Counterfactual Resimulation for Causal Analysis of Rule-Based Models

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Rule-based modeling languages such as Kappa and BioNetGen can be used to write mechanistic models of complex reaction systems. Such models consist in collections of stochastic graph-rewrite rules that are equipped with different firing rates. Techniques have been proposed to analyze the causal structure of simulation traces generated from rule-based models, ideally providing a way to uncover signalling pathways in networks of low-level protein-protein interactions.

These methods take advantage of rule structure to compress a simulation trace into a minimal subset of events that are necessary and jointly sufficient to replicate an outcome of interest, and then highlight causal influences between the remaining events. They suffer from two major drawbacks though. First, compression is blind to kinetics and may therefore discard important events. Second, these methods give no account of inhibitory influences between events, despite these being ubiquitous in molecular biology.

In this talk, we propose a complementary approach to causal analysis that avoids these two drawbacks by enabling counterfactual reasoning on traces. First, we give a semantics to counterfactual statements of the kind "*had event* e_1 *not occurred, event* e_2 *would not have happened*" and describe an efficient algorithm for evaluating them. Then, we show how counterfactual dependencies give rise to explanations in terms of relations of enablement and prevention between events.