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)

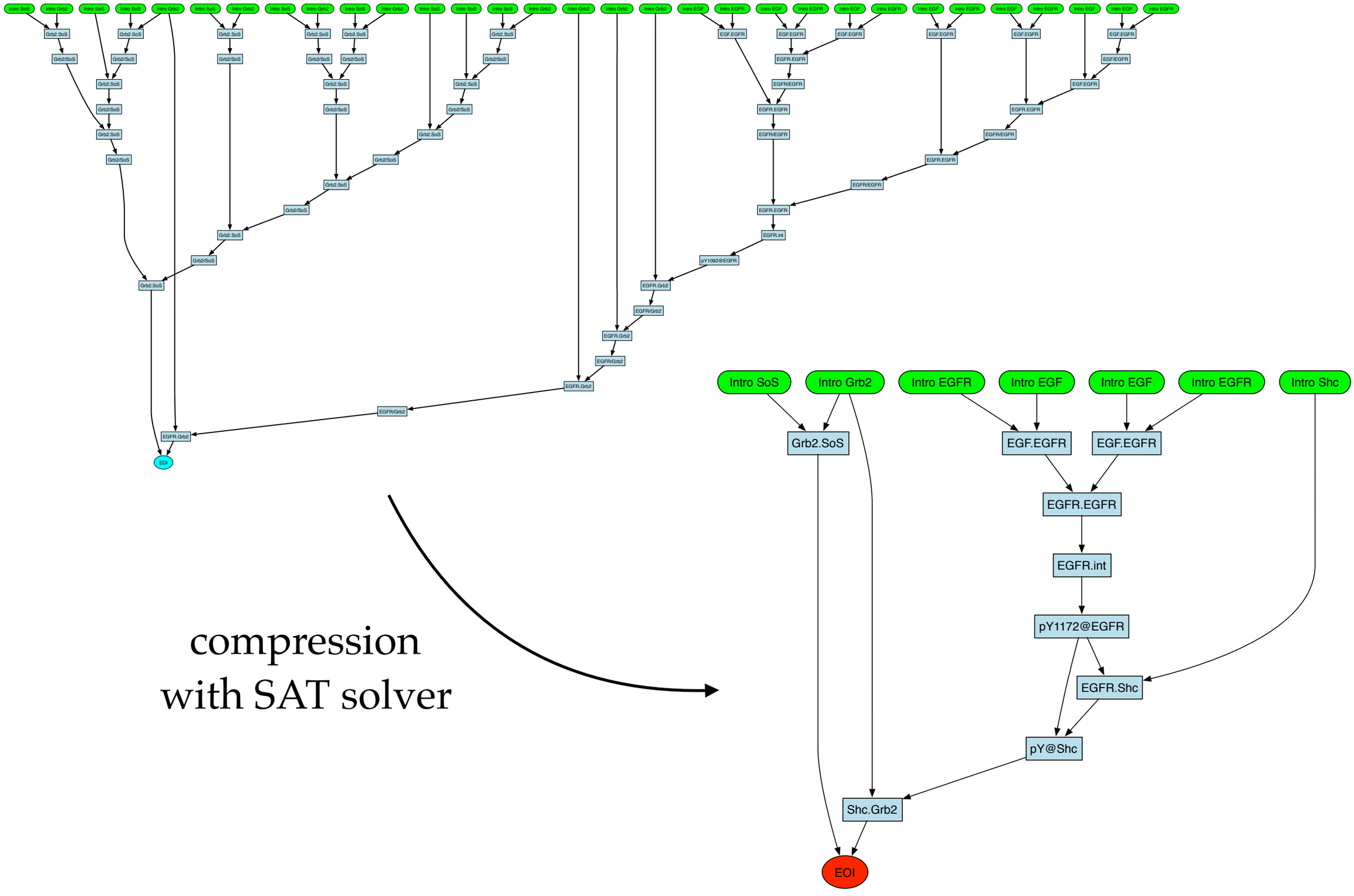
5. Examples of rule-based models
   (Modélisation basé sur les règles; examples)

6. Causality in rule-based dynamics
   (Causalité)

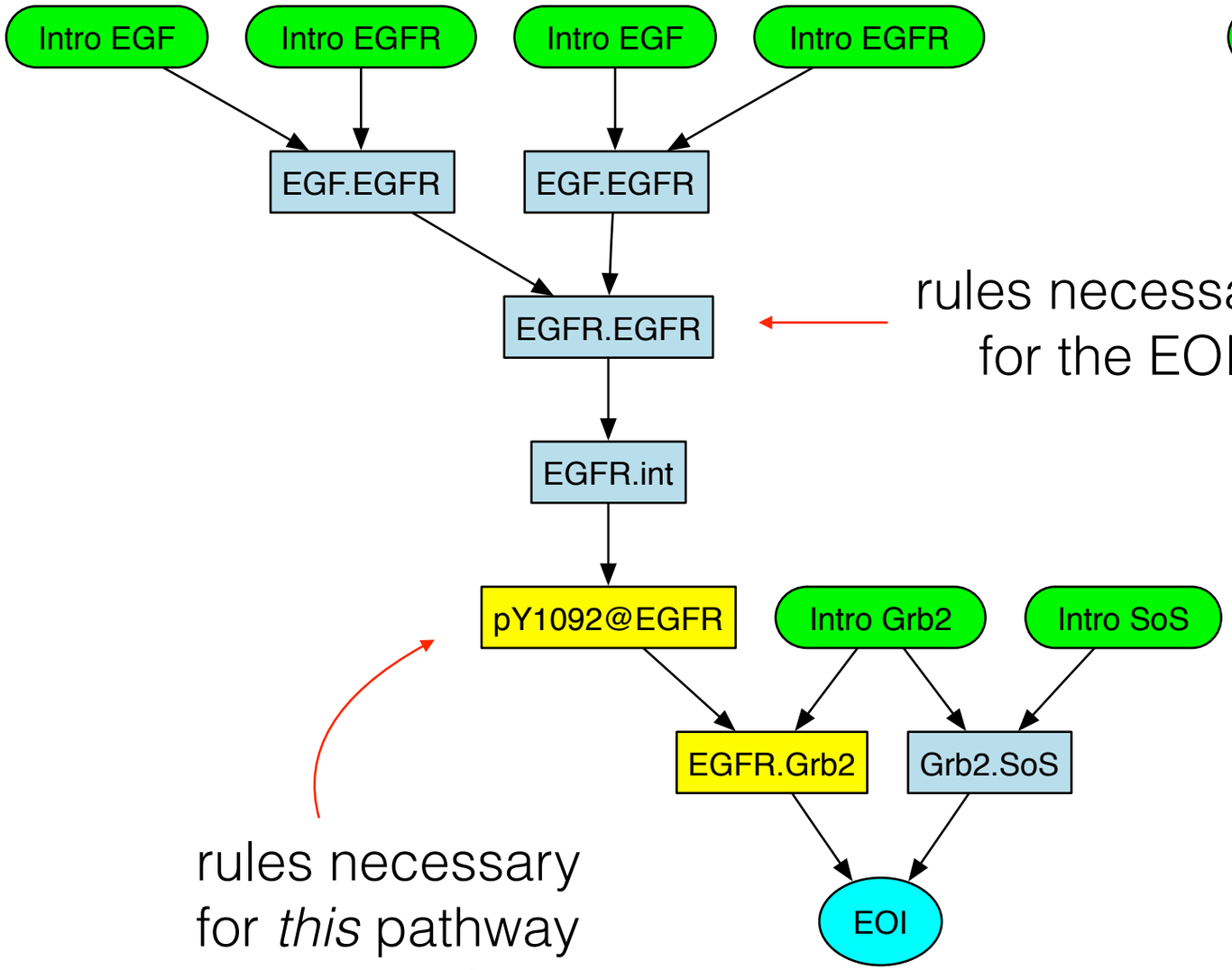
7. Combinatorial scaffolding
   (Echafaudage combinatoire)

8. Cellular learning?
   (Apprentissage cellulaire?)

Sos Recruitment Compressed

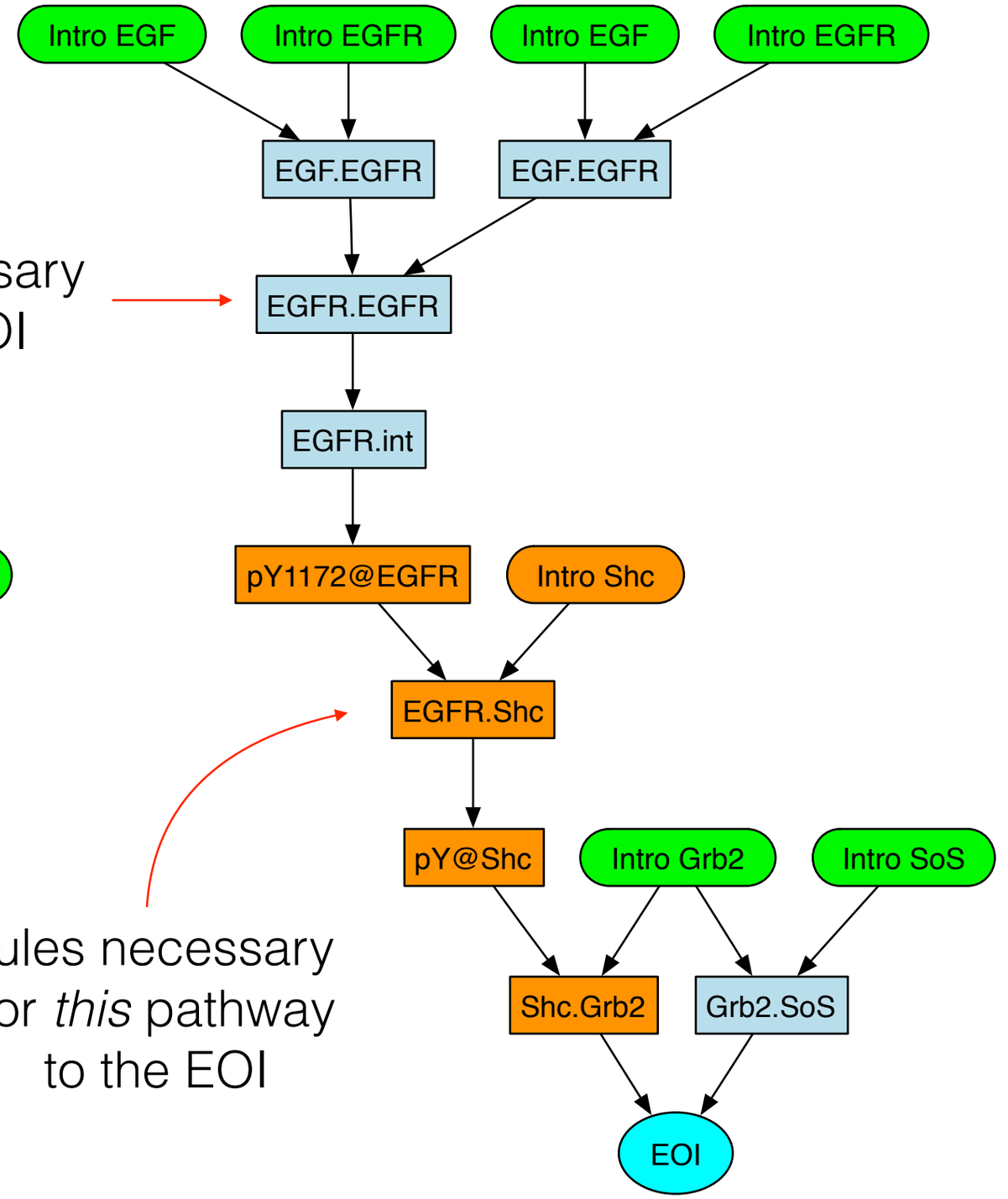


"INUS Causality" (Mackie)



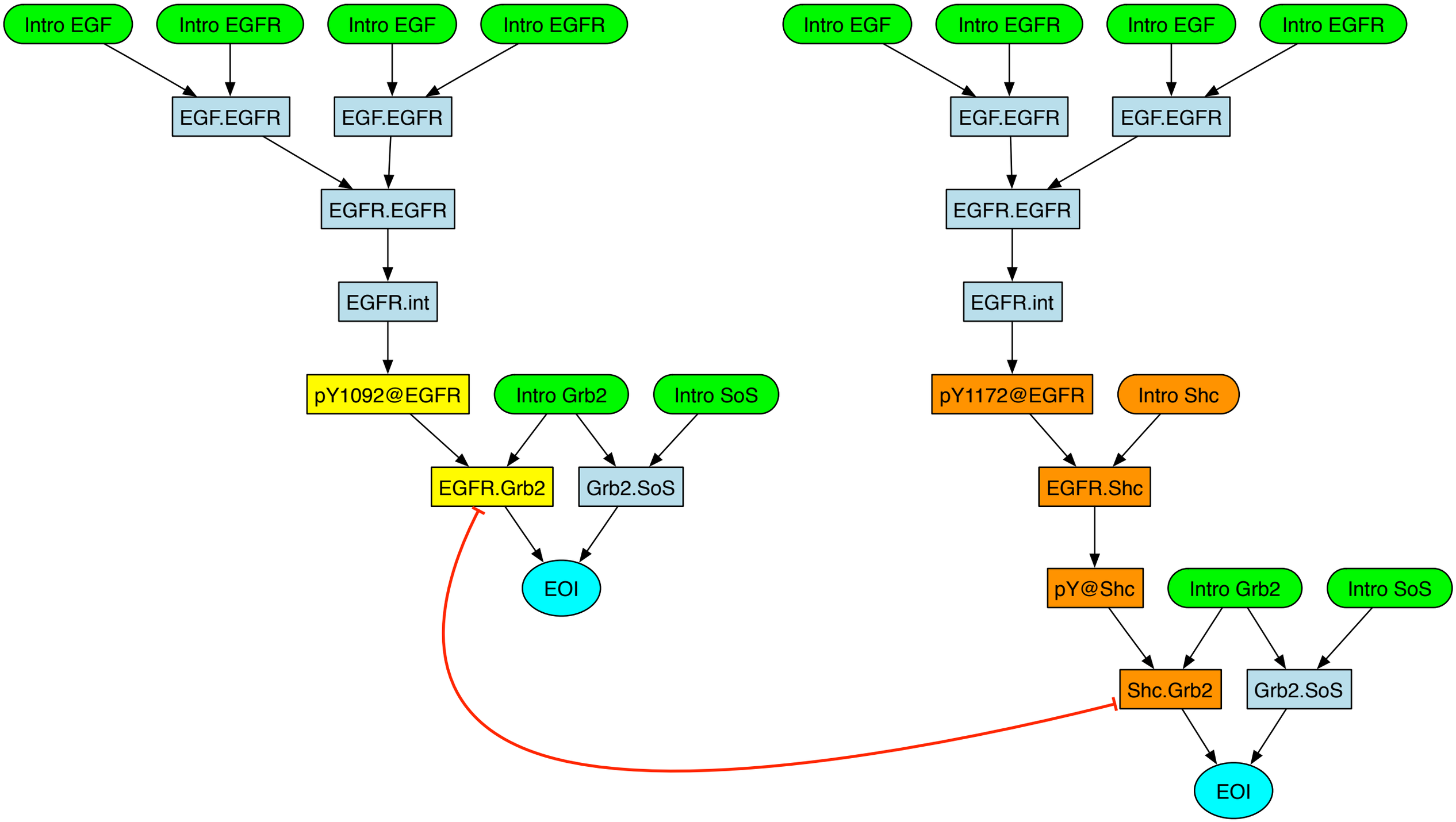
story 2

rules necessary for the EOI



story 1

Story Interaction



story 2

story 1

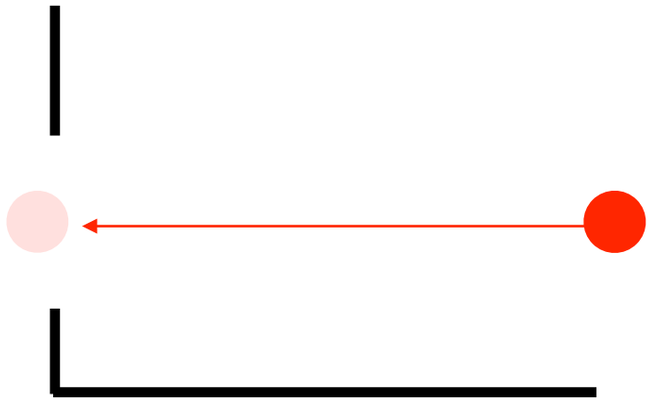
Seeking Explanations

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

via **Jonathan Laurent** @ CMU !

