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Characterization and Control of the Run-and-Tumble Dynamics of *Escherichia Coli*

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We characterize the full spatiotemporal gait of populations of swimming *Escherichia coli* using renewal processes to analyze the measurements of intermediate scattering functions. This allows us to demonstrate quantitatively how the persistence length of an engineered strain can be controlled by a chemical inducer and to report a controlled transition from perpetual tumbling to smooth swimming. For wild-type *E. coli*, we measure simultaneously the microscopic motility parameters and the large-scale effective diffusivity, hence quantitatively bridging for the first time small-scale directed swimming and macroscopic diffusion.

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Swimming is key for many microorganisms to survive [1–8]. Such “active matter” is necessarily far from thermal equilibrium [9–12] and displays peculiar transport properties, which enable foraging [13] and escaping from harm [14]. The flagellated bacterium *Escherichia coli* is a model system for active matter experiments [3,15–21]. Much is known about its genetics, biochemistry, and ultrastructure, but relating this knowledge to the emerging phenotype, for instance to predict the three-dimensional (3D) pattern of locomotion (or gait) of a swimming population, remains a challenge.

The bacterium’s “run-and-tumble” (RT) dynamics [2] alternates between persistent motion along the cell’s axis and sudden changes of direction. While the motion of isolated flagella has been studied in detail using *in vitro* single-motor experiments [22,23], a quantitative characterization of the full

3D gait of swimming populations of multiflagellated bacteria has been out of reach so far. This stems, in particular, from the need for measurements over length scales ranging from the order of the short-time runs ($\sim 1\text{--}10\ \mu\text{m}$) to far beyond the persistence length ($\gtrsim 10^2\ \mu\text{m}$). Assuming exponentially distributed run and tumble durations, the RT dynamics is predicted to lead to a large-scale diffusion [2,24–26], but this claim has seldom been demonstrated experimentally, and the underlying assumptions have recently been questioned [22,27]. The accurate characterization of RT dynamics will therefore fill an important gap.

At the same time, while many aspects of the motility of *E. coli* have been brought under direct experimental control [2,4,18,28–35], including the ability to regulate its run speed by light [36,37], there is currently only limited scope to fine-tune its overall gait compared to synthetic swimmers [38–43] because the bacterium’s tumble dynamics is difficult to control independently. The aforementioned lack of good methods to quantify its RT dynamics contributes to these difficulties, which in turn limits the use of *E. coli* as a model organism for fundamental active matter research.

In this Letter, we report a full characterization of the 3D gait of *E. coli*, which enables us to demonstrate how the RT

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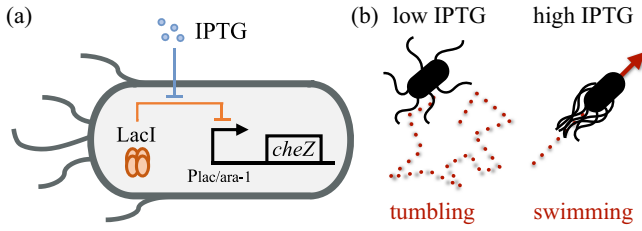


FIG. 1. Engineered strain NZ1. (a) Scheme of the regulation: *cheZ* expression driven by Plac/ara-1 is suppressed by the LacI suppressor. Exogenously adding IPTG induces *cheZ* expression by reducing LacI suppression. (b) Cells are expected to tumble continuously at low IPTG concentration and to enter a smooth swimming state at high IPTG concentration.

dynamics of an engineered strain can be tuned from perpetual tumbling to smooth swimming as the concentration of a chemical inducer is varied. These cells can be used in future work under conditions in which their persistence length can be predicted *a priori* once experimental conditions are specified.

