Role of tumbling in bacterial swarming

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Typical wild-type bacteria swimming in sparse suspensions exhibit a movement pattern called "run and tumble," characterized by straight trajectories (runs) interspersed by shorter, random reorientation (tumbles). This is achieved by rotating their flagella counterclockwise, or clockwise, respectively. The chemotaxis signaling network operates in controlling the frequency of tumbles, enabling navigation toward or away from desired regions in the medium. In contrast, while in dense populations, flagellated bacteria exhibit collective motion and form large dynamic clusters, whirls, and jets, with intricate dynamics that is fundamentally different than trajectories of sparsely swimming cells. Although collectively swarming cells do change direction at the level of the individual cell, often exhibiting reversals, it has been suggested that chemotaxis does not play a role in multicellular colony expansion, but the change in direction stems from clockwise flagellar rotation. In this paper, the effects of cell rotor switching (i.e., the ability to tumble) and chemotaxis on the collective statistics of swarming bacteria are studied experimentally in wild-type *Bacillus subtilis* and two mutants—one that does not tumble and one that tumbles independently of the chemotaxis system. We show that while several of the parameters examined are similar between the strains, other collective and individual characteristics are significantly different. The results demonstrate that tumbling and/or flagellar directional rotor switching has an important role on the dynamics of swarming, and imply that swarming models of self-propelled rods that do not take tumbling and/or rotor switching into account may be oversimplified.

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I. INTRODUCTION

Dense populations of self-propelled microorganisms exhibit a large variety of intricate group phenomena such as collective migration and secretions of wetting agents [1–43]. Multicellular behavior has a major impact on the population level, for example, an increased resistance to antimicrobial compounds [1,2] and reduction of the viscosity of the medium in which the cells are embedded [16]. Bacterial multicellularity has generated interdisciplinary interest and has led physicists to define this state of crowded individuals as a "living active matter" [17]. One fundamental example for such a system is bacterial swarming where hundreds to millions of rod-shaped flagellated cells collectively move on surfaces, forming dynamic whirls and jets [1–15]. Recent work on the physical aspects of collective cell motion has focused on intrinsic parameters such as cluster size statistics, velocity and vorticity distributions, spatial and temporal correlations, and the effect of cell aspect ratio on swarm dynamics and on the trajectories of individuals within the crowd [1,7,9–14,23,24]. Other works have examined the influence of extrinsic parameters on the behavior of the swarm, for instance, depletion of food, lack of oxygen, or dryness of the environment [10,21,37].

At low cell densities, individual swimming wild-type bacteria move by a process called "run and tumble," in which straight trajectories (runs) are interspersed by short, random reorientation (tumbles). Forward movement (run) is generated when multiple flagella rotate in a counterclockwise direction, to generate thrust. During tumbling events, clockwise rotation of even a single flagellum can cause that flagellum to leave the bundle, drag, and cause a change in the direction of the cell [44]. A chemotaxis signal transduction network encodes a short-term memory that allows the bacteria to control the frequency of tumbles and therefore increase run duration in the presence of nutrient gradients, or decrease run duration in the presence of repellent gradients [45].

At high cell densities, however, cell-cell interactions dominate and dictate the behavioral dynamics. Ranging from biological to physical constraints, the number of possible mechanisms for cell communication is enormous, including, for instance, interactions between flagella of neighboring cells [18]. As a result, theories of collective bacterial motility typically consider simplified models (e.g., self-propelled rods) with some effective short-range steric and/or long-range hydrodynamic interactions [27,28]. Tumbling is often ignored, or simplified as angular diffusion, i.e., an additive white noise affecting the direction of cells. In a recent work it was argued that a particular bacterial mutant that is smooth swimmer (cells constantly rotate the flagellar bundle in a counterclockwise direction ("run-only" mode) and swim forward continuously without tumbling) exhibits similar collective motion as the wild-type that does tumble [26]. In other words, these experiments choose a mutant that is thought to be simpler and possibly closer in spirit to a physicist's view of bacterial swimming. However, the precise differences between collective dynamics of wild-type and smooth-swimming bacteria have never been quantified in detail. Sokolov *et al.* [33] and Aranson *et al.* [34] suggested that some of the results they have obtained for collective swimming of wild-type bacteria (that run and tumble) were different than what was obtained in other mathematical models because the cells in experiments tumble, which has not been taken into account in pioneering models.

