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

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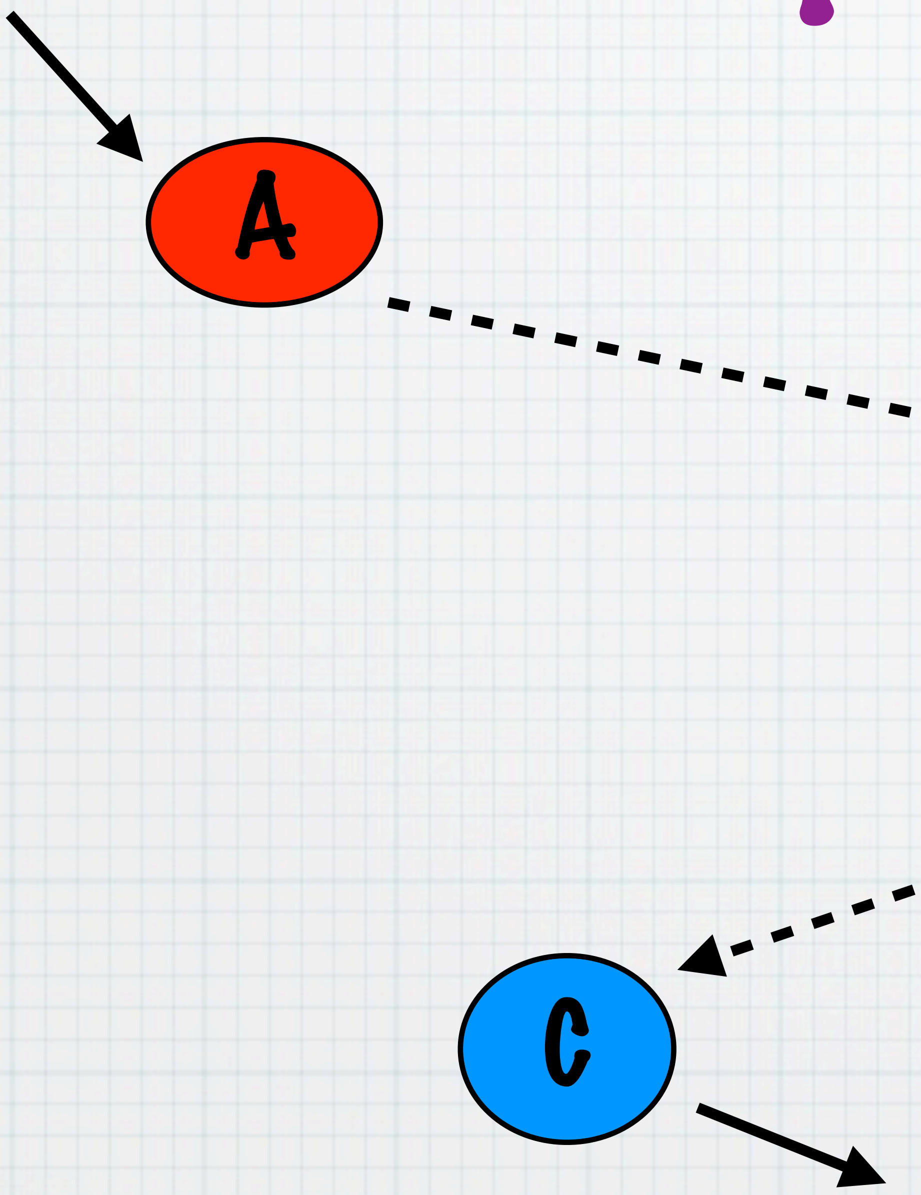
Outline

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

Scaffold proteins

* **organisational role** rather than a signalling role
  - **anchoring function** (binding proteins)
  - **catalytic function** (increasing/decreasing the output of a signaling cascade) under some conditions

Signalling and scaffold proteins



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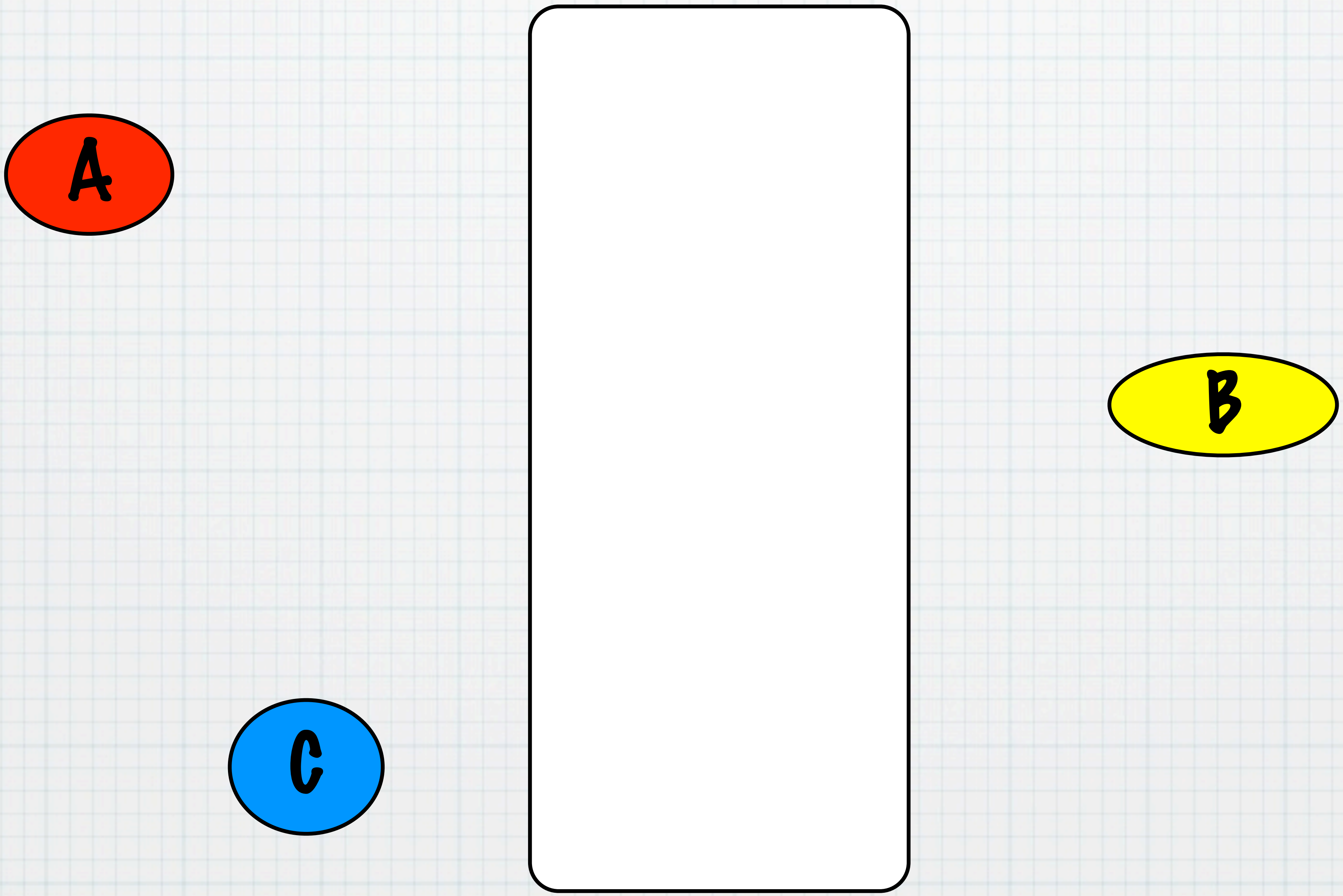

