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Emergent properties of bacterial chemotaxis pathway

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The chemotaxis pathway of *Escherichia coli* is the most studied sensory system in prokaryotes. The highly conserved general architecture of this pathway consists of two modules which mediate signal transduction and adaptation. The signal transduction module detects and amplifies changes in environmental conditions and rapidly transmits these signals to control bacterial swimming behavior. The adaptation module gradually resets the activity and sensitivity of the first module after initial stimulation and thereby enables the temporal comparisons necessary for bacterial chemotaxis. Recent experimental and theoretical work has unraveled multiple quantitative features emerging from the interplay between these two modules. This has laid the groundwork for rationalization of these emerging properties in the context of the evolutionary optimization of the chemotactic behavior.

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Introduction

Bacteria can use flagella-based motility to follow gradients of environmental stimuli, including various chemicals, pH, redox potential, temperature and osmolarity [1]. Evolutionary conservation of this tactic behavior indicates its paramount ecological importance, likely in enabling bacteria to find local niches that are most favorable for their growth and survival. Because bacteria are too small to directly measure chemical gradients along their body, bacterial chemotaxis rather relies on temporal comparisons of environmental conditions [2]. In homogeneous environments, swimming bacteria perform an explorative random walk of seconds-long, more-or-less straight runs, extending over few tens of microns and separated by short random reorientations. These runs are lengthened if an improvement in environmental conditions is detected as the bacterium swims, thus biasing the random walk in a favorable direction (Figure 1a).

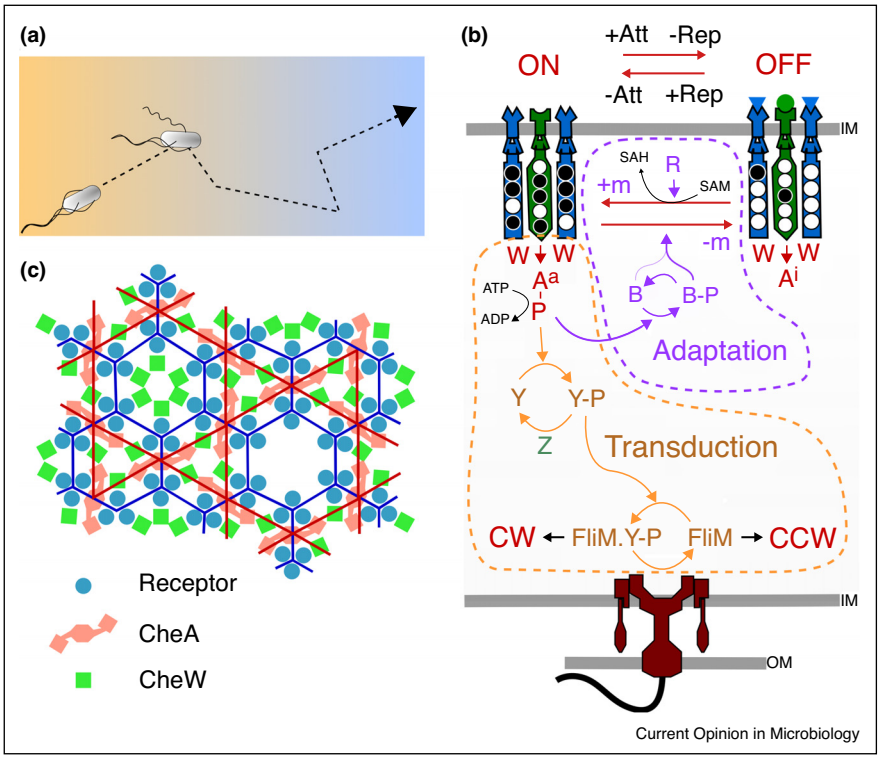
In *Escherichia coli* and other bacteria, this behavior is mediated by the chemotaxis pathway, which consists of two modules, one mediating signal transduction and another adaptation [3,4] (Figure 1b). The signal transduction module is evolutionary related to the broader class of bacterial two-component sensory systems. It includes sensory complexes that respond to changes in environmental conditions and transmit a phosphorylation-based signal to the flagellar motors to control the probability of cell reorientations. The adaptation module is, in contrast, unique to the chemotaxis pathway, although it shows general analogies to adaptation in eukaryotic sensory systems. This module ensures that the signal transduction module stays sensitive in a broad range of conditions and it also provides short-term memory for temporal comparisons. Although the details of the chemotaxis pathway can vary significantly among prokaryotes, its general organization is highly conserved [5,6]. Most information is available for the chemotaxis pathway of *E. coli*, which became one of the most studied bacterial models for quantitative understanding of cell signaling and behavior [3,7–9]. While molecular details of the signal processing by the pathway have been recently reviewed elsewhere [3,6,10], here we focus on recent advances in the understanding of its functional properties.

