Efficient quantification of canalization in automata networks

Keywords: Canalization, automata networks, symmetry, gene regulation, robustness

Extended Abstract

The biomolecular networks underpinning cell function exhibit canalization, or the buffering of fluctuations required to function in a noisy environment [1,2]. In biomolecular regulation, canalization (the buffering of genetic, epigenetic, and environmental fluctuations) plays a key role in establishing a robust mapping from genotype to phenotype [1]. Robustness of sensors to fluctuations, a feature of canalization, requires dynamical redundancy. This manifests in several ways, including: i) multiple signaling pathways, ii) multiple combinations of transcription factors that bind a gene's promoter region, and iii) threshold behaviors that allow depletion of one signal to be overcome by overabundance of another.

We present a new major release of CANA, v1.0.0, an open-source Python package for understanding canalization in automata network models, discrete dynamical systems in which activation of biomolecular entities (e.g., transcription of genes) is modeled as the activity of coupled automata. To study canalization, CANA provides routines that quantify various types of redundancy using rigorous measures. It extends the McCluskey theory of minimization of Boolean functions [3], by compressing the prime implicants of a Boolean function into a set of schemata, where symmetry is also described with symbols for groups of inputs that can permute [4]. Indeed, one understudied putative mechanism for canalization is the functional equivalence of biomolecular regulators (e.g., among the transcription factors for a gene). We study this mechanism using the theory of symmetry in discrete functions [3,4]. We present a new exact method, *schematodes*, for finding maximal symmetry groups among the inputs to discrete functions, and integrate it into CANA. The *schematodes* method substantially outperforms the inexact method of previous CANA versions both in speed and accuracy, as sown in Figure 1.a).

We apply CANA v1.0.0 to study symmetry in 74 experimentally-supported automata network models from the *Cell Collective* (CC) repository [5]. The symmetry distribution is significantly different in the CC than in random automata with the same in-degree (connectivity) and bias (average output) (Kolmogorov-Smirnov test, $p \ll 0.001$), as shoen in Figure 1.b). Its spread is much wider than in a null model (IQR 0.31 vs IQR 0.20 with equal medians), demonstrating that the CC is enriched in functions with extreme symmetry or asymmetry.

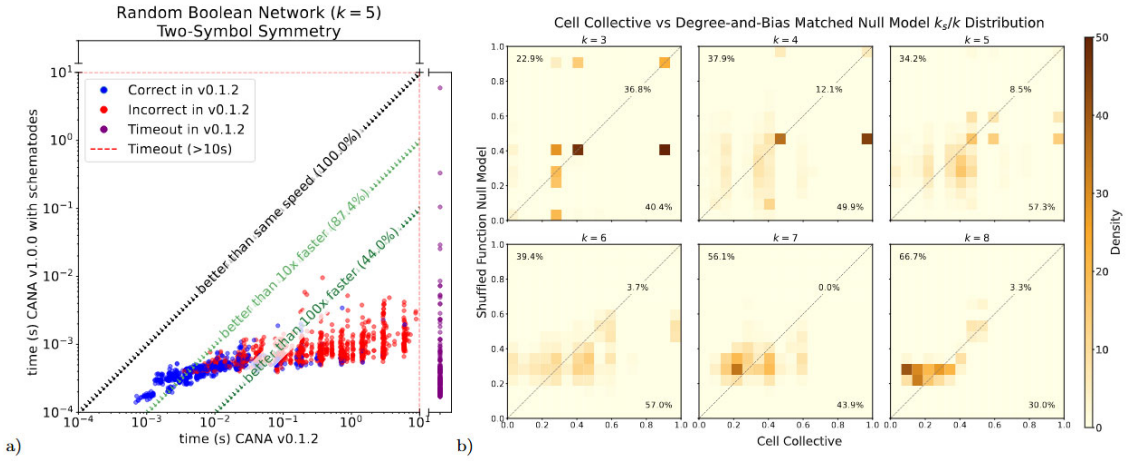

Figure 1: Fig. 1: Benchmarks and symmetry analysis for random and CC automata. a) computation time using CANA v1.0.0 with schematodes (vertical) and CANA v0.1.2 (horizontal). All outputs from CANA v1.0.0 with schematodes were verified to be correct. Correct (incorrect) outputs generated using the heuristic method of CANA v0.1.2 are shown in blue (red). Benchmarks for the CC (not shown) reveal similar behavior. Benchmarks were run on a 3.9GHz Intel core i5 CPU. b) comparisons of normalized symmetry (ks/k) for CC functions before (horizontal axes) and after (vertical axes) random output shuffling, shown separately for each k ∈{3, ..., 8}. Each CC automaton is represented 12 times and is used to produce a "shuffled" null ensemble with equal bias p and in-degree k. Percentages in the top left, top right, and bottom right of each panel indicate how often shuffles result in increased, equal, or decreased symmetry, respectively.

References

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