Note: some slides in the next segment rely heavily on animation, which is absent from this pdf. They might be thus hard to decipher…

Counterfactuals

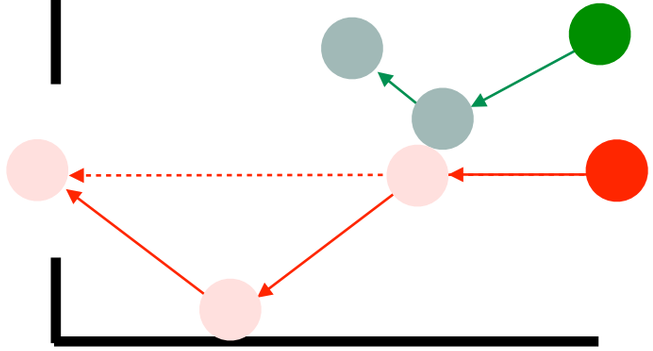


Had the green ball not hit the red ball,
would the red ball have entered goal?

Yes.

Does the green ball cause the red ball to enter goal?

No.



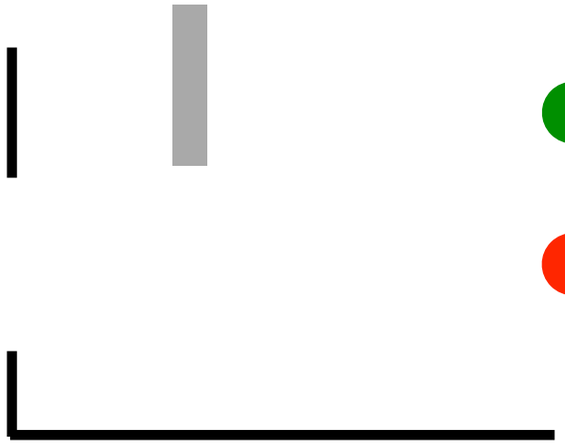
Had the green ball not hit the red ball,
would the red ball have entered goal?

No.

Does the green ball cause the red ball to enter goal?

Yes.

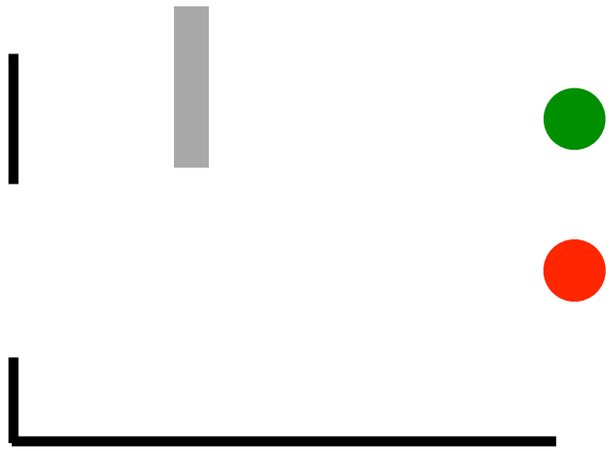
A "Biological" Scenario: Inhibition of an Inhibition



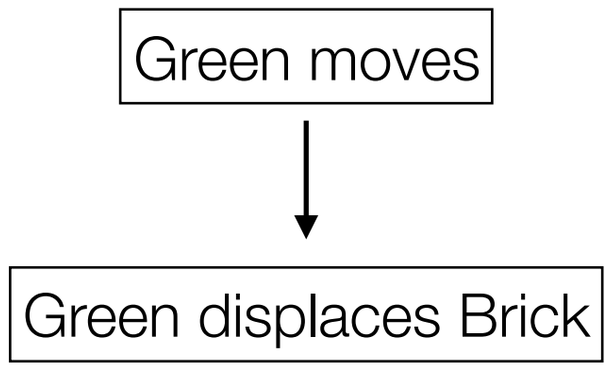
Brick blocks goal a fraction of the time.

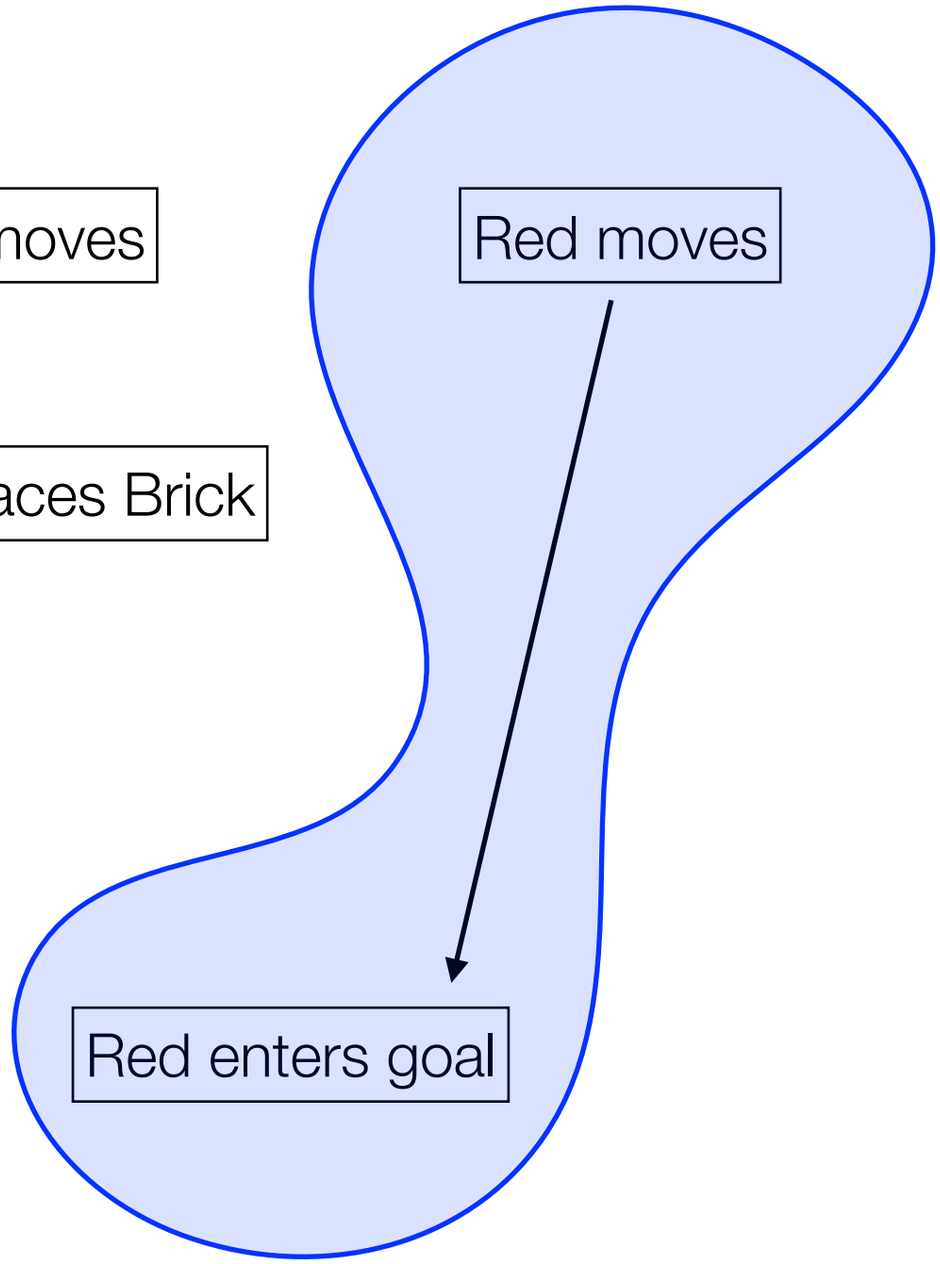
Sometimes Red avoids it and reaches goal.

Standard Analysis of The Factual History



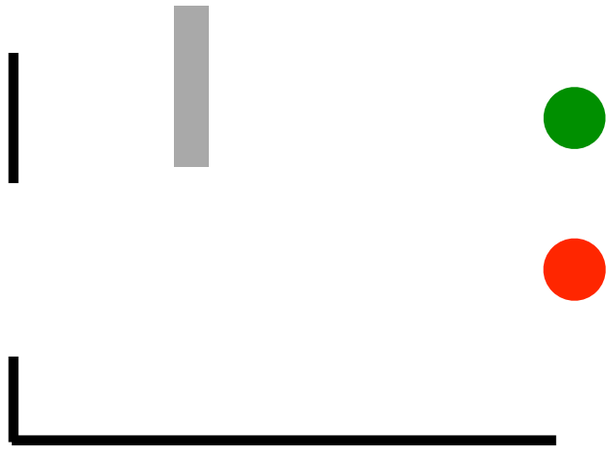
The factual history “F”





The Story

Standard Analysis of The Counterfactual History



The factual history “F”

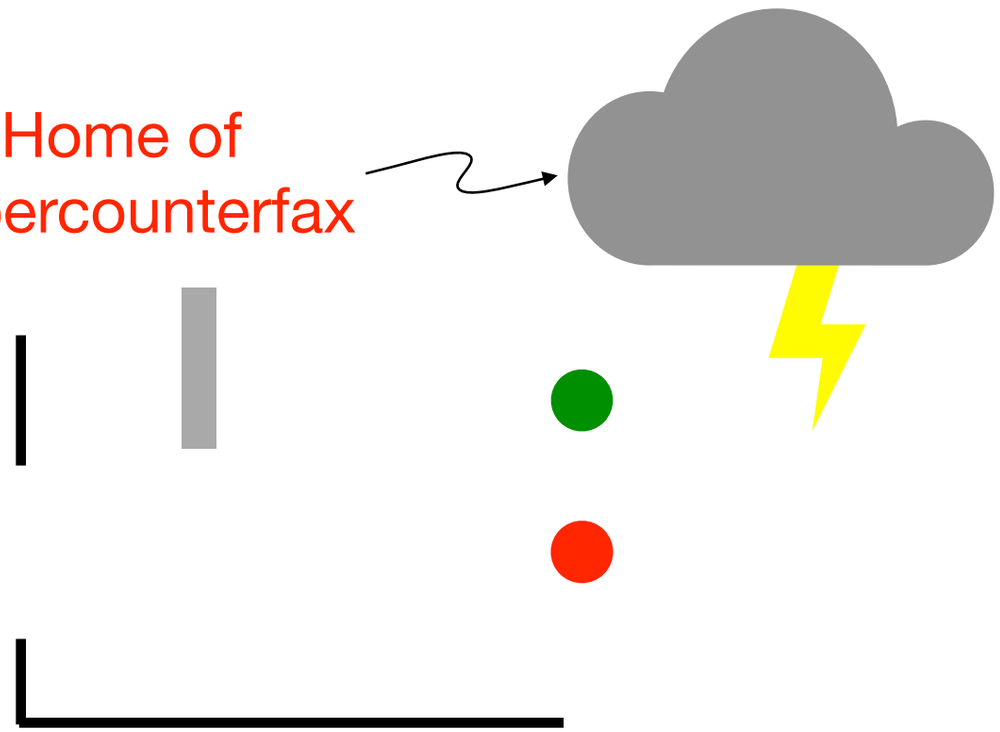
Green moves

Green displaces Brick

Red moves

Red bounces off Brick

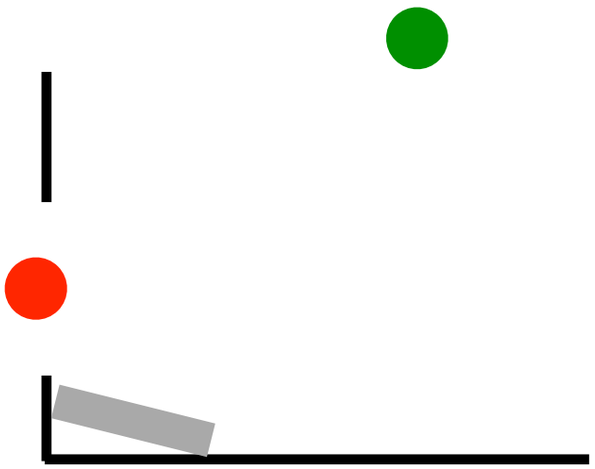
Home of Supercounterfax



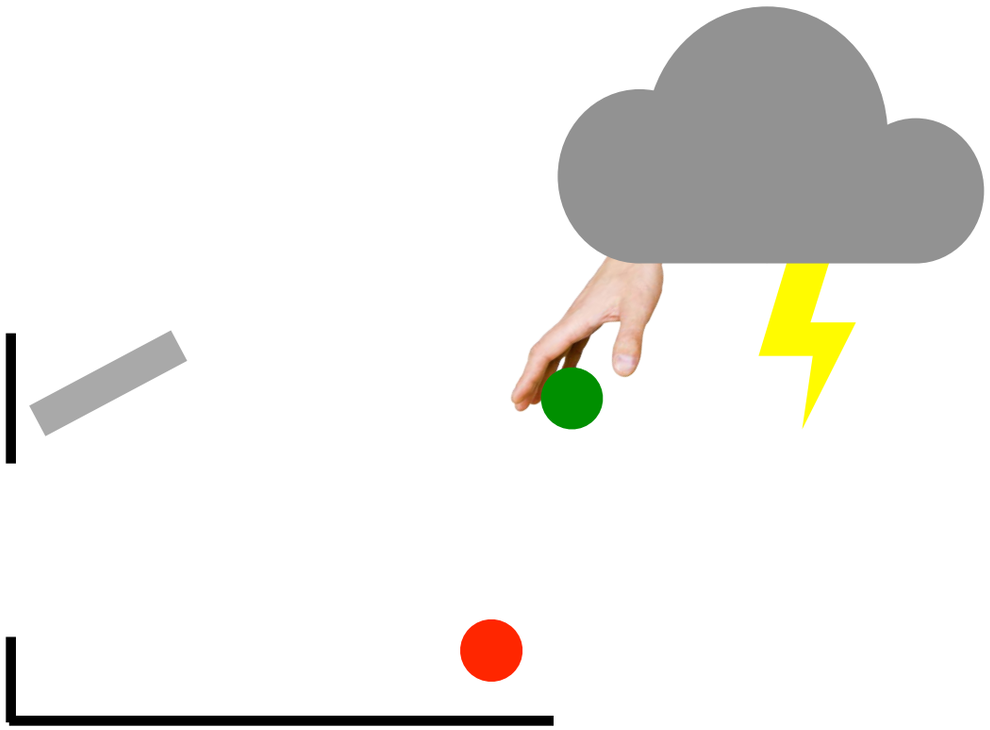
The counterfactual history “CF”

(No Story)

