MPRI 2.19 Biochemical Programming

Rule-based Modeling

Causal analysis

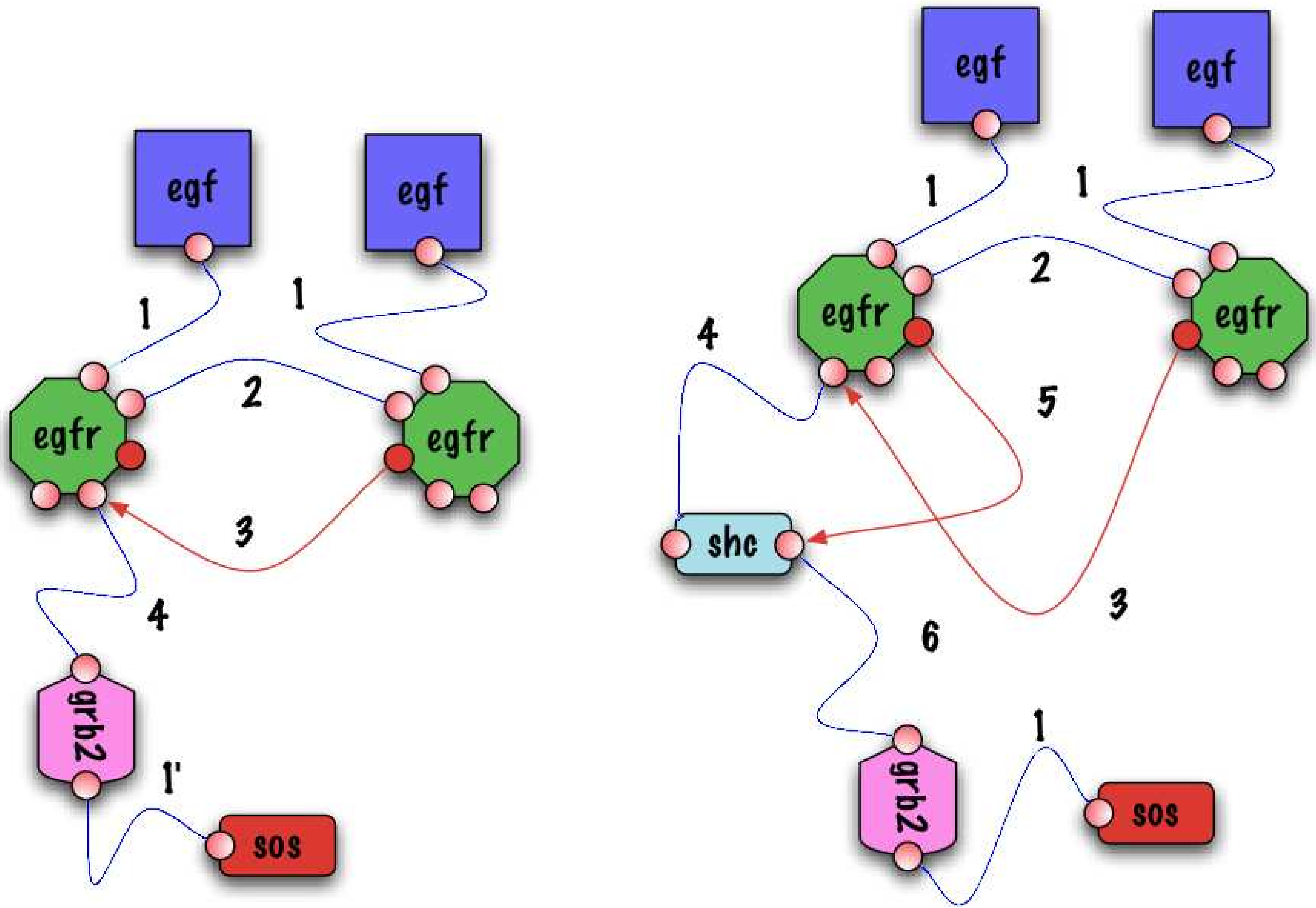
Jérôme Feret

DIENS (ÉNS, CNRS, INRIA, PSL)

kappalanguage.org

Tuesday, the 4th of January, 2022

Causal traces



Challenges

Compute minimal traces up to commutation of concurrent events.

This is parametric with respect to:

- the notion of state
- the notion of event

which can be seen at different levels of abstraction.

The choices of the syntax and of the semantics matter.