We characterize a bacterium's displacement $\Delta\mathbf{r}(\tau)$ at lag time τ in Fourier space using the intermediate scattering function (ISF):

$$f(\mathbf{k}, \tau) = \langle e^{-i\mathbf{k} \cdot \Delta\mathbf{r}(\tau)} \rangle. \quad (1)$$

Analyzing the ISF with a renewal theory then allows us to extract microscopic kinetic parameters such as the particle speed and the run and tumble durations. To measure the ISF, we extend conventional differential dynamic microscopy (DDM) [44] to collect data encompassing both short-length-scale directed-swimming and large-length-scale diffusive regimes. DDM allows us to work in bulk fluid to minimize hydrodynamic interactions with surfaces [45–49]. It also circumvents the need of single-cell tracking, which requires customized Lagrangian [1,2,50,51] or holographic [52,53] microscopy and is limited by the need for low cell concentration, statistical accuracy, and short trajectories. Our data confirm to order of magnitude previous measurements of *E. coli* motility [1], albeit with a significantly larger run time. We find large-length-scale diffusive behavior and compare the extracted diffusivity, D_{eff} , with a theoretical prediction based on the microscopic motility parameters. The predicted D_{eff} is robust against experimental complexities, but speed fluctuations contribute $\sim 10\%$ of its value. Below, we focus on the biophysical implications of our results while our methodology is detailed and validated in a companion paper [54].

Bacterial strain.—We engineered the NZ1 strain by deleting the *cheZ* gene in *E. coli* K12 and adding the inducible plasmid Plac/ara-1-*cheZ* [17] [Fig. 1(a)]. Deleting *cheZ* suppresses the transition from clockwise to counterclockwise flagella rotation, so that cells tumble permanently. The plasmid restores expression of *cheZ* at a rate dependant on the concentration of Isopropyl

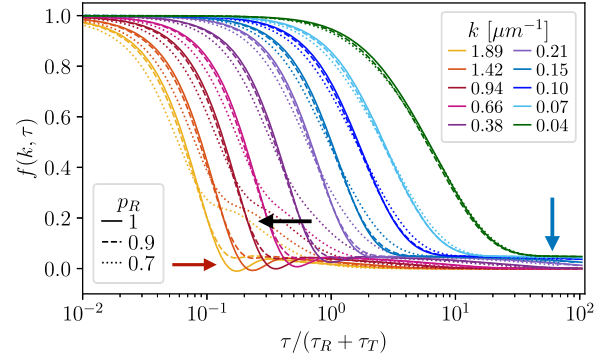


FIG. 2. Theoretical ISFs for a suspension comprising a fraction α of RT bacteria and $1 - \alpha$ of diffusing cells, for several wave numbers k . We consider different fractions of run time $p_R = \tau_R / (\tau_R + \tau_T)$, using $\tau_R = 1$ s and $\tau_T = 0, 0.1, 0.5$ s, with $\bar{v} = 15 \mu\text{m s}^{-1}$, $\sigma_v = 4.5 \mu\text{m s}^{-1}$, $D = 0.3 \mu\text{m}^2 \text{s}^{-1}$, and $\alpha = 0.95$. For smooth swimmers with fixed speed v_0 , $f(k, \tau) = \text{sinc}(v_0 k \tau) \exp(-Dk^2 \tau)$. When $p_R = 1$, this leads to clear oscillations of $f(k, \tau)$ at small length scales (red arrow). As the tumbling rate τ_T^{-1} increases (black arrow), these oscillations are smeared out and the diffusive dynamics of the tumbling bacteria eventually leads to a diffusive plateau around $f \sim 1 - p_R$. At large but finite times, depending on the value of k , the diffusive cells may not have decorrelated, leading to a nonzero plateau of $f(k, \tau)$ (blue arrow).

β -D-1-thiogalactopyranoside (IPTG). It is expected, though never yet confirmed, that tuning the concentration of IPTG during the growth of this strain allows the control of RT dynamics [Fig. 1(b)]. Bacteria were cultured and resuspended carefully in motility buffer [3] to ensure a very high final motile fraction, $\alpha \gtrsim 95\%$ [55].