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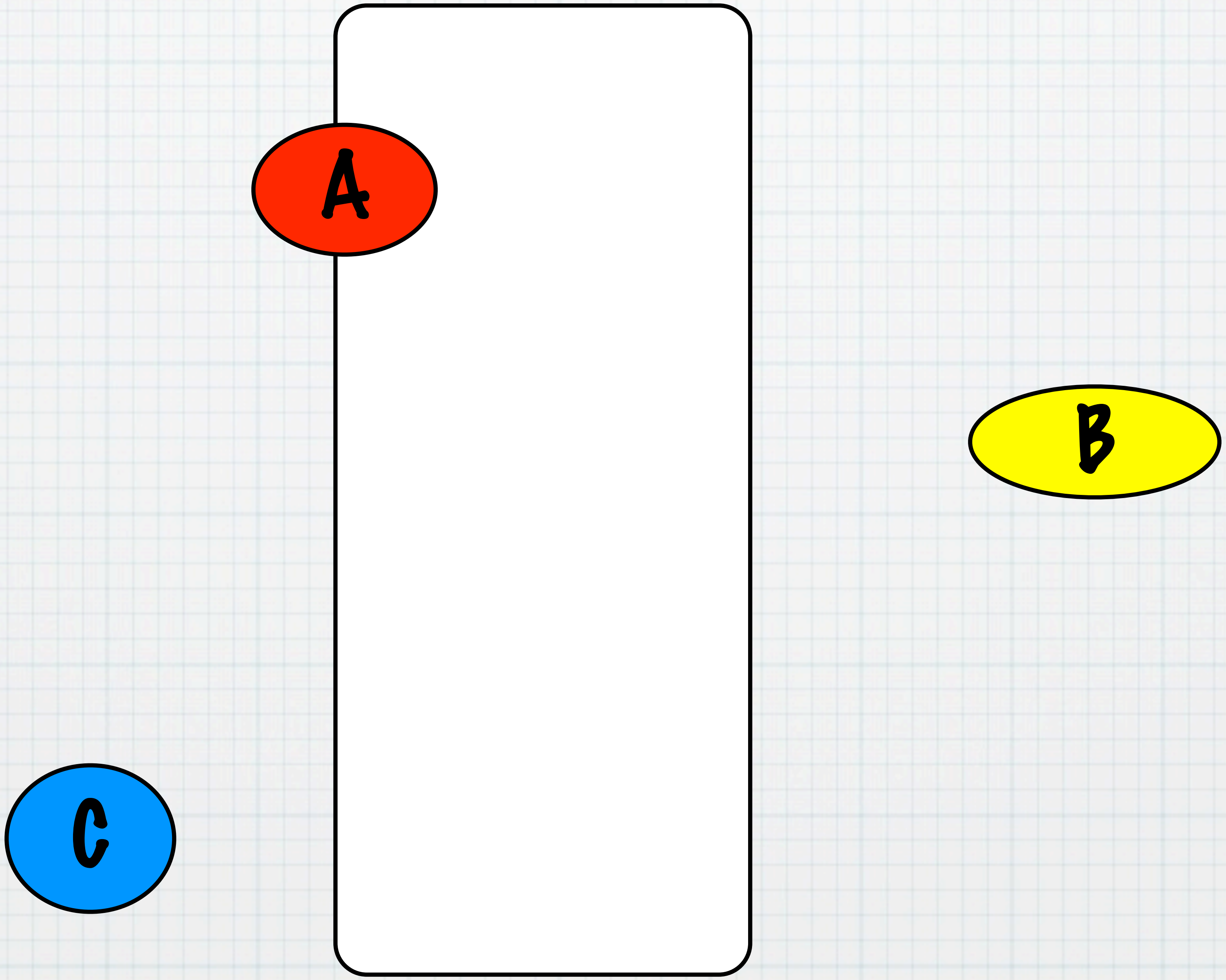

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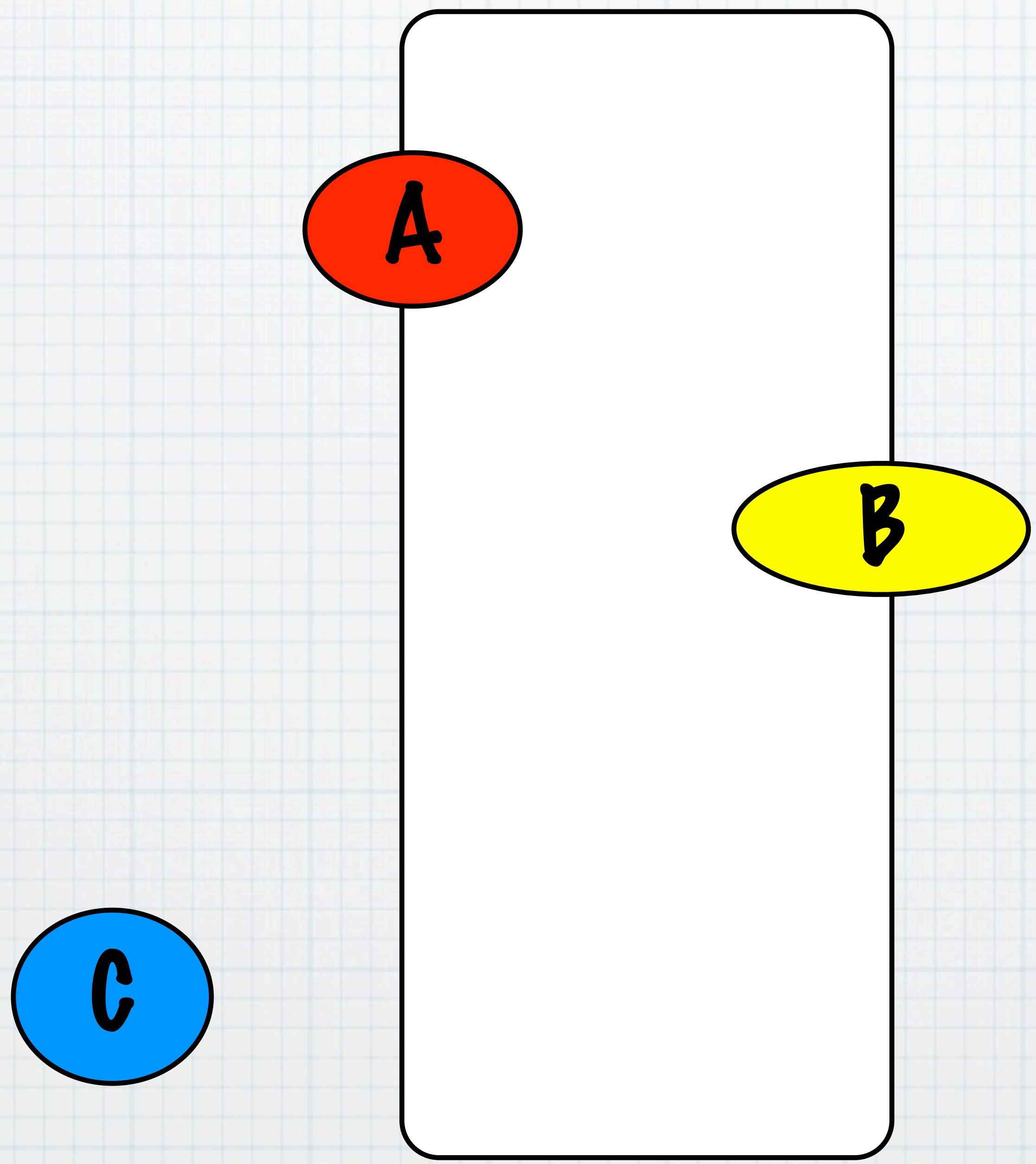