From the biological point of view, the chemotactic system of wild-type flagellated bacteria swimming in liquid bulk enables

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cells to navigate toward, or from, favorable or hazardous chemical gradients. However, it has been suggested that this biased run-and-tumble mechanism (chemotaxis) does not function during swarming on surfaces [38], because experiments showed that flagellar rotor switching between the run and the tumble states (and consequently the frequency of the tumbling events) seems to be uncorrelated with the chemical cues [39]. The role of tumbling (or perhaps the role of rotor switching) during motion on agar or swarming is therefore unclear and models have suggested that rotor reversals either directly pump liquid from the agar [15], or they are thought to strip off lipopolysaccharide (LPS) from the Gram-negative outer membrane to enable wetting of the surface [40,41].

In this paper, we quantitatively compare the individual and the collective swarming dynamics of three strains of the Gram-positive bacterium *Bacillus subtilis* that differ in flagellar activity. Our results demonstrate that while a few of the parameters tested seem to be similar between the strains, other collective and individual characteristics were found to be significantly different. The results show that tumbling, and/or flagellar rotor switching, but not chemotaxis, have an impact on swarm dynamics, emphasizing the importance of including this phenomenon in modeling self-propelled rods.

II. MATERIALS AND METHODS

A. Bacterial strains and growth protocol

Experiments were performed with *Bacillus subtilis* 3610, which is a Gram-positive rod-shaped ($0.8 \times 4.5\,\mu$m; exact number depends on the growth medium) flagellated species, used as a model system in many previous quantitative swarming experiments e.g., [1,2,5,6,8,9,12–14]. Wild-type cells swim within sparse suspensions and individuals control the frequency of rotor switching between states of runs and tumbles, depending on the chemotactic sensing system. Chemotactic signal transduction and the corresponding motor output enable the cells to navigate toward (or away from) chemical gradients in the medium. In sparse situations, the wild-type cells exhibit run durations that last 5.2 ± 3.2 s with tumbling durations of 0.2 ± 0.05 s. By contrast, a *cheB::tet* mutant (DS90, also known as RL2668 [6]) that does not exhibit flagellar rotor switching, because the flagellar rotor is nearly exclusively biased in the counterclockwise direction, experiences the run mode only, and moves in straight trajectories while grown in sparse suspensions (smooth swimmer). Colonies of this strain are wet, large, swarm rapidly, and look similar to the colonies of the wild type [6]. Thus, although the cheB mutant swarms like the wild type, it is defective in chemotaxis. Both strains swim at the same speeds (for the wild type during the run state), $32.1 \pm 4.2\,\mu$m/s for the wild type and $31.7 \pm 3.8\,\mu$m/s.

Because the cheB mutant is both defective in chemotaxis signal transduction and changes in rotor rotation, it is difficult to separate the contributions of the two phenomena to swarming behavior. To study the role of rotor switching in the absence of chemotaxis, we have mutagenized a cheA::tet mutant (DS73 [6]) that tumbles constitutively, with UV radiation, while cells are grown on agar soaked with supernatant of the wild-type cells. Whereas most colonies of the mutagenized cheA::tet strain were small, a few rare colonies were larger and cells extracted from the large colonies exhibited both runs and tumbles during swimming in broth. Importantly, the mutants were resistant to high levels of tetracycline (50 μg/ml) indicating that the mutants were indeed derivatives of the cheA::tet parent. We have checked these cells for chemotactic behavior by growing colonies on 0.6% agar supplemented with NaCl (5 g/l) and K_2HPO_4 (5 g/l) to balance *p*H and osmotic pressure, with no nutrients initially added to the agar. Agar plugs ($1 \times 1.5 \times 1$ cm) of nutrient agar [1.5% agar with 25 g/l Luria Bertani (LB)] were placed on the agar surface at one side to create a nutrient gradient. Cells were inoculated on the plate distal to the gradient origin. Whereas the wild type grew and swarmed preferentially up the nutrient gradient, the cheB:tet (smooth swimmers), the cheA::tet parent (tumbling only), and the rotor switching mutant of the cheA::tet grew symmetrically. We conclude that the latter mutant we have created, in the cheA::tet background, restores rotor switching but does not restore chemotaxis. We will refer to this mutant as nonchemotactic but a rotor switcher (NCbRS) strain. Cells of this strain exhibit durations of both run and tumble very similar to those obtained for the wild-type; 5.1 ± 3.0 and 0.2 ± 0.08 s, respectively, with the same distribution. It should be noted that these values, obtained for sparse situations, reflect rotor switching in nonchemotactic situations (fresh LB broth) where the frequency of tumbling is nonbiased. The strain swims at speeds (during run events) very similar to those obtained for the wild type and the smooth swimmer (31.9 ± 5.0).

