Published in final edited form as:

Annu Rev Microbiol. 2013 ; 67: 417–435. doi:10.1146/annurev-micro-092412-155622.

Biological Consequences and Advantages of Asymmetric Bacterial Growth

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Abstract

Asymmetries in cell growth and division occur in eukaryotes and prokaryotes alike. Even seemingly simple and morphologically symmetric cell division processes belie inherent underlying asymmetries in the composition of the resulting daughter cells. We consider the types of asymmetry that arise in various bacterial cell growth and division processes, which include both conditionally activated mechanisms and constitutive, hardwired aspects of bacterial life histories. Although asymmetry disposes some cells to the deleterious effects of aging, it may also benefit populations by efficiently purging accumulated damage and rejuvenating newborn cells. Asymmetries may also generate phenotypic variation required for successful exploitation of variable environments, even when extrinsic changes outpace the capacity of cells to sense and respond to challenges. We propose specific experimental approaches to further develop our understanding of the prevalence and the ultimate importance of asymmetric bacterial growth.

Keywords

asymmetry; peptidoglycan; sporulation; aging; damage

INTRODUCTION

Asymmetric cell growth—cell elongation and division processes that produce distinct daughter cell morphologies and/or physiologies—enjoys a well-understood and well-recognized place in eukaryotic biology. Cell division asymmetries occur in diverse eukaryotes ranging from single-celled protists and yeasts to multicellular organisms, where asymmetric cell fates underlie complex developmental processes (57, 66, 78, 83).

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Historically less appreciated are the role and prevalence of asymmetric growth and its biological impact on prokaryotes. However, obvious morphological asymmetries exist in numerous bacterial phyla, and inherent asymmetry underlies even morphologically symmetric modes of bacterial division (12, 57). For bacteria and eukaryotes alike, asymmetry proves integral to the process of cell growth and division.

The predominant view of bacteria as simple cells with relatively symmetric cell cycles has changed dramatically over the past few decades as it has become increasingly obvious that bacterial cells are both complex and organized (77). The complexity of bacterial cells is well illustrated by the precise subcellular localization of proteins, DNA, mRNA, and small molecules (15, 36). The poles of rod-shaped bacterial cells serve as localization hubs, and the dynamic changes in macromolecule content at the cell poles control critical aspects of cellular physiology such as the placement of the septum prior to cell division and the onset of sporulation (for review see 10). In addition, the cell poles are a common site for the production of surface organelles such as flagella, pili, stalks, and adhesins, allowing for proper orientation of the cell during complex processes such as swimming through liquid and attaching to surfaces (49, 54). Finally, the cell poles are not identical (one is relatively older), giving rise to asymmetry even in seemingly symmetric rod-shaped cells (Figure 1a).

Here, we describe how different bacterial growth patterns can lead to the establishment of multiple types of asymmetry, including conditional, reproductive, and morphological asymmetries. We explore possible advantages of establishing asymmetry, with a particular emphasis on aging and evolutionary ecology. Throughout this review we highlight some of the remaining questions about bacterial asymmetry and introduce new and emerging approaches that promise to clarify both how cellular asymmetry is established and the significance of asymmetry in bacteria. Improving our ability to assess the degree of bacterial asymmetry will provide a valuable resource for studying the more general question of how cellular organization is utilized to control physiology.

BACTERIAL ASYMMETRIES GENERATED BY GROWTH

Bacterial growth patterning is the result of regulated insertion of new peptidoglycan into the existing cell wall. In many bacteria, insertion of peptidoglycan leads to the production of two distinct poles (Figure 1a). Notably, this is true not only for rod-shaped cells that exhibit dispersed, cylindrical insertion of peptidoglycan, but also for cells with diverse modes of growth. In this section, we discuss how these diverse growth patterns lead to the establishment of reproductive asymmetry and/or morphological asymmetry.

The Cell Wall Growth Process

The growth of most rod-shaped bacterial cells is mediated at least in part by elongation dependent on the actin-like protein MreB, whereby insertion of new peptidoglycan (see sidebar, Peptidoglycan) along the lateral sidewall results in lengthening of the cell (17, 21, 35, 58, 94, 95). Notably, the cell poles in such cells are devoid of new peptidoglycan synthesis (19). Although most models have assumed that synthesis is uniformly distributed along the lateral sidewall, biophysical simulations studying the effects of growth via random insertion of glycan strands predict that rod-shaped cells will lose both their shape and

mechanical integrity due to the stochastic development of density fluctuations in the peptidoglycan (34) (Figure 2a). This indicates that some coordination of growth is necessary to maintain a rod-like shape; coupled with the fact that the copy numbers of peptidoglycan synthesis enzymes may be low, with only ~100 of each enzyme in *Escherichia coli* (22), spatial heterogeneity is likely an inherent property of growth mechanisms even in cells that do not have any obvious morphological asymmetries.

