Motifs emerge from function in model gene regulatory networks

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in collaboration with

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INNOVATIVE ECONOMY
NATIONAL COHESION STRATEGY

FNP
Foundation for Polish Science

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND

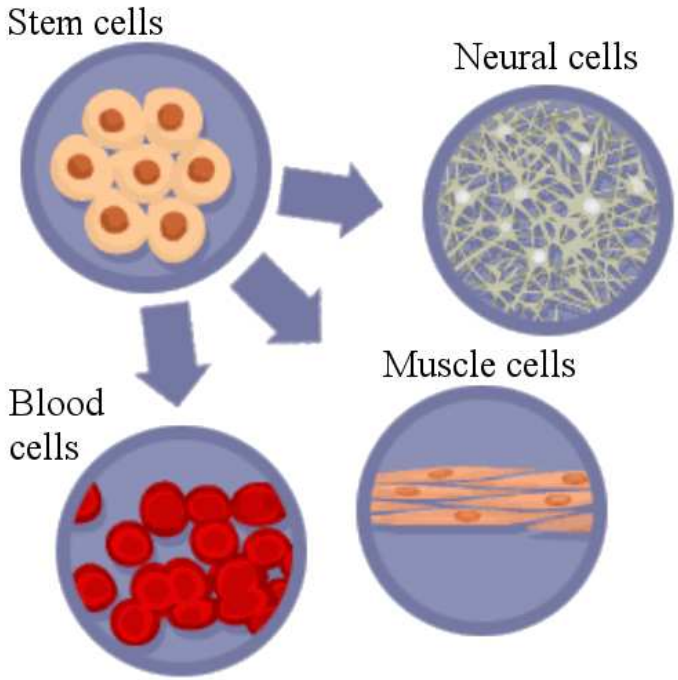
Outline

- Gene regulation
- Transcription factors
- GRN model
- Main results (*motifs*)
- Summary

Gene regulation

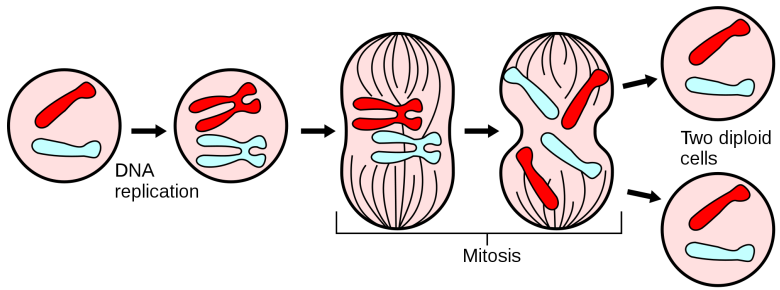
Cell development

- different gene expression patterns correspond to different cell types
- many regulatory mechanisms
- transcription factors (TFs) - promote/block other genes