The biochemical structure is required

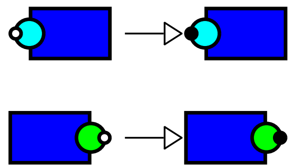
Reactions:

$$
\begin{array}{rcl}
A & \rightarrow & {}^{\bullet}A \\
A & \rightarrow & A^{\bullet} \\
{}^{\bullet}A & \rightarrow & {}^{\bullet}A^{\bullet} \\
A^{\bullet} & \rightarrow & {}^{\bullet}A^{\bullet}
\end{array}
$$

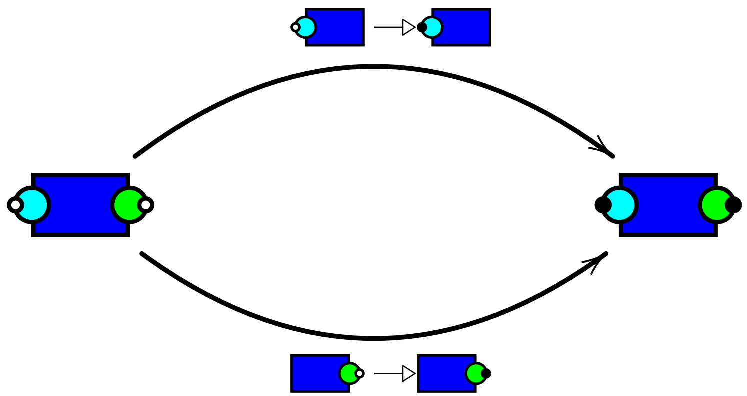
Causal traces:

$$
\begin{array}{l}
A \rightarrow {}^{\bullet}A \rightarrow {}^{\bullet}A^{\bullet} \\
A \rightarrow A^{\bullet} \rightarrow {}^{\bullet}A^{\bullet}
\end{array}
$$

Rules:

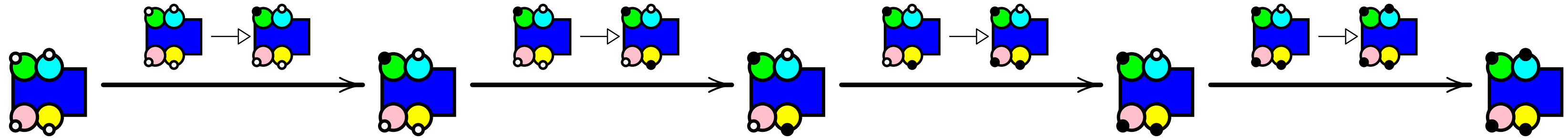


Causal traces:

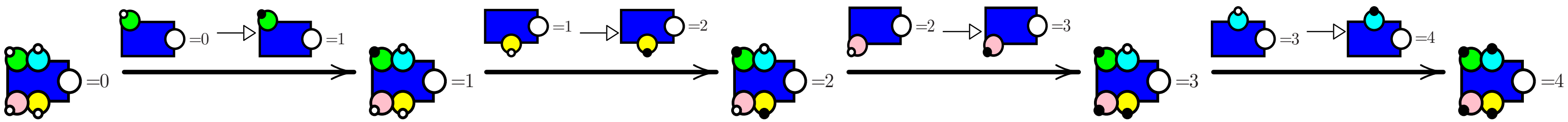


Counters

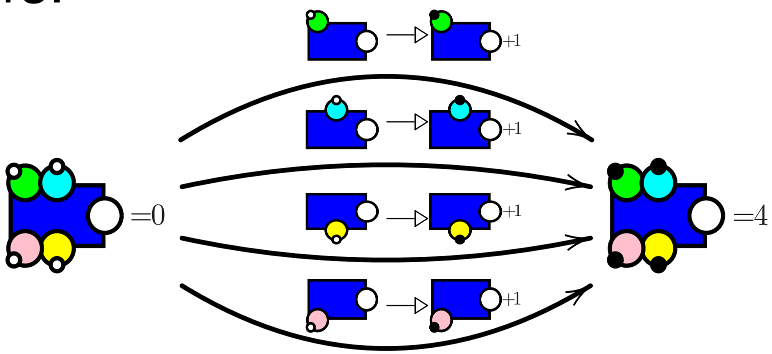
Without counters:



With flat counters:



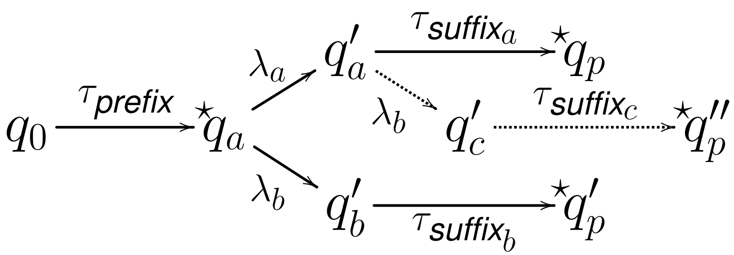
With arithmetic counters:



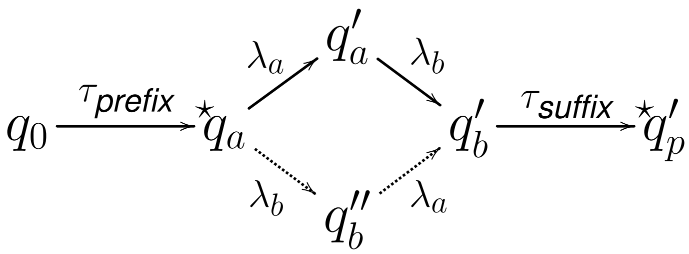
Commutative events

Two events λ_a and λ_b commute if they satisfies the following commutative diagrams:

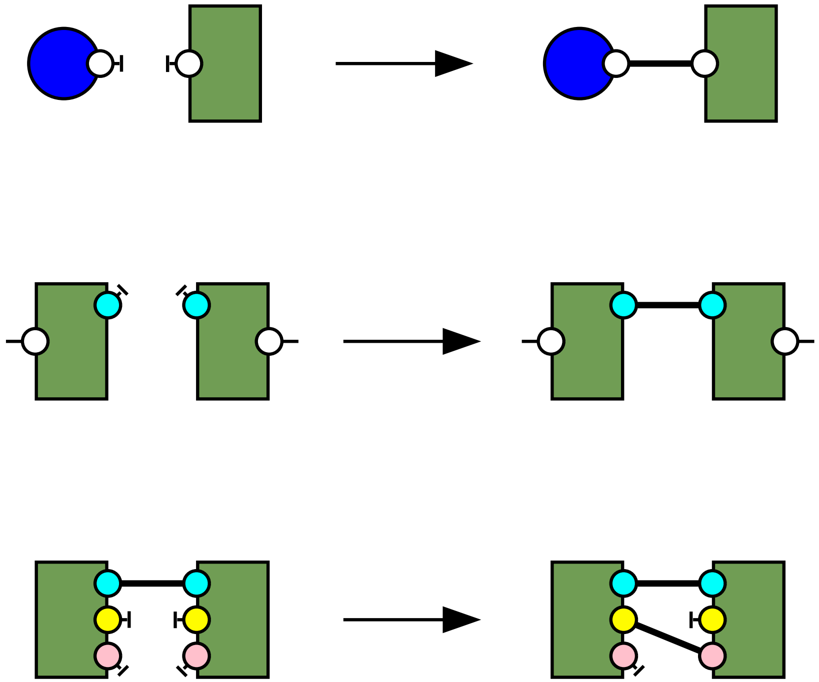
- No conflicts:



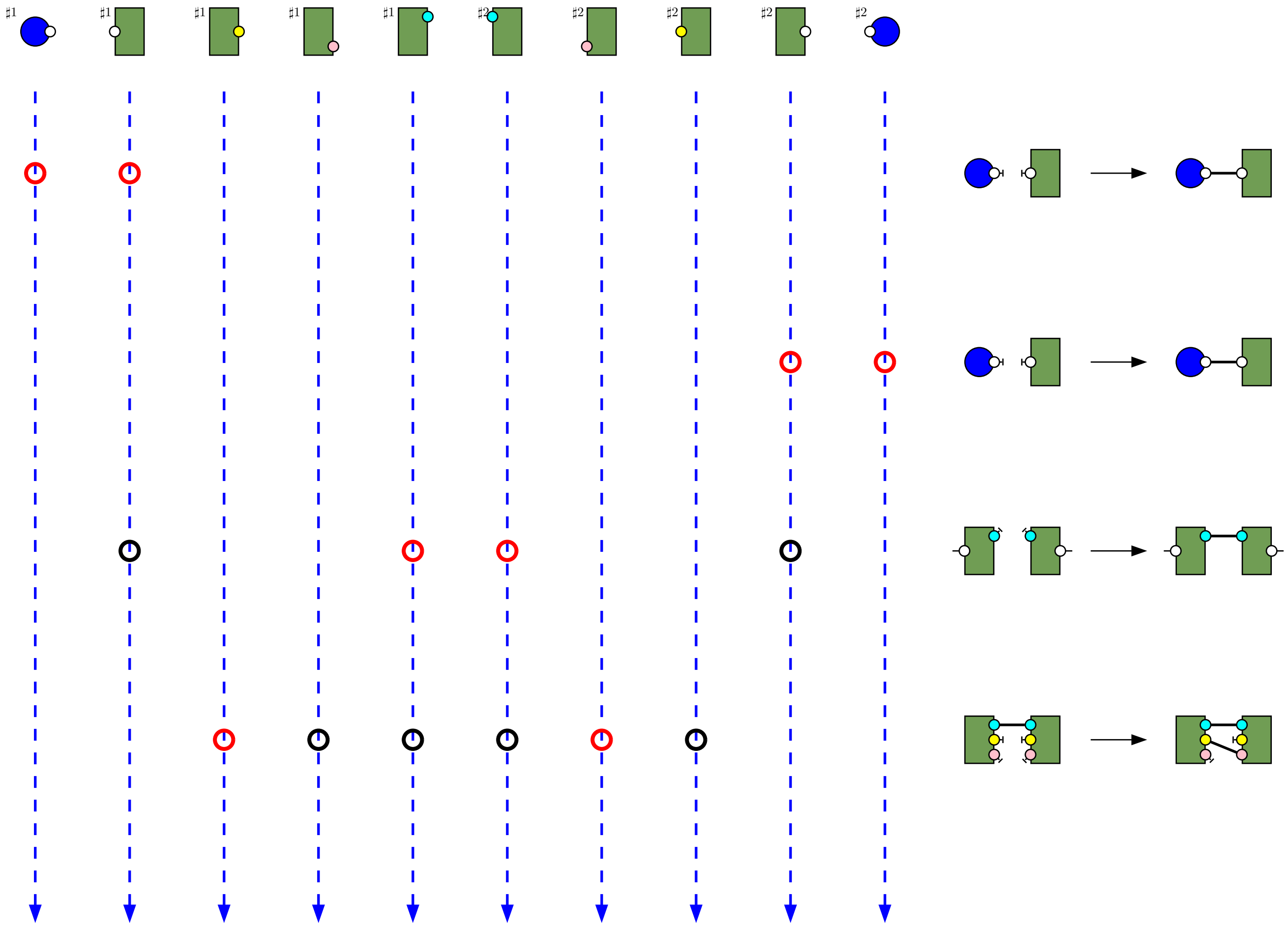
- No precedence:



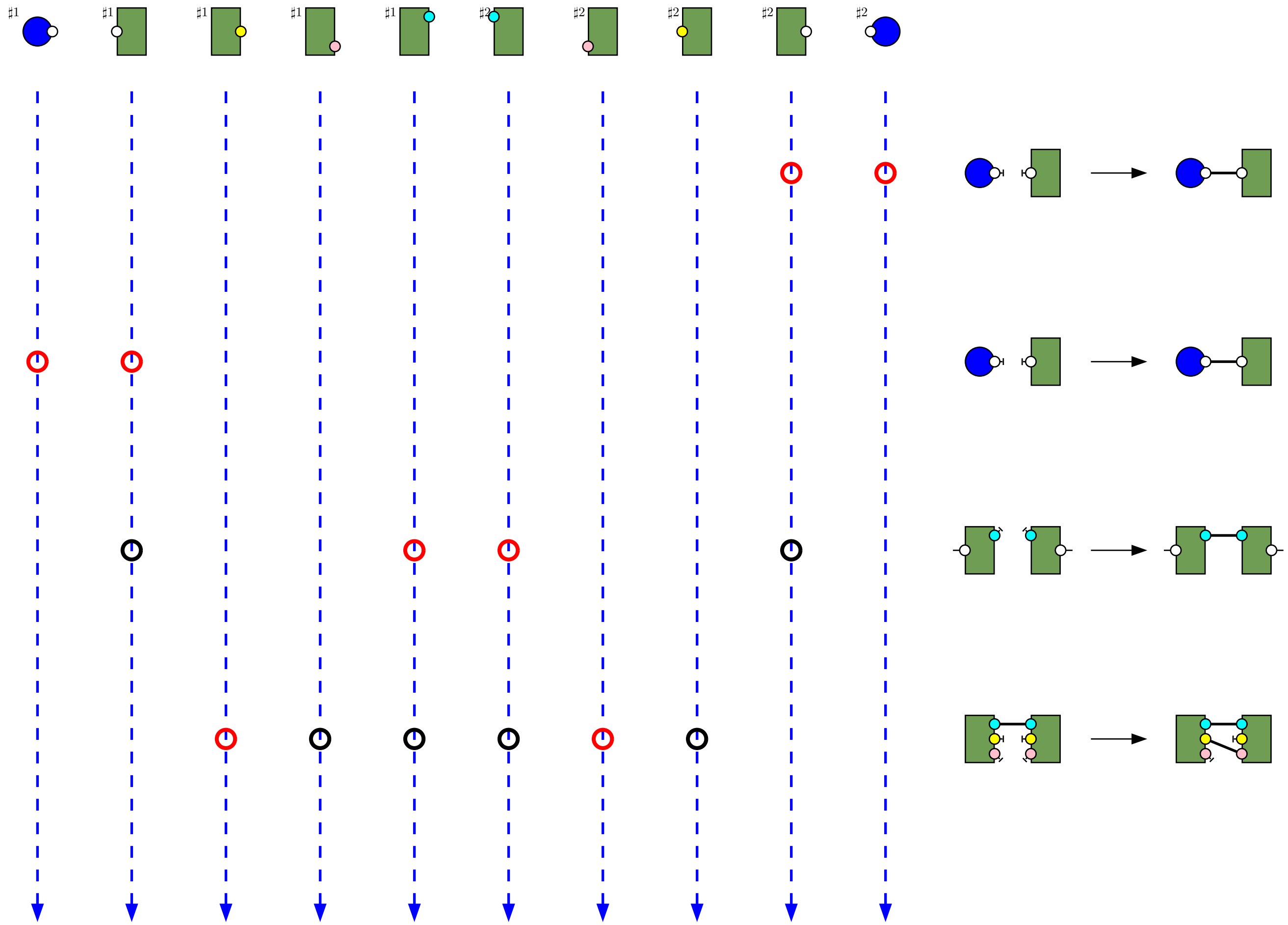
Case study



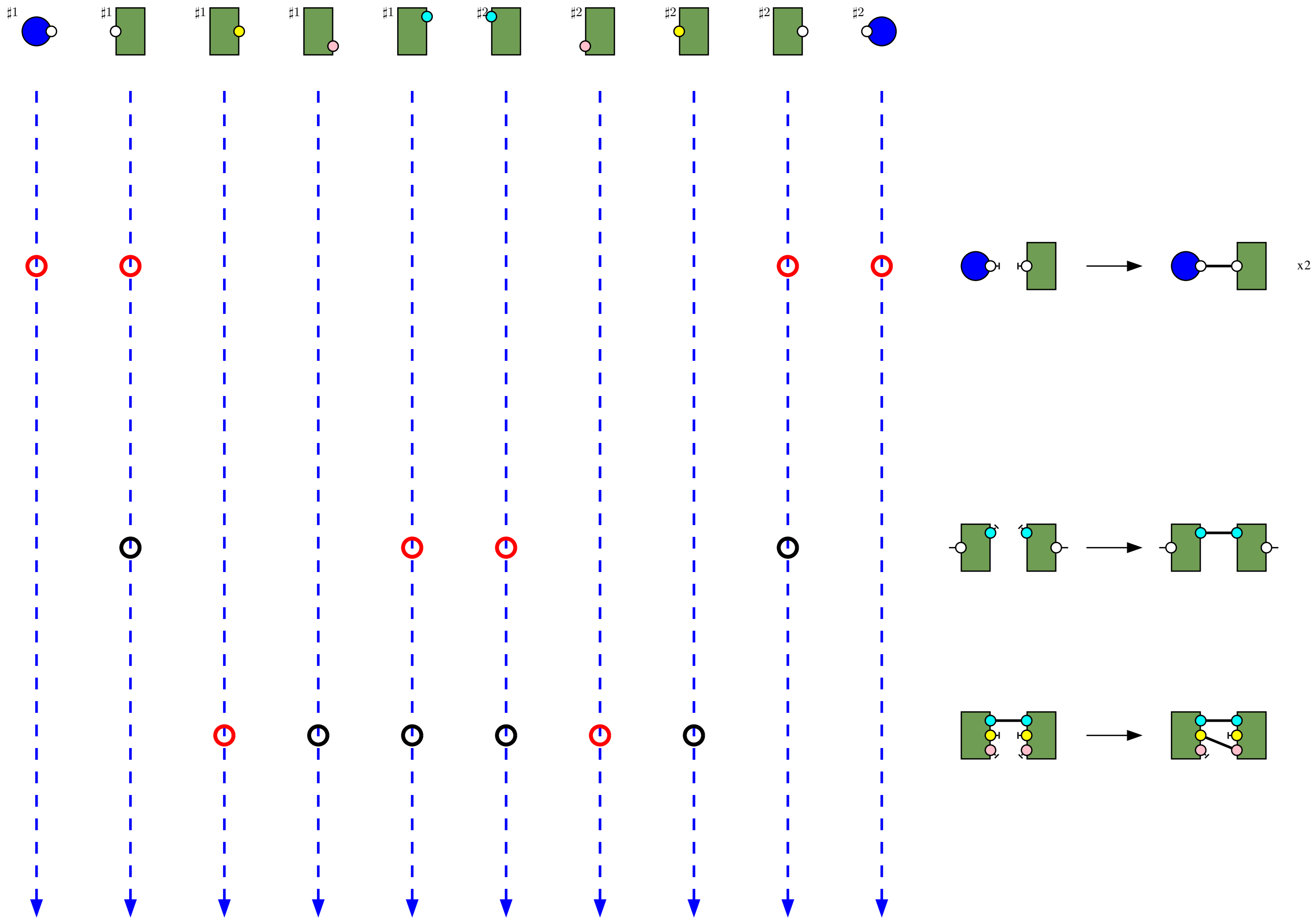
Musical notation



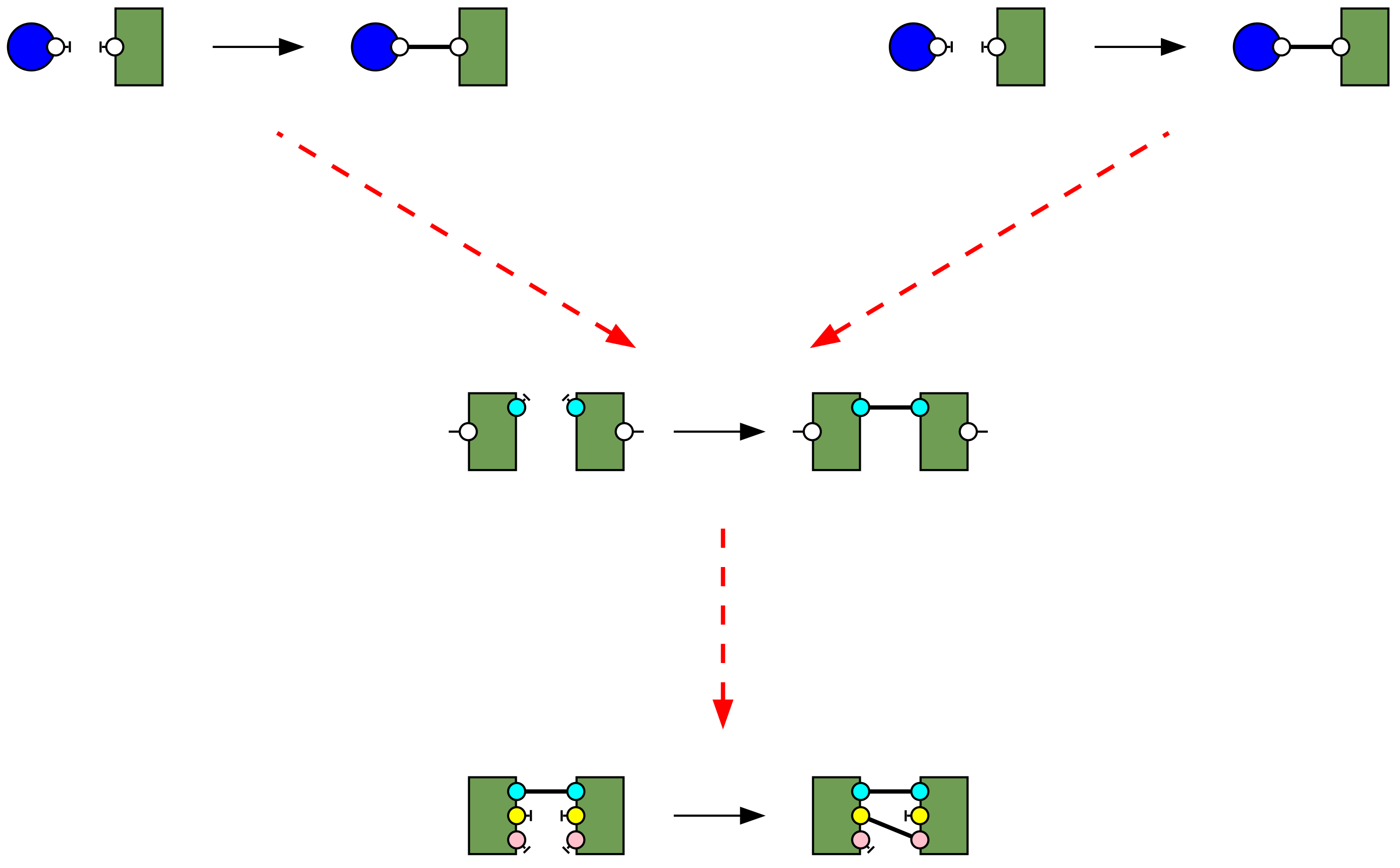
