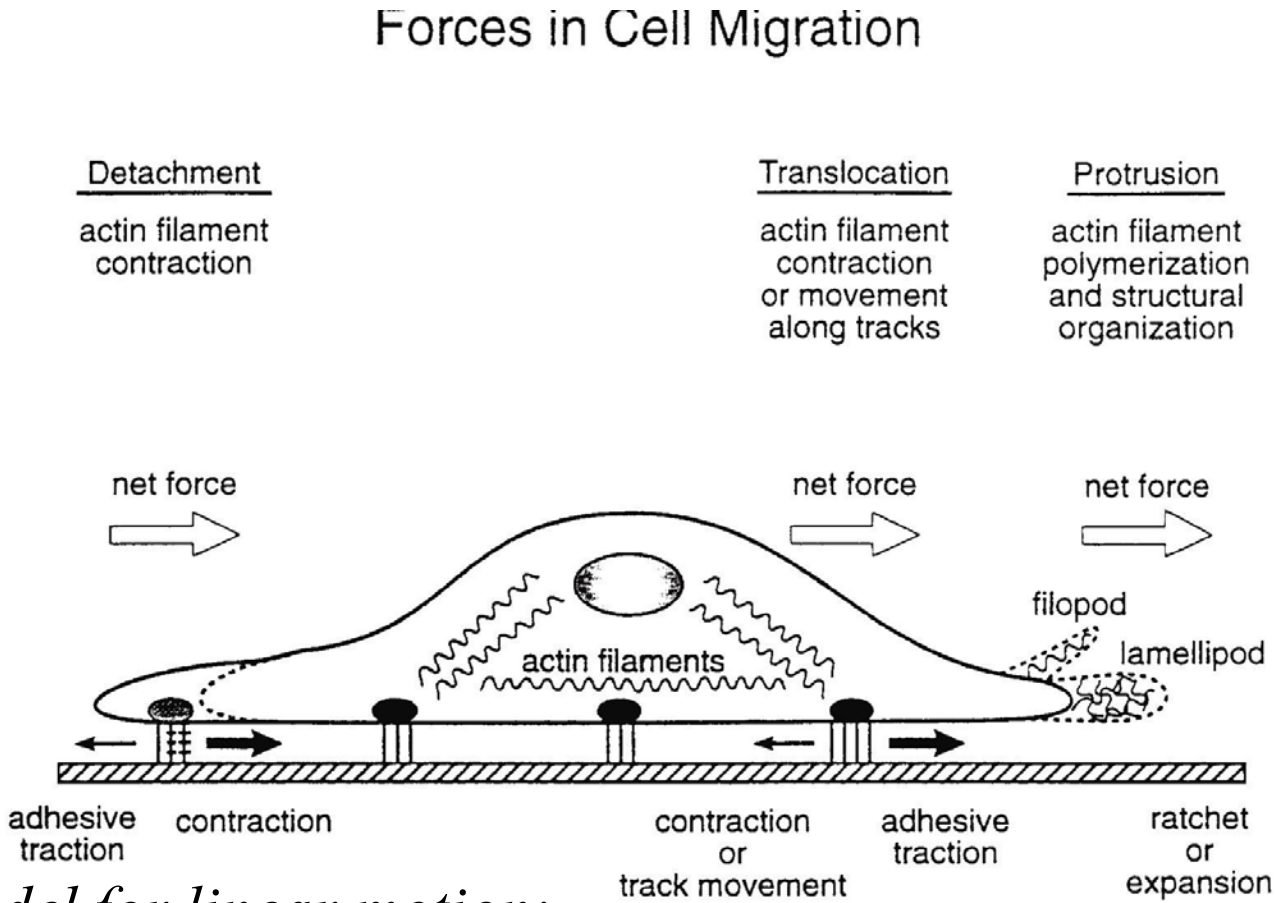
Random Walks and Diffusion

APC 514

December 5, 2002

Cox&Shvartsman

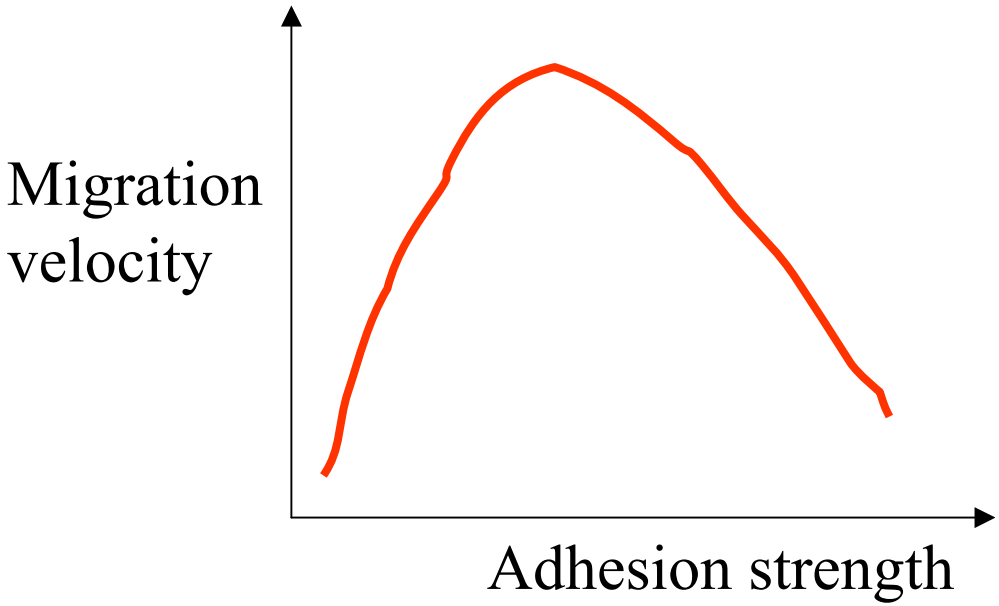
Cell motility over adhesive substrates: a periodic phenomenon

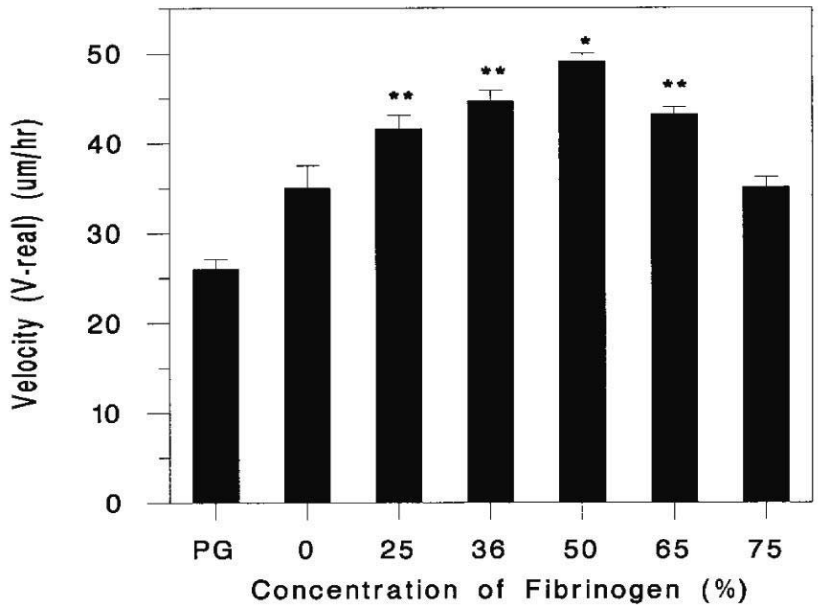


Simple model for linear motion:

DIMILLA PA, BARBEE K, LAUFFENBURGER DA MATHEMATICAL-MODEL FOR THE EFFECTS OF ADHESION AND MECHANICS ON CELL-MIGRATION SPEED BIOPHYS J 60 (1): 15-37 JUL 1991

Models and measurements





Ahmed Z, Underwood S, Brown RA.

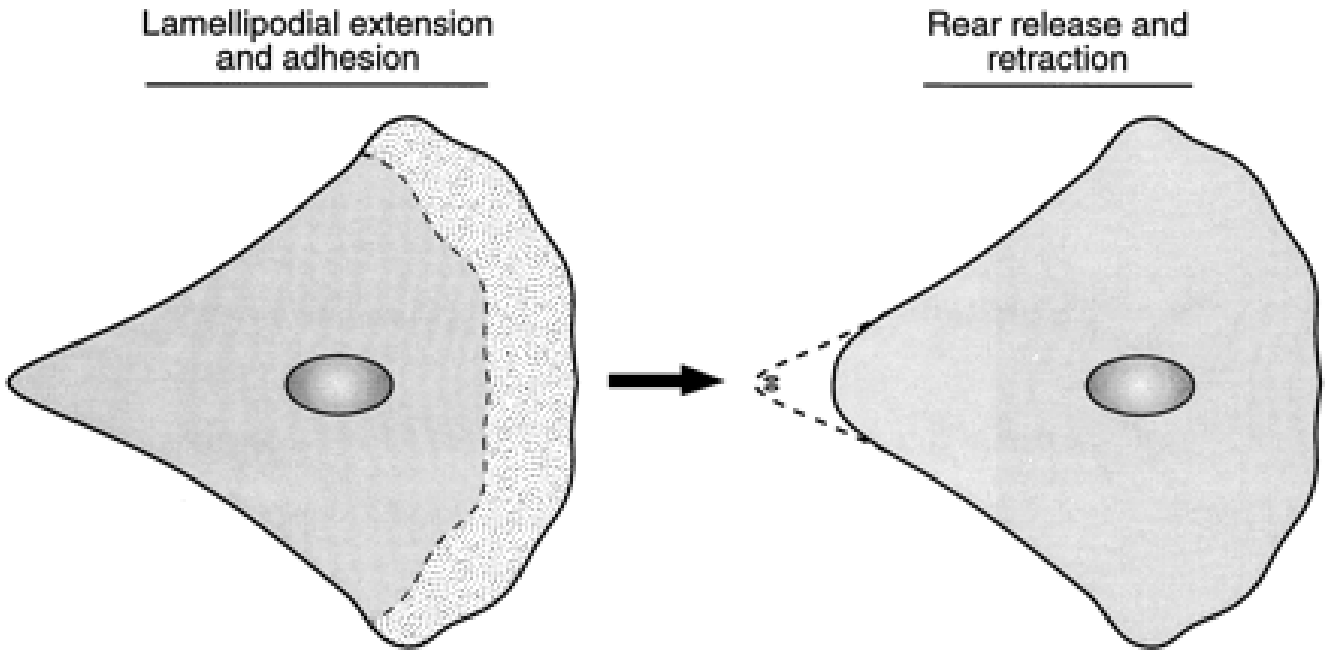
Low concentrations of fibrinogen increase cell migration speed on fibronectin/fibrinogen composite cables.