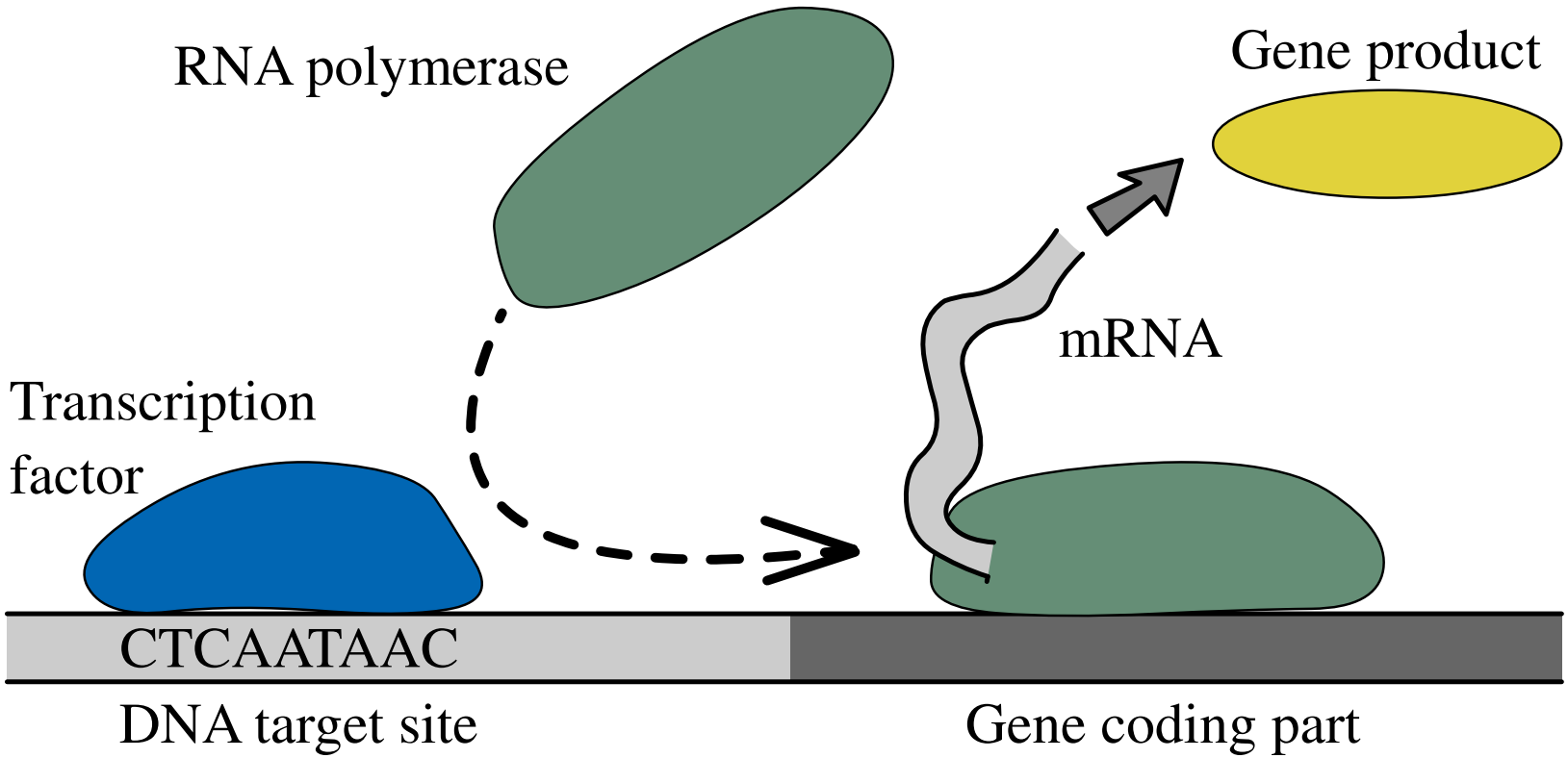
Cell-division cycle

- gene expression patterns correspond to different phases



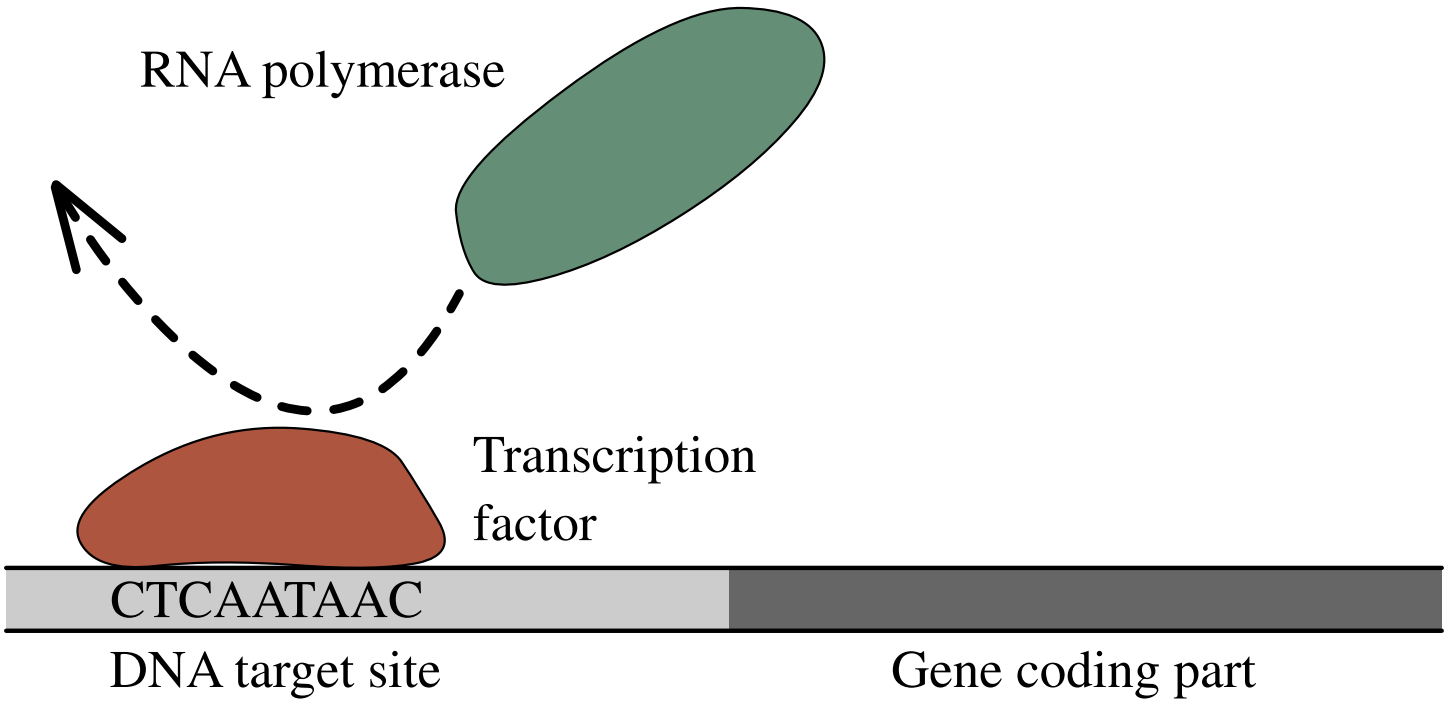
Activators

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.



GRN model

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

- S_i is a level of gene i expression

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

- W_{ij} interaction strength between gene i and TF j

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

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

- $\mathbf{S}^{(target)}$ corresponds to cell's function

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

- we sample space of genotypes leading from $\mathbf{S}^{(initial)}$ to the "vicinity" of $\mathbf{S}^{(target)}$

