Subcellular Organization: A Critical Feature of Bacterial Cell Replication

Ivan Surovtsev[1,2] and **Christine Jacobs-Wagner**[1,2,3,4,*]

[1]Microbial Sciences Institute, Yale University

[2]Howard Hughes Medical Institute, Yale University

[3]Department of Molecular, Cellular and Developmental Biology, Yale University

[4]Department of Microbial Pathogenesis, Yale School of Medicine

Abstract

Spatial organization is a hallmark of all living systems. Even bacteria, the smallest forms of cellular life, display defined shapes and complex internal organization showcasing a highly structured genome, cytoskeletal filaments, localized scaffolding structures, dynamic spatial patterns, active transport, and occasionally intracellular organelles. Spatial order is required for faithful and efficient cellular replication, and offers a powerful means for the development of unique biological properties. Here, we discuss organizational features of bacterial cells and highlight how bacteria have evolved diverse spatial mechanisms to overcome challenges cells face as self-replicating entities.

INTRODUCTION

The second law of thermodynamics dictates that isolated systems evolve toward greater entropy. Organisms, however, are not isolated systems. They exchange energy and matter with the environment, driving them far from thermodynamic equilibrium. As a result, living systems can achieve a stable organized state. Spatial organization is, in fact, evident at all levels of biological complexity.

Bacterial cells are no exception. Spatial order is readily apparent in the highly reproducible cell geometries observed in the bacterial world, ranging from spherical and rod shapes to helical, branched and complex spiny morphologies. Geometrical order in bacterial shapes has been known for a long time, first unveiled by Antonie van Leeuwenhoek at the dawn of microscopy over three centuries ago. However, an appreciation for the internal organization of bacterial cells only emerged in the last 15-20 years, spurred by advances in imaging techniques. In fact, as we will illustrate, bacteria exhibit many of the cell biological complexities once thought to be unique to eukaryotic cells. Granted, apart from notable

*Contact information: christine.jacobs-wagner@yale.edu, tel: +1-203-737-6778, fax: +1-203-737-6715.

exceptions, bacteria lack the membrane-enclosed organelles that help organize the interior of eukaryotic cells. Instead, bacteria have adopted an open plan architectural design of their cytoplasmic space where spatial organization arises in the absence of membrane boundaries.

The first glimpses of intracellular organization in bacteria came with the discoveries that bacterial cells can cluster chemoreceptors at specific locations (Alley et al., 1992; Maddock and Shapiro, 1993), possess cytoskeletal structures (Bi and Lutkenhaus, 1991; Jones et al., 2001; van den Ent et al., 2001; Williamson, 1974), feature protein oscillations (Hu and Lutkenhaus, 1999; Raskin and de Boer, 1999b), and spatially organize and actively segregate chromosomal regions (Glaser et al., 1997; Gordon et al., 1997; Teleman et al., 1998; Webb et al., 1997). These pioneering works were followed by a wealth of studies showcasing the diversity of cell biology among bacterial species and demonstrating the pervasive role of spatial order in many aspects of bacterial life. Cellular organization has emerged as an integral element of the cellular processes that must take place for bacteria to successfully self-replicate in their environment. Bacteria are famous (or infamous) for their proliferative potential. They are also experts in cellular specialization, which has allowed them to colonize almost every corner of the Earth. While much of this colonization success stems from diversification of metabolic functions, diversification of cellular organization is also an important contributing factor.

Because of space constraints, we are unable to describe the vast array of exciting cell biological observations that have been reported in bacteria. This review is not meant to be exhaustive. Our goal is to describe, with illustrative examples, organizational features and self-organizing properties under two different contexts. First, we will discuss the bacterial architecture in the context of the universal tasks that cells must perform to achieve efficient and faithful self-replication. Second, we will discuss spatial organization in the context of specialized biological functions that bacteria have evolved to survive and thrive in their ecological niches.

SHAPING THE CELL

Bacterial cells generally adopt well-defined physical shapes. Cell geometry impacts various aspects of bacterial physiology, such as nutrient uptake, motility, colonization, and pathogenesis (Kysela et al., 2016; Yang et al., 2016). Another critical, but often unappreciated, aspect of cell shape is that it provides geometric features that bacteria use to establish the intracellular organization necessary for various cellular processes, as we will discuss throughout the review. Thus, reproducing a specific cell geometry is a crucial task that bacteria must accomplish at every division cycle.

Cell shape is typically endowed by the peptidoglycan (PG), a major component of the cell wall, that consists of glycan strands crosslinked by peptides. This meshwork, also referred to as the sacculus, encases the cytoplasmic membrane and bears stress generated from cytoplasmic turgor pressure. A loss of PG integrity (e.g., following exposure to β-lactam antibiotics) results in loss of cell shape and eventually lysis. Isolated PG sacculi generally preserve the morphological features of the cells from which they were purified, indicating that the morphology of a cell is dictated by the morphogenesis of the PG sacculus.

Cell division: duplicating round shapes or generating new cell poles

How do PG sacculi obtain their forms? This spatial problem is solved through cellular organization, usually using cytoskeletal elements and scaffolding structures that spatially regulate PG synthesis and remodeling. For instance, part of cell geometry is generated during the cell division process, which involves septal (inward) PG synthesis. In spherical and ovoid bacteria, septal PG growth plays an important role in reproducing the round shape of the cell at every generation, though the cell cycle pattern of PG growth can vary among species (Figure 1Ai) (Monteiro et al., 2015; Turner et al., 2010; Wheeler et al., 2011; Zhou et al., 2015; Zhou et al., 2016).

Apart from a few known exceptions (Jeske et al., 2015; Liechti et al., 2016; Ouellette et al., 2012; Pilhofer et al., 2013), the orchestration of PG synthesis during division is entrusted to the highly conserved FtsZ protein. FtsZ is a GTPase and a structural tubulin homolog that polymerizes upon GTP binding (Bramhill and Thompson, 1994; de Boer et al., 1992; Erickson et al., 1996; Lowe and Amos, 1998; Mukherjee et al., 1993; Mukherjee and Lutkenhaus, 1994; RayChaudhuri and Park, 1992). FtsZ polymers attach to the cytoplasmic membrane through auxiliary proteins, such as FtsA (Pichoff and Lutkenhaus, 2005), and accumulate at the site of division, where they form a ring-like structure (Z-ring) (Figure 1A) (Bi and Lutkenhaus, 1991; Levin and Losick, 1996; Ma et al., 1996).

The structure of the Z-ring (continuous vs. discontinuous) and the exact arrangement of FtsZ polymers within the ring (length, number, orientation, etc.) are the subject of intense debate and may vary between species (Fu et al., 2010; Holden et al., 2014; Jennings et al., 2011; Li et al., 2007; Rowlett and Margolin, 2014; Si et al., 2013; Strauss et al., 2012; Szwedziak et al., 2014; Yao et al., 2017). It is, however, well accepted that the Z-ring provides a scaffold for the recruitment of a number of other division proteins, including components of the PG synthesis machinery that build septal PG during Z-ring constriction (den Blaauwen et al., 2017; Typas et al., 2011).

The Z-ring scaffold is a dynamic structure (Strauss et al., 2012; Stricker et al., 2002). FtsZ polymers move circumferentially around the septal plane (Bisson-Filho et al., 2017; Yang et al., 2017). This motion is achieved by treadmilling, a GTP-hydrolysis-dependent process in which FtsZ monomers are added at one end of the polymer while being removed from the other end. FtsZ treadmilling, which is also observed in vitro (Loose and Mitchison, 2014), is thought to position and distribute PG synthases around the septal plane (Bisson-Filho et al., 2017; Yang et al., 2017).

How the Z-ring constricts and coordinates PG synthesis inward remains an open question. In vitro reconstitution experiments have demonstrated that FtsZ filaments alone can pinch the membrane of tubular liposomes (Osawa et al., 2008; Osawa and Erickson, 2013; Szwedziak et al., 2014). Thus, an attractive possibility is that FtsZ filaments locally pinch the cytoplasmic membrane, perhaps through filament motion, sliding, or bending (Erickson and Osawa, 2017; Lan et al., 2009; Li et al., 2007; Szwedziak et al., 2014). Membrane invagination would help redirect PG synthesis inward, and reiteration of this process would produce concentric PG rings of decreasing size.

Cell elongation: reproducing rod shapes

Rod-shaped bacteria must add a phase of PG growth during which the cylindrical portion of the cell elongates. This can be achieved by inserting new PG material while maintaining the cell width constant. In many rod-shaped bacteria, this process is regulated by the ATPase MreB, a structural homolog of actin that polymerizes upon ATP binding (Jones et al., 2001; van den Ent et al., 2001).

How MreB polymers spatially control PG morphogenesis is not fully understood. Inside cells, MreB filaments bind to the cytoplasmic face of the membrane (Dempwolff et al., 2011; Salje et al., 2011) and connect to the PG synthesis machinery through transmembrane proteins, such as RodZ and MreC/D (Typas et al., 2011). MreB filaments, which are largely oriented orthogonal to the long axis of the cell (Olshausen et al., 2013; Ouzounov et al., 2016), move along the cell circumference together with the PG machinery (Figure 1Bi) (Dominguez-Escobar et al., 2011; Garner et al., 2011; van Teeffelen et al., 2011). MreB motion is unlikely to result from treadmilling because MreB forms antiparallel double-stranded filaments in vitro (van den Ent et al., 2014), indicating that both ends are equivalent. Instead, circumferential motion depends on PG synthesis (Dominguez-Escobar et al., 2011; Garner et al., 2011; van Teeffelen et al., 2011), suggesting that the processivity of PG synthetic enzymes sustains MreB motion. Presumably, the orientation of the MreB filaments helps direct the addition of circular (likely discontinuous) bands of PG oriented perpendicular to the cell length. What sets the width of these PG hoops remains unclear. It does not require a preexisting shape template, as rod shape can arise from spherical PG-deficient cells following restoration of PG synthesis (Kawai et al., 2014; Lederberg, 1956; Miller et al., 1968).

At the cellular scale, the spatial distribution of MreB dictates where new PG will be added. Several patterns have been reported for rod-shaped bacteria. For example, in *Bacillus subtilis* and *Escherichia coli*, MreB filaments are distributed throughout the cylindrical portion of the cell. As a result, PG material is inserted along the entire cell cylinder, in a growth mode referred to as "dispersed" or "lateral" PG synthesis (Figure 1Bi). What prevents PG growth at the poles? The answer is likely related to cell geometry. For instance, the conical shape of anionic phospholipids (e.g., cardiolipin) favors their accumulation in the curved membrane of cell poles (Mukhopadhyay et al., 2008; Renner and Weibel, 2011), which presumably repels MreB filaments, as they tend to avoid anionic phospholipids (Kawazura et al., 2017). On a finer scale, MreB filaments accumulate at the inner curvature of cell bends (Ursell et al., 2014), potentially due to their circumferential motion (Wong et al., 2017). The resulting local accumulation of PG material (Ursell et al., 2014) or PG-strain-dependent growth (Wong et al., 2017) is thought to help straighten the cell cylinder from accidental bends (Figure 1Bi).