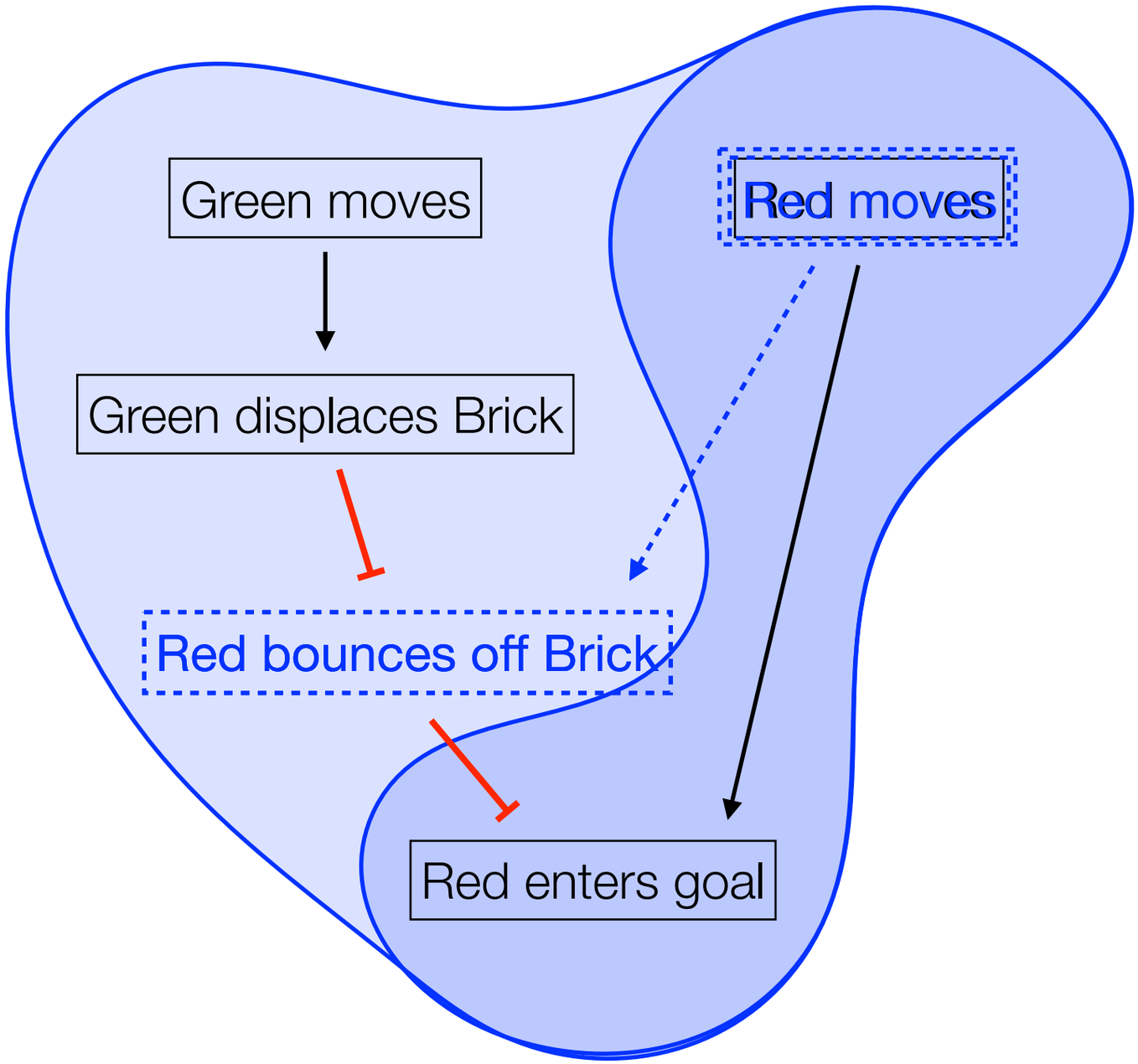
Prevention Shows Up Between F and CF Histories



The factual history “F”



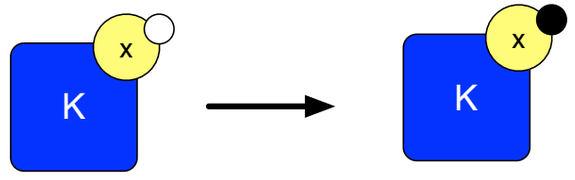
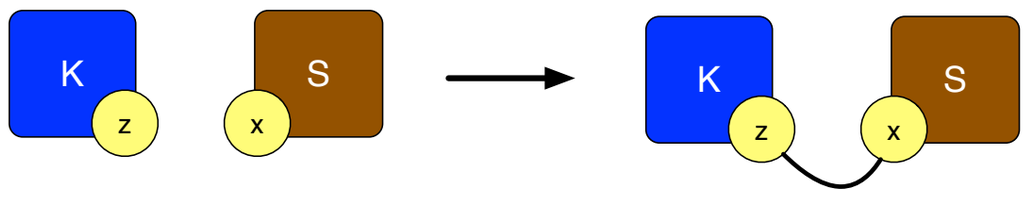
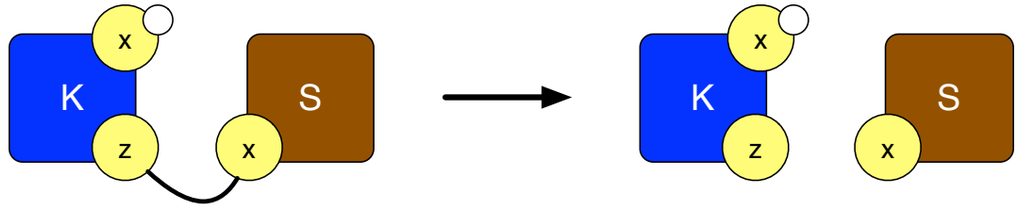
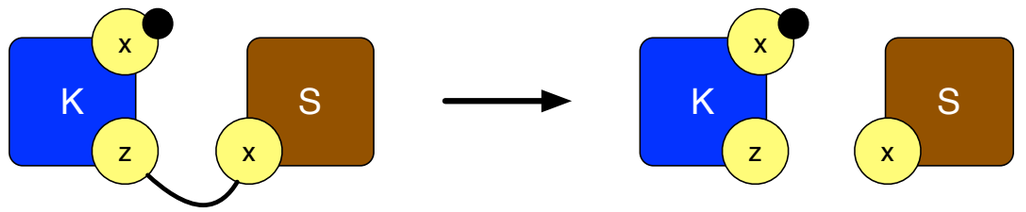
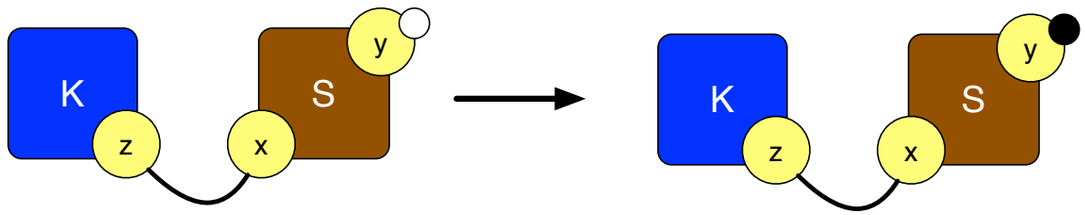
The counterfactual history “CF”



The better Story

The original Story

A Simple Example

pK		0.01
b		1
u		1000
u*		0.01
p (EOI)		1

Limitations of a Story as Explanation

actual trace: init b u pK b p u*

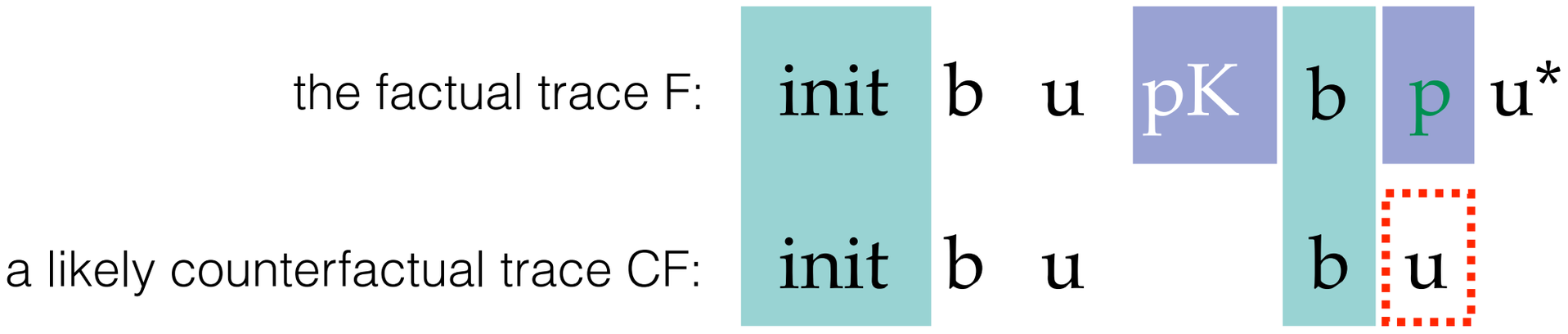
init → b → p

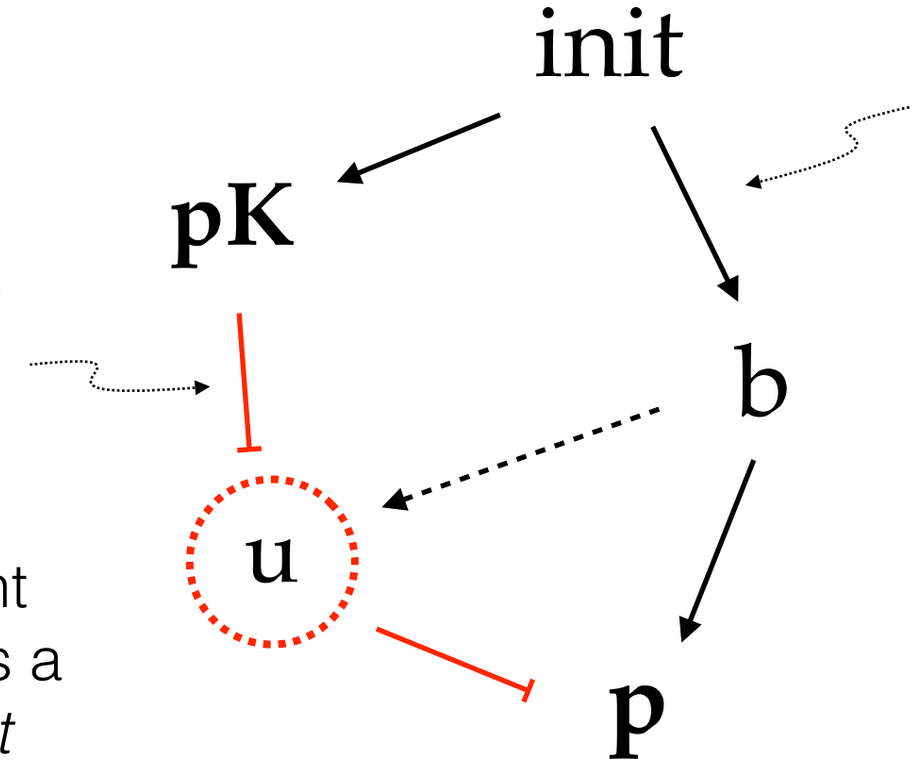
This story is not a satisfactory explanation of ‘p’.

likely alt trace: init b u b u

‘pK’ *prevented* a ‘u’ that would have *prevented* ‘p’:

A Better Explanation





direct causal influence
between E1 < E2
within F or *within* CF

preventative influence
between E1 < E2
across F and CF

(E1 is the last event
before E2 that sets a site
to a value tested by E2)

(E1 in F is the last event
before E2 in CF that sets a
site to a value *different*
than required by E2)

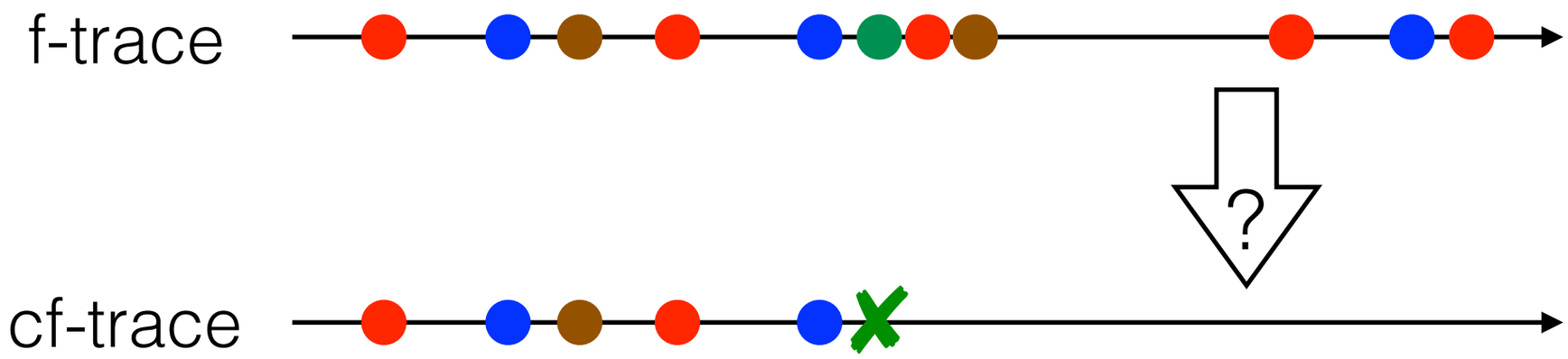
A Metaphysical Cliff

"*If kangaroos had no tails, they would topple over*" seems to me to mean something like this: in any possible state of affairs in which kangaroos have no tails, and which resembles our actual state of affairs as much as kangaroos having no tails permits it to, the kangaroos topple over.

David Lewis, Counterfactuals, 1973

Avoiding the Metaphysical Cliff

Lewis is saying that a counterfactual experiment…

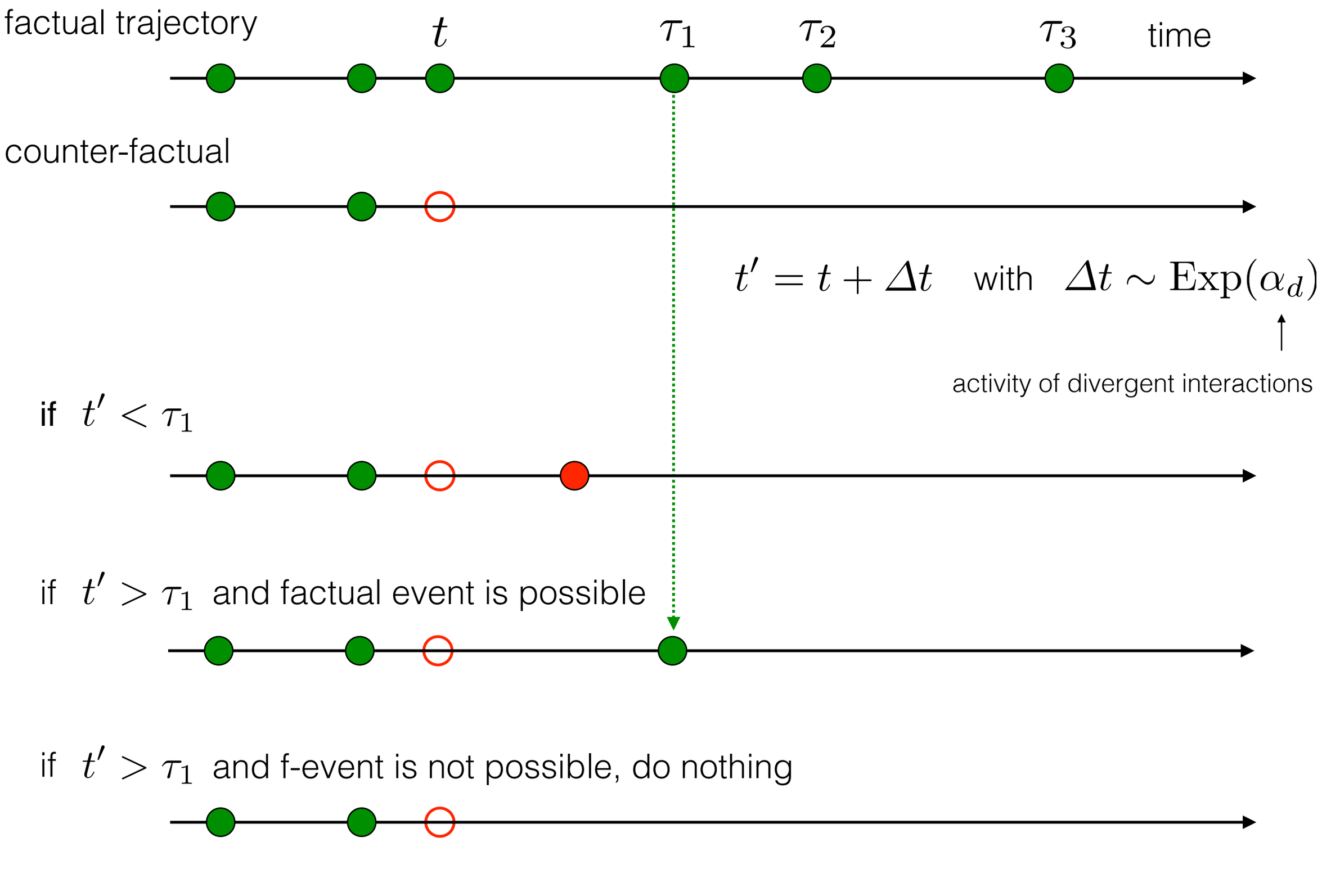


…cannot simply be a fresh simulation after the intervention.

