Modelling scaffold-mediated interaction between the cAMP and the Raf/MEK/ERK pathway

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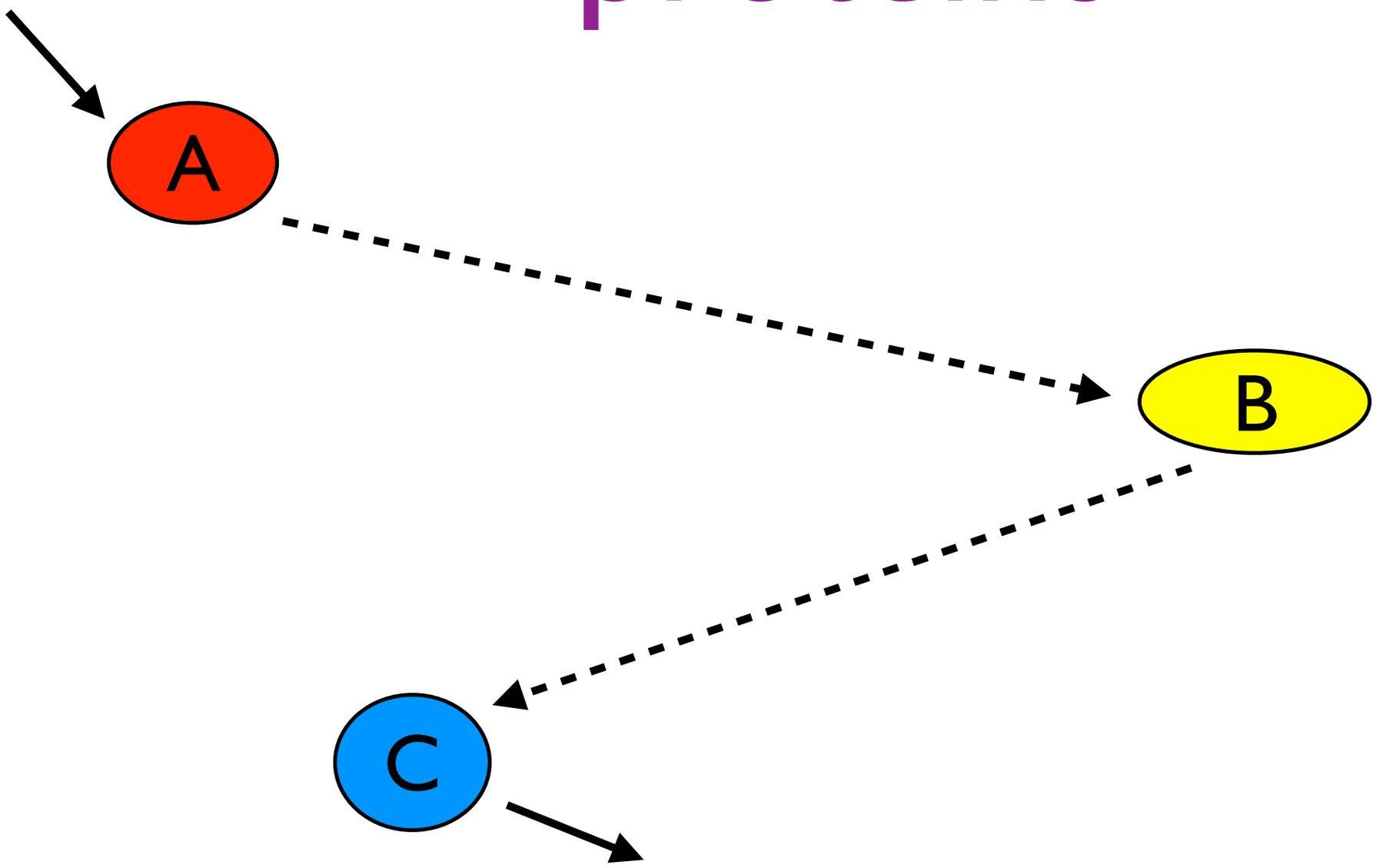
joint work with Muffy Calder

MOAN-CB, September 23, 2009

Outline

- Motivation
- Scaffold model
- Formal model
- Analysis
- Conclusion and perspectives

Signalling and scaffold proteins



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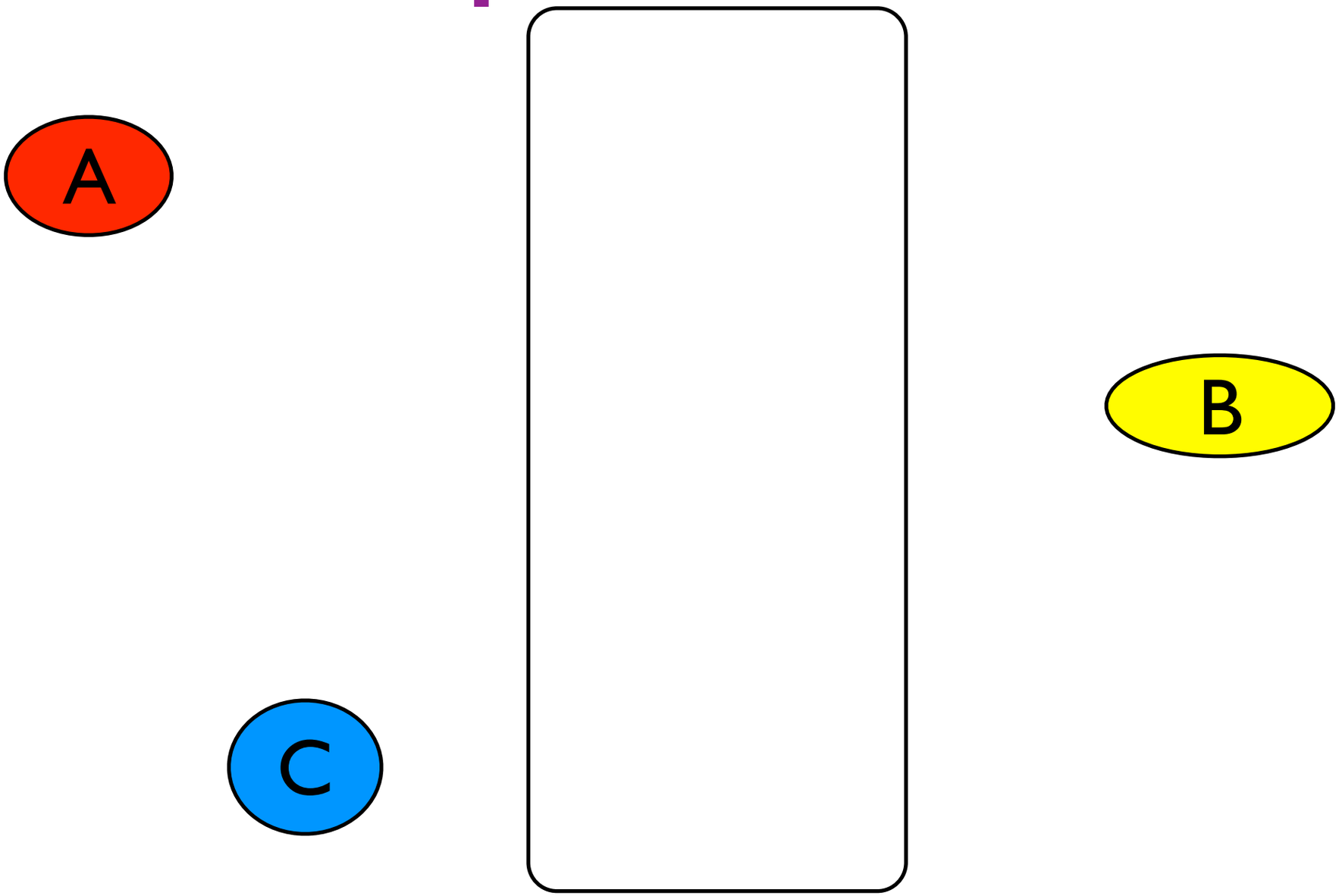

