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SYNTHESIS

An ecological framework for microbial metabolites in the ocean ecosystem

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Scientific Significance Statement

Microbes account for the majority of biomass and metabolic activity in the ocean. Yet, the diversity of metabolites derived from microbial metabolism obscures our view of which metabolites underpin core ecosystem functions. To approach this challenge, we develop an ecological framework to categorize metabolites that shape key characteristics of marine ecosystems. At the core of this framework, we assume the observed complexity in marine communities must be governed by a hierarchical set of rules that explains how life functions. We borrow familiar terms from the macroecology discipline that define important types of ecosystem species, and we adapt these species concepts to marine metabolites. The metabolites we highlight represent the current state of knowledge and future research priorities, to be expanded with continued observations.

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Abstract

The ocean microbe-metabolite network involves thousands of individual metabolites that encompass a breadth of chemical diversity and biological functions. These microbial metabolites mediate biogeochemical cycles, facilitate ecological relationships, and impact ecosystem health. While analytical advancements have begun to illuminate such roles, a challenge in navigating the deluge of marine metabolomics information is to identify a subset of metabolites that have the greatest ecosystem impact. Here, we present an ecological framework to distill knowledge of fundamental metabolites that underpin marine ecosystems. We borrow terms from macroecology that describe important species, namely "dominant," "keystone," and "indicator" species, and apply these designations to metabolites within the ocean microbial metabolome. These selected metabolites may shape marine community structure, function, and health and provide focal points for enhanced study of microbe-metabolite networks. Applying ecological concepts to marine metabolites provides a path to leverage metabolomics data to better describe and predict marine microbial ecosystems.

Microbes account for approximately two-thirds of biomass in the oceans and play vital roles in ecosystem function and stability (Bar-On and Milo 2019). As such, the majority of biological and metabolic diversity in the ocean is contained within microbial communities. Indeed, the ocean microbiome is estimated to harbor over 100,000 microbial taxa (Sunagawa et al. 2020) that generate tens of thousands of different molecules (Moran et al. 2022a). While a remarkable amount of complexity exists within ocean microbe-metabolite networks, this complexity must be governed by a hierarchical set of "rules" for how life functions. Advances in functional characterization of metabolites concurrent with expanding observations in cultures and seawater communities have demonstrated that there is likely a subset of metabolites with outsized ecosystem impacts.

The ocean is replete with signaling and cross-feeding interactions as microbes exchange metabolites with each other and with macroorganisms. Interactions can be context dependent, and they can range from synergistic to antagonistic with considerable variation in the degree of reciprocity (unidirectional vs. bidirectional), the investment by the partners involved (cost to produce a metabolite), and the function of the particular metabolite (e.g., chemoattractant, vitamin; Kost et al. 2023). We can categorize metabolites based on their lability, or flux, in the marine carbon cycle (Moran et al. 2022a). Metabolites can also be characterized by their molecular structure (Catalá et al. 2021), and/or their functional roles as substrates that mediate carbon, nutrient, and energy transfer, facilitators that enable biochemical reactions, or ecological signals that coordinate biotic interactions (Moran et al. 2022b). While current categorizations are practical for capturing broad marine chemical and metabolic diversity, ecological theory suggests that only a small number of metabolites have substantial community impact, and thus, are essential to understanding an ecosystem (Power et al. 1996; Fig. 1). To develop an ecological framework, we focus on small (< 1500 Da), labile (lifetimes of minutes to weeks) molecules with demonstrated potential to impact microbial community composition and activity (Table 1).

There is precedent for borrowing from ecological paradigms in chemical ecology. An analogy between keystone species and metabolites was introduced in 2013 to recognize four molecules of keystone significance in open-ocean (dimethylsulfoniopropionate; DMSP), coastal-ocean (saxitoxin), riparian (tetrodotoxin), and terrestrial (pyrrolizidine alkaloids) ecosystems (Ferrer and Zimmer 2013). More specific to microbial ecology, the keystone metabolite concept in soil microbiomes highlighted the essential function of the B-vitamin cobalamin (Lu et al. 2020) and redox-active phenazines that have fundamental roles in biocontrol of microbial activity and nutrient acquisition (Dahlstrom et al. 2020). Here, we extend the analogy between ecological species and metabolites. We borrow familiar terms from macroecology and adapt classical ecological definitions to define important marine microbial metabolites that have outsized ecosystem impacts, and whose further study may yield transformative insights. Specifically, we use the terms dominant, keystone, and indicator metabolites, envisioned here as microbially transformed small molecules that play fundamental roles in shaping community structure, function, health, and/or stability (Fig. 1; Table 1). This framework will help guide future efforts to probe metabolite activities and roles in structuring communities.

First, dominant metabolites are those that carry most of the available matter and energy and fuel central metabolism (Grime 1987). The ecological concept of dominance is rooted in the idea that certain pervasive species in an ecosystem can exert powerful control over others (McNaughton and Wolf 1970). In our categorization of dominant metabolites, abundance is not the main metric for ecosystem impact as it is with species, but rather a metabolite's flux through the system (Fig. 1d; Table 1). Second, keystone metabolites include compounds with disproportionate influence on communities relative to their abundance (Power et al. 1996). Their addition or removal would cause a fundamental restructuring of the community and consequential changes on biogeochemistry and ecosystem structure, wherein community composition and activity would be substantially different. Keystone