The new simulation has to hug the factual trace probabilistically.

It has to be an instance conditioned on the factual trace.

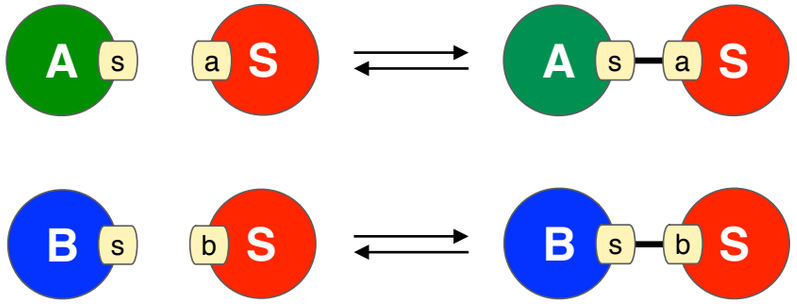
Conditioning on the Factual Trace

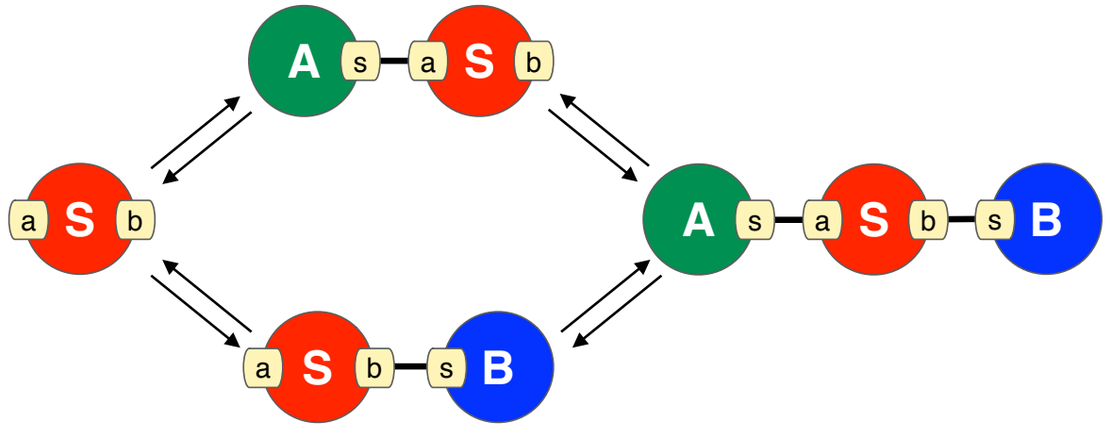


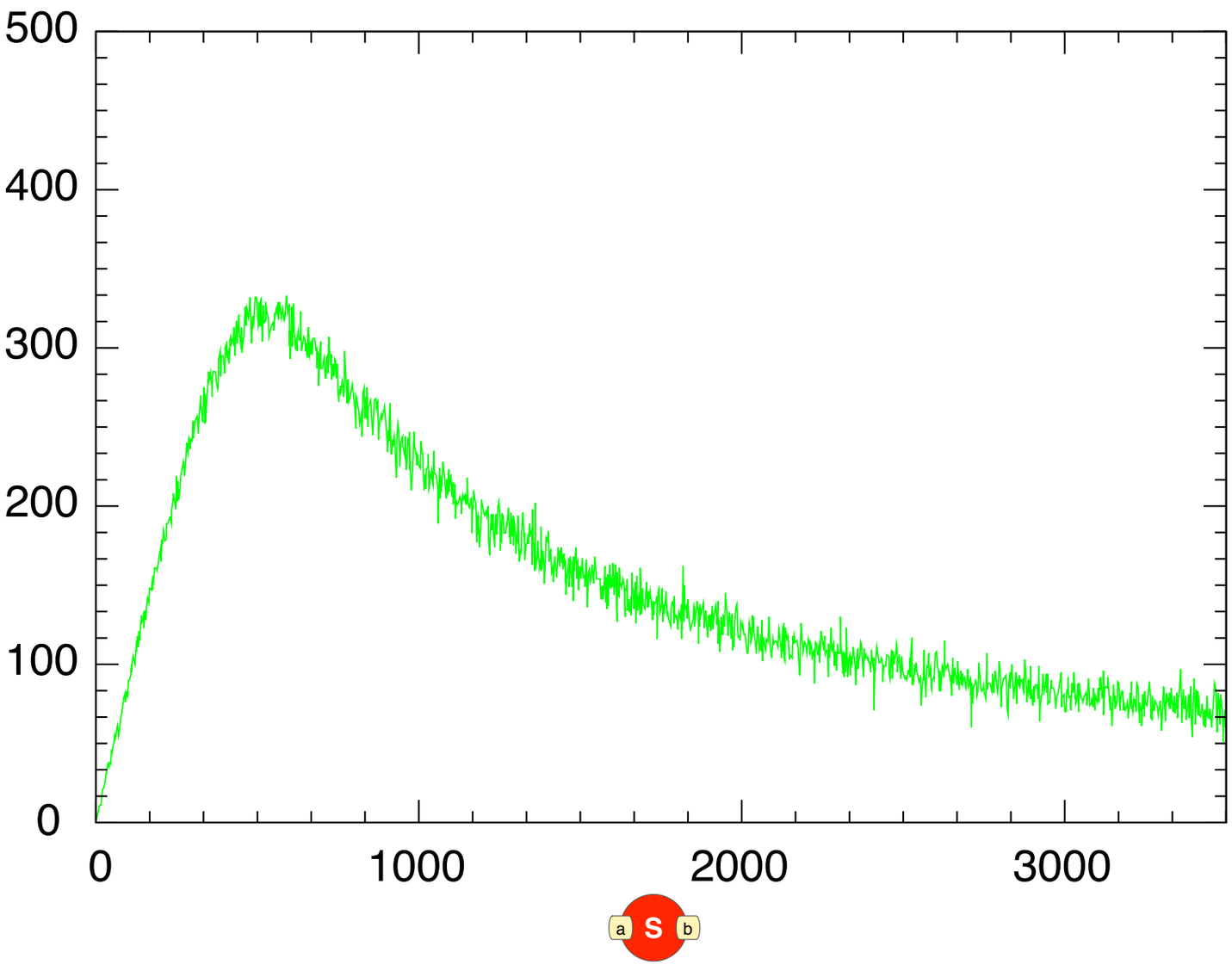
Hard And Soft Causality

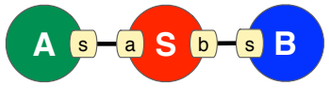
Dependency on kinetics, i.e. timing …

Hard And Soft Causality



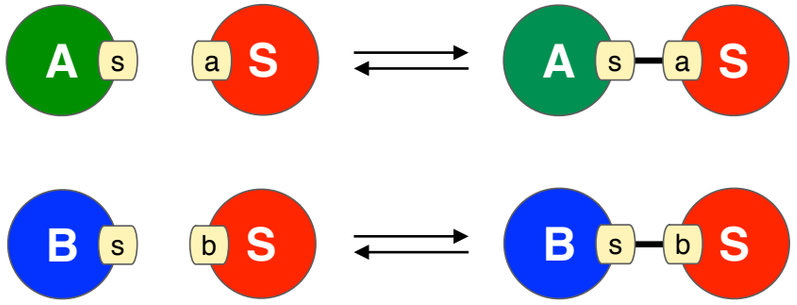


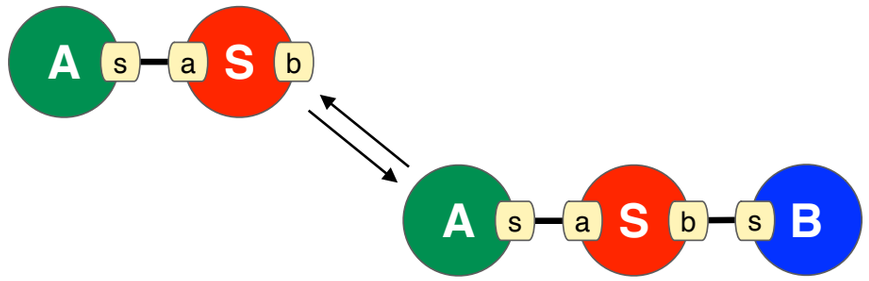


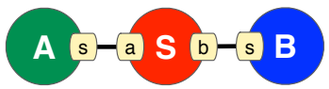


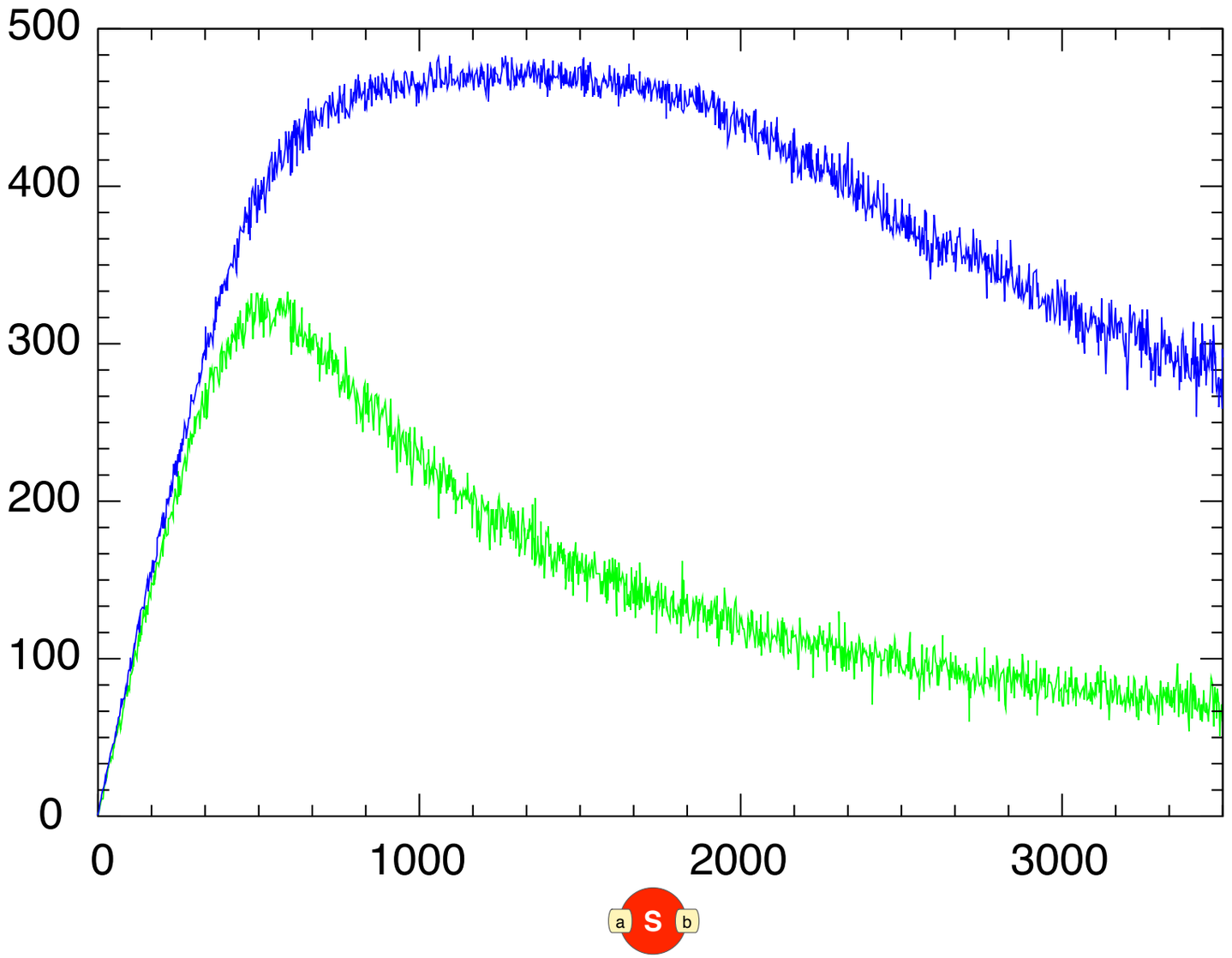
500 A, 500 B, independent

Hard And Soft Causality





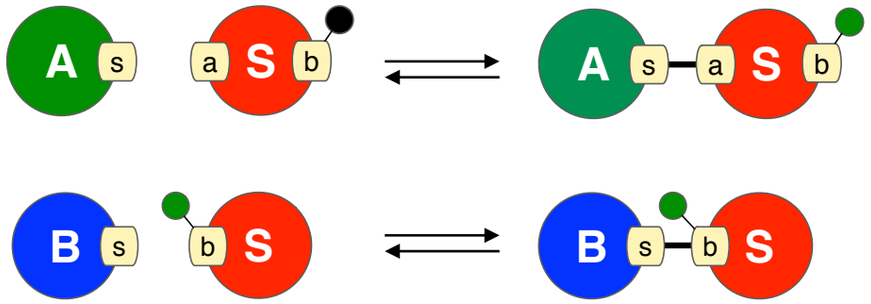


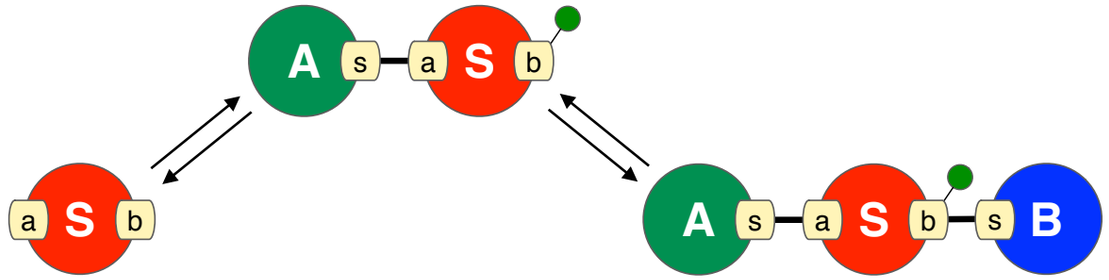


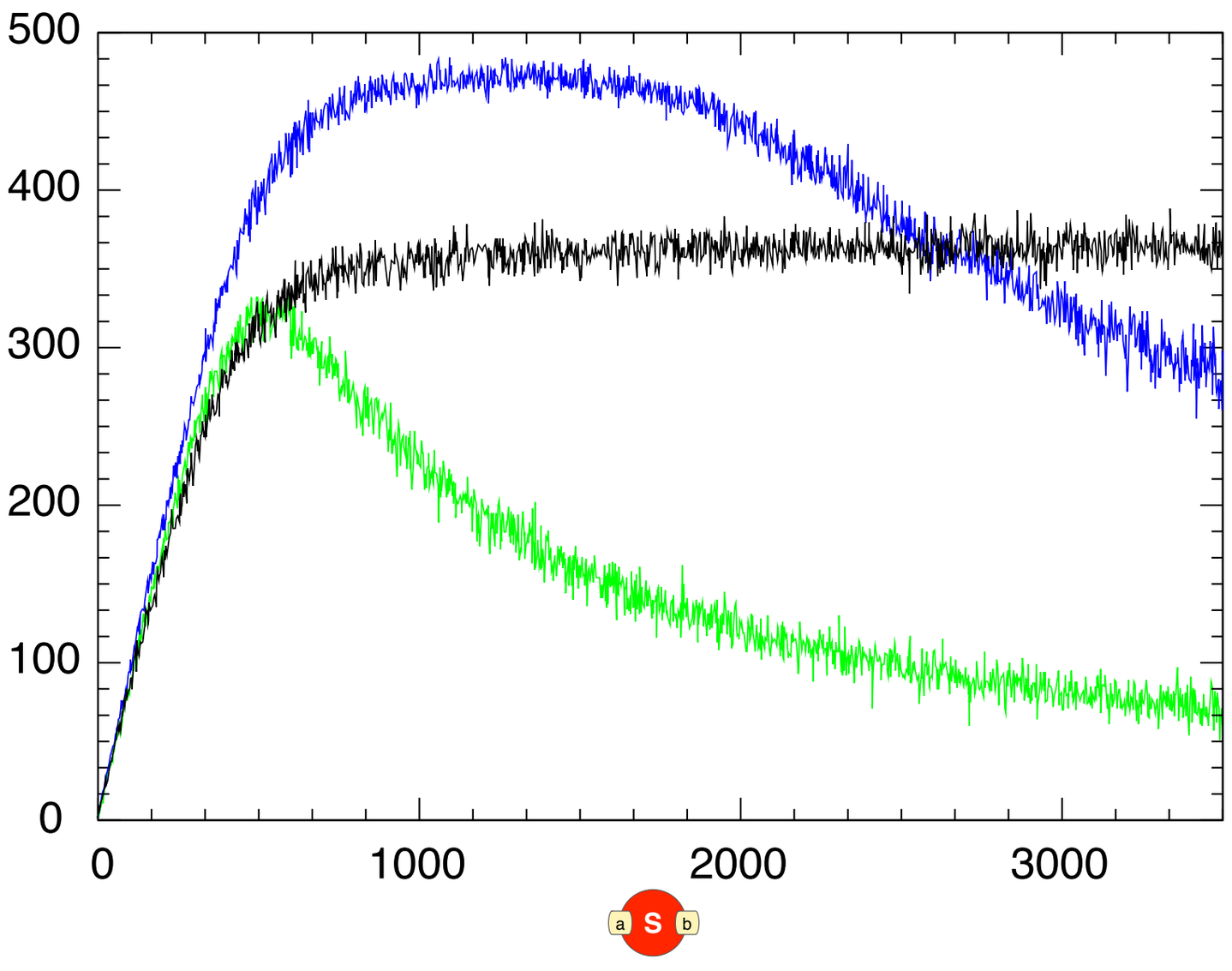
