Effect of receptor clustering on chemotactic performance of E.coli: sensing versus adaptation

Sakuntala Chatterjee

S. N. Bose National Centre for Basic Sciences, Kolkata

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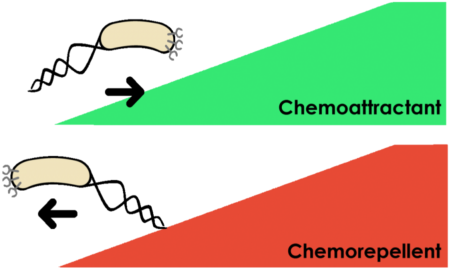
In collaboration with

- Shobhan Dev Mandal
- Subrata Dev (presently at INRAE Paris)

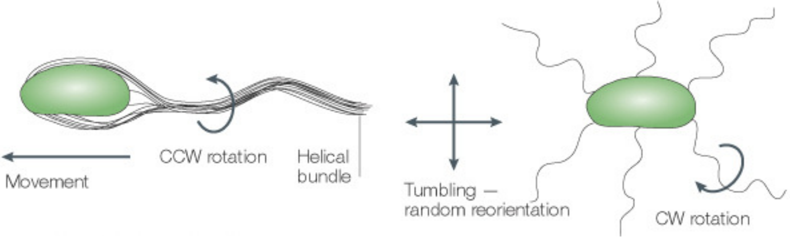
Introduction

- The behavior of a cell is controlled by the biochemical reaction network
- Noisy reaction pathway: fluctuating protein levels
- How pathway noise affects the cell response?
- E.coli chemotaxis: one of the best characterized systems in biology



[http://2016.igem.org/Team:Technion_Israel/Chemotaxis]

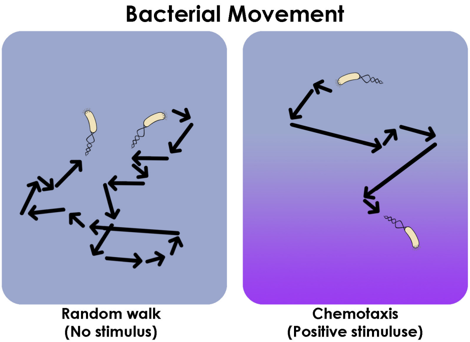
Run and tumble motion



[https://www.ebi.ac.uk/biomodels/content/model-of-the-month?year=2009&month=09]

- Typical size of E.coli cell $\sim 2\mu m$ and $10 - 12$ flagella
- Rotational bias of flagellar motors controls run and tumble motion
- Run: directional motion of the cell with speed $\sim 20\mu m/s$
- Tumble: random rotation without net displacement
- Typical run duration $\sim 1s$ and tumble duration $\sim 0.2s$

- Direct sensing of spatial gradient not possible due to small cell size
- Has to rely on temporal integration
- Switching rates between the modes depend on recent history
- Runs are elongated in the favorable direction and shortened in the opposite direction
- A net chemotactic drift in presence of a chemical gradient