ISF measurement and analysis.—To characterize the gait of the NZ1 strain at different IPTG concentrations, we first measured its ISF by DDM. We then fitted it to the calculated ISF of a well-established model of RT bacteria [1,25,60–62] that is modified to account for recently observed intrinsic fluctuations of the propulsion speed [63]. In this model, bacteria run in quasistraight lines at speed v until they enter a tumbling phase, at rate τ_R^{-1} , during which they fully randomize their orientations. They resume swimming at rate τ_T^{-1} with a new swim speed, sampled from a Schulz distribution $p(v)$ characterized by a mean velocity \bar{v} and a standard deviation σ_v [44]. (For an alternative way to account for swimming-speed fluctuations, see Ref. [54].) In addition, cells diffuse translationally with diffusivity D during both run and tumble phases. There is also a fraction $1 - \alpha$ of nonmotile cells that undergo Brownian motion only, also with diffusivity D [64]. The ISF for a noninteracting *E. coli* suspension predicted by this model reads

$$f(k, \tau) = \alpha f_{\text{RT}}(k, \tau) + (1 - \alpha) e^{-Dk^2 \tau}, \quad (2)$$

where $f_{\text{RT}}(k, \tau)$ is the ISF of RT bacteria [54]. Measuring this ISF for a wide range of k and τ values then allows

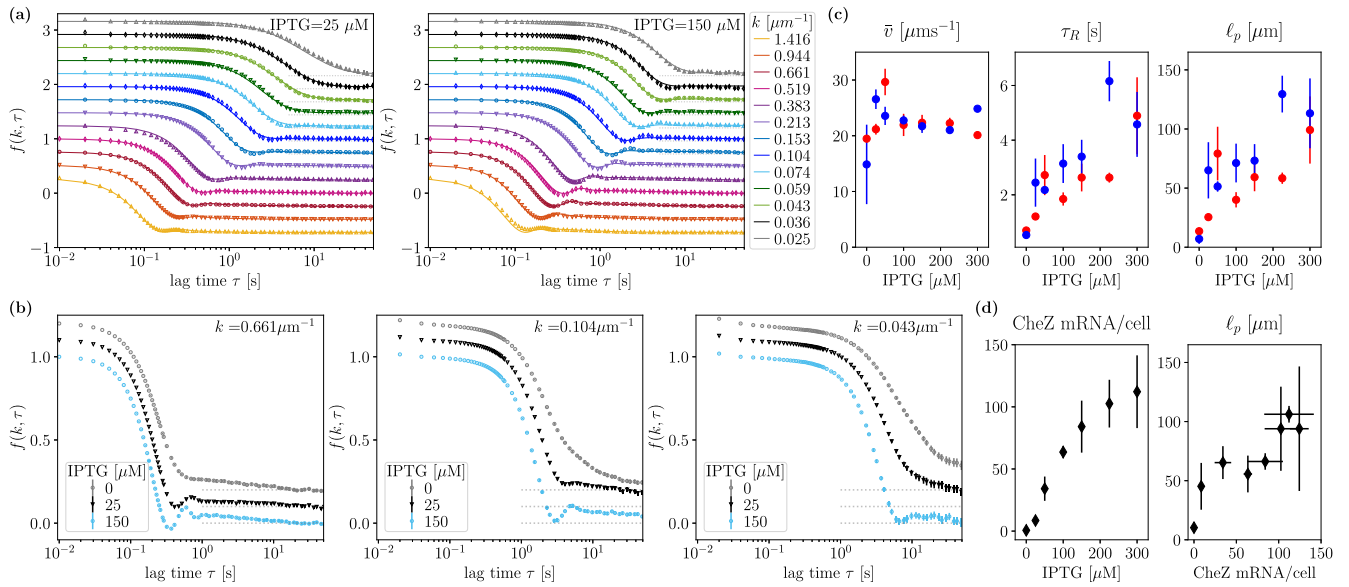


FIG. 3. Engineered *E. coli* strain NZ1. (a) ISFs for IPTG concentrations 25 and 150 μM . The ISFs are shifted vertically and gray dotted lines correspond to $f = 0$. Symbols and lines represent experiments and fits to the theory, respectively, and different colors correspond to different wave numbers k . (b) Comparison of the ISFs for different IPTG concentrations and wave numbers. (c) Average speed \bar{v} , run time τ_R , and persistence length ℓ_p , as a function of IPTG concentration. Red and blue symbols correspond to two biological replicates. The error is estimated from successive measurements of the ISF using the same sample. (d) Independent measurements of the number of CheZ mRNA per cell at various IPTG concentrations (left panel) allow correlating the persistence length ℓ_p and the number of CheZ mRNA per cell (right panel).