PEPTIDOGLYCAN

Bacterial cell walls are composed of a meshwork of peptidoglycan, which serves as an exoskeleton and is responsible for maintaining proper cell shape and providing mechanical strength. Peptidoglycan comprises glycan strands that contain alternating units of β -1-4-linked N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc). The glycan strands are cross-linked by short-stem peptides linked to the carboxyl group of MurNAc. Bacterial cell growth requires the coordination of many enzymes to synthesize peptidoglycan precursors, produce disaccharide chains, break bonds in the existing wall, and insert new material into the growing sacculus. Furthermore, precise temporal and spatial regulation of the peptidoglycan biosynthesis machinery is required to ensure that insertion of new peptidoglycan does not disrupt cell shape. The chemistry, structure, synthesis, and regulation of peptidoglycan are discussed in more detail elsewhere (20, 44, 76, 86, 91).

Several recent studies have demonstrated a feedback between cell wall insertion and MreB dynamics in both gram-negative (89) and gram-positive (21, 35) bacteria, suggesting that MreB serves as a scaffold for wall synthesis. Although the precise spatial distribution of MreB in wild-type cells has not been resolved, simulations of cell wall insertion from a pattern of helical segments predicted that such a rod-shaped cell should establish a chiral peptidoglycan network and should twist during growth, with the two ends rotating in opposite directions (34). Using beads as fiducial markers on wild-type cells with unlabeled MreB, researchers observed that *E. coli* and *Bacillus subtilis* cells indeed twist in an MreB-dependent manner, with a conserved left- or right-handedness, respectively (45, 94) (Figure 2b,c). Therefore, growth itself also imparts a rotational asymmetry to the two halves of the cell and to the wall itself. Intriguingly, a mixture of two populations of *E. coli* cells expressing different fluorescent proteins as neutral markers grew into a colony with spatially segregated sectors of single markers (38). In all cases, the boundaries between sectors curved in a clockwise direction, demonstrating that the community of cells possessed a handedness of its own that could arise from the twisting of single cells during growth (Figure 2d). It remains to be seen whether the patterning of growth leads to fundamental asymmetries in other cell shapes such as spheres; computational models can serve as a quantitative tool to predict morphology from growth mechanisms.

Following elongation, cells must prepare for division in order to complete the reproductive process. In at least *Caulobacter crescentus* and *E. coli*, the transition from elongation to cell division requires penicillin binding protein 3 (PBP3)-independent peptidoglycan synthesis at mid-cell (1, 71, 97). The divisome recruits PBP3 to the mid-cell, resulting in new peptidoglycan synthesis to enable cell division via constriction, septation, or both (58).

Following cell division, each daughter cell contains two poles that differ in their relative ages (Figure 1a). Notably, surface-exposed proteins are immobilized at the old pole (18, 88) as a consequence of outer membrane growth occurring in uniform, discrete bursts only along the lateral sidewall of the cell (88). These results suggest that the growth patterns of the cell wall and the outer membrane strongly influence the organization of the surface-exposed proteins. The asymmetric distributions of surface proteins within a single cell and the variations that can arise throughout subsequent generations of cell growth can by themselves lead to heterogeneity within isogenic bacterial populations.

Reproductive and Morphological Asymmetry

Although it is now clear that even rod-shaped bacteria do not produce identical daughter cells owing to both stochastic fluctuations and active processes (24, 81), asymmetries are often hard to detect. Thus, it is not surprising that the pioneering work on bacterial asymmetry was conducted in systems where morphological differences between mother and daughter cells could be readily observed. Some of the earliest reports of bacterial asymmetry can be found in descriptions of budding bacteria (43, 96). Budding bacteria are classically defined as utilizing a specialized form of growth in which new wall synthesis is confined to a very small area, resulting in the emergence of a bud from the mature mother cell (43). Striking examples of budding can be found among the stalked hyphomonads and hyphomicrobia of the *Alphaproteobacteria*, in which a motile daughter cell emerges from the tip of a stalk-like extension of the cell envelope on the sessile mother cell (43, 62, 93, 96). Detailed observations of these bacteria suggest that cell growth occurs in three distinct phases and locations: stalk elongation at the junction of the stalk and mother cell, daughter cell elongation at the tip of the stalk, and septum formation within the stalk (43, 62, 64, 93, 96). Notably, bioinformatic analyses of sequenced genomes belonging to the *Rhizobiales* family of the *Alphaproteobacteria*, which include many budding bacteria, revealed an absence of known factors involved in cell elongation such as MreB and PBP2, the monofunctional enzymes required for peptidoglycan synthesis during MreB-dependent elongation, suggesting that these bacteria may employ a novel mode of asymmetric cell growth and division (12, 17, 58). In support of this hypothesis, even stalkless bacteria within the *Rhizobiales* exhibit asymmetric cell division and polar elongation of cell wall material (12, 39). Polar elongation results in a high degree of cellular asymmetry because one daughter cell receives nearly all the newly synthesized cell wall components and outer membrane proteins (Figure 1b).