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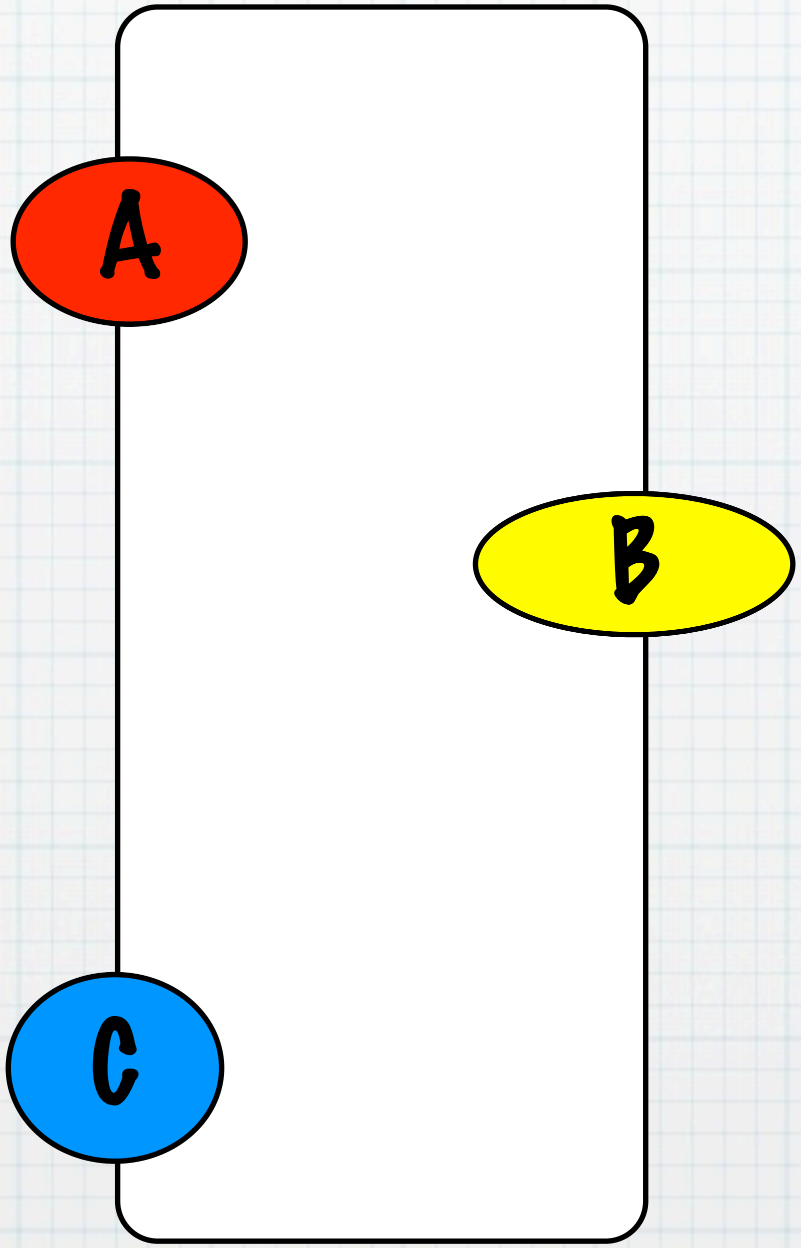

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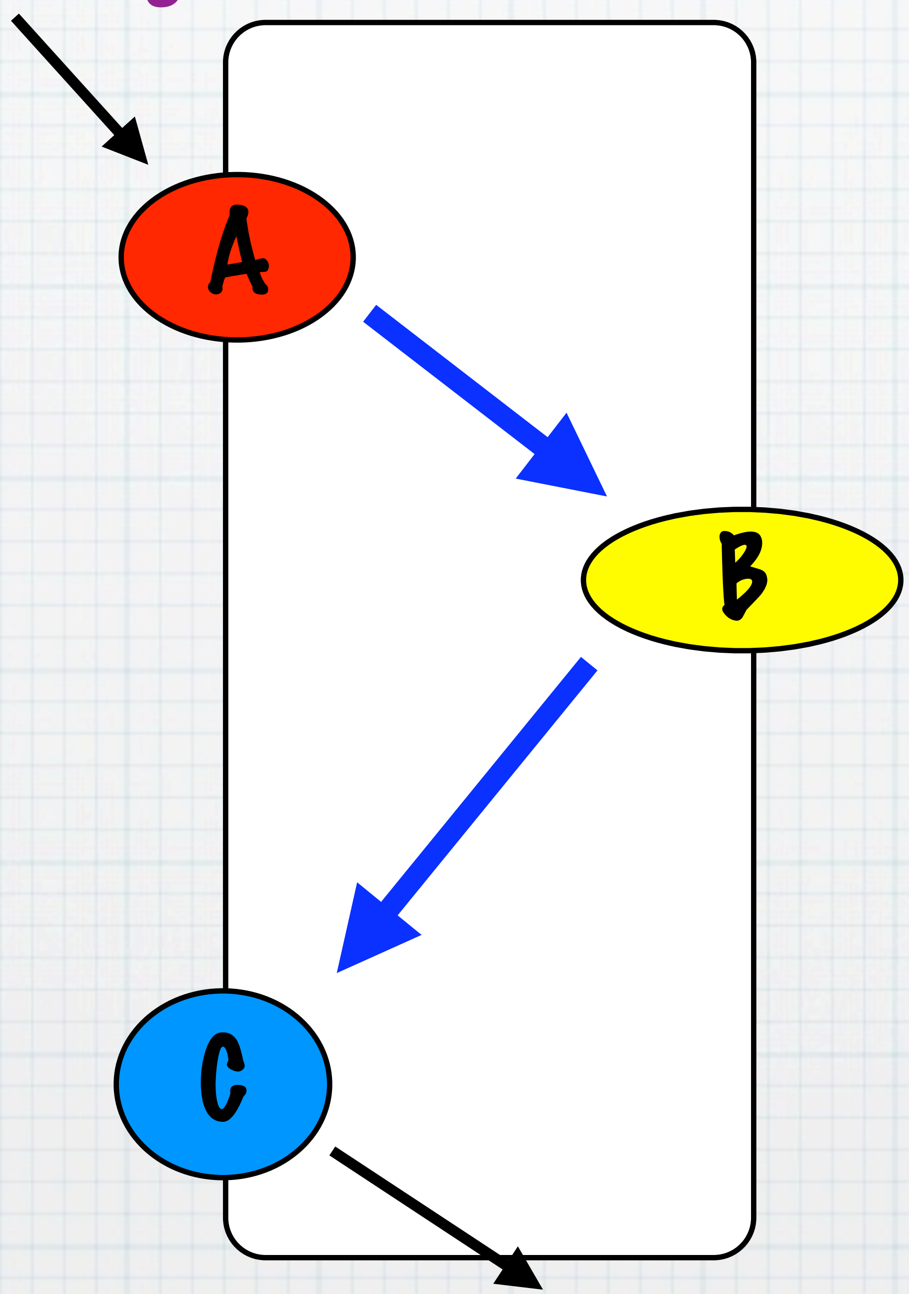
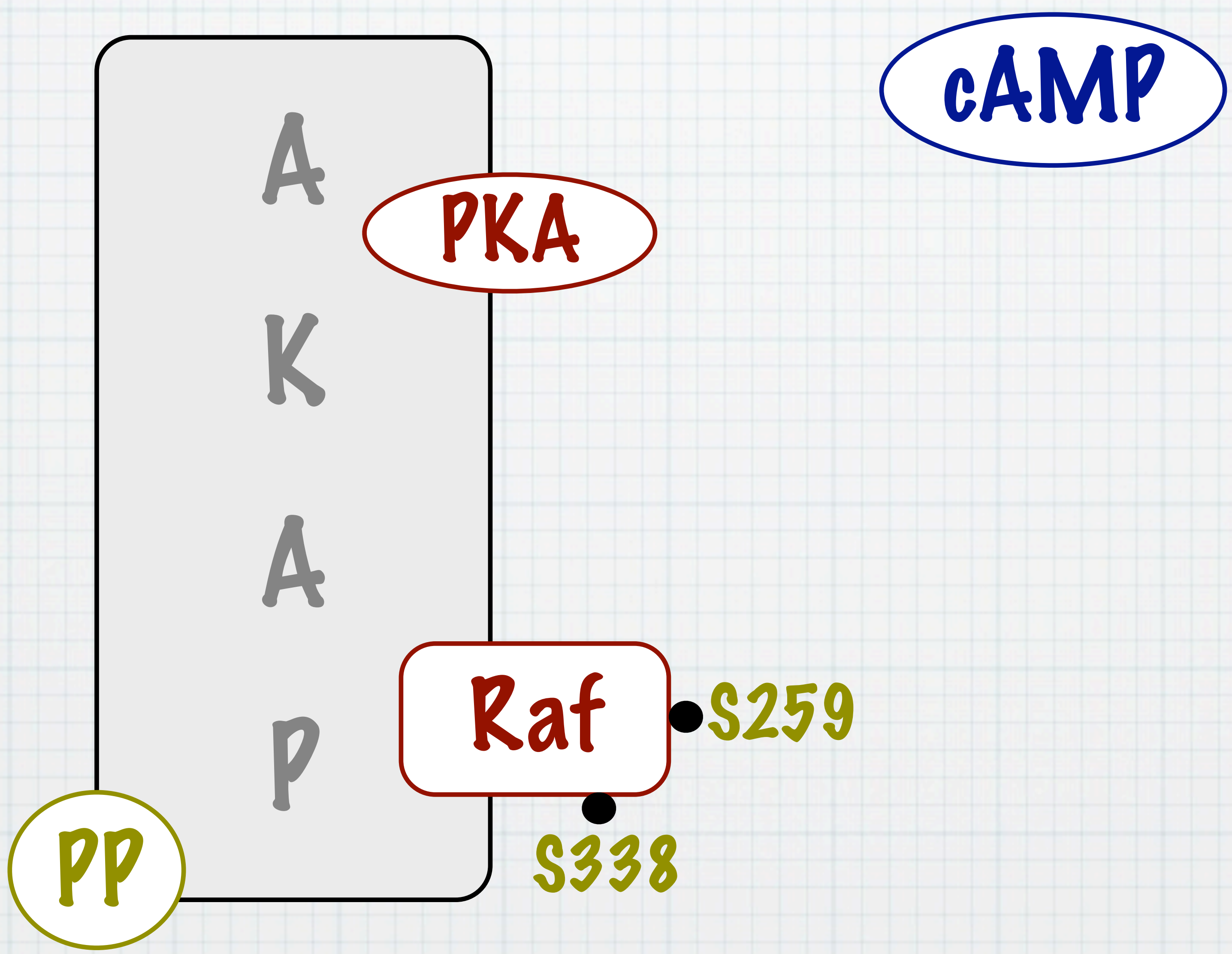


