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Wrapped Up: The Motility of Polarly Flagellated Bacteria

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Abstract

A huge number of bacterial species are motile by flagella, which allow them to actively move toward favorable environments and away from hazardous areas and to conquer new habitats. The general perception of flagellum-mediated movement and chemotaxis is dominated by the *Escherichia coli* paradigm, with its peritrichous flagellation and its famous run-and-tumble navigation pattern, which has shaped the view on how bacteria swim and navigate in chemical gradients. However, a significant amount—more likely the majority—of bacterial species exhibit a (bi)polar flagellar localization pattern instead of lateral flagella. Accordingly, these species have evolved very different mechanisms for navigation and chemotaxis. Here, we review the earlier and recent findings on the various modes of motility mediated by polar flagella.

Contents

INTRODUCTION

The ability to actively move is widely distributed among all domains of life. It gives the key advantage of being able to flee from hostile toward more favorable conditions and allows a population to spread within the environment. The apparent benefits come with the downside of significant amounts of energy that have to be spent on active motility. To efficiently move through the vastly diverse environments they thrive in, bacteria have developed an array of mechanisms (41, 115). Flagella are a widespread means of bacterial motility: rotating helical proteinaceous fibers (12, 98) that extend from the cell body and drive various forms of movement through aqueous environments or across surfaces (45). The first observation of flagellum-mediated motility dates back to the very beginning of microscopy (113) and has, over the centuries, become the best-studied mode of movement in bacteria.

BACTERIAL FLAGELLA

The flagellum is a supracomplex consisting of three major parts: the filament; the basal body, harboring the flagellar motor and associated export system; and the flexible flagellar hook, which connects motor and filament as a universal joint (**Figure 1*a***). The flagellar motor is an intricate molecular nanomachine that converts ion flow, mostly of H^+ or Na^+, across the cytoplasmic membrane into rotational movement (10, 101, 115). The structure of the flagellar motor is generally conserved in its main parts, with some evolutionary modifications, e.g., adaptations to anchor the machine in different cell envelopes (gram-positive and gram-negative) or to adjust the power output according to environmental requirements, e.g., elevated viscosity (9, 42, 105). Most motors function in a bidirectional fashion and can turn in clockwise or counterclockwise direction (**Figure 1*c***). Associated chemotaxis systems induce changes of motor operation, e.g., rotational switching or changes in speed, upon perception and processing of environmental signals, thereby allowing signal-driven navigation (15).

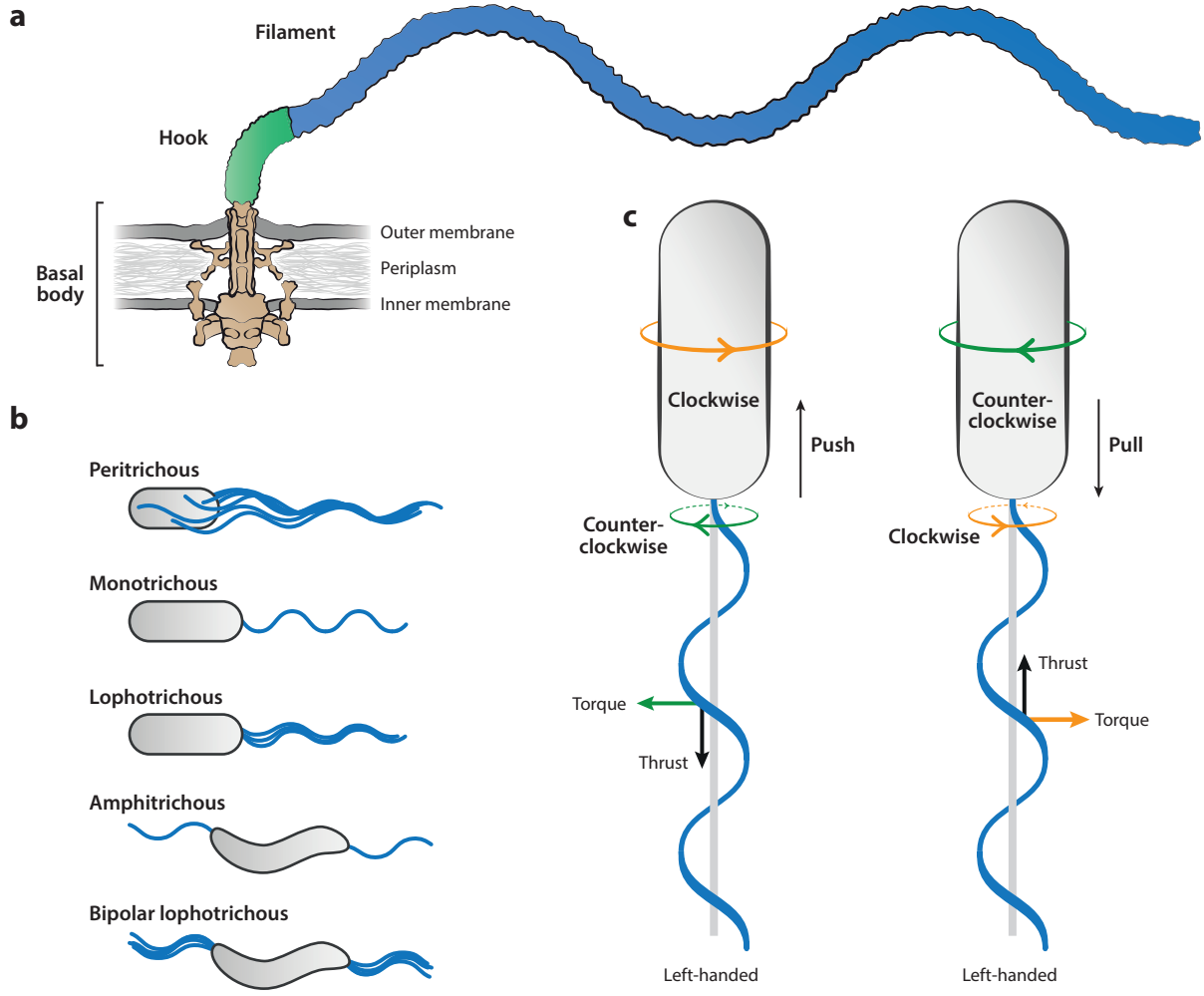


Figure 1

Composition, localization, and function of bacterial flagella. (*a*) The bacterial flagellum consists of three major parts: the helical filament (*blue*); the cell envelope–embedded basal body, including the export apparatus and rotary motor (*brown*); and the hook (*green*), which serves as a universal joint to transfer the rotation to the filament. (*b*) Flagellation is species specific and can occur in various patterns. (*c*) Activity of polar flagella. Here, the filament forms a left-handed helix (when viewed from behind the cell) that, upon counterclockwise rotation, provides thrust that drives the cell forward. When the direction of rotation switches to clockwise, it pulls the cell backward. The cell body exhibits counterrotation in the corresponding direction, as indicated. Note that bacteria may also have right-handed filaments. Panel *c* was inspired by Reference 17.