Polar growth is not restricted to the budding bacteria; it is also the predominant mode of growth in the rod-shaped and filamentous phylum *Actinobacteria*, including *Corynebacterium*, *Mycobacterium*, and *Streptomyces*. In these bacteria, polar elongation requires DivIVA (30, 47, 52), which is broadly conserved among gram-positive bacteria and plays diverse roles in cell growth, cell division, and DNA segregation by functioning as a polar recruitment protein (see 48 for a review of DivIVA functions). In the unicellular actinobacteria such as *Corynebacterium* and *Mycobacterium*, new cell wall growth occurs mostly at the cell poles, and the peptidoglycan along the cylindrical sidewalls is thought to be inert (14, 17). Careful observation of cell elongation in *Mycobacterium* has revealed that polar growth is asymmetric: The old pole elongates more rapidly than the new pole (6, 46).

Furthermore, although each daughter cell inherits an old pole, only one of these poles is already an active growth site. The other old pole, which functioned as a new pole prior to cell division, must initiate new growth, and the corresponding daughter cell grows more slowly than the sibling already primed for growth (6). Consequently, the slower growing daughter exhibits decreased susceptibility to antibiotics that target peptidoglycan synthesis (6). Thus, asymmetric growth results in heterogeneities with respect to cell size and growth rates that can have phenotypic consequences within the bacterial population.

Filamentous actinobacteria belonging to the genus *Streptomyces* display even more marked asymmetry as a result of polar growth. *Streptomyces* species have a complex developmental cycle (see 32 for review) in which spores germinate into germ tubes when nutrients are abundant. The germ tubes grow by tip extension and branching to form vegetative mycelia. The morphology of the mycelia is dictated by precise regulation of apical growth and branching (see 33 for review). DivIVA is part of a multiprotein complex termed the polarisome that guides cell polarity and apical growth (41). In order for branching to occur, an existing polarisome splits; most of the original polarisome continues to promote elongation at the growing tip, whereas a small portion is left behind along the lateral wall (74). Only after the new polarisome remaining on the lateral wall enlarges can new cell wall material be synthesized to initiate branch formation and subsequent growth at the tip. Similar to polar growth in nonfilamentous actinobacteria, cell division during vegetative growth generates two different cell types (31). The apical cell inherits the growing tip and is primed to continue elongation, whereas the subapical cell cannot resume growth until a new lateral branch is established.

Despite a variety of underlying mechanisms, asymmetric synthesis of cell wall material during cell elongation commonly results in the production of heterogeneous populations of cells that vary in features such as cell size, cell fate, and reproductive potential. However, asymmetric growth during elongation is not a prerequisite for generating asymmetric daughter cells. Although *C. crescentus* does not exhibit polar growth (1), this bacterium has become a model system for the study of bacterial asymmetry. The morphological asymmetry of *C. crescentus* is generated by a specialized form of asymmetric growth in which a stalk, a thin extension of the cell wall and membrane, is produced at the old pole at a precise time in the developmental cycle of this bacterium. Every cell division gives rise to two distinct cell types: a stalked cell and a smaller swarmer cell. The sessile stalked cell is primed to commence DNA replication and cell elongation, whereas the swarmer cell is motile by means of a polar flagellum and is not yet competent for DNA replication. Under abundant nutrient conditions, the swarmer cell differentiates into a stalked cell by ejecting the flagellum and synthesizing a stalk. The production of daughter cells with different morphologies and abilities to replicate requires a complex and tightly regulated developmental program (for review see 85). Remarkably, many of the proteins involved in cell cycle regulation are broadly conserved among the *Alphaproteobacteria*, and asymmetric cell division may be an ancestral trait in this group of bacteria (11, 39). The conservation of asymmetric cell division is not linked to a specific mode of growth, as some members of the *Alphaproteobacteria* elongate by peptidoglycan synthesis along the sidewall, whereas others elongate by tip growth.

Conditional Asymmetry

Conditional asymmetry can be triggered by changes in environmental conditions, with endospore formation serving as a classic example. In bacilli and clostridia, nutrient limitation triggers a change in growth patterning to allow endospore production. A key step in successful endospore production is the production of a polar septum. This can be viewed as a symmetry-breaking step because the septum normally forms at mid-cell to produce two morphologically identical cells. How is this dramatic change in growth patterning achieved? In *B. subtilis*, the switch from mid-cell to polar division requires relocalization of the essential division initiation protein FtsZ (8). Under nutrient limitation, FtsZ transiently appears at mid-cell but then reforms into a spiral-like structure and ultimately accumulates near both poles. Either polar Z-ring could form a septum; however, bipolar septum formation is blocked through the coordination of several regulatory proteins (23, 56, 68, 92). The regulated insertion of new peptidoglycan near one pole results in the formation of the polar septum and leads to the production of two morphologically and metabolically distinct cells: the smaller forespore and the larger mother cell. During engulfment, the polar septum curves and eventually surrounds the forespore (for review see 42). The development of the forespore occurs within the mother cell until maturation, when the mother cell lyses and the dormant spore is released into the environment.

How Widespread Is Asymmetry?