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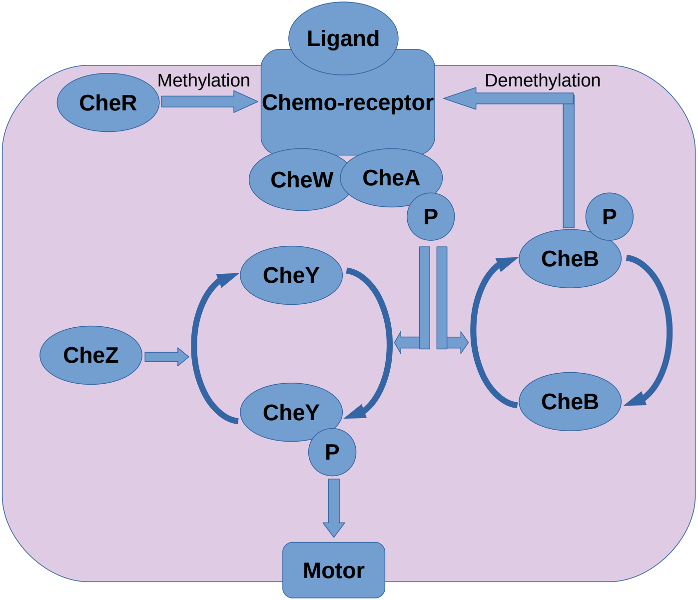
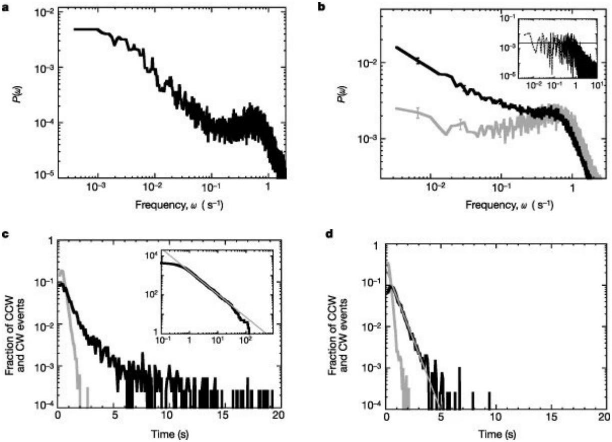
Chemotactic network: sensing and adaptation modules



Power law distribution of run durations

[Korobkova et al. *Nature* 2004]



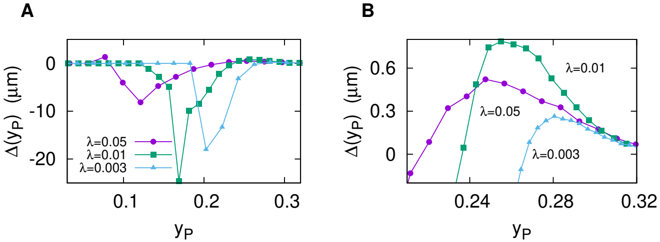
- Large fluctuations in CCW lifetime makes long runs possible
- Chemotactic response or robust adaptation at the population level do not get impaired due to pathway noise
- Emonet and Cluzel, *PNAS* 2008
- Park et al. *Nature* 2010
- Sneddon et al. *PNAS* 2012
- Large variability in a population beneficial for generic nutrient environment
- Each type of behavior may be suitable for a specific environment [Frankel et al. eLife 2014]

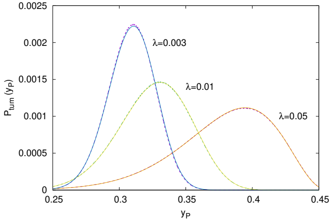
Slow noise from methylation

- What is the effect of noise on single-cell response?
- Most important noise source is methylation
- Methylation of receptors slowest reaction step $\sim 0.01s^{-1}$
- Low abundance of CheR $\sim$ 140 molecules per cell
- Slow noise is not averaged out in the downstream processes
- Noise induced enhancement of chemotactic drift [Flores et al. PRL 2012]
- Long runs control the drift and they are more probable at large noise
- Not the complete story! [Dev and Chatterjee PRE 2018]

Detrimental response at low CheY-P level

- Detailed analysis of CheY-P level statistics
- Average displacement in a run that starts with y_P: negative peak at small y_P followed by a positive peak at large y_P

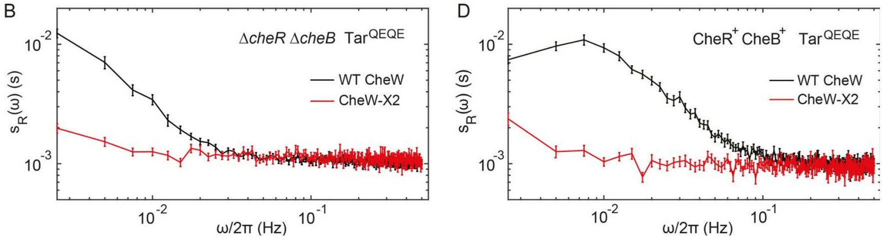




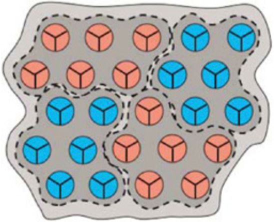
- Zero-crossing of $\Delta(y_P)$ shifts leftward as noise increases
- Noise dependent threshold

