

Cutting through the noise: bacterial chemotaxis in marine microenvironments

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ABSTRACT

The ability of marine microbes to navigate towards chemical hotspots can determine their nutrient uptake and has the potential to affect the cycling of elements in the ocean. The link between bacterial navigation and nutrient cycling highlights the need to understand how chemotaxis functions in the context of marine microenvironments. Chemotaxis hinges on the stochastic binding/unbinding of molecules with surface receptors, the transduction of this information through an intracellular signalling cascade, and the activation and control of flagellar motors. The intrinsic randomness of these processes is a central challenge that cells must deal with in order to navigate, particularly under dilute conditions where noise and signal are similar in magnitude. Such conditions are ubiquitous in the ocean, where nutrient concentrations are often extremely low and subject to rapid variation in space (e.g. particulate matter, nutrient plumes) and time (e.g. diffusing sources, fluid mixing). Stochastic, biophysical models of chemotaxis have the potential to illuminate how bacteria cope with noise to efficiently navigate in such environments. At the same time, new technologies for experimentation allow for continuous interrogation – from milliseconds through to days – of bacterial responses in custom dynamic nutrient landscapes, providing unprecedented access to the behaviour of chemotactic cells in microenvironments engineered to mimic those cells navigate in the wild. These recent theoretical and experimental developments have created an opportunity to derive population-level uptake from single-cell motility characteristics in ways that could inform the next generation of marine biogeochemical cycling models.

Keywords: chemotaxis, bacteria, motility, sensing noise, ocean, microbial ecology, navigation, fluctuations

Introduction

The fine-scale interactions between marine bacteria and both dissolved and particulate organic matter underpin marine biogeochemistry, thereby supporting productivity and influencing carbon storage and sequestration in the planet's oceans (Azam, 1998). It has been historically very difficult to characterise marine environments on the microscales that are most relevant to individual bacteria. Rather, research efforts have typically sampled much larger volumes of water and made comparisons from one sampling site to another (Karsenti *et al.*, 2011; Bork *et al.*, 2015). However, at the length scales relevant to individual microbes, the ocean is an intricate and dynamic landscape of nutrient patches, at times too small to be mixed by turbulence (Kiørboe, 2008; Stocker, 2012). The capacity for microbes to actively navigate these structured environments using chemotaxis can strongly influence their nutrient uptake. Although some work has examined time-dependent chemical profiles (Zhu *et al.*, 2012), past investigations of chemotaxis using *Escherichia coli* and other model organisms have routinely examined steady chemical gradients strong enough to elicit a discernible chemotactic response (Sneddon, Pontius, and Emonet, 2012; Salek *et al.*, 2019). However, the typical chemical gradients wild marine bacteria encounter are often very weak, ephemeral in nature, and with low background concentrations (Stocker, 2012). Shallow gradients are relevant for marine bacteria because, in general, gradients become weaker as one moves away from the source. Yet detecting such gradients at distance has tremendous value, because they point toward nutrient sources. Shallow gradients are important precisely because they can be used to navigate to regions in the vicinity of sources where gradients become steep, concentrations are high, and bacteria can acquire resources at a high rate.

Past experiments have typically been limited in duration to the 1-100 s timescales over which gradient-climbing occurs (Stocker, 2015), but the timescales over which bacteria respond to nutrient uptake – through gene regulation and bacterial reproduction – are much longer. Accurately quantifying the influence of microscale dynamics in oceanic nutrient cycling hinges on (1) interrogating bacterial chemotaxis in realistic microenvironments for extended periods of time and (2) developing mathematical models that capture the essential features of chemotaxis in dilute, dynamic conditions. In this Perspective, we discuss recently developed experimental tools and mathematical frameworks for furthering our understanding of bacterial chemotaxis. We examine the various ways in which noise can enhance or degrade the sensitivity of bacterial navigation, and outline priorities for future research.