Cell Motil Cytoskeleton. 2000 May;46(1):6-16.

Simple model for linear motion:

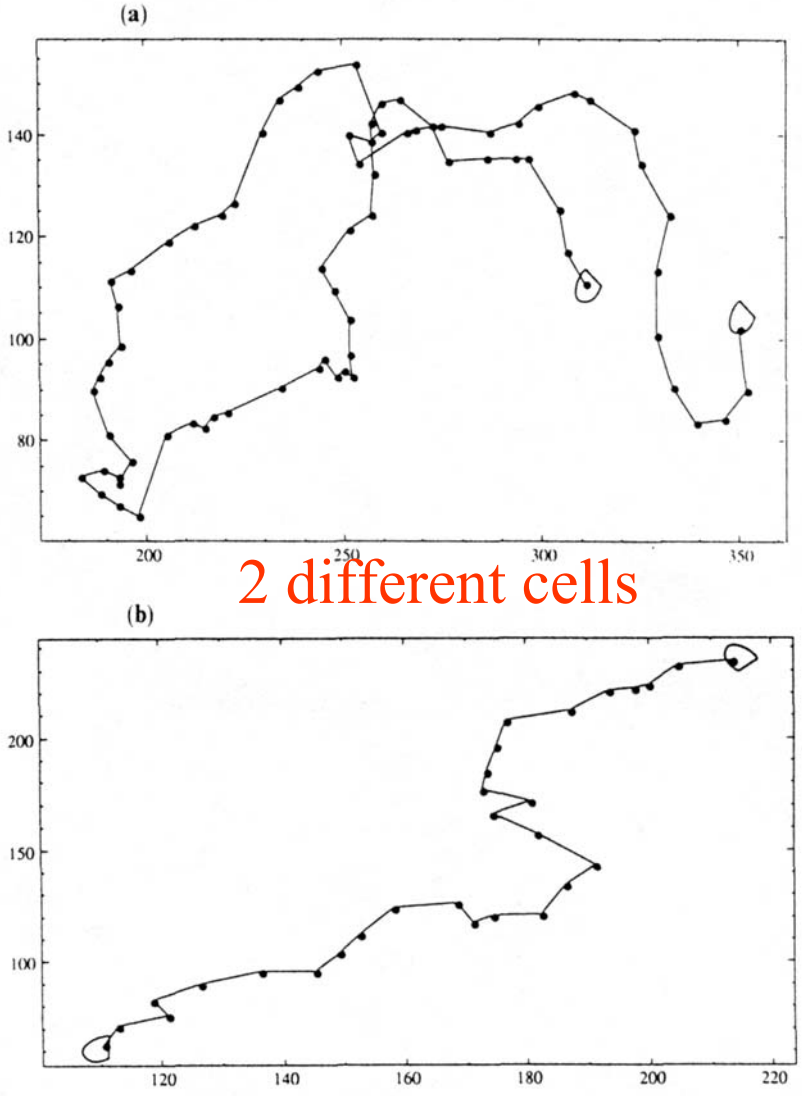
DIMILLA PA, BARBEE K, LAUFFENBURGER DA MATHEMATICAL-MODEL FOR THE EFFECTS OF ADHESION AND MECHANICS ON CELL-MIGRATION SPEED BIOPHYS J 60 (1): 15-37 JUL 1991

Each step of the process is highly regulated



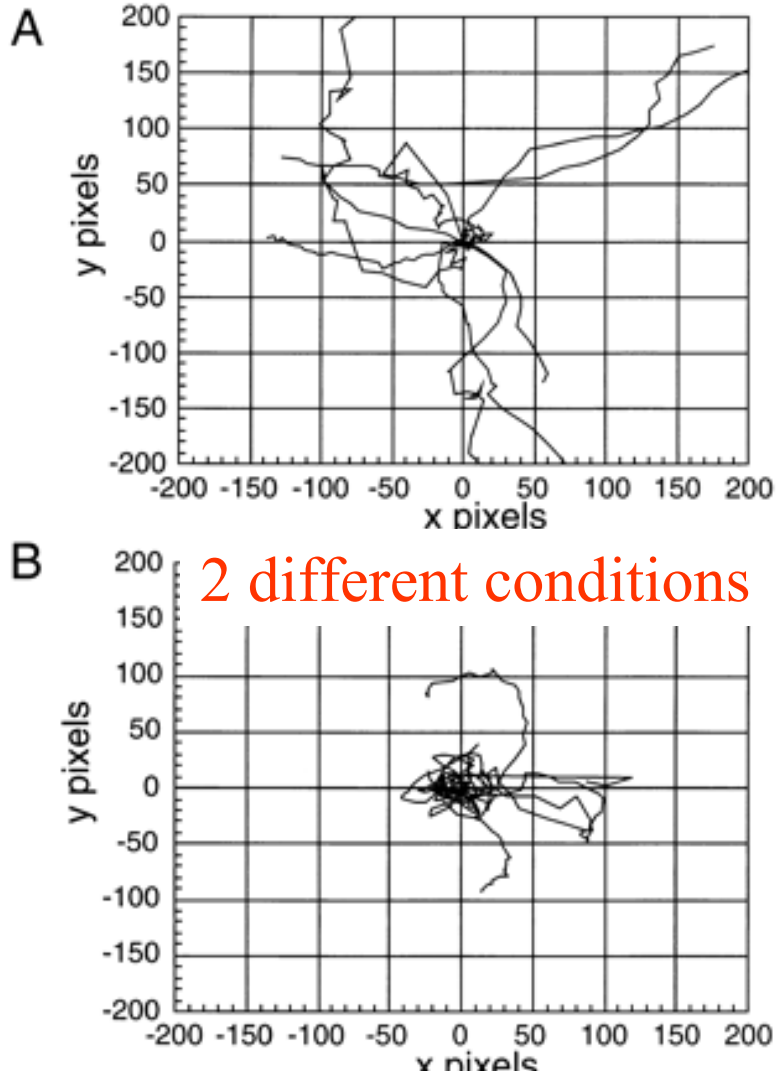
Cell paths are random

Neutrophils



2 different cells

Epithelial cells



2 different conditions

Language for trajectories: random walk theory

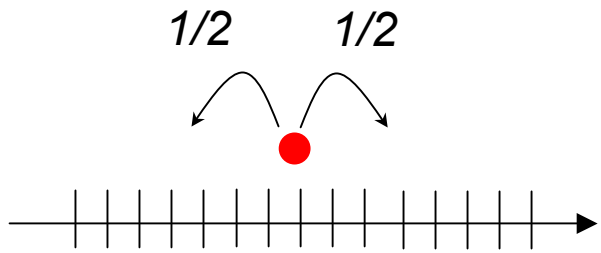
- Probability primer
- Position jump process
  - Exact solution – Binomial distribution
- Mean and variance
- Random variables
  - Distribution function
- Observations of Berg and Brown
  - Exponentially distributed random variable

Position Jump Process (1)

N steps, net displacement - $m : -N \le m \le N$

(N odd/even $\Rightarrow$ m odd/even)

$$P_N(m) = \frac{N!}{(\frac{N+m}{2})!(\frac{N-m}{2})!}\left(\frac{1}{2}\right)^N$$



$< m >= 0 \quad < (m - < m >)^2 >= N \longrightarrow$ ***diffusive behavior***

Approximate solution: $P_N(m) \approx \sqrt{\frac{2}{\pi N}} e^{-\frac{m^2}{2N}}$

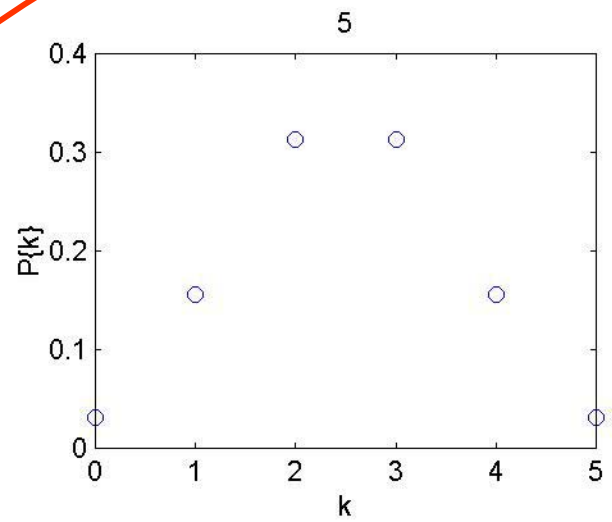
use $\log(n!) \approx (n+1/2)\log n - n + 1/2 \log \pi + O(n^{-1})$ &