2000 A, 500 B, independent
“soft causality”

500 A, 500 B, independent

Hard And Soft Causality







500 A, 500 B, sequentialized
“hard causality”

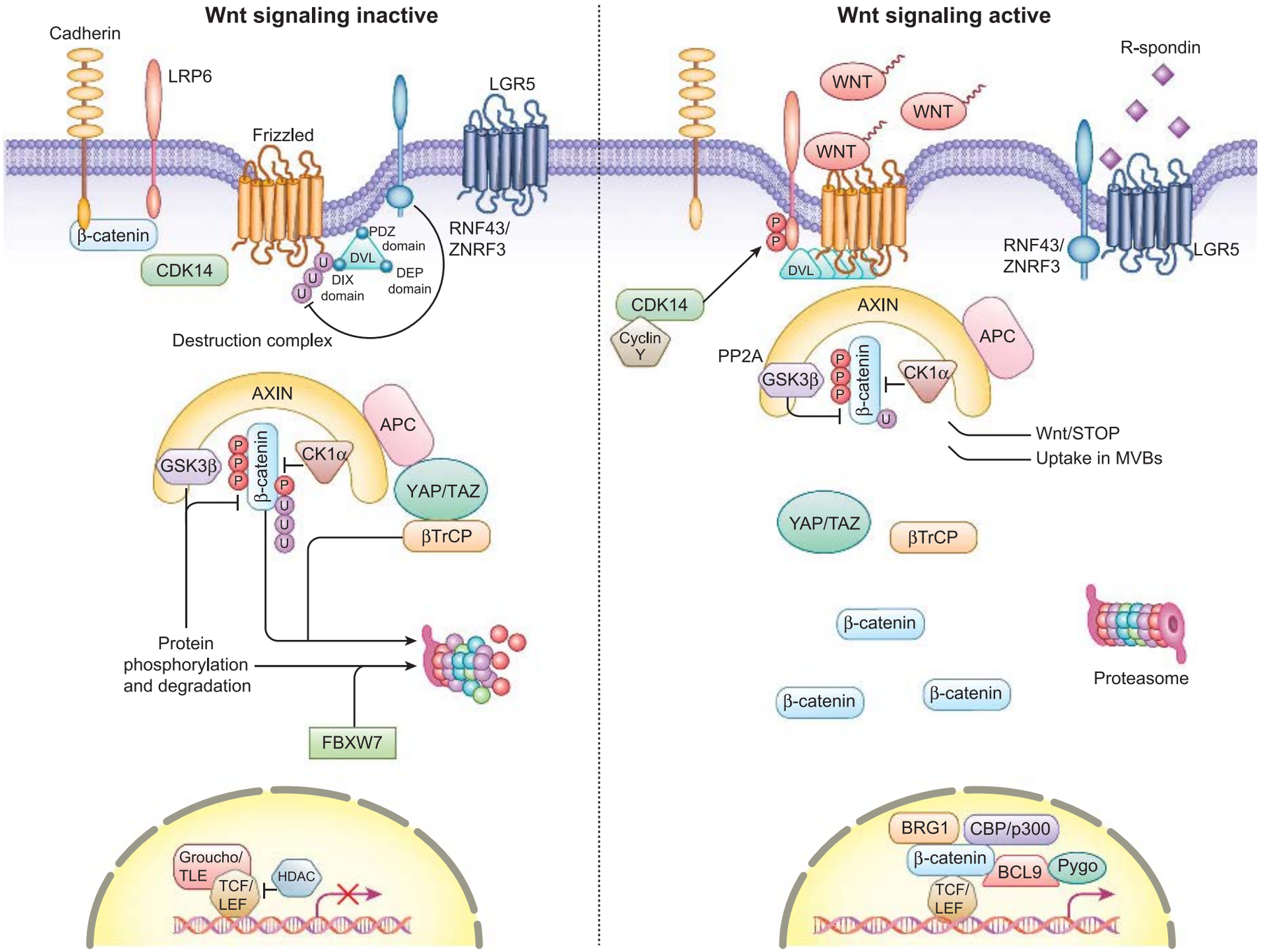
2000 A, 500 B, independent
“soft causality”

500 A, 500 B, independent

Lecture Seven

7.
Scaffolding

Wnt Signaling



A Piece of Wnt Signaling

18 agent types

57 binding sites

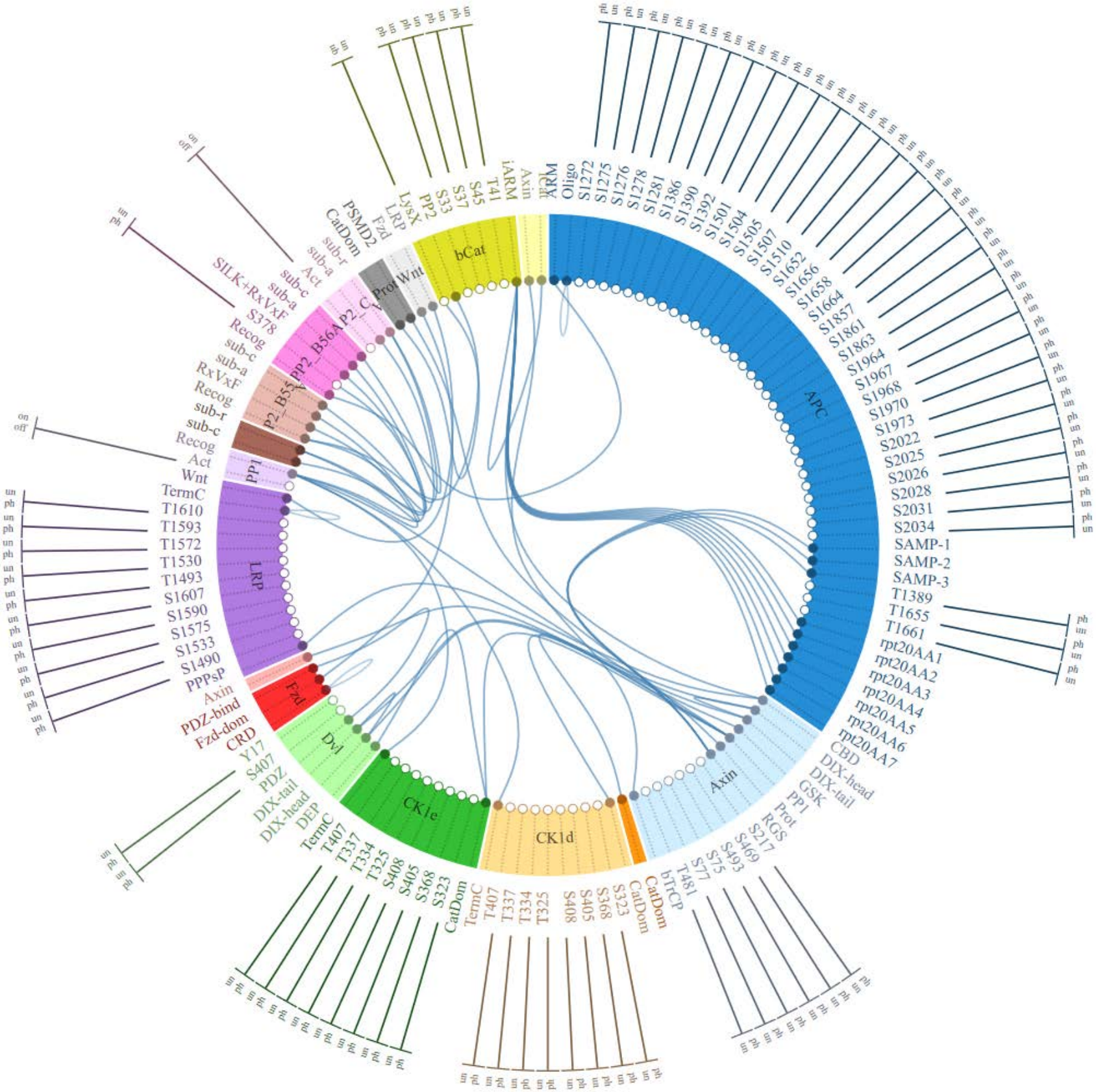
76 taggable sites

31 rule families

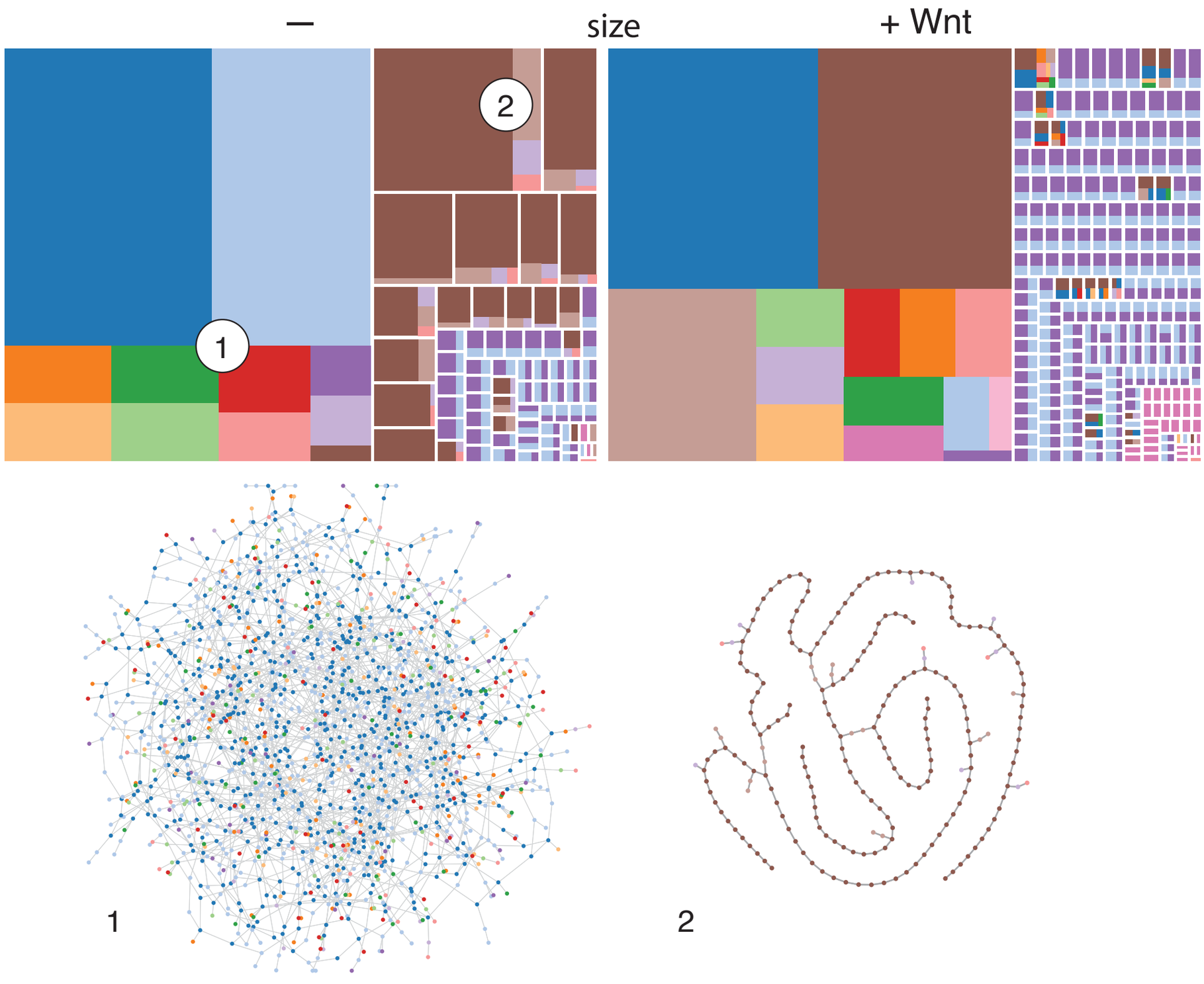
1300+ rules

~750,000 agents

1:1 scale



Protein Aggregates in Wnt Signaling



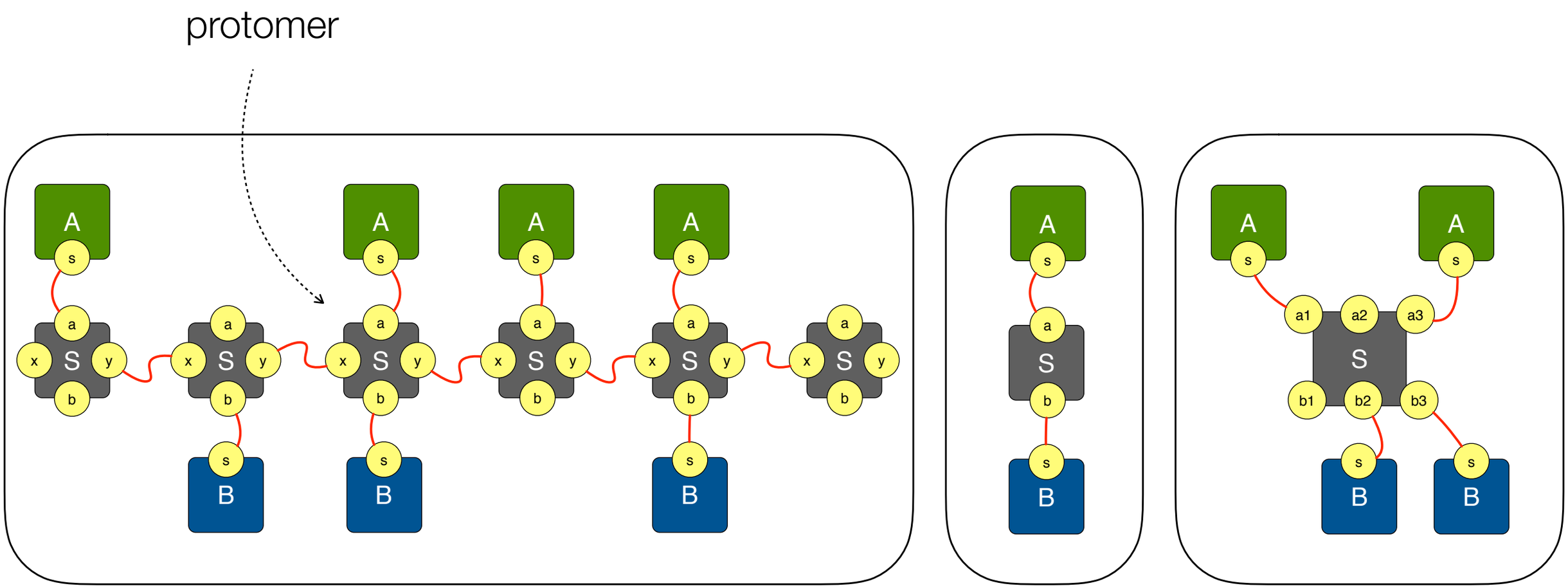
Pleiomorphic Ensembles

A dynamically changing collection of assemblies that are incomplete in reference to the blueprint of a large multi-subunit molecular machine.