Bridging The Timescales of Motility and Metabolism

Bacterial chemotaxis is one of the most thoroughly understood behaviours in all of biology (Berg, 2008; Endres, 2013). Many experimental and modelling approaches have been used to investigate chemotaxis in fine detail, from early capillary assays (Adler, 1973; Brown and Berg, 1974) to experiments in controlled microfluidic environments (Mao, Cremer, and Manson, 2003; Englert, Manson, and Jayaraman, 2009) (Seymour *et al.*, 2010; Son, Brumley, and Stocker, 2015; Salek *et al.*, 2019) and computational modelling of complete biochemical pathways (Morton-Firth, Shimizu, and Bray, 1999; Jiang, Ouyang, and Tu, 2010; Long, Zucker, and Emonet, 2017). Despite the vast literature on bacterial chemotaxis, unanswered questions still remain. In particular, we still know relatively little about the types of microenvironments bacteria navigate in the wild, and how chemotaxis operates and evolves in such environments (Endres, 2013; Wong-Ng *et al.*, 2016).

The distribution of nutrients in the ocean is highly structured, varying strongly with depth, across the globe (Hansell *et al.*, 2009), and with time (Druffel *et al.*, 1996). Moreover, there is tremendous diversity in the types of organic matter available (Riedel and Dittmar, 2014; Benner and Amon, 2015), and substantial exchange of materials between dissolved, particulate, colloidal and gel phases (Verdugo, 2012; Kiørboe,

2001). Although bulk DOC concentrations typically vary between 35 and 70 μM throughout the ocean (Hansell *et al.*, 2009), the vast majority of DOC exists in forms either difficult or impossible to use by bacteria. Low molecular weight, highly labile molecules such as dissolved sugars, amino acids, or nucleotides, have only nanomolar concentrations in the bulk and residence times under one day (Keil and Kirchman, 1999). These molecules can have transiently high concentrations in the aftermath of cell lysis, predation, or nutrient exudation by phytoplankton, but they are not components of more long-lived hotspots such as gels or particles (Verdugo, 2012). The majority of labile or semi-labile organic matter has much higher molecular weight, and consists of biological macromolecules such as proteins or large algal polysaccharides (Benner and Amon, 2015). Too large to pass through bacterial cell membranes, bacteria degrade these molecules into monomers or oligomers using ecto- and exo-enzymes, allowing for their uptake, but also creating public goods which feed other bacteria or give them information on the location of nutrient hotspots.

Dissolved organic matter can be redistributed through ubiquitous fluid flows in the ocean, but at the length scale relevant to microbial motion – less than approximately 1 mm – molecular diffusion predominantly drives the redistribution of chemical cues (Batchelor, 1959). The structure and dynamics of chemical gradients in the ocean thus emerge from the interplay of DOC release by living organisms, the aggregation and disaggregation of DOC into gels and particles, the degradation and uptake of DOC by heterotrophic bacteria, and fluid turbulence.

Experiments (Blackburn, Fenchel, and Mitchell, 1998; Stocker *et al.*, 2008; Smriga *et al.*, 2016) and mathematical theory (Hein *et al.*, 2016a; Mora and Nemenman, 2019) have begun to assess the role of dynamic chemical gradients (Taylor and Stocker, 2012), investigating the interaction between timescales for motility and timescales for changes in the chemoattractant landscape. Experiments have revealed that marine bacteria are capable of rapidly responding to leaking diatoms (Smriga *et al.*, 2016), pulses of phytoplankton exudates (Seymour, Marcos, and Stocker, 2009), model marine particles and sinking aggregates (Kjørboe *et al.*, 2002), exemplifying the importance of chemotaxis throughout the microbial food web. However, previous work has typically been limited to one single unsteady source, and to durations of a few minutes or less. While this may be long compared to the timescales for cell motility and reorientation (seconds), it is still much shorter than the timescales over which bacterial metabolism varies (Lambert and Kussell, 2014) and cell division occurs (hours to days) (Kirchman, 2016). Observations over minute-long timescales cannot detect slow modulations or systematic changes in swimming speed or chemotactic abilities, which could in principle, strongly affect the collective cell dynamics. Chemotaxis assays conducted over short timescales do not necessarily represent the dynamics of wild foraging bacteria throughout their lifetime. Beyond determining the chemotactic *ability* of wild marine bacteria, it will be critical to assess their *propensity* for performing chemotaxis in realistic environments over extended periods of time.

