Noise in Chemotaxis

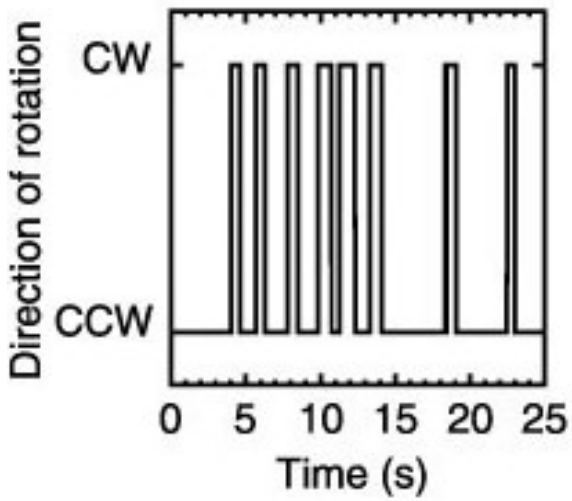
Bangalore School on Statistical Physics XIV

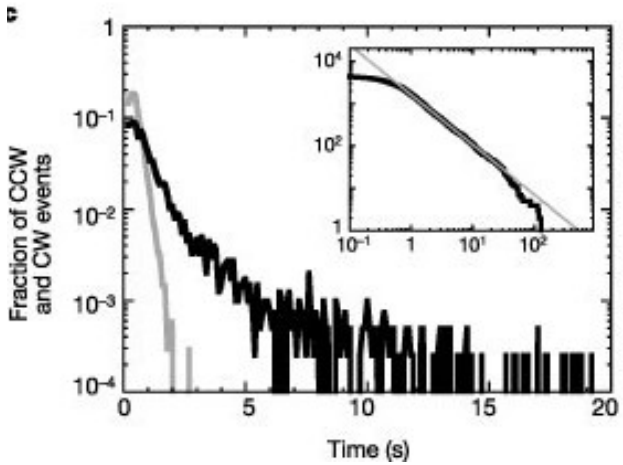
September, 2023

Noise in a single cell

- At the level of populations, chemotaxis network produces a steady output in the absence of external stimuli: adapted steady-states
- Because the network's output from individual cells is noisy, response is averaged across the population of cells
- Averaging eliminates part of the information required to understand how an individual cell performs basic computations
- How the behaviour of an individual bacterium of *E. coli* in a homogeneous environment fluctuates with time?
- Are there specific molecular events that could cause temporal behavioural variability in an individual cell?

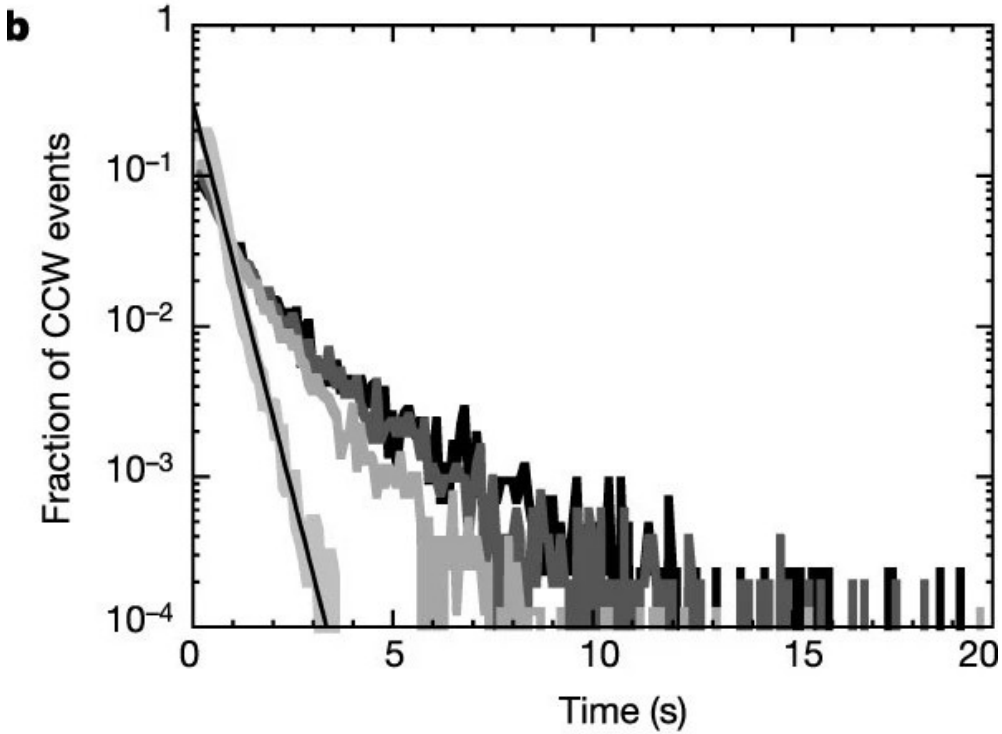
- Switching events of individual flagellar motors from non-stimulated cells in a medium in which attractant was not present
- Binary time series constructed from the clockwise (CW) and the counterclockwise (CCW) rotations of a single motor defined the chemotaxis network output
- If switching events are independent and governed by a Poisson process, then CW and CCW time intervals are uncorrelated and exponentially distributed
- Power law distribution of CCW intervals was observed with exponent ~ 2.2 [Korobkova *et al. Nature* 2004]