Asymmetric growth has evolved multiple times in the bacterial domain (Figure 3). Asymmetric cell elongation occurs in the *Alphaproteobacteria* and the *Actinobacteria* despite their divergent ancestry, strongly suggesting independent origins of asymmetry in these groups (Figure 3). Even within the *Alphaproteobacteria*, multiple asymmetric growth phenotypes occur, including polar cell wall synthesis, dimorphic division, and canonical budding (see Reproductive and Morphological Asymmetry, above). Budding in particular appears to have emerged separately in the hyphomonads (*Hyphomonas*, *Hirschia*) and the rhizobia (*Ancalomicrobium*, *Hyphomicrobium*, *Prosthecomicrobium*, *Rhodomicrobium*, *Rhodopseudomonas*) (Figure 3). This diversity of growth patterns among the *Alphaproteobacteria* suggests that certain taxa may be particularly predisposed to the evolution of asymmetric growth phenotypes.

An increasing number of resources have become available to help address the prevalence of bacterial asymmetry beyond our current understanding. In those cases in which the molecular mechanisms underlying bacterial asymmetry are at least partially understood, bioinformatic approaches exploiting the availability of large numbers of genome sequences allow for rapid assessment of the distribution of genes contributing to particular types of cellular asymmetry. Indeed, as mentioned above, just such an approach suggests an ancient dimorphic life cycle among *Alphaproteobacteria* (11, 39). Although numerous reports of swarmer cell release within the *Alphaproteobacteria* provide support for this notion, a more systematic observation of the morphology and life cycle of diverse *Alphaproteobacteria* is needed.

At present, assessing the prevalence of asymmetric modes of growth bioinformatically is a challenge owing to our limited understanding of their mechanistic basis. Although some

proteins involved in polar growth in the Actinobacteria have been described, homologs of these proteins are not exclusively involved in polar growth, as illustrated by the broad distribution and diverse functions of DivIVA among gram-positive bacteria (48). Furthermore, the mechanism underlying budding/polar growth in the *Alphaproteobacteria* remains undescribed. Finally, although the presence of MreB is often taken as indicator that a bacterium grows by dispersed insertion of peptidoglycan along the lateral cell wall, MreB is present in *Streptomyces* but functions in sporulation rather than cell elongation (59). Thus, the presence or absence of MreB alone does not indicate the mode of elongation in a bacterial cell. A survey of the mode of growth in diverse bacteria is needed to determine the prevalence of asymmetric cell growth. Recent advances in our ability to visualize the sites of peptidoglycan synthesis in living bacterial cells (50, 51) should provide a means for rapid assessment of bacterial growth. Remarkably, labeling of bacteria from environmental samples reveals multiple growth patterns, suggesting that noncanonical modes of growth may be rather common in nature (51).

THE UTILITY OF ASYMMETRY

Aging

The consequences of asymmetric growth extend beyond the simple morphology of a cell and its division process. Asymmetric growth also sets time's arrow in motion for bacterial lineages by establishing a meaningful age for cells, for example, via the age of the old pole in *E. coli* and *B. subtilis* (81, 90). Furthermore, asymmetric inheritance of extant versus newly synthesized macromolecular material (18, 19, 88) implies potentially significant physiological differences between daughter cells born from the same parent. In this section, we consider how these outcomes of asymmetric growth can permit (and perhaps even drive) the evolution of aging in bacteria.

Evolutionary theory of aging—The biology of aging in eukaryotes enjoys a long history of theoretical and experimental study. The widely accepted evolutionary theory of aging first formalized by Medawar (60) and elaborated by Williams (98) relies on the decreasing strength of selection with age to explain the prevalence of alleles with late-acting deleterious effects. Because every individual has a nonzero death rate throughout its lifetime, older individuals will be less abundant even if they never grow frail. The oldest individuals therefore contribute fewer offspring to subsequent generations than do their younger, reproductively mature counterparts, resulting in relaxed selection against deleterious effects occurring late in life (29).

The selective drivers for aging fall into two general categories. The first class involves the introduction of strictly deleterious alleles via mutation (mutation accumulation). Owing to weak selection in older age classes, late-acting deleterious alleles introduced by mutation tend to reach greater equilibrium frequencies compared with early-acting deleterious alleles (75). In the second class, selection favors mutations that enhance individual fitness when young while incurring negative effects late in life (antagonistic pleiotropy). Although selection acts positively to increase the frequency of aging alleles in this case, both antagonistic pleiotropy and deleterious mutation accumulation result from the decreasing

force of selection with age. The resulting decline in vitality with age, termed aging or senescence, typically yields reduced rates of survival and reproduction in old individuals.

Asymmetry, aging, and damage control—Although early work considered the soma–germ line distinction as the basis for the evolution of aging phenotypes, any underlying reproductive asymmetry sufficient for meaningful old and young identity with respect to age-specific deleterious effects should prove sufficient for the evolution of aging (67). Consistent with this prediction, pronounced aging also occurs in the budding yeast *Saccharomyces cerevisiae* (65). Ackermann et al. (4) rationalized that asymmetrically dividing bacteria should also age. Their seminal experiment on *C. crescentus* confirmed that fully developed stalked cells experience a decrease in reproductive output with age, whereas swarmer daughters emerge rejuvenated. Thus, asymmetrically reproducing organisms spanning the eukaryotic and bacterial domains appear susceptible to aging.

