



# A Compass To Boost Navigation: Cell Biology of Bacterial Magnetotaxis

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**ABSTRACT** Magnetotactic bacteria are aquatic or sediment-dwelling microorganisms able to take advantage of the Earth's magnetic field for directed motility. The source of this amazing trait is magnetosomes, unique organelles used to synthesize single nanometer-sized crystals of magnetic iron minerals that are queued up to build an intracellular compass. Most of these microorganisms cannot be cultivated under controlled conditions, much less genetically engineered, with only few exceptions. However, two of the genetically amenable *Magnetospirillum* species have emerged as tractable model organisms to study magnetosome formation and magnetotaxis. Recently, much has been revealed about the process of magnetosome biogenesis and dedicated structures for magnetosome dynamics and positioning, which suggest an unexpected cellular intricacy of these organisms. In this minireview, we summarize new insights and place the molecular mechanisms of magnetosome formation in the context of the complex cell biology of *Magnetospirillum* spp. First, we provide an overview on magnetosome vesicle synthesis and magnetite biomineralization, followed by a discussion of the perceptions of dynamic organelle positioning and its biological implications, which highlight that magnetotactic bacteria have evolved sophisticated mechanisms to construct, incorporate, and inherit a unique navigational device. Finally, we discuss the impact of magnetotaxis on motility and its interconnection with chemotaxis, showing that magnetotactic bacteria are outstandingly adapted to lifestyle and habitat.

**KEYWORDS** magnetotaxis, magnetosome, magnetospirillum, magnetoskeleton, cytoskeleton, cell shape, flagella

In 1975, Richard Blakemore rediscovered what had been observed by Salvatore Bellini in 1963 as “a unique behavior of freshwater bacteria”: some of them seemed able to sense and swim along magnetic fields, apparently by use of magnetic iron minerals (1, 2). Today, 45 and 57 years later, respectively, much has been learned about this exceptional sense in what are now known as “magnetotactic bacteria” (MTB), which actually represent a phylogenetically diverse collection of single and multicellular bacteria that are abundant and widespread in almost any aquatic habitat (3, 4). These bacteria all share the ability to form magnetosomes, which are organelles consisting of dedicated vesicles, each synthesizing a perfect crystal of a magnetic iron mineral that operates as part of a sensor for the Earth's magnetic field. This sensor is assumed to direct the swimming of MTB along magnetic field lines and vertical redox gradients within sediments or oxic-anoxic transition zones of natural waters (5–8). The number, size, shape, subcellular arrangement, and chemical composition of the magnetic crystals vary considerably between phylogenetic groups (4, 9, 10), reflecting a high diversity of biomineralization processes and adaptation to lifestyle, biotope, and cell morphology. This suggests that magnetosomes represent one of the most complex structures found in prokaryotic cells (11, 12). The precise control that is exerted during all stages of biomineralization yields magnetic nanoparticles with exceptionally well-defined

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characteristics such as high crystallinity, strong magnetization, and a uniform size distribution, mostly outcompeting technically produced magnetic nanocrystals (13, 14). Moreover, the particular magnetosome envelope provides an excellent target to add artificial functions by genetic and biochemical coupling of diverse bioactive moieties such as fluorophores, enzymes, antibody fragments, or other ligands (15, 16). Since the organelles can readily be isolated from disrupted cells, they can also be modified *in vitro*, and much of the interest in their biosynthesis has been motivated by their potential use in several biotechnical and biomedical settings. For example, the use of bacterial magnetosomes has been successfully tested in pilot applications such as magnetic imaging techniques like magnet resonance imaging and magnetic particle imaging (17) or magnetic hyperthermia (18, 19). Because of the precisely controlled, unique properties of magnetosomes, MTB have attracted interdisciplinary scientific attention for decades not only from microbiologists and biomedical researchers but also from physicists, materials scientists, geologists, paleontologists, and others. Therefore, much progress has been made in applied research on MTB and the use of magnetosomes, which has been reviewed, for example, by Vargas et al. (16) and others.

Inevitably, MTB have also emerged as an attractive model to study formation of prokaryotic organelles and bacterial cell biology. The increasing and diversifying scientific community and the approach of new techniques in recent years have led to surprising discoveries about the genuine biological function of magnetosomes, the molecular details of their synthesis, and bacterial magnetotaxis in general. On the other hand, the ability of eukaryotic organisms to sense magnetic fields remains a mystery.

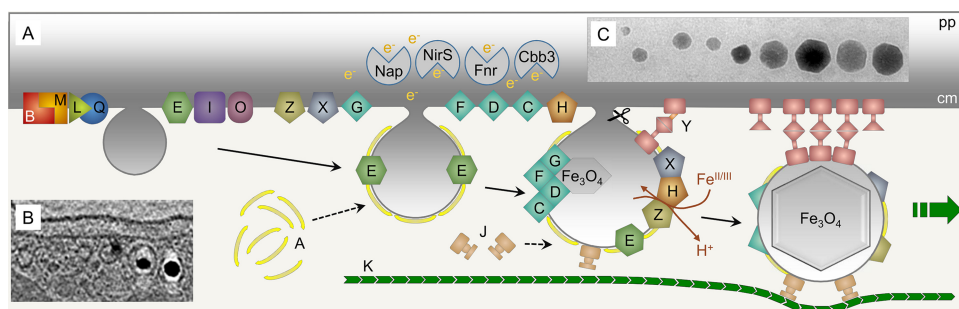
Most of our knowledge about magnetosome structure and biosynthesis comes from studies of the two closely related *Alphaproteobacteria*, *Magnetospirillum magneticum* and *Magnetospirillum gryphiswaldense*, which, compared to most other MTB, can be cultivated and genetically manipulated reasonably well. Both species are microaerophiles that can also grow anaerobically by denitrification; they share many similarities with respect to their magnetosome biosynthesis and cell morphology, and yet they also exhibit several notable differences in magnetosome structure and intracellular organization. While increasing knowledge is accumulating also from other cultured and uncultured MTB, we will mostly focus here on magnetosome structure, biosynthesis, and biological function in magnetospirilla.

### ARCHITECTURE AND STEPWISE BIOSYNTHESIS OF MAGNETOSOMES

In both *M. magneticum* and *M. gryphiswaldense*, magnetosomes consist of single cuboctahedral crystals of magnetite ( $\text{Fe}_3\text{O}_4$ ), which in their mature state are about 45 nm in size (Fig. 1C). Early studies in the related *M. magnetotacticum* indicated that each magnetite particle is enveloped by a membrane containing phospholipids and proteins, and the complete entity comprising the mineral core plus the surrounding membrane was termed a “magnetosome” (20, 21). The presence of a similar magnetosome membrane was later confirmed in *M. magneticum*, *M. gryphiswaldense*, and apparently all other MTB.

The biosynthesis of magnetosomes was subsequently revealed to be a complex, stepwise process that can be genetically dissected (11, 12, 22, 23). First, the magnetosome membrane is invaginated from the cytoplasmic membrane. Second, a set of specific magnetosome proteins is sorted to the magnetosome membrane. Third, iron is transported into the membrane vesicle and mineralized as magnetite crystal. Fourth, a magnetosome chain is assembled, positioned, and partitioned during cell division.

