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An atlas of metabolites driving chemotaxis in prokaryotes

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Chemicals inducing chemotaxis have been characterised for over 60 years across hundreds of publications. Without any synthesis of these scattered results, our current understanding of the molecules affecting prokaryotic behaviours is fragmented. Here, we examined 341 publications to assemble a comprehensive database of prokaryotic chemoeffectors, compiling the effect (attractant, repellent or neutral) of 926 chemicals previously tested and the chemotactic behaviour of 394 strains. Our analysis reveals that (i) not all chemical classes trigger chemotaxis equally, in particular, amino acids and benzenoids are much stronger attractants than carbohydrates; (ii) over one-quarter of attractants tested are not used for growth but solely act as chemotactic signals; (iii) the prokaryote's origin matters, as terrestrial strains respond to 50% more chemicals than those originating from human or marine biomes; (iv) repellents affect cell behaviour at concentrations 10-fold higher than attractants; (v) the effect of large molecules and the behaviour of bacteria other than *Proteobacteria* have been largely overlooked. Taken together, our findings provide a unifying view of the chemical characteristics that affect prokaryotic behaviours globally.

At the scale at which microorganisms live and interact, the environment is often characterised by strong physicochemical heterogeneity[1,2]. Indeed, many microscale processes such as cell lysis, exudation, excretion, or decay release chemicals, creating hotspots where concentrations of solutes can be orders of magnitude higher than in the surrounding environment[1,2]. Some of these chemicals are information-rich, allowing microbes to sense their conspecifics, their competitors, their hosts or their next meal[3]. Within these highly heterogeneous habitats, some prokaryotes can use motility and chemotaxis, allowing them to direct their movements in response to chemical gradients arising from these hotspots[4,5]. Chemotaxis is prevalent among prokaryotes from diverse ecosystems[6–8] and this behaviour has long been considered as a foraging strategy, as it provides a competitive advantage to motile cells by enhancing their access to nutrients[9,10]. Yet, chemotaxis is also used for many other purposes, as it drives population expansion[11], regulates biofilm formation[12], mediates collective behaviours[13], and is key to the onset of symbiosis and pathogenicity[14,15]. In addition, because this behaviour fosters inter-species interactions, chemotaxis also influences key ecological processes, such as primary productivity[16,17], the rate of biochemical transformations[10,18], the production of climate-active molecules[19], the cycling of growth-limiting elements[20], and the long-term storage of carbon in soil and sediments[21–23].

At the cellular level, chemotaxis is arguably one of the best described microbial processes, following extensive description of the biochemistry and biophysics of the chemotactic machinery in *Escherichia coli* and other model bacteria[24–26]. The central signalling pathway involved in this behaviour appears to be largely conserved among prokaryotes, and modulates the rotation of the flagellar motor that propels the cells[25]. The first quantification of chemotaxis was carried out by Julius Adler more than 60 years ago using a capillary assay[27]. Since then, qualitative and quantitative chemotaxis assays have been

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conducted under laboratory conditions using a wide range of approaches, including capillary- and agarose-based assays, as well as microfluidic devices[27–29]. Recently, chemotaxis assays have also been applied directly in the environment, confirming the widespread use of this behaviour in natural populations[28,30]. Together, these approaches have led to the identification of a multitude of chemical compounds that either attract or repel motile bacteria and archaea. However, this wealth of knowledge is scattered across hundreds of publications and a unifying view of the classes and characteristics of molecules that drive prokaryotic chemotaxis, and thereby affect the behaviour of bacteria and archaea, is currently lacking. As new capacities have emerged to identify chemical currencies between microorganisms[31] and to probe for microbial behaviour in the environment[30], it is now more important than ever to look back at the large body of chemotaxis research to guide future studies.

Here, we gathered the results derived from 60 years of chemotaxis assays on prokaryotes to construct a comprehensive database of individual compounds previously tested as chemoeffectors for bacteria or archaea. Through this meta-analysis, we aimed to determine: (i) what the characteristics of the chemicals tested as chemoeffectors are; (ii) if consistent responses to these chemicals exist, based on their physicochemical characteristics (e.g., molecular weight, polarity or structure); (iii) what the diversity of microorganisms responding to these chemicals is, and (iv) if strains isolated from distinct biomes respond differently to specific chemicals. By synthesising and analysing this large body of research, our work sheds light on the chemicals controlling prokaryotic behaviours and highlights avenues for future research.

Results and Discussion

Overview of 60 years of chemotaxis assay methodologies

Quantitative chemotaxis assays (i.e., enumerating cells or measuring their velocity) were performed in 72% of the 341 studies in our database. Capillary-based assays were the most commonly used method (performed in 213 publications, representing 63% of all studies), as this was the first method allowing effective quantitative measurements of the chemotactic response. While being relatively straightforward and sensitive, these assays can be subject to reproducibility issues[29]. Other methods include monitoring chemotactic cells swimming on soft agar plates – which mainly allows qualitative visualisation responses – as well as chamber-based and microfluidic assays. Recent reviews have summarised the most common chemotaxis assays, highlighting their advantages and constraints[29,32]. Cell quantification was mainly performed by plating chemotactic cells (62% of quantitative studies) or by image analysis from microscopy (29% of quantitative studies). Importantly, 77% of the publications exclusively examined attraction, (Table 1) and given this emphasis, we first focus our analyses on chemicals attracting prokaryotes.

Table 1 | Summary of the chemotaxis databases

		Attraction	Repulsion
Number of studies	Attraction or repulsion only	264	15
	Both attraction and repulsion	62	
Tested chemicals	Inorganic compounds	73	56
	Organic compounds	733	365
	Number of Super-classes	13	12
	Number of Sub-classes	127	73
Number of studied prokaryotes	Bacterial strains (genera)	375 (78)	81 (40)
	Archaeal strains (genera)	9 (5)	2 (1)
	Prokaryotic strains per biome (genera)		
	Human/Animal	48 (15)	18 (10)
	Terrestrial	208 (31)	12 (9)
	Freshwater	17 (9)	7 (5)
	Marine	55 (29)	19 (13)
	Polluted	29 (8)	3 (3)

Characteristics of chemoattractants

We identified a total of 806 compounds tested as potential attractants on at least one prokaryotic strain, including 733 organic and 73 inorganic chemicals (Table 1, Fig. 1A). Organic chemicals are scattered across 13 super-classes and of those tested most were organic acids (26% of the organic compounds), organic oxygen compounds (21%), benzenoids (20%), lipids (9%) and organoheterocyclic compounds (7%). Within these super-classes, organic oxygen compounds include mainly carbohydrates and carbohydrate conjugates (85%), while organic acids are mostly comprised of amino acids, peptides and analogues (72%).

