Signalling:

The hourglass, the bomb and the ruler

Or:

Why Reactome, KEGG etc. are in trouble?

Metabolism Vs. Signalling

- Metabolism = Transport of matter and energy

- Signalling = Transport of information

Metabolism Vs. Signalling

- Metabolism = Reversible conversions

- Signalling = Irreversible conversions

☛ Hysteresis

Metabolism Vs. Signalling

- Metabolism = crave for steady-state

- Signalling = exists for perturbation

Metabolism Vs. Signalling

- Metabolic **Networks**

- Signalling **Pathways**

Metabolism Vs. Signalling

- Metabolic **Networks**
- Signalling **Pathways** ~~Networks~~

Metabolism Vs. Signalling

- A Signalling Pathway is a portion of a Signalling Network highlighted by a perturbation

Metabolism Vs. Signalling

- A Signalling Pathway is a Signalling Network filtered by a perturbation

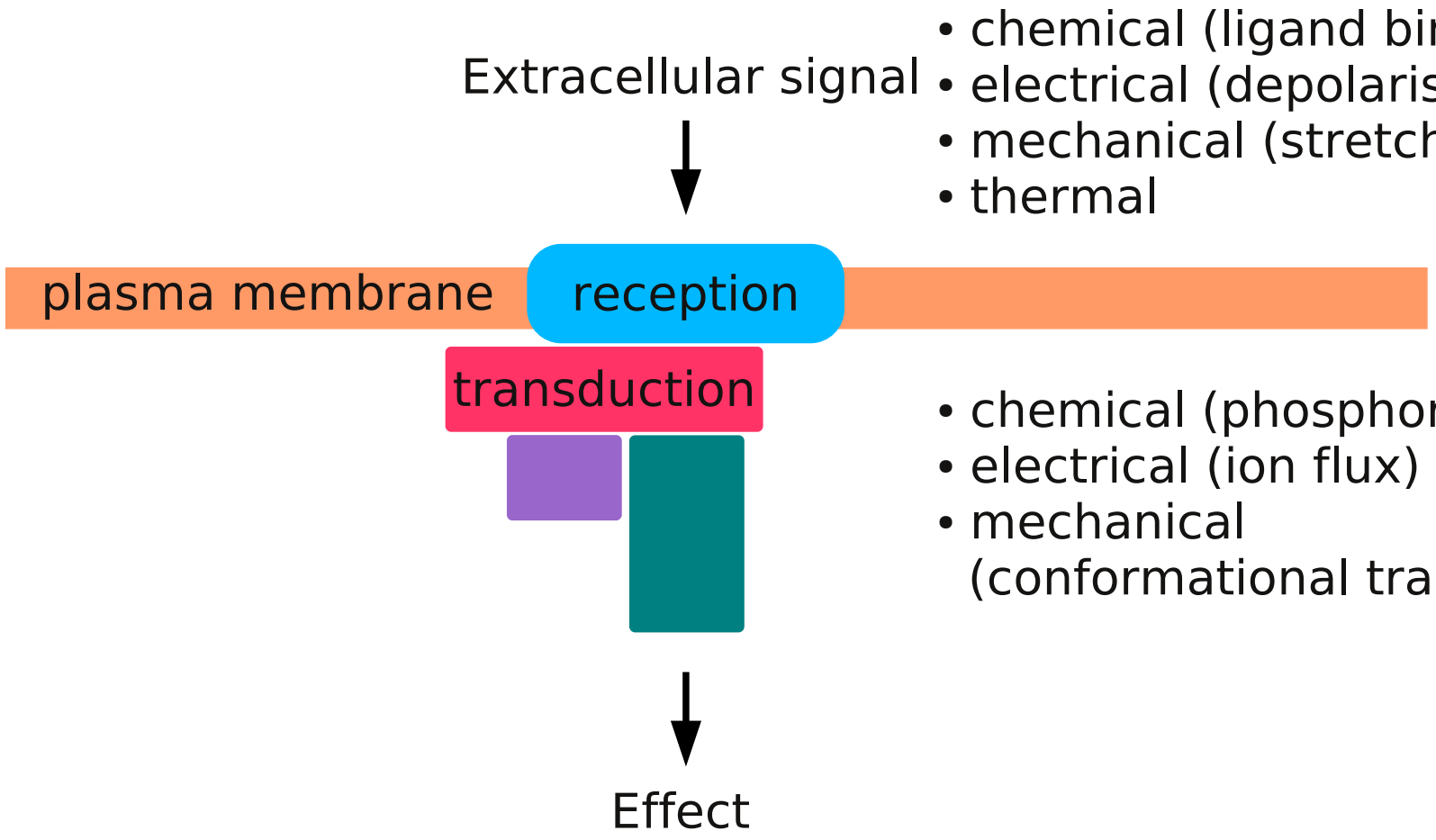
Metabolism Vs. Signalling

- A Signalling Pathway is a Signalling Network filtered by a perturbation*

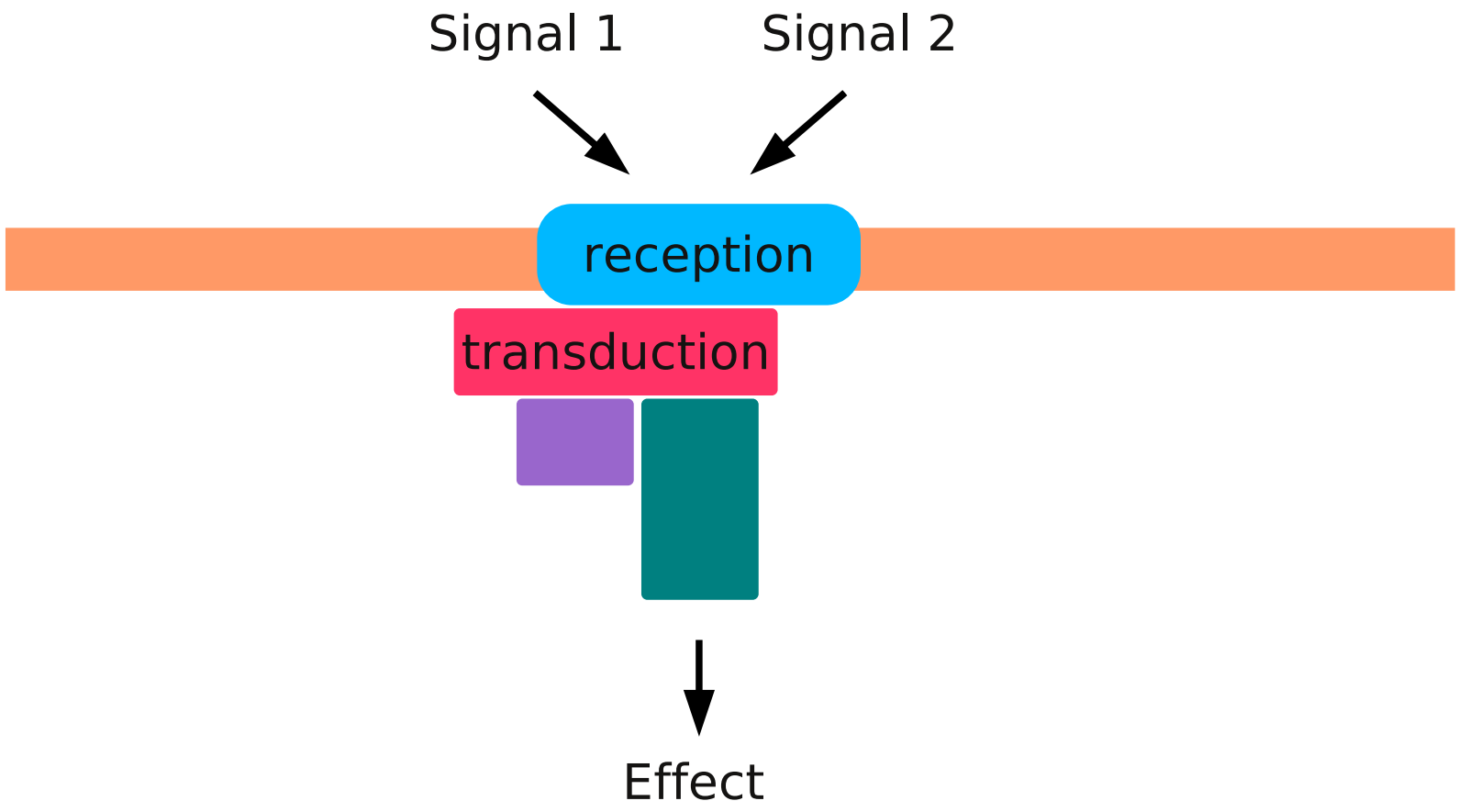
- * A perturbation is not a signal, but a weighted combination of signals