disentangling the contributions of diffusion, swimming, and tumbling to the dynamics (Fig. 2). Fitting Eq. (2) to data finally yields the set of kinetic parameters $\{\bar{v}, \sigma_v, \tau_R, \tau_T, \alpha, D\}$.

To measure the ISF experimentally, we imaged cells in sealed capillaries on a fully automated inverted bright-field microscope with a sCMOS camera. A full characterization of RT dynamics requires accessing length scales much greater than the persistence length ℓ_p in all directions. This necessitated a large depth of field at low k to ensure that bacteria remain in view over large distances in 3D. We thus consecutively recorded movies at $2\times$ and $10\times$ magnifications and extracted the corresponding ISFs for $k < 0.9 \mu\text{m}^{-1}$ and $k \geq 0.9 \mu\text{m}^{-1}$ using DDM [44,56], which are then fitted to our renewal theory using a numerical protocol described elsewhere [54].

IPTG-induced transition from tumbling to swimming.— We grew suspensions of the NZ1 strain at several IPTG concentrations and measured the ISFs. Representative data over approximately four decades in time and two decades in length are shown in Fig. 3(a). Oscillations typical of persistent swimmers (Fig. 2) are seen most clearly at the higher IPTG concentration and high k values.

In more detail, Fig. 3(b) compares the ISFs at a given k for three IPTG concentrations. In the absence of IPTG, diffusion dominates and the oscillations are absent. At IPTG = 25 μM , oscillations are seen for $k = 0.66 \mu\text{m}^{-1}$ and $k = 0.1 \mu\text{m}^{-1}$ (corresponding to length scales of

$\sim 2\pi/k \approx 10$ and $60 \mu\text{m}$, respectively), while data at the smallest k shows a smooth decay: the RT dynamics becomes effectively diffusive on such a large scale. At the highest IPTG concentration, 150 μM , oscillations are seen at all scales, showing a strong enhancement of the persistence length. To our knowledge, this is the first demonstration of a controlled tuning of the 3D gait of *E. coli* by varying external conditions.

Our protocol also allows us to quantify phenotypic heterogeneity. We repeated such measurements for eight IPTG concentrations, using two biological replicates and typically three to four successive measurements of $f(k, \tau)$ per replicate and IPTG concentration. The fitted kinetic parameters are then averaged for each replicate and plotted in Fig. 3(c). The small error bars show that successive measurements of $f(k, \tau)$ at each condition and for each biological replicate yielded consistent results. The observed variability between replicates (compare red and blue data points) therefore quantifies the degree of phenotypic heterogeneity in a clonal population [66].

Increasing IPTG leads to a robust increase of the persistence length, $\ell_p = \bar{v}\tau_R$, which translates into oscillations in the ISF [Figs. 3(a) and 3(b)]. Capturing quantitatively such fine-grained features requires very good statistics, a narrow speed distribution, and a low fraction of nonmotile cells, a challenge that is met by the experimental protocol described in [55]. Finally, note that there is little variability in the average speed ($\bar{v} \approx 23.5 \mu\text{m}^{-1}$ at all finite IPTG concentrations), the tenfold increase in ℓ_p