The prominent flagellar filament is a hollow structure formed by several protofilaments (11 in *Salmonella enterica*), each composed of the main building block flagellin. A fully assembled filament can consist of tens of thousands of flagellin proteins (91, 116). The protofilaments adopt either an L or R conformation; these conformations differ slightly in length, which results in twisting and an overall helical shape of the filament. Depending on the L-to-R ratio of a filament consisting of 11 protofilaments, 12 polymorphic states of the filament are predicted: 2 straight filaments (all L or all R) and 3 left-handed and 7 right-handed helices, each with a different geometry (5, 19, 20, 35, 119). For excellent representations of the filament's composition and polymorphic states, the

reader is referred to References 35 and 64. External strain on the filament, e.g., due to increased torque, may induce complete or incomplete switches between the filament's polymorphic states (25, 37, 62, 116). Bacteria exploit the properties of the hook and flagellar filaments for efficient propulsion and navigation (30).

Roughly half of flagellated bacterial species use more than one specific flagellin building block to assemble their flagella (29), which has been shown to affect the properties and geometry of the filament (22, 29, 47, 54, 55). The bacteria rely on this to modify their swimming behavior. In addition, the flagellins of many bacterial species are modified, e.g., by glycosylation (92), while other flagellar filaments are surrounded by a sheath (21).

BACTERIAL FLAGELLATION PATTERNS

Bacteria exhibit species-specific flagellation patterns (**Figure 1*b***): One or more flagellar filaments can emerge at one or both cell poles [(bi)polar flagellation], a flagellum can locate subpolarly, or several filaments can be distributed along the cell at lateral positions (58, 94). Several species even possess two distinct flagellar systems and thus can produce both patterns, polar and lateral, in parallel (72, 73). The lateral, or peritrichous, flagellation pattern of *Escherichia coli* has become the paradigm for flagellum-mediated movement, including the famous run-and-tumble maneuver for directional switching and chemotaxis (11, 13). However, in many habitats, e.g., marine environments, the majority of swimming bacterial species exhibit polar flagellation (57) and use modes and mechanisms of motility that are quite different from those described for *E. coli*. Recent studies have provided novel insights into how polarly flagellated bacteria move, which is the focus of this review. We will, however, not consider the motility of spirochetes, as the mechanism of their highly original way of moving is covered in an excellent recent review (79).

ORGANIZATION OF POLARLY FLAGELLATED CELLS

As indicated above, polar flagellation comes in several patterns (**Figure 1*b***). The elementary—and highly common—configuration is the monopolar flagellation (monotrichous) that is found, for example, in *Caulobacter crescentus*; in many *Vibrio* and *Pseudomonas* species, such as *V. cholerae* and *P. aeruginosa*; in *Bdellovibrio bacteriovorus*; and in *Shewanella* species, such as *S. oneidensis*. Some species, such as *Campylobacter jejuni* and other species of this genus, sport a single flagellum at each cell pole, a pattern referred to as amphitrichous. Other bacteria have not only one flagellum but bundles (tufts) of several flagella at one pole (a trait referred to as lophotrichous), e.g., some species of *Helicobacter*, *Vibrio*, and *Pseudomonas*. Such a flagellar bundle can also occur at both cell poles (bipolar lophotrichous), as in *Helicobacter suis*.

The exact mechanisms by which the cells establish their specific pattern is still elusive for most systems (94). As flagellar synthesis, from the assembly of the initial structures to the start of propulsion, can easily exceed the doubling time of the cell (31, 44), the formation of one or more polar flagella has to be spatiotemporally regulated. Notably, this can be exploited to achieve asymmetric cell division, with one daughter cell developing or inheriting a flagellar system while the other daughter cell remains nonflagellated and nonmotile. The prime example for this is *C. crescentus*, with its intricate asymmetric cell cycle, which includes a flagellated, highly motile cell and a sessile, nonflagellated stalked cell (111). A recent study showed that surface-attached *P. aeruginosa* cells asymmetrically divide into both nonflagellated and highly motile progeny. Whereas the former has a greater tendency to remain surface-associated, the latter detaches from the surface. This behavior, termed "touch, seed, and go," effectively optimizes the population's balance between colonizing and spreading (56). In cells that are flagellated at a single pole, the associated chemotaxis supracomplex is usually located in direct proximity to the same cell pole.

In this way, the cell ensures efficient chemotactic signaling, as diffusion of the phosphorylated chemotaxis response regulator, CheY, from the chemotaxis system to the flagellar motor(s) may become limiting in cells longer than 2 μm (14). In addition, upon cell division one progeny cell inherits a fully functional chemotaxis system along with the flagellum (43, 68).

SWARMING OF POLARLY FLAGELLATED BACTERIA

For many bacterial species, flagella also allow the rapid movement of groups of bacterial cells across a surface, which is referred to as swarming (45). Of note, swarming must not be confused with bacterial swimming in low-percentage agar, which is commonly used to score flagellum-mediated motility in the lab. Several polarly flagellated bacteria, e.g., some species of *Pseudomonas* (49, 50, 67), are capable of swarming with only their polar flagella. However, a number of bacterial species also employ a helper system: In addition to the main polar flagellum, these species encode a distinct secondary flagellum system (72, 73). This secondary system is usually expressed upon surface exposure, leading to formation of (sometimes numerous) lateral flagella that assist the cells in efficient swarming. Among the polarly flagellated bacteria that swarm by employing such secondary systems are *Vibrio* species such as *V. parahaemolyticus* and *V. alginolyticus*, *Aeromonas* spp., and *Azospirillum brasilense*, to name just a few (2, 32, 95, 96). The transition to swarmer cells may—in addition to formation of multiple lateral flagella—also include suppression of cell division that results in highly elongated cells, which has been studied, for example, in *V. parahaemolyticus* (70, 72, 77).