Chemotaxis in Realistic Microenvironments

What constitutes a *realistic* environment varies wildly between different regions of the ocean, from upwelling of nutrient-rich deep water (Lauro *et al.*, 2009) to the nutrient-poor photic zone; and over time with seasons and bloom conditions (Teeling *et al.*, 2012). The chemical microenvironments are sometimes driven predominantly through the action of physical processes (currents, sunlight) whose effects are known *a priori*. However, in many cases, the nutrient dynamics are strongly coupled to the microbial population itself. Moreover, organic matter may be dissolved (DOM, Fig. 1A(i)), due to phytoplankton exudation or sloppy feeding (Jackson, 2012); particulate (POM, Fig. 1A(ii)) in marine snow and precipitates; or a combination of DOM and POM in, for example, oil droplets and phytoplankton lysis events (Smriga *et al.*, 2016) (Fig. 1A(iii)).

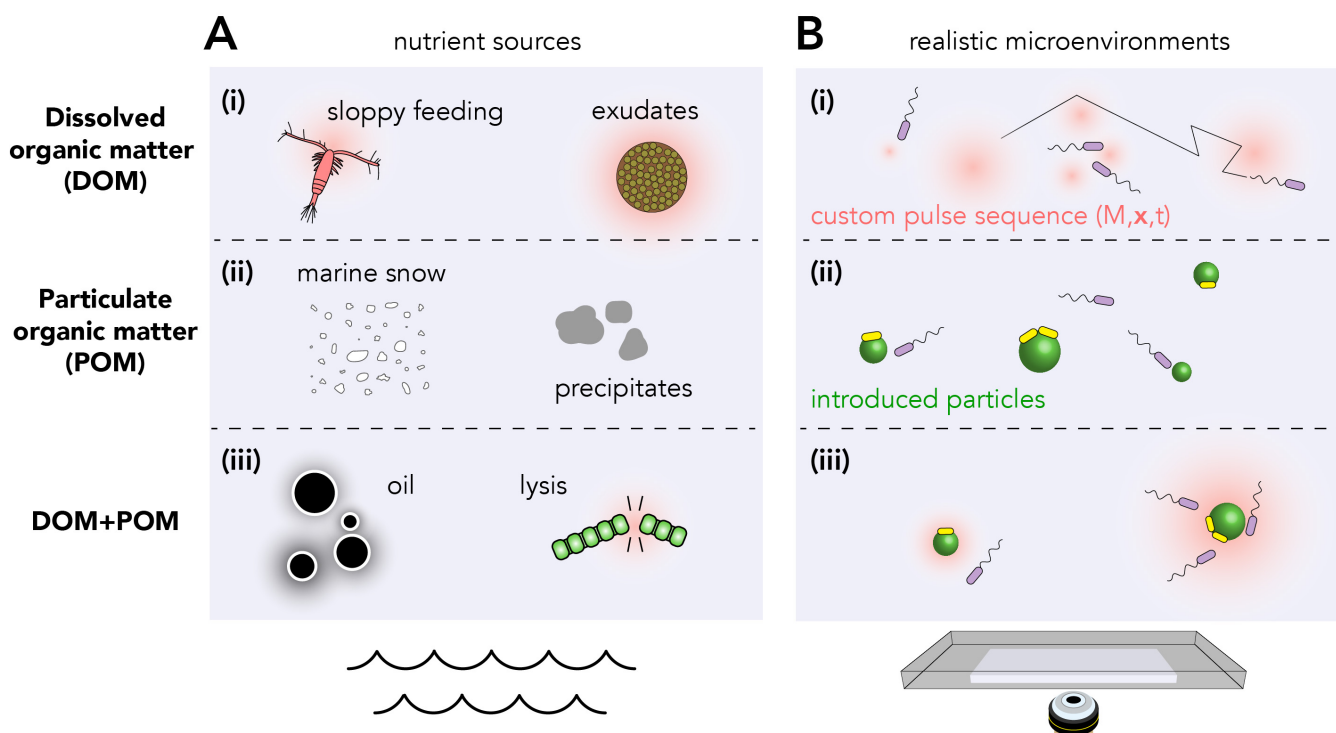


Figure 1. Structured nutrient landscapes found in the ocean can be quantitatively reproduced in laboratory settings using microfluidics, photolysis of caged resources, and discrete nutrient particles. (A) Various biological processes produce resources which may be (i) dissolved, (ii) particulate, or (iii) a combination of both. (B) Realistic microenvironments can be recreated using (i) photolysis of caged compounds to produce custom DOM landscapes (Carrara *et al.*, 2020; Brumley *et al.*, 2019); (ii) spatial arrays of particles (e.g. chitin or alginate) (Datta *et al.*, 2016); or (iii) both. Within these custom arenas, bacterial chemotaxis and population kinetics can be tracked over timescales from milliseconds to days. Transitions between planktonic (purple) and surface-attached bacteria (yellow) can also be quantified (Yawata *et al.*, 2014).

The precise values of the chemical gradients depend on many factors, including the quantity of nutrients released, its molecular diffusivity, the time over which release occurs, the rate of background uptake by bacteria, and any mixing by fluid flows. The phycosphere radius, or distance at which bacteria interact with nutrient pulses, therefore varies from $\lesssim 10 \mu\text{m}$ through to several millimetres (Seymour *et al.*, 2017). Sources can vary in duration from seconds to minutes in the case of lysis events (Blackburn, Fenchel, and Mitchell, 1998), or many hours in the case of continuous leakage.

