Nov 8: **Eric Deeds**, University of California at Los Angeles
"The evolution of cellular individuality"

Nov 15: **Daniel Merkle**, University of Southern Denmark
"Graph rewriting and chemistry"

Nov 22: **Jean Krivine**, IRIF, Université de Paris
"From molecules to systems: the problem of knowledge representation in molecular biology"

Nov 29: **Eric Smith**, Earth Life Sciences Institute, Tokyo
“Easy and Hard in the Origin of Life"

Dec 13: **Yarden Katz**, Harvard Medical School, Boston
"Cells as cognitive creatures"

Jan 10: **Massimiliano Esposito**, University of Luxembourg
"Thermodynamics of Open Chemical Reaction Networks: Theory and Applications"

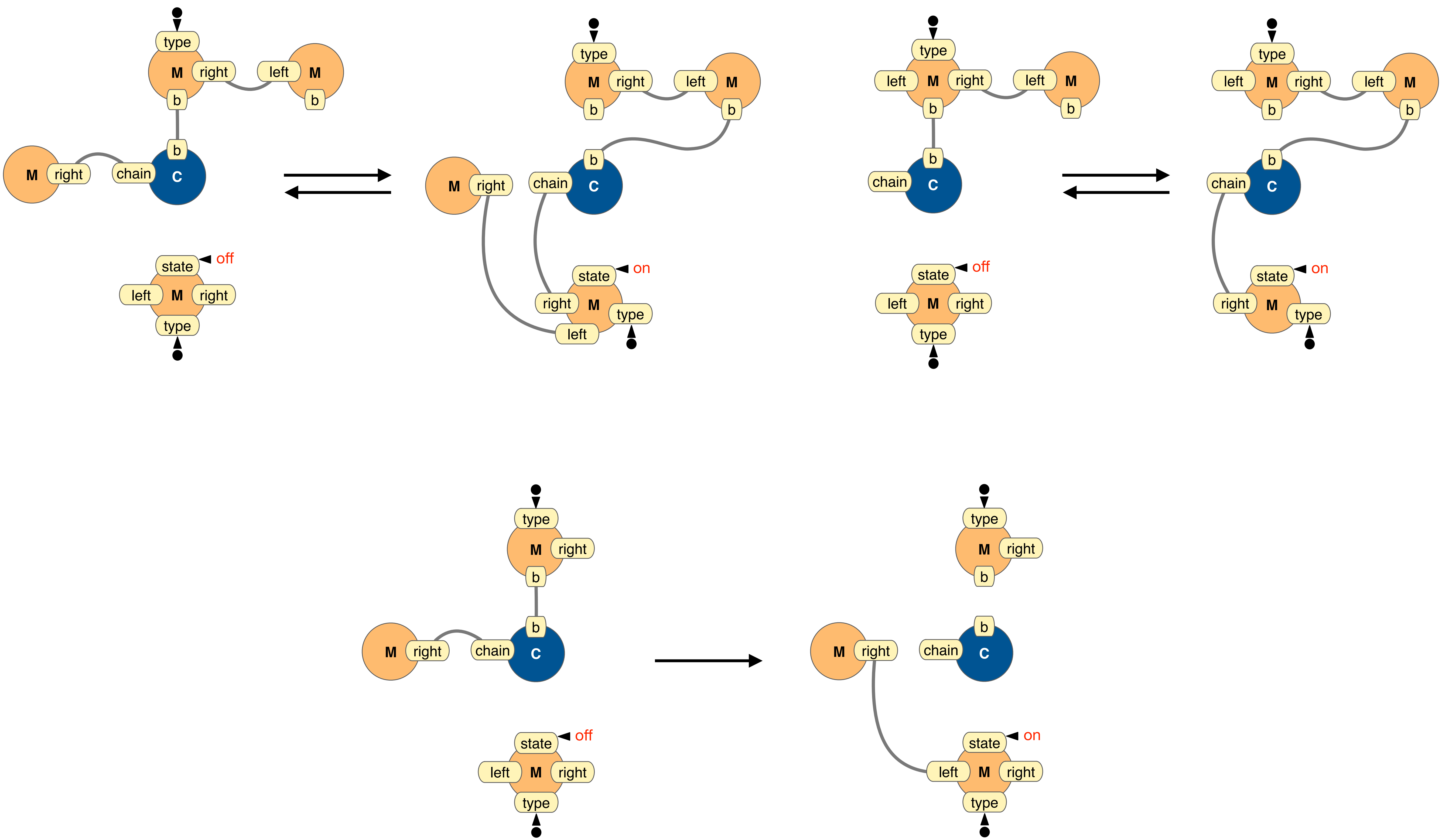
Jan 17: **Aleksandra Walczak**, ENS Paris
"Prediction in immune repertoires"

Jan 24: **Tommy Kirchhausen**, Harvard Medical School
"Imaging sub-cellular dynamics from molecules to multicellular organisms"

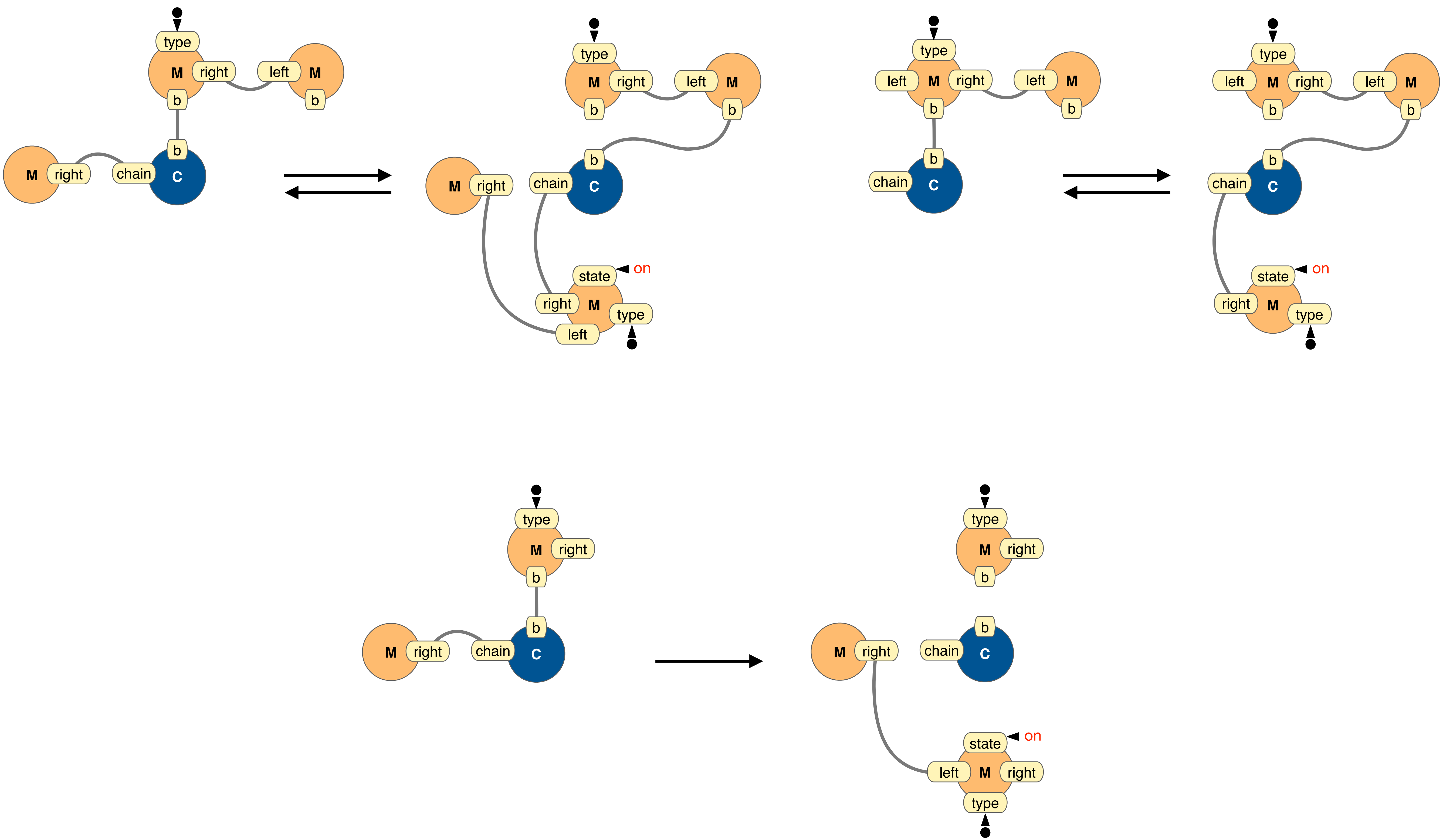
Previous Lectures And Look-Ahead

1. The Topology of the Possible
   (La représentation de l'information biologique)
2. Propagation of Genetic, Phenotypic, and Molecular information
   (Limites de la transmission de l'information biologique)
3. Modeling cellular information processing the classical way
   (Modélisation 'classique' du traitement de l'information cellulaire)
4. Modeling cellular information processing the rule-based way
   (Modélisation basé sur les règles; introduction)
5. Examples of rule-based models
   (Modélisation basé sur les règles; examples)
6. Causality in rule-based dynamics
   (Causalité)
7. Combinatorial scaffolding
   (Echafaudage combinatoire)
8. Cellular learning?
   (Apprentissage cellulaire?)

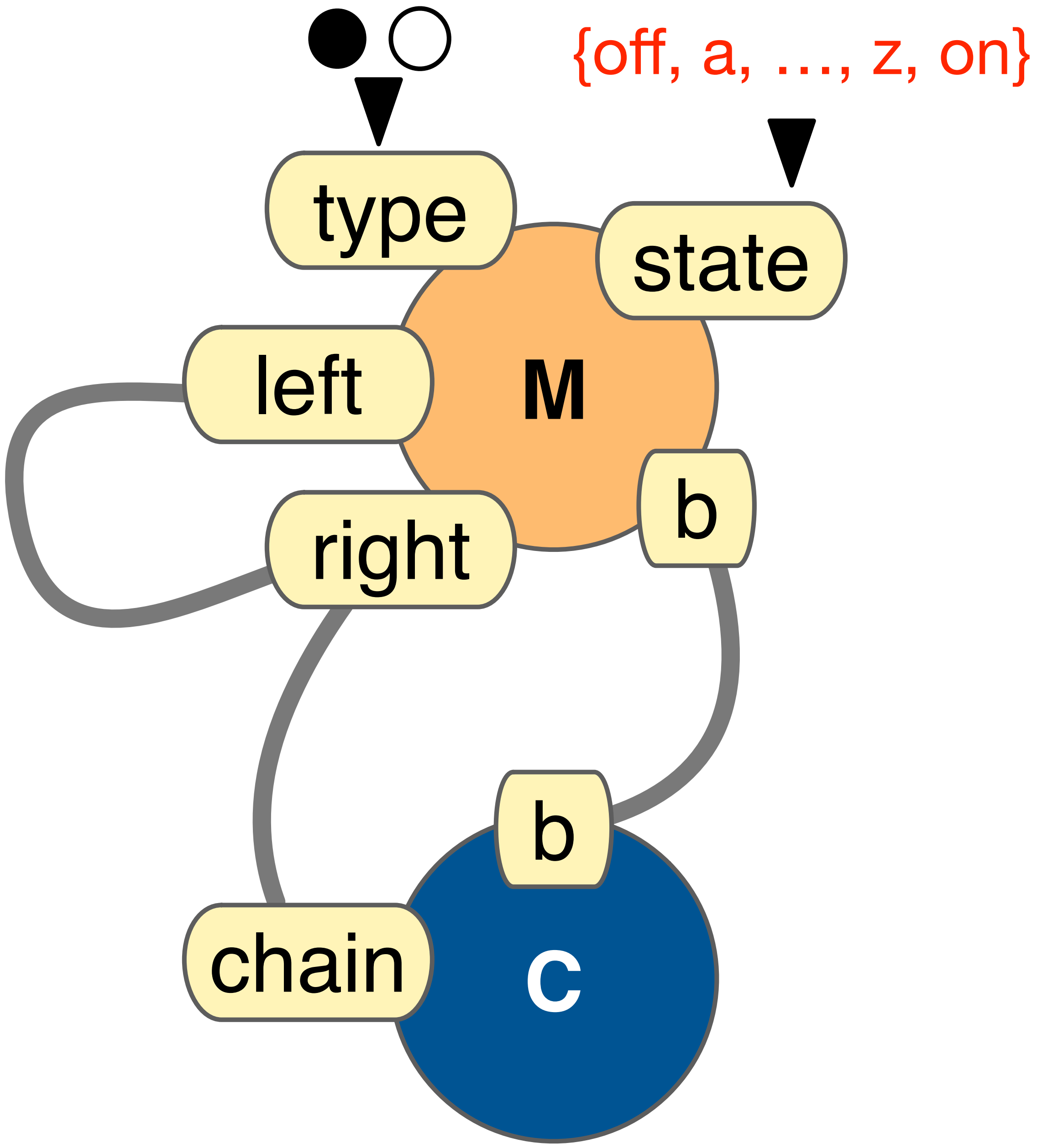
Copying a Polymer (Single-Step)



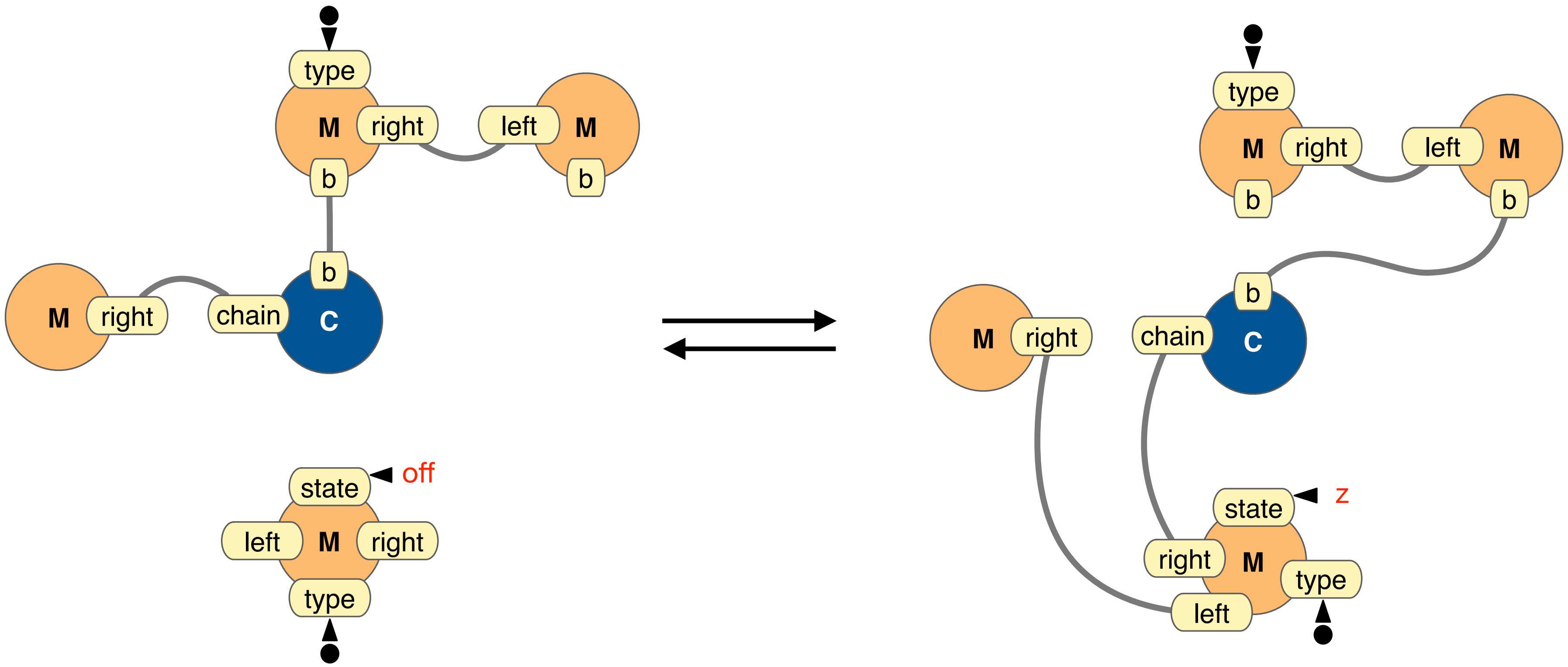
Copying a Polymer (Single-Step)



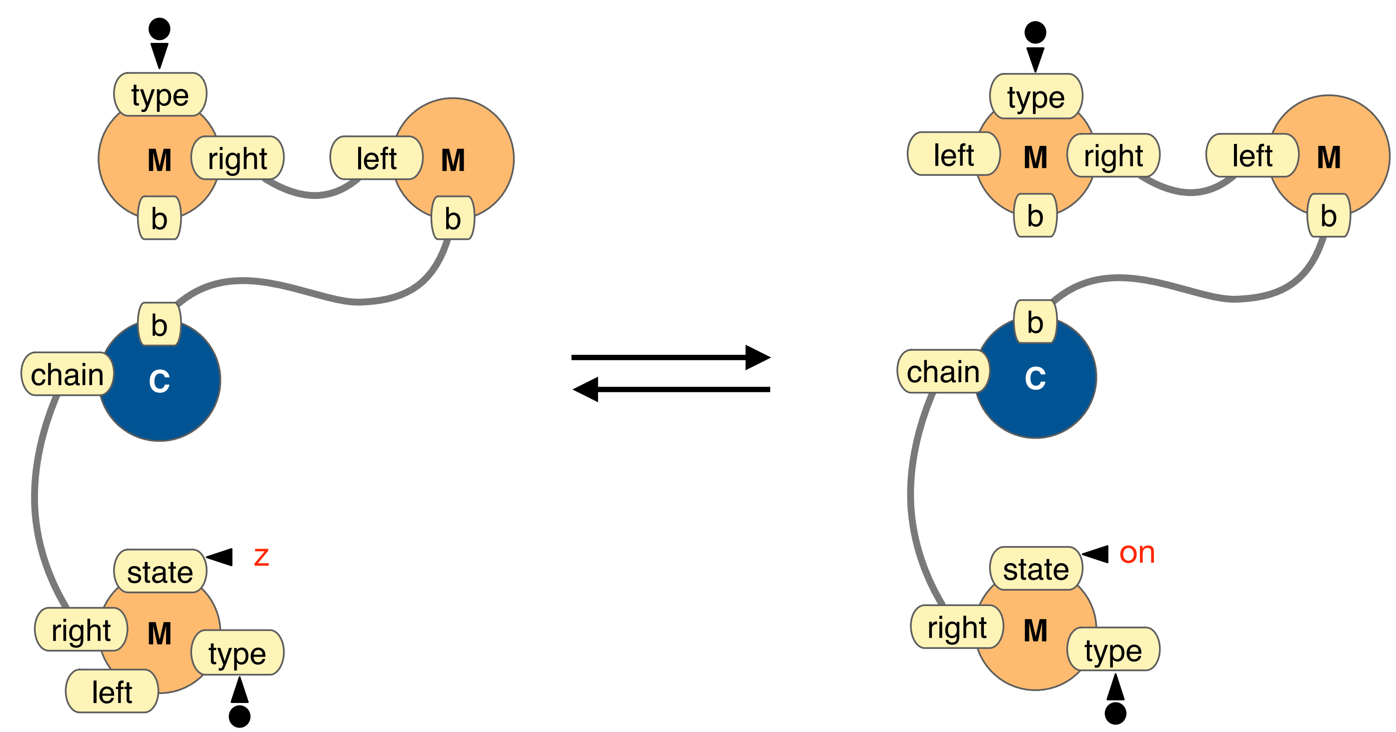
Copying a Polymer (Contact Map)



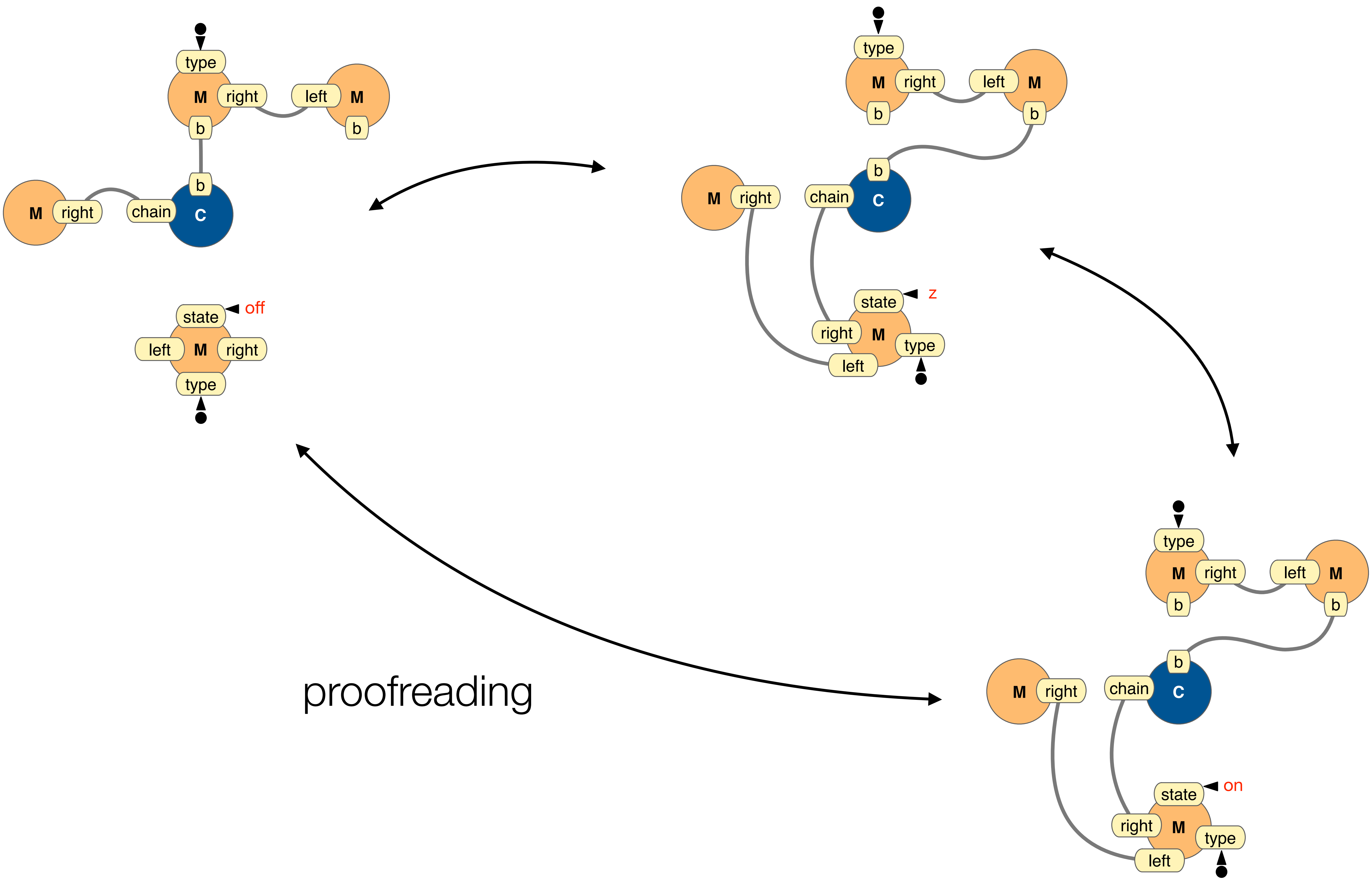
Copying a Polymer (Multi-Step)



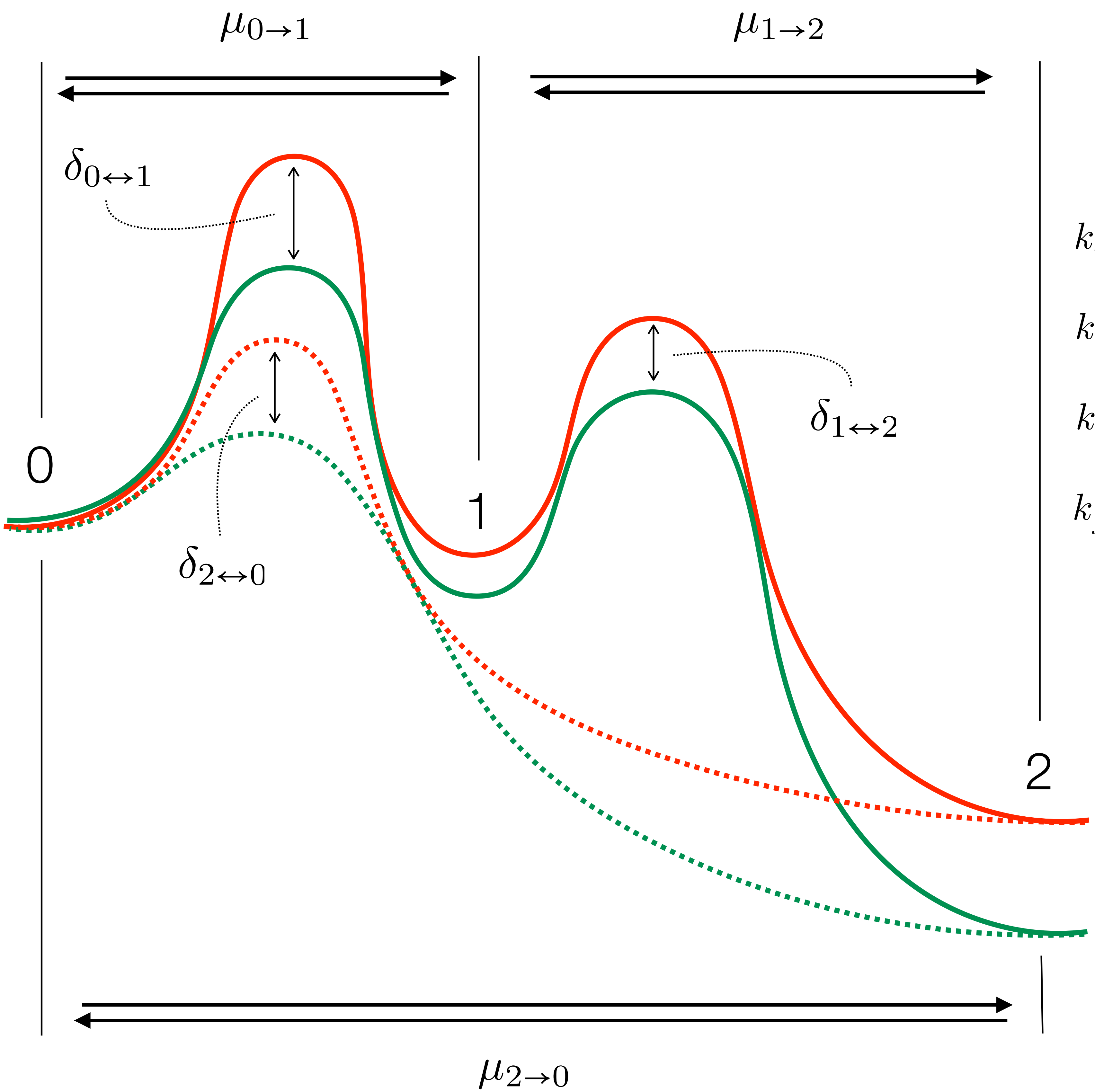
intermediate state



The Purpose of Multi-Step is to Allow for Proofreading



Free Energy Landscape of Proofreading



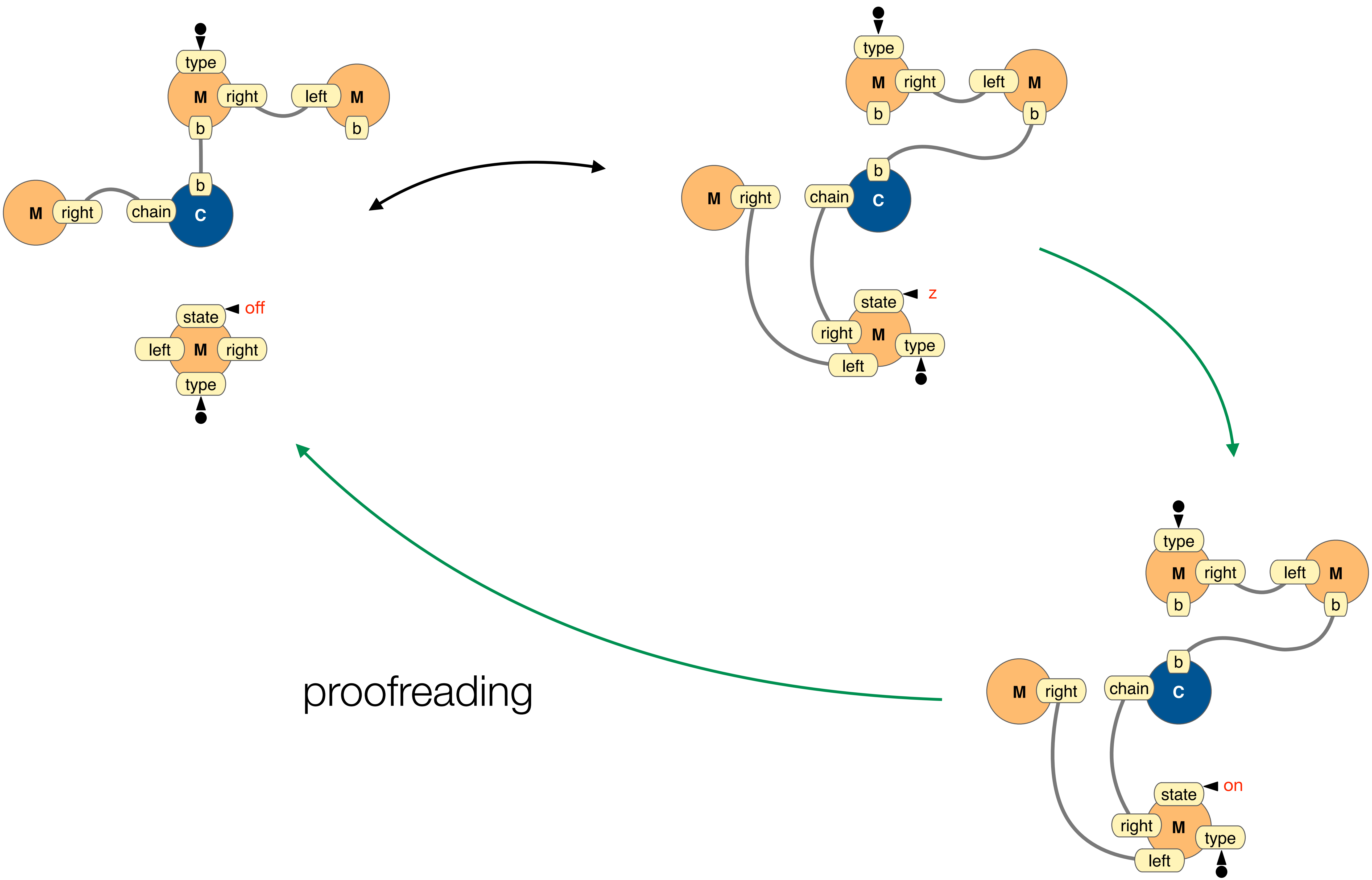
$$k^R_{i\to j} = \omega \ \exp\left((E^R_i + \mu_{i\to j} + \delta_{i\leftrightarrow j})/RT\right)$$

