III B. Bacterial chemotaxis

1. Biological background

Many bacterial species move around in aqueous environment by swimming using flagella.

\[ E. \ coli: \]
\[ \text{Swim speed } v = 25 \mu \text{m/s} = 10 \text{ cm/h} \]

\[ \text{Nutrient gradient } \frac{\Delta n}{\Delta x} = g \]
\[ \Rightarrow v - g = \frac{\Delta n}{\Delta t} = \text{nutrient gain} \]

Nutrient consumption \( \frac{dn}{dt} = r \cdot S / Y \)

\[ \Rightarrow \text{movement can sustain growth of population } \]
\[ v - g = r \cdot S / Y \]

Gradient required: \( g = \frac{r}{v} \cdot S \cdot Y \) \( \frac{S}{10 \text{ cm} \cdot \text{OD}} \)
\(~5 \text{ mM} / 10 \text{ cm} \cdot \text{OD} = 50 \text{ nM} / \mu \text{m} \cdot \text{OD} \)

Q: Can bacteria detect gradient \(~10 \text{ nM} / \mu \text{m}~

\[ \text{Let } V_1 = V_2 = \frac{1}{10} \mu \text{m}^3 \]

Since \( 1 \text{ nM} = 1 \text{ molecule/} \mu \text{m}^3 \)
\[ N_1 - N_2 = 1 \text{ molecule}! \]
requires a detection system with \( \Delta N \ll 1 \)

\( \rightarrow \) can be done by accumulating over time

\[ \text{flux of molecules impinging in value of radius } a: \quad J = 4\pi a D \bar{n} \]

\( \# \) molecule detected in time \( T \):

\[ \bar{N} = J \cdot T \]

\[ \rightarrow \bar{N} = 4\pi a D \bar{n} \cdot T \]

more careful calc: \( \) (Berg + Purcell, 1977)

\[ \bar{N} = \pi a D (1 - \bar{p}) \bar{n} T \]

receptor occup.,

\[ D = 600 \mu m^2/s \text{ (glucose)} \]

\( a = 0.1 \mu m \)

\[ \text{detection limit: } \Delta \bar{n} = \Delta N \cdot \bar{n} \cdot T = \frac{1}{\sqrt{\bar{n} \cdot T}} \]

\[ \Delta \bar{n} \ll 10 \text{nM} \Rightarrow \bar{n} \ll (10 \text{nM})^2 \cdot (100 \frac{\mu m^2}{s} \cdot T) \]

\[ = 10 \mu M \cdot T \]

\( \text{Want to detect gradient when nutrient level high} \)

\[ \bar{n} = 1 \text{mM} \text{ requires } T \sim 100 s \]

\( \text{problem: brownian motion of cell} \)
Rotational diffusivity of object of size $R$

\[ \langle (\Delta \theta)^2 \rangle = 2 D_\theta \cdot \tau \]
\[ D_\theta = \frac{k_B T}{8\pi \eta R^3} \]

$\eta$: Kinetic viscosity $= 10^{-2}$ dyn-sec/cm$^2$ for water

for $R=1$ nm, $D_\theta = 0.16/\tau$.

$\Rightarrow \alpha \theta = 3^\circ$ for measurement time $\tau = 15$.

Bacterial strategy:

Measure difference in time rather than space.

- Take $15\text{sec}$ to measure local conc.
  (knows general direction of motion)

- Move according to temporal change in measured conc.
  - Conc increases: $p > 0.5$ to continue in same direction
  - Conc decrease: $p < 0.5$ to "tumble" and move in random new direction

$\Rightarrow$ net result "biased random walk"
Comments:
* entire cell used as detector: $a = 0.1 \mu m \rightarrow 1 \mu m$
  in $T = 1 sec$, $\Delta n = 10 nm$ for $\bar{n} = 100 \mu M$.
* must have memory element to compare CRC in time
  $\rightarrow$ adaptation dynamics via covalent modification of the chemoreceptors (methylation/demethylation)

* adaptation system also provides "proportional sensing": response $\propto \frac{\Delta n}{\bar{n}}$
2. Population dynamics
Chemotactic bacteria in soft agar (rich medium)

