A path-integral characterization of run and tumble motion and chemotaxis of bacteria

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Abstract
Bacteria such as *Escherichia coli* move about in a series of runs and tumbles: while a run state (straight motion) entails all the flagellar motors spinning in counterclockwise (CCW) mode, a tumble is caused by a shift in the state of one or more motors to clockwise (CW) spinning mode. In the presence of an attractant gradient in the environment, runs in the favourable direction are extended, and this results in a net drift of the organism in the direction of the gradient. Existing theoretical predictions for the drift velocity are limited to exponentially distributed run durations. However, recent experimental observations strongly suggest that the CCW and CW intervals have gamma, rather than exponential distributions. We present a path-integral method which can be used to compute various quantities of interest for the run and tumble walk, with and without chemotaxis, for arbitrary distributions of run and tumble intervals, as power series expansions in the gradient. The effectiveness of the method is demonstrated by deriving a number of existing results for the mean-squared displacement (including motion with directional persistence and algebraically distributed run times) and also chemotactic drift (with exponentially distributed run intervals) in a systematic way, starting from a set of general formulae. New results for chemotactic drift velocity for gamma-distributed run and tumble intervals are then derived, in the limit of weak gradients. Finally, by making use of available experimental data, we make testable predictions for the dependence of the drift velocity on the clockwise bias of the flagellar motor.

Keywords: bacteria, run and tumble, chemotaxis, drift, path-integral

(Some figures may appear in colour only in the online journal)
1. Introduction

The run and tumble motion of the bacterium *Escherichia coli* (*E. coli*) is well-known, and
is characterised by a series of straight runs, interspersed with shorter tumbles, during which
the organism reorients itself [1]. It has been established that a bacterium ‘runs’ when all its
flagellar motors spins counter-clockwise (CCW) [2], while a ‘tumble’ occurs when at least
a single motor switches direction to undergo clockwise (CW) rotation [3]. In the absence of
a chemoattractant (and when the concentration of chemoattractant is uniform), the motion is
globally unbiased in space, but with persistence of direction: after a tumble, the direction of
the new run maintains a mean angle of \( \approx 62^\circ \) with respect to that of the previous one [4].
When an attractant gradient is present, the bacterium extends its runs in the favourable direction
by reducing the frequency of tumbles [4]. As a result, a net drift develops in the direction of the
gradient, which enables the organism to move towards the source. The resulting chemotaxis
in bacterium is, therefore, fundamentally different from similar phenomena in unicellular
eukaryotes like amoeba and neutrophils, in which moving cells reorient themselves in the
favourable direction by sensing concentration difference across their body. For a review of the
experimental literature and a summary of the modelling approaches related to chemotaxis of
*E.coli*, we refer the reader to [5].

In the simplest kinematic description of the run and tumble motion, supported by early
experimental data [4], it is assumed that, in the absence of chemoattractants, tumbling is a
first order process characterised by a single rate \( \lambda \) specifying the switch from CCW to CW
rotation of a single flagellar motor, which initiates the tumbling process. In a bacterium with
a single tethered flagellum, it is observed that a stimulus in the form of a time-dependent
change in attractant concentration \( \delta c(t) \) causes a corresponding change in the clockwise bias,
and hence the switching rate, i.e. \( \lambda \to \Lambda(t) \equiv \lambda + \delta \lambda(t) \). For small stimuli, this change may
be expressed mathematically through a linear response relation of the form [6–8]

\[
\delta \lambda(t) = -\lambda \int_0^t R(t - t') \delta c(t') dt',
\]

where \( R(t) \) is a linear response function. Experiments [9, 10] have shown that at least for some
attractants, the area enclosed by the response function is near-zero [10], which implies that
the organism adapts perfectly to a step-like increase of stimulus. In this case, the response
function has a two-lobe structure, with a positive lobe appearing almost immediately after the
stimulus is applied, and a negative lobe appearing later, with the centres of the lobes being
separated by nearly a second. These properties led de Gennes [7] to suggest the approximate
form

\[
R(t) \simeq \kappa [\delta(t) - \delta(t - \Delta)],
\]

where \( \Delta \) is the time delay between the centres of the positive and negative lobes, \( \kappa \) is an
empirical parameter which depends on the details of the underlying biochemical network and
\( \delta(t) \) is the Dirac delta function. The response function has also been computed explicitly [11, 12]
using variants of the Barkai–Leibler model [13] for the receptor methylation-demethylation
processes, originally introduced to explain the perfect adaptation property of *E. coli*,
and the robustness of the network output to cell-to-cell variations in enzyme concentrations.

Using a combination of heuristic arguments and rigorous calculations, de Gennes [7]
derived the following expression for the drift velocity of a bacterium in two dimensions, in a
concentration gradient \( \nabla c = \alpha \):
\[ \mathbf{v}_d \sim D \alpha \int_0^\infty R(t) e^{-\lambda t} dt, \]  

(3)

where \( D = v^2 / 2\lambda \) is the effective diffusion coefficient for the unbiased run and tumble walk, \( v \) being the run speed. Equation (3) is expected to be valid only when the gradient \( \alpha \) is sufficiently small, which, following [14], shall be referred to as the ‘weak chemotaxis’ limit in the rest of this paper.

More general versions of equation (3), in the same limit, have been derived by other authors. Notably, Locsei [14] provided a rigorous derivation of the drift velocity by adopting a ‘sum over paths’ approach, which generalised equation (3) by including Brownian rotation during runs and directional persistence following tumbles. Erban and Othmer [15] introduced and studied a model of chemotaxis with directional persistence (but without Brownian rotations), where the temporal change in tumble rate of the bacterium is expressed as an integral over the fraction of attractant molecule-bound receptors, as opposed to the attractant concentration directly (as in equation (1)). In their model, temporal comparisons are effected through two internal variables, whose dynamics naturally leads to a bi-lobed response function. Melissa and Gopalakrishnan [11] followed an approach similar to de Gennes [7] (discussed in detail in the next section) to compute the drift velocity, but derived the response function directly from a simplified version of the Barkai–Liebler model [13] for receptor methylation and demethylation. The ‘macroscopic’ approach to chemotaxis has a long history, dating back to the classic papers by Patlak [16] and Keller and Segel [17], which was extended later by several authors [6, 18–21]. Celani and Vergassola [20] obtained the response function from a general Fokker–Planck equation for the run and tumble motion, with a finite number of abstract internal variables included, thus ensuring that the function has the required bi-lobe form. More recently, Seyrich et al [21] constructed an effective Smoluchowski equation for the run-and-tumble bacteria with a history-dependent tumble rate as in equation (1), by defining a history-averaged mean tumble rate at each point in space. In the weak chemotaxis limit, both these approaches [20, 21] lead to Locsei’s result [14] for the drift velocity. The approach in [20] was later extended to study chemotactic drift in fluctuating signalling environments [22].

We now explain the motivations behind this paper. The original derivation of equation (3) by de Gennes [7], elegant as it is, is carried out by making use of a simplifying step. Instead of computing the mean displacement due to a gradient as a single average over all realizable trajectories, de Gennes computes first the mean displacement due to the gradient over a single run event, and multiplies it with the mean number of runs over a certain time interval to find the asymptotic drift velocity. A slightly different definition was adopted by Locsei [14], who obtains the drift velocity by dividing the mean displacement over a run by the mean duration of the same. Locsei’s expression for drift velocity includes de Gennes’ as a limiting case, and has been re-derived by other authors [20, 21] more recently; however, the two-step averaging procedure used in [7] and [14] lacks formal mathematical justification, in our opinion. As a result, the generality of equation (3) is not always apparent even in the weak chemotaxis limit, although simulations have supported it [23]. Beyond this limit, symmetry considerations predict that \( O(\alpha^3) \) terms will become significant in the drift velocity, but it is not clear from the existing approaches how equation (3) is to be extended to include these terms. It is also commonly assumed [7, 14, 22], based on earlier experimental data [4] that the run intervals are exponentially distributed and are (typically) much longer than tumbles. However, more recent experimental observations [24, 25] indicate that time intervals corresponding to CW and CCW modes of rotation of a single motor are, in general, gamma-distributed, the details of which depend on the mean clockwise bias of the motor. To the best of our knowledge, a
generalization of equation (3) to non-exponentially distributed run (and tumble) interval distributions has not been attempted so far.

Here, we develop and present a mathematically rigorous, ‘path-integral’ formulation of the run and tumble motion and chemotaxis in bacteria such as \textit{E.coli}. This method is close in spirit to the ‘sum over paths’ approach developed by Locsei [14] for computation of chemotactic drift velocity, but has a wider scope. In the present theory, an individual trajectory is specified using the set of run and tumble intervals, and angles specifying the directions of runs. The probability distributions of run and tumble intervals are specified using two cumulative (survival) probability functions, while directional persistence is introduced through a conditional probability density connecting the direction of the present run with that of the previous one. A probability functional for a trajectory is constructed using all these quantities, which using any desired statistical average can be computed systematically. The formalism has the structure of a systematic perturbation theory, where the imposed attractant gradient $\alpha$ acts as the small parameter. Also, it naturally includes non-exponentially distributed run (and tumble) intervals, directional correlations between successive runs and finite tumble intervals. Using this new method, we derive a set of new general results for bacterial drift velocity and diffusion coefficient when run and tumble intervals have non-exponential distributions, in the limit of weak gradient. A set of specific results for gamma-distributed runs and tumbles are also derived. In addition, we also show that many existing results can be reproduced using our approach, including (a) equation (3), (b) super and sub-diffusive random motion (without chemotaxis) when run intervals are power-law distributed and (c) modification of the effective diffusion coefficient by correlation between directions of successive runs.

A brief note on the name and historical origins of the formalism is pertinent here. We refer to the technique as ‘path-integral’, as it follows essentially the same reasoning as its more famous namesake in quantum mechanics, quantum field theory and statistical physics [26]; i.e. assigning a probability(density) to every possible path taken by the system during its time evolution, and computing averages by summing over these paths. Different variants of the present technique have been used earlier, in the study of ion channel dynamics [27, 28], reaction–diffusion processes in cells [29] as well as search and capture of chromosomes by microtubules [30]. Here, we develop and expand it further to study the run and tumble motion in bacteria.

The following limitations of the present study may also be noted. All the explicit calculations are presented in spatial dimension $d = 2$; generalisations to $d = 1$ and $d = 3$ are straightforward, but not discussed here. In the present form, our formalism does not include Brownian rotation of the bacterium during runs, an important aspect which has been included in several earlier papers [14, 20, 31]. Also, while the structure of the theory is sufficiently general, owing to practical difficulties, we have not (yet) been able to extend the computations beyond the lowest non-trivial order in $\alpha$, hence our present results are limited to weak gradients.