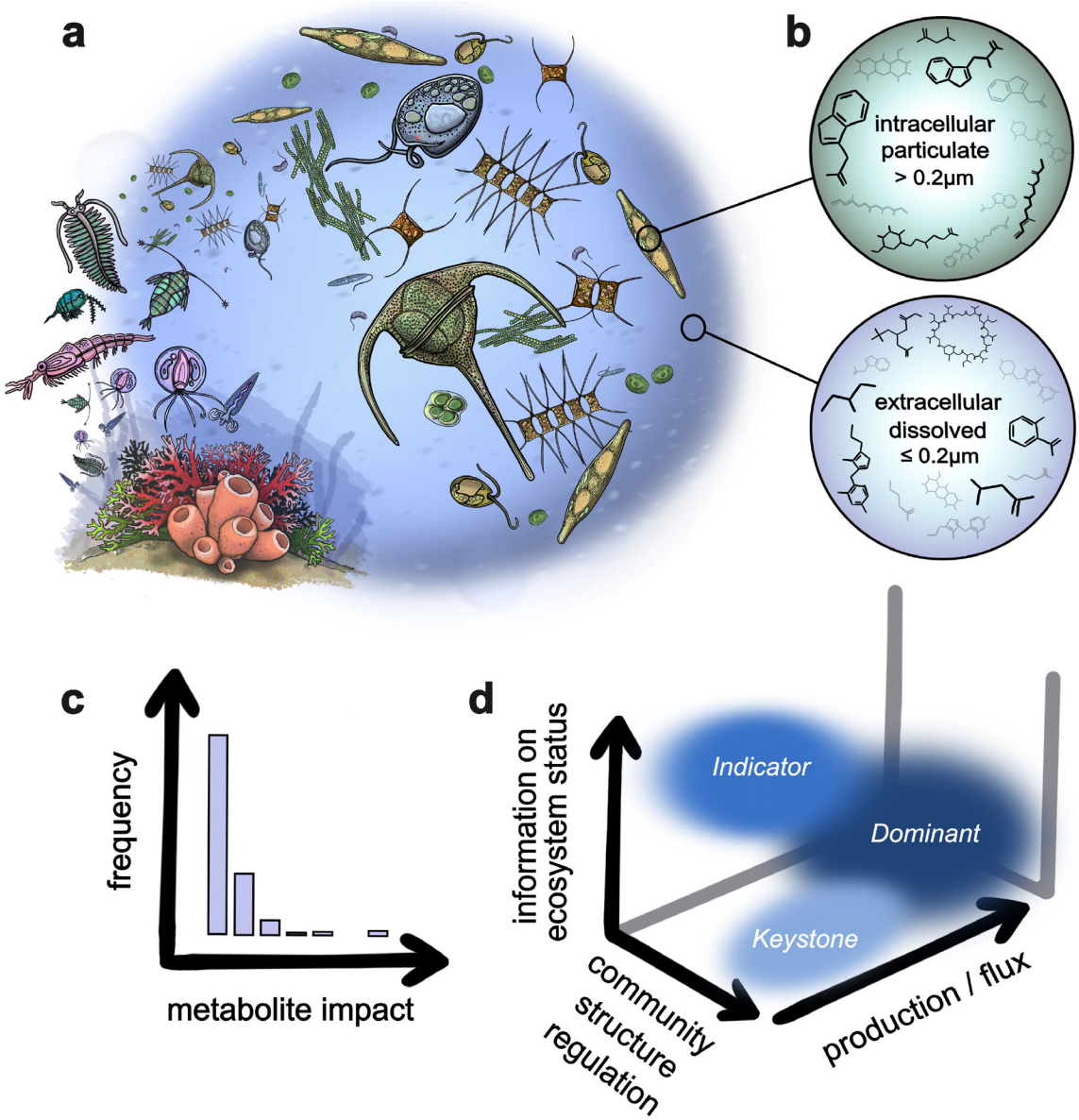
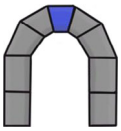
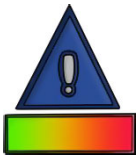


Fig. 1. An ecological framework for marine microbial metabolites. (**a**) Microbes generate and transform a complex pool of metabolites in the ocean that regulates global biogeochemistry and climate and underpins ecological relationships and ecosystem health. (**b**) There are two main standing stocks or "pools" of marine metabolites: a particulate (intracellular) pool and a dissolved (extracellular) pool. Size-fractionation by filtration operationally defines particulate (> 0.2 μm) and dissolved (≤ 0.2 μm) metabolites. The intracellular pool is the reservoir of metabolites inside cells, whereas the dissolved pool is a marketplace of extracellular metabolites and community resources as well as metabolic waste products and inactive metabolites. (**c**) Of the tens of thousands of marine microbial metabolites, a small subset has outsized ecological and ecosystem-scale impact. (**d**) Using ecological species definitions borrowed from macroecology, three categories emerge for an ecological metabolite framework: dominant, keystone, and indicator metabolites. Dominant metabolites carry a substantial fraction of the available matter and energy in the ecosystem, fueling biogeochemical cycles. Keystone metabolites have low functional redundancy and play fundamental roles in structuring communities. Indicator metabolites reveal changes in the biological condition(s) and/or health status of an ecosystem. Figure illustration and design by Rebecca S. Key.

metabolites may include facilitators that enable or regulate critical biochemical reactions and ecological signals that elicit important behaviors. Finally, we propose a third category of indicator metabolites. Their presence, absence, or abundance within the community can reveal the qualitative status of the marine environment or indicate an important change in the ecosystem (Siddig et al. 2016). In particular, we focus on indicator metabolites that reveal aspects of ecosystem health in the context of environmental change. We posit that these three ecological categories are not mutually exclusive, given

Table 1. Definitions and criteria for ecological metabolite categories. Primary evidence gives a high-level of confidence in assigning a metabolite to a particular category, while other pieces of secondary evidence suggest that a metabolite may putatively be assigned to a category. Example metabolites are provided for each line of evidence. The more pieces of evidence, the higher the confidence in category assignment of a metabolite.

	Dominant	Keystone	Indicator
	Metabolites mediate the bulk of community-scale nutrient fluxes and energy transformations	**Metabolites structure and stabilize communities with disproportionate influence relative to abundance**	**Metabolites inform qualitative status or health change in the ecosystem**
			
Primary evidence	Large flux/turnover measured in natural systems over multiple regions	Presence/absence changes community composition and/or biogeochemistry in a natural system	Link between abundance and ecosystem status in a natural system
	DMSP, turnover time of 0.43–10 h[1,2]	*Cobalamin, addition alters community composition*[7]	*PUAs, abundance tracks diatoms and diatom stress/lysis*[11]
Secondary evidence	High particulate abundance and temporal dynamics as a proxy for production	Essential role in community nutrient acquisition that cannot be achieved by other molecules	Relationship between metabolite and a stressor/condition demonstrated experimentally
	Glutamic acid, up to 65 nM in particulate metabolomes with diel cycle[3,4]	*Ferrioxamines, make iron bioavailable*[8]	*DGTA, phosphorus limitation*[12]
	Can fulfill substantial portion of bacterial nutrient demand	Auxotrophy demonstrated experimentally	
	Glycine betaine, up to 7–38% of bacterial carbon demand[5]	*Thiamine, 22% of phytoplankton surveyed are auxotrophs*[9]	
	Taken up by a large portion of microbial community	Biochemical/behavioral response demonstrated experimentally	
	Taurine, 21–65% of prokaryotic cells in seawater take it up[6]	*IAA, can control phytoplankton growth*[10]	

[1–6]*See* Supporting Information Table S2; [7–10]*See* Supporting Information Table S3; [11–12]*See* Supporting Information Table S4.

that metabolites can serve multiple functions in an individual and in an ecosystem, contextual to space, time, and the particular community present.

Our ecological categorization of marine metabolites comes with the challenges of a maturing discipline that will undoubtedly benefit from ongoing methodological advancements and interdisciplinary collaborations. Metabolites within a single ecological category may span several dimensions of chemical heterogeneity (e.g., polarity, size, functional group) not routinely covered in a single metabolomics method (Table 1; Supporting Information Tables S1–S4). Because metabolomics methods often require optimization to target certain metabolites, ecological categorization can serve as a guide in prioritizing measurements of metabolites with the greatest impact. For the few well-characterized metabolites, sufficient information exists to clearly categorize them into one or more ecological definitions. For others, we have limited observations and less understanding of the full extent of their ecosystem impacts. Functional validation is often limited to single observations in a cultured organism and/or field population, making it difficult to attribute generalizable principles for the community impact of a metabolite. Therefore, we note additional "putative" ecologically important metabolites that merit enhanced observation to better define their impact. This includes prioritizing method development to measure these compounds at relevant field concentrations with high

precision and accuracy, incorporating them into rate measurements, and assessing their impact on marine communities. We view the presented ecological categorization of marine metabolites as an initial framework to amend over time as we deepen our understanding of compounds that underpin marine microbe-metabolite networks.