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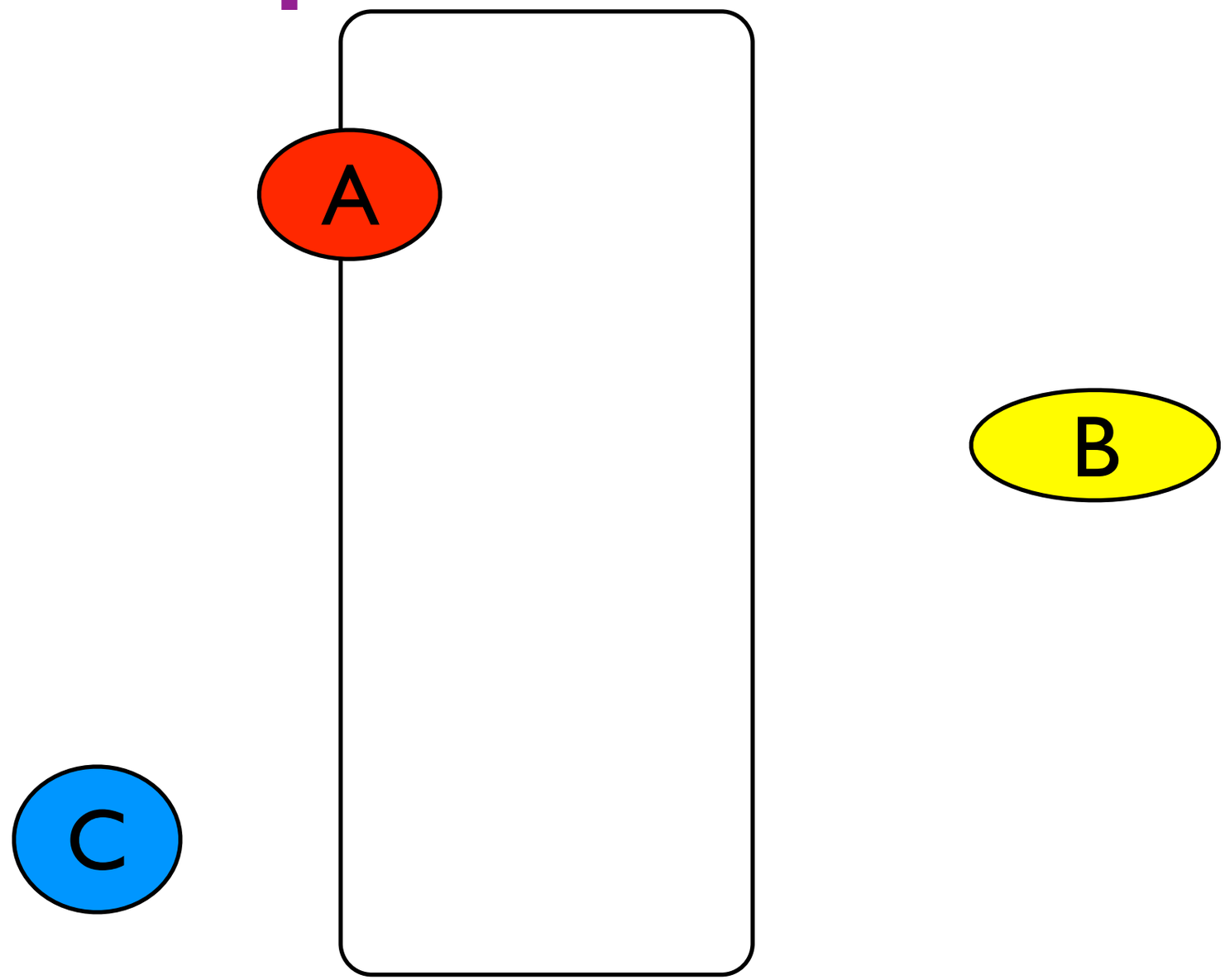

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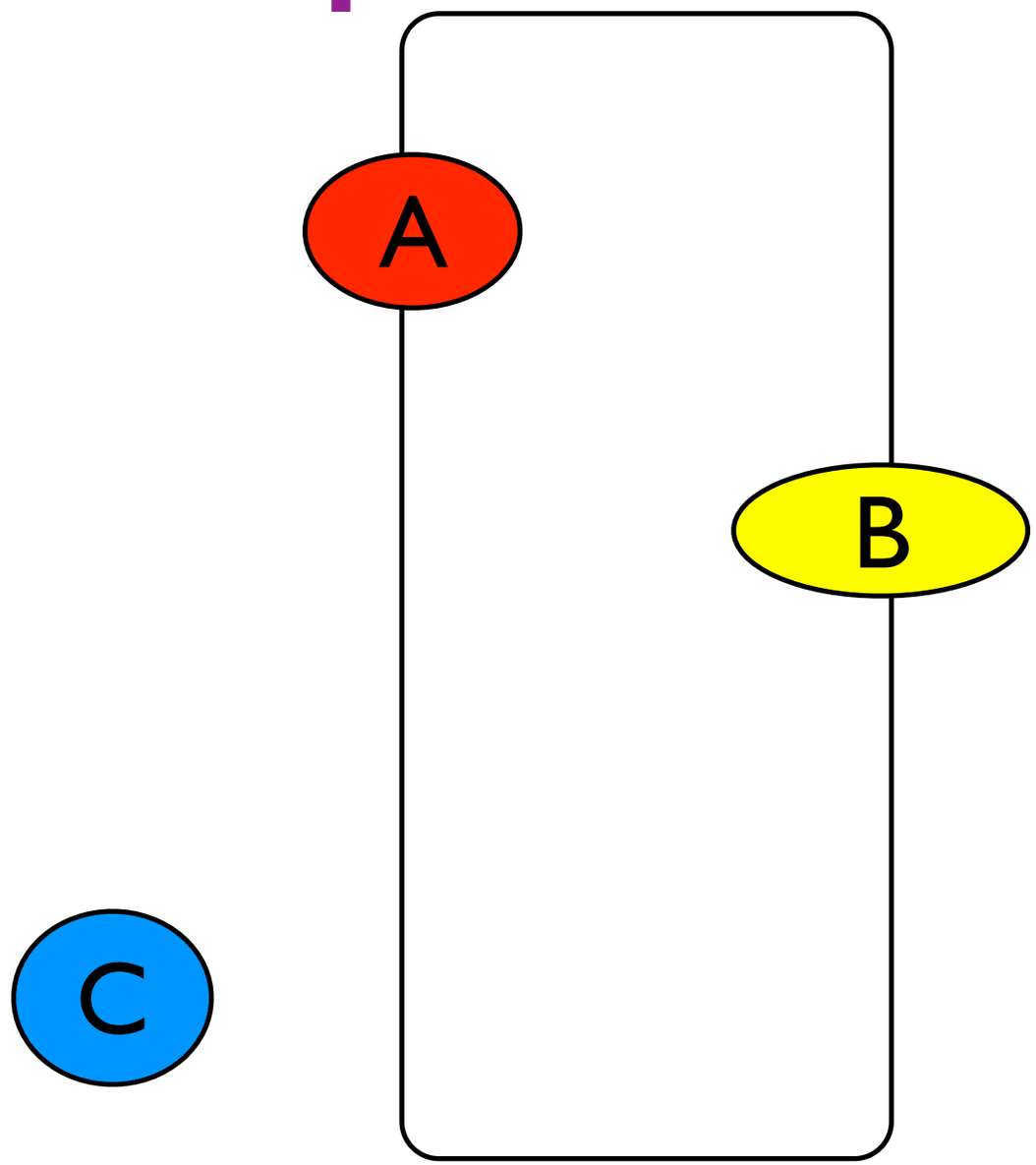

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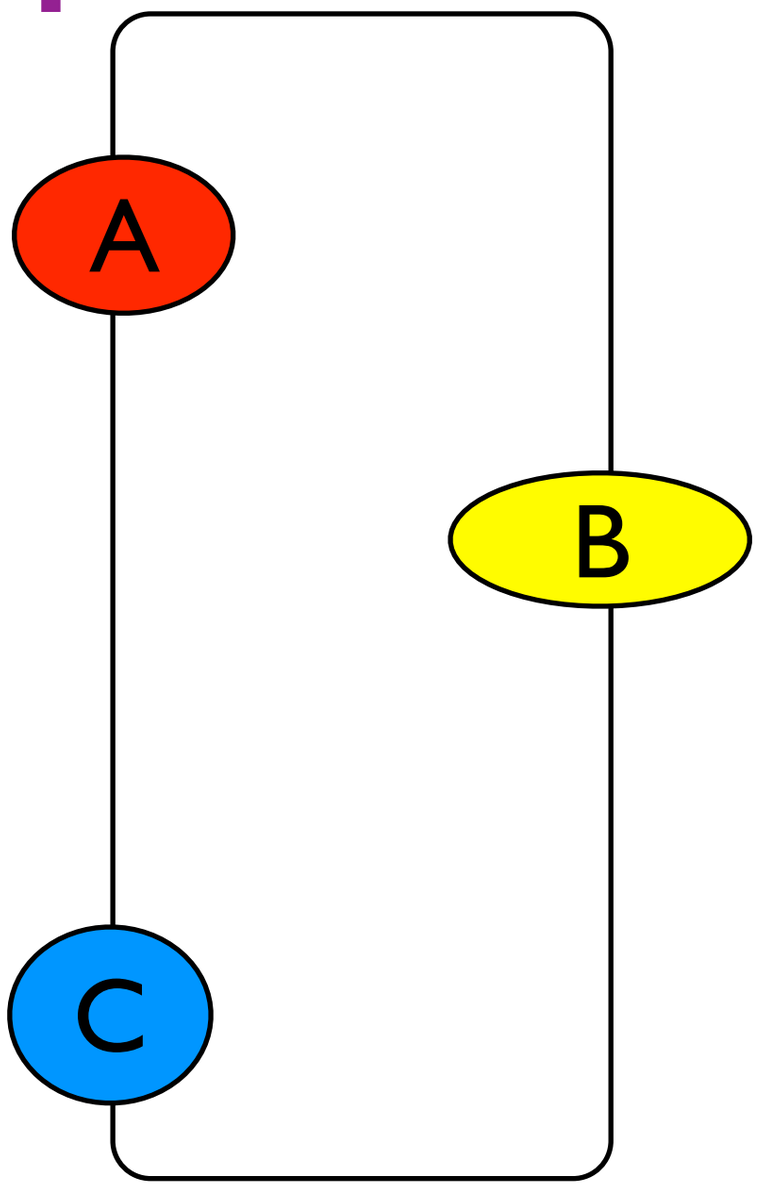

