Interpreting Single Particle Tracking Data with a Correlated Random Walk and a first-passage time algorithm

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Outline

Introduction

Correlated Random Walk Model

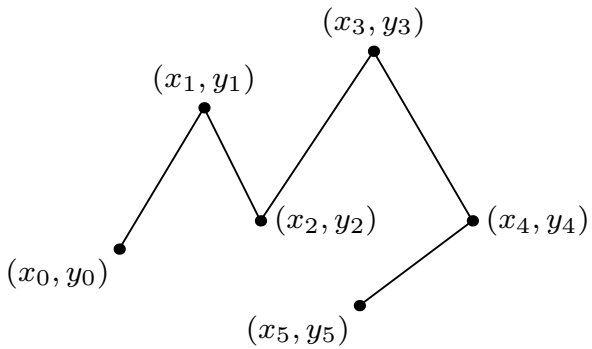
Variance First-Passage Time

Conclusions

Single Particle Tracking

- Single Particle Tracking is an experimental technique used to address the following general question:
  How do individual biomolecules move within the cell?
- Individual particles are labeled with an optical bead or a fluorescent tag, and observed with video microscopy.

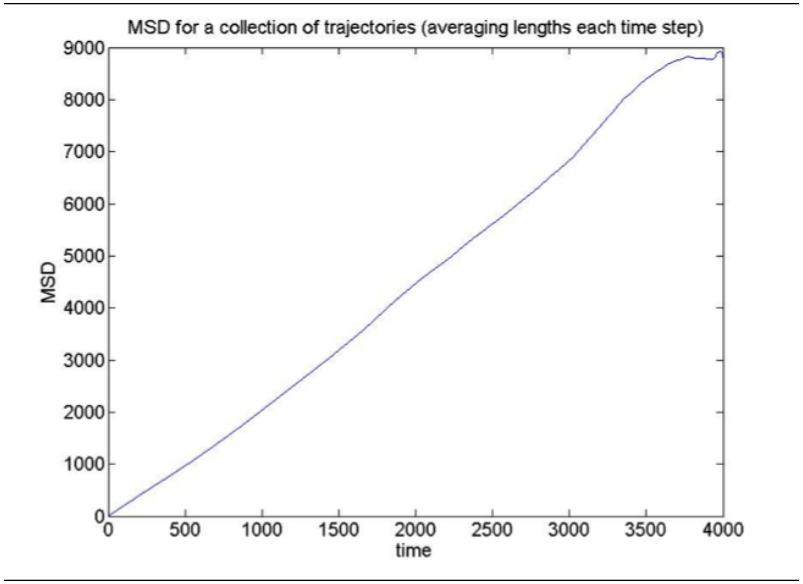
Data from SPT experiments is obtained as $N+1$ position coordinates:



$$\begin{aligned} p_0 &= (x_0, y_0), \\ p_1 &= (x_1, y_1), \\ &\vdots \quad\quad \vdots \\ p_N &= (x_N, y_N). \end{aligned}$$

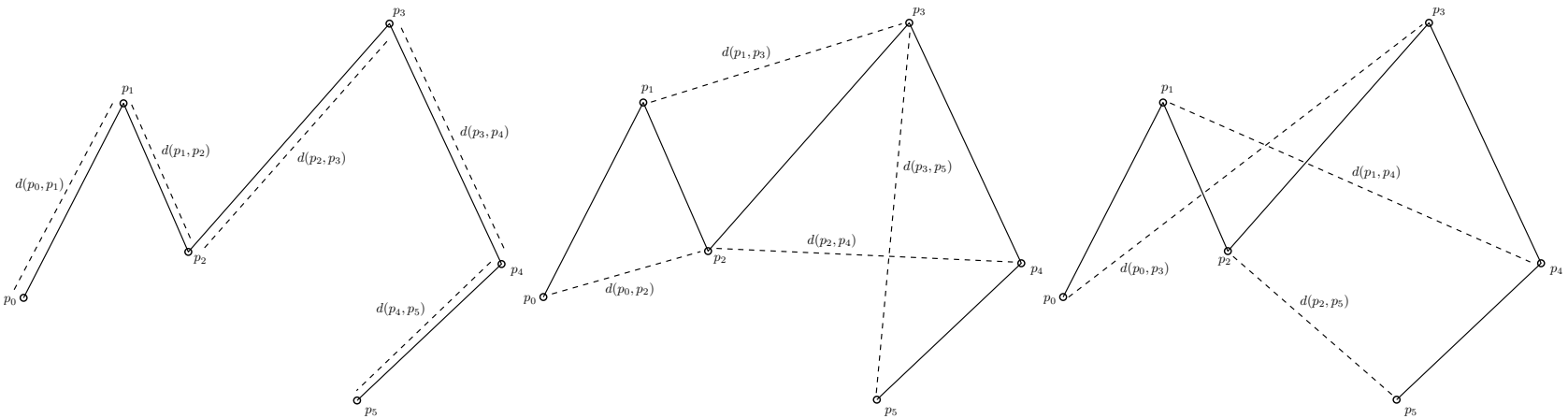
Mean Square Displacement and the Diffusion Coefficient

- A common measure used to characterize the movement of particles is the diffusion coefficient, D.
- D is estimated from Mean Square Displacement (MSD), a quantity that describes the average of the squared displacements of a particle's trajectory.



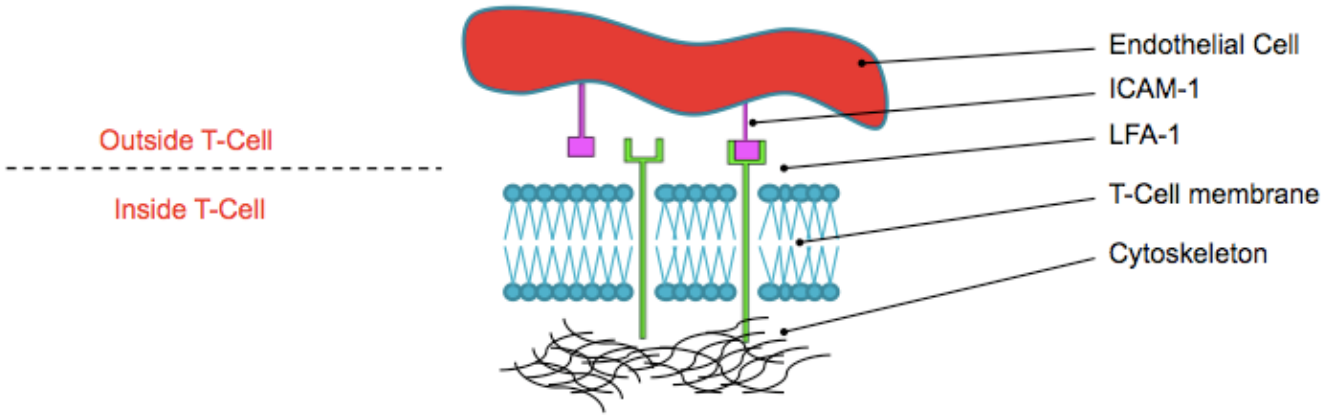
- MSD at time t, is defined by $\rho(t) = \langle (r(t) - r(0))^2 \rangle$.
- In two dimensions, $\rho(t) \approx 4Dt$.

Mean Square Displacement and the Diffusion Coefficient



LFA-1 (Leukocyte function-associated antigen 1)

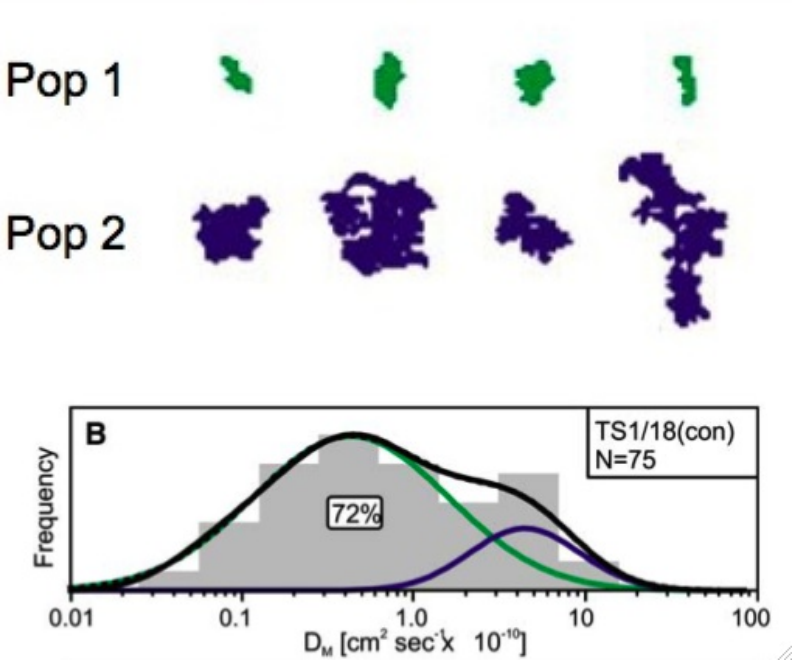
- Integrin - T-cell adhesion receptor - allows T-cells to adhere to endothelial cells by binding to ICAM-1 (intercellular adhesion molecule) on antigen-presenting cells (endothelial cells).
- LFA-1 facilitates transmigration of leukocytes across vascular endothelia in processes such as extravasation and the inflammatory response.