Signal transduction module

The chemotaxis system of *E. coli* and other bacteria detects, integrates and amplifies the environmental cues at the level of the clustered chemoreceptor arrays. These sensory arrays are composed of receptors (also called methyl-accepting chemotaxis proteins, or MCPs) that typically span the cytoplasmic membrane and are associated with dimers of the histidine kinase CheA and the scaffolding protein CheW (Figure 1b). *E. coli* possesses five types of receptors with different ligand specificities. Amino-acid receptors Tar and Tsr, which also sense a number of other stimuli, are highly expressed, whereas more specific receptors for sugars, dipeptides and redox potential (Trg, Tap and Aer, respectively) have lower copy numbers [10].

Conventional chemical effectors bind — either directly (amino acids) or indirectly via a periplasmic binding protein (sugars, dipeptides) — to the periplasmic sensory domains of receptors. This binding induces a shift in the equilibrium between the conformations of the cytoplasmic signaling domain, which either promote (ON) or repress (OFF) the autophosphorylation activity of

Figure 1



Chemotaxis in *Escherichia coli*. **(a)** Swimming behavior in an environmental gradient, biasing the run and tumble choreography by lengthening runs towards more favorable conditions. **(b)** Chemotaxis pathway, with its signal transduction and adaptation modules. (De)methylations of receptors occur according to their activity state. Attractants (Att) favor OFF states and thus CCW motor rotation and cell runs, repellents (Rep) favor ON states, CW rotations and tumbles. **(c)** Scheme of the chemoreceptor cluster organization, as seen from the bottom, highlighting the organization of the receptor TDs (blue) and the kinases (red). Rings of CheW (green) were observed *in vitro* only [13].

CheA [10]. The phosphoryl groups acquired by active CheAs are rapidly transferred to the small diffusible protein CheY, which controls the flagellar motor rotation. In *E. coli*, binding of phosphorylated CheY (CheY-P) to FliM at the cytoplasmic face of the motor promotes a reversal of the motor rotation from the default counterclockwise (CCW) to clockwise (CW), inducing a tumble and cell reorientation. Dephosphorylation of CheY-P mediated by the phosphatase CheZ enables rapid (subsecond) response to the environmental changes, and it further ensures that on the second timescale the level of CheY-P reflects the fraction of active CheA. Chemoattractant binding represses this kinase activity, thus decreasing tumbling probability and extending cell runs. Interestingly, in *Bacillus subtilis* this functioning is doubly inverted, with attractants activating CheA but CheY-P promoting rather than terminating runs [11].

Although the numbers and specificities of chemoreceptors are highly variable among prokaryotes [12], the array organization is generally conserved [13]. Receptors form homodimers, which can bind one ligand molecule each and self-assemble in trimers of dimers (TDs). The minimal signaling unit is believed to consist of two TDs, where receptor of different types can be mixed, associated with one CheA dimer and two monomers of CheW [14]. These units are organized in a large-scale array where a honeycomb TD lattice is intertwined with a kagome lattice of CheA (Figure 1c) [13]. This organization apparently allows cooperative interactions both within [15] and between TDs, so that signaling teams of at least 10–20 receptor homodimers contribute to the regulation of each CheA, thus amplifying changes in ligand binding when converted to kinase activity changes [3,16]. How exactly such cooperativity is mediated at the molecular level remains unclear, but disrupting receptor arrays by specific mutations in CheW abolishes amplification while retaining signaling function [17,18••]. Receptor arrays are stable on the (sub)second time scale of chemotactic signaling, but may undergo slow remodeling on the time scale of minutes [19].