The rest of the paper is organized into three sections. Section 2 introduces the formalism and the tools. Section 3 contains all the results derived in the paper, including confirmation of existing results. Section 4 summarizes the important findings of the paper, and a discussion on possible extensions and further applications of the method.

2. The general path-integral functional for run and tumble motion

Let us consider a bacterium executing run and tumble motion in two dimensions. Denote by $f(T)$, the survival probability of the bacterium in the run state, and let $g(\tau)$ be the same for tumbles, so that $f(0) = g(0) = 1$ by definition. The probability distributions of the run and
tumble interval durations, respectively, are \( -\dot{f} \) and \(-\dot{g} \). Throughout this paper, we assume that rotational diffusion during runs is absent.

A time interval \([0 : t] \) could fall into one of the two following categories: (a) \( N \) completed runs, \( N \) completed tumbles, and one incomplete run \((N \geq 0)\), or (b) \( N \) completed runs, \( N - 1 \) completed tumbles, and one incomplete tumble \((N \geq 1)\). Let \( T_i \) denote the time intervals corresponding to runs, and \( \tau_i \) denote the same for tumbles. During a tumble, the bacterium undergoes a reorientation such that its direction of motion changes. Let \( G_{\tau_i} (\theta_0) \) denote the probability distribution of the final angle \( \theta_i \), given initial angle \( \theta_0 \) and time of tumble \( \tau_i \). Let \( \theta_i \) be the angle specifying the run with duration \( T_i \), which remains constant during the run, we assume. We choose the convention that the bacterium always starts in a run state at \( t = 0 \), and the duration of the first run is \( T_1 \), while that of the first tumble is \( \tau_1 \). Then, the probability functionals describing paths corresponding to situation (a) and (b) are, respectively,

\[
\Phi_N^{(a)}(T, \tau; t) = f(T_{N+1})\delta \left( T_{N+1} + \sum_{i=1}^{N} (T_i + \tau_i) - t \right)
\]

\[
\times \psi(\theta_1) \prod_{i=1}^{N} \dot{f}(T_i) \dot{g}(\tau_i) G_{\tau_i}(\theta_{i+1}|\theta_i)
\]

(4)

and

\[
\Phi_N^{(b)}(T, \tau; t) = -g(\tau_N)\dot{f}(T_N)\delta \left( \sum_{i=1}^{N} (T_i + \tau_i) - t \right)
\]

\[
\times \psi(\theta_1) \prod_{i=1}^{N-1} \dot{f}(T_i) \dot{g}(\tau_i) G_{\tau_i}(\theta_{i+1}|\theta_i),
\]

(5)

where \( \psi(\theta_1) = (2\pi)^{-1} \) is the probability distribution of the initial angle \( \theta_1 \). The functionals are normalized as follows:

\[
\sum_{N=0}^{\infty} \int_a \Phi_N^{(a)}(T, \tau; t) d\Omega + \sum_{N=1}^{\infty} \int_b \Phi_N^{(b)}(T, \tau; t) d\Omega = 1,
\]

(6)

where

\[
\int_a \ldots d\Omega \equiv \int_0^t \int_0^{2\pi} \ldots dT_1 \int_0^{\tau_1} \ldots d\theta_1 \int_0^{\tau_1} \ldots d\tau_1 \int_0^{\tau_1} \ldots dT_2 \int_0^{2\pi} \ldots d\theta_2 \ldots
\]

\[
\times \int_0^{\tau_N} \ldots d\tau_N \int_0^{\tau_N} \ldots dT_{N+1} \int_0^{2\pi} \ldots d\theta_{N+1}
\]

and

\[
\int_b \ldots d\Omega \equiv \int_0^t \int_0^{2\pi} \ldots dT_1 \int_0^{\tau_1} \ldots d\theta_1 \int_0^{\tau_1} \ldots d\tau_1 \int_0^{\tau_1} \ldots dT_2 \int_0^{2\pi} \ldots d\theta_2 \ldots
\]

\[
\times \int_0^{\tau_N} \ldots d\tau_N \int_0^{2\pi} \ldots d\theta_N \int_0^{\tau_N} \ldots dT_{N+1} \int_0^{2\pi} \ldots d\theta_{N+1}
\]

are time-ordered integrals. Using the above functionals, the mean of any dynamical quantity which depends explicitly on the variables \( \{T, \tau, \theta\} \) may be calculated. Let \( \alpha(t) \) be such a quantity (e.g. the net displacement), whose value for a given trajectory may be denoted \( \mathcal{A}_N(T, \tau, \theta) \) [32]. Then, the ensemble average of \( \alpha \) is given by
\[ \overline{a}(t) = \langle A_N(T, \tau, \theta) \rangle = \langle A_N(T, \tau, \theta) \rangle_a + \langle A_N(T, \tau, \theta) \rangle_b, \]  

where

\[ \langle A_N(T, \tau, \theta) \rangle_a = \sum_{N=0}^{\infty} \int_a \mathcal{A}_N(T, \tau, \theta) \Phi_N^{(a)}(T, \tau, \theta; t) \, d\Omega, \]

\[ \langle A_N(T, \tau, \theta) \rangle_b = \sum_{N=1}^{\infty} \int_b \mathcal{A}_N(T, \tau, \theta) \Phi_N^{(b)}(T, \tau, \theta; t) \, d\Omega. \]  

Furthermore, the probability distribution for the variable \( a \) may be expressed as

\[ P(a, t) = \langle \delta(a - A_N(T, \tau, \theta)) \rangle. \]  

In the following subsection, we will discuss a simplified version of the general model introduced here, which will be used for most of the mathematical calculations.

2.1. The ‘minimal’ model: instantaneous tumbles, no directional correlations

In this simplified model, which shall serve as a reference model for us, (i) the tumble durations are assumed to be negligibly small in comparison with run durations (i.e. \( \tau_i \to 0 \) everywhere), and (ii) directional correlations between successive runs are ignored. Condition (i) requires that we choose the tumble time distribution to be \(-\delta(\tau)\). This implies that \( g(\tau) = 0 \) for \( \tau \neq 0 \) while \( g(0) = 1 \). It is then clear that in this case, events corresponding to class (b) in equations (7) and (8) do not contribute to the averages, and may be ignored. Condition (ii) implies that \( G_{\tau_i} (\theta_i+1|\theta_i) = (2\pi)^{-1} \) for \( i \in [1, N] \) in equation (4). As a result, the probability functional in equation (4) reduces to (the superscript ‘m’ denoting ‘minimal’ from now on)

\[ \Phi_N^{(m)}(T, \theta; t) = \frac{1}{(2\pi)^{N+1}} f(T_{N+1}) \delta \left( T_{N+1} + \sum_{i=1}^{N} T_i - t \right) \]

\[ \times \prod_{i=1}^{N} (-1)^{N} f(T_i). \]  

The average of any dynamical quantity \( a(t) \equiv A_N(t; T, \theta) \) associated with the motion may be evaluated as \( \overline{a}(t) = \langle A_N(t; T, \theta) \rangle_m \), where

\[ \langle A_N(t; T, \theta) \rangle_m = \sum_{N=0}^{\infty} \int \cdots \cdots d\Omega \mathcal{A}_N \Phi_N^{(m)}(T, \theta; t) A_N(T, \theta), \]  

with

\[ \int \cdots \cdots d\Omega \equiv \int_0^T \cdots \cdots dT_1 \int_0^{2\pi} d\theta_1 \int_0^{1-T_1} dT_2 \int_0^{2\pi} d\theta_2 \cdots \]

\[ \times \int_0^{1-\sum_{i=1}^{N} T_i} dT_{N+1} \int_0^{2\pi} d\theta_{N+1}. \]  

When \( f(T) \) is non-exponential, it is convenient to use its Fourier transform \( F(\omega) \) in equation (10), defined by the relation \( 2\pi F(\omega) = \int_{-\infty}^{\infty} f(T) e^{i\omega T} \, dT \) (with the understanding that \( f(T) = 0 \) for \( T < 0 \)). In this case, equation (11) becomes
\[\langle A_N(t; \mathbf{T}, \theta) \rangle_m = \sum_{N=0}^{\infty} \frac{1}{(2\pi)^N} \int \mathcal{A}_N(\mathbf{T}, \theta) D\mathbf{T} D\theta \int_a D\omega e^{-i\omega t + i t} F(\omega_{N+1}) \]
\[\times \prod_{i=1}^{N} i \omega_i F(\omega_i) e^{-i(\omega_i - \omega_{N+1}) T_i},\]

where \(\int D\omega \equiv \int \cdots \prod_{i=1}^{N+1} \omega_i\). For \(\mathcal{A} \equiv 1\), equation (13) reduces to the normalisation relation \(\sum_{N=0}^{\infty} P_N(t) = 1\), where

\[P_N(t) = \int D\mathbf{T} D\theta \prod_{i=1}^{N} i \omega_i F(\omega_i) e^{-i \sum_{i=0}^{N} \omega_i T_i} F(\omega_{N+1}) e^{-i \omega_{N+1} (t - \sum_{i=1}^{N} T_i)}\]

(14) gives the probability distribution of the number of tumble events during the time interval [0 : t].

Equation (14) can be expressed in a more compact way using Laplace transforms. For the rhs, we use the following generalisation of the standard convolution theorem in Laplace transforms [28]: given any function \(f(t) = \int_0^t dT_1 h_1(T_1) f(T_1 - T_2) h_2(T_2) \cdots \int_0^{t - \sum_{i=1}^{N} \delta_i} dN h_N(T_N)\), its Laplace transform is \(L_s[f] \equiv \int_0^t f(t) e^{-st} dt = s^{-1} \prod_{i=1}^{N} L_s[h_i]\). Using this theorem in equation (14), we find

\[L_s[P_N] = \int D\omega F(\omega) \left[ i \int D\omega F(\omega) / (s + i\omega) \right]^N.\]

(15)

It is easily verified that \(\sum_{N=0}^{\infty} P_N(t) = 1\), by completing the elementary geometric sum, and noting that \(\int_{-\infty}^{\infty} d\omega F(\omega) \equiv f(0) = 1\) by definition.

2.2. Special cases and extensions of the minimal model

In this subsection, we introduce a few special cases of the functional in equation (10), as well as a few extensions.