While the lateral mode of PG synthesis is common among rod-shaped species, cell elongation can also derive from PG growth in more confined cellular regions, as in *Borrelia* species (Jutras et al., 2016). In *Caulobacter crescentus*, MreB localization and addition of PG material shift during the cell cycle from a dispersed distribution along the cell body to a narrow central zone in an FtsZ-dependent manner (Figure 1Bii) (Aaron et al., 2007; Figge et al., 2004; Gitai et al., 2004).

Given the function of MreB in PG morphogenesis, it is not surprising that most spherical bacteria do not possess an MreB homolog (Pinho et al., 2013). However, some rod-shaped bacteria also lack MreB. Examples include members of Mycobacteriaceae and Rhizobiales. These bacteria display a "polar" or "subpolar" mode of growth. For example, *Agrobacterium tumefaciens* elongates from the "new" pole, which was formed by the last division (Figure 1Biii) (Brown et al., 2012). In *Mycobacterium smegmatis*, PG incorporation occurs at both polar regions, although possibly at a different rate (Figure 1Biii) (Aldridge et al., 2012; Joyce et al., 2012; Kang et al., 2008; Meniche et al., 2014; Santi et al., 2013; Thanky et al., 2007). Polar growth also occurs in the mycelium-forming bacterium *Streptomyces coelicolor* (Flardh, 2003). This bacterium possesses MreB, yet it uses an MreB-independent mechanism to direct polar cell wall growth (Mazza et al., 2006). This mechanism relies on DivIVA, another type of polymerizing protein that self-assembles into a matrix at the incipient growing tips (Figure 1Biii) (Flardh, 2003) with the help of the intermediate filament-like proteins, FilP and Scy (Fuchino et al., 2013; Holmes et al., 2013).

Curvature generation: producing crescent, sigmoid, and helical shapes

Various bacteria form curved rods or spirals. One way to curve a rod is by physically bending it, a strategy that the Lyme disease-causing spirochete *Borrelia burgdorferi* has adopted. This pathogen forms long cells with a flat-wave morphology. The curved morphology is mechanically imparted by the flagella located between the cytoplasmic and outer membranes where flagella wrap around the PG (Charon et al., 2009; Dombrowski et al., 2009; Goldstein et al., 1996; Goldstein et al., 1994; Motaleb et al., 2000). The stiffness of the helical flagella relative to that of the cell cylinder causes the cell to deform into a flat-wave shape (Figure 1Ci). Flagellar rotation propagates waves of cell deformations along the cell length, propelling the cell forward. A flagellar mutant loses the ability to swim and becomes rod-shaped, showcasing the moonlighting skeletal function of the flagella.

Bending the PG to shape the cell is an unusual strategy. More commonly, bacterial curved morphologies are imprinted into the PG fabric itself. Cell curvature can be achieved during growth by adding more PG material to one lateral wall relative to the other (Figure 1Cii). Studies in curved bacteria suggest that anisotropy in PG growth between lateral walls can be achieved with the help of self-assembling proteins, such as crescentin in *C. crescentus* and CrvA in *Vibrio cholerae* (Ausmees et al., 2003; Bartlett et al., 2017). These proteins spontaneously polymerize into filaments in vitro (i.e., without the need of nucleotides) and form static structures that are asymmetrically localized inside the cell. Evidence suggests that these structures generate curvature by mechanically reducing PG synthesis on the side of the cell where the protein structure attaches (Figure 1Cii) (Bartlett et al., 2017; Cabeen et al., 2009), though the precise mechanism is not fully understood. Perhaps the elastic property of the filamentous structure locally opposes the stretching of the PG fabric exerted by the turgor pressure (Cabeen et al., 2009). Reduced mechanical stress on the PG on one side of the cell relative to the other presumably causes an anisotropy in PG growth.

The commonalities between crescentin and CrvA illustrate an interesting case of convergent evolution, as these proteins have important distinguishing features. Like traditional cytoskeletal proteins, crescentin is cytoplasmic. Furthermore, crescentin is a coiled-coil rich

protein that shares the domain organization, the biochemical properties and the in vivo dynamics of eukaryotic intermediate filament proteins (Ausmees et al., 2003; Cabeen et al., 2011; Charbon et al., 2009). CrvA, on the other hand, is periplasmic, and shares little similarity to intermediate filament proteins (apart from two relatively short coiled-coil regions) or to other known cytoskeletal proteins (Bartlett et al., 2017).

Some bacteria combine cytoskeletal and PG-modifying functions to curve their PG fabric. For example, *Helicobacter pylori* uses cytoplasmic intermediate filament-like proteins (coiled-coil-rich proteins Ccrp59, Ccrp1143, Ccrp58 and Ccrp1142) to curve its cells (Specht et al., 2011; Waidner et al., 2009), presumably through anisotropic PG growth. In addition, this bacterium modulates its helical twist through the activity of PG crosslink hydrolases (Sycuro et al., 2010). The PG-relaxing activity of these enzymes affects the material properties of the load-bearing PG mesh. Modeling shows that if these alterations are spatially ordered (e.g., along a helical path), they will lead to curved morphologies under turgor pressure.

Expansion of shape complexity

Spatial regulation of PG morphogenesis can yield a wide diversity of cell shapes (Kysela et al., 2016), though the underlying mechanisms are poorly understood. In some cases, it involves cytoskeletal proteins unique to the bacterial world, such as bactofilins (Lin and Thanbichler, 2013). This is illustrated in *C. crescentus*, which adopts an exotic shape by forming a long, thin cell extension (stalk) at a cell pole (Figure 1D). Full extension of the polar stalk partially depends on bactofilins BacA and BacB (Kuhn et al., 2010). These two proteins self-assemble into a sheet-like structure at the cell pole where a PG synthase is recruited (Figure 1D). Studies of stalk morphogenesis have also provided insight into how morphological transitions may arise during evolution. For instance, changes in the regulation and protein sequence of a morphogen (SpmX) are thought to have driven the evolution of stalk positioning from polar (*C. crescentus*) to subpolar (*Asticcacaulis excentricus*) and bilateral (*Asticcacaulis biprosthecum*) (Jiang et al.,2014).

2. PACKING AND DECODING THE GENOME

Cell geometry defines the intracellular space. An important challenge that all cells face is to pack their oversized genome into this limited space without compromising DNA processes. The contour length of a bacterial chromosome is ~1,000 times larger than the micrometer-sized cell (Figure 2Ai; see also Box 1). To overcome this packing problem, bacteria condense their chromosome(s) into a spatially ordered, yet pliable, three-dimensional (3D) structure composed of domains within domains (Badrinarayanan et al., 2015; Dame and Tark-Dame, 2016; Wang and Rudner, 2014).

Chromosome organization

How do the compaction and domain organization of the bacterial chromosome come about? Physics offers a partial explanation. First, polymer dynamics predicts that even without a cell envelope or other physical confinement, the chromosome should spontaneously shape into a globule (Figure 2Ai), accounting for an ~100-fold compaction (see Box 1). Second,

the high macromolecular crowding of the cytoplasm results in additional compacting forces on the DNA polymer through excluded volume effects (see Box 1) (Cunha et al., 2001; Murphy and Zimmerman, 1997; Odijk, 1998). Third, torsional stress leads to supercoiling, i.e., DNA folding into superhelices (plectonemes) (Figure 2Ai, see Box 1). Various DNA-related activities mitigate or enhance these physical effects. For example, topoisomerases and RNA polymerases modulate torsional stress, thus affecting DNA supercoiling.

Biochemical factors also play important roles in compacting and spatially organizing the chromosome. While bacteria lack histones, they produce various nucleoid-associated proteins (NAPs), which are DNA-binding proteins that generate local and long-distance changes in chromosome organization (Figure 2Aii). The presence and abundance of specific NAPs depend on the species and the growth phase of the culture (e.g., exponential vs. stationary phase) (Dorman, 2014). Some NAPs (e.g., FIS in *E. coli* and IHF in *B. subtilis*) change DNA geometry locally by generating kinks in the DNA polymer (Figure 2Aii) (e.g., Thompson and Landy, 1988). Other NAPs (e.g., H-NS in *E. coli*) bridge different DNA segments and stabilize domains by simultaneously binding to multiple sites (Figure 2Aii) (e.g., Dame et al., 2006). NAPs can have multiple functions. For example, H-NS and HU have also been reported to make a "polymeric coat" on stretches of DNA (Figure 2Aii), locally altering the bending rigidity of the DNA (e.g., Amit et al., 2003; Sagi et al., 2004; van Noort et al., 2004). Other, less abundant DNA-binding proteins organize specific DNA regions on a smaller scale. For example, MatP organizes the terminus (ter) region of the *E. coli* chromosome (Mercier et al., 2008). In vitro observations suggest that MatP creates a cross-connected DNA globule around *ter* through bivalent bridging of multiple high-affinity binding sites (Figure 2Aii) (Dupaigne et al., 2012).

The chromosome is also actively shaped by the Structural Maintenance of Chromosome (SMC) complex, which forms a structure that encircles DNA (Figure 2Aiii) (Gruber, 2014; Kleine Borgmann and Graumann, 2014; Nolivos and Sherratt, 2014). Typically, the SMC complex consists of the ATPase SMC and the auxiliary proteins ScpA and ScpB (Mascarenhas et al., 2002; Soppa et al., 2002). *E. coli* lacks these proteins, but forms an analogous and distantly related complex made of MukB, MukE and MukF (Yamazoe et al., 1999). In *B. subtilis, Streptococcus pneumoniae* and *C. crescentus*, the SMC complex preferentially loads onto the chromosome at the *parS* sequence near the origin of replication (*ori*) (Gruber and Errington, 2009; Minnen et al., 2011; Sullivan et al., 2009; Tran et al., 2017), in a process that requires ATP binding and probably ATP hydrolysis (Wilhelm et al., 2015). The loaded SMC complex then translocates to distal DNA in an ATP hydrolysis-dependent manner (Figure 2Aiii) (Minnen et al., 2016). The current model in *B. subtilis* suggests that continuous loading of SMC complexes, followed by their active translocation from *ori* to *ter*, "zips" and thereby aligns the chromosome arms (Figure 2Aiii) (Marbouty et al., 2015; Wang et al., 2017; Wang et al., 2015). SMC complexes are also thought to mediate intra-arm contact (e.g., Marbouty et al., 2015), which, with active translocation, would result in DNA loop extrusion (Figure 2Aiii).

