products of certain genes (nodes).

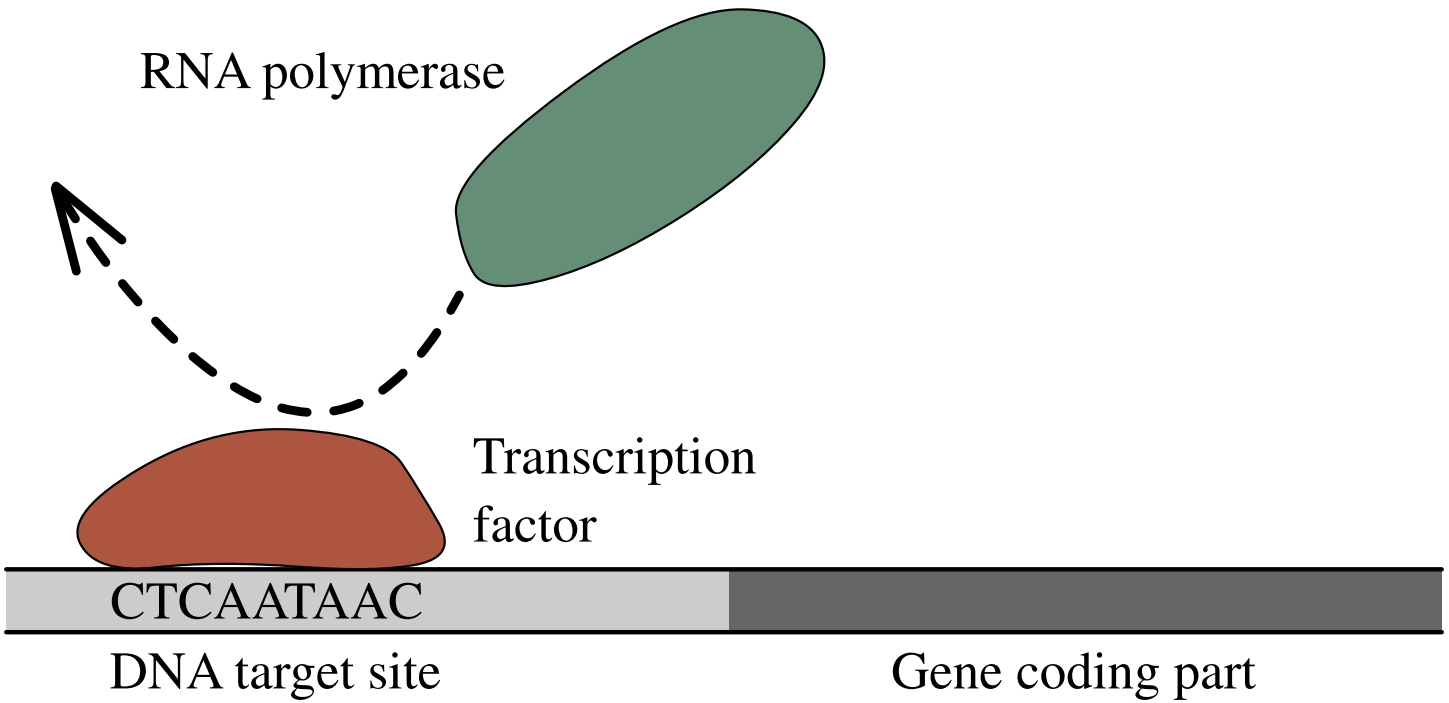
Activators

TF bound to DNA target site in promoter region can enhance protein production rate.



Repressors

In case of repressors the protein production rate is reduced.



Transcriptional Networks

Biological features

- a given gene is generally influenced by a "small" number of other genes
- some genes have effect on multiple target genes (pleiotropic effect)
- GRNs seem to be robust to random change (e.g., to environmental fluctuations or to mutations)

In terms of network terminology, GRNs are sparse with narrow in-degree distribution and broad out-degree distribution.