SWIMMING AND CHEMOTAXIS OF POLARLY FLAGELLATED BACTERIA

Bacteria move through aqueous environments at a low Reynolds number. The Reynolds number measures the ratio of inertial to viscous forces in the surrounding fluid. Due to the small size and low speed of a bacterial swimmer, friction forces that arise from the viscosity of the aqueous surroundings dominate over inertial forces related to the density of the fluid, so that cells instantly stop as soon as they cease their active propulsion (87). While rod-shaped, peritrichous bacteria, such as *E. coli*, reach their maximal velocity at higher viscosities than polarly flagellated bacteria, polar flagellation still allows efficient, high-speed motility under these conditions (93). In *E. coli*, four to six peritrichous left-handed filaments form a bundle behind the cell upon counterclockwise rotation, which pushes the cell forward ("run"). Clockwise rotation of one or more flagella results in a polymorphic transition of this filament to a right-handed flagellar helix, which leaves the bundle and induces a reorientation of the cell ("tumble") that continues in a different direction upon switching back to counterclockwise rotation. By modulating the duration of runs between tumble events, *E. coli* can actively move up or down a gradient in a so-called biased random walk (11, 26, 112), a movement strategy that has become textbook knowledge (**Figure 2*a***). However, owing to differences in flagellation pattern and filament properties, many bacterial species, including the polarly flagellated ones, have evolved mechanisms for swimming and reorientation for chemotaxis that are obviously distinct from the *E. coli* tumbling (107).

Monopolarly Flagellated Bacteria

A common mode of motility of monopolarly flagellated bacteria is the so-called run-reverse-flick pattern (**Figure 2*b***), a mechanism that was first elucidated for *Vibrio alginolyticus* (99, 117). In aqueous environments, *V. alginolyticus* is driven by a single sheathed, left-handed filament that pushes the cell forward when rotated counterclockwise and pulls the cell backward when rotated

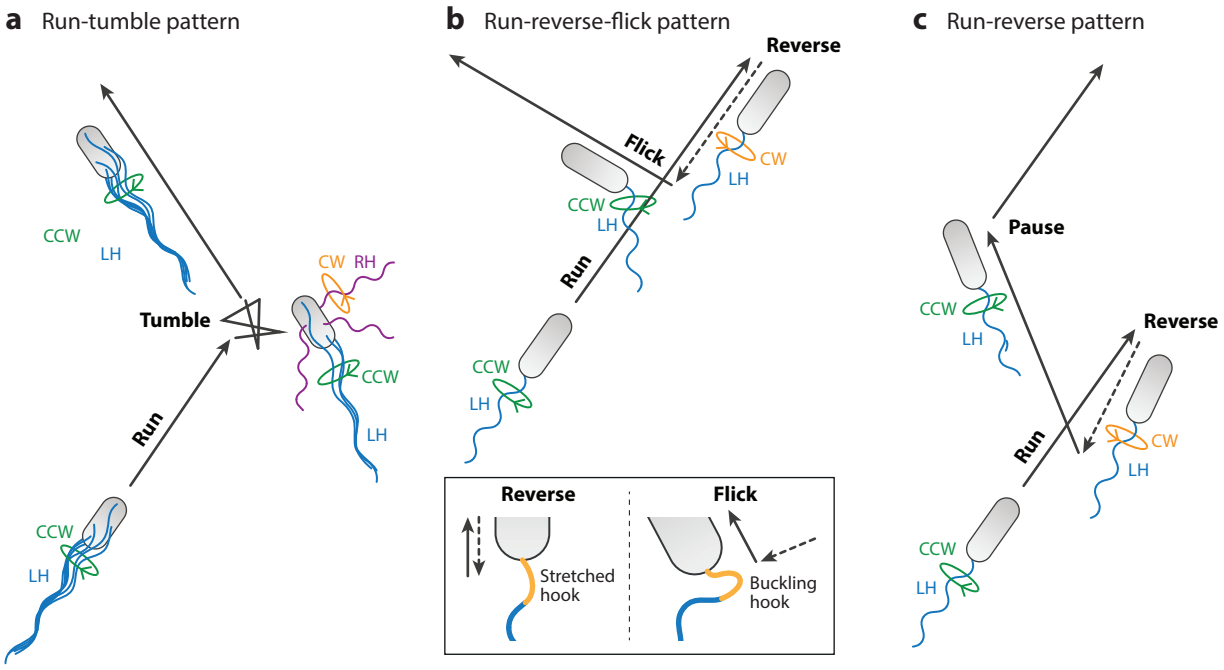


Figure 2

Swimming patterns of flagellated bacteria. (*a*) The paradigm run-tumble pattern of *Escherichia coli*. Efficient movement is achieved only during the pushing mode, when the flagella are rotating counterclockwise. When one or more flagella switch to clockwise rotation, the corresponding filament will become right-handed and leave the bundle, which induces reorientation of the cell body. (*b*) The run-reverse-flick pattern described for some species of *Vibrio*, *Caulobacter crescentus*, and *Shewanella putrefaciens*. Cell realignments are triggered by buckling instabilities of the hook structure upon the switch from pulling to pushing mode. (*c*) The run-reverse pattern observed for some *Pseudomonas* species. Reorientation of the cell body occurs during pauses between runs. Recent studies demonstrate that more effective reorientation can be induced by wrapping and unwrapping the flagellar filament(s) around the cell body. In contrast to peritrichous *E. coli*, monopolarly flagellated species can efficiently move toward a target during both pushing mode and pulling mode. Solid arrows indicate forward swimming (pushing), and dashed arrows indicate backward (pulling) movement. Abbreviations: CCW, counterclockwise; CW, clockwise; LH, left-handed; RH, right-handed.