(a) Exponentially distributed run intervals (exponential model): A particularly simple special case of the minimal model is that of exponentially distributed run durations, where \(-f(T) = \lambda e^{-\lambda T} H(T)\) and \(-g(\tau) = \delta(\tau)\), where \(H(T)\) is the Heaviside step-function: \(H(T) = 1\) for \(T \geq 0\) and 0 otherwise . This implies \(f(T) = e^{-\lambda T} H(T)\) and the corresponding probability functional is

\[\Phi_N^{(e)}(\mathbf{T}, \theta; t) = \frac{1}{(2\pi)^{N+1}} e^{-\lambda T_{N+1}} \delta \left( T_{N+1} + \sum_{i=1}^{N} T_i - t \right) \]
\[\times \lambda^N e^{-\lambda \sum_{i=1}^{N} T_i}.\]

(16)

In the above expression, the superscript ‘e’ denotes ‘exponential’.

(b) Power-law distributed run intervals—Lévy flights : Earlier experimental observations by Korobkova et al [33] had suggested that the cumulative probability of CCW interval durations of a single flagellar motor shows power-law decay for nearly two decades in time. Partly motivated by this observation, we study a model with \(f(T) = (1 + \gamma T)^{-\beta}\) with \(\gamma > 0\) and \(\beta > 0\).

(c) Exponential model with directional correlations between successive runs : The run and tumble motion of *E. coli* observed in experiments is characterized by directional
persistence, i.e. the directions of two consecutive runs are positively correlated. The mean angle between the directions of two consecutive runs separated by a tumble has been reported to be in the range $62^\circ - 69^\circ$ [34]. We assume here that the correlation exists only between two consecutive runs. The probability functional for this case is a straightforward generalisation of equation (16):

$$
\Phi_{N}(e, \theta; t) = e^{-\lambda T_{N+1}} \delta \left( T_{N+1} + \sum_{i=1}^{N} T_{i} - t \right) \lambda^{N} \times e^{-N \sum_{j=1}^{N} \psi(\theta_{j})} \prod_{j=1}^{N} G(\theta_{j+1}\mid \theta_{j}),
$$

(17)

where the additional superscript 'p' represents persistence/antipersistence in run directions, and $\psi(\theta_{1}) = \frac{2\pi}{-1}$ as mentioned earlier (since the initial run direction is chosen randomly). To bring in directional correlations between successive runs, we choose

$$
G(\theta_{j+1}\mid \theta_{j}) = \frac{1}{2\pi} \left( 1 + J \cos(\theta_{j+1} - \theta_{j}) \right), \quad \forall j \in [1, N].
$$

(18)

In the above expression, $J$ is a phenomenological parameter to be chosen such that $|J| < 1$ to ensure positivity of $G(\theta_{j+1}\mid \theta_{j})$. Further, $J > 0$ implies persistence and $J < 0$ implies anti-persistence of motion. It is also easily verified that $\langle \cos(\theta_{j+1} - \theta_{j}) \rangle = J/2$, so that the parameter $J$ may be fixed using the value of the average in the l.h.s, as observed in experiments.

(d) Exponential model with chemotaxis; linear response regime: In E. coli, chemotaxis is achieved by making the tumble rate a function of the previous positions of the bacterium. For a general path and time-dependent tumble rate, denoted as $\Lambda(t) \equiv \Lambda(r; T, \theta)$, equation (10) may be generalised as

$$
\Phi_{N}^{(e)}(T, \theta; t) = \frac{1}{(2\pi)^{N+1}} e^{-\int_{0}^{t} \Lambda(T) dT} \times \prod_{i=1}^{N} \Lambda(t_{i}) e^{-\int_{0}^{t_{i}} \Lambda(T) dT},
$$

(19)

where $t_{i} = \sum_{j=1}^{i} T_{j}$ for $1 \leq i \leq N$. In the minimal model with exponentially distributed run intervals, the dependence of tumbling rate on attractant concentration may be expressed through the linear response relation

$$
\Lambda(t) = \lambda \left[ 1 - \int_{0}^{t} R(t - t') c[r(t')] dt' \right],
$$

(20)

which follows directly from equation (1). Here, $\Lambda(t)$ is the time-dependent tumble rate, $\lambda$ is the tumble rate in the absence of attractant and $r(t)$ is the position of the bacterium at time $t$. In the case of a uniform attractant gradient such that $\nabla c(r) = \alpha$, we have $c(r) = \alpha \cdot r$. Without loss of generality, we choose $\alpha = \alpha \hat{x}$, such that

$$
\Lambda(t) = \lambda \left[ 1 - \alpha \int_{0}^{t} R(t - t') \hat{x}(t') dt' \right].
$$

(21)
Equation (2), when substituted in equation (21), leads to the following ‘path-dependent’ tumble rate:
\[ \Lambda(t) = \lambda [1 - \kappa \alpha (x(t) - x(t - \Delta))] . \] (22)

Equation (22), when used in equation (19) leads to the following expansion of the probability functional, in the limit of weak gradient:
\[ \Phi_N^{(c)}(T, \theta; t) = 1 \pm \frac{\kappa}{2^N} \sum_{i=1}^{N} [x(t_i) - x(t_i - \Delta)] + O(\alpha), \] (23)
where the second superscript, ‘c’ indicates ‘chemotaxis’. In the following section, we present our important results for each of these models.

3. Results

In this section, we present all the results we derived using our formalism. We start with a set of general formulae in section 3.1, while in the following section 3.2, we show that our method reproduces many existing results of interest. A set of new results is derived in section 3.3. Most of the mathematical details of the derivations may be found in a set of appendices at the end of the paper.

3.1. General formulae

3.1.1. Mean-squared displacement. The mean square displacement (MSD) in the minimal model is given by
\[ \langle r^2 \rangle = \langle R_N(t; T, \theta) \cdot R_N(t; T, \theta) \rangle_m, \] (24)
is the displacement vector for a certain path, with \( \mathbf{e}_i = i \cos \theta_i + j \sin \theta_i \) being unit vectors specifying the directions of individual runs. After using equation (11), the following general expression for the Laplace transform of the MSD is arrived at, after a straightforward computation using the convolution theorem:
\[ L_s\left[ \langle r^2 \rangle \right] = \frac{2v^2 I_2(s; F)}{I_1(s; F)}, \] (25)
where the integrals are defined as
\[ I_1(s; F) = \int \frac{\omega F(\omega)}{s + i\omega}; \quad I_2(s; F) = i \int \frac{\omega F(\omega)}{(s + i\omega)^2}. \] (26)

(It is also useful to note that \( I_2(s; F) = I'_2(s; F)/2 \), where \( I'_2(s; F) = 1 - sI_1(s; F) \) and the prime denotes differentiation with respect to \( s \).) As a special case, it follows that, if \( \lim_{s \to 0^+} I_2/I_1 \) is non-zero and finite, \( \langle r^2 \rangle \sim 4Dt \), with the diffusion coefficient \( D \) being given by the general expression
\[ D = \frac{v^2}{2} \lim_{s \to 0^+} \frac{I_2(s; F)}{I_1(s; F)}. \] (27)
3.1.2. Chemotactic drift velocity to the lowest order in \( \alpha \). In appendix A, we show that the general expression for drift velocity for an arbitrary distribution \(-\dot{f}(T)\) of run intervals, in the limit of small \( \alpha \), is

\[
v_d = -\pi \lambda \alpha v^2 \lim_{s \to 0^+} \frac{1}{I_1(s; F)} \int \frac{d\omega}{i(\omega - is)^3} F(\omega) \tilde{R}(-\omega) i(\omega - is)^3,
\]

where \( \tilde{X} \) is a quantity with dimensions of inverse time, defined via equation (A.2), while \( F(\omega) \) and \( \tilde{R}(\omega) \) are the Fourier transforms of \( f(T) \) and \( R(T) \) respectively. The integral \( I_1 \) has been defined in equation (26). The result in equation (28) enables us to study systematically how the drift velocity is affected by deviations in the run interval distribution, from the standard exponential form, for which the result is given by equation (49).

A comparative discussion of our result in equation (28), vis-à-vis the corresponding results of de Gennes [7] and Locsei [14], is given in appendix B.

The general expression for drift velocity when tumble intervals have finite durations is derived in appendix C. The result is

\[
v_d = -\pi \lambda \alpha v^2 \lim_{s \to 0^+} \frac{1}{I_1(s; F + G)} \int \frac{d\omega}{i(\omega - is)^3} F(\omega) \tilde{R}(-\omega) i(\omega - is)^3,
\]

where \( G(\omega) \) is the Fourier transform of \( g(T) \), the tumble interval distribution being \(-\dot{g}(T)\).

3.2. Confirmation of existing results

3.2.1. MSD for Exponential model. The diffusion coefficient can be easily found using the expression in equation (27). Here,

\[2\pi F(\omega) = (\lambda - i\omega)^{-1}\]

which leads to the diffusion coefficient

\[D^{(exp)} = \frac{v^2}{2\lambda},\]

for the exponential model [16, 31, 35]. In appendix D, we also show explicitly that the probability distribution of the displacement in the long-time, large distance limit, for this model, is Gaussian.

3.2.2. MSD for power-law distributed run intervals. The details of the calculations are presented in appendix E. A summary of the results are given below:

\[
\langle r^2 \rangle \propto t^\beta \\
\begin{align*}
0 & < \beta \leq 1, \\
1 & < \beta \leq 2, \\
\beta & > 2.
\end{align*}
\]

Thus, the motion is ballistic for \( \beta \leq 1 \), super-diffusive when \( 1 < \beta < 2 \) and diffusive when \( \beta \geq 2 \). The above results agree with the predictions made in [36], derived using heuristic scaling arguments (a slightly different model is presented in [37], where both run and tumble intervals are assumed to be power-law distributed).

3.2.3. MSD in exponential model with directional correlations between runs. After carrying out the required calculations (see appendix F for details) we find \( \langle r^2 \rangle \sim 4D_J t \), where

\[D_J = \frac{v^2}{2\lambda(1 - J/2)}.\]
is the diffusion coefficient for the run and tumble walk, when directional persistence is present. The expression in equation (32) agrees with the more general expression of Celani and Vergassola [20], derived by a different method for arbitrary spatial dimension \( d \). The corresponding result in \( d = 3 \) was obtained earlier by Lovely and Dahlquist [31], and later by Schnitzer [6].

