Why are chemotaxis receptors clustered but other receptors aren't?

With thanks to:

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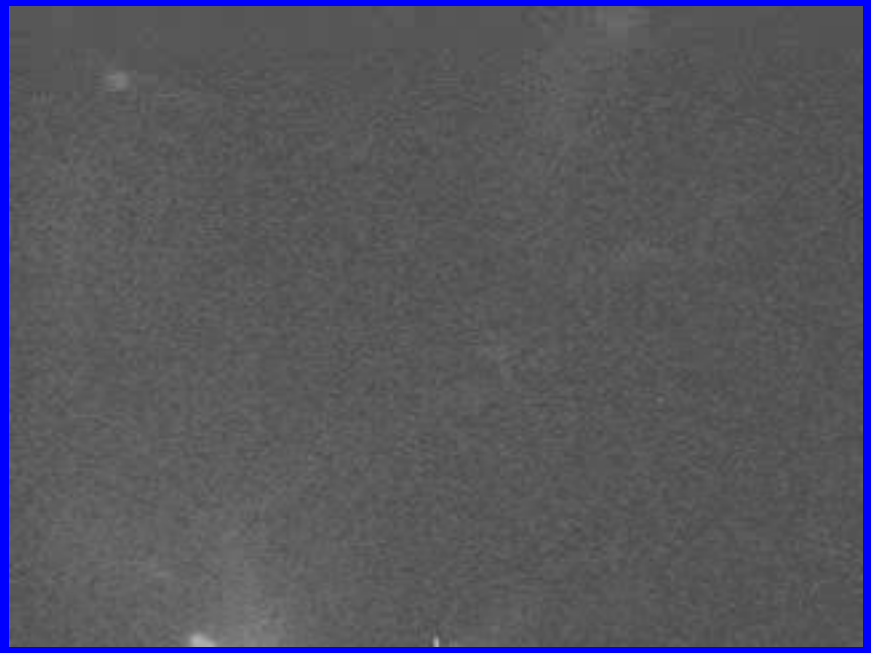
Outline

- Introduction to chemotaxis in *E. coli*
  - The “engineering” challenge
  - The chemotaxis network and receptors
- FRET reveals that receptors cooperate
  - Cooperativity adapts
- Other receptors don’t cluster or cooperate
- Cooperativity and noise
- So why do chemotaxis receptors cooperate?
- Conclusions

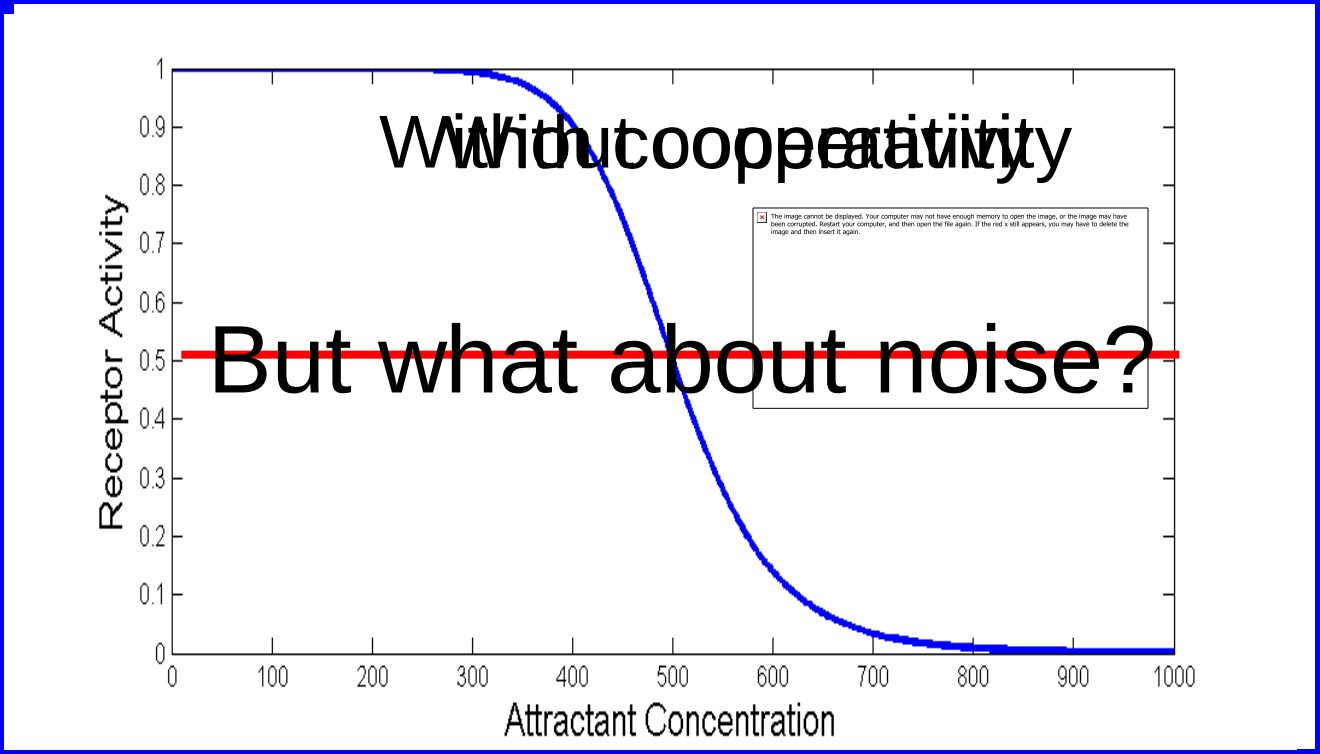
E. coli chemotaxis: runs and tumbles



(Thanks to Howard Berg.)

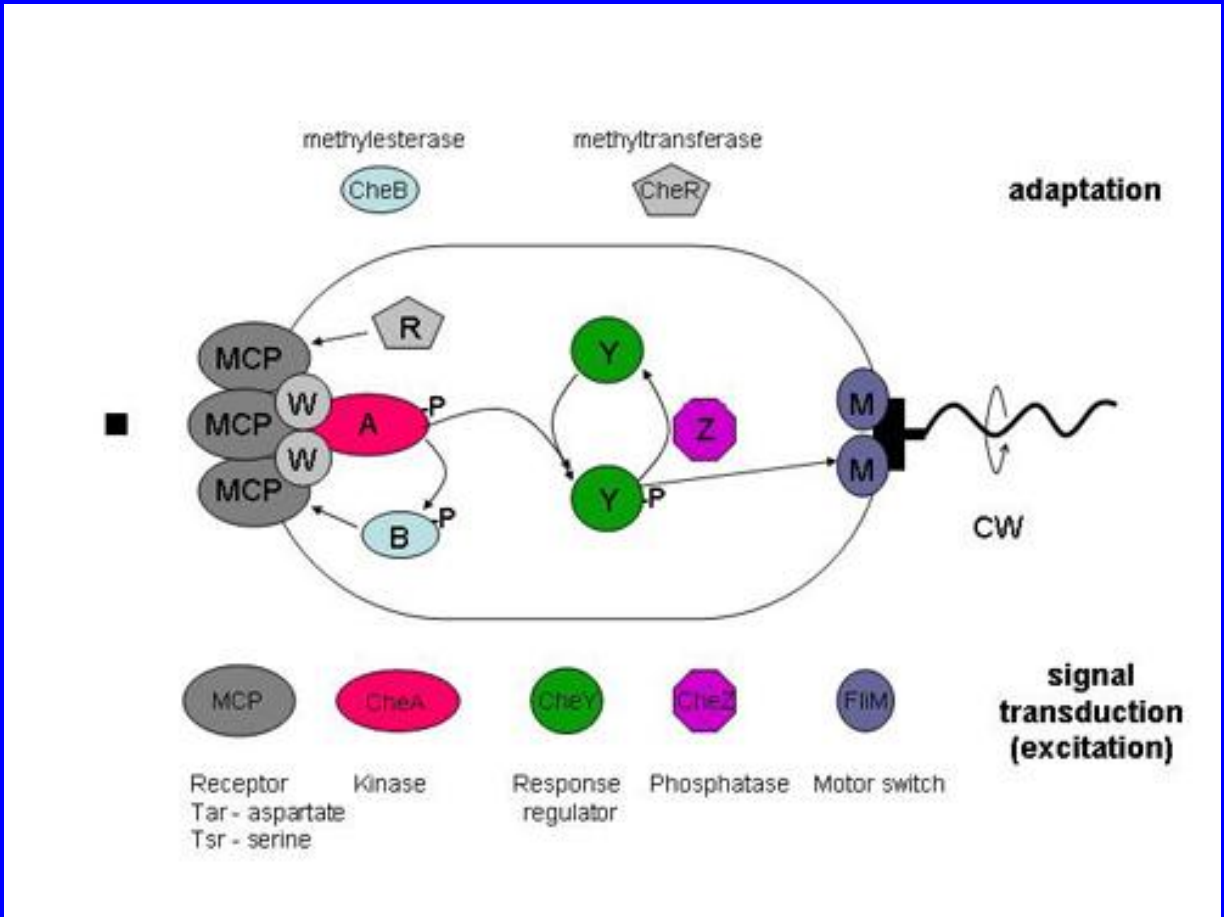
Principles of Chemoreceptor "Engineering"

