Outline

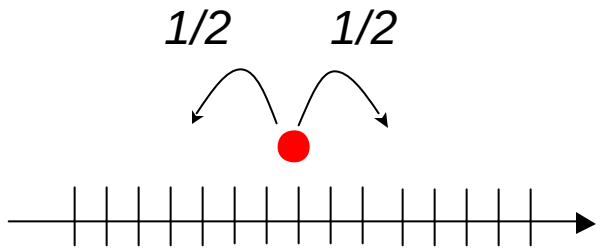
1. Position jump process
2. Velocity jump process
3. Macroscopic flux – dispersion, chemotaxis, chemokinesis
4. Example – biased random walk
5. Chemotactic wave paradox
6. Chemotaxis-driven linear instability

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: $$P_N(m) \approx \sqrt{\frac{2}{p\,N}} e^{-\frac{m^2}{2N}}$$

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

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

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

Position Jump Process (2)

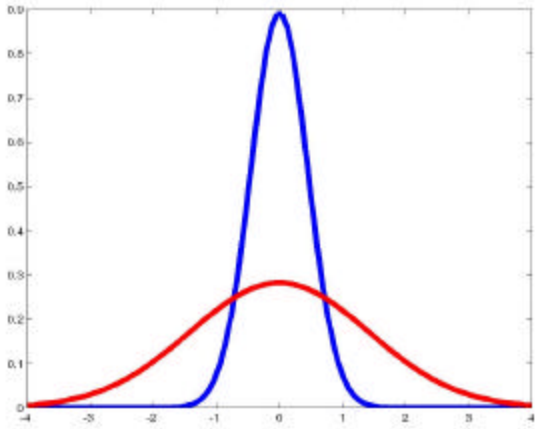
step size: l frequency of jumps: l

Continuous space and time:

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

$$p(x,t) > 0 \text{ for all } t$$

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



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

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

Approximation for large times

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

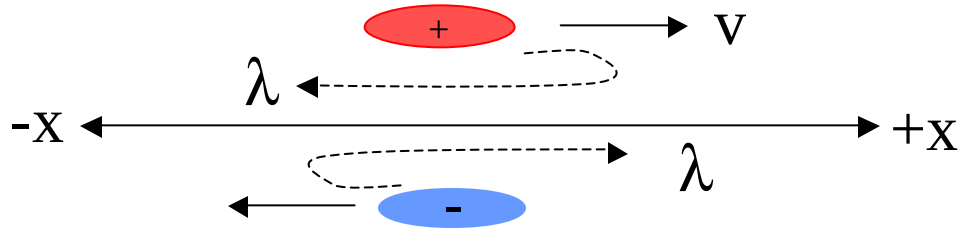
earlier times: correlations in motion -> cell migration is like that

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

Velocity Jump Process (1)

instantaneous changes in velocity

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



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

$$\frac{\partial^2 p}{\partial t^2} + 2l\frac{\partial p}{\partial t} = v^2\frac{\partial^2 p}{\partial x^2}$$
$$p(x,0) = p_0(x), \quad \frac{\partial p(0,x)}{\partial t} = -\frac{\partial j(0,x)}{\partial x}$$

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

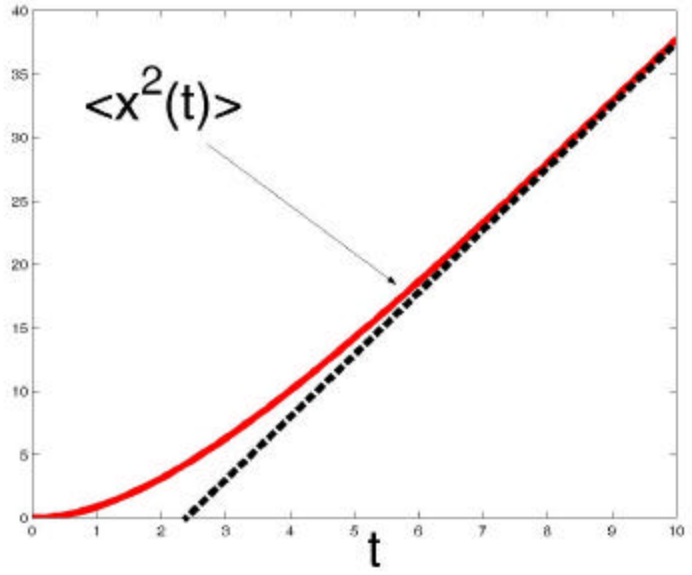
H.G. Othmer, S.R. Dunbar, W. Alt, J.math.Biol, 26, 263-298, 1987