Because receptor dimers of all types are mixed within TDs, the cooperative arrays can further mediate behavioral decisions in complex environmental gradients, by integrating different signals at the kinase level. The net response of the array to several stimuli depends on the abundances of their respective receptors, which allows

bacteria to adjust their ligand preferences by tuning the levels of receptor expression [20,21]. The sensory arrays are also sensitive to environmental stimuli such as osmolarity, temperature or pH that generally perturb receptor conformation [22–24]. Interestingly, some of these stimuli can elicit antagonistic responses via different receptors, resulting in a push-pull mechanism, sometimes called 'precision sensing', that can lead to cell accumulation at an intermediate optimal condition (see Figure 2a) [22,25].

Finally, the sensory arrays can monitor the metabolic state of the cell. In *E. coli*, metabolic sensing in chemotaxis is primarily mediated by the phosphotransferase system (PTS). The overall influx of sugars and certain other metabolites into the cell lowers the phosphorylation state of the PTS proteins [26••] that regulate CheA activity by interacting with the cytoplasmic side of the chemosensory complexes [27]. Notably, chemotactic responses triggered by the PTS are not amplified by the receptor array [26••], indicating that amplification occurs upstream of CheA. Other bacteria possess cytoplasmic clusters that might be dedicated to sensing of the internal cell state [6].

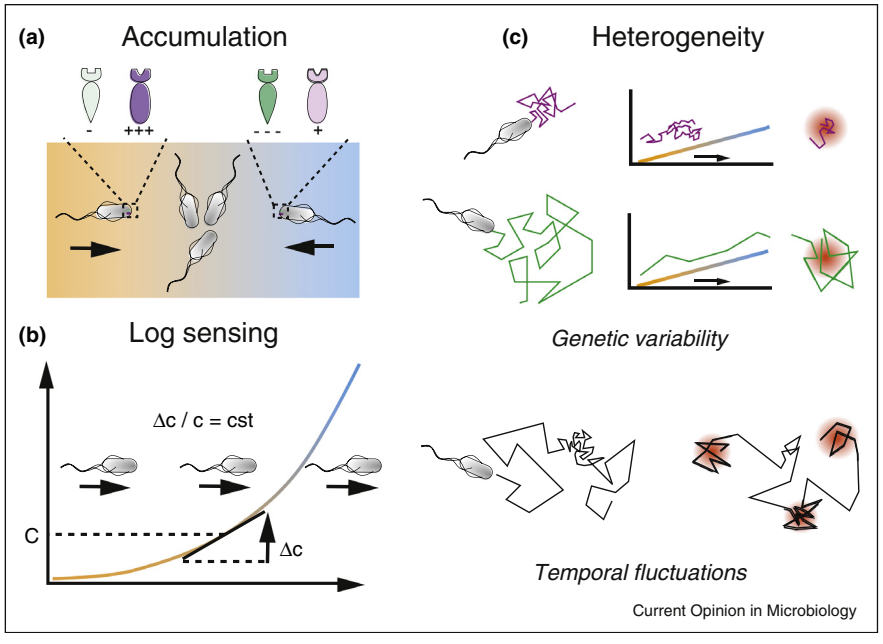
Another level of signal amplification occurs at the motor level through a highly cooperative conformational switch of multiple subunits of the flagellar motor [28]. This cooperativity explains the extremely high sensitivity of the motor to small changes in CheY-P concentration [29,30].