The size of the compounds tested for their potential attraction is not homogeneous. Indeed, 83% have a low molecular weight (<300 g mol^{-1}, LMW; Fig. 1B). Moderate- (between 300 and 1000 g mol^{-1}, MMW) and high- (>1000 g mol^{-1}, HMW) molecular weight compounds represent only 14% and 2% of all tested compounds, respectively. In addition, half of these MMW and HMW compounds were only tested with one prokaryotic strain, highlighting the fact that they have received limited attention to date. Consequently, a large bias toward low molecular weight compounds exists in chemotactic studies and the role of larger molecules, such as polysaccharides or proteins, is still poorly characterised. Yet, both low molecular weight compounds and larger molecules can be released through cellular exudation or lysis[16,33], and therefore likely represent abundant chemical hotspots that chemotactic prokaryotes may respond to[4]. The rationale for preferentially testing LMW compounds is linked to our understanding of the detection of molecules by chemoreceptors. Indeed, all major classes of chemoreceptors are activated by the detection of chemoeffectors at specific ligand-binding domains, which only accommodate small molecules[34,35]. However, our analysis reveals that a large proportion (38%) of the MMW and HMW compounds attracted at least one strain (compared to 58% for LMW) (Fig. 1B). This is of particular importance, as recent studies have begun to demonstrate that terrestrial and marine bacteria are attracted towards polysaccharides, such as alginate, pectin and laminarin[36,37]. Notably, in one study the strongest attraction to laminarin occurred towards the largest size fraction (>3000 g mol^{-1}), compared to smaller laminarin polymers and its monomer constituent[37]. HMW molecules diffuse less quickly, forming sharper gradients that linger for longer periods of time within the detection limit of chemotactic prokaryotes[38]. These large molecules may therefore play important, albeit previously overlooked, roles in shaping the microscale structure of microbial communities and should not be neglected in future chemotactic studies.

Another parameter influencing the diffusion of a compound is its polarity, which is defined by the distribution of electric charges within a molecule. In the context of chemotaxis, polarity dictates if a given compound can freely diffuse across cell membranes and, perhaps more importantly, how soluble it is in water. Indeed, the high polarity of the water molecule means that it typically solubilises other polar molecules, while most non-polar molecules are either poorly soluble or insoluble in water (i.e., hydrophobic). Here, we used four parameters to estimate the polarity of the 70 compounds most frequently used in chemotaxis assays, mainly amino acids and carbohydrates (Supplementary Data 3). The proportion of strains attracted towards carbohydrates was not correlated to any of these parameters (Pearson,

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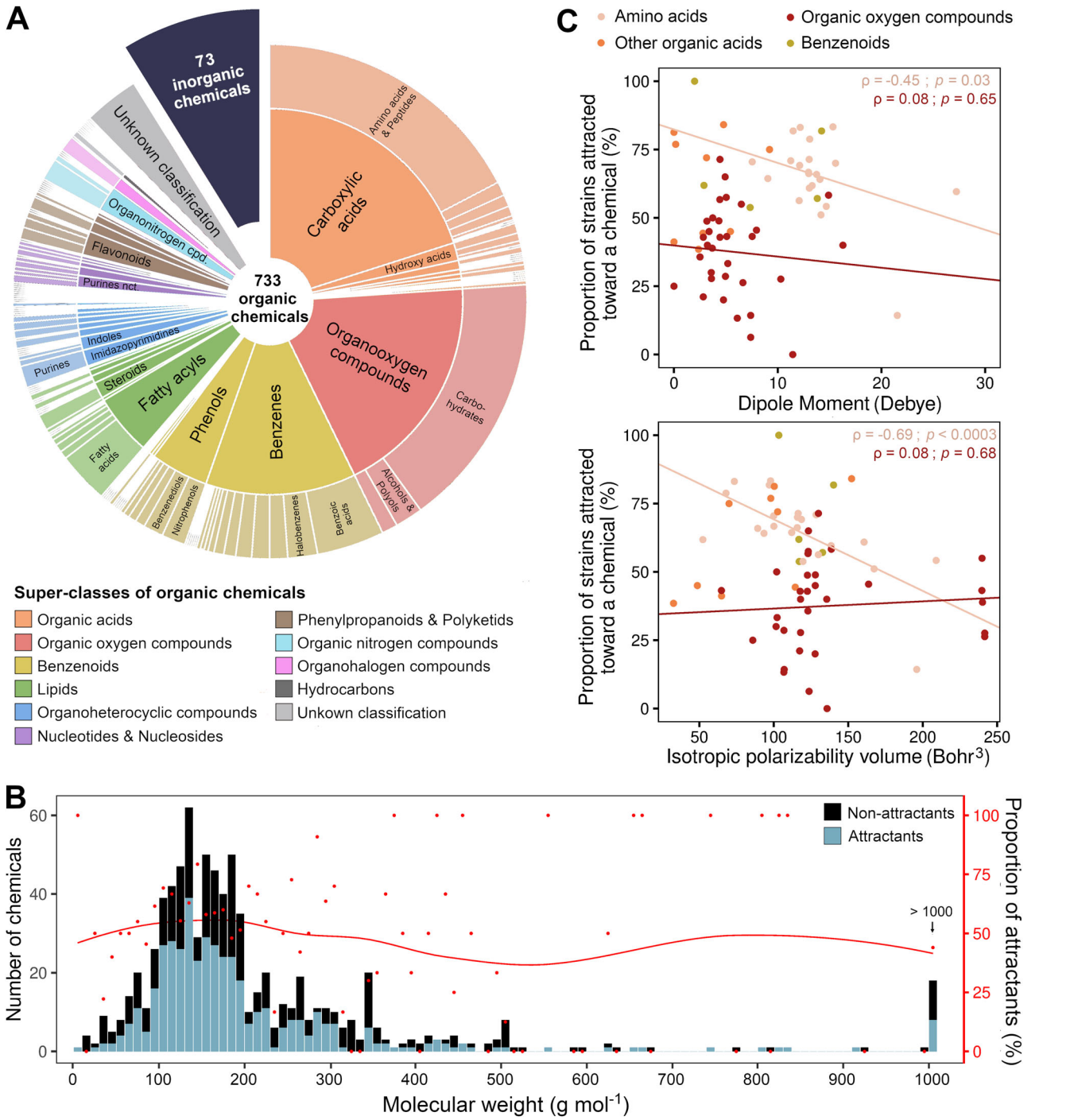

Fig. 1 | Overview of the chemicals used in attraction assays. A Chemical classification of the tested compounds. Colours denote organic chemical super-classes while the inner and outer rings represent classes and sub-classes, respectively. **B** Distribution profile of the chemical used in attraction assays based on their molecular weight. Each bar represents a 10 g mol^{-1} range, except the last bar, which includes all chemicals with a molecular weight exceeding 1000 g mol^{-1}. The red dots indicate the proportion (%) of compounds identified as attractants in a given range and the red trend line was generated using a local regression method. Chemicals were identified as attractants if they acted as such on at least half of the prokaryotic strains tested. **C** Proportion of strains attracted toward a given chemical according to its dipole moment (top) or isotropic polarizability volume (bottom). Linear regressions are displayed for amino acids and organic oxygen compounds and the Pearson correlation coefficient ρ (one-sided) is indicated together with the p-value.

$p > 0.05$; Fig. 1C and Figure S1). Conversely, for amino acids, the proportion of attraction was negatively correlated with both the dipole moment ($\rho = -0.45$, $p = 0.03$; i.e., the net molecular polarity) and the isotropic polarisability volume ($\rho = -0.69$, $p < 0.001$) – the ability of the molecule to acquire a dipole moment in the electric field[39]. These results suggest that chemical polarity may influence chemotaxis towards amino acids. However, the absence of significant correlation observed for carbohydrates is likely explained by their very similar polarity values. Therefore, this analysis should be confirmed on a broader set of compounds with a wider range of polarity.