All three strains look alike under the microscope, with the same typical cell dimensions of $0.8 \times 3.5\,\mu$m in LB broth medium, and $0.8 \times 4.5\,\mu$m on the agar. All bacteria were stored at –80 °C in 50% glycerol stocks [phleomycin 7 μg/ml was added to frozen stocks of the red fluorescent protein (RFP)], selected on an LB plate (with the appropriate antibiotic), and grown overnight in LB broth at 30 °C with shaking (200 rpm) prior to plate inoculation (5 μl at the center of each plate). For swarming experiments, cells were grown on agar plates (1 g/l peptone and 0.5% agar at 30 °C), forming dense colonies (thickness of 3–4 μm); they began expanding outward around 4 h after inoculation. For collective dynamics observations each strain was grown separately with no mixing.

Derivative strains of all three strains were labeled with a red fluorescent protein (RFP), where the protein was expressed from a chromosomal location (ppsB::PtrpE-mCherry). In experiments analyzing the dynamics of individuals in the swarm, the unlabeled cells were mixed with their RFP variant (at a ratio of 1000:1; labeled cells were always the minority) in a small tube prior to inoculation, then coinoculated on swarm agar plates. Labeling does not affect swarming behavior [12]. Under fluorescent microscopy only RFP cells are seen, which enables a precise detection of single-cell trajectories even within a highly dense population.

B. Observations

An optical microscope (Zeiss Axio Imager Z2) equipped with a sensitive high resolution video camera (NEO, Andor) was used to capture the motion of the labeled cells under fluorescence microscopy (50 f/s and 1024×1024 pixels.

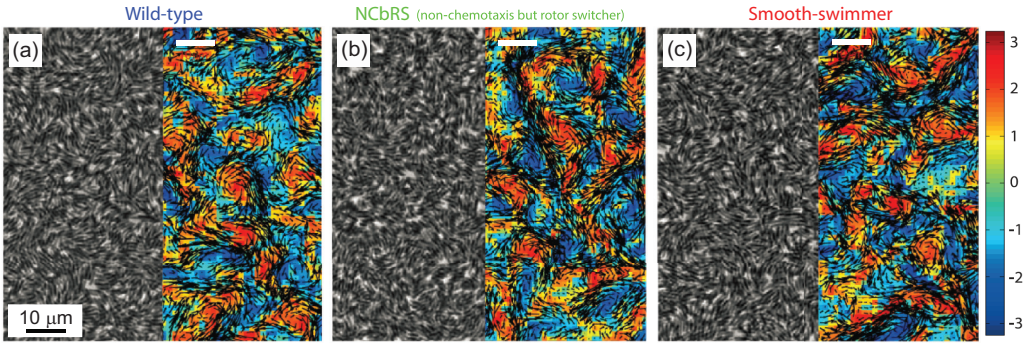

FIG. 1. Swarming colonies of *B. subtilis*. (a) A microscopic phase-contrast image of the edge of a wild-type colony along with the velocity and vorticity fields. Black arrows indicate the local velocity and colors indicate local vorticity (units in rad/s). (b) Same as (a) for the NCbRS (nonchemotactic but rotor switcher) strain. (c) Same as (a) for smooth-swimmers strain.

