Balancing Stability and Complexity in Boolean Models of Biological Networks

Keywords: Boolean networks, robustness, gene regulatory networks, phenotypic complexity, network stability

Extended Abstract

Boolean networks were first introduced by Kauffman as models for gene regulatory networks [1]. These models have gained popularity because of their simplicity and ability to capture the complex behaviors of biological systems. Currently, the repository Biodivine Boolean Models contains more than 230 Boolean network models [2].

A systematic investigation of these biological models suggests that they are incredibly robust. In particular, they are resilient to perturbations and tend to reach the same phenotype despite small disturbances. An explanation of this phenomenon was first given by Kauffman, who showed empirically that a network's connectivity determines the stability of the Boolean network [1]. This was further expanded on by Derrida, who provided a theoretical explanation for the effect of connectivity [3]. This was succeeded by many works that looked at various features of biological networks to prove empirically the relation between a network parameter and stability.

Building upon this foundational understanding of robustness in Boolean networks, our work delves into the intrinsic trade-off between phenotypic complexity and network stability. Using tools from analytic number theory and coding theory [4–6], we prove and extend a conjecture by Willadsen, Triesch, and Wiles. Specifically, we show that network entropy, a measure of complexity, sets a tight upper limit on network stability (see Figure 1). We further demonstrate that this upper bound takes the form of a straight line with a negative slope, where the slope depends on the size of the network. As a consequence, we derive the Pareto frontier between complexity and stability, allowing us to determine exactly how much stability is achievable for any given level of complexity.

References

[1] S.A. Kauffman. "Metabolic stability and epigenesis in randomly constructed genetic nets". In: *Journal of Theoretical Biology* 22.3 (1969), pp. 437–467. URL: `https://www.sciencedirect.com/science/article/pii/0022519369900150`.

[2] Samuel Pastva et al. "Repository of logically consistent real-world Boolean network models". In: *bioRxiv* (2023). URL: `https://www.biorxiv.org/content/early/2023/06/12/2023.06.12.544361`.

[3] B. Derrida and Y. Pomeau. "Random Networks of Automata: A Simple Annealed Approximation". In: *Europhysics Letters* 1.2 (1986), p. 45. URL: `https://dx.doi.org/10.1209/0295-5075/1/2/001`.

[4] L. H. Harper. "Optimal Assignments of Numbers to Vertices". In: *Journal of the Society for Industrial and Applied Mathematics* 12.1 (1964), pp. 131–135. URL: `https://doi.org/10.1137/0112012`.

[5] A. J. Bernstein. "Maximally Connected Arrays on the n-Cube". In: *SIAM Journal on Applied Mathematics* 15.6 (1967), pp. 1485–1489. URL: https://doi.org/10.1137/0115129.

[6] Richard Bellman and Harold N. Shapiro. "On a Problem in Additive Number Theory". In: *Annals of Mathematics* 49.2 (1948), pp. 333–340. URL: http://www.jstor.org/stable/1969281.

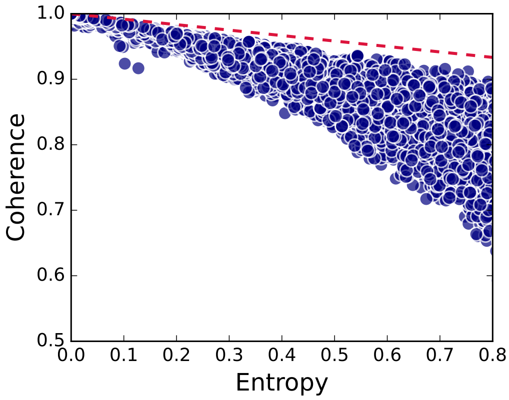

Figure 1: **Coherence versus entropy.** We plotted data from 50,000 randomly generated Boolean networks, each with 12 nodes. In these networks, every node is regulated by two others using a random, non-degenerate function. The dashed red line shows the theoretical upper bound we derived. We clearly observe that coherence never exceeds this bound, and in fact, some networks come very close to it, demonstrating that the bound is not only valid but also tight.