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Spirochetal motility and chemotaxis in the natural enzootic cycle and development of Lyme disease

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Two-thirds of all bacterial genomes sequenced to-date possess an organelle for locomotion, referred to as flagella, periplasmic flagella or type IV pili. These genomes may also contain a chemotaxis-signaling system which governs flagellar rotation, thus leading a coordinated function for motility. Motility and chemotaxis are often crucial for infection or disease process caused by pathogenic bacteria. Although motility-associated genes are well-characterized in some organisms, the highly orchestrated synthesis, regulation, and assembly of periplasmic flagella in spirochetes are just being delineated. Recent advances were fostered by development of unique genetic manipulations in spirochetes coupled with cutting-edge imaging techniques. These contemporary advances in understanding the role of spirochetal motility and chemotaxis in host persistence and disease development are highlighted in this review.

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Introduction

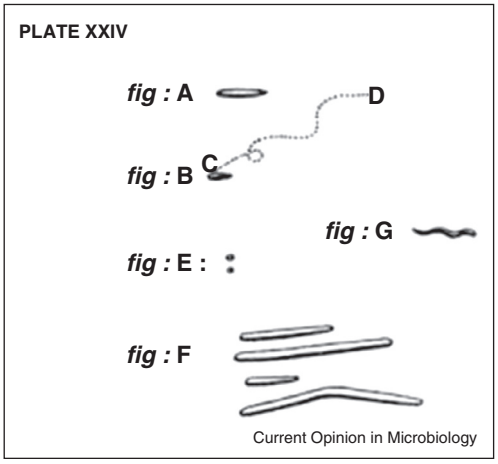
Spirochetes are a group of bacteria with distinctive morphology and motility [1,2•,3,4]. Their morphology is so unique that, upon discovery, Antoine von Leeuwenhoek diagramed spirochetal bacteria as a separate group (Figure 1) [5•]. More than 300 years after the discovery of those spirochetes from the human mouth, numerous spirochetal organisms have been identified, many of which are medically significant. *Borrelia burgdorferi sensu lato* are the causative agents of Lyme disease (i.e. Lyme borreliosis) [6•,7,8•], which is the most commonly reported vector-borne disease in the United States and Europe [9,10]. *Borrelia hermsii* and *Borrelia miyamotoi* species cause tick-borne relapsing fever, while *B. recurrentis* causes louse-borne relapsing fever. Many *Leptospira* species cause leptospirosis, which is a serious health concern for >65% of the world population, particularly in China, India and Brazil [11–15]. *Treponema pallidum* subspecies *pallidum* causes syphilis, which is sexually transmitted and is a major public health problem worldwide [16]. Other closely related treponemes cause yaws, bejel, and pinta. Some *Treponema* spp. are also associated with digital dermatitis in cattle. *Treponema denticola* and other oral treponemes are associated with periodontal disease. *Brachyspira hyodysenteriae* causes swine dysentery, and *Brachyspira pilosicoli* and *Brachyspira aalborgi* are associated with human intestinal infections in developing countries. Together, the spirochetes constitute a major global disease burden and there are tremendous interests in identifying better therapeutic targets for these unique bacterial pathogens.

Notably, recent global signature-tagged mutagenesis studies, as well as infection studies assessing directed mutants, suggested that many genes related to motility and chemotaxis functions are crucial for persistent infection by all pathogenic spirochetes tested to-date [2,17•,18–22]. While there are several excellent review articles on these topics [2•,23–26], the focus of this review is to summarize the most recent research findings and describe how they contribute to the current paradigms on the role of spirochetal motility (and chemotaxis) in the natural enzootic cycle of these bacteria.

Spirochete morphology and motility

Spirochetes are characterized as motile bacteria with distinctive helical or planar flat-wave morphology [2•,24,27]. The outer membrane of most spirochetes is a lipid bilayer that lacks the lipopolysaccharide molecules present in most gram-negative bacteria; the *Leptospira* spp. are the only known exceptions [28]. The inner membrane is typical for prokaryotic cells and is surrounded by a thin peptidoglycan layer that provides strength while being sufficiently flexible for spirochetal motility. Spirochetes flagella are not located externally as in most gram-negative bacteria, but rather reside in the periplasmic space, that is, between the peptidoglycan layer and outer membrane (Figures 2 and 3) [2•]. Each periplasmic flagellum is attached at one pole of the cell,