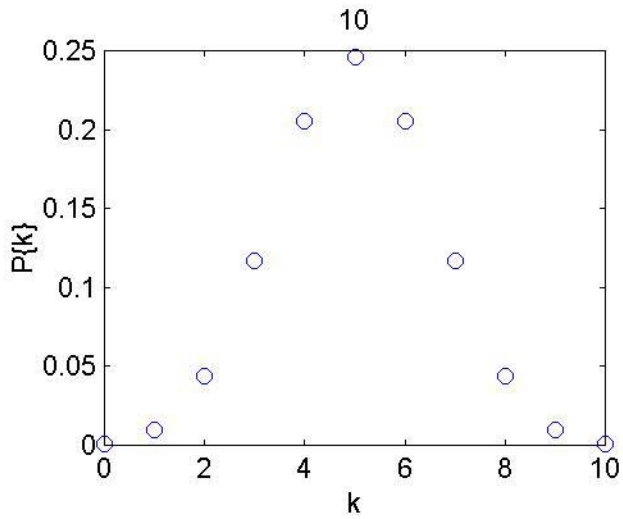
$$\log\left(1 \pm \frac{m}{N}\right) \approx \pm\frac{m}{N} - \frac{m^2}{2N^2} + O(\frac{m^2}{N^2})$$

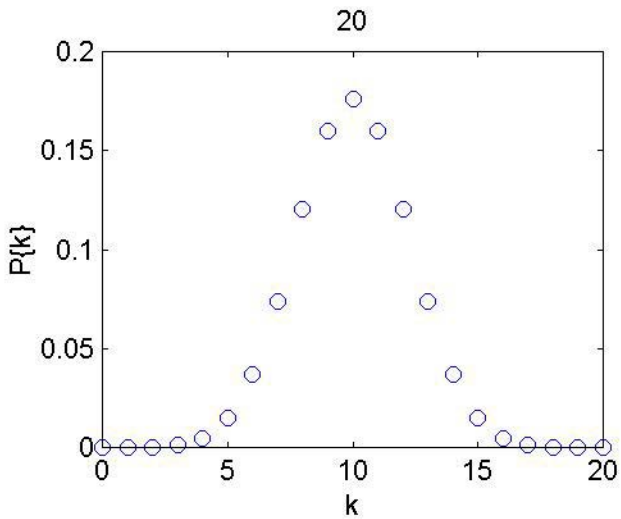
S. Chandrasekhar, Rev. Mod. Phys. 15, 1, 1-89, 1943

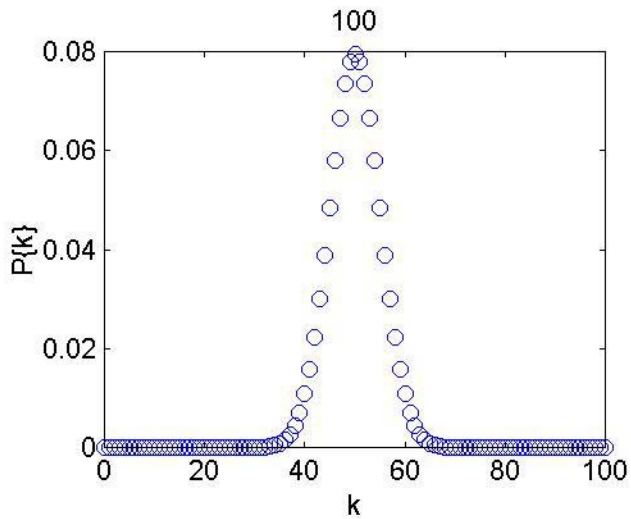
Binomial distribution

N









Position Jump Process (2)

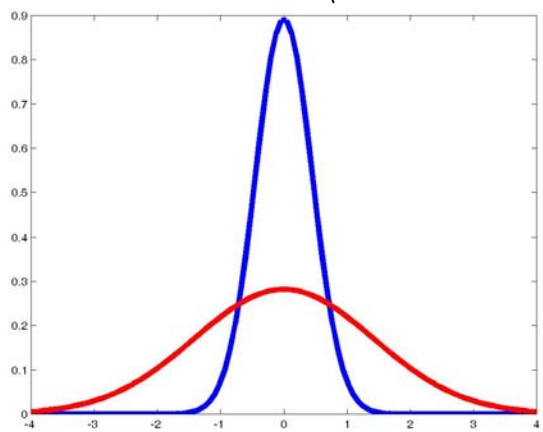
step size: l frequency of jumps: λ

Continuous space and time:

$$p(x,t)dx = P_N(m)\frac{dx}{2l} = \frac{1}{\sqrt{2\pi\lambda l^2 t}} e^{-x^2/2\lambda l^2 t} dx$$

$p(x,t) > 0$ for all t

$$D \equiv \lambda l^2 / 2 \rightarrow p(x,t) = \frac{1}{\sqrt{2\pi Dt}} e^{-x^2/4Dt}$$



Approximation for large times

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial p}{\partial x}\right) \text{ with } p(x,t=0) = \delta(x)$$

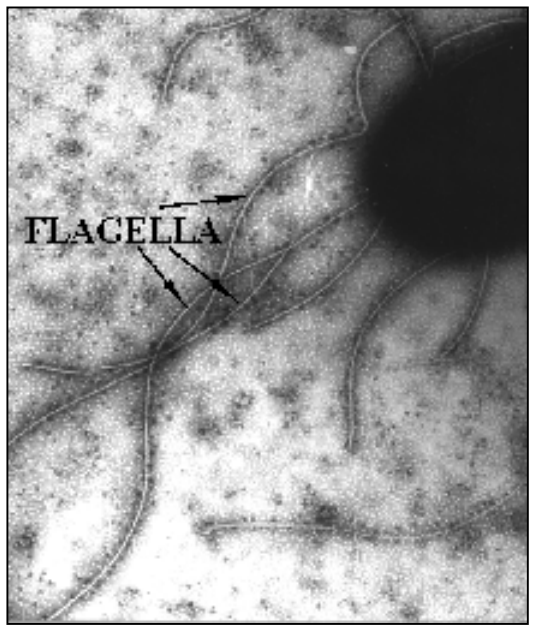
Rewrite: $\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x} J \leftarrow$ flux $J \equiv -D\frac{\partial p}{\partial x}$

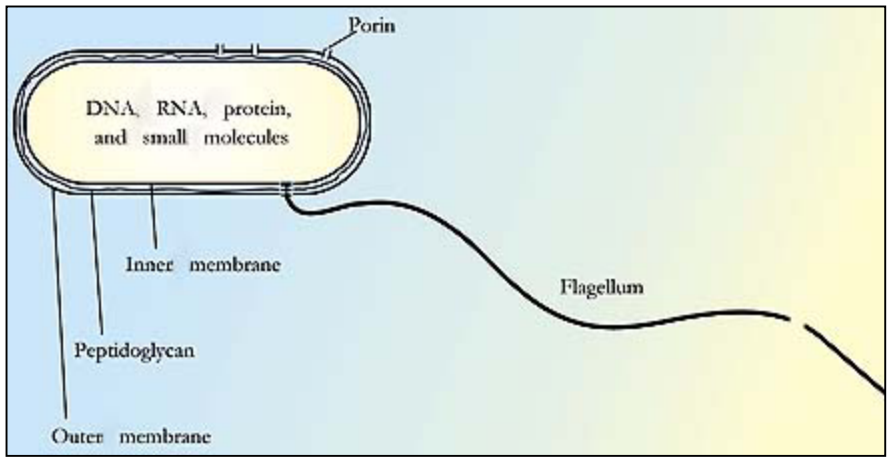
$$< x^2 >= 2Dt$$

earlier times: correlations in motion
-> cell migration is like that

S. Chandrasekhar, Rev. Mod. Phys. 15, 1, 1-89, 1943

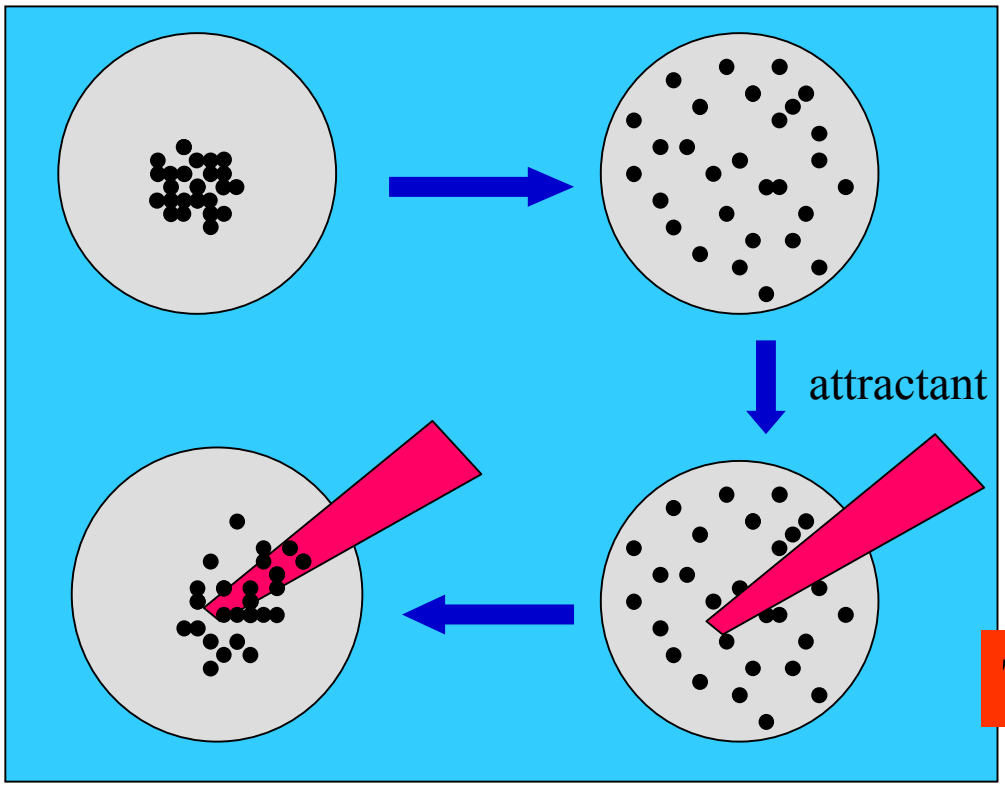
Model Organism: E.Coli





Size: 1 μm
Swims by rotating ~ 6 flagella
Speeds: up to 10 μm/s

Bacteria can be attracted/repelled by chemicals



Mechanism ?