3.2.4. Chemotactic drift velocity in the exponential model. We now use the functional in equation (23) to compute the mean displacement of the bacterium in the long-time limit, and thereby derive an expression for the drift velocity to the lowest order in \( \alpha \). It is easily seen that, in the evaluation of \( \langle x(t) \rangle \), the leading term \( (O(\alpha^0)) \) does not contribute in the long-time limit, and the leading non-zero term can be written as the sum of two terms: \( \langle x(t) \rangle = x_1(t) + x_2(t) \) with

\[
x_1(t) = \alpha \kappa \lambda \int_{t-\Delta}^{t} \langle x(t')x(t) \rangle \, dt'
\]

and

\[
x_2(t) = -\alpha \kappa \sum_{j=1}^{N} \left[ \langle x(t)x(t_j) \rangle e - \langle x(t)x(t_j - \Delta) \rangle e \right],
\]

where the averages need to be carried out using the functional in equation (16). The first average is particularly simple; this is because for the unbiased run and tumble walk, we expect \( \langle x(t)x(t') \rangle \sim 2D^{(\exp)} t' \) for \( t' \leq t \) in the large \( t \)-limit, similar to Brownian diffusion [32], with the diffusion coefficient \( D^{(\exp)} \) being given by equation (30). Substituting this result in equation (33) leads to the asymptotic result \( x_1(t) \sim v_1 t \), with

\[
v_1 = \alpha \kappa v^2 \Delta.
\]

The computation of \( x_2(t) \) is more involved, and the details are to be found below. Let us start with equation (34), and express the rhs in the form

\[
x(t_j) - x(t_j - \Delta) = \sum_{i=1}^{j} P_j^i \cos \theta_i,
\]

where (for \( 1 \leq i \leq j - 1 \)),

\[
P_j^i = v \left( \Delta - \sum_{q=i+1}^{j} T_q \right) \left[ H \left( \Delta - \sum_{q=i+1}^{j} T_q \right) - H \left( \Delta - \sum_{m=i}^{j} T_m \right) \right] + v T_i H \left( \Delta - \sum_{m=i}^{j} T_m \right),
\]

while

\[
P_j^i = v \Delta H (T_i - \Delta) + v T_i H (\Delta - T_i).
\]

Next, we define the integrals

\[
I_m = -v \alpha \kappa \int D T \left( \sum_{j=1}^{N} [x(t_j) - x(t_j - \Delta)] \right) T_m \cos \theta_m
\]
such that

\[ x_2(t) = \sum_{N=0}^{\infty} \lambda^N e^{-\lambda t} \left[ \sum_{m=1}^{N+1} T_m \right], \quad (40) \]

where we can write

\[ T_m = \frac{\sum_{r=m}^{N} T_r}{\sum_{r=m}^{N} T_r} ; \quad T_m = -\frac{V_{\Omega N}}{2} \int DTP^r T_m. \quad (41) \]

The time ordered integral in equation (41) can be done using the convolution theorem in section 2, after expressing the Heaviside functions in equation (37) using the integral representation

\[ 2\pi H(\Delta - \tau) = \int_0^{\Delta} dy \int_0^{\infty} d\psi e^{i\psi(y-\tau)}. \]

Thus, it follows that

\[ L_s[T_m] = \frac{1}{2\pi s^{N+m-r+2}} \int_0^{\Delta} \int_0^{\Delta} e^{i\psi(s+i\psi)m-r} \]

\[ - \frac{1}{2\pi s^{N+m-r+2}} \int_0^{\Delta} \int_0^{\Delta} e^{i\psi(s+i\psi)m-r-1} \]

\[ - \frac{1}{2\pi s^{N+m-r}} \int_0^{\Delta} \int_0^{\Delta} e^{i\psi(s+i\psi)m-r-2} \]

\[ + \frac{1}{2\pi s^{N+m-r}} \int_0^{\Delta} \int_0^{\Delta} e^{i\psi(s+i\psi)m-r-3}. \quad (42) \]

The integrals in the above expression are straightforward; for any \( n \geq 0 \), we have

\[ \frac{1}{s^2} \int_0^{\Delta} dy \int_0^{\infty} d\psi e^{i\psi(s+i\psi)m-r} = \int_0^{\Delta} s^{n-1} e^{-s\tau} dy \]

\[ L_s[I_{N-n}] = \sum_{j=1}^{N+1} \beta_j(s), \quad (43) \]

where, after the rescaling \( sy = \phi \), we find, for \( 2 \leq j \leq N \),

\[ \beta_j(s) = \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^{j-2} d\phi - \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^{j-1} d\phi \]

\[ - \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi + \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^{j+1} d\phi, \quad (44) \]

while

\[ \beta_1(s) = \frac{\Delta}{s^{N+2}} - \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi \]

\[ + \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi \]

\[ + \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi \]

\[ + \frac{\Delta}{s^{N+2}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi. \quad (45) \]

Using equations (43) in (40), it follows that

\[ L_s[x_2(t)] = \sum_{N=0}^{\infty} \lambda^N \left[ \sum_{j=1}^{N} (N-j+1) \beta_j(s + \lambda) \right]. \quad (46) \]

The sum in the rhs of the above equation, after some algebra, is found to be

\[ \sum_{j=1}^{N} (N-j+1) \beta_j(s) = \frac{N\Delta}{s^{N+2}} (2 - e^{-\Delta s}) - \frac{N}{s^{N+3}} \int_0^{\Delta s} e^{-\phi} \phi^j d\phi. \quad (47) \]
After substituting equations (47) into (46) and completing the sum, we find that, in the limit $s \to 0$,

$$L_{\epsilon} [x_2(t)] \sim \frac{\kappa v_2^2 \alpha}{2 \lambda s^2} (1 - e^{-\lambda \Delta} - 2 \lambda \Delta),$$

(48)

which directly leads to the asymptotic result $x_2(t) \sim v_2 t$, where

$$v_2 = \frac{\kappa v_2^2 \alpha}{2 \lambda} (1 - e^{-\lambda \Delta} - 2 \lambda \Delta).$$

(49)

Adding equations (35) and (49) leads to the complete result $\langle x(t) \rangle \sim v_{d}^{(\text{exp})} t$, where the drift velocity $v_{d}^{(\text{exp})} = v_1 + v_2$ for exponentially distributed run intervals is given by

$$v_{d}^{(\text{exp})} = \frac{\kappa v_2^2 \alpha}{2 \lambda} (1 - e^{-\lambda \Delta}),$$

(50)

in agreement with de Gennes [7], and is a special case of the more general expression in equation (3), when the response function is approximated as in equation (2). This follows from the following argument. To derive equations (3) from (50), note that, according to equation (50), a response function $R(t) = \delta(t - \Delta)$ would result in a drift ‘velocity’ $v_d = D \alpha e^{-\lambda \Delta}$, with $D$ given by equation (30). Now, we may express $\delta(t - \Delta) = (2\pi)^{-1} \int_{-\infty}^{\infty} e^{i \omega (t - \Delta)} d\omega$. Since any arbitrary response function may be expressed as $R(t) = \int_{-\infty}^{\infty} R(\omega) e^{i \omega t} d\omega$, it follows that the general expression for drift velocity should be $v_d = 2\pi D \alpha R(-i\lambda)$, in agreement with equation (3) (note that $R(t) = 0$ for $t < 0$).

For later purposes, it is useful to note that the expression in equation (50) is a monotonically decreasing function of the tumble frequency $\lambda$, with the following limiting behaviours:

$$v_{d}^{(\text{exp})} \sim \frac{\kappa v_2^2 \alpha \Delta}{2} \quad \lambda \ll \Delta^{-1},$$

$$v_{d}^{(\text{exp})} \sim \frac{\kappa v_2^2 \alpha}{2 \lambda} \quad \lambda \gg \Delta^{-1}.$$  

(51)

3.3. New results for non-exponential run time distributions

Next, we provide specific results for the drift velocity, when run and/or tumble intervals are not exponentially distributed, for three special cases of interest.

3.3.1. Gamma-distributed run intervals. Recent experimental observations [24, 25, 38] have shown that durations of CW and CCW intervals in a single flagellar motor are best described by gamma distributions, which indicate the presence of multiple hidden Markov steps within a motor (even when decoupled from its signalling network, as in [24]). A characteristic feature of gamma-distributions is the presence of a peak, which implies the presence of a characteristic ‘frequency’ of motor-switching. The observations of Korobkova et al [24] were studied by van Albada et al [39], who proposed that the non-exponential waiting time distributions may be explained in terms of a coupling between switching and rotary dynamics of the motor, and mechanical feedback from conformational dynamics of the flagellum. To separate the effects of filamental dynamics from the intrinsic motor dynamics, Wang, Yuan and Berg [40] studied the statistics of motor rotations in cells lacking flagellar filaments. They concluded that the distributions of CW and CCW intervals are near-exponential, with no visible peak as in [24]. However, according to Park et al [25], their observations [38] fit well with
a phenomenological model that relates the switching behaviour to the magnitude of noise in the chemotaxis signalling network.

We first consider gamma-distributed runs alone (while still keeping tumbles instantaneous) and estimate the drift velocity of the bacterium. Let $\dot{\xi}(t) = \xi(t)$ be the probability distribution of run intervals, where

$$
\xi_n(t) = \frac{\lambda^n}{\Gamma(n)} t^{n-1} e^{-\lambda t},
$$

(52)

where $n \geq 1$ is the number of hidden steps in a single CCW → CW switch. For $n = 1$, the model reduces to the exponential model. For $n > 1$, the run interval distribution has a single peak at $t^* = (n - 1)/\lambda$. Thus, while the model has a preferred run interval, similar to the periodic tumble model, shorter and longer runs are not completely suppressed. In this sense, the present ‘gamma-model’ may be considered an intermediate between the purely exponential model and the periodic tumble model.

The (run state) survival probability in the present model is given by $f_n(t) = \int_t^\infty \xi_n(T) dT$, whose Fourier transform, from equation (52), is given by

$$
F_n(\omega) = \frac{\lambda^n}{\Gamma(n)} \frac{1}{2\pi i \omega} - \frac{1}{2\pi i \omega},
$$

(53)

for $n \geq 1$, where

$$
\mathcal{F}_n = (-1)^{n-1} \frac{\lambda^n}{\Gamma(n)} \frac{d^{n-1}}{d\lambda^{n-1}}
$$

is a linear differential operator, $\Gamma(n) = (n - 1)!$ being the standard gamma function.

