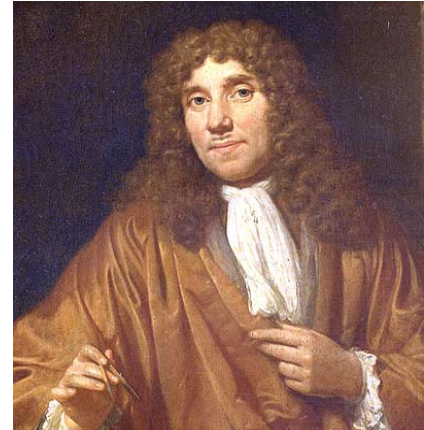


Shape Matters: Why bacteria care how they look

Author: Dr. Kristen Kerksiek
August 12, 2009

In 1683 a particularly curious Dutchman cleaned between his teeth with a toothpick and decided to take a look at the “white matter” underneath his homemade microscope. What Antony van Leeuwenhoek saw and documented was a sensation. In one of the first observations of living bacteria ever recorded, he described at least five different types of tiny “animalcules”: a motile bacillus, a micrococcus and a spirochete as well as curved and thread-like bacteria (most likely *Selenomonas sputigena* and *Leptothrix buccalis*, respectively) - a lively mix representing just a few of the 300+ species that call the human mouth home. (Time to floss and brush again?) With his simple microscope, van Leeuwenhoek not only discovered bacteria, he also documented that they can differ greatly in shape.



Antony van Leeuwenhoek (1632-1723), built simple microscopes that enabled him to magnify objects – clearly and brightly - greater than 250x.

In the mean time we all know that bacteria come in different shapes. And the bacterial repertoire extends far beyond simple rods (bacilli), spheres (cocci) and spirals (spirochetes). In the 325 years since van Leeuwenhoek opened the field of bacteriology, bacteria with a vast array of bizarre and unexpected forms have been discovered: they can be curved, triangular or pointed; they can be shaped like teardrops, lemons, coins or even postage stamps; they can form chains, filaments or clusters; they can grow strange and irregular extensions (to mention just a few possibilities). Yet few scientists have occupied themselves with the question that would seem to logically follow: Why?

Who came first, the rods or the cocci?

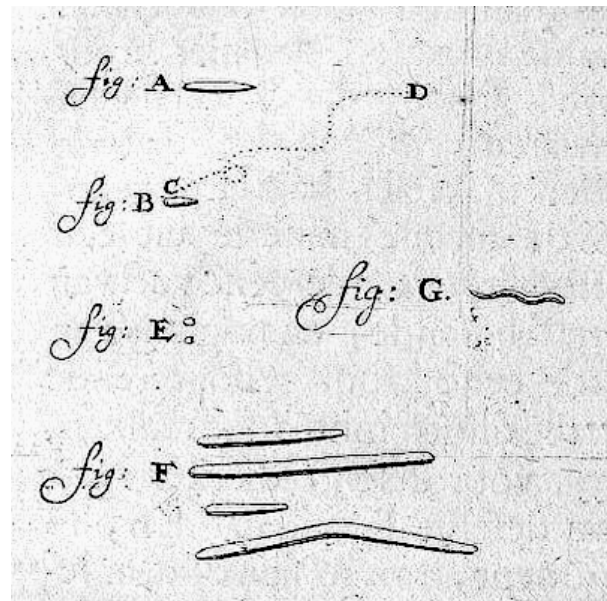
If it came down to pure simplicity, we might assume that the first bacterium was a coccus: without any internal structure, a membranous bag suspended in liquid will assume the shape of a sphere. However, phylogenetic studies performed over the last decade indicate that the first bacteria were rod-shaped; cocci appear to be a “dead-end” shape that has simply arisen many times independently.

The *Why* Question(s)

Why do bacteria have different shapes? Is it an accident or adaptation? A fluke of nature or a selective advantage? Are the cell walls just there to hold important stuff together, or does shape have a specific function? It's a difficult question to address experimentally, but a number of arguments support the view that bacteria take their shape very seriously. For one, although many different bacterial shapes exist, species within the same genus tend to stick to one form – presumably the one that provides the most advantages. On the other hand, prokaryotes occupying entirely different branches of the Tree of Life – Bacteria and Archaea – have evolved very similar morphologies. There must be something special about rods, spheres & Co. that makes these specific shapes so popular in the single-celled world.

Why does a particular bacterium have a specific shape? What selective advantages do different bacterial forms offer? Only recently have bacteriologists started probing their favorite bugs for answers to this question. One of the researchers leading the inquisition is Kevin Young from the University of Arkansas for Medical Sciences. “Most of us have spent many years working on bacteria without ever thinking of why they have shapes,” says Young. “The idea of shape as something useful and important (at least in bacteria) is just beginning to take flight as a scientific specialty.”