The two-inventory challenge: Particulate and dissolved metabolites

When considering ecological species, abundance is a central measure in determining importance. That is, we measure the change in a community or ecosystem trait per unit change in the abundance of a species (Power et al. 1996). In comparison, there are two standing stocks or "pools" of metabolites whose abundance we typically measure: a particulate (intracellular) pool and a dissolved (extracellular) pool (Fig. 1a,b). The particulate pool comprises those metabolites within cells (> 0.2 μm). The dissolved pool is external to cells (≤ 0.2 μm) and is a marketplace for the exchange of metabolites for all organisms in the environment to access with substrate specificity. Dissolved metabolites are generated through a combination of cell mortality, passive leakage, and/or active extracellular release (Moran et al. 2022a). Once labile metabolites enter the dissolved pool, they may be rapidly transported and metabolized, leading to vanishingly low concentrations. An added challenge is that dissolved pools typically harbor an abundance of biologically inactive (recalcitrant) molecules that create a large background that can obscure the detection of metabolites (Moran et al. 2022a).

Traditionally, common and universal metabolites including amino acids and sugars were the target of research examining labile small molecules in the ocean (Lee et al. 2004). The quantitative significance of these compounds goes beyond their metabolite form, as they are also incorporated into macromolecules and are common biosynthetic precursors. With the application of mass spectrometry approaches in conjunction with molecular and biogeochemical measurements, these classes of molecules have been confirmed as important substrates, but many other metabolites have been identified as important components of ocean microbiomes. For example, studies of intracellular metabolites in cultures and surveys of biomass in seawater have revealed a variety of compatible solutes that accumulate in the cytoplasm to balance external osmotic pressure against the high ionic strength of the saline environment (Gebser and Pohnert 2013; Heal et al. 2021). While particulate metabolite measurements are relatively straightforward because metabolites are simply filtered and concentrated from cells in seawater, dissolved metabolites are dispersed throughout the salty seawater matrix. Methods that allow direct injection of salty samples have sensitivity in the 10s of nM range, often higher than typical seawater metabolite concentrations of 10 nM and below (Sogin et al. 2019; Pontrelli and Sauer 2021). Solid phase extraction (SPE)-based methods are more widespread due to their success at concentrating metabolites dissolved in seawater. These include the PPL resin that captures up to 65% of total dissolved organic carbon (Dittmar et al. 2008). However, PPL's extraction efficiency diminishes with small, polar, charged molecules, including amino acids, organic acids, and alcohols (Johnson et al. 2017). Recent methodologies have emerged to surmount these limitations: a method that combines benzoyl chloride derivatization with PPL extraction enables the extraction of metabolites containing alcohol or amine groups (Widner et al. 2021), and a cation exchange method concentrates positively charged and zwitterionic molecules (Sacks et al. 2022).

Dominant metabolites: Major conduits of metabolic exchange and ocean biogeochemistry

Labile microbial metabolites are transformed on timescales of hours to weeks, accounting for the largest flux of organic carbon in the ocean (Moran et al. 2022a). Marine organic matter pools are complex, made up of thousands of different organic molecules that reflect the biochemical diversity of biological processes. These dynamic metabolites serve as conduits in microbe–microbe and microbe–macroorganism metabolic exchanges. In macroecology, dominant species are: (1) abundant with proportional impact on the ecosystem; (2) crucial to the maintenance of communities; and (3) conduits of major energy flow (McNaughton and Wolf 1970; Grime 1987). We propose that dominant metabolites have substantial impacts on carbon, nutrient, and energy flow in microbe-metabolite networks by virtue of their rapid flux in the system (Fig. 1d). We focus less on specific biochemical function(s) of metabolites in cells, and rather highlight those metabolites with the greatest contribution to ecosystem-scale biogeochemistry. Indeed, dominant species typically have generally redundant functions at the community level (Record et al. 2018). Likewise, dominant metabolites may have multiple sources and sinks within the community, overlapping metabolic functions, and widespread occurrence. We focus on metabolites for which measurements exist at the community level. Flux measurements are available for only a handful of metabolites; thus, we use evidence of abundance and temporal dynamics, fulfillment of bacterial carbon demand, and community uptake to discern which metabolites may putatively contribute most to fluxes (Table 1; Supporting Information Tables S1, S2).

Abundant, polar metabolites in microbial biomass

As an initial means to inventory abundant microbial metabolites in biomass, we used previously reported intracellular metabolomics measurements of 80 small, polar molecules in 21 marine microbial phytoplankton cultures, ranging from cyanobacterial to dinoflagellate taxa (Durham et al. 2019; Heal et al. 2021; Fig. 2a; Supporting Information