Next, we use the more general expression for $v_d$ in equation (A.10) (appendix A), and use equation (53), leading to

$$
v_d(n) \sim \lambda \alpha \gamma \frac{\lambda^n}{2I_1(0; F_n)} \mathcal{F}_n \left[ (1 - e^{-\lambda})/\lambda^4 \right],
$$

(55)

which is the required generalisation of equation (49) for arbitrary $n$. To evaluate the integral in the denominator, note that

$$
I_1(s; F_n) = \frac{1}{s} \int \frac{d\omega F_n(\omega)}{\omega^{s}} = J_2(s) - J_1(s),
$$

(56)

where $F_n(\omega)$ is given by equation (53). The integrals $J_1$ and $J_2$ are

$$
J_1(s) = \mathcal{F}_n \int \frac{d\omega F_1(\omega)}{\omega^{s}}; J_2(s) = \int \frac{d\omega}{\omega^{s}}.
$$

(57)

The integrals are evaluated using standard techniques. After a few straightforward calculations, we find that $J_1 = n/\lambda - 1/2s$, and $J_2 = \pi/s$. Combining the two in equation (56), we arrive at the remarkably simple result

$$
I_1(s; F_n) = \frac{n}{\lambda},
$$

(58)
which, when used in equation (55) gives the drift velocity for gamma-distributed run intervals. The effective diffusion coefficient for this case can be evaluated by similar methods. The integral $I_2$ in equation (27) turns out to be

$$I_2(0; F_n) = \frac{n(n + 1)}{2\lambda^2}, \quad (59)$$

so that the effective diffusion coefficient is

$$D^{(n)} = \frac{(n + 1)v^2}{4\lambda}. \quad (60)$$

$D^{(n)}$ is an increasing function of $n$. The same is true for $v^{(n)}$, too, as it is clear from figure 1, where we plot the scaled drift velocity $v^{(n)} = \frac{v^{(n)}}{\kappa_0 \lambda^2}$ as a function of $\lambda$, for a few different values of $n$ and fixed $\Delta$.

An intuitive interpretation of the above observation is as follows. Note from equations (50) and (51) that drift is smaller for large values of $\lambda$, which corresponds to shorter runs, on average. By suppressing shorter runs, compared to purely exponential distribution, the gamma-distribution leads to enhanced drift. The same argument also applies to the random component of the motion, characterized by the effective diffusion coefficient.

Is the enhancement of drift velocity for gamma-distributed runs purely due to suppression of short runs? To answer this question, we investigated an extreme case where the tumbles occur in a perfectly periodic manner.

### 3.3.2. Perfectly periodic tumbles

Here, we choose $-\dot{\phi}(T) = \delta(T - T_0)$, so that the tumbles, in the absence of chemotaxis, occur in a perfectly periodic manner, with time period $T_0$. The survival probability is $f(T) = H(T_0 - T)$, whose Fourier transform is

$$F(\omega) = \frac{\text{e}^{i\omega T_0} - 1}{2\pi i \omega}. \quad (61)$$

For the bi-lobed response function with time delay $\Delta$, the drift velocity can be computed by substitution of equations (61) in (28), while the effective diffusion coefficient is computed using equation (27). The resulting integrals in the numerator and denominator, for both cases, are evaluated using Cauchy’s residue theorem, the details of which are skipped here. Since $T_0$ is the only time scale in the distribution, we use $\lambda = \frac{T_0}{T_0 - 1}$ in equation (28). The final results for drift and diffusion coefficients are

$$v^{(\text{delta})} = \frac{\alpha \kappa_0^2}{12 T_0^2} \left\{ T_0^3 - (T_0 - \Delta)^3 H(T_0 - \Delta) \right\},$$

$$D^{(\text{delta})} = \frac{\nu^2 T_0}{4}. \quad (62)$$

To compare equations (62) with (49) and (30), it is convenient to put $T_0 = \lambda^{-1}$, so that the mean run intervals match in both cases. Figure 2 plots the ratio of the expressions in equations (49) and (62) as a function of the dimensionless number $\frac{\Delta}{T_0}$. The ratio $\eta$ is always found to be larger than unity, and varies in the range 2–6. Hence, we conclude that making the tumbles occur in a perfectly periodic manner is not helpful for the drift.

### 3.3.3. Drift velocity for gamma-distributed run and tumble durations: dependence on clock-wise bias

We now consider the case where both runs and tumbles are gamma-distributed,
as suggested by experiments [24, 25]. The general expression for drift velocity when tumble intervals have finite durations was given by equation (29).

We again make the simplifying assumption that runs correspond to CCW mode of a motor, tumbles correspond to CW mode, and define the probability distributions $\xi_n(t)$ for run intervals and $\xi^{\ast}_n(t)$ for tumble intervals, with Poisson rates $\lambda$ and $\lambda^{\ast}$, and number of 'hidden' Markov steps $n$ and $n^{\ast}$, respectively. Their respective survival probabilities are denoted $f_n(T) = \int_T^\infty \xi_n(t) dt$ and $g^{\ast}_n(\tau) = \int_\tau^\infty \xi^{\ast}_n(t) dt$, with Fourier transforms $F_n(\omega)$ and $G^{\ast}_n(\Omega)$. 

**Figure 1.** The scaled drift velocity $\tilde{v}^{(n)}_d$ for gamma-distributed run-lengths and instantaneous tumbles (equation (55)) as a function of the Poisson rate $\lambda$, for response time delay $\Delta = 1.0$ s.

**Figure 2.** The ratio $\eta = v^{\text{exp}_d}/v^{\text{delta}_d}$ of the drift velocity for exponential (equation (50)) and delta (equation (62)) distributions of run intervals is plotted against the dimensionless delay time $\Delta/T_0$. 

as suggested by experiments [24, 25]. The general expression for drift velocity when tumble intervals have finite durations was given by equation (29).
The general expression for drift velocity with arbitrary run and tumble distributions is given in equation (29), in which the integrals \( I_{1}(s;F/G) \) are to be replaced by \( I_{1}(s;Fn/Gn^{*}) \). From equation (58), it follows that \( I_{1}(s;F_n) = n/\lambda \), and \( I_{1}(s;Gn^{*}) = n^{*}/\lambda^{*} \). Using these results in equation (29), it follows that the drift velocity, in this case, is given by the expression

\[
v_{d}^{(n,n^{*})} = \frac{\lambda_{0}k_{01}^{2}}{2I_{1}(0;Fn+Gn^{*})} \hat{F}_{\lambda}^{n}[(1-e^{-\lambda\Delta})/\lambda^{4}],
\]

which generalizes equation (55). The parameters \( n, n^{*}, \lambda, \lambda^{*} \) have been estimated in the experiments reported by Park et al [25], as a function of the mean clockwise bias \( b \) of a motor, and are summarized in table 1. Using these values in equation (63), we computed the drift velocity \( v_{d}^{(n,n^{*})} \) as a function of the clockwise bias by using the software package Mathematica.

### Table 1. Details of the parameters used in figures 1 and 3. Here, \( b \) denotes the CW bias.

| Symbol | Quantity | Numerical values | Source |
|--------|----------|------------------|--------|
| \( n \) | Number of hidden steps (CCW \( \rightarrow \) CW) | \( 8b + 1 \) (0 \( \leq \) \( b \) \( \leq \) 0.5) | [25] |
| \( n^{*} \) | Number of hidden steps (CW \( \rightarrow \) CCW) | 5 (0 \( \leq \) \( b \) \( \leq \) 1) | [25] |
| \( \lambda \) | Poisson rate (CCW \( \rightarrow \) CW) | \( nk_{01} \) | [25] |
| \( \lambda^{*} \) | Poisson rate (CW \( \rightarrow \) CCW) | \( n^{*}k_{10} \) | [25] |
| \( \Delta \) | Time delay | 1 s | [10] |

The scaled drift velocity \( \tilde{v}_{d}(n,n^{*}) \) (see definition in text) is plotted as function of the CW bias \( b \). The plot is constructed using the expression in equation (63) and the experimental data in table 1. Inset: the ratio of the predicted drift velocity at various CW bias to its value for purely exponential (\( n = n^{*} = 1 \)) CW and CCW interval distributions.

Figure 3.

![Diagram](image-url)
Figure 3 shows the plot of $\tilde{v}(n, n^*) d_0 = v(n, n^*) d_0 / \kappa \alpha v^2$ as a function of the mean clockwise bias $b$. Interestingly, while the drift velocity itself appears to follow a monotonic decay (note, however, that only a small set of bias values were used in the plot, corresponding to integer values for $n$ and $n^*$, see table 1), the ratio $\tilde{v}(n, n^*) d_0 / \tilde{v}(1,1) d_0$ (see inset, figure 3) has a weak non-monotonic nature, with a maximum of around 1.6, which is attained at $b \approx 0.5$. (The mean clock-wise bias of wild-type $E. coli$ cells has been reported to be around 0.13 [41].)

For the sake of completeness, we also derive the expression for the effective diffusion coefficient $D(n, n^*)$ in this case. Upon substituting equations (58) and (59) in (C.3), we find that

$$D(n, n^*) = \frac{n(n + 1)v^2}{4\lambda(n + n^*) \frac{\alpha}{\kappa}}.$$  \hspace{1cm} (64)

Table 2 collects all the results for diffusion coefficient and drift velocity derived or re-derived in this paper, except those for power-law distributed run intervals, which were summarized in equation (31).

4. Summary and conclusions

In this paper, we have presented a novel, path-integral-inspired method to compute various dynamical quantities of interest in run and tumble motion of bacteria, with and without chemotaxis. Similar to a few earlier papers [11, 14, 20, 23], our study is also motivated by the pioneering work of de Gennes [7], who computed an expression for drift velocity of a bacterium, after neglecting rotational diffusion and persistence of direction. In this derivation, the drift velocity is assumed to be the product of the mean displacement of the bacterium over a single (representative) run and the mean number of run/tumble events per unit time. Since it involves two independent averages, de Gennes’ derivation is clearly of a ‘mean-field’ nature. Locsei [14] provided an alternative definition of drift velocity, as the ratio of mean displacement during a run event to the mean time taken to complete the run. Locsei’s formalism includes Brownian rotations during runs and directional persistence following a tumble, and

| Model                    | Run interval distribution | Tumble interval distribution | Diffusion coefficient | Drift velocity |
|--------------------------|---------------------------|------------------------------|-----------------------|---------------|
| General, non-power law   | $-f(T)$                   | $-g(\tau)$                  | Equation (27)         | Equation (29) |
| Exponential, non-persistent | $\lambda e^{-\lambda T}$ | $\delta(\tau)$              | Equation (30)         | Equation (50) |
| Exponential, persistent  | $\lambda e^{-\lambda T}$ | $\delta(\tau)$              | Equation (32)         | [14]          |
| Periodic tumbles         | $\delta(T - T_0)$         | $\delta(\tau)$              | Equation (62)         | Equation (62) |
| Gamma, runs              | $\frac{\lambda^* n \Gamma(n)}{\Gamma(n^*)} e^{-\lambda^* T} \delta(\tau)$ | $\delta(\tau)$              | Equation (60)         | Equation (65) |
| Gamma, runs and tumbles  | $\frac{\lambda^* n \Gamma(n)}{\Gamma(n^*)} e^{-\lambda^* T} \delta(\tau)$ | $\delta(\tau)$              | Equation (64)         | Equation (63) |

(Wolfram Research Inc., 2008).
is, therefore, a significant generalisation of de Gennes’ result. However, similar to de Gennes’, Locsei’s definition also involves computing two different averages. A general formalism where all required statistical averages could be computed using a single probability density functional was missing so far, and it is this gap we sought to fill with our new approach. Furthermore, the formalism is sufficiently general to include non-Poissonian run-tumble and tumble-run transitions, the existence of which has been observed in recent experiments [24, 25]. By construction, the formalism allows us to express any required average as a power-series in the chemo-attractant gradient, but we find that explicit computations become rather lengthy beyond the lowest order. In the present form, it is a challenge to include Brownian rotations during the run phase in this formalism. This may be possible by suitably expanding the same, the details of which are yet to be worked out.

