shaped by their activity — both intrinsic and environment induced — and how these networks support the brain computations that underlie externally observable behavior.

The second major challenge facing our young field will be applying the basic discoveries we are making to important real-world issues. It is a widely held view that understanding the brain bases of cognitive and behavioral development has potential for application to clinical issues, educational strategies, and societal policies. With a few notable exceptions, however, this still remains largely a promissory note.

What do you think is the future of scientific publication? As a long-standing journal editor, I get to see both sides of the publication process. The changes currently occurring in scientific publishing are probably the most rapid and dramatic since the original founding of the oldest scientific journals. Some of these changes are clearly positive, as web publication allows a move towards a more flexible and multi-dimensional version of the classic scientific paper: a new form of publication in which different levels of detail of information can be accessed and presented at the press of a key. Further, I suspect that web-publication will also lead to more creative ways to present complex data sets, as we move away from the limitations of the printed page. However, with rapid change there are also some potential negatives. Foremost among these concerns is the increasing difficulty in sorting out the wheat from chaff with the plethora of new web journals. While scientists can apply their critical faculties to papers post-publication, journalists often do not have the necessary background and assume that all journals have the same values and standards. Another concern is that a paradoxical side-effect of some search-engines is that only more recent literature gets cited. As a journal editor I am often reminding young authors about critical studies conducted before the advent of pdf files and doi numbers!

MRC Programme Leader, and Director, Centre for Brain & Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, Malet Street, London WC1E 7HX, UK.
E-mail: mark.johnson@bbk.ac.uk

Quick guide

Caulobacter crescentus

Velocity Hughes, Chao Jiang, and Yves Brun

What is* Caulobacter crescentus*? *Caulobacter crescentus* is an aquatic Gram-negative bacterium that thrives in nutrient-poor environments and exhibits an elaborate life cycle. It features regulated changes in cell shape and surface adhesion within the context of a dimorphic cell cycle that culminates in asymmetric cell division (Figure 1).

Why study* Caulobacter crescentus*? *Caulobacter*'s cell cycle allows easy synchronization of populations based on developmental stage, and cells display clear polarity that distinguishes their two ends. These properties facilitate spatiotemporal tracking of gene expression, protein subcellular localization, chromosome segregation, and growth over the course of *Caulobacter*'s life cycle. This has enabled detailed understanding not only of the mechanisms of bacterial differentiation and development, but also of widely conserved processes in chromosome replication and cell cycle regulation that were less tractable in symmetrically dividing model species such as *Escherichia coli.*

What happens during* Caulobacter*'s extensive metamorphosis? The cell cycle of *Caulobacter* is a visually striking display of bacterial development, with each life stage having a distinctive appearance (Figure 1). Major functional transitions accompany the morphological changes of the cell as it progresses through the cell cycle. The newborn swarmer cell is equipped with a flagellum and pili at a single pole. Incapable of DNA replication, the swarmer cell dedicates its energy towards motility and dispersal. With time, the flagellar pole of the swarmer cell undergoes differentiation. It secretes a polysaccharide adhesin known as the holdfast, which mediates permanent surface attachment of the cell. Then the flagellum and pili are lost from that pole and replaced by the growing stalk, which is a thin extension of the cell envelope. The stalked cell is reproductively mature and gives off daughter swarmer cells, marking the completion of the dimorphic life cycle.

How are the events of the* Caulobacter *life cycle coordinated so precisely? First of all, *Caulobacter* tightly regulates DNA replication initiation, allowing it to occur exactly once per cell cycle in the stalked stage. Overseeing this important routine is a protein called CtrA, which belongs to the response regulator family of transcription factors. CtrA not only prevents extraneous initiation of DNA replication, it also controls the expression and activity of a large number of important regulons involved in cell cycle progression. CtrA prevents the initiation of new rounds of DNA replication by binding to the chromosomal origin of replication; however, it undergoes timed degradation during the swarmer-to-stalked cell transition. This allows replication initiation and tightly coupled activation of various pathways involved in polar differentiation, growth and cell division, maintaining synchrony between the various events of the cell cycle. The activity of CtrA and its effectors marks the crucial transition that enables the emergence of complex development from the mechanistic foundations of functionally symmetric binary fission, in *Caulobacter* and other related organisms. The details of the functioning of this pathway therefore continue to be an extensive area of research in developmental microbiology.

