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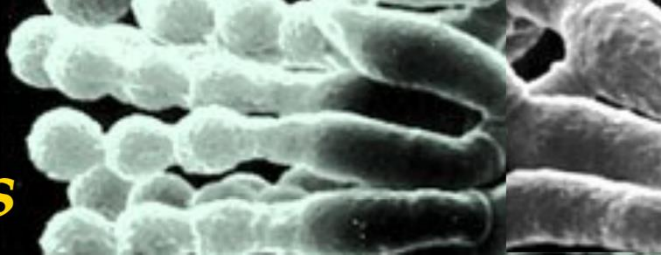

A random walk through life

Judy Armitage

I was about 16 when I first looked at a drop of pond water through a microscope. What I saw changed the direction of my life. I watched a complex world of different, tiny, organisms of different sizes, shapes and colours, all apparently going about their business, oblivious of the macroscopic world I was part of. Up to that point, I was unsure of my own focus. I was at a small, girl's grammar school in Yorkshire where few pupils went to university and even fewer to do science. I made two decisions, to study Microbiology as a degree, even though I had no idea whether it would lead to any sort of a job, and to go to London to take that degree, rather than the expected northern university - after all it was 1969.

I went to University College London and had an amazing time. Not only was the course varied, engaging and taught by giants in their field (although I often didn't realise it until much later!) there was exotic food, theatre, clubs *etc*. and I took full advantage of everything. At the end of my degree I was offered a PhD place, funded by the then Science Research Council (SRC). The SRC eventually became the BBSRC (Biotechnology and Biological Sciences Research Council), which has more or less funded the whole of my scientific career.

My PhD, jointly supervised by Robin Rowbury and David Smith, was to study the biochemical and morphological changes that occurred when the bacterium *Proteus mirabilis* was inoculated onto a surface. On a surface it initially grows as single short rods, but when the density reaches a critical number, the cells stop dividing and become long filaments. They sprout massive numbers of flagella and then move en-masse over the surface for a centimetre or so before dividing back into short rods and repeating the process every few hours until the petri dish is covered in rings of bacteria.

While I was doing my PhD, researchers in the US showed that bacterial flagella are completely different to flagella on eukaryotes. The filament is made of a polymer of a single protein, flagellin, which forms a rigid corkscrew. If you make an antibody to the flagellin protein and use it to coat a glass slide, you can tie a bacterium to the slide by its flagellum. Surprisingly the tethered bacterium rotates smoothly, like holding a submarine by its propeller and watching the submarine rotate. This strongly suggested that the bacterial motor is a rotary motor embedded in the cell membrane. The cell body switched between clockwise (CW) and counter-clockwise (CCW) rotation, and the frequency of switching changed if the cell was given a pulse of, for example, an amino acid, but after a few seconds returned to the pre-stimulus switching *i.e.* it sensed a stimulus, responded and then adapted.

Bacteria are too small to sense a spatial gradient and we now know that they swim about their environment at speeds of up to 100 µm/s using helical flagella rotated using the flow of ions, usually protons, through the motor. The motor rotates in either CCW or CW directions and the frequency of switching

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depends on chemosensory signals from the environment activating receptors. This produces a signal that binds to the motor to increase CW rotation. The increased switching when heading in an unfavourable direction or decrease if the direction is favourable biases the random swimming pattern to a better environment for growth. The system needs a memory of the recent past and the ability to reset the receptors. Using this chemosensory system most bacteria can respond to a change of about 1% in the background concentrations of a wide range of stimuli, over a background range from nanomolar to millimolar.

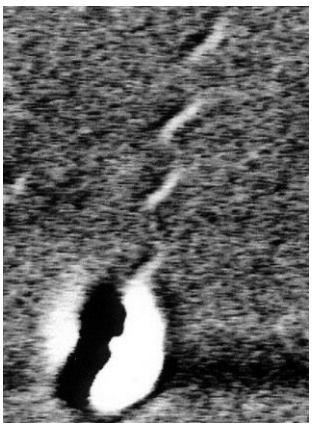

Figure 1. Electron Micrograph of *Rhodobacter sphaeroides* showing the single flagellum.