AKAP

* AKAP = A-kinase anchoring protein
* crosstalk between the cAMP and Raf/MEK/ERK pathways

AKAP



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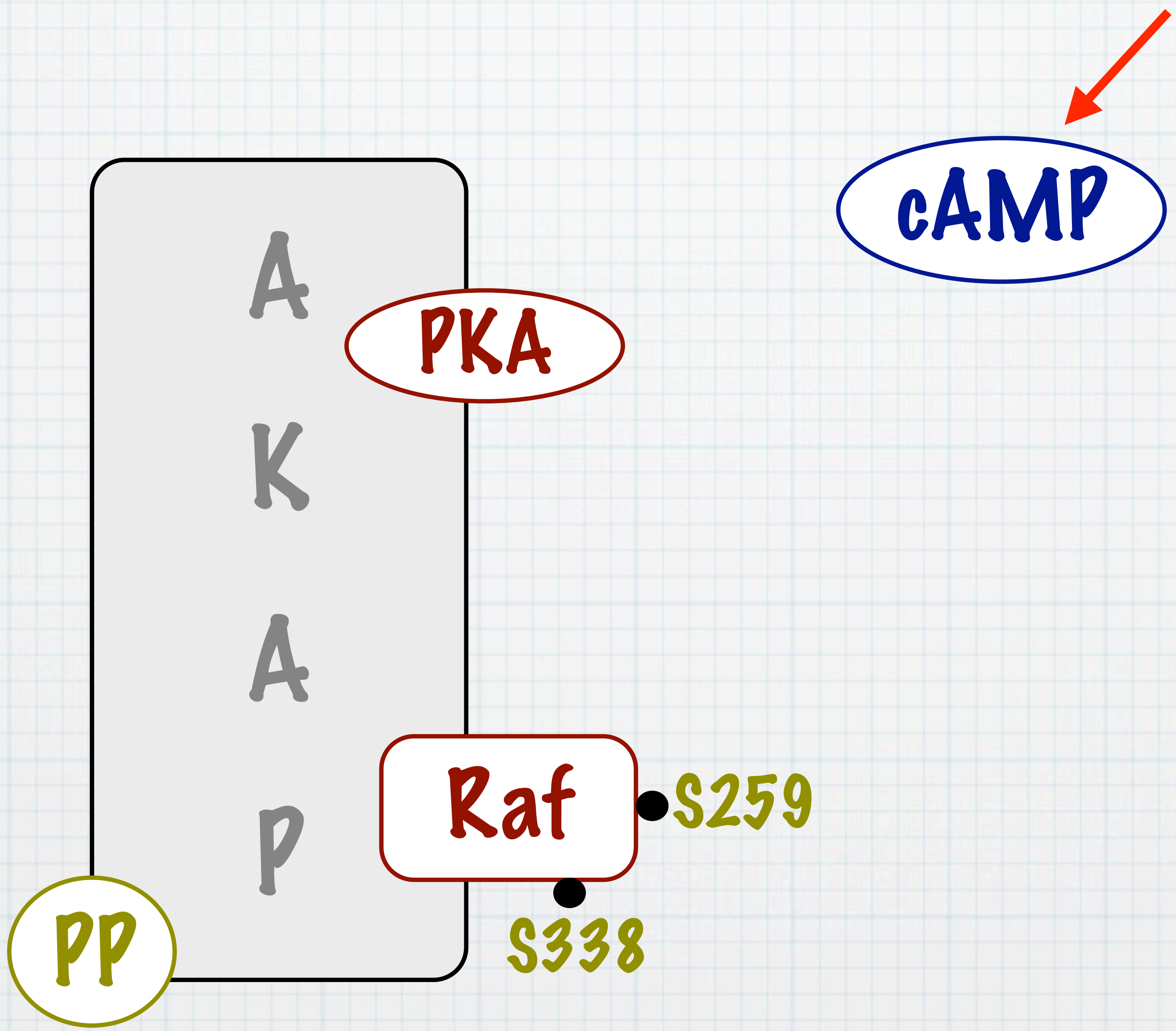

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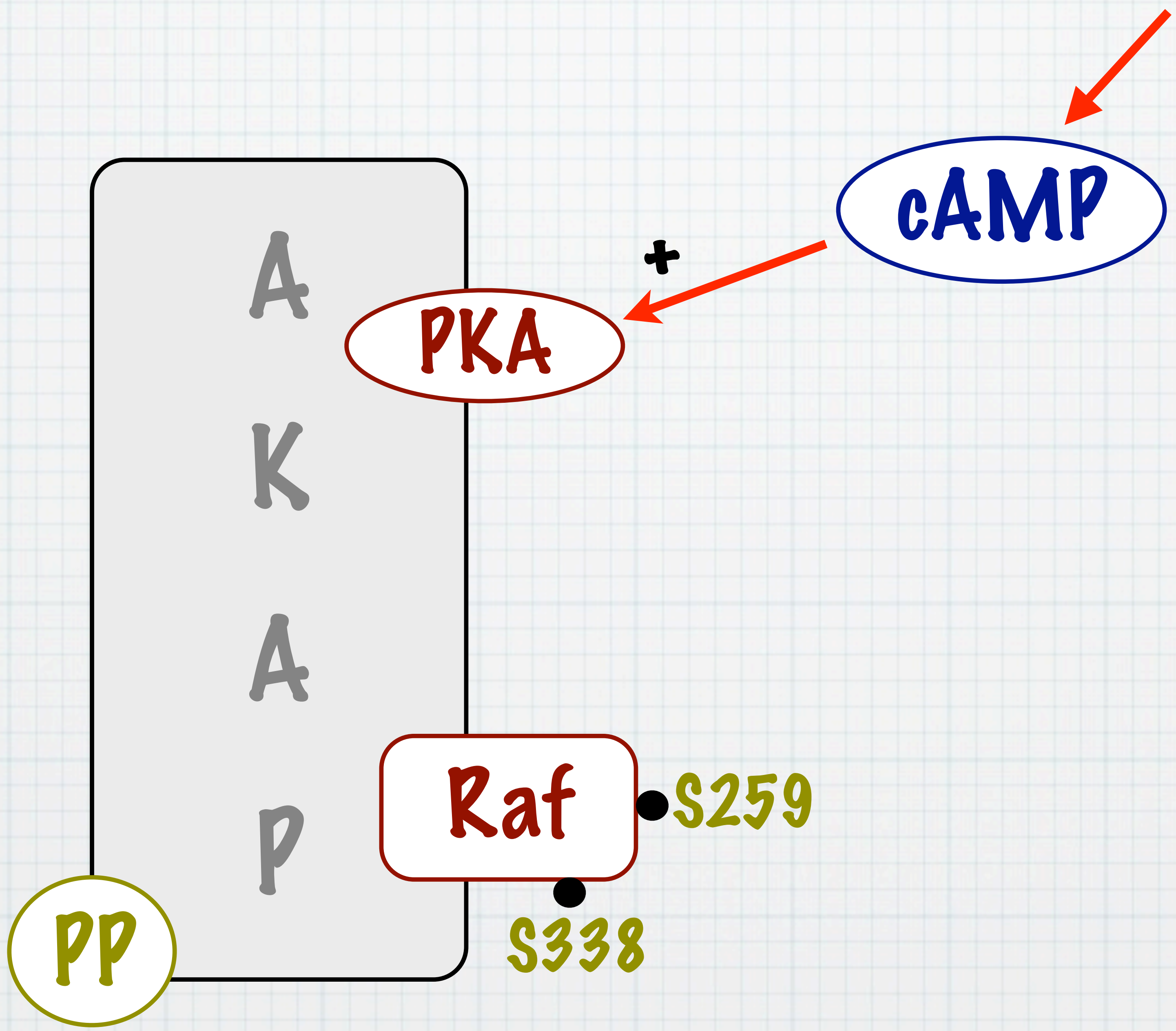