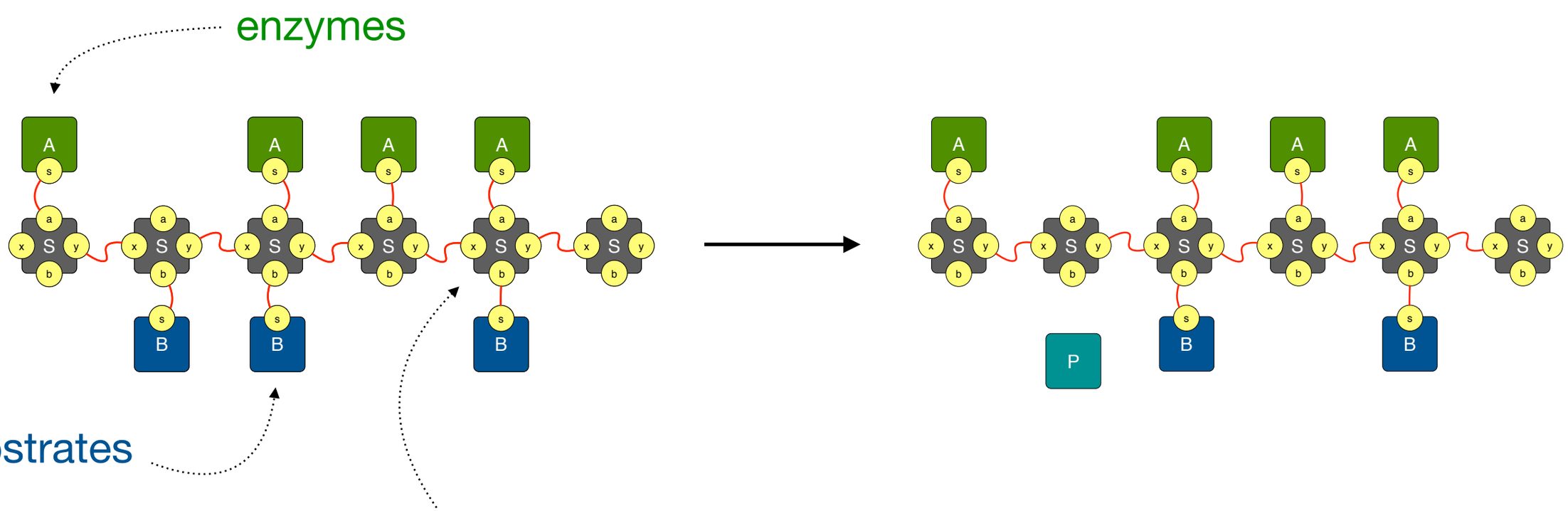
Yet, the ensemble as a whole might nonetheless function as if it was a fully assembled machine.

Mayer BJ, Blinov ML, Loew LM. Molecular machines or pleiomorphic ensembles: signaling complexes revisited. *Journal of Biology* 8(9):81 (2009)

Scaffold Types



Catalytic Potential



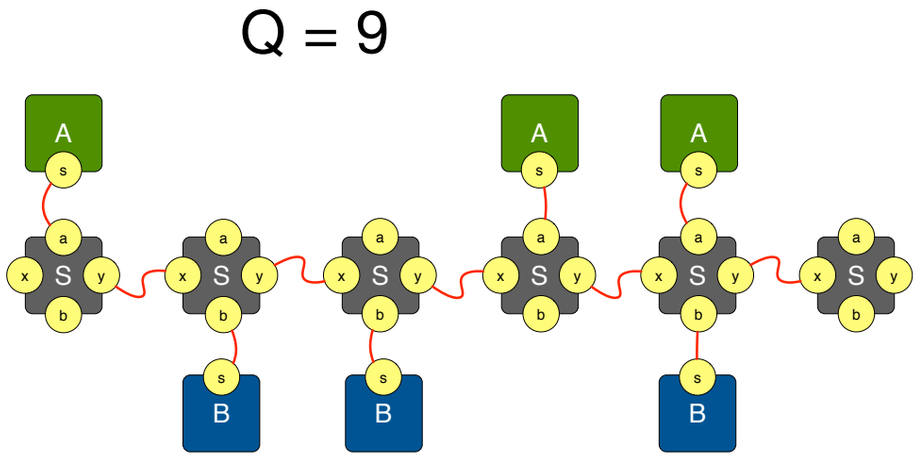
catalytic event occurs with rate

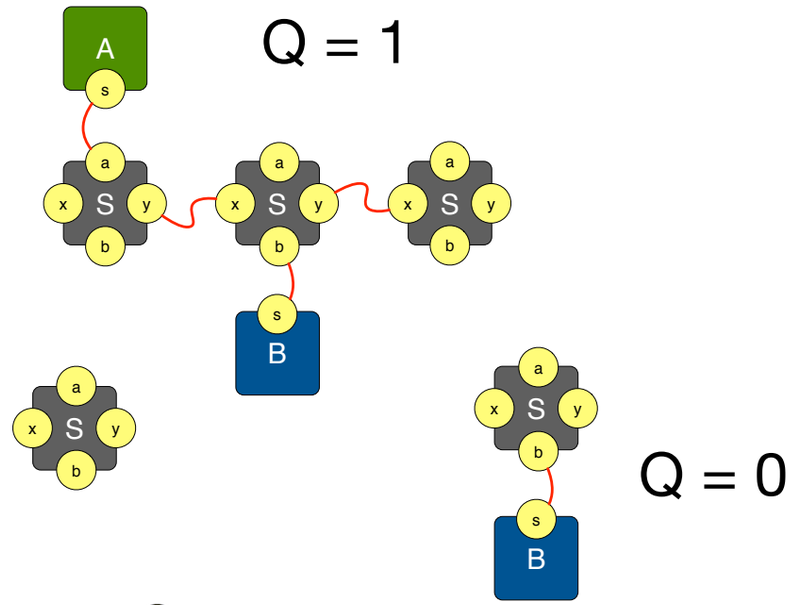
$12\,k_{\mathrm{cat}}$

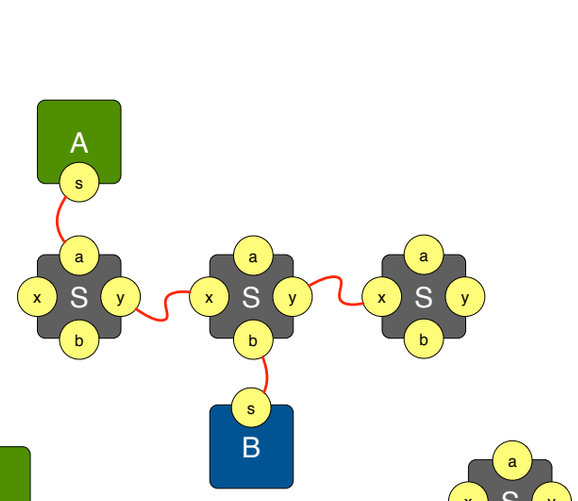
“catalytic potential” *Q* of this configuration

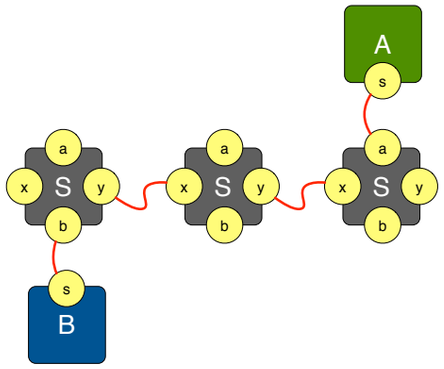
rate of an AB interaction

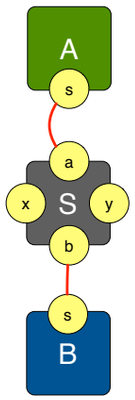
A Mixture

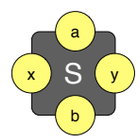


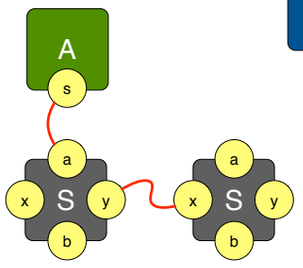


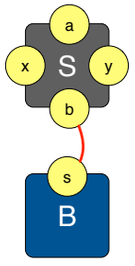


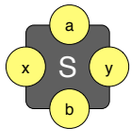


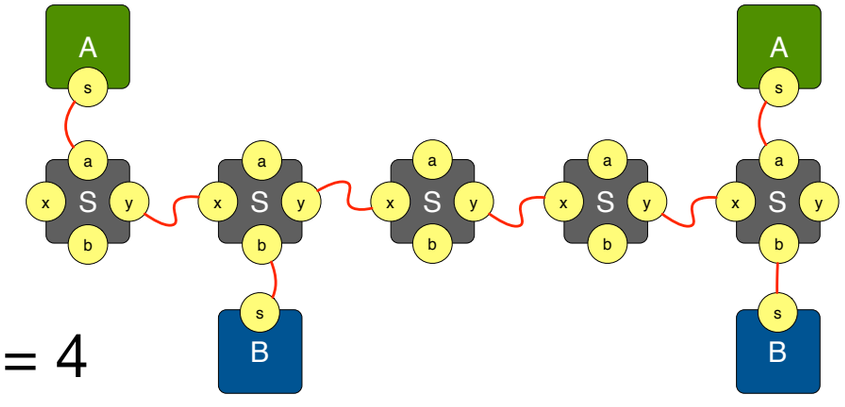












Q = 4

$$Q = \sum_i Q_i = 17$$

Generalizing Michaelis-Menten

$$\mathrm{A} + \mathrm{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{AB} \xrightarrow{k_{cat}} \mathrm{P} + \ldots$$

$$\frac{dP}{dt} = k_{cat} \quad t_A \quad \frac{[B]}{[B] + \frac{1}{\alpha} + \frac{k_{cat}}{k_f}}$$

free substrate (B)

equilibrium constant $\alpha = \frac{k_f}{k_r}$

initial rate of product formation

Generalizing Michaelis-Menten

fraction of enzyme (A) bound

$$\mathrm{A} + \mathrm{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{AB} \xrightarrow{k_{cat}} \mathrm{P} + \ldots \qquad \frac{dP}{dt} = k_{cat} \quad t_A \quad \frac{\alpha t_B - \alpha t_A - 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}{\alpha t_B - \alpha t_A + 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}$$

equilibrium constant $\alpha = \frac{k_f}{k_r}$

initial rate of product formation

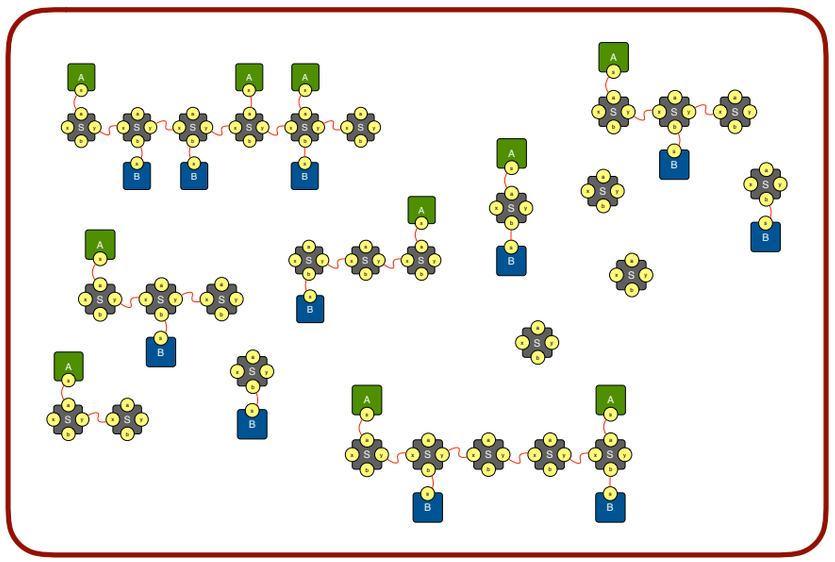
major assumption: the contents of the box are in equilibrium

Generalizing Michaelis-Menten

$$\mathrm{A} + \mathrm{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{AB} \xrightarrow{k_{cat}} \mathrm{P} + \ldots$$

equilibrium constant $\alpha = \dfrac{k_f}{k_r}$

polymerizing scaffold



a *pleiomorphic* ensemble

$$\frac{dP}{dt} = k_{cat} \quad t_A \quad \frac{\alpha t_B - \alpha t_A - 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}{\alpha t_B - \alpha t_A + 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}$$

fraction of enzyme (A) bound

"catalytic potential" Q of Michaelis-Menten

initial rate of product formation

$$\xrightarrow{k_{cat}} \mathrm{P} + \ldots \qquad \frac{dP}{dt} = k_{cat} \quad Q \qquad Q = ??$$

major assumption: the contents of the box are in equilibrium

Criticality

just polymerization

$$s_n = \sigma^{n-1} s^n \longrightarrow W(s) = \sum_{n=1}^{\infty} \sigma^{n-1} s^n = \frac{s}{1-\sigma s} \longrightarrow s\frac{dW(s)}{ds} = t_S$$

$$\downarrow$$

$$s = \frac{1}{4\sigma}\left(\sqrt{4+\frac{1}{\sigma t_S}} - \sqrt{\frac{1}{\sigma t_S}}\right)^2$$