Adaptation module

The resulting rapid integrated and amplified response to changes in environmental condition is followed by slower adaptation process. The adaptation gradually resets the average kinase activity of the receptor arrays towards an intermediate operating point. This negative feedback is carried out by the methyltransferase CheR and the methylesterase CheB, which respectively modify the OFF or ON receptors by adding or removing methyl groups at specific glutamate residues, with methylation activating and desensitizing receptors. The adaptation is enhanced by receptor clustering [17], likely because CheR and CheB transiently dock at the C-terminus of high-abundance receptors and act on several neighboring receptors [31]. The time scale of adaptation depends on the strength but not on the nature of the stimulus [32•]. For small stimuli, as experienced by cells swimming in gradients, adaptation takes several seconds [33,34]. Thanks to the slow kinetics of adaptation, the methylation level of the receptors encodes recently experienced conditions and provides the short-term memory required for temporal comparisons [2,3,7].

Adaptation to small stimuli is in first approximation precise, meaning that the average kinase activity always returns to its pre-stimulation value, which is then a robust property of the cell [35]. Precise adaptation requires that the rates of (de)methylation depend on receptor activity

Figure 2



Emergent features of the chemotactic behavior. **(a)** Two receptors responding antagonistically to the same signal, with varying strengths as the background conditions change, allow for cell accumulation around an optimum condition. **(b)** Precise adaptation and the functional form of the free energy allow for logarithmic sensing, with bacteria responding according to relative rather than absolute changes in concentration and therefore having constant drift velocity in an exponential gradient. **(c)** Exploitation of genetic variability and stochasticity in biochemical reactions allows for bet hedging strategies.

Box 1 Modeling the chemotaxis pathway

Models of the chemotaxis pathway of *E. coli* aim at explaining the intracellular dynamics of the pathway response to chemical and other stimuli as well as cell behavior in gradients of these stimuli [16].

At the intracellular level, single receptors are typically modeled as two-state objects, either kinase activating (ON) or kinase inhibiting (OFF). The free-energy difference between these two states, $\Delta f = f_{ON} - f_{OFF} = \ln((1 + c/K_{OFF})/(1 + c/K_{ON})) + \gamma(m)$, determines receptor propensity to be in the OFF state, depending on ligand concentration c and methylation level m [3,16]. The function γ is usually considered linear, in line with experimental data [37]. This model can account for responses to stimuli other than chemical ligands (e.g. temperature) by integrating these additional dependences [25].

Two alternative formulations account for receptor cooperativity: Monod–Wyman–Changeux (MWC) models assume the receptor cluster is composed of independent teams of infinitely coupled signaling subunits (receptors and associated kinases), whereas Ising models treat the whole cluster as a network of receptors and kinases with finite couplings [16,97,98]. In MWC models, the probability of the signaling team to be in an active state is determined by the net free energy difference over all receptors of different types, $A = 1/(1 + \exp\sum_k \Delta f_k)$. In Ising models, the receptor states a_k are determined by minimization of the Hamiltonian of the whole sensory cluster $H = H_{int} + \sum_{k=1}^{N_R} a_k \Delta f_k$. The interaction term H_{int} usually accounts for couplings among receptors, of all types, by introducing an energy penalty to two coupled elements being in opposite states. Average kinase activity is then given by the average receptor state [97]. Alternative Ising formulations considering only kinase-receptor and inter-kinase couplings have also been proposed [99]. The dynamics of the receptor array is well described by both MWC and Ising models [98], but whereas Ising models normally need to be analyzed using numerical simulations, the MWC models can be solved analytically.

Adaptation is treated similarly in all model types, by assuming that demethylation preferentially (or exclusively) occurs on active receptors and methylation occurs on inactive receptors. Precise adaptation requires that the rates of methylation and demethylation do not depend on the methylation levels of receptors [35,100], but such dependence can be included to describe imprecise adaptation [46,47,100]. The effect of CheB phosphorylation can be included by using non-linear dependence of the demethylation rate on activity [37]. More refined treatments also account for transient tethering of the adaptation enzymes on receptors and resulting adaptation neighborhoods [31,51]. Ising models, contrary to MWC, allow for receptor-specific adaptation and may be preferred when modeling responses to multiple stimuli or stimuli with antagonistic actions on different receptors [51].