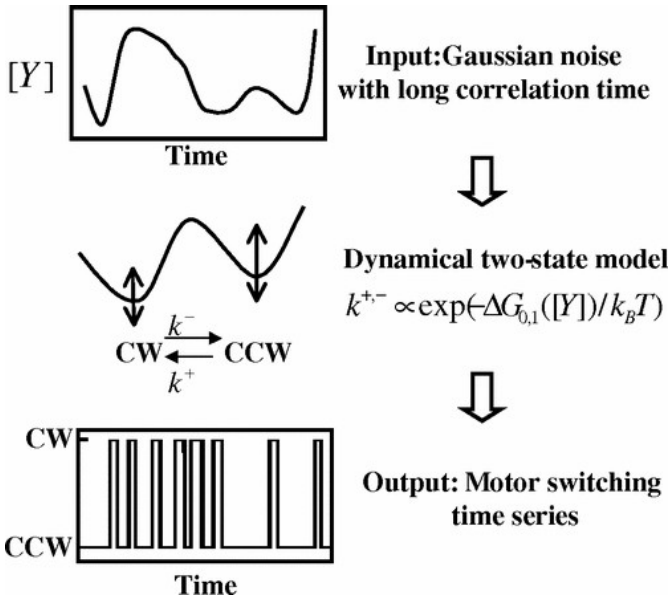


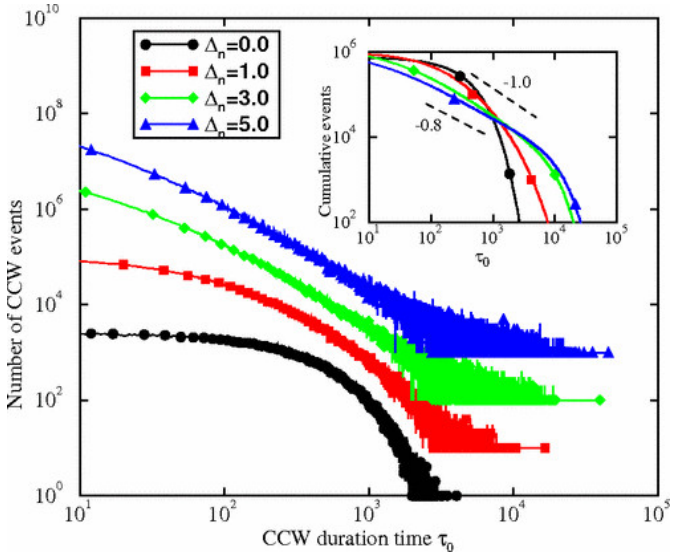
Correlated noise from methylation

- For increasing [CheR] power law changes to exponential



Two state model with fluctuating energy level





- Bacterial motor system as a two-state model with each state (CW or CCW) sitting in a potential well, transitions between the states governed by thermal fluctuations over an energy barrier

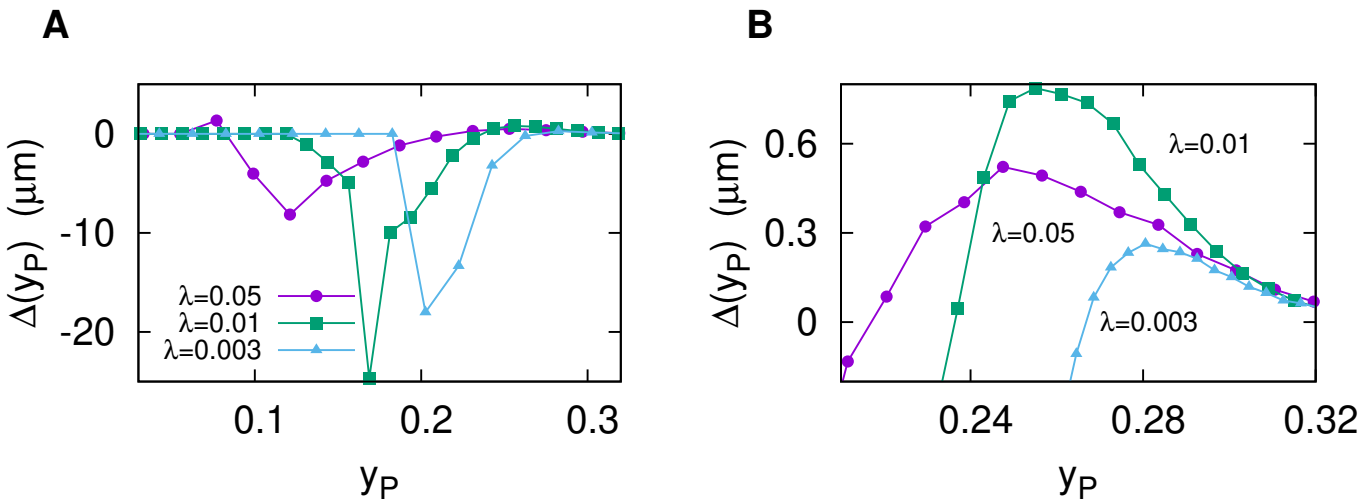
$$\frac{d[Y]}{dt} = -\frac{[Y] - [Y]_0}{\tau} + \eta(t)$$

- Large noise strength gives power law distribution with exponent ~ 2 [Tu and Grinstein *PRL* 2005]

Effect of noise on chemotactic performance

- Quantify performance: chemotactic drift velocity and localization
- Average velocity with which the cell climbs up the chemical concentration gradient
- Nutrient concentration, averaged over the steady state distribution of the cell position $\int dx P(x)c(x)$
- Localizaton takes a high value, when in the long time limit most of the cells are present in the regions which contains maximum nutrient
- High values of localization and drift velocity ensures a good chemotactic performance in the long time limit
- How methylation noise affects performance?

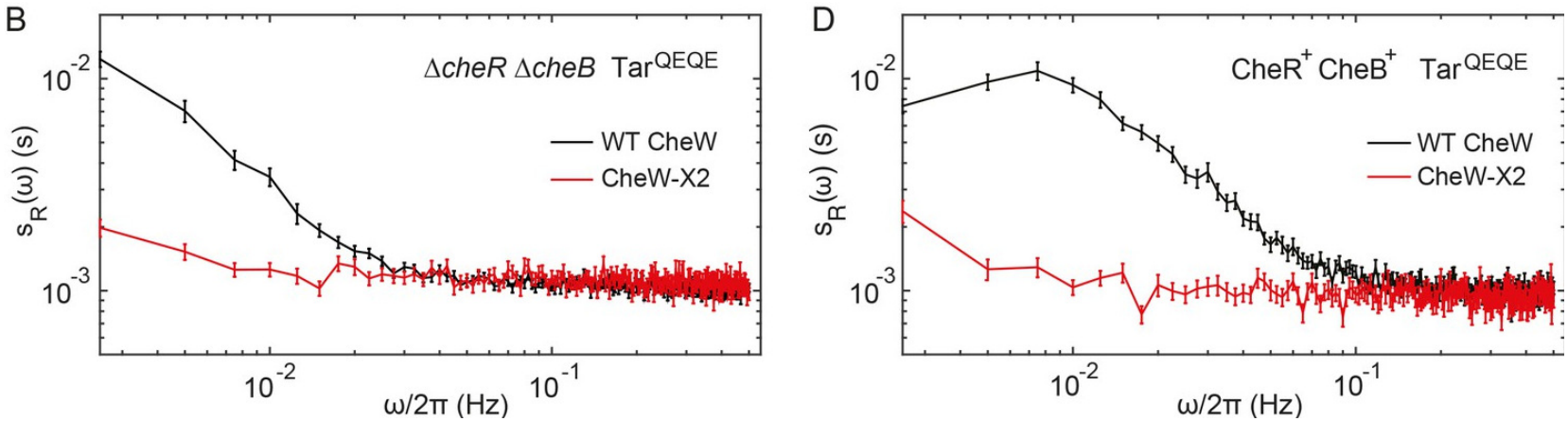
- In a shallow nutrient gradient drift velocity shows a peak with methylation noise strength, while localization remains constant for low noise and decreases for high noise [Flores *et al. PRL* 2012]
- Low activity states correspond to long runs and makes significant contribution to drift velocity
- With increasing noise smaller activity values are accessible: results in increase in V
- Not the complete story! [Dev and Chatterjee *PRE* 2018]
- Detailed analysis of CheY-P level fluctuations in presence of signaling noise is needed