Proteomic and comparative genomic studies revealed that all steps are highly controlled by a distinct set of genes that are harbored within a genomic island in *M. gryphiswaldense* (24, 25) but also in the related *M. magneticum* and, apparently, in all MTB (9, 26–30) (Table 1). A core set of these so-called *mam*, *mms*, *mad*, and *man* genes seems conserved and proved useful as genomic signature for the potential to build magnetosomes (31). Transfer of 32 essential and accessory *mam* and *mms* genes from *M. gryphiswaldense* into the photosynthetic alphaproteobacterium *Rhodospirillum rubrum* resulted in its “magnetization,” that is, it caused the biosynthesis of magneto-



**FIG 1** Steps and some key proteins of magnetosome biogenesis. (A) Essential membrane-bound Mam proteins (labeled with respective letters) (see also Table 1) are thought to tightly interact at the cytoplasmic membrane and eventually facilitate formation and growth of vesicles. Later, more proteins that function in iron transport, redox control, and magnetite precipitation are recruited. Soluble proteins are associated with the periphery of the vesicles and either play a role in magnetosome membrane assembly, e.g., MamA, or are involved in the positioning and mobility of the vesicles, e.g., MamJ and MamK. Magnetite precipitation and crystal growth require not only magnetosome vesicles equipped with Mam and Mms proteins as a “nanoreactor” but also appropriate cellular redox conditions, depending on nitrate and oxygen respiration controlled by Nap, NirS, Fnr, and Cbb3 that act in the periplasmic (pp) space or the cytoplasmic membrane (cm). In *M. gryphiswaldense*, vesicles eventually become pinched off the cytoplasmic membrane by an unknown mechanism. Note that only a subset of the essential and accessory factors is shown. For a synopsis of magnetosome-associated proteins in magnetospirilla, refer to Table 1. (B) Cryo-electron tomography image of nascent magnetosomes in an *M. gryphiswaldense* cell. (Adapted from *PLoS Genetics* [22].) (C) Transmission electron microscopy (TEM) image of magnetite crystals in a wild-type cell close to the end of a chain highlighting their even cuboctahedral shape.

somes resembling those of the donor *M. gryphiswaldense* and demonstrated that these genes are basically sufficient to confer magnetosome biosynthesis to this hitherto-nonmagnetic microbe (32). This also highlights that the genetic equipment to form magnetosomes can be transmitted horizontally (33, 34), although magnetotaxis capabilities of the recent MTB mostly seem to descend from a common ancestor (31, 35, 36).

**FORMATION OF MAGNETOSOME MEMBRANE VESICLES**

Magnetosome vesicles are formed by invagination of the cytoplasmic membrane and apparently become pinched off at later stages of biogenesis in *M. gryphiswaldense* (Fig. 1A and B) but seemingly remain connected to it in *M. magneticum*, raising the possibility of a continuum between magnetosome interior and periplasm at least temporarily during vesicle growth. However, plug-like structures that separate the magnetosome lumen from the periplasm are conceivable and probable.

The formation of the magnetosome membrane is independent of magnetite biomineralization, as shown by the presence of empty vesicles in iron-starved cells or biomineralization-defective mutants. Likewise, empty vesicles are formed when cells are cultivated under aerobic conditions which suppress magnetite biomineralization,

**TABLE 1** Synopsis of genes known to control magnetosome biosynthesis in magnetotactic spirilla<sup>a</sup>

| Genes  | Affected function upon deletion                                     |
|--|---|
| <i>mamA</i> (“ <i>mms24</i> ”), <i>mamB</i> , <i>mamQ/mamQ-like</i>  | Vesicle formation   |
| <i>mamC</i> (“ <i>mms13</i> ”), <i>mamD</i> (“ <i>mms7</i> ”)/ <i>mamD-like</i> , <i>mamE/limE/mamE-like</i> , <i>mamF/mamF-like</i> , <i>mamG</i> , <i>mamH</i> , <i>mamI</i> , <i>mamL/mamL-like</i> , <i>mamM</i> , <i>mamN</i> , <i>mamO/limO</i> , <i>mamP</i> , <i>mamR</i> , <i>mamS</i> , <i>mamT</i> , <i>mamX</i> , <i>mamZ</i> , <i>mms5</i> , <i>mms6</i> , <i>mms36</i> , <i>mms48</i> , <i>mmsF</i> , <i>mmsX</i> , <i>feoB1</i> , <i>feoB2</i> , <i>ftsZm</i> , <i>feR5</i> , <i>feR6</i> , <i>amb411</i> | Iron transport/magnetite biomineralization and crystal size control |
| <i>mamJ/limJ/mamJ-like</i> , <i>mamK/mamK-like</i> , <i>mamY</i>   | Magnetosome chain formation, localization and dynamics              |
| <i>mamU</i> , <i>mamV</i> , <i>mamW</i> , <i>mms5</i>  | Uncertain   |
| <i>nap</i> , <i>nirS</i> , <i>nirN</i> , <i>norC</i> , <i>norB</i> , <i>fnr</i> , <i>cbb3</i> , <i>fur</i> (not magnetosome island encoded)  | Redox balance or iron homeostasis                                   |

<sup>a</sup>All essential and most of the accessory genes cluster in a genomic island (“magnetosome island”). A few genes have been identified and named twice, such as *mamA/mms24*. The “-like” genes are restricted to *M. magneticum* and have been identified as paralogs of the respective *mam* genes in a genomic “islet” of this organism. This redundancy is partially responsible for some differences in deletion mutant phenotypes of *M. gryphiswaldense* and *M. magneticum*. In other MTB, homologs for most of the *mam* and *mms* genes have been detected as well. However, with increasing phylogenetic distance to magnetospirilla, distinctive genes occur such as *mad* genes in greigite mineralizing *Deltaproteobacteria* or *man* genes in *Nitrospirae*. Moreover, some gene functions are redundant and some deletion phenotypes are pleiotropic so that unique functions cannot yet be assigned to all of the listed genes (for example, MamB plays a crucial role in vesicle formation but also in iron transport [47]). Biomineralization phenotypes owing to *nap*, *nir*, *nor*, *fnr*, *cbb3*, and *fur* deletion are likely an indirect effect of perturbed cellular redox balance or iron homeostasis. Products of further genes (not listed) have been found associated with magnetosomes (43), but their significance is not yet clear.

likely due to inappropriate redox conditions (37–39). In both *Magnetospirillum* strains, these invaginations originate simultaneously from several nonspecific cellular locations, as was revealed by tracking *de novo* magnetosome biogenesis by time-lapse fluorescence microscopy and cryo-electron tomography (22, 23, 40).