Together, physical and biochemical factors shape the chromosome into a domain-within-a-domain structure (Figure 2Ai), which was recently mapped at high resolution in chromosome conformation capture experiments (Le et al., 2013; Marbouty et al., 2014;

Marbouty et al., 2015; Val et al., 2016; Wang et al., 2015). At the cellular scale, the chromosome maintains a general linear arrangement inside the cell, such that the cytoplasmic position of each gene locus can be predicted based on its chromosomal coordinate (Figure 2Ai) (David et al., 2014; Vallet-Gely and Boccard, 2013; Viollier et al., 2004; Wiggins et al., 2010). The orientation of the chromosome during the non-replicating phase can, however, vary. In the "longitudinal" arrangement, *ori* and *ter* are located at opposite cell ends, with the left and right chromosomal arms side-by-side (Figure 2Ai) (Deghelt et al., 2014; Fogel and Waldor, 2005; Harms et al., 2013; Jensen and Shapiro, 1999; Srivastava et al., 2006; Teleman et al., 1998; Vallet-Gely and Boccard, 2013). In this arrangement, the left and right arms are thought to wrap around each other (Umbarger et al., 2011). In the "transverse" arrangement, *ori* and *ter* are in the middle of the cell, with the left and right arms at opposite ends (Figure 2Ai) (Nielsen et al., 2006; Niki et al., 2000; Wang et al., 2006). Some bacteria can switch between longitudinal and transverse arrangements depending on the cell cycle stage and the growth conditions (Bates and Kleckner, 2005; Cass et al., 2016; Niki et al., 2000; Wang et al., 2014a).

Chromosomal organization and compaction result in a discrete, albeit dynamic, coiled structure whose shape depends on the geometry of the cell (Fisher et al., 2013; Hadizadeh Yazdi et al., 2012). This compacted DNA structure is called the nucleoid.

Spatial organization of gene expression

The nucleoid and cell geometry are the most salient features of bacterial cell architecture. These two cellular features serve as foundational elements from which other aspects of cellular organization can develop.

To start with, the nucleoid and cell geometry help spatially organize the transfer of genetic information from DNA to proteins. This is best studied in rod-shaped bacteria, where the nucleoid is centrally located in the cytoplasm leaving the cell poles largely free of DNA (Figure 2Bi). The open plan of the bacterial cytoplasm means that ribosomes have direct access to the DNA. Free ribosomes diffuse through the nucleoid (Sanamrad et al., 2014) and load onto nascent mRNAs, such that translation initiates during transcription. However, as translation proceeds, polysomes (mRNAs loaded with multiple ribosomes) relocate outside of the nucleoid, resulting in ribosome accumulation at the poles (Figure 2Bi), as shown in *E. coli, B. subtilis* and *Lactococcus lactis* (Bakshi et al., 2012; Lewis et al., 2000; van Gijtenbeek et al., 2016). The partial physical separation between the nucleoid and ribosomes suggests that transcription and translation are partially separated in space, despite the lack of a nuclear envelope.

mRNA degradation is also under spatial control. The major component of the degradation machinery (RNase E in *E. coli* and RNase Y in *B. subtilis)* is enriched at the cytoplasmic membrane (Figure 2Bi) (Lehnik-Habrink et al., 2011; Liou et al., 2001). This membrane localization indicates that even though mRNA degradation can begin on nascent mRNAs during transcription (Morikawa and Imamoto, 1969; Morse et al., 1969), most of mRNA degradation likely occurs near the membrane, away from the nucleoid. In *E. coli*, mRNAs encoding inner membrane proteins are found in greater abundance near the membrane; accordingly, they have shorter lifetimes relative to mRNAs located elsewhere (Moffitt et al.,

2016). Some mRNAs have also been shown to localize to specific regions where their protein products are needed (dos Santos et al., 2012; Nevo-Dinur et al., 2011). Thus, in spite of their open plan layout, bacteria spatially regulate processes involved in the transfer of genetic information (transcription, translation and mRNA degradation), drawing a parallel to eukaryotic biology.

What accounts for the physical separation between polysomes and the condensed chromosome meshwork? In the prevailing model, this separation has been, at least in part, attributed to excluded volume effects (Castellana et al., 2016; Mondal et al., 2011). This explanation makes physical sense: the DNA polymer avoids the cell boundary to maximize conformational entropy, and the polysomes occupy the available space outside the DNA to maximize translational entropy. But apparent contradictions are found in bacteria such as *C. crescentus*, which exhibits a fundamentally different spatial organization of gene expression. In this bacterium, DNA and ribosomes are spread throughout the cytoplasm, and RNase E appears to associate (directly or indirectly) with the DNA instead of the membrane (Figure 2Bii) (Briegel et al., 2006; Montero Llopis et al., 2010). The same physical laws, including excluded volume effects, should apply to *C. crescentus*. Yet, we do not see the DNA of *C. crescentus* at the center of the cell with polysomes enriched at the cell poles, as in the prevailing model. Solving this mystery will help us understand the evolutionary constraints and physiological consequences of spatially organizing gene expression.

PARTITIONING THE CELLULAR CONTENT

Decoding the genome creates biomass, and biomass must be properly partitioned between daughter cells at every generation. In this respect, the small size of bacterial cells presents a big advantage, as diffusion—a passive process driven by thermal fluctuations—is an effective means of molecular transport over short distances. For freely-diffusing components, diffusion will randomize position, and for any component in high-copy number, random distribution will ensure that each daughter cell gets about half of the cellular components at division. However, diffusion alone is not a reliable means of partitioning low-copy-number cellular components, as the probability that a daughter cell receives zero copies increases exponentially with decreasing copy number (see Box 1). The solution, here again, is intracellular organization: bacteria have evolved means of spatially ordering low-copy-number cellular components inside cells to ensure their proper partitioning between daughter cells. Development of this spatial order generally depends on either the nucleoid or cell geometry, as exemplified below.

Bipolar distribution of low-copy-number components

In rod-shaped bacteria, one way to ensure inheritance of a low-copy-number factor upon division is by segregating copies to opposite ends of the cell. This strategy is used by a subset of low-copy-number plasmids whose segregation mechanisms are based on active transport and dynamic cytoskeletal filaments made of distant actin or tubulin homologs (Fink and Aylett, 2017; Gayathri and Harne, 2017). This is illustrated by the ParM/R system encoded by the low-copy-number *E. coli* plasmid R1 (Moller-Jensen et al., 2003). ParM is an actin homolog that polymerizes into a bipolar spindle comprised of two or more

antiparallel filaments (Bharat et al., 2015). In an interesting evolutionary twist, the ParM structure behaves more like microtubules than actin filaments by displaying dynamic instability, switching from steady elongation to rapid shrinking (Figure 3Ai) (Garner et al., 2004). This dynamic property provides a "search-and-capture" mechanism, as shrinking stops when one end of the ParM filaments becomes bound by the plasmid via the ParR protein (Garner et al., 2007; Gayathri et al., 2012). Disassembly from the other filament end is prevented through antiparallel pairing with another ParM filament (Gayathri et al., 2012). With both ends unable to disassemble, the bipolar spindle continues growing, pushing sister plasmids apart (Figure 3Ai). The rod-shaped geometry of the cell plays a critical role in this mechanism. Through elongation, the spindle naturally orients itself along the long axis of the cell, leading to plasmid translocation toward opposite cell poles.

Other segregation mechanisms that depend on actin- or tubulin-like proteins have been described (Fink and Lowe, 2015; Ni et al., 2010; Polka et al., 2014), which differ in their mechanism of generating polymer instability. For example, in the case of the *Bacillus thuringiensis* pBtoxis plasmid system, filaments of the tubulin-like protein TubZ do not display dynamic instability. Instead, they treadmill (Fink and Lowe, 2015; Larsen et al., 2007). In the case of the *B. subtilis* plasmid pLS32 system (Becker et al., 2006), the actin-like protein AlfA polymerizes into stable bundles of filaments (Polka et al., 2009; Popp et al., 2010), and their destabilization is driven by the accessory protein AlfB (Polka et al., 2014).

It is also worth noting that some cellular components (e.g., chemoreceptor arrays) preferentially localize at the cell pole membranes (Figure 3Aii). Any mechanism underlying such bipolar localization could work as a potential partitioning mechanism because each daughter cell inherits a cell pole from the mother cell. Such mechanisms do not necessarily involve protein filaments. We will present several examples in a later section (see "Functionalization of the cell poles").

Equidistant distribution of low-copy-number components

Segregating low-copy-number components to opposite ends of the cell is not the only way to achieve proper partitioning. Equidistant distribution of component copies along the long axis of the cell will also ensure equal inheritance between daughter cells (Figure 3Aiii). Such spatial patterning has been reported for low-copy-number plasmids (Adachi et al., 2006; Ebersbach et al., 2006; Lioy et al., 2015; Sengupta et al., 2010), storage granules in *C. crescentus, Pseudomonas aeruginosa* and *Pseudomonas putida* (Galan et al., 2011; Henry and Crosson, 2013; Racki et al., 2017), cytoplasmic chemotaxis protein clusters in *Rhodobacter sphaeroides* (Thompson et al., 2006), and carboxysomes (protein organelles for carbon fixation) in *Synechococcus elongatus* (Savage et al., 2010).

The best studied system driving such a striking spatial pattern is the ParA/B partitioning system, which is expressed by a large number of low-copy-number plasmids (Gerdes et al., 2000). Note that ParA/B systems are also expressed by many bacterial chromosomes (Livny et al., 2007), as discussed later. How do ParA/B systems regularly space plasmids? Once again, the mechanism involves active transport of plasmids. However, here, the active transport does not appear to involve cytoskeletal filaments (Hwang et al., 2013; Lim et al.,

2014; Vecchiarelli et al., 2013). Furthermore, the plasmids travel within the nucleoid volume (Le Gall et al., 2016). A large body of work has revealed that ParA/B-dependent transport relies on the following core biochemical features of the DNA-binding protein ParB and the P-loop ATPase ParA (Baxter and Funnell, 2014). ParB associates with the plasmid cargo through the recognition of a specific DNA sequence, whereas ParA binds to the nucleoid non-specifically in an ATP-bound dimeric form. The ParB-decorated cargo diffuses until it interacts with one or more nucleoid-bound ParA dimers, resulting in a complex. Each ParA-ParB interaction is transient because ParB stimulates ParA ATPase activity, releasing freely diffusible ParA monomers. Following nucleotide exchange and redimerization, ParA rebinds to the nucleoid, restarting the cycle (Figure 3Bi). Iteration of this cycle leads to the ParB-decorated cargo being "pulled" by a retracting ParA concentration gradient (Figure 3Bii) (Fogel and Waldor, 2006; Hatano et al., 2007; Ringgaard et al., 2009). These correlated dynamics lead to oscillatory behaviors of the plasmid and ParA waves across the nucleoid when a single plasmid cargo is present (Figure 3Bii). When multiple plasmids are present, the correlated dynamics between ParA and the ParB-decorated plasmids create depletion zones of ParA between approaching plasmids (Surovtsev et al., 2016). This depletion presumably causes plasmids to change direction each time they come close to each other, resulting in localized motion and equidistant distribution of plasmids on time average (Figure 3Biii).