- Linear ligand profile with a positive slope
- 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
- A negative $\Delta(y_P)$ means that the net displacement of the cell is down the attractant concentration gradient, which is opposite to what one expects for chemotaxis.
- This behavior is detrimental to chemotaxis, and the threshold level of CheY-P below which this happens decreases as noise increases.
- Noise induces enhancement of chemotactic performance

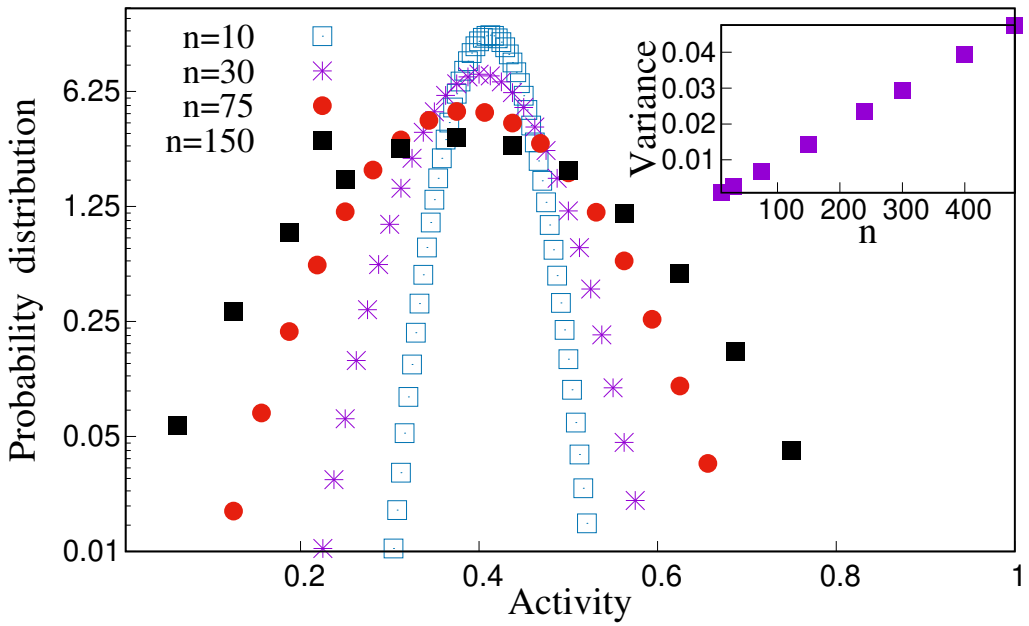
Noise in absence of methylation

- Receptor clustering is an independent and equally important noise source in the pathway
- Colin et al. eLife 2017, Keegstra et al. eLife 2017
- For large n fewer clusters $\Rightarrow$ large fluctuations in total activity



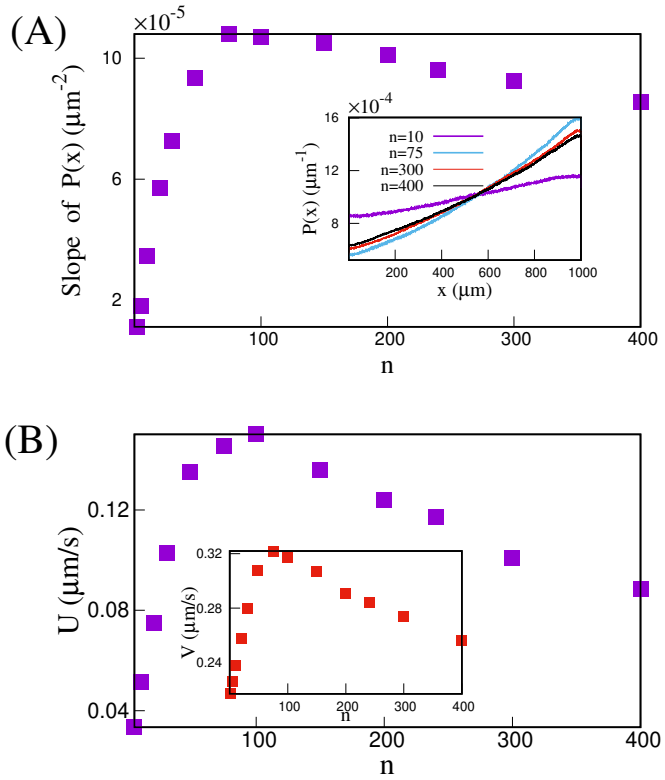
- How this newly found noise source affects chemotactic efficiency?

Activity fluctuations increase with receptor clustering



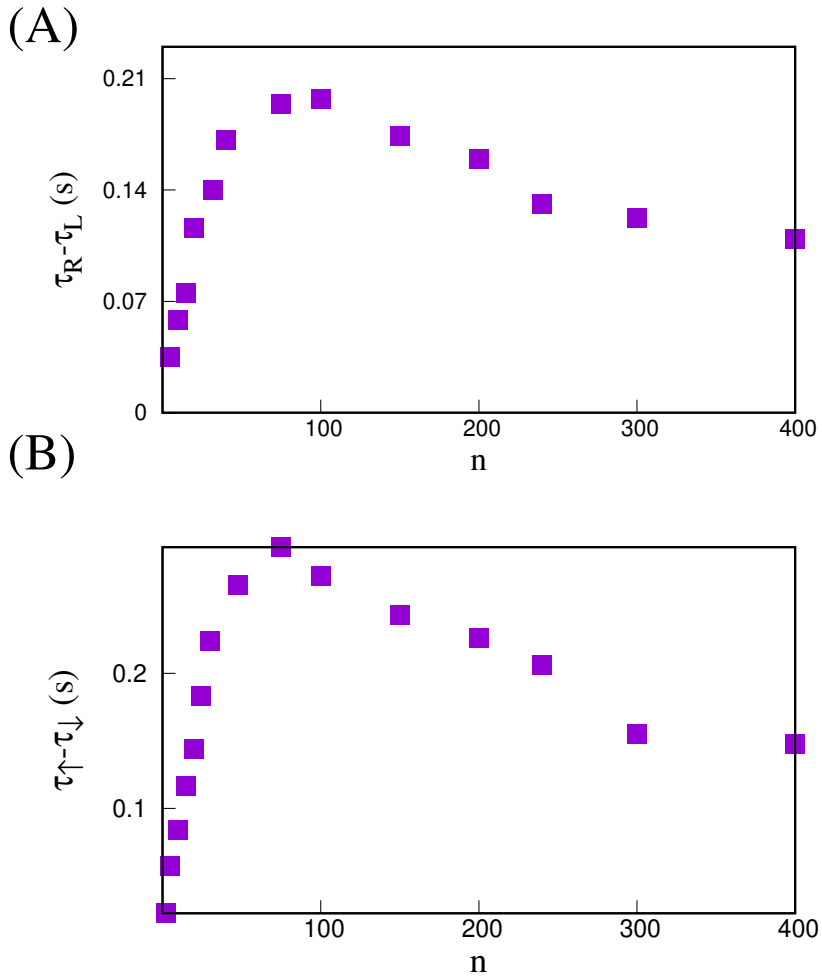
- Activity distribution gets wider for large receptor clusters
- Variance scales linearly with cluster size