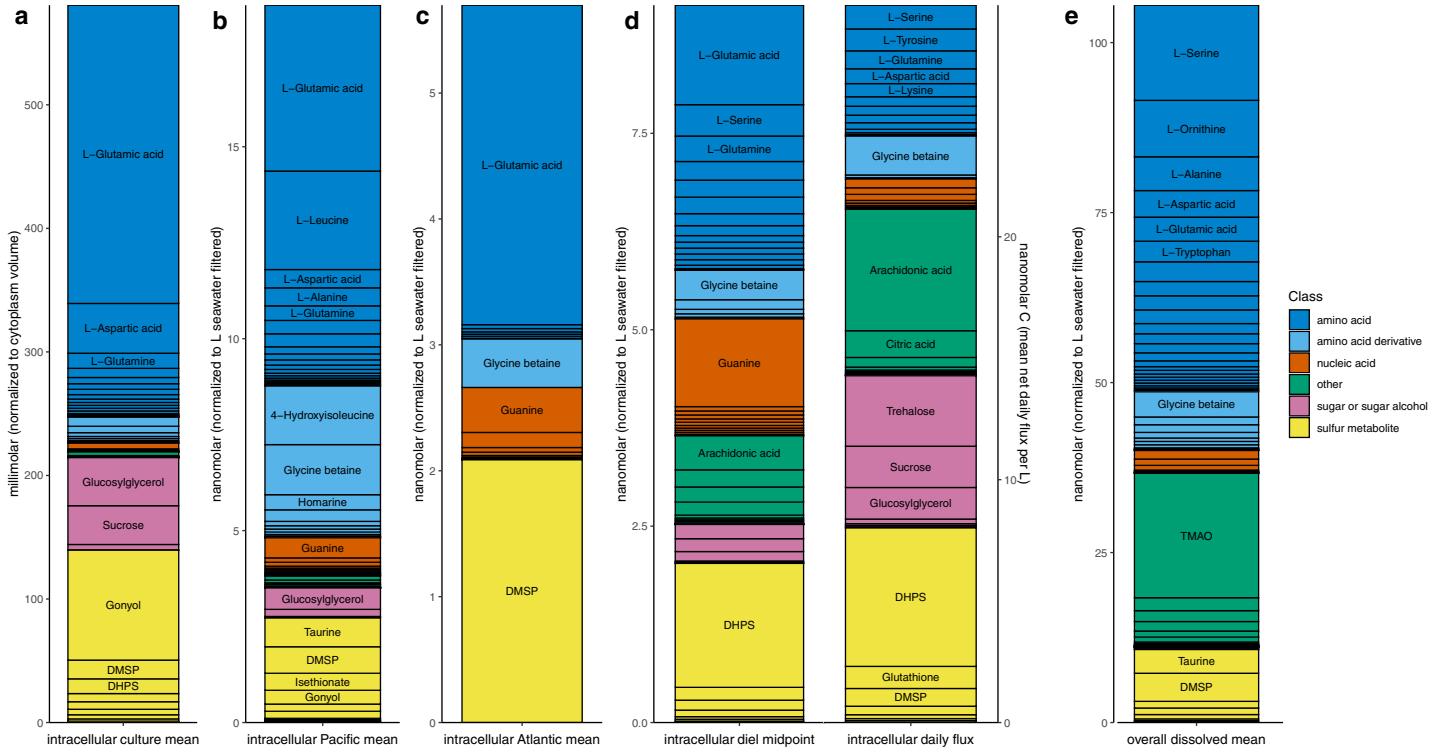


Fig. 2. Abundance and temporal dynamics inform identification of dominant metabolites. (**a**) Intracellular pools of small, polar metabolites are typically dominated by a few compounds. Intracellular metabolite concentrations averaged across 21 phytoplankton monocultures normalized to cell cytoplasmic volume. Data replotted from Heal et al. 2021. Data represent a compilation of metabolite concentrations ($n = 80$ metabolites) across phytoplankton taxa; that is, not all organisms make sucrose or gonyol, but when present, those metabolites are quite abundant in cells. (**b**) Intracellular metabolite abundances in North Pacific particulate samples normalized to filtered seawater volume. Data replotted from Heal et al. 2021 using average surface (15 m depth) sample values ($n = 39$ samples; $n = 84$ metabolites). (**c**) Intracellular metabolite abundances in western Atlantic particulate samples normalized to filtered seawater volume. Data replotted from Johnson et al. 2023 using average surface (1–6 m depth) sample values ($n = 12$ samples; $n = 24$ metabolites). (**d**) Temporal dynamics demonstrate a subset of metabolites with rapid flux. Intracellular metabolite abundances and fluxes in particulate samples from the North Pacific Subtropical Gyre during a diel study. Data replotted from Boysen et al. 2021. Midpoint values are based on estimated or absolutely quantified minimum and maximum values from replicates ($n = 3$) collected every 4 h. Of 73 metabolites quantified, 51 had sufficient diel resolution to estimate a flux through the intracellular particulate pool of 32 nmol C L^{-1} d^{-1} as calculated by the mean daily swing from maximum to minimum. (**e**) Dissolved pools include those metabolites available to the community and inform metabolite activity. Dissolved metabolite concentrations in surface ocean samples. Values are a compilation of average metabolite concentrations across three extraction methods (Widner et al. 2021; Sacks et al. 2022; Johnson et al. 2023) with taurine values from Clifford et al. 2020 (*see* details in Supporting Information Fig. S2). Metabolites are colored according to broad chemical classes, as noted in Supporting Information Table S1. All measurements should be considered incomplete metabolite inventories as variable numbers of metabolites are measured across datasets (*see* Supporting Information Tables S1, S5a–e, S6a–e for compiled values and full chemical names; *see* Supporting Information Summary for details). All data are redistributed under the terms of their Creative Commons Attribution License.

Fig. S1 and Tables S5a,b). While these data do not cover the full repertoire of cellular metabolites, this information allows us to begin to estimate a total intracellular metabolite concentration and to determine key compounds. On average, the sum of the concentrations of 80 labile metabolites in phytoplankton cytoplasm is ~ 560 mM (Heal et al. 2021). For comparison, the sum of the concentrations of 103 intracellular metabolites in *Escherichia coli* is ~ 300 mM (Bennett et al. 2009). In *E. coli*, relatively few metabolites account for most of the total metabolomic inventory (10 metabolites accounted for 77% of molar concentration). We found similar results in phytoplankton (10 metabolites accounted for 85% of molar concentration), with the greatest contributions from amino acids and other compatible solutes (Fig. 2a). Averaging individual metabolite concentrations across 21 phytoplankton metabolomes, we find the metabolome consists of 57% free amino acids, 25% organic sulfur metabolites (excluding methionine and cysteine), and 13% sugar and sugar alcohols dominated by compatible solutes sucrose and glucosylglycerol (Supporting Information Tables S1, S2).

Next, to categorize abundant metabolites from a broader ecosystem and biogeochemical perspective, we leveraged several existing metabolomic field measurements to identify metabolites that constitute a large portion of standing stocks

in microbial community biomass (Fig. 2b–d; Supporting Information Tables S1, S2, S5c–e). Particulate surface water samples from latitudinal transects of the Atlantic (Johnson et al. 2023) and North Pacific (Heal et al. 2021) and a time series in the North Pacific Subtropical Gyre (Boysen et al. 2021) generally agree on abundant metabolites in microbial biomass, and these data are largely consistent with the intracellular metabolomes from phytoplankton cultures (Heal et al. 2021). There is some variation across these datasets, including reordering of the most abundant metabolites within some functional groups like amino acids, their derivatives, and organic sulfur (Fig. 2b–d). Typically, a handful of ~ 20 metabolites comprises over three-quarters of the metabolite signal in terms of molarity (Boysen et al. 2021; Heal et al. 2021). Measurements of amino acid pools show recurring abundance of glutamic acid followed by more variable contributions from leucine, aspartic acid, alanine, serine, and glutamine. Of further interest are abundant amino acid derivatives glycine betaine and homarine, sugars glucosylglycerol, trehalose, and sucrose, and organic sulfur compounds DMSP, gonyol, taurine, isethionate, and 2,3-dihydroxypropane-1-sulfonate (DHPS), all of which are known to act as compatible solutes. While the majority of these abundant metabolites are described in plankton and can act as microbial substrates, notable exceptions that require further investigation include 4-hydroxyisoleucine, the fourth-most abundant metabolite in North Pacific metabolomes (Heal et al. 2021) whose function is not described in marine ecosystems, and nucleobase guanine, consistently one of the most abundant metabolites in intracellular metabolomes across study regions (Boysen et al. 2021; Heal et al. 2021; Johnson et al. 2023) where it may act as a nitrogen storage molecule (Mojzeš et al. 2020).

While measuring flux directly is challenging, one clue comes from observations of metabolite concentrations over short time scales. For instance, daily oscillation of light drives diel rhythms in various microbes, either directly or indirectly, for functions related to photosynthesis, organic matter production and consumption, and circadian rhythm (Boysen et al. 2021). Particulate metabolite concentrations reflect this daily oscillation in the North Pacific with diel patterns in amino acids like serine, glutamine, glutamic acid, aspartic acid, alanine, and (iso)leucine, compatible solutes DHPS, DMSP, taurine, glucosylglycerol, trehalose, and sucrose, as well as the taurine derivative isethionate (Boysen et al. 2021; Fig. 2d; Supporting Information Tables S1, S2, S5e). Notably, several metabolites had net flux rates > 1 nmol C L^{-1} d^{-1}: DHPS, trehalose, sucrose, glycine betaine, glucosylglycerol, and arachidonic acid. Both trehalose and sucrose are sugar dimers that are intermediates between monomers and the macromolecules glycogen and starch and whose standing stocks do not necessarily reflect rapid flux over the diel cycle. Indeed, the authors estimated that up to 11% of nitrogen fixation could be fueled by nighttime catabolism of the standing stock of intracellular trehalose in the cyanobacterium *Crocosphaera*. Overall, these data support the concept that a subset of metabolites within the community have high flux over short timescales.