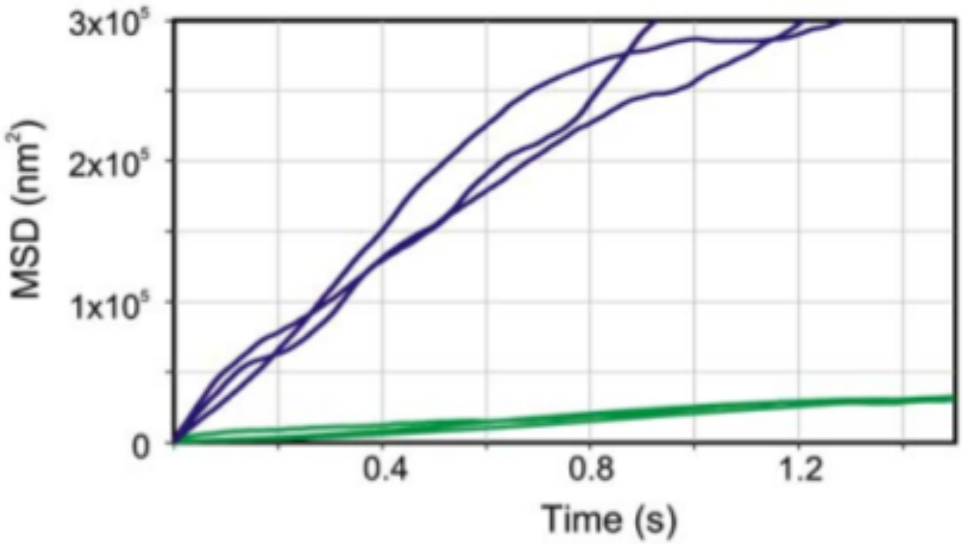


Receptor affinity $\iff$ lateral diffusion

How does the protein move along the membrane?

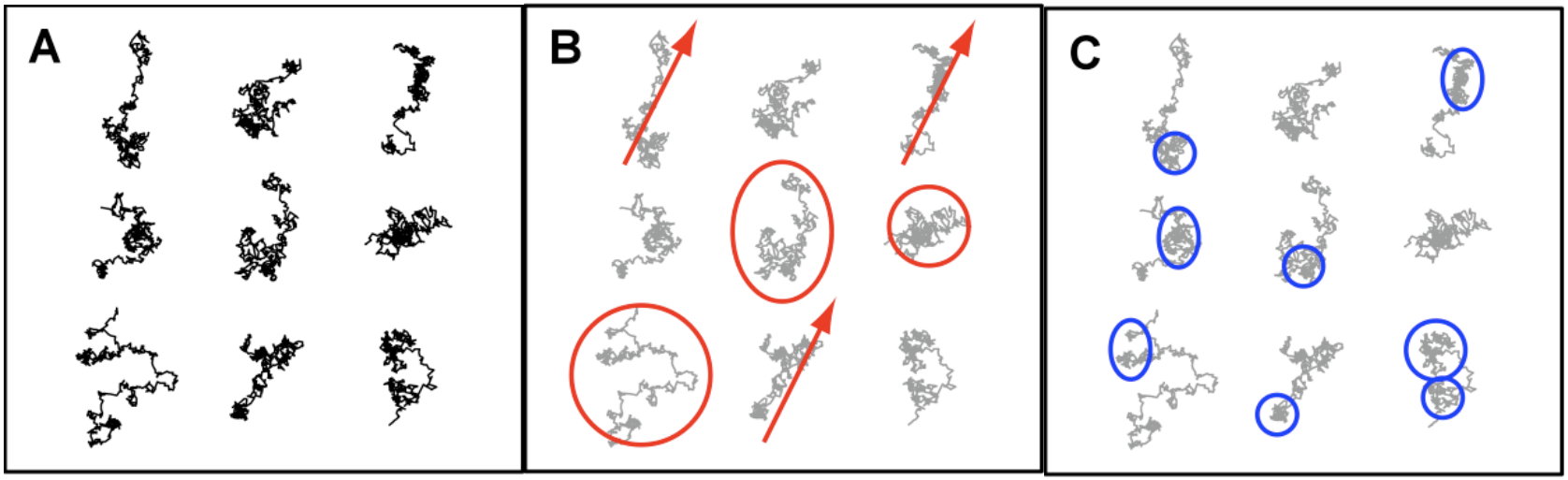
Macroheterogeneity Observed in LFA-1





Cairo et al., 2006

Macroheterogeneity – Microheterogeneity



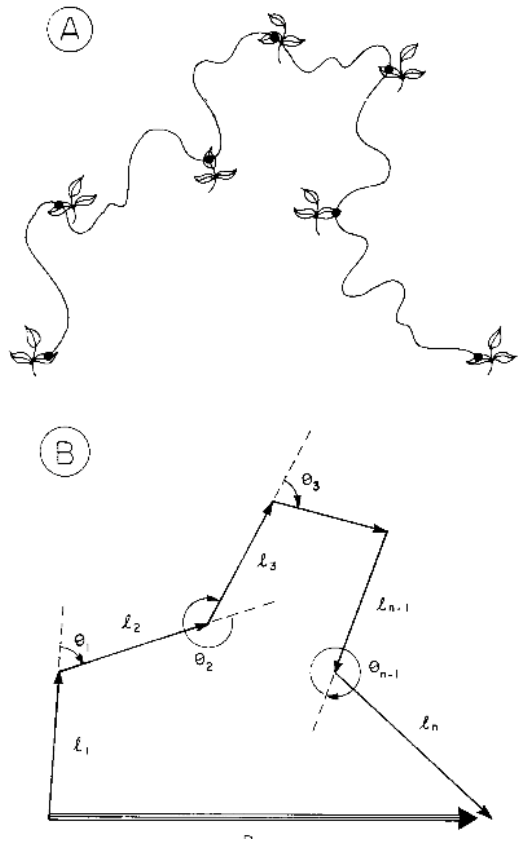
Some Questions

- What is the mechanism of movement of LFA-1 proteins?
- Is there a common mechanism that governs the whole population or multiple movement mechanisms?
- Is there movement heterogeneity within the population (macroheterogeneity) and/or within individual trajectories (microheterogeneity)?

Our Approach

Movement tracks are also analyzed in ecology, to understand the movement of animals.

- Can ecological models be used to provide information about SPT data?
- Move lengths and turning angles are often used in Ecology. What can length and turning angle distributions tell us about SPT movement tracks?
- How can we use ecological tools to tell us more about both macro and micro heterogeneity?



Kareiva et al., 1983.