No photobleaching was observed during acquisition times (2 min for each experiment; 6000 frames). In each field of view we typically had about five fluorescent cells at 63× magnification. The data summarize results from tens of experiments with hundreds of cells from each strain. The RFP expressing cells, designed initially for mCherry illumination setup, were observed by a standard Rhodamin (RFP) Zeiss illumination setup (filter set 20 Rhodamin shift free: excitation 546/12; beam splitter 560; emission 607/80). Trajectories were obtained and analyzed using MATLAB, and were smoothed using the malowess function which locally fits a polynomial (second order) to a moving window (11 frames) [12].

A second camera (GX 1050, Allied Vision Technologies) detecting simultaneously the exact field of view by phase-contrast illumination, was operated at 100 f/s and similar spatial resolution. The series of images capturing the motion of all bacteria in the field of view (not only fluorescently labeled ones) were analyzed by optical flow measurements. Following standard preprocessing for noise reduction, the optical flow between each two consecutive frames was obtained using the Horn-Schunck method. Vector fields were reduced to a 64×64 grid by simple averaging, generating an approximated velocity field [1].

III. RESULTS

A. Collective dynamics

Wild-type swarm colonies were grown on agar plates, observed by optical microscopy, and studied using optical flow analyses. The same procedure was repeated for the nonchemotactic but rotor switching mutants (NCbRS) and the smooth swimmers. Microscopic images of the swarm colonies are shown in Fig. 1 along with the velocity and vorticity fields derived by our analyses. To the naked eye, there are no apparent differences between the three strains. Both spatial and temporal correlation functions of the velocity and vorticity fields [Figs. 2(a) and 2(b)] were found to decay exponentially with similar time and length scales. In addition, the standard deviation of the velocity and vorticity distributions is the same for all strains (about 19.4 μm/s and 3.1 rad/s, respectively; the smooth swimmers were slower than the wild type and the NCbRS by 4%). This suggests that the collective dynamics of all the strains is essentially the same. However, the shapes of the distributions were found to depend on the strain [Fig. 2(c)]. Both the wild type and the NCbRS

