

Active and passive mechanisms of intracellular transport and localization in bacteria

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Spatial complexity is a hallmark of living organisms. All cells adopt specific shapes and organize their contents in such a way that makes possible fundamental tasks such as growth, metabolism, replication, and division. Although many of these tasks in bacteria have been studied extensively, only recently have we begun to understand the influence of spatial organization on cell function. Clearly, bacteria are highly organized cells where proteins do not simply diffuse in a 'cytoplasmic soup' to exert function but can also be localized to specific subcellular sites. In this review, we discuss whether such order can be achieved solely by diffusive capture mechanisms or if active intracellular transport systems are required.

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Introduction

Because they are relatively 'simple' organisms, bacteria have been widely used as model systems to study basic biological mechanisms. However, owing to its small size, the bacterial cell was long considered a primitive 'bag of enzymes', held together by a rigid cell wall, in which proteins reach their sites of action through simple diffusion. Strikingly, however, cytoskeletal elements such as homologs of actin and tubulin, that were thought to be restricted to eukaryotic cells, were also found in bacteria revealing that the prokaryotic cell has a complex underlying architecture. The prokaryotic cytoskeleton was originally shown to be involved in orchestrating cell wall synthesis and cytokinesis, but accumulating evidence also points to roles in other essential processes such as chromosome segregation, the positioning of subcellular orga-

nelles, and the control of cell polarity [1–4]. Recently developed high-resolution fluorescence techniques revealed that many proteins are sorted to specific locations to achieve their functions. These include not only receptors and signaling proteins but also proteases and other metabolic enzymes. An extreme example is the localization of a hybrid polyketide/nonribosomal peptide synthetase in *Bacillus subtilis* that assembles at a unique subcellular location into a 2.5 MDa membrane-associated, organelle-like structure [5].

The complexity of the bacterial cell has so far been underestimated and questions that were until recently only relevant for eukaryotic cells need to be studied in bacteria. Despite a decade of study, the exact roles of the cytoskeleton and subcellular protein localization remain undefined. In this review, we will touch on several mechanisms that have been hypothesized to contribute to intracellular transport and localization of macromolecules in bacteria addressing such questions as: Do bacteria possess or even need active transport systems? Can diffusion be used to create the observed complexity, or are directed processes required? Are the cytoskeletal filaments in bacteria polarized and can they give rise to transport phenomena?

Passive transport

Diffusion in the cytoplasm

The interior of a bacterium is a crowded place. However, diffusion still dominates the positioning of free proteins in the cytoplasm. Pioneering work by Elowitz *et al.* measured the diffusion of proteins in the cytoplasm of *Escherichia coli* and found that proteins move randomly with a diffusion coefficient of 3–8 $\mu\text{m}^2/\text{s}$ [6]. This value is about 10 times smaller than in water and lower than found in eukaryotic cells. However, on the cellular scale these diffusion coefficients lead to efficient mixing on the second timescale. For a diffusion coefficient of 5 $\mu\text{m}^2/\text{s}$, a protein will travel the length of an *E. coli* cell (about 2 μm) in 0.4 s and will encounter a fixed, protein-sized target in the cell every few seconds [7]. This diffusion-limited rate is most likely fast enough to allow a protein to find a localized binding partner in a search and capture process. For proteins and small macromolecular complexes in the cell cytoplasm or periplasm, therefore, it is not clear that an active mode of transport is necessary for intracellular transport.

Diffusion in the membrane

Membrane proteins can also reach their final destination by diffusion, although with substantially reduced

mobility. The diffusion coefficient for membrane-bound proteins has been measured to be in the range of 0.01–0.1 $\mu\text{m}^2/\text{s}$, one to two orders of magnitude less than that for cytoplasmic proteins [8–11]. Although slower than in the cytoplasm, diffusion in the membrane will lead to mixing on the minute time scale. One example of diffusion and capture in bacterial membranes is SpoIVFB, a protein from *B. subtilis* that is first uniformly inserted into the membrane and then diffuses freely to be specifically sequestered into the septal membrane [12].

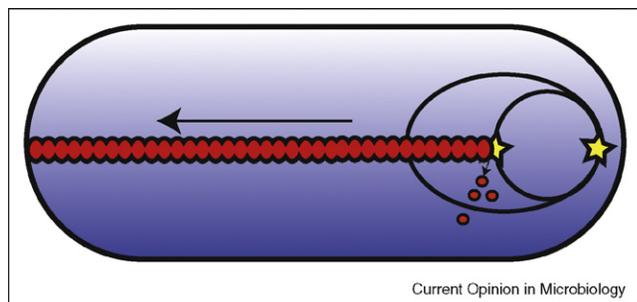
Active transport

Large objects, such as whole chromosomes, need to be moved over long distances in the cell and require active machinery. To date, several distinct systems have been implicated in the process of chromosome segregation. Different species of bacteria appear to use different subsets of these mechanisms (see [13–15] and references therein). Two of these systems, however, are found in a large majority of bacteria and are required for high-fidelity segregation.

