The Role of Gene Circuit Motifs and their Coupling in State Distributions

Benjamin R. Clauss[1,2,4], and Mingyang Lu[1,2,3,4]

***Short Abstract* — We present a novel method for the identification of functional properties of gene circuits through the comprehensive analysis of 4-node circuits by ODE based simulations. Our approach can identify circuits, motifs, and coupling of motifs capable of recapitulating any state distribution. We identify specific functional properties of circuits responsible for multiple distinct classes of state distributions and show how our method can be applied to single cell RNA-seq data.**

I. Purpose

Gene circuit motifs are functional units of circuits that occur at greater than expected frequencies and contain important regulatory patterns[1]. Each motif contains distinct information processing functions and helps to define the behavior of the circuit. In-sillico analysis of synthetic circuits capable of specific functions has led to the identification of biologically meaningful regulatory motifs [2]. Unfortunately, motif searches typically use very narrow parameter ranges for exploring the behavior of circuits and fail to use networks large enough to explore how coupling of motifs can impact the behavior of the circuit.

When multiple motifs are present in a circuit there are several ways in which they can be connected [3]. The specific coupling in a circuit can impact the way each motif process information and therefore plays an important role in determining circuit behavior [4]. Currently, coupling of motifs is often overlooked when considering the contribution of motifs to circuit behavior.

We present a novel method for the identification and analysis of the functional properties of circuits capable of generating distinct state distributions. Our method robustly explores the behavior of all four-node circuits and identifies circuits, motifs, and motif coupling responsible for distinct arrangements of multiple states. Contrary to other methods for assigning function to motifs, our method defines a function and identifies motifs responsible. We also show how our method can be applied to single-cell RNA-seq data to gain important insight into biological processes.

Acknowledgements: This work was funded by R35GM128717, Lu (PI)

1. Tufts Graduate School of Biomedical Sciences. Tufts University, Boston, MA
2. The Jackson Laboratory for Genomic Medicine. Bar Harbor, ME
3. Department of Bioengineering, Northeastern University. Boston, MA
4. Center for Theoretical Biological Physics, Northeastern University. Boston, MA

II. Results

We began by generating all possible 4-node circuits containing activating, inhibiting and self-regulatory edges. All unique topologies were simulated with RACIPE [5] for a comprehensive and robust exploration of circuit behavior using an extremely wide parameter range.

Circuit behavior was evaluated to identify distinct state distributions. One such distribution describes a triangular arrangement of three states. Analysis of the circuits most able to generate a triangular state distribution revealed a repeating two node motif of mutual activation and self-inhibition occurring twice in each of our top circuits and never with overlapping nodes.

Next, we developed a state distribution comparison score to determine the similarity in behavior of any two circuits. Our score allows us to start with any state distribution and identify similarly behaving circuits, enriched motifs and motif coupling. Comparison of the behavior of all our circuits has identified multiple distinct classes of state distributions.

Finally, we use our method to compare the behavior of synthetic circuits to experimental data. In an application to human glutamatergic neuron differentiation, we identify four-node circuits capable of recapitulating gene expression state distribution. Analysis circuits most able to recapitulate the experimental data yields insights into important regulatory motifs and their coupling for human glutamatergic neuron differentiation.

III. Conclusion

We present a robust method for the identification of functional properties of circuits capable of any function that can be defined with a score. We identify novel circuit motifs involved in generating distinct state distributions. Finally, we show how our method can be applied to gain insight into the regulation of biology.

References

[1] Alon, U. (2007) Network motifs: theory and experimental approaches. Nature Reviews Genetics **8,** 450–461
[2] Ye Y, Kang X, Bailey J, Li C, Hong T (2019) An enriched network motif family regulates multistep cell fate transitions with restricted reversibility . PLOS Computational Biology 15(3) : e1006855
[3] Jiménez A et al. (2017) A spectrum of modularity in multi-functional gene circuits, Molecular Systems Biology 13:925
[4] Kishore Hari et al. (2022) Emergent properties of coupled bistable switches bioRxiv 2021.06.15.448553
[5] Kohar, V., Lu, M. (2018). Role of noise and parametric variation in the dynamics of gene regulatory circuits. npj Systems Biology and Applications **4,** 40