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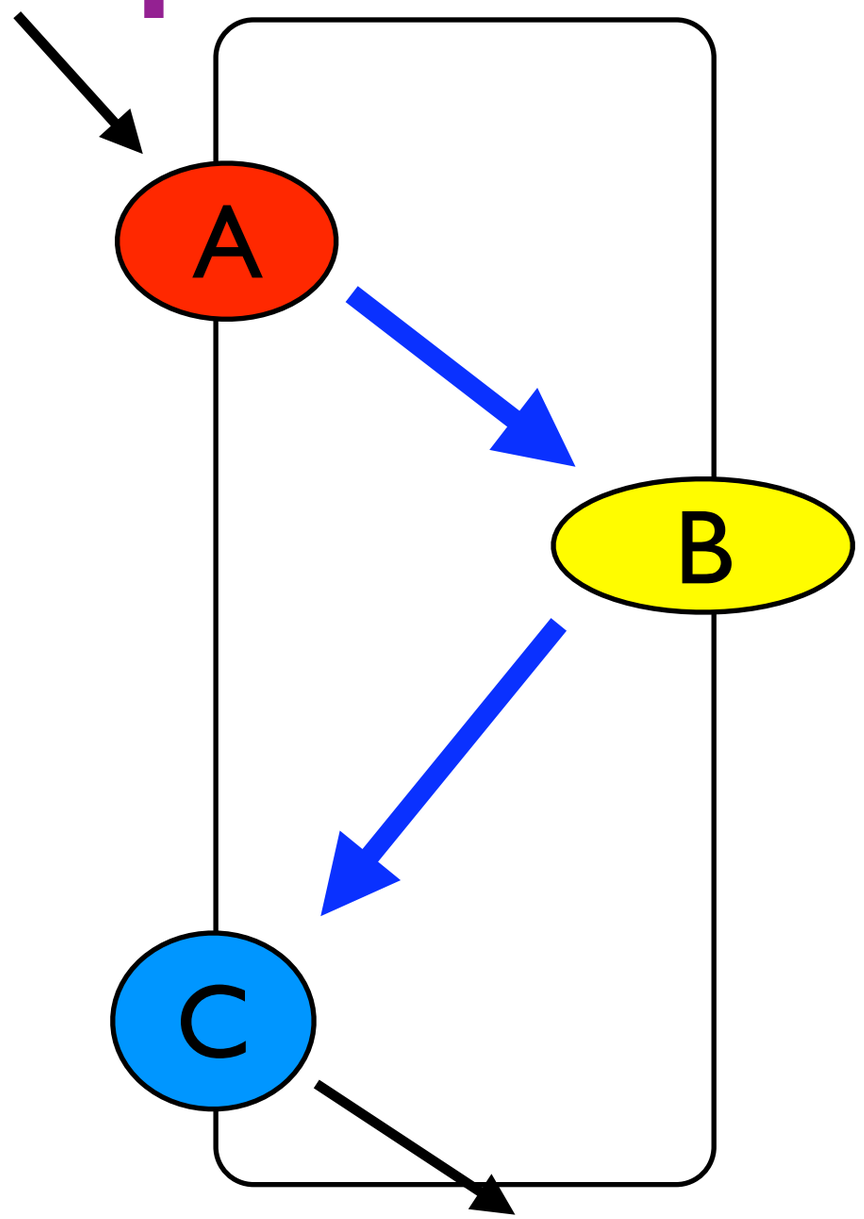
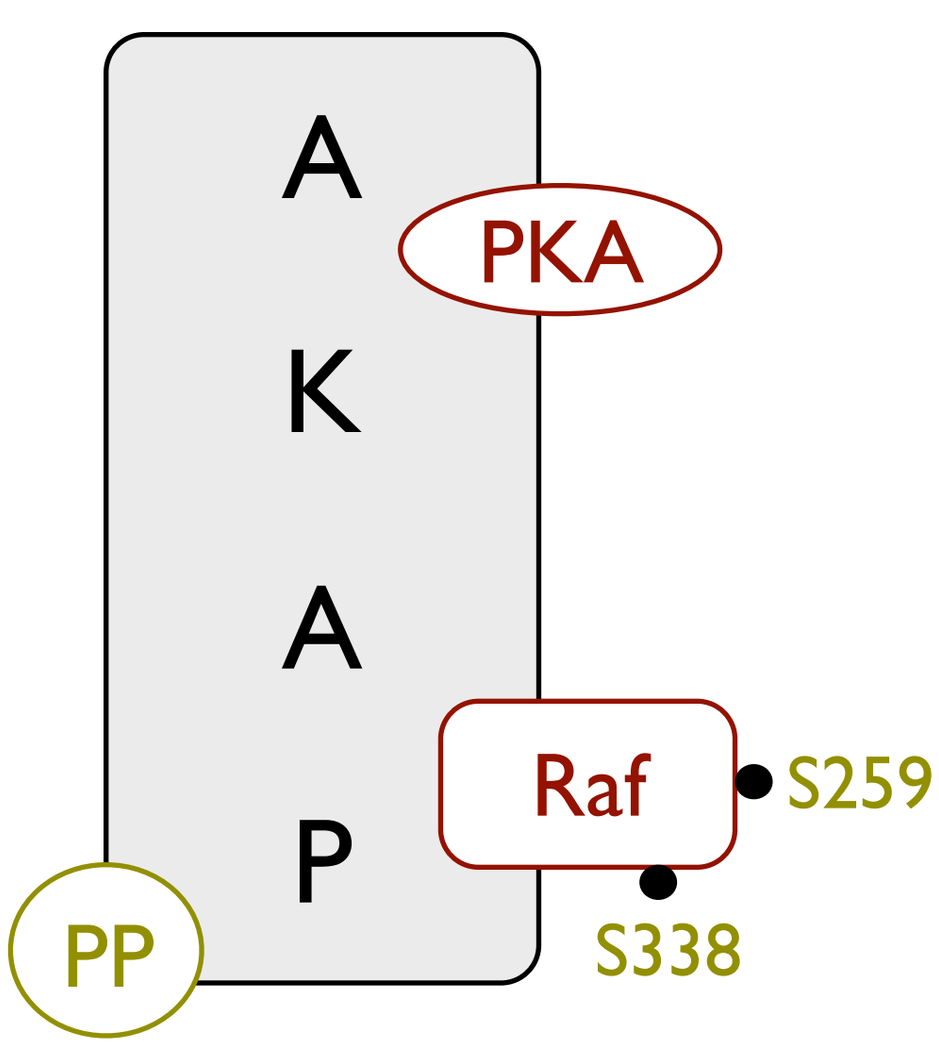


AKAP

(A-kinase anchoring protein)