- High gain via receptor cooperativity
- Broad range via adaptation (integral feedback)



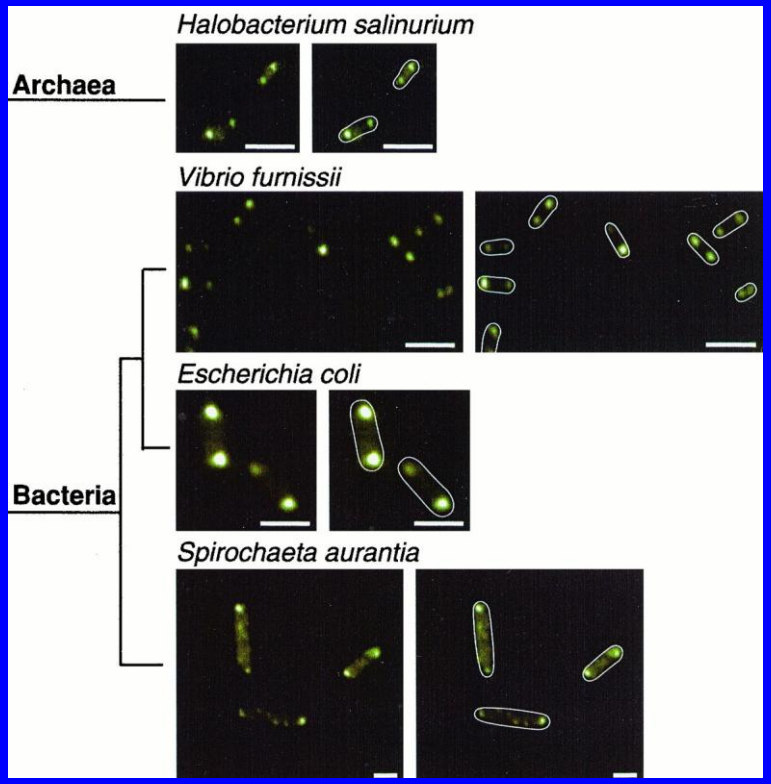
The chemotaxis network (best studied network in biology)

http://www.rowland.harvard.edu/labs/bacteria/projects_fret.html

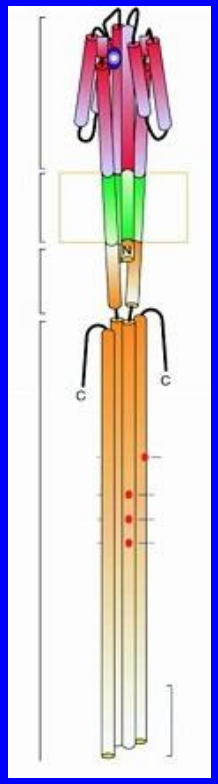


Chemoreceptor clustering

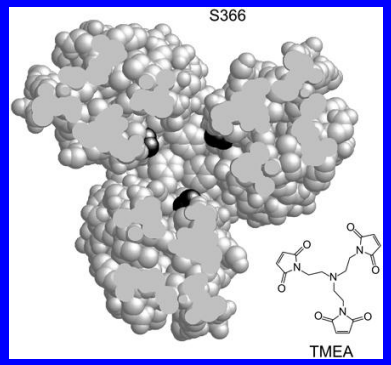
Receptors are clustered globally,
and locally form trimers of dimers, arranged in a honeycomb lattice.



Gestwicki *et al.* (2000)

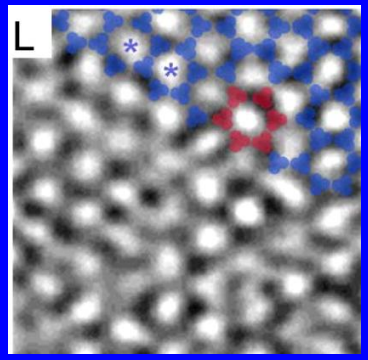


Stock (2000)



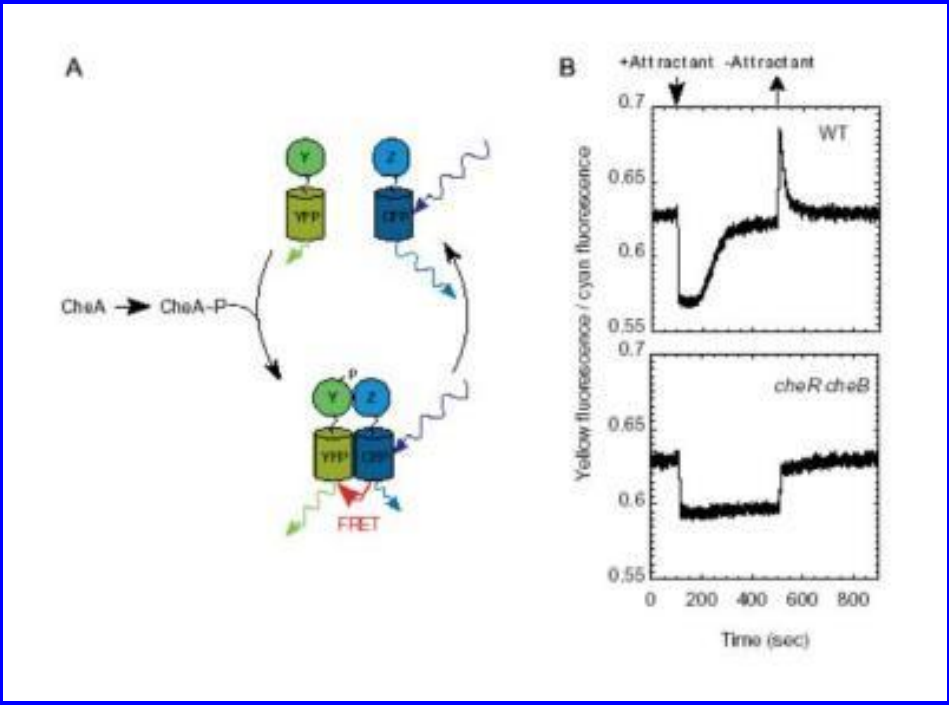
Kim *et al.* (1999); Studdert and Parkinson (2004)

V. cholerae



Briegel *et al.* (2009)

In vivo FRET studies of receptor activity

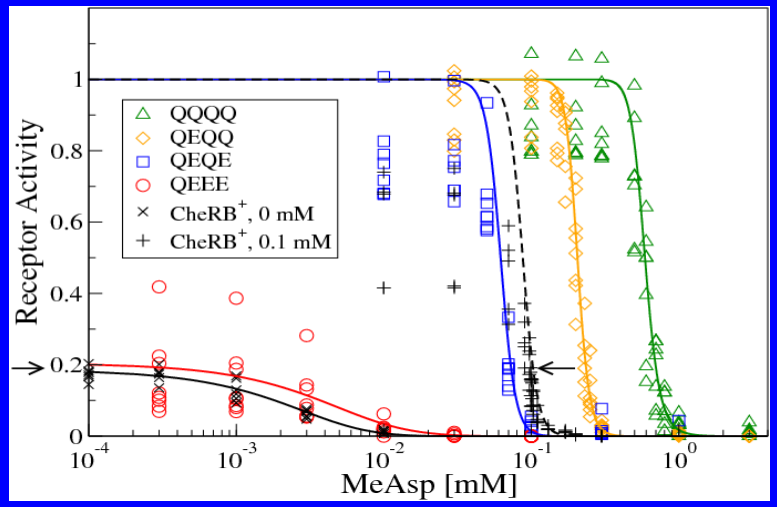


Sourjik and Berg (2002)

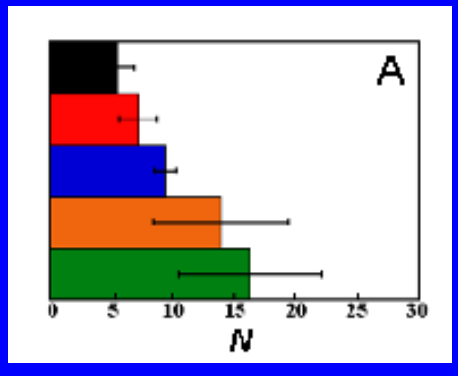
Real-time measurement of rate of phosphorylation of CheY.