The magnetosome membrane has a lipid composition similar to that of the cytoplasmic membrane, but it contains a distinct set of proteins encoded in the genomic magnetosome island and with functions in magnetite biomineralization (21, 41). Magnetosome proteins are present in different quantities from one or few (e.g., MamZ) up to 120 copies (MamC) per particle (41–43). The high protein content of the magnetosome membrane suggests a crowded composition and a tight packing with transmembrane domains of integral proteins. It has been proposed that a lipid raft-like association of magnetosome-membrane proteins takes place prior to the magnetosome invagination (22). How proteins are specifically targeted to the magnetosome membrane is not known, and no conserved motifs that encode sorting signals to the magnetosome membrane have been identified.

The four proteins MamB, MamI, MamL, and MamQ were recognized as key factors in the early biogenesis of the magnetosome membrane (22, 26, 29). Among them, elimination of MamB completely abolished formation of regular magnetosome membranes, while mutants of MamI, MamL, or MamQ still contained fewer immature vesicles in *M. gryphiswaldense* (22). The crucial role of the cation diffusion facilitator (CDF) protein MamB in membrane biogenesis is independent from its function in iron transport but involves interactions with other magnetosome proteins, including the paralogous CDF transporter MamM and the protease MamE, which acts in processing and protein sorting to magnetosomes (44–47). From available genetic and biochemical data, a model for magnetosome membrane formation has been proposed in which MamB serves as landmark protein that interacts with a subset of proteins at the inner cell membrane (Fig. 1A). This initial protein complex is then thought to recruit further interaction partners that by protein crowding eventually induce lateral pressure to generate membrane curvature and finally membrane vesicles, possibly by a “blebbing” mechanism (22).

### BIOMINERALIZATION OF MAGNETITE CRYSTALS

Compartmentalization of biomineralization by the magnetosome membrane provides a specialized “nanoreactor” in which the iron redox species and pH environments of biomineralization can be strictly regulated for the formation of single crystals of magnetite. Most available evidence supports a model in which extracellular iron is first imported into the cytoplasm by generic transporters. Subsequently, iron is transported from the cytoplasm into membrane vesicles by the magnetosome-specific transporters MamB and MamM (for ferrous iron), which are members of the Fe/Zn-transporting subfamily of divalent metal CDF proteins (47), as well as MamH and MamZ (for ferric iron), which are members of the major facilitator superfamily (48). The proper Fe<sup>2+</sup>/Fe<sup>3+</sup> ratio for production of the mixed-valence iron mineral magnetite inside magnetosome membrane vesicles is thought to be regulated by MamE, MamP, MamT, and MamX, which are also constituents of the magnetosome membrane (41). These proteins each contain two or three conserved MTB-specific CXXCH c-type cytochrome heme-binding motifs denoted the “magnetochrome” domain that may oxidize magnetosomal Fe<sup>2+</sup> for biomineralization (49, 50). In addition, the redox balance for magnetite biomineralization is also affected by the activity of cellular electron transport chains (Fig. 1). For instance, magnetite formation is linked to dissimilatory nitrate reduction, and *M. gryphiswaldense* cells are impaired in magnetosome biomineralization upon deletion of genes encoding the periplasmic nitrate and nitrite reductases Nap and NirS, as well in cells lacking the fumarate and nitrate reduction regulator protein Fnr. In a similar manner, inactivation of the terminal oxidase Cbb3 involved in aerobic respiration caused pleiotropic effects on magnetosomes under microaerobic conditions, probably by disturbing the redox balance required for proper magnetite biomineralization (38, 39, 51).

After nucleation of the magnetite crystal, several magnetosome proteins regulate their maturation into particles of defined size and shape in a positive (MamG, MamF, MamD, MamC, MamS, MamR, MamN, Mms6, and MmsF) or negative (Mms36 and Mms48) manner (Fig. 1 and Table 1). However, an understanding of how they exactly interact with the surface of the nascent magnetite crystals is just emerging (27, 52–54). Mature magnetosomes finally contain a single-domain magnetite (or greigite) crystal of species-specific shape and size, mostly between 30 and 100 nm. Under optimal growth conditions, an *M. gryphiswaldense* cell contains up to 100 cuboctahedral magnetosome particles of about 40 nm in size. However, the molecular mechanisms which ensure an optimal number of magnetosomes are not well understood. Apparently, the key biosynthetic genes are constitutively expressed (25), as well as poorly regulated, and simultaneous overexpression of almost all *mam* and *mms* gene clusters substantially increases the numbers and sizes of magnetosomes (55).

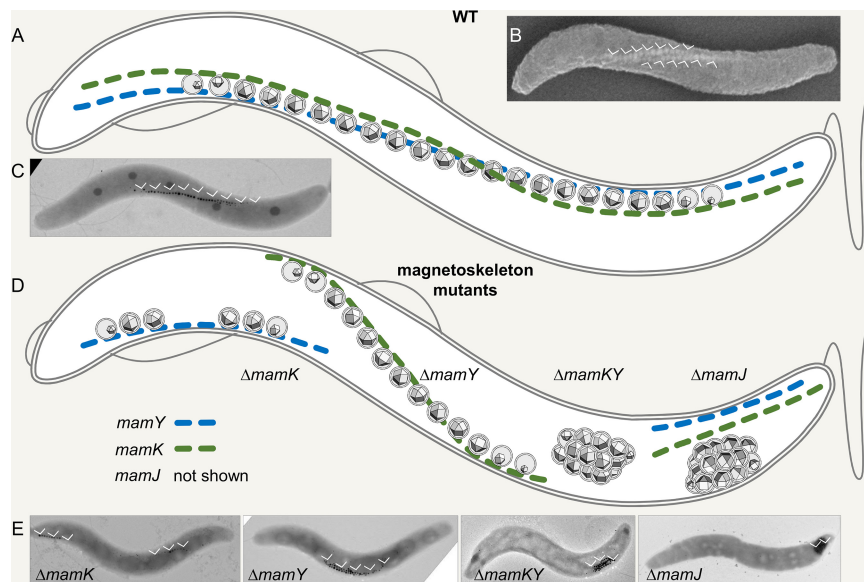
However, synthesis of magnetosomes alone is not sufficient for magnetotaxis because mature but disorganized magnetosomes would be still unsuitable to guide the cell within magnetic fields.

### COMPASS CONSTRUCTION AND MAGNETOTAXIS

Magnetotaxis differs from conventional chemotaxis paradigms known from, e.g., *Escherichia coli*. Here, chemotactic swimming resembles a three-dimensional (3D) trial-and-error walk where periods of straight movement are interrupted by tumbling pauses where cells turn randomly before they resume straight swimming. These so-called run-and-tumble sequences are biased by chemosensory signal cascades, which control the frequency of runs and tumbling by interaction with flagellar motor proteins in response to detected gradients of nutrients, repellents or electron acceptors (reviewed, for example, in reference 56). Magnetospirilla and all other characterized MTB thus far also use flagella for motility, and aerotaxis or even phototaxis have been described (57, 58), but in contrast to *E. coli*, magnetospirilla were observed to swim in long runs interrupted by short reversals, resulting in an immediate change of direction of almost 180° (10). So, what is the benefit of detecting the Earth's magnetic field in addition to chemical gradients, and how does this sense feed into motility of MTB?