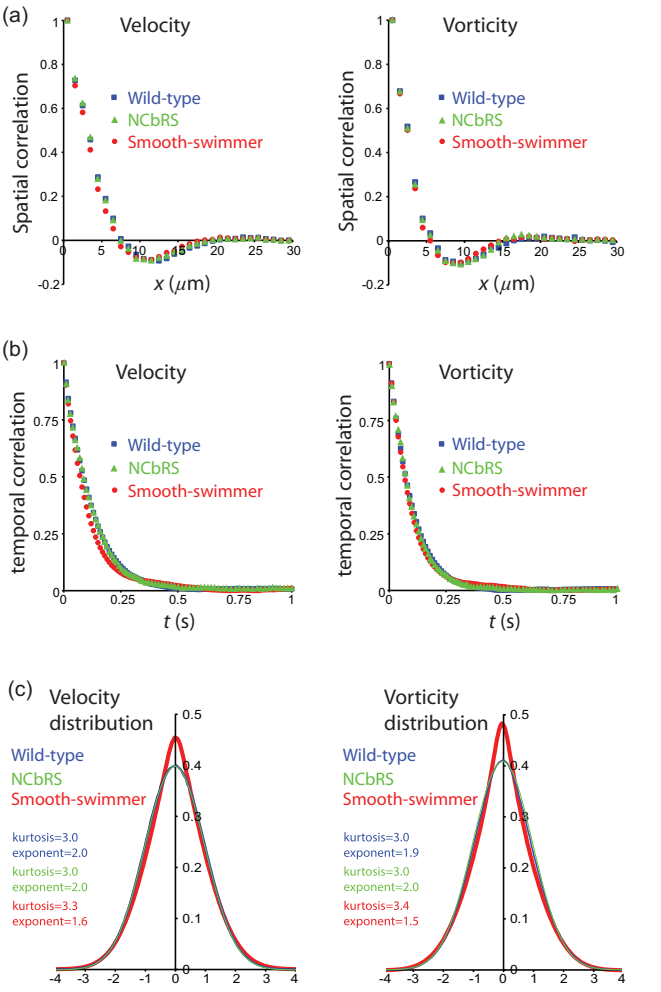

FIG. 2. Collective swarm statistics. Left column: velocity; right column: vorticity. (a) The spatial correlation functions of the velocity and vorticity fields of the three strains decay similarly. (b) The temporal correlation functions of the velocity and vorticity fields of all strains decay similarly. (c) Velocity and vorticity distributions of the wild-type swarmers, and the NCbRS (nonchemotactic but rotor switcher), obey a Gaussian curve while the smooth swimmers exhibit deviations from the Gaussian.

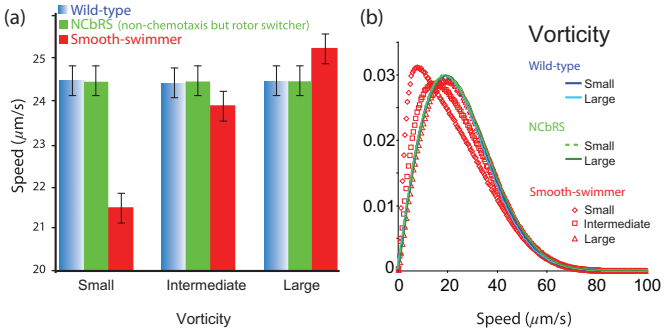

FIG. 3. Correlation between speed and vorticity. (a) The average speed of the swarming cells at three different vorticity ranges (in absolute values). Correlation is found for the smooth swimmers only. (b) Speed distribution for different vorticity ranges; the smooth swimmers show different distributions, but the wild-type and the NCbRS (nonchemotactic but rotor switcher) strains show similar distributions independent of the vorticity.

exhibited Gaussian distributions with kurtosis = 3.0. Fitting to a stretched exponential distribution of the form $z^{-1}e^{-(v/v_0)^{\gamma}}$, where v_0 is the characteristic speed and z a normalization constant, yields an exponent $\gamma \cong 2.0$. Approximate Gaussian velocity distribution of wild-type *B. subtilis* has previously been reported [1,12,27]. In contrast, the smooth swimmers exhibited a slight deviation from the Gaussian curve with kurtosis $\cong 3.4$ and $\gamma \cong 1.5$, indicating that the collective dynamics of the smooth swimmers is different. However, the most surprising difference between the wild type and the NCbRS on one hand, and the smooth swimmers on the other hand, was found in the correlation between linear speeds (normal of the vector field) and the rotational speed (absolute value of the curl). Figure 3(a) shows that linear and rotational speeds are uncorrelated in swarms of the wild-type and the NCbRS cells. This is not the case for smooth swimmers for which high speeds are correlated with fast angular velocities. In addition, the distribution of speeds at each regime—and not only the mean—is different as seen in Fig. 3(b). These results demonstrate that the collective dynamics of rod-shaped smooth-swimming cells is indeed different from the one obtained for the wild-type strain.

B. Dynamics of individuals

Trajectories of RFP labeled cells embedded in a dense swarm of nonlabeled cells, from the same strain, were obtained and analyzed as seen in Fig. 4. Figure 4(b) shows the mean square displacement (MSD) of cell trajectories. All strains exhibit similar behavior with a mean slope of approximately