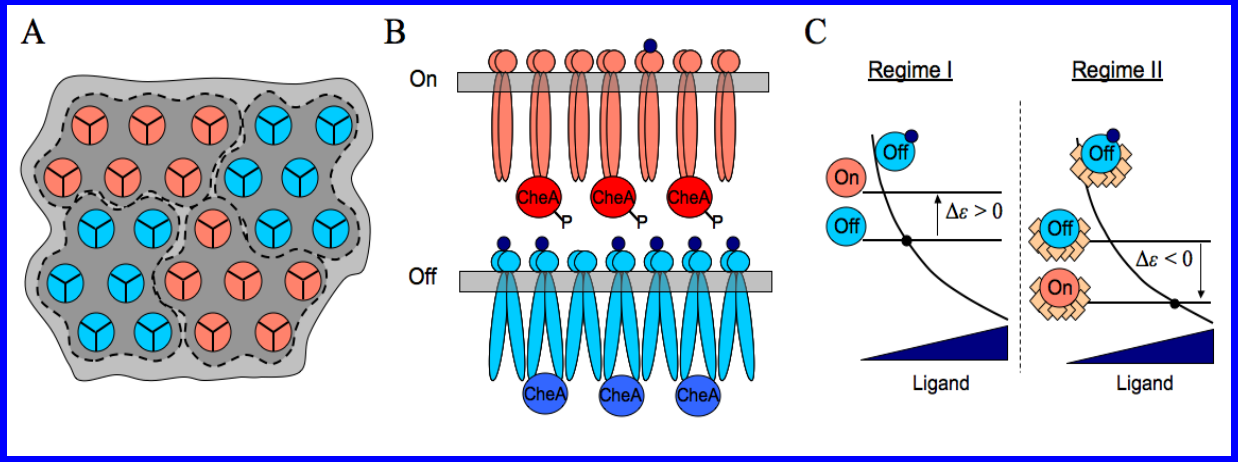
Receptors cooperate in teams

PCA of FRET data (Tar-only strains)



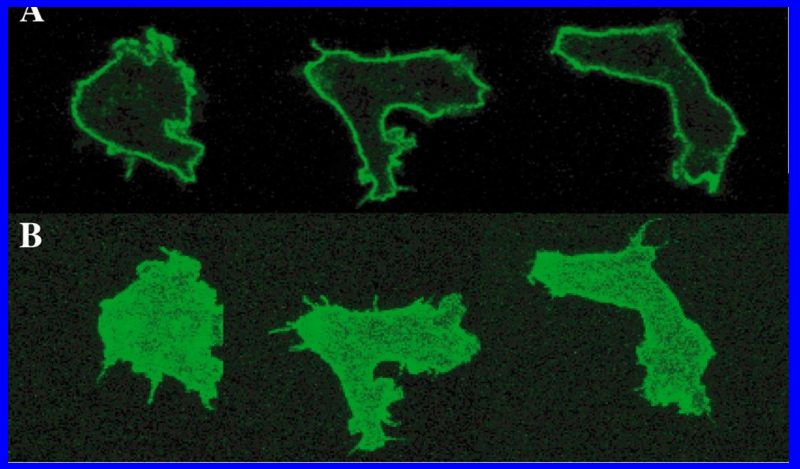
team size





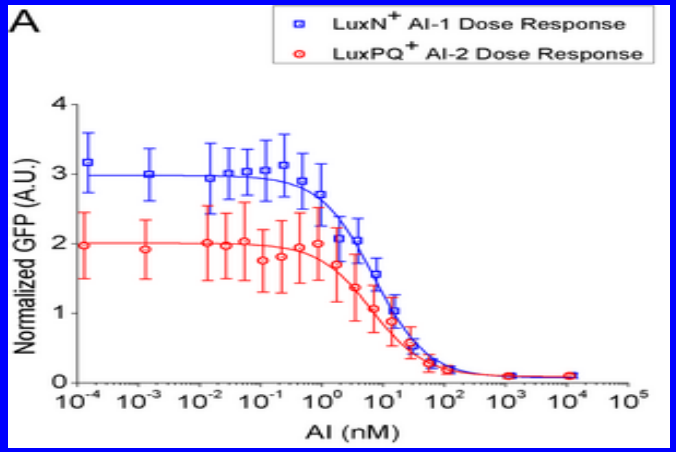
Why don't other receptors cooperate?

Dictyostelium cells have ~uniform cAR1-GFP distribution (cAMP receptor)



Traynor *et al.* (2007)

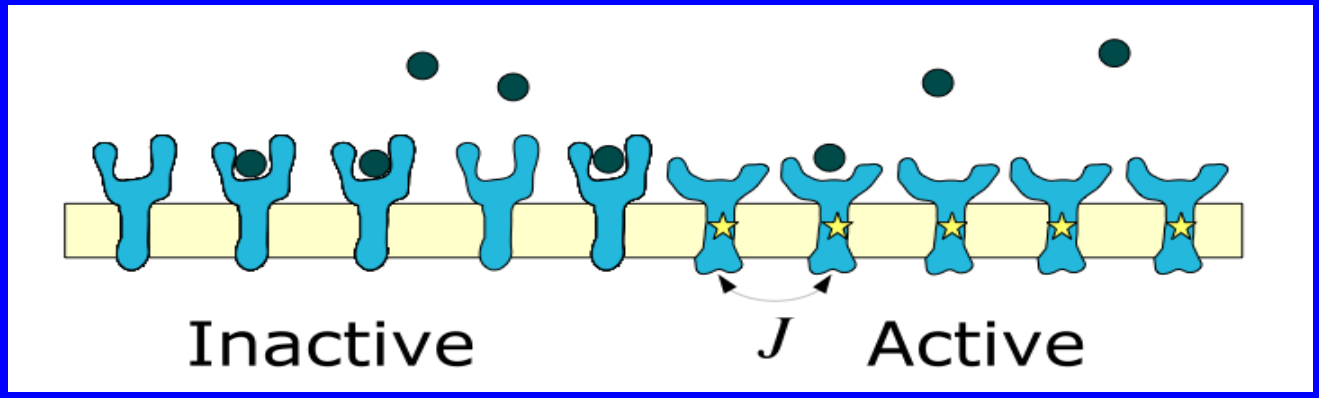
V. harveyi quorum-sensing dose-response curves have no gain



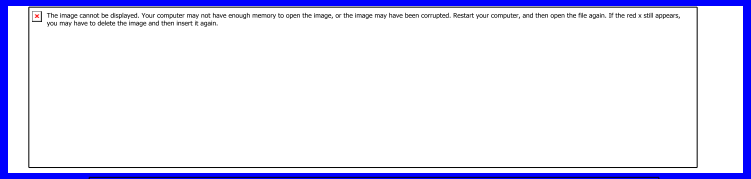
Long *et al.* (2009)

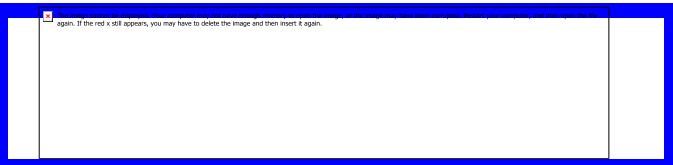
Could cooperativity increase noise?

Model for cooperative receptors with switching noise

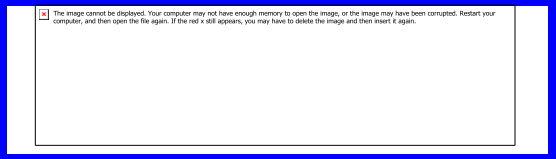


Ising model of receptor clusters:

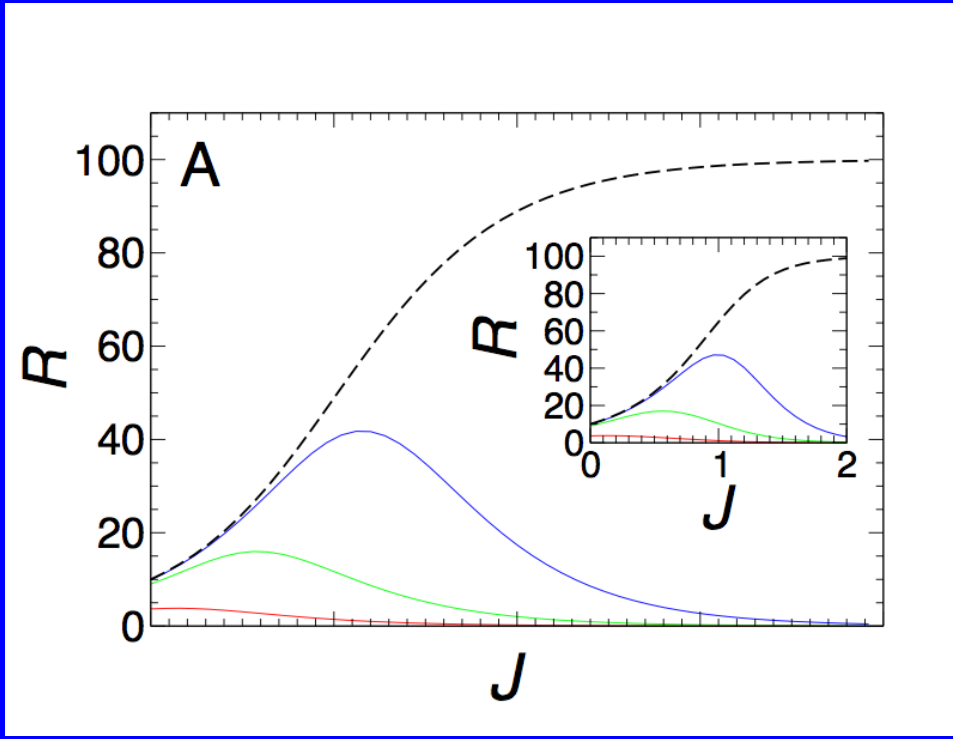


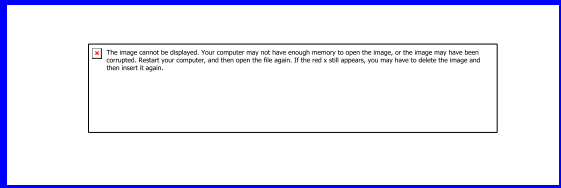


With Glauber's "heat bath" dynamics:



Signal

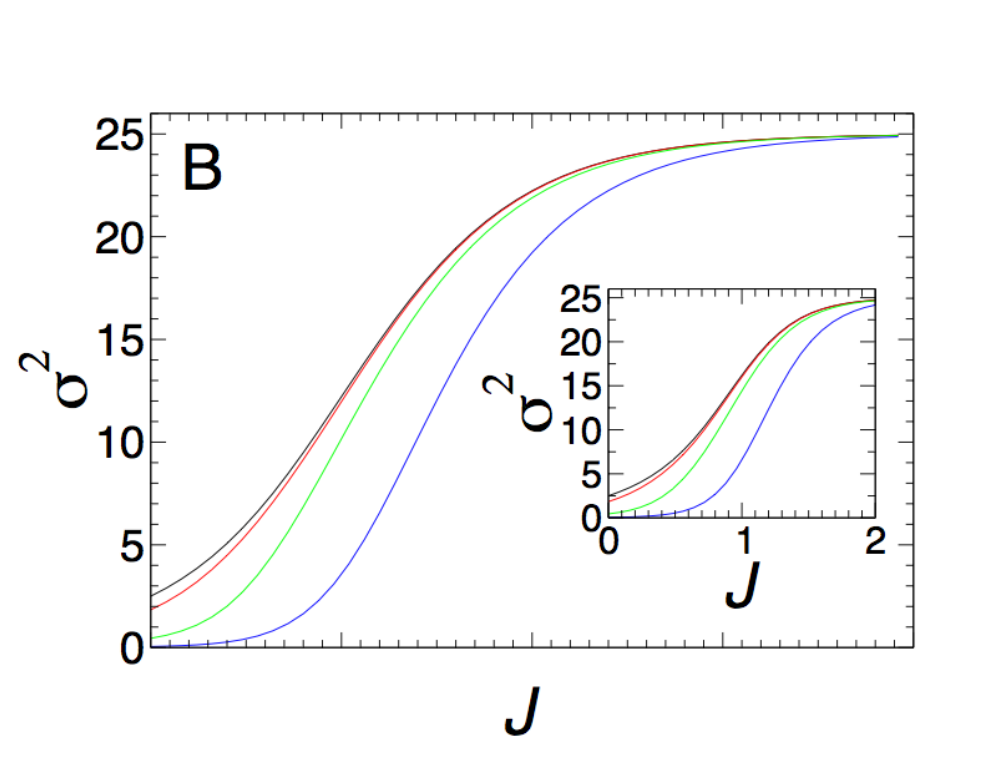




1D chain with
n = 10 receptors

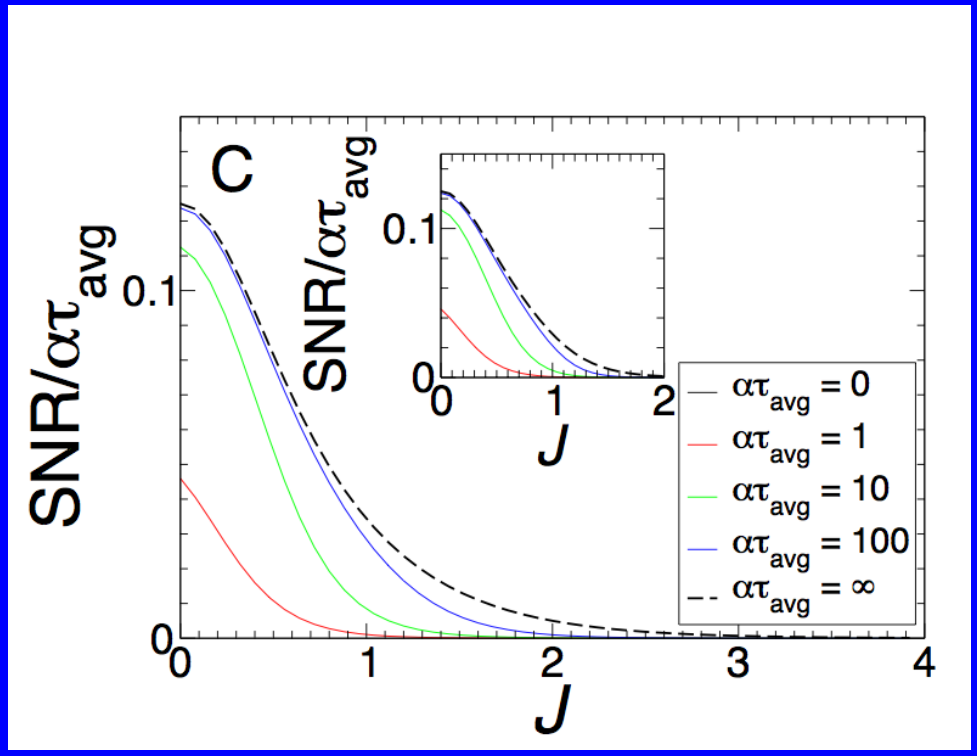
- Signal increases with coupling J (cooperativity).
- Then signal decreases as response slows.

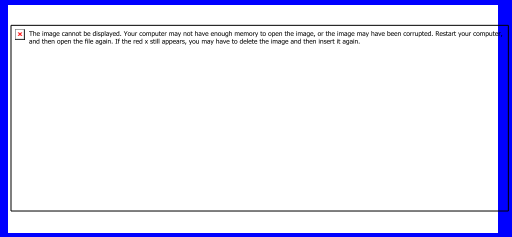
Noise



- Noise increases with coupling *J*.
- Longer τ_{avg} reduces noise.

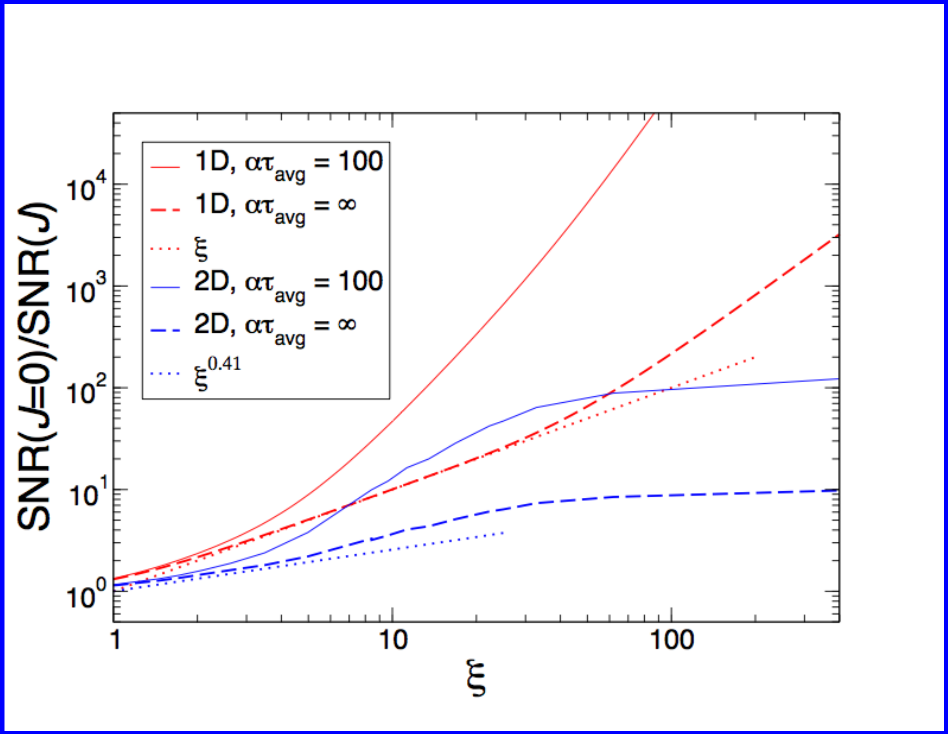
Signal-to-Noise Ratio (SNR)