Even in bacteria that reproduce by morphologically symmetric modes of division, underlying asymmetry can still arise in the reproductive process. In particular, as discussed earlier, inert material at the poles of rod-shaped cells gives rise to an older, extant pole and a nascent, septal pole upon division. If such inherent asymmetry does indeed establish a physiologically meaningful age for cell poles, then the classical evolutionary theory predicts that aging will occur in such bacteria. Further probing the taxonomic extent of bacterial aging, experiments by Stewart et al. (81) and Veening et al. (90) tracked the persistent old poles of *E. coli* and *B. subtilis*, respectively, across multiple generations and measured vegetative growth rates. As observed for *C. crescentus*, significant aging occurred in these bacteria despite the outward apparent symmetry of their division processes. Indeed, these results echo observations of aging in the fission yeast *Schizosaccharomyces pombe*, whereby careful maintenance of cells that had repeatedly inherited the old pole at cell division revealed a drastic increase in mortality with age in this eukaryote despite the production of daughter cells with essentially identical morphologies (7). These findings suggest that aging may be a universal phenomenon among cellular organisms.

The ubiquity of aging should perhaps come as no surprise, given the asymmetries that arise even in morphologically symmetric modes of division. But whereas the classical evolutionary theory of aging explains aging in the presence of reproductive asymmetry, it offers no explanation for the origin of asymmetry itself. How, then, does asymmetry arise in bacteria? Is there a fundamental driving force for the emergence and persistence of asymmetric modes of growth and reproduction?

A relatively recent theory of aging suggests that the asymmetric inheritance of accumulated cellular damage can provide a selective advantage (2, 13, 26, 28). Much like natural selection against deleterious mutations requires the presence of competing alleles, selection to purge damage such as misfolded proteins from bacterial populations requires differences in the amount of damage found in individual cells. By biasing damage segregation into one cell upon division, a relatively damage-free daughter enjoys higher fitness at the expense of the aging cell, thereby increasing the overall damage tolerance of the population (Figure 4). Detailed analysis of aging in *E. coli* confirms a progressive (but ultimately limited) accumulation of damage and corresponding reproductive decline in aging cells (55, 72, 73).

Although this theory is motivated by controlling damage rather than the more general classical theory that considers phenotypic effects more generally, the damage control theory serves as a special case of antagonistic pleiotropy, as damage clearance in young cells trades off for damage loading in older counterparts. Making no assumptions about the initial level of reproductive asymmetry, this hypothesis instead provides a mechanism that could drive the simultaneous evolution of asymmetric reproduction and aging via natural selection for asymmetric damage inheritance.

Looking ahead: experimental verification of aging models—Numerous unresolved questions surround the evolution and physiological properties of aging in bacteria. First and foremost, what mechanisms mediate the aging process? Segregation of misfolded protein aggregates into aging cells may explain at least some aging effects in *E. coli* (55), although visualization of such aggregates via fluorescence microscopy may introduce other complications by creating artificial damage via phototoxicity or through the introduction of potentially toxic fluorescent protein fusions (73). Do protein aggregates correlate with aging in other model bacteria such as *C. crescentus* and *B. subtilis*? Protein oxidative damage segregates preferentially into aging yeast mother cells (5); do aging bacteria exhibit a similar bias in the allocation of damaged proteins or other macromolecules? Moreover, the mechanism by which cells drive biased segregation of protein aggregates (and any other aging factors) remains undetermined. Mutations that disrupt segregation bias should help both to identify mechanisms responsible for bias and to establish the role of the affected macromolecules in the aging process; mutations reducing segregation bias should alleviate aging, whereas mutations enhancing bias should accelerate it. The phenotypes of these mutants will also provide insight into the physiological consequences of aging at the single-cell and population levels. Such experiments into the bacterial aging apparatus will elucidate not only how bacteria age, but also the utility of bacterial models in understanding the eukaryotic aging process.

Future research should also seek to determine the prevalence of aging among bacteria. Although current observations of bacterial aging span a broad phylogenetic range, several candidate organisms with distinct modes of reproduction merit additional research. Unipolar growth in *Agrobacterium tumefaciens* leaves extant peptidoglycan and outer membrane proteins in the daughter cell bearing the old pole upon division, with essentially completely de novo synthesis of these materials in the other daughter (12) (Figure 1b). Other bacteria, such as those from the genera *Hyphomonas* and *Hyphomicrobium*, reproduce by pronounced unipolar budding (63). Is damage to the cell wall and outer membrane proteins stably inherited by the mother cell in these diverse bacteria with unipolar growth? Does the mother cell retain other components such as inclusion bodies, or even certain diffusible proteins, upon division? We suspect that the relatively extreme degree of asymmetry in *A. tumefaciens* and canonical budding bacteria should yield rapid aging in these populations.

