MINIMAL MODEL OF BACTERIAL RUN-&-TUMBLE CHEMOTAXIS

We will discuss here a minimal (1D) model of bacterial chemotaxis à la E.coli, based on modulation of run & tumble dynamics.

A lot is known on E.coli chemotaxis (see e.g. work by Howard Berg & his book "Random Walks in Biology").

Here we will use material from:

- S. Goldstein, Q. J. Applied Math. 4, 2, (1951)
- M. J. Schnitzer, PRE, 48, 2553 (1993)
- V. Méndez, D. Campos, F. Bartumeus, "Stochastic Foundations in Movement Ecology", Springer Series in Synergetics (2014).

• It is well known (now) that E.coli performs chemotaxis through a temporal comparison of the concentration of chemoattractant c

If $c(t)$ is the concentration it measures at time t, the tumbling rate $\alpha(t)$ will be given by

$$\alpha(t) = \int_0^\infty c(\tau)\, I(t-\tau)\, d\tau$$

$\int_0^\infty I = 0$

$I(\tau)$ = response kernel → Implements a "time derivative"

→ Interesting properties (e.g. adaptation) & Interesting biological "implementation"

We will not deal with these here. I only mentioned them to provide a novel idea.

[A natural question to ask: why not biasing α just dependent on the local concentration $C(x)$?]

- SPACE DEPENDENT DIFFUSIVITY

Biasing α with the local chemoattractant concentration $c(x)$ amounts to $\alpha(x) \Rightarrow \boxed{D(x) \sim \frac{v^2}{\alpha(x)}}$ SPACE DEPENDENT DIFFUSIVITY

(v = swimming speed)

Naive intuition: bacteria will accumulate when D is low.

$\boxed{\text{PROBLEM}}$: Not so simple! When $D = D(x)$, knowing the function $D(x)$ is $\boxed{\text{NOT ENOUGH}}$ to predict what will happen.

↓

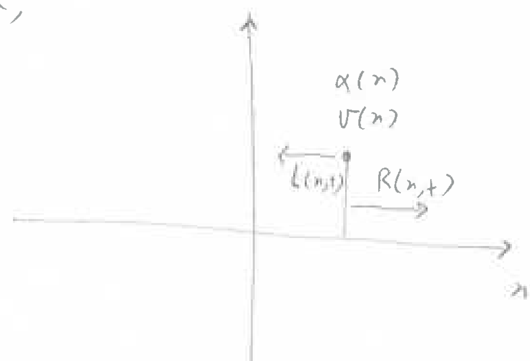
Let's see

↓

1D model of run-and-tumble bacteria,

swimming speed $v(x)$, tumbling rate $\alpha(x)$

two populations



$$\begin{cases} L(x,t) & \text{moving at speed } -v(x) \\ R(x,t) & \text{moving at speed } +v(x) \end{cases}$$

After each tumble, equal prob. to become R or L.

CONTINUITY EQNS

$$\begin{cases} \dfrac{\partial R}{\partial t} = -\dfrac{\partial (vR)}{\partial x} - \dfrac{\alpha R}{2} + \dfrac{\alpha L}{2} \\[2ex] \dfrac{\partial L}{\partial t} = +\underbrace{\dfrac{\partial (vL)}{\partial x}}_{\text{DRIFT}} \underbrace{+ \dfrac{\alpha R}{2} - \dfrac{\alpha L}{2}}_{\text{Transitions b/w } R \,\&\, L} \end{cases}$$

Recast in terms of $\begin{cases} \rho = R+L \\ \sigma = R-L \end{cases}$

$$\begin{cases} \dfrac{\partial \rho}{\partial t} = -\dfrac{\partial (v\sigma)}{\partial x} \quad \left(= -\dfrac{\partial J}{\partial x} \quad J = \text{net particle current} \right) \\[2ex] \dfrac{\partial \sigma}{\partial t} = -\dfrac{\partial (v\rho)}{\partial x} - \alpha\sigma \end{cases}$$

Two relevant timescales here:

(i) $\dfrac{1}{\alpha} = \tau_t$ tumbling time. (for a 'typical' α)

(ii) $\dfrac{L}{v} = \tau_b$ ballistic time (v characteristic velocity) (L " length e.g. size of box)

We are interested in the regime

$$\boxed{\tau_t \ll \tau_b}$$

EX Given typical values of τ_t & v, how large does the "chemoattractant profile" need to be to satisfy this requirement?