Peak in localization and drift velocity



- Attractant concentration profile $c(x) = c_0(1 + x/x_0)$
- Chemotactic drift velocity measured from net displacement in a run, or in a fixed time interval T

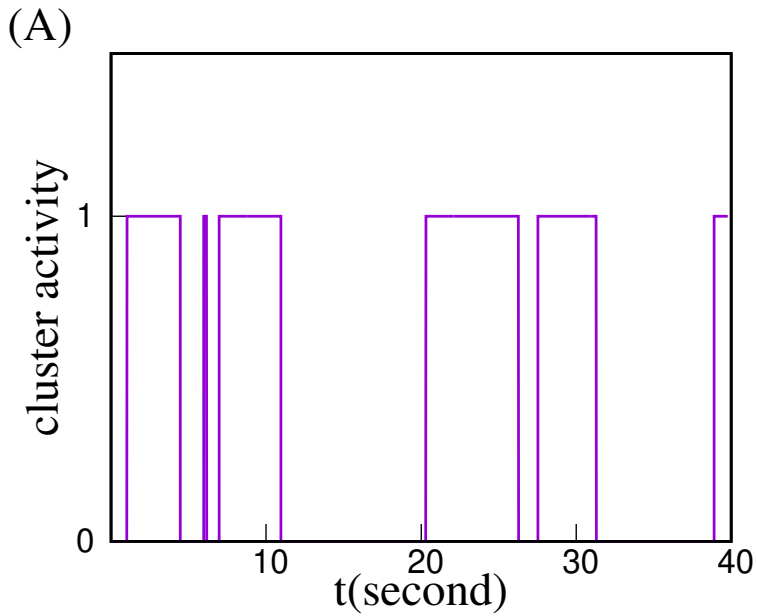
- Differential behavior of the cell when the nutrient level in its environment goes up or down
- Time till the first tumble during an uphill run and downhill run
- Even works for a tethered cell

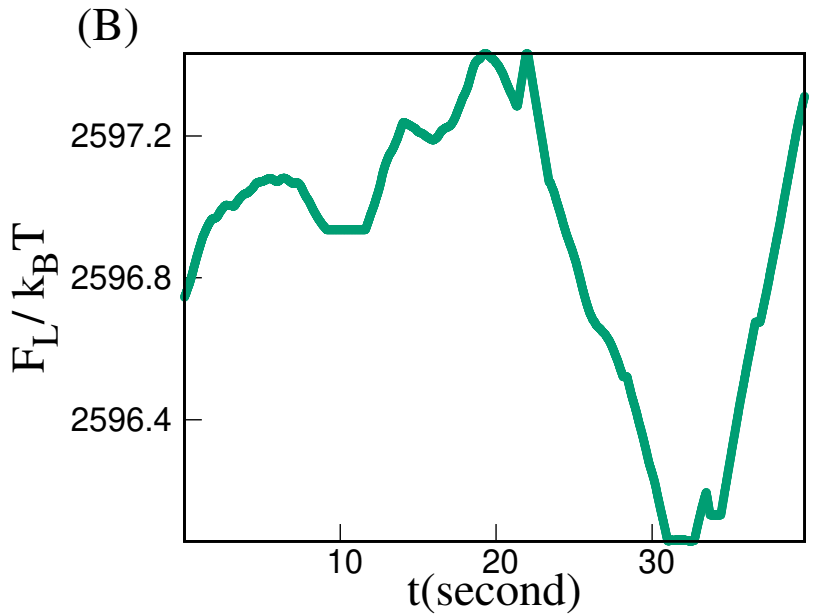


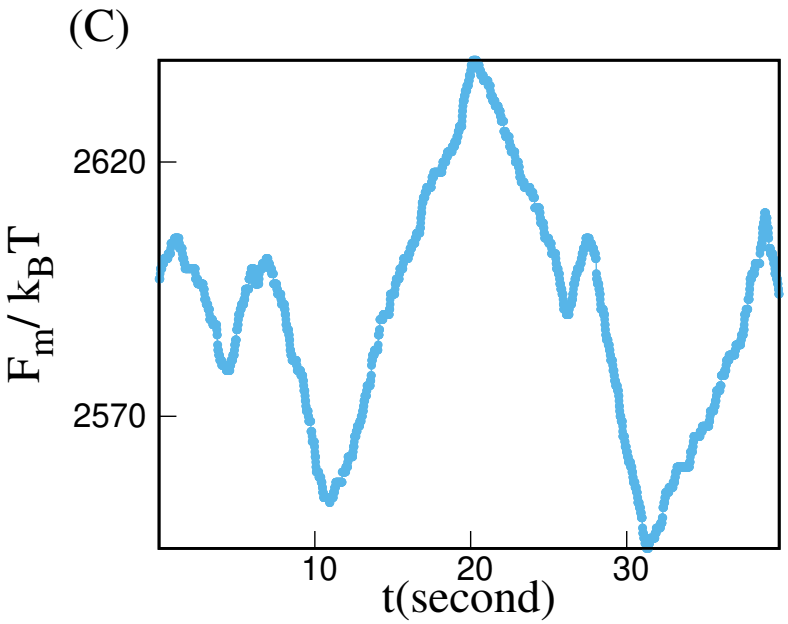
- Ramp up (down) the nutrient level in CCW mode and measure time till transition to CW mode
- Nutrient level changed at the same rate as that experienced by a swimming cell during a run