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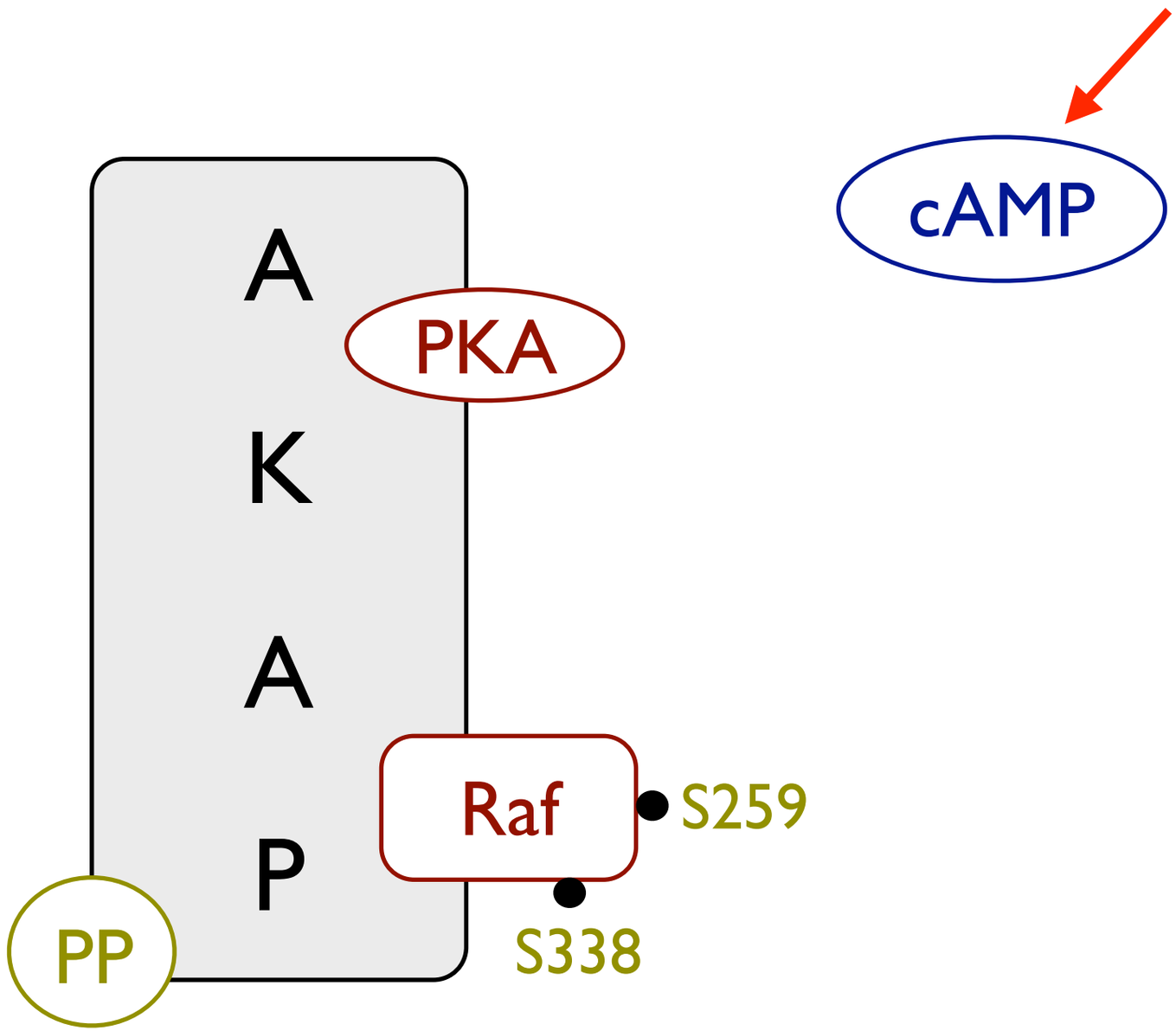

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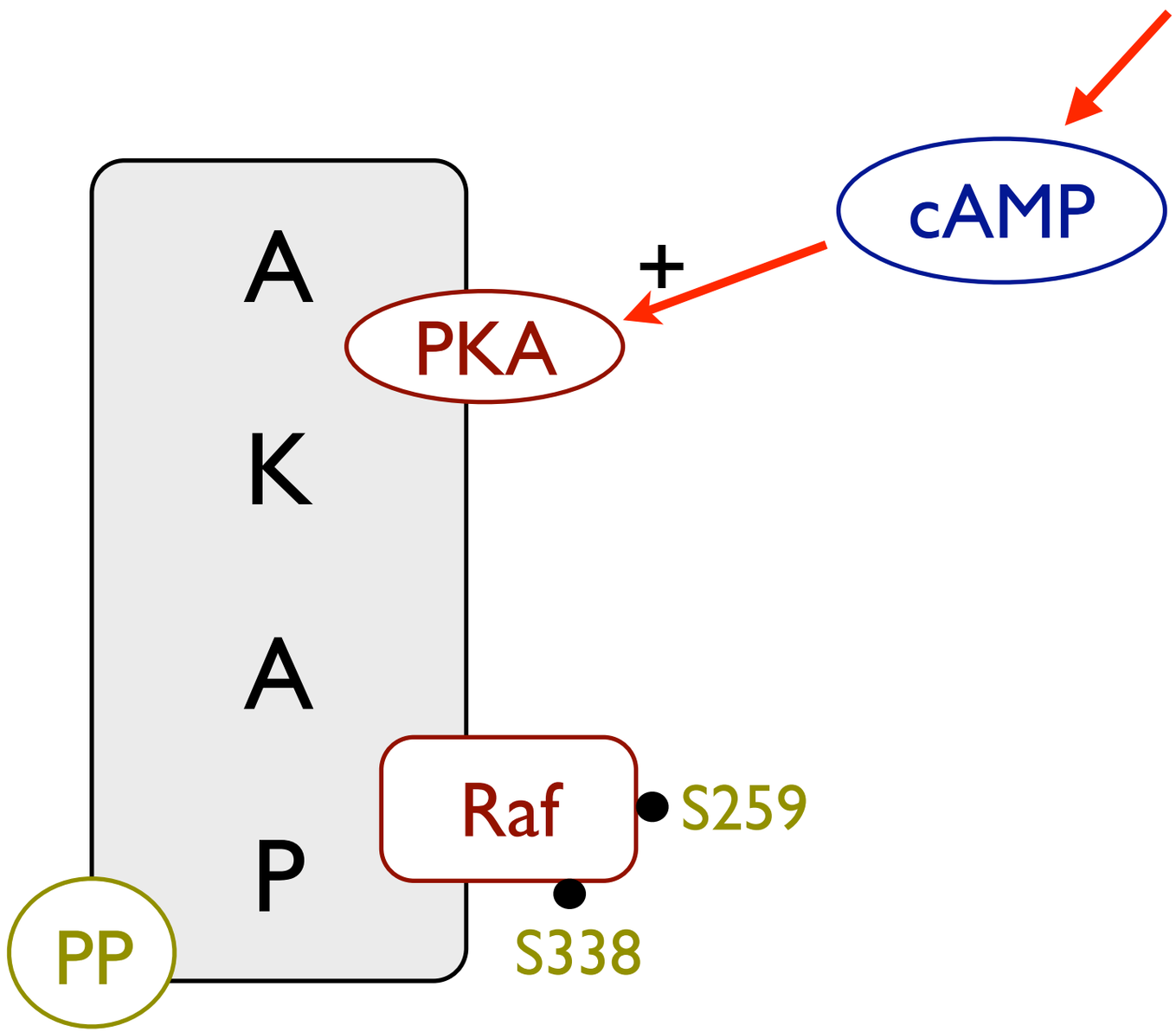