Where do I come into this story? At the end of my PhD I had the opportunity to continue my research, initially funded by a Departmental Fellowship and then a Lister Institute Research Fellowship. In the lab next to mine Mike Evans was working on the bioenergetics of photosynthesis using a bacterium *Rhodobacter sphaeroides* (**Figure 1**). This species can grow as an aerobe or as an anaerobic phototroph. When growing aerobically it swims towards oxygen, but as a phototroph it is repelled by oxygen but attracted to light. I set out to answer how the bacterium "decides" to be attracted or repelled by oxygen. I have spent the subsequent 35+ years investigating the workings of the tiny nanomachine that is the flagellar motor and its control by environmental signals (**Figure 2**).

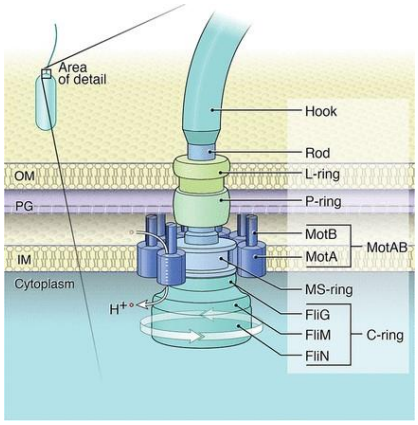

Figure 2. Cartoon of the structure of the transmembrane flagellar motor. OM-outer membrane, PG-peptidoglycan, IM-inner membrane. FliM and FliN are sites of interaction of chemosensory signals and FliG is the rotor ring. As ions flow through the stator complex, MotA and MotB, the electrostatic interaction with FliG changes, causing rotation of the rotor, the MS ring, the rod and thus the helical hook and filament. The L and P rings form a 'grommet' through which the rod threads. Picture modified from Baker AE, O'Toole GA. 2017. Image credit: William Scavone.

During that period I trained over 40 graduate students and employed the same number of postdoctoral researchers. I have had the pleasure of working in interdisciplinary teams, with physicists and mathematicians. We have shown that while the static images of the flagellar motor show something like an electric motor, it is in fact constantly remodelling. Different protein components can swap in and out while the motor turns, adding new or different parts to cope with different environments, whether it is a change in the prevailing ions or the load on the motor. We have shown that while a bacterium like *Escherichia coli*, the workhorse of bacteriology, has hundreds of copies of only four types of chemoreceptor, all in the membrane, other species have tens of different types of receptor, with some in the cytoplasm, allowing the bacterium to sense its metabolic needs and balance its response to external signals. A swimming bacterium needs to have chemoreceptors to compete

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therefore, when it divides, each daughter needs to inherit a cluster of receptors. Membrane receptors are located at the poles of the bacterial cell, and therefore each daughter gets a pole with a cluster of receptors. Cytoplasmic receptors are more difficult. We showed that they form clusters that loosely associate with the surface of the chromosome and, when the cell duplicates its chromosome upon division the cluster splits, one half piggy-backing on a chromosome to end up in each daughter cell. It is now understood that other, unrelated, proteins can hitch a ride on duplicating chromosomes to ensure segregation into daughter cells.

In the 40+ years since starting this adventure our understanding of the world of bacteria has been transformed, from a suggested few thousand species to tens of millions (at least). We now know they live in complex interacting communities and, while a few can make us ill, some very ill, the majority are essential for the health of the planet and everything that lives on it. We are entering a new era where we will need new approaches and ideas to understand these dynamic interacting communities and their place in the world.

REFERENCE: Baker AE, O'Toole GA. (2017). Bacteria, rev your engines: stator dynamics regulate flagellar motility. *J Bacteriol* 199: 1-8.

AUTHOR PROFILE

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