$$k^W_{i\to j} = \omega \ \exp\left((E^W_i + \mu_{i\to j})/RT\right)$$

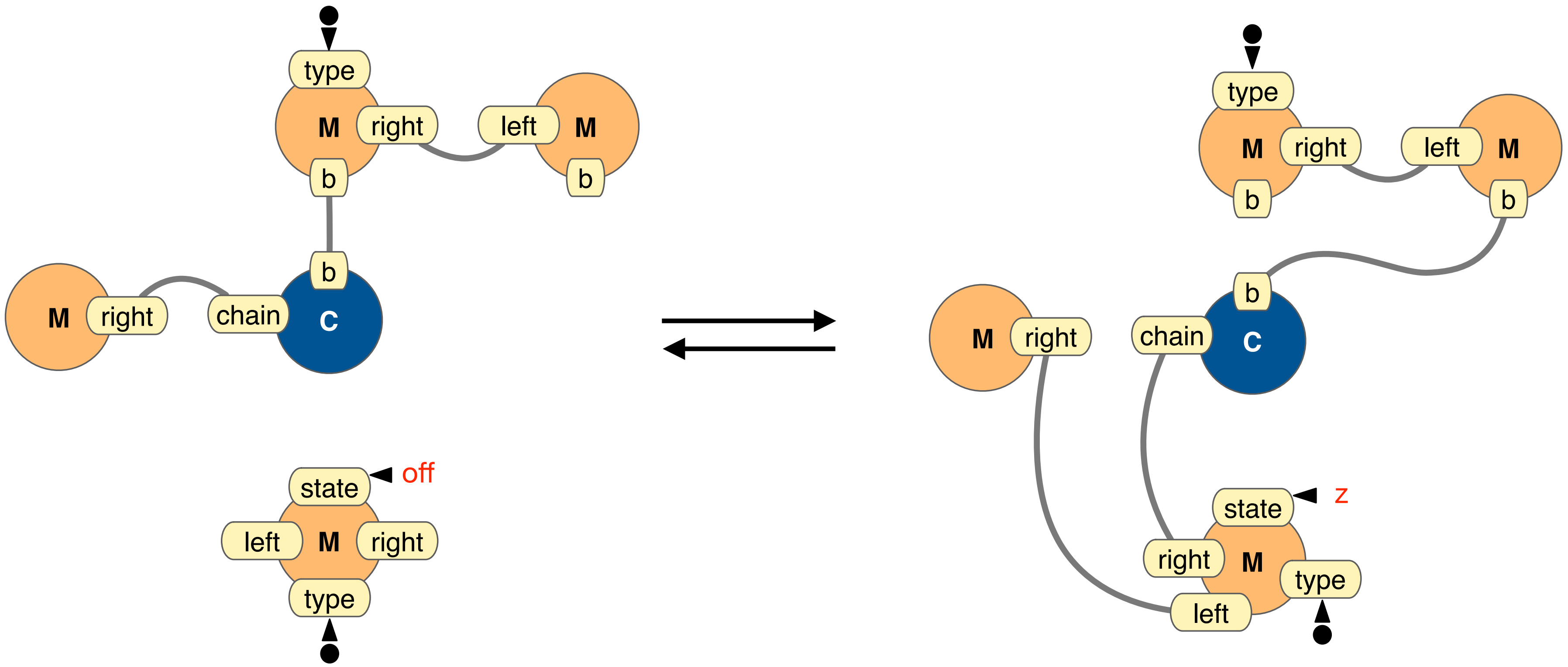
$$k^R_{j\to i} = \omega \ \exp\left((E^R_j + \delta_{i\leftrightarrow j})/RT\right)$$

$$k^W_{j\to i} = \omega \ \exp\left(E^W_j/RT\right)$$

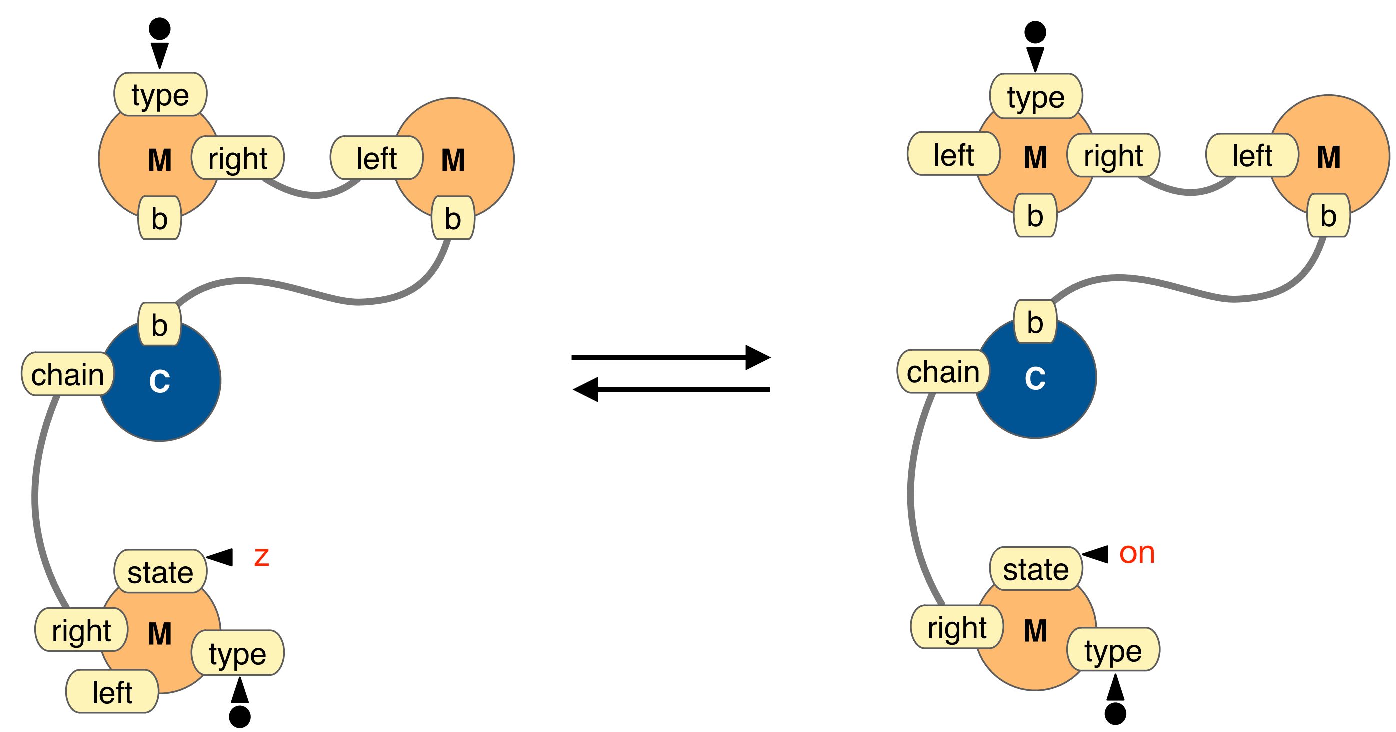
The Purpose of Multi-Step is to Allow for Proofreading



Copying a Polymer (Multi-Step)

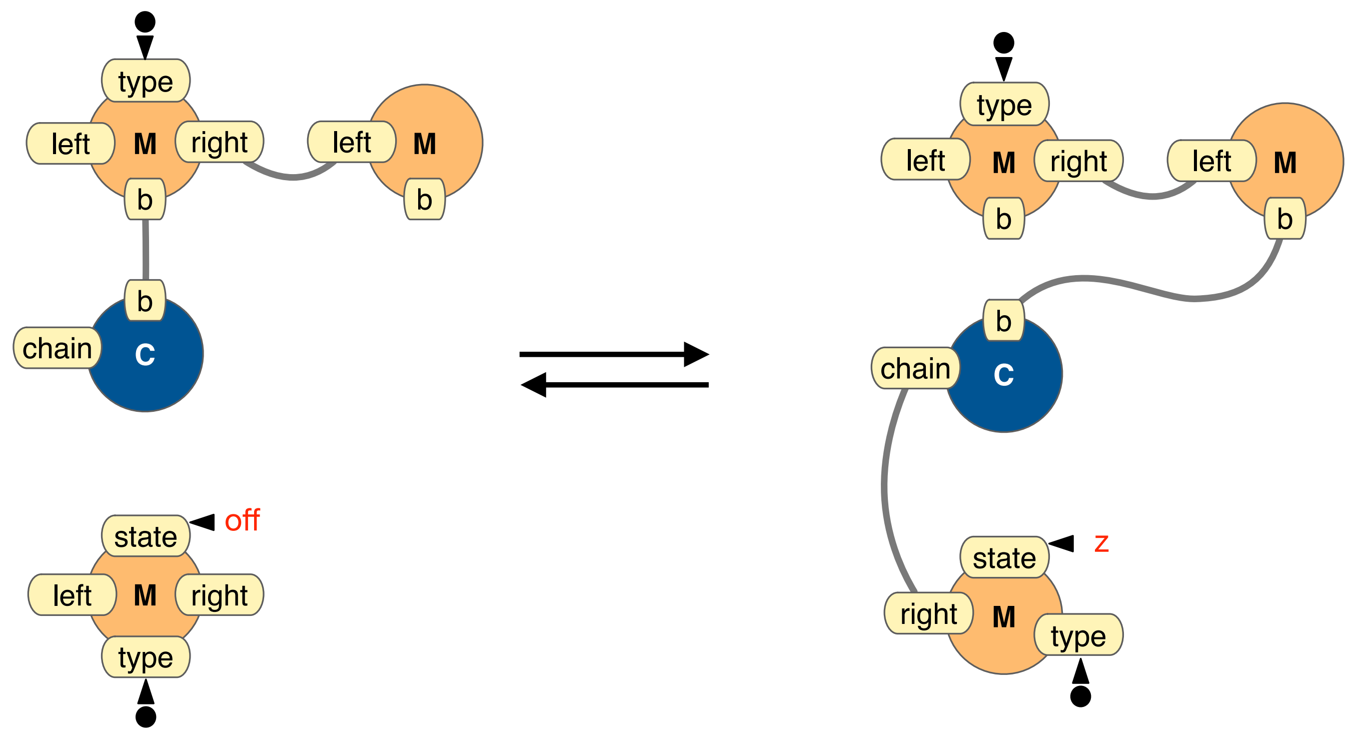


intermediate state

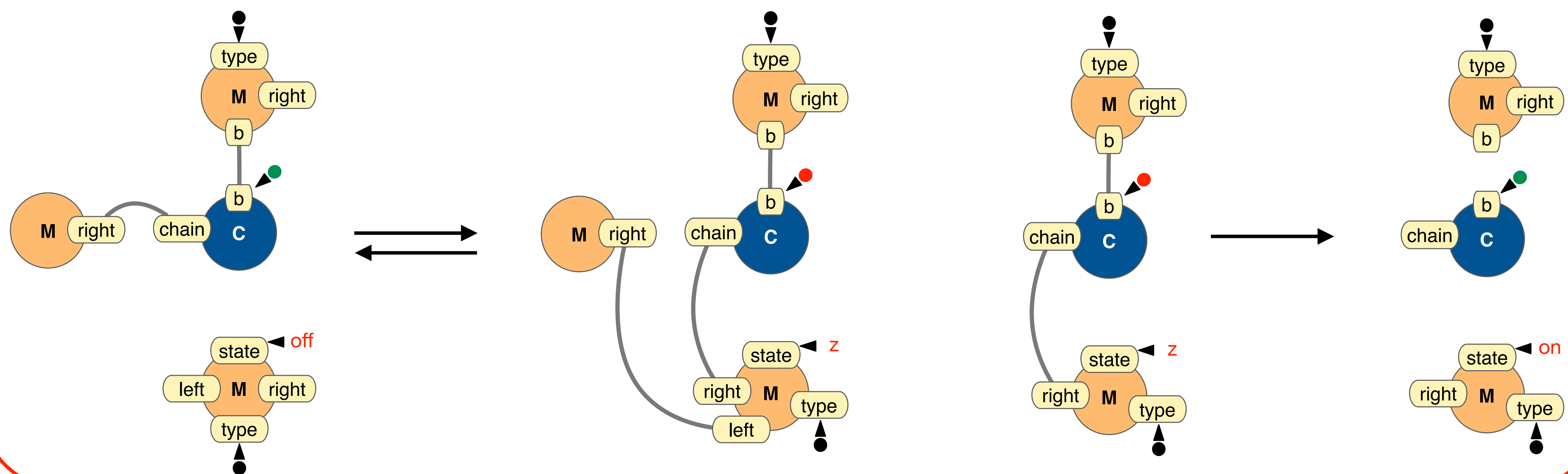


Copying a Polymer: End Cases

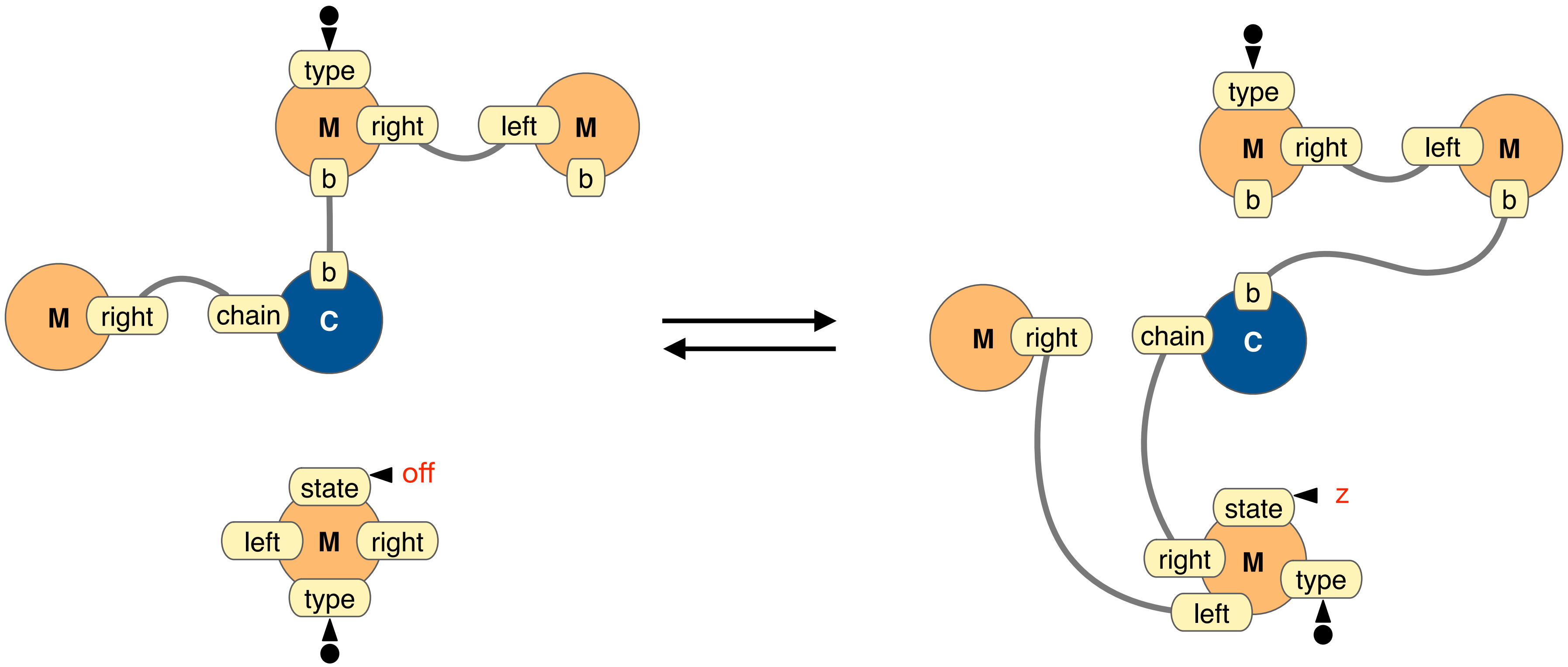
chain start



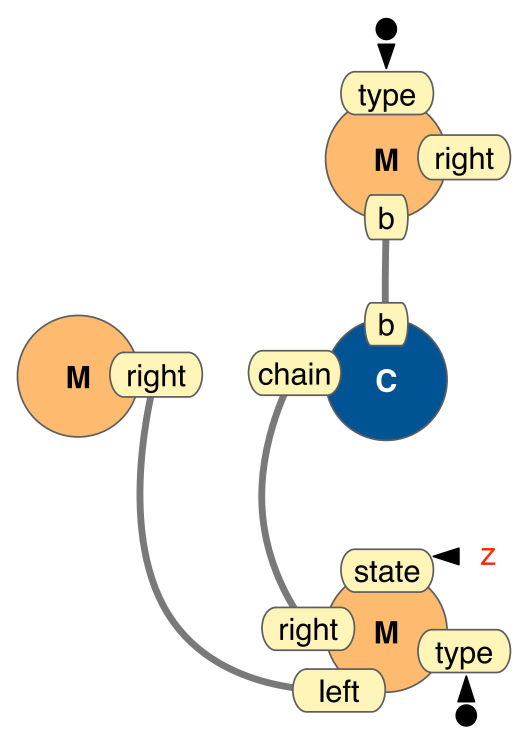
chain end



Copying a Polymer: End Cases

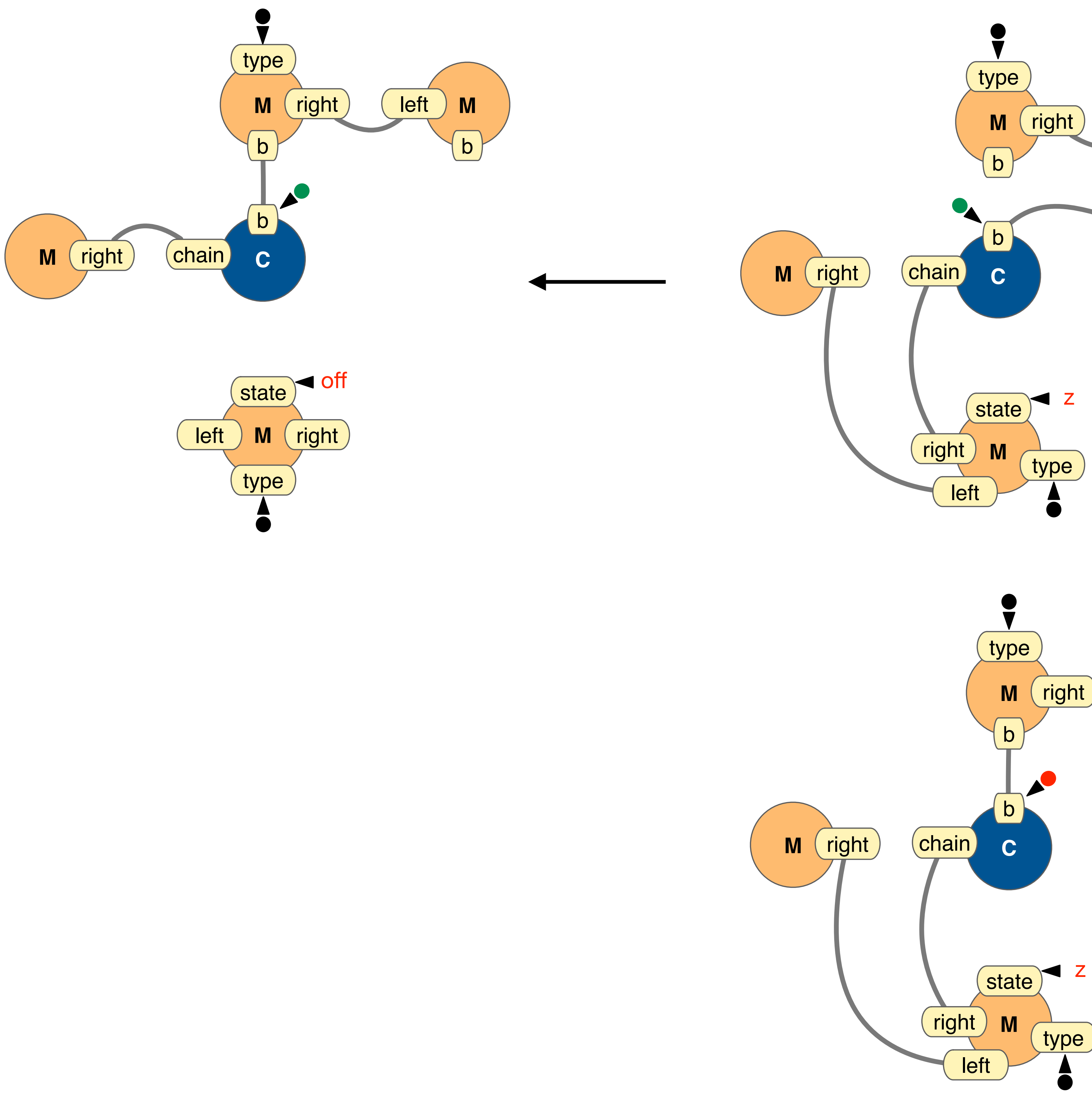


intermediate state



a problem…

Copying a Polymer: End Cases



“test” unbinding

Vincent Danos (ENS Paris)

Jérôme Feret (ENS Paris)

Jean Krivine (Paris Diderot)

Jonathan Laurent (Carnegie Mellon)

Pierre Boutillier (Harvard Med)

Russ Harmer (ENS Lyon)

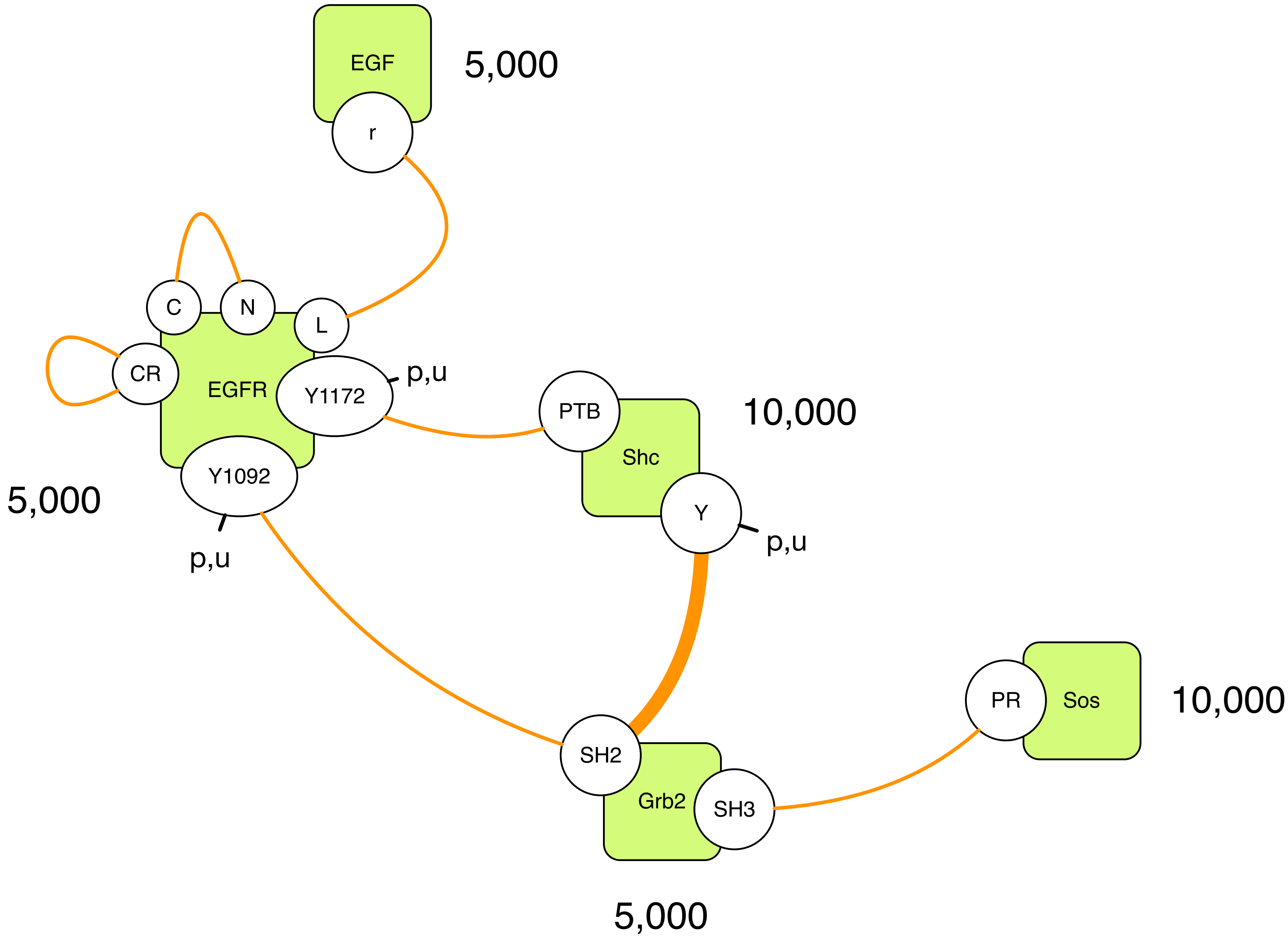
6.
Causality

Models as Programs

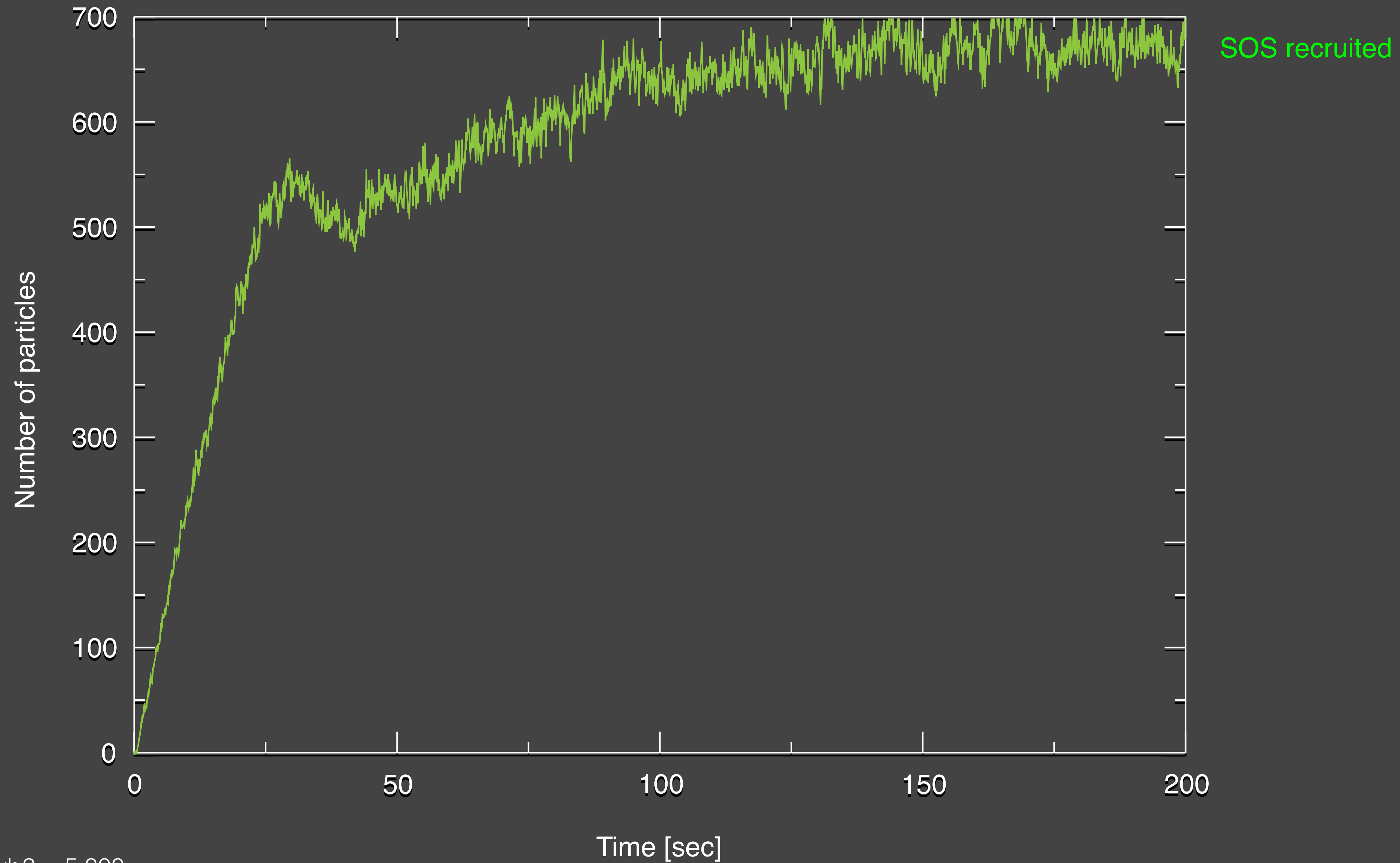
```
'EGFR.EGFR'    EGFR(L[_],CR[.],N[.],C[.]), EGFR(L[_],CR[.],N[.],C[.]) ➜ EGFR(L[_],CR[1],N[.],C[.]), EGFR(L[_],CR[1],N[.],C[.])  @ 'k_on'/2
'EGFR/EGFR'    EGFR(L[_],CR[1],N[.],C[.]), EGFR(L[_],CR[1],N[.],C[.]) ➜ EGFR(L[_],CR[.],N[.],C[.]), EGFR(L[_],CR[.],N[.],C[.])  @ 'k_off'/2
'EGF.EGFR'     EGF(r[.]), EGFR(L[.],CR[.]) ➜ EGF(r[1]), EGFR(L[1],CR[.])  @ 'k_on'
'EGF/EGFR'     EGF(r[1]), EGFR(L[1],CR[.]) ➜ EGF(r[.]), EGFR(L[.],CR[.])  @ 'k_off'
'Shc.Grb2'     Shc(Y{p}[.]), Grb2(SH2[.]) ➜ Shc(Y{p}[1]), Grb2(SH2[1])  @ 5 'k_on'
'Shc/Grb2'     Shc(Y{p}[1]), Grb2(SH2[1]) ➜ Shc(Y{p}[.]), Grb2(SH2[.])  @ 'k_off'
'EGFR.Grb2'    EGFR(Y1092{p}[.]), Grb2(SH2[.]) ➜ EGFR(Y1092{p}[1]), Grb2(SH2[1])  @ 'k_on'
'EGFR/Grb2'    EGFR(Y1092{p}[1]), Grb2(SH2[1]) ➜ EGFR(Y1092{p}[.]), Grb2(SH2[.])  @ 'k_off'
'EGFR.Shc'     EGFR(Y1172{p}[.]), Shc(PTB[.]) ➜ EGFR(Y1172{p}[1]), Shc(PTB[1])  @ 'k_on'
'EGFR/Shc'     EGFR(Y1172{p}[1]), Shc(PTB[1]) ➜ EGFR(Y1172{p}[.]), Shc(PTB[.])  @ 'k_off'
'Grb2.SoS'     Grb2(SH3n[.]), SoS(PR[.],S{u}) ➜ Grb2(SH3n[1]), SoS(PR[1],S{u})  @ 'k_on'
'Grb2/SoS'     Grb2(SH3n[1]), SoS(PR[1]) ➜ Grb2(SH3n[.]), SoS(PR[.])  @ 'k_off'
'EGFR.int'     EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.]) ➜ EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2])  @ 'k_on'
‘EGFR/int'     EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2]) ➜ EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.])  @ 'k_off'
'pY1092@EGFR'  EGFR(N[1]), EGFR(C[1],Y1092{u}[.]) ➜ EGFR(N[1]), EGFR(C[1],Y1092{p}[.])  @ 'k_cat'
'pY1172@EGFR'  EGFR(N[1]), EGFR(C[1],Y1172{u}[.]) ➜ EGFR(N[1]), EGFR(C[1],Y1172{p}[.])  @ 'k_cat'
‘uY1092@EGFR'  EGFR(Y1092{p}[.]) ➜ EGFR(Y1092{u}[.])  @ 'k_cat'
'uY1172@EGFR'  EGFR(Y1172{p}[.]) ➜ EGFR(Y1172{u}[.])  @ 'k_cat'
'pY@Shc'       Shc(PTB[_],Y{u}[.]) ➜ Shc(PTB[_],Y{p}[.])  @ 'k_cat'
'uY@Shc'       Shc(Y{p}[.]) ➜ Shc(Y{u}[.])  @ ‘k_cat'

‘EOI'          Grb2(S[_],SH3n[2]),SoS(PR[2]) ➜ Grb2(SH2[_],SH3n[2]),SoS(PR[2])  @ 100
```