From the 806 chemicals tested, 513 acted as chemoattractant for at least one prokaryote strain. Analyses revealed that all chemicals do

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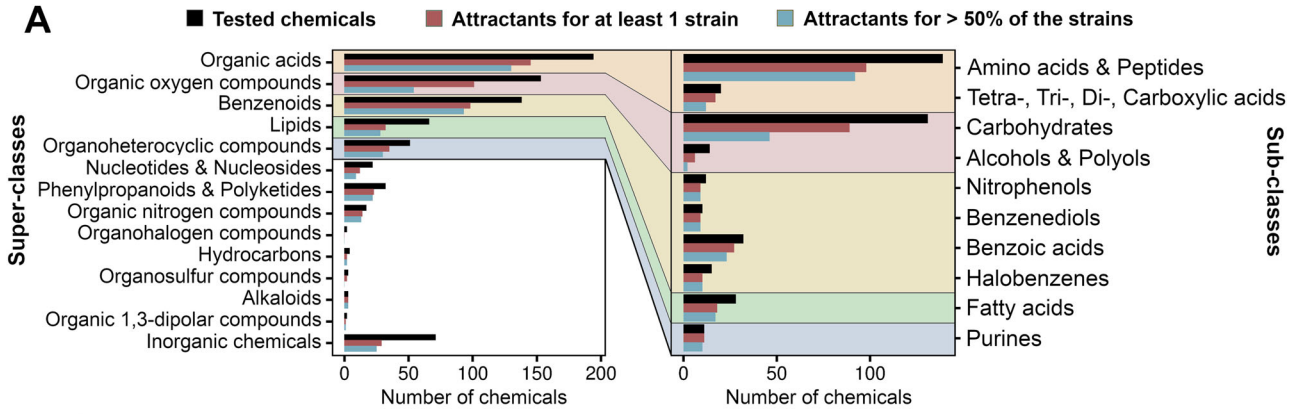

B

	Compounds	MW	Classification	Number of Genera	Number of Strains	Number of Studies	Strains per biome H	T	F	M	P	N/A
Never attractant	D-glucuronate	194.1	Carbohydrates	6	7	7	4	1	.	.	.	2
	Fe(III) chloride	162.2	Inorganic compounds	10	12	3	3	.	.	.	.	9
Always attractant	Malate (unknown configuration)	134.1	Beta hydroxy acids and der.	20	101	37	8	82	1	2	4	4
	DL-malate	134.1	Beta hydroxy acids and der.	4	6	4	.	5	1	.	.	.
	Alginate	>1000	Carbohydrates	4	6	3	1	1	.	4	.	.
	Catechol	110.1	Benzenediols	5	10	7	1	5	.	1	2	1
	Luteolin	286.2	Flavones acids	4	5	5	.	5	.	.	.	.

Fig. 2 | The effect of chemical classification on chemoattraction. A Number of chemicals per super-class (left) and main sub-class (right). Only sub-classes containing at least 10 tested compounds are shown. **B** Compounds never (top) or always (>97%; bottom) found as attractants in the collected assays. Only compounds whose effect was assessed with at least five different strains belonging to at least three distinct genera among at least three studies are reported. A red colour gradient was applied to reflect the number of genera tested. Compounds are coloured based on their classification at the super-class level. Red: organic oxygen compounds; Orange: organic acids; Yellow: benzenoids. The abbreviation "der." stands for "derivatives". The number of prokaryotic strains tested with each compound is indicated per biome. MW: Molecular weight; H: Human/Animal; T: Terrestrial; F: Freshwater; M: Marine; P: Polluted; N/A: Not available.

not attract prokaryotes equally. The sub-classes that stood out as the most appealing to prokaryotes were amino acids and peptides (66% attract at least half of the strains tested), benzenoids sub-classes (>67%) and purines (91%) (Fig. 2A). In comparison, only 35% of carbohydrates and 14% of alcohols and polyols attracted at least half of the tested strains. A few compounds always induced the same effect (Fig. 2B). Two compounds (tested with more than five strains across different genera and studies), D-glucuronate and ferric chloride, never attracted prokaryotes (Fig. 2B). Conversely, five compounds always triggered attraction, malate (DL- and unknown enantiomer), alginate, catechol and luteolin (malate was attractant in 97% of the assays, the others in 100%). In particular, malate consistently attracted members of 21 genera found in all biomes (from eight different classes and four different phyla). Studies of the chemosensing apparatus of model prokaryotes, such as *E. coli* and *Rhodobacter sphaeroides* revealed that individual compounds are sensed by specific receptors[40]. Although our results are based on a limited number of genera, the ubiquitous response to malate across eight bacterial classes suggests that malate receptors might be widespread in chemotactic bacteria, hinting at the possibility that malate may play an important signalling role in the environment.

Chemotactic responses were also affected by optical isomerism (i.e., enantiomers). Several bacterial and archaeal strains were attracted towards specific L-amino acids but did not respond to their D-form[41–43], or with a threshold concentration 100 to 1000-fold higher[44] (Table S1). Natural proteins are exclusively built from L-amino acids as D-amino acids cannot be incorporated into proteins via ribosomal synthesis[45]. The lower metabolic value of D-amino acids likely explains the chemoreceptors' specificity towards L-forms. In addition, several studies reported that D-amino acids have a role in biofilm disassembly[46,47], suggesting that they could be more effective as chemorepellents[43]. A notable exception is aspartate, as both enantiomers were frequently attractant (in 62 out of 88 tested strains and four out of five for the L- and D-forms, respectively). Three out of the four strains attracted to D-aspartate are known plant pathogens, belonging to the species *Pseudomonas syringae* and *Pectobacterium atrosepticum*. As D-aspartate is found in plant cell wall[48], chemotaxis towards this molecule may facilitate pathogens' entry into plant tissues[49]. Specific attraction towards the natural enantiomer was also observed for chemicals from other sub-classes, such as the hydroxy acid malate whose natural L-form is a major component of plant exudates. The L- and DL-forms triggered attraction in 75% of the tested strains (15 out of 20; the five non-attracted strains were only assayed at lower concentrations)[50] and 100% of the tested strains (six out of six), respectively. Moreover, malate of unknown configuration attracted 97% of the tested strains (97 out of 101). While not mentioned, these assays were likely conducted with the L- or DL-forms as the utilisation of D-malate, which is scarce in nature, would have certainly been specified. Conversely, only 28% of the strains tested (two out of seven) were attracted to D-malate and exhibited a weaker response than L-malate[50–52]. Such distinct responses depending on the molecule configuration were not observed for all compound classes. Indeed, similar attraction behaviour was observed towards both enantiomers for several monosaccharides, such as arabinose, arabitol, fucose, galactose or lyxose (Table S1). In nature, most sugars occur in their D-conformation, while their L-form is extremely rare. However, L-arabinose and L-lyxose are the most common enantiomers, and both forms of fucose, galactose and arabitol are found widely[53–55]. The finding that chemotactic specificity towards one enantiomer depends on the class of the compound likely reflects the relative abundance of the different enantiomeric forms in the environment.