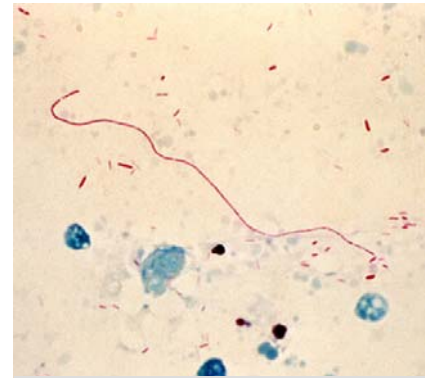
The answer will be complex. Bacterial morphology is affected by a combination of selective pressures - access to nutrients, cell division, attachment/dispersal, predation and motility (among others). Among these different factors, our understanding of the relationship between motility and cell shape is most complete; for example, highly motile bacteria are usually rods with a specific (optimal) shape and size, and movement through viscous fluids seems to favor a spiral shape. But since multiple selective forces are always in play, there is – at the moment – no way to predict cell shape based on the environment or *vice versa*.



van Leeuwenhoek described (and illustrated) his observations of bacteria in a letter sent to the Royal Society of London in September, 1683.

Masters of change

We tend to think of bacteria as having fixed morphologies. We even name them after their shape (*e.g.* Streptococcus). But environments aren't static, and neither is bacterial shape. Some bacteria – including a number of human pathogens – change their form dramatically as they go through different development pathways. For example at least eight different morphological forms are adopted by *Legionella pneumophila* during its developmental cycle. *Helicobacter pylori* is usually identified as short spiral rods but can appear as corkscrews (filaments) in biopsy specimens. And an impressive study of uropathogenic *Escherichia coli* identified four distinct morphological forms as the bacteria infected bladder epithelial cells: nonmotile rods, cocci, motile rods and filaments. Does shape change have anything to do with pathogenesis? For fungi we know it does. Most pathogenic fungi are dimorphic, with yeast and hyphal (filamentous) stages, and only one form is pathogenic. The study of bacterial morphology and virulence is still in its infancy, but at least for *E. coli* shape change seems to play a central role during infection.



Legionella pneumophila, a causative agent of Legionnaires' disease, can take on different shapes (here singular, paired and filamentous in red) © CDC

The role of filamentation in bacterial survival is drawing particular attention. Filaments form when bacteria continue to grow but don't divide, and they can reach lengths 10–50 times that of the corresponding rods. *E. coli* filaments – like the filamentous (hyphal) form of the fungus *Candida albicans* – are resistant to phagocytosis, enabling the bacteria to persist. Filamentous forms of other pathogenic bacteria – *Haemophilus influenzae*, *Legionella pneumophila*, *Mycobacterium tuberculosis* and *Salmonella enterica* among others – have also been observed and may be associated with increased survival. And filamentation of *Burkholderia pseudomallei* (the causative agent of melioidosis) results in resistance to antibiotics at a concentration that kills the bacillary form.



E. coli are usually rods ~2 µm in length. Uropathogenic strains (causing urinary tract infections) can form filaments that reach a length of 70 µm. © HZI

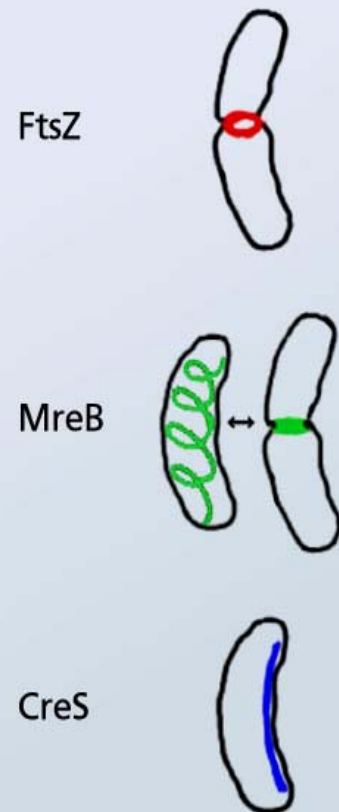
Shape – and shape change – seem to be a key part of the survival strategy of many pathogenic bacteria. It's a factor that hasn't been considered in studies of bacterial pathogenesis but may be of crucial importance for the understanding of – and treatment of – bacterial diseases. For treatment of *C. albicans*, an opportunistic pathogen that is increasingly resistant to standard antifungal therapies, anti-filamentation agents are already being developed. Drugs targeting filamentation might also be an alternative therapeutic strategy for bacterial infections. As the effectiveness of standard antibiotics continues to wane and the search for new antimicrobials becomes more critical, it may pay to remember bacterial shape: they take it very seriously, and we just may be able to use that against them.