"Chemoreceptors in bacteria."

Adler, 1969 "Science" – READ!

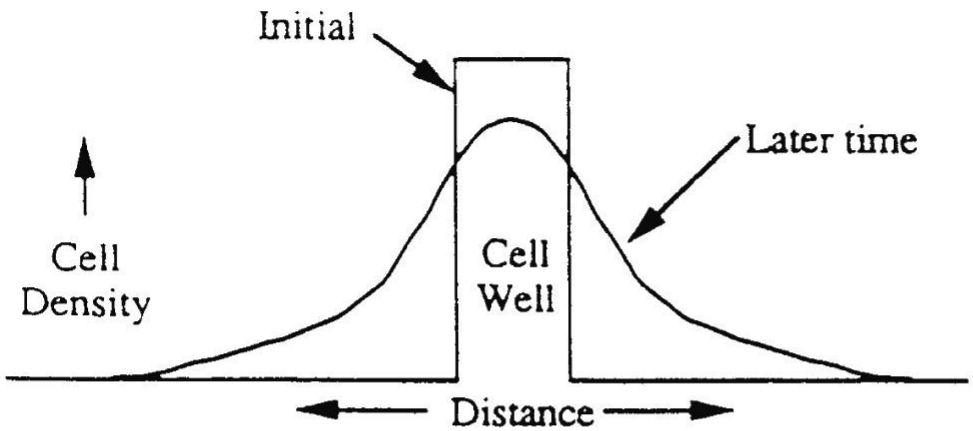
This is sensing, not metabolism

Based on genetic approach!!!
No molecules yet

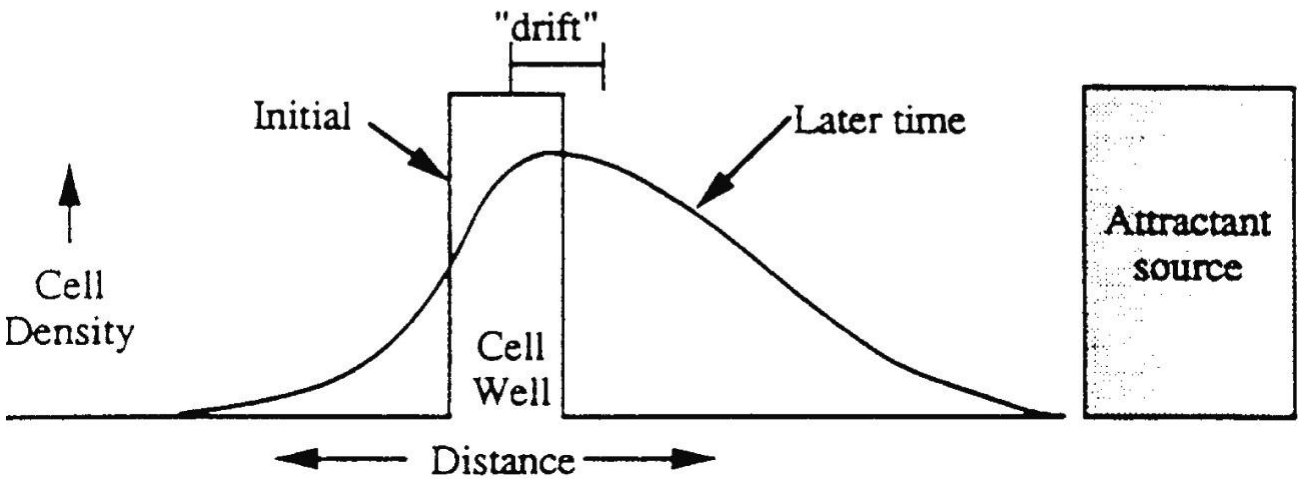
Macroscopic phenomenon:

flux of bacteria = F(gradient of chemicals)

Random Motility and Chemotaxis

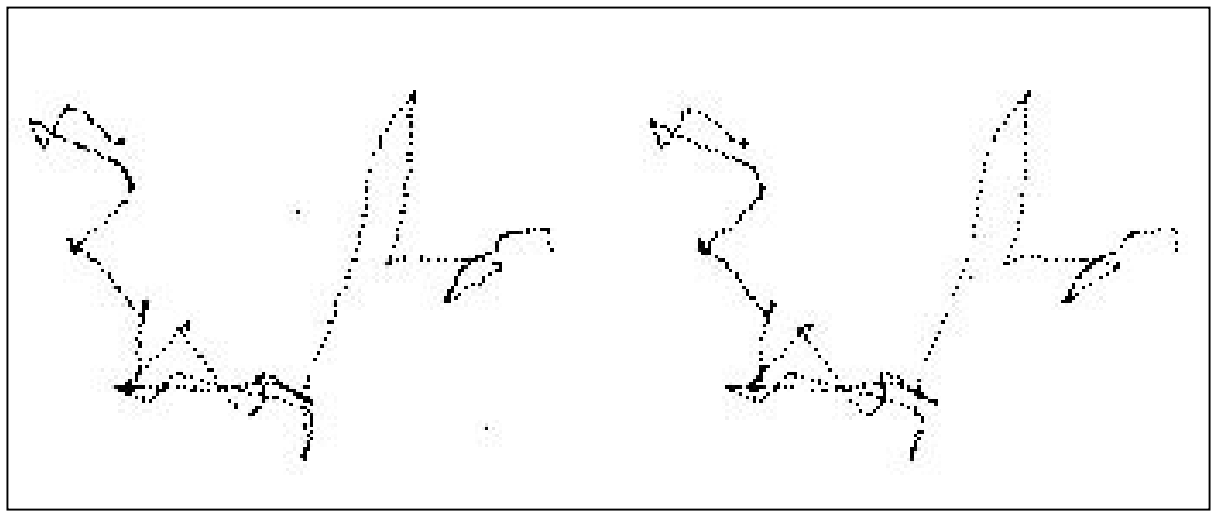


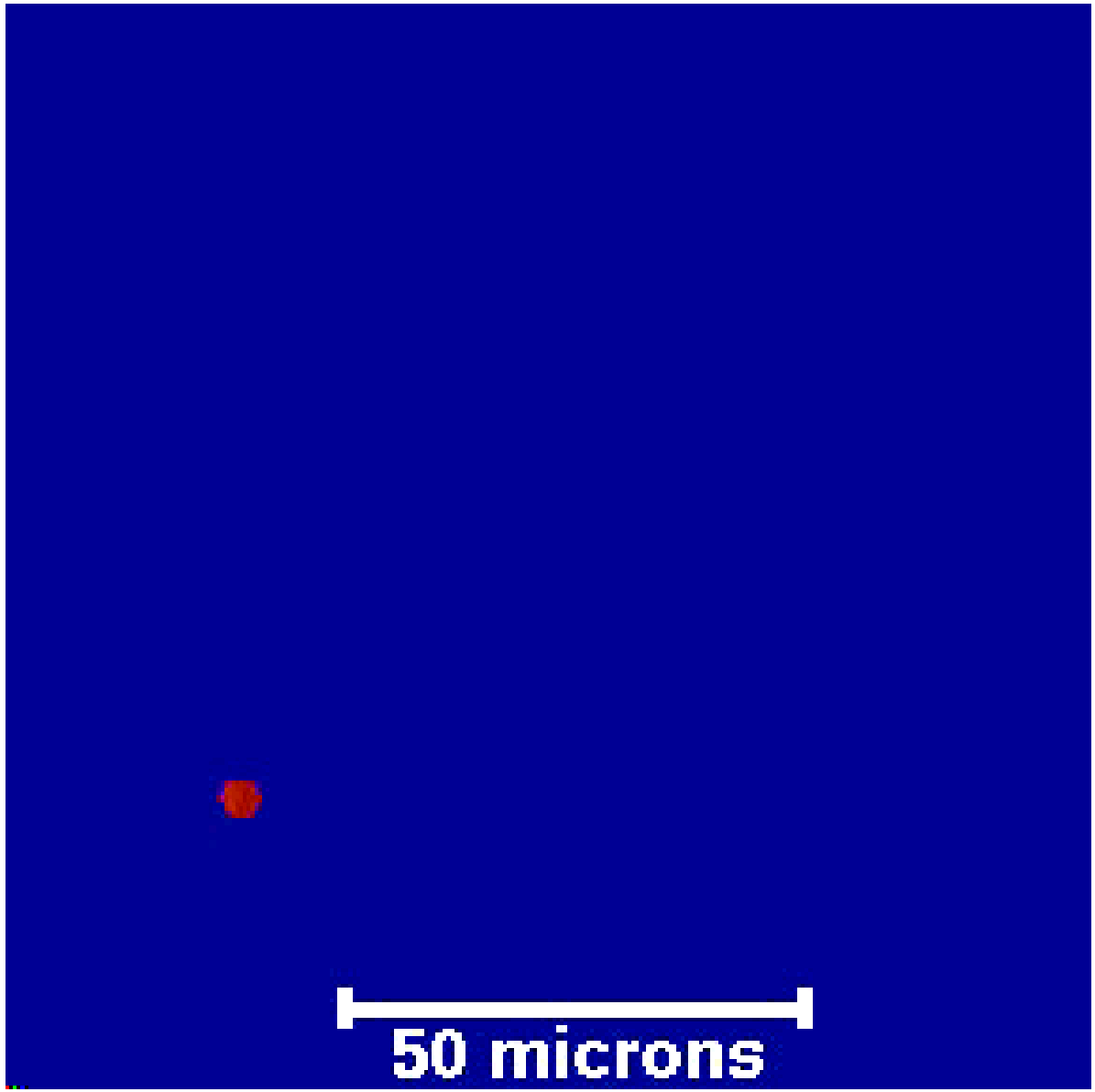
b. Migration in a chemical attractant gradient:
Random motility (μ), chemokinesis ($\frac{d\mu}{da}$) and chemotaxis (χ)