The hourglass

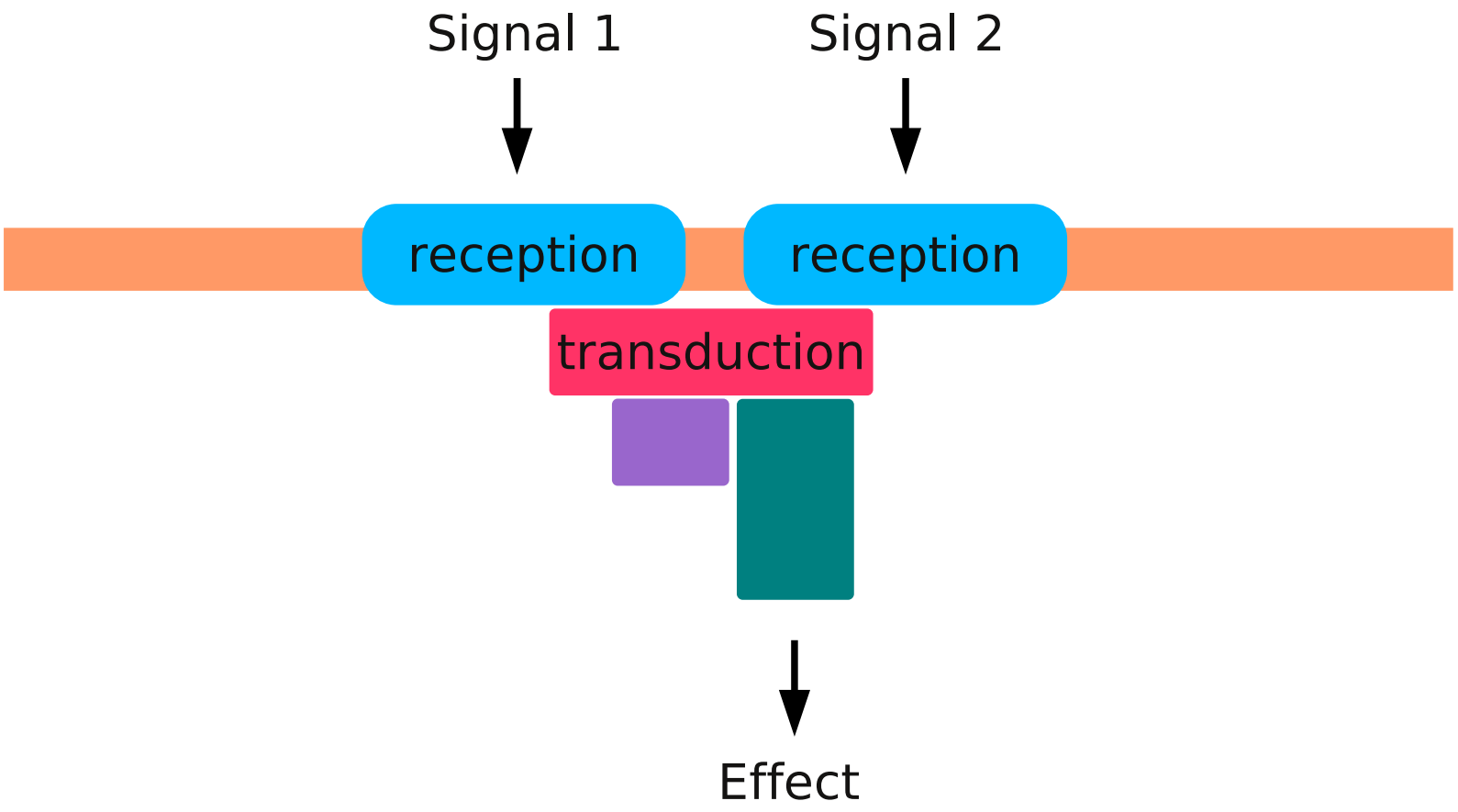
Signal transduction



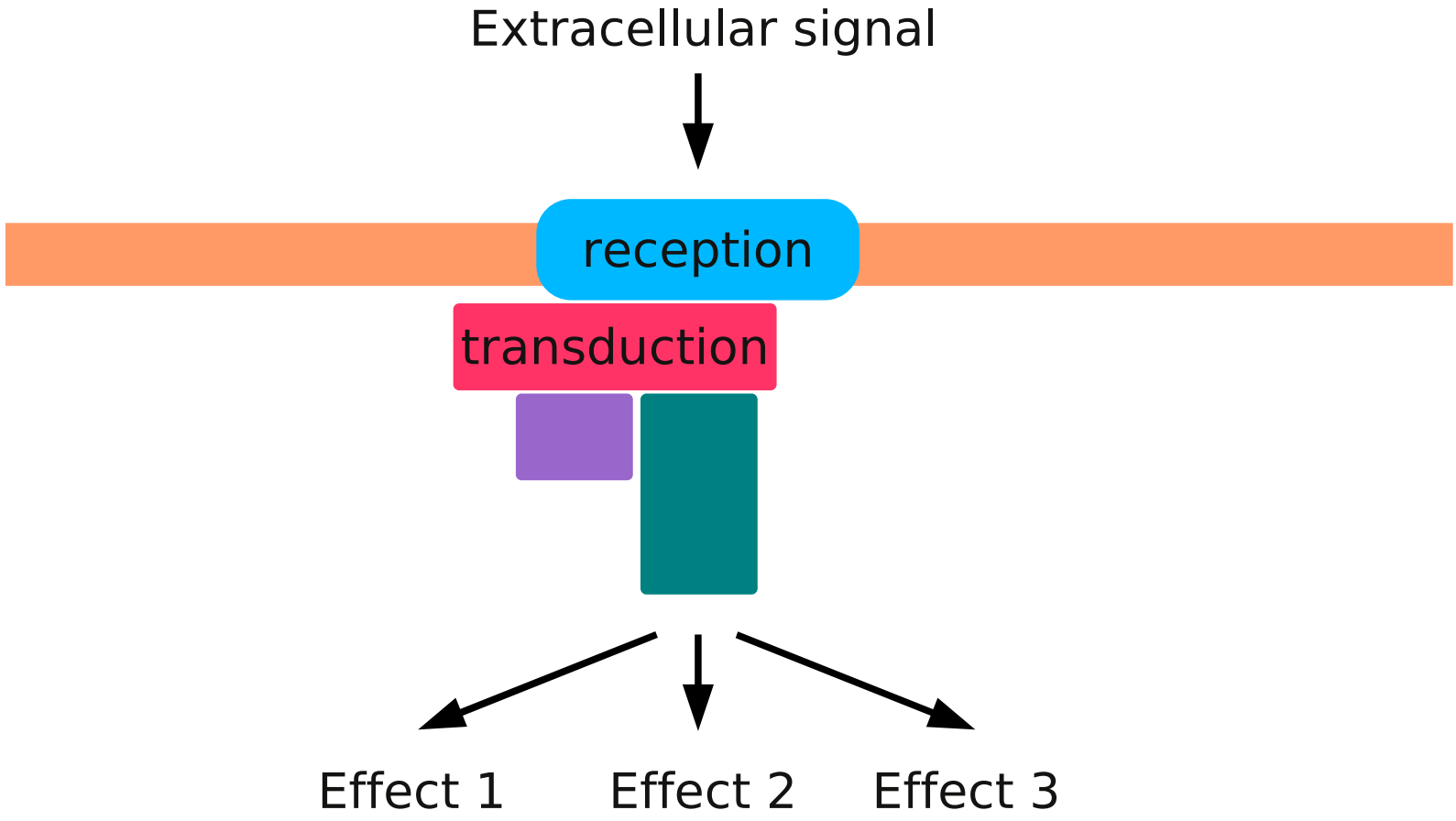
Signal convergence



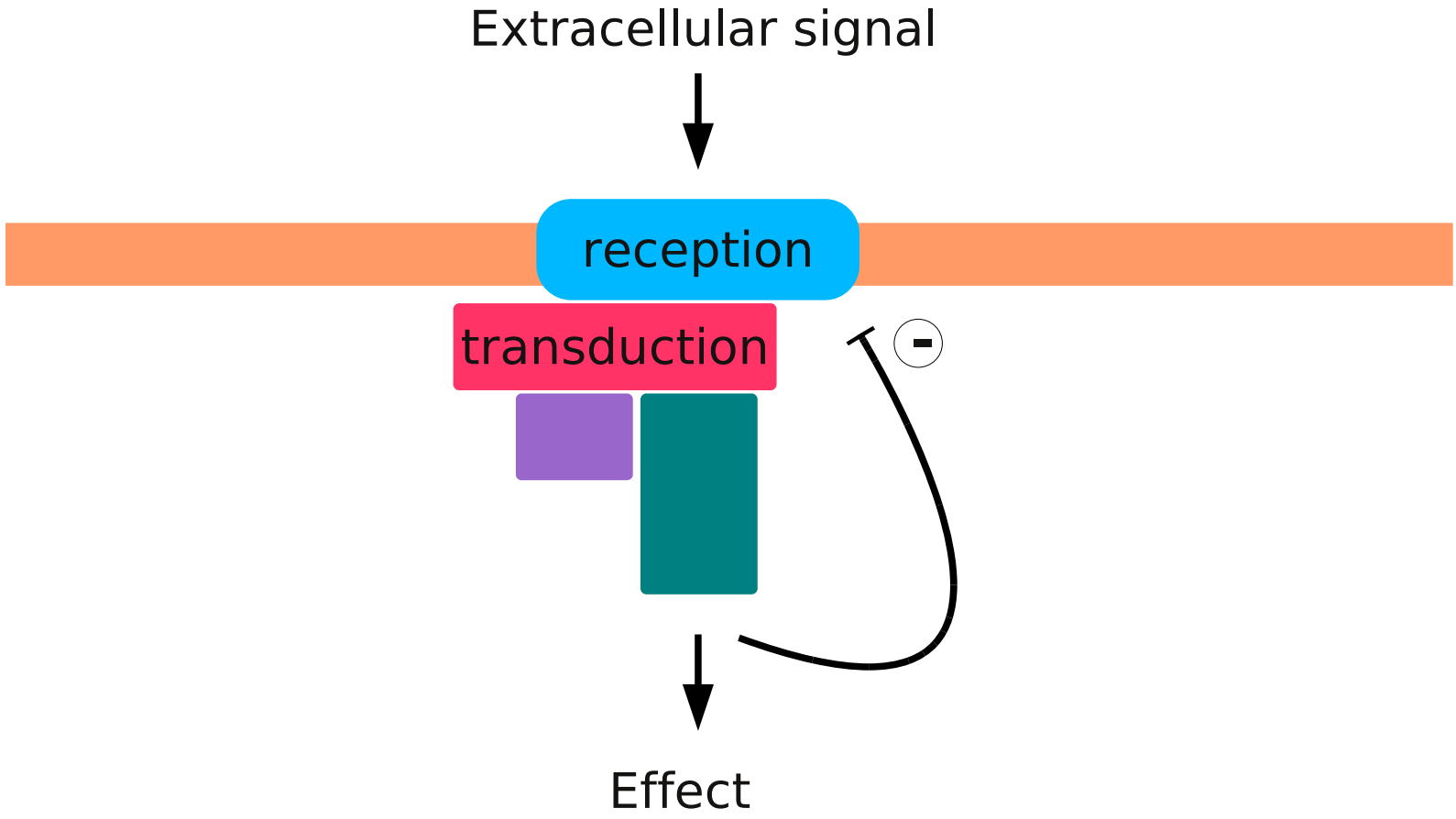
Signal convergence



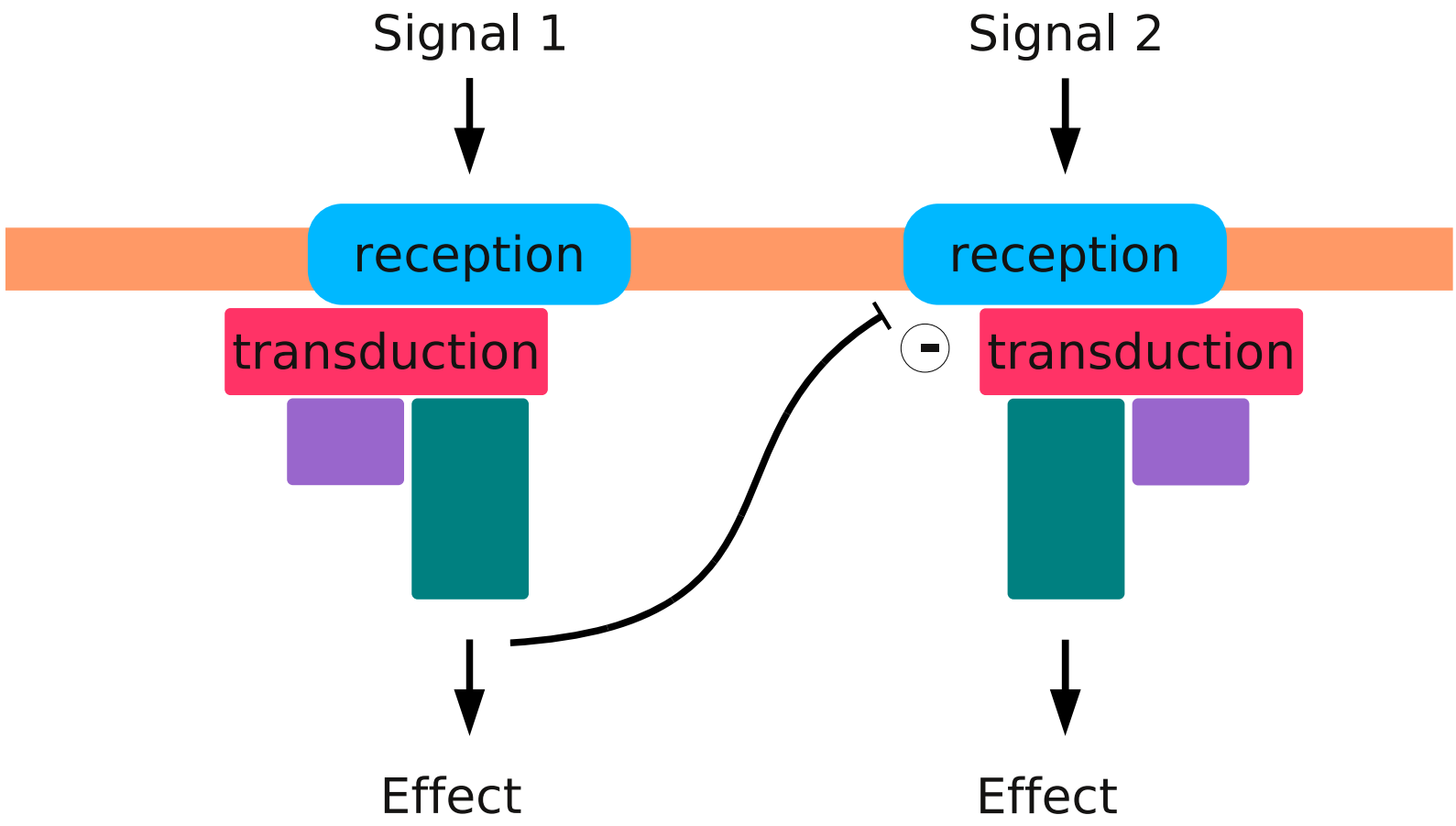
Signal divergence