Contact Map


EGF
r
5,000
C
N
L
CR
EGFR
Y1172
p,u
Y1092
p,u
5,000
PTB
Shc
Y
p,u
10,000
PR
Sos
10,000
SH2
Grb2
SH3
5,000

Dynamics of Occurrences of an Event of Interest



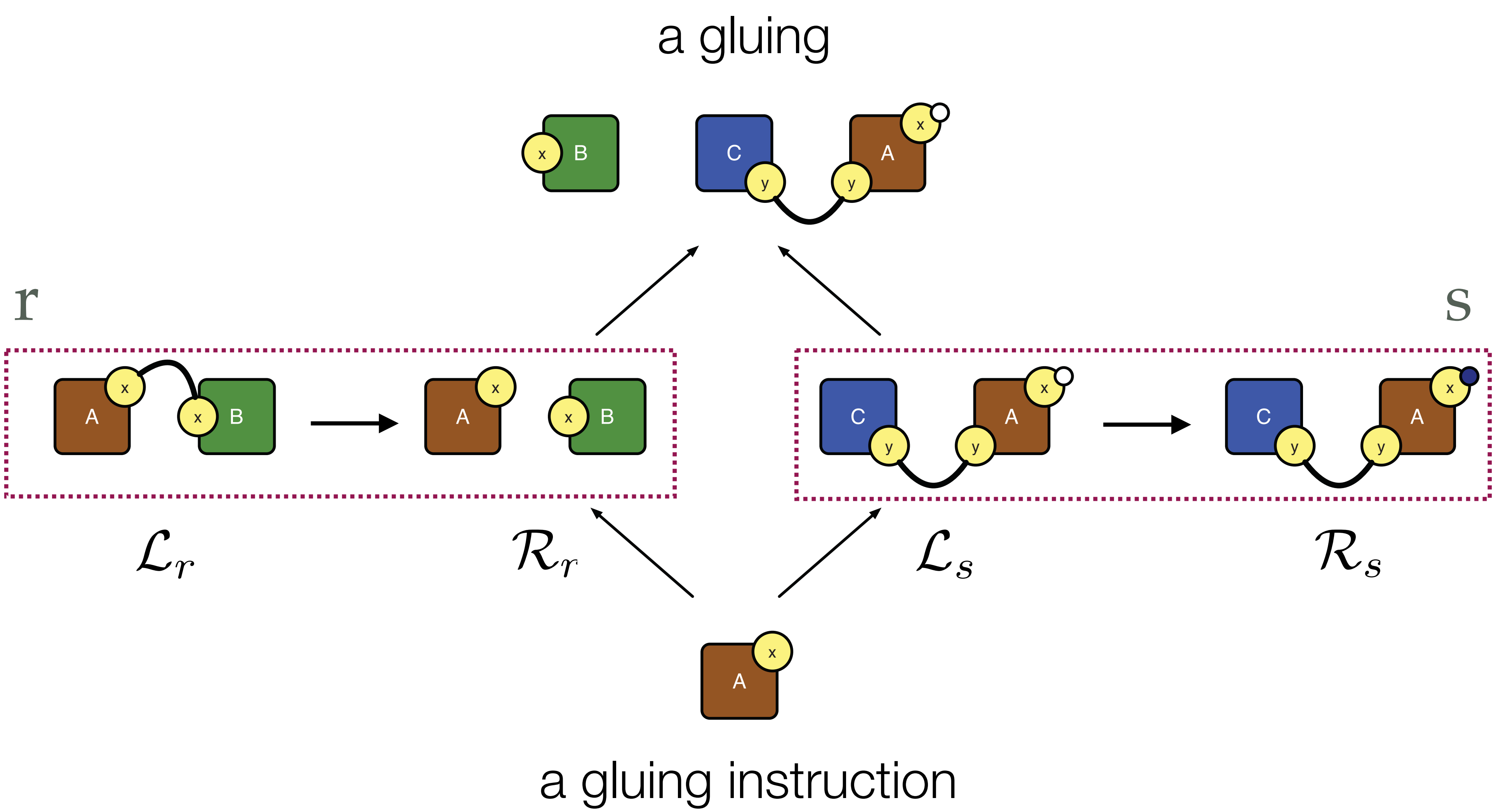
EGF, EGFR, Grb2 = 5,000
Sos = 10,000
Shc = 8,000
total agents = 33,000

volume = 2 10^{-14} l
Kd = 10 nM (= 2,400 molecules)

Seeking Explanations

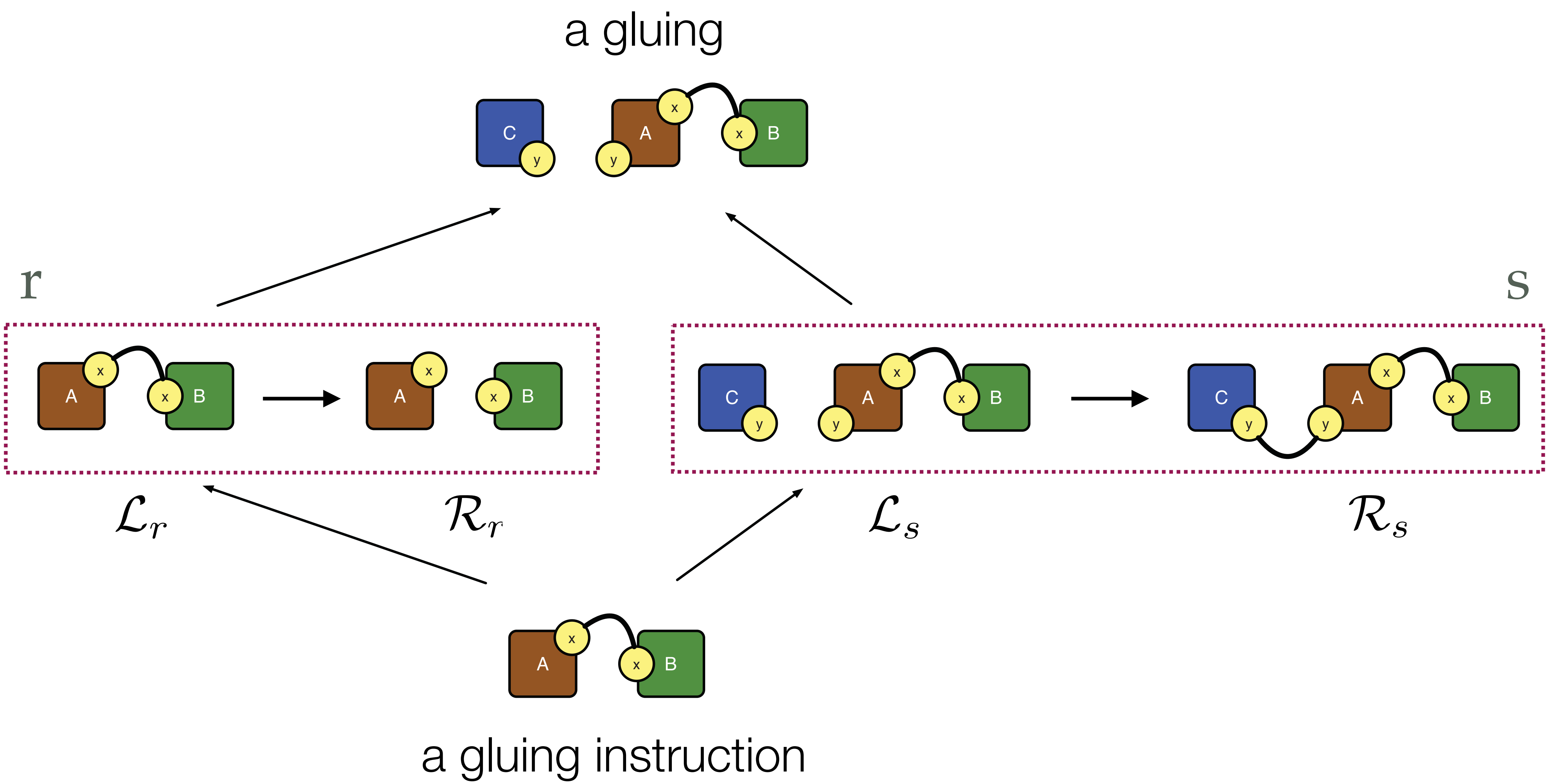
- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals

Direct Positive Static Influence



A direct positive influence exists if the pattern that constitutes the gluing instruction between $\mathcal{R}_r$ and $\mathcal{L}_s$ is modified by rule r.

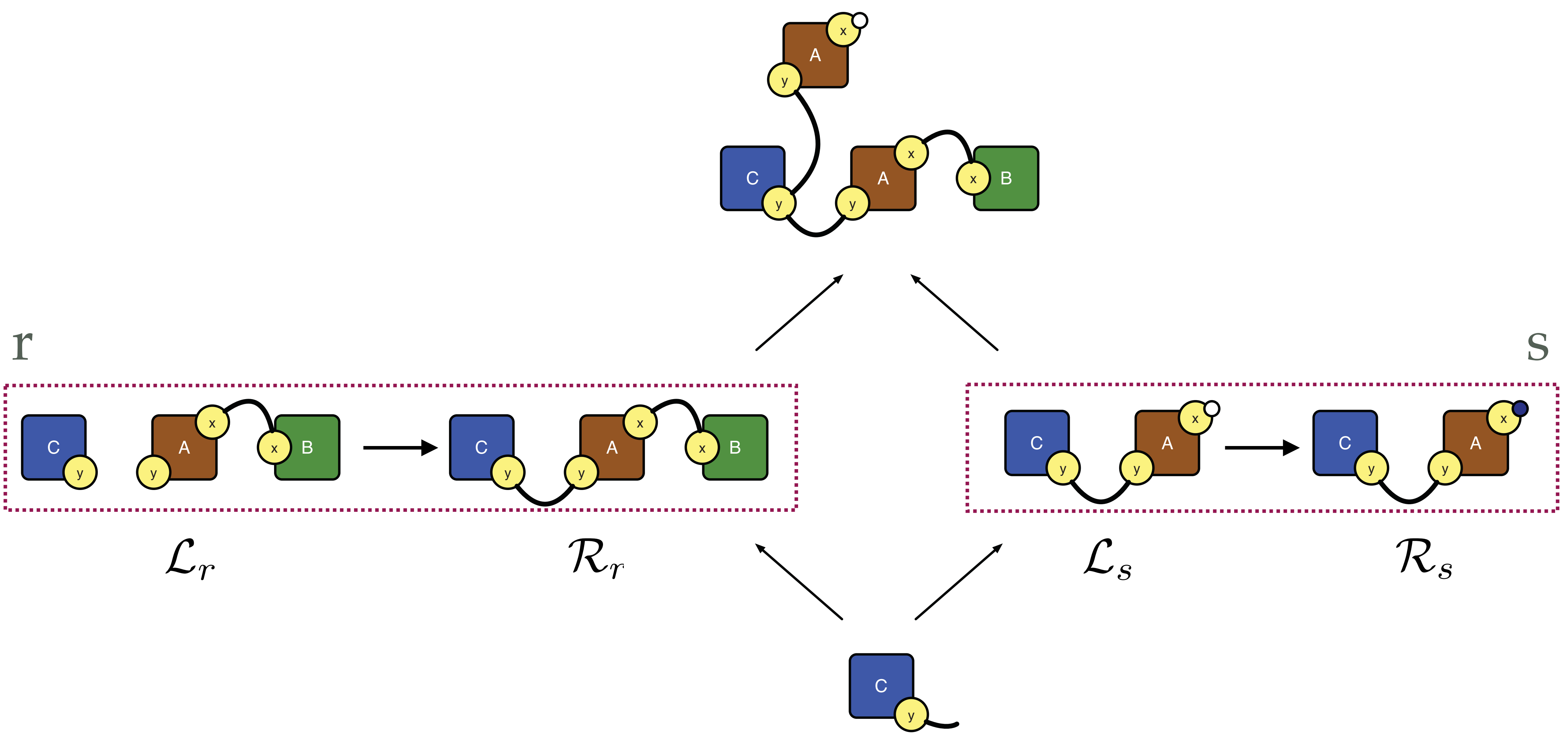
Direct Negative Static Influence



A direct negative influence exists if the pattern that constitutes the gluing instruction between $\mathcal{L}_r$ and $\mathcal{L}_s$ is modified by rule r.

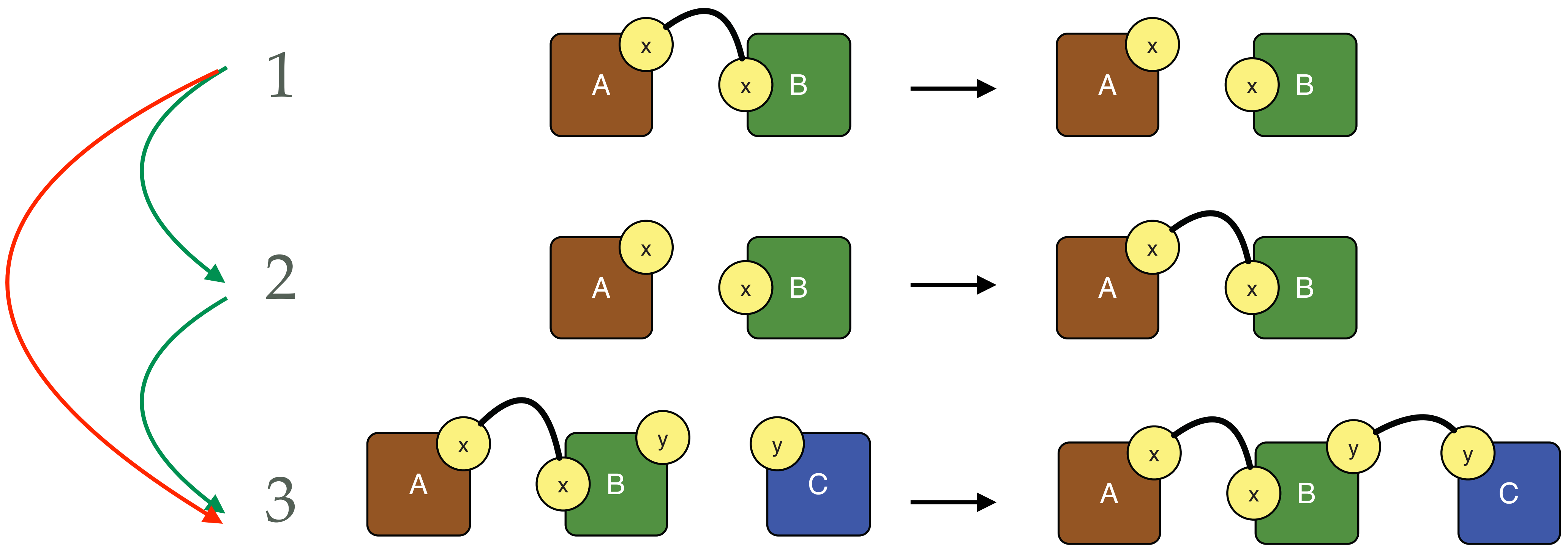
Indirect Positive Static Influence

An indirect positive influence of rule r satisfies only part of the $\mathcal{L}_s$ condition of rule s.

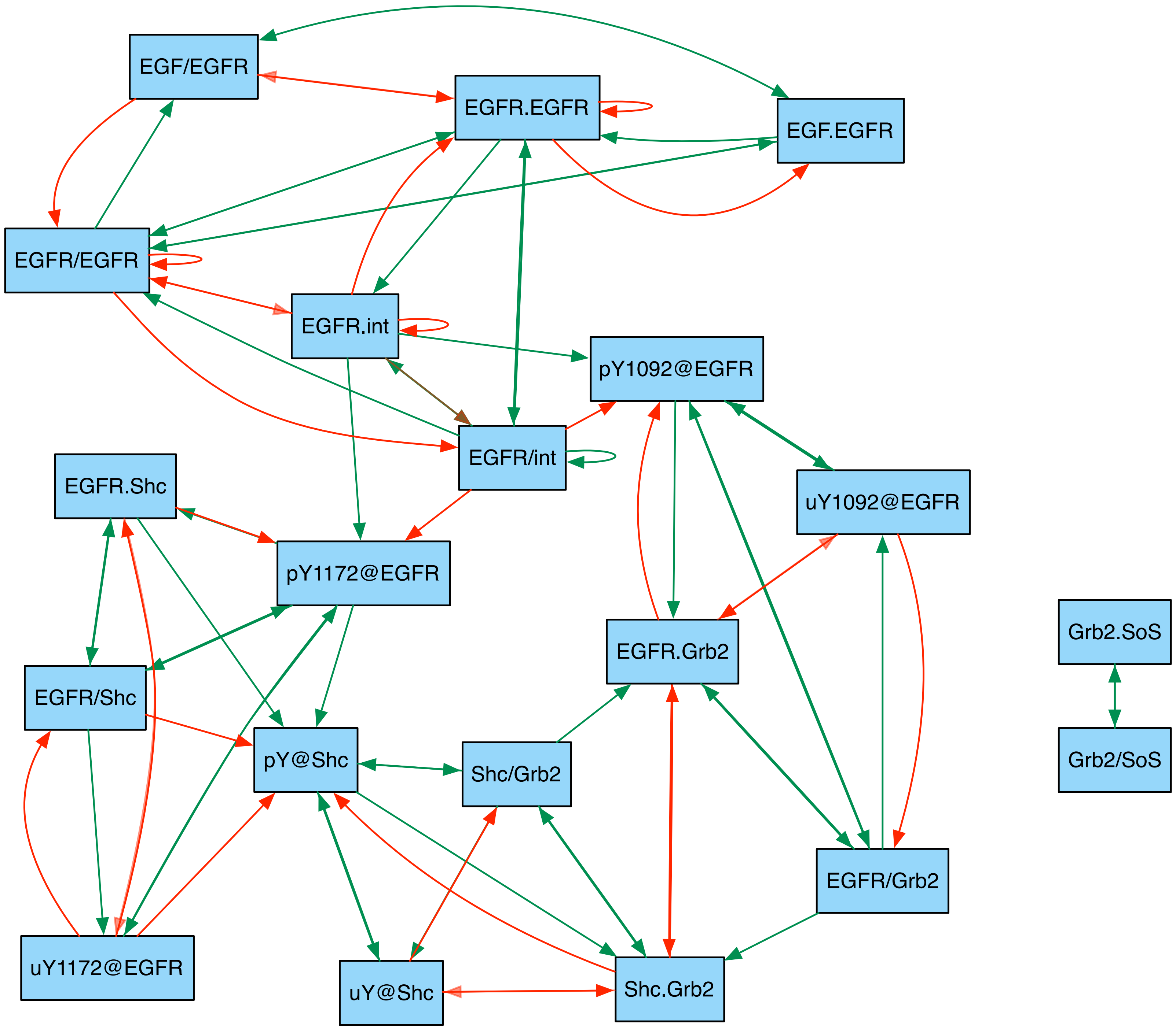


An indirect positive influence exists if the pattern that constitutes the gluing instruction between $\mathcal{R}_r$ and $\mathcal{L}_s$ is modified by rule r and the gluing is not a site graph.

Influence is Not Transitive



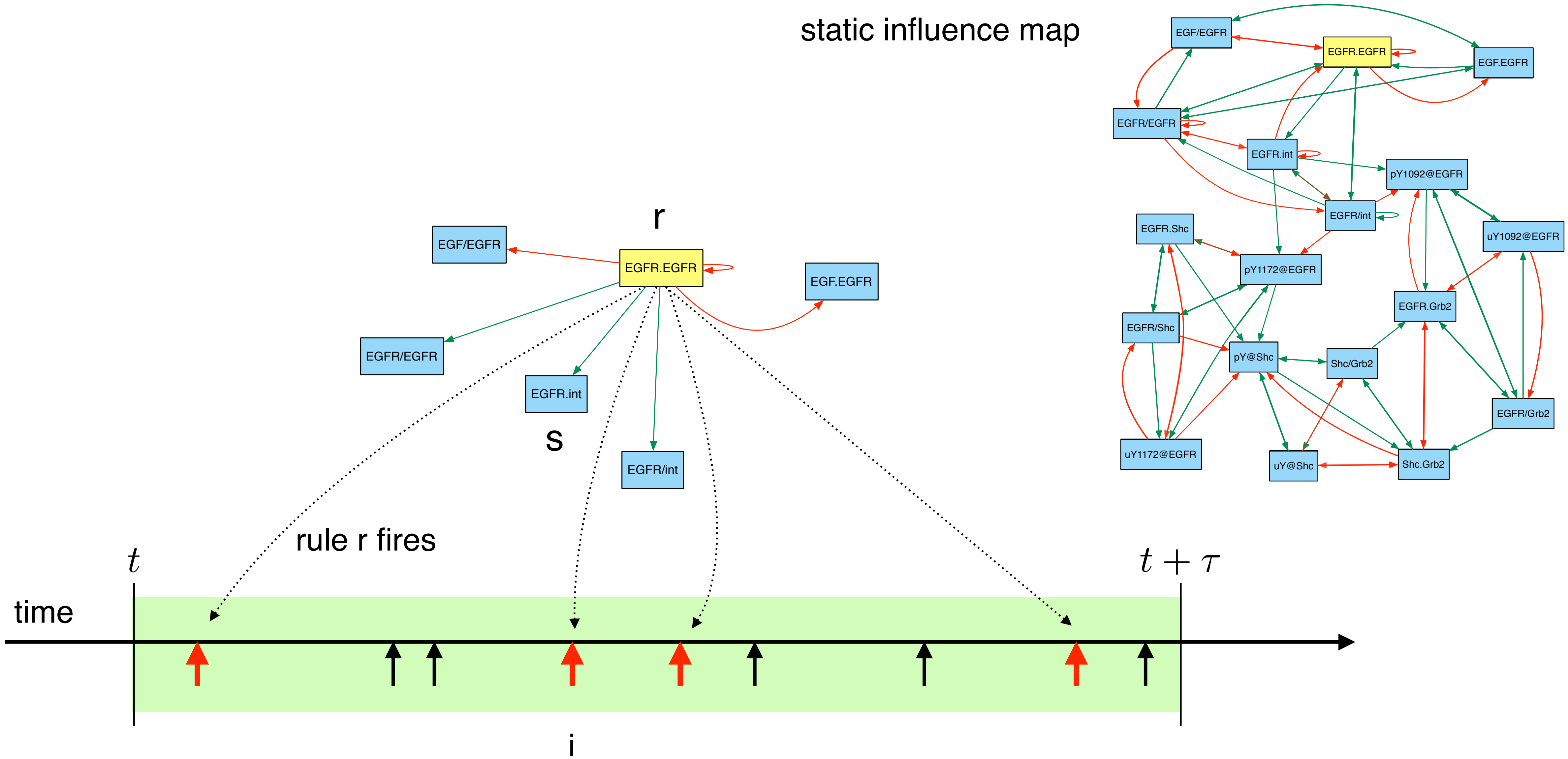
The Static Influence Map



Seeking Explanations

- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals

Dynamic Rule Influence

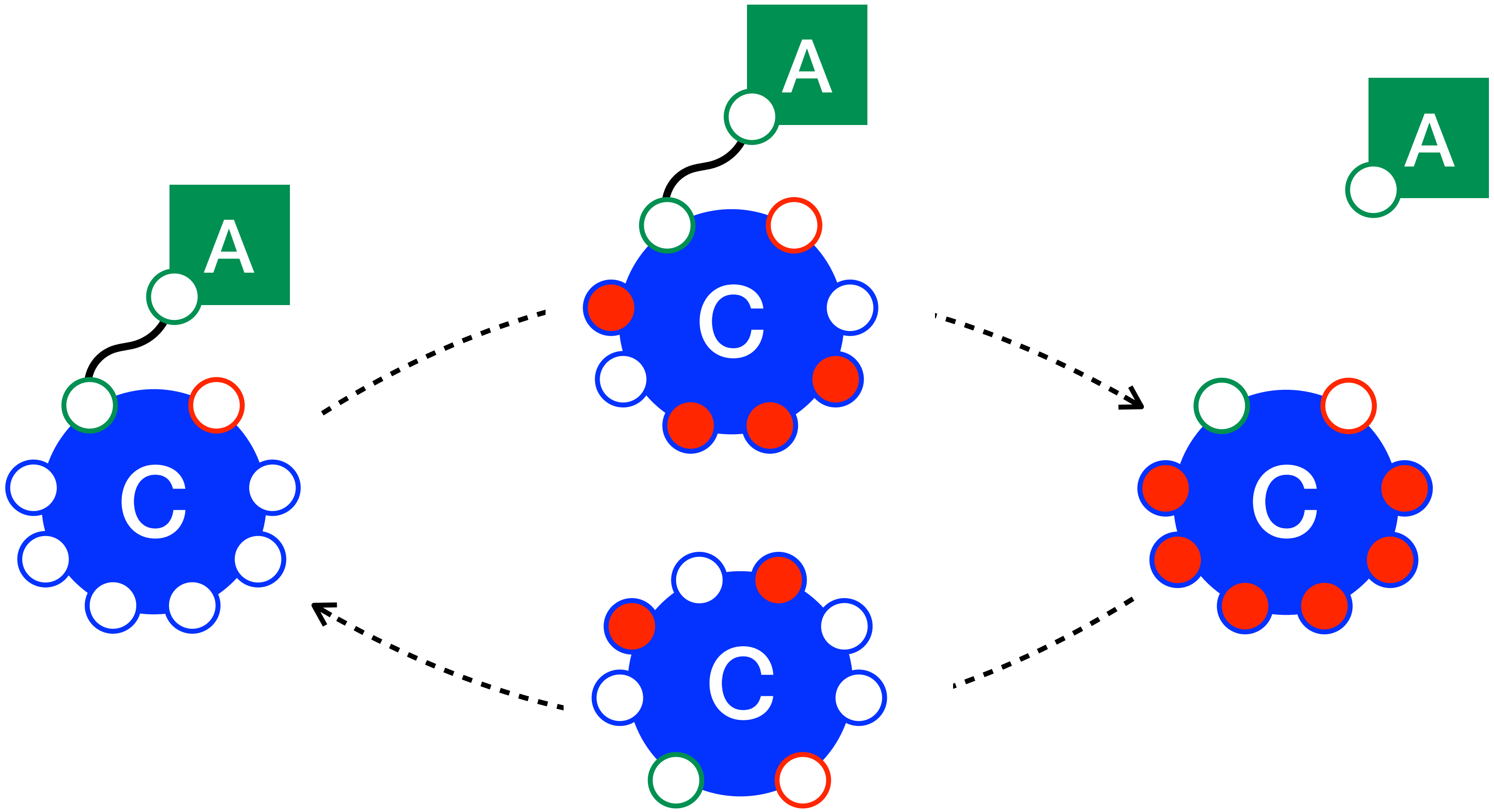


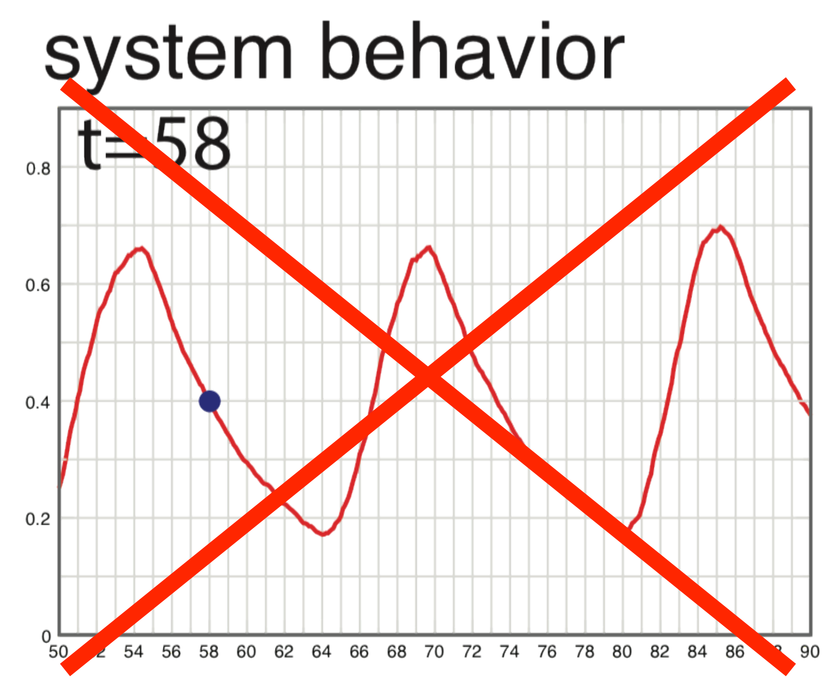
$$\Delta_i(r \rightsquigarrow s) = \begin{cases} \dfrac{\alpha_s(i+1) - \alpha_s(i)}{\alpha_s(i)} & \text{if event } i \text{ is due to rule } r \\ 0 & \text{otherwise} \end{cases}$$

$$\langle \Delta_t(r \rightsquigarrow s) \rangle_\tau = \frac{1}{\#r} \sum_i \Delta_i(r \rightsquigarrow s)$$