Magnetotaxis could, for example, be beneficial for a bacterium if it combined the sense of direction provided by magnetosomes with decisions on locomotion, i.e., on run-and-tumble/reversal frequencies which could be conveyed by interaction of MamK with the chemosensory system (as suggested previously [59–61]). However, until now, neither deviant chemotaxis patterns in a *mamK* mutant nor direct evidence for a biochemical signal transduction between magnetosome chain and flagellar motor have been found. This and the lack of any canonical signal transduction motif (as, for example, in kinases or methylases) in the magnetosome gene clusters suggest that magnetotaxis functions in a different way and exploits magnetic forces directly. In recent years, the evidence for the latter idea has increased, but some biophysical considerations are necessary to comprehend this paradigm.

It has been shown that the force generated by a single magnetosome in the geomagnetic field is too weak to align a cell effectively to the field vector (62, 63). On the other hand, multiple free magnetosomes within a cell agglomerate by their own magnetic pull, which again minimizes their net magnetic moment close to zero (64–66). Hence, to serve as efficient magnetic field receptor, single magnetosomes must become stacked into a linear structure that adds the single magnetic moment of each unit to form a much stronger magnetic dipole. In fact, almost all MTB regardless of their phylogenetic affiliation, cell morphology, or lifestyle seem to carefully organize their magnetosomes into chains, most likely by conserved actin-like proteins. This also suggests that the number of magnetosomes per cell is controlled so that the assembled magnet becomes strong enough to align whole cells to the rather weak geomagnetic field akin to a compass needle (62, 67–69). Indeed, the cell size and number of magnetosomes appear to be correlated. Whereas ~45 particles on average within a single chain (70) are sufficient to align a cell of the model organism *M. gryphiswaldense*



**FIG 2** Magnetosome organization in wild-type and phenotypes of magnetoskeleton mutants in *M. gryphiswaldense*. (A to C) Wild type. (A) Magnetosomes in wild-type cells are organized in extended straight chains along the magnetoskeleton formed by membrane-bound MamY, the cytoplasmic actin-like MamK, and MamJ proteins (MamJ is not shown). Due to the two-dimensional (2D) nature of the scheme, the chain seemingly detaches from the cell envelope in its central part but actually stays in close proximity to it. (B) Scanning electron microscopy image of an *M. gryphiswaldense* wild-type cell harboring two magnetosome chains (arrowheads, iron detected by energy dispersive X-ray spectroscopy) and indicating the twisted cell morphology. (C) TEM (2D) image of an *M. gryphiswaldense* wild-type cell. Arrowheads indicate the magnetosome chain. (D and E) Phenotypes of magnetoskeleton mutants in *M. gryphiswaldense*. (D) Schematic view of magnetosome organization in *mamK*, *mamY*, *mamKY*, and *mamJ* mutants. *mamK*, short, fragmented, off-center chains attached to positive membrane curvature; *mamY*, chain shifted to the negative inner cell curvature; *mamKY*, agglomerated magnetosomes or magnetic flux-closed rings; *mamJ*, similar to *mamKY*. (E) Representative TEM images are shown in the lower panel. The position of the magnetosomes is indicated by arrowheads.

(66), MTB with larger cells, such as members of the *Nitrospirae* phylum or multicellular *Deltaproteobacteria*, tend to possess a multitude of magnetosomes and chains (9, 71), which increase the magnetic force for their alignment. These findings suggest both that cell alignment to the magnetic field is a passive, physical effect and that MTB possess a dedicated cytoskeleton allowing them to form, stabilize and (re)position a modular magnetic field sensor suitable for navigation.

With such systems in place, the need for cell tumbling motion in MTB is likely obviated. The spatial orientation of their cells is controlled by the magnetosome chain, and their motility axis is preset by the position of flagella (incidentally even in fast swimming magnetotactic cocci [72]). The alignment to the geomagnetic field then reduces three-dimensional trial-and-error-swimming to a linear (or quasilinear for cocci and spherical multicellular MTB [73]) movement along vertical inclines of the Earth's magnetic field. In this way, together with integration of chemotactic responses such as aerotaxis, MTB are efficiently guided to their preferred oxygen concentration in stratified environments (74). However, it turned out recently that spirilla, in particular, have evolved sophisticated adaptations to optimize and inherit their magnetic navigation skills, which will be highlighted in the following section.

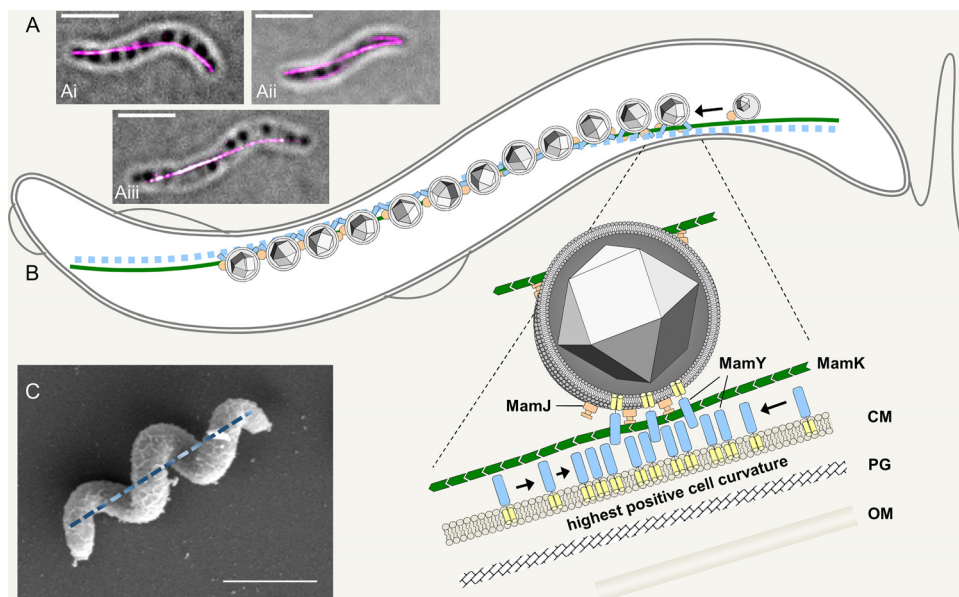
### DYNAMICS AND PARTITIONING OF MAGNETOSOME CHAINS