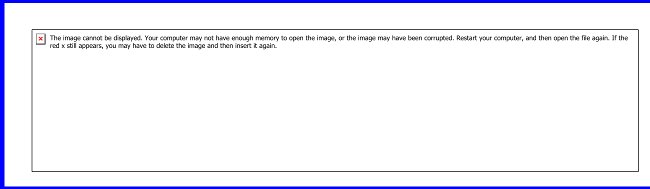


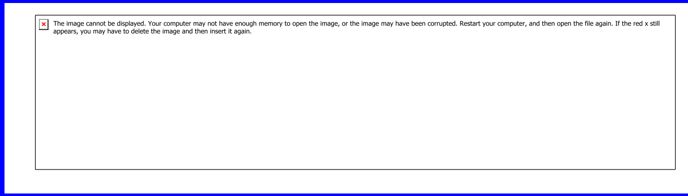


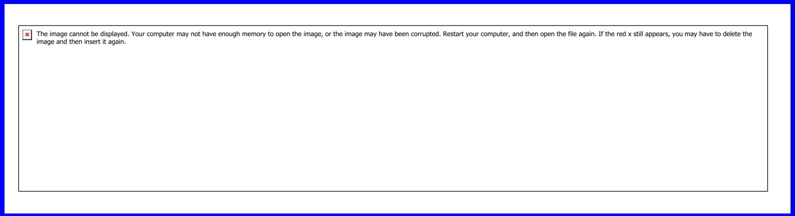
SNR is best for independent receptors!

Scaling relations for SNR









SNR is *always* best for independent receptors!

So why do chemoreceptors cooperate?

- Slow ligand dynamics?
- Extrinsic noise?
- We’re asking the wrong question?

So why do chemoreceptors cooperate?

- Slow ligand dynamics?
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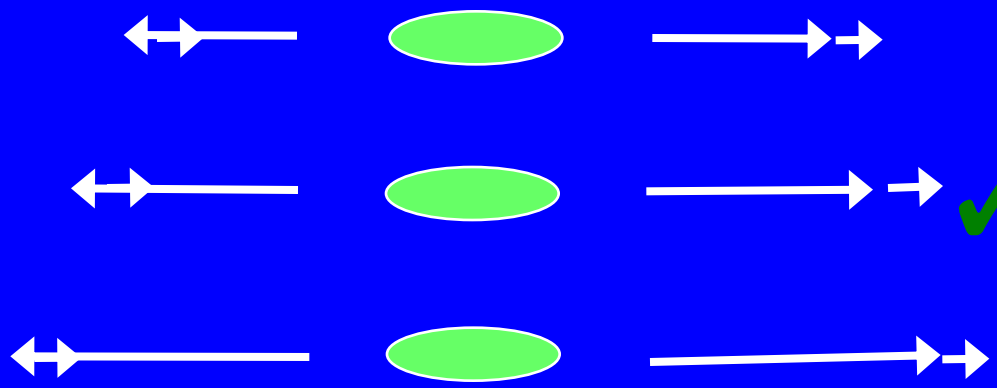
So why do chemoreceptors cooperate?

- Slow ligand dynamics? ✗
- Extrinsic noise? ✗
- We're asking the wrong question? ✓

We should be asking how to optimize chemotactic velocity, not SNR.

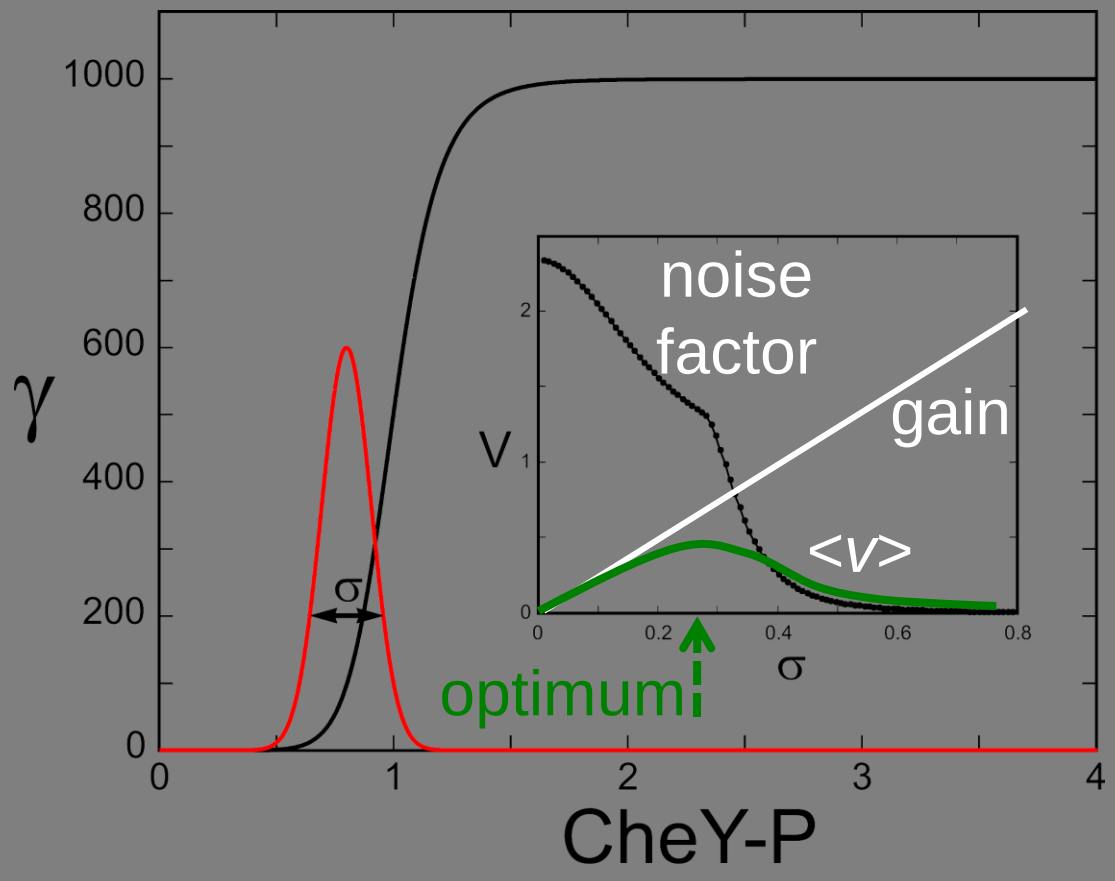
Effect of signal and noise on chemotaxis



✓ Optimum: $1/\tau_{tumble} = 2D_{rot}$

- Noise reduces $\langle v \rangle_{drift}$, but only gradually
- Signal increases $\langle v \rangle_{drift}$ *linearly*

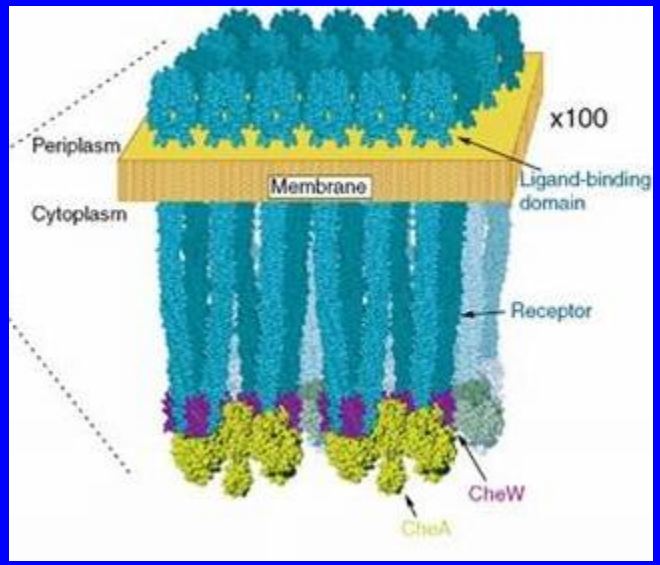
Maximizing chemotactic velocity



"Run and tumble" strategy implies noise threshold, which sets optimal cooperativity.

Open questions

- When is cooperativity advantageous?
- In *E. coli* chemotaxis, what controls cooperativity and its adaptation, and why does cooperativity adapt?
- Why ~5,000 chemoreceptors?