Phenotype $\mathbf{S} = (S_1, S_2, \ldots, S_N)$
$S_i \in [0, 1]$

Genotype $\mathbf{W}$ is matrix $N \times N$

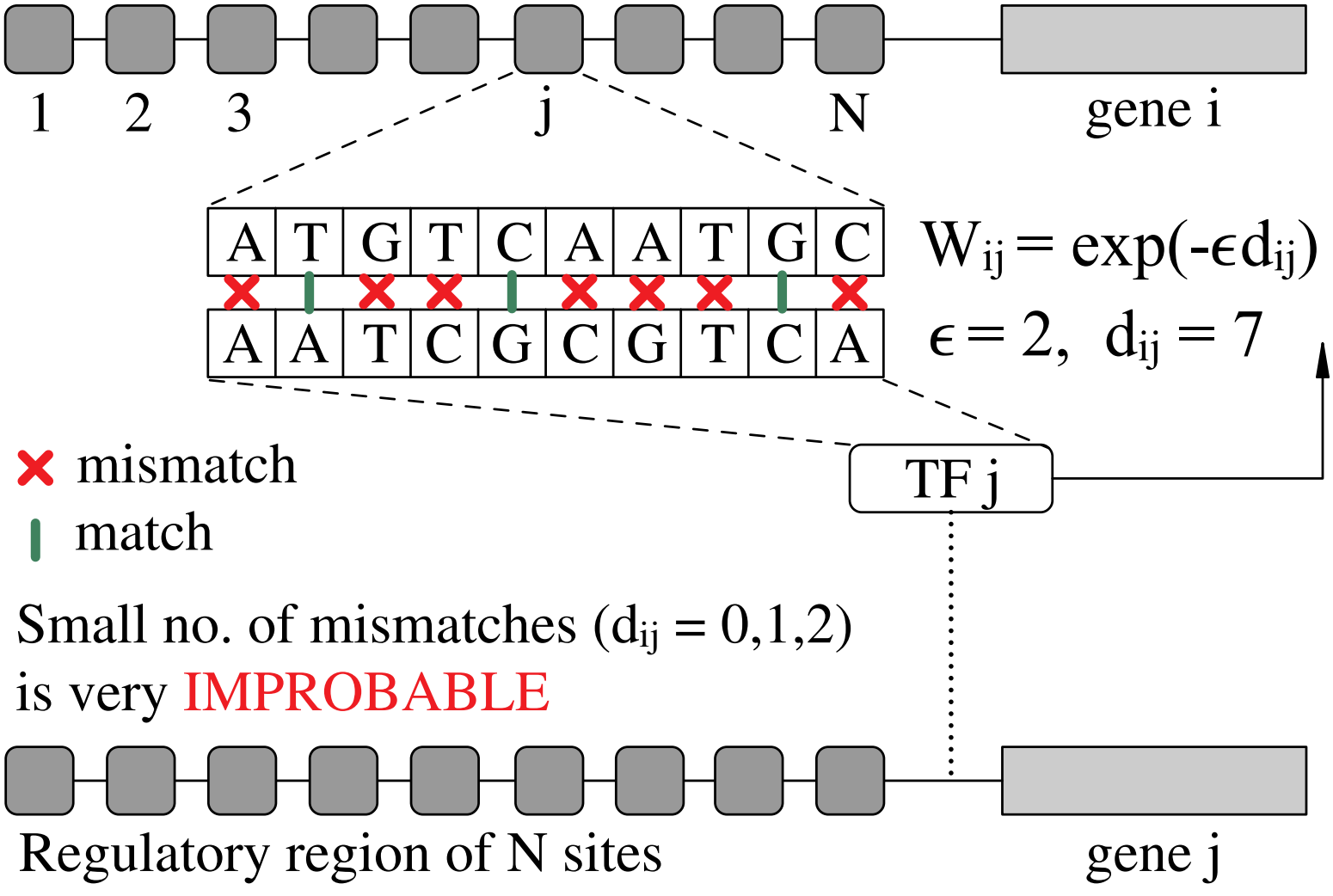
Dynamics $\mathbf{S}(t+1) = G(\mathbf{S}(t), \mathbf{W})$

$$\underbrace{\mathbf{S}(0)}_{\mathbf{S}^{(initial)}} \xrightarrow{\mathbf{W}} \mathbf{S}(1) \xrightarrow{\mathbf{W}} \ldots \xrightarrow{\mathbf{W}} \underbrace{\mathbf{S}(t) \xrightarrow{\mathbf{W}} \mathbf{S}(t+1)}_{\text{fixed point phenotype}}$$