Generating Controlled, Dynamic Chemical Landscapes

A promising method for creating custom dissolved (DOM) nutrient landscapes utilises the photo-release of caged chemoattractants (McCray and Trentham, 1989; Jasuja *et al.*, 1999; Sagawa *et al.*, 2014; Jikeli *et al.*, 2015). Dissolved organic compounds such as the amino acid glutamate, which naturally occurs in coastal environments and acts as a chemoattractant for marine bacteria (Barbara and Mitchell, 2003; Duursma and Dawson, 2011), can be chemically appended using a “cage” molecule. When bound to the cage, this attractant is undetectable by bacteria. Calibrated exposure to light causes photolysis of the cage, and the precise release of chemoattractant hotspots. Since the illumination can be easily varied in space and time, this method facilitates the creation of custom two-dimensional nutrient landscapes, with exquisite precision (Carrara *et al.*, 2020; Brumley *et al.*, 2019).

Alginate beads (Yawata *et al.*, 2014), chitin particles (Datta *et al.*, 2016) and oil droplets (Desai, Shaik, and

Ardekani, 2018) can be used to mimic particulate organic matter (POM), investigate bacterial chemotaxis, and study the physics of attachment/detachment dynamics (Fig. 1). However, controlled sequential introduction of multiple particles can be difficult to achieve experimentally. Moreover, particulate matter in the ocean tends to sediment, making visualisation in realistic environments challenging. Microscopy techniques that continuously follow individual marine snow particles for days at a time (Krishnamurthy *et al.*, 2019) have the potential to provide tremendous insight into the long-time dynamics of bacterial chemotaxis and particle colonisation. Reconciling the known resource landscape with bacterial trajectories measured using high throughput techniques (Taute *et al.*, 2015; Waite *et al.*, 2016; Brumley *et al.*, 2019), is key to teasing apart the mechanisms bacteria use to navigate their microenvironment.