Caulobacter*'s division gives rise to two cell types with distinct developmental fates — how does this occur?* Polarity in CtrA regulation between the two halves of the dividing cell drives developmental asymmetry between *Caulobacter*'s two daughter cell types. CtrA is synthesized and activated in the stalked cell shortly after DNA replication initiation. As the stalked cell progresses towards division, two important regulatory proteins,

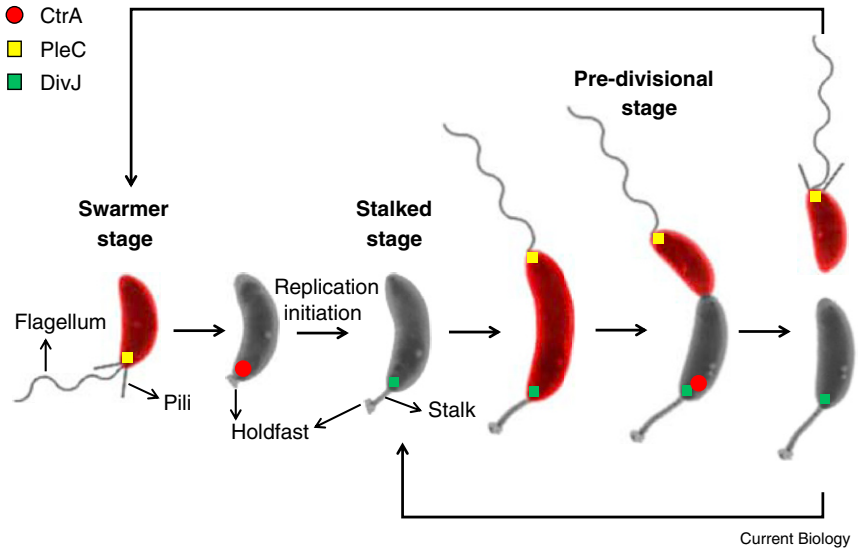

Figure 1. The dimorphic cell cycle and asymmetric division of *Caulobacter crescentus*.
Precise spatiotemporal patterning of key regulatory proteins coordinates development and cell polarity during cell cycle progression. Cells are false colored red to indicate the presence of dispersed, active CtrA.

the histidine kinases DivJ and PleC, localize to opposite poles of the cell (Figure 1). At the stalked pole, DivJ signaling favors localization, degradation, and inactivation of CtrA. Conversely, at the pole opposite the stalk, PleC signaling promotes the dispersal and activity of CtrA. When both are present in the elongating stalked cell, PleC's effect dominates and CtrA remains active. But upon cell constriction at the predivisional stage, the two daughter cell compartments differentially inherit either DivJ or PleC. In the stalked compartment, DivJ signaling abolishes CtrA activity, allowing immediate initiation of a new round of DNA replication and growth in the stalked daughter. Conversely, in the swarmer compartment, PleC signaling maintains CtrA activity, which continues to inhibit differentiation and DNA replication until its timed degradation. Thus, differential localization of regulatory proteins at the two ends of the pre-divisional cell drives developmental asymmetry between the daughter cells of *Caulobacter*'s division.