Whereas bacteria with marked asymmetries are likely candidates for strong aging effects, species without obvious signatures discriminating young from old cells provide a compelling test of the true prevalence of aging. Unlike their rod-shaped counterparts, many cocci exhibit no obvious polarity, and *Staphylococcus aureus* in particular divides via orthogonally oriented, equatorial septa (87). Without a clear bias in the inheritance of extant

material by specific cells, the mode of division may preclude aging in such bacteria. However, if natural selection does indeed tend to favor asymmetric damage allocation in all bacteria, then perhaps inherent but unidentified asymmetries (and hence aging) exist in these species. Asymmetry need not extend beyond damage itself in order to satisfy the variable damage load favored under the damage control theory of aging.

Beyond comparative approaches, the proposed functional link between asymmetry, damage allocation, and aging lends itself to direct experimental tests. Previous work has already identified numerous mutations that modulate cell symmetry phenotypes, particularly in the developmental model *C. crescentus* (16). Do disruptions in native developmental asymmetry and cell fate determinants interfere with the aging process in *C. crescentus*? Such mutations could also provide a useful test of the fundamental adaptive argument behind the damage control theory of aging, as any disruption of aging mechanisms should result in a concomitant decrease in the capacity of the cell population to tolerate induced damage. Similarly, experimental evolution under high rates of damage accumulation should select for strong reproductive asymmetry, whereas low rates of damage may lift selection for aging and facilitate the erosion of asymmetry. Notably, experimental evolution of *C. crescentus* by repeated batch culture transfer resulted in the frequent emergence of slowly aging mutants, although the symmetry phenotypes of these strains were not reported (3). It seems possible that lab culture conditions afford lower rates of damage than the natural environment of *C. crescentus*, and additional experiments with controlled rates of damage and thorough characterization of experimentally evolved strains can provide a rigorous test of aging theories.

Adaptive Variation

Reproductive asymmetry factors critically into bacterial evolutionary ecology. Asymmetric division generates distinct cell types that may help bacteria exploit patchy, variable, and unpredictable environments more effectively. Such heterogeneous environments favor phenotypic variability, which populations can generate via genetic variation or by varying the phenotypes achieved through a shared genotype (61). The particular spatial and temporal patterns of environmental variation determine how organisms can best respond to challenges, but phenotypic variation from a single genotype facilitates a relatively quick and directed response to environmental fluctuations both within and between generations.

In cases in which environmental changes can be rapidly detected and transduced into phenotypic responses, phenotypes can vary along environmental gradients. This phenomenon, termed phenotypic plasticity, applies to numerous, well-described aspects of bacterial physiology and development. Among the most familiar are physiological responses to stress and nutrient changes that may not rely on cellular asymmetry (37, 82). Sporulation, on the other hand, is one example that relies fundamentally on asymmetric growth and division. Sporulation provides adaptive variation in response to cues indicating environmental deterioration, in which asymmetric cell division produces durable spores that can survive adverse conditions (27). Bacteria capable of sporulation thus probabilistically generate cell types to match the current environmental context: more spores in lean times or more vegetative cells in times of plenty.

In other cases, environmental shifts may occur too rapidly or unpredictably to favor the generation of phenotypic variation on demand. Even for populations with high average fitness over time, bottlenecks resulting from an occasional poor phenotypic fit to a fluctuating environment can disproportionately harm long-term fitness (53). Instead, the production of multiple phenotypes can help ensure a consistent, moderate fit to the environment by some portion of the population. This bet-hedging strategy can maximize the long-term fitness of the population in unpredictable environments (61).

The hardwired developmental program in *C. crescentus* and phylogenetically related bacteria (69, 79) may provide a bet-hedging strategy for contending with unpredictable environmental variation. In particular, the swarmer and stalked cell types in *C. crescentus* facilitate exploitation of patchy resources. Stalked cells attach to surfaces via an adhesive holdfast situated at the stalk tip. On the one hand, the resulting permanent attachment permits stalked cells to take advantage of locally suitable environments, including established biofilms, while preventing washout into potentially unsuitable habitat patches (25). On the other hand, swarmer cells permit colonization of new habitat patches but necessarily assume some degree of risk because some swarmer cells disperse away from the habitat patch of the stalked parents. This dimorphic life cycle thus potentially provides a mode of bet hedging through the deterministic production of both sessile stalked cells and motile swarmer cells within a clonal *C. crescentus* population. Notably, dispersal is not left entirely to chance; extracellular DNA release by mature and presumably deteriorating biofilms specifically inhibits swarmer cell settling (9). This phenomenon thus affords some degree of environmentally responsive tuning in an otherwise rigid developmental strategy.

This proposed ecological role of the bacterial developmental cell cycle lends itself to direct experimental validation. If bet hedging via the balance of sessile and dispersing cell types indeed affords *C. crescentus* an advantage in patchy environments, wild-type cells should outcompete dispersal- and colonization-deficient types (e.g., holdfast and motility mutants) in artificially generated, spatially structured environments with patchy resource availability. Conversely, spatially unstructured environments should favor mutants that bypass the developmental process, particularly in light of the replication initiation delay observed in wild-type swarmer cells prior to differentiation. Indeed, simulations of competition between these life-history strategies confirm a potential advantage to the dimorphic life cycle that is specific to spatiotemporally variable environments (Figure 5).