Velocity Jump Process (2)

ballistic and diffusive regimes

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

$$D \equiv \frac{n^2}{2l}$$



$T \equiv 2l$ – "persistence time"

v – velocity

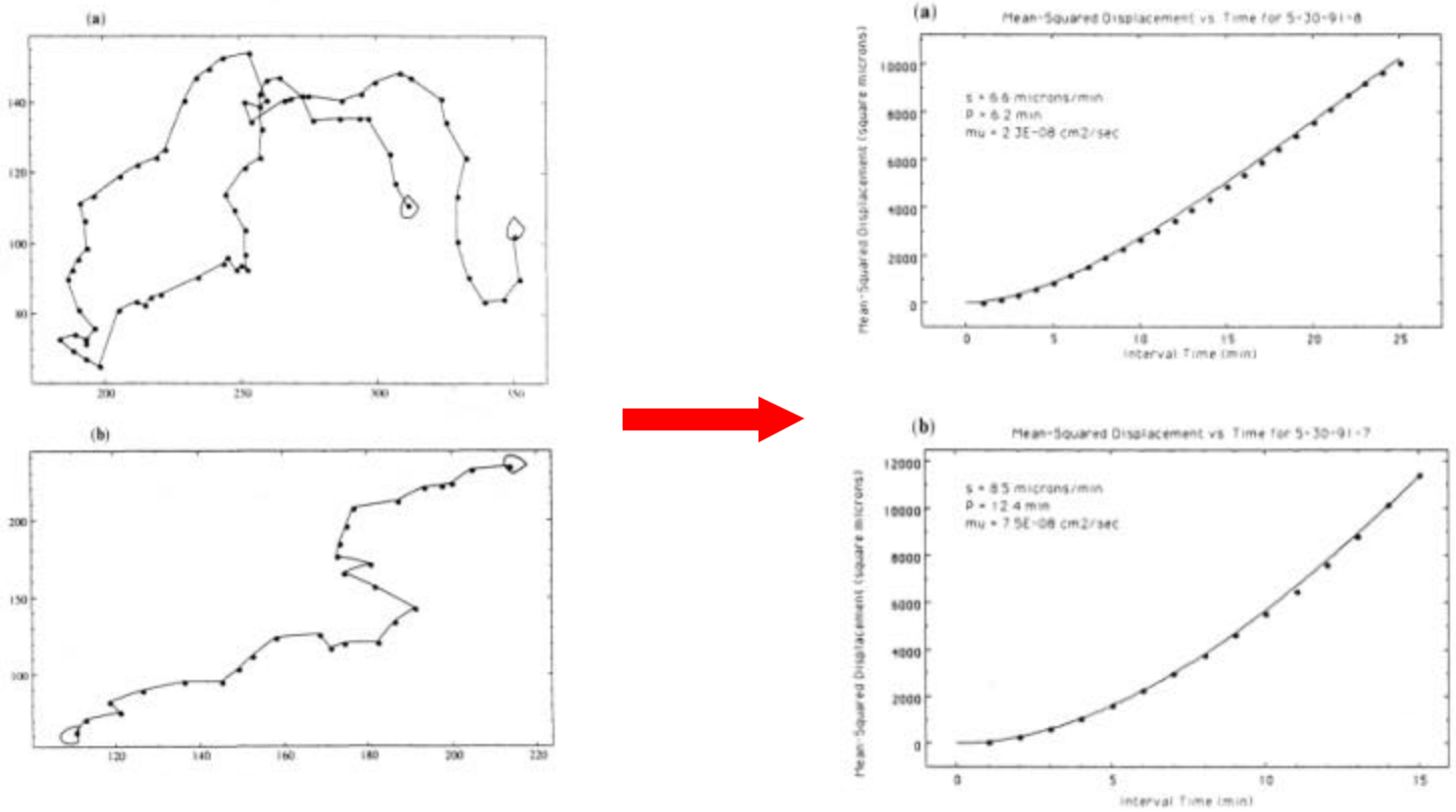
$$j(x,t) = -D\frac{\partial p(x,t)}{\partial x} \quad \text{only when } l \to \infty$$