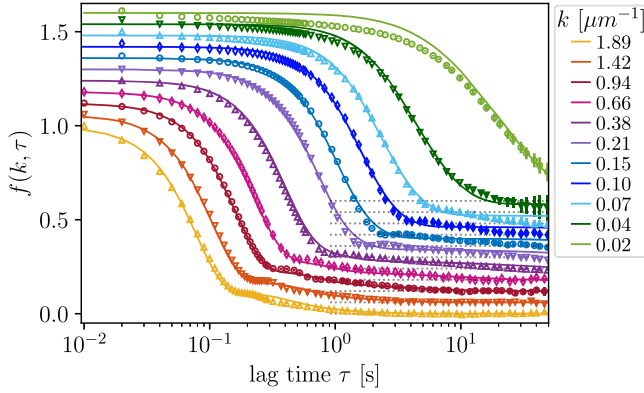


FIG. 4. Measurements of the ISFs for a WT *E. coli* suspension (symbols). Fits to Eq. (2) (lines) lead to $\bar{v} = 15.95 \mu\text{m s}^{-1}$, $\sigma_v = 5.78 \mu\text{m s}^{-1}$, $D = 0.24 \mu\text{m}^2 \text{s}^{-1}$, $\alpha = 0.96$, $\tau_R = 2.39 \text{ s}$, and $\tau_T = 0.38 \text{ s}$. The ISFs are shifted vertically as in Fig. 3(a).

results from longer run durations. This shows that the expression level of CheZ thus impacts tumbling statistics without altering the bacteria swimming speed.

Given the high speed of our NZ1 strain and the long run durations at high IPTG concentrations, the extraction of τ_R requires sampling large length scales, at which we find that the tumbling times τ_T cannot be reliably measured. We have tested the robustness of our results with respect to τ_T by fixing it at $\tau_T = 0.1, 0.2, 0.3 \text{ s}$ and extracting the remaining kinetic parameters. We find that the average velocity of the bacteria remains unaffected and the systematic increase of the persistence length persists (Fig. S1 [55]). Finally, while measurements of the evolution of single-motor statistics of wild-type (WT) *E. coli* in different environments have been reported before [23], Fig. 3(d) shows for the first time the measured correlation between ℓ_p and the number of CheZ mRNA in the cell.

Wild-type E. coli.—Figure 4 shows the measured ISFs for a dilute suspension of WT *E. coli* over approximately four decades in time and two decades in length. The ISFs display an intermediate plateau at large k , which is a signature of the diffusive motion of both the small non-motile fraction ($\lesssim 5\%$) and of the tumbling cells. The plateau disappears at low k and long times, which reflects the randomization of the swimming direction.

The WT data are well fitted by our renewal theory [54] at all k (Fig. 4, solid lines). We find that $96 \pm 0.1\%$ of the bacteria swim at a mean speed $\bar{v} = 16 \pm 0.1 \mu\text{m s}^{-1}$ with standard deviation $\sigma_v = 5.78 \pm 0.13 \mu\text{m s}^{-1}$ (errors are obtained by a jackknife resampling method [67]).

The lower WT speed (cf. $\bar{v} \approx 24 \mu\text{m s}^{-1}$ for NZ1) allows us to fit the mean run and tumble durations: $\tau_R = 2.39 \pm 0.11 \text{ s}$ (so that $\ell = \bar{v}\tau_R = 38 \pm 2 \mu\text{m}$) and $\tau_T = 0.38 \pm 0.02 \text{ s}$, giving a run fraction of $p_R = \tau_R / (\tau_R + \tau_T) \approx 0.86$. Original, and still widely cited, measurements also gave $p_R \approx 0.86$, but with $\tau_R = 0.86 \pm 0.20 \text{ s}$ and $\tau_T = 0.14 \pm 0.03 \text{ s}$ [1]. These results were obtained by