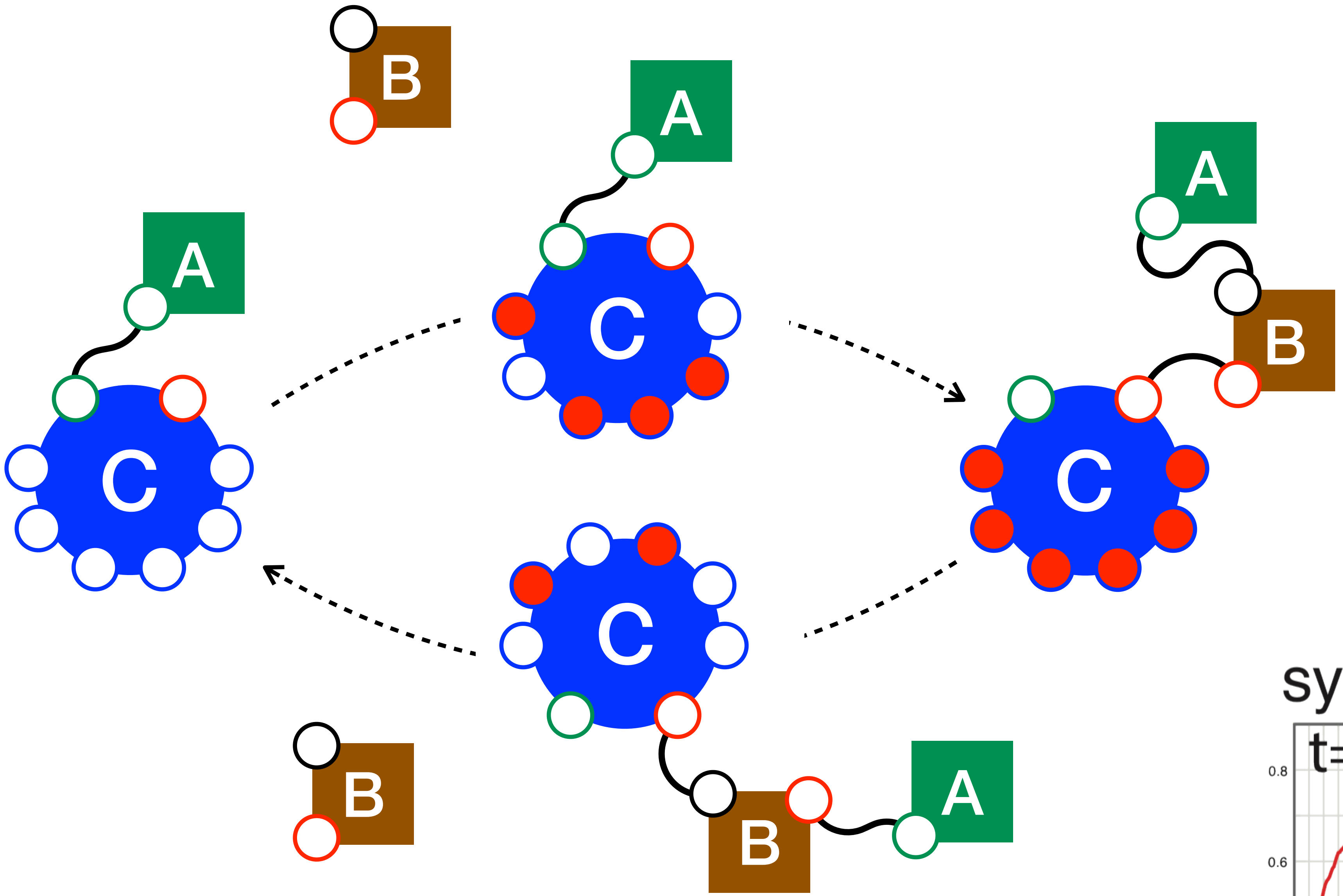
change of s-activity due to r in $[t, t+\tau]$

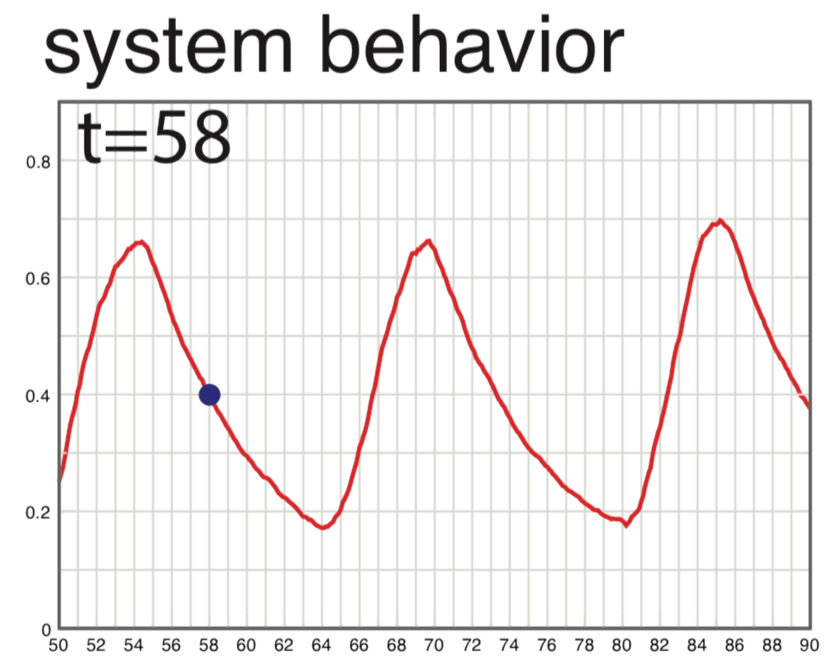
KaiABC Oscillator (Simplified)





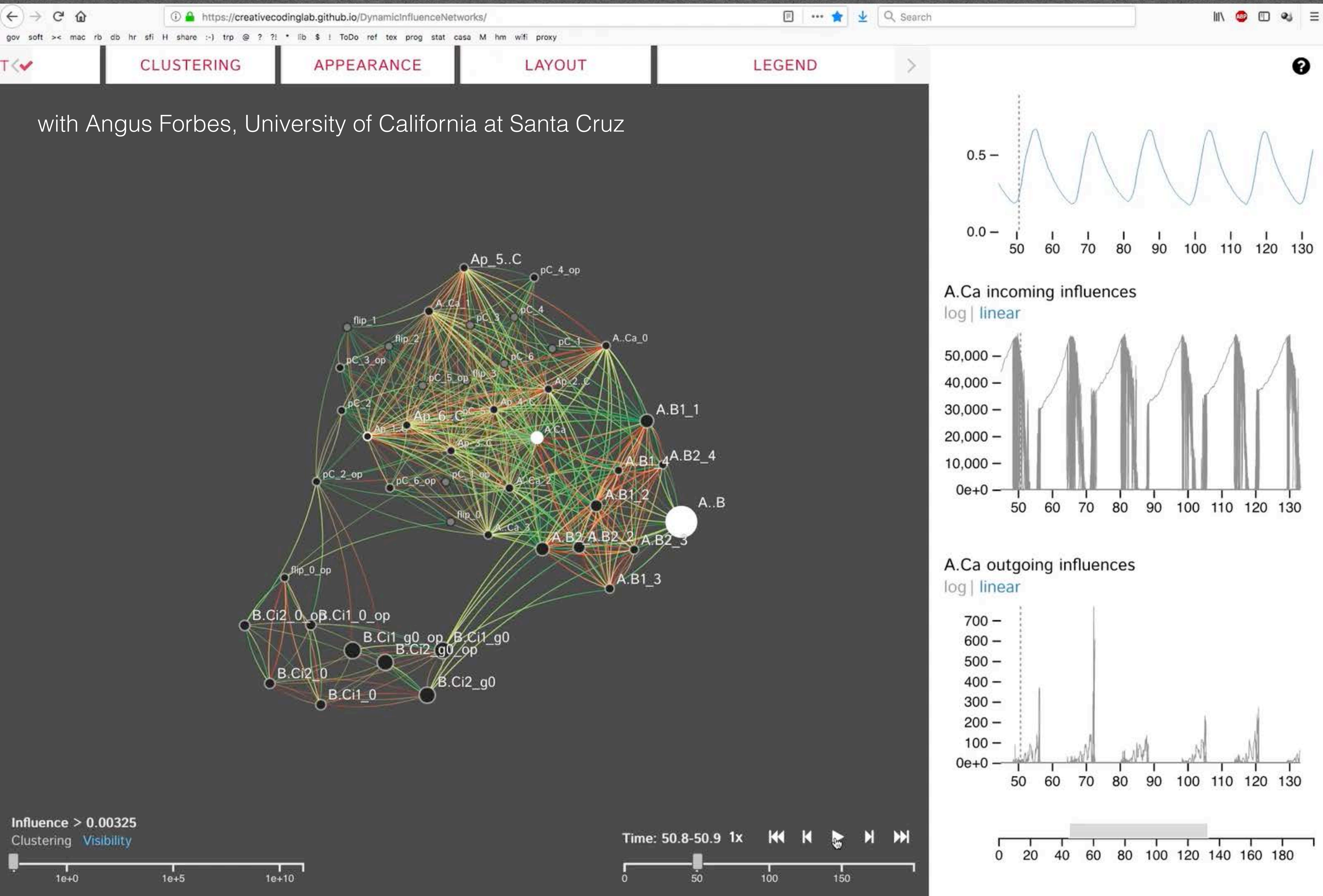
KaiABC Synchronisation (Simplified)



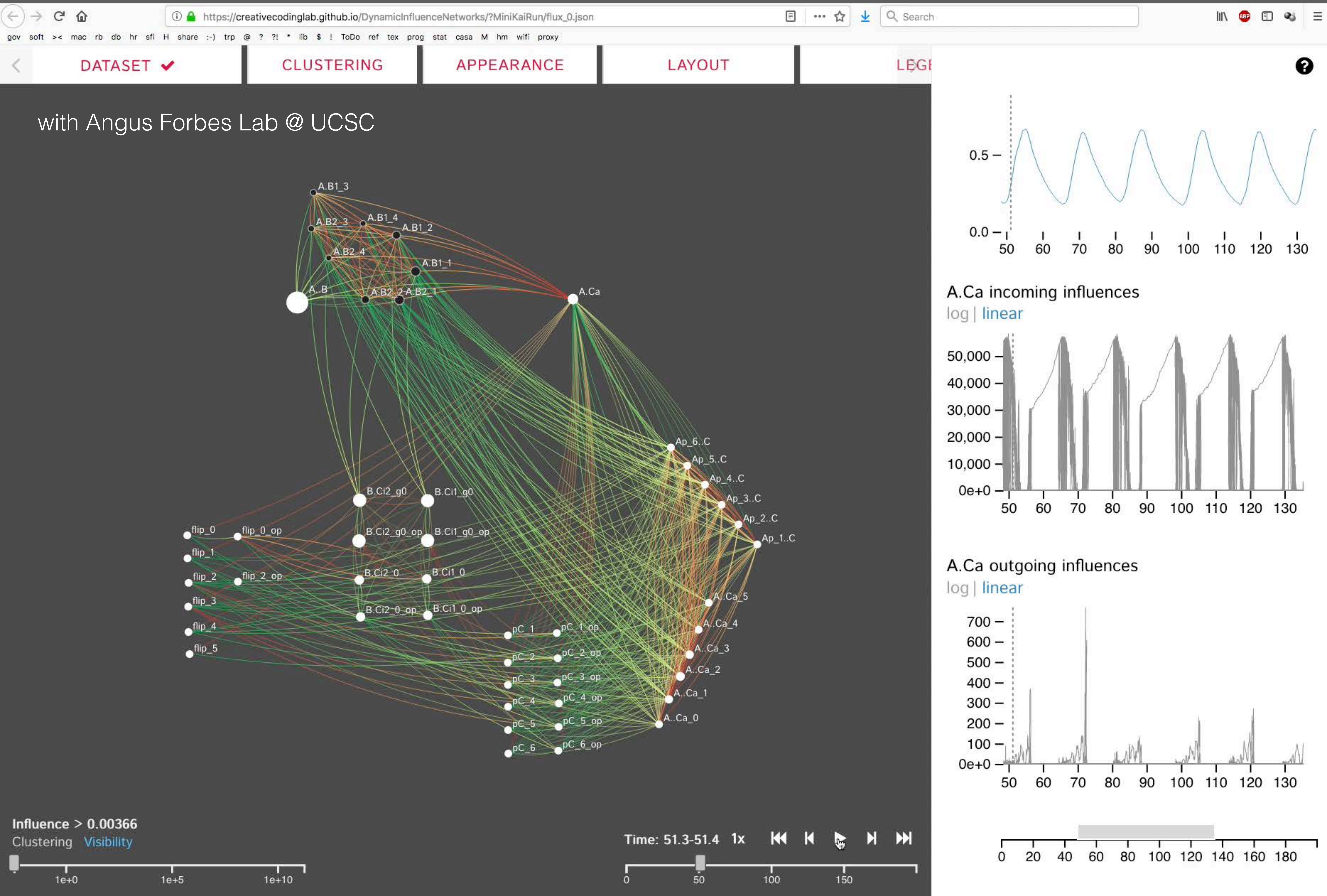


Dynamic Influence Networks in a Molecular Clock (Kai-ABC)

with Angus Forbes, University of California at Santa Cruz



The dynamic influence network



Seeking Explanations

- Static influence
- Dynamic influence
- Causality as “non-independence”
- Causality via counterfactuals

Causality

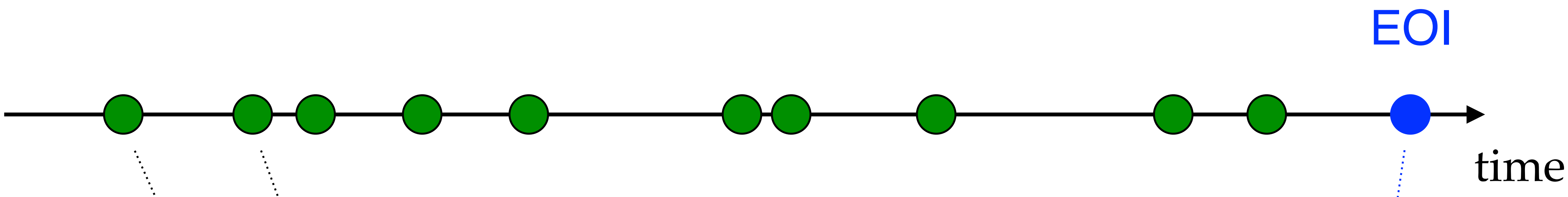
Type causality

- general statements
- predictions
- forward-looking

Actual causality

- focus on particular events
- less useful for prediction, but still useful for intervention
- backward-looking

Events and Traces



trace: $e_1\, e_2\, e_3\, e_4 \;\cdots\cdots\; e_n$

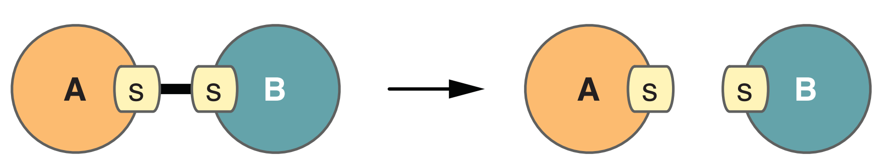
states of the world

an event: $e \quad , \quad \mathrm{pre}(e) \subseteq Q \quad , \quad \mathrm{eff}(e) : \mathrm{pre}(e) \rightarrow Q$

label — context (before) — context (after)

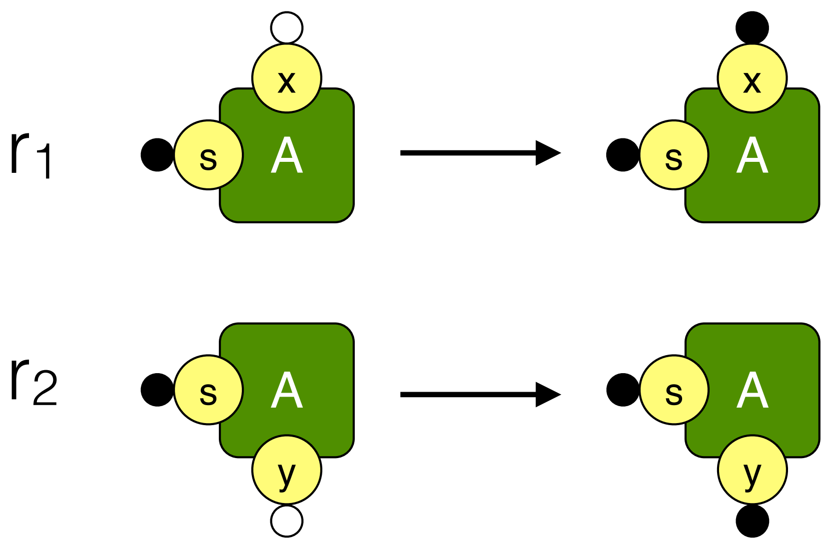
$\mathcal{L}_r \qquad \mathcal{R}_r$

rule r + embedding

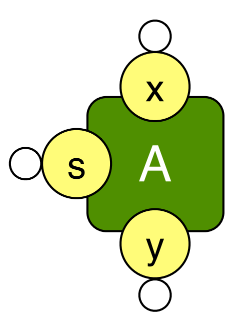


Causality via Non-Independence

$e_1 \diamond e_2$ iff for every context c it is the case that



these events are independent,
but cannot occur in this context:



$$c \vdash e_1$$

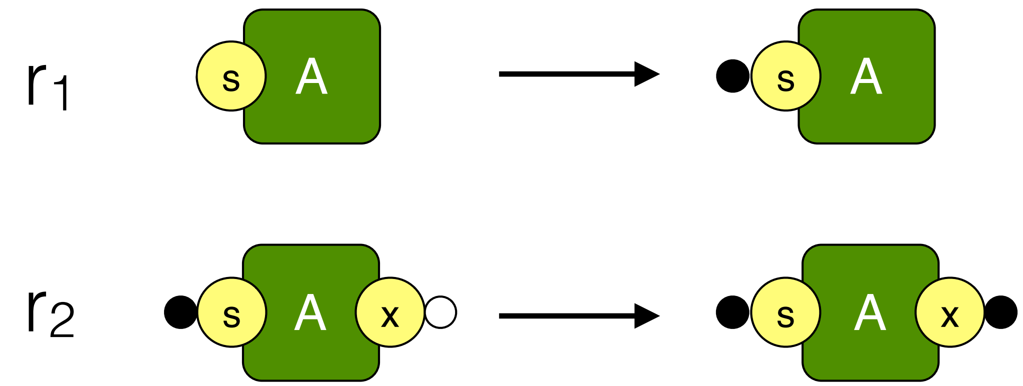
$$c \vdash e_2$$

implies

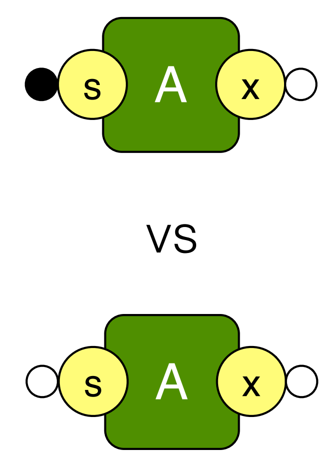
$$c \vdash e_1 e_2$$

$$c \vdash e_2 e_1$$

$$\mathrm{eff}(e_1 e_2) = \mathrm{eff}(e_2 e_1)$$



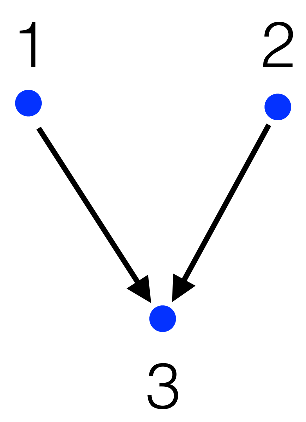
whether these events are independent,
depends on context:



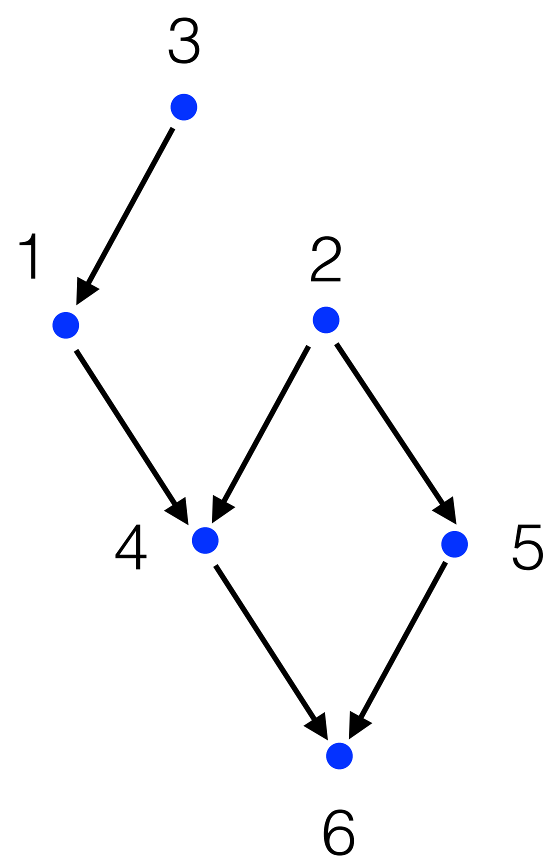
Trace Equivalence

trace equivalence $e_1 \diamond e_2 \Rightarrow t.e_1 e_2.t' \sim t.e_2 e_1.t'$

precedence $(\neg(e_i \diamond e_j) \wedge i < j) \Rightarrow e_i < e_j$



= {123, 213}



= {312546, 231546, …}

precedence-preserving permutations

Causal and Non-Causal Precedence

With regard to causality, precedence

$$e_i < e_j$$

comes in two flavors:

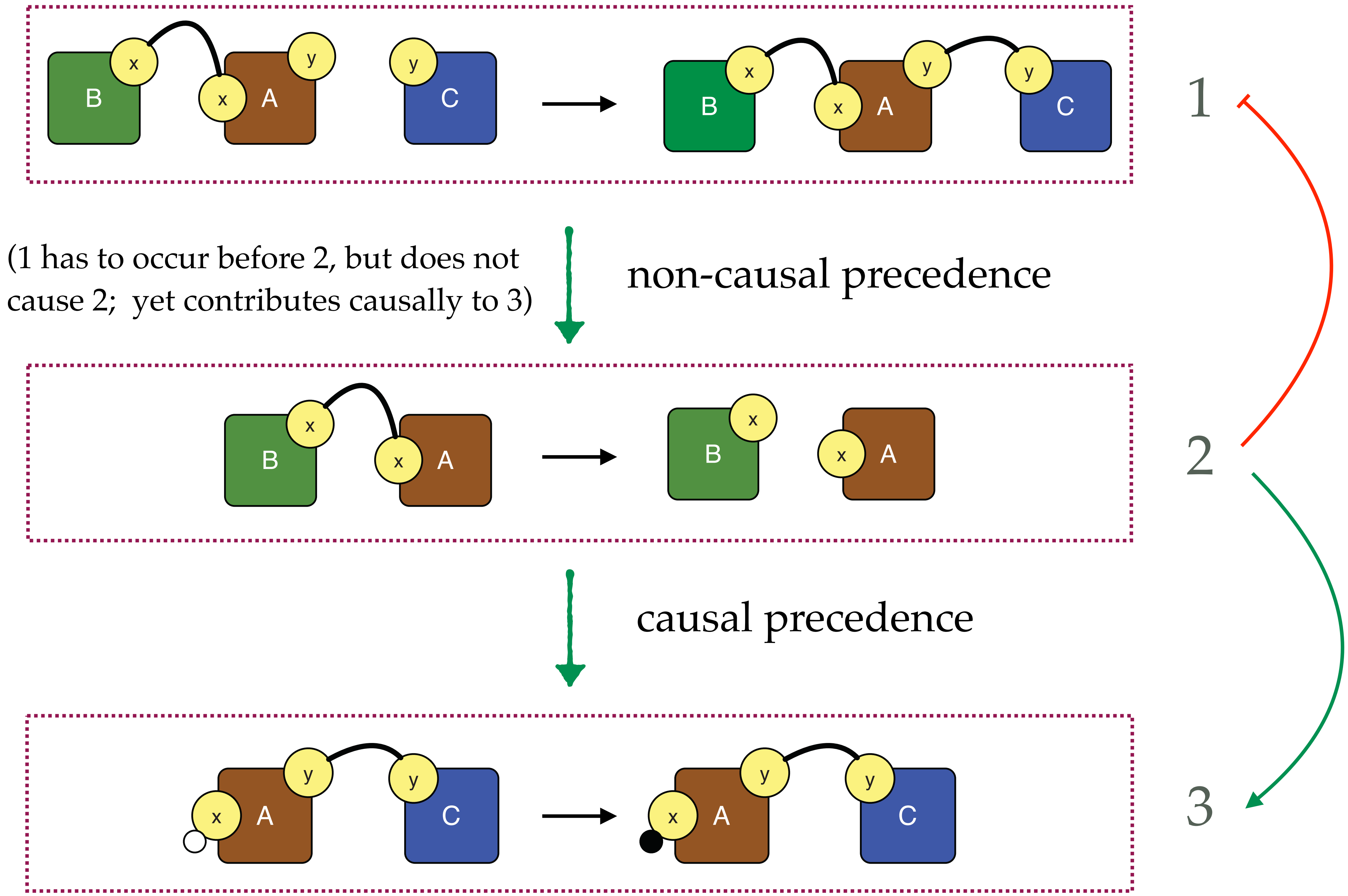
“immediate causality”

$$e_1 \rightarrow e_2 \quad \text{if} \quad \exists c \quad c \vdash e_1 e_2 \wedge c \nvdash e_2$$