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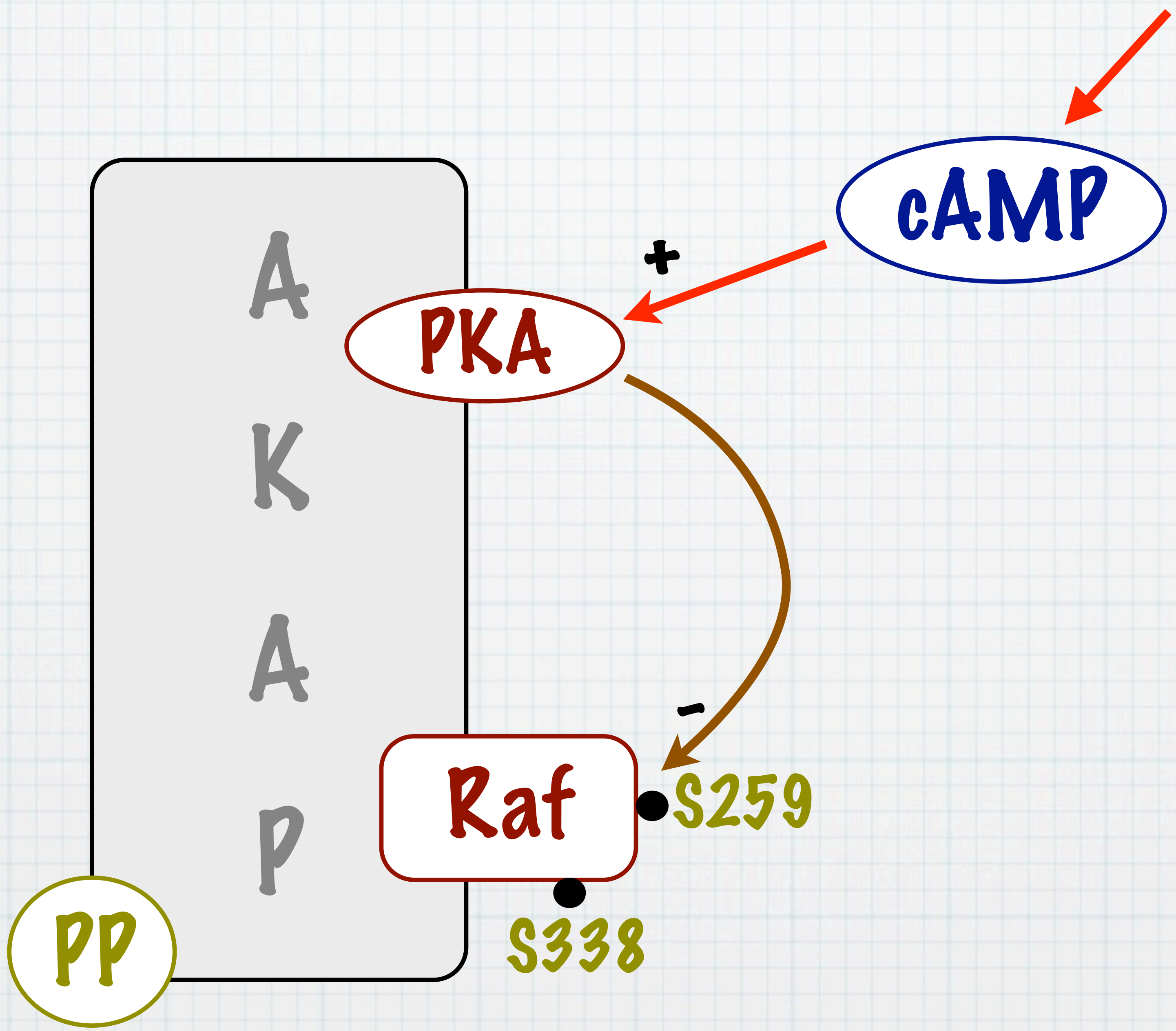

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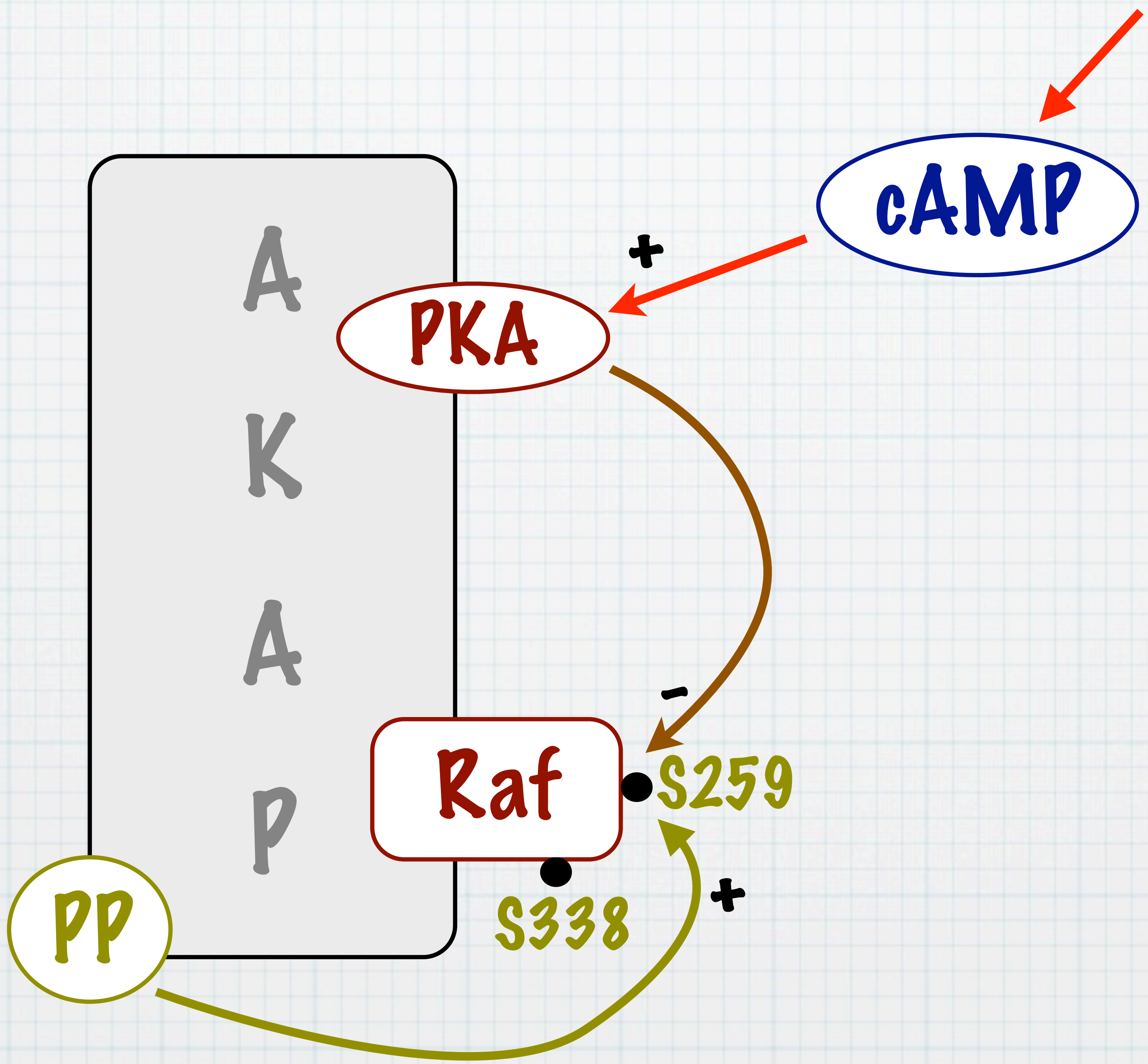