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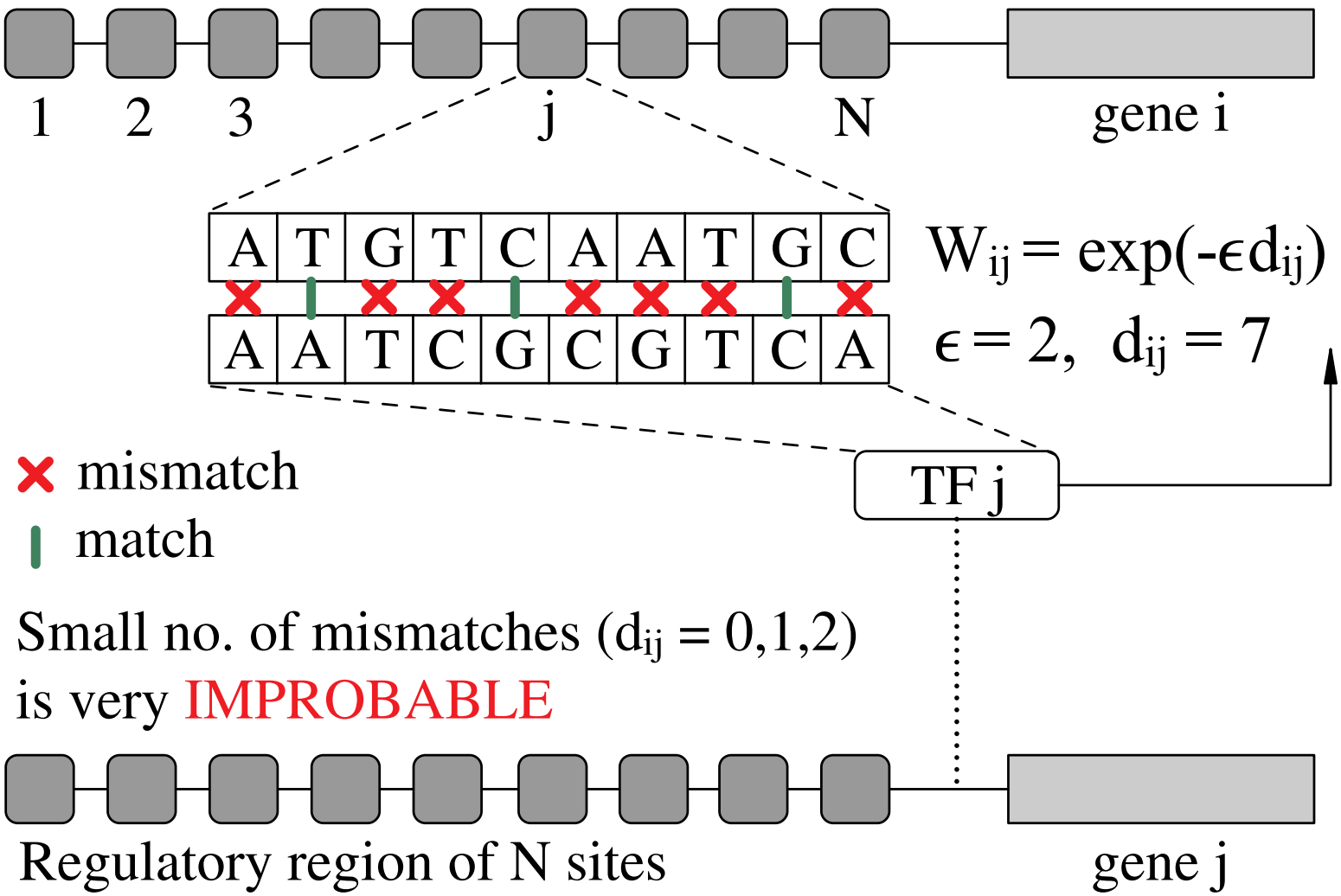
Molecular genotype

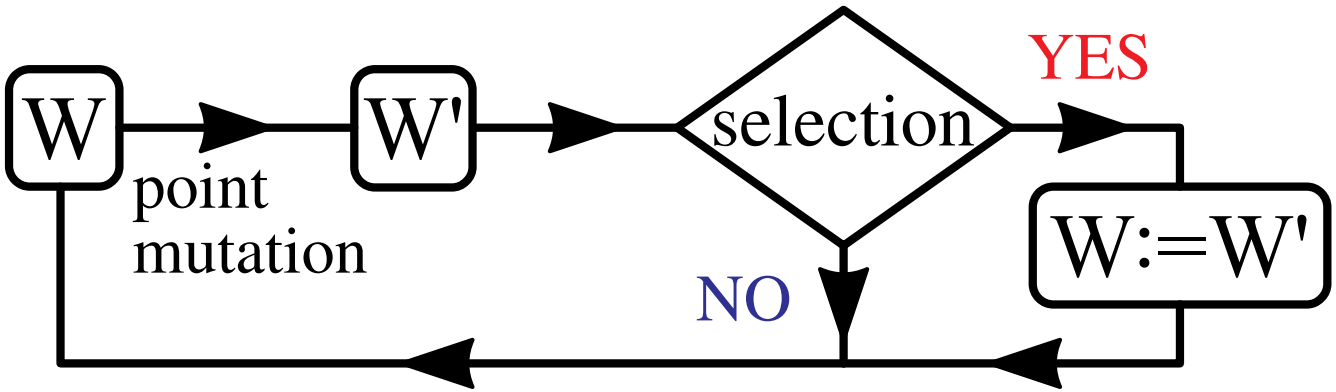


Expression pattern dynamics

$$S_i(t+1) = \underbrace{\left[1 - \prod_j (1 - p_{ij}(t))\right]}_{\text{Activators}} \underbrace{\prod_{j'} (1 - p_{ij}(t))}_{\text{Repressors}}$$