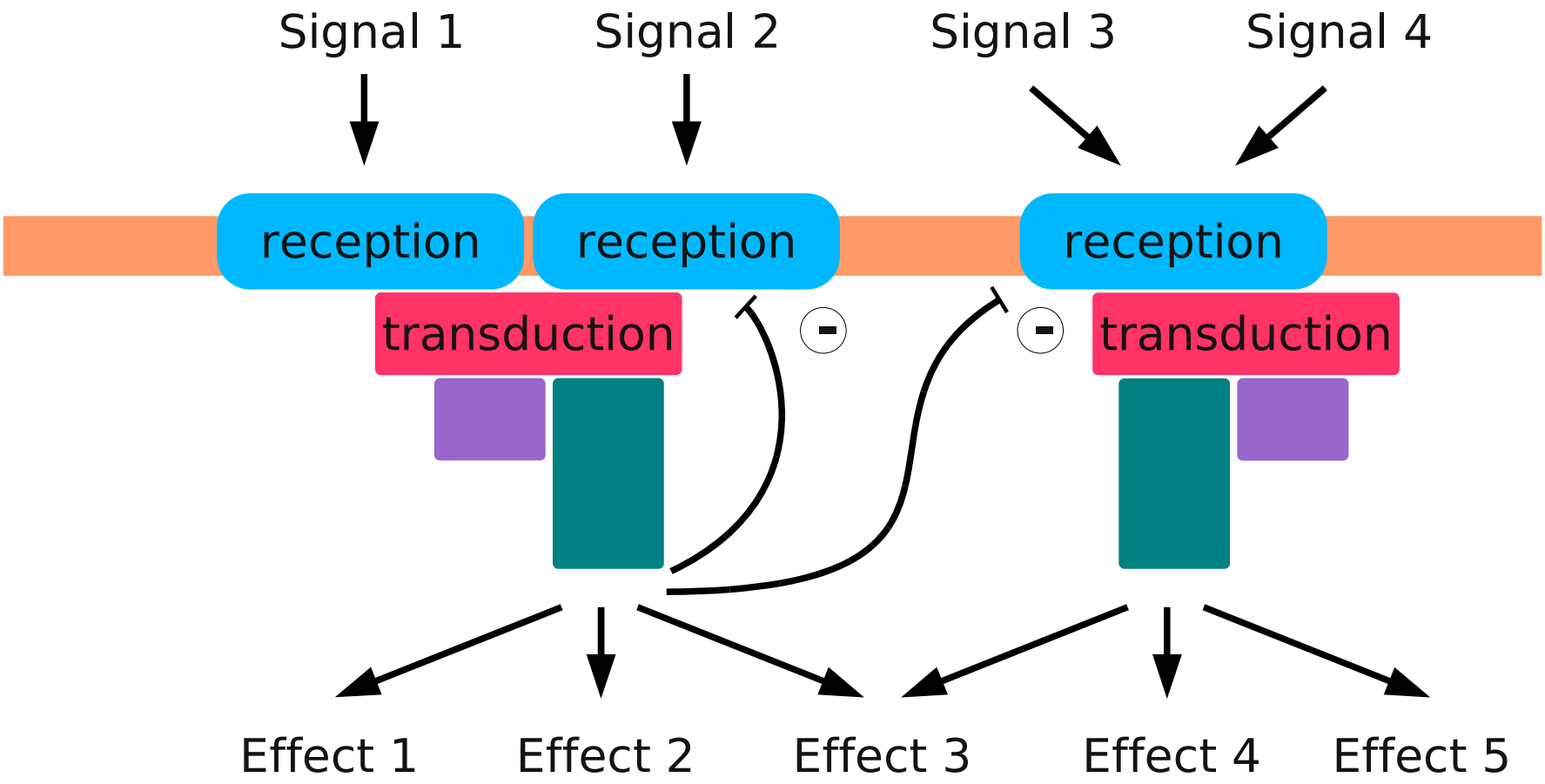
Signal adaptation



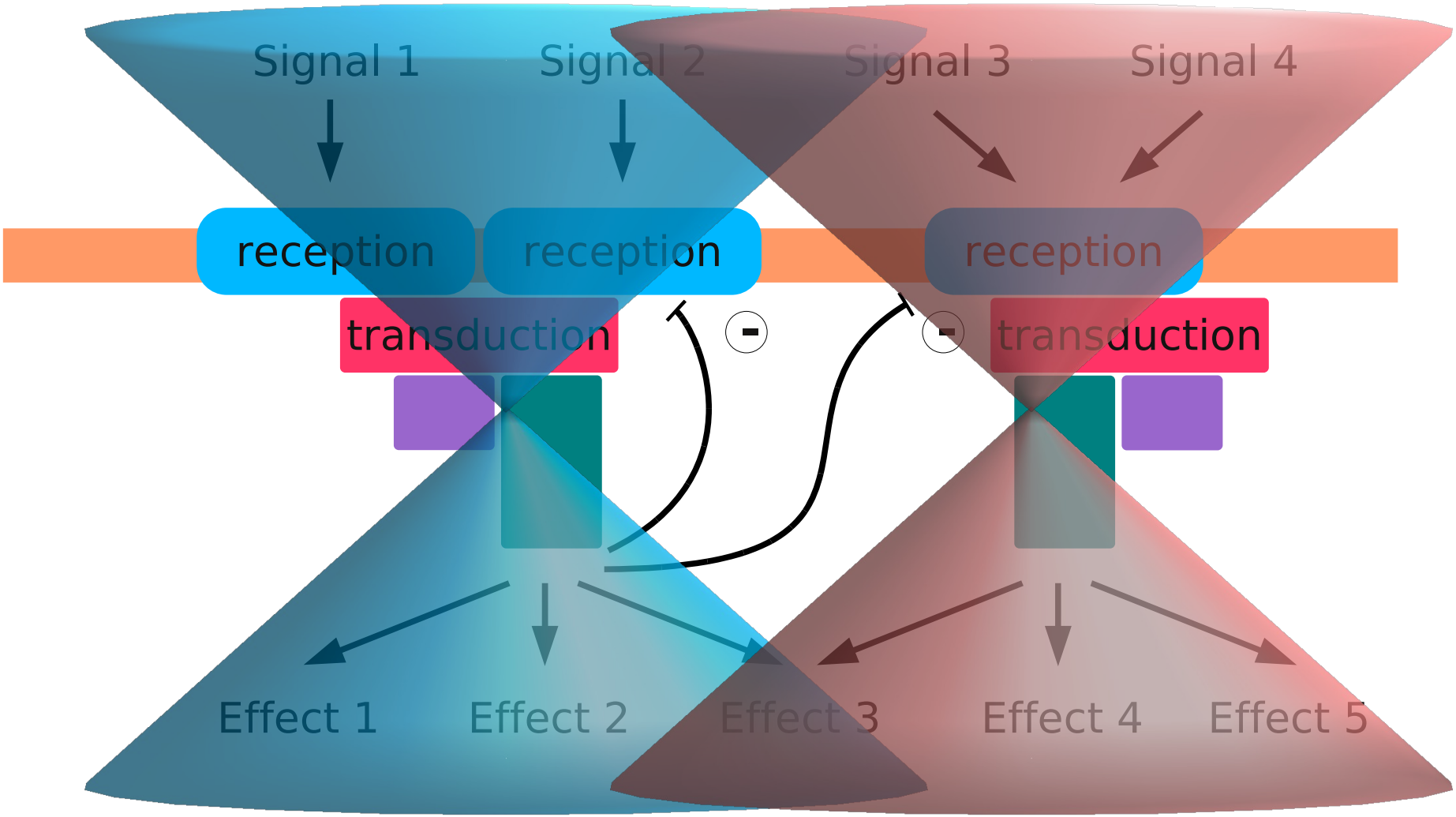
Cross-adaptation



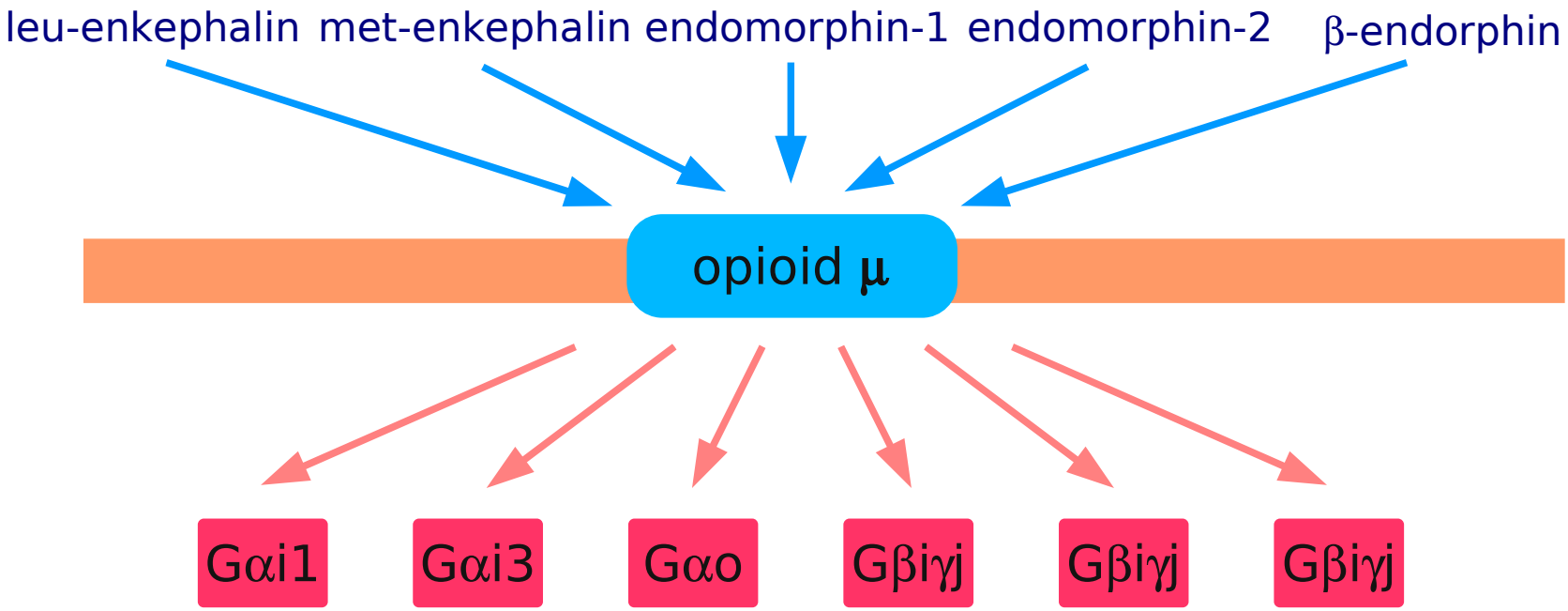
The full monthy



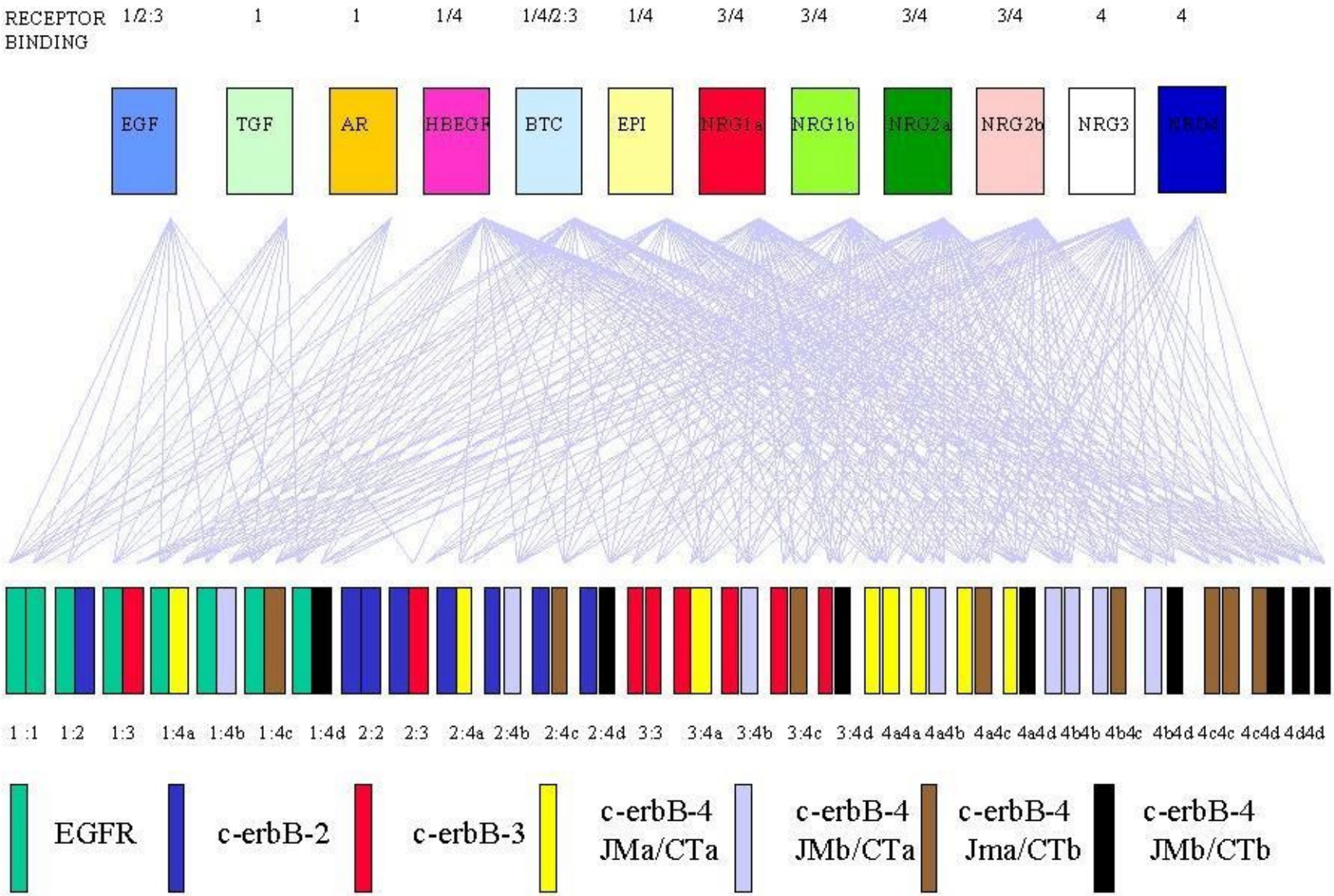
The full monthy



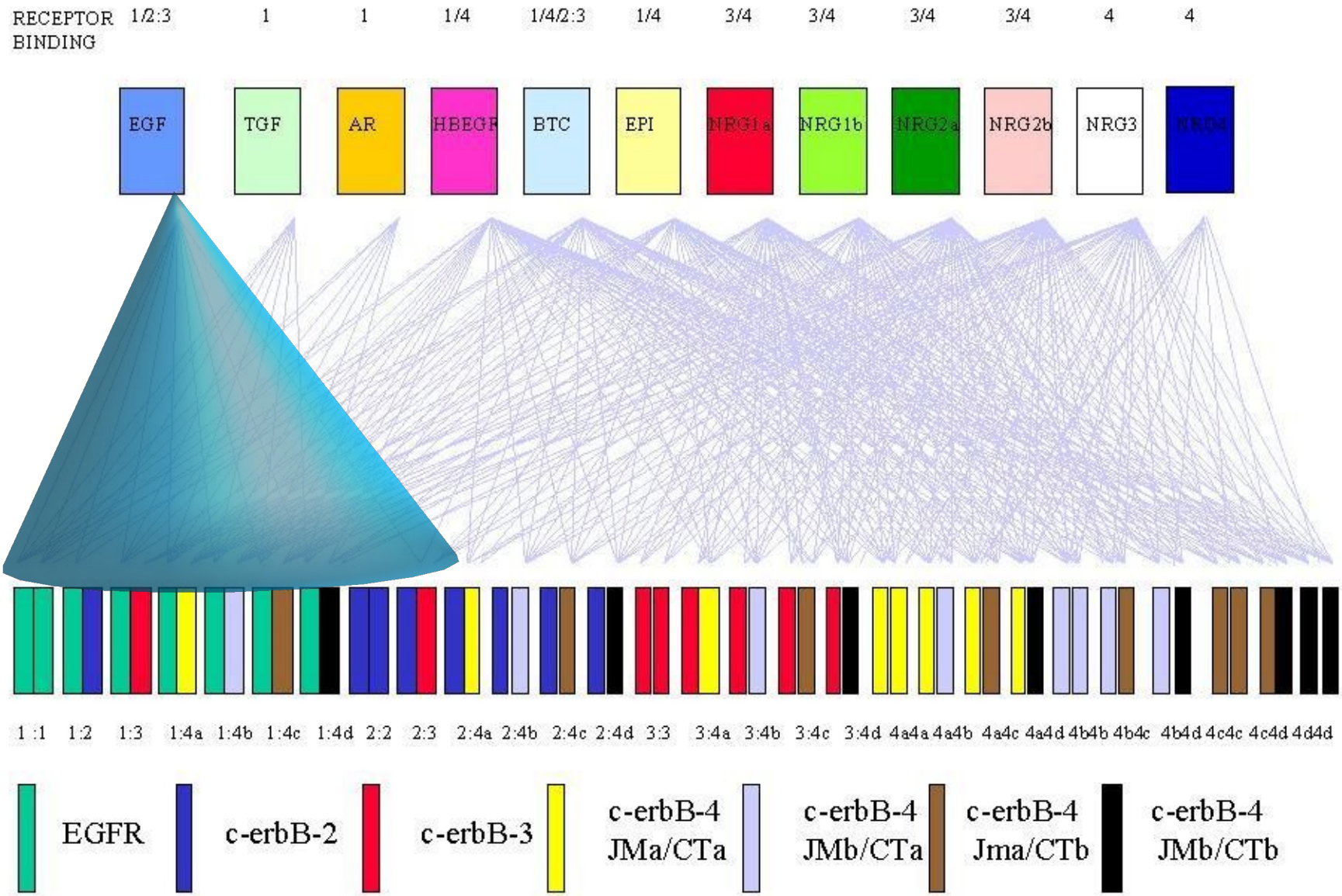