Molecules with high abundances in particulate matter typically have dissolved concentrations in the picomolar to low nanomolar range, consistent with rapid uptake (Fig. 2e; Supporting Information Fig. S2, Tables S1, S2, S6a–e; Widner et al. 2021; Sacks et al. 2022; Johnson et al. 2023). Some abundant particulate metabolites (e.g., glucosylglycerol, sucrose, trehalose) do not currently have a routine method for measurement in the dissolved phase, making this a research priority. Despite challenges with measuring and interpreting dissolved metabolite data, laboratory and compound-specific isotope-tracer experiments have provided evidence of rapid flux and ecological significance for several aforementioned metabolites. For example, compatible solute DMSP can fulfill up to 6% of carbon and nearly 100% of bacterial sulfur demand (Simó et al. 2009). Dimethylsulfoniopropionate is also involved in host-algal relationships in corals, sponges, and clams (Guibert et al. 2020). Taurine, a sulfur- and nitrogen-containing metabolite commonly produced by microbes and zooplankton, is taken up by 21–65% of prokaryotic cells in seawater communities (Clifford et al. 2020). Taurine is also highlighted in sponge–microbe interactions and nutrient cycling, with concentrations up to 6.6 mM in sponge tissue (Moeller et al. 2023). Nitrogen-containing and widely used compatible solute glycine betaine has reported turnover values ranging from minutes to days (Boysen et al. 2022). Further, glycine betaine is an important metabolite in the coral microbiome as well as in interactions between bacterial symbionts and marine annelids (Kleiner et al. 2012). Notably, 16% of worldwide coral tissue nitrogen is stored as glycine betaine (Ngugi et al. 2020). Studies on community uptake and turnover for dissolved free amino acids indicate they supply as much as 20% of the carbon and nitrogen required to support bacterial growth (Suttle et al. 1991). In particular, serine, leucine, glutamate, aspartate, and alanine are among those amino acids with high uptake and/or turnover rates (Williams et al. 1976; Suttle et al. 1991).

Metabolites with high flux

Metabolites with high flux are not necessarily maintained in constitutively high concentrations in cells. For example, phytoplankton actively release glycolate under nutrient limitation or periods of intense light as a product of photorespiration (Fogg 1983). Concentrations of dissolved glycolate vary over three orders of magnitude with a clear diel cycle indicative of a tight link between production and consumption by heterotrophic bacteria (Leboulanger et al. 1997; Supporting Information Table S2). A diel cycle in bacterial glycolate uptake rate has also been observed in the North Pacific (Casey et al. 2017). Furthermore, cross-feeding of glycolate is a

proposed currency in the metabolic coevolution of specific cyanobacterial lineages of *Prochlorococcus* and heterotrophic bacterial lineages of SAR11 (Braakman et al. 2017). Thus, unidirectional transfer of glycolate between microbes likely serves as a substrate driving phytoplankton–bacteria interactions.

Saccharides are another important component of marine organic matter (Kirchman and Rich 1997; Sogin et al. 2019). Chitin is one of the most abundant polymers in the ocean, and its enzymatic degradation releases the monomer N-acetyl glucosamine (GlcNAc; Pollak et al. 2021). This amino sugar is an important substrate across a variety of bacteria associated with phytoplankton (Ferrer- González et al. 2021) and facilitates important cross-feeding and stress resistance within communities (Pontrelli et al. 2022; Amarnath et al. 2023). In experimental systems, GlcNAc-consuming bacteria produce organic acids (pyruvate, acetate, glutamate) that complementary organic acid-consuming bacteria then use as substrates, a process that regulates acid stress and maintains stable microbial coexistence.

Though the metabolomic inventory data we compiled primarily focuses on polar metabolites, dominant metabolites also include nonpolar constituents. For example, triacylglycerols (TAGs) are nonpolar, energy-rich molecules that are made in abundance by eukaryotic phytoplankton for energy storage. In the open ocean, the concentration of TAGs can undergo a two-fold change over the course of the day, accumulating during the day and depleting overnight (Becker et al. 2018). The sheer abundance of TAGs and their diel flux indicate they are a major component of the daily carbon cycle in the surface ocean (calculated as $7.5 \pm 0.5\%$ of total daytime net primary production at Station ALOHA; Becker et al. 2018). The extent to which TAGs are released to the microbial loop or transferred up the food web through grazing, rather than being used by the same organism that produces them, remains unresolved.

Putative dominant metabolites: Insights from the dissolved pool

Nearly all metabolites within cells have the potential to become dissolved; however, selective release and intense processing (biological or physicochemical) of the dissolved pool mean that its composition can greatly differ from the intracellular metabolome (Moran et al. 2022b; Fig. 2). Paired intracellular and extracellular metabolomes of phytoplankton monocultures (in the absence of heterotrophic consumers) can reveal decoupling between the production of metabolites within and external to phytoplankton cells. For example, experiments with both major cyanobacterial groups, *Synechococcus* and *Prochlorococcus*, show substantial extracellular release of thymidine with minimal intracellular accumulation (Fiore et al. 2015; Kujawinski et al. 2023; Supporting Information Table S2). Thymidine cannot be assimilated into nucleic acids in these organisms because they lack the thymidine kinase enzyme required to phosphorylate thymidine prior to incorporation. High levels of thymidine release by abundant cyanobacteria, in addition to detectable assimilation and catabolic activity in seawater bacterioplankton (Hollibaugh 1994), suggest thymidine exchange in oligotrophic regions. Subsequent laboratory and computational data have revealed cross-feeding of thymidine between globally abundant microbial groups (Braakman et al. 2025).

There are some metabolites that can be quantified in dissolved metabolite pools for which we have limited particulate data and spatiotemporal information. For example, trimethylamine-N-oxide (TMAO), an osmolyte that can be produced from glycine betaine or carnitine, is abundant in dissolved metabolomes with concentrations up to 76.9 nM (Gibb and Hatton 2004; Sacks et al. 2022). Trimethylamine-N-oxide has demonstrated pathways for uptake and catabolism as an energy, carbon, and/or nitrogen source by key marine bacterial taxa including the abundant SAR11 and Roseobacter clades (Lidbury et al. 2014). Indeed, the trimethylamine monooxygenase (Tmm) protein that produces TMAO from precursor trimethylamine is one of the most abundant proteins in Pacific Ocean communities (Saunders et al. 2022). As TMAO acts as a precursor to marine aerosols and is a critical piezolyte for organisms from bacteria to fish that deal with hydrostatic pressure (Yancey et al. 2014; Qin et al. 2021), it warrants further community-scale investigation.