=> Linear propagation of "swarm ring" (Adler, 1966)

At the population level, biased random walk is described by diffusion equation with drift

\[ \frac{\partial p}{\partial t} = D \nabla^2 p - \nabla \cdot (\bar{v} p) , \quad \bar{v} = \text{drift velocity} \]

if \( \bar{v} \) is constant, then \( \bar{p}(\vec{x},t) = \hat{p}(\vec{x} - \bar{v} t, t) \)

follows the diffusion eqn: \( \frac{\partial}{\partial t} \hat{p} = D \nabla^2 \hat{p} \)

Note RTHS is in the form \( -\nabla \cdot \bar{J} \),

where \( \bar{J} = -D \hat{v} p + \bar{v} p \) is the cell flux.

\( \hat{p} \) conserved since no cell growth/death
a) Keller-Segel Model (KS, 1971)

propose \( \dot{v} = x \frac{\nabla a}{a} \) → perfect proportional sensing; Weber’s law.

\( a = \) attractant conc.
\( x = \) chemotactic coefficient.

Then in 1D: \( \partial_t p = D \partial_x^2 p - x \partial_x (p \partial_x a - a) \)

Note 1: \( \partial_t x(t, \mathbf{x}) \) still conserved (no growth)
Note 2: \( x \) has same dimension as \( D \).

Supplement with the effect of cells on \( a \):

\( \partial_t a = D_a \partial_x^2 a - k(a) p \)

\( k(a) \): attractant uptake rate (KS set to const)
\( D_a \): attractant diff coeff (KS set to zero)

\( \Rightarrow \) \begin{cases} \partial_t p = D \partial_x^2 p - x \partial_x (p \partial_x a - a) \\ \partial_t a = -k(p) \end{cases} \) Keller-Segel eqn

main idea:
- bacterial pop. create attractant gradient through their own consumption
- pop chase the receding att. gradient
Expect a traveling band of bacteria

**Init Cond:** $a(x,0)=a_0$

**b.c.** \( \frac{da}{dx} = 0 \quad \text{and} \quad \frac{dp}{dx} = 0 \)

\[ \begin{align*}
  a(x,0) &= a_0, \\
  p(x,0) &= p_0(x) & \text{init # cells}
\end{align*} \]

Look for \( p(x,t) = \tilde{p}(z), a(x,t) = \tilde{a}(z) \) with \( z = x - ct \)

\[ \begin{align*}
  -c\tilde{p}' &= D\tilde{p}'' - x(g\tilde{a}/a)' & (1) \\
  -c\tilde{a}' &= -kp & (2)
\end{align*} \]

\( c \) obtained from conservation of \( p \) (Note: Same with \( D\frac{da}{dx} \))

Integrate \( 2): \frac{c}{k}(a(x)-a(0)) = k \int_{-\infty}^{x} p(z) \, dz = k \int_{-\infty}^{\infty} \phi(p,0) \, dp \equiv N \)

\[ c = \frac{kN}{a_0} \]

**Geometric Interpretation:**

- In time \( T \), \( a(x) \) has receded by a distance \( l = c \cdot 2 \).
- The loss of \( da = a_0 \cdot l \) is given by the total uptake = \( k \cdot N \cdot 2 \)

\[ \Rightarrow a_0 \cdot l = kN \cdot 2, \quad a_0 c = kN/a_0 \]

\( \Rightarrow \) problem: KS soln cannot accommodate cell growth
b) Sol'n of K Segn: asymptotes
\[ \begin{cases} -c p' = D p'' - X(p a'/a)' & (1) \\ c a' = k p & (2) \end{cases} \]

look for \( p = p_1 e^{-\lambda z} \), \( a = a_0 - a_1 e^{-\lambda z} \) as \( z \to \infty \)

2: \( c X a_1 e^{-\lambda z} = k p_1 e^{-\lambda z} \) \( \Rightarrow \)
\[ a_1 = \frac{k p_1}{c X} \]