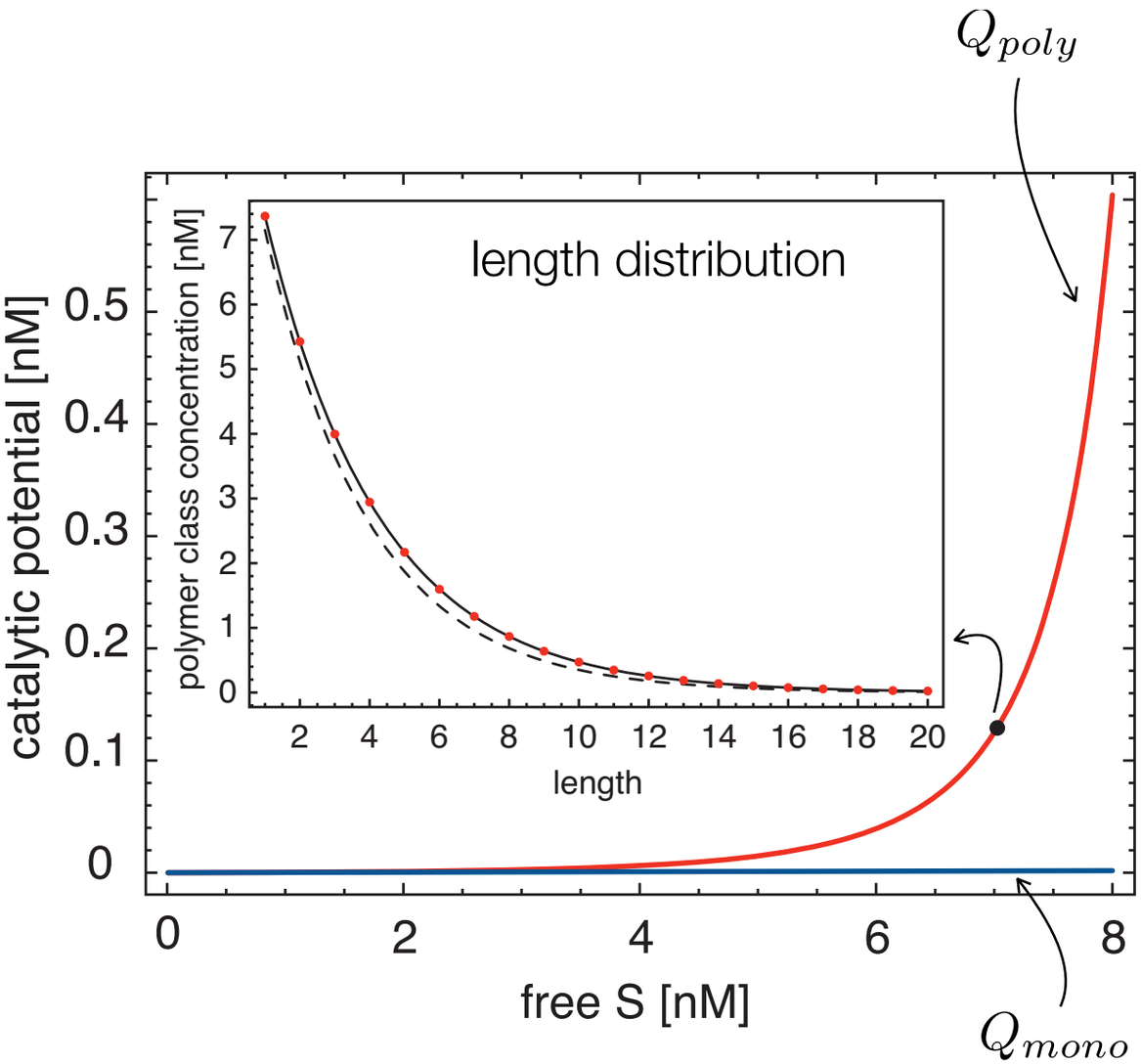
polymerizing scaffold with ligands

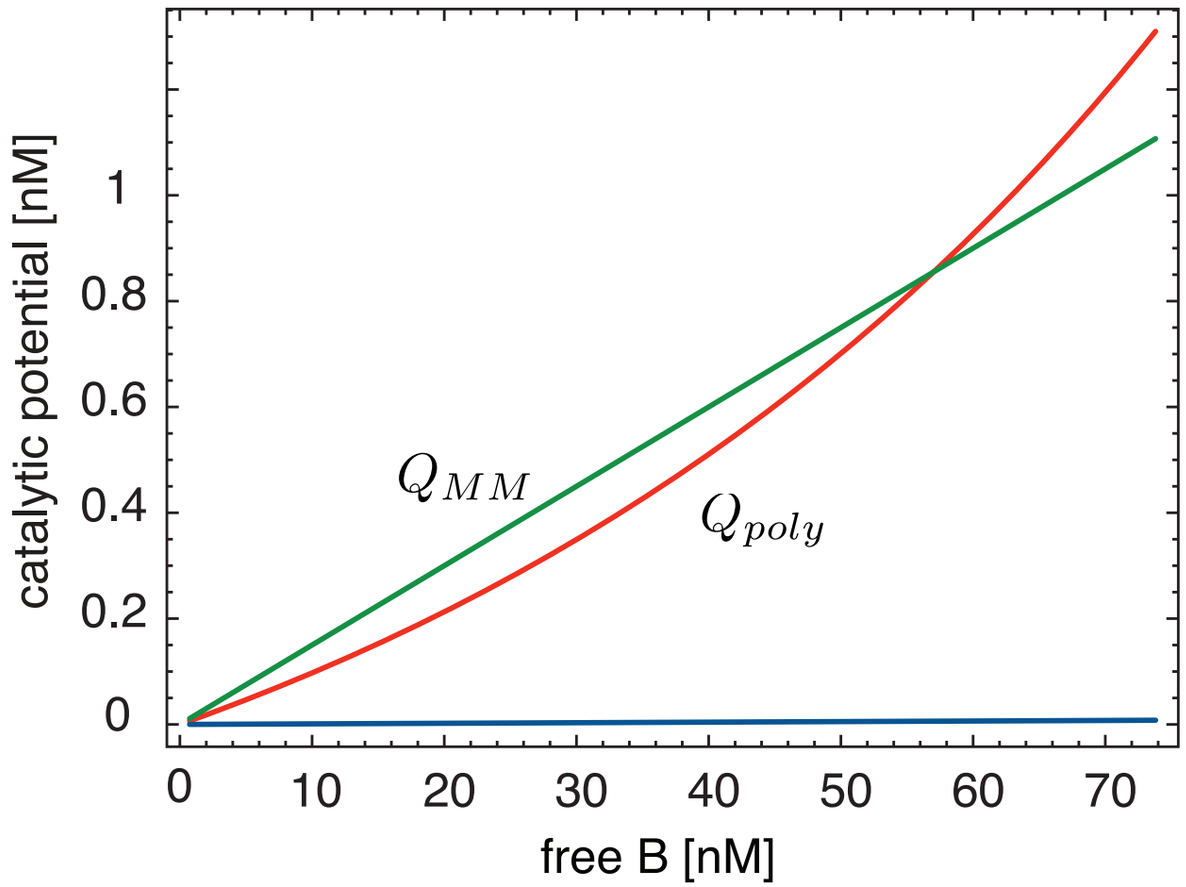
$$W(a,b,s) = a + b + \frac{s(1+\alpha a)(1+\beta b)}{1-\sigma s(1+\alpha a)(1+\beta b)}$$

$$Q_{\text{poly}} = a\,b\,\frac{\partial^2}{\partial a\,\partial b} W = \alpha a\,\beta b\,s\,\frac{1+\sigma\,s(1+\alpha a)(1+\beta b)}{(1-\sigma\,s(1+\alpha a)(1+\beta b))^3}$$

+ explicit expressions for a, b, and s (that are ugly & tedious)

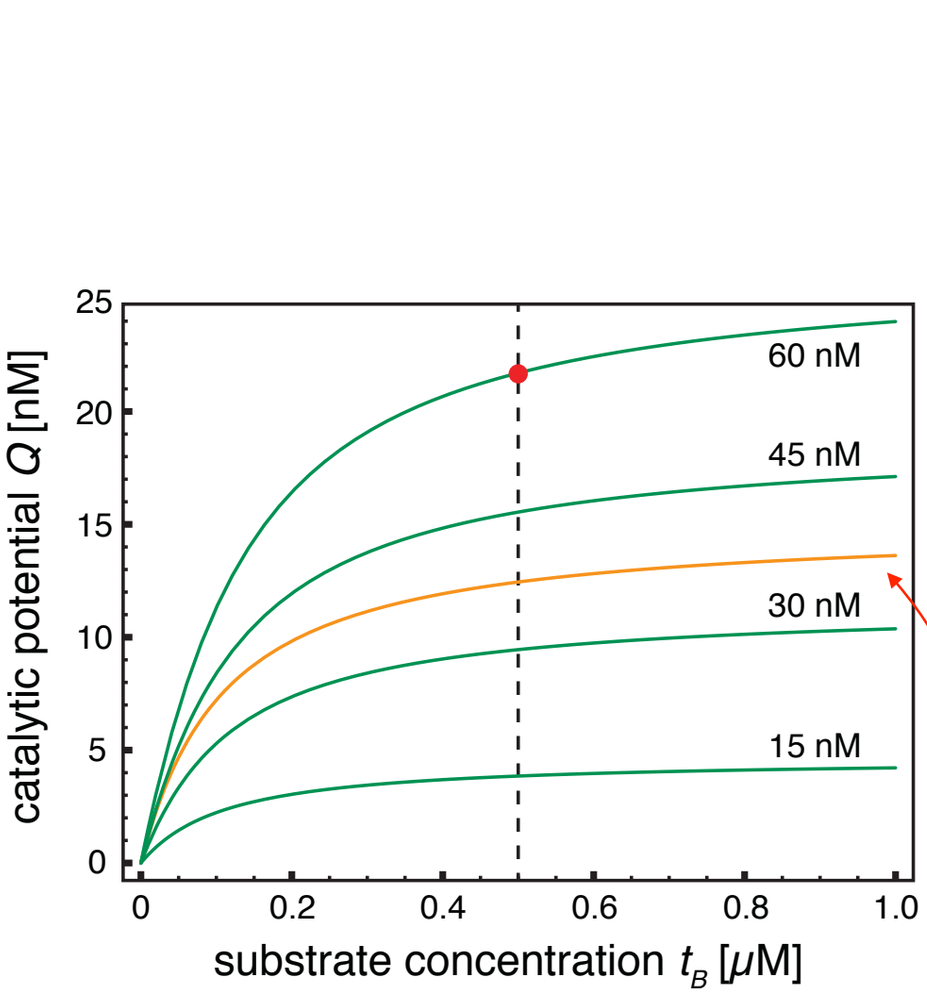
At Constant Chemical Potential



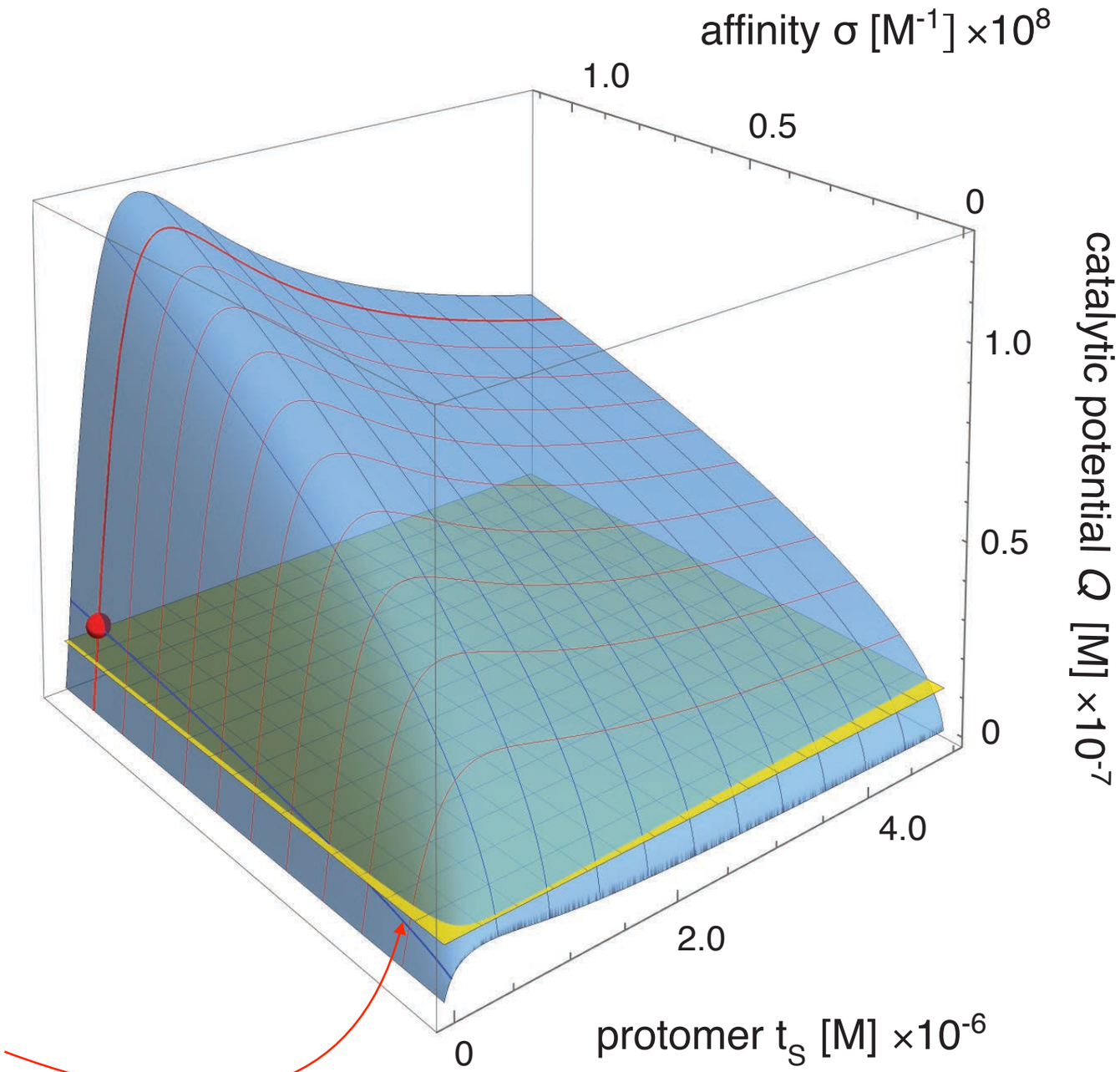


$\alpha = \beta = 10^6\ \mathrm{M}^{-1}$, $\sigma = 10^8\ \mathrm{M}^{-1}$, and $a = b = 15 \cdot 10^{-9}\ \mathrm{M}$

The Equilibrium Q-surface

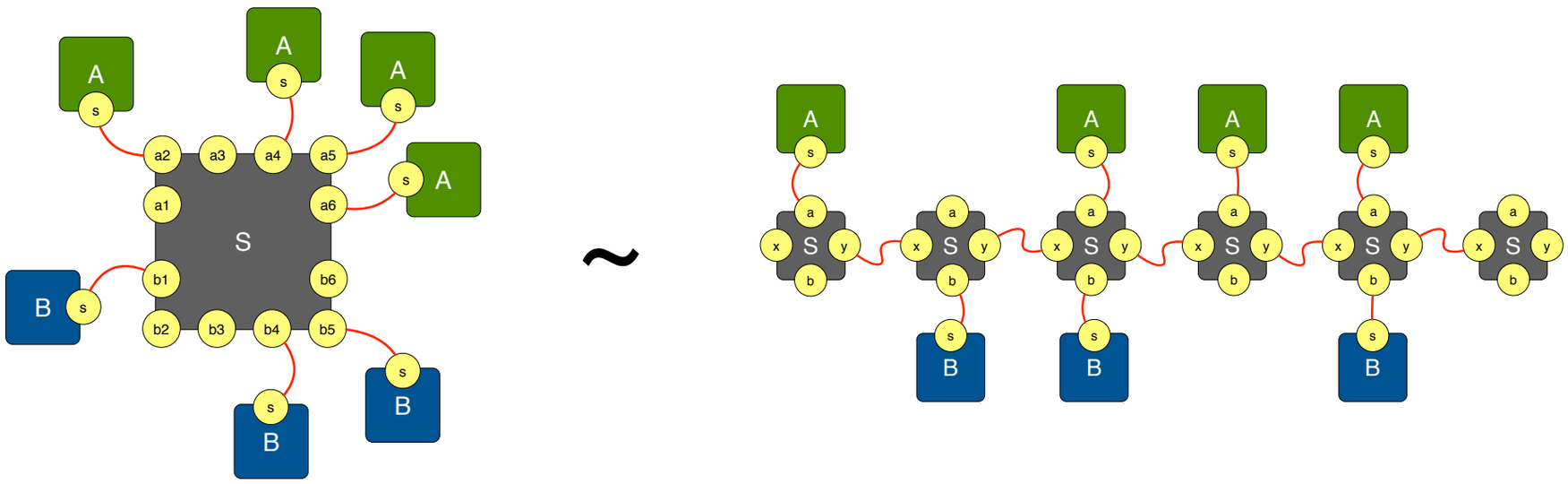


MM



$\alpha = \beta = 10^7\ \mathrm{M}^{-1}$, $t_A = 15 \cdot 10^{-9}\ \mathrm{M}$, and $\sigma = 10^8\ \mathrm{M}^{-1}$