CONCLUDING REMARKS AND FUTURE ISSUES

Asymmetry in bacteria takes on numerous forms, with even simple, morphologically symmetric modes of growth giving rise to inherent asymmetries. An appreciation for the prevalence of bacterial asymmetry has developed relatively recently within the microbiology community, with much still to be determined regarding its taxonomic extent and mechanistic basis. A much greater challenge lies ahead in carefully describing the ecology and evolution of asymmetry—not merely its consequences, but also the selective basis for the initial emergence of asymmetry. Although we have reviewed certain evolutionary forces that may help explain asymmetric growth phenotypes, these are admittedly speculative arguments that enjoy frequent mention in article discussion sections but little experimental support. Future

work should seek to test such hypotheses by direct experimentation in order to better resolve the ultimate causes and consequences of widely observed asymmetric bacterial growth.

Acknowledgments

D.T.K. was supported by NIH Research Service Award GM083581. K.C.H. was supported by NSF CAREER Award number 1149328. Y.V.B. was supported by NIH grants GM051986 and GM102841 and by a grant from the Indiana METACyt Initiative of Indiana University. D.T.K. and P.J.B.B. contributed equally to this review.

Glossary

Morphological asymmetry	cell division that produces two daughter cells with distinct shapes
Aging (senescence)	a loss of vitality with age, manifested through increasing mortality or decreasing reproductive output
Reproductive asymmetry	cell division that produces daughter cells with underlying asymmetry, which may or may not include obvious morphological asymmetry
MreB	a bacterial actin homolog that serves as a determinant of cell shape and coordinates the sites of peptidoglycan synthesis
DivIVA	a coiled-coil protein that accumulates at membrane regions of higher curvature and serves as a cell polarity determinant
Conditional asymmetry	cellular asymmetry that results from a response to changing environmental conditions
Endospore	metabolically dormant and environmentally resistant cell that is morphologically distinct from the mother cell
FtsZ	a bacterial tubulin homolog that forms a constricting ring and recruits additional proteins to the division plane, enabling cell division
Mutation accumulation	in aging theory, the evolution of alleles that decrease fitness in old age; results from weakened selection in older individuals
Antagonistic pleiotropy	opposing, age-dependent effects of alleles that enhance fitness early in life but decrease fitness later in life
Phenotypic plasticity	the capacity of a single genotype to generate different phenotypes in response to environmental variation

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SUMMARY POINTS

1. Bacterial growth patterning is required to maintain cell shape and generate asymmetry. Different growth patterns result in varying degrees of asymmetry.
2. Conditional triggering of bacterial asymmetry enables endospore formation and allows survival in adverse conditions.
3. Asymmetric division establishes a meaningful age for cells, thereby enabling the evolution of age-specific phenotypes that dispose populations to aging.
4. Asymmetric distribution of damage in dividing cells can cause aging by loading damage into “old” cells while rejuvenating their counterparts. This process provides a possible adaptive solution to managing cellular damage, and it is thus a plausible evolutionary force driving the emergence of asymmetry.
5. Reproductive asymmetries generate phenotypic variation that can help populations to contend with environmental change.

FUTURE ISSUES

1. Findings of polar growth in taxonomically diverse bacteria suggest that a broad set of species may share this pattern of growth, but many details of polar growth processes remain to be described. Additional work should identify polar growth mechanisms and determine whether diverse bacteria employ common or unique polar growth machinery.
2. It remains uncertain how widespread polar growth is among bacteria. A survey of bacterial growth using small molecules that allow rapid visualization of the site of peptidoglycan synthesis (50, 51) is now a viable option.
3. Asymmetries generated by growth patterning have been almost exclusively studied in rod-shaped bacteria. Observation and computational modeling of growth in bacteria with diverse morphologies should reveal the extent of cellular asymmetry.
4. Recent theory suggests an intimate link between reproductive asymmetry and aging as a means of damage control. In order to test this theory, future studies should measure aging rates in bacteria with varying reproductive asymmetry. In addition, experimental evolution of bacteria exposed to varying rates of damage should examine whether exposure to damage actively selects for the emergence and persistence of division asymmetry.

Figure 1.

Asymmetry generated during cell growth. (a) During dispersed cell elongation, as in *Escherichia coli*, new cell material is inserted into the existing network along the lateral sidewall, generating the active growth zone (yellow). The yellow color reflects the mixture of newer and older patches of wall material in the cylindrical sidewall. The cell poles are devoid of new peptidoglycan synthesis, and age during elongation. New peptidoglycan (red) is synthesized at the mid-cell to enable cell division. Following cell division, each daughter cell contains a new pole and an old pole, giving rise to cellular asymmetry. (b) During polar elongation, as in *Agrobacterium tumefaciens*, new cell wall material is inserted into existing peptidoglycan at the new pole, comprising the active growth zone (red). The old cell pole and cell body are inert, generating a gradient of cell material from old to new. Following elongation, new peptidoglycan (red) is synthesized at the mid-cell to enable cell division. After cell division, one daughter cell inherits newer cell material (orange), whereas the other daughter cell contains old material (blue). Each daughter cell inherits a new pole (red) generated by cell division that is primed for a subsequent round of elongation.