Noise in Bacterial Chemotaxis

From the stochastic encounters with chemoattractant molecules to the actuation of the flagellar motors, there are many sources of noise that can influence the capacity of microbes to detect and respond to chemical gradients (Sourjik and Wingreen, 2012; Micali and Endres, 2016; Kromer *et al.*, 2018). Individual microbes experience the chemical environment as a sequence of encounters with individual molecules (Berg and Purcell, 1977) (see Fig. 2A). The randomness in this sequence is particularly important within marine environments, where resource hotspots may be very small ($\lesssim 1$ pmol) (Blackburn, Fenchel, and Mitchell, 1998; Davis and Benner, 2007) and short-lived (seconds-minutes) (Smriga *et al.*, 2016). The discrete molecular nature of the chemoattractant means that even in a steady, uniform environment, the number of chemoattractant molecules reaching the surface receptors per unit of time will fluctuate (Endres and Wingreen, 2008; Mora and Wingreen, 2010), and may be as small as a few molecules per second (Brumley *et al.*, 2019). Provided that bacteria rely on temporal signalling to perform chemotaxis (Macnab and Koshland, 1972; Segall, Block, and Berg, 1986), a *gradient* can only ever be defined in an average sense, and requires integration of the arrival sequence over an appropriate timescale, T . If the cell's uncertainty in the gradient estimate is larger in magnitude than the gradient itself, a typical measurement will not be able to resolve the signal. The photo-release of glutamate in sub-picomole quantities – explicitly designed to mimic an individual lysing phytoplankton cell (Blackburn, Fenchel, and Mitchell, 1998) – was used to assess the role of sensory noise in realistic environments (Brumley *et al.*, 2019). The chemotactic precision of *Vibrio ordalii* was found to be close to the fundamental limit set by this molecule counting noise. While these results assume sampling through discrete time intervals, it will be important for future work to examine the role of continuous integration of ligand binding events (Mora and Nemenman, 2019), determine exactly how cells average measurements, and ascertain how noise propagates through the chemotaxis networks of different model organisms (Micali and Endres, 2019). Phenotypic variation may also influence the collective chemotactic response of many cells (Frankel *et al.*, 2014; Waite, Frankel, and Emonet, 2018).

Intracellular noise can also influence the capacity of bacteria to respond to chemical gradients (Korobkova *et al.*, 2004) (see Fig. 2A). The discrete nature of signalling molecules places limits on a cell's chemotactic ability in a manner similar to extracellular counting noise (Bialek and Setayeshgar, 2005). Suppressing internal noise in biochemical networks generally requires a cell to produce and maintain an increased number of signalling molecules (Lestas, Vinnicombe, and Paulsson, 2010; Govern and ten Wolde, 2014). Depending on the dynamics of the chemical environment, the extra cost in noise suppression (Sartori and Tu, 2015) may exceed the additional resources acquired through greater sensitivity. For systems in which the noise frequency is much higher than that of the signal, it may be possible to filter noise (Andrews, Yi, and Iglesias, 2006). However, for realistic marine environments, the timescales over which chemoattractant concentrations vary and signalling molecules fluctuate may be similar. The conflation of these timescales could thwart the ability for cells to successfully filter the intracellular noise.