Variations of the chemotactic response depending on the different type of molecules might be linked to their biochemical and ecological functions, and metabolic value. Three main types of attractants can be distinguished, with (i) those that are only used as substrates, to sustain biomass production, (ii) those acting as signals only, helping

cells to reach a specific environment, and (iii) those with a dual role, acting both as substrate and signalling molecule[3,56,57]. One-third of chemoattraction studies also investigated (for at least one metabolite-strain pair) the ability of the strain to use the chemical for growth. Our analysis revealed that if a strain was attracted towards a chemical, it was able to use it as a carbon source in 73% of cases. This proportion drops to 34% when the chemical does not affect the chemotactic behaviour of a strain. This trend was verified for all compound sub-classes (Table S2). Such findings suggest that strains that acquired the ability to catabolize specific chemicals also developed an ability to sense them in the environment.

Among the compounds that did not support the growth of the targeted strain, 44% still induced attraction (Table S2). This proportion varied depending on the chemical sub-class, ranging from 56–59% for amino acids and benzoic acids to twice less (28–29%) for carboxylic acids and carbohydrates. Chemotaxis has predominantly been recognised as a foraging strategy, wherein chemoattractants directly function as sources of nutrients or energy[58], but this behaviour also serves many other ecological processes[3,5], including signalling the presence of host organisms[14,15] and attractants could also act as chemical cues to reach other energy sources. However, it is also important to note that, while 80% of the studies assessing prokaryotic growth used the tested chemicals as the sole carbon source, some compounds can only be used for growth in the presence of additional carbon and nitrogen sources.

Who are the prokaryotes attracted by these metabolites?

Our analysis also allowed for investigation of behavioural patterns based on the taxonomy of the chemotactic prokaryote. Overall, we collected data on the chemoattraction behaviour of more than 384 motile prokaryotic strains belonging to at least 153 different species and 83 genera (Table 1, Fig. 3A). Members of the class *Gammaproteobacteria* are the most represented (207 strains, i.e., 53%), followed by *Alphaproteobacteria* (60 strains, i.e., 16%), *Betaproteobacteria* (27 strains, i.e., 7%) and *Bacilli* (28 strains, i.e., 7%). The most studied genera include *Pseudomonas*, *Escherichia*, *Bacillus*, and *Vibrio*. In comparison, archaeal chemotaxis has been much less studied with only nine publications, testing nine archaeal strains (five genera), accounting for only 2.5% of all prokaryotic strains tested, and with these largely restricted to halophilic archaea[59].

The tested prokaryotic strains were initially isolated from a wide range of environments, mostly from terrestrial (56%, 273 different compounds tested), marine (14%, 137 compounds), or human/animal biomes (12%, 384 compounds). A few strains were also derived from polluted (6%, 139 compounds) or freshwater (4%, 89 compounds) environments. An important proportion (70%, 469 compounds) of chemicals was only tested with strains from one biome. Organic oxygen compounds and organic acids were the chemicals most tested with strains from all biomes, with the exception of polluted habitats (Fig. 3C). These chemicals play a central role in cellular metabolism and are widespread in nature, including within microhabitats where chemotaxis is prevalent, such as the phycosphere[57,60,61] or the rhizosphere[62,63]. In contrast, the effect of benzenoids, hydrocarbons and organohalogens was especially characterised in strains isolated from polluted habitats. These compounds are released in high quantities in the environment through anthropogenic activities and are considered as ubiquitous pollutants[64]. Addressing the chemotactic behaviour of strains found in contaminated sites in response to these pollutants is therefore essential, since chemotaxis is an important determinant of microbial bioremediation[65].

The diversity of physicochemical conditions experienced by microorganisms originating from different biomes and occupying a wide variety of ecological niches may also foster distinct behavioural responses in prokaryotes. Terrestrial strains displayed a chemotactic behaviour towards a significantly larger proportion of chemicals (on average 72%) than strains from the human/animal (50%) biome (Tukey's HSD test, $p = 0.01$) (Fig. 4A). Interestingly, the lower chemotactic abilities of the human/animal strains might be explained by a low number of chemoreceptors in their genome. Indeed, 55% of the chemotactic assays of the human/animal biome were conducted with *Escherichia coli*, *Campylobacter jejuni* or *Helicobacter pylori* strains. These strains possess on average only five, 10 and four chemoreceptors, respectively, while the average for chemotactic bacteria is 14[66–68]. In comparison, at least 40 out of the 66 tested terrestrial species (used in 65% of terrestrial assays) possess more sophisticated chemotaxis system with 20 to 64 chemoreceptors. Although not statistically significant (likely due to the limited number of values for the other biomes), the proportion of chemicals that terrestrial strains were attracted to was also higher compared to polluted (64%), marine (54%) and freshwater (50%) biomes.

We found no strong effect of biome of origin on chemotaxis across chemicals and their subclasses. This may be because many prokaryotic taxa and tested compounds can be found in multiple biomes. However, a few caveats to this pattern must be considered. For instance, terrestrial strains frequently responded to organic acids: 69% of them were attracted to at least three-quarters of the organic acids tested, while this proportion drops to 38% and 11% for strains isolated from human/animal and marine biomes, respectively (Fig. 4B). Among organic acids, amino acids were particularly potent attractants in terrestrial environments as all of them (i.e., 20) triggered chemoattraction in more than 75% of the terrestrial strains tested (Fig. 4C). In comparison, only three and seven amino acids were potent attractants in human/animal and marine environments, respectively. Between 35–40% of human/animal and terrestrial strains responded to at least 75% of tested organic oxygen compounds, but this proportion was 2.5-times lower for marine strains. Carbohydrates – the most represented chemical sub-class of organic oxygen compounds – also attracted a similar proportion of human/animal and terrestrial strains.

The effect of repulsion

While chemoattraction has received a lot of attention over several decades, the investigation of chemorepulsion has been relatively limited. Nevertheless, the effect of 421 chemicals was examined (although we could consider that all chemicals that are an attractant at a specific concentration are not acting as repellent) across 77 publications that either specifically focused on evaluating repulsion (15 studies) or conducted assays allowing the identification of both attractants and repellents (62 studies; Table 1). Half of the studies (38) assaying repulsion were carried out on enteric strains isolated from the human/animal biome. Consequently, 317 chemicals were tested on members of this biome, while only 79 and 67 were tested on strains from the marine and terrestrial biomes, respectively, and less than 30 on strains from freshwater and polluted habitats (Fig. 5A). Altogether, 186 chemicals were reported as repellents at least once in the literature, three times less than the number of known attractants.

As was seen with attractants, analyses based on molecular weight revealed that LMW compounds represented 88% (i.e., 370) of the compounds tested as repellents (Figure S2A). The proportion of repellents was similar among MMW/HMW compounds (36%) and LMW compounds (38%), suggesting that large chemicals also likely play key roles in chemorepulsion and need to be better integrated in chemotaxis studies.

