Explorations of causal probabilistic programming approaches for rule-based models of biological signaling pathways

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Rule-based models handle the complexity of biological signaling pathways

Biological signalling pathways are complex systems that underlie many cellular process and whose dysregulation is the source of many morbidities. To address the combinatorial complexity of interactions, patterns of transitions between model states can be compactly represented as probabilistic events using rule-based models.

Implementation of a simple rule-based model in 3 causal PPLs

We implemented a simple rule-based model using three different causal PPLs and compared their advantages and limitations. Kappa[1] is designed for rule-based modeling of signaling pathways and was recently extended for counterfactual inference. Omega[2] is a causal PPL implemented in Julia and is designed for general counterfactual inference. Probability trees[3] are among the simplest models of causal generative processes and can compactly represent conditional independencies as a probabilistic program.

Rules for substrate-kinase binding and phosphorylation

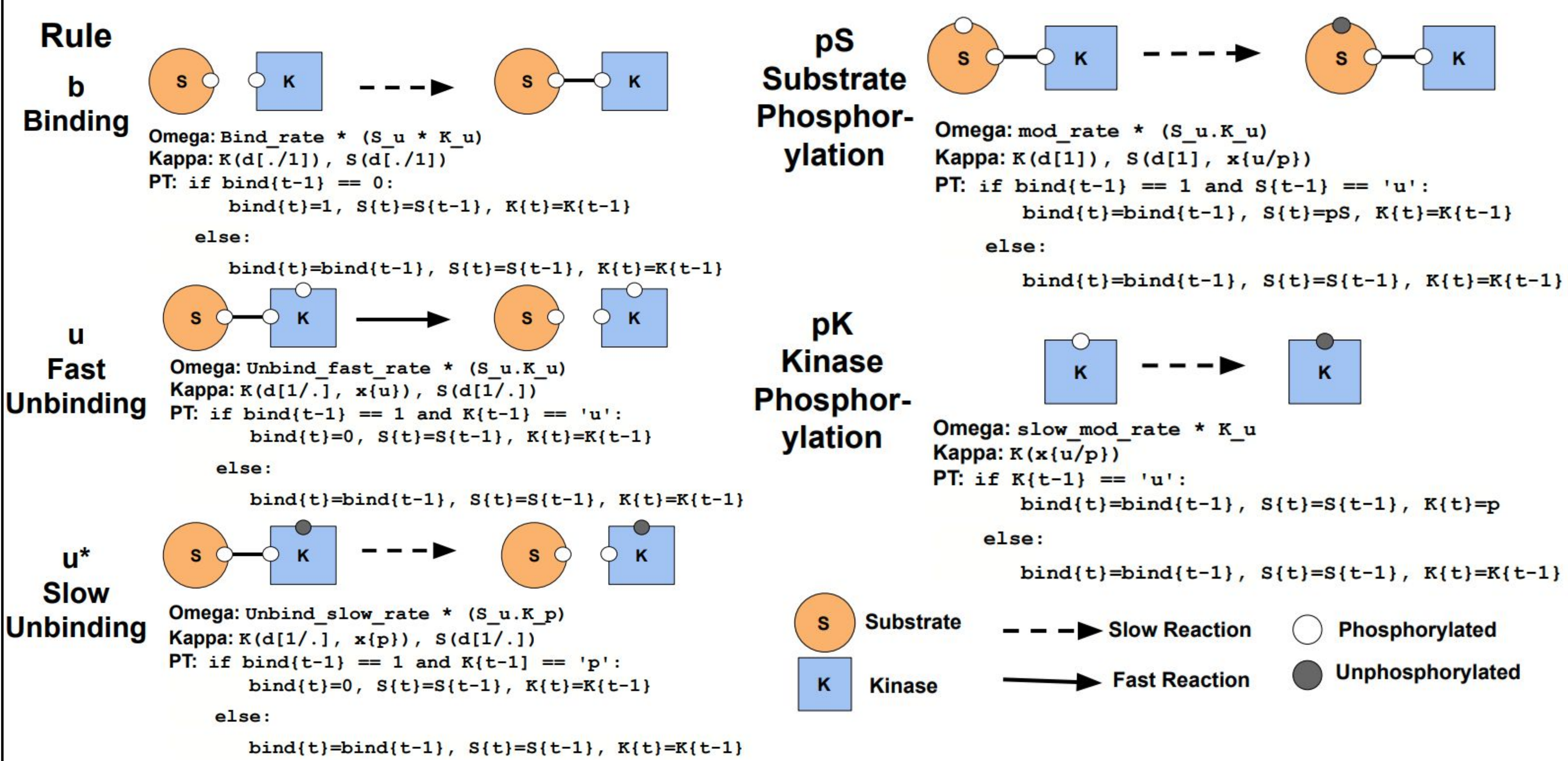

Figure 1: Rules governing the kinetics of substrate and kinase binding and phosphorylation. Left-hand side are patterns that when fired result in the state change on the right-hand side. Below each rule is its Omega, Kappa, and Probability Tree implementation.

References and Acknowledgments

1. J. Laurent, J. Yang, and W. Fontana. "Counterfactual resimulation for causal analysis of rule-based models". Proceedings of the Joint Conference on Artificial Intelligence. 2018.
2. Z. Tavares et al. "A language for counterfactual generative models". Tech. rep. MIT, 2019.
3. T. Genewein et al. "Algorithms for causal reasoning in probability trees". In:arXiv:2010.12237(2020).