During maturation, nascent magnetosomes become organized and assembled into chains. Essential active parts of this assembly and positioning machinery consist of dedicated cytoskeletal proteins first identified years ago in the two model organisms *M. gryphiswaldense* and *M. magneticum*. In both bacteria, the magnetosomes become concatenated by the joint action of the actin-like MamK, which polymerizes into cell-spanning dynamic filaments (75–78) (Fig. 2A to C), and MamJ, an adaptor protein

with less understood function that seems to be weakly structured, and central parts of it are dispensable (79, 80). In *M. magneticum*, both proteins exist as two paralogs with overlapping but also slightly different functions causing less pronounced phenotypes upon gene deletion compared to *M. gryphiswaldense* (81, 82). *mamK* mutants fail to assemble wild-type-like continuous magnetosome chains but contain either disordered chains (in *M. magneticum* [75]) or short and fragmented chains in *M. gryphiswaldense* (77) (Fig. 2D and E). The *mamJ* deletion mutant phenotype in *M. gryphiswaldense* is striking since magnetosomes are completely detached from MamK filaments and cluster irregularly, or they form magnetic flux-closed rings due to their unconstrained magnetic interaction (79, 83, 84) (Fig. 2D and E). In *M. magneticum*, which contains two MamJ paralogs, the phenotype is less pronounced, but magnetosome chain formation is also perturbed (78). These phenotypes and suggested MamK-MamJ interactions (79) led to the early model of an only two-part cytoskeletal structure, consisting of a presumably static backbone made of MamK filaments and MamJ, which attaches magnetosomes to that scaffold. However, this model recently proved incomplete in at least two aspects: first, the magnetosome chain was revealed to be highly dynamic, and second, the localization of the chain in spirilla is much more controlled than initially assumed.

MamK has been analyzed extensively *in vitro*, and the pure protein was found to polymerize into filaments when ATP or GTP are present (85–87). The crystal structure of the protein and molecular details of its polymeric form have been solved (88) and underpinned its structural relatedness to eukaryotic actin proteins. *In vivo* studies analyzed the dynamics of polymeric MamK filaments in their cellular context. By fluorescence recovery after photobleaching experiments it was found that MamK treadmilling speed in *M. gryphiswaldense* is about 300 nm/min (89) and depends on its ATP hydrolysis capacity. Similar observations were made in *M. magneticum* (78, 82, 90). Interestingly, the dynamics of the MamK filaments was found to also depend on MamJ, which therefore seems not only necessary to tether magnetosomes to MamK filaments but also necessary for tuning MamK turnover rates.

The dynamics of MamK filaments in *M. gryphiswaldense* already suggested that a magnetosome chain may be not a static structure and that individual magnetosomes are moved along the track. In fact, active movement of the organelles seems a crucial prerequisite to assemble a chain: magnetosome vesicles emerge more or less randomly at the cytoplasmic membrane (22). Mature magnetosomes, however, are regularly found in chains, suggesting an active collecting and positioning mechanism, although spontaneous incorporation of maturing magnetosomes based on their increasing magnetism may also play a role (91). The function of MamK in *M. magneticum* seems somewhat different, but MamK is still needed to restrict movement and to position magnetosomes (23, 92). There is, however, other evidence for active translocation of magnetosomes: when *M. gryphiswaldense* cells divide, each daughter cell receives exactly half the number of magnetosomes from the mother cell indicating that cells distribute their magnetosomes with highest possible precision to their offspring (89, 93). This is achieved by strict positioning of the chain center at the cell division site. After cytokinesis, the daughter chains undergo repositioning from the new cell poles to midcell, and they are maintained at this position during growth by an unknown mechanism. Photobleaching experiments suggest that MamK filaments in *M. gryphiswaldense* nucleate close to the cell poles and grow toward midcell, i.e., into the direction where magnetosomes do migrate. In catalytic site mutants with severely impaired dynamics of MamK filaments, chain dynamics are also perturbed (i.e., chains are not efficiently relocalized to midcell), leading to unequal distribution of the organelles, a phenotype that is also seen in *mamK* and *mamJ* deletion mutants (89, 94). Despite these data, the molecular mechanism by which magnetosomes move along MamK filaments is still unknown. On one hand, effective repositioning of magnetosomes seems to depend on intact MamK turnover rates. On the other hand, the treadmilling speed of MamK filaments seems much higher than the speed of magnetosomes (89). Since MamK monomers are immobile once incorporated into the fila-



**FIG 3** Localization and function of magnetoskeleton constituents. (A) Localization of mCherry-MamK (i and ii) and mCherry-MamY (iii) in live *M. gryphiswaldense* cells imaged by 3D structured illumination microscopy (3D-SIM; maximum-intensity projection overlaid with a bright-field image; scale bar, 2  $\mu$ m). (B) 2D model of the current view of the “magnetoskeleton” in *M. gryphiswaldense*, as suggested by Toro-Nahuelpan et al. (99). The actin-like MamK (green) polymerizes into cell-spanning dynamic cytoplasmic filaments that nucleate at the cell poles and “treadmill” toward midcell. Maturing magnetosomes become attached to this filament via MamJ (orange). MamY is a protein of the cytoplasmic and magnetosome membranes (membrane helices, yellow; cytoplasmic domain, blue) with high potential to self-interact. MamY assemblies are suggested to become curvature sensitive and localize to sites of highest positive inner membrane curvature coinciding with the geodetic cell axis, where they recruit magnetosome chains. CM, cytoplasmic membrane; PG, peptidoglycan; OM, outer membrane. The model is not drawn to scale. (C) SEM image of an *M. gryphiswaldense* cell illustrating a corkscrew-like cell morphology. The geodetic cell axis is indicated as a dashed line. Scale bar, 2  $\mu$ m.

ment, and homologs of myosin-like cargo proteins that might walk along the actin-like MamK filaments have not been found, the mechanism of magnetosome dynamics cannot yet be fully explained. However, a candidate for further studies might be the so far poorly characterized MamJ protein.

Potential factors that possibly control nucleation of MamK filaments and their polarity are also unknown. It is also not clear what happens if the filaments of opposite polarity converge at midcell and if MamK filaments stop growing at all. For example, it has been observed that filaments that reach the opposite cell pole bend and turn, sometimes even at physiological expression levels (Fig. 3Aii) (75, 89, 94), which has never been observed for magnetosome chains. The reason for the different phenotypes of the *mamK* and the *mamJ* mutants (fragmented chains versus clustered magnetosomes) in *M. gryphiswaldense* has been also enigmatic for many years but this mystery became elucidated recently.

### SOPHISTICATED POSITIONING OF MAGNETOSOME CHAINS IN HELICAL CELLS

On top of the amazingly organized assembly, dynamics, and partitioning of magnetosome chains, magnetospirilla have evolved even more sophisticated means to reconcile helical cell morphology with a straight magnetoreceptor and to optimize magnetotaxis. Again, we will discuss some biophysical considerations that can help to appreciate these remarkable adaptations.