Receptor hourglass



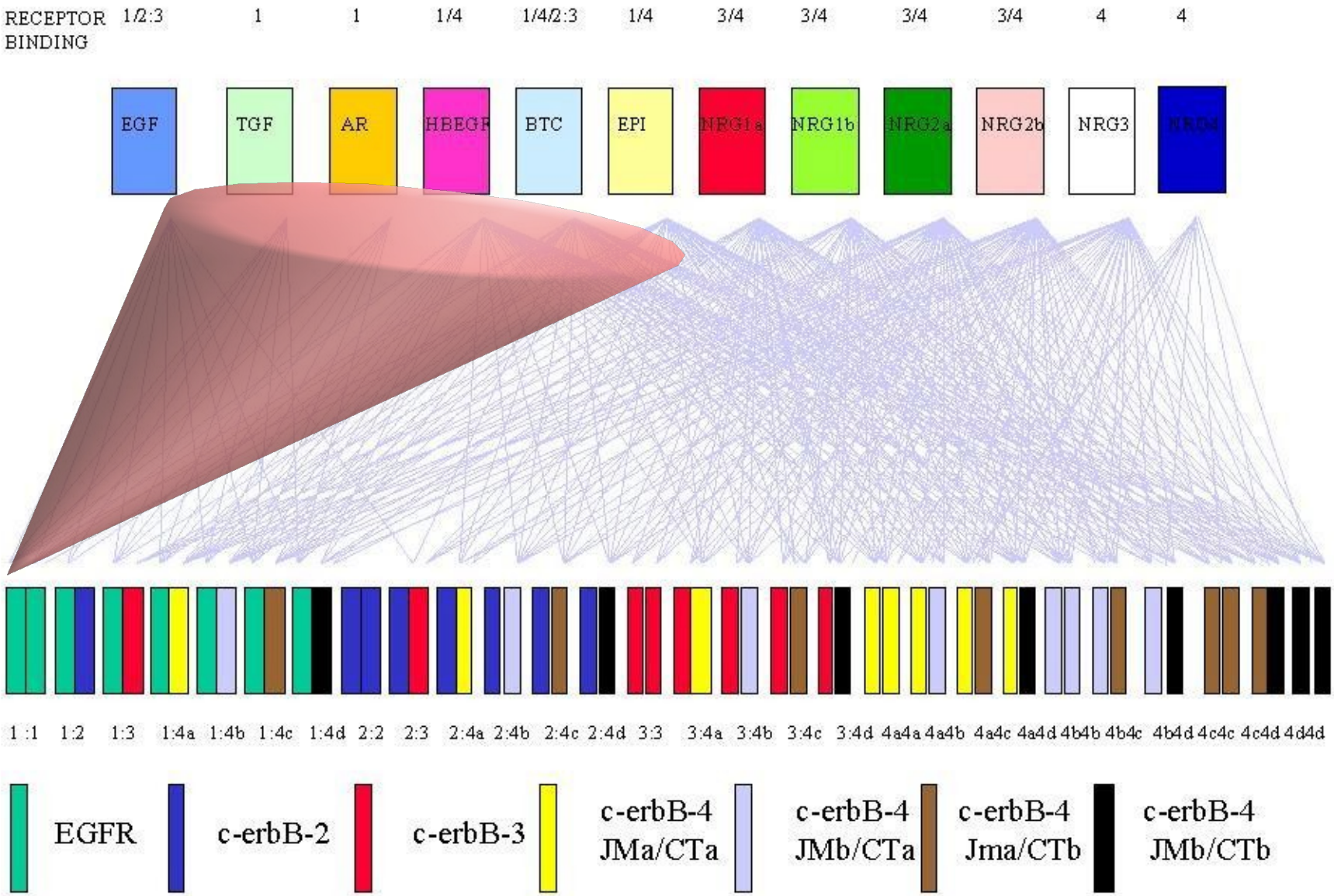
Receptor hourglass



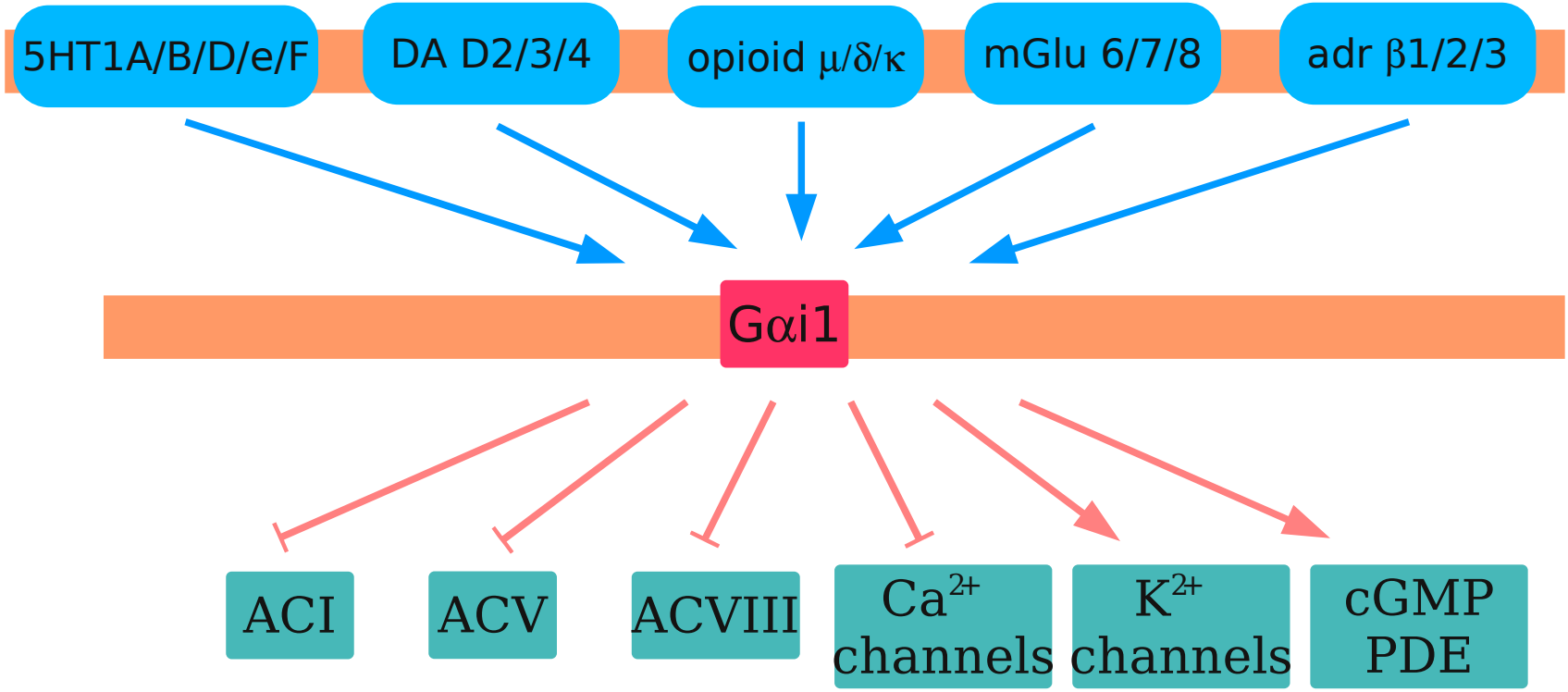
Receptor hourglass



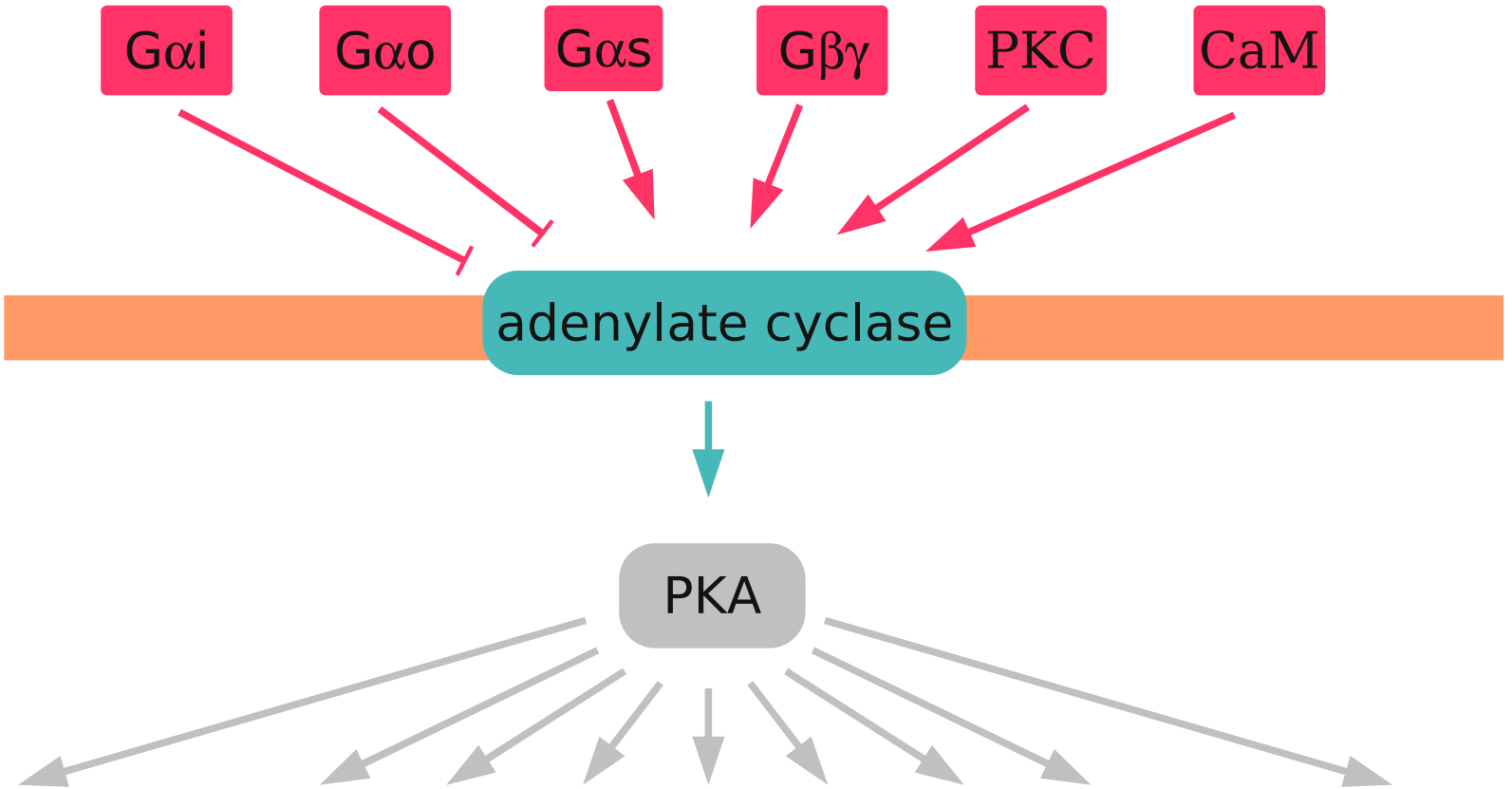
Receptor hourglass



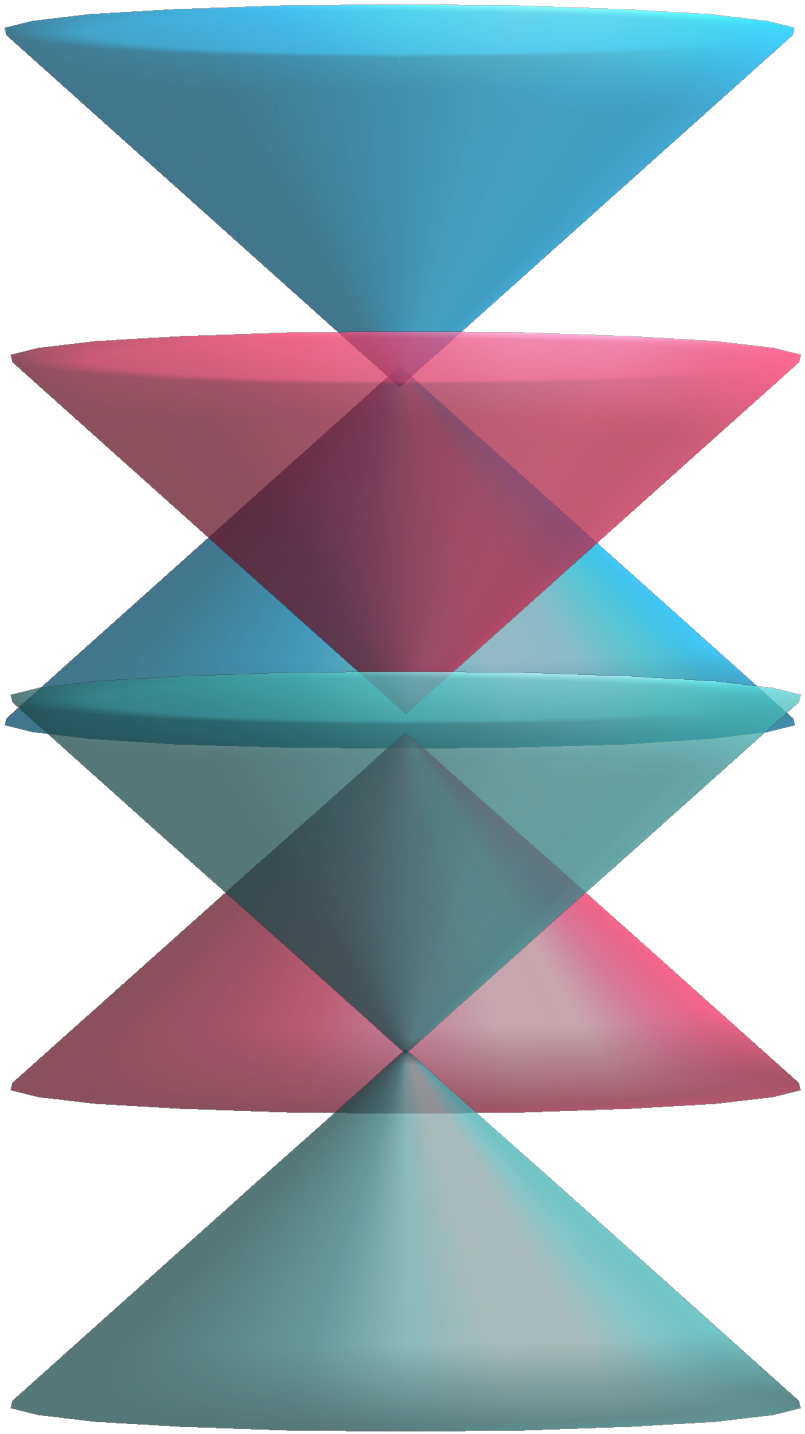
2nd messenger hourglass