A number of existing results were re-derived by us using the new method. These include (a) de Gennes’ classic result for drift velocity [7], (b) the effective diffusion coefficient for the unbiased run and tumble walk with ‘built-in’ directional persistence [6, 14, 20, 31] and (c) the occurrence of ballistic, super-diffusive and diffusive behaviour of the MSD when the run intervals are algebraically distributed [36]. The principal new, general results are (a) the chemotactic drift velocity (equation (28)) and (b) the effective diffusion coefficient in the absence of chemotaxis (equation (27)), for arbitrary, non-exponentially distributed run intervals. As examples, we used equation (28) to compute drift velocity for two specific cases, gamma-distributed and delta-distributed run intervals (periodically spaced tumbles). We show that while gamma-distributed run intervals uniformly lead to enhancement in drift velocity, spacing the tumbles apart in a perfectly periodic manner reduces the same.

In recent experiments [24, 25], the distributions of CW and CCW intervals of a single flagellar motor in an immobilised bacterium were measured as a function of the mean clockwise bias $b$ of the motor. It was found that both intervals are, in general, gamma-distributed, but the number of hidden steps in each transition (CW $\rightarrow$ CCW and vice-versa) depends continuously on the bias [24, 25]. Although the CCW and CW spinning states of a single motor may not directly correspond to run and tumble events of a bacterium, it is likely that the latter also displays similar statistical behaviour. Assuming this to be the case, we applied our formalism to make predictions for the drift velocity of such a bacterium. While the drift velocity appears to follow a monotonic decay with bias (at least for the selected set of values of $b$), the enhancement ratio of the same (with reference to the purely exponential run/tumble distributions) shows a maximum in the vicinity of $b \simeq 0.5$. We are hopeful that a future experiment may explore the statistics of run and tumble durations in more detail, and measure the drift velocity as a function of the mean clockwise bias; the latter could be tuned by e.g. selecting cells with lower/higher values of intracellular concentrations of important signalling proteins like CheR or CheB.

The model we studied here assumes that run durations are modulated by an attractant gradient, but tumble durations are not. However, observations by Saragosti et al [34], and more recently by Pohl et al [42] reported larger directional persistence following a tumble (i.e. smaller value of the difference in angle) when swimming in favourable directions (along the gradient) when compared to unfavourable directions (against the gradient). Using a statistical parameter inference method to analyze a large number of individual bacterial trajectories, Seyrich et al [43] showed recently that the increased persistence when swimming ‘upstream’ can be accounted for by shorter tumbles and smaller rotational diffusivity during a tumble, when compared to run. In an earlier paper, Saragosti et al [44] showed that tumbles may be modelled as Brownian rotations of the bacterium; hence, shorter the tumble, smaller would be the tumble angle (with reference to the original direction). Taken together, the above
observations strongly suggest the possibility of existence of a gradient-dependent modulation of the mean tumble time [44], with the corresponding Poisson rate satisfying a linear response relation similar to equation (1), which should make an additional contribution to the drift velocity. It would be interesting to explore the consequences of this ‘tumble time-modulation’ using our formalism.

The technique presented in the paper has been developed with the run and tumble walk of *E. coli* in mind, which has multiple flagella uniformly distributed over its body. On the other hand, many marine bacteria like *Shewanella putrefaciens* and *Vibrio alginolyticus* (*V. alginolyticus*) are mono-flagellated, while the soil bacterium *Pseudomonas putida* (*P. putida*) has multiple flagella, but localized at one pole of the cell body. Unlike *E. coli*, such bacteria typically employ a run and reverse mode of locomotion, where, instead of tumbling between runs, the cell undergoes abrupt reversals in its direction of motion by $\sim 180^\circ$. Observations show that *V. alginolyticus* has a more complex run-reversal-flick swimming pattern, where, during the last step (‘flick’) the cell chooses a new direction with a preferred angle of $\sim 90^\circ$ [45]. Interestingly, Xie *et al* [45] also observed that the time intervals of both forward and reverse motion have non-exponential distributions, with a single well-defined peak in each. Similar observations have also been in *P. putida* [46]. With appropriate modifications, it should be possible to adapt our formalism to run-reverse and run-reverse-flick modes of random motion by introducing additional memory terms in the angular Green’s function.

It is also likely that our formalism may find applications in other, related fields. Anomalous, non-Brownian signatures in the transport of intracellular organelles on networks of filaments have been receiving considerable attention lately [47, 48]. It has been suggested that non-Markovian, effective models of molecular motor-driven cargo motion could offer a possible explanation of the observed anomalous features of transport [48]. Indeed, an earlier theoretical study had also shown rigorously that the bidirectional motion of intracellular cargoes pulled by multiple molecular motors has an inherent non-Markovian character, and is characterized by non-exponential survival probabilities of different motility states [49]. We believe that the path-integral method presented here will be found useful in these and other, similar transport problems in biology where the presence of hidden, ‘internal’ variables makes the observed dynamics appear non-Markovian.

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Appendix A. Diffusion coefficient and drift velocity for general \( f(T) \)

In this section, we present the calculation of drift velocity under chemotaxis, for arbitrary run interval distribution \( f(T) \), but assuming that the unbiased motion is diffusive in the long-time limit. Let us start from equation (10): the attractant gradient modifies the survival probability in the run state, which we express in the general form

\[
f(T; T, \theta) = f^{(0)}(T) \left\{ 1 - \int_{t=1}^{t} \delta R(t; T, \theta) dt + \ldots \right\},
\]

\[\text{(A.1)}\]
where
\[
\delta R(t; T, \theta) = -\alpha \lambda \int_0^t R(t - t')x(t')dt'
\]  
(A.2)
is the perturbation due to the gradient and \( \lambda \) is a baseline switch rate. From equation (A.1), we find
\[
\dot{f}(T; T, \theta) = f^{(0)}(T_i) - \delta f_i(T, \theta),
\]  
(A.3)
where the dot denotes differentiation with respect to the first variable, and
\[
\delta f_i(T, \theta) = f^{(0)}(T_i) \int_{t_{i-1}}^{t_i} \delta R(t; T, \theta)dt + f^{(0)}(T_i)\delta R(t; T, \theta).
\]  
(A.4)

After using equations (A.1) and (A.4), the probability functional in equation (10) may be expanded in the form
\[
\Phi^{(mc)}_N(T, \theta; t) = \frac{1}{(2\pi)^{N+1}} f^{(0)}(T_{N+1}) \delta \left( T_{N+1} + \sum_{i=1}^{N} T_i - t \right)
\]
\[
\times \prod_{i=1}^{N} (-1)^{N_i} f^{(0)}(T_i) \left[ 1 - \int_0^t \delta R(t'; T, \theta)dt' - \sum_{i=1}^{N} \delta R(t_i; T, \theta)f^{(0)}(T_i) + \ldots \right],
\]  
(A.5)
which replaces equation (23), for general \( f(T) \). The mean position \( \langle x(t) \rangle = x_1(t) + x_2(t) \) again, with the slightly modified expressions:
\[
x_1(t) = \alpha \kappa \lambda \int_{t-\Delta}^t \langle x(t')x(t) \rangle dt',
\]
\[
x_2(t) = -\alpha \kappa \lambda \sum_{j=1}^N \left( x(t)[x(t_j) - x(t_j - \Delta)]f^{(0)}(T_j) \right) / f^{(0)}(T_j),
\]  
(A.6)
where the averages are to be computed using the distribution function in equation (10). Note that for \( f(T) = e^{-\lambda T}H(T) \), the expressions in equation (A.6) reduce to those in equations (33) and (34). We again use the standard result \( \langle x(t)x(t') \rangle \sim 2D \Delta \) (for \( t' \leq t \)) in the long time limit to find \( x_1(t) \sim v_1 \Delta \) where
\[
v_1 = 2\kappa \lambda \alpha D \Delta,
\]  
(A.7)
with \( D \) given by equation (27). The Laplace transform of \( x_2(t) \) turns out to be
\[
\mathcal{L}_s [x_2] = -\frac{\kappa \lambda \alpha \Delta}{2} \sum_{N=0}^{\infty} \int D\omega \sum_{i=1}^{N} (N - i + 1) \beta_i(s + i\omega_i)
\]
\[
\times F(\omega_i) \prod_{j \neq i} i\omega_j F(\omega_j),
\]  
(A.8)
which is a generalisation of equation (46) in appendix A. The explicit expressions for the integrals \( \beta_i(s) \) are given in equations (44) and (45). After completing the summation, we find that \( x_2(t) \sim v_2 \Delta \) for large \( t \), where
\[
v_2 = -\lim_{s \to 0^+} \frac{\lambda \kappa \alpha \Delta^2}{2 \Gamma(\frac{s}{F})} \int d\omega F(\omega) \left\{ -\frac{2\Delta}{(\omega - is)^2} + \frac{1}{i(\omega - is)^3} \right\}.
\]  
(A.9)
It may be easily verified that, for the exponential model with \( F(\omega) = [2\pi(\lambda - i\omega)]^{-1} \) (and the substitution \( \lambda \to \lambda \)), the rhs of equation (A.9) reduces to that of equation (49), as expected.

The net drift velocity is given by the sum of the expressions in equations (A.7) and (A.9):

\[
\nu_d = \lim_{s \to 0^+} \frac{\overline{\lambda} \alpha v^2}{2I_1(s; F)} \int d\omega F(\omega) \frac{(e^{-i\omega \Delta} - 1)}{i(\omega - is)^3},
\]

which generalises equation (50) for arbitrary \( f(T) \).