expression for flux has memory:

$$j(x,t) = e^{-2lt} j(x,0) - v^2 \int_0^t e^{-2l(t-t)} \frac{\partial p(x,t)}{\partial x} dt$$

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

Macroscopic Flux (1)

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

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

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

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

steady state for the flux ($t \gg (l^+ + l^-)^{-1}$)

$$j_{eq} = \frac{-v^2 \frac{\partial n}{\partial x} - nv \frac{\partial v}{\partial x} - vn(l^+ - l^-)}{(l^- + l^+) - v^{-1} \frac{\partial v}{\partial t}}$$

Macroscopic Flux (2)

$$T_p \equiv [(l^- + l^+) - v^{-1}\frac{\partial v}{\partial t}]^{-1} \quad \text{persistence time}$$

$$m \equiv T_p v^2 \quad \text{random motility coefficient}$$

$$V_c \equiv T_p v(l^- - l^+) \quad \text{chemotactic velocity}$$

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

in phenomenological models

$$j_{eq} = -m\frac{\partial n}{\partial x} + \underline{a}n$$

Three contributions to flux:

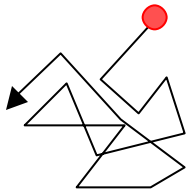
1. random motility
2. chemotaxis (right- and left- moving cells reverse differently)
3. chemokinesis (gradient in cell velocity)

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

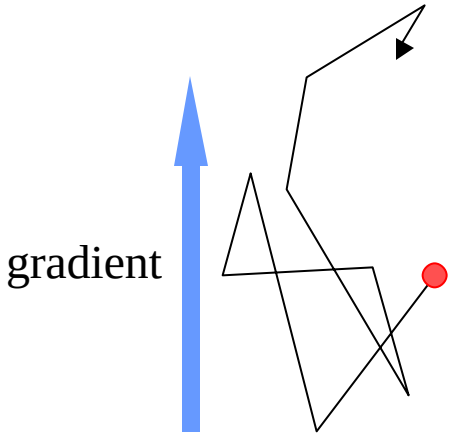
Flux in a 1D Gradient (1)

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

$$T_p = (l^- + l^+)^{-1}$$

$$l^{+/-} = p_T^{+/-}(1-y)/2$$

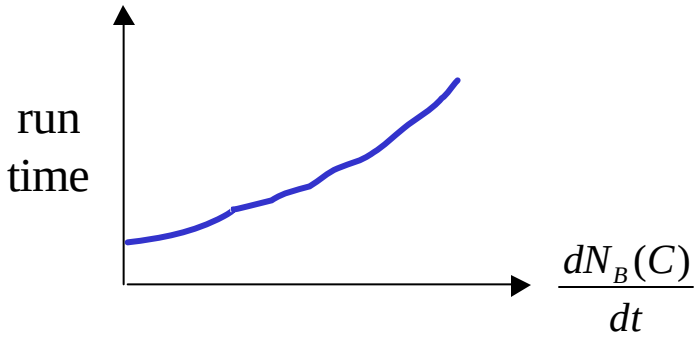
p_T: is the tumbling probability

y : "directional persistence"

probability of reversing after tumbling

receptor-mediated mechanism:

N_B – # of occuppied receptors



Flux in a 1D Gradient (2)

$$t = t_0 e^{s \frac{dN_b}{dt}}$$

relate to the frequency of tumbles

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

time derivative seen by the "bacterium"

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

$$l^+ + l^- = (1-y) e^{-s \frac{\partial N_b}{\partial t}} \cosh(s\, v \frac{\partial N_b}{\partial x})$$

$$l^+ - l^- = p_0 (1-y) e^{-s \frac{\partial N_b}{\partial t}} \sinh(s\, v \frac{\partial N_b}{\partial x})$$

$$m = \frac{v^2}{p_0 (1-y)} e^{s \frac{\partial N_b}{\partial t}} \sec h(s\, v \frac{\partial N_b}{\partial x})$$

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

Flux in a 1D Gradient (3)

Simple Ligand/receptor Equilibrium

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

$$m = \frac{v^2}{p_0(1-y)} e^{s \frac{\partial c}{\partial t} \frac{dN_B}{dc}} [\cosh(s\, v \frac{\partial c}{\partial x} \frac{dN_B}{dc})]^{-1}$$

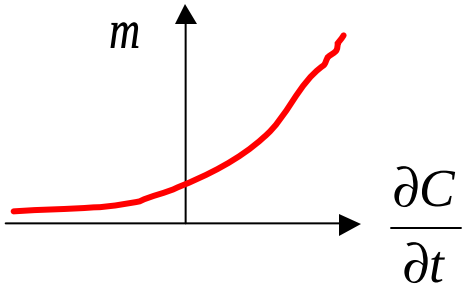
$$V_c = v \tanh(s\, v \frac{\partial c}{\partial x} \frac{dN_B}{dc})$$

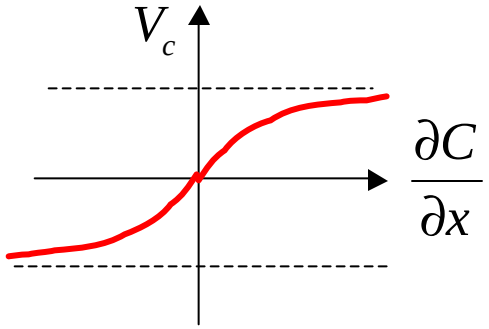
chemotactic coefficient, χ

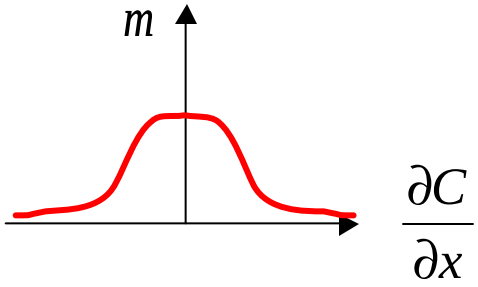
small gradients: $m = \frac{v^2}{p_0(1-y)} [1 + s \frac{\partial c}{\partial t} \frac{dN_B}{dc}]$, $V_c = \boxed{s\, v^2 \frac{dN_B}{dc}} \frac{\partial c}{\partial x}$