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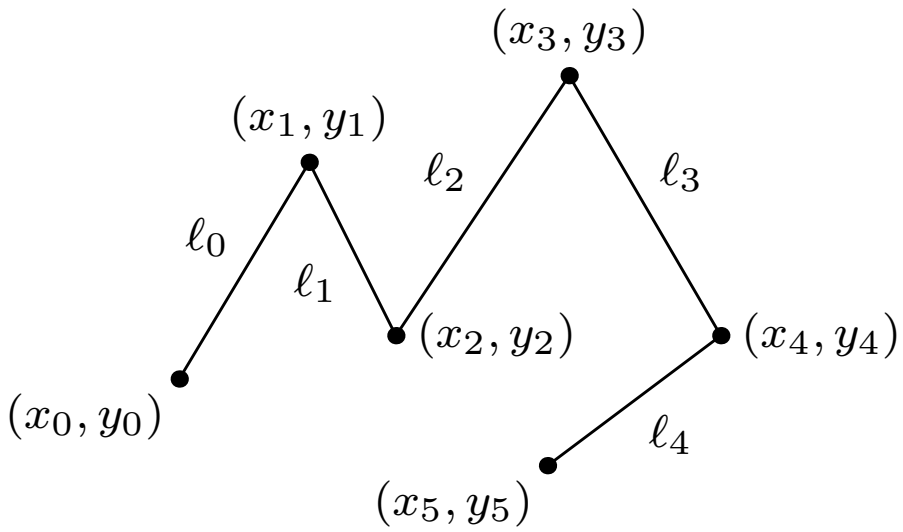
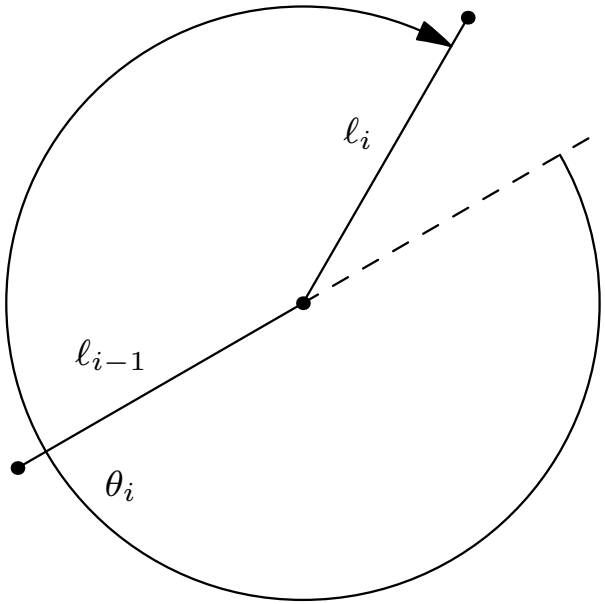
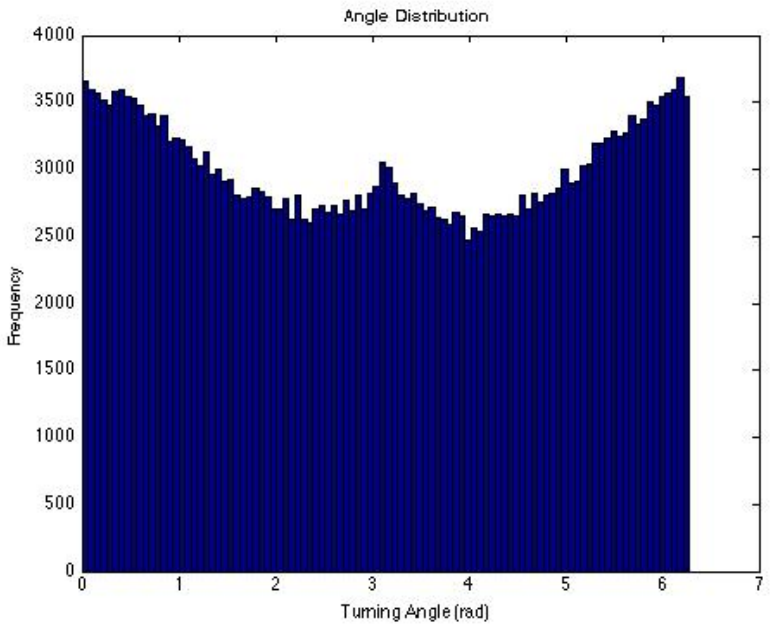
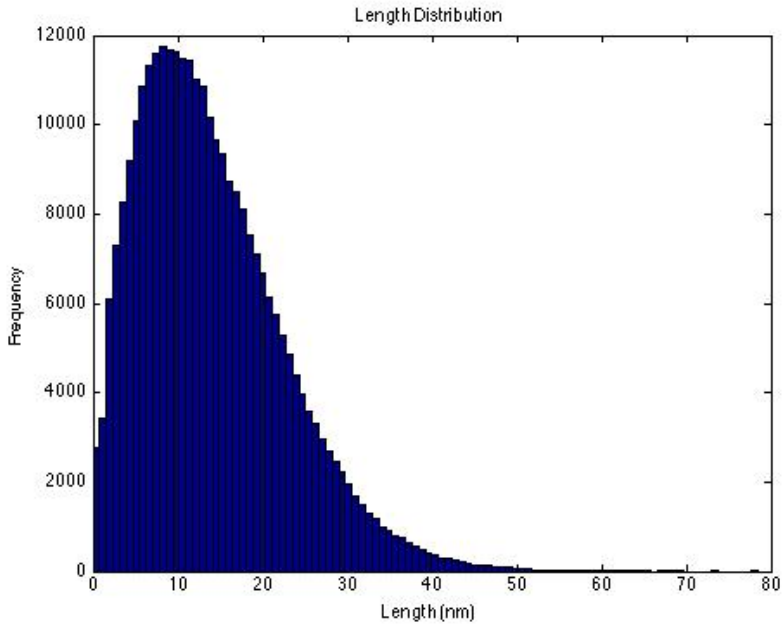
Turning Angles and Step Lengths





Angle and Length Distributions





Are these distributions alone enough to describe the observed LFA-1 trajectories?

Correlated Random Walk

- A random walk in which the directions of subsequent moves are correlated.
- Data is measured in terms of move lengths and turning angle probabilities.
- Conclusions are derived from analyzing collective distributions of data.

Can the movement mechanism of the LFA-1 protein be described by the length and turning angle distributions?

Correlated Random Walk: The Patlak Model

The model is given by the partial differential equation:

$$\frac{\partial u}{\partial t} = \frac{1}{n}\nabla\cdot\left[\frac{1+\psi\left(2\frac{m_1^2}{m_2}-1\right)}{1-\psi}\nabla\left(\frac{m_2}{2\tau}u\right) - \frac{\psi m_1^3}{\tau m_2\left(1-\psi\right)}\nabla\left(\frac{m_2}{m_1}\right)u\right]$$

$$\begin{aligned} m_1 &= \text{average move length} \\ m_2 &= \text{average squared move length} \\ \tau &= \text{average move duration} \\ \psi &= \text{average of the cosines of turning angles} \end{aligned}$$

Correlated Random Walk: The Patlak Model

This model gives rise to a theoretical formulation for MSD, called Net Squared Displacement:

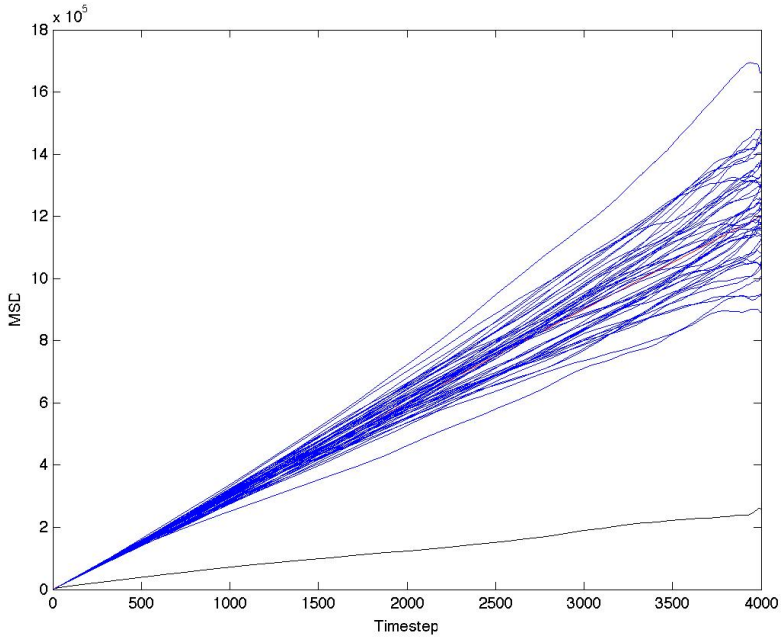
$$\overline{R_n^2} = nm_2 + 2m_1^2 \left[\frac{(\psi - \psi^2 - s^2)n - \psi}{(1-\psi)^2 + s^2} + \frac{2s^2 + (\psi + s^2)^{\frac{n+1}{2}}}{((1-\psi)^2 + s^2)^2} \gamma \right]$$