Under this assumption, for times $\tau_t \ll t \ll \tau_b$ we can simplify the eqn. for σ to its "steady state" solution (slave σ to ρ):

$$\begin{cases} \dfrac{\partial \rho}{\partial t} = -\dfrac{\partial (v\sigma)}{\partial x} \\[2ex] 0 = -\dfrac{\partial (v\rho)}{\partial x} - \alpha\sigma \quad \longrightarrow \quad \sigma = -\dfrac{1}{\alpha}\dfrac{\partial v\rho}{\partial x} \end{cases}$$

$$\boxed{\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}\left[\frac{v}{\alpha}\frac{\partial (v\rho)}{\partial x}\right]}$$

$$J = -\frac{v}{\alpha}\frac{\partial (v\rho)}{\partial x}$$

$$= \underbrace{-\frac{v^2}{\alpha}\frac{\partial \rho}{\partial x}}_{-D\frac{\partial \rho}{\partial x}} \underbrace{- \frac{v\frac{\partial v}{\partial x}}{\alpha}\rho}_{+v_{drift}\rho}$$

Diffusive term — Advective term

- $D(x) = \dfrac{v^2(x)}{\alpha(x)}$ EFFECTIVE DIFFUSION
- $v_{drift} = -\dfrac{v}{\alpha}\dfrac{\partial v}{\partial x}$ EFFECTIVE DRIFT $\left(\propto -\dfrac{\partial v(x)}{\partial x}\right)$

Towards small v!

Ex Estimate the ratio b/w characteristic times τ_ρ, τ_σ (5)
for the evolution of ρ & σ.

From the eqns above,

$$\begin{cases} \dfrac{\rho}{\tau_\rho} \sim \dfrac{v\,\sigma}{L} \\[2ex] \dfrac{\sigma}{\tau_\sigma} \sim \alpha\,\sigma + \dfrac{v\rho}{L} \end{cases} \longrightarrow \underline{\frac{1}{\tau_\sigma} \sim \alpha + \tau_\rho \frac{v^2}{L^2}}$$

Using the approx. $\underbrace{\text{above}}$ (σ slaved to ρ), $\alpha\sigma \sim \dfrac{v\rho}{L} \Rightarrow \underline{\dfrac{1}{\tau_\rho} \sim \left(\dfrac{v}{L}\right)^2 \dfrac{1}{\alpha}}$,

and

$$\frac{1}{\tau_\sigma} \sim \alpha + \alpha \quad \Rightarrow \quad \tau_\sigma \sim \frac{1}{\alpha}$$

which implies

$$\boxed{\frac{\tau_\rho}{\tau_\sigma} \sim \tau_\rho\,\alpha \sim \alpha^2\left(\frac{L}{v}\right)^2 \sim \left(\frac{\tau_b}{\tau_t}\right)^2}$$

So, indeed, for $\tau_t \ll \tau_b$ we also have $\tau_\sigma \ll \tau_\rho$.

The steady state profile is obtained for J = constant

We are interested in the case constant = 0, i.e. no net current @ steady state.

What is the general solution?

$$\frac{v(x)}{\alpha(x)} \frac{\partial v(x) \rho(x)}{\partial x} = 0 \quad \Leftrightarrow \quad \boxed{\rho(x) = \rho_0 \left[\frac{v_0}{v(x)}\right]}$$

for some constants
ρ_0 density
v_0 velocity

$$\boxed{\rho(x) \sim \frac{1}{v(x)}}$$

Let's see what does this mean in some typical examples.

(i) $v(x)$ & $\alpha(x)$ = const.

This means $D = \frac{v^2}{\alpha}$ = const, and we expect the steady state to be ρ = const. OK!

(ii) v = const. & $\alpha = \alpha(x)$

This implies that the effective diffusivity $D = \frac{v^2}{\alpha}$ is space dependent. However, the current J takes the form $J(x) = -D(x)\frac{\partial \rho}{\partial x}$, w/o a drift term (!).

As a consequence, the steady state is still ρ = const.