For efficient magnetotaxis, the magnetosome chain must adopt and maintain a very distinct position in the cell for several reasons. First, a mechanically fixed position is important because a flexible, “floating” magnetosome chain would move within the cell rather than aligning it. However, a physical connection of magnetosome chains to dynamic cytoplasmic content such as DNA (as described for other organelles such as carboxysomes [95] or carbonosomes, i.e., polyhydroxybutyrate granules [96, 97]) seems



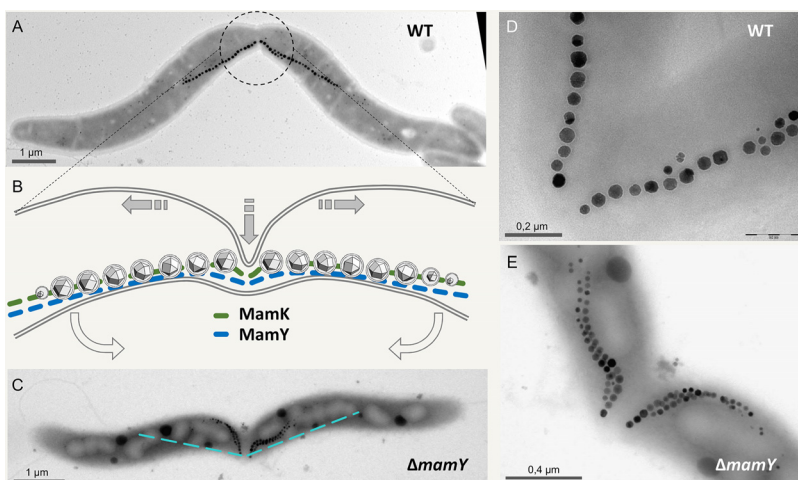
not sufficient. Tethering the chain to a rigid and more static structure such as the cell envelope would meet this requirement much better. Second, for efficient magnetotaxis, the magnetic moment of the magnetosome chain must perfectly match the swimming direction of the cell, which is predefined by the position of the flagella on the cell surface (62). Spirilla are propelled by polar flagella and hence move along the longitudinal cell axis, accompanied by fast rotations of the cell body. If swimming direction and magnetosome chain were misaligned, cells would tumble when they swim because two forces pull in slightly different directions. Third, to maximize the net magnetic moment similar to a corresponding bar magnet, the magnetosome chain must be maintained as straight as possible and stabilized against its inherent tendency to bend or to even form energetically favored, magnetic flux-closed rings (98). This is intriguing because unlike rod-shaped bacteria, spirilla lack any straight cell surface to support a rod-like magnetoreceptor. Nevertheless, a three-dimensional analysis of magnetosome chain positioning in *M. gryphiswaldense* wild-type cells revealed that the chains indeed meet all these criteria: they tightly follow a path along the inner cell envelope with the highest positive curvature. This path coincides with the shortest connection between the cell poles and hence represents the geodetic axis of the helix, i.e., the track which comes closest to a bar (Fig. 2A to C). Importantly, this path also coincides with the cellular motility axis (99). The question of how spirilla could achieve this has remained unaddressed for a long time, and mechanisms for magnetosome chain positioning in curved cells have been unknown until recently, when an in-depth analysis of the magnetosome protein MamY and the *mamY* mutant in *M. gryphiswaldense* have shed light on this phenomenon.

MamY is found among the magnetosome-associated proteins and conserved in magnetotactic spirilla and vibrios, i.e., in MTB of curved cell shape. Initially proposed to be involved in vesicle formation in *M. magneticum* (100), it represents a protein of the inner of the cytoplasmic and associated with the magnetosome membranes in *M. gryphiswaldense*. The protein self-interacts and forms higher-ordered structures at the cytoplasmic membrane. Upon achieving a certain size, these polymers are supposed to become curvature sensitive and further enrich along the membrane with highest positive curvature (99), eventually resulting in an extended assembly reaching from pole to pole and designating the geodetic cell axis. With its cytoplasmic domain, MamY recruits the magnetosome chain made by MamK and MamJ and forces it to a path that is parallel to the cellular motility axis (Fig. 3) (99).

Upon deletion of *mamY*, magnetosome chains lose their straight appearance, detach from the inner (convex) curvature of the helical cell, and shift to the outer (concave) curvature (Fig. 2D and E). Consequently, the ability of the cells to align to the magnetic field drops similar to the *mamK* mutant (66). Additional evidence that MamY functions as a scaffold for the chain comes from a *mamKY* double deletion mutant, which phenocopies a *mamJ* mutant where all magnetosomes agglomerate due to the missing tether to MamK filaments (Fig. 2D and E). This also suggests that in the *mamK* mutant, the magnetosomes are likely still attached to MamY structures but not concatenated into coherent chains because the cytomotive MamK filaments are missing. Correspondingly, short, fragmented chains of the *mamK* mutant are still observed at sites of inner positive cell curvature (Fig. 2D and E). The formation of short chains may be explained by the linear localization of MamY and magnetic attraction of the particles (91).

Taking these results together, MamY seems to be the key to (i) connect the magnetosome chain to the cell envelope ensuring efficient force transmission and cell alignment, (ii) keep the magnetosome chain straight to maximize its magnetic moment, and (iii) bring the chain into alignment with the cellular motility axis. Finally, its discovery reconciles the previously observed different phenotypes of the *mamK* and *mamJ* mutants.

However, the tightly fixed “compass” poses a challenge during cytokinesis when not only the magnetoskeleton but also the magnetic forces that act between magnetosomes or even chains must be overcome. Experimental data and biophysical calcula-



**FIG 4** Cytokinesis in the presence of a magnetosome chain, as suggested by Katzmann et al. (94). (A) TEM image of a dividing *M. gryphiswaldense* wild-type cell. The center of the magnetosome chain is precisely localized at the division plane, ensuring that each daughter cell inherits exactly half of the magnetosomes (89, 93). Note the “buckling” cell center reflecting a distortion of the otherwise preserved helical cell morphology. (B) 2D scheme of the center from a dividing wild-type cell. Shaded arrows indicate direction of main cell wall growth at the division plane. Open arrows indicate the direction of cell bending. (In three dimensions, some twisting may occur as well.) Within the division plane, the septum grows by asymmetric indentation starting unilaterally from the site of negative inner cell curvature, resulting in a fracture-like appearance of the magnetosome chain. (C) In the *mamY* mutant, the magnetosome chain seemingly becomes disrupted by the wedge-like growing division septum. However, the buckling cell shape upon division is still apparent. The dashed line indicates the magnetosome chain position in wild-type cells. (D and E) Magnification of magnetosome chains immediately after splitting in the wild type (D) and the *mamY* mutant (E).

tions suggest that the magnetoskeleton of *M. gryphiswaldense* withstands forces up to 25 pN (84, 101, 102). The magnetic force that attracts magnetosomes was calculated to be at least 40 pN (94). These resistances must be mastered in addition to the turgor and cell wall tension, which may add up to 400 pN (103). Two mechanisms can be inferred to facilitate chain splitting and hence cell division. First, the magnetoskeleton may reverse its polarity, i.e., the direction of MamK treadmilling may become inverted at the nascent septum, weakening the overall rigidity of the scaffold. This idea is supported by nonseparating, chained cells that occur in a mutant where MamK dynamics is perturbed (89). Second, a mechanical trick could help to “crack” the pulling magnetosome chains. Within the division plane of a magnetospirillum cell, the septum grows asymmetrically starting from the side of highest negative inner curvature toward positive curvature, resulting in a buckling-like deformation of the dividing cell (93) (Fig. 4A). Placing the chain at the positive curvature, i.e., opposite to the indentation results in a leverage-like mechanism, which has been interpreted as specific adaptation to overcome the magnetostatic interactions between separating daughter chains (94) (Fig. 4B and D). Obviously, this peculiarity is lost in the *mamY* mutant (Fig. 4C and E) and yet seems not to compromise cell division under laboratory conditions. However, it might matter in natural, energy-limiting environments.