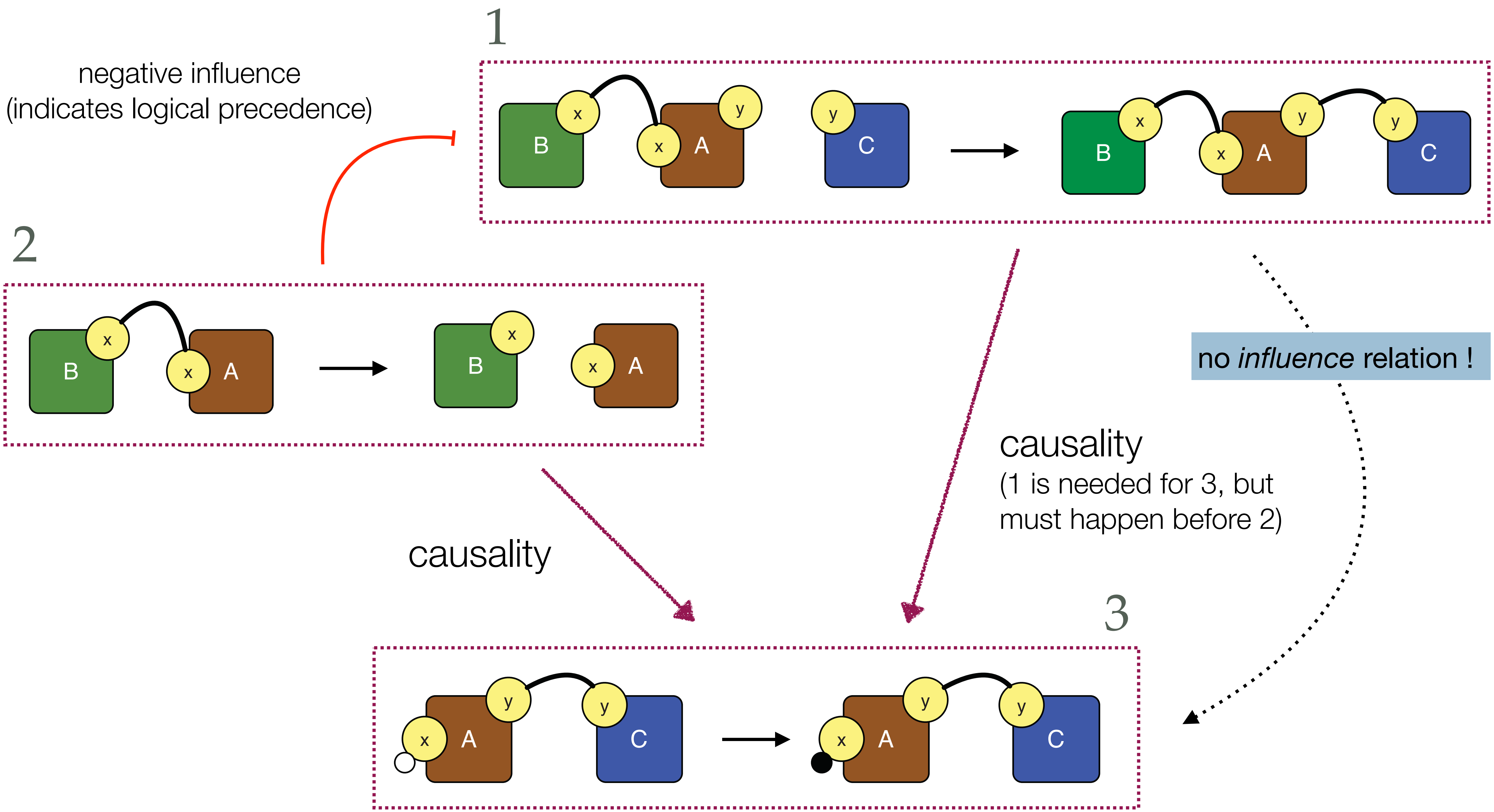
“non-causal precedence”

$$e_1 \dashv e_2 \quad \text{if} \quad \exists c \quad c \vdash e_2 \wedge c \nvdash e_1 e_2$$