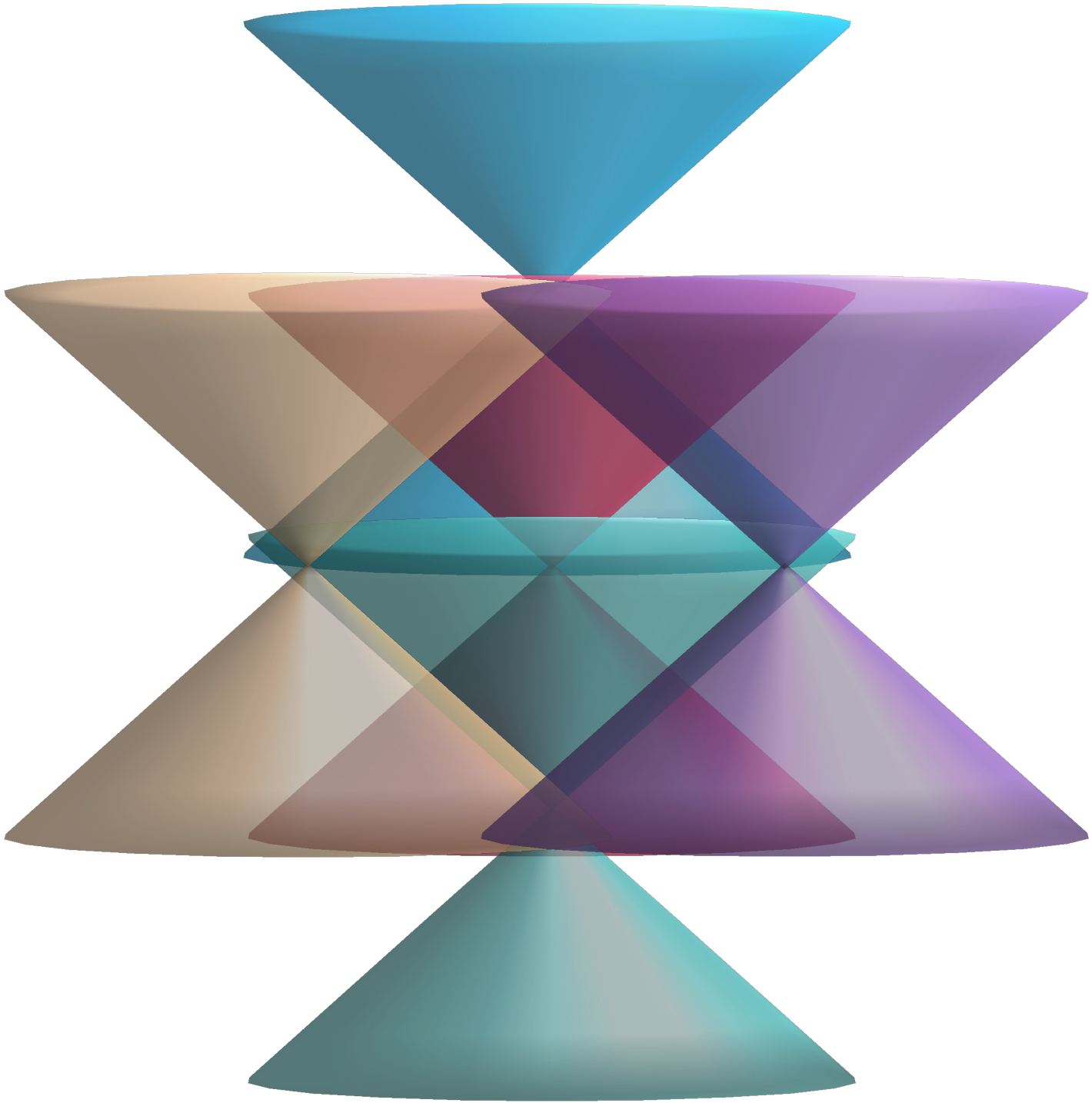
“further down” hourglass



Everything together

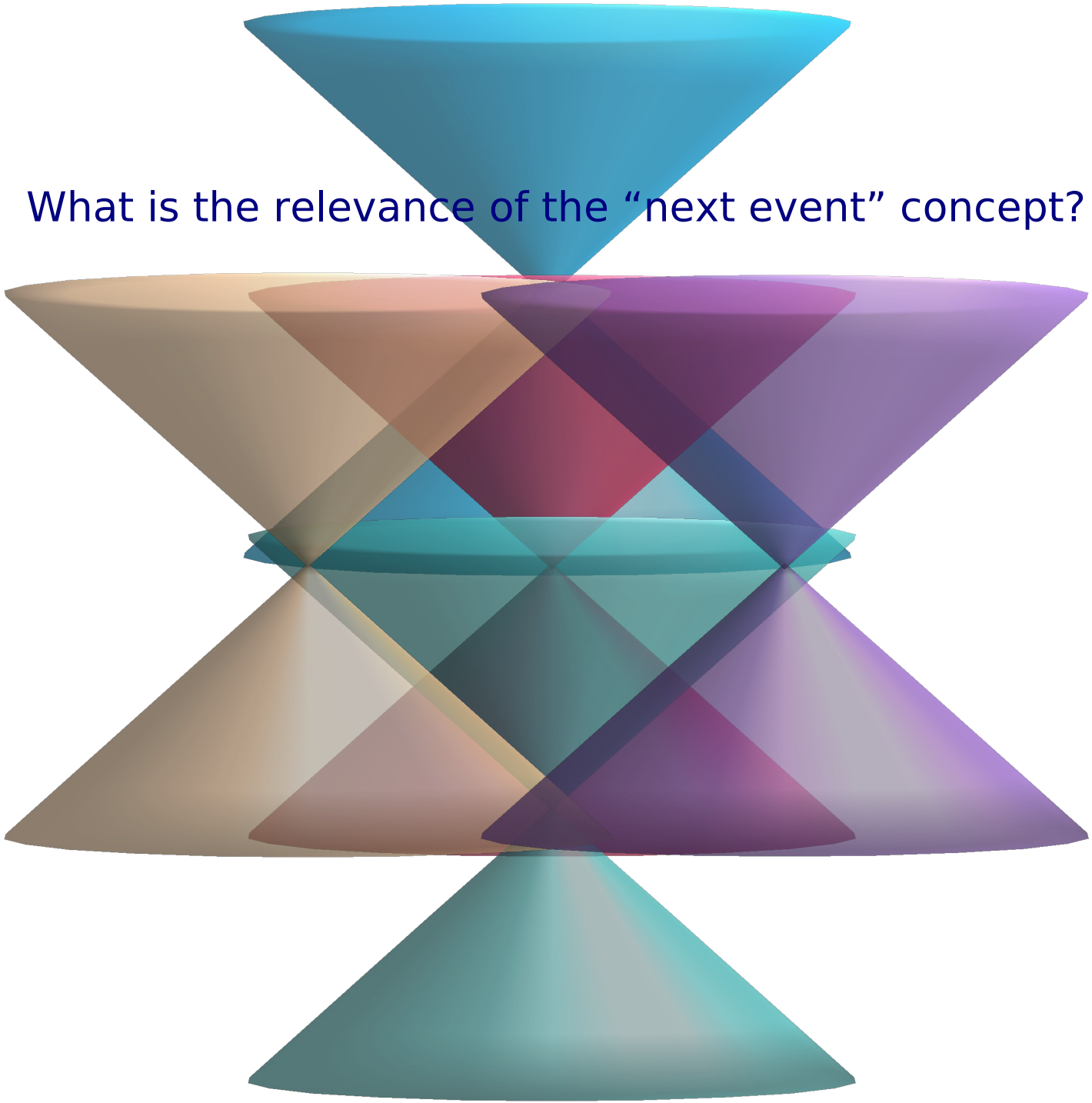


Everything together

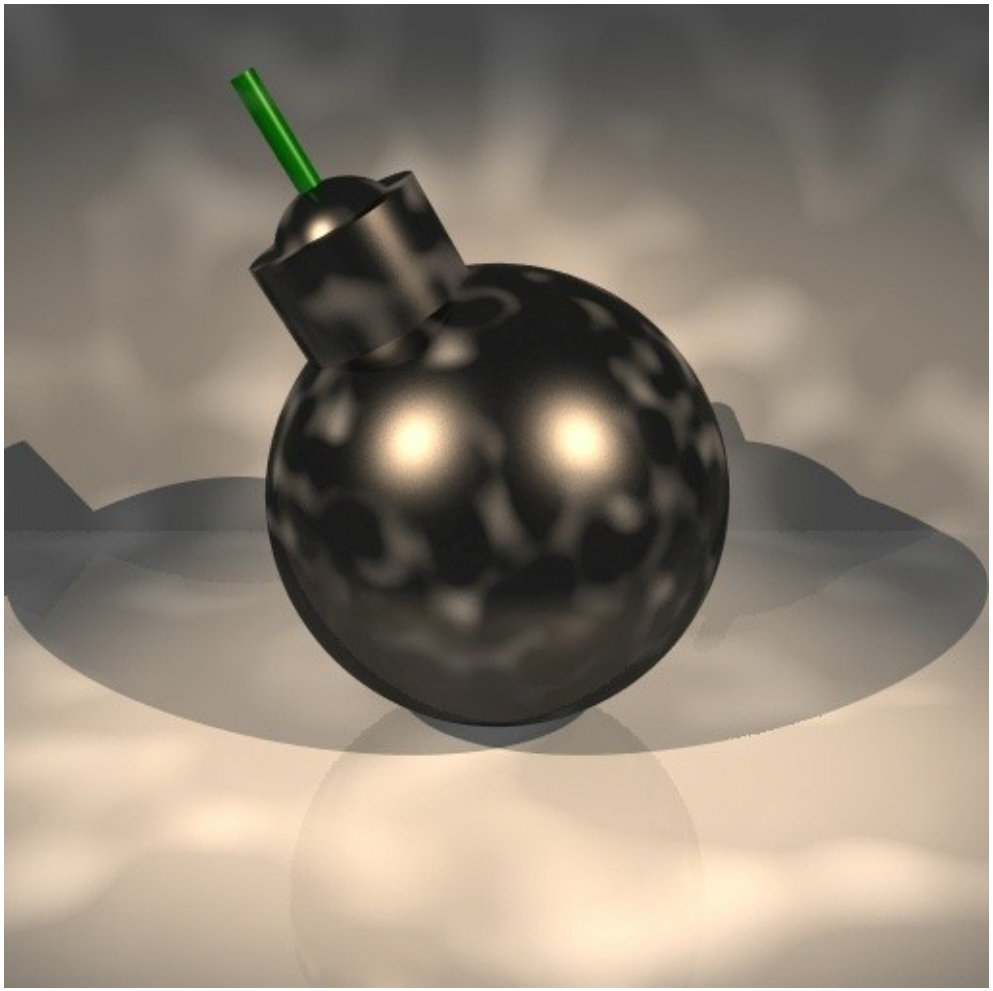


Everything together

What is the relevance of the “next event” concept?