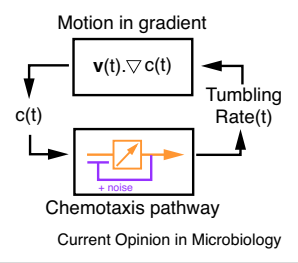
Finally, the kinetics of CheY phosphorylation in most simulations is assumed to be fast, so that the CheY-P level follows the activity of the sensory arrays. Nevertheless, this kinetics can be specifically considered, for example to investigate the effects of spatial localization of the sensory arrays [101]. Motor tumbling rates are usually deduced from CheY-P levels using the experimentally measured motor response function [29].

At the cellular level, the behavior in a gradient is modeled by solving the dynamics of the intracellular pathway as the cell swims, either through agent-based numerical simulations [64,84] or analytically [25,39,56,59]. The pathway response dynamics to small stimuli can alternatively be coarse grained using an effective memory kernel [49•,56]. The cell behavior results from interplay between the internal pathway dynamics and the swimming of the cells in the gradient (see scheme). For example, in a shallow steady 1D gradient, the expression for the average drift velocity of the cells

$$v_d(\nabla c, c) = NHv^2(1-a)\frac{df(c)}{dc}\nabla c \tau_r g\left(\frac{\tau_a}{\tau_r}, D_R\tau_r, \langle\cos\phi\rangle\right)$$

integrates pathway parameters — steady state activity (a) and average run duration ($\tau_r(a)$), rate of adaptation ($1/\tau_a$), gains at the receptor (N) and motor (H) level — with motility parameters — rotational diffusion coefficient (D_R), average turning angle during tumbles ($\langle\cos\phi\rangle$) and swimming speed (v) — and with the gradient of receptor free energy due to environmental changes $\frac{df}{dc}\nabla c$. The actual dimensionless function g is complex and can be estimated theoretically under various assumptions [25,46,49•,56].

To reproduce the naturally observed variation in the chemotactic behavior within populations, modeling fluctuations in chemotactic and swimming behavior of individual cells has recently gained importance. Typically, noise terms were introduced *ad hoc* in the mean-field equations of the pathway dynamics to model stochastic effects [8,67,102]. Multiple features of the adaptation enzymes dynamics were also analyzed in detailed simulations as sources of temporal activity fluctuations [31].



state, but not on the number of methylated glutamates, which is a natural implementation of the integral feedback control also used in engineering [36]. Although an additional feedback to the adaptation module is provided by the phosphorylation of CheB that increases its enzymatic activity (Figure 1b), precise adaptation does not require CheB phosphorylation [35]. Instead, one role of CheB phosphorylation might be to accelerate repellent escape [37].

Precise adaptation confers to the cell the ability to sense and respond to gradients in a wide range of ambient attractant concentrations, at least for the ligands that directly bind to the sensory domains of receptors [16,21]. The pathway response to these attractants depends on fractional — rather than absolute — changes in concentrations, a property called the Weber–Fechner law or logarithmic sensing [38,39] (see Figure 2b), that is common to sensory systems and is observed not only in *E. coli* but also in other chemotactic bacteria [40,41]. In *E. coli* chemotaxis, logarithmic sensing requires precise adaptation and specific dependence of the free energy difference between ON and OFF states of the receptors (see Box 1) on ligand concentration [4,16]. The range of ambient ligand concentrations of logarithmic sensing is bounded by the difference between binding affinities of

the ligand to the OFF and ON receptors [39], which is indeed large for the directly binding ligands but small for the indirectly binding ligands [21]. For directly binding attractants, not only the strength of the response but also the adaptation kinetics remains unchanged at a given relative strength of stimulation, a property called fold-change detection (FCD) [42,43].

Precise adaptation is a costly active process fueled by S-adenosyl methionine (SAM), and maintenance of the adapted state requires idle cycles of methylation/demethylation, each consuming 30 kT of energy [44]. Precision of adaptation increases with the rate of energy dissipation, which might explain why SAM rather than lower-energy ATP is used as the energy donor. Energy consumption may further enhance the amplitude of chemotactic responses while reducing noise [45•] and ensure efficient information transfer through the pathway [7].