clockwise (**Figure 1*c***). Backward swimming was found to be even faster than forward movement (63). Thus, a rotational switch from counterclockwise to clockwise results in a 180° reversal. For directional changes other than reversals, the cells have evolved a mechanism that exploits an instability of the hook structure, which connects filament and motor. Backward swimming with the flagellum pulling the cell stretches the hook structure. When the cell switches back to counterclockwise rotation, the sudden pushing of the flagellar filament results in compression and buckling of the hook, which in turn effectively reorients the cell body at an angle of about 90°, depending on cell size and speed (100, 106). In addition to the mechanism of cell reorientation, the chemotactic behavior of *V. alginolyticus* is different from that of *E. coli*. First, it is proposed that a fast chemotactic response to changes in chemical signals allows the cells to quickly correct a wrong turn that points down instead of up a chemoattractant gradient (3, 102). In addition, for a bidirectional swimmer like *V. alginolyticus*, it does not matter whether the target is approached in a forward or backward direction. Accordingly, *V. alginolyticus* increases the duration of runs upon positive stimulation in both directions (118), and thus it outperforms *E. coli* with respect to chemotactic speed. Such run-reverse-flick maneuvers are likely prevalent in polarly flagellated marine bacteria, such as *V. alginolyticus* or *Pseudoalteromonas haloplanktis*, and enable the cells to efficiently roam

their natural environment and to respond to microscale nutrient gradients (8, 103). Other species for which the flicking was demonstrated include *C. crescentus*, which operates a right-handed flagellum for swimming (51, 60). *Shewanella putrefaciens* also navigates by a run-reverse-flick behavior similar to that of *V. parahaemolyticus* (8, 16). Notably, *S. putrefaciens* is one of the species with a secondary flagellar system and can produce, in addition to the polar flagellum, several distinct lateral flagella during swimming. These additional filaments have been proposed to assist spreading of swimming cells by lowering the turning angle to increase directional persistence (16).

A strategy partly different from run-reverse-flick navigation is used by the monotrichous *P. aeruginosa*, which swims and navigates by a run-reverse-pause pattern (**Figure 2*c***). Similar to *V. alginolyticus*, *P. aeruginosa* is capable of responding to and moving up or down a gradient in both forward and backward swimming directions (18). However, no flicking is observed. Instead, the cells pause their motility, which is proposed to promote realignments of the cell body (88). Recently, more efficient directional switching of *P. aeruginosa* cells was assigned to wrapping and unwrapping of the flagellar filament (110), which will be explained in detail below. The run-reverse pattern is similarly observed in other monopolarly flagellated species of *Pseudomonas*, such as *P. fluorescens* and *P. citronellolis* (85, 107).

And as these two strategies, pausing and flicking, are obviously successful, why not combine them? Such a combination has been observed for the monotrichous soil bacterium *Azospirillum brasilense*, which exhibits forward-backward movement with pausing and, occasionally, also a run-reverse-flick pattern (76, 120).

Lophotrichous Bacteria

In the case of the plant root–colonizing soil bacterium *Pseudomonas putida*, five to seven flagella form a polar tuft that propels it forward in liquid media (33). Its motion pattern consists of straight runs interrupted by reversals in swimming direction and occasional pauses (28). In contrast to the unimodal turning angle distribution of *E. coli*, this is accompanied by a bimodal distribution of turning angles for *P. putida* (28), where two peaks at angles below and above 90° can be attributed to the pauses and reversals, respectively (108). The bimodal distribution of the turning angles is robustly maintained for a wide range of different conditions, such as different cell densities (27) and swimming under confinement (89, 109). Notably, reversals in the swimming direction of *P. putida* are typically associated with a change in swimming speed by a factor of two on average (108), a prominent feature that can be understood only in conjunction with the mechanism of flagellar wrapping and is explained in more detail below.

The run-time distribution of *P. putida* was found to be nonexponential (108), indicating that, in contrast to the case of *E. coli*, the duration of runs is controlled by a more complex underlying stochastic process (80). As chemoattractant concentrations are increased over time, the frequency of directional changes is decreased (33, 34). This is in line with a classical chemotaxis strategy where runs in gradient direction elongate on average, compared to runs pointing away from the source of chemoattractant (80, 86).

The bioluminescent marine bacterium *Vibrio fischeri* is also lophotrichous (71, 82). It relies on flagellum-driven motility to colonize the light organs of the Hawaiian bobtail squid (6). *V. fischeri* swims in a run-reverse pattern, as does the lophotrichous bean bug symbiont *Burkholderia* sp. RPE64 (48). Similar to *P. putida*, both of these polar swimmers exhibit pronounced changes in their swimming speed upon directional reversals (48). *Helicobacter pylori*, which is associated with the formation of peptic ulcers and gastric cancer, also displays a tuft of flagella attached to one pole of its helical cell body (65). *H. pylori* exhibits helical trajectories and, similar to the other lophotrichous swimmers, propagates in a run-reverse fashion (38), showing a broad distribution of swimming speeds that depends on the number of flagella and on variations in the geometrical

parameters of its helical cell body (23, 66). Also in *H. pylori*, alternating swimming speeds in conjunction with directional reversals were recently detected. They were associated with pushing and pulling configurations of the flagellar bundle and allowed quantification of changes in the rotational bias in response to chemoattractant stimuli (4).