Stock (2000)

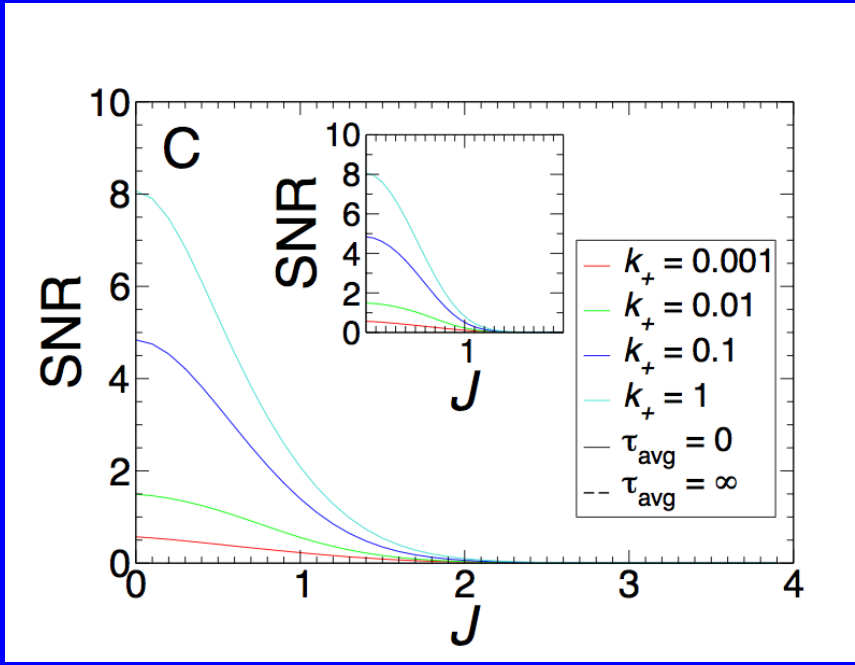
Conclusions

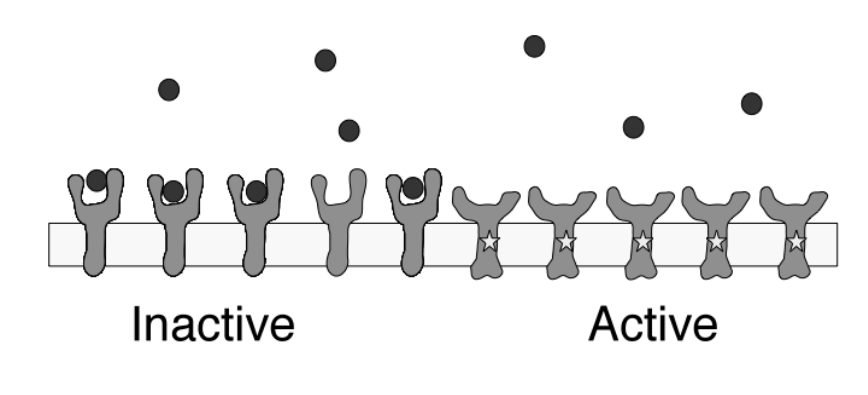
- *E. coli* chemotaxis receptors cooperate
  - increase of gain
  - cooperativity adapts
- Cooperativity is bad for SNR
- Chemotactic velocity optimized by increasing signal, up to noise threshold
- Do other receptors optimize SNR?

Keymer *et al*., PNAS (2006)
Endres and Wingreen, PNAS (2006)
Skoge, Endres, and Wingreen, Biophys J (2006)
Hansen, Endres, and Wingreen, PLoS CB (2007)
Endres *et al.,* MSB (2008)

Wang *et* al., PRL (2008)
Greenfield *et al*., PLoS Biology (2009)

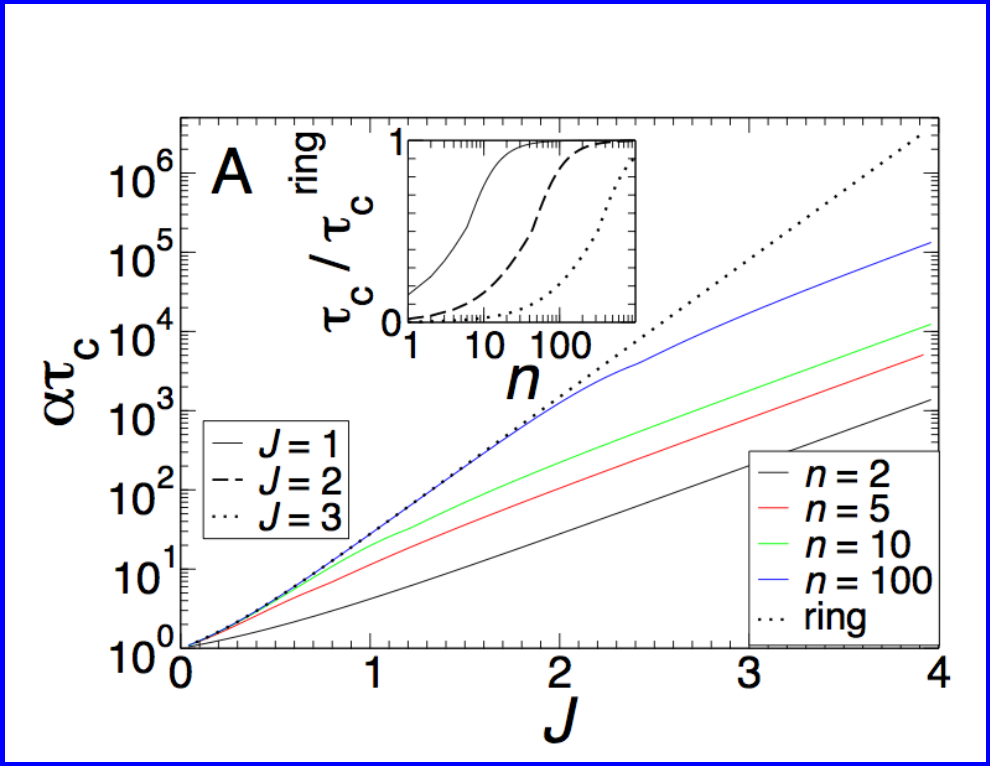
Slow ligand dynamics

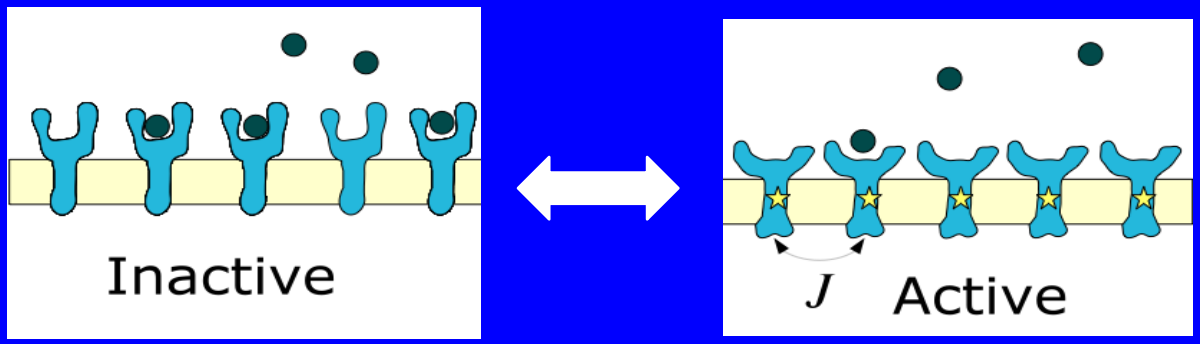




- SNR still best for independent receptors
- Correlation time is multiplied by ligand binding time, due to domain wall pinning