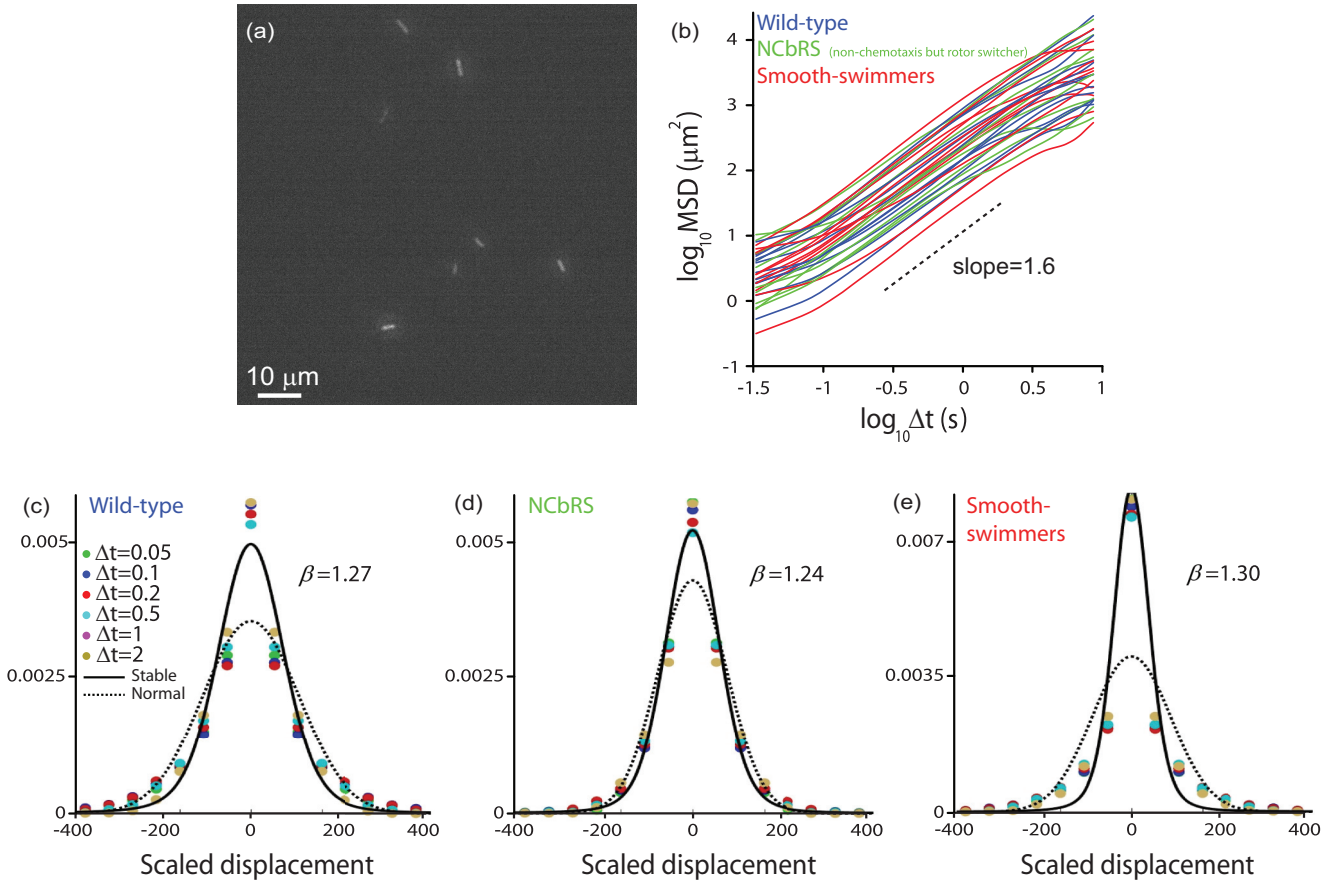

FIG. 4. Microscopic statistics of individuals in the swarm. (a) Fluorescent microscopy showing the fluorescently labeled bacteria only. (b) Mean square displacement of single bacteria. A slope of ~1.6 is obtained for all cells, independently of strain type. (c) The distribution of cell displacements of wild-type cells along each axis between a fixed number of frames. Following a scaling of $\Delta t^{1/\beta}$, the distribution approximately fits a Lévy-stable distribution with parameter $\beta = 1.27$. (d) Same as (c) for the NCbRS (nonchemotactic but rotor switcher) with $\beta = 1.24$. (e) Same as (c) for smooth swimmers with $\beta = 1.30$.