Despite its apparent importance in the overall function of the chemotaxis pathway, precise adaptation breaks down under strong stimulation, where the methylation level of receptors approaches saturation [37,46–48]. Nevertheless, imprecise adaptation might be an evolutionary selected trait, not an 'imperfection', as it increases the average length of the cell runs and therefore their performance in static gradients [33,49•,50•]. Moreover, it might limit chemotactic accumulation to the sources of certain chemicals, such as serine, that are beneficial at low but toxic at high concentrations [46].

Although the highly cooperative initial response of the sensory array suggests strong coupling between receptors of different types, adaptation is mostly specific to the receptor that recognizes the stimulus [51]. This ensures that environmental information is specifically encoded into the methylation levels of cognate receptors. Methylation of non-cognate receptors ('cross-talk') exists only transiently if adaptation is precise, although it persists when the cognate receptor fails to adapt. Such specificity could not be accounted for by the simple Monod–Wyman–Changeux (MWC) models of receptor cooperativity, indicating some degree of receptor decoupling [51] or slow reorganization of the MWC-postulated receptor signaling teams [52] (see Box 1).

Although the methylation-based adaptation module is nearly universally conserved in bacterial chemotaxis [5], additional mechanisms of adaptation are found in other bacteria, such as *B. subtilis* [11]. Moreover, even in *E. coli* additional levels of adaptation apparently exist. Acetylation of CheY might modulate its binding to the motor thus contributing to adaptation [53]. Further adaptation occurs through remodeling of the motor, which gradually shifts the motor sensitivity range around the steady state concentration of CheY-P [54,55]. Theoretical analysis suggests that such tuning should improve the chemotactic performance in gradients, by preventing cells from being trapped in tumbly states [56].

Cell behavior in gradients

In nature, the chemotaxis pathway needs to function in different environments and for gradients of various shapes. Extended sources of chemicals such as plant roots or the epithelial surface of the gastro-intestinal tract will create locally one-dimensional gradients, whereas point sources of organic material will form radial gradients. Theoretical analyses showed that these situations pose conflicting optimization problems to chemotactic bacteria, with requirements for fast gradient climbing partly conflicting with those for efficient localization around concentration maxima [57]. Importantly, microfluidic devices now permit to create controlled gradients of various shapes [58••,59–62] and length scales [63] at relatively low cost, where cell behavior can be directly compared with theoretical predictions (see Boxes 1 and 2).

Generally, the behavior of a cell in a gradient depends both on pathway parameters (response sensitivity, steady-state activity and the rate of adaptation) and on motility parameters (swimming speed, angle of reorientation during tumbles and Brownian diffusion). Predictions for the drift velocity in linear steady gradients, derived for various limit cases [25,49•,56,64], capture well the behavior of dilute suspensions of cells in shallow gradients of non-metabolized chemoattractants [49•,59] and allow studying effects of various pathway parameters on the chemotactic drift [50•,64]. Such analyses were used for example to show that bacteria with low steady state activity are most efficient in one-dimensional gradients [50•,58••] and that the difference in turning angles while swimming up versus down the gradient enhances the chemotactic drift [65,66].

So far, more complex situations were mostly studied theoretically and in numerical simulations [46,67,68,69•,70], although experimentally creating complex concentration patterns might be possible [71]. In two-dimensional gradients, accurate positioning at maximal concentrations depends on the memory time and adaptation accuracy as well as on the steady-state activity [67,68,70]. When the gradient is transient, as common in nature, its accurate detection requires high speed [69•].

