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ARTICLE

P.-G. de Gennes

Chemotaxis: the role of internal delays

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Abstract When exposed to certain chemoattractants, bacteria like *Escherichia coli* move up the concentration gradient ∇c with a velocity $\kappa \nabla c$. Microscopically, *E. coli* moves at constant speed when it's flagellum is rotating counter-clockwise (ccw) and tumbles when the rotation is clockwise (cw). The lifetime of a ccw interval, τ_+, is a function of the concentration $c(t')$ experienced at earlier times. The corresponding response function was measured long ago by Berg and co-workers. We present here a detailed description of the motion taking place during one ccw interval. This gives an explicit formula relating the chemotactic coefficient κ to the response function; the formula has some surprising features.

Keywords Bacterial motion · Chemotaxis · *Escherichia coli* · Random walks

Introduction

When *Escherichia coli* is exposed to a weak gradient in an aspartate concentration, c, it moves up against the gradient with an average velocity:

$$\bar{V} = \kappa \nabla c \tag{1}$$

The basic biochemical processes involved are relatively well understood. Aspartate binds to a Tar receptor, and this starts a chain of coupled protein phosphorylations (see, for instance, Bray 2001; Webre et al. 2003). The final result is a change in the activity of the flagellar motors. When the motors rotate counter-clockwise (ccw), the bacterium advances in a straight line, with a velocity of order 20 μm/s. When some motors rotate clockwise (cw), the bacterium tumbles randomly, and does not move.

P.-G. de Gennes
Collège de France and Institut Curie, 11 rue P. et M. Curie,
75231 Cedex 05 Paris, France
E-mail: pgg@curie.fr

There are two lifetimes: one (τ_+) for the ccw intervals (also called "the runs"), and one (τ_-) for the cw intervals. Both lifetimes depend on the asparte concentration c at earlier times. This has been studied in detail by Segall et al. (1986). We shall be mostly concerned by the lifetime τ_+ (we assume that in the cw phase the motions are negligible). The rate $\frac{1}{\tau_+(t)}$ has a certain average τ^{-1}, plus a chemotactic term. We assume for the moment that this term is linear in c for small c:

$$\frac{1}{\tau_+(t)} = \frac{1}{\tau_+}\left[1 - \int^t \mathrm{d}t' R_+(t-t')c(t')\right] \tag{2}$$

One may also define a response function R_- for the lifetime τ_- of the tumbling intervals:

$$\frac{1}{\tau_-(t)} = \frac{1}{\tau_-}\left[1 - \int^t \mathrm{d}t' R_-(t-t')c(t')\right] \tag{3}$$

The time fraction ϕ of the ccw operation is the central object of Segal et al. (1986); it is given by:

$$\begin{aligned}\phi(t) &= \tfrac{\tau_+(t)}{\tau_+(t)+\tau_-(t)} \\ &\approx \bar{\phi}\left[1 + \left(1-\bar{\phi}\right)\int^t \mathrm{d}t' R_+(t-t') - R_-(t-t')c(t')\right]\end{aligned} \tag{4}$$

to first order in c.

We shall see that R_+ alone controls chemotaxis. We start the discussion by a special case:

$$R_+(t) = \alpha\delta(t-\theta) \tag{5}$$

with a unique delay time θ, because the presentation is more simple. The extension to a distribution $R_+(t)$ is performed later.