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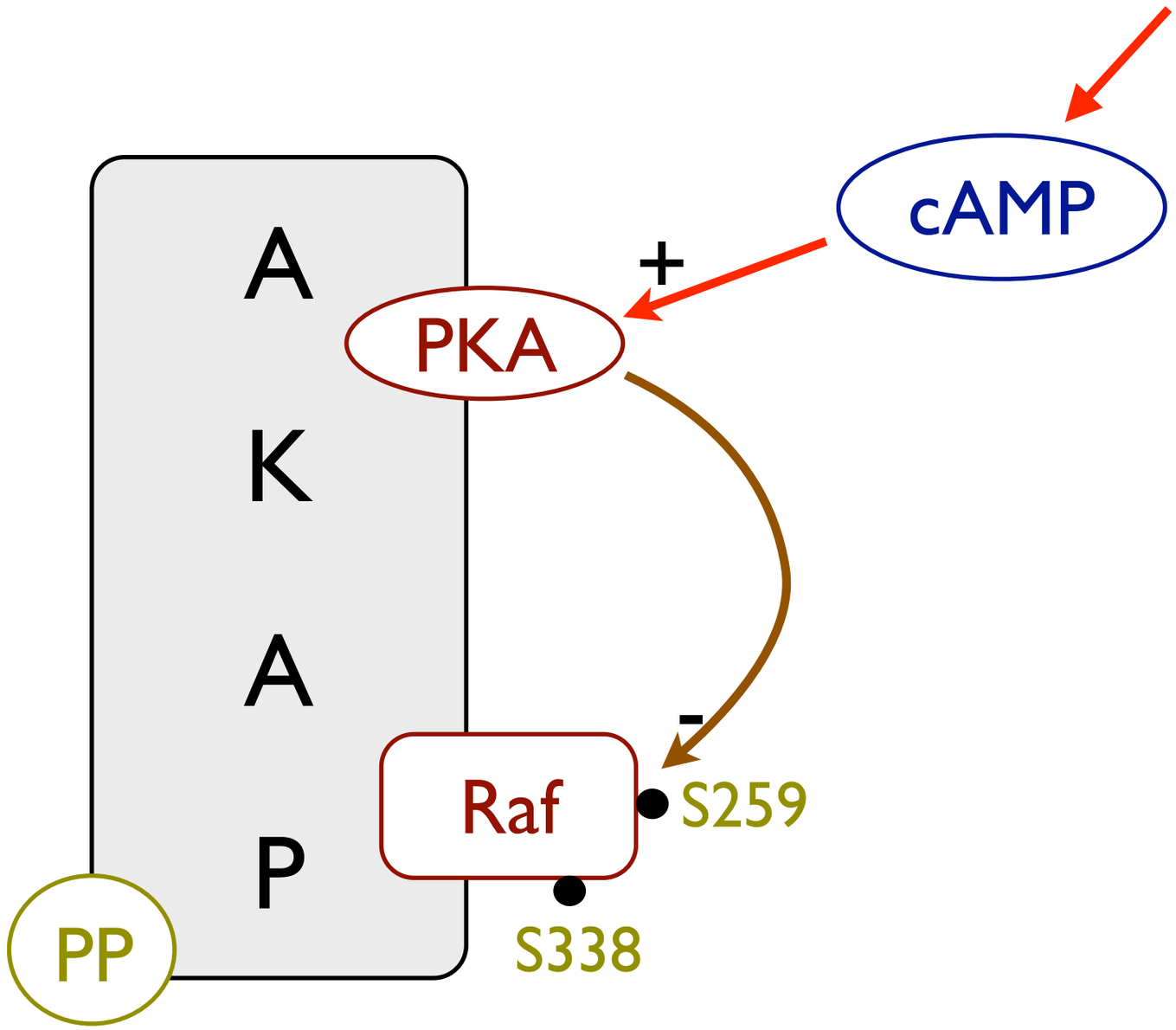

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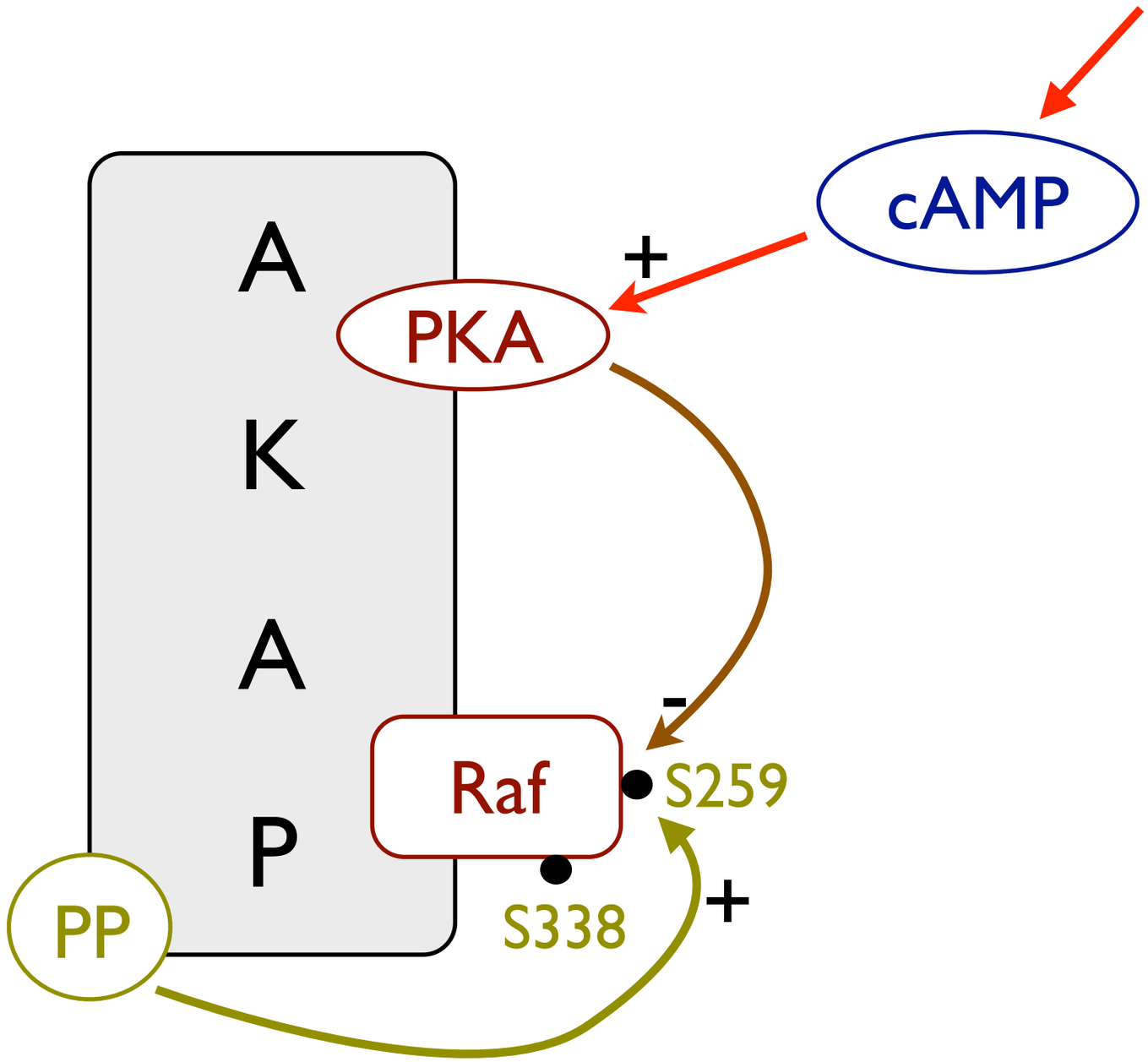

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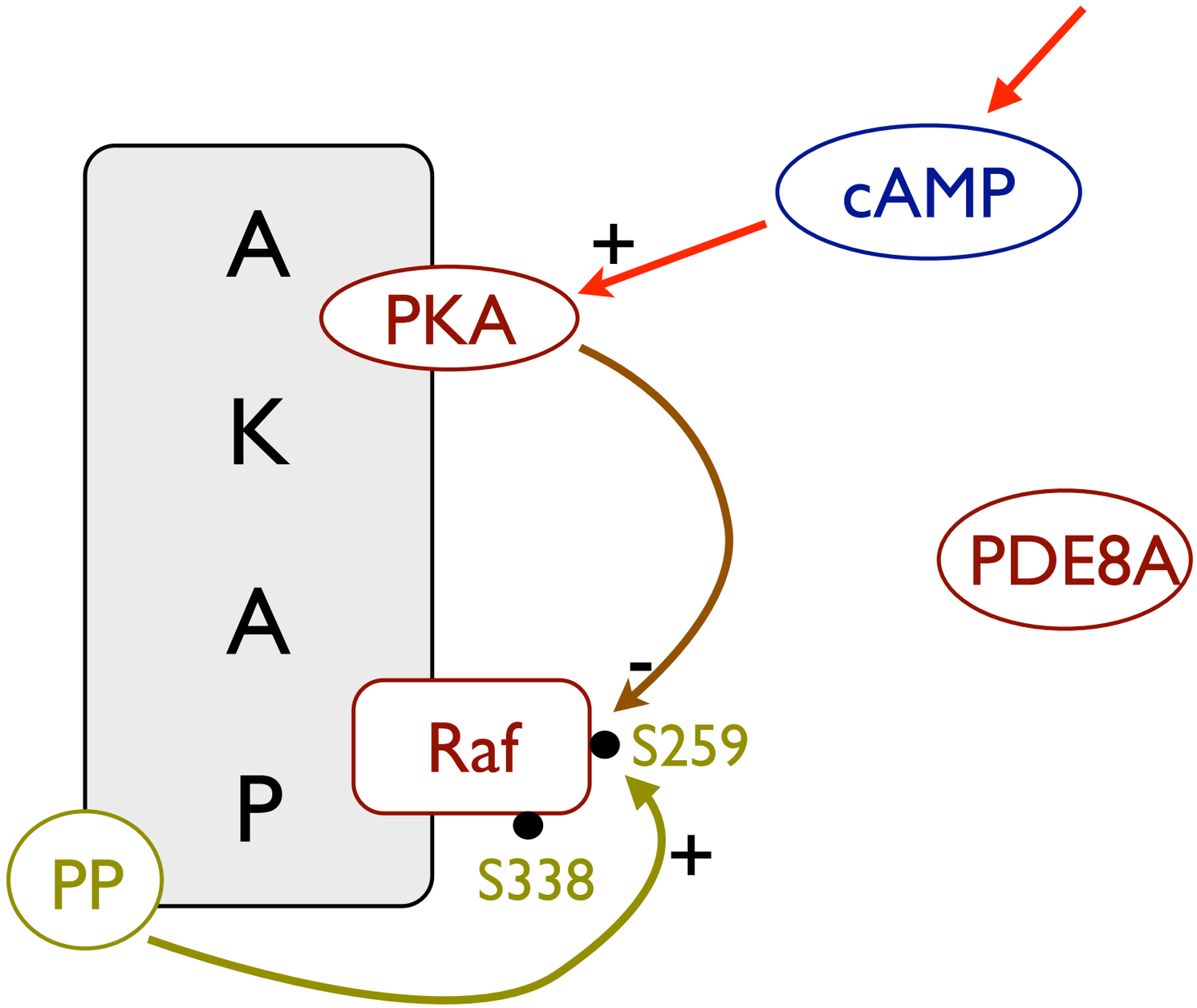