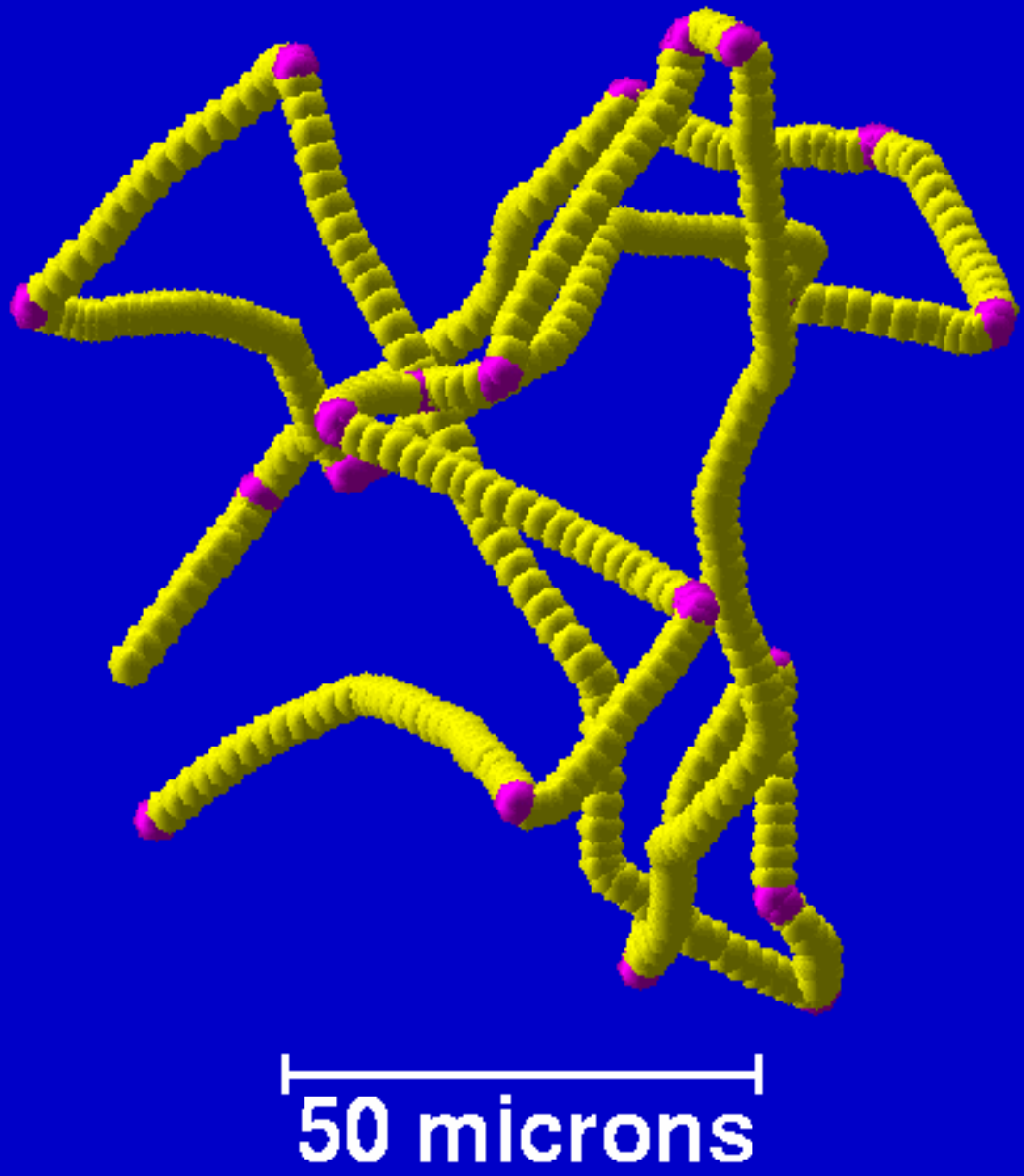
Trajectories

In the absence of chemical gradients, a swimming bacterium executes a three-dimensional random walk consisting of **runs** of swimming in a straight line punctuated by tumbles





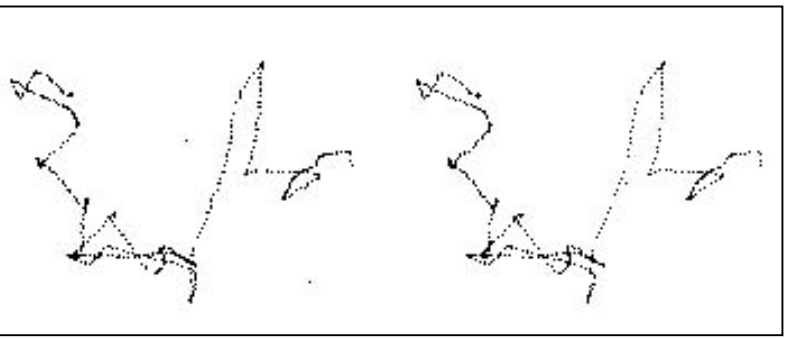
http://curie.che.virginia.edu/cleb/clebmain.html


50 microns

From Trajectories to Microscopic Parameters of Cell Migration

(Velocity Jump Process)

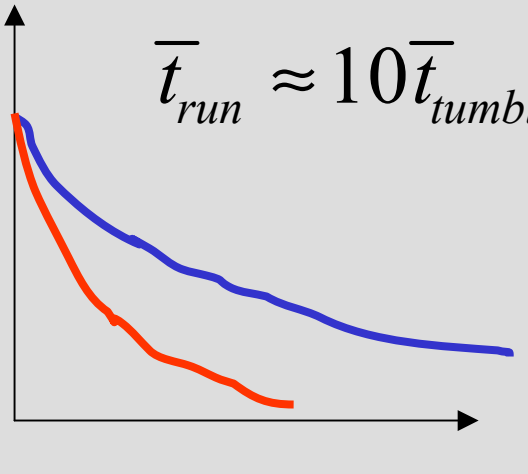
Berg and Brown, 1972



$P\{T_{run} > t\}$

or

$P\{T_{tumble} > t\}$

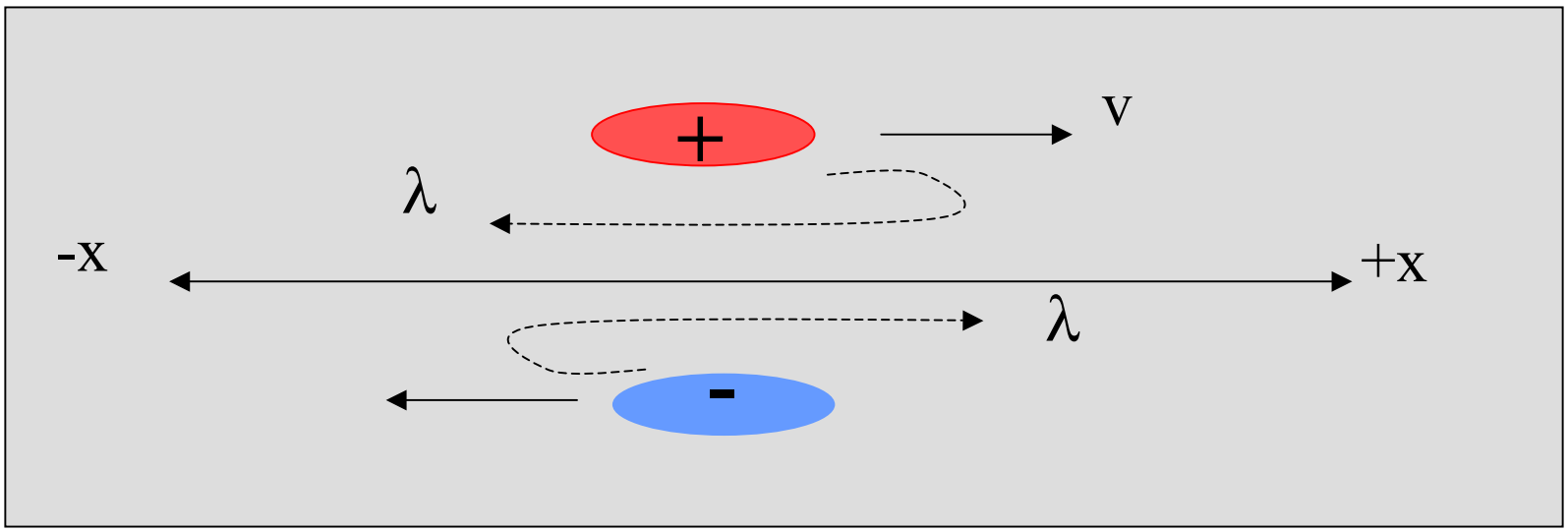


1. Runs punctuated by tumbles
2. Both runs and tumbles are exponentially distributed
3. Runs are longer than tumbles
4. Constant velocity

MODEL: instantaneous tumbles (neglect tumble time)

MODEL: instantaneous tumbles (neglect tumble time)

Velocity Jump Process



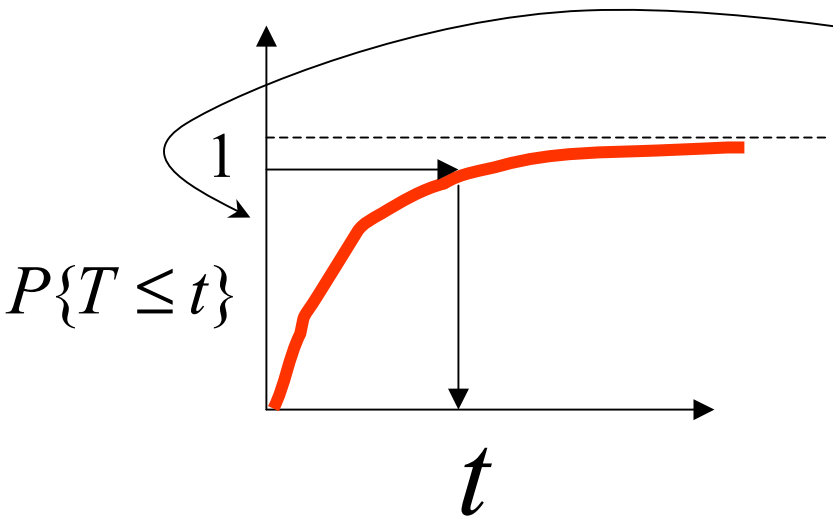
1. Continuous space & Continuous time
2. At every point: right- and left-moving cells
3. Follow a single cell & a population of cells