Fitness $F(\mathbf{S}) = \exp(-f \sum_i |S_i - S_i^{(target)}|)$

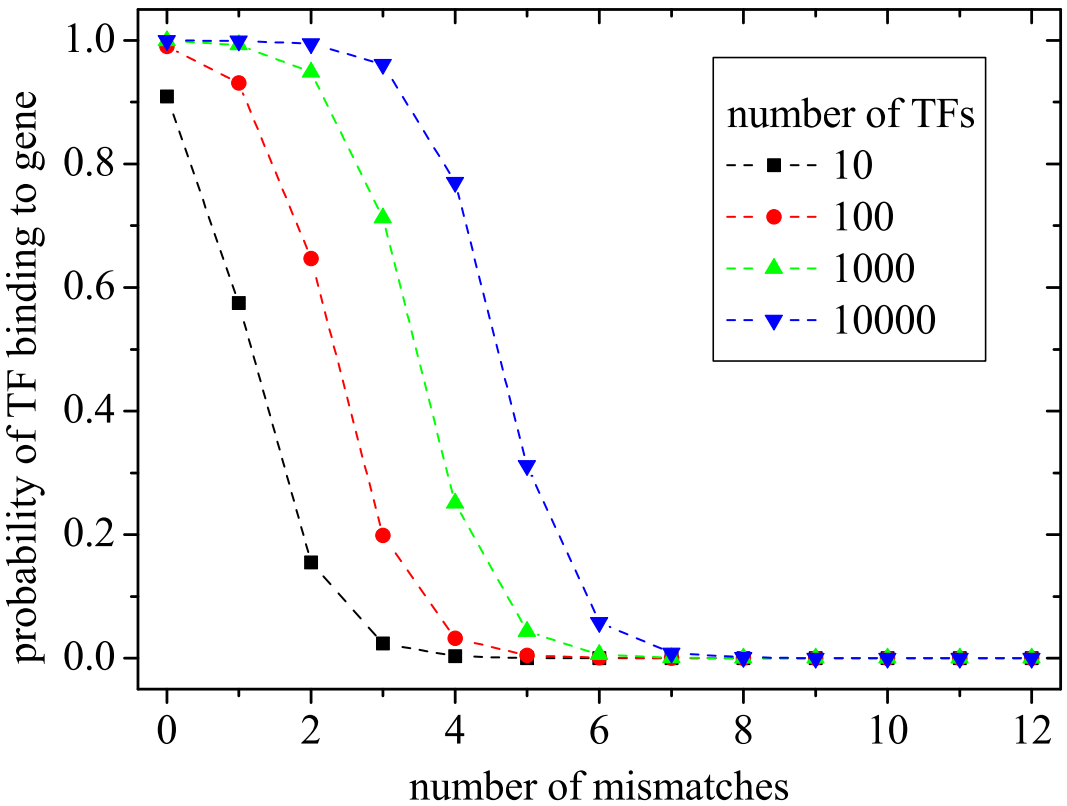
- S_i a level of gene i expression
- W_{ij} interaction between gene i and TF j
- $\mathbf{S}^{(target)}$ corresponds to cell's function
- we sample space of genotypes which lead from $\mathbf{S}^{(initial)}$ to $\mathbf{S}^{(target)}$

Molecular genotype



Specific binding

$$p_{ij} = \frac{1}{1 + \exp\left(\varepsilon d_{ij} - \log nS_j\right)} = \frac{1}{1 + 1/W_{ij} n_j}$$