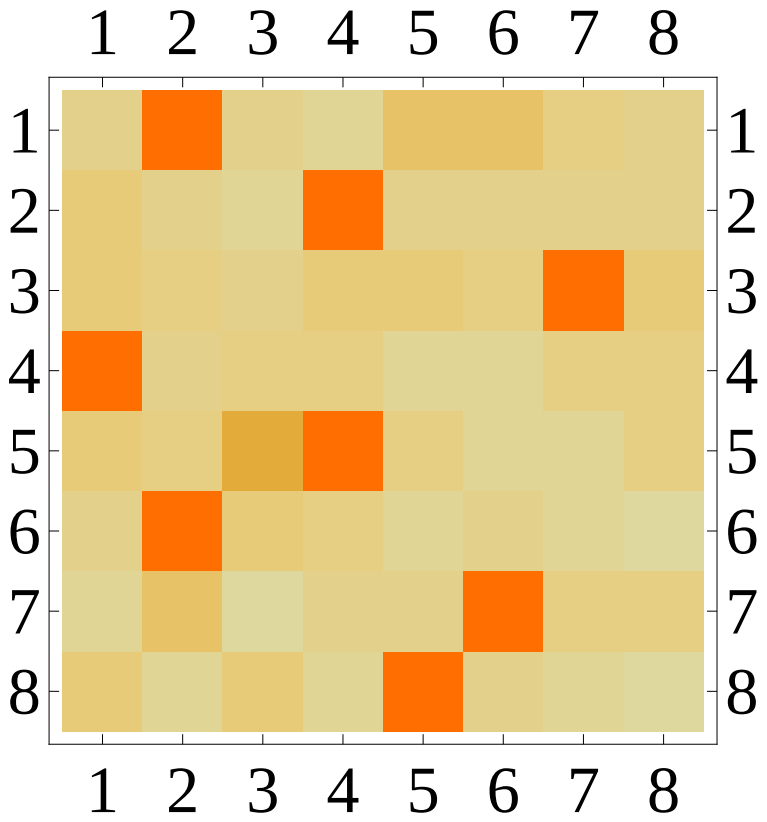
$$p_{ij}(t) = \frac{1}{1 + \exp\left(\varepsilon d_{ij} - \log n S_j(t)\right)}$$

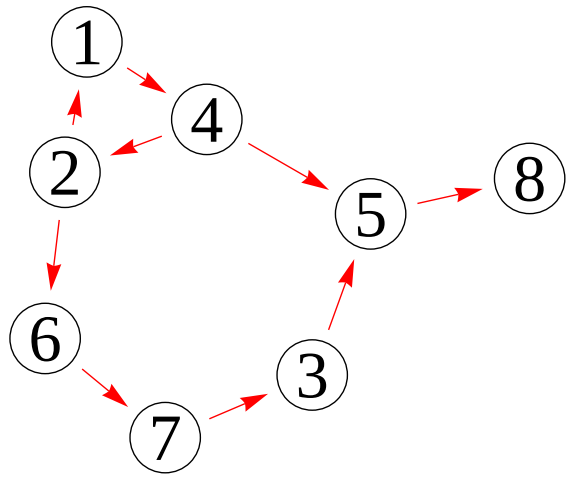
Metropolis sampling of space of viable genotypes.



GRN made of essential interactions

Matrix **W** with corresponding GRN (one target phenotype).





Multi-stability

Target phenotypes

16 genes

8 being ON, 8 being OFF

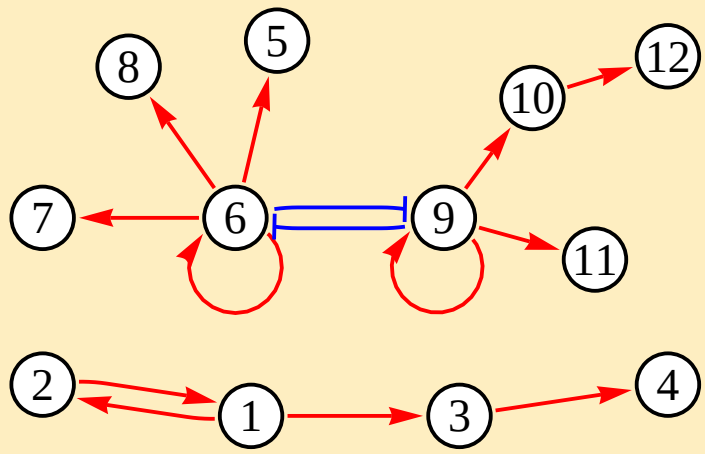
1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0