The expression in equation (A.10) is easily generalised to an arbitrary response function \( R(t) \) through the replacement \( \kappa(1 - e^{-i\omega \Delta}) \to 2\pi \tilde{R}(-\omega) \), where \( \tilde{R}(\omega) \) is the Fourier transform of \( R(t) \), as defined following equation (50). The result is equation (28).

Appendix B. Comparison of our result with those of de Gennes [7] and Locsei [14]

Equation (28) has the following intuitive interpretation, following de Gennes’ approach [7]. In the long time limit, the mean displacement, \( \langle x \rangle \sim \nu_d t \), as given by equation (28), may be expressed as

\[
\langle x \rangle = \langle \Delta x \rangle_{\text{run}} \overline{N}(t),
\]

where \( \overline{N}(t) \) is the mean number of tumbles (completed runs) during \([0 : t]\), and \( \langle \Delta x \rangle_{\text{run}} \) is the mean displacement of the bacterium per run, when measured with respect to its starting location at the start of the run. The mean number of tumbles can be computed using the distribution in equation (15), and the result turns out to be

\[
\overline{N}(t) \sim \frac{t}{I_1(0; F)}. \tag{B.2}
\]

Using equation (B.2), we deduce that the mean displacement per run is

\[
\langle \Delta x \rangle_{\text{run}} = -\pi \alpha v^2 \lim_{s \to 0^+} \int d\omega F(\omega) \tilde{R}(-\omega) \frac{i(\omega - is)^3}{i(\omega - is)^3}.
\]

Locsei [14] defines the drift velocity through the relation (equation (5) in [14])

\[
\nu_d'(L) = \frac{\langle \Delta x \rangle_{\text{run}}}{\langle T \rangle_{\text{run}}}, \tag{B.4}
\]

where \( \langle T \rangle_{\text{run}} \) is the mean run duration, and it is assumed that both the averages in equation (B.5) have stationary values, and are hence independent of the ‘location’ of the run in the time interval concerned. In the limit of weak chemotaxis, the numerator in equation (B.5) is \( O(\alpha) \), hence the denominator needs to be computed only in the absence of chemotaxis to obtain the lowest order term in drift velocity. In this limit, \( \langle T \rangle_{\text{run}} = -\int_0^\infty T f dT = \int_0^\infty f(T) dT = 2\pi F(0) \), and hence Locsei’s expression for drift velocity, in our notation, would be

\[
\nu_d'(L) = \frac{\overline{\lambda} \alpha v^2}{2F(0)} \lim_{s \to 0^+} \int d\omega F(\omega) \tilde{R}(-\omega) \frac{i(\omega - is)^3}{i(\omega - is)^3} \tag{B.5}
\]

If we now assume that the Fourier transform \( F(\omega) \) has no singularity in the upper half-plane (as is, for example, the case with single or multi-exponential functions which decay with time), then it is easy to see that \( \lim_{s \to 0^+} I_1(s; F) = 2\pi F(0) \), in which case the expressions in

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Appendix C. Results for general $f(T)$ and $g(\tau)$

In this case, the tumbles are no longer assumed to be instantaneous. After a few straightforward calculations, it emerges that the generalisation of the result in equation (27) is

\[ D = D_a + D_b, \tag{C.1} \]

with

\[ D_a = \frac{v^2}{2} \lim_{s \to 0^+} \frac{I_1(s; F)I_2(s; F)}{I_1^2(s; F + G)}; \]
\[ D_b = \frac{v^2}{2} \lim_{s \to 0^+} \frac{I_1(s; G)I_2(s; F)}{I_1^2(s; F + G)}, \tag{C.2} \]

where the integrals have been defined in equation (26); note that $I_1(s; F + G) = I_1(s; F) + I_1(s; G)$. Upon using this property in equation (C.2), we find

\[ D = \frac{v^2}{2} \lim_{s \to 0^+} \frac{I_2(s; F)}{I_1(s; F + G)}, \tag{C.3} \]

which is the most general expression for the diffusion coefficient in the (unbiased) run and tumble motion, in the absence of directional persistence. For $v_2$, the corresponding generalisation of equation (A.9) turns out to be

\[ v_2 = - \lim_{s \to 0^+} \frac{\lambda \kappa \alpha v^2}{2I_1(s; F + G)} \int d\omega F(\omega) \left\{ - \frac{2\Delta}{(\omega - i\alpha)^2} + \frac{1 - e^{-i(\omega + \alpha)\Delta}}{i(\omega - i\alpha)^3} \right\}. \tag{C.4} \]

The modification of drift on account of finite tumble durations, as displayed in equation (C.4) may be understood as follows: the replacement of $I_1(s; F)$ in the denominator equation (A.9) by (the larger) $I_1(s; F + G)$ in equation (C.4) arises from the reduction in the number of run/tumble events in a given time interval on account of the finite durations spent by the organism in the (unproductive) tumble state. On the other hand, the chemotactic sensing mechanism (equations (1) and (2)) only affects the run durations in the present model, hence the numerator is unaffected.

The net drift velocity is $v_d = v_1 + v_2$, with $v_1$ given by equation (A.7), with $D$ replaced with the expression in equation (C.1), and $v_2$ given by equation (C.4). The final result is

\[ v_d = \lim_{s \to 0^+} \frac{\lambda \kappa \alpha v^2}{2I_1(s; F + G)} \int d\omega F(\omega) \left( \frac{e^{-i\omega\Delta} - 1}{i(\omega - i\alpha)^3} \right), \tag{C.5} \]

which differs from the expression in equation (A.10) only in the integral term in the denominator. The generalization of equation (C.5) to include an arbitrary form of the response function is given in equation (29). Note that equations (C.5) includes (50) and (A.10) as special cases.

Appendix D. Probability distribution of displacement in the exponential model

Here, we calculate the probability distribution of the displacement vector $r$ of the bacterium after time $t$. Note that for a given trajectory with $N$ tumbles in all, the displacement vector is
given by the expression in equation (24). The probability distribution \( P(\mathbf{r}, t) \) is evaluated using the functional in equation (16); \( P(\mathbf{r}, t) = \langle \delta^2(\mathbf{r} - \mathbf{R}_N(t; \mathbf{T}, \mathbf{\theta})) \rangle \), whose Fourier transform \( \tilde{P}(\mathbf{k}, t) = (2\pi)^{-1} \int P(\mathbf{r}, t)e^{i\mathbf{k} \cdot \mathbf{r}} \) turns out to be

\[
\tilde{P}(\mathbf{k}, t) = \sum_{N=0}^{\infty} \frac{1}{(2\pi)^{N+2}} \lambda^N e^{-\Delta t} \int_0^{2\pi} \cdots d\theta_{N+1} \int_0^t dT_1 e^{i\lambda T_1} \int_0^{t-T_1} dT_2 e^{i\alpha T_2} \times \cdots \int_0^{t-\sum_{j=1}^{N-1} T_j} dT_N e^{i\alpha T_N},
\]

where \( A = \lambda + iv \mathbf{k} \cdot \mathbf{e}_{N+1} \) and \( \alpha_j = v \mathbf{k} \cdot (\mathbf{e}_{N+1} - \mathbf{e}_j) \). After using the generalised convolution theorem in section 2, we find the Laplace-transformed distribution \( \tilde{P}(\mathbf{k}, s) = \int_0^\infty \tilde{P}(\mathbf{k}, t)e^{-st}dt \):

\[
\tilde{P}(\mathbf{k}, s) = \sum_{N=0}^{\infty} \frac{1}{(2\pi)^{N+2}} \lambda^N \left[ \int_0^{2\pi} \frac{d\theta}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}(\theta)} \right]^{N+1},
\]

where \( \mathbf{e}(\theta) = \cos \theta \mathbf{i} + \sin \theta \mathbf{j} \) are unit vectors. After carrying out the straightforward angular integration, we find

\[
\tilde{P}(\mathbf{k}, s) = \frac{1}{2\pi} \left( \frac{1}{\sqrt{(s + \lambda)^2 + v^2k^2}} \right),
\]

where \( k = |\mathbf{k}| \). For small \( k \), one can expand the denominator in powers of \( k^2 \). After carrying out the \( s \rightarrow t \) inverse Laplace transform of the resulting expression, we find

\[
\tilde{P}(\mathbf{k}, t) \sim \frac{1}{2\pi} \exp \left( \frac{-v^2k^2t}{2\lambda} \right) \left( \frac{\nu k}{\lambda} \rightarrow 0 \right).
\]

The inverse Fourier transform (\( \mathbf{k} \rightarrow \mathbf{r} \)) of equation (D.4) yields the large distance asymptotic form

\[
P(\mathbf{r}, t) \sim \frac{1}{4\pi D^{(\exp)}_t} \exp \left( \frac{-r^2}{4D^{(\exp)}_t} \right) \left( r \gg \nu/\lambda \right),
\]

where \( r = |\mathbf{r}| \) is the net displacement and the diffusion coefficient \( D^{(\exp)} \) is given in equation (30).