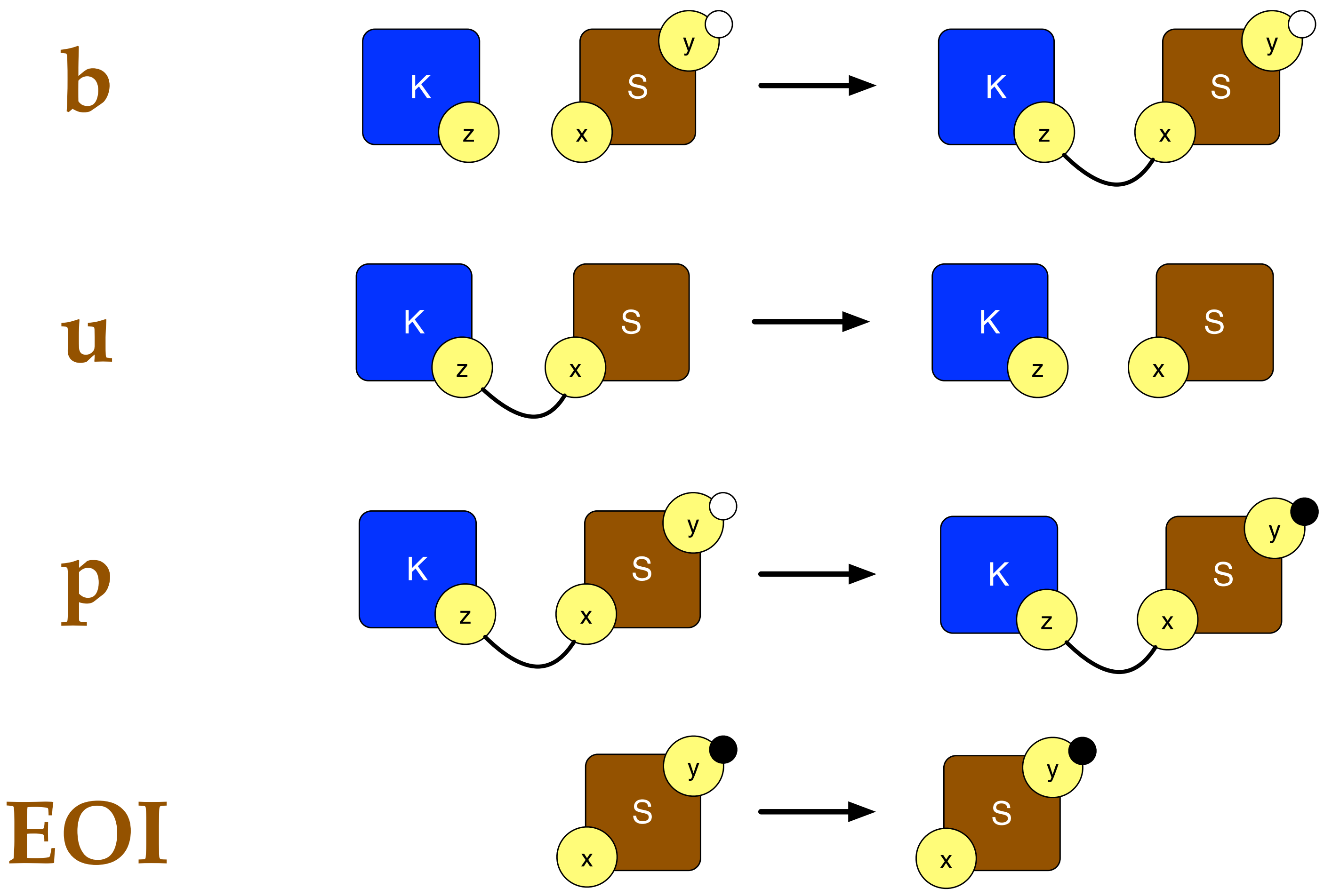
Causal and Non-Causal Precedence



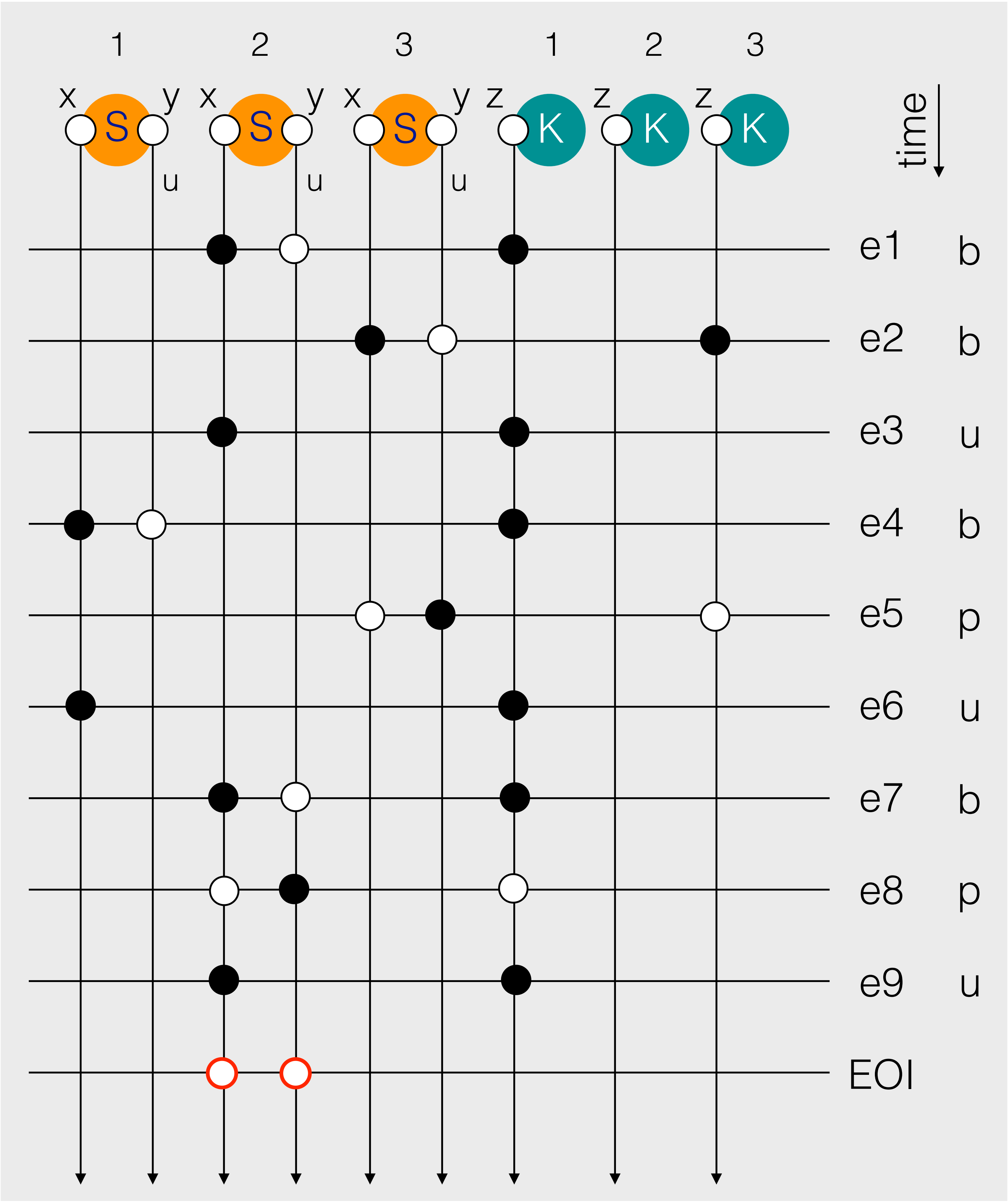
Causal and Non-Causal Precedence

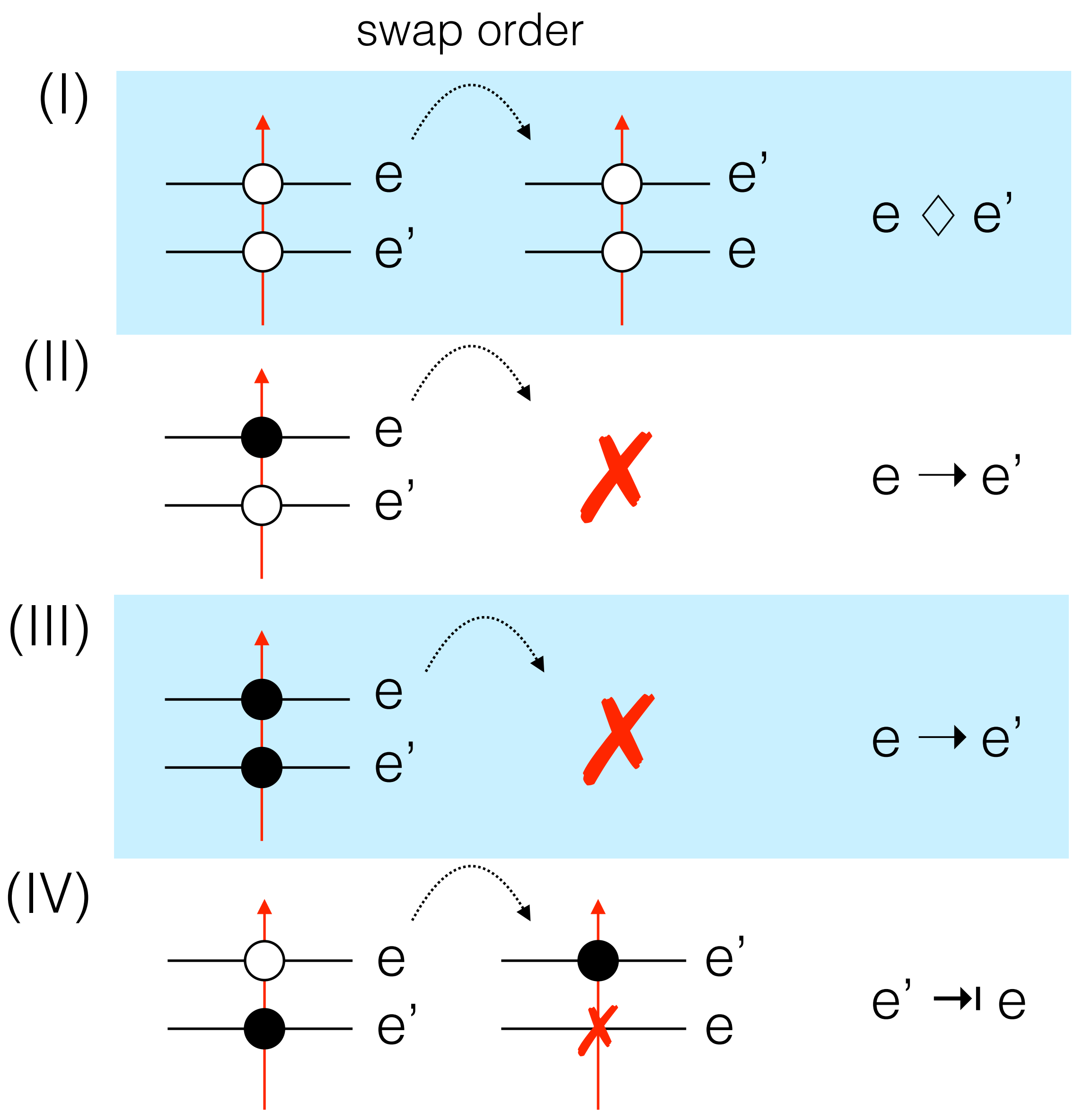


A Simple Example

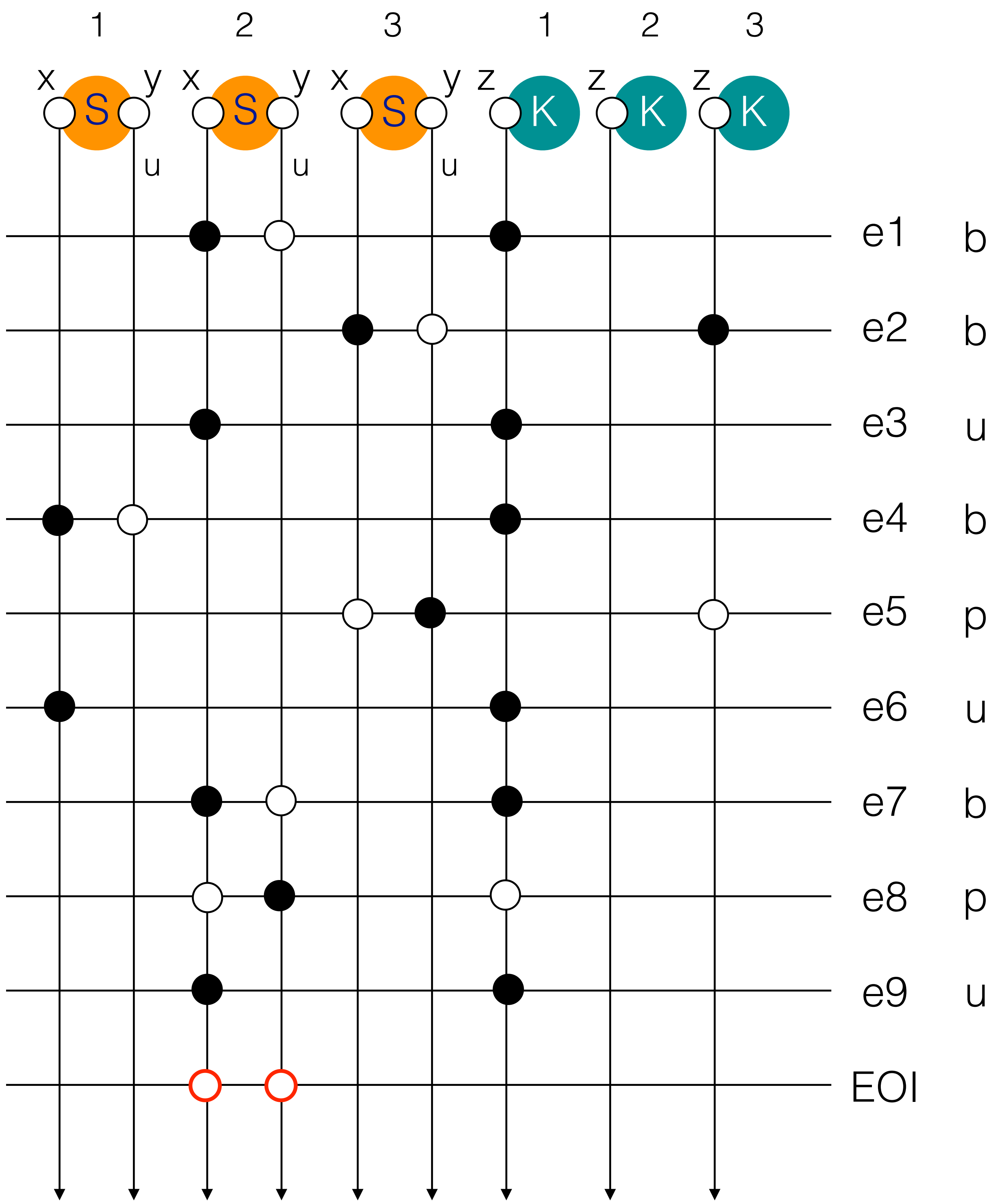


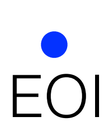
From Trace to Causal Past



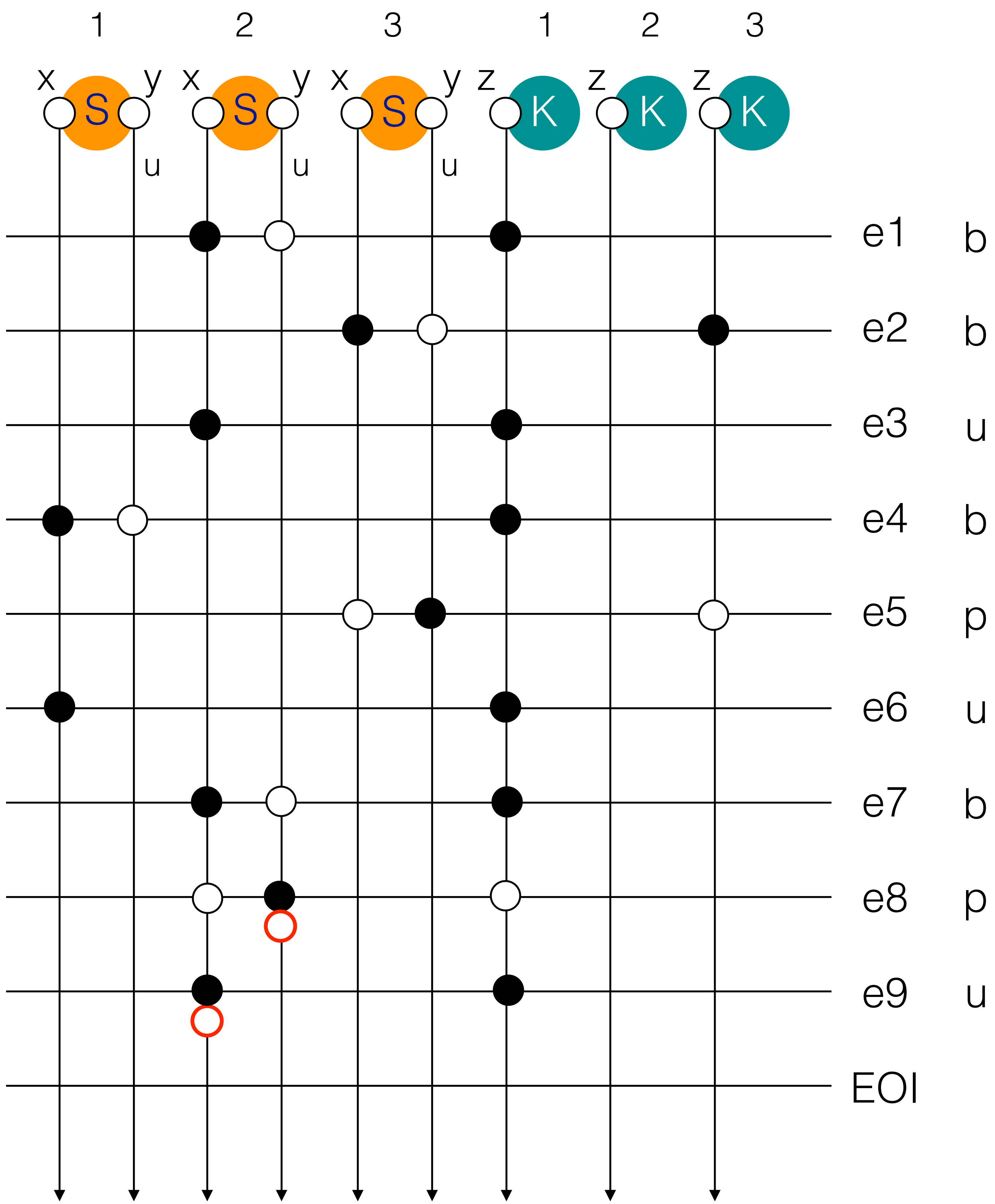


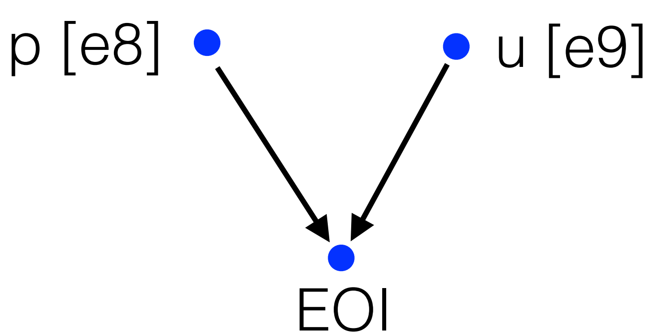
From Trace to Causal Past



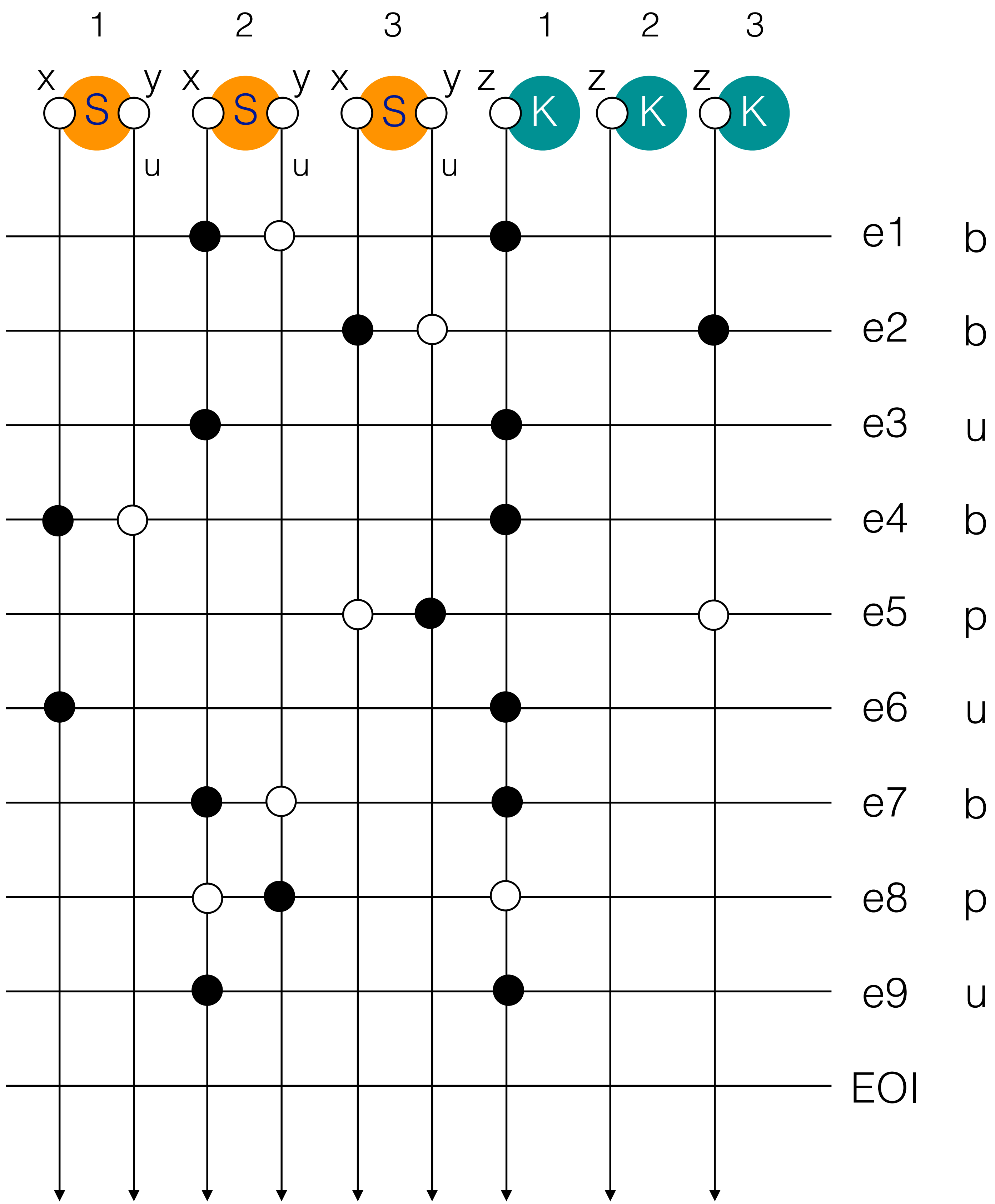


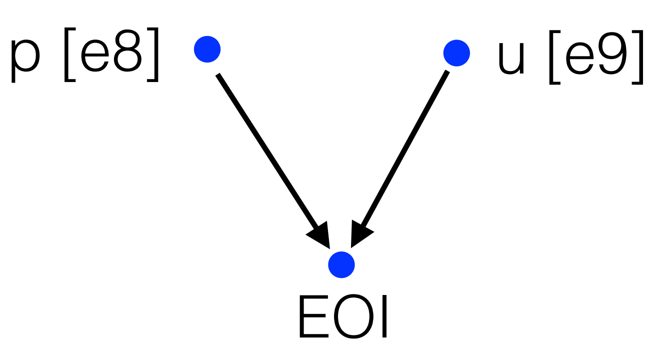
From Trace to Causal Past



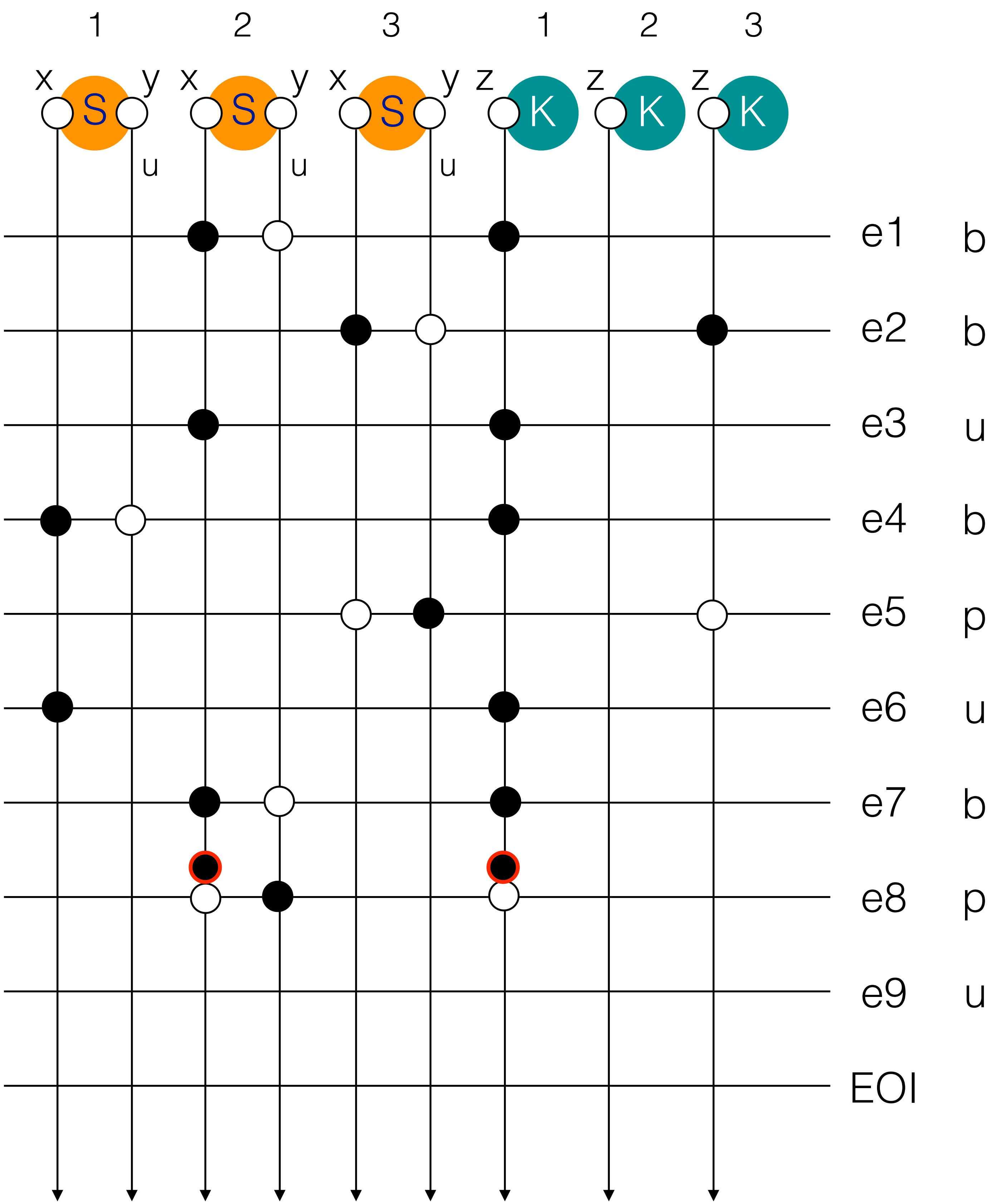


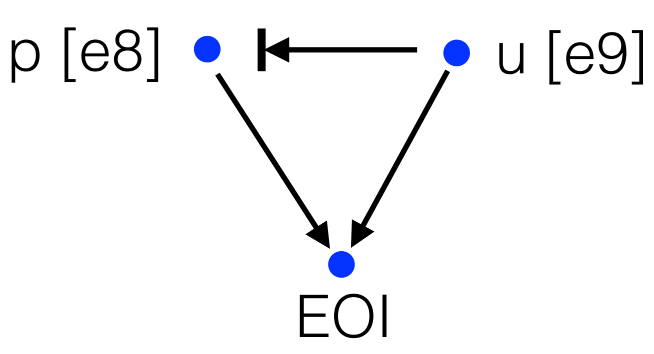
From Trace to Causal Past



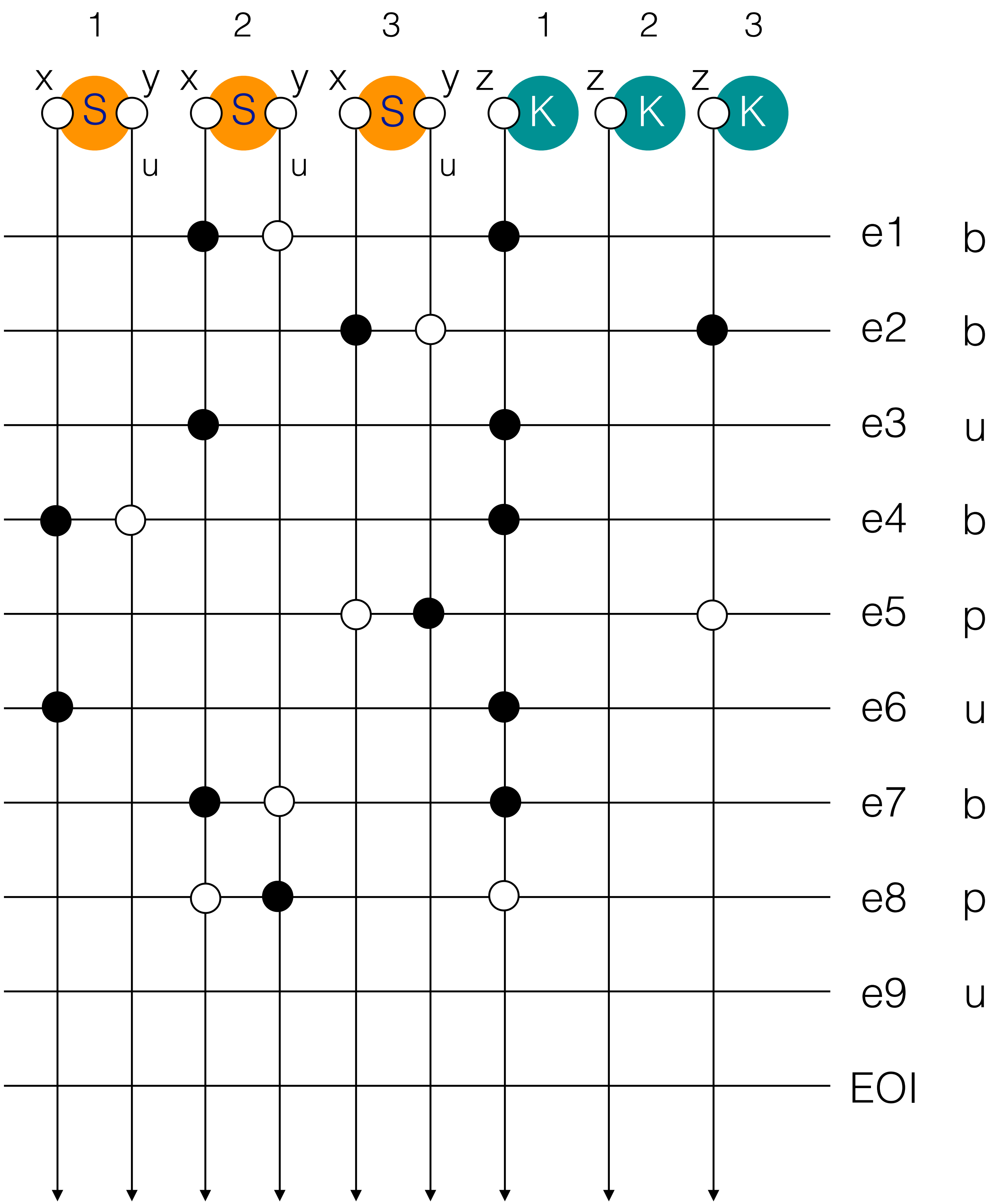


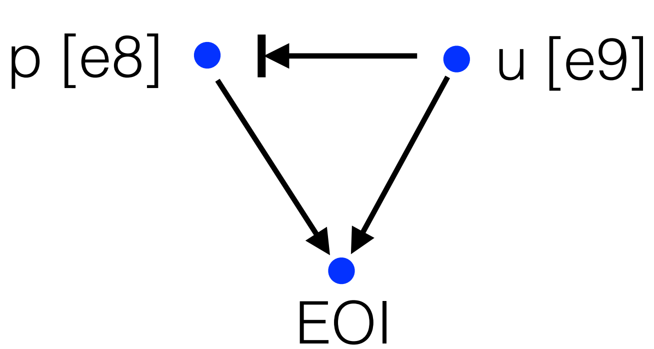
From Trace to Causal Past



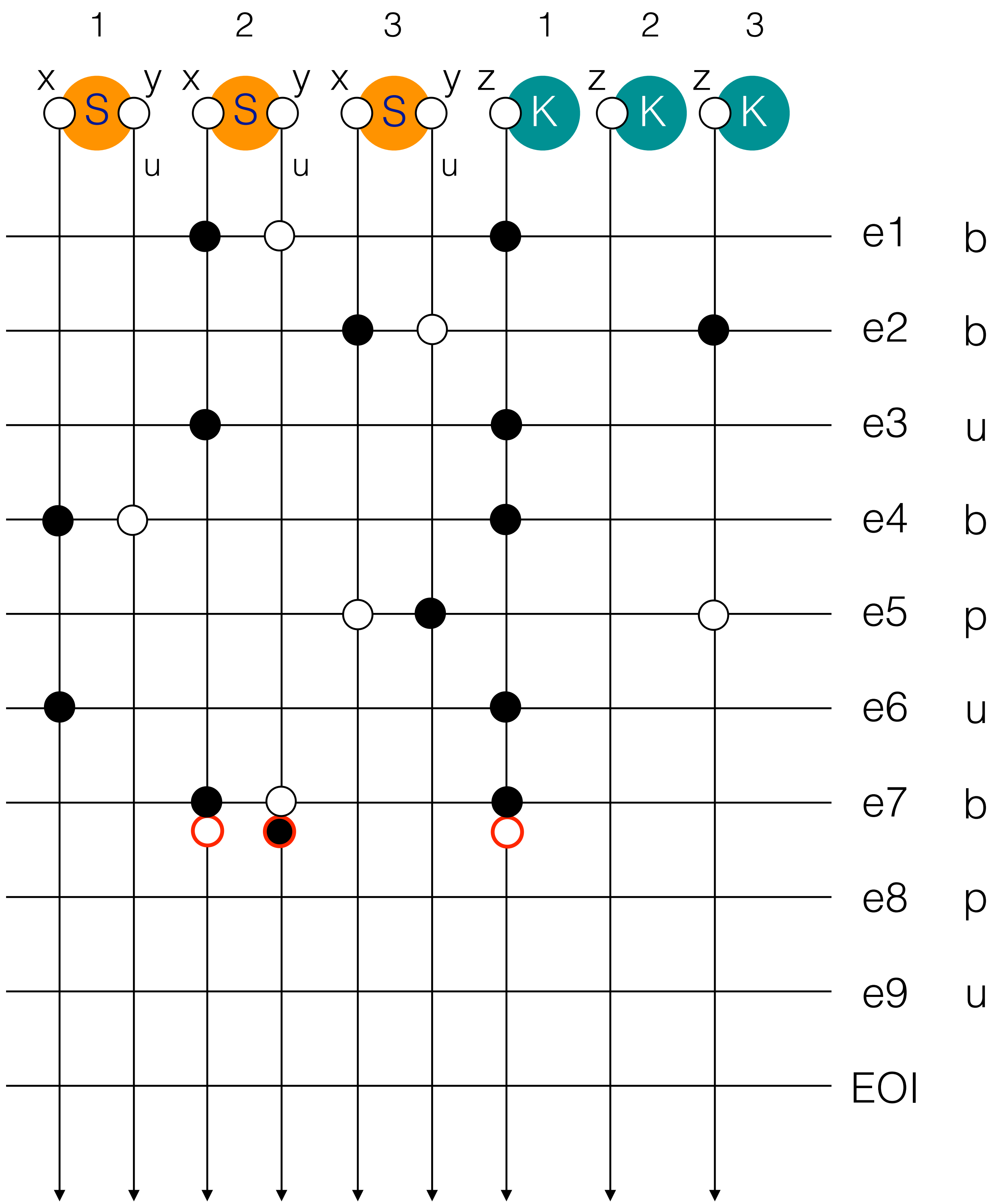


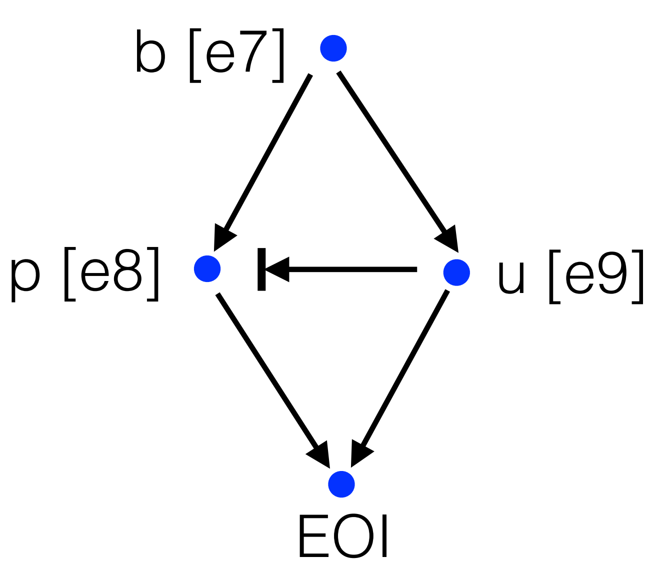
From Trace to Causal Past



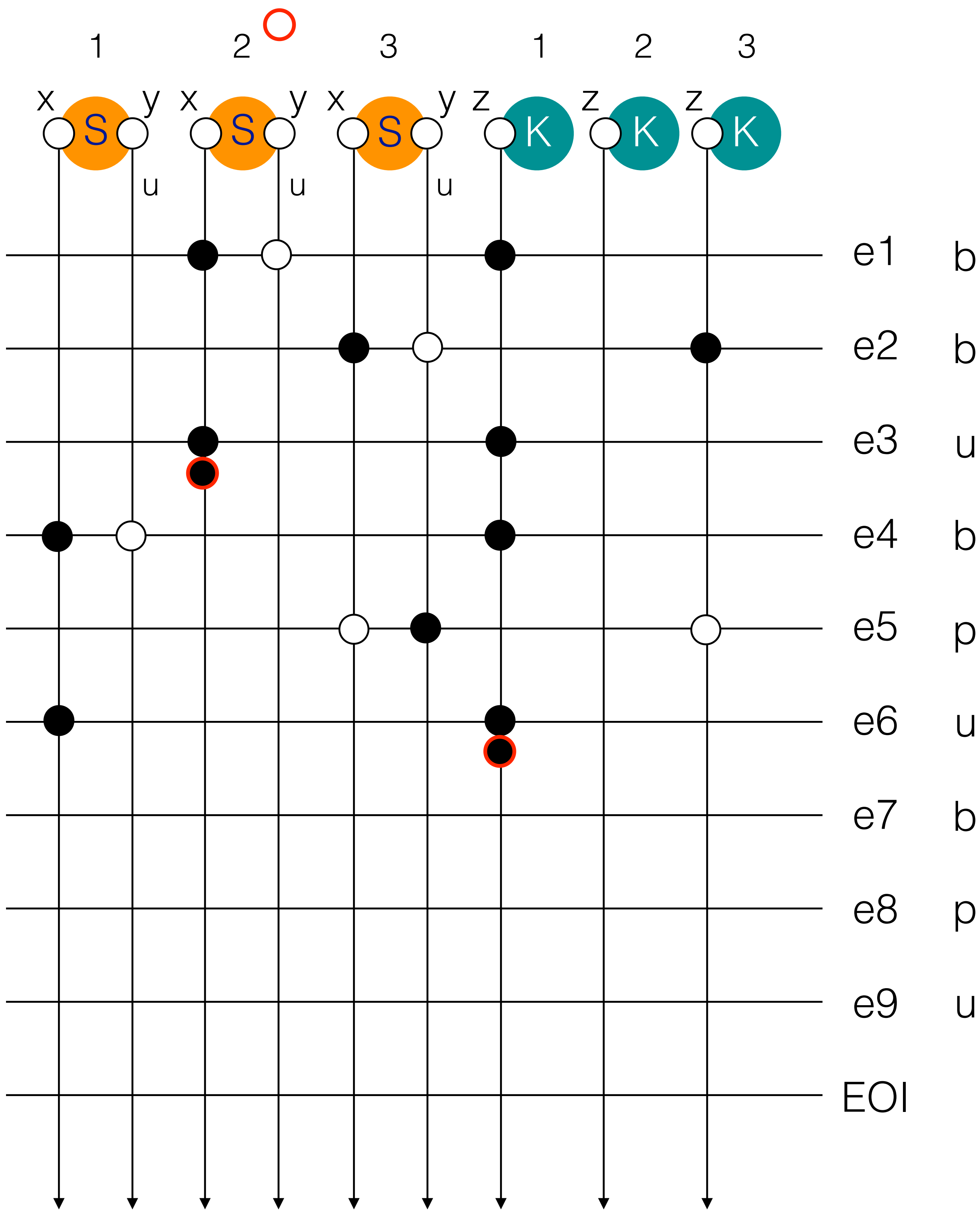


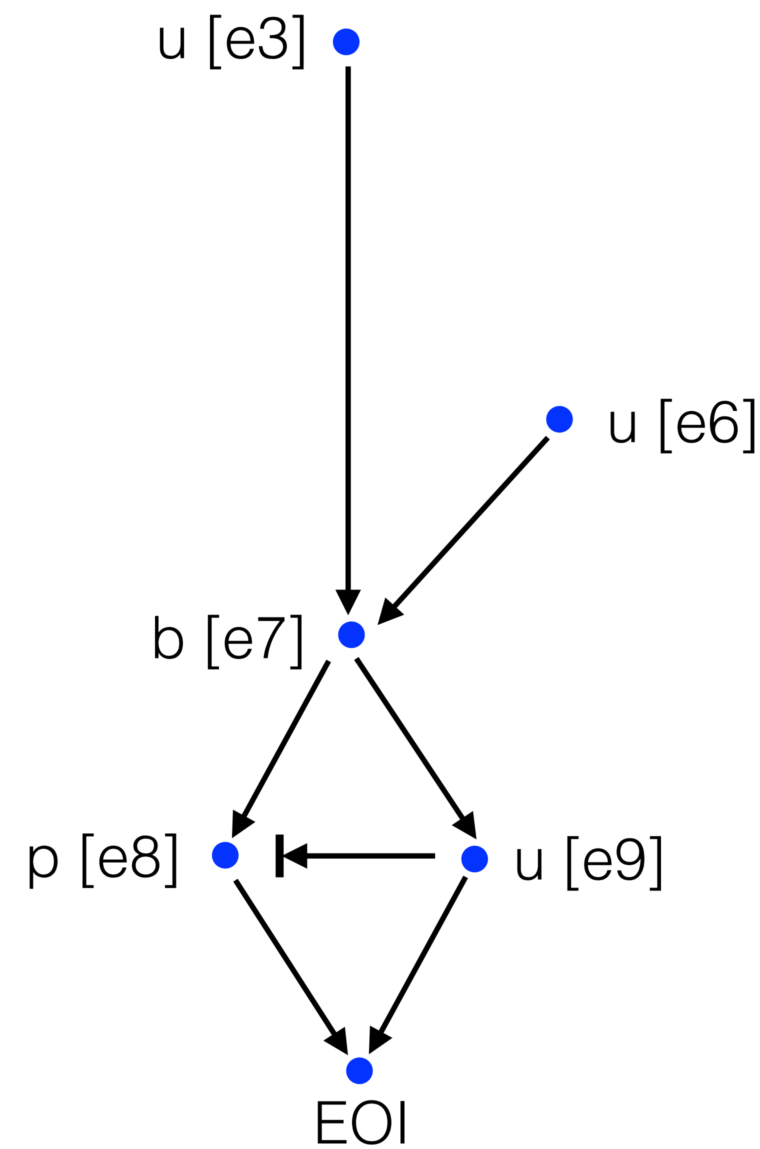
From Trace to Causal Past



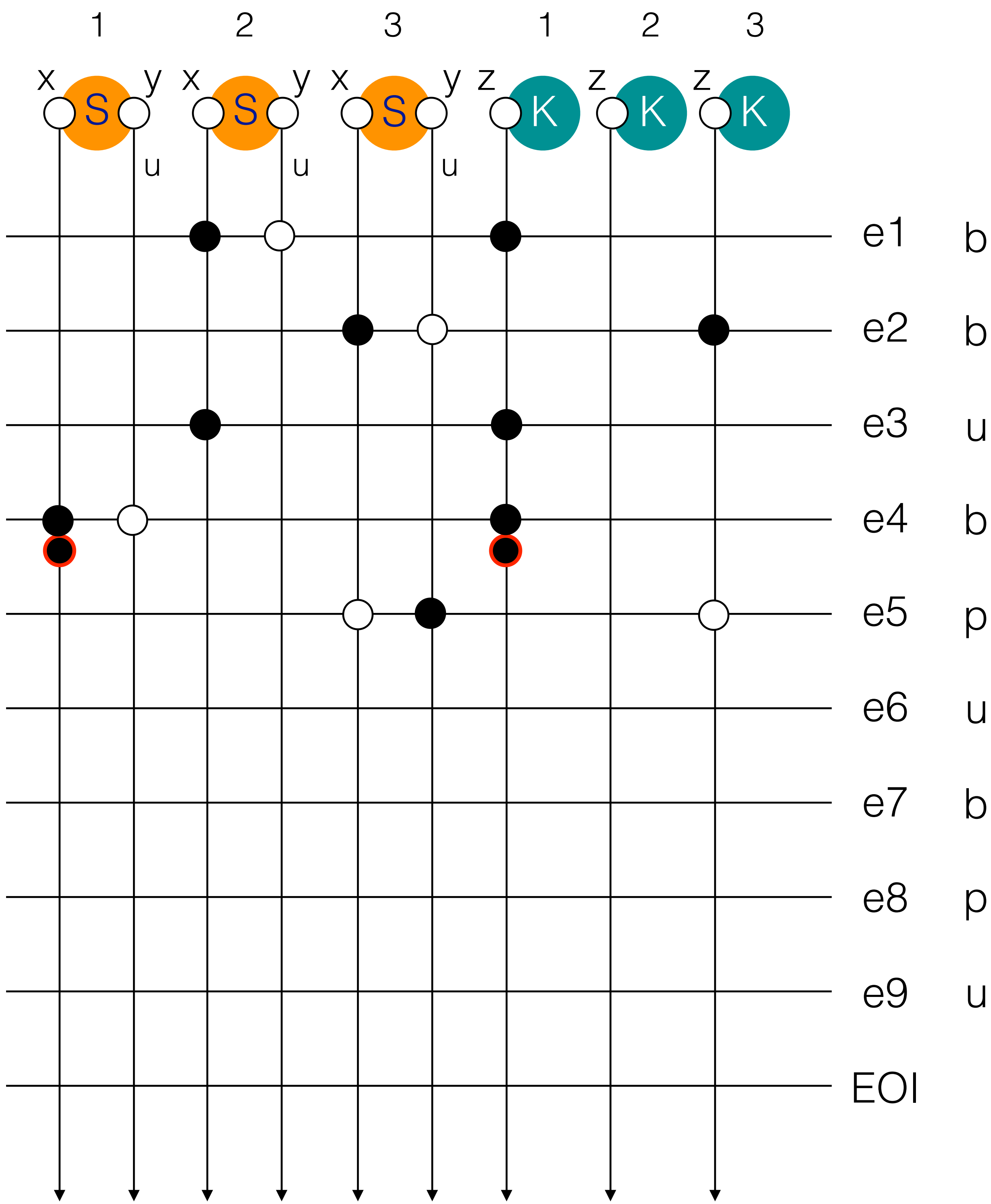


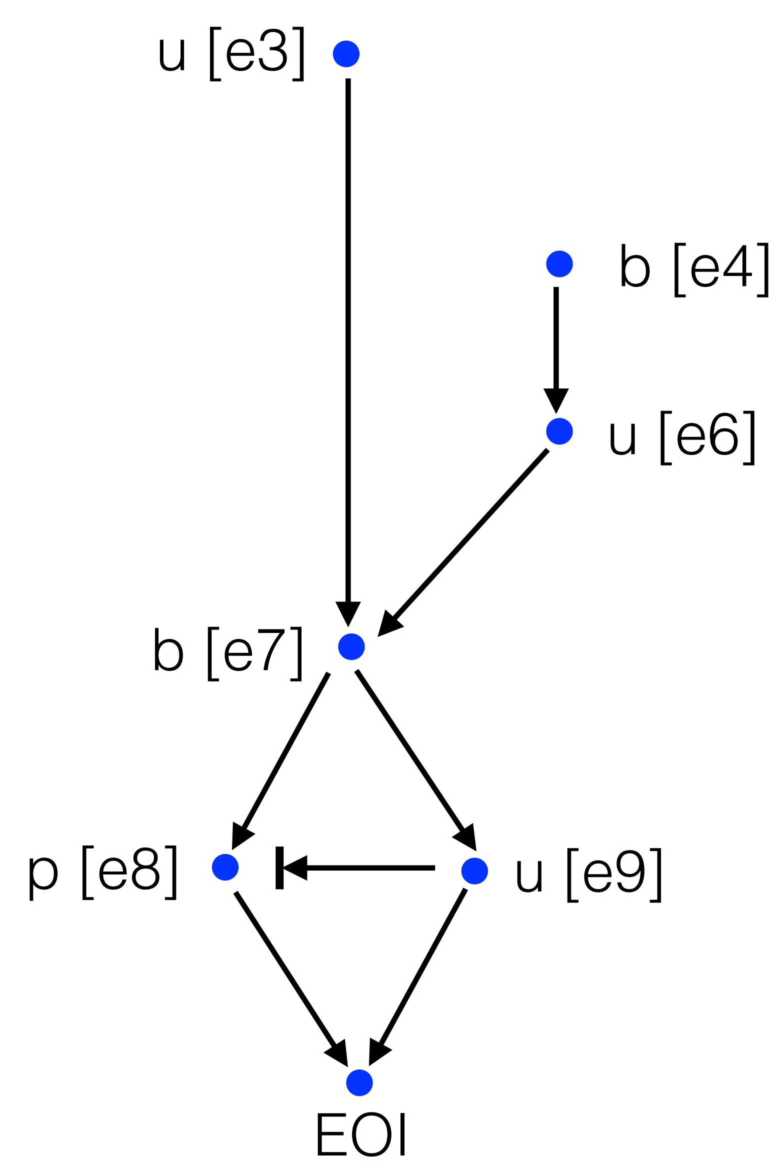
From Trace to Causal Past



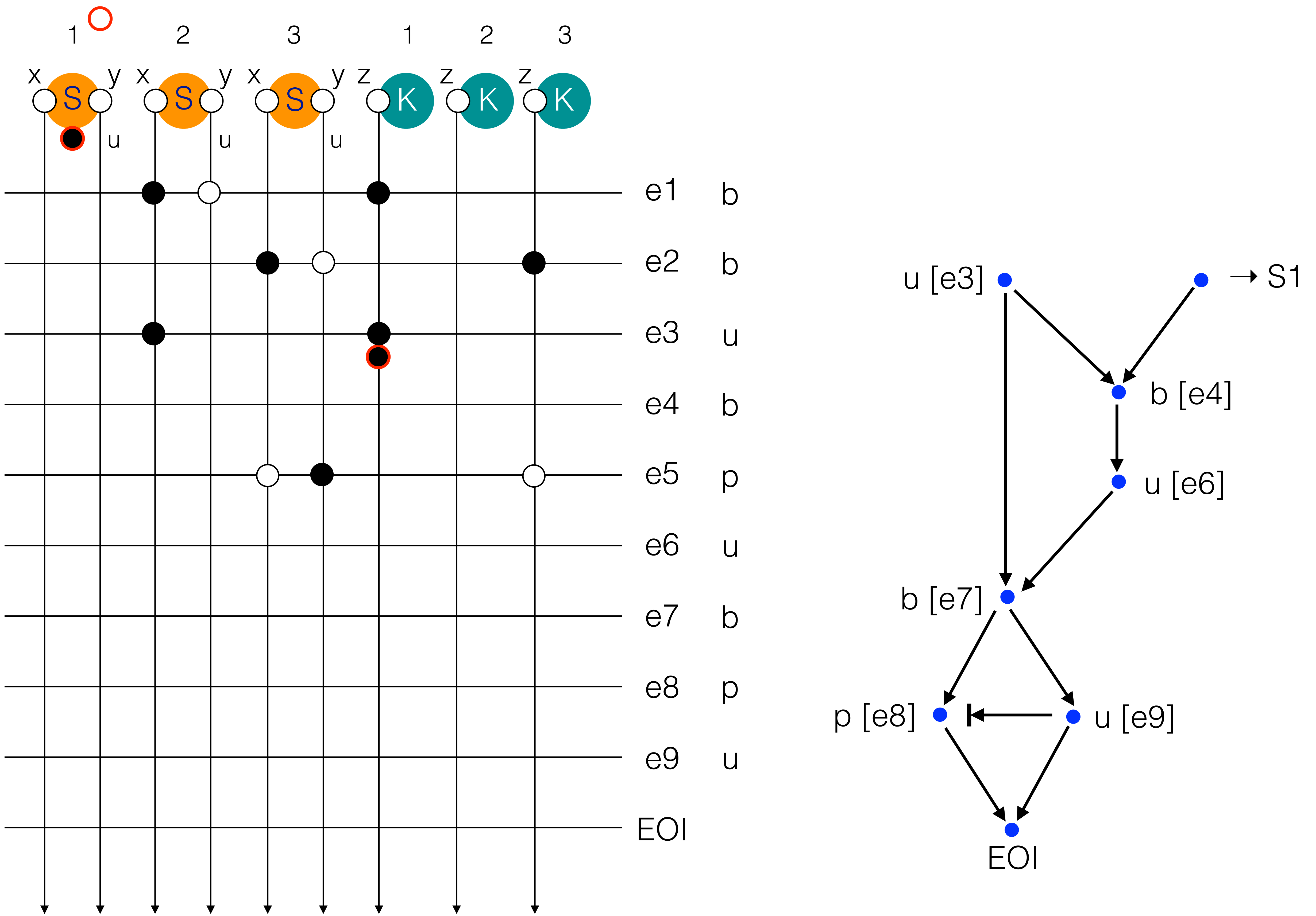


From Trace to Causal Past

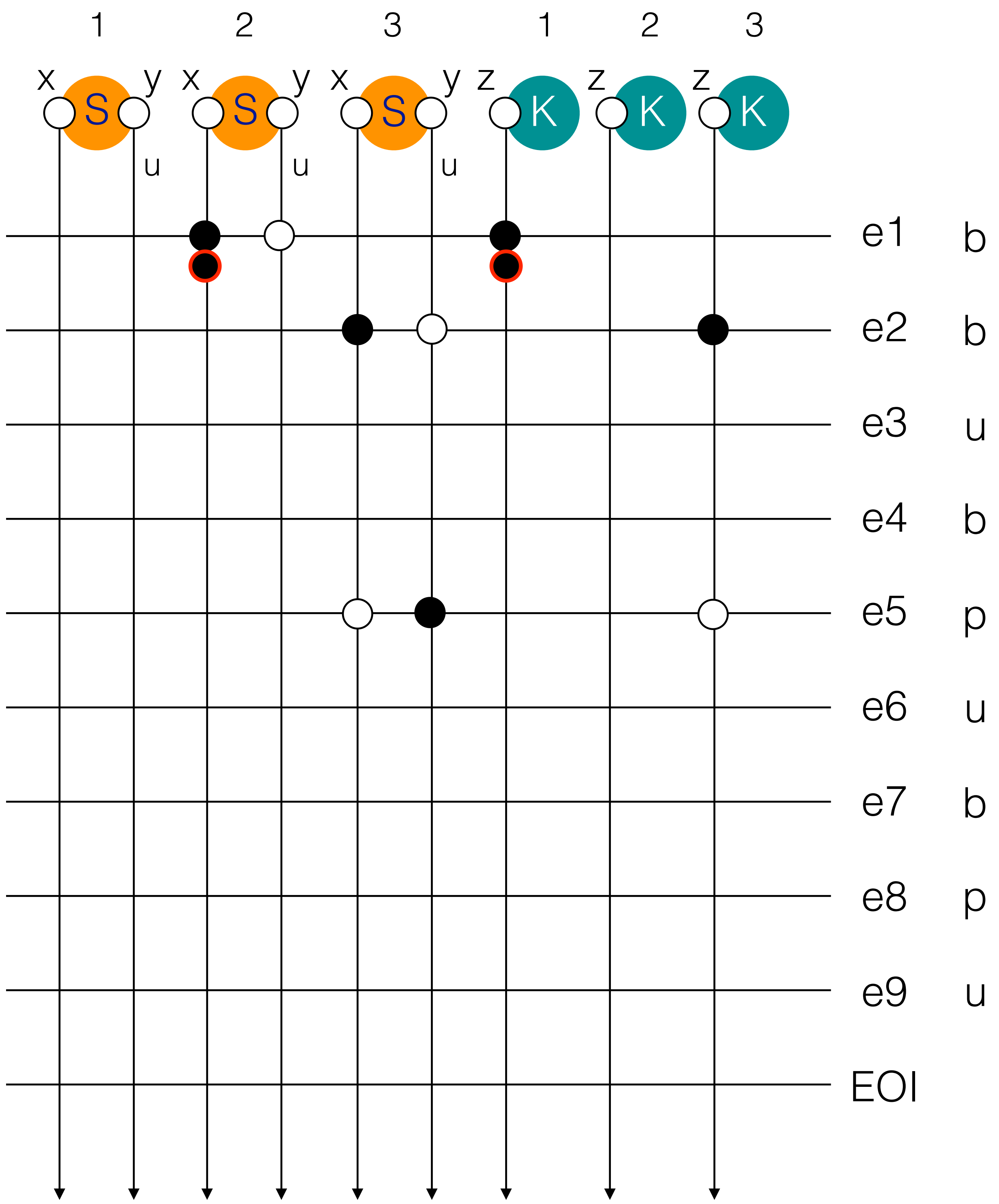


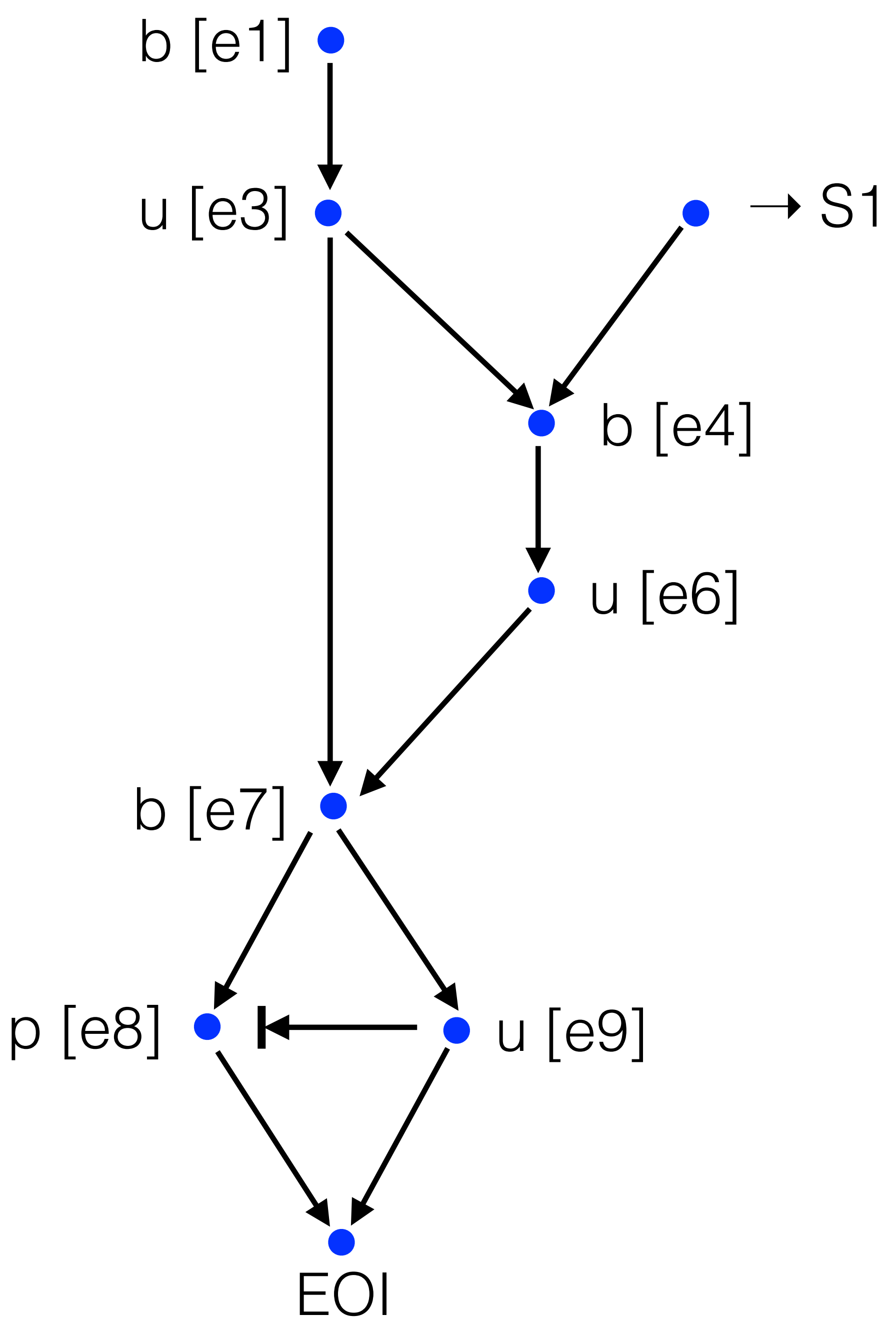


From Trace to Causal Past

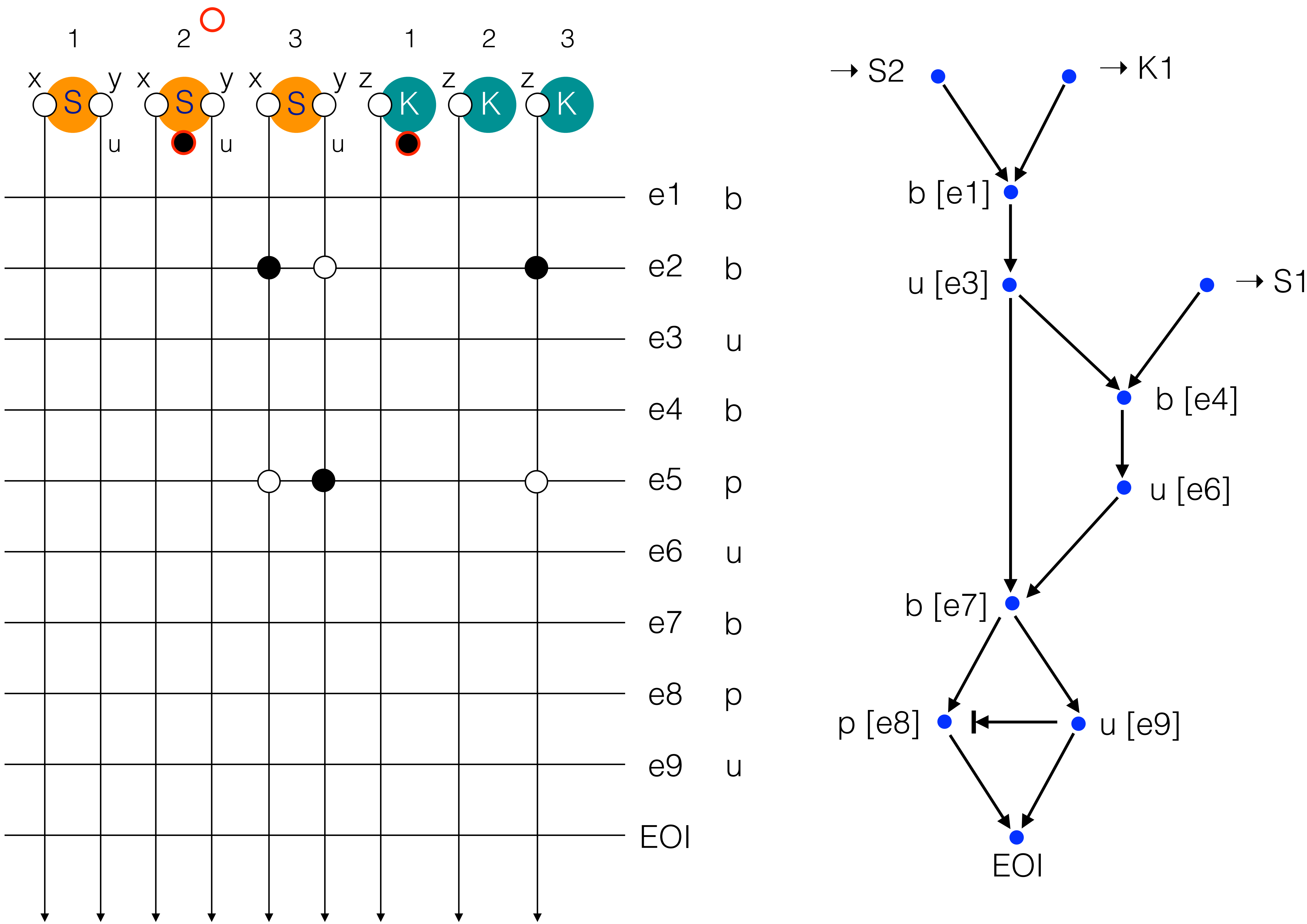


From Trace to Causal Past

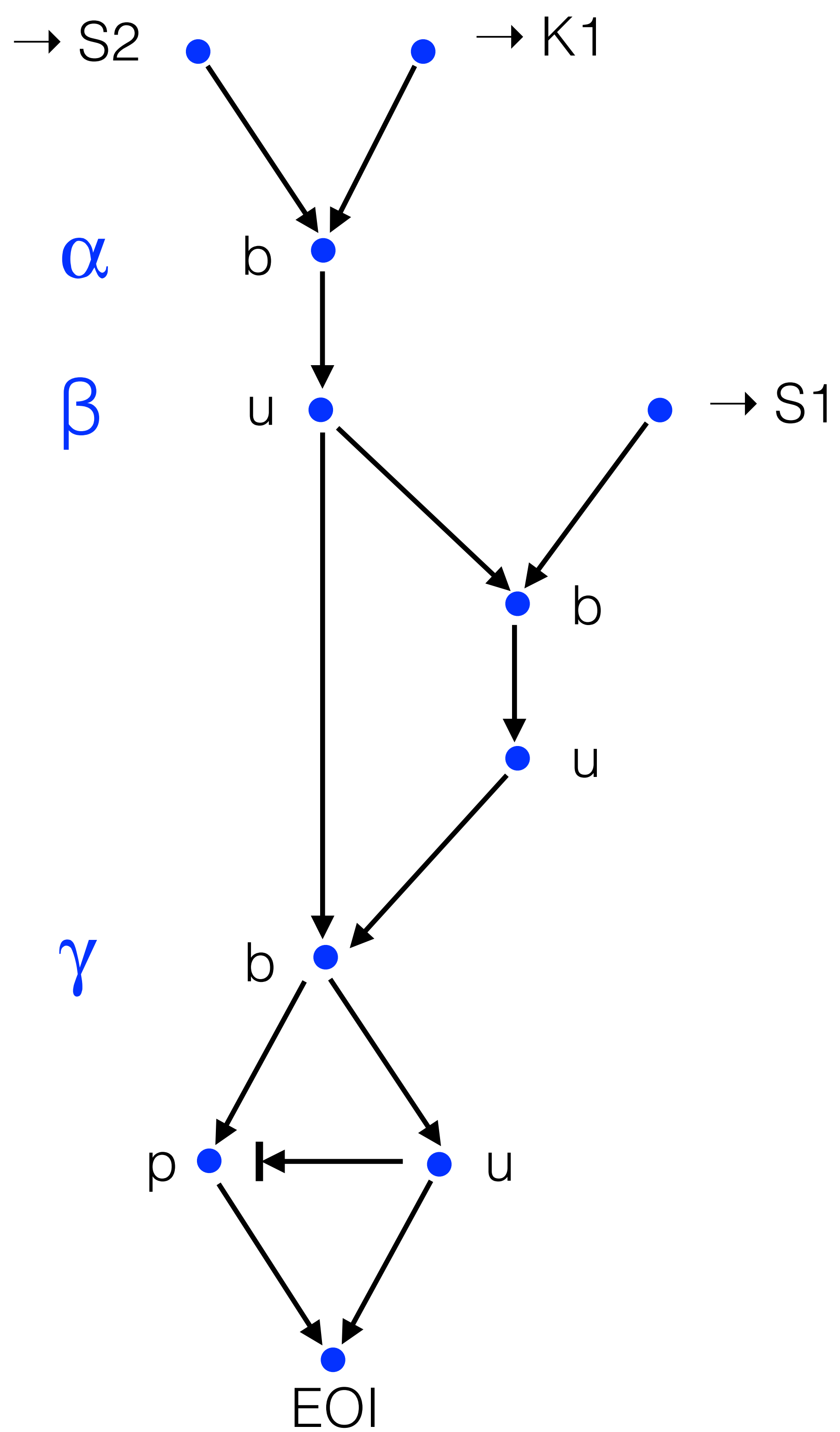




From Trace to Causal Past



The Causal Past Does not Capture Necessity

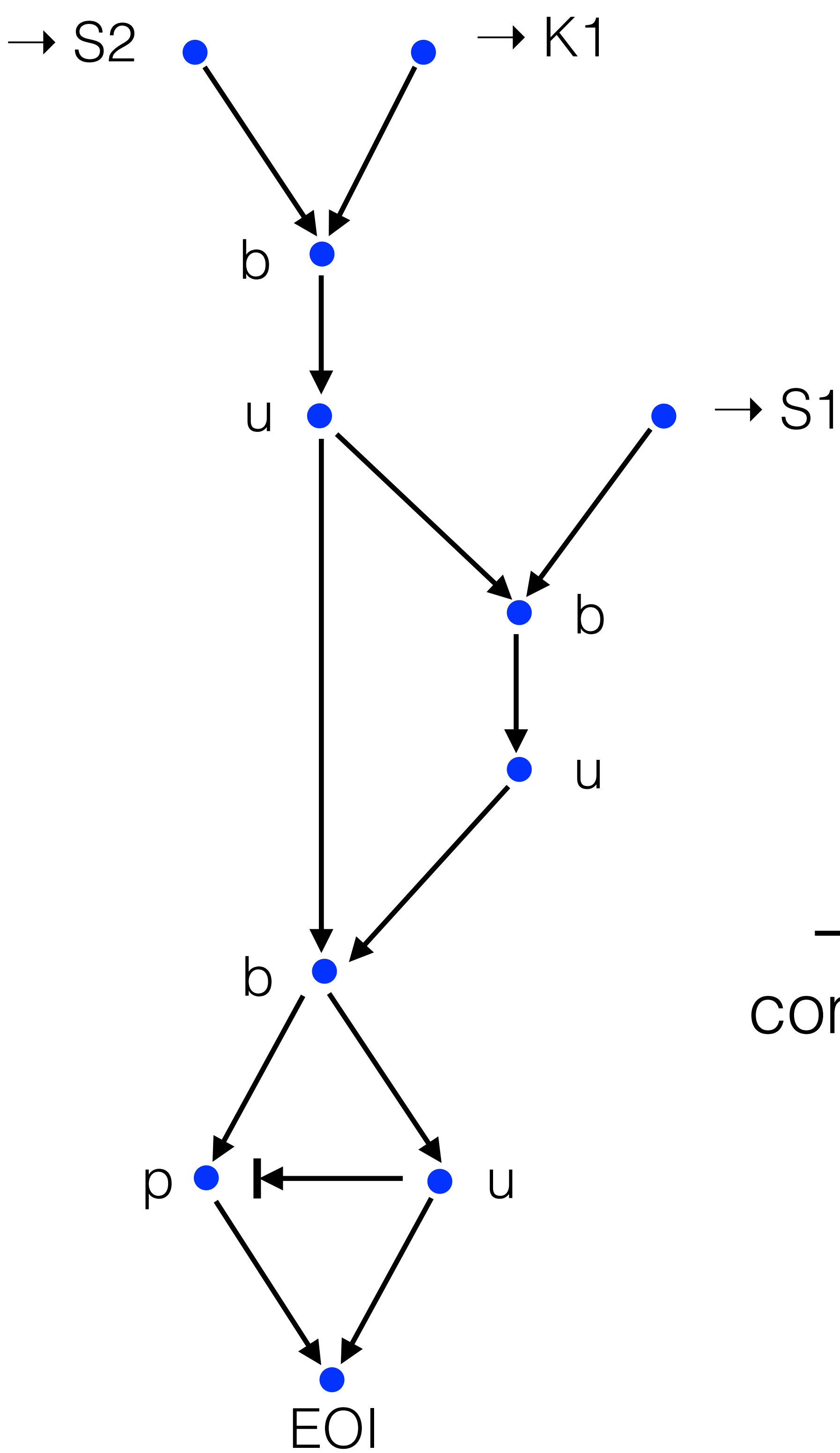


causal past

Does not capture necessity!

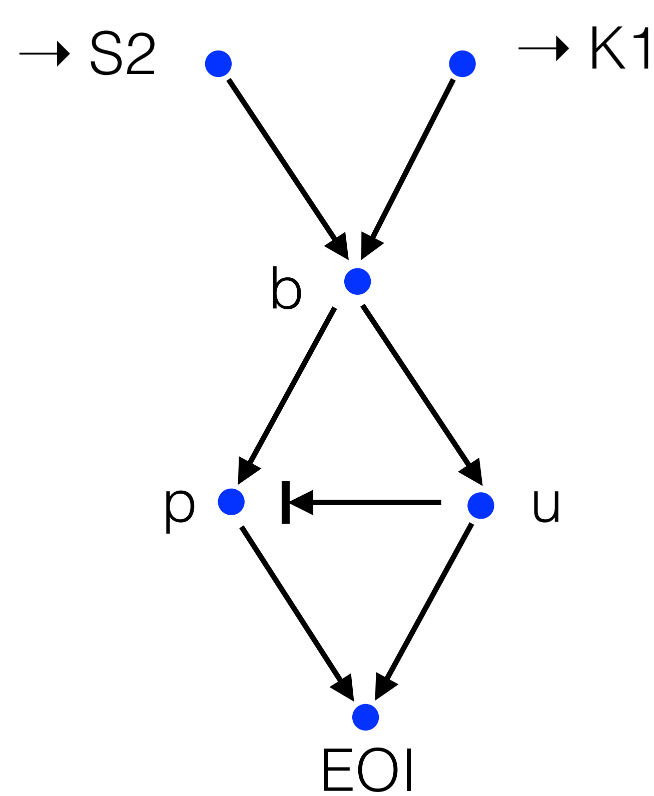