As observed for chemoattractants, organic acids (29% of the organic compounds), benzenoids (19%), organic oxygen compounds (18%), lipids (11%) and organoheterocyclic compounds (11%) were the most tested repellents (Figure S2B). Among the chemicals tested as repellents, 29% (120 compounds) were never tested as attractants, including some amino acids and derivatives (13%), fatty acids (8%), benzoic acids (7%), and indoles (7%) (Fig. 5B). Benzoic acids, nitrophenols, halophenols and phenylhydrazines (from the super-class

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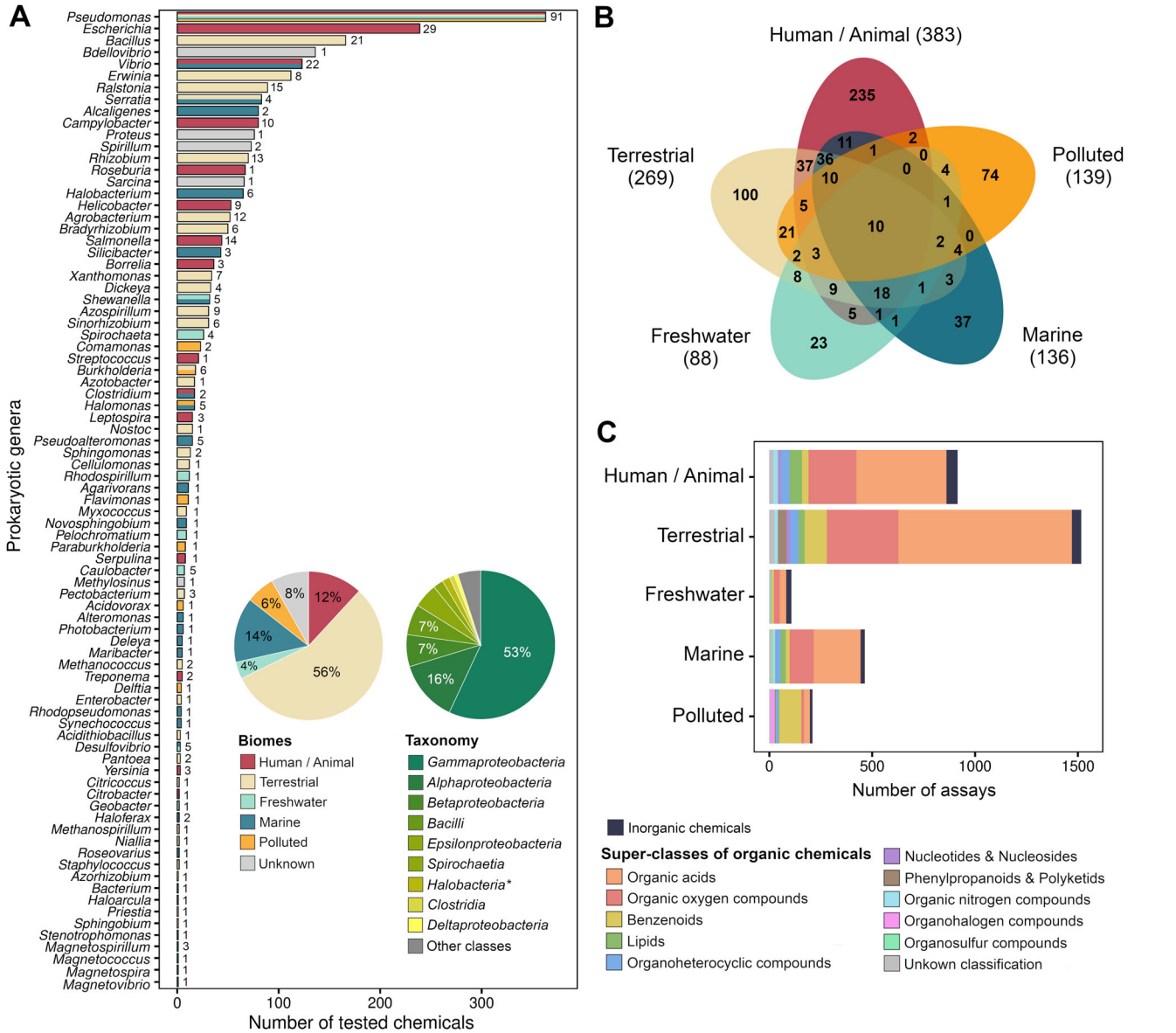

Fig. 3 | Origin and identity of the prokaryotes used in attraction assays. **A** Number of tested chemicals per prokaryotic genus. Genera are coloured by biome. The number of publications that performed chemotaxis assays with each genus is indicated at the end of the respective bar. Pie charts representing strain distribution depending on biome (left) and taxonomy (class level; right) are shown. Asterisks denote archaeal genera/classes. Unknown taxonomy and classes containing less than three tested strains (*Acidithiobacillia*, *Actinomycetia*, *Cyanophyceae*, *Flavobacteriia*, *Methanococci**, *Methanomicrobia** and *Oligoflexia*) are referred to as "Other classes". **B** Venn diagram showing the number of chemicals tested with strains from only one biome or with strains from multiple biomes. The total number of chemicals tested per biome is indicated in brackets. **C** Super-class profile of the chemicals tested with strains from each biome. Each time a chemical was tested with a different strain, it was counted as a separate occurrence. Super-classes containing less than 10 occurrences in all biomes are included in "Other and unknown classification".

benzenoids) and alcohol and polyols were often identified as potent repellents (more than 80% of these compounds displayed a repulsive effect on at least half of the tested strains; Fig. 5C). Conversely, only 4% of the carbohydrates and 17% of the amino acids displayed a repulsive effect.

Contrasting the results from the two databases (i.e. chemoattractants and repellents) revealed that the concentration threshold prompting chemotaxis is on average 10 times higher for repellents than for attractants (Fig. 5D; t-test, $p < 0.001$). This difference could potentially be the result of distinct sensing pathways or feedback loop regulations. However, such comparisons should be considered carefully as (i) repulsion assays determining threshold concentrations were mainly performed with *E. coli* and *B. subtilis* (56% and 13%, respectively) and might not be fully representative of prokaryotic behaviours, and (ii) sensitivity differs from one chemotactic assay to another. To date, the detection mechanisms for repellents remain elusive as very few repellent-sensing chemoreceptors have been characterised[34]. Several chemoreceptors are implicated in binding both attractants and repellents[35,69]. In addition, recent studies showed that some repellents bind to the exact same binding pockets as attractant molecules[70–72]. In this scenario, attractants and repellents bind with varying affinity as they form different hydrogen-bond interactions with the residues of the ligand-binding pocket, leading to different chemotactic effects[70–72]. Studies on *E. coli* revealed that, depending on its concentration, a compound could act either as an attractant or repellent and that different types of chemoreceptors are involved[69,73–75].