Velocity Jump Process

$$P\{T \le t\} = 1 - \exp(-\lambda t)$$

$$v = \pm V$$

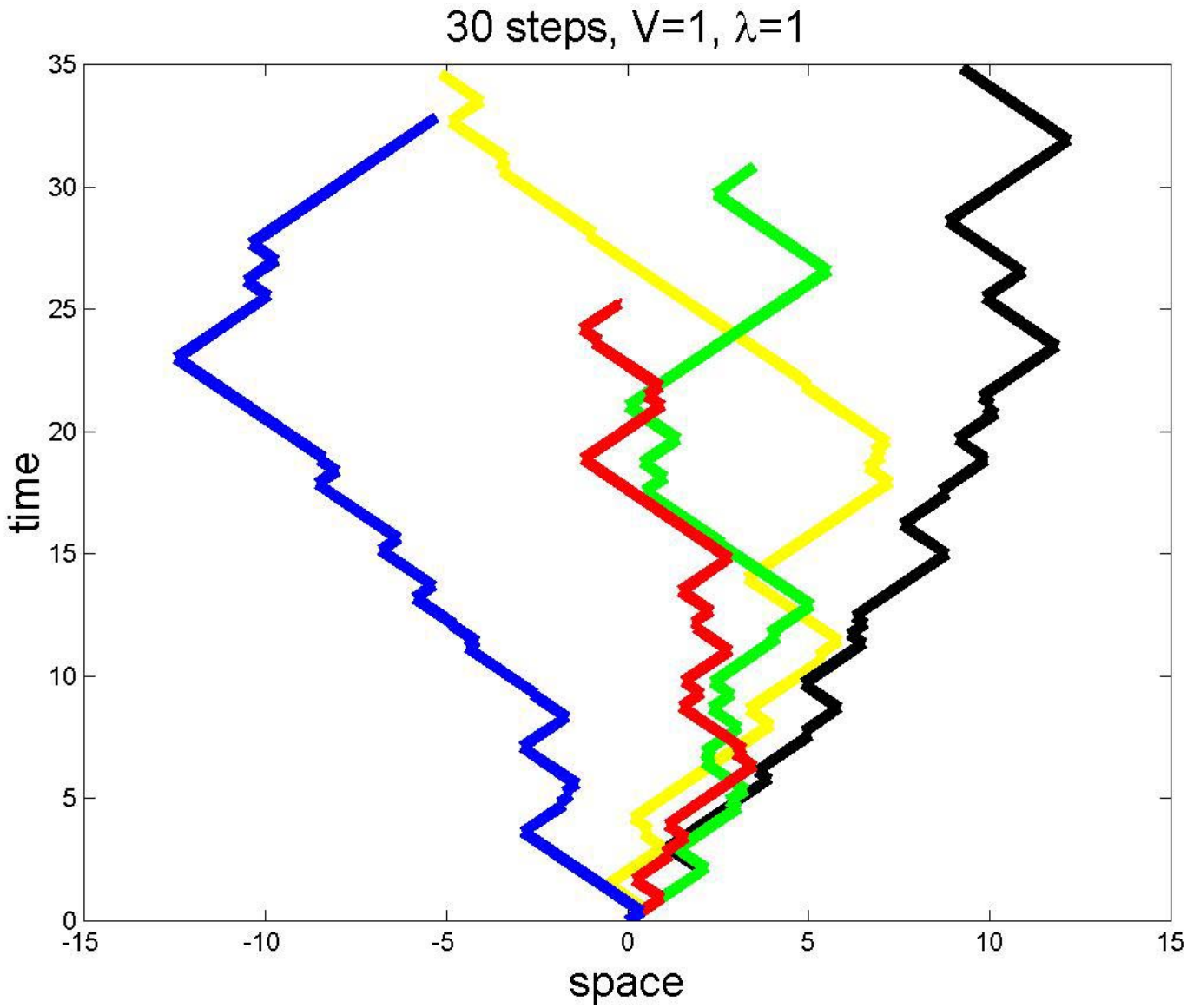
Inversion method



Simulation

```
λ =1; t=[0];
x=[0]; V=1; STEPS=30
for j=1:5
   for i=1:STEPS;
        T=-log(1-rand(1))/λ;
        N=length(t);
        t=[t;t(N)+T];
        x=[x;x(N)+V*T];
        V=-V;
    end; plot(x,t); hold on;
end;
```

Velocity Jump Process

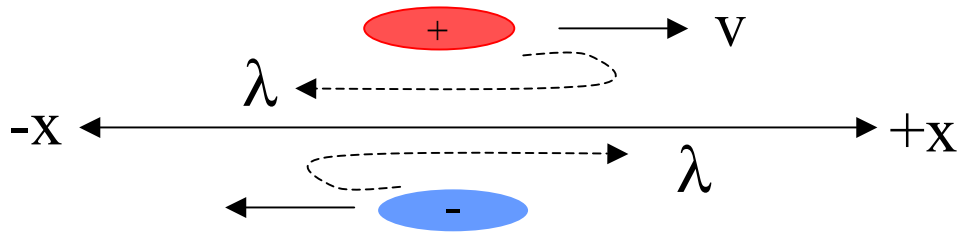


Velocity Jump Process (1)

instantaneous changes in velocity

$$\frac{\partial p^+}{\partial t} + v\frac{\partial p^+}{\partial x} = -\lambda p^+ + \lambda p^-$$

$$\frac{\partial p^-}{\partial t} - v\frac{\partial p^-}{\partial x} = -\lambda p^- + \lambda p^+$$



$$p(x,t) \equiv p^+(x,t) + p^-(x,t) \qquad \text{total probability}$$

$$j(x,t) \equiv v(p^+(x,t) - p^-(x,t)) \qquad \text{flux}$$

$$\frac{\partial^2 p}{\partial t^2} + 2\lambda\frac{\partial p}{\partial t} = v^2\frac{\partial^2 p}{\partial x^2}$$

$$p(x,0) = p_0(x), \quad \frac{\partial p(0,x)}{\partial t} = -\frac{\partial j(0,x)}{\partial x}$$

$$\left\langle x(t)^2 \right\rangle \equiv \int_{-\infty}^{\infty} x^2 p(x,t)dx = \frac{v^2}{\lambda}\left\{t - \frac{1}{2\lambda}(1 - e^{-2\lambda t})\right\}$$

H.G. Othmer, S.R. Dunbar, W. Alt, J.math.Biol, 26, 263-298, 1987

Velocity Jump Process (2)

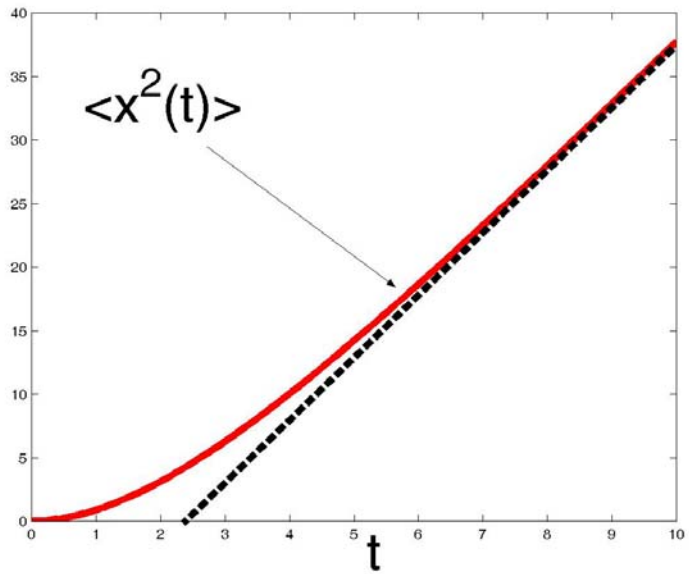
ballistic and diffusive regimes

$$\left\langle x(t)^2 \right\rangle = \begin{cases} t \ll 1 : \left\langle x^2(t) \right\rangle \sim v^2 t^2 \\ t \gg 1 : \left\langle x^2(t) \right\rangle \sim \dfrac{v^2 t}{\lambda} \end{cases}$$

$$D \equiv \frac{v^2}{2\lambda}$$

$T \equiv 2\lambda -$ "persistence time"

$v -$ velocity



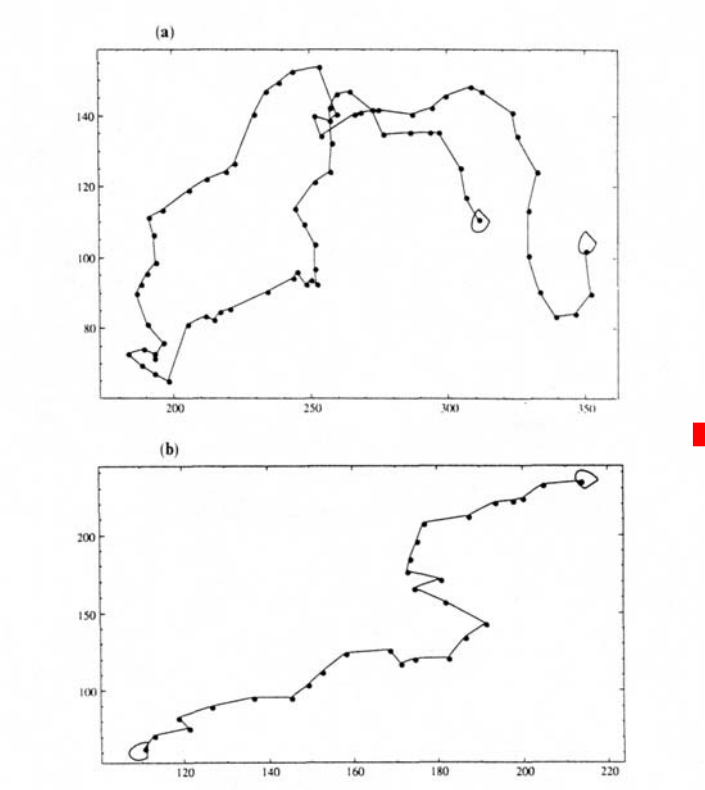
$j(x,t) = -D\dfrac{\partial p(x,t)}{\partial x}$ only when $\lambda \to \infty$