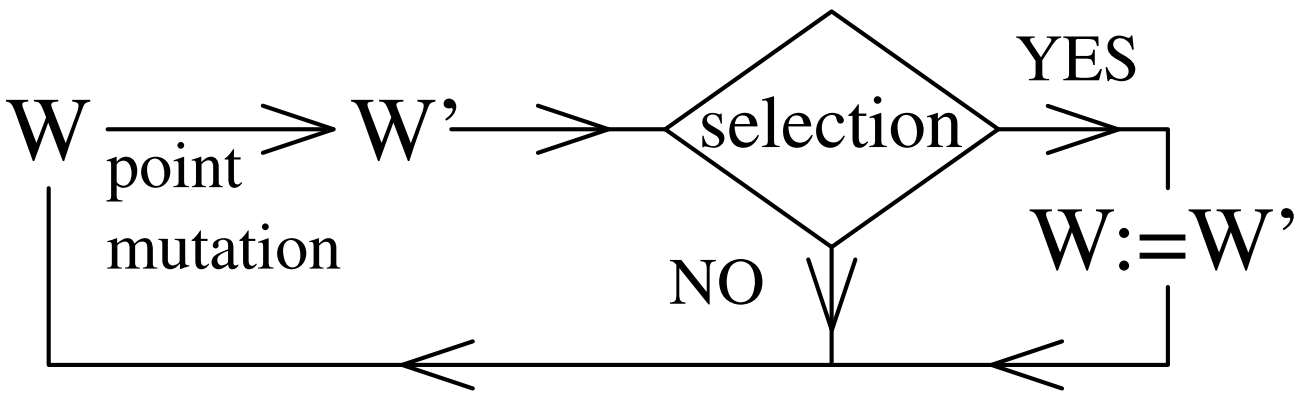


Expression pattern dynamics

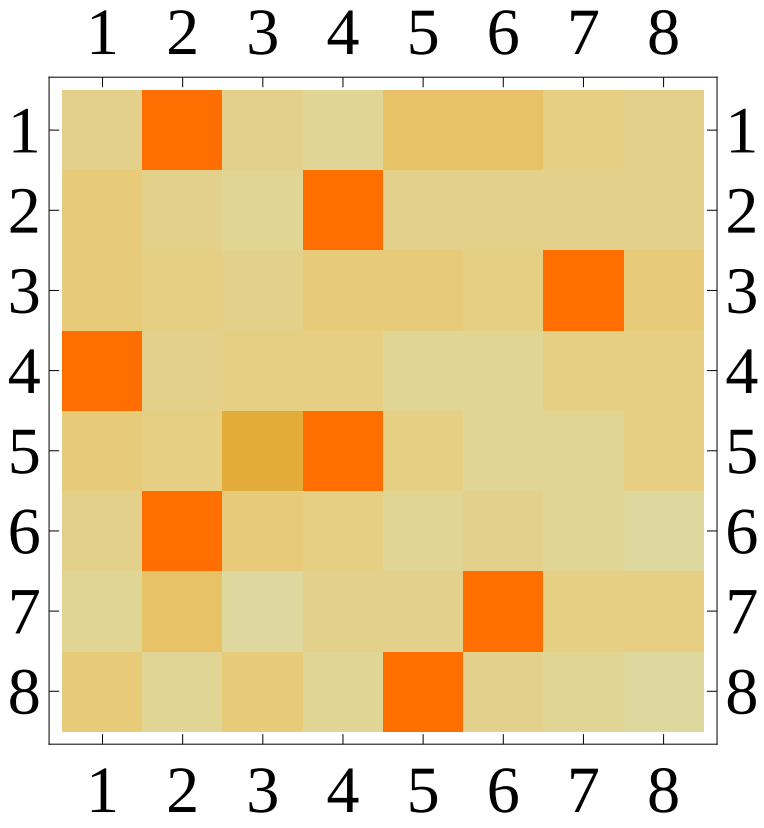
$$S_i(t+1) = 1 - \prod_j (1 - p_{ij}(t))$$

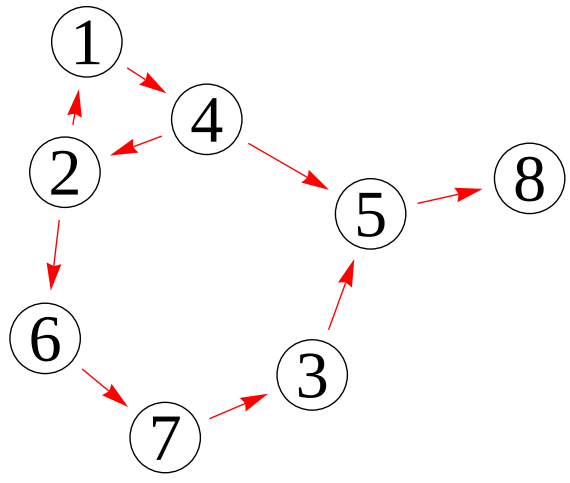
$$p_{ij}(t) = \frac{1}{1 + \exp\left(\varepsilon d_{ij} - \log n S_j(t)\right)}$$

Metropolis sampling of space of viable genotypes.