1 1 1 1 0 0 0 0 1 1 1 1 0 0 0 0

1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0

1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0

Two fixed points



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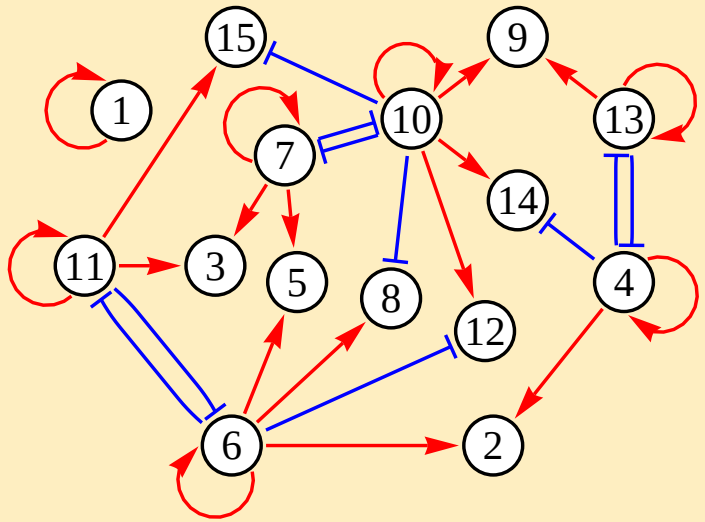
1 1 1 1 0 0 0 0 1 1 1 1 0 0 0 0

1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0

1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0

Four fixed points

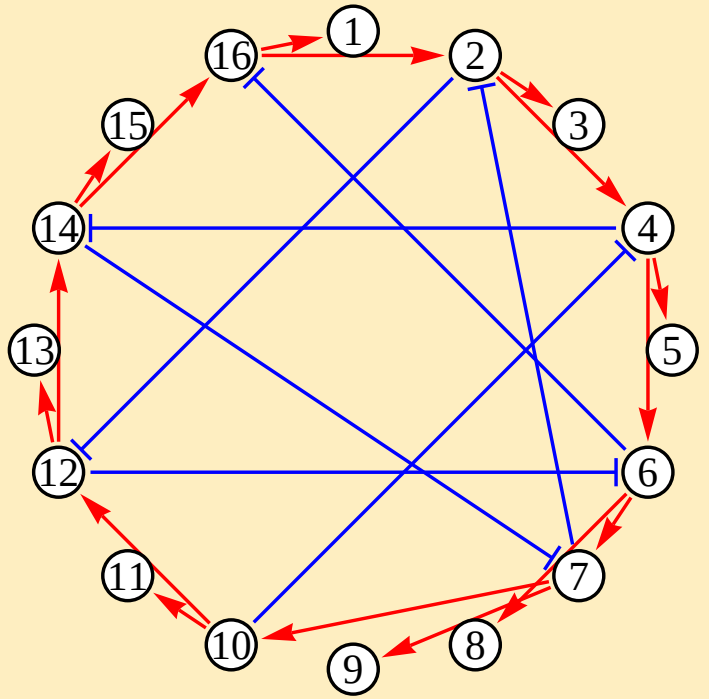


Cycle limiting behavior

Cycle

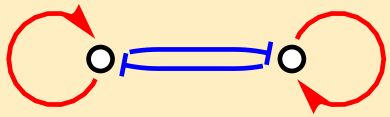
Alternating phenotypes with
8 genes ON and 8 OFF

1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0
0 0 1 1 1 1 1 1 1 1 0 0 0 0 0 0
0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0
0 0 0 0 0 0 1 1 1 1 1 1 1 1 0 0
0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1
1 1 0 0 0 0 0 0 0 0 1 1 1 1 1 1
1 1 1 1 0 0 0 0 0 0 0 0 1 1 1 1
1 1 1 1 1 1 0 0 0 0 0 0 0 0 1 1
1 1 1 1 1 1 1 1 0 0 0 0 0 0 0 0