NOTICE this implies that modulating the frequency of INSTANTANEOUS tumbles on the local chemoattractant concentration will NOT lead to accumulation.

iii $v = v(x)$ & $\alpha = \text{const}$

Again, space dependent diffusivity $D = \frac{v^2(x)}{\alpha}$. However, this time

$$J = -D(x)\frac{\partial \rho}{\partial x} - \frac{1}{2}\left(\frac{\partial D}{\partial x}\right)\rho$$

There is an effective drift. The steady state conc.

$$\rho = \rho_0 \frac{v_0}{v} = \rho_0 \sqrt{\frac{D_0}{D}} \Rightarrow \rho \sim \frac{1}{\sqrt{D}}$$

iv $v = v(x)$ & $\alpha = \alpha(x)$ But $\frac{v}{\alpha}$ = CONSTANT

$\frac{v}{\alpha}$ = mean free path

Again, we have a space dependent diffusivity $D(x)$, J has a drift contribution, and at steady state

$$\rho(x) = \rho_0 \frac{v_0}{v(x)} = \rho_0 \frac{D_0}{D(x)} \Rightarrow \rho \sim \frac{1}{D}$$

$$\left(J = -D(x)\frac{\partial \rho}{\partial x} - \left(\frac{\partial D}{\partial x}\right)\rho \right)$$

NOTICE That in the cases ii, iii, iv I can choose α & v in such a way as to produce always the SAME function $D(x)$, BUT the resulting ρ @ steady state will depend differently on $D(x)$

ii	iii	iv
$\rho = \text{const}$	$\rho \sim \frac{1}{\sqrt{D}}$	$\rho \sim \frac{1}{D}$

Knowing $D(x)$ is NOT ENOUGH!

NOTICE A generic choice of $v(x)$ & $\alpha(x)$ leads to an equation for ρ which cannot be written as a simple generalization of Fick's law.

This example highlights that:

(a) Knowledge of $D(x)$ is not enough

(b) Implementing $D(x)$ by changing the tumbling rate α will not, by itself, lead to chemotaxis.

(c) Chemokinesis, i.e. "v" increases w/ chemical concentr. "c", leads, by itself, to accumulation in regions of LOW "c".

– CHEMOTAXIS BASED ON SWIMMING DIRECTION

Now we suppose that the two populations, R & L, move with species-dependent speed ($v_{R,L}$) & tumbling rate ($\alpha_{L,R}$). The continuity equations become

$$
\begin{cases}
\dfrac{\partial R}{\partial t} = -\dfrac{\partial(v_R R)}{\partial x} - \dfrac{\alpha_R}{2} R + \dfrac{\alpha_L}{2} L \\[2ex]
\dfrac{\partial L}{\partial t} = \dfrac{\partial(v_L L)}{\partial x} + \dfrac{\alpha_R R}{2} - \dfrac{\alpha_L L}{2}
\end{cases}
$$

Recast in terms of (ρ, σ) we get

$$
\begin{cases}
\dfrac{\partial \rho}{\partial t} = -\dfrac{1}{2}\left[\dfrac{\partial}{\partial x}\left[(v_R - v_L)\rho\right] + \dfrac{\partial}{\partial x}\left[(v_R + v_L)\sigma\right] \right] \\[2ex]
\dfrac{\partial \sigma}{\partial t} = -\dfrac{1}{2}\left[\dfrac{\partial}{\partial x}\left[(v_R + v_L)\rho\right] + \dfrac{\partial}{\partial x}\left[(v_R - v_L)\sigma\right] + (\alpha_R - \alpha_L)\rho + (\alpha_R + \alpha_L)\sigma \right]
\end{cases}
$$

As before, we can slave σ to ρ, and the "equilibrium" steady state will be characterised by $\rho(x)$ being the solution to

$$
0 = J(x) = -2\frac{(v_R + v_L)}{(\alpha_L + \alpha_R)} \frac{\partial}{\partial x}\left[\frac{v_R v_L}{v_R + v_L}\rho\right] + \frac{(\alpha_L v_R - \alpha_R v_L)}{\alpha_L + \alpha_R}\rho
$$

$\boxed{\text{Ex}}$ Derive the 'equilibrium' condition above.

The formal solution to the eq. condition is

$$\rho(x) = \left[\rho(x_0)\,\frac{v_R(x_0)\,v_L(x_0)}{v_R(x_0)+v_L(x_0)}\right]\left[\frac{v_R(x)+v_L(x)}{v_R(x)\,v_L(x)}\right] e^{\int_{x_0}^{x} dx\left(\frac{\alpha_L(x)\,v_R(x) - \alpha_R(x)\,v_L(x)}{2v_R(x)\,v_L(x)}\right)}$$

A few comments:

(i) The current $J(x)$ above is the sum of a diffusive component $-2\left[\frac{v_R v_L}{(\alpha_L+\alpha_R)}\right]\frac{\partial\rho}{\partial x}$ with effective diffusivity $D = \frac{v_R v_L}{(\alpha_R+\alpha_L)}$ (cfr. expression for $D(x)$ in previous sect.); and a drift term

$$\underbrace{\left[\left(\frac{\alpha_L v_R - \alpha_R v_L}{\alpha_R+\alpha_L}\right) - 2\left(\frac{v_R+v_L}{\alpha_R+\alpha_L}\right)\frac{\partial}{\partial x}\left(\frac{v_R v_L}{v_R+v_L}\right)\right]}_{v_{drift}}\rho\,.$$

The drift velocity has a (potential) contribution if $v_{R,L}$ depend on space (fair enough), AND a contribution from asymmetries b/w L & R motion, regardless of whether these are space dependent.