Fluctuations, robustness and bet hedging

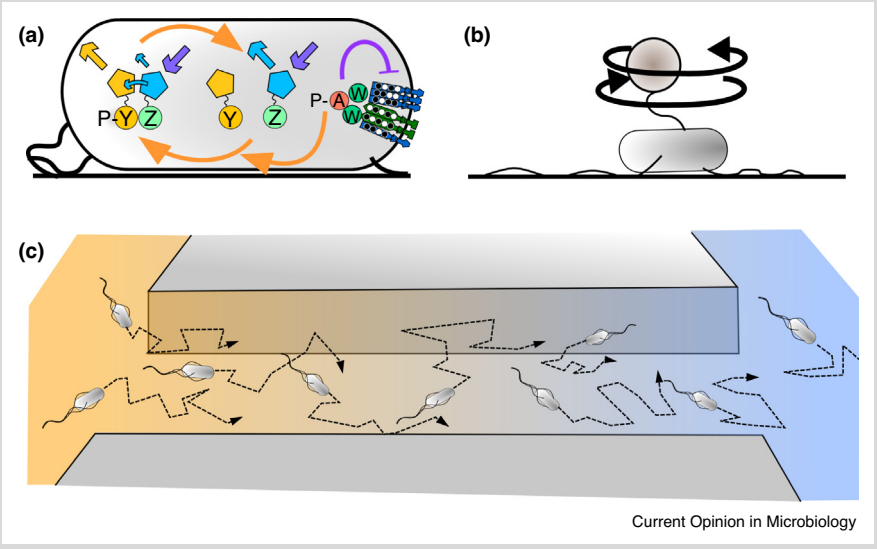
Cellular signaling networks are noisy systems dealing with noisy signals. Fluctuations in the chemotaxis pathway activity arise both on the longer time scale, due to the stochasticity of gene expression, and on shorter times due to noise in biochemical reactions.

Analyses of the chemotaxis pathway revealed multiple mechanisms conferring robustness against gene expression noise to the average operating point of the pathway

Box 2 Measuring chemotaxis

The bacterial chemotactic behavior can be assessed at three different levels. First, Förster (Fluorescence) Resonance Energy Transfer (FRET) between two fluorophores tagged to proteins of interest can be used to measure their level of interaction *in vivo* (scheme a). In *E. coli*, using tagged CheY/CheZ as a phosphorylation-dependent FRET interaction pair provides a reporter of the kinase activity, which allows to evaluate the behavior of the pathway [103]. Second, using cells tethered to a microscopy slide, either directly by their flagella or with their flagella attached to beads (scheme b), the dynamics of motor rotation and its changes upon stimulation can be monitored [28,54,55,79]. In both of these methods, the cells are not moving and are stimulated by changes in effector concentrations in the medium flowing over them, often but not necessarily step-like. Finally the swimming dynamics of population of cells can be monitored in gradients of chemoeffectors (scheme c), using video-microscopy and microfluidics devices [62] combined with particle tracking [39] or other image analysis techniques [59]. This enables taking into account feedbacks of the motion in a gradient on the pathway operating point [50•], as well as monitoring intercellular interactions. An older, simpler but less controlled and informative version of this method is the classical capillary assay, where bacterial accumulation towards a capillary filled with attractant is monitored [1].

Typically, microfluidic devices are used to form controlled one-dimensional chemical gradients. These devices usually feature two reservoirs with different concentrations of chemoeffector, linked by a straight channel where a linear gradient forms, within 1 to 2 hours in a 2-mm-long channel [59]. Non-linear gradients can also be created, by modulating the shape of the intermediate channel [62]. The gradients formed in these configurations are relatively shallow, but sharper gradients can also be created in flow devices [63].



(adapted activity and thus the tumbling rate) [35,72,73]. Above a certain threshold, the topology of the network makes the adapted activity a function of relative rather than absolute amount of proteins [72,73], thus making it robust against correlated fluctuations in the expression of chemotaxis genes [9,74]. In contrast, the pathway is highly sensitive to fluctuations in protein ratios, and the relative abundances of CheR and CheB or CheY and CheZ are under strong selection [58••,73,75•]. However, these fluctuations are reduced by the polycistronic organization and common regulation of chemotaxis genes, which ensures tight coupling of their expression in single cells [73]. Competition between CheB and CheY for phosphorylation may further allow tuning the adapted kinase activity according to CheY expression [72]. Finally, cell-to-cell variations in average CheY-P level are also partly compensated by adaptation at the motor level [55,56].

The chemotaxis system also apparently evolved robustness against external perturbations, such as variations in temperature. This robustness of the adapted activity is achieved by the multilevel compensation of the temperature dependences of the pathway components' behaviors, while the adaptation kinetics is tuned to optimal performance at the respective growth temperature [76].