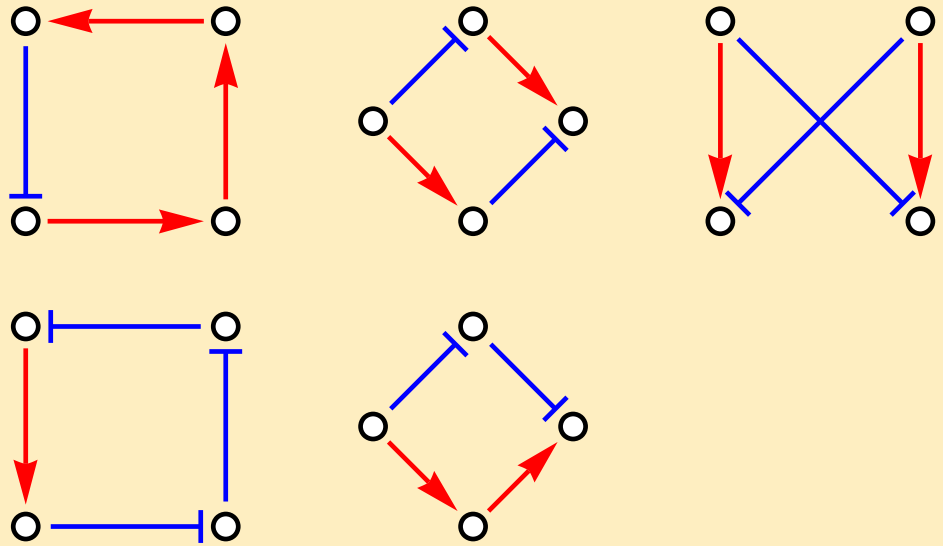


Motifs summary

Multi-stationarity



Cycle limiting behavior



Summary

Motifs

Different motifs emerge due to *functional* capabilities of GRN

- multi-stability: bi-stable switch
- cycling expression: bi-fan, negative loops, diamonds

Outlooks

Getting closer to biological regulatory networks

- including cooperativity
- other constraints (not only functional)

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Acknowledgments

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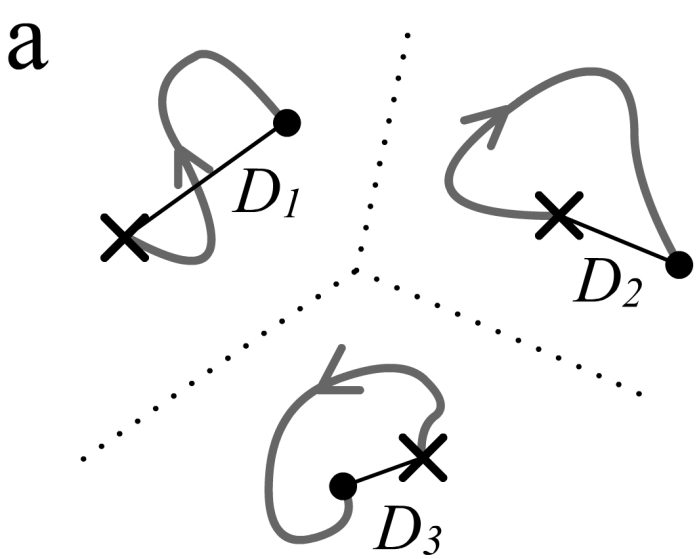
References

- Z. Burda, A. Krzywicki, O.C. Martin, M. Zagorski, *Motifs emerge from function in model gene regulatory networks*, PNAS **108**, 17263-17268 (2011).
- Z. Burda, A. Krzywicki, O.C. Martin, M. Zagorski, *Distribution of essential interactions in model gene regulatory networks under mutation-selection balance*, Phys. Rev. E **82**, 011908 (2010).
- U. Alon, *Network motifs: theory and experimental approaches*, Nat. Rev. Genet. **8**, 450 (2007).

Thank you for your attention

MCMC process

Multi-stability



Cycling phenotypes