Emergence of motifs in model gene regulatory networks

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Gene regulatory networks arise in all living cells, allowing the control of gene expression patterns. The study of their circuitry has revealed that certain subgraphs of interactions or "motifs" appear at anomalously high frequencies. We ask here whether this phenomenon may emerge because of the functions carried out by these networks. Given a framework for describing regulatory interactions and dynamics, we consider in the space of all regulatory networks those that have a prescribed function. Monte Carlo sampling is then used to determine how these functional networks lead to specific motif statistics in the interaction circuitry. In the case where the regulatory networks are constrained to exhibit multi-stability, we find a high frequency of gene pairs that are mutually inhibitory and self-activating. In contrast, networks constrained to have periodic gene expression patterns (mimicking for instance the cell cycle) have a high frequency of bifan-like motifs involving four genes with at least one activating and one inhibitory interaction.

GENERAL DESCRIPTION

We have proposed a gene regulatory network (GRN) model [1, 2] which incorporates the microscopic interactions between genes and transcription factors. In particular the gene's expression level is determined by deterministic synchronous dynamics with contribution from both excitatory and inhibitory interactions. We study the structure of networks that have a specific "function" and are subject to the natural selection pressure. Particularly, within formulated framework we analyse certain subgraphs of interactions (motifs [3]) that appear at anomalously high frequencies in GRNs having a prescribed gene expression pattern. By using Markov Chain Monte Carlo sampling procedure we are able to produce many regulatory networks, and therefore we can address this question *in silico*.

Obtained GRNs are evolvable and a given target expression pattern can be realized through different topologies. Having such framework, we can ask whether functional constraints shape the network structure. Particularly, we consider two classes of constraints which resemble two types of biological processes: (i) different stable gene expression patterns can be interpreted as different types of cells during cell development, (ii) cyclic gene expression is characteristic for cell cycle,

where different genes are excited/inhibited during different stages of cell division process. In the case of multistability we observe two node motif that works as a bistable switch between situations with one gene being "on" and the other being "off". In the case of target phenotypes being periodic in time the bistable switch is not present, and four node motifs like bifan, diamond and "frustrated" loop appear and are highly overrepresented. Hence, we can conclude that different classes of motifs are observed for different types of functional capabilities of GRN. This result is very striking if we realize that no motif structures are incorporated inside our framework on any level. Instead motifs emerge from purely random background due to imposed functional patterns and selection pressure.

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[1] Z. Burda, A. Krzywicki, O.C. Martin and M. Zagorski, Proc. Natl. Acad. Sci. U.S.A. **108**, 17263 (2011).

[2] Z. Burda, A. Krzywicki, O.C. Martin and M. Zagorski, Phys. Rev. E **82**, 011908 (2010).

[3] S. Shen-Orr, R. Milo, S. Mangan, U. Alon, Nature Genetics **31**, 64 (2002).