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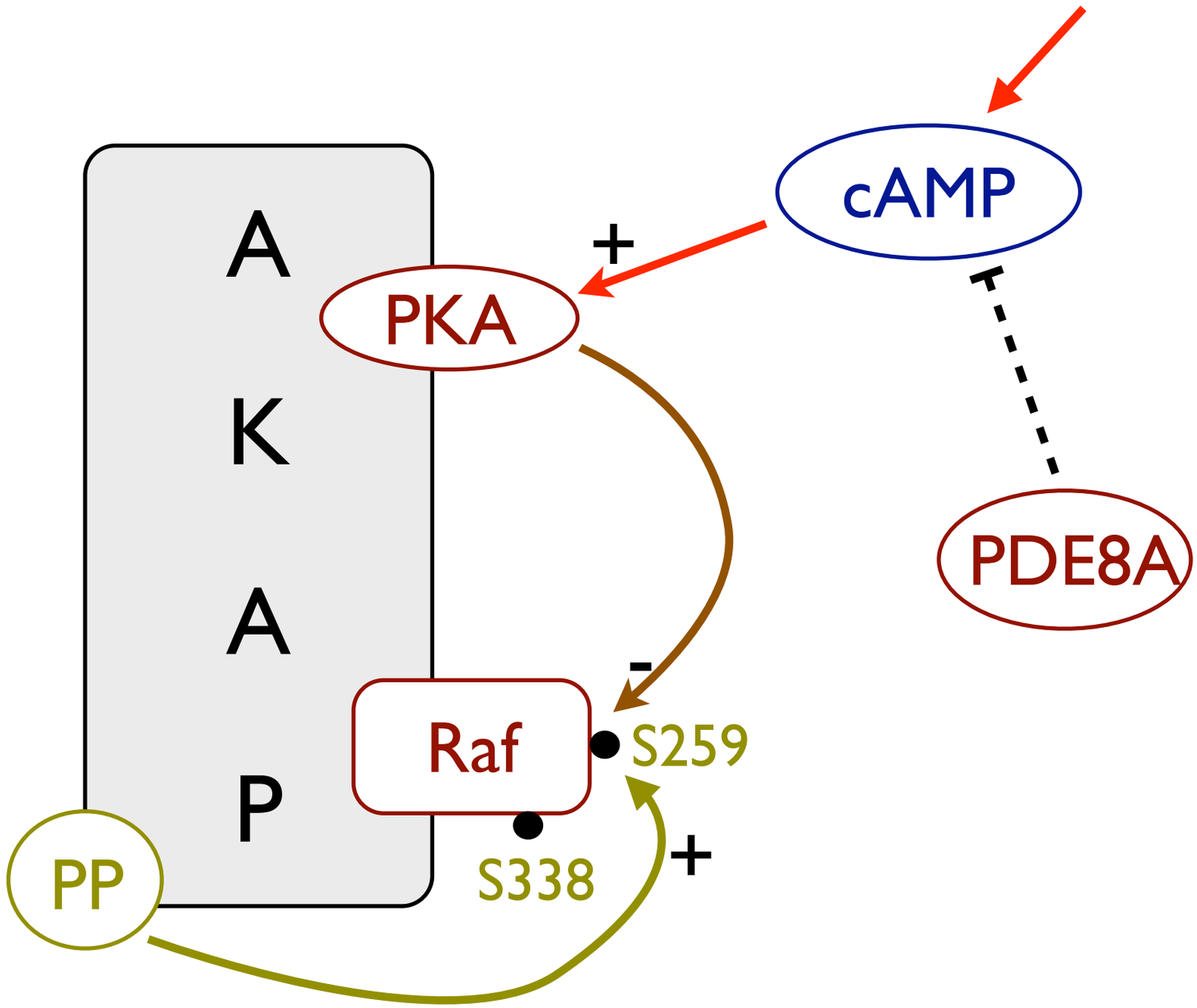

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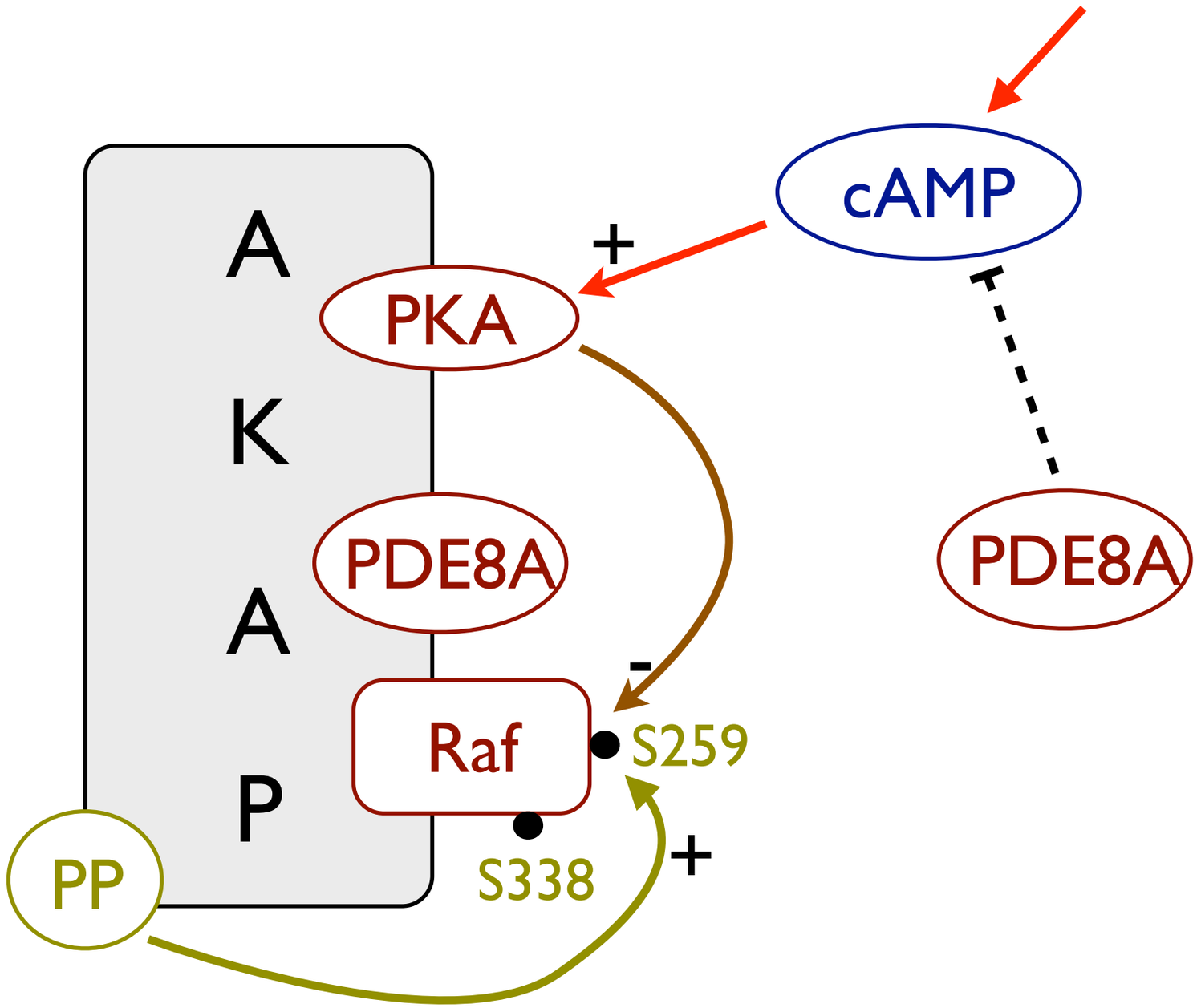