γ could have occurred before α
α then voided the conditions for γ
β reintroduced them

Minimality and the Concept of "Story"



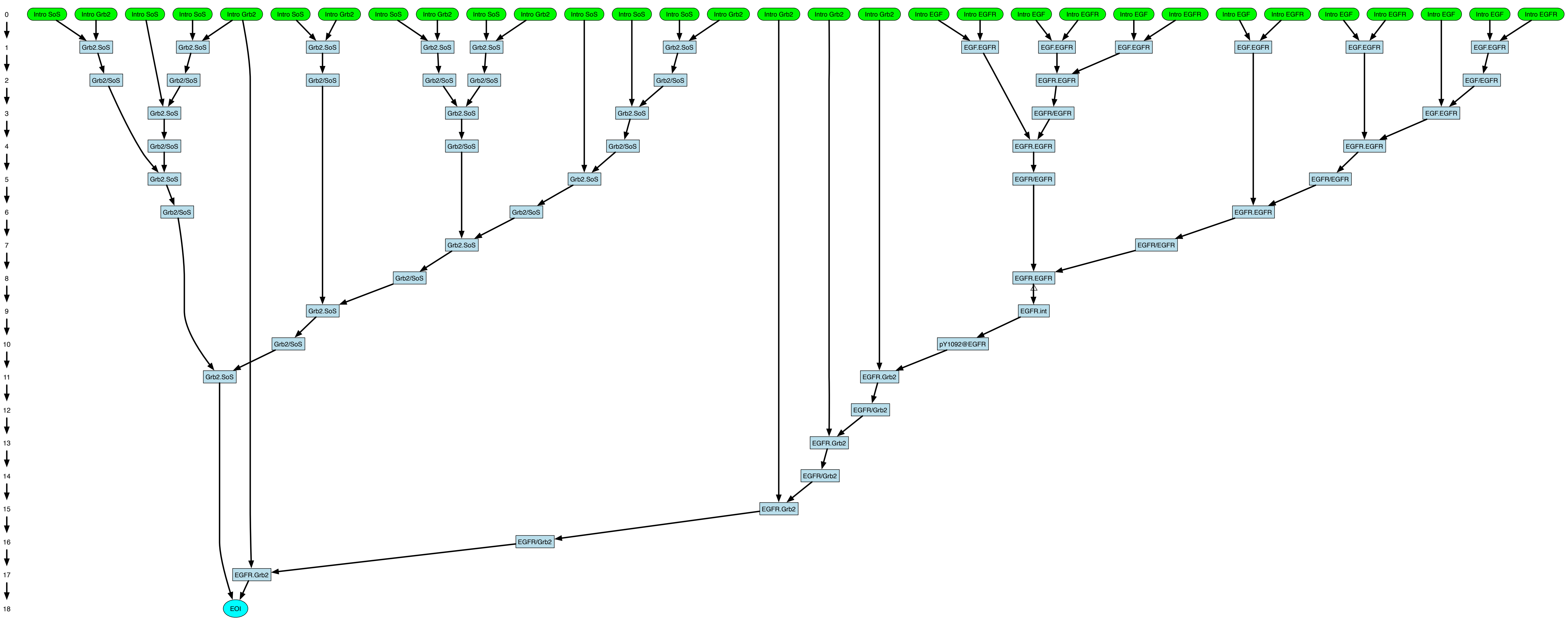
causal past

compress



"story"

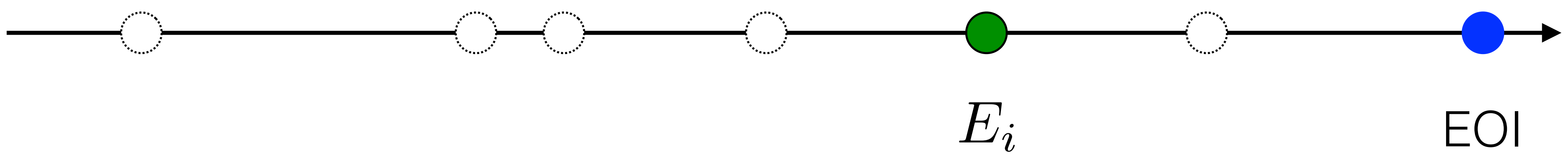
The Causal Past of Sos Recruitment



Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \text{pre}(E_i)$

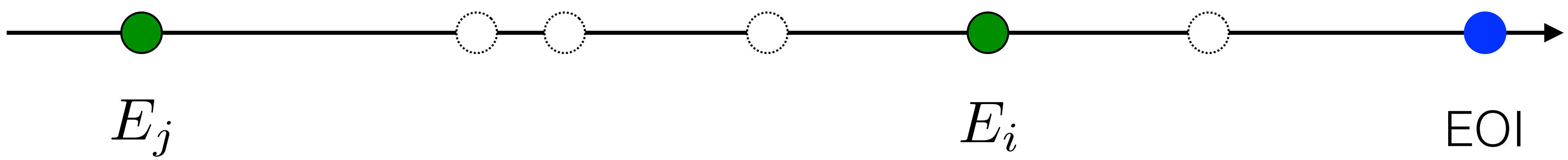


$$e_i \Rightarrow$$

Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \text{pre}(E_i)$



sets

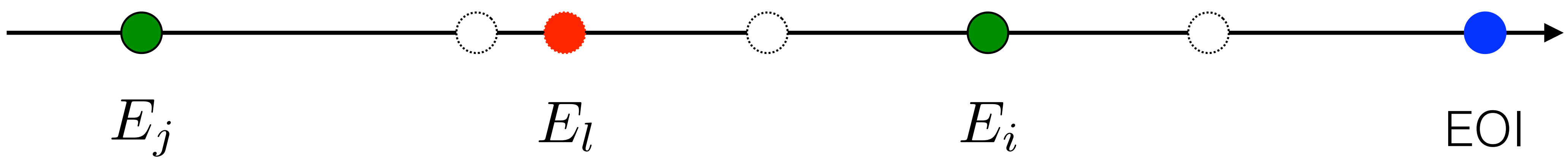
$(x, v) \in \text{pre}(e_i)$

$$e_i \Rightarrow \qquad e_j$$

Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \text{pre}(E_i)$



sets $(x, v) \in \text{pre}(e_i)$

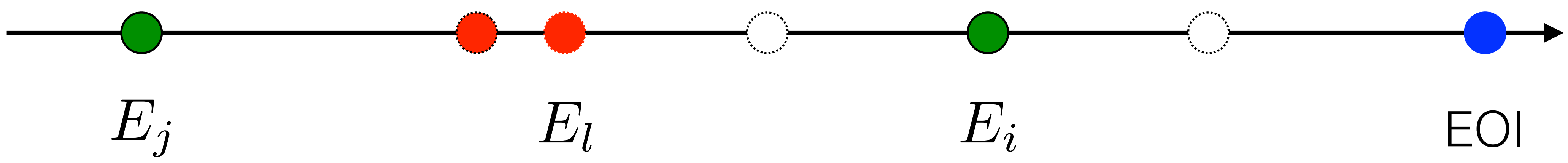
destroys $(x, v) \in \text{pre}(e_i)$

$$e_i \Rightarrow \quad e_j \wedge \neg e_l$$

Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \mathrm{pre}(E_i)$



sets $(x, v) \in \mathrm{pre}(e_i)$

destroys $(x, v) \in \mathrm{pre}(e_i)$

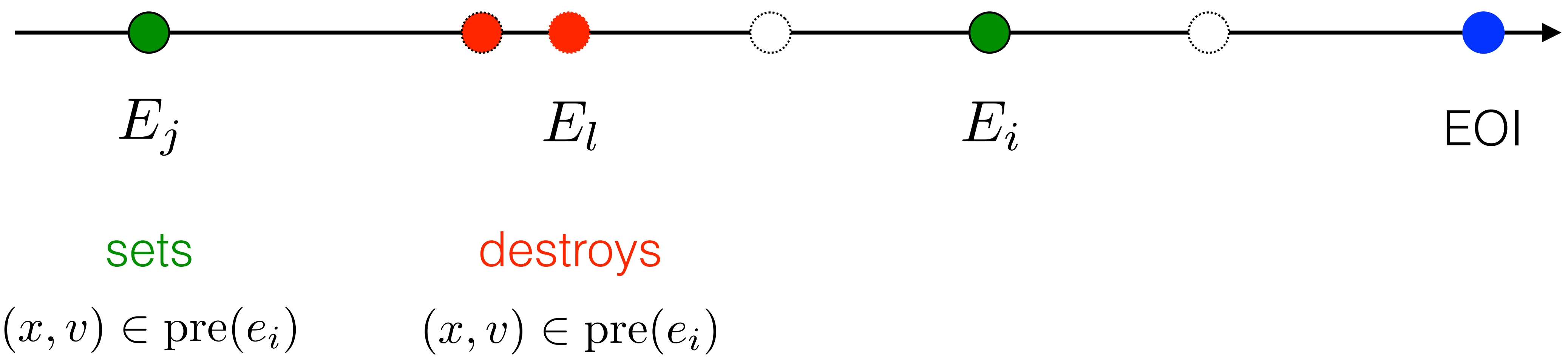
$$e_i \Rightarrow \quad e_j \wedge \left[\wedge_{l \in B_{ji}} \neg e_l\right]$$

with $B_{ji} = \{l \,|\, j < l < i \wedge (x, v') \in \mathrm{eff}(E_l) \wedge v' \neq v\}$

Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \text{pre}(E_i)$



$$C_{i,x,v} \equiv \; e_i \Rightarrow \bigvee_{j \in A_{ji}} \left(e_j \wedge \left[\bigwedge_{l \in B_{ji}} \neg e_l\right]\right)$$

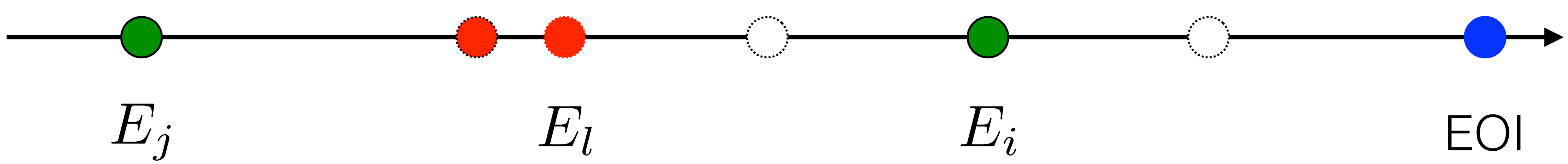
with $A_{ji} = \{j \mid j < i \wedge (x, v) \in \text{eff}(E_j)\}$

with $B_{ji} = \{l \mid j < l < i \wedge (x, v') \in \text{eff}(E_l) \wedge v' \neq v\}$