Musical notation



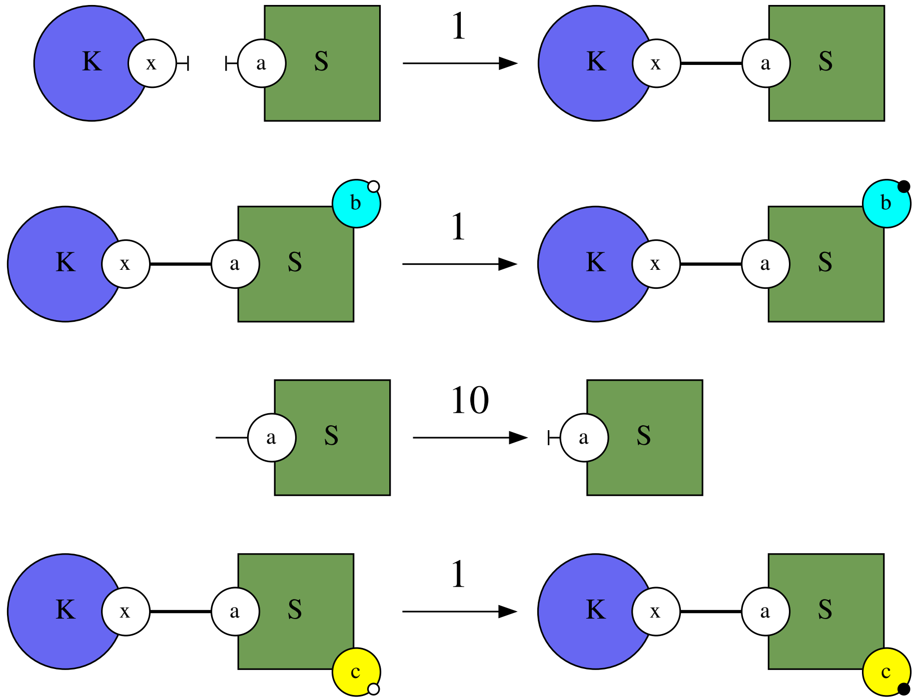
Musical notation



Causal flow



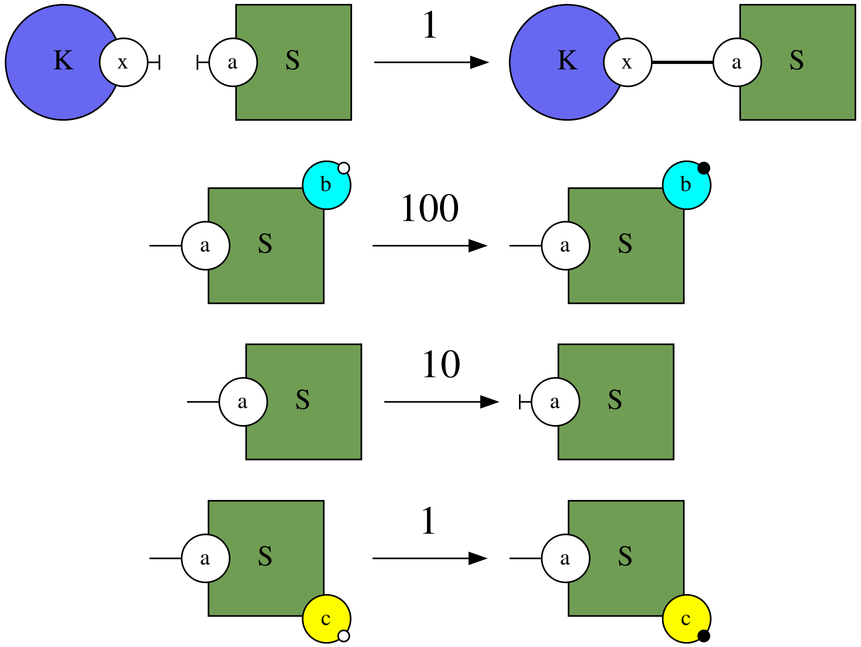