A key question remains: how does ParA "pull" the ParB-decorated plasmids? Computational simulations suggest that ParA/B biochemistry and plasmid diffusion alone cannot account for the observed active transport and patterning—a translocating force is required (Figure 3Bi) (Ietswaart et al., 2014; Surovtsev et al., 2016). Indeed, all recent mathematical models that reproduce the active motion and spatial patterning observed in vivo include a non-Brownian, ParA-dependent force (Hu et al., 2017; Ietswaart et al., 2014; Jindal and Emberly, 2015; Sugawara and Kaneko, 2011; Surovtsev et al., 2016; Walter et al., 2017). But what is the source of the force? In some models, motion is proposed to be driven by "chemophoresis" (or "proteophoresis") in which the force originates from ParB and ParA binding in a chemical (ParA) gradient (Sugawara and Kaneko, 2011; Walter et al., 2017). Such a force is predicted by theoretical thermodynamic considerations (Sugawara and Kaneko, 2011), though the scale of this force inside cells remains to be determined. In other models, motion is driven by an elastic force originating from chromosomal fluctuations (Hu et al., 2017; Surovtsev et al., 2016). The compacted chromosome behaves as an elastic body, with chromosomal loci (and therefore anything bound to them) experiencing an elastic force on the scale of 0.04 pN (see Box 1) (Surovtsev et al., 2016; Wiggins et al., 2010). Importantly, this chromosomal force is on the same scale as the translocating force plasmids experience inside cells (see Box 1). The chromosomal elastic force would act on the plasmid cargo whenever it interacts with the nucleoid via ParA/ParB interaction.

Chromosome segregation

A low-copy-number component that all cells must partition without fail is the chromosome. Unlike in eukaryotes, bacterial chromosome segregation happens simultaneously with DNA replication, and can be divided into three major steps: a) separation and translocation of the freshly duplicated *ori* regions, b) segregation of the bulk of the chromosome, and c)

separation of the *ter* regions (Badrinarayanan et al., 2015; Bouet et al., 2014; Wang and Rudner, 2014). Here again, intracellular organization facilitates proper chromosome segregation. This is particularly apparent in the first and last steps of chromosome segregation, which will therefore be the focus of our discussion.

Segregation of the *ori* regions dictates the directionality of chromosome segregation and sets up the final configuration of the chromosome. In some bacteria, *ori* translocation is driven or assisted by a chromosomally-encoded ParA/B system that is closely related to the ParA/B plasmid system described above. For example, in *V. cholerae* (for the large chromosome) and *C. crescentus*, one of the replicated ParB-bound *ori* regions stays at one pole while the other moves to the opposite pole in the wake of a retracting ParA wave over the nucleoid (Figure 3Biv) (Fogel and Waldor, 2006; Ptacin et al., 2010; Schofield et al., 2010; Shebelut et al., 2009). The translocated ParB-bound *ori* is then anchored to the pole through a direct interaction between ParB and a pole-organizing element, PopZ in *C. crescentus* (Bowman et al., 2008; Ebersbach et al., 2008) and HubP in *V. cholerae* (Yamaichi et al., 2012). In Actinobacteria such as *Corynebacterium glutaminicum*, the polar anchor for the ParB-bound *ori* likely is DivIVA (Donovan et al., 2012).

The correlated localization dynamics between the ParB-bound *ori* region and the ParA waves are visually similar to one leg of the single-plasmid oscillation described above (Figure 3Bii). The underlying mechanism is likely similar: the ParB-bound *ori* region harnesses the chemophoretic force and/or the chromosomal elastic force through iterative interactions with nucleoid-bound ParA to propel itself along the ParA gradient (Lim et al., 2014; Sugawara and Kaneko, 2011). Remarkably, the ParA and ParB localization patterns can differ among species. For instance, instead of being anchored at the cell poles, ParB-bound *ori* displays a near-midcell position in *M. smegmatis* or a subpolar position in *M. xanthus* during the non-replicating phase (Ginda et al., 2017; Harms et al., 2013; Iniesta, 2014; Trojanowski et al., 2015). Furthermore, instead of localizing to the nucleoid, ParA is largely confined to the large DNA-free regions between the cell poles and the nucleoid in *M. xanthus* (Harms et al., 2013; Iniesta, 2014). These differences suggest a diversification in ParA/B-dependent mechanisms, highlighting the importance of studying different bacterial models.

Other bacteria, such as *E. coli*, lack *parA* and *parB* genes (Livny et al., 2007). In these cases, other non-exclusive physical phenomena play a role in the translocation of the chromosomal *ori* regions. Polymer dynamics in confined space predicts that duplicated *ori* regions will naturally separate from each other by entropic forces (Youngren et al., 2014), especially if these *ori* regions are condensed into compact domains (e.g., via NAP and SMC activity) (Marko, 2009). In *B. subtilis*, self-condensation and disentanglement of *ori*-proximal loops may also be actively driven by SMC complexes that load close to *ori* via the ParB homolog (Spo0J) and then thread left and right chromosomal segments presumably by a loop-extrusion mechanism (Gruber and Errington, 2009; Marbouty et al., 2015; Sullivan et al., 2009; Wang et al., 2017). Inactivation of SMC leads to interconnected sisters *ori* (Gruber et al., 2014; Wang et al., 2014b). A "snap-release" mechanism has been proposed for *ori* segregation in *E. coli*, based on the observation that sister *ori* regions remain in close proximity for an extended amount of time before they abruptly separate (Bates and

Kleckner, 2005; Joshi et al., 2011). Release of accumulated mechanical stress, perhaps due to the entropic repulsion of polymer segments, is thought to drive the sister *ori* regions apart (Fisher et al., 2013). Similar physical phenomena are thought to also underlie bulk chromosome segregation (Fisher et al., 2013; Hadizadeh Yazdi et al., 2012; Hong and McAdams, 2011; Hong et al., 2013; Jun and Mulder, 2006; Junier et al., 2014; Lampo et al., 2015; Marko, 2009; Youngren et al., 2014).

To ensure that chromosomes are fully segregated before division completes, DNA "pumps" made of proteins such as FtsK (SpoIIIE during *B. subtilis* sporulation) actively translocate DNA from one daughter cell compartment to the other (Figure 3C) (Aussel et al., 2002; Lesterlin et al., 2008; Sharp and Pogliano, 2002). FtsK associates with the division machinery at the growing septum (Wang and Lutkenhaus, 1998; Yu et al., 1998) and recognizes specific sequences on the chromosome (Bigot et al., 2006; Bigot et al., 2005; Levy et al., 2005; Lowe et al., 2008; Pease et al., 2005). The *ori*-to-*ter* orientation of these recognition sites sets the directionality of DNA translocation relative to the septum (Figure 3C). Effectively, FtsK transforms the orientation of the replicating chromosome and the geometry of the dividing cell into a directed translocation of chromosomal DNA across the division plane.

DIVIDING AT THE RIGHT PLACE

Speaking of the division plane, another critical event that occurs at every generation is the selection of the division site. While some bacteria divide asymmetrically, most divide in the middle of the cell. But how is the midcell point identified? This inherently geometrical problem is, not surprisingly, solved through intracellular organization. Selection of the division site occurs through positive and/or negative spatial regulation of Z-ring assembly (Monahan et al., 2014; Rowlett and Margolin, 2015). Positive regulation involves protein complexes or cell-wall markers that recruit FtsZ to the middle of the cell. In contrast, negative regulation generally involves protein patterns that restrict FtsZ ring formation everywhere except the cell midpoint. Bacteria often have multiple redundant mechanisms of Z-ring positioning (Bailey et al., 2014; Rodrigues and Harry, 2012), and the mechanisms themselves vary among species. However, a recurring theme is, again, the reliance on the nucleoid or cell geometry to provide spatial cues, as illustrated by three examples below.

Negative regulation by nucleoid occlusion

The Z-ring preferentially assembles in DNA-free-regions through a phenomenon known as "nucleoid occlusion". Unrelated DNA-binding proteins, SlmA in *E. coli* and Noc in *B. subtilis*, contribute to nucleoid occlusion (Bernhardt and de Boer, 2005; Wu and Errington, 2004). SlmA depolymerizes FtsZ polymers (Cabre et al., 2015; Cho et al., 2011; Du and Lutkenhaus, 2014) or prevents FtsZ polymers from coalescing into a Z-ring (Tonthat et al., 2011; Tonthat et al., 2013). Noc is thought to interact with both the nucleoid and the cytoplasmic membrane to form large membrane/DNA complexes that physically occlude Z-ring assembly and cell constriction (Adams et al., 2015). These inhibitory activities are spatially regulated by the intracellular arrangement of the chromosome. While Noc and SlmA bind across the chromosome, their binding sites are specifically depleted in the *ter*

domain (Figure 4A) (Cho et al., 2011; Tonthat et al., 2011; Wu et al., 2009). This uneven distribution of binding sites helps prevent assembly of the functional Z-ring in the middle region of the cell until segregation of replicated *ori* regions leaves the *ter* region at midcell (Figure 4A).

Negative regulation by the *E. coli* Min system

E. coli uses cell geometry and a reaction-diffusion mechanism to establish a pole-to-pole oscillating wave of the FtsZ polymerization inhibitor MinC (Hu and Lutkenhaus, 1999; Raskin and de Boer, 1999a). Oscillations of MinC from one end of the cell to other results in a minimum of MinC concentration and inhibitory activity at the middle of the cell on time average, thereby confining Z-ring assembly to that location. MinC oscillations are driven by the antagonistic relationship between two other Min proteins, the P-loop ATPase MinD and its regulator MinE (Kretschmer and Schwille, 2016; Rowlett and Margolin, 2015). While details vary among current models (Bonny et al., 2013; Park et al., 2011; Vecchiarelli et al., 2016; Wu et al., 2016), the core features of the oscillatory mechanism are as follows (Figure 4B). MinD associates with the cytoplasmic membrane upon ATP binding and dimerization. Membrane-associated MinD recruits MinE. This is followed by enhanced binding of MinD to the membrane. MinE antagonizes MinD's membrane binding by stimulating its ATPase activity, causing the release of MinD monomers into the cytoplasm. Following nucleotide exchange and diffusion, MinD redimerizes and rebinds to the membrane. The antagonism between MinD and MinE, coupled with the positive feedback of MinD binding to the membrane, drives oscillations of MinD and MinE between the most distant locations of the cell, the cell poles (Figure 4B). The FtsZ inhibitor MinC rides on the oscillatory waves simply by interacting with MinD.