Compressing The Causal Past

"keep event E_i in the causal past" $e_i \in \{T, F\}$

value of quark x in the precondition of E_i $(x, v) \in \mathrm{pre}(E_i)$



sets $(x, v) \in \mathrm{pre}(e_i)$

destroys $(x, v) \in \mathrm{pre}(e_i)$

$$(\wedge_{i,x,v} C_{i,x,v}) \wedge e_{EOI}$$

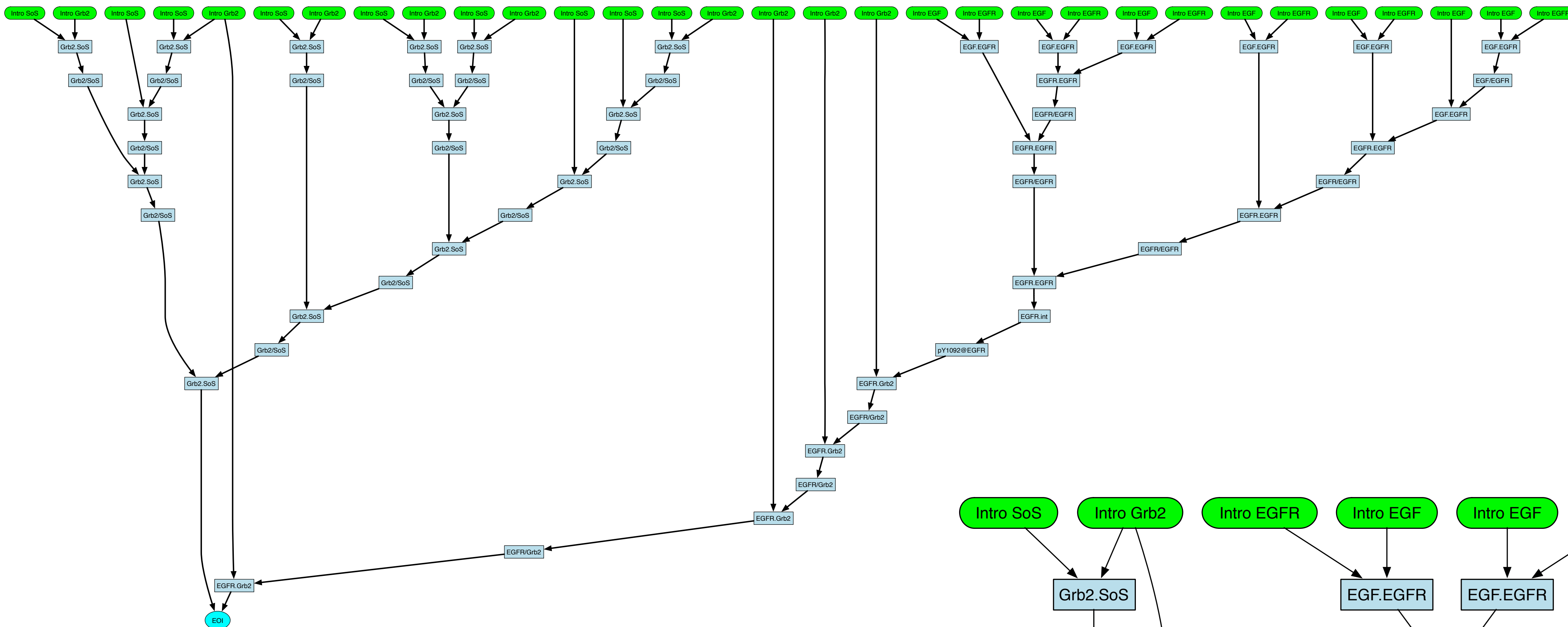
find the minimum number of truth-value assignments such that this is satisfied!

with $C_{i,x,v} \equiv \; e_i \Rightarrow \vee_{j \in A_{ji}} \left(e_j \wedge \left[\wedge_{l \in B_{ji}} \neg e_l\right]\right)$

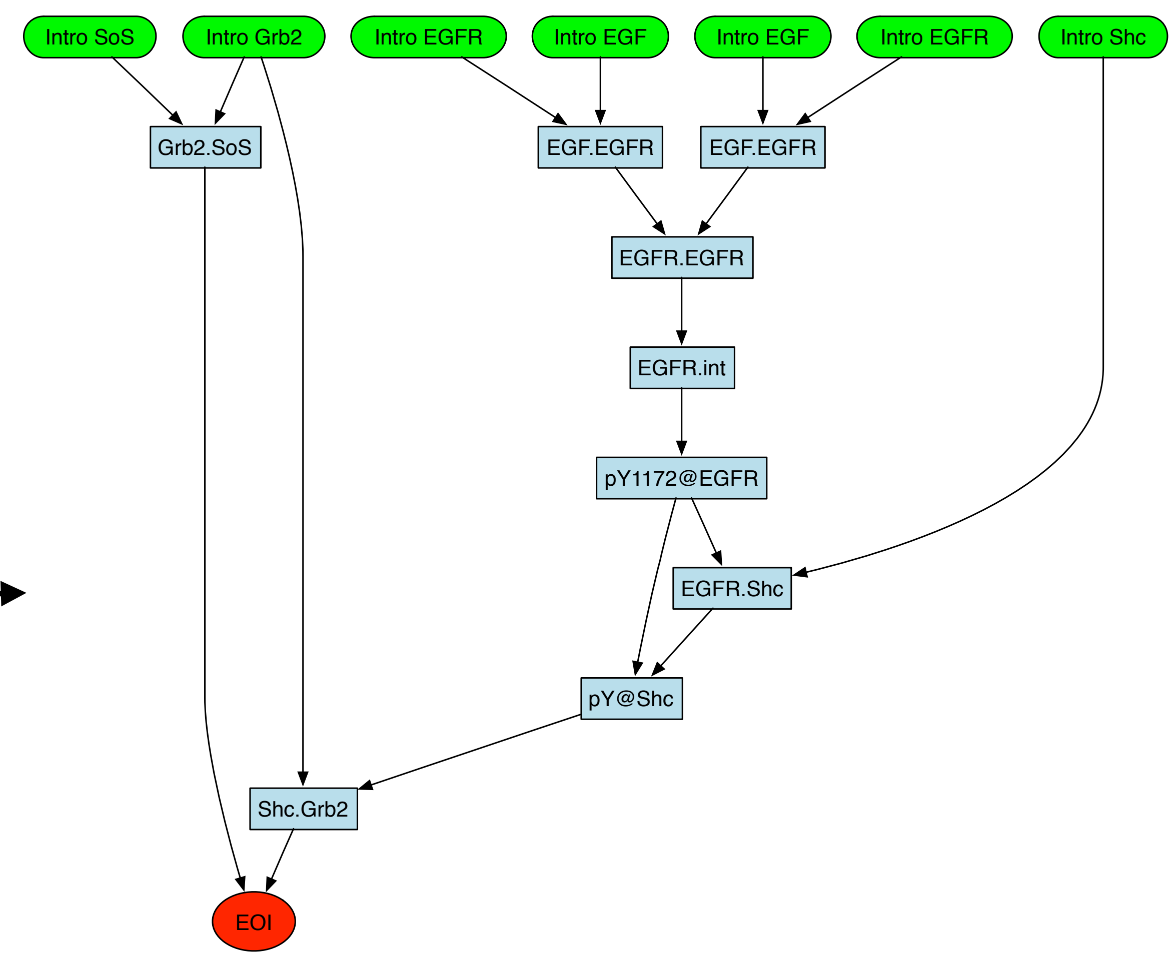
with $A_{ji} = \{j \,|\, j < i \wedge (x, v) \in \mathrm{eff}(E_j)\}$

with $B_{ji} = \{l \,|\, j < l < i \wedge (x, v') \in \mathrm{eff}(E_l) \wedge v' \neq v\}$

Sos Recruitment Compressed

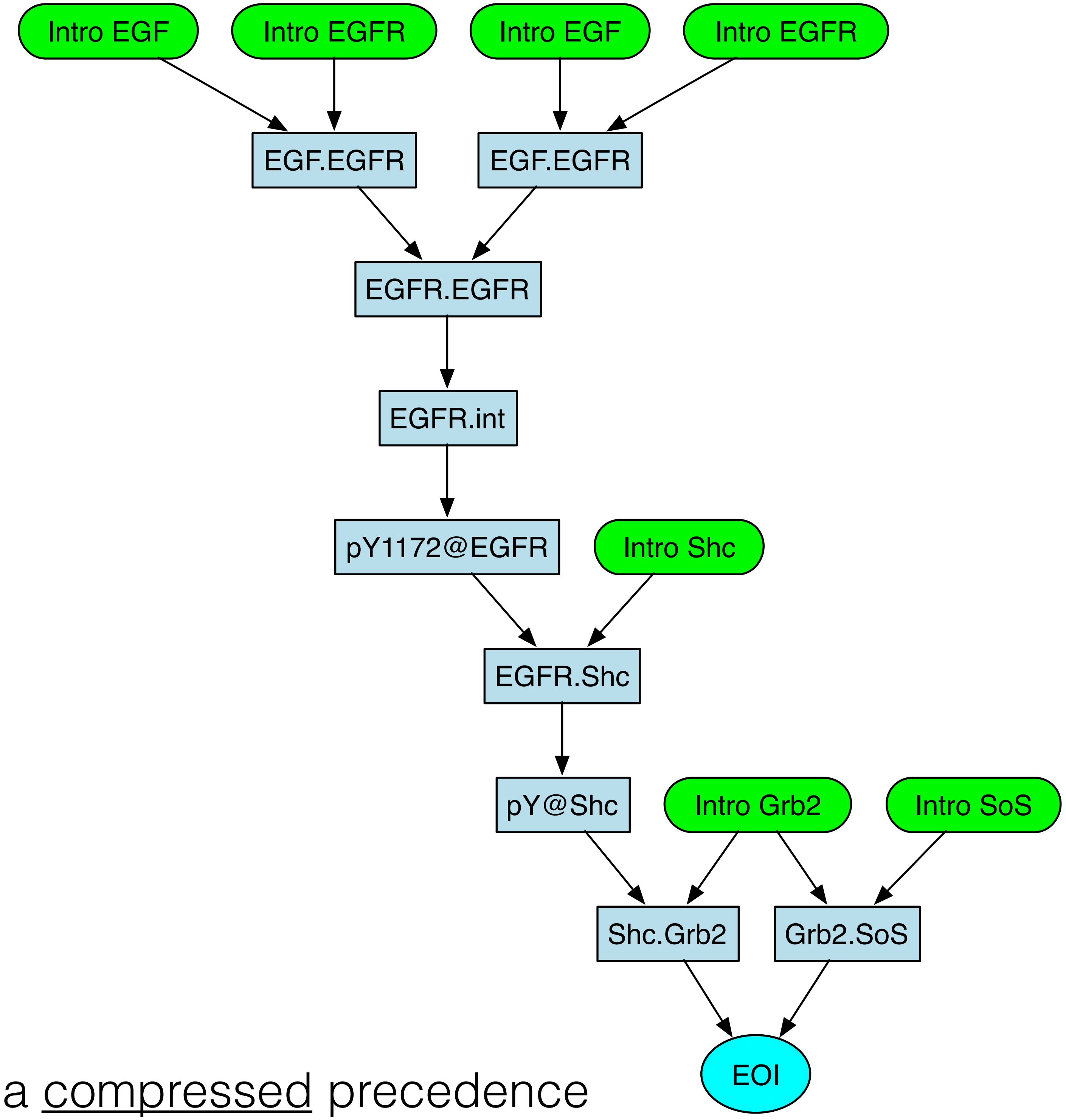


compression
with SAT solver



A Formal Pathway

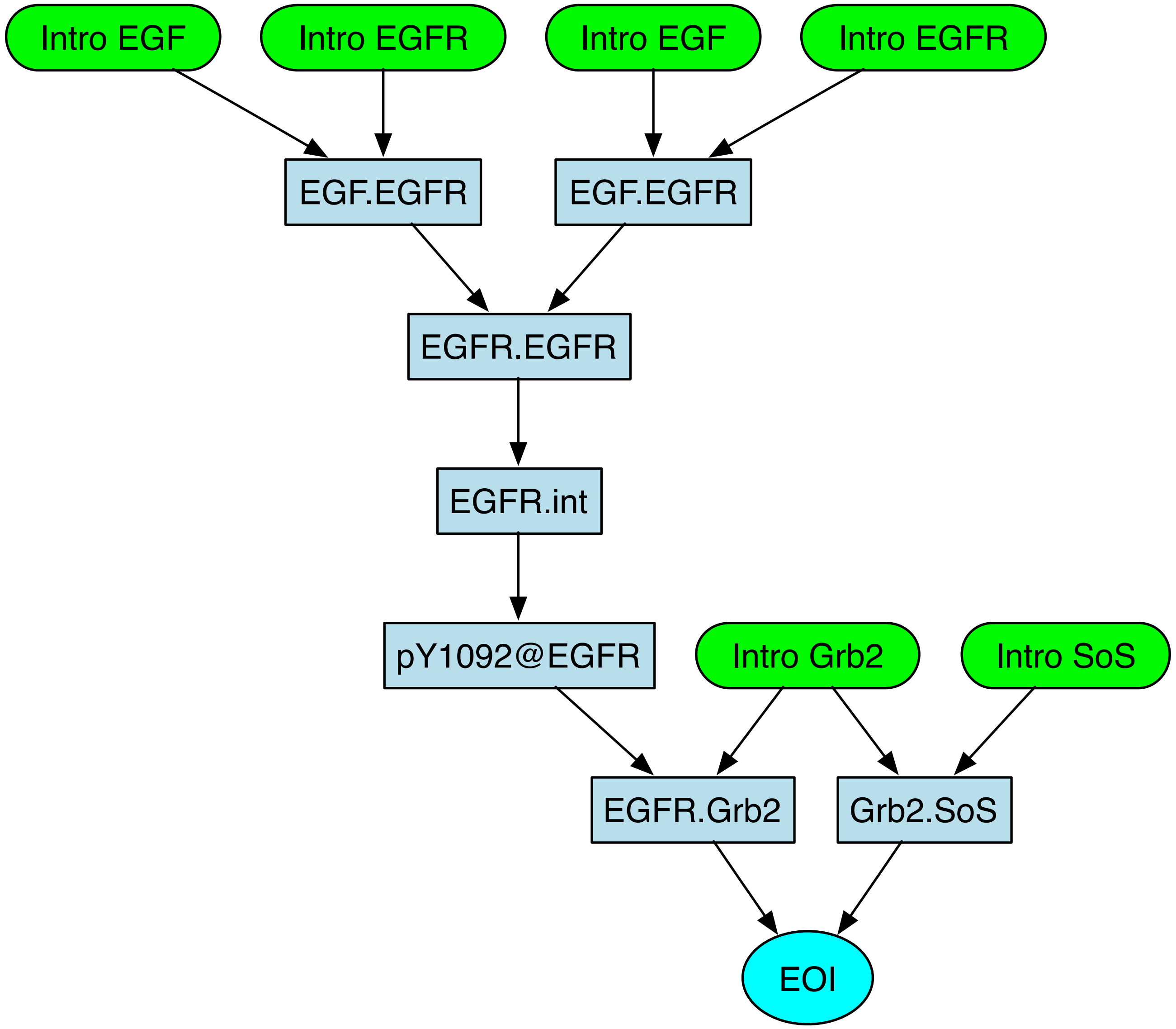
story 1



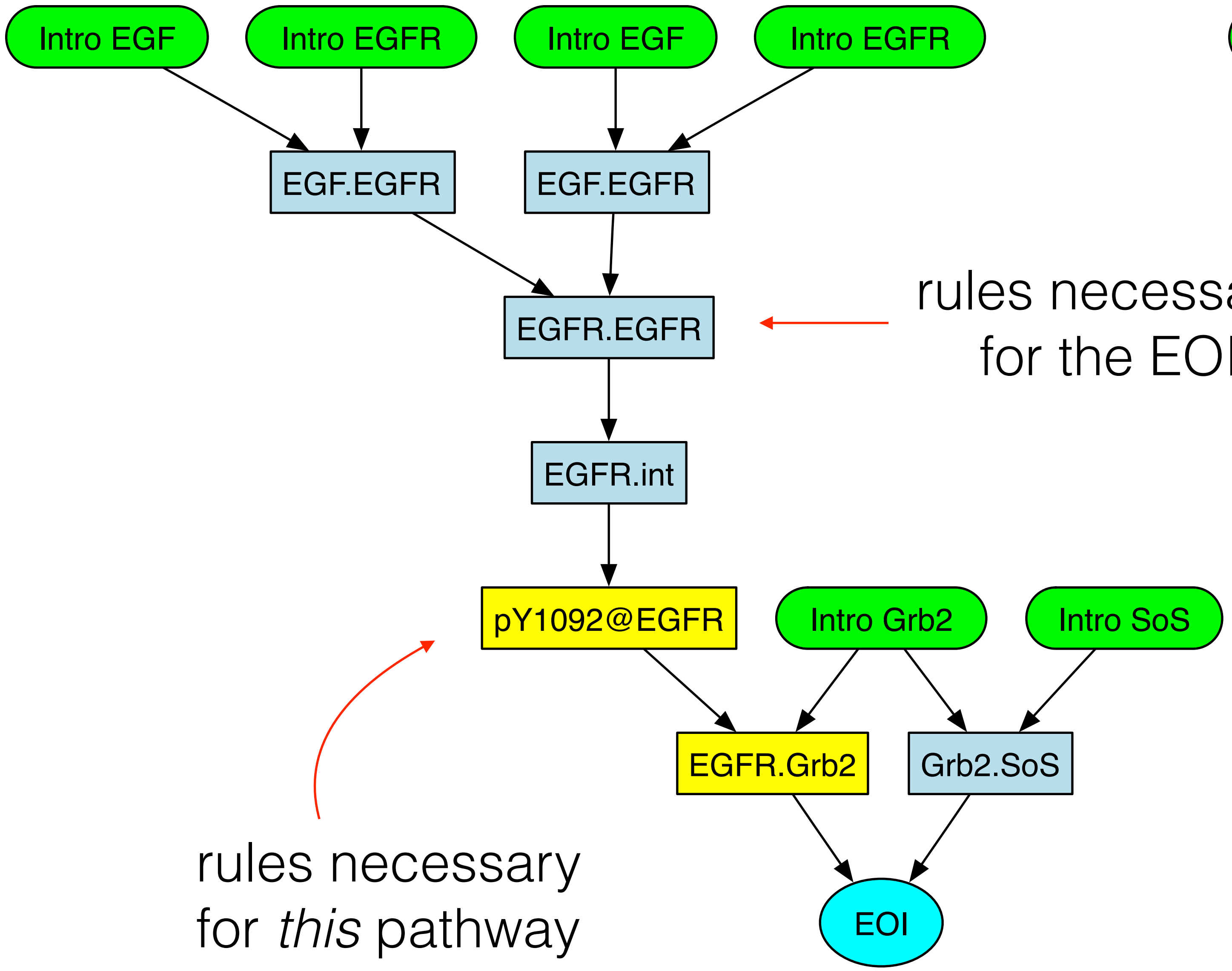
A formal pathway is a <u>compressed</u> precedence relation among events that were <u>necessary</u> to obtain <u>an instance of</u> the EOI

Another Formal Pathway

story 2

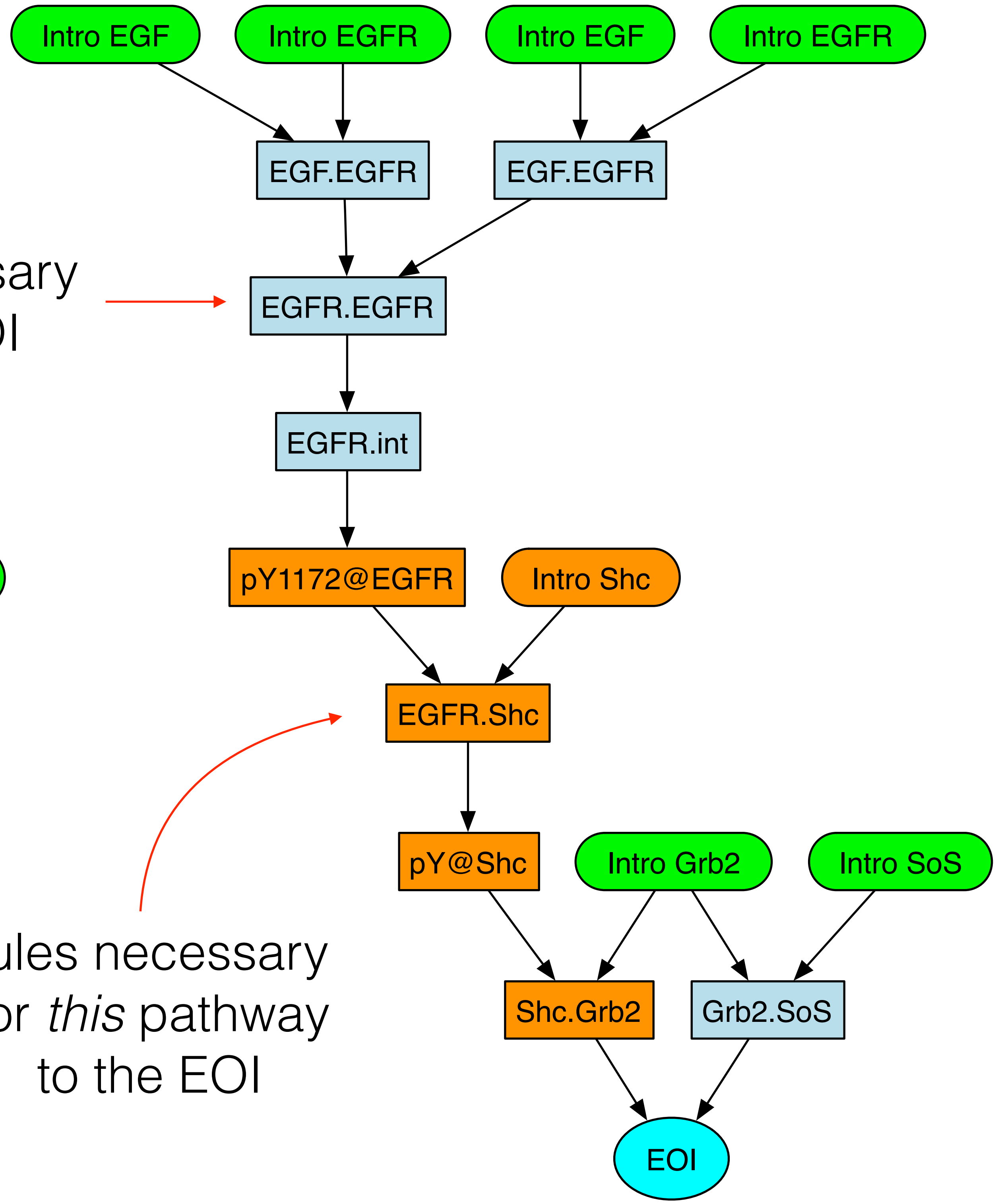


"INUS Causality" (Mackie)



rules necessary
for the EOI

rules necessary
for *this* pathway
to the EOI

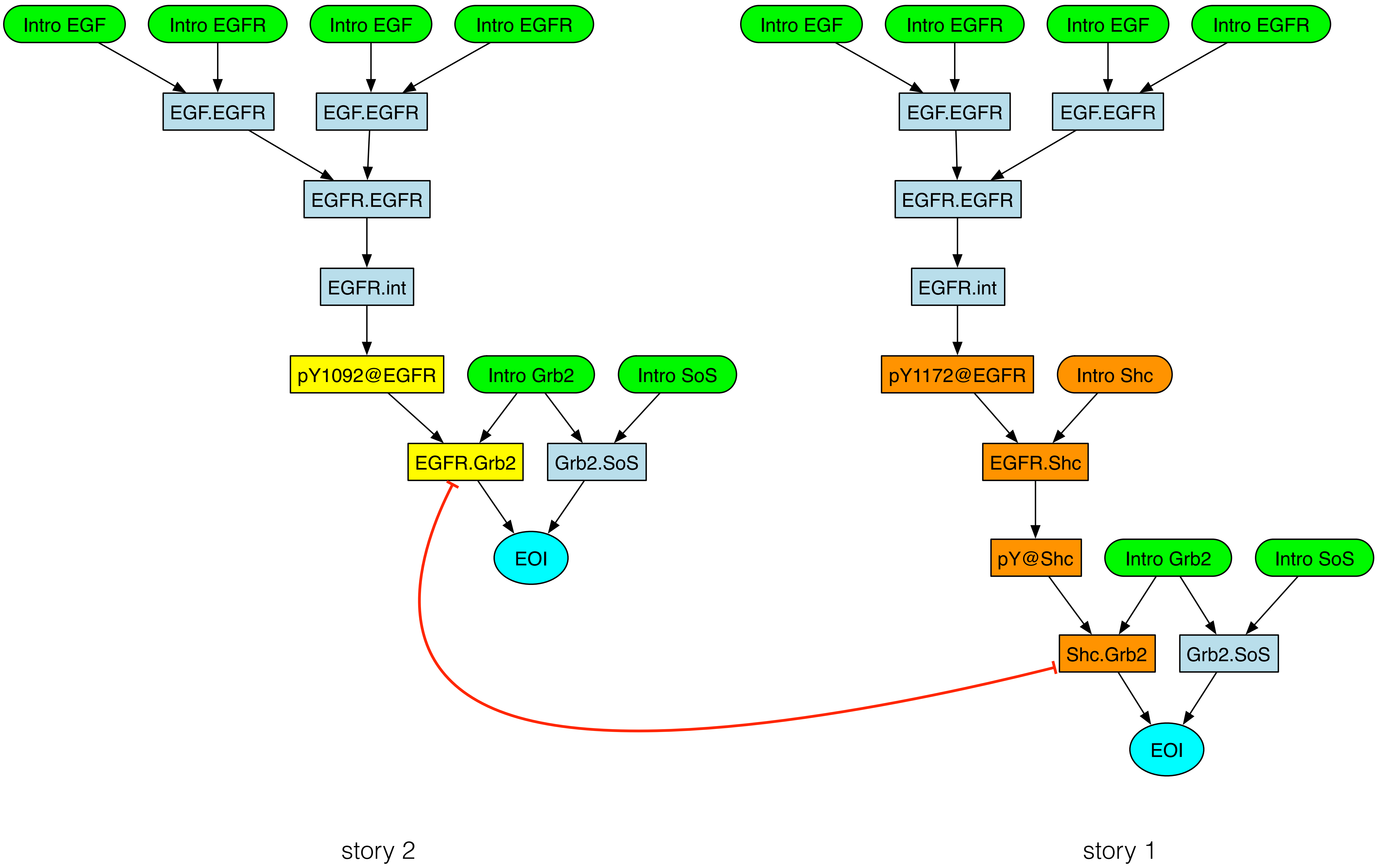


rules necessary
for *this* pathway
to the EOI

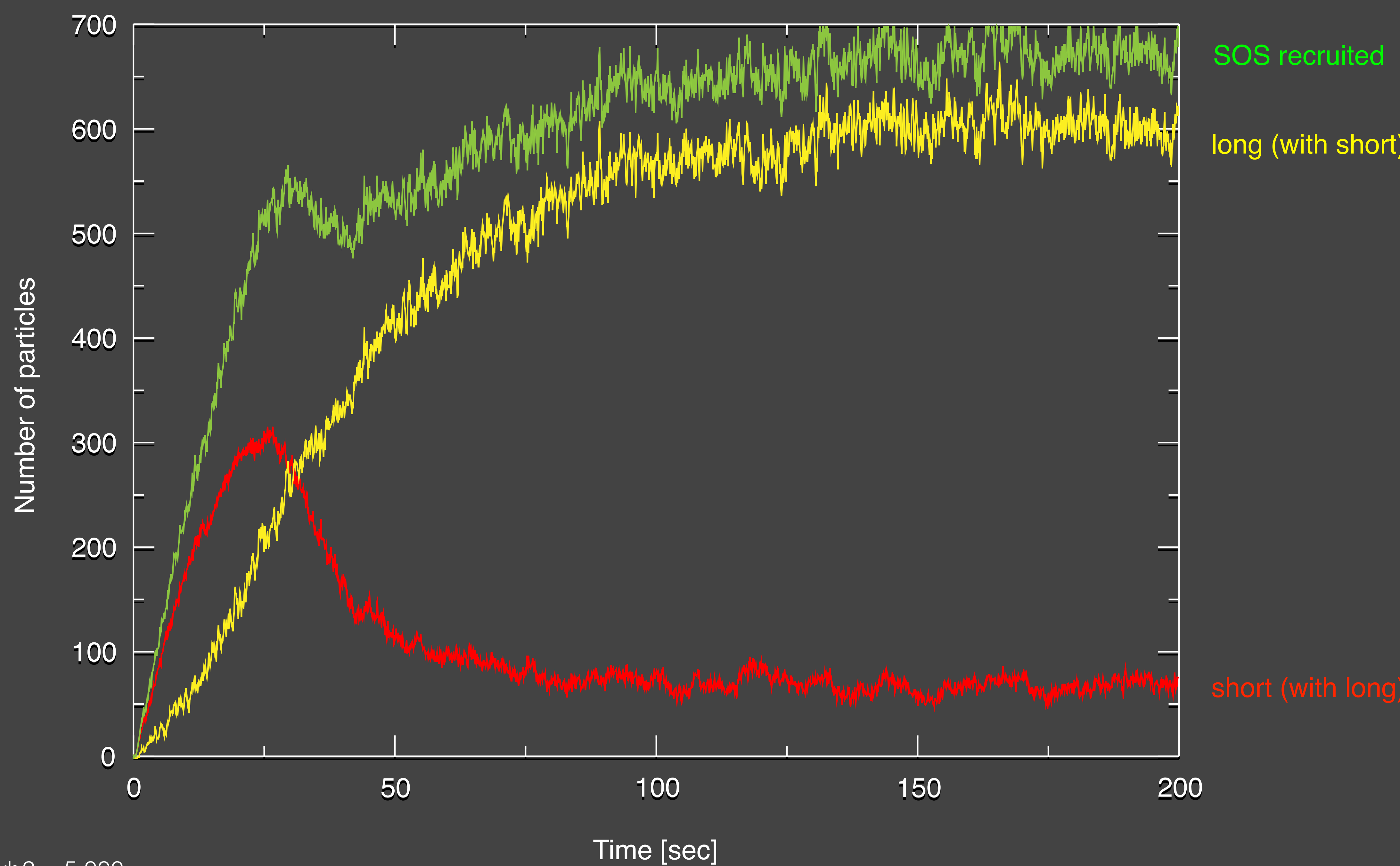
story 2

story 1

Story Interaction



Sos Recruitment Dynamics Revisted



EGF, EGFR, Grb2 = 5,000
Sos = 10,000
Shc = 8,000
total agents = 33,000

volume = 2 10^{-14} l
Kd = 10 nM (= 2,400 molecules)