1: \( c X p_1 e^{-\lambda z} = D X^2 p_1 e^{-\lambda z} - X(p_1 e^{-\lambda z} a_1 e^{-\lambda z}) \)
\[ c \lambda = D \lambda^2 \]
\[ \Rightarrow \lambda = \frac{c}{X D} \]

\( \) for \( z \to -\infty \), look for \( a = a_1 e^{\lambda z} \), \( p = p_1 e^{\lambda z} \)

2: \( c X a_1 = k p_1 \)

1: \( -c X p_1 = D X^2 p_1 - X X p_1 \) \( \Rightarrow \)
\[ \lambda = \frac{c}{X D} \]

C) Full sol'n by Keller and Segel:

Integrate (1): \(-c p = D p'' - X p a'/a + c a'\) \( \Rightarrow \) (b.c.)
\[ \Rightarrow D \frac{p'}{p} = X \frac{a'}{a} - c \]

Integrate (3): \( D \ln p = X \ln a - c z + \text{const} \)
\[ p(z) = a^\frac{X}{c} e^{-c z / D} \]

\( \)
Insert (4) into (2) and integrate:

\[ \frac{d}{dz} \ln \frac{a}{a_0} = Q k \cdot \frac{x}{c^2} e^{-cz/D} \]

\[ a = \frac{a_0}{e^{-cz/D}} \int \frac{a^{x-1}}{1-x} \cdot \frac{k (x-D)}{c^2} e^{-cz/D} \, dz \]

\[ a(z) = a_0 \left[ 1 + e^{-cz/D} \right]^{-\frac{D}{x-D}} \]

Note: requires \( x > D \)

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Corresponding expression for $p(z)$

$$p(z) = A \frac{z}{XD} \left[ 1 + e^{-c^2 z/D} \right] e^{-c z/D}$$

$$= \frac{N c}{XD} \left[ 1 + e^{-c^2 z/D} \right] e^{-c z/D}$$

$$= \begin{cases} 
\frac{N c}{XD} e^{-c^2 z/D} & z \to \infty \\
\frac{N c}{XD} e^{c^2 z/D} & z \to -\infty 
\end{cases}$$

Max $p$ at $e^{-c^2 z/D} = \frac{X}{D}$

$$p_{\text{max}} = \frac{N c}{D} (X/D)^{1/2} = \frac{c^2 a}{k D} \left( \frac{X}{XD} \right)$$

$\frac{N}{2} = \frac{X}{XD}$

Drift speed:

$$v(z) = X \frac{a^1}{a} = \begin{cases} 
\frac{c X}{X D} e^{-c z/D} & z \to +\infty \\
\frac{c X}{X D} & z \to -\infty 
\end{cases}$$

$\text{larger than C, needed to counter back diffusion}$
3. Limit in proportional sensing

Note: constant $v$ for small $z$ (behind the pulse) arise from perfect proportional sensing

In reality, there is a Cme cutoff to adaptation

$$ v = X \frac{a'}{a + a^*} \mid a^* = 1 \mu M \text{ (Asp, E. coli)} $$

For $a \ll a^*$, $v \propto a' \to 0$ for $z \to -\infty$.

Let the position where $a(z) = a^*$ be $z^*$.

Then cells for $z \ll z^*$ are left behind, i.e., they are removed from the traveling band.

$\to$ Since total pop size $N$ determines wave speed $c$, expect the leakage to slow down propagation.

$\Rightarrow$ Quantitative effect of leakage on $c$?

Novick - Cohen + Segal (84): Systematic expansion in $D/X$

Here: heuristic analysis (to be expanded below)

Assume KS soln. to be unaffected for $a \geq a^*$

At $z = z^*$, $v = X \frac{a'}{a + a^*} = \frac{V_{KS}}{2}$.