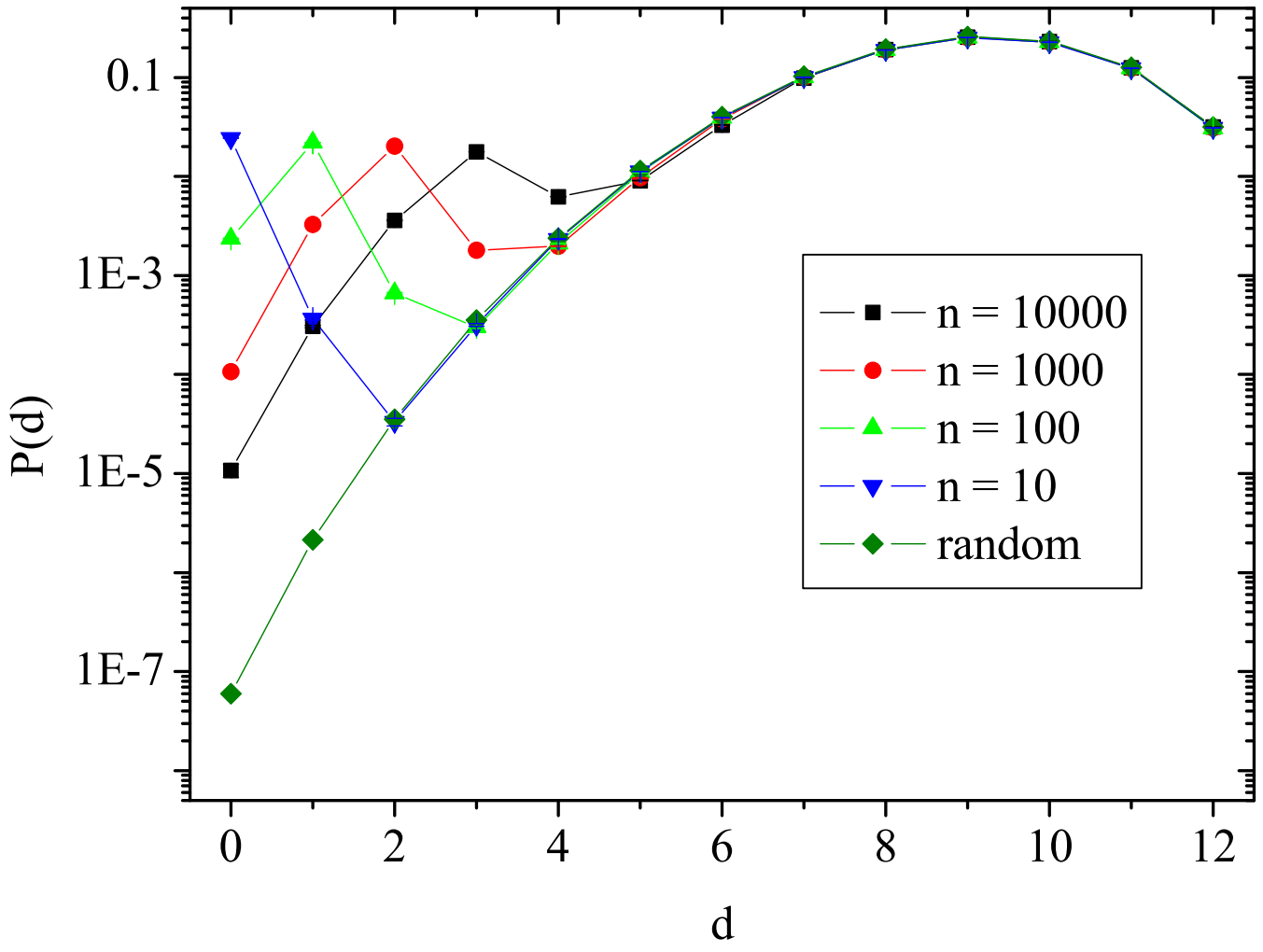
GRN as a directed weighted graph