Bipolarly Flagellated Bacteria

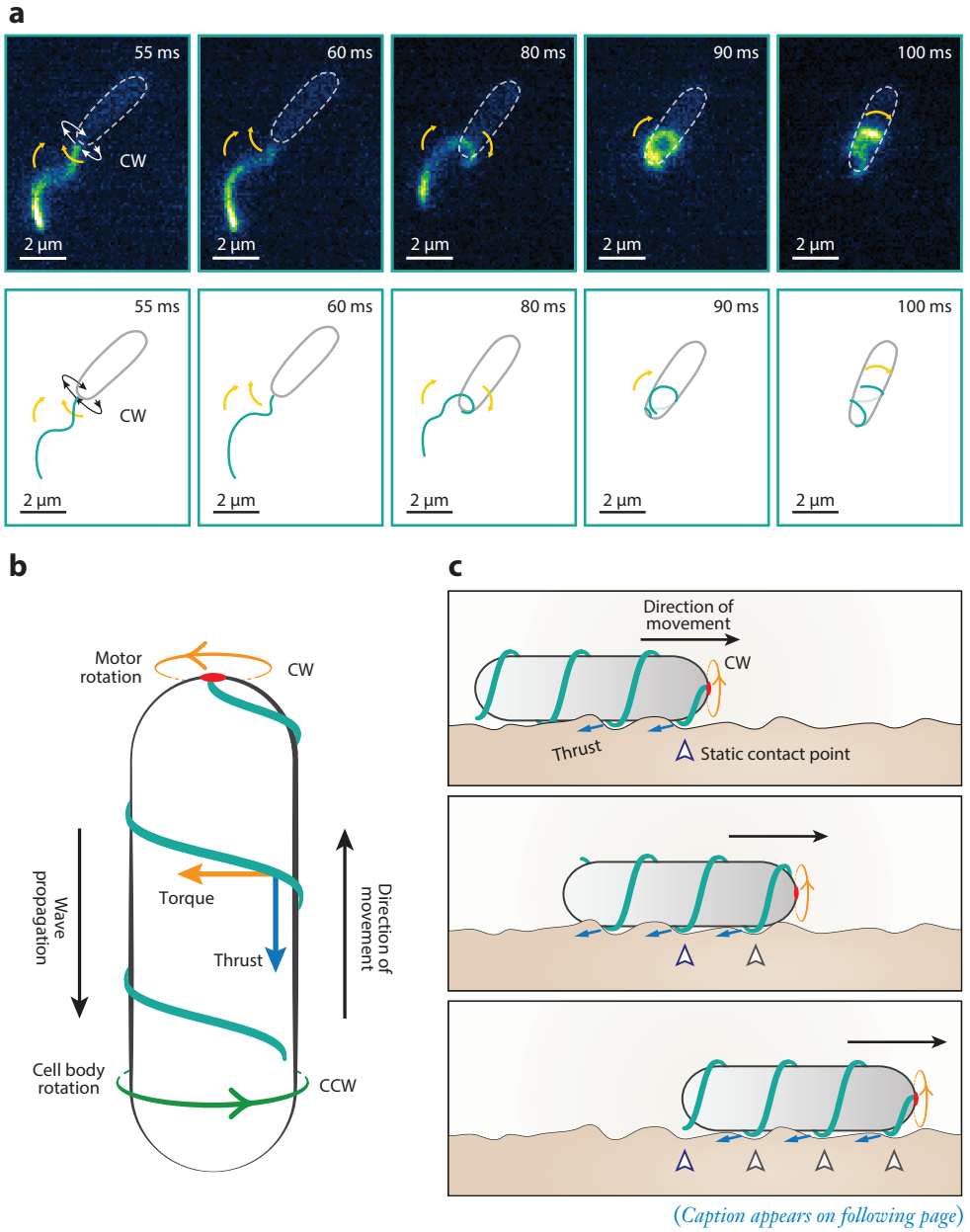
Several bacterial species outside the group of spirochetes form one or more flagella at both poles of the cell, among them *Spirillum volutans*, *Magnetospirillum magneticum*, *C. jejuni*, and *H. suis* (7, 52, 59, 78). The bipolar flagellation pattern comes with several challenges with respect to efficient motility and navigation, as now two flagellar motors or motor clusters have to be coordinated. Notably, these bacteria are helical rods, and it was proposed that the flagellar rotation primarily drives rotation of the cell body to generate propulsion in high-viscosity environments. However, straight-rod mutants of *S. volutans* are well able to swim (83), and the role and benefit of body propulsion may not be as pronounced as originally thought (23). An important question is how rotational switches are coordinated to avoid flagella or flagellar bundles pushing or pulling from both sides for extended periods. While many questions about the chemotactic coordination remain unsolved, more insights with respect to navigation have been gained by the rediscovery of another flagellar mode of function, flagellar wrapping, which is explained below.

FLAGELLAR WRAPPING

First hints that flagella may not only function when pointing away from the cell date back more than 100 years when microbiologists determined the behavior and position of flagellar filaments of swimming bacteria by means of dark-field microscopy. At that time, it was noted that cells of the lophotrichous species, at that time referred to as *Pseudomonas cyncyanea*, moved with a flagellar bundle pushing the cells. However, the filaments folded down along the cell body when the leading pole became the lagging pole due to a switch in swimming direction (90). A similar observation was made for the bipolarly lophotrichous *Thiospirillum* (17): A bundle of flagella pushed the cell from the lagging pole; however, the flagella at the leading pole seemed to rotate around the cell body rather than pulling the cells. Upon a switch of direction, these flagella would extend again to form a bundle that pushed the cells, while the filaments at the opposite, now leading, cell pole would instantly flip down, "eine Erscheinung, die eine verblüffende Ähnlichkeit mit dem Überschnappen eines Regenschirms hat"—astoundingly reminiscent of an umbrella flipping over (17, p. 555). Similarly, the flagellar bundle at the leading pole of swimming *Spirillum* cells was observed to bend around the cell, taking the shape of a wide bell (74). These early examples already suggested that polar flagella may undergo a functional switch between two modes, pointing away from the cell or operating close to the cell body. The latter was next observed for amphitrichous bacteria that had just divided and not regrown flagella at the new cell pole. These cells occasionally moved with their filaments not only bent down but also wrapped around the cell body (40).

It took some time until studies using more advanced microscopy approaches on swimming cells confirmed the earlier observations and, finally, began to shed new light on the role of this flagellar behavior. During swimming of amphitrichous *Magnetospirillum magneticum*, the flagellar filament at the lagging pole was observed to push the cell while pointing away from the cell (tuft) (78). In contrast, the filament at the leading pole was often not extended but performed rotation around the cell (parachute), similar to the umbrella that was reported by Buder in 1915 (17). Independent research groups later described more examples of these phenomena in the monopolarly flagellated species *S. putrefaciens* (53) and *P. aeruginosa* (110), and the lophotrichous species *P. putida* (36), *Burkholderia* sp., and *V. fischeri* (48). Except for *P. aeruginosa*, these species exhibited

a similar behavior: Upon switching from pushing to pulling mode, the flagellar filament or filament bundle would wrap around the cell in a spiral-like form and continue to rotate around the cell body, in "a motion like that of a ribbon streamer in rhythmic gymnastics" (48, p. 838). The cell body itself rotated in the opposite direction (**Figure 3*b***). In all cases, the wrapped filaments would unwrap from the cell body to point away from the cell upon switching the direction of swimming, showing that the wrapping is a reversible process. In *P. aeruginosa*, flagellar wrapping appears to occur upon switching from clockwise (pulling) to counterclockwise (pushing) rotation (110). The



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Mechanism of flagellar wrapping and screw thread motility. (*a*, *Top*) Micrograph stills of a high-speed movie of a monopolarly flagellated *Shewanella putrefaciens* cell wrapping a fluorescently labeled filament, and (*bottom*) corresponding drawings. High-force clockwise rotation induces an incomplete perversion within the base of a left-handed helix, which pulls the residual filament down and around the cell. The process takes about 50 ms. The scale bars represent 2 μm. Adapted from Reference 53. The yellow arrows indicate the movement of the flagella during the wrapping process. (*b*) Rotation and function of a wrapped flagellum. The filament remains a left-handed helix that rotates around the cell, with the cell body exhibiting counterrotation. While the wave of the helix propagates toward the nonflagellated cell pole, the cell is moved backward toward the flagellated pole (compare **Figure 1*c***). (*c*) Screw thread motility. When the cell has contact with a substratum, irregularities at the substratum's surface serve as static contact points for the flagellar helix, which allows efficient movement of the cell across a surface or through a narrow space. Abbreviations: CCW, counterclockwise; CW, clockwise.

reversible helical wrapping of the flagellar filament around the cell body was also demonstrated for the bipolarly lophotrichous *H. suis* (24) and the amphitrichous *C. jejuni* (22). Also, the above-mentioned parachute-like filament formation reported for the amphitrichous *M. magneticum* (78) may correspond to a rotating wrapped flagellum observed at a lower spatiotemporal microscopic resolution, and it is quite conceivable that the reports from Reichert (90) and Buder (17) 100 years ago described the very same phenomenon. But how is this flagellar filament state achieved, and is this connected to a biological function?