Depolymerization-based transport

A number of bacteria possess homologs of the plasmid partitioning proteins ParA and ParB. During chromosome segregation, ParB binds a specific region of the chromosome near the origin of replication and ParA filaments, which are anchored to a cell pole, ‘drag’ the origin of replication poleward (Figure 1 [16–19,20*,21]). Because ParA filaments are seen to extend and then retract, it has been proposed that depolymerization of ParA might drive segregation similar to the shrinking microtubules during mitosis [20*,22]. However, unlike the Dam1 kinetochore complex which forms rings around depolymerizing microtubules which have frayed ends [23], it is unclear how ParB might connect the chromosome to the depolymerizing end of a ParA filament.

Figure 1



Proposed mechanism for ParAB-mediated chromosome segregation. Segregation of a replicating chromosome is shown. A polar-bound ParA filament (red) binds to ParB (Star) at the origin of replication. ParA then pulls the chromosome poleward as it depolymerizes.

Motor-driven transport

Second, the helical actin homolog MreB appears to play a role in chromosome segregation as well. Depletion of MreB yields defects in segregation of the origins of replication and, sometimes, of the entire chromosome [4,24–26]. How these processes are affected by MreB remains elusive. MreB was found to interact with regions proximal to the replication origin and by analogy with the eukaryotic kinetochore, it was suggested that MreB could serve as a track for a motor protein to pull the origin to the other pole [24]. This putative motor has not been characterized, and it was suggested that it could be RNA polymerase itself [4]. To date, cytoskeletal motors have not been found in bacteria.

Treadmilling-based transport

The MreB filament might also be used for transport without the aid of a cytoskeletal motor. Current evidence points to the helical bundle of MreB being made up of short, laterally associated protofilaments ~ 400 nm in length [27*]. On the basis of this evidence and some assumptions about the polymerization kinetics of MreB based on our knowledge of actin biophysics, Allard and Rutenberg have created a theoretical model of transport that uses protofilament treadmilling to generate bidirectional transport modes if a cargo binds either the monomers bulk or the end of a protofilament [28]. In support of treadmilling, single-molecule fluorescence experiments have revealed the motion of individual MreB monomers within the bundle [27*]. These results show the movement of MreB monomers within the polymerized MreB bundle, but no consistent directionality of the monomer motion. In their theoretical model Allard and Rutenberg touch on the idea that directional motion may still be possible for bundle geometries in which the filaments are not directionally aligned, but more work needs to be done to expand this idea.

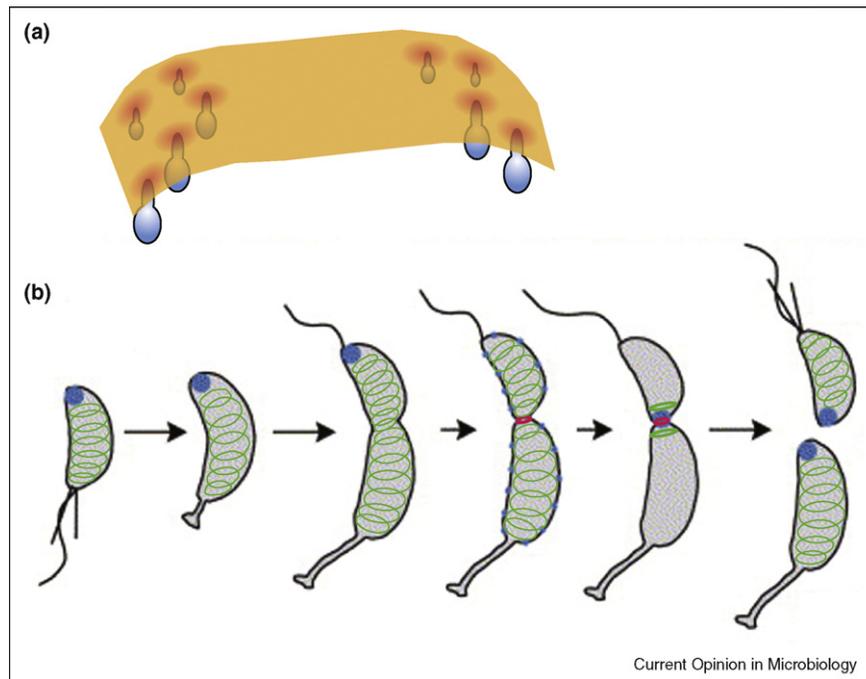
Static localization

Protein localization is a general bacterial trait that is involved in an increasing number of functions: not only the positioning of polar organelles, type-IV pili, flagella, and stalks but also signal transduction complexes, chemoreceptors, and two-component systems. For extensive reviews on bacterial cell polarity the reader is referred to Refs. [29,30]. Two types of locations in the cell appear to be used extensively: the poles and the midcell.