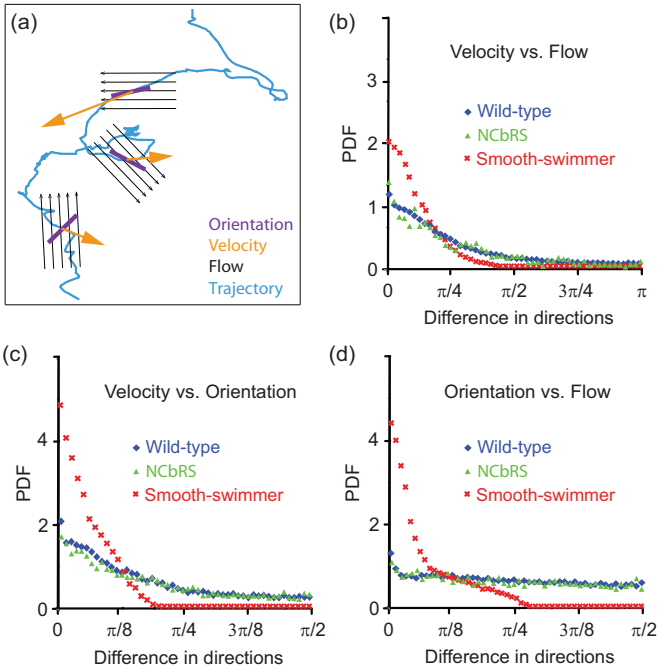

FIG. 5. Differences in directions. (a) An example trajectory of an individual bacterium (light-blue line), superimposed with the collective flow (black arrows), cell orientation (purple bar), and instantaneous cell velocity (orange arrow). (b) Distribution of angles between the cell velocity and the flow vector field at the same position and time. Smooth-swimming cells (red crosses) are more aligned with the flow while wild-type cells (blue diamonds) and the NCbRS (nonchemotactic but rotor switcher; green triangles) exhibit much larger deviations. (c) Distribution of angles between the cell velocity and its orientation. Smooth-swimming cells tend to be aligned with the actual direction of motion while wild-type bacteria and the NCbRS exhibit significantly larger deviations. (d) Distribution of angles between cell orientation and the flow vector field at the same position and time. Smooth-swimming cells tend to be aligned with the flow while wild-type and NCbRS exhibit larger deviations.

1.6. Embedding RFP labeled wild type in a swarm of smooth swimmers and vice versa gave a similar result, indicating that the dynamics of the individuals is largely the same for all strains. Next, we have looked at the distribution of cell displacements along each axis between a fixed number of frames [Figs. 4(c)–4(e)]. Following a scaling of $\Delta t^{1/\beta}$, all distributions approximately fit a Lévy-stable distribution in which β is not significantly different between the three strains. The fit to a Lévy-stable distribution is the fingerprint of a Lévy walk, as was recently reported for wild-type cells [12].

On the other hand, we have found a major difference in the way wild-type, NCbRS, and smooth swimmers move through the collective flow. Simultaneous acquisition of the flow field and individual trajectories of RFP labeled bacteria (no mixing between the strains) showed that smooth-swimming cells follow the flow of their crowd, and align their principal axis with the flow significantly much more than the wild-type and the NCbRS (Fig. 5). This implies that tumbling—or rotor switching—is not entirely suppressed during swarming and has a significant effect on the ability of cells to maneuver or switch between local streams and jets, which was also observed in the past [6]. The strong similarity between the wild type and the NCbRS supports the observation that chemotaxis during swarming is indeed suppressed.

Surprisingly, in experiments performed with a mixture of two populations (e.g., few RFP smooth swimmers inside the swarm of nonlabeled wild type); at very late stages of the experiment, namely, when the colony was nearly reaching the edges of the plate, we have found that no matter what the initial proportion of the two populations was, the population of the smooth swimmers in the outer regions of the colonies was zero. They were always outcompeted by the wild type or by the NCbRS even if their fraction was larger in the population; RFP smooth-swimming cells were simply not detected in the outer regions of the mixed colony (e.g., in the last 1.8 cm off the edges of a fully grown colony 7.2 cm in diameter. Experiments were repeated with larger Petri dishes (14 cm) yielding the same results for the same distances, excluding boundaries effects). This is despite the fact that all strains have the same speeds, the same structure, and the same size, and they secrete surfactants at the same quantity. It all indicates that the tumbling events are mandatory for better dispersion in a colony, especially for large time scales.