**Appendix E. Mean square displacement for (Lévy-like) algebraically decaying \( f(T) \)**

**E.1. Case \( 0 < \beta \leq 1 \)**

The Fourier transform of the function \( f(T) = (1 + \gamma T)^{-\beta} \) is defined as

\[
F(\omega) = \frac{1}{2\pi} \int_0^\infty \frac{e^{i\omega T}}{(1 + \gamma T)^\beta} dT.
\]

Substituting \( 1 + \gamma T = x \) in the above integral, we obtain

\[
F(\omega) = \frac{e^{-i\omega/\gamma}}{2\pi \gamma} \int_1^\infty \frac{e^{i\omega x/\gamma}}{x^\beta} dx = F'(\omega) - F''(\omega),
\]

where \( F'(\omega) = \lim_{x \rightarrow \infty} \frac{e^{i\omega x/\gamma}}{x^\beta} \) and \( F''(\omega) = \lim_{x \rightarrow 1} \frac{e^{i\omega x/\gamma}}{x^\beta} \).
\[ F'(\omega) = \frac{e^{-i\omega/\gamma}}{2\pi\gamma} \int_0^\infty \frac{e^{i\omega x/\gamma}}{x^{3/2}} dx; \quad F''(\omega) = \frac{e^{-i\omega/\gamma}}{2\pi\gamma} \int_0^1 \frac{e^{i\omega x/\gamma}}{x^{3/2}} dx. \]  

(E.3)

Note that $F''(\omega)$ does not diverge as $\omega \to 0$, while $F'(\omega)$ does (see below); therefore in the long-time limit we are interested in, $F(\omega) \sim F'(\omega)$. Consider now the complex-valued integral

\[ F(z) = \oint \frac{e^{iz}}{z^{3/2}} dz, \]  

(E.4)

with the contour of evaluation chosen as in figure E1 where $z = x + iy$. In the limit $R \to \infty$, the integral over the quarter-circle vanishes according to Jordan’s lemma, and we arrive at

\[ \int_0^\infty \frac{e^{i\omega x/\gamma}}{x^{3/2}} dx + \int_0^1 \frac{e^{i\omega iy/\gamma}}{(iy)^{3/2}} idy = 0, \]  

(E.5)
where the rhs is zero since \( F(z) \) has no pole inside the contour. Therefore

\[
F(\omega) \sim \frac{e^{-i\omega/\gamma}}{2\pi\gamma^\beta} \omega^{1-\beta} \Gamma(1-\beta).
\]  
(E.6)

The integral \( I_1(s;F) \) in equation (26) becomes

\[
I_1(s;F) = \frac{\Gamma(1-\beta)\gamma^{-\beta}e^{\pi(1-\beta)}}{\pi} I_A(s),
\]  
(E.7)

where

\[
I_A(s) = \int_0^\infty \frac{e^{-i\omega/\gamma}}{s+i\omega} \omega^{\beta-1} d\omega.
\]  
(E.8)

To evaluate the integral, we use the contour in figure E2; along the branch cut, \( \omega \) will be replaced by \( \omega e^{i2\pi} \), while along the imaginary axis, \( \omega = iy \). Applying Cauchy’s residue theorem again, we find

\[
e^{i2\pi(\beta-1)} I_A + i\beta \int_{-\infty}^0 y^{\beta-1} \frac{e^{i\gamma y}}{s-y} dy = 0.
\]  
(E.9)

Substituting \( \xi = -y \), we find

\[
I_A = e^{-i\pi\beta/2} \int_0^\infty \xi^{\beta-1} \frac{e^{-\xi/\gamma}}{s+\xi} d\xi.
\]  
(E.10)

The integral in the rhs of equation (E.10) can be evaluated by introducing an auxiliary variable \( \lambda \) through the integral representation \( 1/(s+\xi) = \int_0^\infty e^{-\lambda(s+\xi)} d\lambda. \) After substituting in the above equation, we find

\[
\int_0^\infty \xi^{\beta-1} \frac{e^{-\xi/\gamma}}{s+\xi} d\xi = \Gamma(1-\beta).
\]  
(E.11)

where \( \eta = \lambda s \). In the limit \( s \to 0 \), the integral becomes \( \Gamma(1-\beta) \). We now substitute the resulting limiting expression for \( I_A(s) \) in equation (E.7) to find that \( I_1(s,F) \propto s^{\beta-1} \) as \( s \to 0 \). It follows that \( I_2(s,F) \propto s^{\beta-2} \) and hence, from equation (26), we find \( \langle r^2 \rangle \propto \tau^2 \) for large \( \tau \). The motion is, therefore, ballistic in this regime.

**E.2. Case II: 1 < \beta < 2**

For \( \beta > 1 \), the Fourier transform of the survival probability can be expressed as

\[
F_{\beta}(\omega) = \frac{1}{2\pi\gamma(1-\beta)} \int_0^\infty e^{i\omega t} d[(1+\gamma t)^{1-\beta}],
\]  
(E.12)

which can be simplified to

\[
F_{\beta}(\omega) = \frac{1}{2\pi\gamma(\beta-1)} \left[ 1 + i\omega F_{\beta-1}(\omega) \right].
\]  
(E.13)

For \( \beta < 2 \), after using the expression given in (E.6), we get

\[
F_{\beta}(\omega) = \frac{1}{2\pi\gamma(\beta-1)} \left[ 1 + \Gamma(2-\beta)e^{i\pi(3-\beta)/2} e^{-i\omega/\gamma (\omega/\gamma)^{\beta-1}} \right].
\]  
(E.14)
For this case, one can write $I_1(s; F) = I_1^{(1)} + I_1^{(2)}$, which are defined as follows:

$$I_1^{(1)} = \int_{-\infty}^{\infty} \frac{d\omega}{2\pi \gamma (\beta - 1)(s + i\omega)} = \frac{-i}{2\pi \gamma (\beta - 1)} \equiv A_1,$$

$$I_1^{(2)} = \Gamma(2 - \beta) e^{\pi(3 - \beta)/2} \int_{-\infty}^{\infty} \frac{e^{-\omega/\gamma \omega^{\beta - 1}}}{s + i\omega} d\omega = A_2 s^{\beta - 1},$$

(E.15)

where $A_1$ and $A_2$ are constants. Therefore $I_1(s; F) = A_1 + A_2 s^{\beta - 1}$ and $I_2 \propto s^{\beta - 2}$. From equation (26), it follows that $\mathcal{L}_2(\langle r^2 \rangle) \propto s^{4 - \beta}$, and hence $\langle r^2 \rangle \propto t^{\beta - 3/2}$. Thus, the run and tumble motion is super-diffusive in this regime.

**E.3. Case III: $\beta \geq 2$**

Here, we apply the recursion relation in equation (E.13) one more time to find that $I_1(s; F) = B_1 + B_2 s + B_3 s^{\beta - 1}$, where $B_1, B_2, B_3$ are non-zero constants. It then follows that in the long time limit, $\langle r^2 \rangle \propto t$, i.e. the motion is purely diffusive in this regime.

**Appendix F. Mean square displacement in unbiased motion with directional persistence**

The Fourier–Laplace transform of the probability distribution $P(r, t)$ of the position $r$ at time $t$ is given by the following generalisation of equation (D.2):

$$\tilde{P}(k, s) = \sum_{N=0}^{\infty} \lambda^N \int D\theta \frac{\psi(\theta_1)}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}_1} \prod_{j=1}^{N+1} \frac{G(\theta_{j+1} | \theta_j)}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}_j},$$

(F.1)

where, the unit vectors $\mathbf{e}_j$ have been defined following equation (24). Let us now define a set of $N$ integrals,

$$I_1(\theta_N) = \int_0^{2\pi} \frac{d\theta_{N+1} G(\theta_{N+1} | \theta_N)}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}_{N+1}} ,$$

$$I_2(\theta_{N-1}) = \int_0^{2\pi} \frac{d\theta_{N} G(\theta_{N} | \theta_{N-1}) I_1(\theta_N)}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}_N} ,$$

$$\vdots$$

$$I_N(\theta_1) = \int_0^{2\pi} \frac{d\theta_{2} G(\theta_{2} | \theta_1) I_{N-1}(\theta_2)}{s + \lambda + iv \mathbf{k} \cdot \mathbf{e}_2}. $$

(F.2)

After substituting equations (18) in (F.2), it turns out that, for general $n$, the integral $I_n$ can be expressed as

$$I_n = C_n + D_n \cos(\theta_{N-n+1}),$$

(F.3)

where

$$\begin{bmatrix} C_n \\ D_n \end{bmatrix} = \begin{bmatrix} (s + \lambda) A_1 & -ivk A_2 \\ -ivk A_2 & (s + \lambda) A_2 \end{bmatrix}^{n-1} \begin{bmatrix} C_1 \\ D_1 \end{bmatrix}; \quad \forall n \geq 2$$

(F.4)
and \( k \equiv |\mathbf{k}| \). The constants \( A_1 \) and \( A_2 \) in the above equation are given by the following integrals:

\[
\begin{align*}
A_1 & \equiv \frac{1}{2\pi} \int_0^{2\pi} \frac{d\theta}{(s + \lambda)^2 + v^2 k^2 \cos^2 \theta}, \\
A_2 & \equiv \frac{1}{2\pi} \int_0^{2\pi} \frac{\cos^2 \theta d\theta}{(s + \lambda)^2 + v^2 k^2 \cos^2 \theta},
\end{align*}
\]

whose explicit expressions are

\[
\begin{align*}
A_1 &= \frac{1}{(s + \lambda) \sqrt{(s + \lambda)^2 + v^2 k^2}}, \\
A_2 &= \frac{1}{v^2 k^2} \left[ 1 - \frac{s + \lambda}{\sqrt{(s + \lambda)^2 + v^2 k^2}} \right].
\end{align*}
\]

where \( C_1 = (s + \lambda)A_1 \) and \( D_1 = -ivkA_2 \). The rhs of equation (F.4) is evaluated using Cayley–Hamilton theorem, which uses the following eigenvalues of the \( 2 \times 2 \) matrix in equation (F.4):

\[
\begin{align*}
\lambda_1 &= \frac{(s + \lambda)(A_1 + JA_2) + \sqrt{(s + \lambda)^2(A_1 + JA_2)^2 - 4J[(s + \lambda)^2A_1A_2 + v^2k^2A_2^2]}}{2}, \\
\lambda_2 &= \frac{(s + \lambda)(A_1 + JA_2) - \sqrt{(s + \lambda)^2(A_1 + JA_2)^2 - 4J[(s + \lambda)^2A_1A_2 + v^2k^2A_2^2]}}{2}.
\end{align*}
\]

The final exact result, after some simplifications, is

\[
\hat{P}(k, s) = \frac{1}{2\pi} \left( \frac{1}{\sqrt{(s + \lambda)^2 + v^2k^2} - \lambda} \right) \left( J\lambda v^2 k^2 A_2^2 \right)
\]

\[
2\pi \left[ (s + \lambda)^2A_2^2 - J \left( 2v^2k^2A_2^2 + (s + \lambda)^2A_1A_2 \right) \right] \left( \sqrt{(s + \lambda)^2 + v^2 k^2} - \lambda \right)^2
\]

which, as expected, reduces to equation (D.3) when \( J = 0 \). The Laplace transform of the MSD \( \langle r^2 \rangle = \langle x^2 \rangle + \langle y^2 \rangle \) is given by

\[
\mathcal{L}_s[\langle r^2 \rangle] = 2\pi \left\{ \left. \frac{\partial^2 \hat{P}(k, s)}{\partial (-ik_x)^2} \right|_{k=0} + \left. \frac{\partial^2 \hat{P}(k, s)}{\partial (-ik_y)^2} \right|_{k=0} \right\},
\]

which we use in equation (F.8) to find that \( \mathcal{L}_s[\langle r^2 \rangle] \sim 4D_J/s^2 \) as \( s \to 0 \), or, equivalently, \( \langle r^2 \rangle \sim 4D_J t \) as \( t \to \infty \), with the diffusion coefficient \( D_J \) given in equation (32).

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