Noise in absence of methylation

- Receptor clustering is an independent and equally important noise source in the pathway [Colin et al. eLife 2018]



Cooperativity of chemoreceptors



[www.embopress.org/doi/full/10.1038/msb.2008.49]

- Receptors form clusters or 'signaling teams'
- Synchronous switching of activity
- Amplification of input signal from ligand binding $\Rightarrow$ sensitive response to weak concentration gradient
- For large n fewer signaling teams $\Rightarrow$ large fluctuations in total activity

Chemotactic performance

- How this newly found noise source affects single-cell chemotactic performance?
- How fast the cell is able to climb up the gradient?
- How strongly it localizes in the nutrient-rich region?
- Ability of the cell to distinguish between regions of high and low nutrient levels
- An optimum size of the receptor cluster for best chemotactic performance

Model of signaling pathway

- Chemoreceptors form trimers of dimers
- Free energy difference between active and inactive states

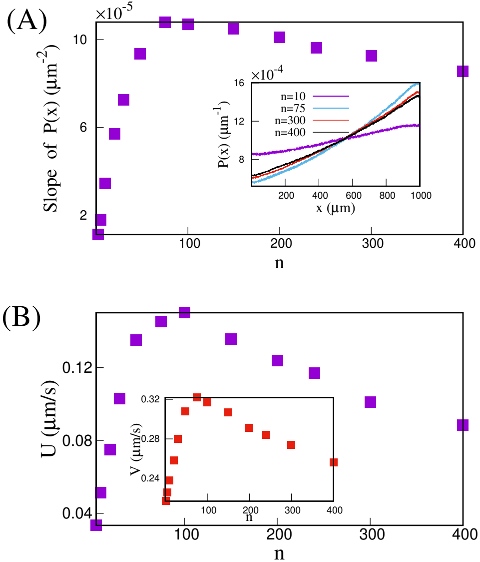
$$F = 3n \left(1 + \log \frac{1 + c(x)/K_{min}}{1 + c(x)/K_{max}} \right) - \sum_{i=1}^{3n} m_i$$

- Monod-Wyman-Changeux model [Monod et al. *J. Mol. Biol.* 1965]
- All receptors within a cluster switch their activity state simultaneously
- Switching rate depends on F

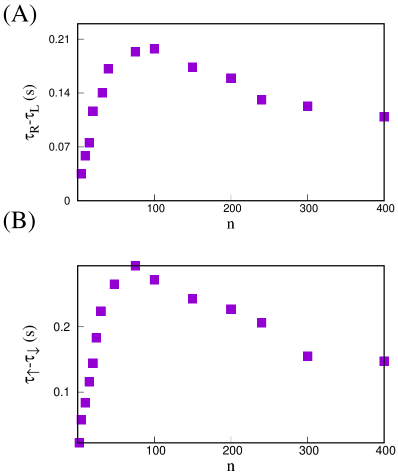
Assistance neighborhood and brachiation

- Number of enzyme molecules far too low compared to the number of receptor dimers
- It takes a long time for a dimer to bind to an unbound enzyme molecule in the cell cytoplasm
- How to reconcile low abundance with perfect adaptation?
- Assistance neighborhood: a bound enzyme can modify methylation level of the neighboring dimers
- Brachiation: a bound enzyme can perform random walk on the receptor array before it unbinds
- We include a flavor of these mechanisms in our model
- Pontius et al. PLoS Comp Biol 2013

Peak in localization and drift velocity



- Differential behavior of the cell when the nutrient level in its environment goes up or down
- Time till the first tumble during an uphill run and downhill run
- Even works for a tethered cell