Putative dominant metabolites: Insights from molecular and analytical approaches

Examining high-flux metabolites presents a challenge, especially in the natural environment where the concentrations of a given metabolite may be low or the metabolite may fall outside the analytical window of current approaches. For instance, isotopic labeling coupled with GC–MS revealed mannitol as a major immediate carbon storage molecule in the haptophyte *Gephyrocapsa huxleyi* (formerly *Emiliania huxleyi*; Obata et al. 2013) yet additional extraction and analytical methods are required for broader detection of this analyte in environmental communities (Sogin et al. 2019). Advances in biological approaches have also pointed the way toward ecologically relevant metabolites. For example, transporters for organic substrates citrate and 3-hydroxybutyrate were the most highly expressed bacterial genes in a dinoflagellate bloom, suggesting these metabolites are actively transferred between microbes (Schroer et al. 2023), and field measurements of citrate further support fairly rapid production rates (Boysen et al. 2021).

Keystone metabolites: Fundamental regulators of community and ecosystem activity

In macroecology, keystone species are those whose impact on the community or ecosystem is disproportionately large relative to their abundance (Power et al. 1996). Keystone

species fundamentally structure and stabilize communities to the point that the community could not return to its previous state if the species were removed. This concept has formerly been applied to metabolites in soil microbiomes (Dahlstrom et al. 2020; Lu et al. 2020). In this literature, a keystone metabolite, through either growth-deterring or growth-promoting properties, may have an outsized role in shaping community structure development (Dahlstrom et al. 2020). Dahlstrom also notes that several keystone metabolites can exist, but certain ones will have outsized effects in particular spatiotemporal contexts, suggesting their keystone roles are time- and space-specific.

Keystone metabolites may fall into the functional categories of facilitators and signals that indirectly contribute to elemental cycling by affecting the rates and routes of carbon flux without constituting a substantial fraction of mass flux themselves (Moran et al. 2022b). Here, we suggest that keystone metabolites typically have low abundance and low functional redundancy in addition to stabilizing communities, such that their removal from the organic matter reservoir would cause a fundamental restructuring of the community and consequential changes to the larger ecosystem (Fig. 1d). Few metabolites are conclusively shown to play such roles in natural marine ecosystems, so we leverage experimental evidence of metabolites that support auxotrophy, nutrient acquisition, and signaling activities (Table 1; Supporting Information Tables S1, S3). We investigate several keystone metabolite case studies and highlight additional putative keystones that require further validation.

Keystone marine metabolites: three case studies

a. *Vitamins*. Vitamins have been recognized for over a century as important metabolites to marine microbial communities. In the 1950s, culture work uncovered the prevalence of microalgal auxotrophy, or absolute requirement for exogenous sources (Droop 1957). Continued experimental work and field observations have since demonstrated that B vitamins underpin an intricate web of exchange and interaction within marine communities where one subset requires a resource that only another specific subset can produce (Bertrand et al. 2015; Heal et al. 2017; Bannon et al. 2022).

   Many marine organisms spanning bacteria and algae are auxotrophic for cobalamin, vitamin B_{12}, the cofactor for B_{12}-dependent methionine synthase (METH; Croft et al. 2006; Zoccarato et al. 2022). B_{12} limitation can cause substantial metabolic consequences as shown in phytoplankton (Heal et al. 2019). However, B_{12} biosynthesis is limited to select heterotrophic bacteria and archaea (Heal et al. 2017; Lu et al. 2020; Zoccarato et al. 2022). Thus, exchange of B_{12} underpins a range of microbial relationships with algae and marine invertebrates (Bertrand et al. 2015; Durham et al. 2015; Zoccarato et al. 2022). In seawater, B_{12} is typically present at femto- to pico-molar levels (Heal et al. 2017; Bannon et al. 2022, 2023; Fig. 3a,b; Supporting Information Tables S3, S7a,b). Demand for B_{12} can exceed supply, as B_{12} has been shown to limit phytoplankton growth and alter microbial community composition in various parts of the ocean (Bannon et al. 2022; Fig. 3c,d; Supporting Information Tables S7c,d). For example, during spring in the Northwest Atlantic, addition of nitrogen and cobalamin in combination led to increased chlorophyll *a* concentrations (Fig. 3c) and B_{12} enrichment in particulate samples compared to dissolved (Bannon et al. 2024). Beyond B_{12}'s impact on primary productivity is its influence on community composition. In the Gulf of Alaska, cobalamin addition stimulated growth of $> 2\ \mu$m phytoplankton (Koch et al. 2011). Limited results suggest that larger phytoplankton may be disproportionately influenced by cobalamin availability (Gobler et al. 2007; Koch et al. 2011), with consequences for the biological carbon pump yet to be determined (Fig. 3e).

   Thiamine, vitamin B_1, serves as an essential cofactor for amino acid synthesis and central carbon metabolism by all domains of life and is present at picomolar concentrations in the marine environment (Paerl et al. 2023; Supporting Information Table S3). An exogenous source of B_1 is required by a substantial fraction of bacterioplankton and phytoplankton (Croft et al. 2006; Paerl et al. 2018), and B_1 has been shown to significantly enhance the biomass of larger ($> 5\ \mu$m) phytoplankton (Gobler et al. 2007). Though few studies examine the community impact of B_1, evidence suggests it may be a keystone metabolite at some places and/or times. Furthermore, widespread episodic B_1 deficiency has been observed in bivalves, fishes, and birds, suggesting microbial production may have a cascading influence up the trophic web (Balk et al. 2016).

b. *Siderophores*. Iron-chelating siderophores solubilize ferric iron, allowing cells to maintain iron in the dissolved phase and compete for iron in marine ecosystems. As most sources of iron to the surface ocean are in particulate forms not directly accessible for internalization (e.g., dust), siderophores are essential for transforming this non-labile iron into bioavailable pools (Bundy et al. 2018; Manck et al. 2022; Hoffman et al. 2024). Siderophore biosynthesis and uptake genes have been found in every ocean environment where they have been examined (Garber et al. 2020), and dissolved siderophores are present in picomolar concentrations across large gradients in dissolved iron concentrations (Park et al. 2023; Supporting Information Table S3). Thus far, ferrioxamines and amphibactins are the most common siderophores detected in seawater (Bundy et al. 2018; Boiteau et al. 2019; Park et al. 2023). Synechobactins (Boiteau et al. 2019; Park et al. 2023) and photochemically reactive petrobactin (Manck et al. 2022) have also been observed. While siderophore production and uptake appear globally distributed, there is mounting evidence that siderophore cycling is particularly important in nutrient-limited ecosystems. For example, diatoms in