Positive regulation by the *Myxococcus xanthus* Pom system

M. xanthus uses another P-loop ATPase, PomZ, but, in this case, for positive regulation of Z-ring formation (Schumacher et al., 2017; Treuner-Lange et al., 2013). PomZ is a ParA-like protein. Thus, instead of binding to the membrane like MinD, PomZ binds to the nucleoid upon ATP binding and dimerization (Figure 4C). PomZ dimers also associate with a protein cluster of PomX and PomY, which synergistically stimulates PomZ monomerization. After fast cytoplasmic diffusion and nucleotide exchange, PomZ reforms dimers and rebinds to the nucleoid. As a result, the PomX/Y cluster acts as a localized sink for PomZ dimers while the nucleoid serves as a broadly distributed source, resulting in a diffusive flux of PomZ dimers into the PomX/Y cluster (Figure 4C). When the cluster is away from midcell, the fluxes on each side of the cluster are unequal, resulting in a higher accumulation of PomZ dimers on one side of the cluster relative to the other. This asymmetry results in active translocation of the cluster toward the higher concentration of PomZ dimers. The translocating force likely emanates from chemophoresis or the elastic properties of the chromosome, as discussed above for the ParA/B system involved in DNA segregation. The asymmetry and the force vanish when the PomX/Y cluster reaches the middle of the nucleoid (i.e., midcell) because the fluxes of PomZ dimers from each side of the cluster become equivalent (Figure 4C) (Schumacher et al., 2017). Stabilization of the cluster at midcell stimulates Z-ring assembly through an unknown mechanism.

SPECIALIZING THE CELL

As illustrated in the sections above, spatial organization of the bacterial cell is an integral element of processes required for cellular replication. Often, different bacteria have evolved different spatial mechanisms to complete the same task. Over the course of evolution, diversification of cellular organization has also offered ways for bacteria to expand their metabolic capability and evolve new phenotypic traits. In some cases, cell specialization has come from the functionalization of specific cellular regions, in particular, the cell poles. In others, the development of new biological properties has been associated with cellular compartmentalization, generally through the formation of endomembranes and intracellular organelles.

Functionalization of the cell poles

While the vast majority of bacterial proteins have dispersed distribution in the cell, some proteins accumulate at one or both cell poles in diverse non-spherical bacteria. These pole-localized proteins are involved in a variety of functions including chemotaxis, motility, pathogenesis, cell differentiation, cell-cycle regulation, energy production, and secretion. Polar localization can offer various benefits. For example, in the aquatic bacterium *C. crescentus*, polar protein localization establishes cellular asymmetry and creates regulatory hubs that coordinate developmental programs with cell cycle progression (Kirkpatrick and Viollier, 2012; Lasker et al., 2016). During each cell cycle, *C. crescentus* produces two distinct daughter cells: a motile cell with pili and a flagellum for exploring new territories, and a sessile cell with an appendage (stalk) and an adhesin (holdfast) for colonizing the local environment. In this organism, temporally orchestrated localization of regulatory and signaling proteins at a specific pole couples the synthesis or activation of polar organelles (flagellum, pili, holdfast, and stalk) with DNA replication, chromosome segregation or cell division (Figure 5Ai). Functionalization of each cell pole with distinct regulatory pathways is necessary to accommodate the polar morphogenesis and the dimorphic lifestyle of this bacterium.

Another striking example of cell specialization through pole functionalization is the actin-based motility that propels diverse intracellular pathogens in the cytosol of eukaryotic host cells, allowing them to spread to neighboring cells (Figure 5Aii). In these pathogens, polymerization of the host actin occurs at one cell pole and is usually promoted by an asymmetrically distributed actin-organizing protein, such as ActA in *Listeria monocytogenes*, IcsA/VirG in *Shigella flexneri*, BimA in *Burkholderia pseudomallei* and Sca2 in *Rickettsia parkeri* (Goldberg et al., 1993; Haglund et al., 2010; Kocks et al., 1993; Stevens et al., 2005).

How is polar localization achieved? Some bacteria first reduce the problem by relying on pole-organizing proteins. For example, *B. subtilis* DivIVA, *C. crescentus* PopZ, and *V. cholerae* HubP recruit multiple proteins at the poles either by interacting directly with them or by self-assembling into a multivalent scaffolding matrix (Bowman et al., 2008; Ebersbach et al., 2008; Holmes et al., 2016; Lenarcic et al., 2009; Ramamurthi and Losick, 2009; Yamaichi et al., 2012). But how do pole-organizing proteins (or other polar proteins that do

not use their help) accumulate at the pole in the first place? Various physical mechanisms relying on cell geometry (cell pole shape) or the nucleoid have been proposed.

Such a mechanism is based on protein interaction with lipids, like cardiolipin, that preferentially accumulate at curved polar membranes due to their conical shape (Figure 5Bi) (Lin and Weibel, 2016; Mukhopadhyay et al., 2008), as mentioned earlier. Another geometry-dependent mechanism is based on proteins directly sensing membrane curvature. For example, a transmembrane protein oligomer can gauge the curvature of the membrane when the curvature radius of the membrane is on the same scale as the intrinsic curvature of the protein oligomer, as shown for cone-shaped trimers-of-dimers of the *B. subtilis* chemoreceptor TlpA (Figure 5Bii) (Strahl et al., 2015). Similar membrane curvature recognition by bent oligomers may underlie DivIVA localization (Lenarcic et al., 2009; Oliva et al., 2010; Ramamurthi and Losick, 2009). Since the cell poles of *E. coli* do not display the sharp corners of *B. subtilis* cell poles, they lack membranes with a curvature radius small enough to recruit individual oligomers. One model proposes that curvature sensing and polar localization of *E. coli* chemoreceptors are achieved through the clustering of trimers-of-dimers (Figure 5Biii) (Draper and Liphardt, 2017), potentially with the help of the Tol-Pal complex (Santos et al., 2014). The requirement for clustering is an example of spatial pattern emerging from collective interactions, a concept usually referred to as collective phenomena in physics. Another model for the polar accumulation of *E. coli* chemoreceptors does not involve membrane curvature; instead, it is based on the idea that large chemoreceptor clusters act as a sink for diffusing smaller clusters through agglomeration (Figure 5Biv) (Thiem and Sourjik, 2008; Wang et al., 2008). Small clusters can develop into a new large one only when the cell grows sufficiently for the cluster to be out of range of the sink (the old large cluster). Since one of the cell poles is always the most distant location from any arbitrary position in the cell, a large cluster will develop there.

For the polar matrix-assembling PopZ protein in *C. crescentus*, theoretical and experimental evidence suggests that nucleoid-dependent size exclusion effects are at play (Ebersbach et al., 2008; Laloux and Jacobs-Wagner, 2013; Saberi and Emberly, 2010). In *C. crescentus*, the nucleoid spreads throughout most of the cell (Figure 2Bii), limiting the volume available for large structures, such as the PopZ matrix, to the DNA-free cell tips (Figure 5Bv). When there is a pre-existing matrix (from the previous division cycle), PopZ self-affinity dictates continuous growth of this matrix. To break this pattern and nucleate PopZ assembly at the opposite pole, *C. crescentus* is thought to exploit the local accumulation of the ParA protein during chromosomal *ori* segregation (Laloux and Jacobs-Wagner, 2013). ParA would recruit PopZ oligomers through direct interaction, seeding the assembly of a new pole-organizing matrix right on time to attach the segregating *ori* region. Other molecular factors may be involved in regulating PopZ localization (Berge et al., 2016; Ptacin et al., 2014).

In diverse rod-shaped bacteria, the two poles are not functionally equivalent. This is readily obvious in any bacterium that exhibits unipolar features or properties (e.g., Figure 5Ai-ii). Pole identity is generally defined by the age of the pole: the "new" pole results from the latest division whereas the "old" pole originates from an earlier division. Little is known about how pole identity is achieved and reset at every division. In *C. crescentus*, TipN, a "birthmark" protein, regulates flagellar biosynthesis and marks the new pole until the end of

the cell cycle, when it relocates to the division site to mark the new pole of the daughter cells at birth (Huitema et al., 2006; Lam et al., 2006). TipN relocation to the developing poles is dependent on the Tol-Pal complex, which bridges the cell envelope layers during division (Yeh et al., 2010). In *Agrobacterium tumefaciens*, PopZ plays a similar birthmark function to mark the location of polar growth at the new pole (Grangeon et al., 2015).

The functional identity of the pole is not always associated with its age. Powerful examples are the motility systems of *M. xanthus*, in which the identity of the pole (leading vs. lagging) is associated with the direction of cell motion on surfaces (Schumacher and Sogaard-Andersen, 2017). This soil bacterium has two motility systems that are important for individual and social cell behaviors such as chemotaxis, group predation, and multicellular development. The so-called S-motility system relies on type IV pili, which are protein filaments that extrude from the leading pole. Cycles of pili extension, surface attachment, and retraction result in cell motion (Figure 5Aiii). The A-motility machinery, which consists of the cell envelope Agl-Glt complex, also assembles at the leading pole (Figure 5Aiii). Its active translocation toward the lagging pole, combined with its adhesion to the underlying surface at focal adhesion sites, results in propulsion of the cell in the opposite direction (Faure et al., 2016; Mignot et al., 2007). When the A-motility machinery reaches the lagging pole, it disassembles. Upon sensing environmental cues through the Frz chemosensory system, both the Agl-Glt complex and the type IV pili switch their polarity axis (Keilberg et al., 2012; Zhang et al., 2012). The leading pole becomes the lagging one, and vice versa, resulting in a reversal of motility direction (Figure 5Aiii). The leading-lagging polarity control system consists of three proteins, MglA, MglB and RomR, which simultaneously switch pole location to direct cell motion reversal (Figure 5Aiii) (Keilberg et al., 2012; Leonardy et al., 2010; Mauriello et al., 2010; Miertzschke et al., 2011; Treuner-Lange et al., 2015; Zhang et al., 2010; Zhang et al., 2012). MglA is a Ras-like GTPase that recruits the motility engines when bound to GTP. MglA-GTP is excluded from the lagging pole by the GTPase-activating protein (GAP) MglB and is recruited to the leading pole by the response regulator RomR. The involvement of a small GTPase and a GAP in the polarity of a bacterial motility system draws a remarkable parallel to the cell polarity role of small GTPases and GAPs in eukaryotic cell migration (Artemenko et al., 2014).

Compartmentalization of the cytoplasm

A number of diverse species deviate from the conventional open plan of the bacterial cytoplasm by forming endomembranes and specialized intracellular compartments that confer unique biological properties. For example, green sulfur bacteria (phylum *Chlorobi)* and filamentous anoxygenic phototrophs (phylum *Chloroflexi)* build intracellular organelles known as chlorosomes comprised of a lipid monolayer and a proteinaceous baseplate (Figure 5Ci) (Nielsen et al., 2016). These chlorosomes serve as ultra-efficient light-harvesting antennae that allow the organism to perform photosynthesis in near complete darkness (Beatty et al., 2005; Manske et al., 2005). But perhaps the bacterial organelle most similar to a eukaryotic membrane-enclosed organelle is the anammoxosome found inside anaerobic ammonium oxidizing planctomyces (Figure 5Cii) (Neumann et al., 2014). The purpose of this compartment is to catalyze anaerobic ammonium oxidation and to prevent the extremely toxic and unstable intermediate hydrazine (a rocket fuel propellant!) from

reacting with the cytoplasmic milieu. Hydrazine readily diffuses across most biological membranes. However, the anammoxosome membrane is rich in ladderane lipids (lipids containing fused cyclobutane rings), which creates an exceptionally dense membrane that limits hydrazine diffusion (Sinninghe Damste et al., 2002).