Many studies pointed out that most of the identified repellents were harmful for the targeted strain[76–78]. The higher threshold

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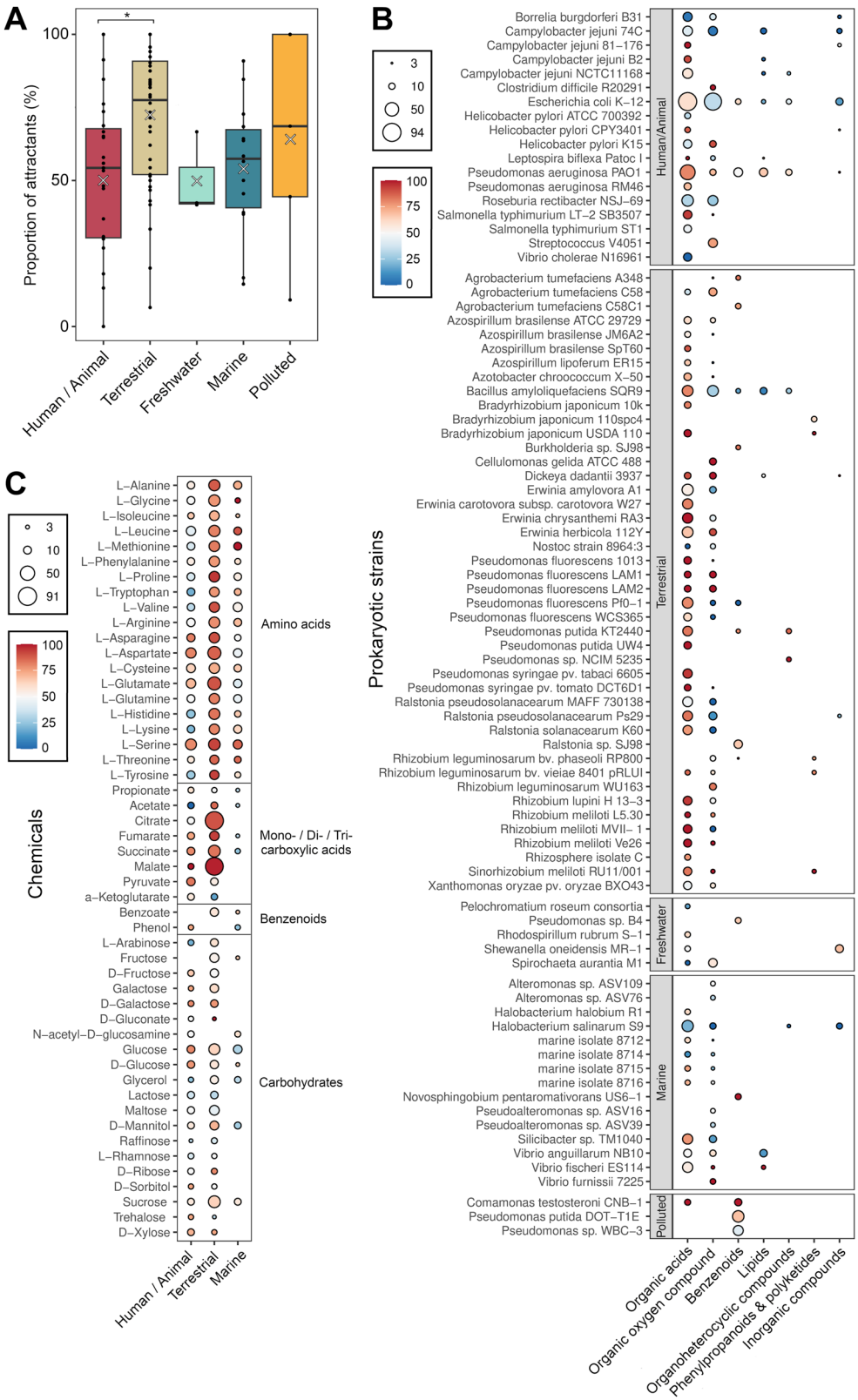

Fig. 4 | Response to attractant across different prokaryotic biomes. **A** Proportion (%) of chemicals attracting a given strain. Only strains tested with at least 10 chemicals are included ($n = 23, 44, 3, 14$ and 5 for Human / Animal, Terrestrial, Freshwater, Marine and Polluted environments, respectively). The box plots represent the first quartile, median, third quartile, and minimum and maximum values (i.e., whiskers). The white crosses denote the average values. ANOVA followed by post hoc Tukey HSD test (one-sided) were conducted, the asterisk denotes significant differences ($p = 0.01$). **B** Chemicals were scattered at the super-class level. Dot colour represents the proportion (%) of chemicals within a super-class attracting each prokaryotic strain. Strains are organised depending on their isolation biome. Only the strains that were tested with at least six chemicals of one super-class are represented. Dot size is proportional to the number of chemicals within each super-class tested with each strain. **C** Dot colour represents the proportion (%) of prokaryotic strains attracted towards different chemicals. Only chemicals that were tested at least three times in at least two out of the biomes "Human/Animal", "Terrestrial" and "Marine" are represented. Dot size is proportional to the number of tested strains.

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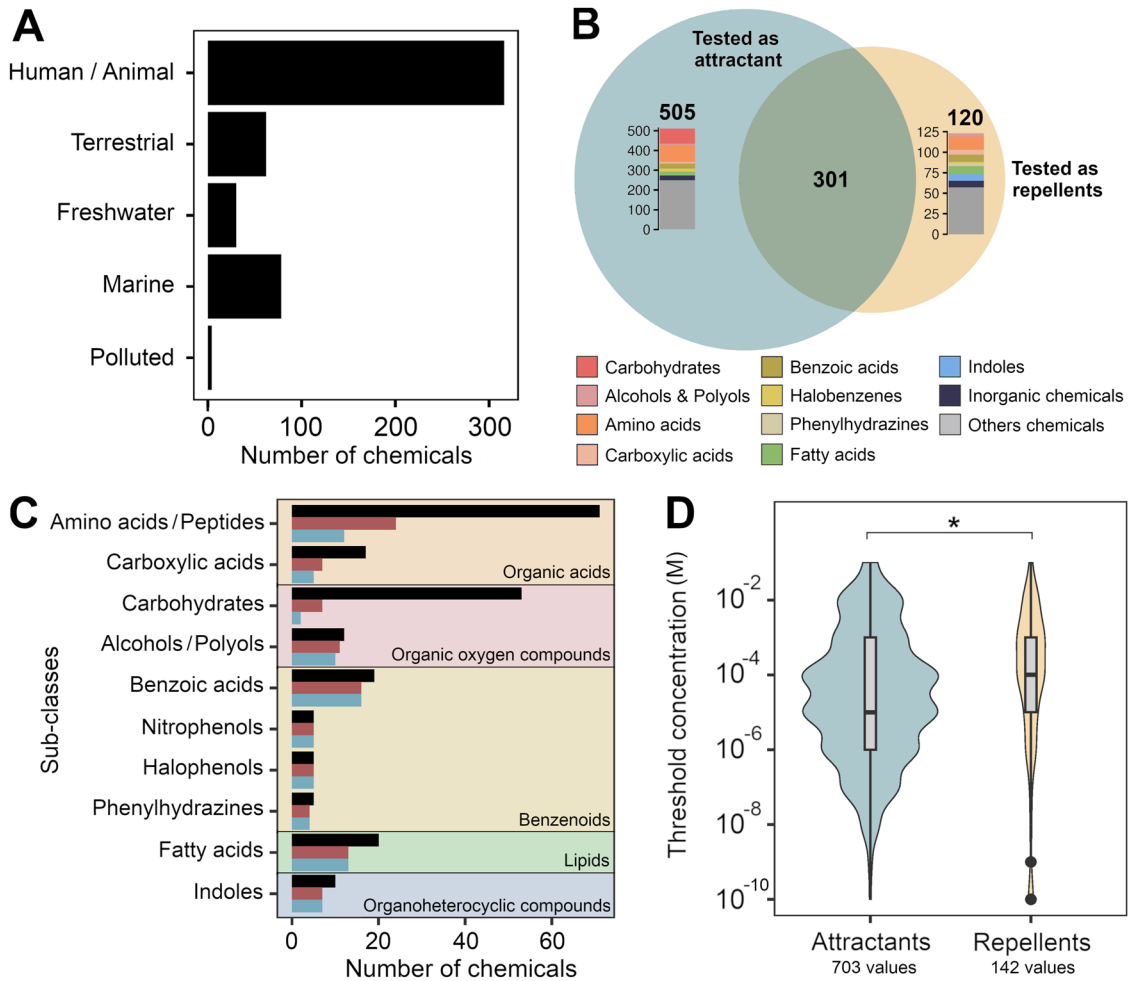