IV. DISCUSSION

We compared the individual and swarming dynamics of three bacterial mutants: (1) Wild-type cells performing run and tumble, and chemotaxis. (2) A mutant termed NCbRS that tumbles at random times which are independent of the environment. As a result, it cannot chemotax. (3) Smooth-swimming cells that do not tumble. This comparison allows us to shed light on the role of rotor switching and chemotaxis on swarming.

Our results indicate subtle differences between the collective dynamics of wild-type and NCbRS cells on one hand, and smooth-swimming cells on the other hand. These differences do not seem significant when studying collective properties of the swarm dynamics such as velocity distributions or correlation functions, and definitely not when studying macroscopic properties such as the expansion of the colony. Indeed, qualitative phenomena such as collective swimming *per se*, of wild-type *B. subtilis*, was seen also in the smooth-swimming mutant [26]. Experiments with smooth swimmers are also important for gaining insight on the physical properties of "living active matter" and comparison with theories of self-propelled particles. The correlation between speed and vorticity has not been well studied in active fluid models. Even if it was done, the cell that better matches a specific fluid model is the cell with the characteristics used to build this model. One of the points in this study is to show how different can a system be, if tumbling is added or excluded from the swimming. It is important to note that our results do not determine the precise effect of rotor switching while swarming—do bacteria tumble, i.e., reorient to a new random direction as they do while swimming in sparse suspensions? Another option, which was observed experimentally in swarming *Escherichia coli* is that rotor switching causes cell reversals and other intricate maneuvers [15].

Finally, it is important to discuss the differences between *B. subtilis*, a Gram-positive species, and Gram-negative

swarming species such as *E. coli*, *Serratia marcescens*, and *Salmonella typhimurium*. Wild-type strains of these Gram-negative species form swarming colonies under conditions similar to those described here for *B. subtilis* [4]. However, their smooth-swimming mutants are unable to swarm at all [42]; they either do not move on the agar or show poor movements of individuals within an immobile crowd. Some studies report that swarming of smooth-swimming Gram-negative strains is rescued if water is spritzed on the agar [40] or when grown on specific agar makes, such as Eiken agar [43]. Also, with CheY missing and FliM defective, the flagellar motors are uncoupled from the chemotaxis signaling pathway and swarming is obtained even in the absence of chemotaxis. This is because rotor switching and/or tumbling exist [4]. In addition, smooth-swimming cells of Gram-negative *E. coli* were able to form some type of collective motion if trapped in water in thin chambers ($\sim 2\,\mu$m) of poly(dimethylsiloxane) (PDMS) containing channels bonded to a glass slide covered with PDMS [31]. These findings lie in the base of the assumption that Gram-negative bacteria use rotor switching to promote surface wetting, perhaps through enhanced extraction of water from the agar, facilitating the collective motion. In the absence of rotor switches (in smooth-swimming cells) this mechanism does not work.

Our results were obtained for *B. subtilis*, a Gram-positive bacterial species that does not use LPS as a wetting mechanism. Therefore, in *B. subtilis* rotor switching is not needed for surface wetness. In this case, rotor switching, or perhaps the tumbling *per se*, may play a role in physical maneuvers by increasing short-range interactions, explaining why wild-type and NCbRS cells behave the same while smooth swimmers are different. For instance, Fig. 5, as well as the results on the absence of smooth swimmers in the outer regions of a mixed colony, indicates that flagellar switching is mandatory for the cells to reach the outer parts of the colony even if the entire crowd is active. The similarity between the NCbRS and wild type implies that the chemotaxis system is not required for swarming. In addition, we conclude that flagellar propulsion of wild-type cells during swarming are not necessarily operating in the counterclockwise direction almost solely, as was previously thought. Lastly, because wild-type colonies do not move toward richer nutrient regions in rich (e.g., 25 g/l LB), or nutrient-limited (e.g., 1 g/l peptone), swarming plates (saturation inhibits receptors; see [46] for more details), we find that the chemotaxis system is also suppressed. However, chemotaxis does play a major role in very poor nutrient medium, because the wild-type colonies move toward the richer regions.

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