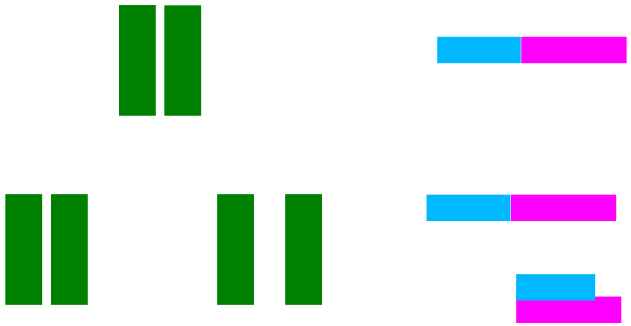


The bomb



Combinatorial explosion

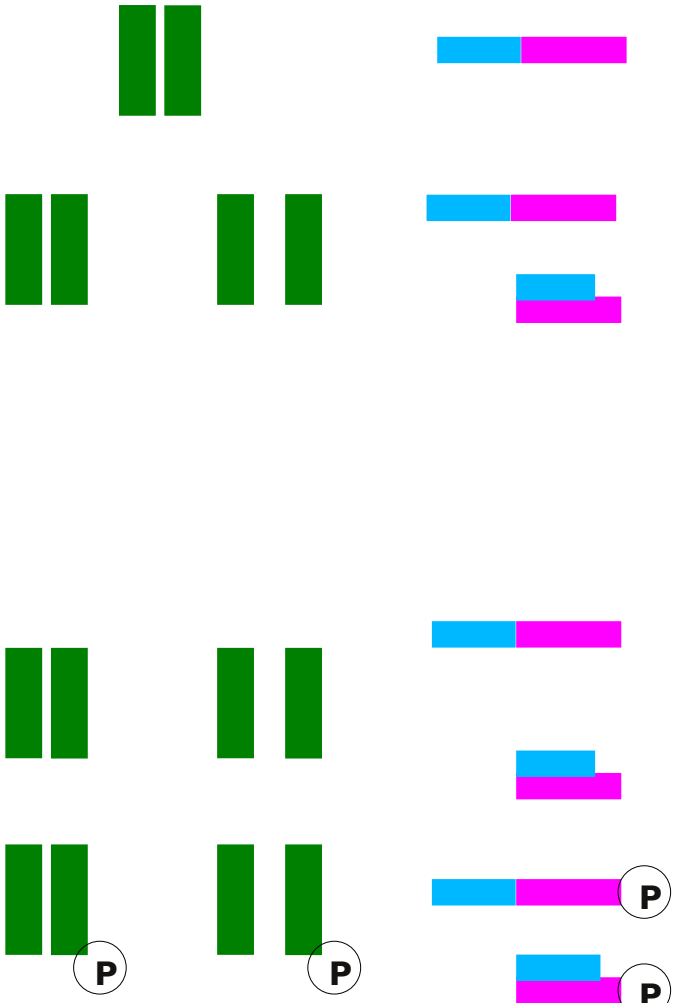
Combinatorial explosion



NMDA + CaMKII <=> NMDA-CaMKII

NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo

Combinatorial explosion



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NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo
pNMDAc + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAo + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAc + CaMKIIo <=> pNMDAc-CaMKIIo
pNMDAo + CaMKIIo <=> pNMDAc-CaMKIIo
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pNMDAc + pCaMKIIo <=> pNMDAc-pCaMKIIo
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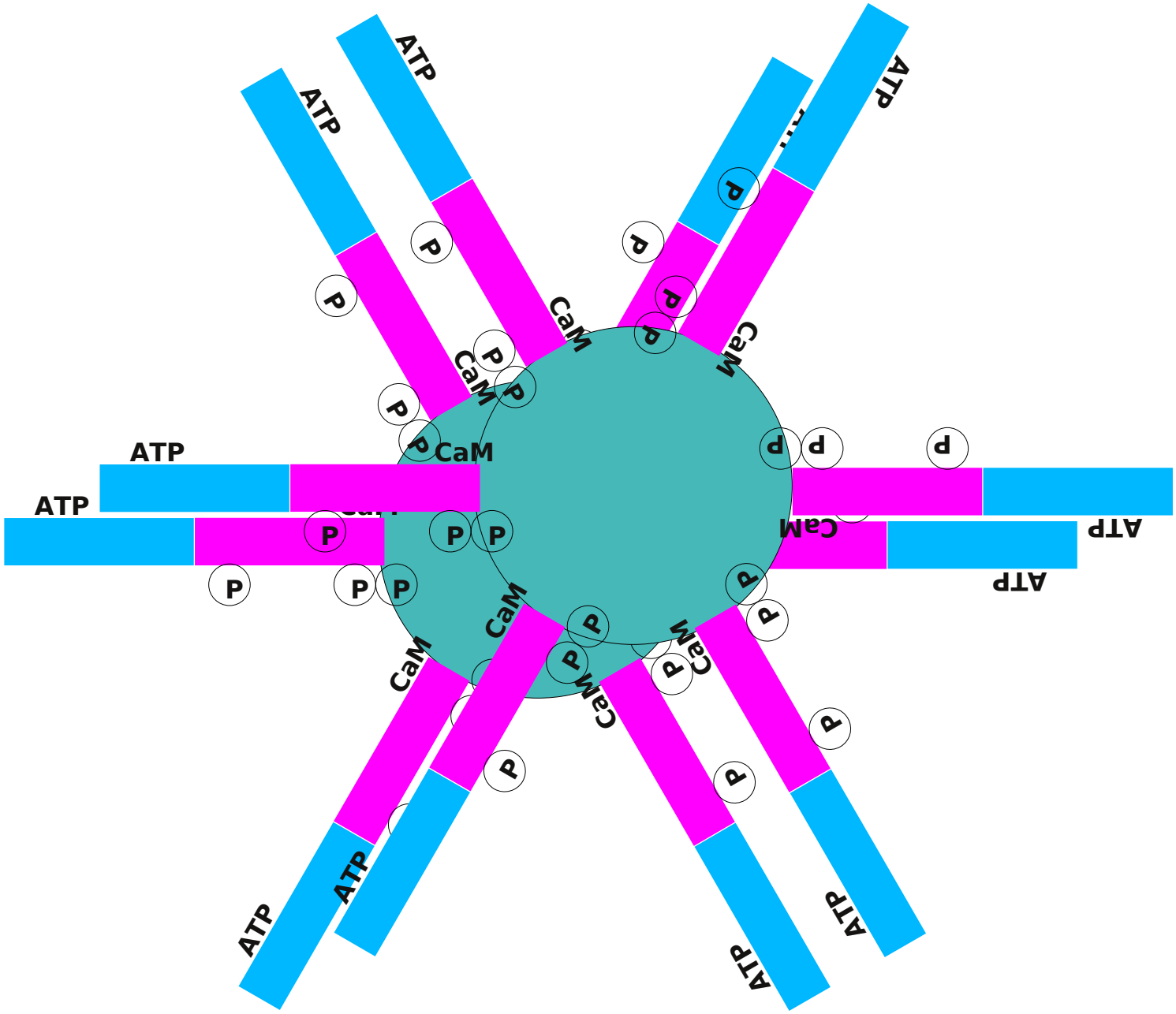
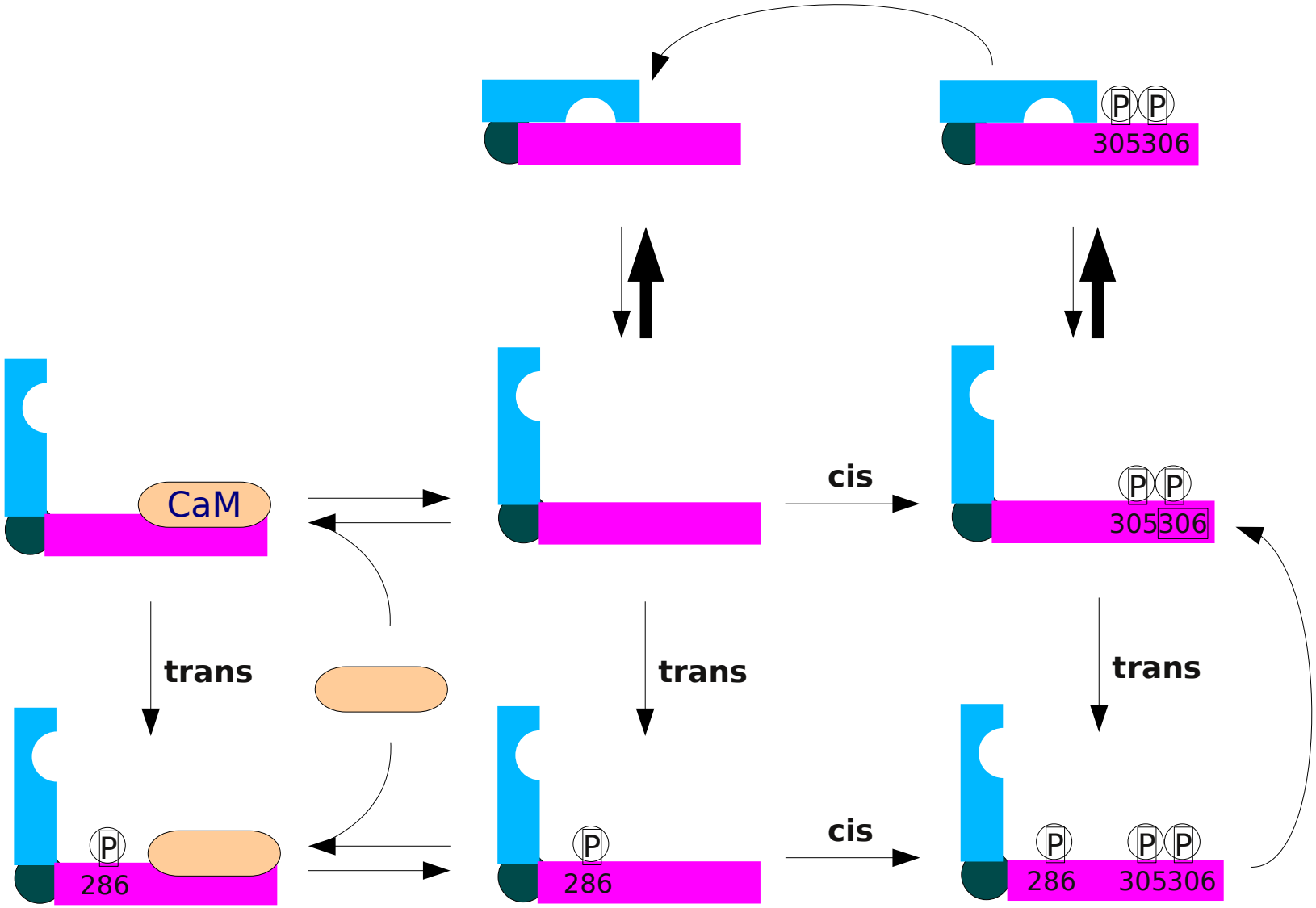
Combinatorial explosion

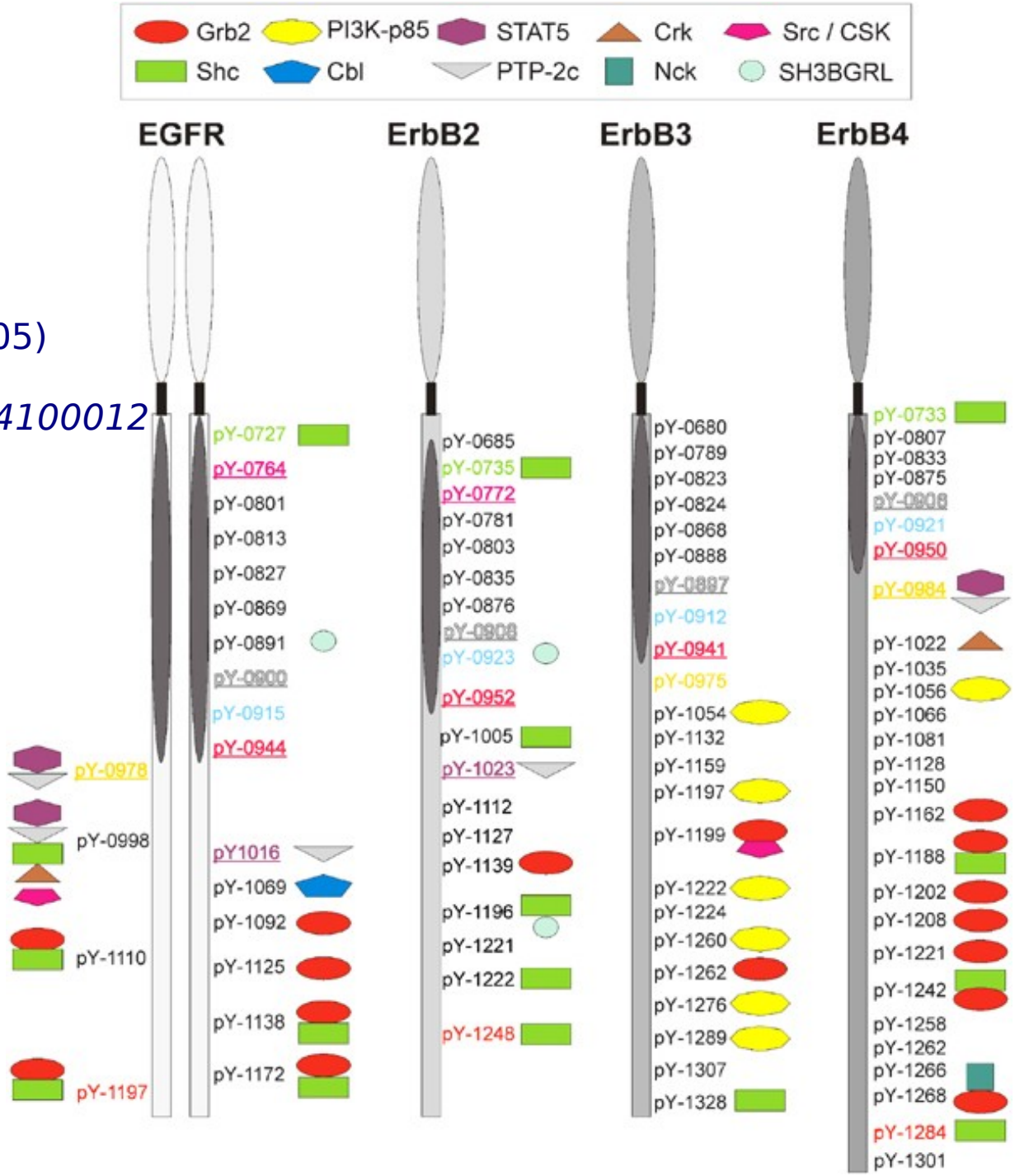


Additional reactions



Combinatorial explosion

Schulze *et al*. (2005)
Mol Sys Bio,
doi: 10.1038/msb4100012



Combinatorial explosion

- A molecule with 10 features = 2^{10} = 1024 states
- A molecule with 10 features reacting with a molecule with 10 features = 1 048 576 possible reactions.

  ... plus all the interconversions.

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  Do-we want (can-we) store millions of reactions in a pathway database?

Combinatorial explosion

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  ... plus all the interconversions.

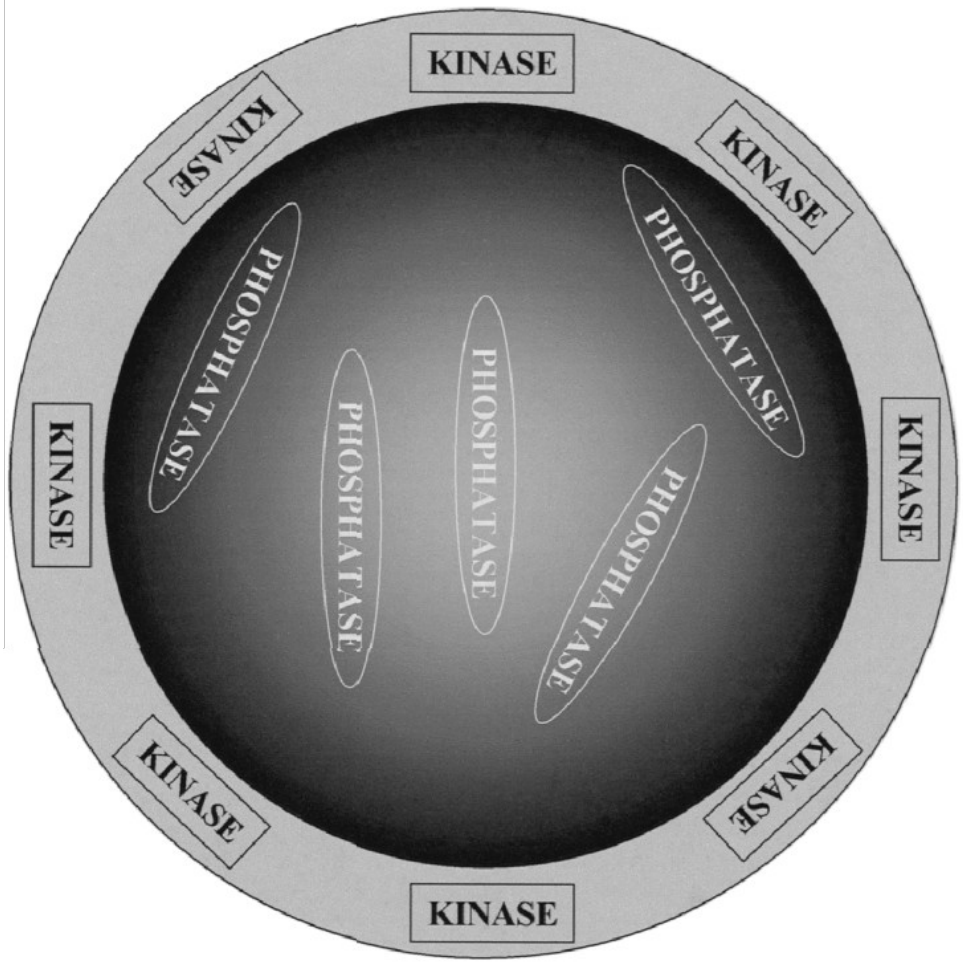
  Do-we want (can-we) store millions of reactions in a pathway database?