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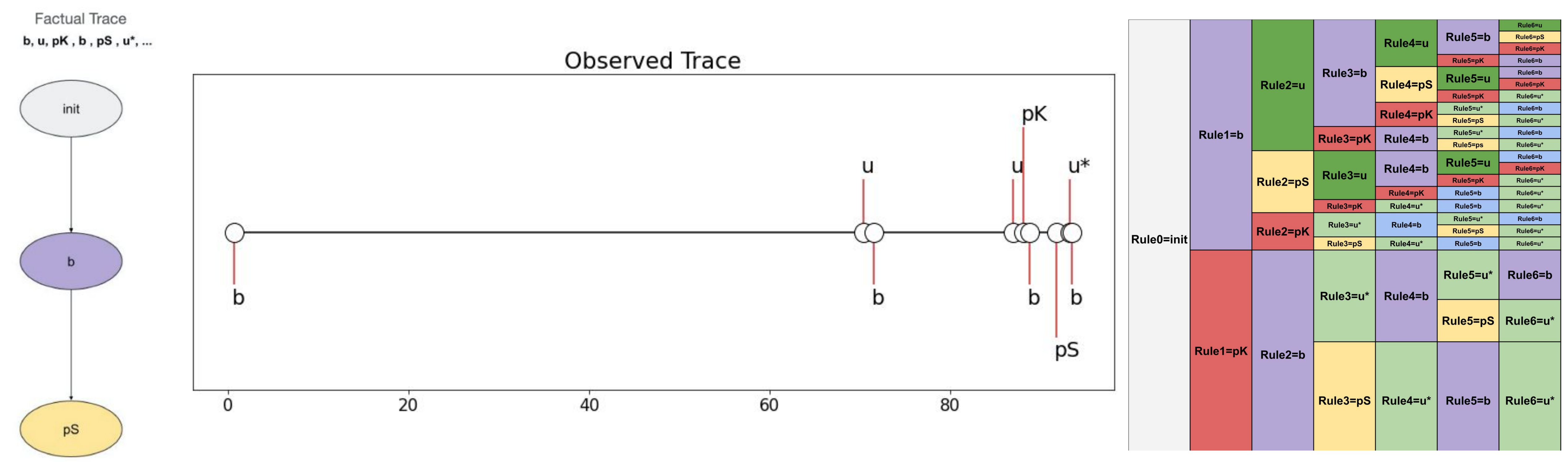
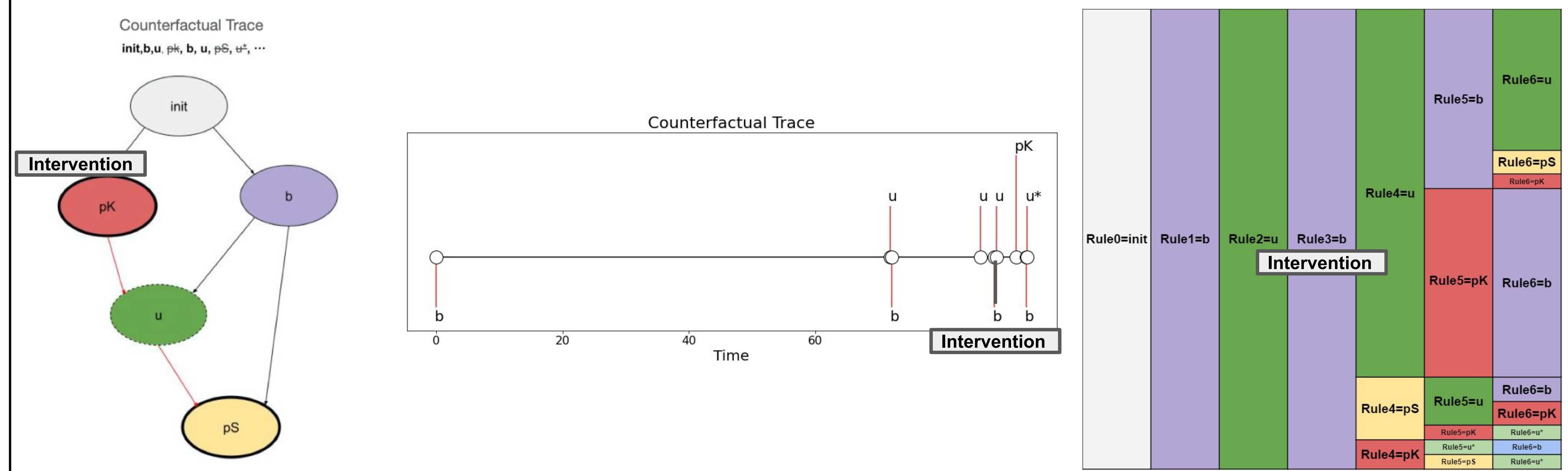
Factual (Observed) Trace: `init => b => u => pK => b => pS = u*`



Kappa | Omega | Probability Tree

Counterfactual trace: What would have happened if `pK` had not fired at Step 3?



Kappa | Omega | Probability Tree

Comparison of language advantages

Model	Unique Counterfactual	Continuous Variables	Visualization of outcomes	Run Time	Applicable to other problems
Kappa	Yes	Yes	No	2.5 Minutes	No
Omega	Yes	Yes	No	10 Minutes	Yes
Probability Trees	No	No	Yes	--	Yes

Figure 4: Omega and Kappa generate a unique counterfactual given a factual trace and intervention. They are both applicable to continuous variables whereas for probability trees continuous variables are intractable. Probability trees give the best visualization of possible outcomes, although the size of tree can quickly become intractable as the event space increase. Omega took a long time to train compared the other two models because it relies on an efficient inference implementation by the user.