Fig. 5 | General features of the repulsion assays. A Number of unique chemicals tested on strains from each biome. **B** Venn diagram of chemicals used in chemotaxis assays. Bars indicate the organic chemical classification at the sub-class level. **C** Number of chemicals per sub-class. Black: tested chemicals; Red: chemicals identified as attractant with at least one strain; Blue: chemicals identified as attractant with at least 50% of the strains tested. **D** Threshold chemical concentrations (M) assessed for attractants and repellents. The box plots represent the first quartile, median, third quartile, and minimum and maximum values (i.e., whiskers). The asterisk denotes a significant difference (t-test, one sided, $p = 0.007$).

concentration observed for repellents could be due to the fact that repellents only exhibit harmful effects at relatively high concentrations. For example, bacteria can cope with toxic compounds by expelling them via multidrug exporters and efflux pumps[79]. However, at high concentration, a movement response might be required to avoid potential lethal effects. Interestingly, not all repellents elicited a toxic effect. As observed for chemoattraction, some repellents might not directly impact the cells but could act as chemical cues. For example, under stressful conditions, *Vibrio cholerae* cells release some D-amino acids that act as repellents on conspecifics, allowing the cells to escape unfavourable ecological niches[43]. The toxicity of repellents on the targeted strain was evaluated based on the information available in the collected studies. However, toxicity data is available for only 22% of the repellents in our database (i.e., 42/186; and 26 of them have been tested on only one strain), preventing any robust analysis. Our understanding of compounds prompting repulsion is still in its infancy. Future studies should focus on the behaviour of non-enteric strains and on the link between harmfulness and repulsion, in order to determine the ecological roles of prokaryotic repulsion in the environment.

Aerotaxis

Aerotaxis is the movement of cells in response to an oxygen gradient. While the signal transduction mechanisms used in aerotaxis generally differ from the ones involved in classical chemotaxis[80,81], several receptors sense both oxygen and other chemicals[35]. We identified a total of 46 prokaryotic strains (45 bacteria and one archaeon) from 19 genera for which aerotaxis behaviours have been tested (Figure S3). Among them, only two strains, from the species *Rhizobium meliloti*[82], were not aerotactic. This behaviour is therefore widespread in the prokaryotes tested, and homologues of specific aerotaxis transducers (*aer* and *hemAT*) are found in thousands of sequenced genomes, across 10 bacterial and archaeal phyla (Table S3). Sensing oxygen levels is a survival strategy for most of these taxa, as the exposure to inadequate oxygen concentrations is often growth-limiting. As a consequence, oxygen has been reported to act both as an attractant and a repellent for at least 22 strains that migrated to their preferred oxygen concentration and were repelled by suboptimal oxygen concentrations (Figure S3).

Using the database

Our meta-analysis proved a powerful method to identify clear patterns in the way compounds affect prokaryotic behaviours. Users of the database should however keep in mind that these patterns are based on the literature available at the time of writing. In addition, the nature of a meta-analysis implies that all compounds were not tested with the same strains, type of assays and experimental conditions. It is also likely that compounds hypothesised to be effectors were more prone

to be tested, which implies that the proportion of chemicals having no chemotactic effect is likely underestimated in the literature. Conversely, the responses observed in specific laboratory conditions might not reflect the breadth of chemotactic behaviours of a strain toward a chemical. Indeed, similarly to other biochemical process, chemotactic sensing pathways can be only expressed under specific growth conditions (e.g., medium enriched with[83] or limited by the tested effector[84]). Together, these considerations emphasise the need for a greater, and better-integrated understanding of chemotactic behaviours, not only in laboratory settings, but also in the field. By highlighting the heavy skew in the study of certain bacterial strains, biomes and compounds, our database represents a map to guide the design of experiments addressing these caveats.

Conclusion and future directions

This study aimed to synthesise 60 years of chemotaxis assays conducted on prokaryotes. We constructed a database of chemoeffectors, highlighting their behavioural effect on different prokaryotic strains and containing a rich set of contextual data. By classifying chemicals per size and structural groups, and organising strains according to their biome of origin, we generated a unifying view of the existing knowledge on the identity of compounds eliciting chemotactic behaviour in prokaryotes. In particular, we found that all chemical classes do not trigger chemotaxis equally. Specifically, amino acids and benzenoids were much stronger attractants than carbohydrates, and benzenoids were also found to be potent repellents. In terms of chemical structure, our analysis revealed that the two enantiomers of a given molecule can elicit very distinct chemotactic responses, and further analysis led us to hypothesise that the "chemotactic capacity" of an enantiomer depends on its prevalence in the environment. We also underlined that one third of attractants are not used as energy or carbon sources and likely only act as signalling cues. The effect of the biomes of origin was weak, even though a general pattern indicated that terrestrial strains typically exhibited stronger responses than other prokaryotes, notably towards amino acids. Conversely, chemical solubility likely influences chemotaxis and the effect may differ across the different biomes. Finally, we showed that the chemotactic threshold concentration was one order of magnitude lower for attractants than repellents, which calls for additional research to identify the underlying cause.

The comprehensive nature of our analysis allowed us to highlight five important knowledge gaps in the 60 years of chemotaxis research analysed. First and foremost, we revealed that chemotaxis towards large molecules (i.e., carbohydrates or proteins) has been largely overlooked despite their prevalence in organic matter hotspots and their important signalling role, and that the diversity of molecules tested has remained quite low, with amino acids, carbohydrates and benzenes most frequently tested. Second, we demonstrated that our understanding of the chemicals eliciting repulsion is still rudimentary and mostly restricted to enteric biomes, even though chemorepulsion plays crucial roles in many ecological processes. A third major gap lies in the fact that the chemotactic behaviour of archaea is rarely investigated. This is important because archaea are key microorganisms within all natural environments[85]. In addition, archaea and bacteria can inhabit different ecological niches and their motility and chemotaxis machinery present structural dissimilarities[59]. Increased efforts now need to be made to characterise archaeal responses towards various chemicals, to shed light on potential differences with bacterial behaviour. Furthermore, despite the astonishing microbial diversity, only a small proportion of studies have focused on bacteria outside the *Proteobacteria* phylum. While *Bacteroidetes* is one of the most represented phyla in various biomes, with key roles in biogeochemical processes[86], the behaviour of only two strains of this phylum was retrieved in this study. Many *Bacteroidetes* members do not possess a flagellar machinery and rely on gliding motility[87], yet the chemotactic behaviour of prokaryotes that use such motility mechanisms is poorly characterised. Finally, to date, chemotactic studies largely focused on characterising the effect of individual chemicals. While this allowed the identification of key chemotactic drivers and their role in microbial interactions, they do not represent the complexity of chemical hotspots found in the environment, which contains a multitude of metabolites potentially acting in synergy. Consequently, substantial efforts are needed to investigate the prokaryotic responses towards mixtures of diverse chemicals, in order to gain a deeper understanding of the determinants controlling chemotactic-mediated processes[38].