The *How* Question

A meshwork of peptidoglycan (also known as murein) forms the cell wall of nearly all bacteria. It keeps the bacterial innards in place, resisting osmotic pressure to prevent rupture and influencing cell shape. But since the structure of peptidoglycan is similar in bacteria with vastly different forms, it can't be the determining force in bacterial morphology. How do bacteria keep a specific shape?

There must be a scaffold of sorts to support the peptidoglycan shell, and researchers are finding that recently described components of a prokaryotic cytoskeleton serve exactly this function. For example, the actin homologue MreB, which is found in almost all non-spherical bacteria, controls cell diameter and rod morphology by a mechanism that seems to involve control of the enzymes that synthesize and organize peptidoglycan. FtsZ, a tubulin homologue responsible for cell division, may also be involved in shaping cells by managing peptidoglycan-synthesizing enzymes. Another cytoskeletal homologue – crescentin (CreS), the prokaryotic version of intermediate filaments – is the difference between run-of-the-mill rods and crescent-shaped cells.

(For more information about the *How* of bacterial shape, check out the reviews by Matthew Cabeen and Christine Jacobs-Wagner, Kevin Young (Bacterial Shape) and Zemer Gital listed below).



Localization of the homologues of tubulin (FtsZ), actin (MreB) and intermediate filaments (Cres) as detected in *Caulobacter crescentus*. © Tim Vickers

References and additional reading:

A website with extensive information – and documentation – about Antony van Leeuwenhoek:
www.euronet.nl/users/warnar/leeuwenhoek.html

A concise review for an overview of the field:

- Young, K.D. Bacterial morphology: why have different shapes? *Curr. Opin. Microbiol.* (2007) 10: 596–600. doi:10.1016/j.mib.2007.09.009.
<http://dx.doi.org/10.1016/j.mib.2007.09.009> Free article at PubMed Central
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=17981076>

A comprehensive (but very readable) review covering various selective pressures:

- Young, K.D. The selective value of bacterial shape. *Microbiol. Mol. Biol. Rev.* (2006) 660–703. doi:10.1128/MMBR.00001-06 <http://dx.doi.org/10.1128/MMBR.00001-06> (free full text)

Reviews focusing on the *how* question of bacterial shape:

- Cabeen, M.T. and Jacobs-Wagner, C. Skin and bones: the bacterial cytoskeleton, cell wall, and cell morphogenesis. *J. Cell. Biol.* (2007) 179: 381–387. doi: 10.1083/jcb.200708001
<http://dx.doi.org/10.1083/jcb.200708001> (free full text)
- Gitai, Z. The new bacterial cell biology: Moving parts and subcellular architecture. *Cell* (2005) 120: 577–586. doi: 10.1016/j.cell.2005.02.026
<http://dx.doi.org/10.1016/j.cell.2005.02.026>
- Young, K.D. Bacterial shape. *Mol. Microbiol.* (2003) 49: 571–580. free full text
<http://www3.interscience.wiley.com/journal/118845516/abstract> (Erratum in: *Mol Microbiol.* 2003 50: 723. free full text <http://www3.interscience.wiley.com/cgi-bin/fulltext/118845645/HTMLSTART>)

A discussion of the role of stress-induced filamentation in bacterial survival:

- Justice, S.S., Hunstad, D.A., Cegelski, L. and Hultgren, S.J. Morphological plasticity as a bacterial survival strategy. *Nat. Rev. Microbiol.* (2008) 6: 162–168. doi:10.1038/nrmicro1820
<http://dx.doi.org/10.1038/nrmicro1820>

Research articles:

- Justice, S.S. et al. Differentiation and developmental pathways of uropathogenic *Escherichia coli* in urinary tract pathogenesis. *Proc. Nat. Acad. Sci. USA* (2004) 5: 1333–1338. doi:10.1073/pnas.0308125100 <http://dx.doi.org/10.1073/pnas.0308125100> (free full text)
- Chen, K. et al. Modified virulence of antibiotic-induced *Burkholderia pseudomallei* filaments. *Antimicrob. Agents Chemother.* (2005) 49: 1002–1009. doi:10.1128/AAC.49.3.1002-1009.2005 <http://dx.doi.org/10.1128/AAC.49.3.1002-1009.2005> (free full text)
- Saville, S.P. et al. Inhibition of filamentation can be used to treat disseminated candidiasis. *Antimicrob. Agents Chemother.* (2006) 50: 3312–3316. doi:10.1128/AAC.49.3.1002-1009.2005 <http://dx.doi.org/10.1128/AAC.49.3.1002-1009.2005> (free full text)