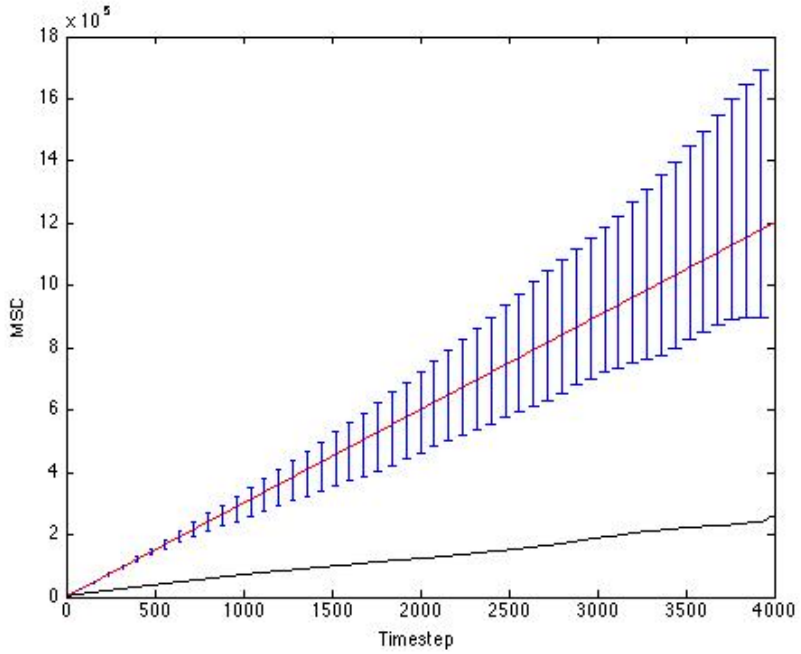
$$\gamma = ((1-\psi)^2 - s^2)\cos((n+1)\alpha) - 2s(1-\psi)\sin((n+1)\alpha)$$

where m_1, m_2, ψ and s are calculated from data as

$$\begin{aligned} m_1 &= \frac{1}{k}\sum_{i=1}^{k} \ell_i \\ m_2 &= \frac{1}{k}\sum_{i=1}^{k} \ell_i^2 \\ \psi &= \frac{1}{k}\sum_{i=1}^{k} \cos(\theta_i) \\ s &= \frac{1}{k}\sum_{i=1}^{k} \sin(\theta_i) \end{aligned}$$

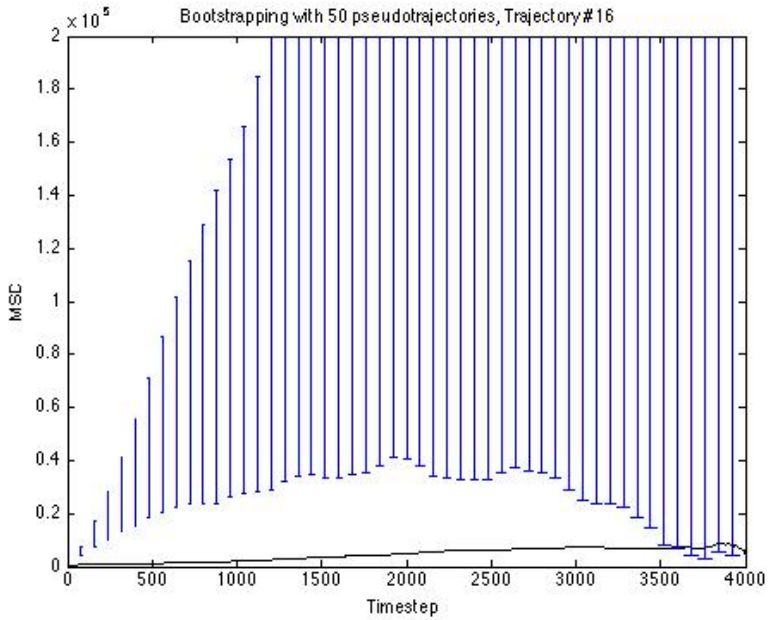
Testing the CRW with a Bootstrapping Procedure

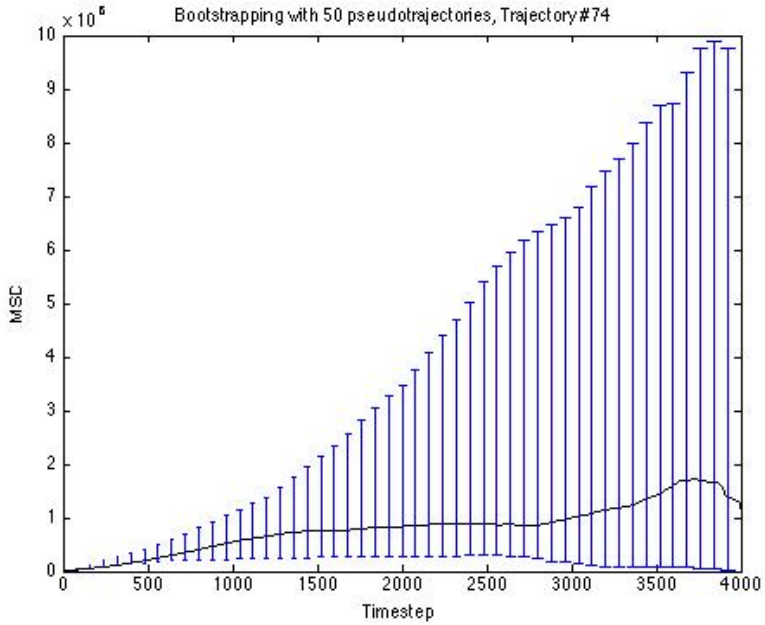




- The MSDs of the pseudotrajectories (blue) surround the theoretical Net Squared Displacement (red) of the experimental data.
- They do not encompass the MSD of the experimental data (black).

Testing the CRW for Individual Trajectories

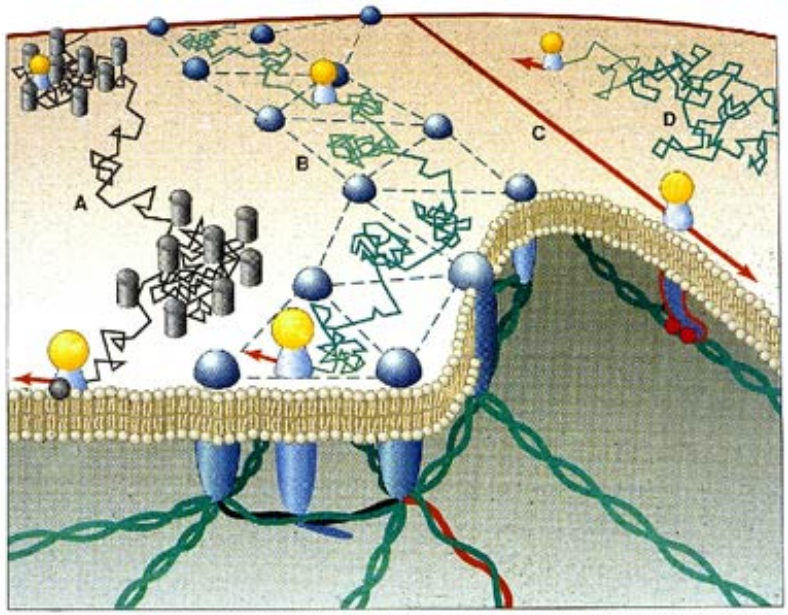




Out of 75 experimental trajectories, only 10 passed the bootstrapping procedure.

What about the rest?

Anomalous Diffusion



Lateral transport modes on the cell surface. (**A**) Transient confinement by obstacle clusters (**B**) or by the cytoskeleton, (**C**) directed motion, and (**D**) free random diffusion.

www-cellbio.med.unc.edu

(A) Transient Confinement Zones due to obstacles

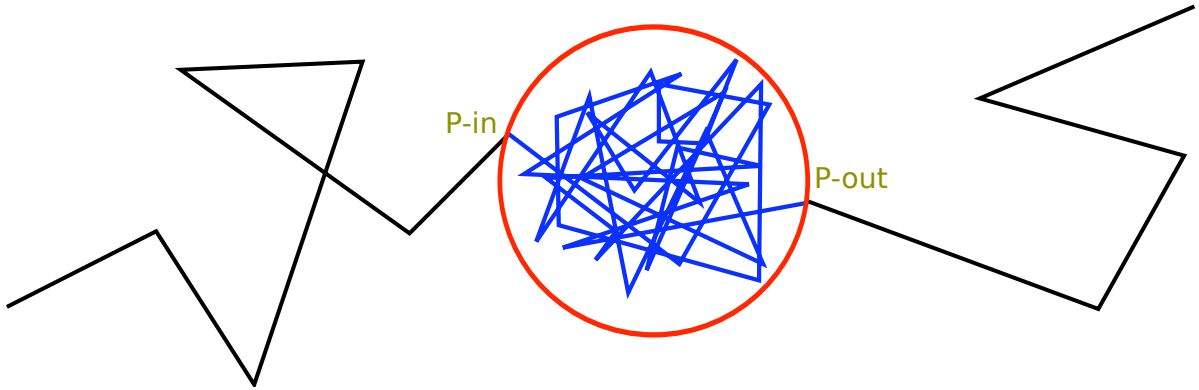
(B) Transient Confinement Zones due to cytoskeleton binding