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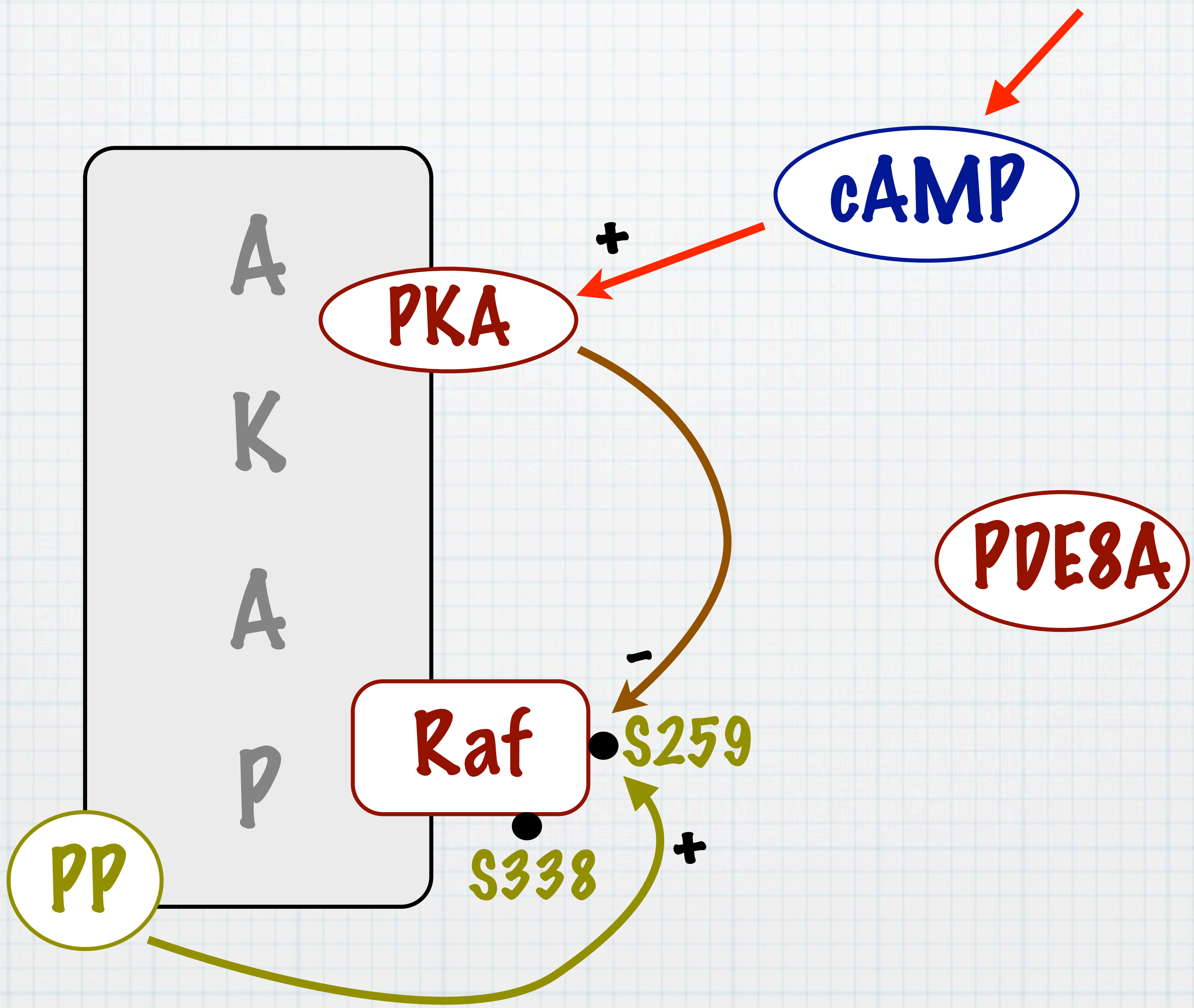

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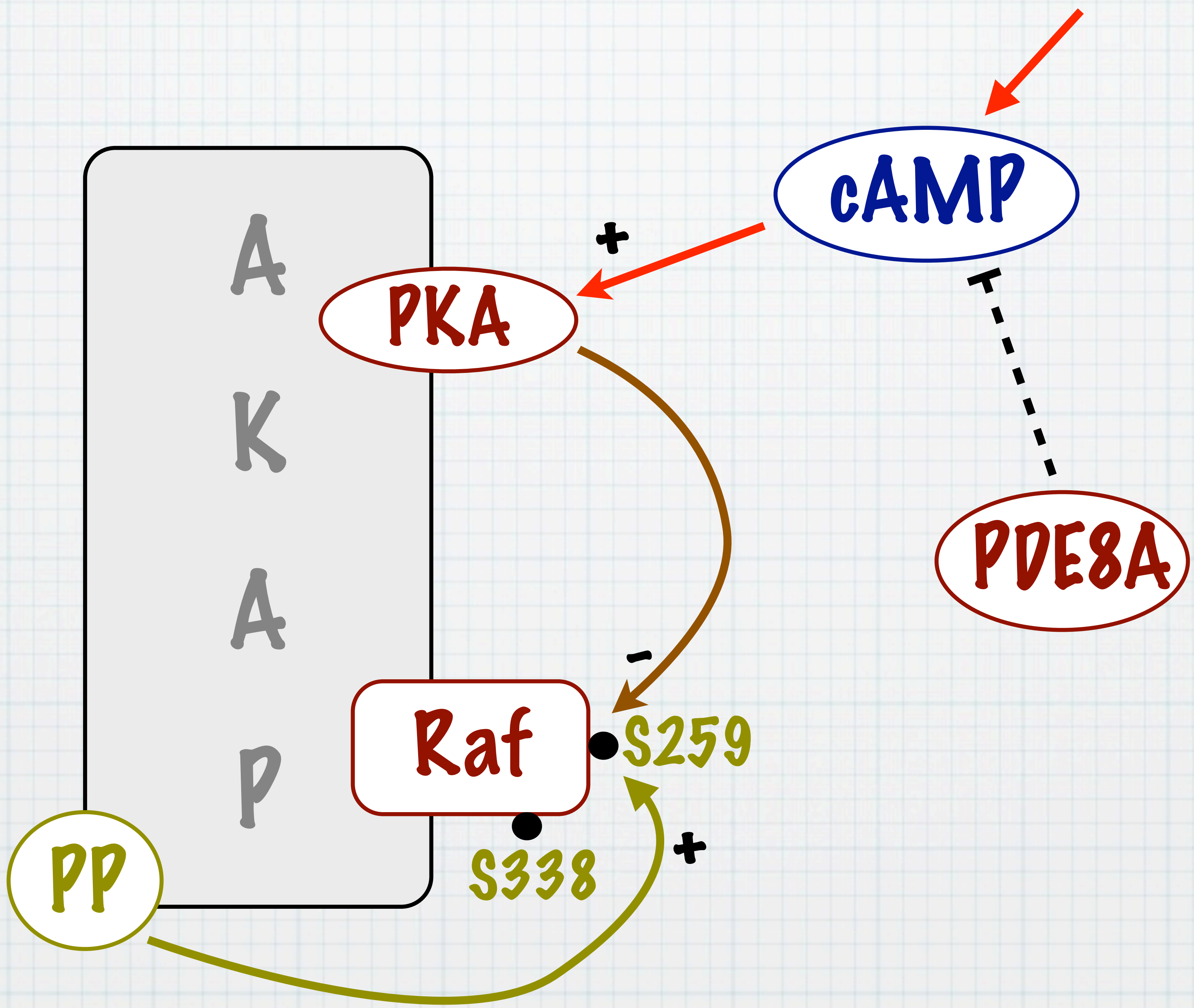