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





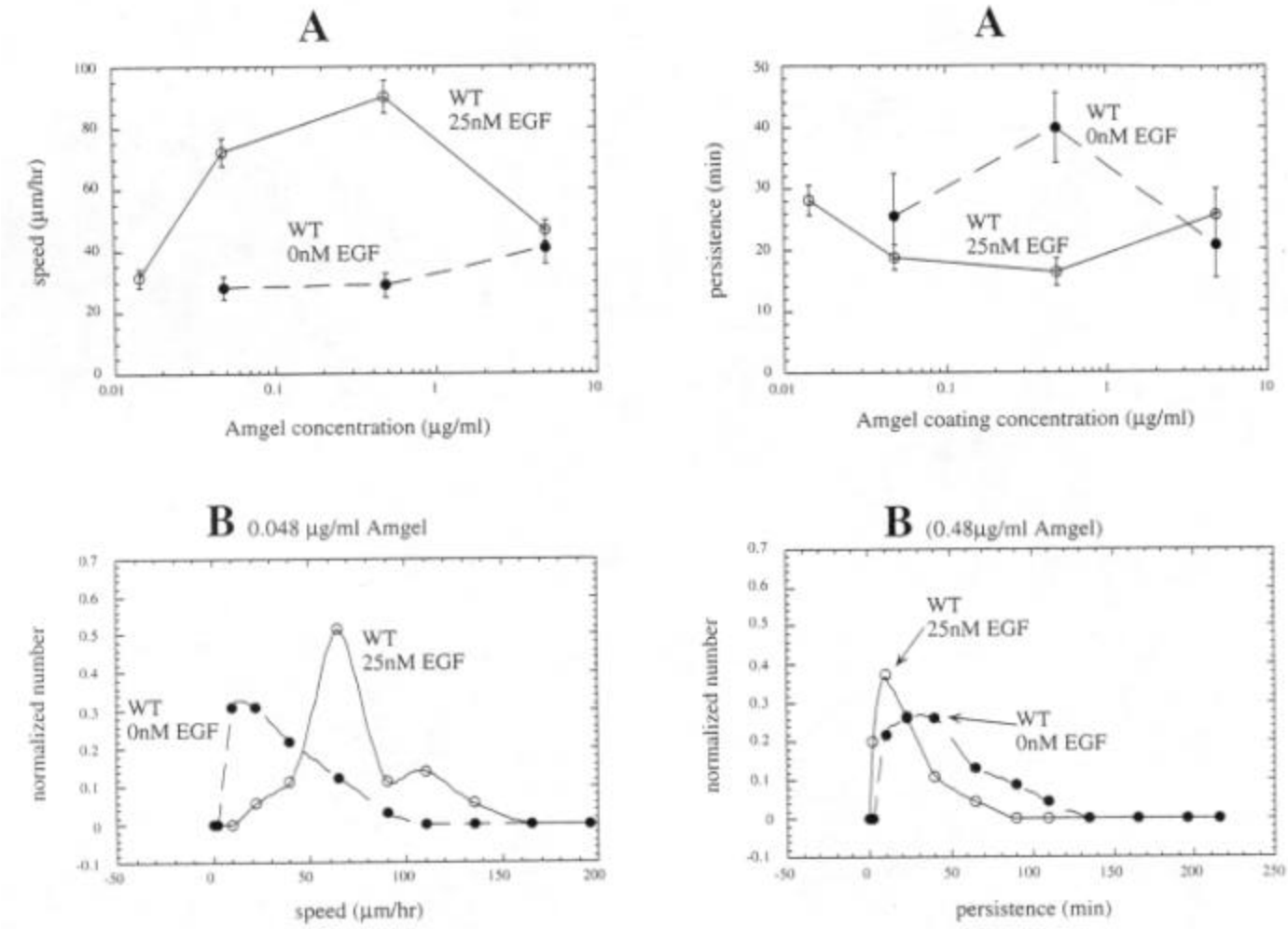


1. Random motility coefficient increases with temporal gradient

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

Example: Growth Factor Mediated Cell Motility



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

“Chemotactic Wave Paradox”