(C) Directed Motion

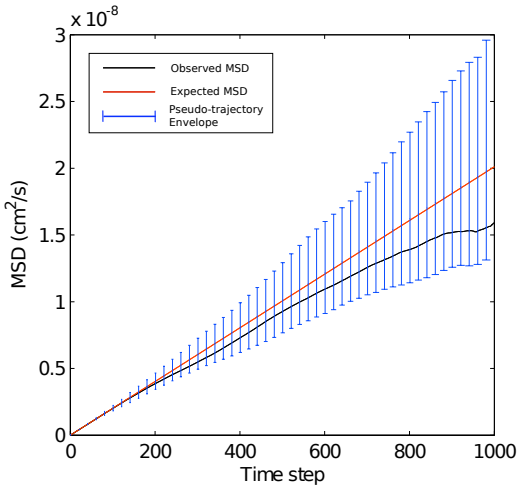
(D) Random Brownian Motion

Modeling Transient Confinement

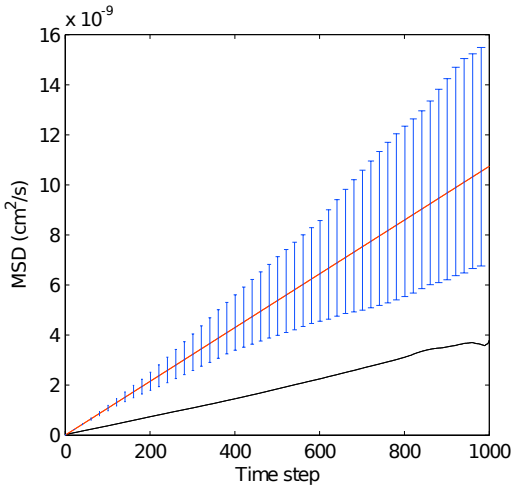
- At each step of a CRW, decide whether the particle should become confined with probability $P - in$
- If confined, decide whether the particle should leave the confinement zone with probability $P - out$



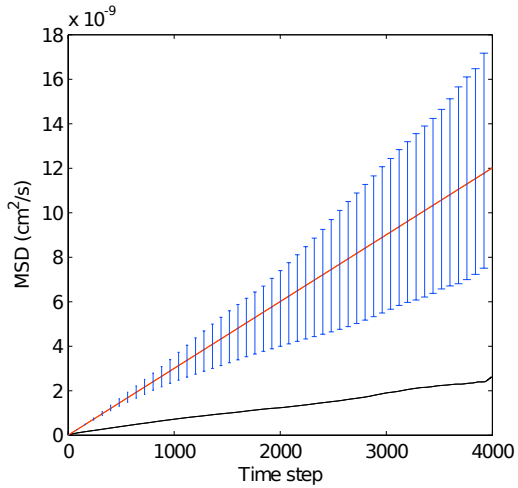
Transient Confinement and the Patlak Model



Simple random walk



Transient Confinement



LFA-1

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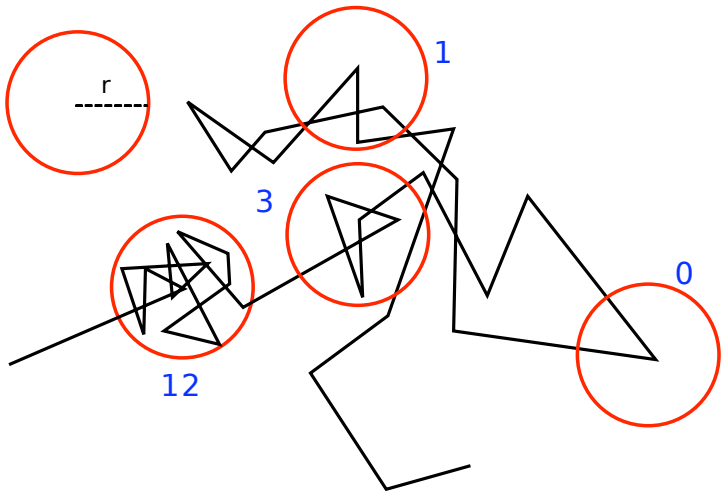
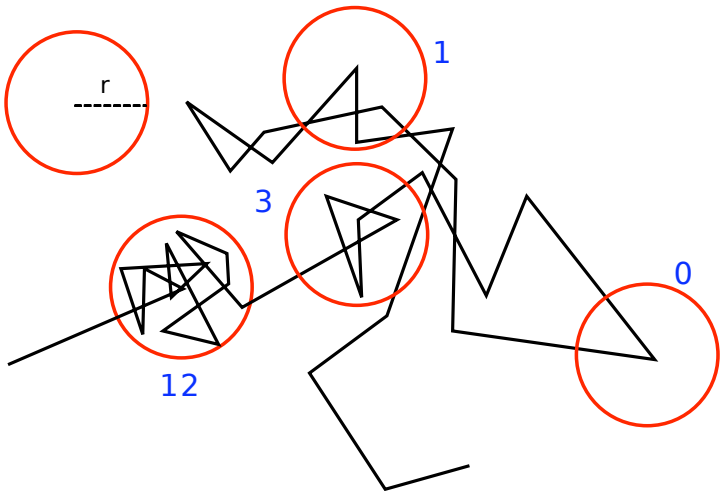
First-Passage Time and its Distribution

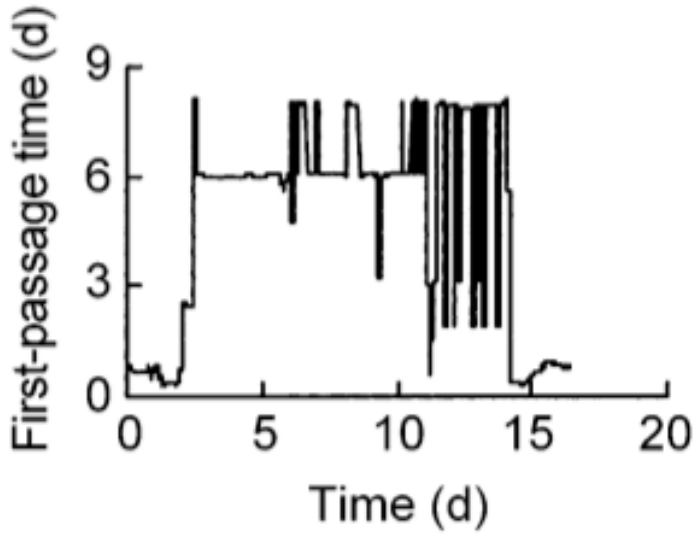


FPT (First Passage Time): number of steps that a particle or individual takes in a circle of radius r centered on each step of the trajectory.

First-Passage Time and its Distribution

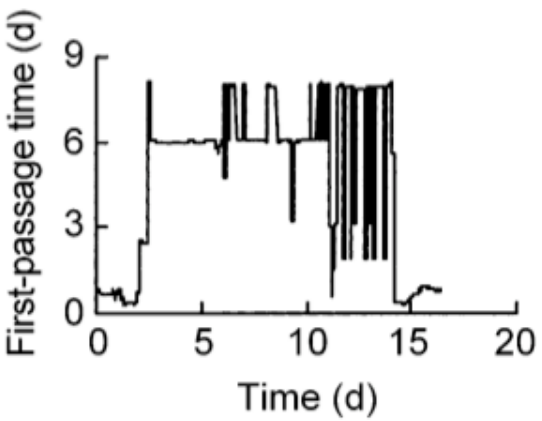


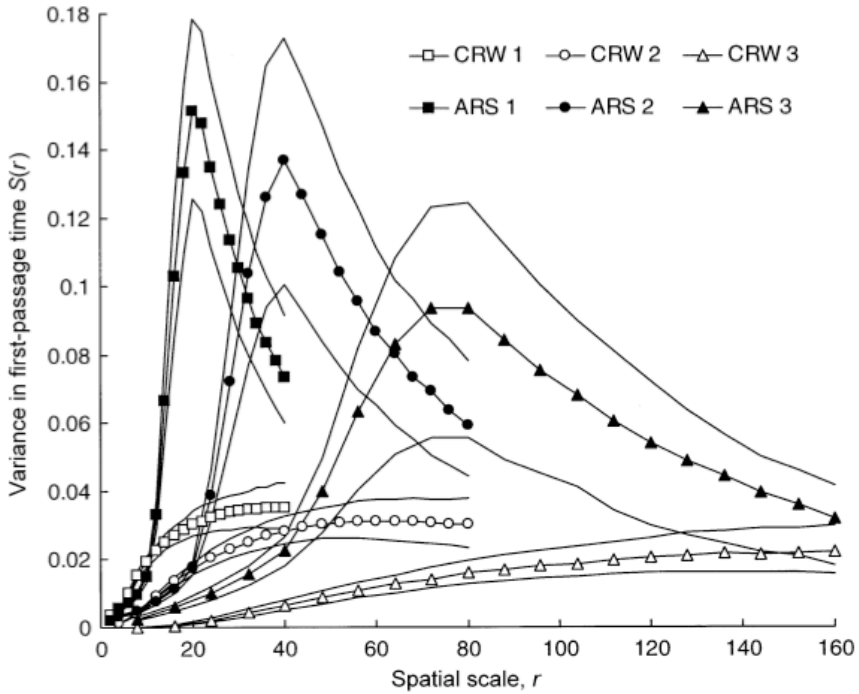
FPT (First Passage Time): number of steps that a particle or individual takes in a circle of radius r centered on each step of the trajectory.