But why does a bacterium need such a complex cell cycle? The French biologist François Jacob once said that the dream of a cell is to become two cells. Indeed, many rapidly growing bacteria like *E. coli* initiate several simultaneous rounds of DNA replication per cell cycle in preparation for multiple successive divisions. But *Caulobacter*'s strategy constrains the energetically expensive process of chromosome replication to occur just once per cell cycle, perhaps to help it thrive in comparatively nutrient-starved environments (*E. coli* gets to live in guts, *Caulobacter* in pristine lakes). Furthermore, from an ecological perspective, the diphasic development of *Caulobacter* ensures the persistence of two cell types in any given population. Stalked cells may form a core community that maximizes reproductive yield through dedicated use of resources for daughter cell production. But through asymmetric division, stalked cells afford their swarmer daughters the opportunity to colonize new ground that may be more bountiful. Bet-hedging strategies of this type have support from theoretical models and are seen in diverse bacteria (and indeed eukaryotes) as a way to balance the benefits of communal lifestyles, niche exploitation, and dispersal.

What allows a single-celled organism like Caulobacter to form a community? Like many bacteria, *Caulobacter* can form surface-attached communities called biofilms. Permanent attachment of *Caulobacter* cells within these communities occurs using their holdfast polysaccharide, which is among the strongest and most versatile biological adhesives known. Holdfast synthesis can be initiated through two mechanisms. One is a temporal trigger that coincides with the swarmer-to-stalked cell transition as described above. But intriguingly, holdfast synthesis can also be triggered during dispersal when the flagellum and pili of the swarmer cell form weak, reversible attachments with a suitable substrate for adhesion. Such surface contact stimulated holdfast attachments may predispose swarmers born in a surface-attached community to rapidly settle within the existing biofilm, furthering the communal lifestyle.

If attachment is permanent, wouldn't it be impossible for cells to leave a biofilm? Though existing cells in a biofilm are permanently attached, each new generation of swarmer cells they produce has the option of dispersal from the biofilm. Indeed, swarmer cells born in a dying biofilm in a deteriorating environment are actively prevented from settling in that biofilm. Under these circumstances, genomic DNA debris from dead *Caulobacter* cells can bind to the nascent swarmer cells' holdfasts and inhibit their adhesive properties. The death of neighboring cells thereby favors dispersal and may enable newborn swarmers to find more hospitable environments. Interestingly, this response is specific to the death of *Caulobacter* cells, and DNA even from closely related species binds ineffectively to holdfast. The foundations for such specificity are a topic of ongoing research.

What is the role of the stalk in* Caulobacter*'s lifestyle? The stalk is a thin, continuous extension of the cell body, comprising a narrow cytoplasmic core surrounded by each layer of the Gram-negative cell envelope. Stalk synthesis is regulated by two independent mechanisms. Under developmental control, the stalk is initiated during the swarmer-to-stalked cell transition and then continues to elongate slowly with each subsequent round of division by the stalked cell. But much more dramatically, stalks elongate up to several times the length of the cell

body in cells that are starved for phosphate, a nutrient that is typically low in abundance in *Caulobacter*'s aquatic ecosystems. The phosphate starvation response has long suggested that the *Caulobacter* stalk might specialize in nutrient uptake. Consistent with this hypothesis, the stalk is particularly rich in nutrient transport proteins of the outer membrane and periplasm and can take up and process nutrients even when purified away from the rest of the cell. By increasing cell surface area and especially cell length relative to volume, the stalk thus better permits sessile, reproductively active cells to take up nutrients that aid in growth and division. In addition to nutrient uptake, the stalk might serve other purposes. Though stalks are not required for attachment to surfaces using holdfast, stalks allow cells to extend away from surfaces to which they are attached, providing access to more nutrients. Stalks also increase the buoyancy of unattached cells and facilitate their ability to stay close to air/water interfaces, a desirable trait for aerobes like *Caulobacter*.