Figure 2.

Maintenance of cell shape requires growth patterning that can lead to inherent asymmetries in cell wall architecture and surface patterning. (a) Computational modeling predicts that random insertion of peptidoglycan would lead to rapid loss of cell shape, resulting in bending, cell width fluctuations, and the formation of large pores in the cell wall. (b) In contrast, growth from a pattern of helical segments maintains the rod-like shape. Blue spheres represent fiducial markers labeling a particular site on the cell wall. The model predicts that the cell wall will develop a handedness opposite that of the helical pattern (*inset*) and that cells will twist with the same handedness as the helical pattern. (c) Wild-type *Escherichia coli* cells, treated with cephalixin to inhibit cell division, always exhibit a left-handed twist during growth, evidenced by the opposite rotation of the beads bound to each end, demonstrating that the two ends of the cell are rotationally asymmetric with respect to each other. (d) Fluorescent image of an *E. coli* colony grown from a mixture of cells labeled with different fluorescent proteins. The colony spatially segregates into “sectors” expressing only one of the two neutral markers. The boundaries between the sectors exhibit a tendency to curve in a clockwise direction, indicating that colonies of cells may grow with a preferred handedness and that cellular asymmetries can be transduced to multicellular communities. Black circles indicate the colony boundaries at 12-h time points. Panels *a–d* modified from References 34, 89, 94, and 38, respectively. Panel *a*, copyright 2007, National Academy of Sciences, USA.

Figure 3.

Phylogeny of asymmetric growth. Colored labels indicate species with known asymmetric growth patterns, with sites of cell wall growth colored as follows: budding, green; polar/tip growth, red; stalk elongation, purple; sporulation, blue. Topology reflects maximum-likelihood reconstruction of *gyrA* alleles using the JTT protein substitution matrix and a four-category gamma-distributed model of rate variation plus an additional invariant category (80).

Figure 4.

A simplified model of aging by asymmetric damage segregation and accumulation. (a) Symmetric damage segregation yields identical damage levels in both daughter cells. (b) Highly asymmetric damage segregation shunts all damage into one daughter cell, leaving the other daughter free of damage. Both populations start with a single, undamaged cell and experience a net damage increase at the same fixed rate between divisions. This simple model considers no effects of damage until a fatal dose is reached, at which point cells stop dividing altogether. In the case of symmetric damage allocation, each generation experiences an increase in the damage level by one-fourth of the fatal threshold level in all cells. With asymmetric damage segregation, one cell from each daughter pair receives one-half of a fatal damage dose each generation, resulting in rapid deterioration of one daughter (the aging cell) and rejuvenation of the other. After several generations, the symmetric population dies out completely, whereas asymmetric damage segregation ensures continued exponential population expansion.

Figure 5.

Simulations of ecological competition demonstrate that a life cycle that includes a mixed strategy of attachment and dispersal is more fit in a fluctuating environment. Individual-based stochastic simulations modeled competition on a lattice of environmental patches. Three different strategies compete: a surface-attached cell with minimal dispersal (*blue*), a motile cell with no attachment (*red*), and a mixed-strategy cell that is born motile and later differentiates and attaches (*green*). White regions remain unoccupied. The mixed strategy mimics the dimorphic bacterium *Caulobacter crescentus* and incurs a reproductive rate cost relative to that of other strategies, as it achieves reproductive ability only upon development into the attached form. (*a*)

Simulation of a stable environment with constant resource availability in all patches; in 100 simulations, the mixed strategy eventually suffered extinction in all cases. (*b*) Simulation of a patchy environment in which habitat patches occasionally switch between availability and absence of resources; the mixed strategy achieved fixation in 99 out of 100 simulations. Simulations used a 4×4 patch lattice with periodic boundary conditions. Dispersal events occur to one of the four adjacent patches, selected at random. Motile cells disperse at a rate of 0.5 h^{-1} , and attached cells disperse at a rate of 0.001 h^{-1} . The mortality rate was 0.01 h^{-1} in patches with resources and 0.05 h^{-1} in the absence of resources. Cell division occurred at a rate of 0.1 h^{-1} , scaled according to a logistic model (40) with a carrying capacity of 100 cells per patch; mixed-strategy cells switch to the attached, reproductive state 3 h after birth. In panel *b*, patches switch from resource absence to availability at a rate of 0.03 h^{-1} and in the reverse direction at 0.015 h^{-1} . Initial seeding assigned 400 individuals of each cell type randomly across the lattice. Simulations were updated at 1-h intervals, with birth, death, and dispersal events occurring randomly with a probability determined by the corresponding rate. The metapopulation lattice model takes its general form from Reference 84. Parameterization of birth and death rates was selected to conform approximately to field observations of naturally occurring *Caulobacter* species (70).