Distribution given by the FPT for r

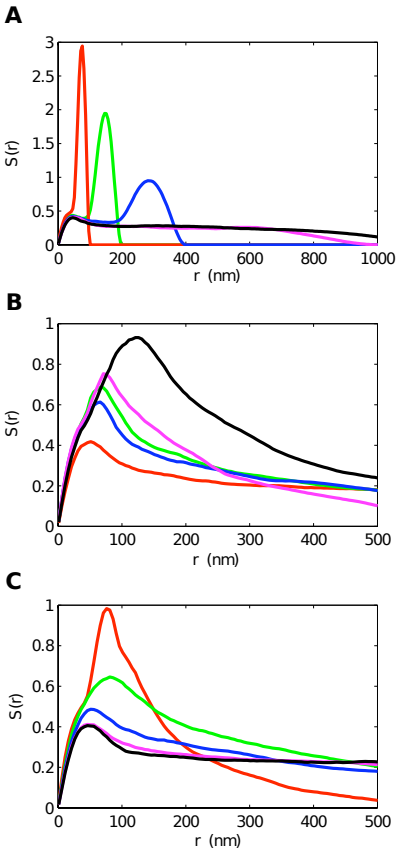
Variance First-Passage Time

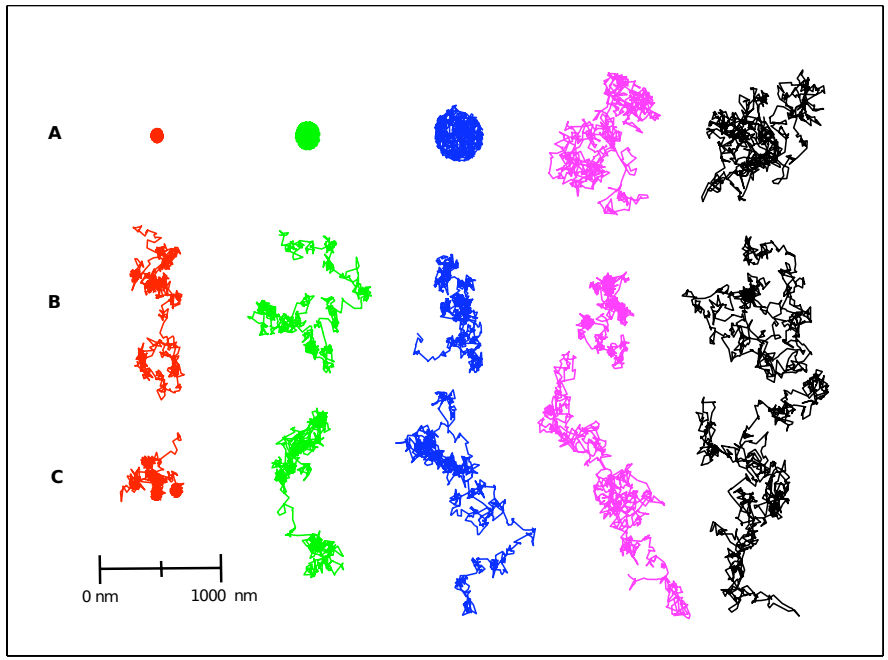




$S(r)$(Variance First-Passage Time): Variance of the distribution given by the FPT for r. It is a measure of the amount of heterogeneity at the spatial scale r.

How does variance FPT look for different transient confinement parameters?