One run in a concentration gradient

Let us assume that the bacterium started its ccw operation at a certain time t. During the following interval, it has a constant velocity V_i along the x axis. After a time

Δ, the motor stops. The probability of not stopping before $t+\Delta$ is:

$$p(\Delta) = \exp\left[-\int_t^{t+\Delta} \mathrm{d}t' \tfrac{1}{\tau_+(t')}\right] = \exp -\left[\tfrac{\Delta}{\tau} - \tfrac{\alpha}{\tau}\int_t^{t+\Delta} c(t'-\theta)\mathrm{d}\theta\right] \quad (6)$$

$$\approx \left[\exp\left(-\frac{\Delta}{\tau}\right)\right]\left[1+\frac{\alpha}{\tau}\int_t^{t+\Delta} c(t'-\theta)\mathrm{d}\theta\right] \quad (7)$$

The probability of stopping during the interval (Δ, $\Delta+\mathrm{d}\Delta$) is $-\frac{\mathrm{d}p}{\mathrm{d}\Delta}$, and the average length traveled during the run is:

$$x_i = <\int_0^{\infty} \mathrm{d}\Delta\left(-\frac{\mathrm{d}p}{\mathrm{d}\Delta}\right)V_i\Delta> = <V_i\int_0^{\infty} p(\Delta)\mathrm{d}\Delta> \quad (8)$$

where the symbol $<>$ denotes an average over the orientations of V_i. We may write Eqs. (7) and (8) in the form:

$$x_i = \frac{\alpha}{\tau}\int_0^{\infty} \mathrm{d}\Delta \exp\left(-\frac{\Delta}{\tau}\right)<V_i\int_t^{t+\Delta} c(t'-\theta)\mathrm{d}t'> \quad (9)$$

The concentrations c, and the bacterium positions x, are related through the imposed gradient ∇c:

$$c(t'-\theta) = (\nabla c)x(t'-\theta) + \text{const} \quad (10)$$

If the time $t-\theta$ occurred before our active interval (t, $t+\Delta$), the corresponding position $x(t-\theta)$ is not correlated to V_i (we assume that each active interval corresponds to a value of V_i which was uncorrelated with the previous ones). Then there is no contribution to Eq. (10). Thus we may substitute:

$$\begin{array}{ll} x(t'-\theta) \to V_i(t'-t-\theta) & t' > t+\theta \\ x(t'-\theta) \to 0 & t' < t+\theta \end{array} \quad (11)$$

Then the average displacement during one ccw interval is:

$$x_i = \frac{\alpha}{\tau}\nabla c<V_i^2>\int_{\theta}^{\infty} \mathrm{d}\Delta\frac{1}{2}\exp\left(-\frac{\Delta}{\tau}\right)(\Delta-\theta)^2 \quad (12)$$

$$= \alpha\nabla c<V_i^2>\tau^2\exp\left(-\frac{\theta}{\tau}\right) \quad (13)$$

The average velocity over many successive intervals is:

$$V = \frac{x_1}{\tau_1}\bar{\phi} \quad (14)$$

where:

$$\bar{\phi} = \frac{\tau_+}{\tau_+ + \tau_-} \quad (15)$$

is the global time fraction in the active state.

We can now superpose Eqs. (13) and (14), and also sum up other all possible delays θ, using a general response function $R(\theta)$. The result is:

$$\kappa = D\int_0^{\infty} R(\theta)\exp(-\frac{\theta}{\tau})\mathrm{d}\theta \quad (16)$$

where D is the diffusion coefficient in zero gradient:

$$D = \bar{\phi}<V_i^2>\tau \quad (17)$$

Discussion

The conclusions of this note are in complete disagreement with the theoretical paper by Schnitzer et al. (1990). Their conclusion was that $\kappa = 0$ for fast responses $R(\theta) = \delta(\theta)$. The discussion in Schnitzer et al. (1990) is based on a macroscopic approach, with time and space intervals much longer than what happens during one run; it ignores crucial features during each run.