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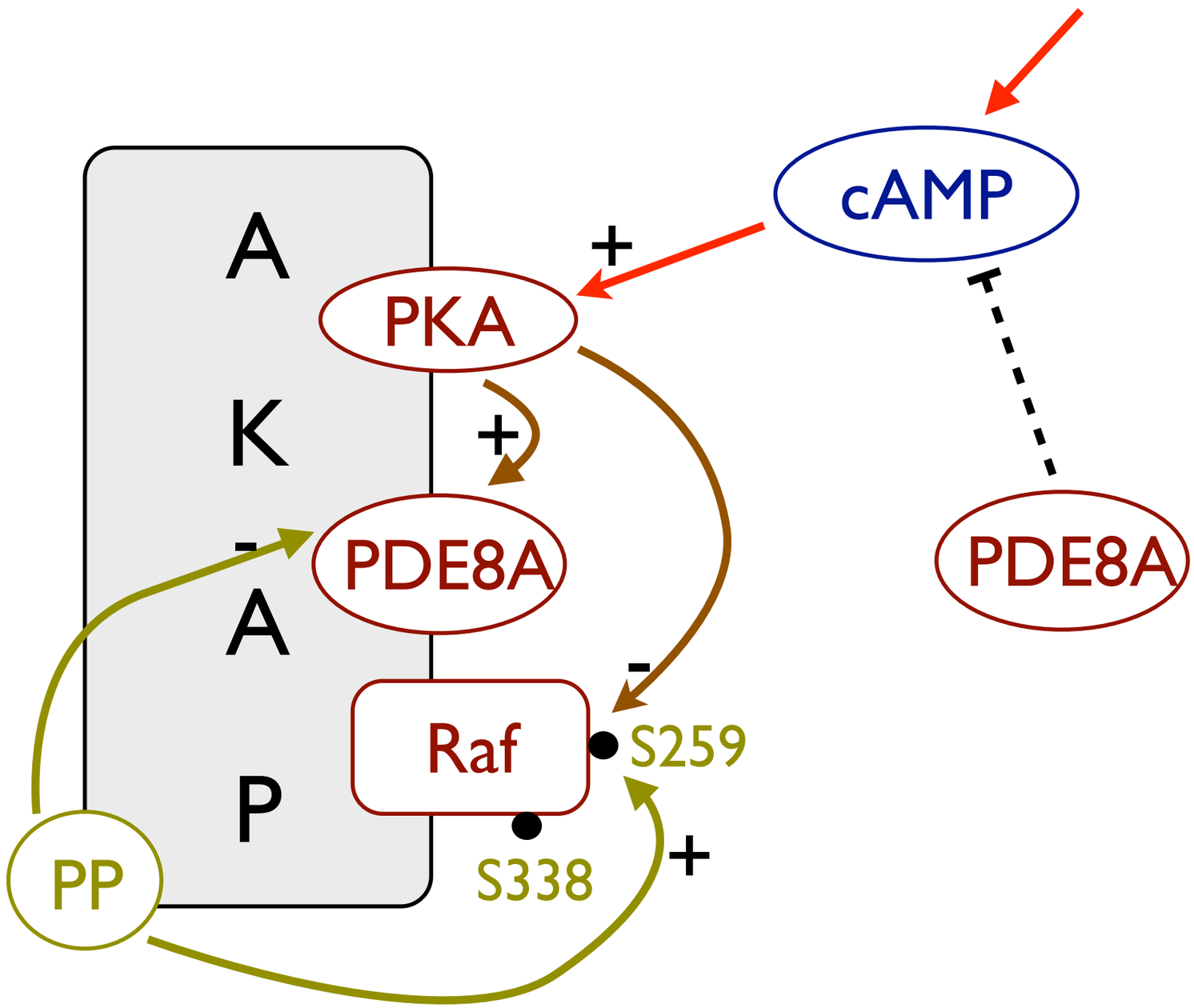

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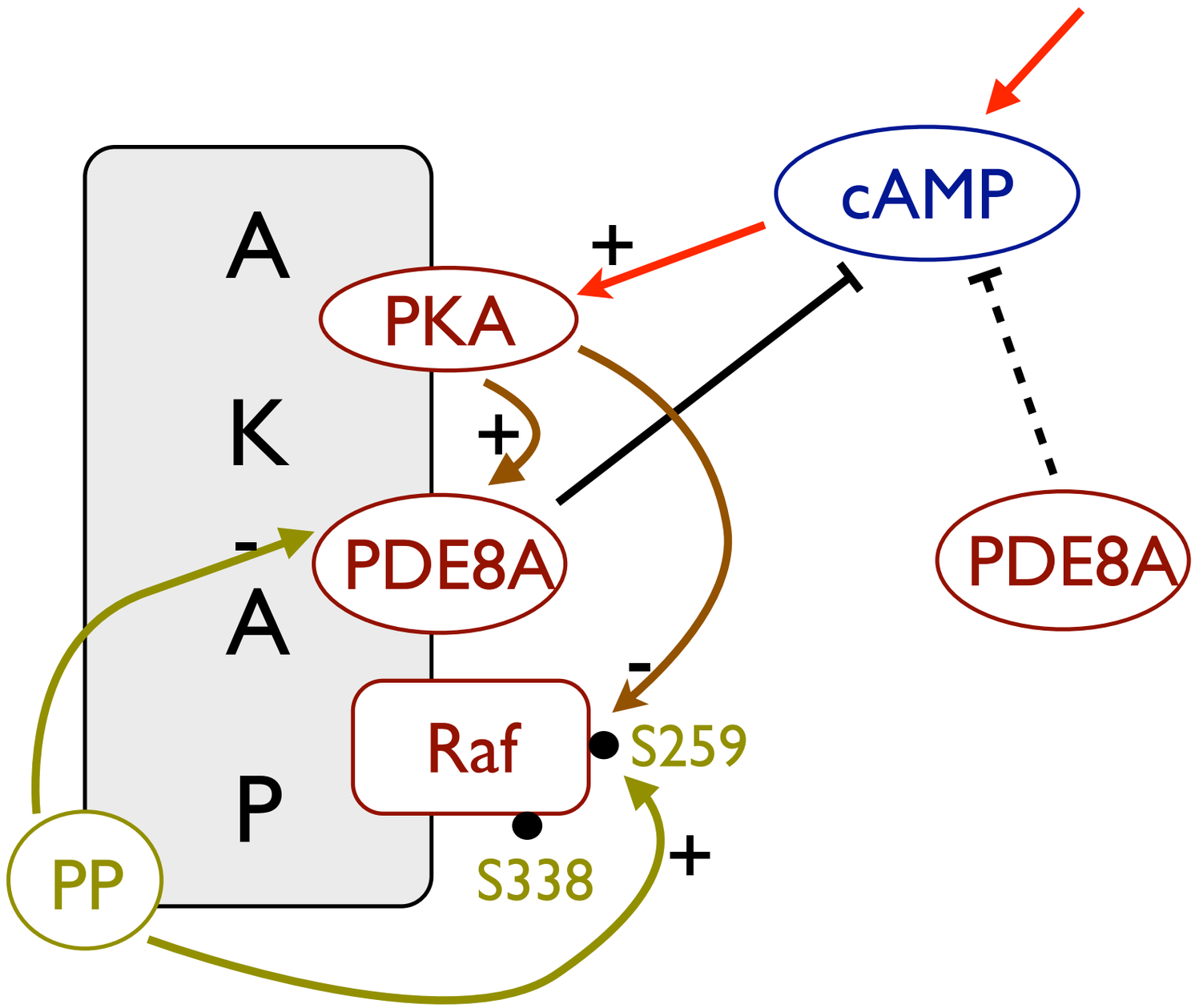
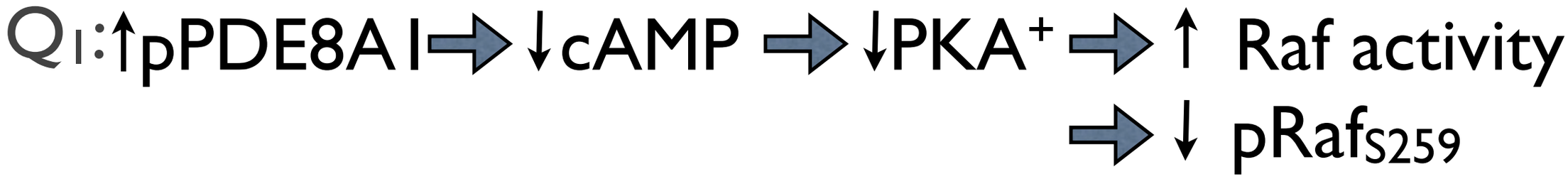


Expected Behaviour



What is the time relation or causality between events?