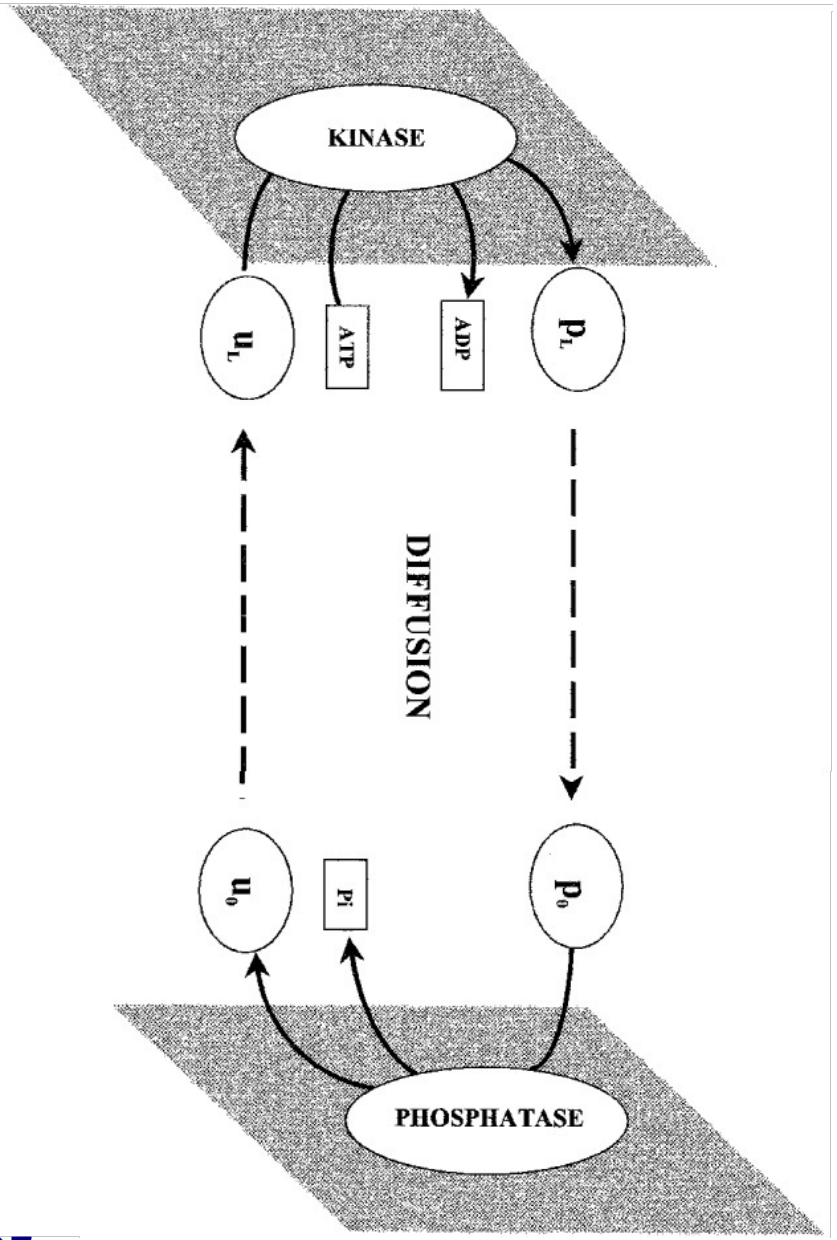
  However, all the states do not affect all the reactions:

  ☛ Reduction of dimensionality needed

The ruler

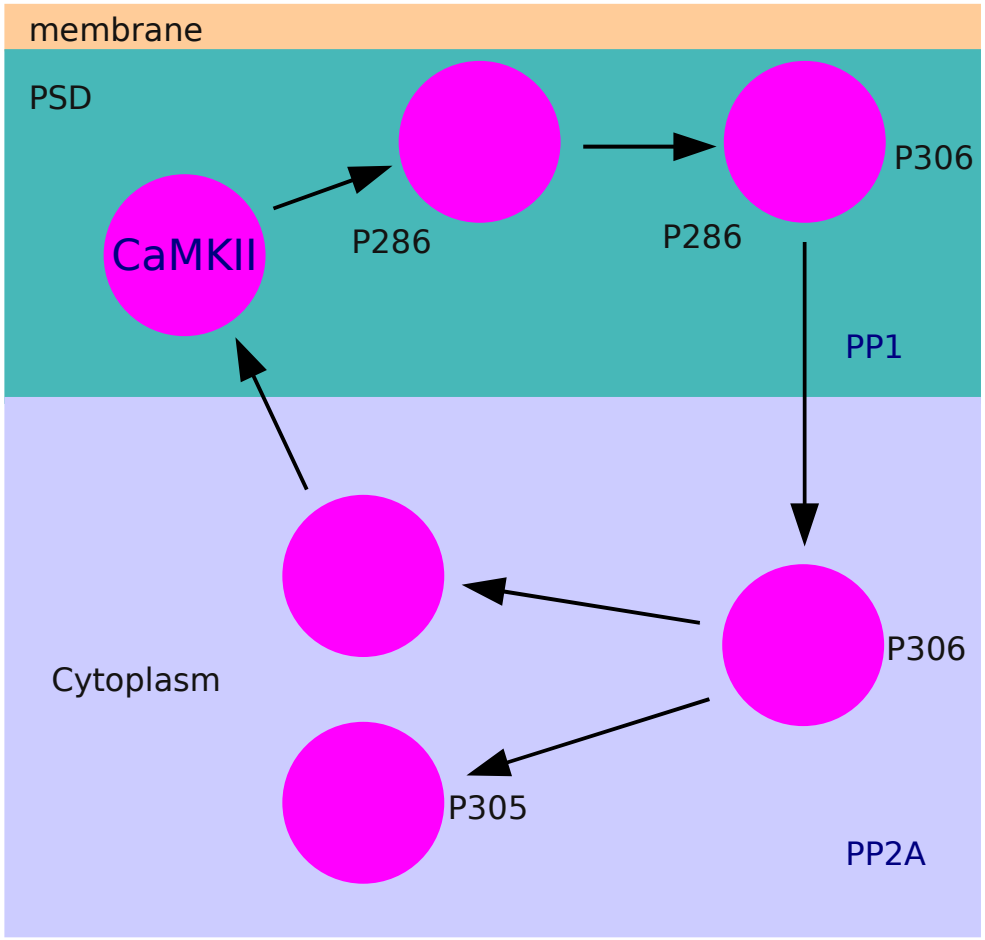
Spatial hysteresis





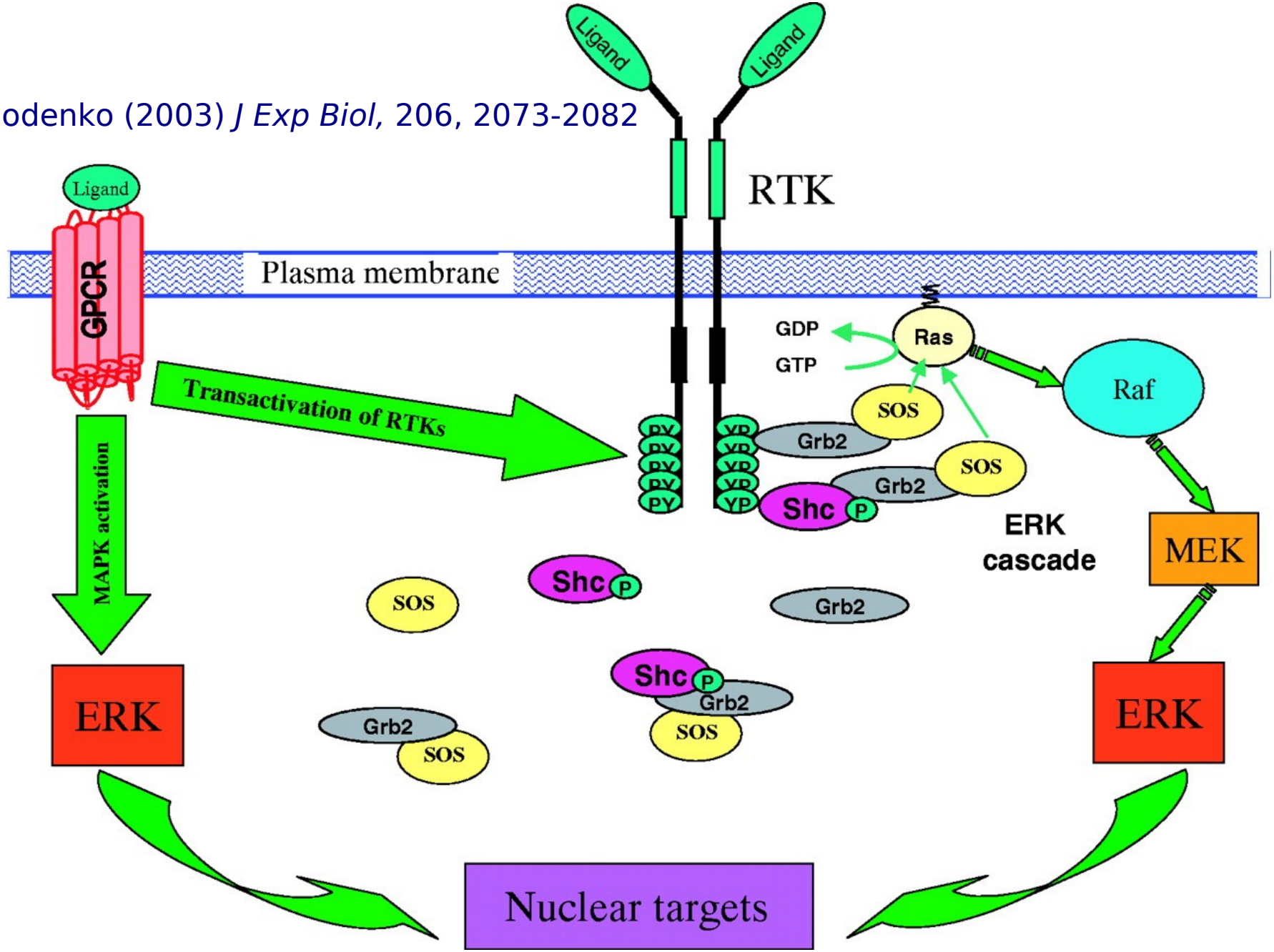
Kholodenko et al. *Biochem. J.* (2000) 350: 901–907

Spatial hysteresis

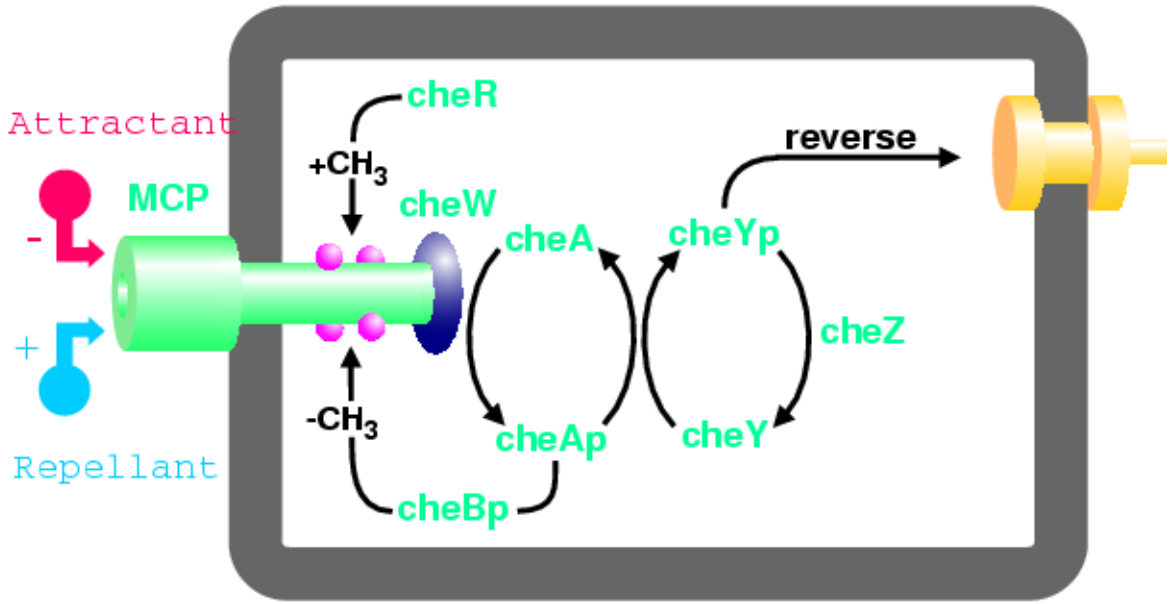


Spatial cascades

Kholodenko (2003) *J Exp Biol,* 206, 2073-2082

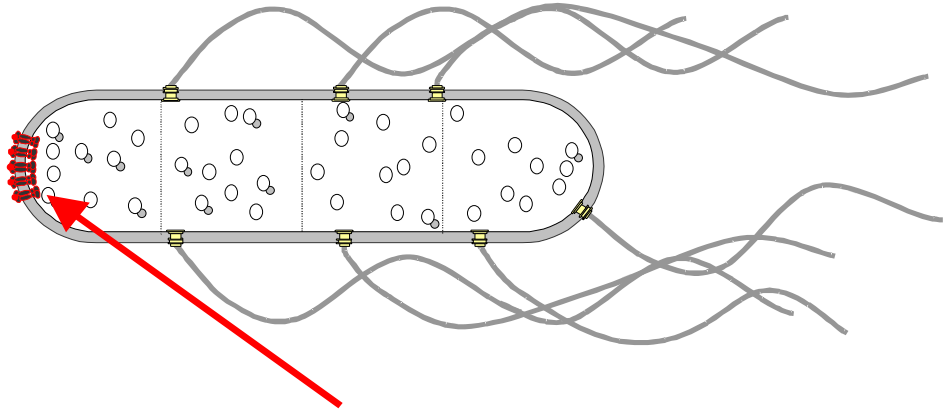


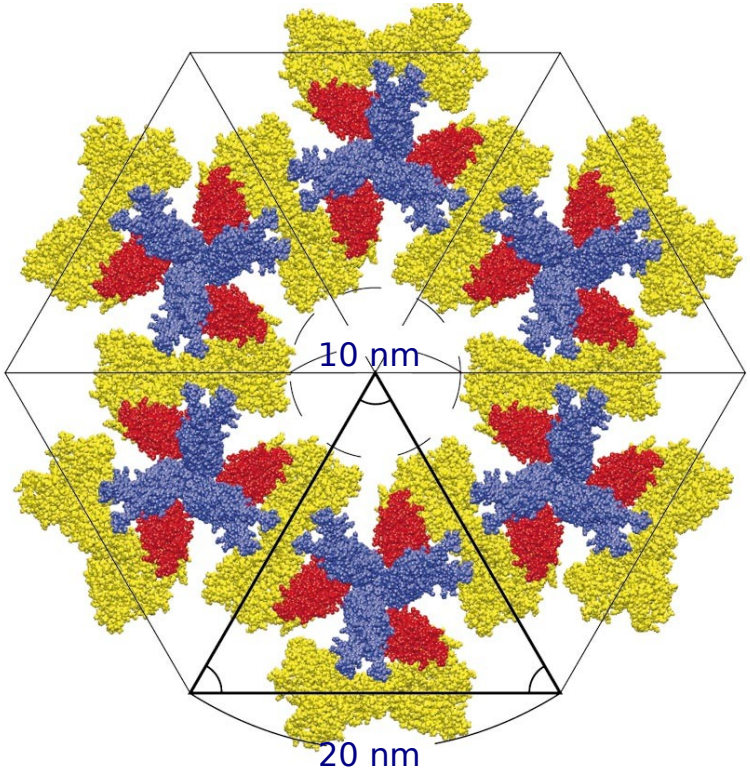
Importance of topology : the nose of the bacteria