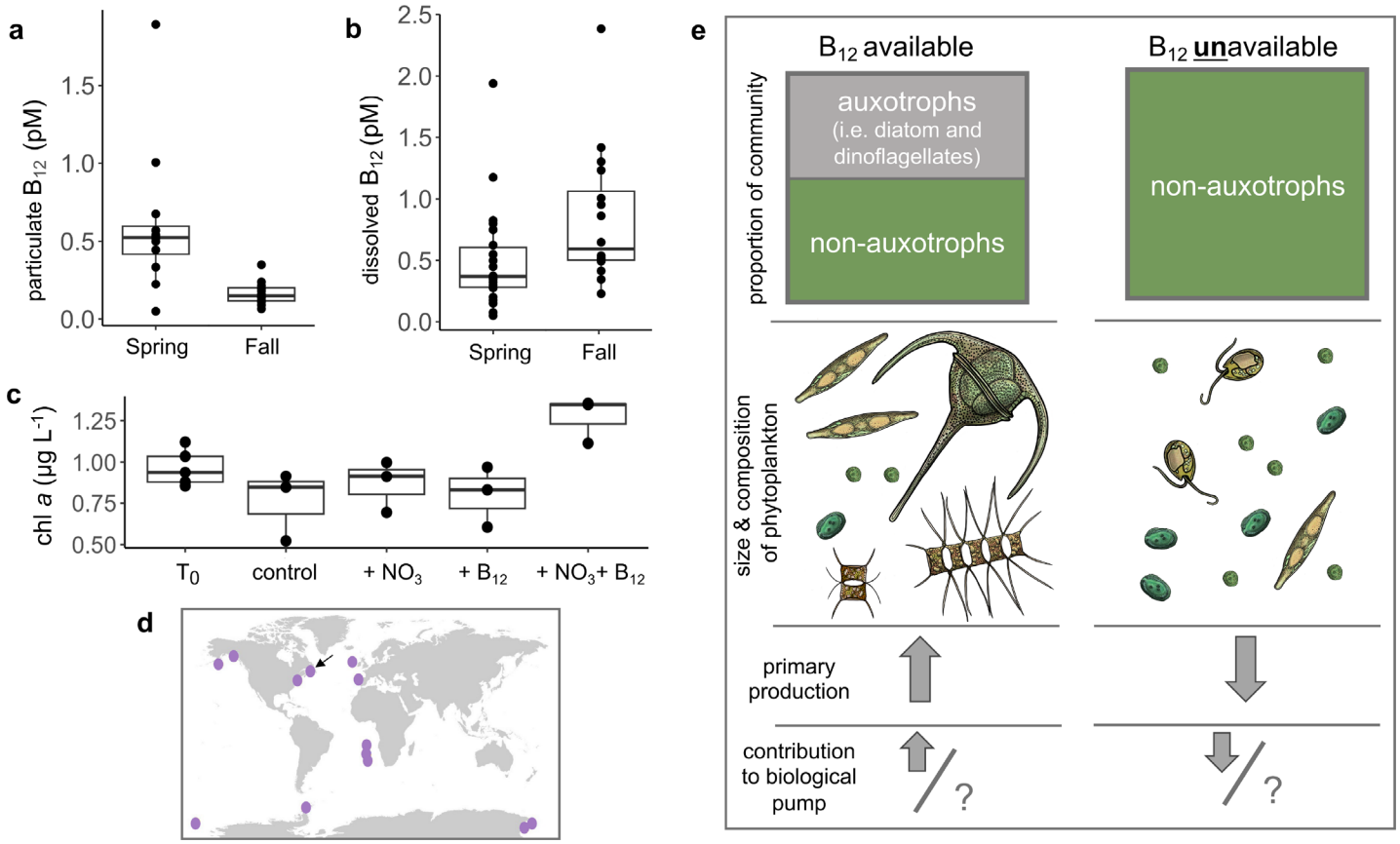


Fig. 3. Vitamin B_{12} is a keystone metabolite in the surface ocean. B_{12} is found in low pM concentrations in both cells and seawater, but sometimes enriched in particulate phase. Average (**a**) particulate ($n = 28$) and (**b**) dissolved ($n = 33$) concentrations (pM) of (a) total B_{12} (Ado-, Me-, OH- and CN-combined) and (b) OH-B_{12} (adjusted for percent recovery) at a coastal station in the Northwest Atlantic Ocean during Spring and Fall from 2016 to 2020. Data replotted from Bannon et al. 2024 with author permission. (**c**) B_{12} and nitrogen added together stimulate chlorophyll a production in a microbial community from the coastal Northwest Atlantic Ocean during Spring. Chl *a* concentrations ($\mu g\ L^{-1}$) measured initially (T0) and 4 d after addition of $+NO_3$ (10 μM), $+B_{12}$ (100 pM) and $+NO_3 + B_{12}$ (10 μM, 100 pM; $n = 3$; Bannon et al. 2024). (**d**) B_{12} co-limits phytoplankton growth in various regions. Global map of study sites where B_{12} co-limitation was observed (modified from Bannon et al. 2022 under the terms of the Creative Commons Attribution License). Arrow highlighting sampling site of data shown in (a–c). (**e**) B_{12} availability impacts microbial community structure and the biological carbon pump. Simplified illustration of conclusions from Gobler et al. 2007, Koch et al. 2011, and Bertrand et al. 2015. Note that the influence of B_{12} on the biological carbon pump has not been systematically tested. This is inferred by evidence that B_{12} availability selects for larger phytoplankton, which in turn have been shown to increase sinking rates and impact grazing rates. *See* Supporting Information Summary and Table S7a–d for details on compiled data. Figure illustrations by Rebecca S. Key.

iron-limited waters have adapted to internalizing siderophore-bound iron (Kazamia et al. 2018). Researchers have also demonstrated siderophore-mediated iron uptake by *Synechococcus* and *Prochlorococcus*, both of which lack biosynthetic pathways for siderophores, in oligotrophic regions of the ocean (Hogle et al. 2022).

Siderophores also underpin specific microbial interactions, where siderophore producers facilitate the transformation of bioavailable iron for their partners (Manck et al. 2022). Culture studies demonstrate that algal-associated bacteria produce siderophores (Amin et al. 2009) and improve the growth of iron-limited algal hosts (Keshtacher-Liebson et al. 1999). Macroalgae-associated microbes also produce siderophores, which could provide nutritional and antimicrobial benefits to their hosts (Chakraborty et al. 2022). Specific interactions involving siderophores in natural communities have yet to be elucidated. However, the number of siderophore measurements is increasing, revealing additional siderophores for further investigation, like mycobactins and vibrioferrin (Hoffman et al. 2024), and the importance of siderophores in not only surface waters but also the mesopelagic (Bundy et al. 2018; Li et al. 2024) and deep oceans (Hoffman et al. 2024).

c. *Polyunsaturated fatty acids* (*PUFAs*). Marine microbial communities are an important source of omega (ω)-3/6 polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA; c22ω3), eicosapentaenoic acid (EPA; c20ω3),

arachidonic acid (ARA; c20ω6), stearidonic acid (SDA; c18ω3), and linoleic acid (LA; c18ω6). Long-chain PUFAs (those with ≥20 carbon atoms such as EPA and DHA) are required for the development of vertebrates, though many lack the de novo ability to produce them. Instead, they rely on a dietary supply of PUFAs from microbial producers such as microalgae, heterotrophic protists, and select bacteria (Nichols 2003). Although there are notable exceptions (Kabeya et al. 2018), higher trophic organisms' long-chain PUFAs originate from these select marine producers, supporting their categorization as keystone. A comprehensive field dataset spanning the Atlantic Ocean showed temperature dependence, with less production of PUFAs under higher temperatures and implications for cascading effects for fisheries under global warming scenarios (Holm et al. 2022).