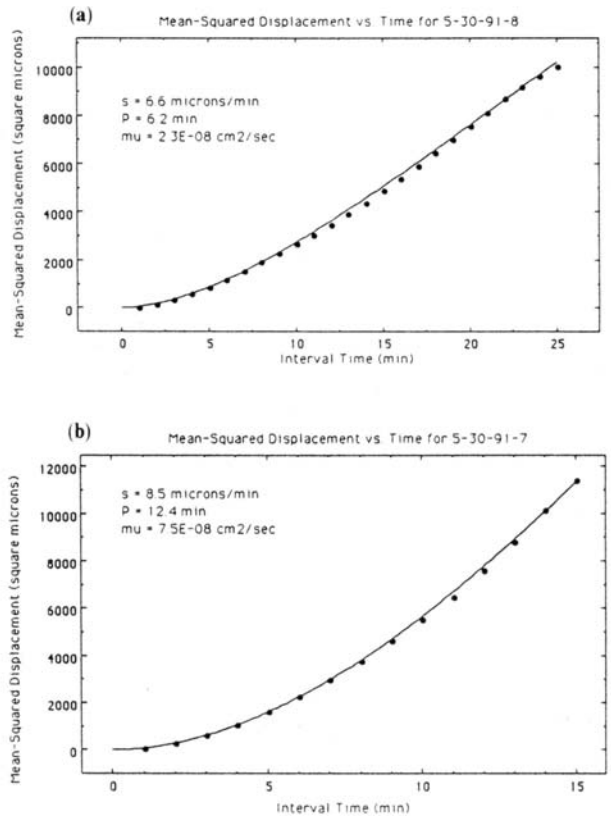
expression for flux has memory:

$$j(x,t) = e^{-2\lambda t} j(x,0) - v^2 \int_0^t e^{-2\lambda(t-\tau)} \frac{\partial p(x,\tau)}{\partial x} d\tau$$

H.G. Othmer, S.R. Dunbar, W. Alt, J.math.Biol, 26, 263-298, 1987

Velocity Jump Process (3) fitting data

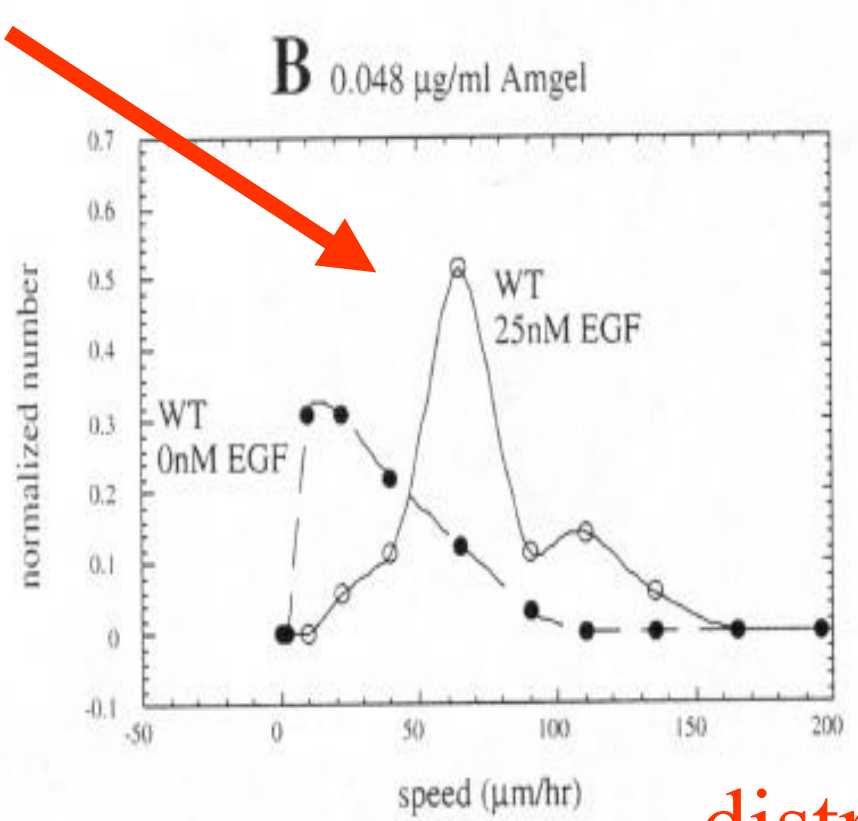


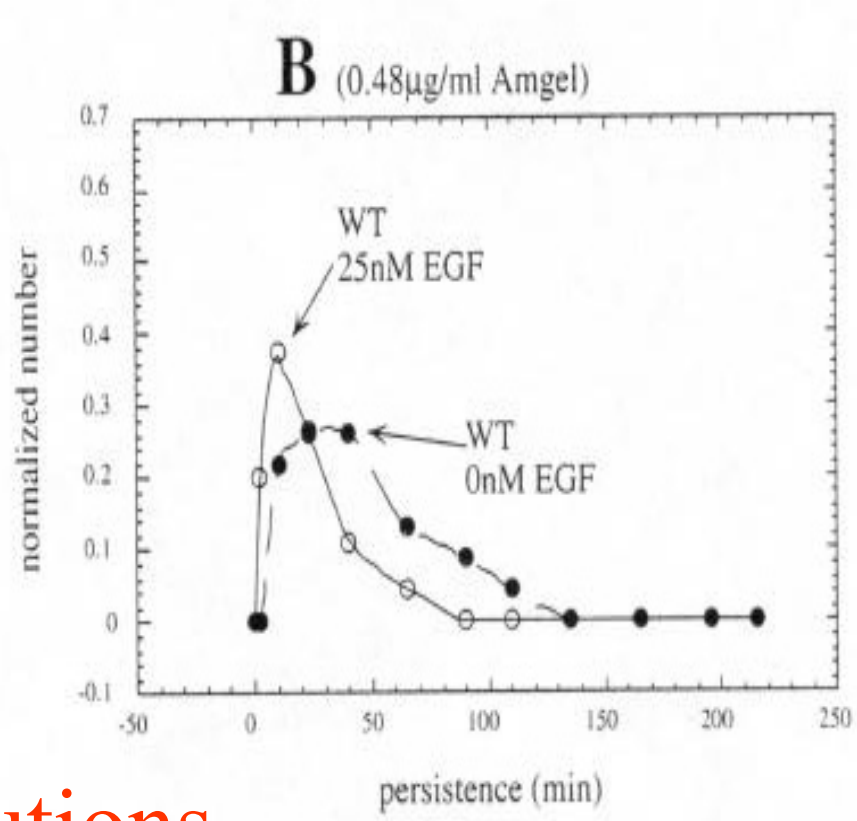


1. Microscopic parameters can be extracted from data
2. Next step: expressions for macroscopic fluxes

BE Farrell et al, Cell Motil Cytoskeleton, 16:279-293, 1990 - example
RB Dickinson, RT Tranquillo, AICHE J, 39 (12): 1995, 1993 - estimation algorithms

Example:
Growth Factor-Mediated Cell Motility





distributions

MF Ware, A Wells, DA Lauffenburger, J.Cell Science, 111, 2423-2432, 1998

Cancer Lett 1997 Oct 14;118(2):173-80

Locomotory phenotypes of human tumor cell lines and T lymphocytes in a three-dimensional collagen lattice.

Niggemann B, Maaser K, Lu H, Kroczek R, Zanker KS, Friedl P.

Active cellular locomotion is a feature of such diverse cell types as lymphocytes and cancer cells. **The locomotory phenotype of a cell should ultimately reflect the biochemical basis of different migratory strategies.** We investigated the locomotory behavior of five epithelial cell lines and one non-epithelial human cell-line as well as human CD4+ T lymphocytes in a three-dimensional collagen type I matrix using time-lapse video microscopy and computer assisted cell-tracking.

Migration velocity was up to 70 times lower in tumor cells (0.1-0.3 microm/min) as compared to T lymphocytes (7-7.5 microm/min), whereas the percentage of spontaneously active cells was up to twice as high in tumor cells (80-90%) in comparison to T lymphocytes (54%). Persistence, i.e. the degree of roaming, varied appreciably between the different cell types.

In conclusion, velocity and persistence may describe distinct migration strategies in different cell types.