Chemotaxis is one of the most important microbial behaviours, underpinning interspecies interactions, foodweb dynamics and biogeochemical cycling. Our study provides an overarching view of the current knowledge on the effector molecules mediating prokaryotic behaviours. This synthesis, together with the chemoeffector database, will provide a useful resource to guide future efforts deciphering the chemicals structuring microbiomes.

Methods

Coverage of the literature

A comprehensive literature search was performed in June 2024 using the search terms "chemotaxis assays bacteria" and "chemotaxis assays archaea" in Google Scholar. Relevant studies cited in these publications were also collected. To be considered in our analysis, studies had to: (i) report original data quantifying chemotaxis in prokaryotes (i.e., bacteria and archaea); (ii) use identified chemicals. Only data obtained with wild-type strains were collected. This resulted in a total of 341 publications, which we used to build the chemotaxis databases. While we included every study that fitted these criteria, we acknowledge that some might have been missed in our search.

Building of the chemotaxis databases

Two databases were constructed, reporting compounds tested as attractants (Supplementary Data 1) or repellents (Supplementary Data 2). In total, 926 compounds are reported across the two databases. Each entry reports whether a compound is attractant ("+"), repellent ("−") or without any chemotactic effect ("0") on a given prokaryotic strain. In addition, an extensive set of contextual information was included in the databases – encompassing several features.

First, for each compound, we report the chemical formula and molecular weight (g mol^{-1}), as well as their chemical classification, from the Human Metabolome Database (HMDB; https://hmdb.ca) 5.0[88]. The HMDB uses a hierarchical classification with four main levels that are analogous to taxonomic ranks: "Kingdom", "Super-class", "Class" and "Sub-class". The Kingdom level informs if the compound is organic or inorganic. The three lower levels are based on the structure of the organic compounds. When no classification was available, "NA" is displayed (i.e., for 3.5 % (33 out of 926) compounds). As chemotaxis might vary depending on the molecule's configuration (see[89]), the different isomers of a given compound were reported separately. For chiral molecules, if the enantiomer configuration was not mentioned in the original study, we did not specify the configuration in our databases. Molecules with unknown configuration (i.e., not mentioned in the study) were not counted as a different compound unless no specific configuration of this molecule was already reported (e.g., in the database, Malate appears under four different denominations ("Malate", "DL-Malate", "D-Malate" and "L-Malate") but was counted as three different compounds). For the analyses, all amino acids were considered as L enantiomers if not stated otherwise. Indeed, L-amino acids are the predominant building blocks of natural proteins, and we therefore assumed that authors would have explicitly stated if the D configuration had been used. Protonated acids (suffix "-ic acid") and their deprotonated form (suffix "-ate") were not distinguished and the suffix "-ate" was used throughout by convention.

Second, the environments from which the prokaryotic strains were first isolated are reported. We grouped these environments into five different biomes: "human/animal", "terrestrial", "freshwater", "marine" and "polluted" environments. "NA" indicates that the origin of the strains was not reported. The human/animal biome contains strains from human and terrestrial animal faeces, urine, gut and wound. The terrestrial biome includes all strains isolated from plants (e.g., root, leaf or fruit), soil, mud and rock. The freshwater biome is composed of strains isolated in lakes, rivers, groundwater/freshwater sediments. Strains isolated from marine animals (e.g., coral, fish or clam) were counted in the marine biome, which also includes strains from seawater, sand, sediments or hypersaline environments. The polluted biome encompasses strains isolated from polluted soils, sediments, seawater and freshwater. The different derivatives of the *E. coli* K-12 strain were not counted as different strains in the analyses.

Third, the following methodological parameters were considered: the type of chemotaxis assay, the cell counting method and the incubation time. In addition, when assessed in the original study, we reported the capacity of the strain to use the chemical for growth, the range of tested chemical concentrations (in mol L^{-1}; M), the threshold and optimal chemical concentration (M), and the chemotactic index at the optimal concentration. The chemotactic index is calculated by dividing the number of cells affected by the tested compound by the number of cells present in the control condition. When another calculation method was used to quantify chemotaxis, this is mentioned in the "Additional Information" column. When a study reported the same effect with both capillary assay and a non-quantitative method, only the capillary assay was reported in the database (as it brings additional information on the strength of the response).

Polarity estimation

For the 70 most widely tested compounds, four different parameters were used to estimate polarity (Supplementary Data 3): the dipole moment (apparent measure of the overall polarity), the isotropic polarisability volume, the polarisation density (both assessing the capacity of the molecule to polarise) and the hydrophilic-lipophilic balance (HLB) (measuring the degree of hydrophilicity). Values were calculated for the amphoteric form of amino acids and ionic form of other organic acids and benzenoids, as they mainly exist under this form in neutral or weakly basic aqueous solutions. To assess the dipole moment, the isotropic polarisability volume and the polarisation density of the compounds, density functional computations were conducted using Gaussian 09 software at the B3LYP/6-311++g(d,p) level of theory[90]. The solvation effect by water was considered using a polarisable continuum model. HLB was simulated using MarvinSketch software developed by ChemAxon in order to present the lipophilic/hydrophilic nature of those molecules as a measure of polarity. The ChemAxon method was used for the HLB computations.

Statistical analyses

A chemical was considered as an effector (attractant or repellent) if it acted as such in at least 50% of the tested strains. Unclear and variable chemotaxis effects ("0/+" or "0/−") were considered as having no effect. Induced chemotaxis assays (i.e., when the tested strain was initially grown with a compound, subsequently tested as effector) were not considered for the analyses (but are reported in the databases). Attractant and repellent databases were analysed separately.

All figures and statistical tests were generated with the R Statistical Software (v4.1.2[91]) with the packages *ggplot2* (v3.4.0[92]), *reshape2* (v1.4.4[93]), *psych* (v.2.4.1[94]), *RcolorBrewer* (v1.3.3[95]), *webr* (v0.1.5[96]), *moonBook* (v0.3.1[97]) and *VennDiagram* (v1.7.3[98]). A Student's t-test was used to assess the difference in response between attractants and repellents ($p < 0.05$). A one-way analysis of variance (ANOVA), followed by pairwise post-hoc Tukey's HSD, was performed to test if the proportion of chemicals attracting a strain was affected by its origin (biome). The proportion of strains attracted to a given chemical was correlated with the four polarity parameters using Pearson's correlation.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All primary data are available as supplementary information and in the online source data file. Source data are provided with this paper.

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Author contributions

M.B., S.A.A., J.R.S., and J.B.R. designed the study. M.B. and J.B.R. assembled the databases. M.B. and J.B.R. analysed the data. I.B. and U.K. calculated the polarity of the selected compounds. M.B. and J.B.R. wrote the manuscript, and all authors edited subsequent versions.

Competing interests

The authors declare no competing interests.

Additional information

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