MECHANISM OF FLAGELLAR WRAPPING

The mechanism of the flagellar wrapping was first characterized in the monopolarly flagellated *S. putrefaciens* (53). This species has a left-handed helical flagellar filament that pushes the cell when rotated counterclockwise and pulls the cell when the rotational direction switches to clockwise. However, when rotating clockwise under conditions of high load on the filament, e.g., when the cell gets stuck or is moving in a medium with increased viscosity, the flagellar helix becomes unstable: The first loop of the helix above the hook is bent toward a right-handed helix, a so-called incomplete perversion (**Figure 3*a***). This results in pulling the entire filament following the first loop, which remains a left-handed helix, toward and around the cell. The process is accompanied by a polymorphic conversion of the flagellar filament toward a broader helical form, which alleviates the wrapping procedure. Initiation of filament wrapping was similarly observed for the lophotrichous cells of *P. putida*, *Burkholderia* sp., and *V. fischeri* (36, 48). Here, high-speed imaging demonstrated that clockwise rotation of the left-handed filament's helix results in a loop opening at the base of the flagellar bundle close to the cell pole, before the whole bundle is pulled down to wrap around the cell (36). Similar to the case of monopolarly flagellated *S. putrefaciens*, this may be triggered by an incomplete perversion of the left-handed helical bundle close to the cell pole. In contrast to what was observed in *S. putrefaciens*, wrapping of the flagellar bundle in the latter three lophotrichous species readily occurred also in the absence of additional strain on the filaments. It may thus be related to the unstable configuration of a pulling helical bundle or to spontaneous changes in the motor torque. This is confirmed by mathematical modeling showing that transitions to the wrapped mode critically depend on the bending modulus of the hook and the applied motor torque (84). The wrapped state of the flagellar bundle remains stable as a left-handed clockwise-rotating helix around the cell as long as the motor continues to rotate clockwise, while the cell body counterrotates in counterclockwise direction (48) (**Figure 3*b***). The filament or filament bundle readily unwinds to resume the normal pushing configuration, pointing away from the cell, upon switching of the flagellar motor to a counterclockwise direction, and the cell then continues its regular forward motion. Flagellar wrapping in *P. aeruginosa* is thought to be based on

a different mechanism: Switching from the pulling (clockwise rotation) to pushing (counterclockwise rotation) mode results in a buckling of the flagellar hook, reminiscent of the flicking mode of *V. alginolyticus* (99, 117). However, in *P. aeruginosa* this buckling instability can result in flagellar wrapping and then unwrapping once the hook straightens, after a short period of time (110).

As in the monopolarly flagellated species *S. putrefaciens*, a shift in rotational direction to clockwise is thought to initiate the parachute state of the single polar left-handed flagellum at the leading pole in amphitrichous *M. magneticum* (78). Assuming that this parachute state represents a flagellar filament that is wrapped around the right-handed helical cell body of this species, this may be based on a similar mechanism as described above for the monopolarly flagellated *S. putrefaciens*. This may also apply to the bipolar bundles of *H. suis* (24). However, the details of wrapping initiation for these two species remain unclear and require further studies. More data are available for the initiation of flagellar wrapping in amphitrichous *C. jejuni* (22). Both flagellar filaments exhibit a left-handed helix, and both motors synchronously rotate either counterclockwise (as a default direction) or clockwise. In either case, the flagellum at the lagging pole pushes the cell, while the flagellum at the leading cell pole folds down, apparently without an incomplete perversion at the proximal end of the left-handed helix. The helical shape of the filament fits into the groove of the opposite-handed helical shape of the cell body, which exhibits the corresponding counterrotation (**Figure 4*a***). Flagellar wrapping was promoted by increasing drag on the filament, e.g., by higher viscosity, and did not depend on the direction of rotation (22).

PHYSIOLOGICAL ROLE OF FLAGELLAR WRAPPING

Motility in Structured Environments

The observed flagellar wrapping could just be the result of a simple structural failure of a flagellar helix not sufficiently rigid to mediate pulling of the cell. However, there is solid evidence that the phenomenon has, in fact, important biological functions for the corresponding species.

Mutations affecting the flagellin composition of the *S. putrefaciens* filament allowed the generation of a strain unable to perform flagellar wrapping (54). Although exhibiting vigorous swimming under planktonic conditions, the cells had severe defects in spreading through structured environments, such as a polysaccharide matrix (54). Accordingly, cells that got stuck in constricted environments were observed to wrap the flagellar filament and escape the constriction by a screw-like backward motion (53). During the backward movement, the waveform of the filament did not change relative to the substratum (**Figure 3*c***), while the cell was moved backward through the helix. In contrast, when wrapping was induced by increased viscosity without a solid substratum, the waveform of the flagellar helix moved relative to the medium, and no efficient translation of the cell body occurred. Similar cell translation, without changing the waveform of a wrapped flagellar filament or a filament bundle, was observed for *Burkholderia* sp. RPE64 in close contact with a surface (48), indicating a form of flagellum-mediated gliding of bacteria, which we will henceforth term screw thread motility.

The mechanistic concept of this form of motility is reminiscent of other surface-dependent modes of movement: A-motility gliding, which is well studied in *Myxococcus xanthus*, and the gliding of *Flavobacteria*. Despite fundamental differences in the components of the underlying machinery, all of the abovementioned modes of movement rely on a rotating helical cellular structure for propulsion. While *M. xanthus* and *Flavobacteria* use designated adhesins as surface focal adhesion points (39, 69, 75, 97), screw thread motility of *S. putrefaciens* and *Burkholderia* sp. RPE64 rather relies on natural surface irregularities to efficiently move the cell.