More Complex Models

1. **Higher dimensions: turning operators, anisotropy, etc**
   - Dickinson RB.A generalized transport model for biased cell migration in an anisotropic environment. J Math Biol. 2000 Feb;40(2):97-135.
   - Othmer HG, Dunbar SR, Alt W. Models of dispersal in biological systems. J Math Biol. 1988;26(3):263-98.
2. **Finite tumble time**
   - Schnitzer MJ.Theory of continuum random walks and application to chemotaxis. Phys Rev E, 1993 Oct;48(4):2553-2568.
3. **Internal state random walks**
   - Grunbaum D Advection-diffusion equations for internal state-mediated random walks SIAM J APPL MATH 61 (1): 43-73 JUL 19 2000

From Microscopic Parameters to Macroscopic Balances

(Expression for the Chemotactic Flux)

Macroscopic Flux (1)

$$\frac{\partial n^+}{\partial t} + \frac{\partial}{\partial x}(vn^+) = \lambda^- n^- - \lambda^+ n^+$$

$$\frac{\partial n^-}{\partial t} - \frac{\partial}{\partial x}(vn^-) = \lambda^+ n^+ - \lambda^- n^-$$

total cell density: $n \equiv n^+ + n^-$

flux: $j \equiv v(n^+ - n^-)$

steady state :

$$j_{eq} = \frac{-v^2 \frac{\partial n}{\partial x} - nv\frac{\partial v}{\partial x} - vn(\lambda^+ - \lambda^-)}{(\lambda^- + \lambda^+)}$$

Macroscopic Flux (2)

$T_p \equiv [\lambda^- + \lambda^+]^{-1}$ persistence time

$\mu \equiv T_p v^2$ random motility coefficient

$V_c \equiv T_p v(\lambda^- - \lambda^+)$ chemotactic velocity

$$j_{eq} = -\mu \frac{\partial n}{\partial x} + V_c n - T_p v n \frac{\partial v}{\partial x}$$

in phenomenological models

$$j_{eq} = -\mu \frac{\partial n}{\partial x} + \underline{\alpha} n$$

Three contributions to flux:

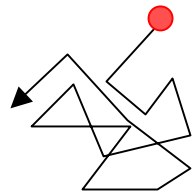
1. random motility
2. chemotaxis (right- and left- moving cells reverse differently)
3. chemokinesis (gradient in cell velocity)

To couple to external concentration field, combine with the experimentally determined dependencies of $\boldsymbol{\mu}$ *and* $\boldsymbol{T_p}$

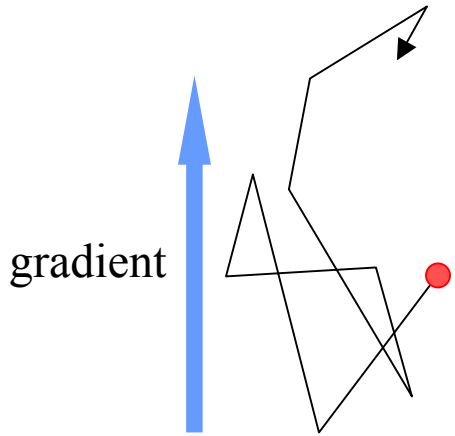
Flux in a 1D Gradient (1)

Motivated by Berg & Brown 1972 Experiments

- runs & tumbles
- tumble duration is zero
- use velocity jump process in 1D
- motion in a gradient



random motility



chemotaxis

$$T_p = (\lambda^- + \lambda^+)^{-1}$$

$$\lambda^{+/-} = p_T^{+/-}(1-\psi)/2$$

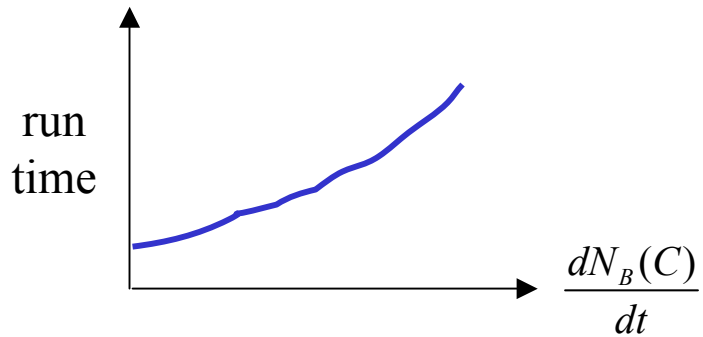
p_T: is the tumbling probability

ψ: "directional persistence"

probability of reversing after tumbling

receptor-mediated mechanism:

N_B – # of occuppied receptors



Flux in a 1D Gradient (2)

$$\tau = \tau_0 e^{\sigma \frac{dN_b}{dt}}$$

relate to the frequency of tumbles

$$p_T^{+/-} = 1/\tau^{+/-} = p_0 e^{-\sigma \frac{dN_B}{dt}}$$

time derivative

seen by the "bacterium"

$$\frac{dN_B}{dt} = \frac{\partial N_B}{\partial t} \pm v \frac{\partial N_B}{\partial x}$$

$$\lambda^+ + \lambda^- = (1-\psi)\cosh(\sigma v \frac{\partial N_b}{\partial x})$$

$$\lambda^+ - \lambda^- = p_0(1-\psi)\sinh(\sigma v \frac{\partial N_b}{\partial x})$$

$$\mu = \frac{v^2}{p_0(1-\psi)} \sec h(\sigma v \frac{\partial N_b}{\partial x})$$

$$V_c = v \tanh(\sigma v \frac{\partial N_b}{\partial x})$$

Flux in a 1D Gradient (3)

Simple Ligand/receptor Equilibrium

$$N_B = \frac{N_{total} c}{K_D + c} \Rightarrow \frac{dN_B}{dc} = \frac{N_T K_d}{(K_d + c)^2}$$

$$\mu = \frac{v^2}{p_0(1-\psi)}[\cosh(\sigma v \frac{\partial c}{\partial x}\frac{dN_B}{dc})]^{-1}$$

$$V_c = v \tanh(\sigma v \frac{\partial c}{\partial x}\frac{dN_B}{dc})$$

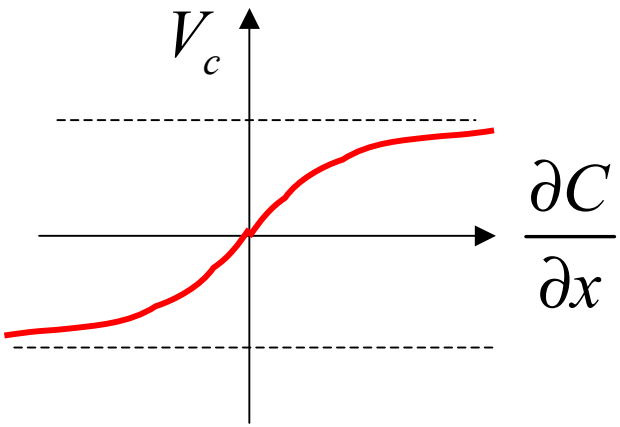
chemotactic coefficient, χ

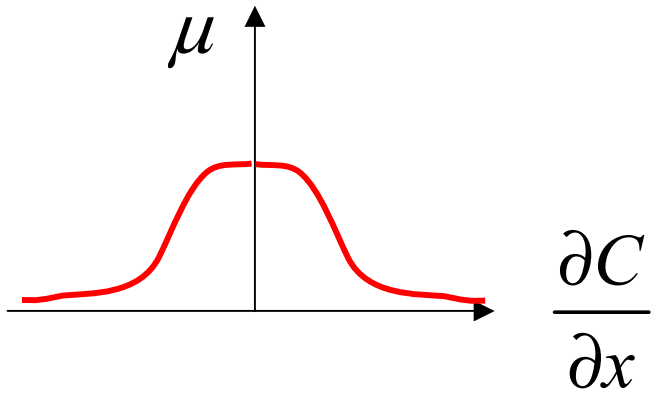
small gradients:

$$\mu = \frac{v^2}{p_0(1-\psi)}, \qquad V_c = \sigma v^2 \frac{dN_B}{dc}\frac{\partial c}{\partial x}$$

If the model is correct: macroscopic flux can be estimated from data on binding and microscopic parameters for cell migration

Flux in a 1D Gradient (4): Analysis





1. Random motility coefficient increases with temporal gradient

2. Random motility coefficient is a decreasing function of spatial gradient: at large gradients all cells swim in one direction

3. Chemotactic velocity has a limiting value: the population can not move faster than the maximal cell speed

"Chemotactic Wave Paradox"

Observation

aggregation to the source of chemical wave

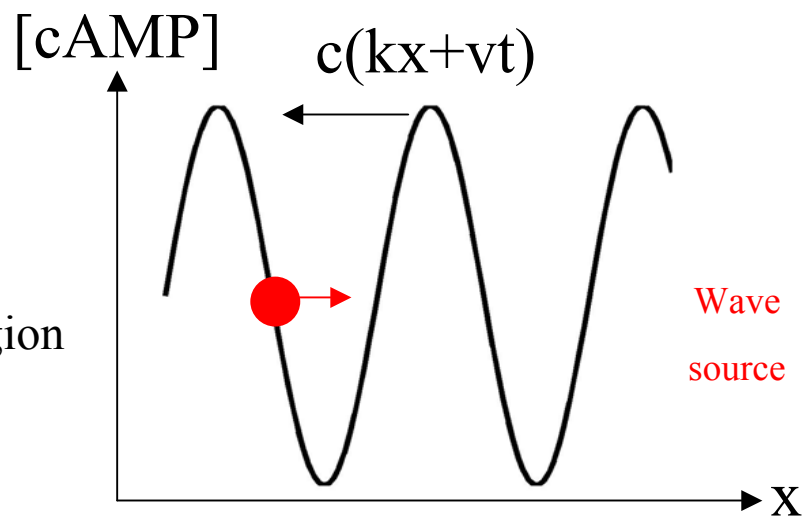
pulse of cAMP is nearly symmetric

Devreotes & Tomchik, *Science* 212, 443-6, 1981

Simple-model:

symmetric chemotactic velocity

no net directed motion



Worse: cells stay longer in the negative gradient region

Prediction: cells move away from the wave source

What is the problem?

Experiment: Cells move only in the wave front and not in the back => chemotactic response can not be determined by the concentration gradient alone

$$\chi = \chi(\alpha)$$

chemotactic sensitivity

Model: Soll, Wessels, Sylwester, 1993

Translocation phase:
Rapid & persistent translocation; suppressed lateral pseudopods formation; elongate shape

Peak of the wave:
suppression of pseudopod formation and cellular translocation; freeze in cell morphology

Decision phase:
high frequency of random pseudopod formation; nonpolar cell morphology; no net translocation

Back of the wave:
increased frequency of random pseudopod formation; loss of elongate cell morphology; little net translocation