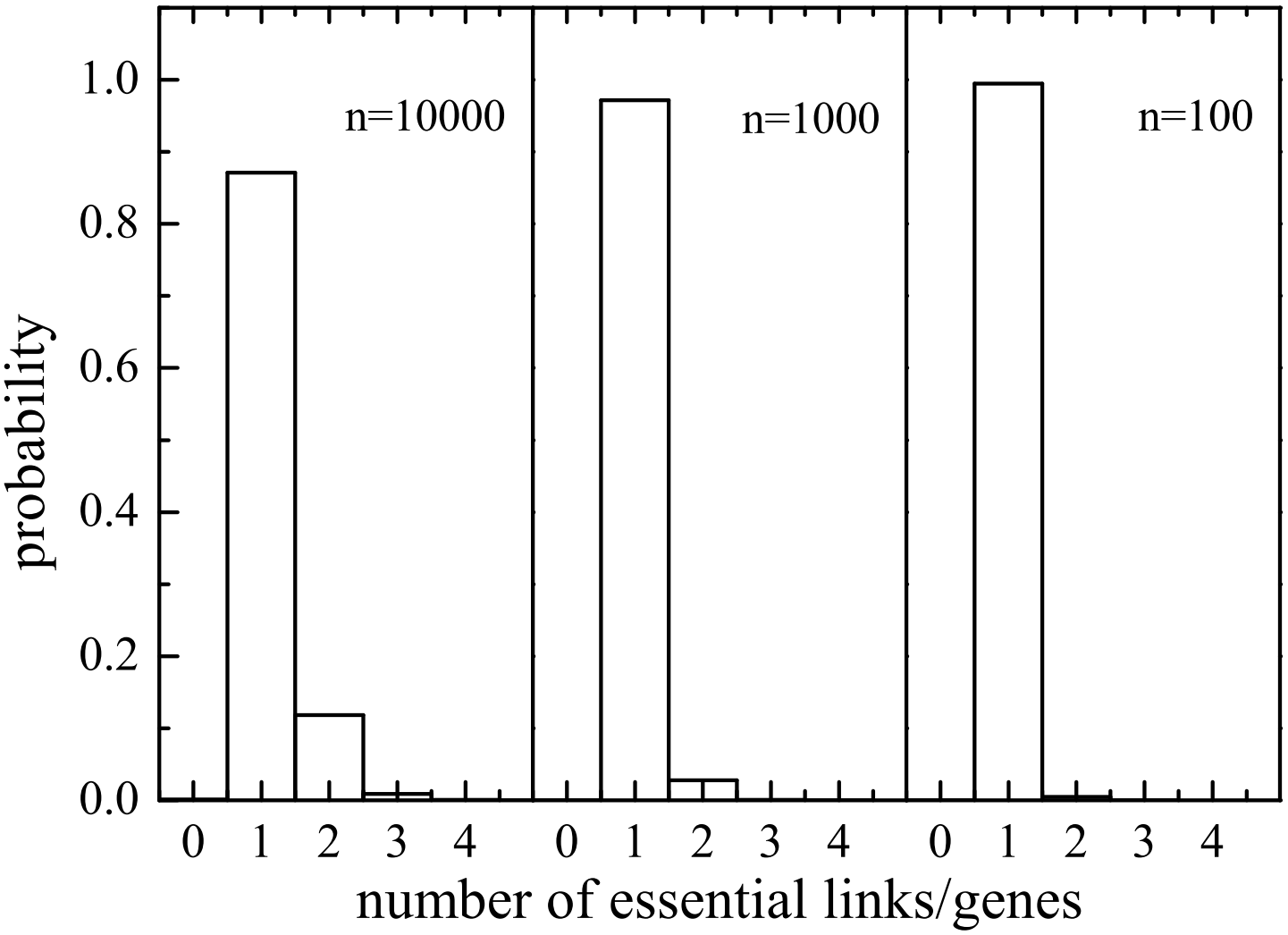


Matrix **W** with corresponding GRN (only strong interactions).