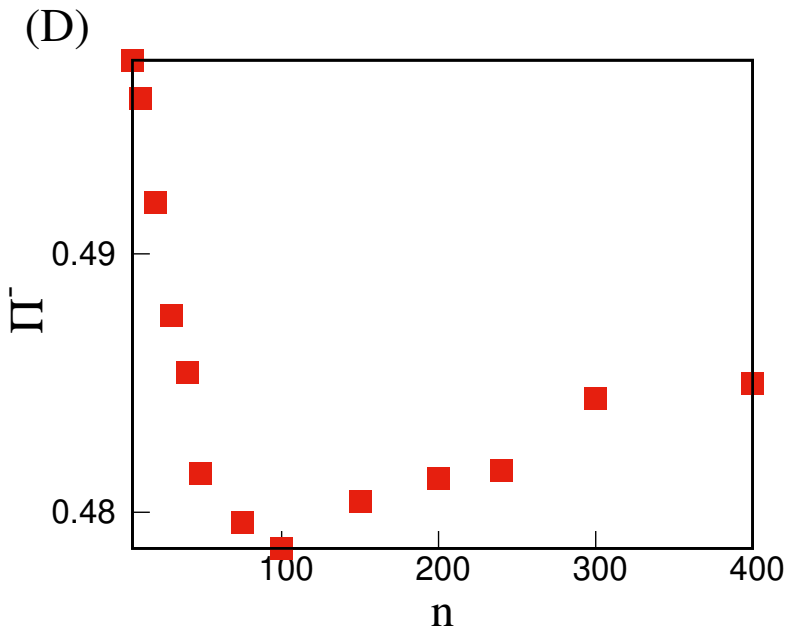
Sensing vs adaptation

- $F = F_L - F_m$
- As the cell swims uphill or downhill, the change in F_L is proportional to n
- As n increases, activity changes more quickly during a run
- Uphill runs get elongated and downhill runs get shortened : better performance
- But large n also increases activity fluctuations and adaptation module gets triggered
- F is now controlled by F_m and activity is less sensitive to ligand variation: performance worsens
- A shorter uphill run and a longer downhill run now become increasingly likely
- Probability to find a negative net displacement of the cell during a time interval T shows a minimum with n

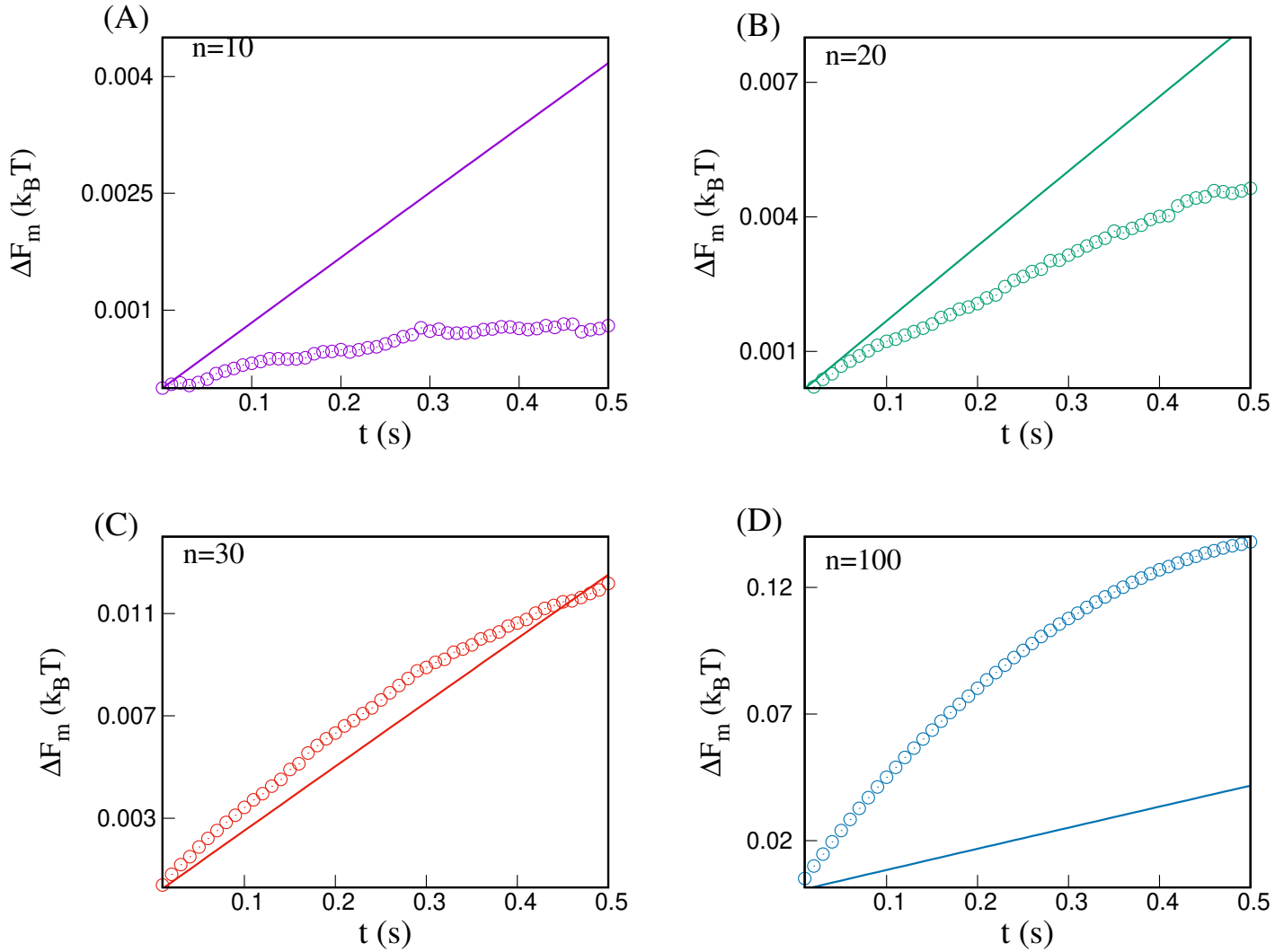

(A)
cluster activity
1
0
10
20
30
40
t(second)


(B)
2597.2
2596.8
2596.4
$F_L / k_B T$
10
20
30
t(second)


(C)
2620
2570
$F_m / k_B T$
10
20
30
t(second)