Is Caulobacter *unique among bacteria in its interesting features?*

Yes and no. Though *Caulobacter crescentus* has developmental features that contrast sharply with *E. coli*, it shares these features with many other organisms. Closely related to *Caulobacter* within the order *Caulobacterales* are many prominent freshwater and marine genera that have dimorphic cell cycles, polar holdfasts, and stalks (Figure 2). Such conservation suggests the importance of these features for the fitness of bacteria living in oligotrophic environments (Figure 2). Genetic, genomic and ecological approaches comparing these diverse organisms could reveal more of the essential genes, functions and selective forces that drive the evolution and persistence of dimorphic developmental life histories in bacteria.

What else can we learn from Caulobacter *and its relatives?*

The developmental features seen in *Caulobacter* have diverged profoundly in other species, perhaps to meet the specific needs of unique environmental niches. For example, *Caulobacter*'s marine relative *Hyphomonas neptunium* has evolved the ability to bud off daughter cells from the tip of its stalk (Figure 2). While retaining the overall scheme of a dimorphic cell cycle, these cells differ in their site of daughter cell synthesis, not to mention having to translocate their entire genome through the stalk into their progeny with each cell cycle. Variation also arises in stalk positioning and number in *Caulobacterales,* ranging from a few non-stalked species of *Brevundimonas* to the single polar stalk of *Caulobacter* and the dramatic bilateral stalks of an *Asticcacaulis* species (Figure 2). Similarly, composition and the subcellular location of the holdfast can vary from species to species. All of this taken together, the differences between *Caulobacter* and its relatives are ripe for understanding how and why developmental phenotypes diversify. Since they share similar genetics and ecology, relevant changes that bring about the diversification of these relatives may prove easier to identify.

So Caulobacter *is a model organism for diversity!*

An oxymoron, but it's true. *Caulobacter* has long been a powerful and prominent system for addressing mechanistic questions in bacterial cell cycle control and development. But now, especially with the availability of genomic tools in several close but different organisms, we are poised to begin using our knowledge of *Caulobacter* to address how and why cellular organization and developmental processes diversify in the particular ways they do.

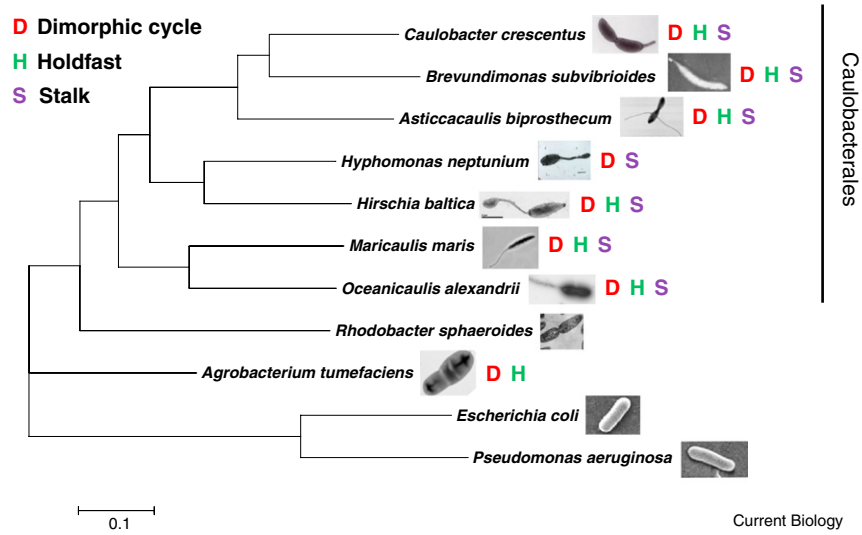

Figure 2. Dimorphic cell cycles, polar adhesives and stalks are conserved across diverse Alphaproteobacteria.
Maximum likelihood tree is inferred from GyrA sequences of various alphaproteobacteria, the gammaproteobacteria *E. coli* and *Pseudomonas aeruginosa* serving as an outgroup.

Where can I find more about Caulobacter *and its relatives?*

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Department of Biology, Indiana University, Bloomington, IN 47405, USA.
E-mail: ybrun@indiana.edu