#### CELL SHAPE, MOTILITY, AND MAGNETOCHEMOTAXIS

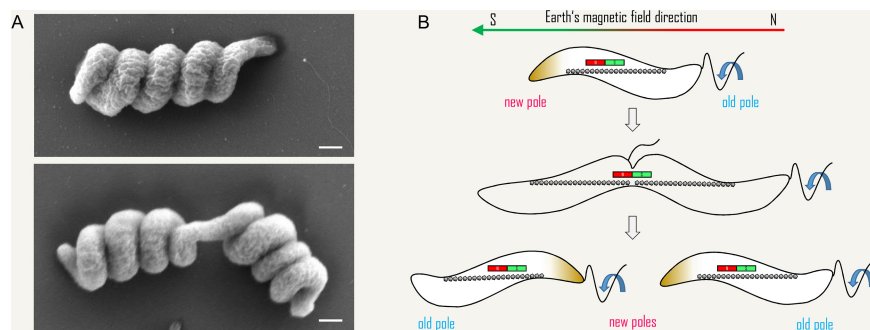
In contrast to the magnetoskeleton, knowledge of the generic cytoskeleton in MTB is very limited, and yet some recent insights again from magnetospirilla allow a first glimpse of its organization. Genomic data suggest that magnetospirilla possess the common cytoskeletal elements and cytokinesis key organizers known from other *Alphaproteobacteria* such as FtsZ, MipZ, PopZ, MreB, and others (104–108). Interestingly, however, some of the factors, such as MipZ or FtsZ, have paralogous or even xenologous counterparts. For example, the essential tubulin-like cell division organizer FtsZ possesses a C-terminally truncated duplicate called FtsZm (or FtsZ-like) intriguingly encoded in the magnetosome island and seemingly colocalizing with its canonical

equivalent at the future division site readily suggesting an interplay of cyto- and magnetoskeleton. Yet, the function of the paralogous genes is not fully understood. Deletion of *ftsZm* does not cause a cell or magnetosome chain division phenotype under standard growth conditions. Instead, the mutant seems to have a biomineralization defect in the absence of the anaerobic electron acceptor nitrate (51, 109), suggesting that the tubulin-like FtsZm is not a core constituent of the magnetoskeleton in contrast to the actin-like MamK, although its polymerization properties seem conserved (51, 110). The second MipZ (*midcell positioning of FtsZ*) (108) protein (encoded outside the magnetosome island) was found to localize to the division plane as well, which stands in stark contrast to its canonical counterpart that forms pole-to-midcell concentration gradients that inhibit FtsZ polymerization (111). Again, deletion of *mipZ2* does not elicit an obvious phenotype under standard conditions.

The polar organizing protein Z PopZ was found to have slightly different properties than in the related *Caulobacter crescentus* and *Agrobacterium tumefaciens*, since it localizes not predominantly to one but to both cell poles throughout the cell cycle. Its essential role as landmark for accurate cell division and chromosome segregation still seems conserved in *M. gryphiswaldense*. Upon deletion or overexpression severe defects in magnetosome segregation occur that are, however, likely an indirect effect of perturbed cell division (112).

The obvious corkscrew-like cell morphology of magnetospirilla (Fig. 3C) suggests the presence of a particular cell shape-determining cytoskeleton. Several factors for curved cell shape are known from non-MTB with vibroid or helical cell shape. In these examples, commonly, intracellular scaffolding structures were found acting in concert with the actin-like MreB and periplasmic cell wall biosynthetic enzymes to introduce curvature and helical twist via spatial patterning of peptidoglycan synthesis (113). Whereas MreB promotes elongated rod cell shape by organizing centers of predominant cell wall synthesis (114, 115), nucleotide-independent elements such as coiled-coil rich proteins or bactofilins (which are characterized by a right-handed  $\beta$ -helix core domain structure [116]) introduce curvature by functioning as a mechanical support with intrinsic curvature preference and/or scaffold for cell wall synthesis-related enzymes in a rather static manner (113). Knowledge of cell shape determinants in magnetospirilla is still very limited and hardly based on experimental evidence, but the presence of mostly uncharacterized genes in *M. gryphiswaldense* and *M. magneticum* coding for MreB (90), a putative bactofilin, a structural coiled-coil rich protein, as well as multiple enzymes involved in peptidoglycan remodeling, suggest that their helical cell morphology is likely controlled by a multifactorial cell shaping system. Time-lapse microscopy of *M. gryphiswaldense* further indicates that cells elongate by an unequal predominant polar mode of cell growth (94, 112), although it has not been analyzed quantitatively whether new cell wall material is incorporated more toward the old or new cell pole. Future studies related to the function of a shape-determining cytoskeleton in magnetospirilla might reveal novel insights into the control of helical cell morphology, e.g., by use of fluorogenic cell wall labels, and also focus on the intriguing question whether underlying structures are interconnected with the magnetoskeleton.

The morphology of magnetospirilla is part of the motility system because in helical cells, the cell body rotates in the opposite direction of flagellar rotation (117). This agrees with live-cell observations on *M. magneticum* with fluorescently labeled cell poles which revealed right-handed helical trajectories, indicating that the cell body of magnetospirilla rotates clockwise during swimming (118). Fluorescent labeling of flagella in bipolarly flagellated *M. magneticum* revealed that the leading flagellum forms a parachute-like structure, likely caused by wrapping around the cell body, with the lagging counterclockwise-rotating flagellum forming a "tuft" oriented away from the cell body (118). The rotational direction of the leading flagellum could not be clearly resolved due to its association with the cell body but was suggested as clockwise (if observed from the tip of the flagellum toward the cell pole), i.e., suggesting that the two flagellar motors rotated in opposite directions. Bipolarly flagellated *M. gryphiswal-*



**FIG 5** Helicity of *M. gryphiswaldense* cells grown on solid media and a hypothetical mechanism for preservation of cell polarity upon cytokinesis in MTB. (A) SEM images of *M. gryphiswaldense* cells that were recovered from a colony growing on agar-solidified medium. Note the highly spiralized cell morphology in comparison to cells grown in liquid medium (e.g., Fig. 2B). Cell division (lower image) seems to require (or to cause) some “unwinding” of the tight helix at the division plane, and yet the “buckling” appearance of the dividing cell (Fig. 4) is still visible. Scale bars, 500 nm. (B) Maintenance of polarity during cytokinesis in a monopolarly flagellated MTB. Before cytokinesis, swimming polarity is defined by the internal magnetic dipole (indicated by the bar magnet) and a gradient in redox potential (data not shown), leading to preferred swimming toward one pole of the external magnetic field. However, cell division generates daughter cells of opposite magnetic polarity with respect to the new cell pole. To ensure that both cells have the same magnetic polarity with respect to their flagellated pole, the daughter cell that does not inherit the flagellum must synthesize a new flagellum at the new cell pole (127).