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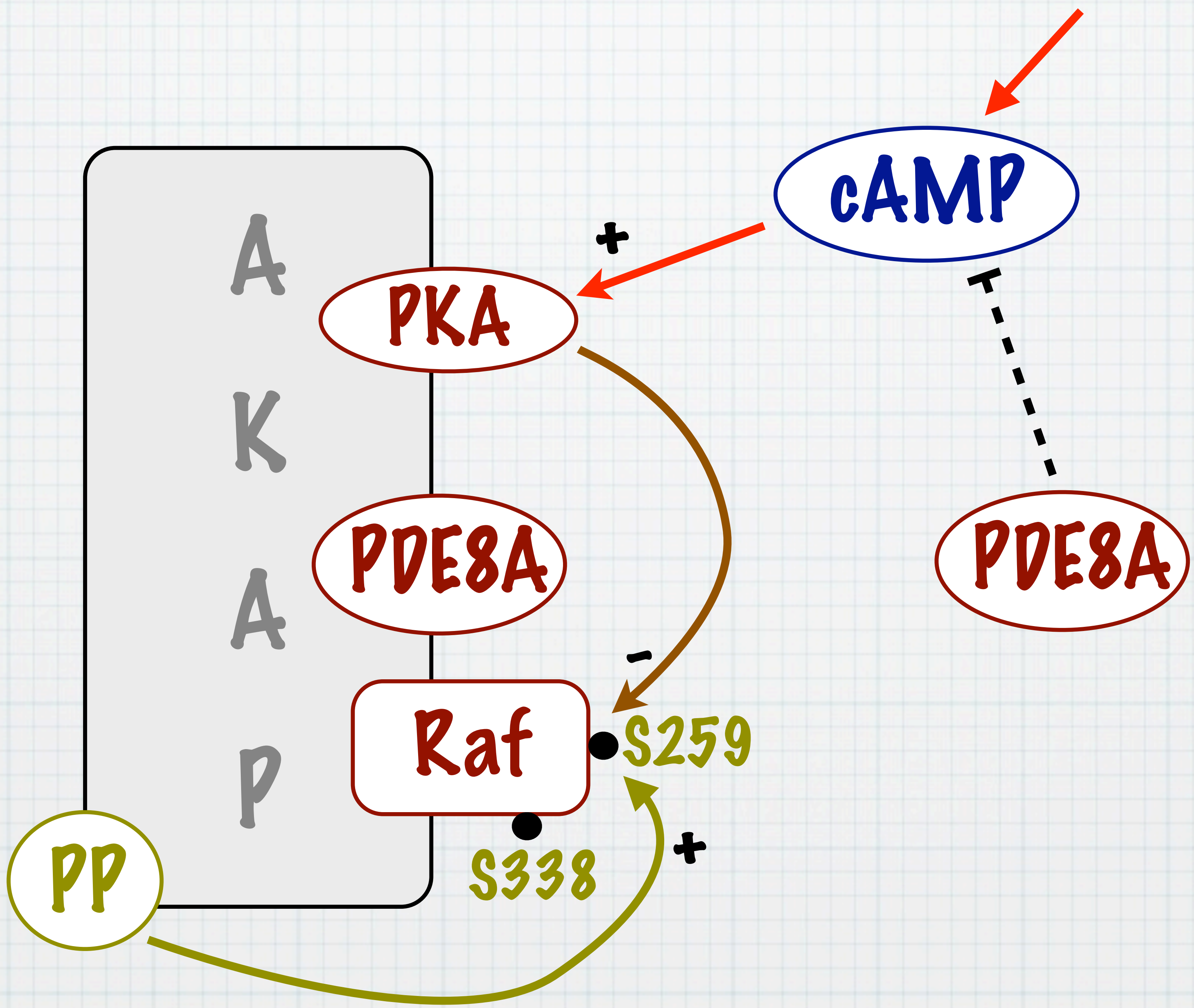

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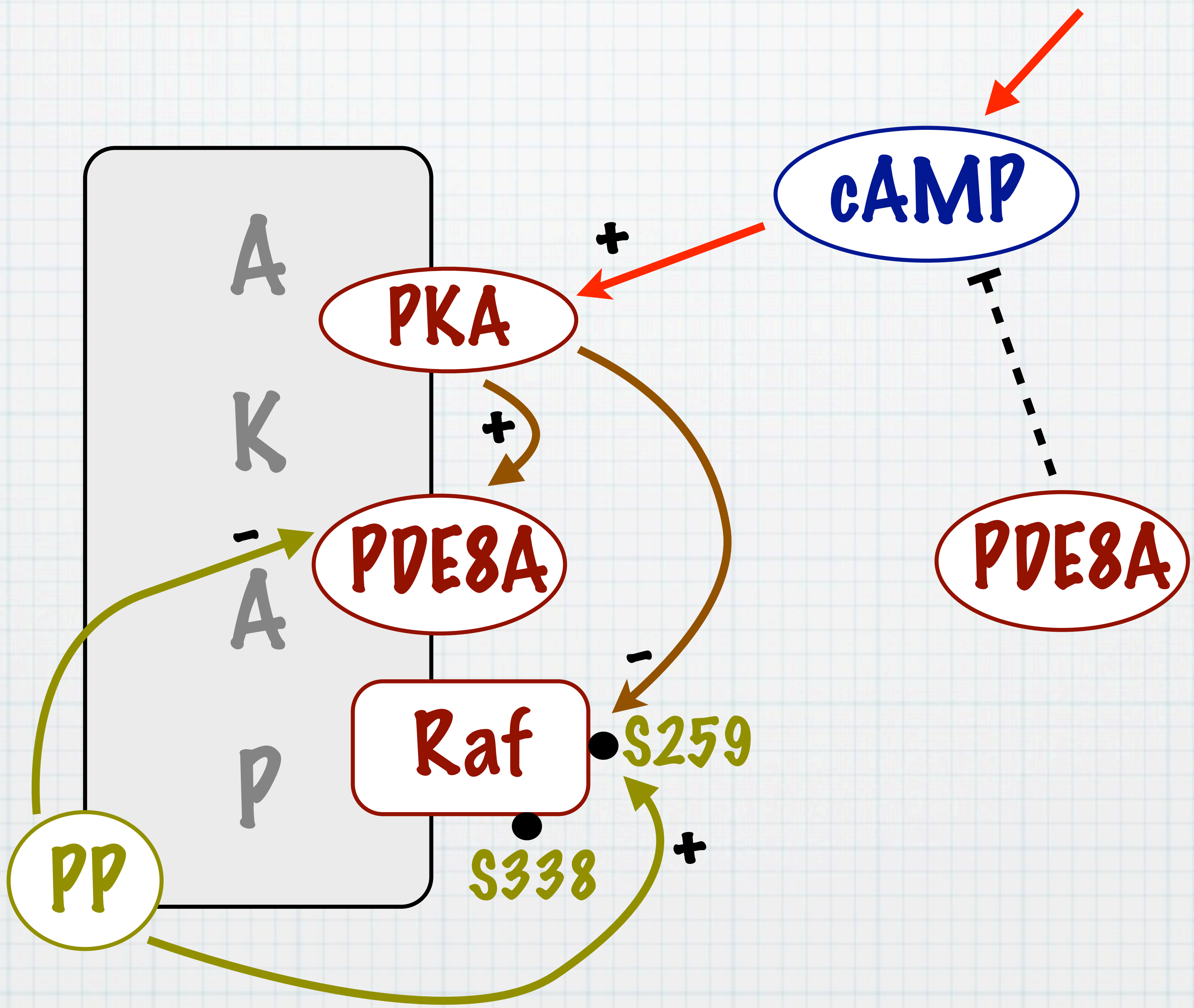