(D)
0.49
0.48
Π
100
200
300
400
n

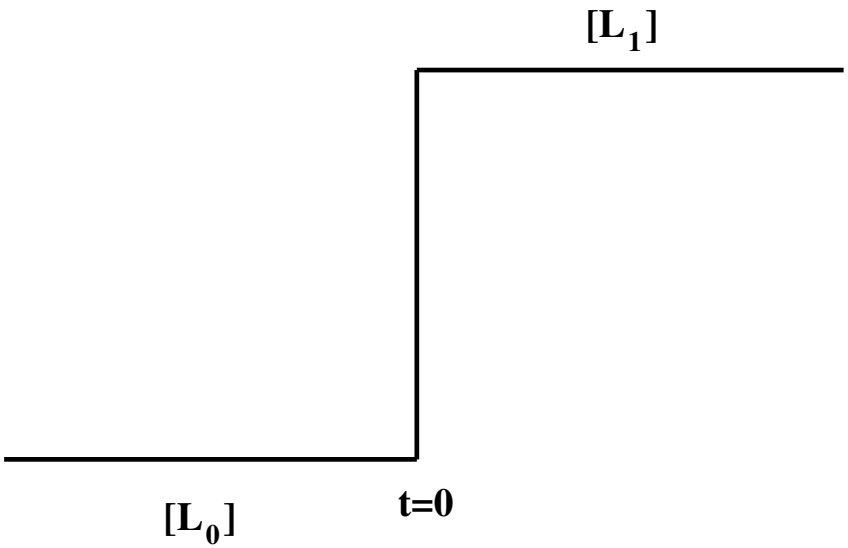
Interplay between F_L and F_m



- Free energy variation during first few steps of an uphill run

- Enhanced sensitivity comes at the cost of increased biochemical noise
- Optimum strength of cooperative interaction between the receptors
- Origin of optimality distinctly different from noisy input signal [Aquino et al. 2011]
- We find optimality even in absence of any noise in the ligand environment
- Mandal and Chatterjee, *PRE Lett* 2021

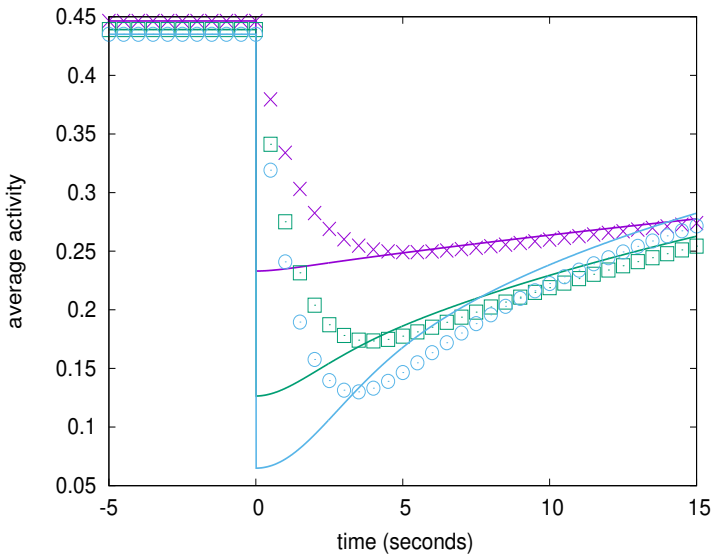
Response to step stimulus at short times

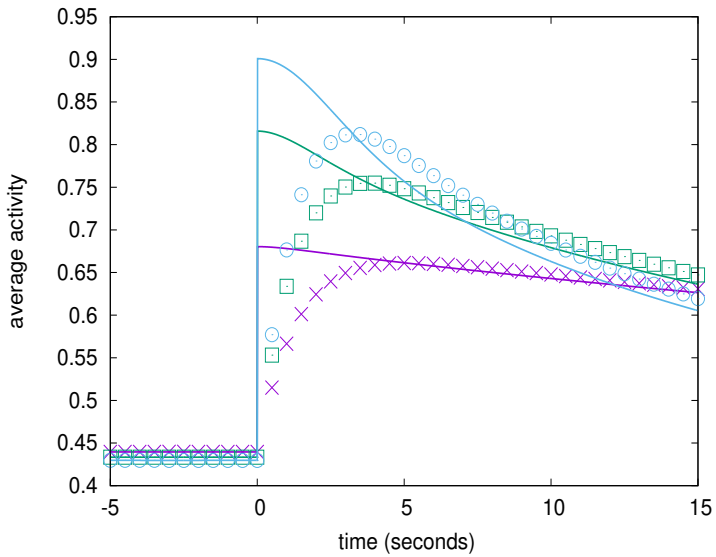


- Pre-stimulus state ($t < 0$) perfectly adapted
- Post-stimulus re-adaptation for $t \to \infty$

- Receptor activity and CW bias have time-independent average values for $t < 0$ and $t \to \infty$
- But at short times they show rapid variation and reach extremal values
- How long does the cell need to reach its extremal response and how to characterize the properties of the signaling network at this time?
- Our exact calculations agree well with numerics

Extremal value for receptor activity





- Step addition: $200 \rightarrow 250\mu M$; step removal: $300 \rightarrow 200\mu M$
- average activity $\langle a(t) \rangle$ and $\langle [1 + e^{F(t)}]^{-1} \rangle$ for $n = 5, 10, 15$
- At the extremal point $t = t_a$, these two quantities coincide
- Such equality is only expected in adapted state!!

Exact calculation for extremal activity

- $P(N_1, t)$ probability to find N_1 active receptor clusters at time t

$$\begin{aligned}\frac{\partial P(N_1,t)}{\partial t} &= \Gamma_{0\to1}(t)\left[P(N_1-1,t)(N-N_1+1)-P(N_1,t)(N-N_1)\right] \\ &+ \Gamma_{1\to0}(t)\left[P(N_1+1,t)(N_1+1)-P(N_1,t)N_1\right]\end{aligned}$$

- Total transition rate from inactive to active state $\Gamma_{0\to1}(t) = \sum_m \frac{w_a}{1+e^F} p(m,t|0)$
- Multiplying by N_1 and summing over all N_1

$$\frac{d\langle N_1(t)\rangle}{dt} = \Gamma_{0\to1}(t)(N-\langle N_1(t)\rangle) - \Gamma_{1\to0}(t)\langle N_1(t)\rangle$$

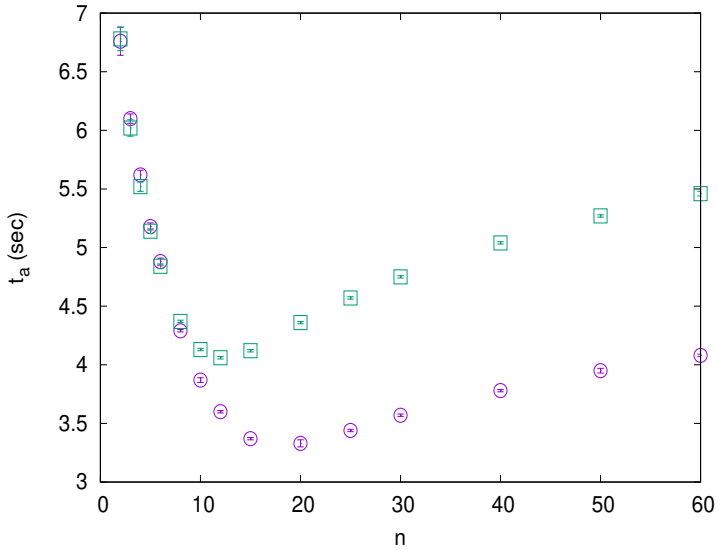
- Average activity $\langle a(t) \rangle$ is nothing but $\langle N_1(t) \rangle / N$
- At $t = t_a$ time-derivative must vanish