*dense* and *M. magneticum* were described to reach swimming speeds up to  $\sim 70 \mu\text{m s}^{-1}$  (58, 66, 119) and  $\sim 100 \mu\text{m s}^{-1}$  (120), respectively, in liquid, but the corkscrew-like cell morphology of magnetospirilla might be of particular advantage for motility in complex structured habitats such as aquatic sediments (117, 121) since the helical cell shape might prevent slipping of the rotating cell body under such conditions and hence facilitates to achieve higher swimming speeds (113). An increase in average swimming speeds of soft agar-grown *M. gryphiswaldense* (66) suggests that cells might undergo specific ultrastructural alterations to increase flagellar torque in more viscous environments (e.g., changes in flagellum [motor] architecture or number [122, 123]) or even increased helicity of the cell body (Fig. 5A).

Magnetotaxis, aerotaxis, and flagellum-mediated swimming motility are likely integrated with complex sensory systems, since multiples of putative chemotaxis-related proteins (i.e., Che proteins and methyl-accepting chemotaxis transducers) are encoded within magnetospirillum genomes, and the first experimental evidence (58) underpins this notion. Chemoreceptor arrays are located near flagellar motors at both cell poles in *M. gryphiswaldense*, as revealed by cryo-electron tomography and fluorescent labeling of the chemoreceptor-associated adaptor protein CheW<sub>1</sub> (77, 124). Since the flagellar polymorphic structure and conformational changes during clockwise/counterclockwise rotation are likely physically imprinted (i.e., determined by the ultrastructure of the flagellum), as well as motor switching by CheY response regulators, it is currently unknown how motor rotation in opposite senses (as proposed earlier [118]) might be integrated with chemotactic signaling and switched in a coordinated manner. Given the vast number of putative motility- and chemotaxis-related proteins in magnetospirilla, it was suggested that distinct proteins might govern some sort of motor asymmetry (58, 118). Other models suggest simultaneous counterclockwise rotation of both flagellar motors in a nonmagnetotactic bipolarly flagellated spirillum (125) or pausing of one flagellum in *M. gryphiswaldense* (119). Whereas rotation of both motors in the same direction during straight swimming is conclusive in terms of chemotactic signaling, pausing of one motor appears to be unlikely due to the observation of tethered magnetospirilla, which change rotational direction without extended pauses, as well as “tumbling-like” motions observed in *M. magneticum* cells with both flagella spinning at the same time in an uncoordinated manner (58, 118).

## NORTH- AND SOUTH-SEEKING SWIMMING POLARITY

An intriguing phenomenon was observed in early studies when populations of MTB enriched from environmental samples were observed under the light microscope. When exposed to a magnetic field, the cells not only aligned to it and moved along the field lines, but they also seemed to prefer one direction over the other, i.e., they ran either toward the magnetic north or south pole (5, 8, 126). This behavior was termed “swimming polarity” (to be distinguished from the magnetic polarity which is a physical property set by the magnetosome chain). Even more exciting was the observation that in the Earth’s northern hemisphere predominantly north-seeking cells and in the southern hemisphere predominantly south-seeking cells were isolated. Because the magnetic south pole currently coincides with the geographic north pole and vice versa, and because the Earth’s magnetic field is inclined, the north-seeking cells of the northern hemisphere swim actually down toward a magnetic south pole. This swimming polarity is thought to assist magnetotaxis to efficiently guide cells from oxic zones down into regions of preferred low oxygen concentration toward the bottom of the water column (6). Interestingly, swimming polarity was lost in lab strains of magnetospirilla, but could be restored within only few generations by cultivation in an oxygen gradient with superimposed magnetic field, suggesting that this characteristic is an individually acquired adaptation rather than a “hardwired” physical or genomic trait (10, 58). This means that swimming polarity in magnetospirilla is set by the direction of the oxygen gradient with respect to the magnetic field orientation during growth but is lost in the absence of an oxygen gradient (for example, if cell cultures are stirred) and is reversibly triggered and switched by changes in oxygen concentration (58). These observations also suggest that swimming polarity is closely linked to aerotaxis at the molecular level, which was confirmed by the finding that deletion of the chemosensory pathway *cheOp1* in *M. gryphiswaldense* results in loss of aerotaxis and swimming polarity (58). Currently, it is not understood how magnetotactic swimming polarity is exactly controlled and perhaps inherited at the cellular and molecular levels. Faithful segregation of magnetosome chains by the magnetoskeleton might be important. As stated above, the magnetosome chain is divided into half during cell division. For a polarized cell, this results in daughter cells with opposing magnetic polarities with respect to their new cell poles but similar directional preferences toward one of the magnetic poles (58, 112, 118, 127) (Fig. 5B). It was hypothesized that asymmetric activity or localization of motility-related structures such as flagella might determine a cellular asymmetry with respect to the physically imprinted magnetic polarity of the magnetosome chain leading to equal cellular and magnetic polarity of the offspring. In other words, direction of polarized swimming could be maintained by a monopolar flagellation pattern for both cells when one of them synthesized a new flagellum at the division site (127), so that the flagellated cell pole of both daughter cells is oriented toward the same pole of the magnetic field (Fig. 5B). Interestingly, in magnetospirilla, synthesis of new flagella at the division site has been observed to occur before cytokinesis has completed (89, 94), raising the question about their rotational sense (as discussed above) and how swimming polarity is determined in cells with two flagella.

## CONCLUSIONS

Altogether, past and present studies emphasize that MTB are a unique and rewarding model to study a plethora of bacterial adaptations. Apart from micro- and anaerobic physiology, iron metabolism and biomineralization, organelle formation, applied research, and ecology/phylogeny, which were only briefly touched upon in this minireview, recent work highlighted that magnetospirilla possess distinctive cellular adaptations to take advantage of their magnetic sense and to link it to life style and motility. A sophisticated “magnetoskeleton” can now be defined, which in *M. gryphiswaldense* to date consists of three cytoskeletal factors dedicated to magnetotaxis. The actin-like MamK and its adaptor MamJ represent the dynamic part of the magnetoskeleton as they actively concatenate magnetosomes and position the chain at midcell, thereby

also ensuring precise equipartitioning of the magnetoreceptor upon cell division. The static MamY structure by contrast is responsible to identify and to tether the dynamic assembly to the geodetic cell axis, i.e., to fix it along the shortest path from cell pole to cell pole, where the flagella are inserted. This straightens the “compass needle” within the helix and aligns it with the motility axis, thereby perfectly superimposing the Earth’s magnetic field vector on swimming movements. These recent results highlight that magnetosomes are not only one of the most complex structures found in bacteria, but they require dedicated cytoskeletal elements to form a dynamic and distinctly localized higher ordered structure and to function in a cooperative manner. Moreover, magneto-aerotaxis turned out not only to comprise magnetosome chains but also to require dynamic integration of chemosensory signals, coordination with motility systems, and even cell shape to perfect magnetic navigation.

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