Curvature-induced phase separation at the poles

In rod-shaped cells, the poles are clearly defined as unique locations by pure geometry. They are curved in two dimensions whereas the cell axis is only curved in one direction. This difference can be used, in principle, for protein localization. For example, the phospholipid cardiolipin is known to naturally form small microdomains at cell poles and has been shown to localize the protein ProP in *E. coli* [31–34]. Two recent papers have described how

Figure 2



Possible mechanisms to define the poles in bacteria. **(a)** Cardiophilin patches form spontaneously at the poles (red circles) thereby localizing cardiophilin-binding proteins (blue). **(b)** Definition of the flagellated pole in *Caulobacter*. Upon asymmetric cell division, TipN (blue) is directed to the new pole through potential interactions with the FtsZ division ring (red). TipN is then proposed to act as a polar landmark to direct differentiation of the flagellated pole. By analogy with observations made in *E. coli*, TipN could be important to establish a polarity axis by recruiting MreB rings at the division septum during cytokinesis and thus ensuring proper segregation and polarization of the cytoskeleton (green). The TipN cycle is resumed after the dispersal of TipN from the old flagellated pole and relocalization to the division septum. The mechanism of this relocalization remains enigmatic. Image was obtained and modified from [37,38].

a lipid phase-separation phenomenon can lead to this polar localization (Figure 2a [35,36]). By combining an inherent curvature preference for this lipid species with an interaction energy between lipid molecules, the authors show that cardiophilin will form patches at the two cell poles. Thus, a protein that interacts with cardiophilin will naturally localize to a cell pole.

Differentiation of the new and old pole

True cell polarity, that is a directionality of the cell axis, requires the cell to differentiate between the two poles. One method for doing this that is used by several bacteria is the distinction between the newer and older poles in the cell. In *Caulobacter crescentus*, for example, the search for initial localization factors led to the discovery of TipN, a coiled-coil rich protein that acts as a polar landmark to localize pilus, flagellar, and signaling proteins (Figure 2b [37,38]). TipN was proposed to be a 'birthscar protein' by localizing to the septum in an FtsZ-dependent manner, thus marking the new pole. Direct interactions with the septal FtsZ ring have not been shown yet, but if it were the case TipN could be the first intrinsic cue toward polarization of the flagellated pole. Interestingly, MreB is affected in the assembly of the divisional ring in the

absence of TipN [37,38]. In *E. coli*, the formation of such a ring before cell division has been linked to proper segregation of the cytoskeleton upon cell division [39]. Thus, TipN could act upstream of crucial cytoskeletal rearrangements leading to segregation and the establishment of a polarity axis (Figure 2b).

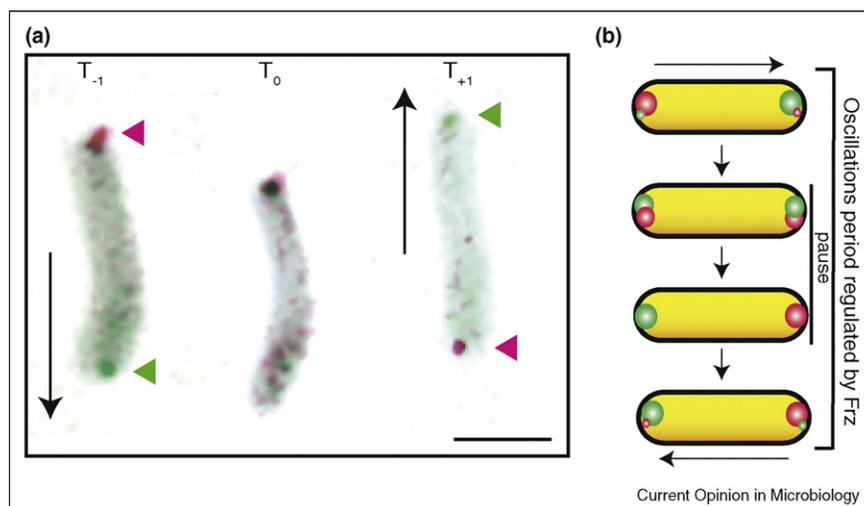
MreB has been shown to directly affect the localization of at least some polar proteins. Depletion or overexpression of MreB leads in both cases to mislocalization of several *C. crescentus* polar markers [1]. When depleted cells were replenished with MreB, polar markers such as DivK and PleC relocalized to the cell poles but to the wrong pole in half of the cells. This would suggest that the cytoskeleton is globally polarized, in seeming contrast to the single molecule data of Kim *et al.* [27]. Perturbation of the MreB cytoskeleton has also been shown to lead to abnormal localization of polar proteins in *E. coli* [40].