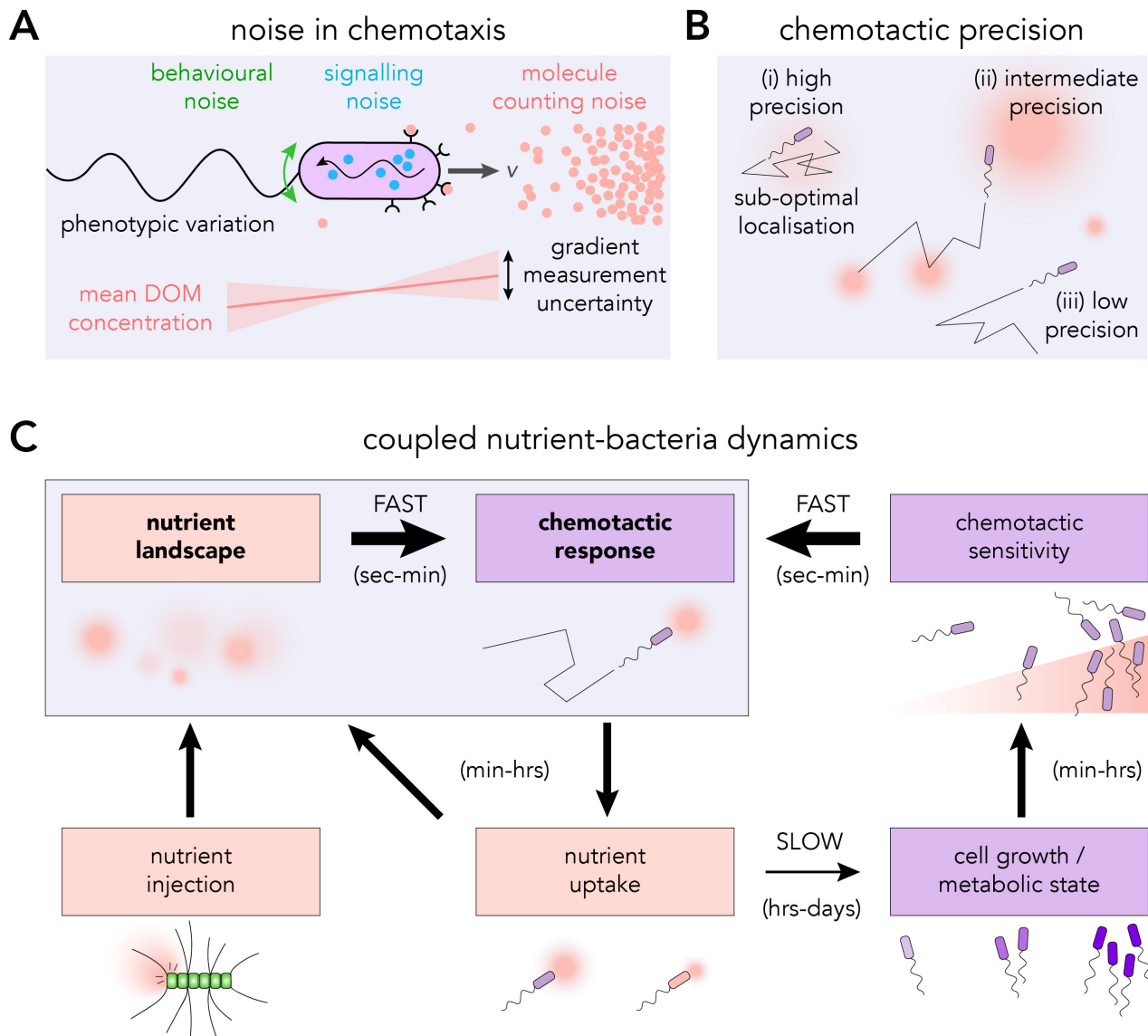


Figure 2. (A) The discrete nature of dissolved chemoattractants introduces molecule counting noise into the bacterium's measurement of the gradient. In conjunction with other sources of noise in the signalling pathway, the flagellar response as well as rotational diffusion, the cell executes an effective chemotactic response. (B) The level of chemotactic precision governs the ability of bacteria to navigate towards, and reside at, regions of high DOM concentration. (i) High chemotactic precision may result in sub-optimal localisation at local nutrient maxima; (ii) intermediate precision allows for both exploration and exploitation; and (iii) low precision results in undirected motility. (C) Highly coupled nutrient-bacteria dynamics in chemotactic foraging cycle. The traditional means of studying chemotaxis is to assess the motility response to prescribed nutrient landscapes (seconds to minutes). However, over timescales of hours to days, feedback loops exist which have the capacity to reshape the nutrient landscape and modify the chemotactic response.