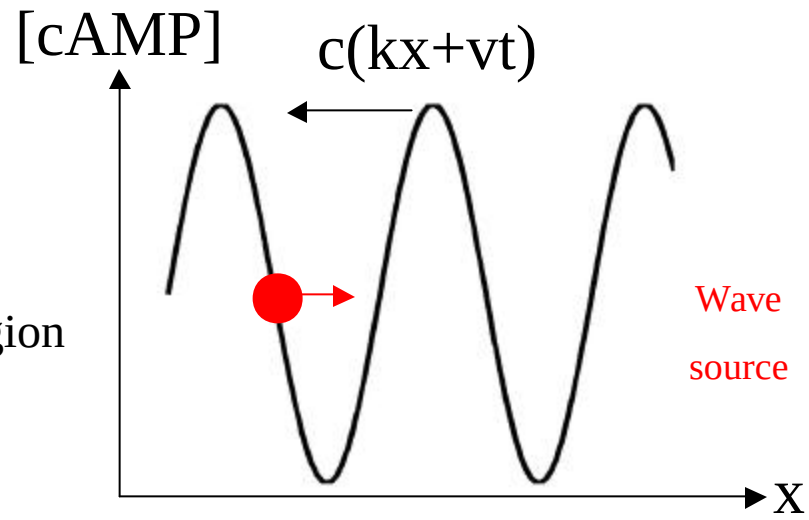
Observation

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

$$c = c(a)$$

chemotactic sensitivity

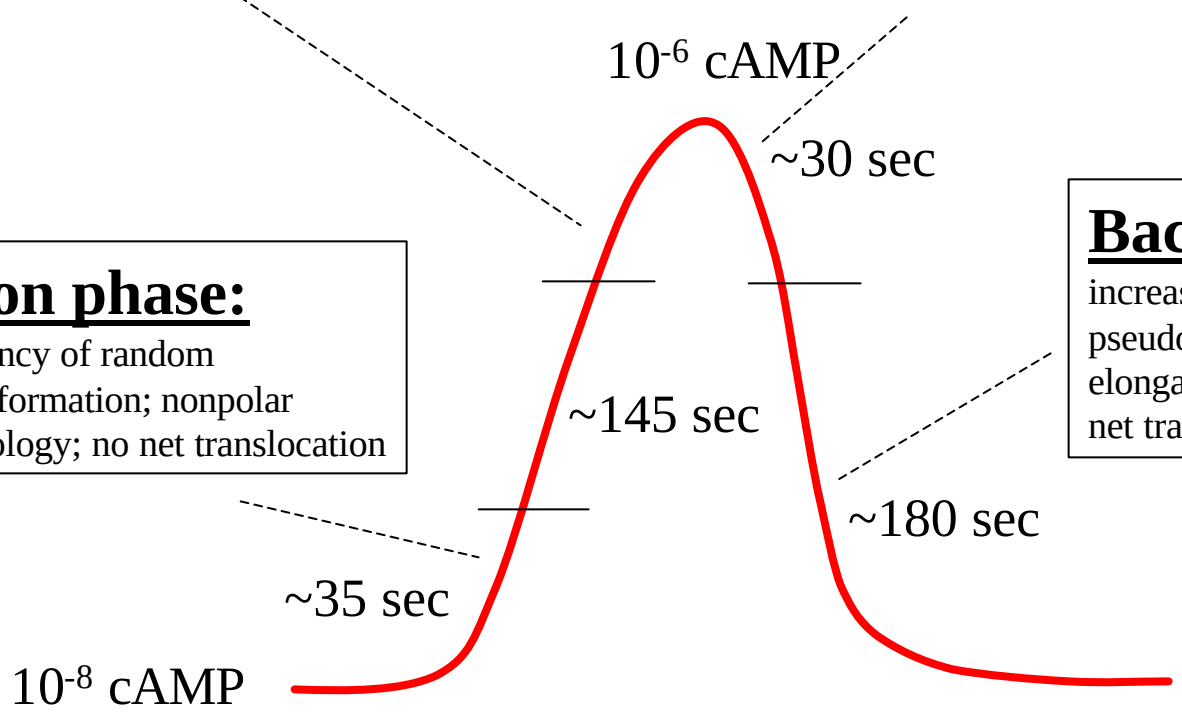
Model: Soll, Wessels, Sylwester, 1993

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



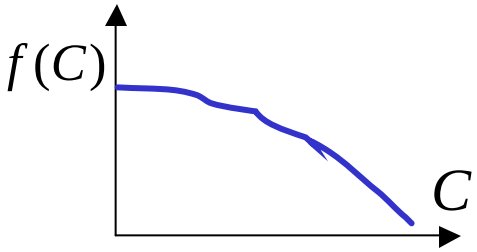
Chemotactic Sensitivity Is Dynamic

$$\frac{dx_{cell}}{dt} = c(C)\frac{dC(kx+vt)}{dx}$$

$$t\frac{dc}{dt} = f(C) - c$$

$$t/T \sim 1$$

Wave period



- Cells are sensitive in the wave front
- Refractory in the wave back
- Recovered by the next pulse