$\Rightarrow$ Reduction in speed: $\Delta V = V_{KS} - v = \frac{V_{KS}}{2} = \frac{1}{2} \frac{Xc}{x-D}$.
$x^* = z^* + ct$ where $a(z^*) = a^*$
$v(z^*) = v^* < V_{ks}$

A cells remaining in the front: $N(t) = \int_{x^* + ct}^{\infty} dx P(x, t)$

- Loss rate due to leakage

$$\frac{dN}{dt} = \frac{d}{dt} \int_{x^* + ct}^{\infty} dx P(x, t)$$

$$= -c \cdot P(z^* + ct, t) + \int_{x^* + ct}^{\infty} dx \frac{\partial P}{\partial t}$$

- Compute 2nd term using KS eqn:

$$\frac{\partial P}{\partial t} = D \frac{\partial^2}{\partial x^2} P - \frac{\partial}{\partial x} (vP)$$

$$\int_{x^* + ct}^{\infty} dx \frac{\partial P}{\partial t} = D \frac{\partial P}{\partial x} \bigg|_{z^* + ct}^{\infty} - (vP) \bigg|_{z^* + ct}^{\infty}$$

$$= -D P'(z^* + ct, t) + v(z^* + ct, t) P(z^* + ct, t)$$

$$= -D P'(z^*) + (V_{ks} - \Delta v) P(z^*)$$

Since $-DP' + V_{ks} P = cP$

$$\Rightarrow \frac{dN}{dt} = -\Delta v P(z^*)$$
Using $p(z) = \frac{N_c}{x-D} e^{-c^2/x-D}$ (for $z^* \ll \frac{D}{x-D}$)

\[
\Delta V = \frac{1}{2} v_{ks}(z^*) = \frac{1}{2} \frac{c x}{x-D}.
\]

\[\Rightarrow \quad \frac{dN}{dt} = -\frac{xN}{2} \left( \frac{c}{x-D} \right)^2 e^{c^2/x-D}.\]

Note: $\Delta V = \frac{1}{2} v_{ks}$ form a simple approx. with step function effect on drift speed.

More generally, expect reduction to be

\[\Delta V = b v_{ks} = b x \frac{c}{x-D}, \quad \text{with } b < 1\]

(detailed calc showed $b = \frac{1}{2}$; see below)

⇒ Loss rate across boundary at $z = z^*$

\[\frac{dN}{dt} = -b x N \left( \frac{c}{x-D} \right)^2 e^{c^2/x-D}.\]

Further, from $a(z^*) = a^*$, and $a(z) = a_0 e^{c^2/x-D}$

\[a^* = a_0 e^{c^2/x-D}, \quad \text{(for } z \ll z_{max})\]

\[\Rightarrow \quad \frac{dN}{dt} = -b x N \left( \frac{c}{x-D} \right)^2 \frac{a^*}{a_0} \]

\[\text{Note: since } e^{c^2/x-D} = \frac{D}{x-D}, \quad z_{max}^* = \frac{x-D}{c} \ln \left( \frac{a^*}{a_0} \right) / \frac{D}{c} \ln \left( \frac{D}{x-D} \right)
\]

\[|z^*| \gg |z_{max}| \quad \text{corresponds to } X \gg D\]
from \( c = kN/a_0 \), we have
\[
\frac{dN}{dt} = -bX \left( \frac{k/a_0}{X-D} \right) N^3 = -\alpha N^3; \quad \alpha = bXa_0 \left( \frac{k/a_0}{X-D} \right)^2
\]

\( \rightarrow \) Solve ODE with initial condition \( N(t=0) = N_0 \)

\[
-\int_{N_0}^{N(t)} \frac{dn'}{(N')^3} = \int_0^t \alpha dt' \quad \Rightarrow \quad \frac{1}{N(t)} - \frac{1}{N_0} = 2\alpha t
\]

\[
\rightarrow \quad N(t) = \frac{N_0}{1+2\alpha N_0^2 \alpha t} \propto \sqrt{1-2\alpha t}
\]

Insert into \( C(t) = kN(t)/a_0 \)

\[
C(t) = C_0 \cdot \left( 1 + 2bXc_0^2 \left( \frac{a^*}{X-D} \right) \frac{a^*}{a_0} t \right)^{-\frac{1}{2}}
\]

where \( C_0 = kN_0/a_0 \) is speed if \( a^* = 0 \).