Another remarkable example of specialization through organelle formation is found in magnetotactic bacteria. These organisms form magnetosomes, which are made of magnetic iron crystals surrounded by a membrane derived from cytoplasmic membrane invaginations (Figure 5Ciii) (Uebe and Schuler, 2016). In some *Magnetospirillum* species, filaments of the actin homolog MamK help align the magnetosomes along the cell body through an interaction with MamJ (Figure 5Ciii) (Komeili et al., 2006; Pradel et al., 2006; Scheffel et al., 2006). This cellular-scale order effectively endows the cell with a compass. Such a built-in navigation system allows the cell to orient itself along the Earth's magnetic field and swim toward a position in the water column where growth is optimal.

Many bacteria can also form intracellular organelles surrounded by a protein shell, offering unique properties compared to membrane-bound organelles. For example, different types of aquatic bacteria (e.g., cyanobacteria and anoxygenic phototrophic bacteria) carry hollow gas-filled proteinaceous vesicles in their cytoplasm (Pfeifer, 2012). The rigid protein wall, which primarily consists a highly hydrophobic protein (GvpA), is impermeable to liquid water, but permeable to gases (Sivertsen et al., 2010; Walsby, 1969). As a result, the vesicles fill with air and cells become buoyant, preventing them from sinking and adjusting them to the right water depth.

Most protein-based intracellular organelles in bacteria are, however, not filled with air. Instead, they encapsulate enzymes (Bobik et al., 2015). Genomic analyses suggest that about 20% bacteria across phyla can compartmentalize metabolic reactions within a protein shell (Abdul-Rahman et al., 2013). The best characterized bacterial microcompartments (BMCs) are the cyanobacterial carboxysomes (Figure 5Civ), which encapsulate CO_2-fixing enzymes, and the enteric metabolosomes that carry out ethanolamine and propanediol degradation (Bobik et al., 1999; Kofoid et al., 1999; Shively et al., 1973). The selectively permeable protein shell of BMCs serves not only to colocalize enzymes of a specific pathway, but also to confine toxic intermediates and volatile compounds(Bobik et al., 2015). For instance, carboxysomes help reduce the loss of CO_2 (Dou et al., 2008), a small, nonpolar molecule that readily crosses lipid membranes. The microcompartments for ethanolamine and propanediol utilization are thought to sequester a volatile aldehyde intermediate that is toxic to the cell (Havemann et al., 2002; Penrod and Roth, 2006; Sampson and Bobik, 2008). Structural studies of carboxysomes have shown that the icosahedral protein shell shares assembly principles with viral capsids and consists of facets of tightly packed hexamers and vertices of pentamers (Kerfeld et al., 2005; Tanaka et al., 2008; Tsai et al., 2007). Pores within the protein shell are thought to control what goes in and out of the microcompartment (Cai et al., 2013; Klein et al., 2009; Sagermann et al., 2009). BMCs typically range from 80 to 500 nm in size. Similar, but smaller (20-40 nm) proteinaceous compartments called encapsulins are also widespread in bacteria (Giessen and Silver, 2017; Sutter et al., 2008). Protein targeting to the BMC or encapsulin interior only requires a short peptide sequence, allowing encapsulation of foreign proteins through genetic engineering (Cassidy-Amstutz et

al., 2016; Choudhary et al., 2012; Fan and Bobik, 2011; Rurup et al., 2014; Tamura et al., 2015). This property, together with their stability (e.g., to temperature, pH or denaturants), makes BMCs and encapsulins promising platforms for biotechnology and biomedical applications (Giessen, 2016; Giessen and Silver, 2016).

An extreme case of cytoplasmic compartmentalization in bacteria is endospore formation, a developmental process that members of the *Bacillus* and *Clostridium* genera undergo in response to starvation. The endospore is a cell maturing into a resilient spore within the cytoplasm of a nurturing "mother" cell (Figure 5Cv). This organization presents a new cell geometrical cue—a convex membrane inside the cell—that can be exploited for protein localization. This is elegantly illustrated by SpoVM, a small protein that specifically accumulates to the endospore's outer surface by sensing, through a cooperative interaction, small differences in lipid packing between convex and non-convex membrane curvatures (Figure 5Cv) (Gill et al., 2015; Ramamurthi et al., 2009). This geometry-driven localization of SpoVM provides positional information for the deposition of a protective proteinaceous coat on the developing spore.

IN CLOSING

The examples presented above demonstrate how ingrained cellular organization is in many aspects of bacterial replication and lifestyle. Order at the cellular scale emerges from interactions at the molecular scale through protein polymerization, reaction-diffusion mechanisms, excluded volume effects, and collective phenomena. The examples also highlight the crucial role that physical factors play in organizing the cell.

A recurring theme in bacterial cellular organization is the reliance of self-organizing mechanisms on ATPases or GTPases. These proteins render the system dynamic by cycling between different states. At the same time, the activity of these proteins pushes the system out of thermodynamic equilibrium by continuously consuming ATP or GTP. This less appreciated aspect of their activity allows cells to maintain spatial order by "fighting back" against the natural increase in entropy.

Another theme is the role of the nucleoid and cell geometry in providing spatial cues for the development of finer organization. This dependence emphasizes the importance of studying how geometrical cell features (e.g., cell shape, cell size, curved membranes) and aspects of nucleoid organization (nucleoid shape, DNA compaction, chromosome orientation, and spatial gene positioning) are established and maintained. Most of our current knowledge comes from studies of rod-shaped, monoploid bacteria, and much remains to be learned from them. In recent years, bacteria with different shapes or ploidy have gained momentum as experimental systems. Further expanding the repertoire of bacterial models will be important to develop a complete understanding.

In the context of cell biology, bacterial systems have emerged from virtual irrelevance into excellent experimental models for investigating how spatial order can spontaneously arise from disorder. In the field of residential and office architecture, an open layout provides flexibility and efficient use of the space. Perhaps, by analogy, the open plan of the bacterial

cytoplasm offers a flexible platform for the evolution of different intracellular organizations. The study of evolutionary divergent species has, indeed, taught us that bacteria have often found different solutions to the same biological problem. In this context, the breadth of bacterial diversity gifts us with a unique opportunity to explore the space of design principles and to study the evolution of cellular organization. Understanding the self-emergent and evolvable organization of the cell will bring us closer to understanding life itself.

Acknowledgments

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BOX 1

PHYSICAL CONSIDERATIONS

Here, we briefly describe some physical aspects that contribute to intracellular organization.

Polymeric nature of the DNA

Most bacteria have a single circular chromosome. Given that the distance between adjacent nucleotides is 1/3 nm, the contour length of a typical bacterial chromosome (4.5×10^6 base pairs, bp) is 1.5 mm. At the cellular scale, the chromosome can be modeled as a very long flexible polymer, as the persistence (rigidity) length (L_p) of double-stranded DNA is small (~150 bp or ~50 nm) relative to the length of the chromosome (1.5 mm). This polymeric nature emphasizes the role of entropic effects, as the chromosome has an intrinsic tendency to adopt a conformation that maximizes available degrees of freedom for its segments. These entropic effects would drive spontaneous condensation of the chromosome into a soft globule of size $L \sim L_p(N)^{1/2} \approx 10$ μm, considering the chromosome as an ideal polymer of length N in persistence-length units.

Crowding and excluded volume effects on chromosome organization

Inside cells, the DNA is not in an ideal solvent. The high macromolecular crowding of the cytoplasm causes the collapse of large polymer loops through excluded volume effects. This effect is entropy-driven; a decrease in the conformational freedom of the polymer is overcompensated by the gain in accessible volume by the large number of crowding particles.

DNA supercoiling

Another crucial aspect of DNA physics is that the DNA is an oriented helix with a natural pitch of about 10.5 bp per twist. Addition or removal of twists imposes a torsional (mechanical) strain. In the case of a circular DNA, the strain is partially released by the folding of the DNA into superhelices. A classic (albeit outdated) analogy for this supercoiling effect is the coiling of a telephone cord generated by repetitive rotations of the phone's handset.

Elastic properties of the chromosome

From a statistical physics perspective, the probability to find a particle (a chromosomal locus, in our case) at position x is given by the Boltzmann distribution: $P(x) \sim e^{\frac{-E(x)}{kT}}$, where $E(x)$ is the potential energy of the particle, k is the Boltzmann constant, and T is the absolute temperature. From the experimental measurement of such a distribution, one can infer the energy potential E(x) in which the particle moves. For chromosomal loci, experiments show that the probability of finding a chromosomal locus away (at position

x) from its mean position x_0 follows a Gaussian distribution: $P(x) \sim e^{\frac{-(x-x_0)^2}{2\sigma^2}}$, with the deviation ($\sigma$) from the mean position being ~ 100 nm (Lim et al., 2014; Surovtsev et al., 2016). This implies that a chromosomal locus moves in a "harmonic" potential $E(x) =$

$a(x-x_0)^2$ with $a = kT/2\sigma^2$ and with the particle experiencing a force $F = 2a(x-x_0)$, i.e., an elastic force with a spring constant $k_{sp} = 2a = kT/\sigma^2$. In other words, the chromosomal locus moves like a particle on a spring experiencing a characteristic force: $F = k_{sp}\sigma \sim$ 0.04 pN.

ParA-dependent translocating force on plasmid cargos

A force F applied to a particle in a viscous liquid is related to the particle velocity v as:

$F = \dfrac{kT}{D}v$, where D is the diffusion coefficient of the particle. The average velocity of a single plasmid cargo can be estimated from experiments as $v = 2l/t = 0.007$ μm/s, where l is the length of nucleoid (~ 2 μm) and t is the period of plasmid oscillation (~ 10 min) (Ah-Seng et al., 2013; Ringgaard et al., 2009). Given the experimentally measured diffusion coefficient of plasmids $D \sim 0.001$ μm^2/s (Ietswaart et al., 2014; Surovtsev et al., 2016), the estimated translocating force on plasmid cargos is $F \sim 0.03$ pN.