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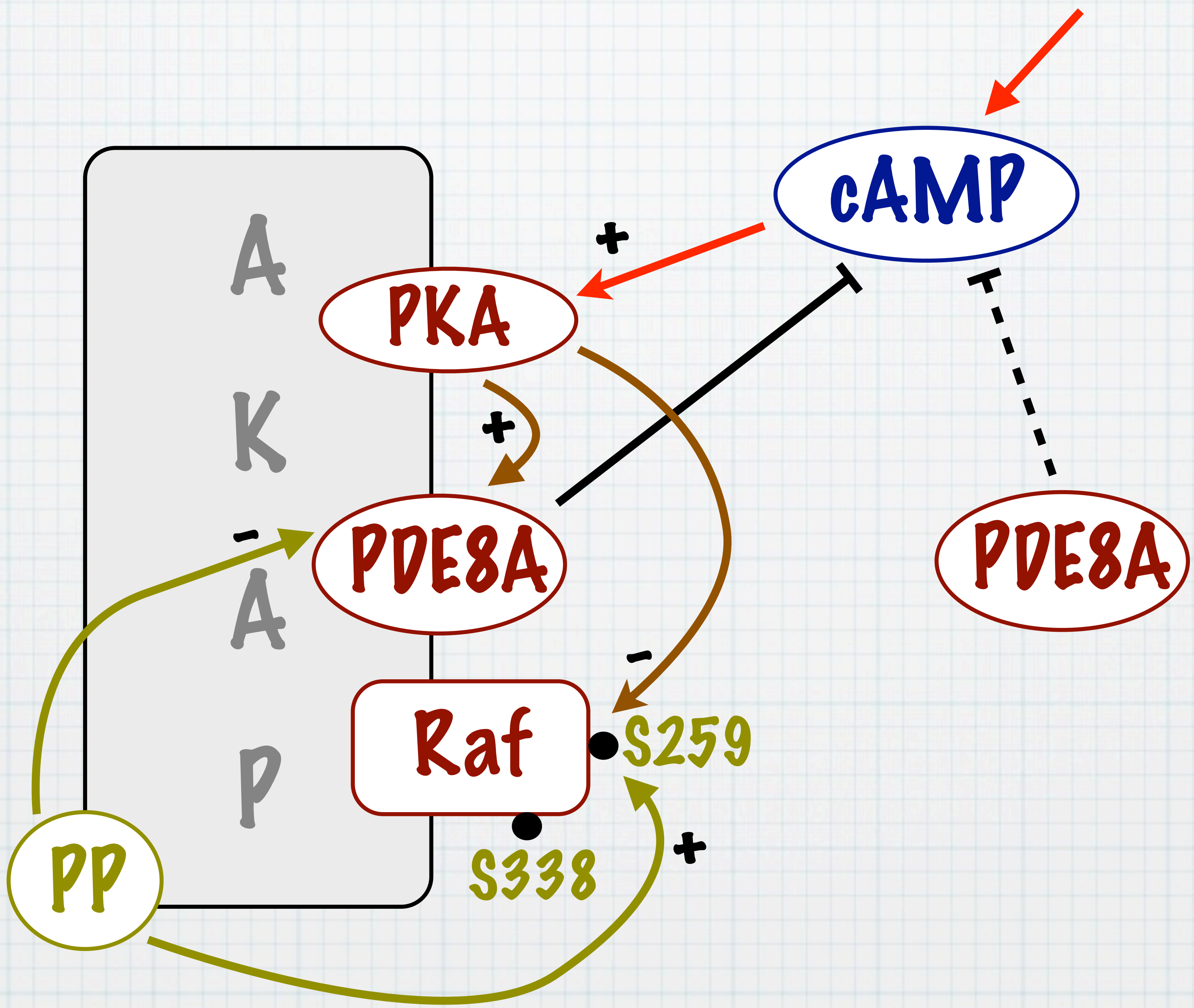

Expected Behaviour

Q_1: ↑pPDE8A1 → ↓cAMP → ↓PKA$^+$ → ↑ Raf activity

→ ↓ $pRaf_{S259}$

What is the time relation or causality between events?

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Q2: Pulsating behaviour.

Formal model

* continuous time Markov chains with levels
* properties expressed as formulas in CSL
* symbolic probabilistic model checker PRISM

PRISM model

* modules for cAMP, scaffold, free PDE8A1 and PP
* filled scaffold (S000, S100, S101,...) and unfilled scaffold (S00, S10, S01, S11)
* mass action law
* information on constant rates ratios

PRISM model

The PKA activation reaction S00 + 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

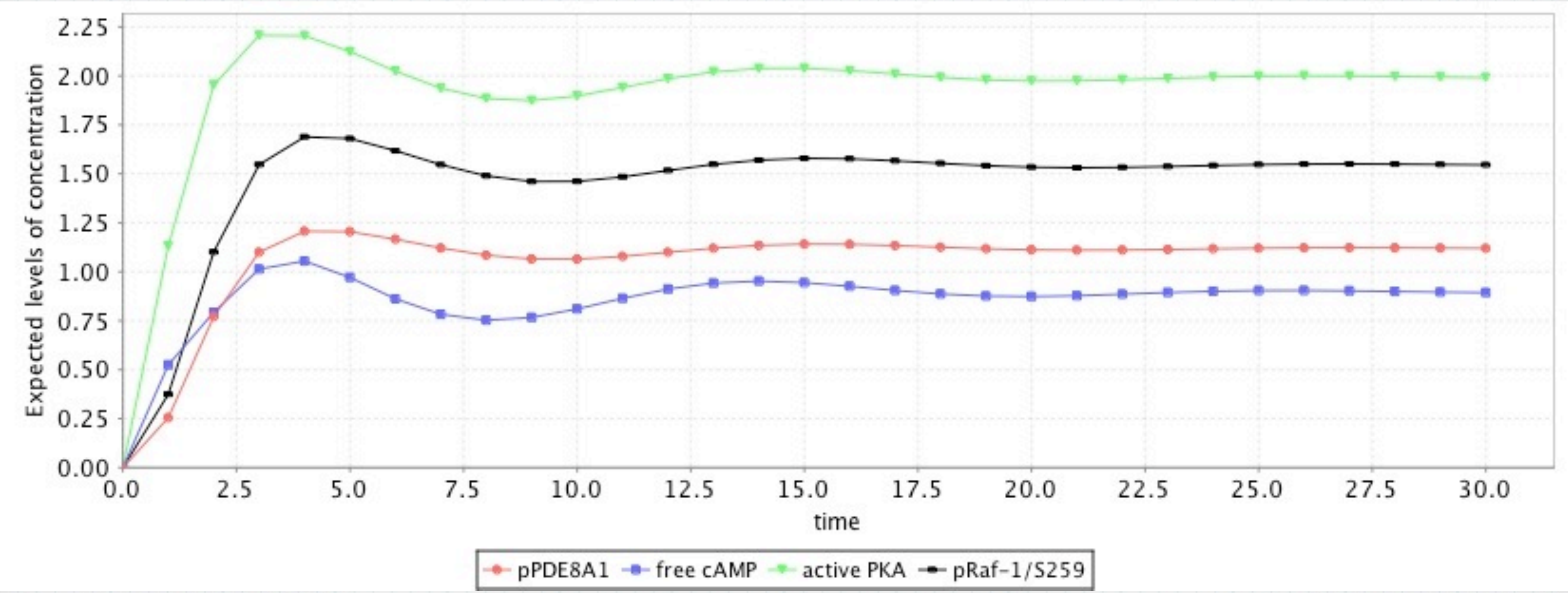
State formulae	$\Phi ::= \top \mid a \mid \neg\Phi \mid \Phi \wedge \Phi \mid \mathsf{P}_{\bowtie p}[\phi] \mid \mathsf{S}_{\bowtie p}[\Phi]$
Path formulae	$\phi ::= \mathsf{X}\,\Phi \mid \Phi\ \mathsf{U}^{I}\ \Phi$

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 level for cAMP, pPDE8A1, PKA^{+}, pS259



Derivatives

* use of signs of derivatives to keep track of decreasing or increasing variable values
* add new variables in the PRISM modules for cAMP, PKA^{+} and pS259
* $\downarrow x$ ($\uparrow x$) negative (positive) derivative

  for variable x

Necessarily Preceded

- ➡ 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: $(EF\ \phi) \wedge AG((\neg \psi) \Rightarrow AG(\neg\ \phi))$

Necessarily Preceded

For ϕ = $\downarrow$ cAMP $\wedge$ $\downarrow$ PKA^{+} and ψ = $\uparrow$ pPDE8A1

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

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

Pulsations

For ϕ = $\uparrow$ pPDE8A1 $\wedge\downarrow$ cAMP $\wedge$ $\downarrow$ PKA^+

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

a pulsation in CTL [Fages05,Ballarini et al. 09]:

$AG((\phi \Rightarrow EF\,\psi) \wedge (\psi \Rightarrow EF\,\phi))$

to obtain in CSL the formula:

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

Conclusions

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- [x] formal model of a biological process
- [x] the biologists validated our results
- [ ] refine the model with more experimental data
- [ ] derivatives, amplitude of oscillations
- [ ] formulate new properties and express them using a temporal logic

Acknowledgement

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Bibliography

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Thank you!