Practical activity



We want to observe the formation of doubly phosphorylated substrate.

1. Compare the result of causal and weak compression.

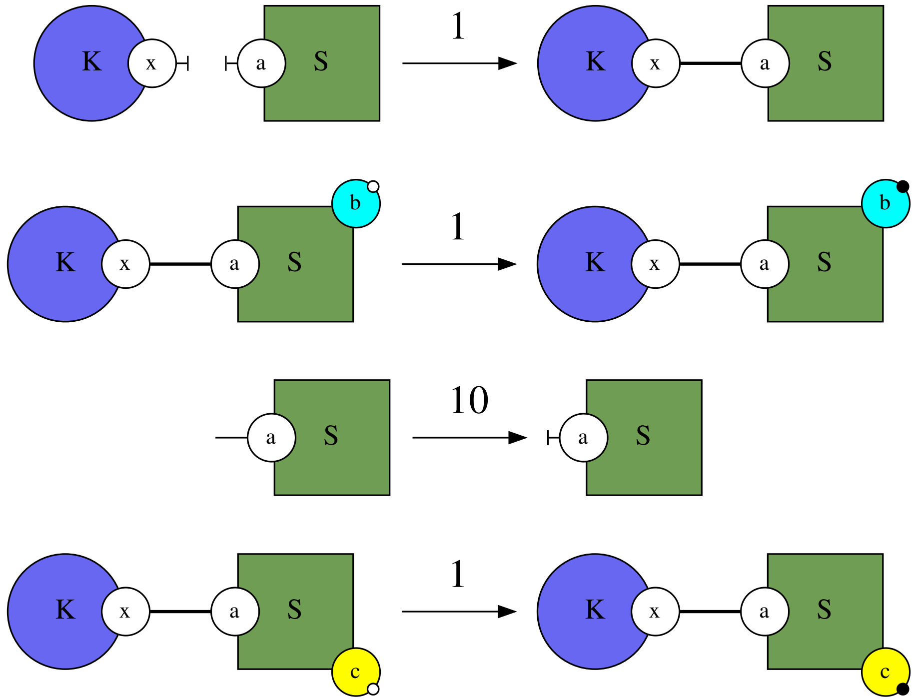
Practical activity



We want to observe the formation of doubly phosphorylated substrate.