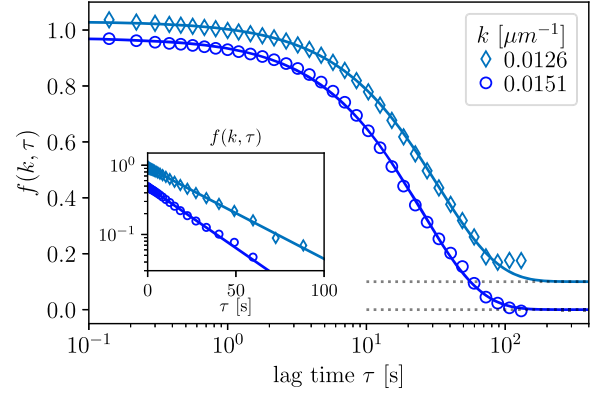


FIG. 5. Measured ISFs of WT *E. coli* at $k = 0.0126 \mu\text{m}^{-1}$ and $k = 0.0151 \mu\text{m}^{-1}$ (symbols) fitted against the ISF of diffusive particles (lines), giving effective diffusivities $D_{\text{eff}} = 192 \mu\text{m}^2 \text{s}^{-1}$ and $D_{\text{eff}} = 178 \mu\text{m}^2 \text{s}^{-1}$, respectively. The ISFs are shifted vertically as in Fig. 3(a).

tracking 35 bacteria, while we averaged over $\sim 10^4$ – 10^6 bacteria.

Finally, our data allow us to probe a range of length and time scales large enough to bridge short-scale directed swimming and large-scale diffusive motion. This is an important challenge since recent experiments have questioned the experimental relevance of exponentially distributed run and tumble durations [22,27]. The ISF of purely diffusive particles, $f(k, \tau) = A \exp(-k^2 D_{\text{eff}} \tau)$, where A is a constant, gives a good account of our large-scale data (shown for two values of k in Fig. 5). Averaging over our two smallest values of k leads to $\langle D_{\text{eff}} \rangle = 185 \pm 7 \mu\text{m}^2 \text{s}^{-1}$.

In an RT model with exponentially distributed run and tumble durations, $\langle D_{\text{eff}}^{\text{th}} \rangle = (\bar{v}^2 + \sigma_v^2) \tau_R^2 / (3\tau_R + 3\tau_T)$. Using parameters from fitting the measured ISF (caption, Fig. 4), we find $\langle D_{\text{eff}}^{\text{th}} \rangle = 198 \pm 11 \mu\text{m}^2 \text{s}^{-1}$, which is remarkably close to the measured value. Interestingly, the σ_v^2 term arising from velocity fluctuations contributes to $\sim 10\%$ of the value of $\langle D_{\text{eff}}^{\text{th}} \rangle$. Note that our measured D_{eff} is 3 orders of magnitude larger than the fitted single-particle diffusivity, $D = 0.24 \pm 0.01 \mu\text{m}^2 \text{s}^{-1}$, which highlights the ability of our protocol to provide information on active-particle dynamics over a large spatiotemporal range.

Conclusion.—By characterizing the dynamics of *E. coli* over a wide range of length and time scales, we demonstrated for the first time how the tumbling dynamics of an engineered strain can be tuned independently of the swimming speed. Furthermore, we have characterized to a high statistical accuracy the full 3D gait of WT *E. coli* in bulk suspensions, directly characterizing for the first time both the small-scale persistent motion and the large-scale diffusion. We have shown that a microscopic run and tumble model with exponentially distributed run and tumble durations describes both regimes. The use of more realistic distributions [27] can be accommodated in our approach, but is unlikely to change significantly any of our

conclusions. We also note that, while our bulk approach is well suited to characterize the population-scale distribution of motility gaits, cell tracking remains a very useful tool to investigate more precisely the detail of single-cell trajectories and investigate their diversity [1,27,63,68].

Our Letter lays the foundation for the high-throughput study of the swimming gait of a variety of microorganisms, such as the RT pattern of *Bacillus subtilis* [63] or the run-reverse motion of marine bacteria [69] and archaea [70], using standard microscopy. We hope that this will allow for a more systematic characterization of the role of cell motility in collective self-organization, which is often studied at a purely macroscopic scale due to the long-standing difficulty in characterizing cell motion at the microscopic level [71]. We note that the ability of microorganisms to respond to chemical fields or gradients, through quorum sensing or chemotaxis, is a vital part of their foraging and survival strategy. Our method, in combination with spatiotemporally resolved DDM [20], opens the way to the high-throughput study of such response at the population level.

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