While it is intuitive that noise in the incoming chemical signal and the internal signalling pathway can degrade chemotactic performance, there are cases in which cells actually appear to benefit from noise (Flores *et al.*, 2012). For bacteria with multiple flagella such as *E. coli*, stochastic coordination of flagellar motors can reduce the latency below that of an individual motor, which can assist in steep gradients (Sneddon, Pontius, and Emonet, 2012). Random fluctuations in the signal protein CheY-P have also been

shown to increase the chemotactic sensitivity of *E. coli* at the level of the flagellar motors (Hu and Tu, 2013; He, Zhang, and Yuan, 2016). Yet, these particular mechanisms are generally not accessible to marine bacteria, which typically possess one flagellum (Xie *et al.*, 2011) and operate in shallow, ephemeral gradients.

Greater chemotactic abilities do not necessarily lead to enhanced resource acquisition or growth (Ni *et al.*, 2020). The level of bacterial chemotaxis which confers the greatest advantage for individual cells depends on the structure of the chemical microenvironment (Celani and Vergassola, 2010). For bacteria in the vicinity of a single isolated nutrient source, a greater chemotactic precision will generally lead to an enhancement in the nutrient exposure and uptake rate (Smriga *et al.*, 2016). However, in an environment with multiple nutrient sources of different magnitude, a cell which perfectly follows the gradient may become trapped in a locally favourable, but globally sub-optimal position (see Fig. 2B(i)). Sources of noise which reduce the cell's chemotactic sensitivity may actually improve the overall nutrient acquisition by allowing the cell to more thoroughly explore its environment (see Fig. 2B(ii)). The optimal bacterial behaviour will therefore be sensitively linked to the precise spatiotemporal dynamics of the chemical microenvironment (Passino, 2002). Theoretical frameworks linking organismal navigation with the overall resource landscape structure (Hein *et al.*, 2016b; Seymour *et al.*, 2017; Hein and Martin, 2019) provide predictions about the optimal strategies for bacterial foraging, which can be explicitly tested, for example using microfluidic platforms.

Bacterial Uptake Kinetics in Structured Microenvironments

Because of fluctuations in nutrient exposure within the structured microenvironments of the ocean, the generation times, and therefore biomass production, of wild bacteria are likely to be fundamentally different from those measured during experiments in homogenous batch culture (Fenchel, 2002; Azam and Malfatti, 2007). In fact, temporal fluctuations can drive distinct growth physiologies and strategies (Yan, Nadell, and Bassler, 2017), even for environments with the same mean nutrient concentration. Bacterial chemotaxis has the capacity to systematically redistribute the cells, and therefore may provide a feedback loop between the microbial population and the resource landscape (Cremer *et al.*, 2019). In cases where there is strong two-way coupling between the bacterial dynamics and the nutrient field – i.e. nutrient field drives chemotaxis, and bacterial consumption shapes nutrient profile – it is important to study the system for an extended period of time (Carrara *et al.*, 2020). This will provide great utility in determining realistic cell growth rates that are often very difficult to measure *in situ* (Kirchman, 2016).

Chemotaxis, as well as plasticity in physiology and behavioural strategy, can enhance the ability of bacteria to respond to spatial and temporal variation in resources. This, in turn, has the potential to influence ecosystem level processes such as remineralisation rates or carbon export fluxes. Rates of these microbially mediated processes exhibit considerable regional variation (Hansell, Carlson, and Schlitzer, 2012; Mouw *et al.*, 2016), and they also strongly influence the distribution of carbon throughout the oceans and atmosphere (Kwon, Primeau, and Sarmiento, 2009). Global-scale biogeochemical models rely on highly simplified, phenomenological parameterisations of remineralisation of particulate and dissolved organic matter, which prevents them from detecting carbon-cycle feedbacks induced by the ecological dynamics of marine microbes (Mislan *et al.*, 2014). The ability to assess long-term changes in microbial motility presents a unique opportunity for determining the influence of physiological states in bacterial chemotaxis (Jordan *et al.*, 2013; Cremer *et al.*, 2019), which is a key step to understanding how to link microbes and biogeochemistry.