These studies indicate that flagellar wrapping and screw thread motility enable the release of cells that are trapped in narrow passages and allow cells to move more efficiently through

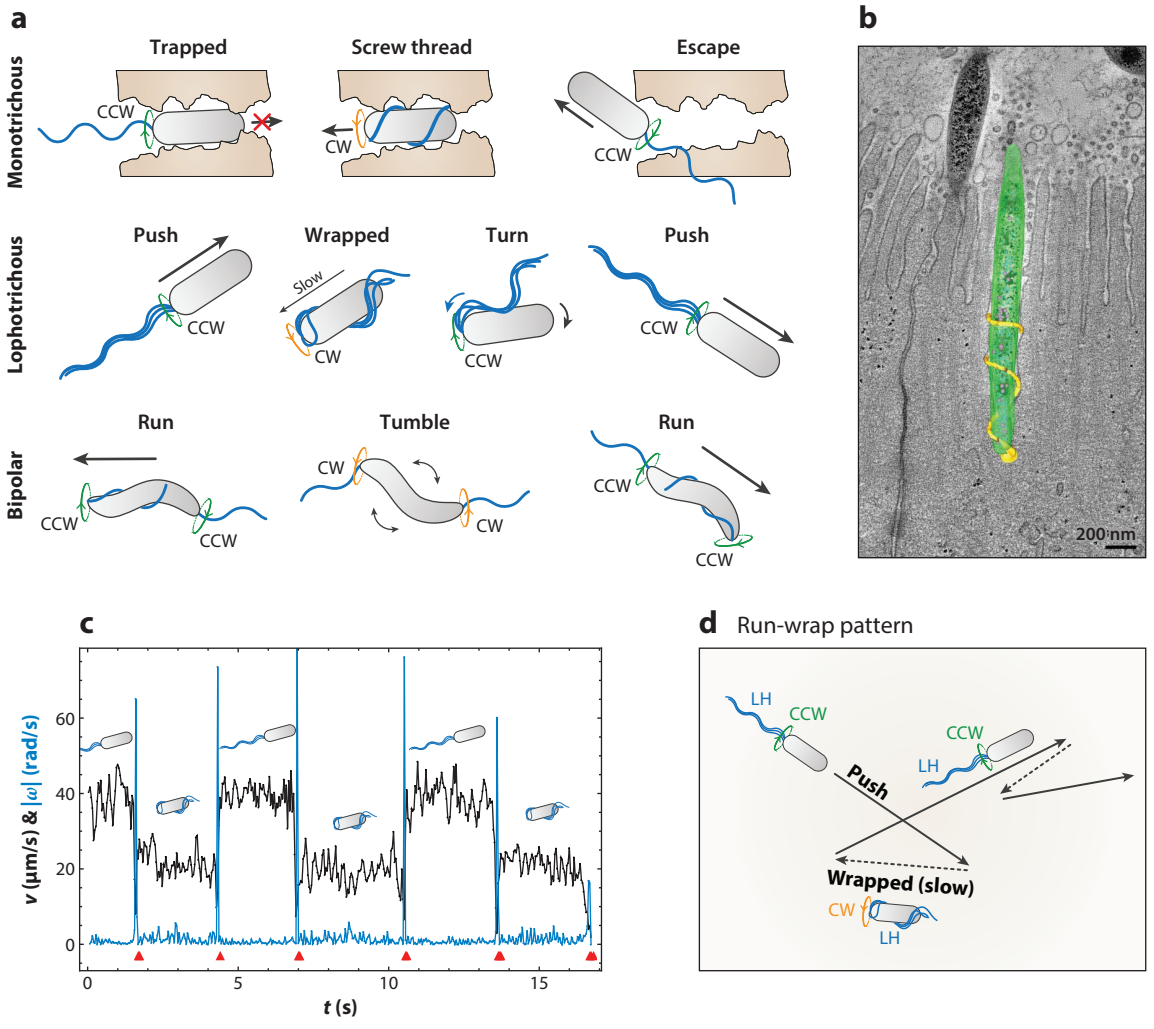


Figure 4

The physiological roles of flagellar wrapping. (*a*, *Top*) Screw thread motility enables cells to escape from traps and move through narrow, structured spaces (see also **Figure 3*c***). (*Middle*) The unwrapping of a filament or filament bundle realigns the cell for more efficient navigation. (*Bottom*) For bipolarly flagellated species, wrapping of the filament at the leading pole enables efficient, straight movement. Cellular realignments during wrapping or unwrapping benefit directional changes and navigation. Black arrows indicate the direction of the cell's movement. (*b*) Screw thread motility might enable cellular drilling. The tomography image of a cell of a yet unidentified species invading an epithelial cell with the flagellar filament (*yellow*) wrapped around the cell body (*green*). Image provided by Mark Ladinsky and Pamela Bjorkman (Caltech, California, USA). (*c*,*d*) *Pseudomonas putida* cells alternate between a fast pushing and a slow reverse wrapped mode, which benefits spreading of the cells (see also **Figure 2**). (*c*) Cell speed (v, *black*) and absolute value of the angular velocity ($|\omega|$, *blue*) over time. The red triangles mark the time points of the speed-change events. (*d*) Swimming pattern of *P. putida* cells in the push mode (*solid arrows*) and the wrapped mode (*dashed arrows*). Abbreviations: CCW, counterclockwise; CW, clockwise; LH, left-handed. Panel *c* adapted from Reference 108.

constricted environments, such as a polysaccharide matrix. Notably, both *V. fischeri* and *Burkholderia* sp. RPE64 are endosymbionts of the internal crypts of the bobtail squid's (*Euprymna scolopes*) light organ and of the lumen of the midgut crypts of the bean bug *Riptortus pedestris*. This requires active movement of the cells through mucus-filled ducts (81, 104, 114), and it was therefore proposed that flagellar wrapping facilitates the establishment of a persistent association (48).