Random distribution and inheritance of cellular components

If a cellular component in n copies are distributed randomly in the cell, the probability to find all copies in the same half of the cell is $P = \dfrac{1}{2^{n-1}}$.
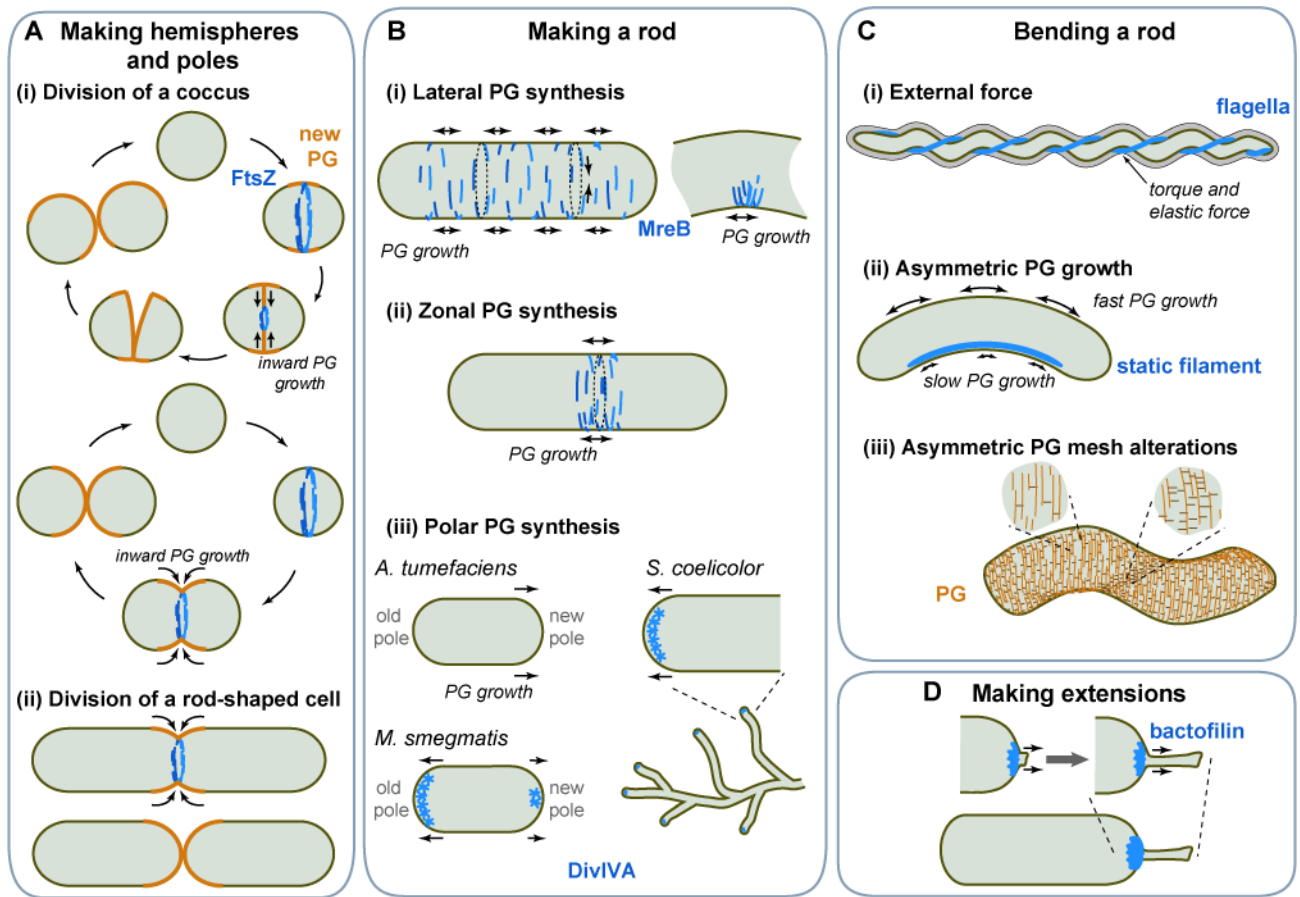
Figure 1. Shaping the cell

A. (i) FtsZ-dependent inward growth of PG during division produces new cell halves in spherical bacteria. Two types of cell cycle are shown. The top panel showcases septal PG synthesis followed by an abrupt separation of daughter cells, as in *Staphylococcus aureus*. The bottom panel illustrates the hypothetical case of septal PG synthesis occurring concurrently with cell constriction. A good candidate for this cell cycle pattern is *Moraxella catarrhalis* (Zhou et al, 2016). (ii) Septal PG growth gives rise to cell poles in rod-shaped bacteria. **B**. Rod shapes can be created by MreB-dependent (i) lateral or (ii) zonal PG incorporation. Preferential localization of MreB to the inner curve of a bent cell cylinder has been proposed to help restore straight shape. (iii) Rod shape can also derive from polar growth, which, in some bacteria, is DivIVA-dependent. **C**. Curved cell shapes can be achieved (i) by a filamentous structure such as periplasmic flagella applying an external force on the PG, (ii) through asymmetric PG growth between lateral walls caused by a static protein filament, (iii) via local modifications of the PG mesh, affecting its material properties. **D**. Stalk formation is achieved through localized PG growth with the assistance of a bactofilin structure.
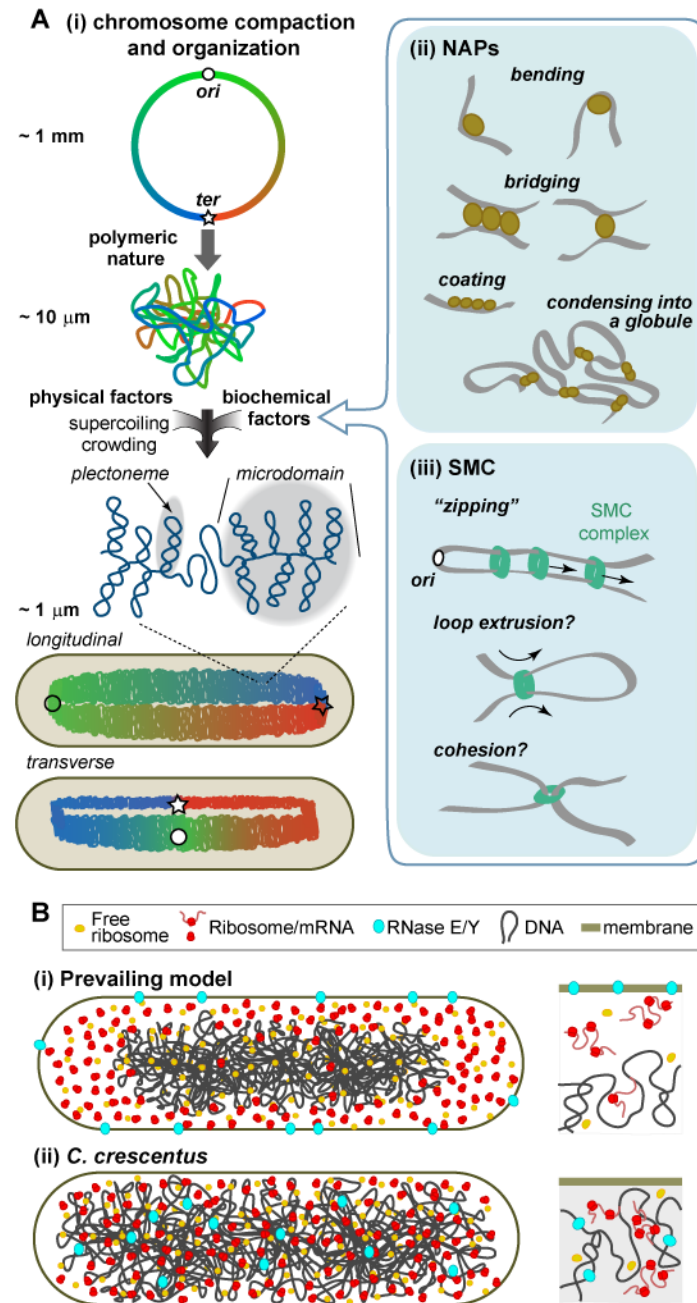
Figure 2. Folding and decoding the genome

A. (i) Bacterial chromosomes can fold into two major configurations: longitudinal or transverse. Folding is driven by physical factors and DNA-binding proteins such as (ii) NAPs and (iii) SMC complexes. SMC complexes may travel in pairs (Badrinarayanan et al., 2012; Wang et al., 2017), but just a single complex is shown for simplicity. **B**. (i) Prevailing view of nucleoid (transcription), polysome (translation) and RNase E or Y (mRNA degradation) arrangement in bacterial cells. (ii) Unconventional organization of the chromosomal DNA, ribosomes and RNase E in *C. crescentus*.
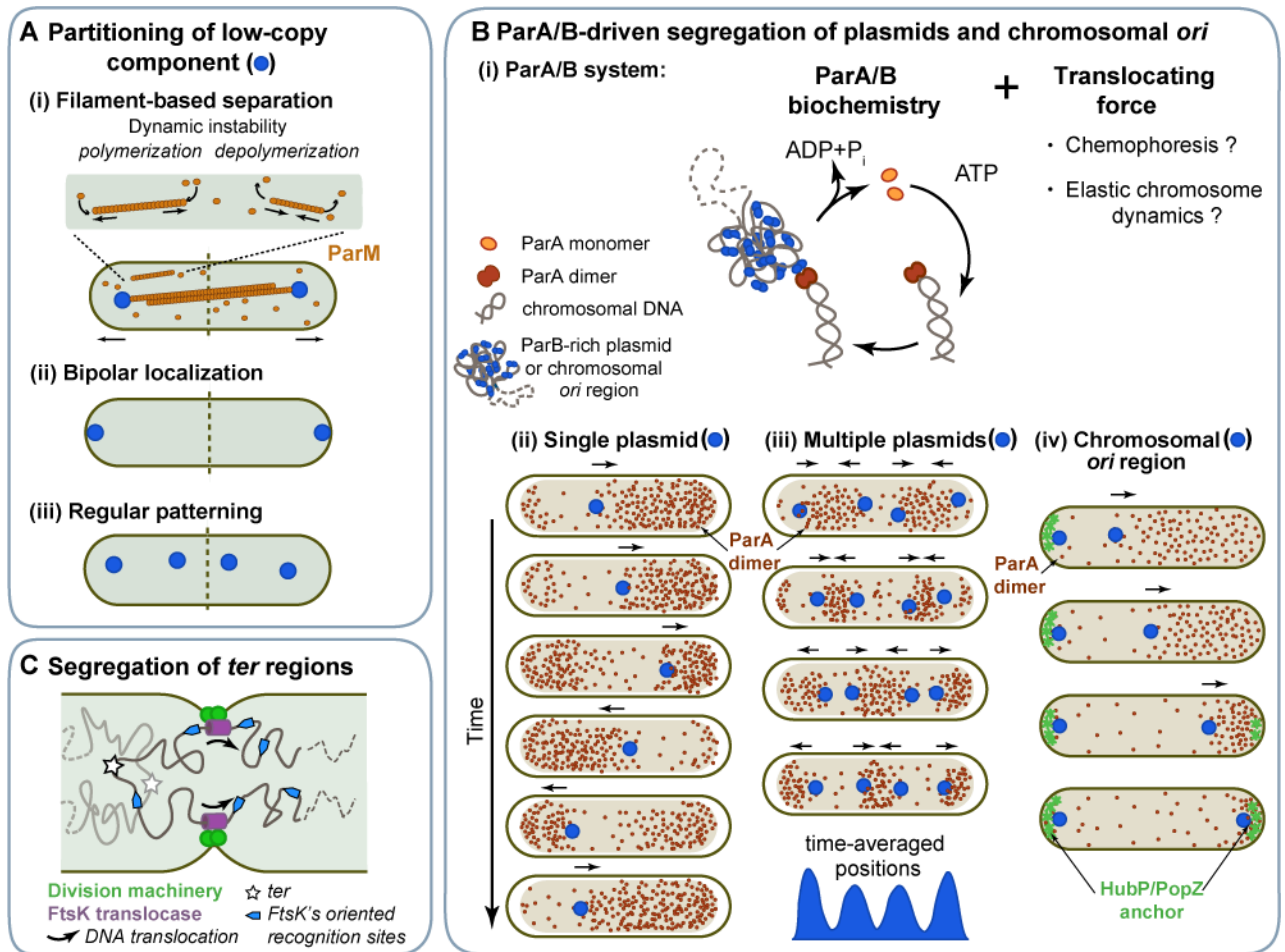
Figure 3. Partitioning cellular components