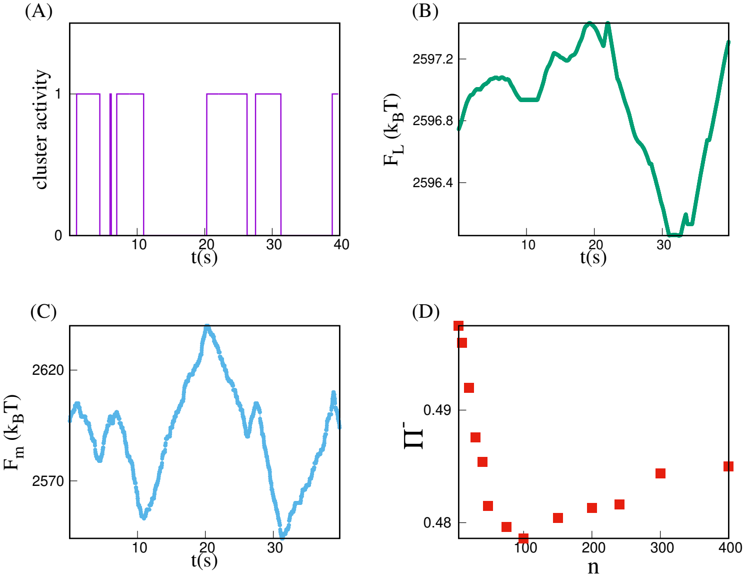


- Ramp up (down) the nutrient level in CCW mode and measure time till transition to CW mode
- Nutrient level changed at the same rate as that experienced by a swimming cell during a run

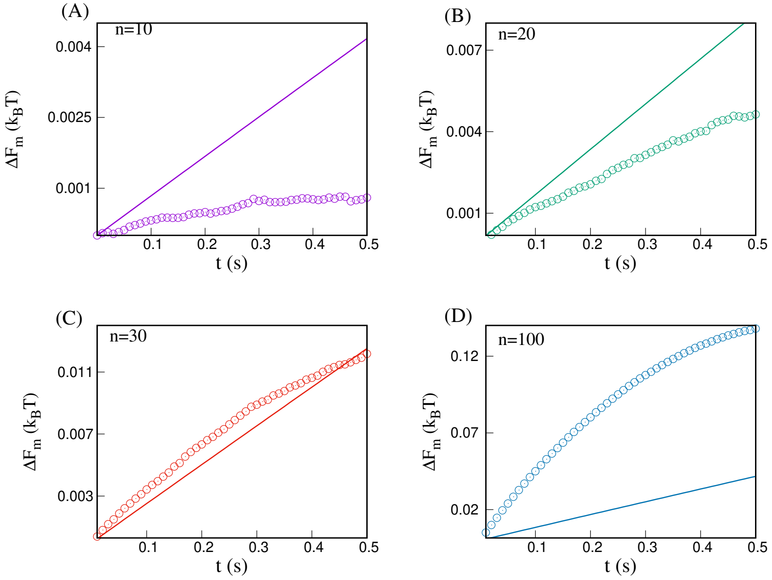
Competition between sensing and adaptation

- Activity controls the tumbling rate
- Probability to find a receptor cluster in the active state is $[1 + \exp(F_L - F_m)]^{-1}$
- As the cell swims uphill or downhill, the change in F_L is proportional to n
- As n increases, the activity of a receptor cluster decreases (increases) quickly during an uphill (downhill) run, thereby elongating (shortening) the run $\Rightarrow$ better performance
- But for large n activity fluctuations increase and adaptation kicks in
- Variation in cluster free energy is now controlled by F_m
- A shorter uphill run and longer downhill run become increasingly likely: less sensitive to F_L
- Performance goes down

Typical time series for $n = 200$



Average change in F_m during first few steps of an uphill run



Conclusions

- Competition between sensing and adaptation gives rise to a performance peak
- Hexagonal geometry of receptor array and membrane curvature energy not considered in our model
- Interplay between ligand free energy and methylation free energy can be investigated as the receptor cooperativity is varied
- A stronger cooperativity among the receptors has been experimentally shown to induce larger activity fluctuations in a tethered cell [Colin et al. eLife 2017, Keegstra et al. eLife 2017]
- Whether the variation of methylation free energy increases for stronger receptor cooperativity and its effect on the chemotactic efficiency, $(\tau_{\uparrow} - \tau_{\downarrow})$ can be investigated in experiments
- In a wide variety of biological systems sensing-adaptation competition can be relevant