Motility and Chemotaxis in Free Liquid Environments

In addition to surface/substratum-dependent screw thread motility, flagellar wrapping was shown to benefit efficient free movement away from a substratum. This is somewhat intuitive for the amphitrichous or bipolarly lophotrichous *C. jejuni* and *H. suis*. In both species, the flagella on both poles are assumed to rotate counterclockwise or clockwise, which would lead to synchronous pushing or pulling from both poles, preventing efficient translation of the cell without wrapping of the filament of the leading pole. Accordingly, fast and efficient movement of both species occurred with the lagging flagella extended and the leading filaments wrapped (22, 24). This was similarly observed for *M. magneticum*, with the filament at the lagging pole turning counterclockwise and pushing the cell and the filament at the leading pole rotating clockwise either extended from the cell or, more frequently, in the parachute state around the cell body (78). In addition, for all species intermediate states were observed with both filaments wrapped or extended, or one filament in the process of wrapping while the other unwrapped. This could be triggered by synchronized (or asynchronized) motor reversals and resulted in an efficient realignment of the cell body (**Figure 4*a***), which is therefore likely to benefit efficient chemotaxis (22, 24, 78).

Three modes of propagation were observed for free-swimming lophotrichous *P. putida*: Their left-handed helical flagellar bundle can push, pull, or wrap around the cell body (36). By changing the sense of motor rotation, cells can switch between push (counterclockwise) and pull (clockwise) modes. In addition, starting from a pulling bundle, a transition to the wrapped mode can occur without changing the sense of motor rotation. As the motors keep turning in the clockwise direction, how this transition is initiated remains an open question. Mathematical modeling suggests that this may be related to changes in the motor torque (84), but instabilities of pulling flagellar bundle configurations could also play a role (46, 61). The latter aspect seems particularly plausible, as the transition back from wrapped to pull mode has never been observed. Instead, upon a switch from clockwise to counterclockwise rotation, the bundle changes from wrapped to push mode. Moreover, the instability of the pull mode is additionally highlighted by the observation that swimming *P. putida*, on average, spends most of the time in either push or wrapped mode, whereas the pull mode is less frequently observed and is often only a short-lived intermediate state during transitions from push to wrapped mode (1). The swimming speed of the wrapped mode in free aqueous environments is, on average, reduced by a factor of two compared to runs in the push and pull modes (**Figure 4*c***). Thus, regular transitions to the wrapped mode explain the earlier observation that reversals in the swimming direction of *P. putida* are associated with changes in the swimming speed (108). This was also confirmed for *Burkholderia* sp. RPE64 and *V. fischeri* (48). A swimming pattern that involves sequences of push-pull-wrap transitions with a decreased swimming speed in the wrapped mode was recently also observed for *P. aeruginosa* (110). For *H. pylori* a similar change in swimming speed was attributed to a transition from push to pull mode (4, 23). However, we expect that also in this case, direct fluorescence imaging of the flagellar dynamics may reveal that wrapping of the flagella around the cell body is involved. Compared to the push and pull modes, the helix of the wrapped flagellum typically exhibits a larger radius and a lower frequency of rotation, which may be related to increased frictional forces resulting from the close proximity to the enclosed cell body. The lower frequency of rotation may also cause a decreased swimming speed (36).

For run-reverse swimmers, switching between a fast and a slow mode of propagation results in an enhanced diffusive spreading compared to swimmers that move at a constant intermediate speed (108) (**Figure 4*d***). By introducing regular episodes of slow swimming, a population of bacterial swimmers may thus expand faster, which can be seen as a key advantage when they are competing for resources by exploring and colonizing the environment. Also the broader turn angle distribution of the pull-wrap-push transition contributes to more efficient spreading dynamics

and may even impact the chemotactic performance (110). Theoretical estimates based on active particle models provide explicit expressions for the long-time diffusion coefficient, depending on the probability of switching to the wrapped mode (36) and also for arbitrary speed ratios between the fast and slow modes of propagation (4).

In the case of *P. putida*, it was observed that the wrapped mode also plays a distinct role in chemotaxis. While runs in push mode are insensitive to the presence of a chemoattractant gradient, runs in wrapped mode display a clear run-time bias. They are, on average, shorter when oriented down the gradient as compared to runs up the gradient, which are comparable to runs in the absence of a concentration gradient (1). Theoretical estimates of the long-time chemotactic drift coefficient show that the presence of a nonresponsive run mode positively affects the robustness of the chemotactic response. Moreover, the lower swimming speed during the chemotactically active wrapped runs may enhance the chemotactic efficiency in dense, crowded environments (1).

CONCLUSIONS: WHAT IS STILL OUT THERE?

Flagellar wrapping has now been reported for a growing number of bacterial species with different polar flagellation patterns. The wrapping mechanism is a universal physical process and could, potentially, occur for all rod-shaped species with polar flagella. Initiation of flagella wrapping depends on several factors, such as the load acting on the flagellum and the inherent properties (e.g., the ability to undergo polymorphic changes) and geometry of the filament. Wrapping may thus be a common behavior that benefits or may even be critical for bacterial spreading. It needs to be mentioned, though, that more nonwrapping mutants of different species are required to directly investigate potential roles of this flagellar behavior in more detail. While the benefit of screw thread motility and wrapping for efficient movement under confinement is rather intuitive, other functions of this flagellar behavior could be imagined. This is highlighted by cryotomographic images of yet uncharacterized bacteria invading epithelial cells with their flagella wrapped around their cell bodies that may use screw thread motility as a drill (M. Ladinsky & P. Bjorkman, unpublished data) (**Figure 4*b***).

In addition, the phenomenon of flagellar wrapping sheds new light on previously identified cell or flagellar properties.

1. A role for helical cell bodies: While it was proposed that the counterrotation of a helical cell shape, as for *Helicobacter* and *Campylobacter*, provides an advantage in viscous environments, the effect of this body propulsion may be smaller than originally thought (23). It was recently shown that the helical shape of *C. jejuni* significantly benefits the flagellar filament's unwrapping and, thereby, environmental spreading, providing a novel hypothesis for the nature of the cell shape's impact on motility (22).
2. A role for decoration of the filament: The helical wrapping of the flagellum leads to a close proximity or even interaction between the filament and the cell surface or the substratum. Thus, some of the filaments may require modifications to allow smooth movement of the filament across the cell. Notably, with the exception of *P. putida*, the flagellar filaments of species for which flagellar wrapping was demonstrated are either sheathed or decorated by carbohydrates. However, such a role for a flagellar filament's decoration remains to be investigated.

Motility of polarly flagellated bacteria is emerging as a vibrant field of research on a rich variety of novel phenomena that are clearly distinct from the classical picture of peritrichous species like *E. coli*. This field holds many open questions, including the roles of the different flagellins, chemotactic coordination, and adaptation to new and changing environmental conditions. In

particular, we expect further exciting insights into how these newly discovered swimming strategies are related to the diverse and often complex heterogeneous habitats of bacterial swimmers.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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