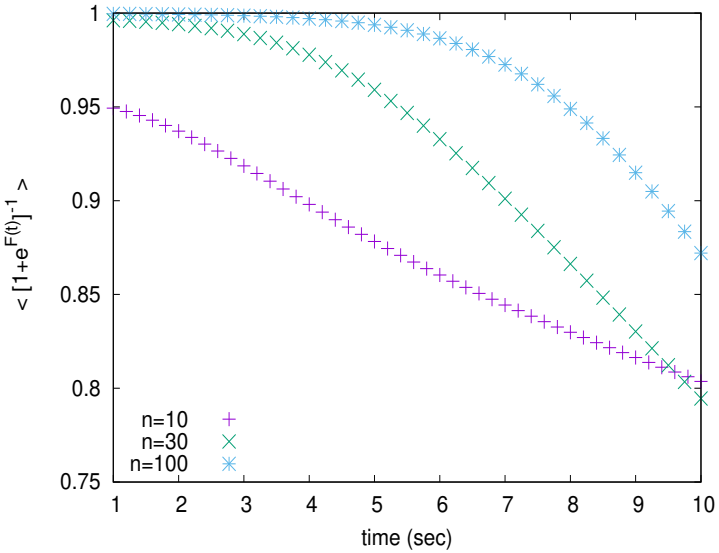
$$\sum_m p(m, 1, t = t_a) = \sum_m \frac{\mathcal{P}(m, t = t_a)}{1 + e^F}$$

$$\langle a(t) \rangle \Big|_{t=t_a} = \langle [1 + e^{F(t)}]^{-1} \rangle \Big|_{t=t_a}$$

- An 'equilibrium-like' relationship between time-varying activity and free energy holds momentarily when the system is farthest away from any adapted state!

Quickest extremal response





- After the application of a step stimulus the system reaches its extremal response in the shortest possible time for a specific size of the receptor cluster
- Define $z(t) = \langle [1 + e^{F(t)}]^{-1} \rangle - \langle a(t) \rangle$
- $z(t_a) = 0$

t_a increases with n for large n

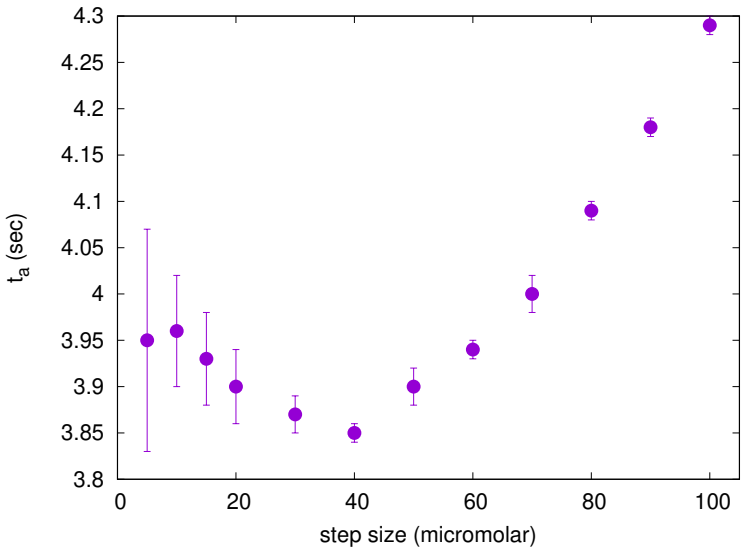
- Step removal: for large n drop in F is so large that $\langle [1 + e^F]^{-1} \rangle$ reaches very close to unity
- Active to inactive state transitions remain effectively blocked
- $z(t) \approx 1 - \langle a(t) \rangle$
- $\langle a(t) \rangle$ can only increase during this time
- As n increases, it takes longer for the system to lower its methylation level enough such that reverse transition is possible again
- t_a increases with n

t_a decreases with n for small n

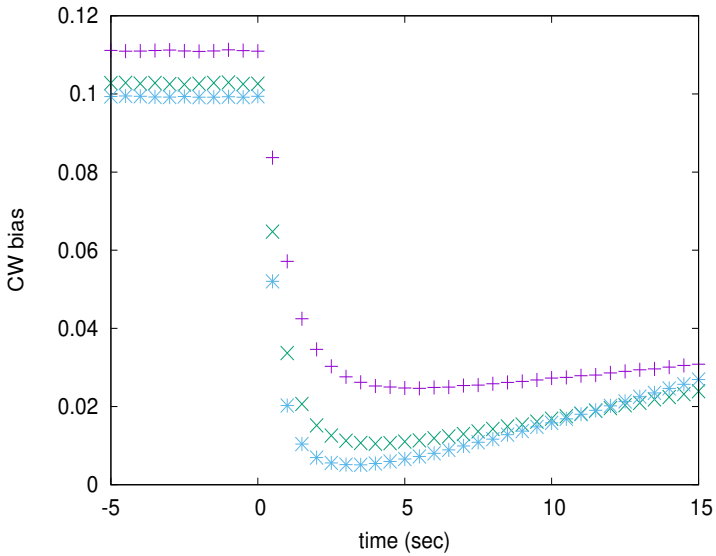
- For small n change in F is scaled down
- $\langle [1 + e^F]^{-1} \rangle$ remains significantly below unity
- Both forward and reverse transitions have non-zero rates but their difference grows with n
- Activity increases faster and $z(t)$ reaches zero quicker
- t_a decreases with n
- There exists a minimum for intermediate n

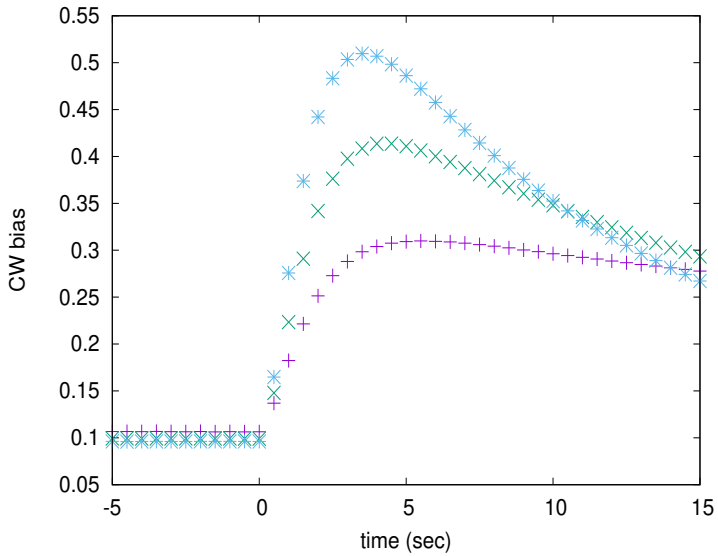
Optimum step size for quickest extremal response