Systematic expansion (Novick-Cohen & Segal, '84)

\[
\frac{C(t)}{C(0)} \rightarrow \left( \frac{XC_0^2}{2(X-D)^2} \frac{a^*}{a_0} t \right)^{-\frac{1}{2}} \quad \text{(corresponds to } b = 4 \text{ instead of } \frac{1}{2})
\]

\( \Rightarrow \) No steady propagation due to leakage behind the density pulse
Numerical Simulation

KS Soon

KS Soon with leakage

4. Include population growth
a) background: inclusion of pop growth attempted immediately after KS

\[
\begin{align*}
\frac{\partial P}{\partial t} &= D \frac{\partial^2 P}{\partial x^2} - \frac{3}{5} (v \cdot P) + r(a) P \\
\frac{\partial a}{\partial t} &= D_a \frac{\partial^2 a}{\partial x^2} - k(a) P
\end{align*}
\]

- never worked well (too slow)

\[C_{KS} = kN/a_0\]

- fast expansion favored by small \(a_0\)

- large \(a_0\) needed to support growth

\[C < C_{FK}\]

What sets "N" for a growing population?

Origin of Adler ring prop. remained mysterious
b) biological picture (Cremer et al, 2019)

Separate growth from chemotaxis
i.e., attractant ≠ nutrient (significance later)

\[ \begin{align*}
\frac{dx}{dt} &= v(x) (1 - \frac{x}{x_c}) + D \frac{d^2x}{dt^2} - 2x(vp), \quad v = \frac{2a}{a + a_c} \\
\frac{d\theta}{dt} &= D_a \frac{d^2\theta}{dt^2} - k(a) \theta; \quad k(a) = \kappa \frac{a}{a + a_k}
\end{align*} \]

Numerical simulation yields steady propagation with a density peak at first followed by a trailing plateau

Directly measure density profile in agar

Adhering? optical illusion!
3) Heuristic sol'n:
- soln composed of two regions

\[ \begin{array}{c}
\text{back} & \text{front} \\
\ln s & \ln a
\end{array} \]

front \( (z > z^*) \):
- KS with leakage + growth

back \( (z < z^*) \):
- \( \nu = 0 \rightarrow \) Fisher wave
  (\( \phi \) and \( \alpha \) decoupled)

* front region:
  - for \( \ln \alpha > \ln c \), can neglect \( \phi^2 \) term in growth
  - for \( \ln \alpha < \ln c \), \( k(\alpha) = k \frac{\alpha}{\alpha + \alpha_0} \approx k \) (const)
  - further neglect \( D_0 \) as in KS (will restore later)
  - \( \rightarrow \) front dynamics = KS + leakage + const growth

\[ \begin{align*}
\frac{\partial \phi}{\partial t} &= r \phi + D_2 \frac{\partial^2 \phi}{\partial x^2} - \phi (\nu \phi) ; \\
\frac{\partial \alpha}{\partial t} &= -k \phi
\end{align*} \]

let \( N \) = # cells in the front bulge

\[ \frac{dN}{dt} = rN - b \chi \left( \frac{c}{\alpha_0} \right)^2 \frac{\partial^2 \alpha}{\partial \alpha_0^2} N \]

\( \chi(c) = \) leakage rate
Steady propagating state \( \Rightarrow r = Y(c) \)

\[ c = (X-D) \left( \frac{a_0}{6Xa_x^2} \right)^{1/2} \]

\[ = \sqrt{\frac{a_0}{6a_x^2}} B (1-D) \cdot C_{FK}; \quad C_{FK} = 2\sqrt{rD} \]

- Boost of expansion speed by \( \sqrt{rD} \) compared to Fisher wave (\( fn X \gg D \))

- \( c \) increases with \( a_0 \) - opposite of \( KS \).
  (lower if \( a_0 \) too large, \( P_{\max} \) exceeds \( P_c \))

\(*\) back region:

\[ \frac{\partial}{\partial t} \phi = \nabla \phi + D \nabla^2 \phi \quad (\phi^2 \text{ term neglected}) \]

\[ \phi \propto e^{-\lambda (X-ct)} \]

\[ + \lambda c = r + D \lambda^2 \]

\[ \lambda = \frac{c \pm \sqrt{c^2 - 4rD}}{2D} \quad \Rightarrow \quad c \geq 2\sqrt{rD} \]