Figure 1



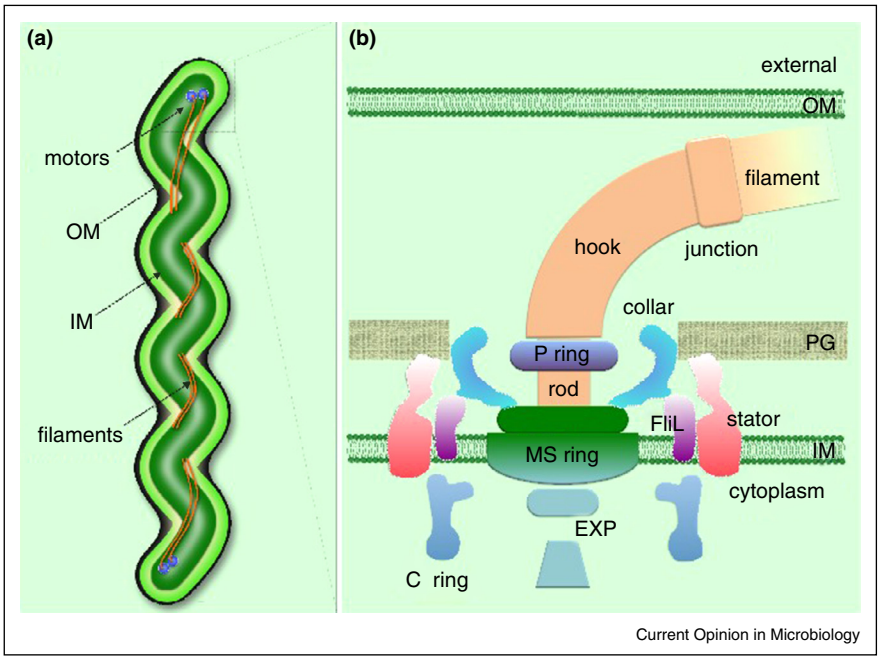
Antonie Van Leeuwenhoek's illustrations of various bacteria isolated from a human mouth that was published in September 1683, which he referred to as 'animalcules.' Bacteria shown are **(a)** a rod-shaped bacterium, **(b)** a motile bacterium moving from points **(c)** to **(d)**, **(e)** micrococci, **(f)** fusiform bacteria and **(g)** a spirochete illustrating characteristic wave-like shape.
Adapted from Ref. [5•].

then extends towards the opposite pole of the cell. The flagella from both poles may overlap in the middle of the cell. Spirochete species vary with respect to the size and number of periplasmic flagella they possess. For example, *Cristispira* spp. are 0.5–3 μm wide, 30–180 μm long, and have over 100 periplasmic flagella attached at each pole. In contrast, the *Leptospiraceae* (which include *Leptospira* and *Leptonema* spp.) are approximately 0.1 μm in diameter, 10–20 μm long, and have only one periplasmic flagellum at each end (total of 2 flagella per cell) [2,24,27,3,29•].

B. burgdorferi is the best-studied organism among the spirochetes, and will constitute the major focus of this review. *B. burgdorferi* cells are 5–20 μm long, ~0.3 μm in diameter, and possess 7–11 periplasmic flagella (endoflagella) attached to each pole [3,30–32]. During swimming, these flagella located at the poles of the cell must coordinate in order to run, reverse, or flex/tumble. *B. burgdorferi* asymmetrically rotate their flagella during these swimming patterns [24,33]. Prototypical gram-negative bacterial flagella and periplasmic flagella share substantial amino acid sequence and functional homology, but do possess some unique characteristics. For example, periplasmic flagella bear collar proteins that are unique to the spirochetes (Figure 2) [34,35]. Another unique aspect is that, while external flagella only provide motility for most bacteria, endoflagellar activity (i.e. motor rotation) also produces the spirochetal morphology that is characteristic for these bacteria [29•,36•,37•].

The periplasmic flagellum can be subdivided into three main portions: basal body, hook, and filament (Figure 2)

Figure 2



General morphology and periplasmic flagellar structures in spirochetes. **(a)** Schematic model of a spirochete cell showing the periplasmic flagellar filaments located between the outer membrane (OM) and the inner membrane (IM), causing the characteristic flat-wave morphology. **(b)** Schematic model of the periplasmic flagellar motor illustrating various flagellar motor components. PG, peptidoglycan layer; EXP, export apparatus.Adapted from Ref. [38•].