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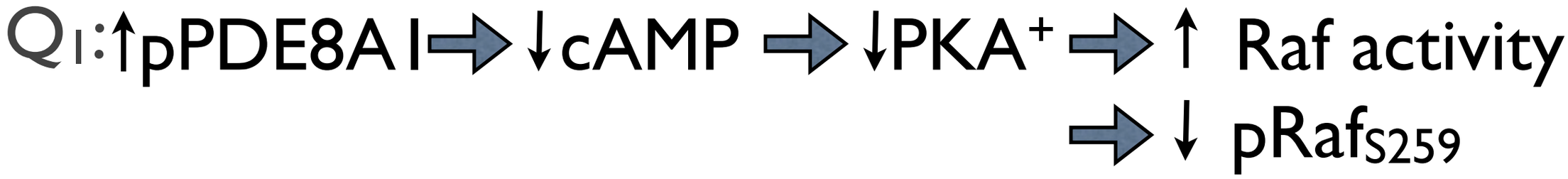


What is the time relation or causality between events?

Q_2: Pulsating behaviour

Formal model

- continuous time Markov chains with levels
- properties expressed as formulas in Continuous Stochastic Logic (CSL)
- symbolic probabilistic model checker PRISM

PRISM model

- modules for cAMP, scaffold, free PDE8A1, PP
- mass action kinetics
- information on constant rates ratios

PRISM model

The PKA activation reaction S000 + cAMP $\rightarrow_{r2}$ S100 is modeled as follows:

- in the module for cAMP:

```
[activate_PKA] (cAMP > basal_camp) -> (cAMP) : (cAMP' = cAMP-1);
```

- in the module for the scaffold:

```
[activate_PKA] (S000 > 0) & (S100 < scaffold_max) ->
               (r2*S000) : (S100' = S100+1) & (S000' = S000-1);
```

Continuous Stochastic Logic

- extension of non-probabilistic CTL
- probability operator P
- steady-state operator S

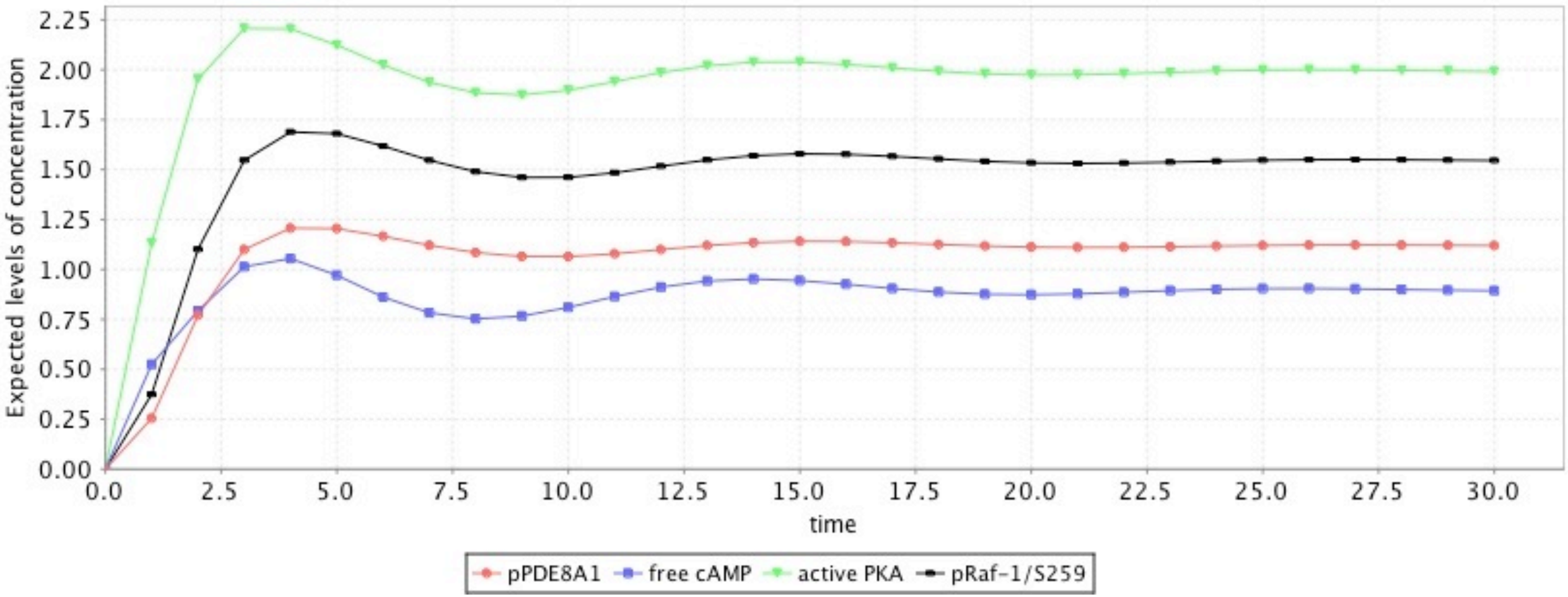
$$\begin{array}{ll} \text{State formulae} & \Phi ::= \top \mid a \mid \neg\Phi \mid \Phi \wedge \Phi \mid \mathsf{P}_{\bowtie p}[\phi] \mid \mathsf{S}_{\bowtie p}[\Phi] \\ \text{Path formulae} & \phi ::= \mathsf{X}\,\Phi \mid \Phi\ \mathsf{U}^{I}\ \Phi \end{array}$$

Reward-based properties

- use of rewards (or costs) in CSL
  - real values assigned to states or transitions
  - to track variable values in states
  - to compute the expected value of a variable at a given time

Reward-based properties

- state rewards for computing the expected levels for cAMP, pPDE8A1, PKA^{+}, pS259



Trend Variables

- keep track of decreasing or increasing variable values
- define new variables in the PRISM modules for cAMP, PKA^+ and pS259

  cAMP' = cAMP-1 & trend_cAMP' = -1

- $\downarrow x$ ($\uparrow x$) ascending (descending) trend for variable x

Necessarily Preceded

We use the requirement / necessarily preceded pattern [Monteiro et al. 08]:

"a state φ is reachable and is necessarily preceded all the time by a state ψ"

CTL: $(EF\ \varphi) \wedge AG((\neg\psi) \Rightarrow AG(\neg\ \varphi))$

Necessarily Preceded

For $\varphi = \downarrow cAMP \wedge \downarrow PKA^{+}$ and $\psi = \uparrow pPDE8A1$

CTL: $(EF\ \varphi) \wedge AG((\neg\psi) \Rightarrow AG(\neg\ \varphi))$

CSL: $P_{>0}[F\ \varphi] \wedge P_{\leq 0}[F(\neg((\neg\ \psi) \Rightarrow P_{\geq 1}[F(\neg\ \varphi)]))]$

Pulsations

Show that the levels of pPDE8A1 fluctuate:

- φ = $\uparrow$pPDE8A1 and ψ = $\downarrow$pPDE8A1
- pulsation in CTL [Fages05,Ballarini et al. 09]:

$$AG((\varphi \Rightarrow EF\psi) \wedge (\psi \Rightarrow EF\varphi))$$

- pulsation in CSL:

$$P_{\leq 0}[F\ (\neg(\varphi \Rightarrow P_{>0}[F\psi]) \vee \neg(\psi \Rightarrow P_{>0}[F\varphi])$$

Pulsations

- for cAMP: $\varphi = \uparrow cAMP$ and $\psi = \downarrow cAMP$
- for PKA^+: $\varphi = \uparrow PKA^+$ and $\psi = \downarrow PKA^+$
- coordinated pulsations:

$\varphi = \uparrow pPDE8A1 \wedge \downarrow cAMP \wedge \downarrow PKA^+$ and

$\psi = \downarrow pPDE8A1 \wedge \uparrow cAMP \wedge \uparrow PKA^+$

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- ☑ formal model of a biological process
- ☑ the biologists validated our results
- ☐ refine the model with more experimental data
- ☐ trend variables, amplitude of oscillations
- ☐ formulate new properties and express them using a temporal logic

Acknowledgement

- Walter Kolch, George Baillie and Kim Brown from the Faculty of Biomedical & Life Science, University of Glasgow

Bibliography

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- **[Ballarini et al. 09]** Paolo Ballarini, Radu Mardare, and Ivan Mura. *Analysing Biochemical Oscillation through Probabilistic Model Checking*. ENTCS, 229(1):3--19, 2009

- **[Fages05]** François Fages. *Temporal Logic Constraints in the Biochemical Abstract Machine BIOCHAM.* LOPSTR'05, volume 3901 of LNCS, pages 1--5. Springer, 2005.

Thank you!

Questions?