Correlation time

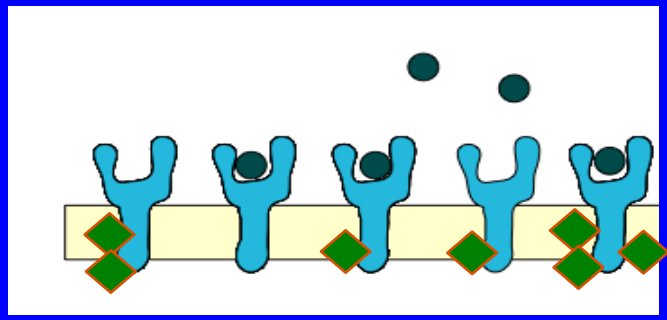


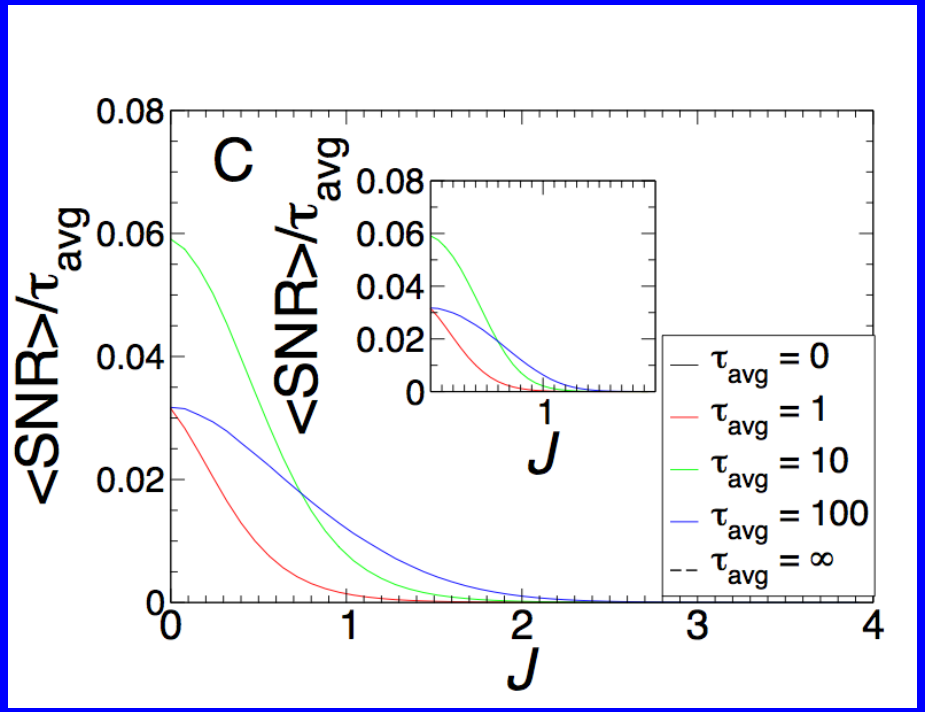


$\tau_c \sim \exp(2J)$

Static, extinsic receptor noise

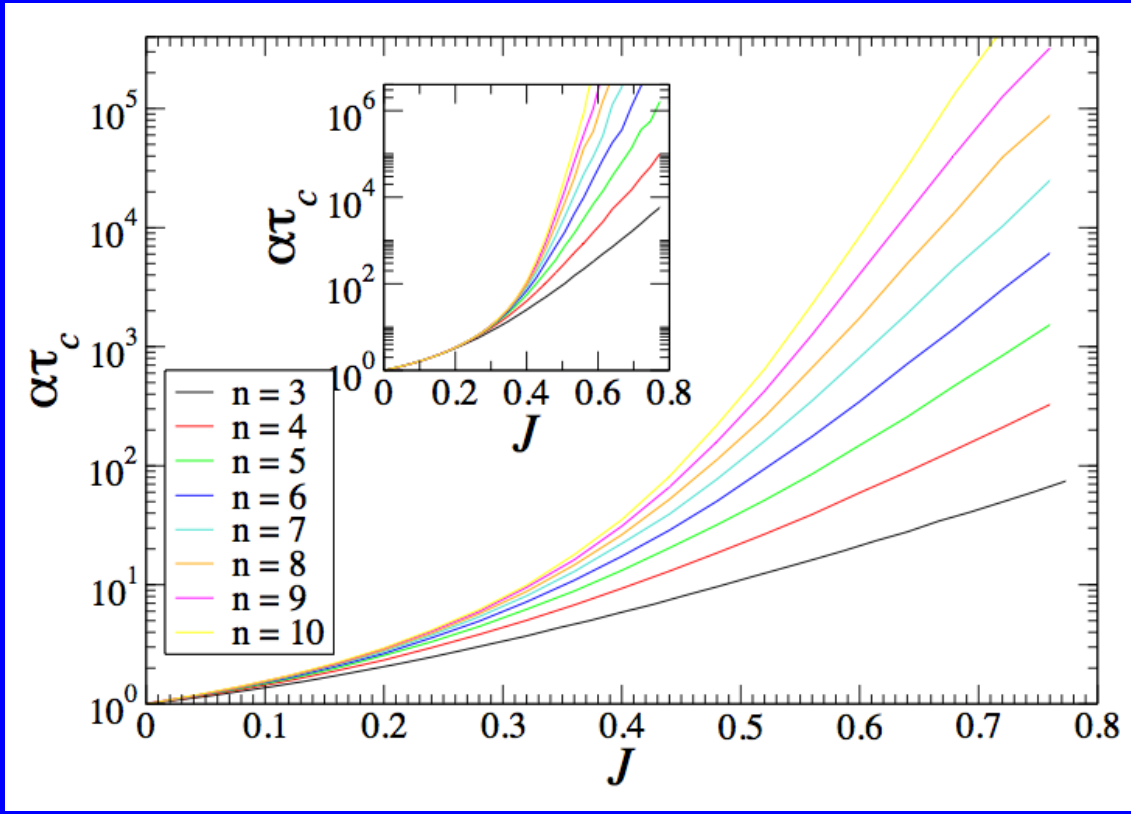
E.g. noise from receptor methylation:





- Cooperativity amplifies static noise
- SNR still best for independent receptors

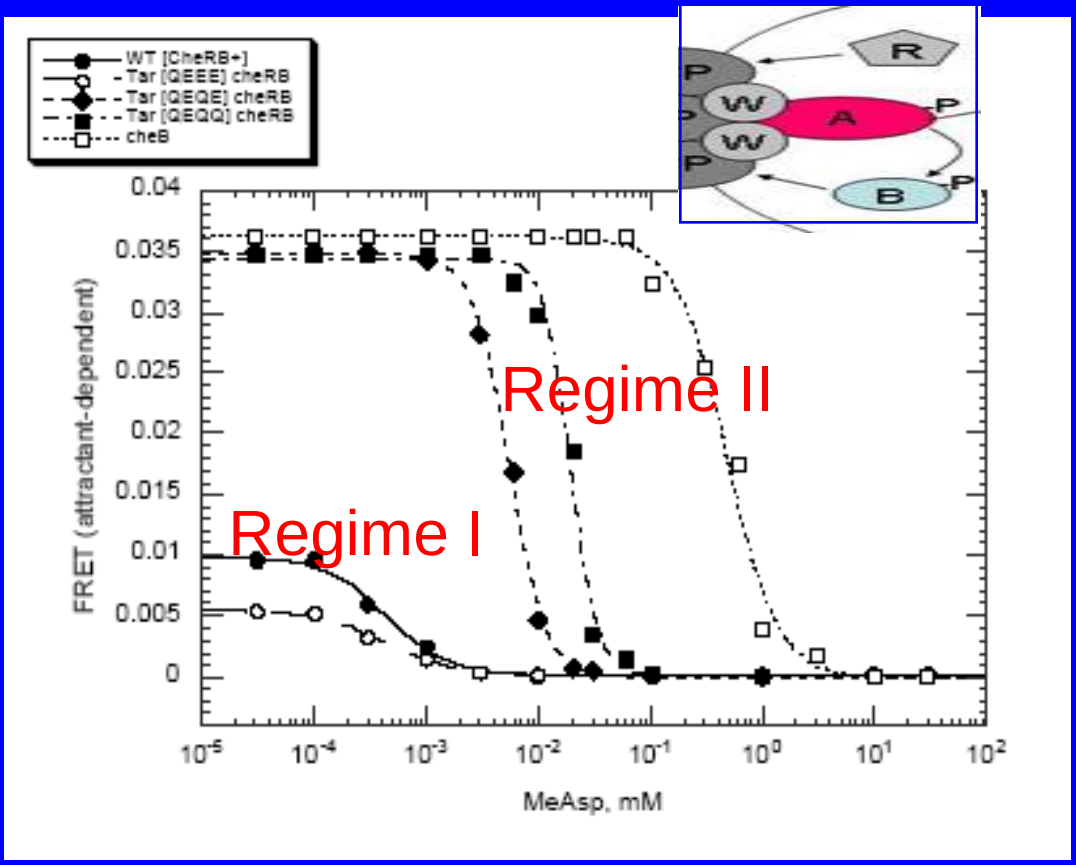
Correlation time in 2D



$\tau_c \sim \exp(?)$

FRET data: two regimes of activity

Sourjik and Berg (2002)

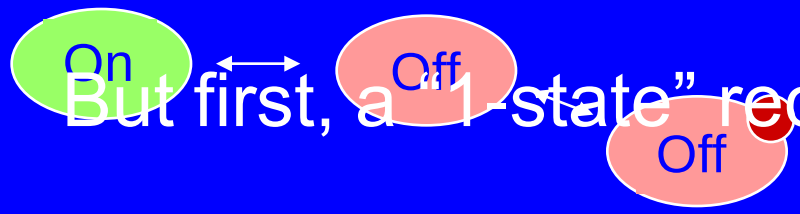


Regime I:
- Activity low at zero attractant
- K_i small and ≈ constant

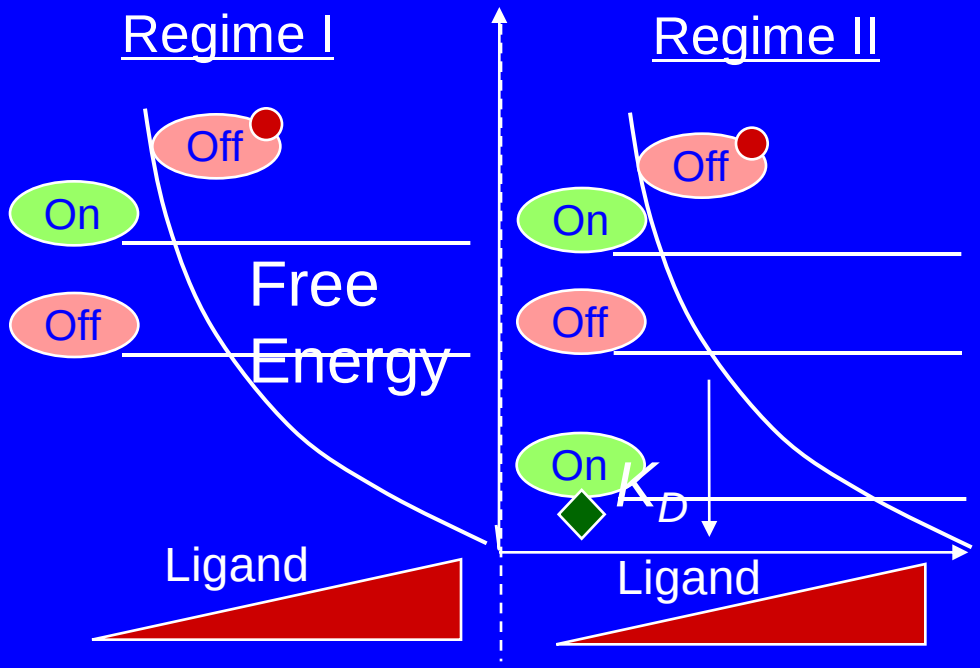
Regime II:
- Activity high (saturated) at zero attractant
- K_i large and increases with methylation

Two regimes of receptor activity consistent with 2-state receptor model.