A. Different approaches ensure faithful partitioning of low-copy-number cellular components between daughter cells: (i) Cytoskeleton-based active transport of component copies to opposite poles, as illustrated with the plasmid ParM/R system. (ii) Localization of copies at opposite poles. (iii) Regular distribution of copies along the long cell axis. **B**. (i) Current models of the ParA/B DNA partitioning system propose different sources of the translocating force, which, together with the ParA/B biochemistry, drive (ii) oscillations of a single plasmid, (iii) regular patterning of multiple plasmid copies, and (iv) segregation of chromosomal *ori* regions in some bacteria. **C**. Segregation of chromosomal *ter* regions across the septal plane is driven by the hexameric FtsK translocase, which interacts with the division machinery. FstK recognizes DNA sequences on the chromosome that have an *ori*-to-*ter* orientation, which determines the directionality of DNA translocation across the septal plane.
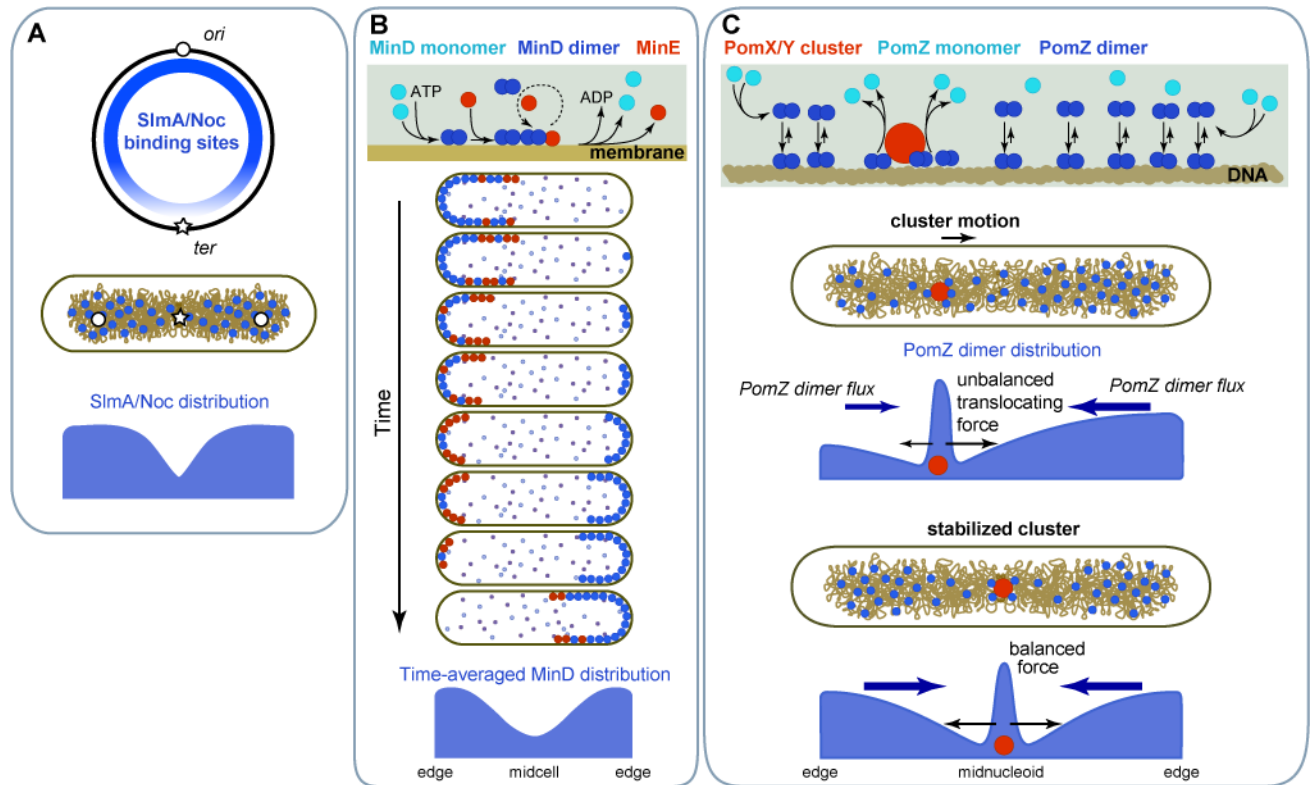
Figure 4. Selecting the division site

A. Nucleoid occlusion of Z-ring formation is facilitated by the asymmetry in DNA-binding sites of FtsZ inhibitors SlmA (*E. coli*) or Noc (*B. subtilis*) along the chromosome. **B**. The *E. coli* Min system prevents Z-ring formation in the polar regions through protein oscillations driven by a reaction-diffusion mechanism. These oscillations result in time-averaged accumulation of an FtsZ-assembly inhibitor at the polar regions. **C**. The Pom system in *M. xanthus* identifies midcell by positioning an FtsZ assembly activating complex, the PomX/Y cluster, at mid-nucleoid through a localized-sink/distributed-source mechanism coupled to a translocating force of chemophoretic or chromosomal origin.
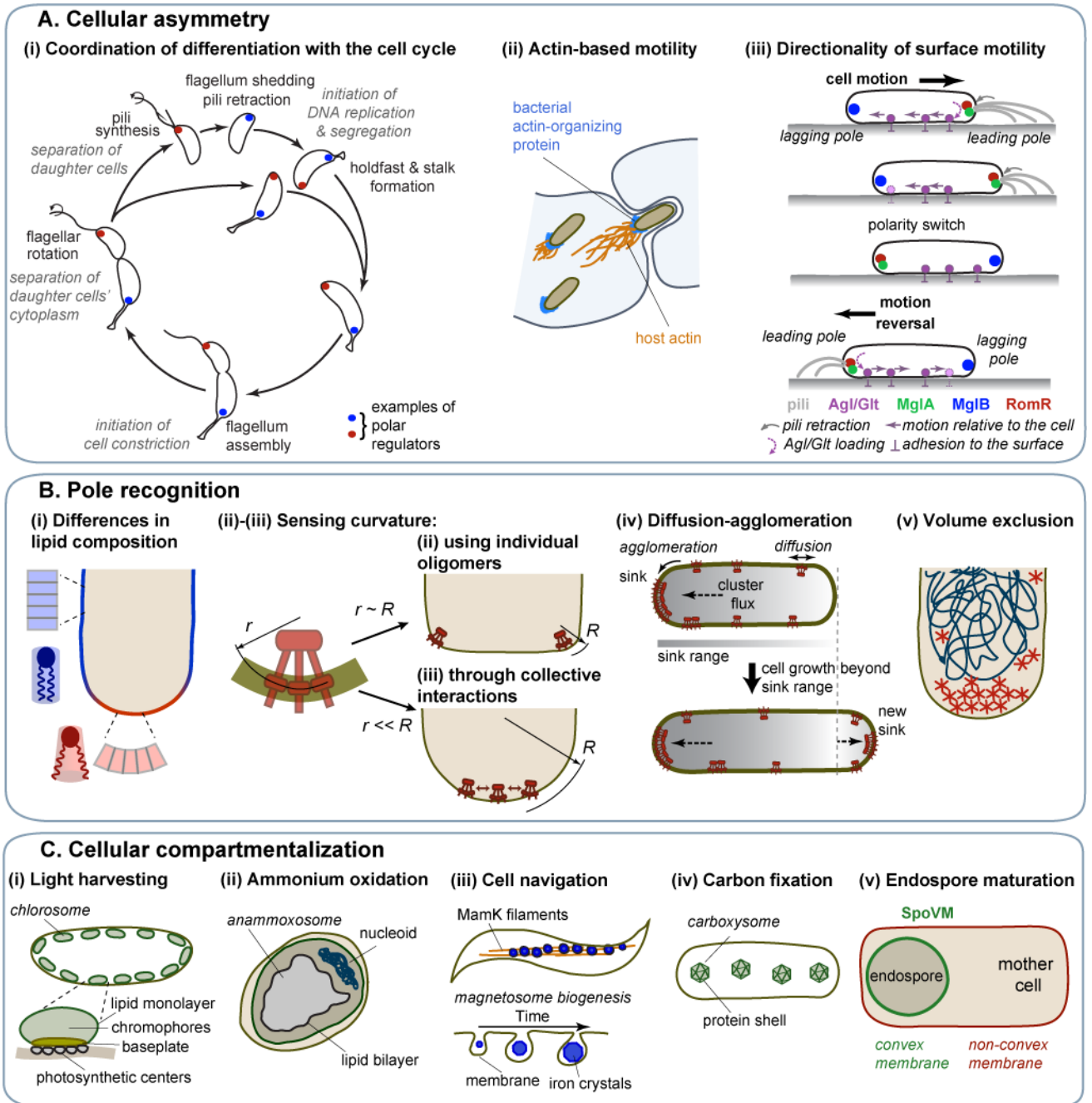
Figure 5. Specializing the cell

A. Protein localization at a specific cell pole results in cellular asymmetry that underlies (i) the coordination between developmental and cell cycle events in *C. crescentus* (the polar localization of only two histidine kinases, DivJ and PleC, are shown for clarity (Wheeler and Shapiro, 1999); in reality, there are at least a dozen regulators that display polar accumulation during the cell cycle), (ii) the actin-based motility of some intracellular pathogens and their cell-to-cell spread in eukaryotic host tissues, (iii) the directional motility in *M. xanthus*. **B**. Pole recognition can be based on (i) differences in lipid composition between membrane regions of different curvatures, (ii) sensing of high curvature by

individual protein oligomers, (iii) sensing of moderate curvature through collective oligomer interactions, (iv) interplay between protein cluster diffusion and protein cluster agglomeration, (v) volume exclusion that promotes formation of large protein structures outside the nucleoid. **C**. Examples of bacterial microcompartments: (i) chlorosomes bound by a single lipid layer and a protein baseplate, (ii) an anammoxosome enclosed by a lipid bilayer, (iii) iron-containing magnetosomes, (iv) carboxysomes, which confine reactions involved in carbon fixation in a protein shell, (v) an endospore maturing into a spore inside the mother cell. *B. subtilis* SpoVM localizes to the outer surface of the endospore to facilitate spore coat formation.