(ii) The drift velocity contribution $v_d^* = \left(\frac{\alpha_L v_R - \alpha_R v_L}{\alpha_R+\alpha_L}\right)$ can be derived easily from a quick estimate of the time spent moving rightward vs. leftward. Notice that the drift up the chemical gradient can be increased either by decreasing the corresponding tumbling rate, or by increasing the swimming speed, or both.

EX Derive the expression of v_d^* by estimating the fraction of time spent by the cell moving leftward vs rightward.

iii Given tumbling rates

$$\alpha_L = -\beta \frac{\partial c}{\partial x} \; ; \quad \alpha_R = \beta \frac{\partial c}{\partial x}$$

Idealization of the effect of the response kernel $I(\tau)$ (see 1)

for some value β, and assuming

$v_L(x) = v_R(x) = v$ const.

we get the "equilibrium" concentration

$$\rho(x) = \rho(x_0)\, e^{\frac{\beta}{v}[c(x)-c(x_0)]}$$

→ Accumulation @ high $c(x)$!!

(or the opposite if $\beta < 0$)

EX Derive the equilibrium distribution above.

EX Derive the equilibrium $\rho(x)$ for $\alpha_{R,L} = \left[\pm \frac{\gamma}{c}\frac{\partial c}{\partial x} + \alpha_0\right]$.

A cell response $\alpha \sim \frac{1}{c}\frac{\partial c}{\partial x}$ follows what is known as Weber's law or Fold Change Detection. See e.g.

Shoval O. et al. "Fold-change detection of scalar symmetry of sensory input fields", PNAS 107(36), 15995 (2010).

(iv) Effect of a finite tumbling time? Is it important?

Tumbles take time, so tumbling more will decrease the mean cell velocity & impact on cell accumulation.

For a cell swimming at speed v & tumbling at rate α, if the tumbles take a time τ, the overall swimming speed for a (swim + tumble) event will be

$$v_{eff} = \frac{v}{1+\alpha\tau}$$

[EX] Derive the expression above.

So, for us, $v_{L/R} \longrightarrow v_{L/R,eff} = \dfrac{v_{L/R}}{1+\alpha_{L/R}\,\tau}$

and the drift speed v_d^* will become

$$v^*_{d,eff} = \frac{\dfrac{\alpha_L v_R}{1+\tau\alpha_R} - \dfrac{\alpha_R v_L}{1+\tau\alpha_L}}{\alpha_L+\alpha_R}$$

For E. coli, "typical" values are

$$\tau \sim 0.1\,s$$

$$\alpha = \begin{cases} 0.1\,s^{-1} & \text{upstream} \\ 1\,s^{-1} & \text{downstream} \end{cases}$$

$$v \sim 30\,\mu m/s$$

$\Rightarrow$ $\tau\alpha$ is small, typically less than 10%.

$$\Rightarrow \boxed{v^*_{d,eff} \simeq v^*_d - \underbrace{\frac{\tau\alpha_L\alpha_R}{\alpha_L+\alpha_R}(v_R - v_L)}_{\text{IS THIS BIG?}}}$$

$$\frac{\left|\frac{\tau \alpha_L \alpha_R}{\alpha_L+\alpha_R}(v_R - v_L)\right|}{|v_d^*|} = \frac{|\tau \alpha_L \alpha_R (v_R - v_L)|}{|\alpha_L v_R - \alpha_R v_L|} \sim \frac{\tau \alpha^2 v}{\alpha v} \sim \tau\alpha$$

In reality much less because $v_R \simeq v_L$.

So we can expect the effect of finite tumbling time on the drift velocity to be <u>at most</u> of order $\tau\alpha$: <u>SMALL</u> for normal conditions.

<u>NOTICE</u> that the effect is to <u>DECREASE</u> the drift speed: can you think <u>why</u>?

<u>BOTTOM LINE</u>: Direction-dependent chemotaxis works better than position-dependent.

If you want to know more (e.g. extend to 2D / 3D) see e.g. paper by Schnitzer cited @ the beginning.