Multivalent Scaffolds as Stepping Stones



$$Q_{\text{multi}} = p(nt_S, t_A, \alpha)p(nt_S, t_B, \beta)\; n^2\, t_S$$

with $$p(t_{\text{sit}}, t_X, \gamma) = \frac{\gamma t_X - \gamma t_{\text{sit}} - 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}{\gamma t_X - \gamma t_{\text{sit}} + 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}$$

MM Flashback

Q_{max} of Michaelis-Menten

fraction of enzyme (A) bound

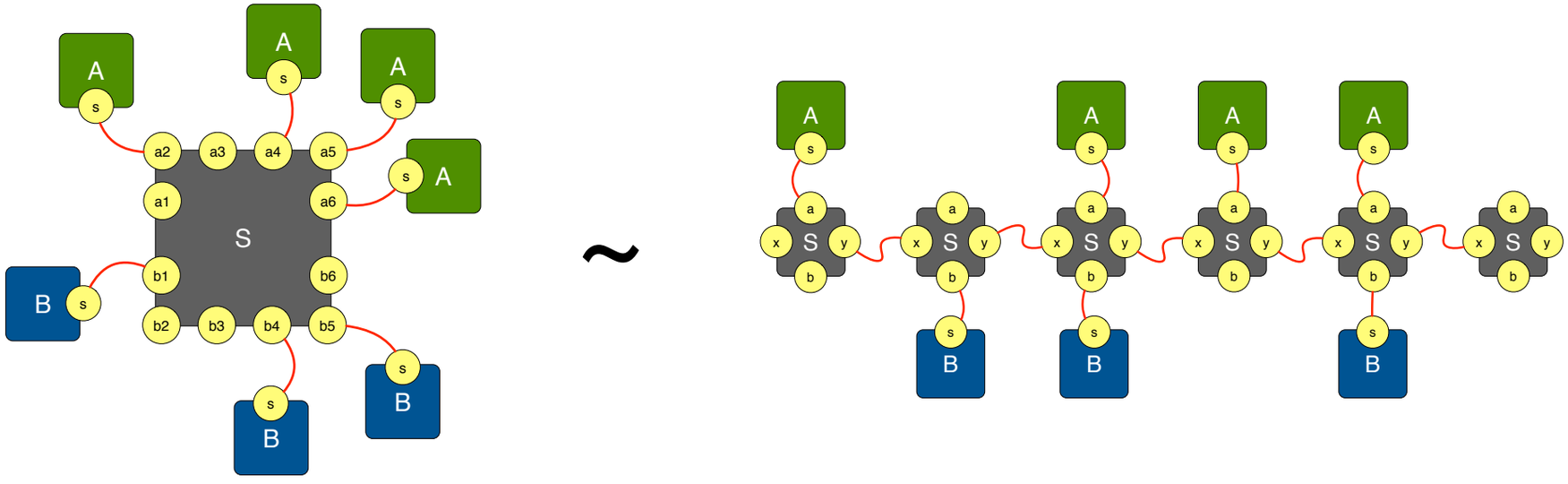
$$\mathrm{A} + \mathrm{B} \underset{}{\overset{\alpha}{\rightleftharpoons}} \mathrm{AB} \xrightarrow{k_{cat}} \mathrm{C}$$

$$\frac{dP}{dt} = k_{cat}\, t_A \, \frac{\alpha t_B - \alpha t_A - 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}{\alpha t_B - \alpha t_A + 1 + \sqrt{4\alpha t_B + (\alpha t_B - \alpha t_A - 1)^2}}$$

equilibrium constant $\alpha = \frac{k_f}{k_r}$

"catalytic potential" Q of Michaelis-Menten

Multivalent Scaffolds as Stepping Stones



$$Q_{\text{multi}} = p(nt_S, t_A, \alpha)p(nt_S, t_B, \beta)\, n^2\, t_S$$

not dependent on partitioning of sites
only dependent on ligand binding

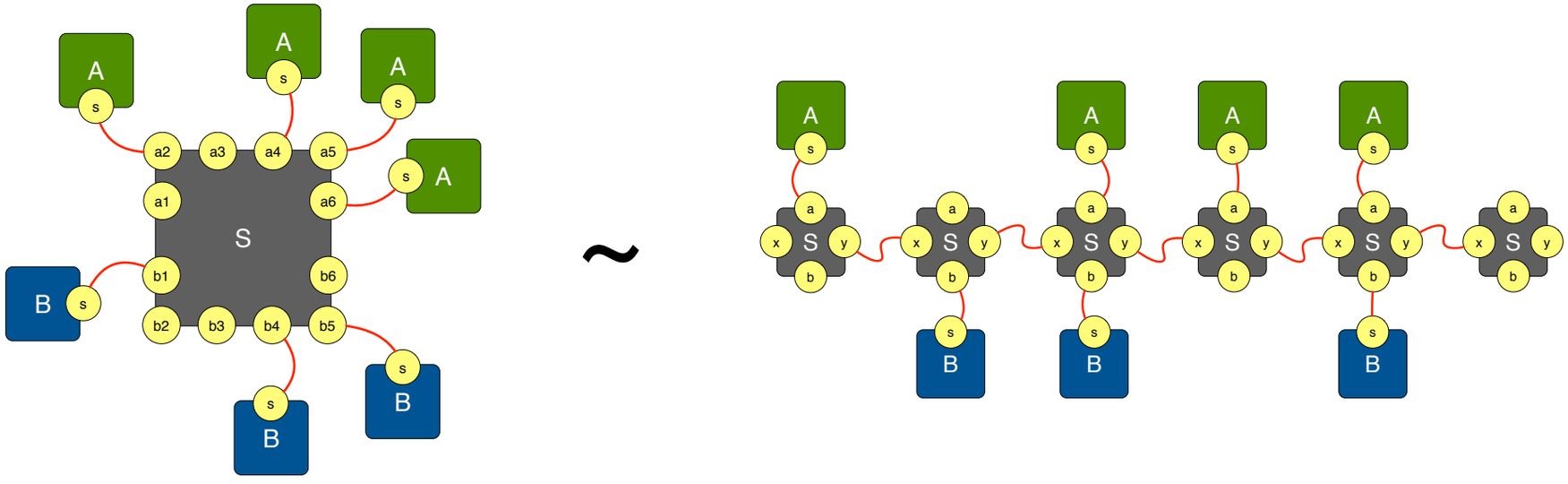
$$Q = \underbrace{p(t_{\text{sit}}, t_A, \alpha)p(t_{\text{sit}}, t_B, \beta)}_{I}\,\underbrace{Q_{\max}(\vec{t}_S)}_{II}$$

not dependent on ligand binding
only dependent on partitioning of sites

$$Q_{\text{poly}} = p(t_S, t_A, \alpha)p(t_S, t_B, \beta)\sum_{n=1}^{\infty} n^2\sigma^{n-1}s^n = p(t_S, t_A, \alpha)p(t_S, t_B, \beta)\frac{s(1+\sigma s)}{(1-\sigma s)^3}$$

with $$p(t_{\text{sit}}, t_X, \gamma) = \frac{\gamma t_X - \gamma t_{\text{sit}} - 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}{\gamma t_X - \gamma t_{\text{sit}} + 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}$$

Multivalent Scaffolds as Stepping Stones



$$Q_{\text{multi}} = p(nt_S, t_A, \alpha)p(nt_S, t_B, \beta)\, n^2\, t_S$$

not dependent on partitioning of sites
only dependent on ligand binding

$$Q = \underbrace{p(t_{\text{sit}}, t_A, \alpha)p(t_{\text{sit}}, t_B, \beta)}_{I}\,\underbrace{Q_{\max}(\vec{t}_S)}_{II}$$

not dependent on ligand binding
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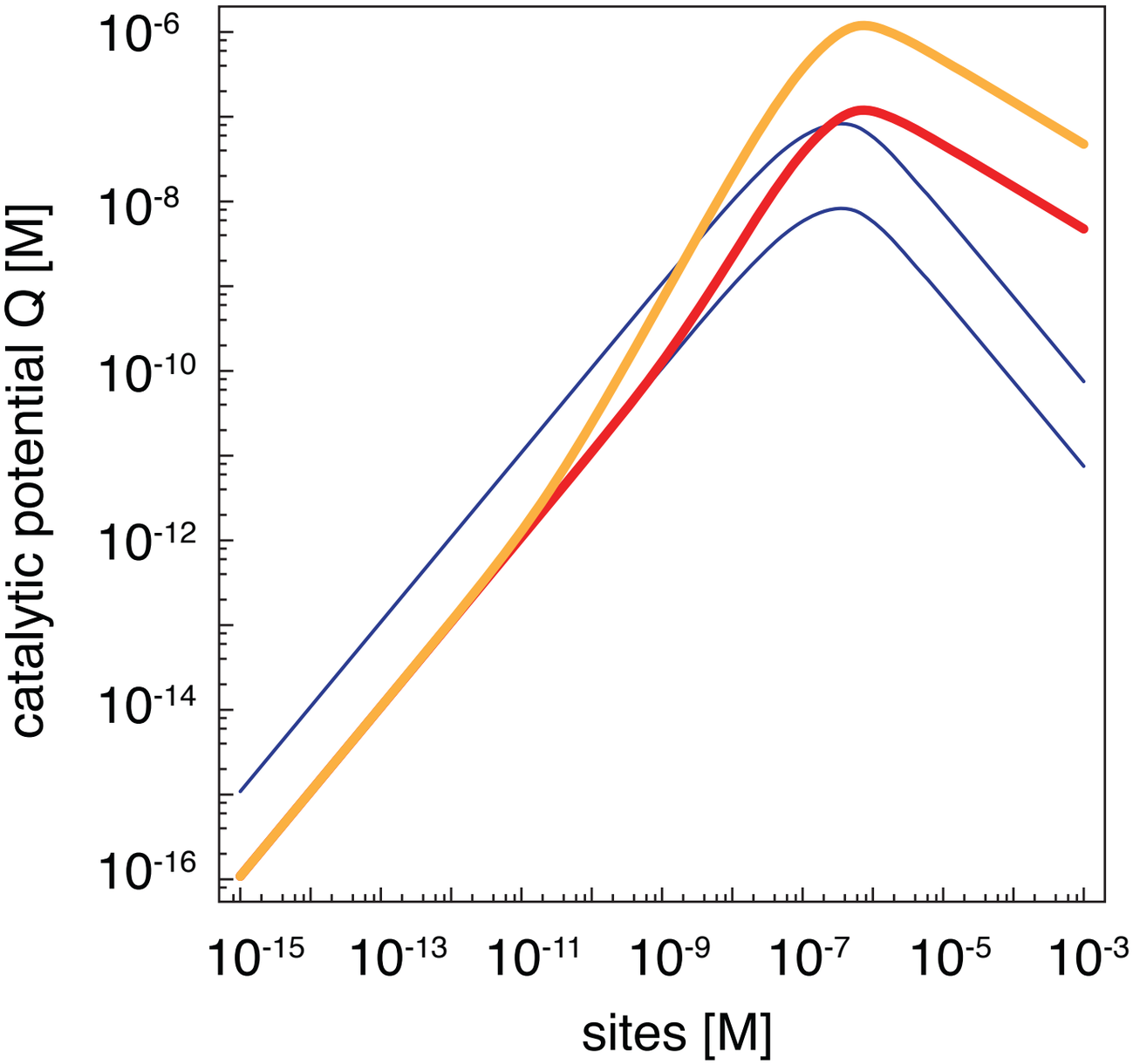
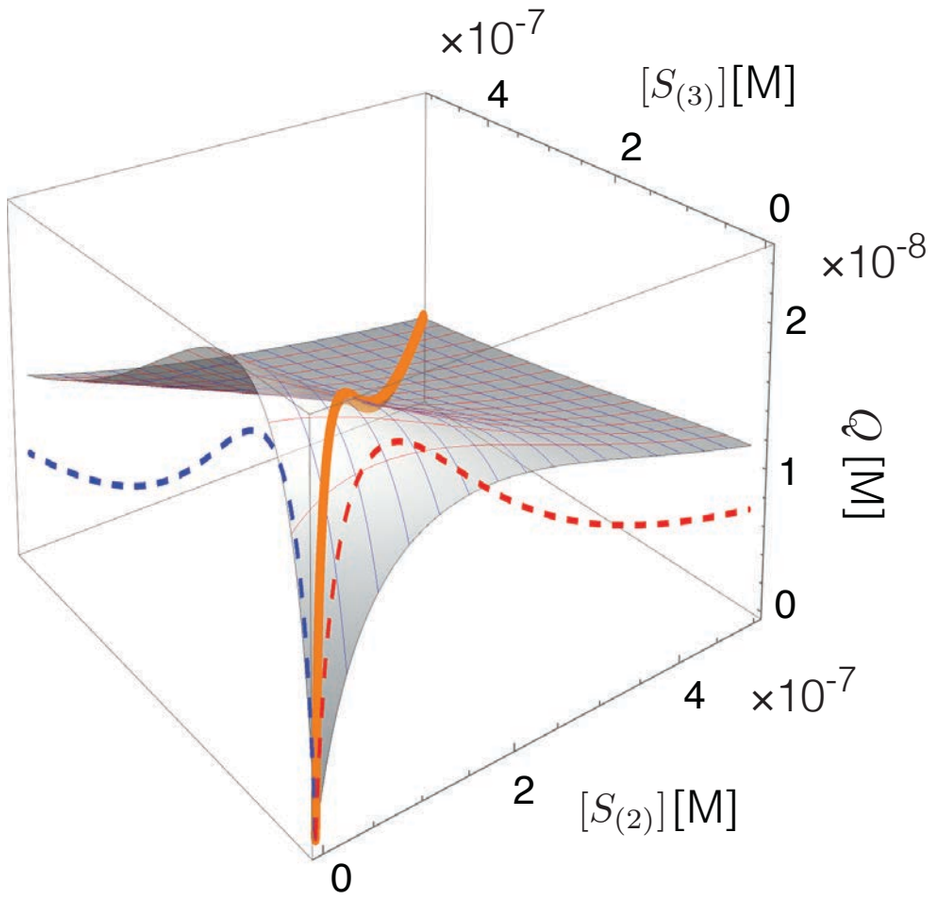
$$Q_{\text{poly}} = p(t_S, t_A, \alpha)p(t_S, t_B, \beta)\sum_{n=1}^{\infty} n^2\sigma^{n-1}s^n = p(t_S, t_A, \alpha)p(t_S, t_B, \beta)\frac{s(1+\sigma s)}{(1-\sigma s)^3}$$

with $$p(t_{\text{sit}}, t_X, \gamma) = \frac{\gamma t_X - \gamma t_{\text{sit}} - 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}{\gamma t_X - \gamma t_{\text{sit}} + 1 + \sqrt{4\gamma t_X + (\gamma t_X - \gamma t_{\text{sit}} - 1)^2}}$$

Multivalent Scaffolds and Poly-Scaffold



mixture of bi- and tri-valent scaffolds



$\alpha = \beta = 10^7\ \mathrm{M}^{-1}, \sigma = 10^8\ \mathrm{M}^{-1}, t_A = 15 \cdot 10^{-9}\ \mathrm{M}, t_B = 0.5 \cdot 10^{-6}\ \mathrm{M}$