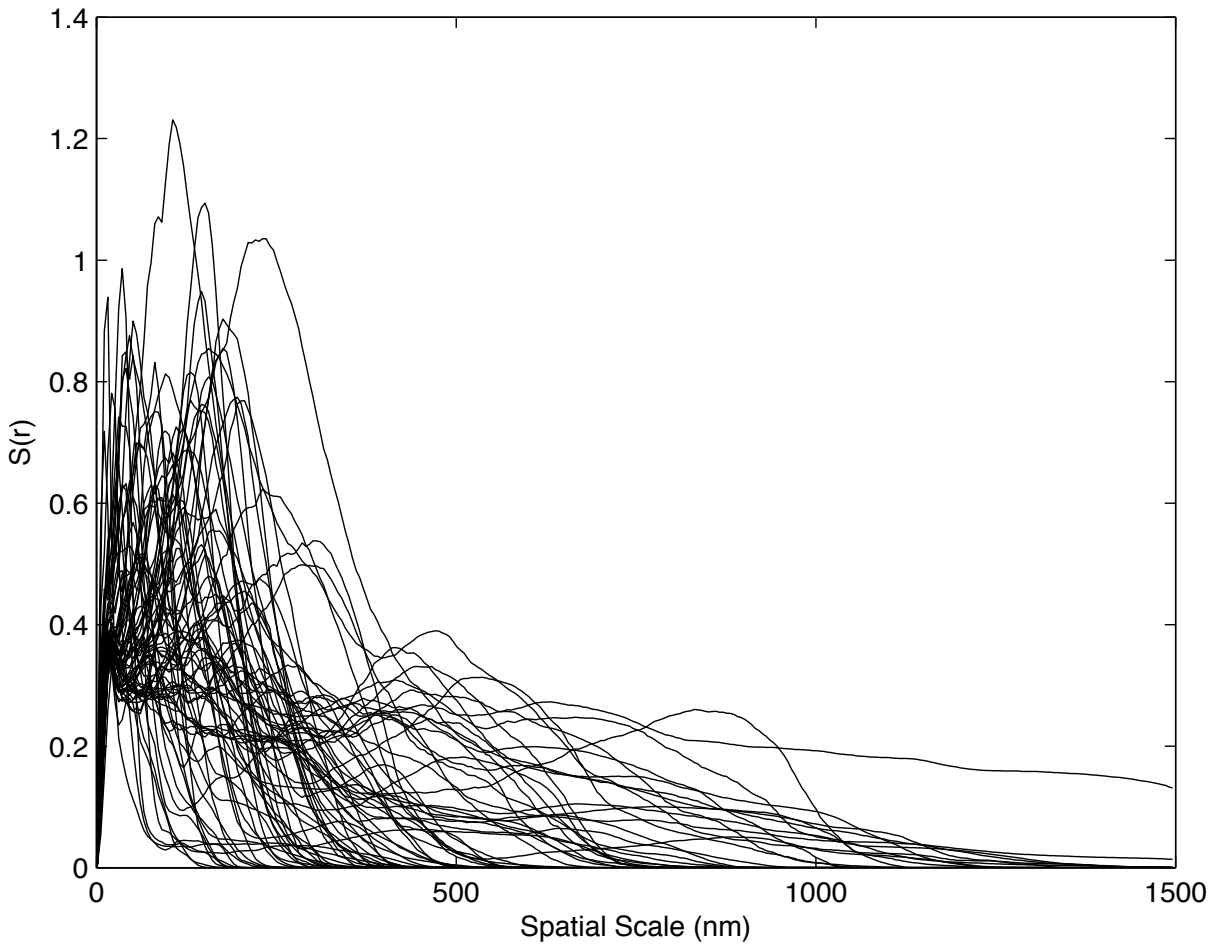


(A) $p_i = 1$ and $p_o = 0$;
50nm, 100nm, 200nm,
500nm, 1000nm

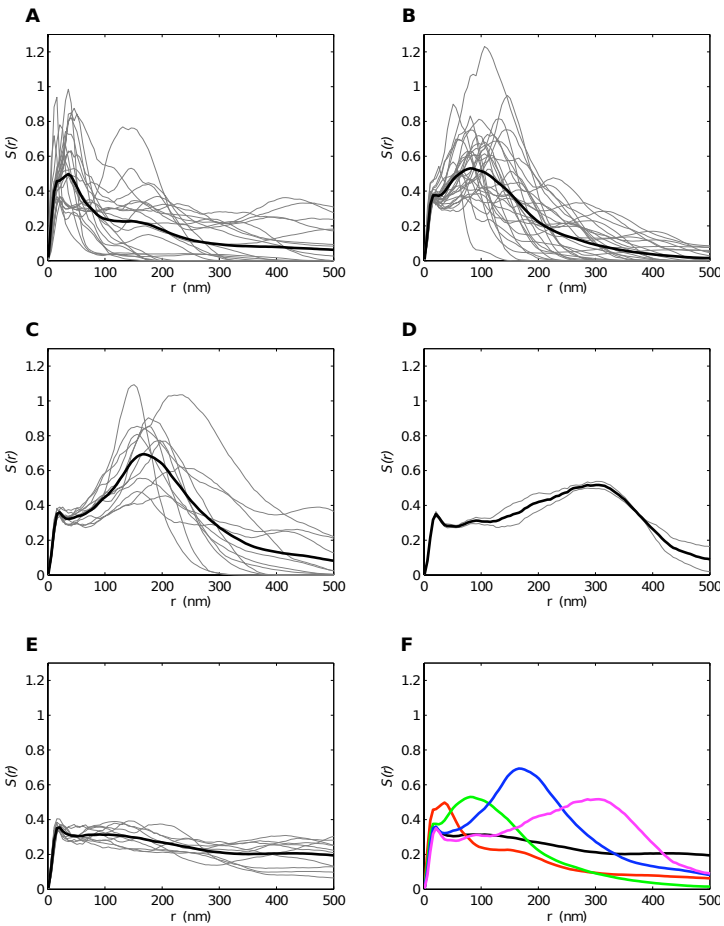
(B) $r_c = 50nm$;
$p_i = 0, 0.2, 0.4, 0.8, 1$
$p_o = 0.1$

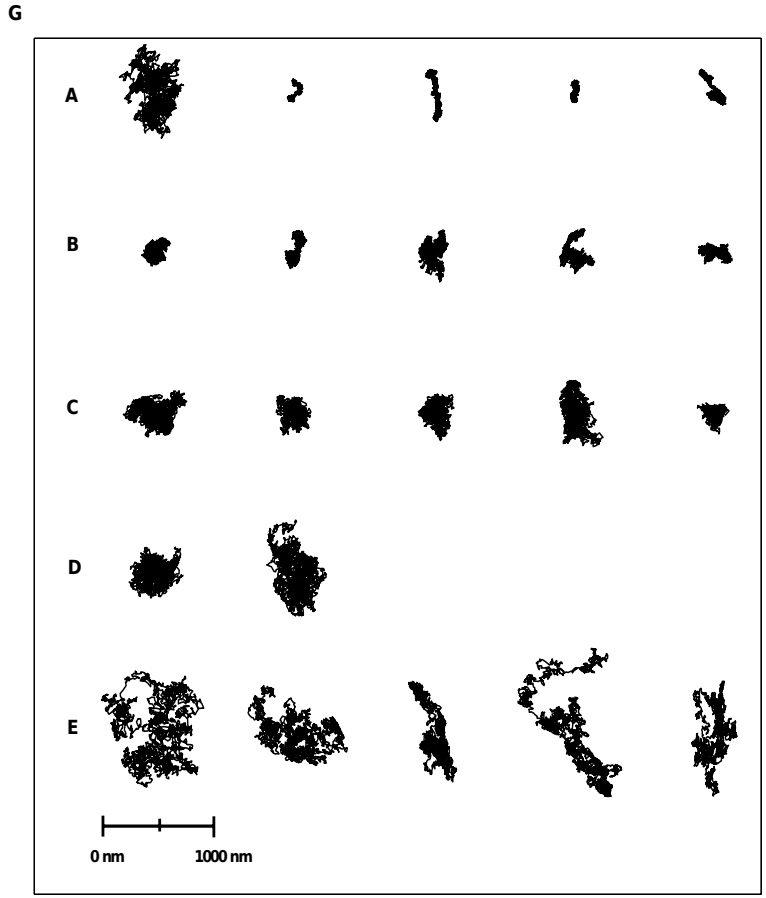
(C) $r_c = 50nm$;
$p_o = 0.05, 0.2, 0.4, 0.8, 1$
$p_i = 0.9$