Despite these elaborate compensatory mechanisms, experiments showed a substantial cell-to-cell variability in the parameters determining the average drift of a cell in a gradient [34,58••], attributed to gene expression noise. This intercellular variability may also be exploited by bacterial populations [64,75•] (see Figure 2c, top). These bet hedging strategies may enable the population as a whole to thrive in multiple environments [77]. For example, the diversity of adaptation time and steady state activity due to variable expression of CheR and CheB enables a population to maintain performance in large variety of gradients while individuals get segregated in each gradient [56,58••,64,78].

Temporal fluctuations of the run duration in individual cells, on a time scale of 10 s [34,79], might also be

beneficial (see Figure 2c, bottom). These fluctuations are believed to arise because of the stochasticity in the receptor methylation dynamics resulting from low expression levels of CheR and CheB, as well as their transient tethering to the receptor arrays [31,80]. The swimming behavior of adapted bacteria should then take the form of a Levy walk [67], with periods of long runs exploring large distances alternating with periods of short local searches. Although direct experimental evidence for such swimming behavior is scarce because of the technical challenges of cell tracking on large time scales [81], the long explorations are believed to be beneficial in environments with scarce food sources. They may further improve the chemotactic behavior in gradients, by allowing bacteria to jump from one food source to the next, by increasing the maximum drift speed [67,82,83] or by counterbalancing the detrimental effects of having several uncoordinated motors on the sensing in shallow gradients [84,85].

Perspectives

Bacterial motility and chemotaxis are physiologically expensive, requiring in *E. coli* approximately 3% of the total cellular protein amount and consuming per second 3×10^6 kT [86], energetic equivalent of 3×10^5 ATP molecules, for operation. Given these high costs, the bacterial chemotaxis system is likely to have been evolutionary fine-tuned for optimal performance. Indeed, it has been speculated that multiple features of the *E. coli* pathway, including levels and activities of individual proteins [44,67,74,84], can be explained as products of such selection. Furthermore, the assumption of evolutionary optimization has been used to infer the probable shapes of the most frequently encountered amino-acid gradients [87]. Experimental evolution under defined conditions could then be used to test theoretical predictions. Indeed several recent studies demonstrated that bacteria are able to rapidly adjust their motile behavior under selective pressure [88–90].

Nevertheless, rationalizing properties of the pathway in the context of evolutionary optimization remains a challenge that requires even better quantitative understanding of the chemotactic behavior as well as of the metabolic requirements and the nature of gradients present in bacterial habitats. Although it was recently shown that chemotactic preferences of *E. coli* are strongly correlated with the respective metabolic values of individual amino acids [91] or sugars [26••], the overall chemoeffector spectrum of *E. coli* and other bacteria still awaits explanation in the context of cell physiology, and at least some chemoeffectors appear to serve signaling rather than metabolic function [92•]. It would be also important to understand why gradients of some attractants — amino acids in the case of *E. coli* — are detected by binding to specific receptors and therefore can be followed with very high sensitivity and over a wide dynamic range, whereas detection of other attractants, such as sugars, occurs via indirect binding or via the PTS that both enable only a narrow dynamic range of detection [21,26••,27].

More generally, it remains to be shown how the observed differences in the composition of the chemotaxis pathway and in motility among bacteria [5] could be explained by their different environmental niches. For example, marine bacteria can experience dramatic changes of their environment on a time scale of seconds due to turbulent flows [93]. These challenges might explain several important differences in their motility and chemotaxis from the *E. coli* model, including chemokinesis [68] and reorientations by flicking [94].

Another remaining challenge is to elucidate how chemotactic behavior at the level of populations is influenced by chemical and physical interactions between bacteria. Indeed, chemical gradients generated by bacteria can mediate chemotaxis-dependent self-aggregation, thus creating seeds of multicellular communities [92•]. Physical interactions control bacterial motility at high density, such as during swarming on the surface, but understanding their implications for chemotaxis requires further investigation [95,96].

Conflicts of interest

None.

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- • of special interest
- •• of outstanding interest

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