1. Compare the result of causal and weak compression.
2. Compare with what had been obtained on the previous slide.

Practical activity



We want to observe the formation of doubly phosphorylated substrate.

1. Compare the result of weak and strong compression.

Bisimulation/group action

$\mathbb{G}$ is a group of symmetries compatible with the set of rules.
Let r be a rule, and $(\sigma_L, \sigma_R) \in \mathbb{G}$ be a pair of transformations.
If the following diagram:

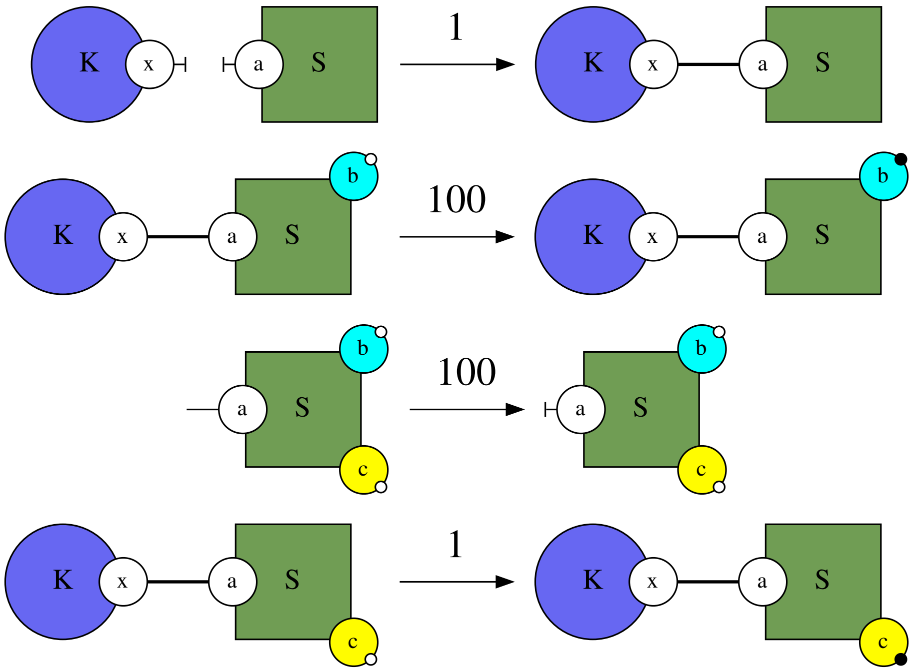
$$\begin{array}{ccc} L' & \xrightarrow{\quad r \quad} & R' \\ {\scriptstyle h_L}\uparrow & & \uparrow{\scriptstyle h_R} \\ L & \xrightarrow[\quad r' \quad]{} & R \end{array}$$

is a push-out, then the following diagram:

$$\begin{array}{ccc} \sigma_L.L' & \xrightarrow{\quad (\sigma_L,\sigma_R).r \quad} & \sigma_R.R' \\ {\scriptstyle \sigma_L.h_L}\uparrow & & \uparrow{\scriptstyle \sigma_R.h_R} \\ (h_L.\sigma_L).L & \xrightarrow[\quad (h_L.\sigma_L,h_R.\sigma_R).r' \quad]{} & (h_R.\sigma_R).R \end{array}$$

is a push-out as well.

Practical activity



We want to observe the phosphorylation of the site c.

1. Compute the result of causal compression.
2. Is the result satisfying ?

Take home message

- Causality analysis aims at capturing which events are necessary in potential scenarii.
- Several approaches from different fields.
- Ours is based on concurrency theory based on lack of commutation, combined with combinatorial optimization.
- We do not capture counter-factual causal relationships.

Bibliography

- Vincent Danos, Jérôme Feret, Walter Fontana, Russell Harmer, Jonathan Hayman, Jean Krivine, Christopher D. Thompson-Walsh, Glynn Winskel: Graphs, Rewriting and Pathway Reconstruction for Rule-Based Models. FSTTCS 2012: 276-288
- Jonathan Laurent, Jean Yang, Walter Fontana: Counterfactual Resimulation for Causal Analysis of Rule-Based Models. IJCAI 2018: 1882-1890
- Pierre Boutillier, Ioana Cristescu, Jérôme Feret: Counters in Kappa: Semantics, Simulation, and Static Analysis. ESOP 2019: 176-204