Application to LFA-1



Looking at Macroheterogeneity





0 - 50 nm

50 - 150 nm

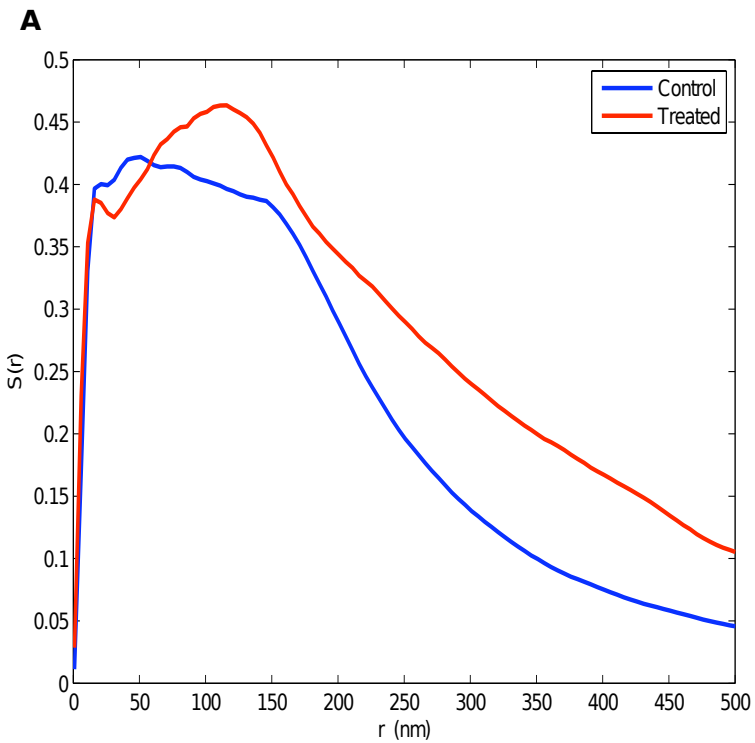
150 - 250 nm

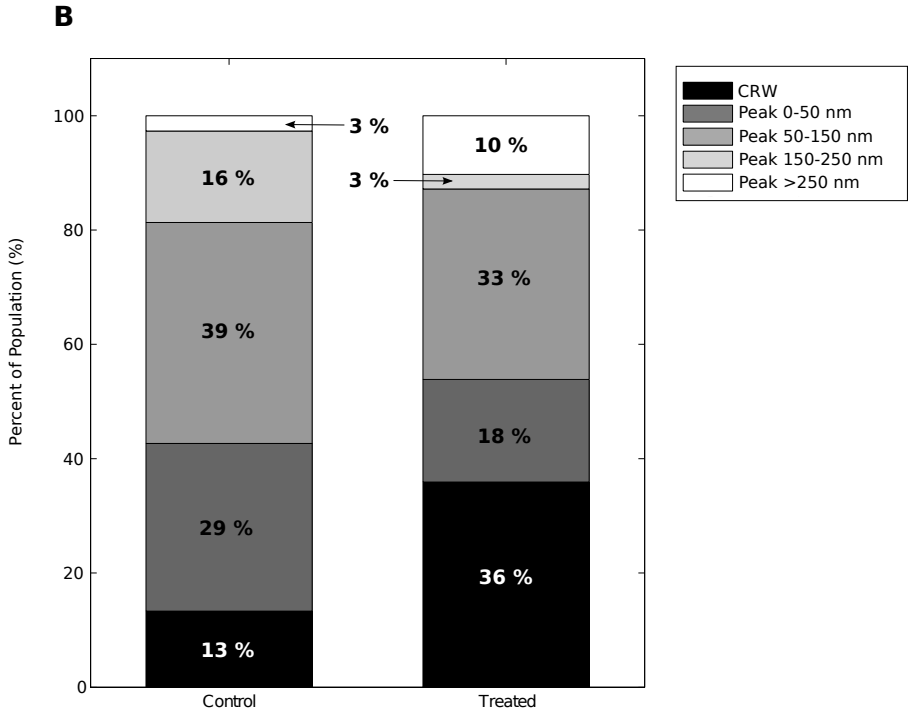
$\geq$ 250 nm

CRW

Classifying Population Structure

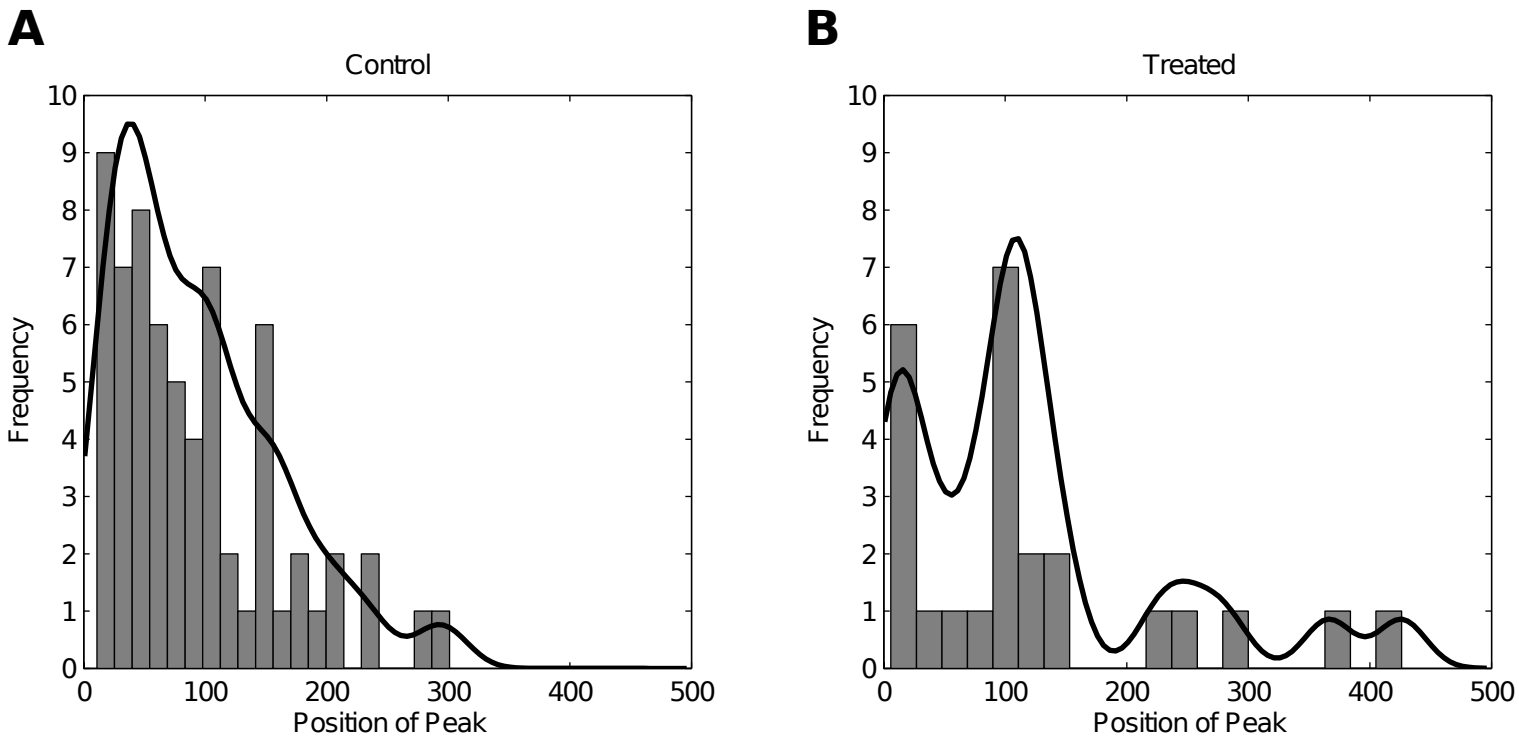
- Changes in population structure after treatment of PMA
- For a particular label (TS1/18), PMA activates the cell: increases mobility of LFA-1 proteins





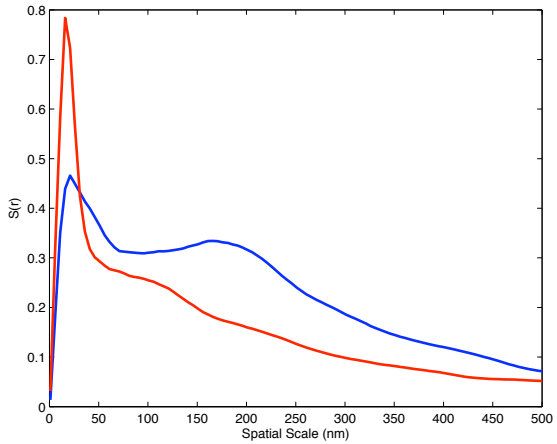
Distribution of Peaks in Variance First-Passage Time

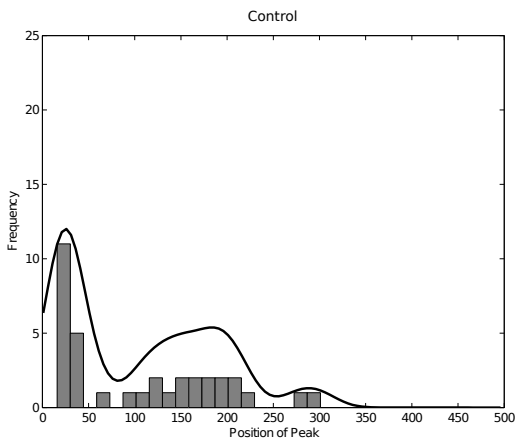
- The areas of concentrated movement change after treatment of PMA

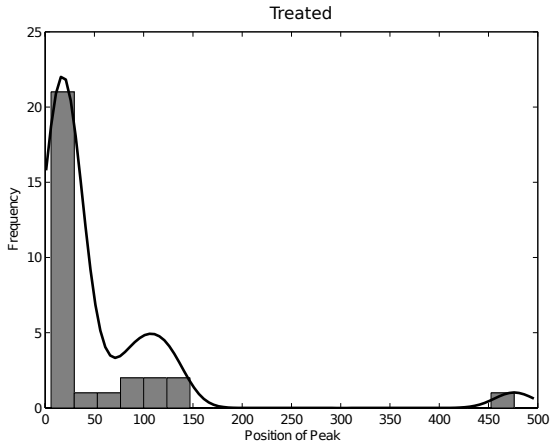


Detecting Cluster Sizes

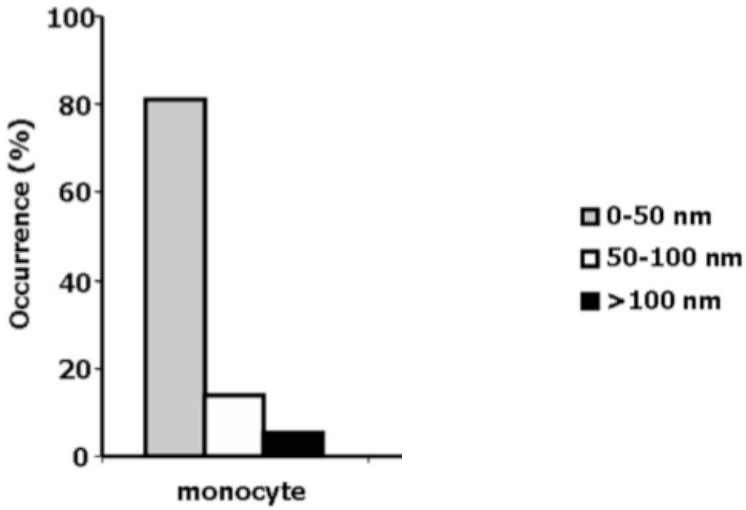
- Combining MEM148 Antigen with PMA shows concentrated diffusion within $\leq 50nm \Rightarrow$ clustering?

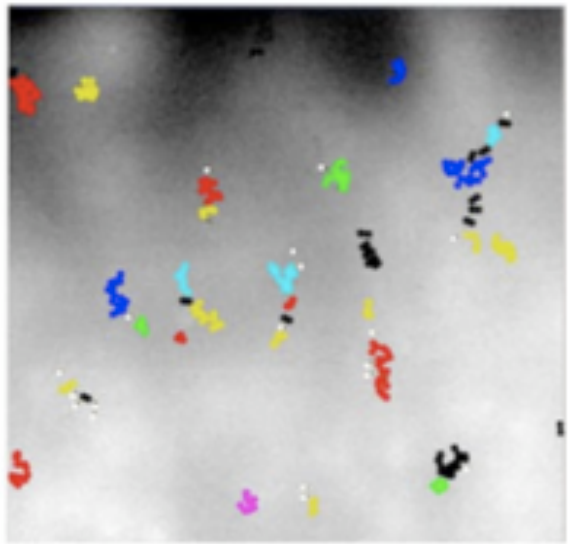






LFA-1 Receptor Clustering





Cambi et al., 2006

- Experimental evidence for LFA-1 clusters on activated cells is limited

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- Ecological approaches can provide insights into the movement mechanism of individual proteins.
- Both the CRW model and variance FPT provide some ability to monitor and filter macroheterogeneity.
- Variance FPT is a useful method to detect microheterogeneity and suggests receptor clustering.

THANKS YOU!