Marginal stability \( \Rightarrow c = 2\sqrt{rD} = C_{FK} \)

\[ \text{But in the above soln fn C,} \]

\[ c \gg 2\sqrt{rD} \quad \text{if} \quad \frac{D}{X} \gg 1 \quad \text{and} \quad \frac{a_0}{a_x^2} \gg 1 \]

\[ \rightarrow \text{How do bacteria beat "marginal stability"?} \]

\[ \phi^2 \text{ How is prop. speed c "passed on" to the trailing region?} \]
1) Connection between front and back region:

leakage rate from front:

\[ \frac{\partial N}{\partial t} = \Delta \nu \cdot S(z^*) \]

where \( \Delta \nu = \nu_{KS} - \nu^* = \frac{b}{x-D} \)

\[ \Rightarrow \text{"source" of new cells for trailing region} \]

\[ S(x,t) = S_0 \cdot S(x-(z^*+ct)) ; S_0 = \frac{P_{KS}(z^*) \cdot \Delta \nu}{\nu_{KS}} \]

dynamics in the back region:

\[ \frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial x^2} + \gamma P + S_0 \cdot S(x-ct-z^*) \]

\[ \text{necelt} \]

let \( P(x,t) = e^{rt} \cdot y(x,t) \)

then \[ \frac{\partial y}{\partial t} = S_0 \cdot e^{-rt} \cdot S(x-ct-z^*) \]

\[ y(x,t) = \frac{S_0}{c} \cdot e^{-\frac{r}{c} \cdot (x-ct-z^*)} \]

\[ \Rightarrow P(x,t) = \frac{S_0}{c} \cdot e^{-\frac{r}{c} \cdot (x-ct-z^*)} \]

In moving frame:

\[ P_{FK}(z) = \frac{\Delta \nu}{c} \cdot P_{KS}(z^*) \cdot e^{-\frac{r}{c} \cdot (z-2^*)} \]

\[ \approx b \frac{x}{x-D} \]

Apparent "gap" between \( P_{FK} \) and \( P_{KS} \)

width of trough region
5. Compare to numerics (test of heuristic soil)
Simulation difficult with Da = 0.

→ Repeat heuristics for finite Da.

\[ C = C_{FK} \cdot \sqrt{\frac{4b}{a^2}} \cdot \frac{X}{D} \cdot (1 - \frac{D}{X}) \cdot \left( \frac{X - D}{D + X - D} \right) \]

\[ \alpha = \frac{X}{D \cdot Da} \quad \text{for } Da < X < D \]

Compares well with numerics

A few more notes:
- The case \( k(a) = a \) can also be treated (\( X \to X + D \))
- Include carrying capacity: \( \alpha_c = \frac{k_c}{P_c} = 2 \text{mM} \cdot P_c \quad \text{(in OD)} \)

\[ \frac{C^2}{C_{FK}^2} = \frac{1}{4b} \cdot \frac{a_0}{a^2} \cdot \frac{X}{D} \cdot (1 - \frac{D}{X})^2 \cdot \left[ 1 + \frac{Da}{X - D} + \frac{a_0^2}{a_c^2} (1 - \frac{D}{X}) \right] \]

\[ C \xrightarrow{\alpha_c} \text{peak attr. conc.} \]
attractant not necessary used as nutrient!
refutes classical notion of chemotaxis for nutrient scavenging

New picture for chemotaxis (Cremer et al, 2019)
- bacterial pop. employ chemotaxis in nutrient-replete condition
- boost of range expansion (by factor \( (\frac{X}{D})^2 \approx (\frac{X}{D})^1 \))
- requires low attr. conc. (attr. ≠ nutrient)

\( \Rightarrow \) attractant is an environmental "marker", whose destruction provides directional cue to navigate chemotaxis

\( \Rightarrow \) expand the pop. even w/ exp. growth, faster GR, faster expansion