Dynamic localization

Oscillatory mechanism defines mid-cell position

Perhaps the best studied example of a dynamic localization is the pole-to-pole oscillations of the MinCDE proteins first shown in 1999 [41]. The oscillation of these

Figure 3



Protein dynamics during bacterial motility. **(a)** Dynamic pole-to-pole oscillations of motility proteins during cellular reversals in *Myxococcus*. Time-lapse microscopy of a moving cell expressing dual fluorescent proteins, RomR-mCherry (red) and FrzS-GFP (green). At T_0 , the cell pauses for a short time before it reverses. At the time of reversal, FrzS-GFP and RomR-mCherry are targeted to the leading and lagging poles, respectively. Image was obtained and modified with permission from [45**]. Scale bar = 2 μm . **(b)** Proposed dynamic cycle for FrzS and RomR. Following a reversal, FrzS is mostly condensed at the leading cell pole and RomR accumulated at the lagging pole. As the cell starts moving in the new direction, FrzS accumulates at the lagging pole, while RomR moves to the leading pole until they reach equal amounts at both poles. At this stage, the cell pauses and each protein is rapidly redirected to the new pole, the cell then resumes movement in the opposite direction. The behavior of RomR and FrzS is tightly regulated by the Frz chemosensory-like system.

proteins between the poles along with an inhibition of FtsZ polymerization largely defines the midplane of the cell and prevents Z-ring formation at and near the poles (see [42] for a review). It has been shown that the Min proteins form filamentous structures that oscillate via polymerization [43]. A large number of theoretical models have treated various aspects of this system (see citations 132–140 in [42]). The main feature of these models is that the dynamic behavior of the Min proteins is hard wired in their biochemical properties of membrane binding, polymerization, and catalysis.

Dynamic polarity during gliding motility

In *Myxococcus xanthus*, the localization of motility proteins appears to be not only dynamic, but also controlled. During gliding motility, cells do not change direction by doing ‘U-turns’ but occasionally undergo cellular reversals during which the leading cell pole is converted to the lagging cell pole [44]. Cellular reversals imply that polar determinants can be rapidly switched from one pole to another. Indeed, key regulators of motility, the FrzS and RomR proteins, were found to specifically localize to the leading and the lagging cell poles, respectively where they interact with elements of the motility machinery (Figure 3a and b [45**,46,47]). These proteins oscillate between the cell poles when cells reverse [45**,46]. Remarkably, a signal transduction pathway regulates the periodicity of the oscillations (Figure 3b). It is difficult to imagine that these abrupt switches in cell polarity

could result from a passive mechanism. Consistent with this, pole-to-pole movements of FrzS and RomR do not depend on *de novo* protein synthesis, ruling out localized degradation of these proteins at the old poles. When analyzed by Fluorescence Recovery After Photobleaching (FRAP), a fluorescent FrzS-GFP fusion was shown to traffic from one pole to another at a speed 10 times slower than the speed expected for diffusion [46]. Large FrzS-GFP clusters moved from one pole to the other along a seemingly helical path and a FrzS mutant unable to localize to the poles assembled along a helical path that spanned the cytosol. These results were interpreted as evidence for pole-to-pole transport of FrzS along a cytoskeletal filament, implying that regulated polarization is an active process in *Myxococcus*. Although definitive evidence for active transport is still missing, *Myxococcus* motility seems to be an excellent model to investigate active mechanisms for polarity and intracellular transport.

Conclusions

It is now widely accepted that the bacterial cell is a highly organized structure where proteins are sorted to specific locations. It is also clear that diffusion alone can account for the targeting of many proteins to their destination, leaving open the question for the necessity and existence of active transport mechanisms. Even though the mechanism of chromosome segregation remains largely mysterious, it seems clear that transport mechanisms are involved. By analogy with eukaryotic cell systems, it is

tempting to imagine that both passive and active mechanisms are also used by prokaryotes. However, as pointed in this review, there is no hard evidence for active protein trafficking in bacteria. Recent developments in high-resolution microscopy will be instrumental in unraveling the mechanisms of intracellular protein trafficking and localization. Ultimately, definitive evidence for active transport will depend on the identification and characterization of the molecular motors involved. The discovery of tubulin-like and actin-like proteins has raised the question of the existence of kinesin-like, dynein-like, and myosin-like proteins in bacteria. However, genomic and biochemical analyses have failed to identify such motor proteins, but it is useful to remember that cytoskeletal elements were only isolated after generations of research in bacteria. Possibly, strains carrying mutations in motor genes may already be in laboratory collections labeled as genes of unknown functions or localization genes. New experimental designs will probably need to be developed to find the elusive motors. For example, an *in vitro* system that recapitulates the tracking of complexes on polymerized MreB will be instrumental.

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