- For a fixed n if step size of stimulus is increased, change in F is also larger
- Therefore, our argument predicts an optimum step size
- Verified in simulations
- Can be tested in experiment



Extremal value of CW bias





- Probability to find the motors in the CW rotation mode
- Extremum value at t_{cw}

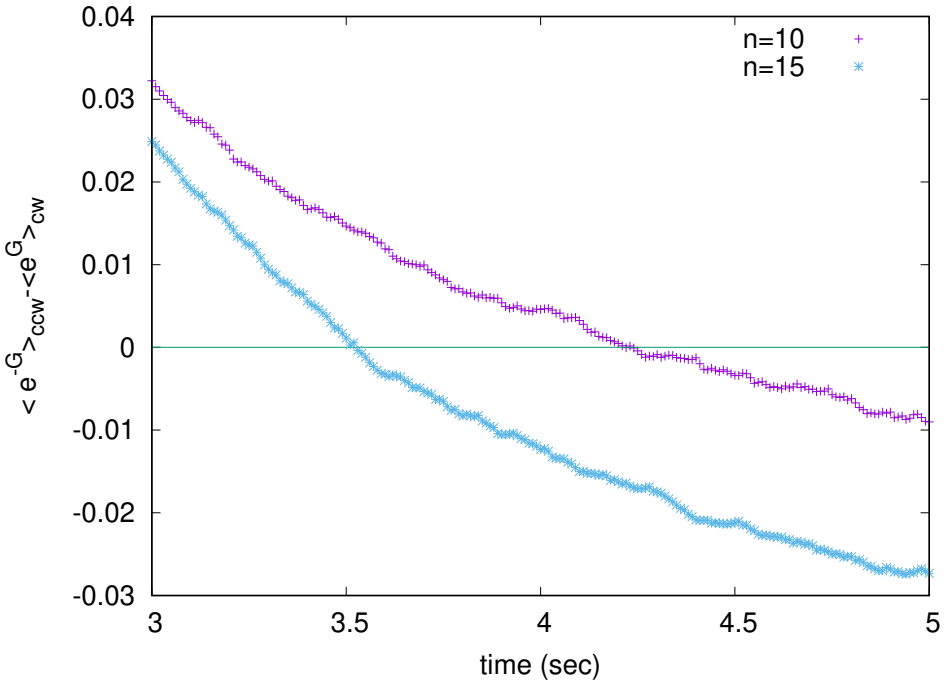
Exact calculation for extremal CW bias

- $Q(cw, N_1, t)$ joint probability to find the motors in CW rotation mode and N_1 active receptor clusters at time t

$$\begin{aligned}
\partial_t Q(cw, N_1, t) &= \omega e^{-G(N_1)} Q(ccw, N_1, t) - \omega e^{G(N_1)} Q(cw, N_1, t) \\
&+ \Gamma_{1\to 0}(t)[(N_1+1)Q(cw, N_1+1, t) \\
&- N_1 Q(cw, N_1, t)] \\
&+ \Gamma_{0\to 1}(t)[(N - N_1 + 1)Q(cw, N_1 - 1, t) \\
&- (N - N_1)Q(cw, N_1, t)]
\end{aligned}$$

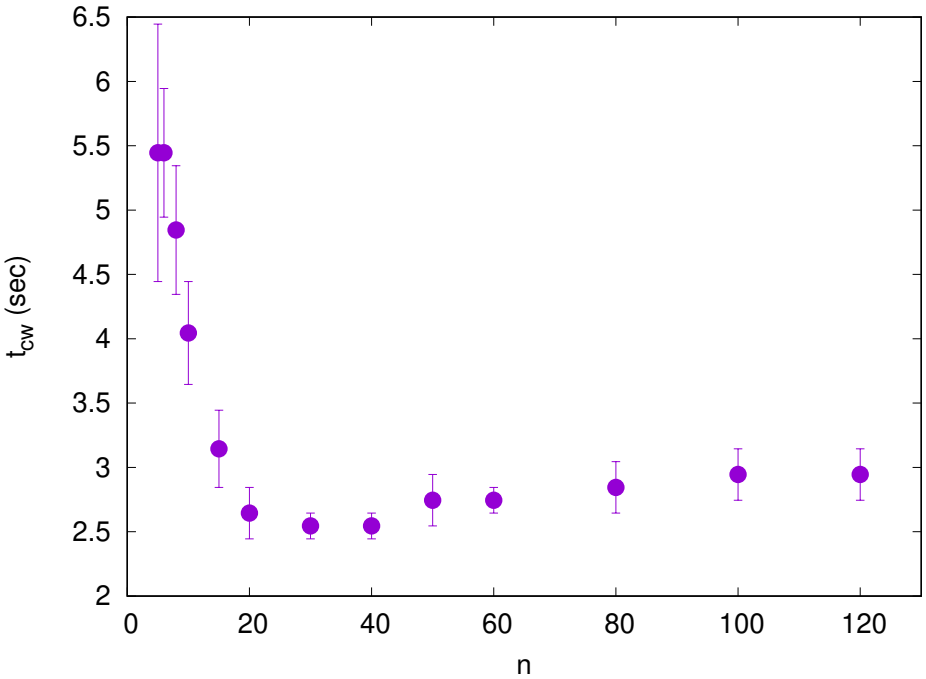
- $\omega e^{\pm G}$ are the activity dependent switching rates between the CCW and CW modes
- Summing both sides over N_1

$$\partial_t \mathcal{Q}(cw, t) = \omega \left(\langle e^{-G} \rangle_{ccw} - \langle e^{G} \rangle_{cw} \right)$$



- Step removal: $220 \rightarrow 200 \mu M$
- $t_{cw} = 4.3 \pm 0.2$ sec for $n = 10$ and 3.6 ± 0.2 sec for $n = 15$
- Zero-crossing matches reasonably well
- $\langle e^{-G} \rangle_{ccw} = \langle e^{G} \rangle_{cw}$ expected only in adapted state

t_{cw} shows a minimum with n



- $200 \rightarrow 220 \mu M$
- Shallower minimum owing to larger error-bars

- Most experimental and theoretical studies consider long time behavior of post-stimulus recovery
- We show short time response also provides useful insights about adaptation kinetics
- Using tethered assays and FRET based setup our prediction of optimum step size can be verified
- Cooperative interaction between the receptors can be tuned in experiments [Colin et al. 2018, Keegstra et al. 2018]
- By measuring extremal activity typical methylation level can be estimated even far from adaptation
- Our calculations do not depend on enzyme kinetics that modulate (de)methylation reactions
- Results should remain valid for other models
- Chatterjee *J Stat Mech* 2022