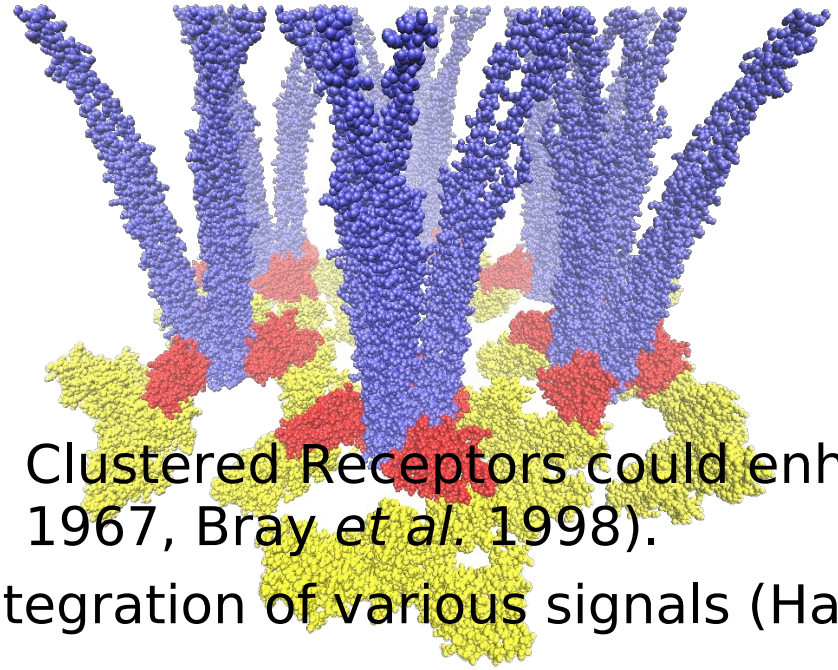


Receptor clustering and sensitivity

Chemotactic receptors form clusters at cell poles in E. coli (Shimizu, Le Novère et al. (2000) *Nat Cell Biol* 2: 792-796).



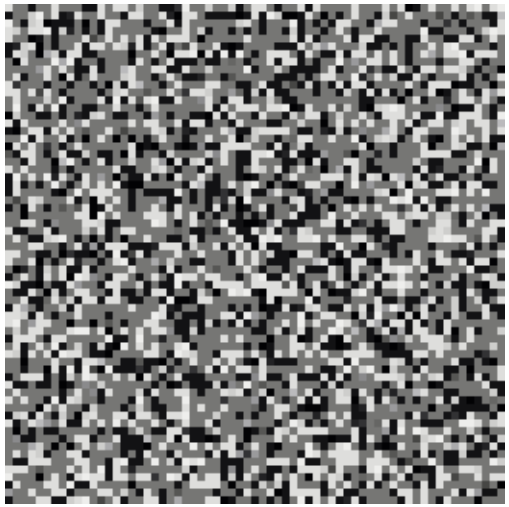
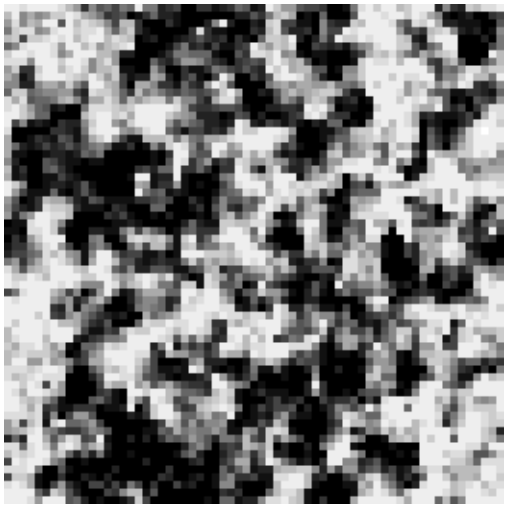
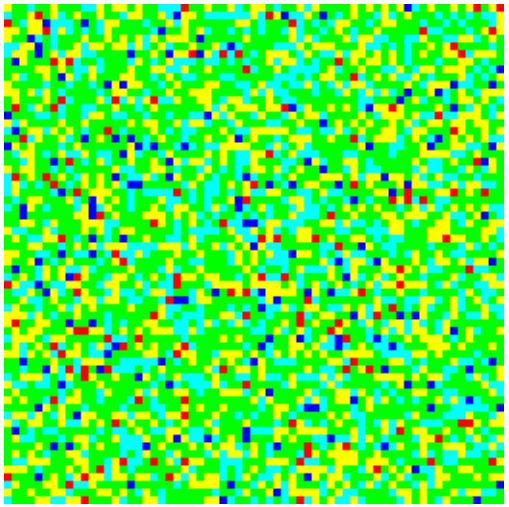
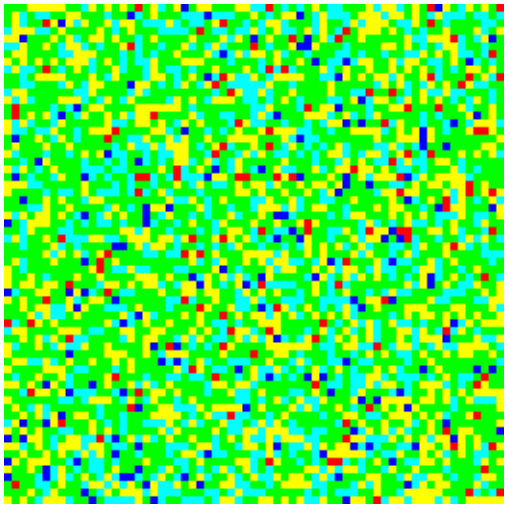




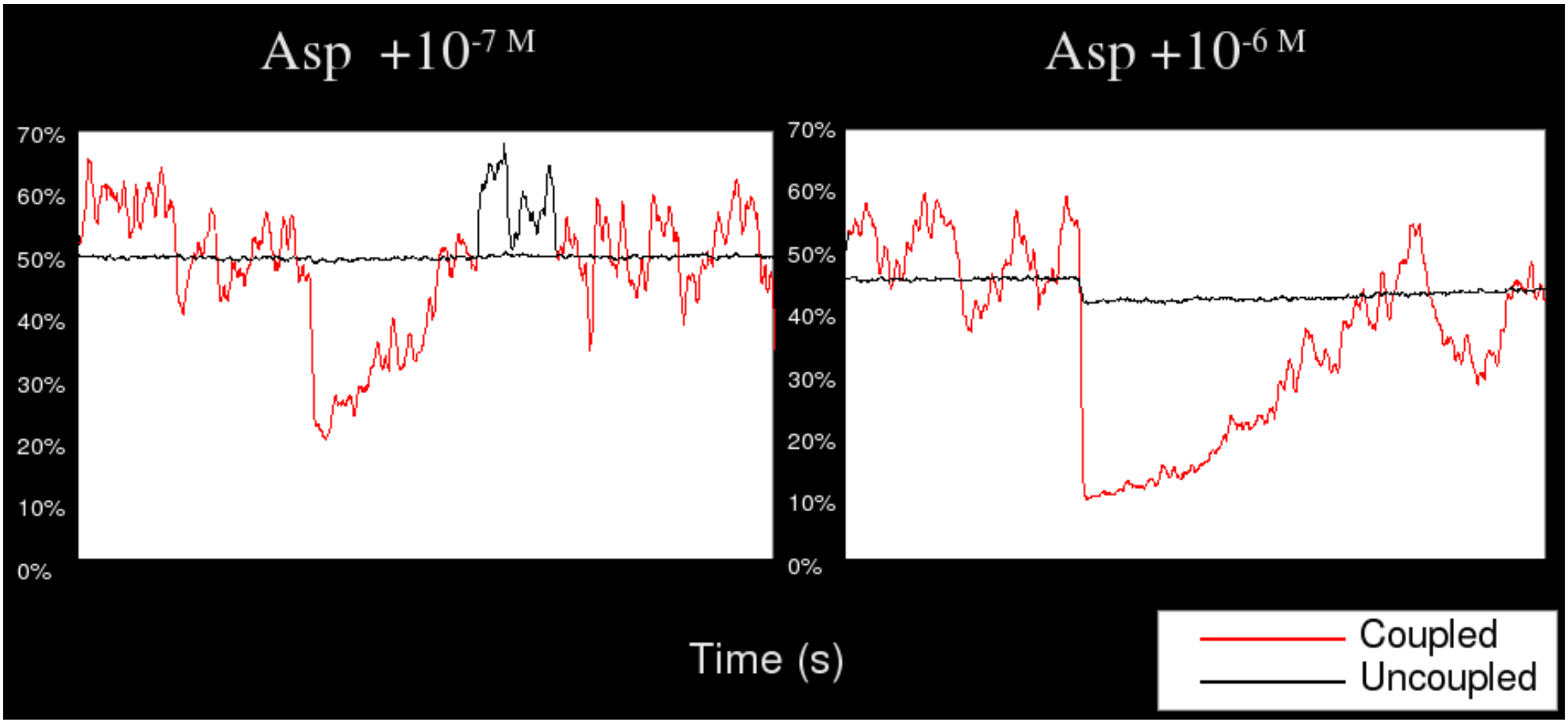
Clustered Receptors could enhance sensitivity (Changeux *et al.* 1967, Bray *et al.* 1998).

Integration of various signals (Hazelbauer et al. 1989).

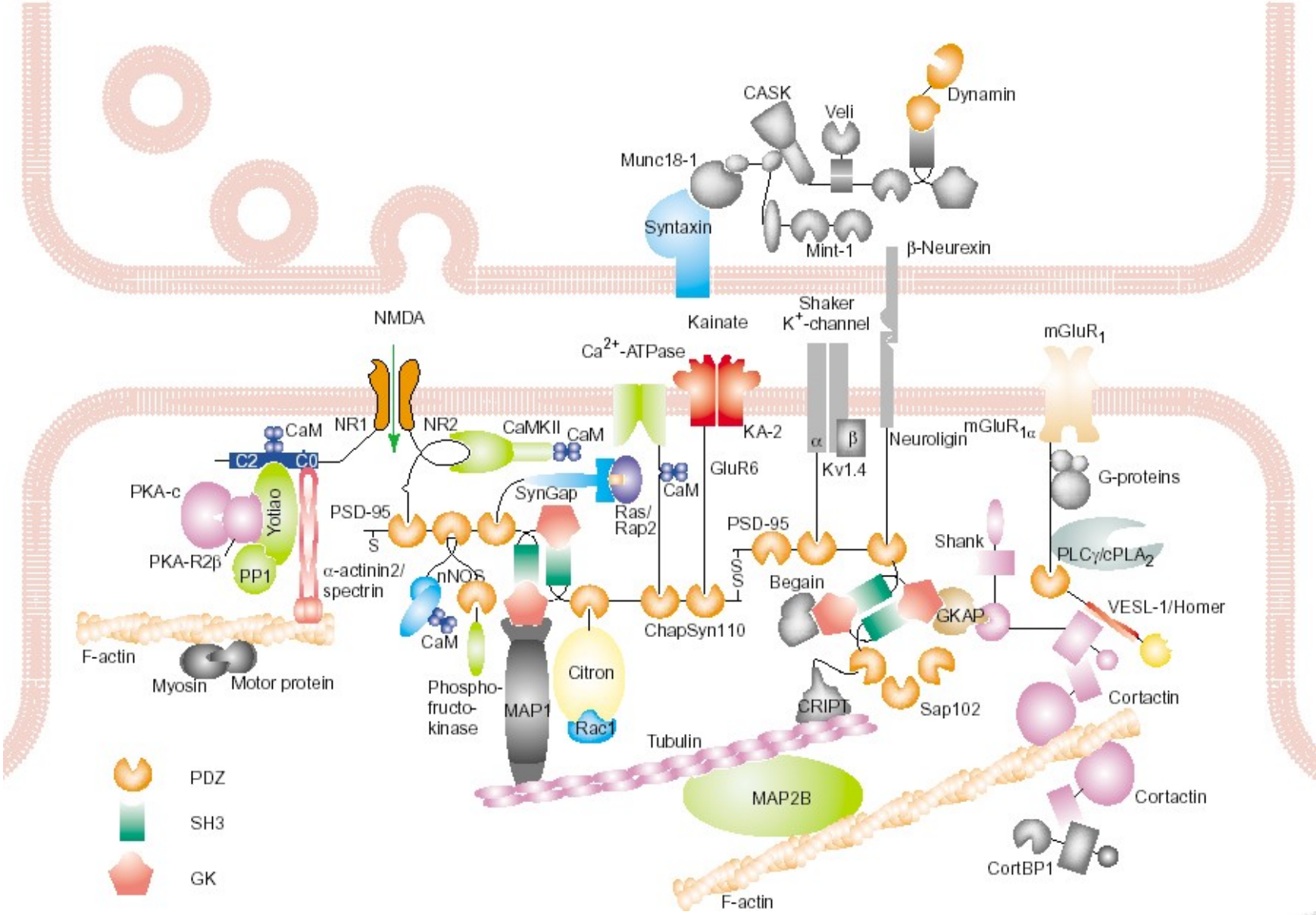
Effect of conformational spread

	uncoupled	coupled
activity		
methylation		

Effect of conformational spread



Complex post-synaptic machinery



Husi & Grant (2001) *TINS, 24*: 259-266

Conclusion: a brain map of signalling