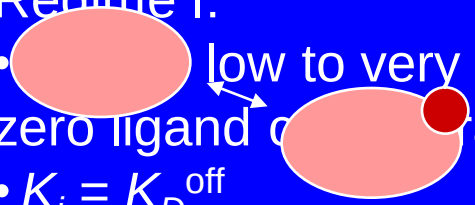
Two regimes of a 2-state receptor



But first, a "1-state" receptor:



Regime I:



- low to very low at zero ligand c ration
- $K_i = K_D^{off}$

Regime II:

$$P_{\text{noligandbound}} = \frac{1}{1+\frac{C}{K_D}}$$

) at n

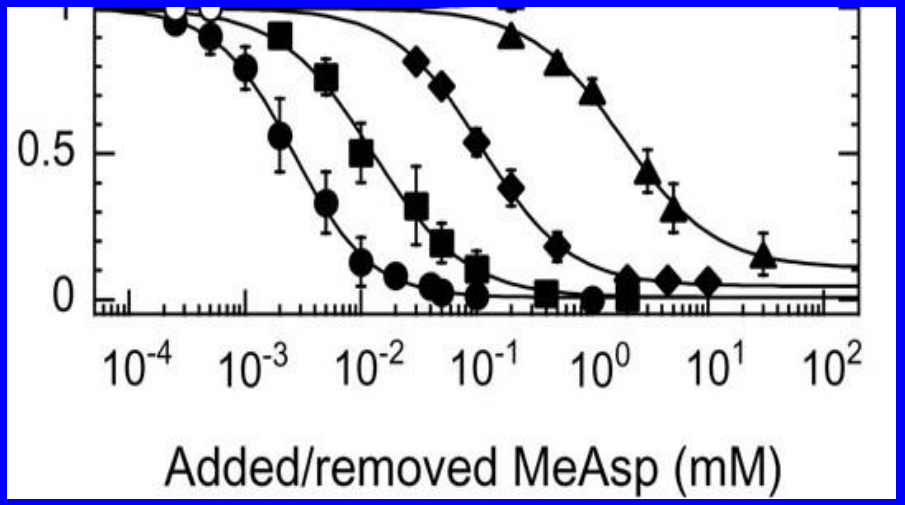
$$\text{Activity} = P_{\text{on}} = \frac{e^{-\varepsilon^{\text{on}}}}{e^{-\varepsilon^{\text{on}}} + e^{-\varepsilon^{\text{off}}} + \frac{C}{K_D^{\text{off}}} e^{-\varepsilon^{\text{off}}}}$$

However, single receptor does not account for low apparent K_i in Regime I.

Data collapse

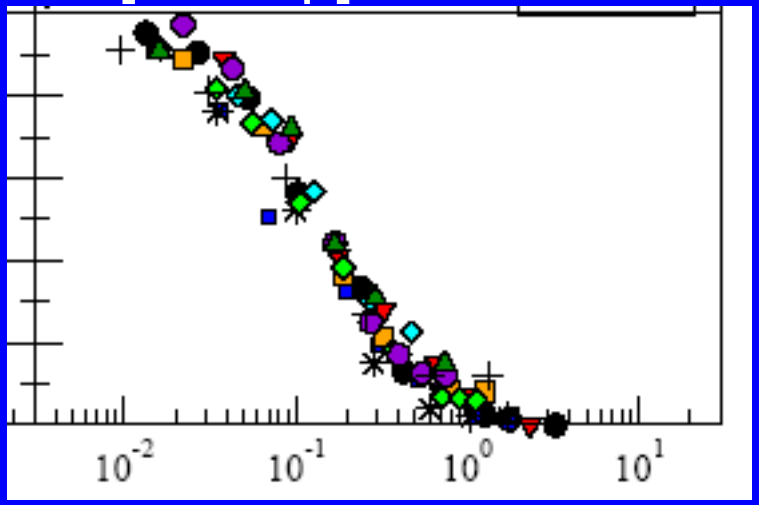
Receptor activity depends only on difference between on and off state free energies.

Sourjik and Berg:
Δ[MeAsp] → ΔFRET



Sourjik and Berg (2002)

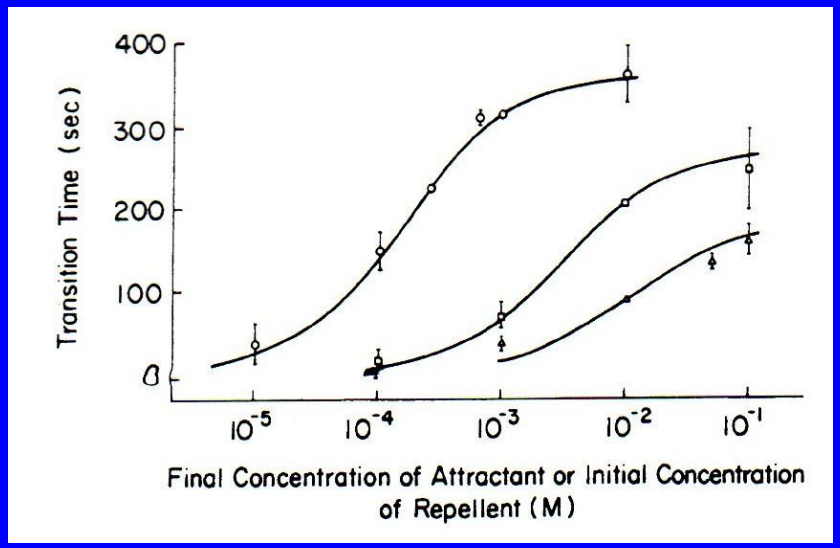
"Free energy" data collapse:
Δ[MeAsp] → ΔF



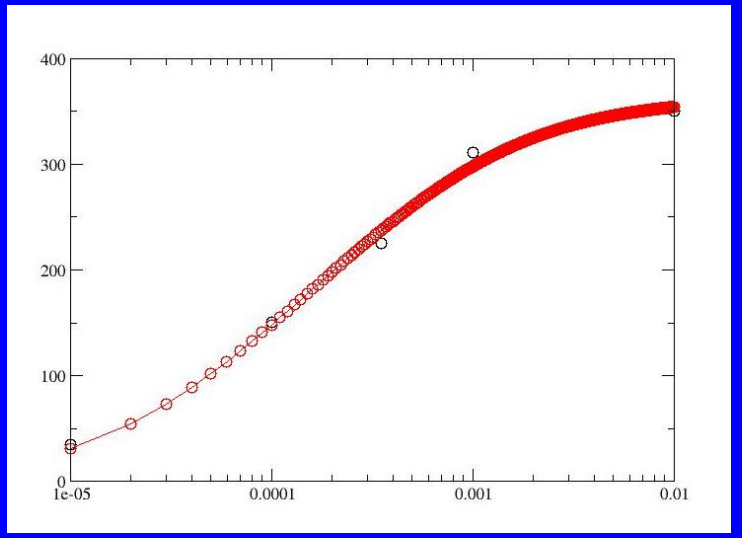
And data collapses and yields K_Ds:

K_D^{off} = 25 μM, K_D^{on} ≈ 0.5 mM

Recovery time – confirms K_D values



Berg and Tedesco (1975)



$$t \sim \Delta f \sim \log\left(\frac{1+C/K_D^{off}}{1+C/K_D^{on}}\right)$$

→ K_D^{off} = 27 μM, $K_D^{on} \approx$ 0.9 mM

So why do chemoreceptors cooperate?

- Slow ligand dynamics? ✗
- Extrinsic noise? ✗
- We're asking the wrong question? ✓

We should be asking how to optimize chemotactic velocity, not SNR.