References:

1. T. Hofer et. al, Appl. Math. Lett. (7), 1-5, 1994
2. R.E. Goldstein, Phys. Rev. Lett.(77), 775-778, 1996

Chemotaxis-driven Linear Instability (1)

Keller & Segel, 1971: cells migrate in a self-imposed field of chemoattractant

$$\frac{\partial n}{\partial t} = -\frac{\partial}{\partial x}\left(-m\frac{\partial n}{\partial x} + cn\frac{\partial c}{\partial x}\right), \qquad \left.\frac{\partial n}{\partial x}\right|_{0,L} = 0$$

$$\frac{\partial c}{\partial t} = -\frac{\partial}{\partial x}\left(-D\frac{\partial c}{\partial x}\right) + fn - kc, \qquad \left.\frac{\partial c}{\partial t}\right|_{0,L} = 0$$

$$s.s.: \bar{n} = N/L, \bar{c} = \bar{n}f/k$$

$$n(x,t) = \bar{n} + n'(x,t)$$

$$c(x,t) = \bar{c} + c'(x,t)$$

Linearized equations:

$$\frac{\partial n'}{\partial t} = m\frac{\partial^2 n'}{\partial x^2} - c\bar{n}\frac{\partial^2 c'}{\partial x^2}$$

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c'}{\partial x^2} + fn' - kc'$$

Solution:

$$\begin{pmatrix} n'(x,t) \\ n'(x,t) \end{pmatrix} = \sum_{i=1}^{\infty} \begin{pmatrix} A_i \\ B_i \end{pmatrix} \cos(q_i x) \exp(l_i t)$$

why $i \neq 0$?

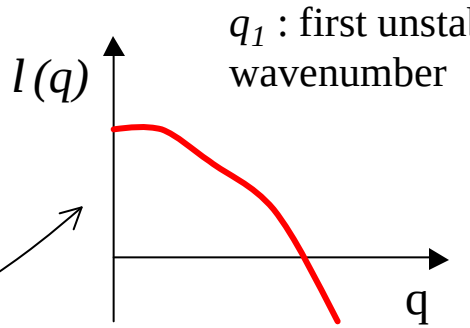
Linear instability of uniform state: $l_i > 0$

Keller-Segel (2)

For every wavenumber q : $\begin{bmatrix} l + mq^2 & -c\bar{n}q^2 \\ -f & l + Dq^2 + k \end{bmatrix} \begin{pmatrix} A \\ B \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$

Nontrivial solutions $(A \neq 0, B \neq 0)$ when $\det(M) \neq 0$

$l_{1,2}$ satisfy $(l + mq^2)(l + Dq^2 + k) - c\bar{n}q^2 f = 0$



q_1 : first unstable wavenumber

Condition for instabilit y : $m(Dq^2 + k) < c\bar{n}f$

Using the B.C. : $m\left[\frac{D(pi)^2}{L^2} + k\right] < c\bar{n}f$

Interpretation :

1) small m, D, k, i

2) large L

3) large $c, \bar{n}, f$

This is just linear analysis ...

Keller-Segel (3)

- Instability is promoted by

  low random motility & chemoattractant degradation
  high chemotactic sensitivity, secretion rate, cell density

- Problems

  no saturating effect: $\lim_{t\to\infty} n(x,t) = d(x)$
  instability does not appear to involve linear mechanism
  mechanism is more complicated

References:
1. E.F. Keller and L.A. Segel, J. theor. Biol. (26), 399-415, 1970
2. T. Hillen and K. Painter, Adv. Appl. Math. (26), 280-315, 2001