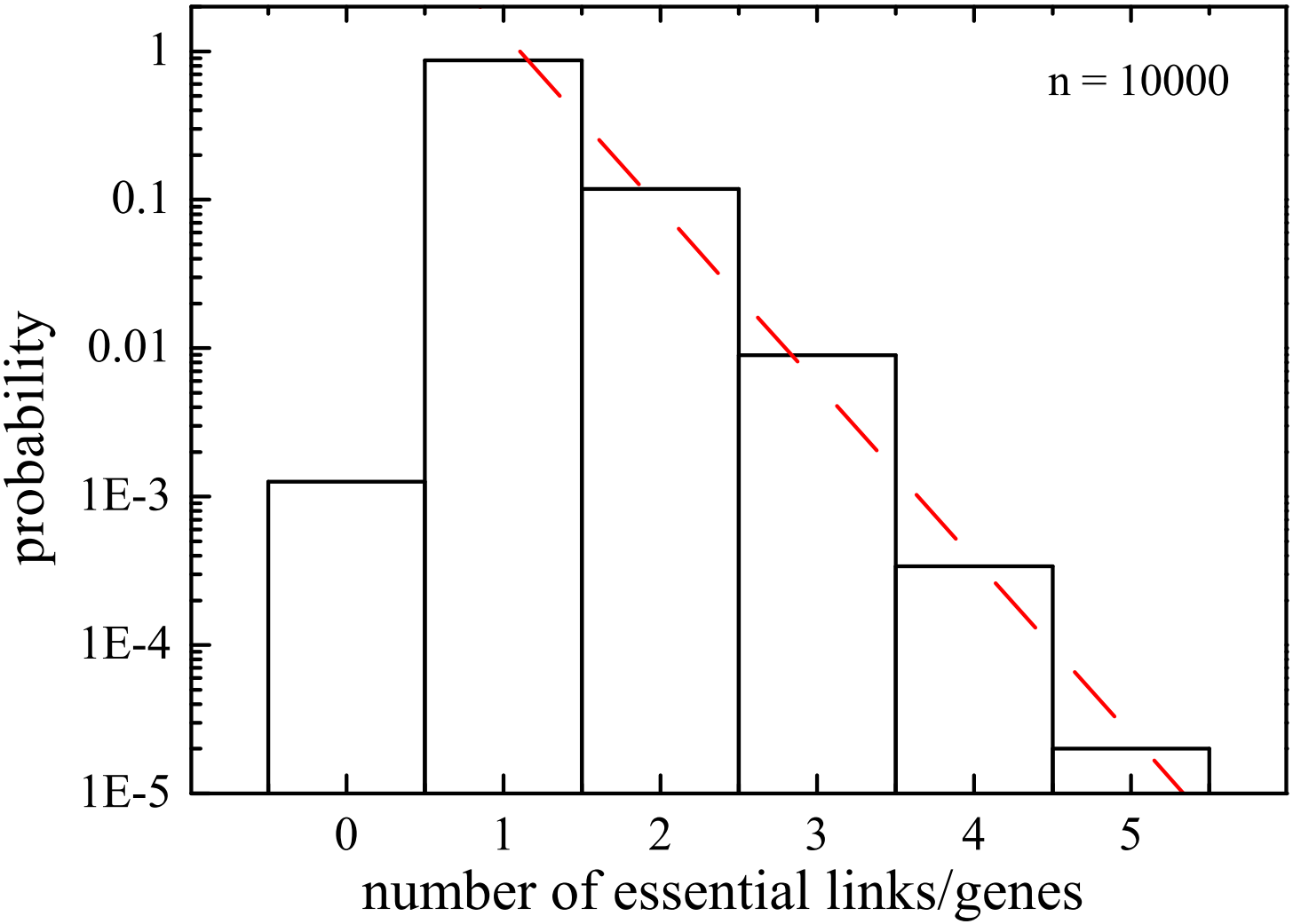
Mismatch distribution



Essential interactions



In-degree distribution



Conclusions

Ensemble of GRNs having one biological function

- GRNs as *sparse* as possible to maintain their function
- in- and out-degree distribution qualitatively agree with those observed in real GRNs
- heterogeneous mutational robustness

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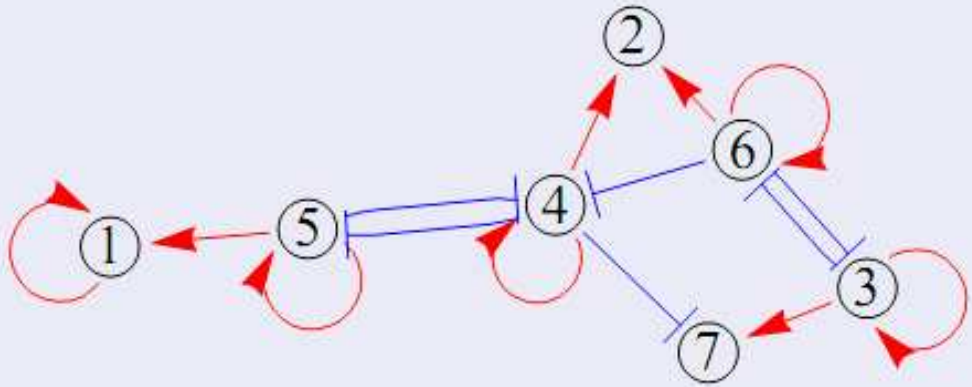
Outlook

GRNs having two or more functions



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Thank you for your attention