Following early evidence that aspects of *E. coli* chemotaxis are independent of uptake or metabolism (Adler, 1969), research has largely overlooked the capacity for uptake or physiological states to influence motility. Studies of microbial motion often use highly specific culturing conditions. If the nutrients are

too scarce cells may not grow, swim or navigate. Similarly, cell motility and chemotaxis may also be reduced by overly abundant nutrients, since they are not advantageous when resources are plentiful (Ni *et al.*, 2020). Additional work suggests that *E. coli* (Taylor and Zhulin, 1998), *Azospirillum brasilense* (Alexandre, Greer, and Zhulin, 2000) and other species of bacteria (Alexandre and Zhulin, 2001) exhibit metabolism-dependent chemotaxis. Bacteria appear to modulate the way they perform chemotaxis – and indeed whether they even swim at all – based on their metabolic state, which presumably helps cells cope with the conditions they experience in natural environments (Ni *et al.*, 2020). Correlations between cellular motility and other copiotrophic traits (Koch, 2001), such as ribosomal copy number, hydrolytic enzymes, and genes for environmental sensing and signalling (Lauro *et al.*, 2009; Roller, Stoddard, and Schmidt, 2016) hint at the capacity for motile bacteria to rapidly expand their population, to adapt their behavioural and trophic strategies in response to their environment, and to structure local nutrient fields by being the primary degraders of biological macromolecules. The feedback loop between nutrient exposure, swimming speed (Son, Menolascina, and Stocker, 2016) and ultimately chemotactic sensitivity (Ni *et al.*, 2020; Hein *et al.*, 2016a) exemplifies the need to interrogate bacteria in realistic environments for extended periods of time, and investigate temporal variations in motility and chemotactic performance (see Fig. 2C), within and between successive generations. Since biogeochemical cycling will be driven not only by the spatial distribution of cells with respect to the nutrient field, but also by their metabolic state, modelling both of these processes (Egbert, Barandiaran, and Di Paolo, 2010) may prove to be important in predicting nutrient cycling in the ocean.

Priorities for Future Research

The capacity to generate controlled, dynamic chemical landscapes, while simultaneously visualising bacterial responses from milliseconds through to days, represents a uniquely powerful approach to investigating marine microbial processes. An important area for future exploration will be considering multiple interacting species of bacteria and other organisms (Amin, Parker, and Armbrust, 2012; Hol *et al.*, 2016; Raina *et al.*, 2019), where population and community dynamics may depend on the nutrient properties and organismal phenotypes. This will be particularly important in assessing the spatial patterning of metabolic handoffs (Anantharaman *et al.*, 2016), density dependent competition dynamics (Gude *et al.*, 2020), and the role of quorum sensing (Hmelo, 2017).

Investigating the rich interplay between multiple chemoattractants represents another important direction for future research. Except in some simplified domains (Kalinin *et al.*, 2010), bacterial chemotaxis is routinely studied in response to single molecular species. Yet, phytoplankton exudates and other dissolved organic matter exist as complex mixtures of compounds which differ in their abundance, diffusivity and propensity to elicit chemotaxis (Duursma and Dawson, 2011; Davis and Benner, 2007). Emerging analytical methods of characterising chemical microenvironments, exudation rates and nutrient exchanges (Wessel *et al.*, 2013) will further inform models for microbial motion (Keller and Segel, 1970; Jackson, 1987; Bray, Levin, and Lipkow, 2007; Desai, Shaik, and Ardekani, 2019) through to ocean-scale dynamics of microbial populations (Barton *et al.*, 2010; Worden *et al.*, 2015; Kuhn *et al.*, 2019).

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

D.R.B. wrote the first draft of the manuscript. All authors revised the manuscript and approved it for publication.

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