On the experimental side, as mentioned in the Introduction, what has been measured mainly is:

$$R(t) = [\,R_+(t) - R_-(t)]\big(1-\bar{\phi}\big) \quad (18)$$

However, looking at some numerical data of Segall et al (1986), it may be that there is no major difference between $R_+(t)$ and $R(t)$:

1. Certain mutants of *E. coli* (cheR, cheB) have been studied by Segall et al. (1986) and by Berg and Turner (1986). They show a "single lobe" of constant sign for $R(\theta)$. Also, they do not seem to swim up a concentration gradient: $\kappa = 0$! This speaks in favor of the Purcell conclusion (Schnitzer et al. 1990). However, it must be realized that all chemotactic effects are reduced by a factor $\sim 10^{-2}$ in these mutants.
2. If we return to the wild-type behavior of *E. coli*, we find that $R(\theta)$ has a *positive* peak (over $\sim$1 s) followed by a *negative* peak (over $\sim$3 s). Also, the overall area $\int R(\theta)\mathrm{d}\theta$ vanishes. Berg pointed out that the latter property is of some particular interest. It means that if *E. coli* is submitted to a change of concentration c (without any spatial gradients), it will adapt and show the same behavior (the same rates $\frac{1}{\tau}$) at long times after the c jump.

The effect on κ of this two-lobe structure is presented as follows in Segall et al. (1986): "a wild-type cell compares the stimulus experienced during the past second with the stimulus experienced during the previous 3 s, and responds to the difference"; see also Berg and Turner (1986).

However, if our calculation holds, the difference procedure does not seem to increase κ. Consider, for instance, a response $R(\theta)$ which is the difference of two equal peaks:

$$R(\theta) = \alpha\left[\delta(\theta) - \delta\left(\theta - \bar{\theta}\right)\right] \tag{19}$$

where $\bar{\theta}$ is a fixed delay time (~3 s). The resulting chemotactic coefficient is:

$$\kappa = \alpha D\left[1 - \exp\left(-\bar{\theta}/\tau\right)\right] \tag{20}$$

and it shows no enhancement. Because of the averaging over random walks, the difference procedure is not beneficial for κ (although it is beneficial for adaptation). Simulations have been performed on this problem (Berg 1988; Mittal et al. 2003), but we have not found one simulation which would correspond to short delays and give $\kappa = 0$ as predicted by Purcell and co-workers (Schnitzer et al. 1990).

In real life, one complication is present and was not taken into account in our presentation. From experiments by Berg and Brown (1974), it appears that $1/\tau_+$ changes linearly when the aspartate concentration c increases, but that it stays constant when c decreases! This is challenging from a biochemical point of view. It is not easy to set up a kinetic model for the phosphorylate cascades which could produce such an abrupt nonlinearity. We suspect that the Berg–Brown effect is due to hysteresis in a strongly cooperative (allosteric) response. However, this would require a separate study.

From the point of view of the present calculation, the effect of this anomalous response is simple: only one half of the directions of the movement contribute (those where V_i is pointing towards ∇_c). Thus the net result is simply to add a factor 1/2 in Eq. (16).

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Appendix: the Langevin bacterium

Equation (16) may be derived by a slightly different way, which is less transparent but more direct. The starting point is an equation of motion for the velocity V, somewhat similar to that which Langevin used for Brownian motion (Langevin 1908):

$$\frac{\mathrm{d}V}{\mathrm{d}t} + \frac{V}{\tau_+} = f(t) \tag{A1}$$

where $f(t)$ is a random "force" (actually a random signal describing the switching between ccw and cw rotation). We assume that $f(t)$ is a "white noise", and is independent of the chemoattractant concentration:

$$< f(t_1) f(t_2) > = K\delta(t_1 - t_2) \tag{A2}$$

We then separate $\frac{1}{\tau_1}$ into an average $\frac{1}{\tau}$ plus a perturbation (Eq. 2), and write $V = V_0 + V_1$, where V_1 is a linear functional of c. V_0 has the classical correlation form:

$$< V_0(0) V_0(t) > = K \exp(-t/\tau) \tag{A3}$$

Solving for V_1 and taking averages, we return to Eq. (16).

Equation (A1) leads to a concise derivation, but it suffers from the unclear origin of the noise $f(t)$: this is why we used the more precise discussion of time intervals in the main text.

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