Putative keystone metabolites: Additional vitamins plus derivatives and precursors

Several other vitamins are emerging as critical currencies in microbial communities. Riboflavin (B_2), an important precursor and co-factor involved in electron transport, is implicated in exchange within microbial communities. B_2 has distinct variability in the water column implying active uptake or degradation, with both diel and seasonal cycling where highest concentrations are observed at night and during winter periods when mixed layer depths were deepest, respectively (Longnecker et al. 2024; Supporting Information Table S3). Algal growth can also be stimulated by riboflavin or lumichrome, a photochemically-derived product of riboflavin (Lopez et al. 2019; Brisson et al. 2021). In addition, riboflavin is enriched in coral holobiont exudates (Weber et al. 2022), and it can induce larval development in benthic invertebrates (Burns et al. 2014). How much influence B_2 has on communities remains unclear, but it is an exciting avenue for future research.

Further investigating auxotrophy assists in the characterization of additional putative keystone metabolites. Some eukaryotic phytoplankton are auxotrophic for biotin (B_7), though this auxotrophy is less widespread than cobalamin and thiamine (Croft et al. 2006). B_7 is a cofactor for carboxylase enzymes, including the essential acetyl coenzyme A carboxylase. In culture experiments, auxotrophy for para-aminobenzoic acid (pABA), precursor to folate (B_9), and niacin (B_3) has been observed in the heterotrophic bacterium *Dinoroseobacter shibae*, and these requirements can be satisfied by co-culture with the picoeukaryotic alga *Ostreococcus tauri* along with the exchange of B_1 and B_{12} (Cooper et al. 2019). Further, auxotrophy for B_1, B_3, B_7, and B_9 is common in bacterial communities that degrade particulate organic matter and likely influences community composition and activity (Gregor et al. 2024), suggesting broader ecosystem impact(s) than previously appreciated. The few existing environmental observations of these metabolites demonstrate interesting dynamics. For example, B_3 has diel periodicity in North Pacific particulate metabolomes (Boysen et al. 2021), and in the northwestern Sargasso Sea during seasonal deep convective mixing, dissolved pABA accumulates in the mixed layer (Liu et al. 2022). The role(s) of B_3, B_7, and B_9 in marine communities are gaining interest, and future research exploring their community scale influence will illuminate potential keystone roles.

B vitamin cycles are even more complex due to active use and exchange of precursors, moieties, and degradation products collectively called "vitamers." Evolving research suggests microbial community members use vitamers to satisfy vitamin requirements and/or maintain ecological interactions. For example, certain microorganisms can fulfill B_1 requirements by using vitamin precursors [4-methyl-5-thiazoleethanol (HET), 4-amino-5-hydroxymethyl-2-methylpyrimidine (HMP)] or degradation products [5-(2-hydroxyethyl)-4-methyl-1,3-thiazole-2-carboxylic acid (cHET), N-formyl-4-amino-5-aminomethyl-2-methylpyrimidine (FAMP), 4-amino-5-aminomethyl-2-methylpyrimidine (AmMP)] (Paerl et al. 2023), and complex relationships are underpinned by thiamine intermediates like HMP (Sathe et al. 2022). Recently, the biotin precursor desthiobiotin has been identified as "an escape route for B_7 auxotrophy" (Wienhausen et al. 2022a). Additionally, moieties of the cobalamin molecule alpha-ribazole and 5,6-dimethylbenzimidazole (DMB) are both implicated in the ability of microbes to remodel cobalamin and are present in the environment (Lu et al. 2020; Wienhausen et al. 2022b; Bannon et al. 2024), and culture work demonstrates bacterial release of alpha-ribazole in response to DMSP (Johnson et al. 2016). Additional insights into the role of vitamers in community interactions may support such metabolites as keystone metabolites.

Putative keystone metabolites: Infochemicals

Microbial-derived infochemicals, those metabolites that mediate information and shape interactions, may positively or negatively modify community physiology and behavior in ways that alter biogeochemistry and ecosystem function. They establish important routes of communication and interaction that can stabilize the community (Seymour et al. 2017). Despite their low concentrations and transient occurrence, infochemicals affect not only the fate of individual microbial cells but also the flux of carbon and energy via the induction of cascading effects on the marine food web. Infochemicals in marine plankton have been recently reviewed (Kuhlisch et al. 2023). Here, we highlight a few prominent examples.

Specialized communication molecules are important in establishing active metabolic interactions and behavior in many organisms. Quorum sensing (QS) is a process of cell-to-cell communication that bacteria use to coordinate behavior in response to their population density by producing, releasing, perceiving, and reacting to chemical signals such as acylated homoserine lactones (AHLs) among others (Hmelo 2017). Of > 100 bacterial

isolates from corals, ~ 30% have the ability to produce AHLs (Golberg et al. 2011). Acylated homoserine lactones are implicated in phytoplankton-bacterial signaling and density-driven physiology changes based on bacterial lifestyle, that is, free-living vs. particle-associated (Johnson et al. 2016; Krupke et al. 2016). Despite limited community measurements of AHLs, observations of *N*-(3-oxooctanoyl)-L-homoserine lactone (3O-C8-HSL) show it can trigger processing of high molecular weight organic matter on marine snow through stimulation of extracellular enzyme activity on sinking particles (Krupke et al. 2016; Hmelo 2017; Supporting Information Table S3). The alkylquinolone 2-heptyl-4-quinolone (HHQ) produced by marine gammaproteobacteria arrests cell division and confers protection from virus-induced mortality in the bloom-forming coccolithophore *G. huxleyi* (Garrett and Whalen 2023) in addition to restructuring microbial community structure (Whalen et al. 2019). More extensive observations in natural populations are required to better understand community impacts of QS metabolites.

Other infochemicals alter growth and/or physiology of particular taxa and, as such, may have community-scale influence. For example, the brominated compound tetrabromopyrrole (TBP) produced by the bacterium *Pseudalteromonas* sp., acts as a settlement cue for coral larvae (Sneed et al. 2014) and contributes to the immobilization or death of pre-competent coral larvae (Tebben et al. 2015). In addition, TBP has implications for plankton interactions. In a study with seven phytoplankton species, including diatoms, cryptophytes, and coccolithophores, TBP exposure induced algal mortality in all species (Whalen et al. 2018). To our knowledge, there are no published measurements of TBP in seawater, warranting further investigation. Indole-3-acetic acid (IAA; auxin) is a phytohormone documented in algae–bacteria interactions (Seymour et al. 2017; Kuhlisch et al. 2023) and produced by sea fan holobionts (Weber et al. 2022). Indole-3-acetic acid biosynthesis is encoded by many marine bacteria (Zoccarato et al. 2022) and can stimulate the growth of certain phytoplankton (Amin et al. 2015) and potentially coral algal symbionts (Matthews et al. 2020). Azelaic acid and rosmarinic acid are additional signaling molecules with implications for phytoplankton–bacteria interactions. In culture, the diatom *Asterionellopsis glacialis* regulates bacterial growth using these molecules; specifically, azelaic acid stimulates the growth of beneficial bacterial associates, while rosmarinic acid promotes the attachment of beneficial bacteria to the diatom while inhibiting opportunistic bacteria from attaching (Shibl et al. 2020). Copepods, the most abundant zooplankton in the oceans, produce copepodamides that induce a range of impacts on phytoplankton traits, from reduction in size to induction of toxin production, with implications for community restructuring (Selander et al. 2019). The impact of these various infochemicals on microbial activity at a broader community scale requires further investigation.

Indicator metabolites: Signals of ecosystem status

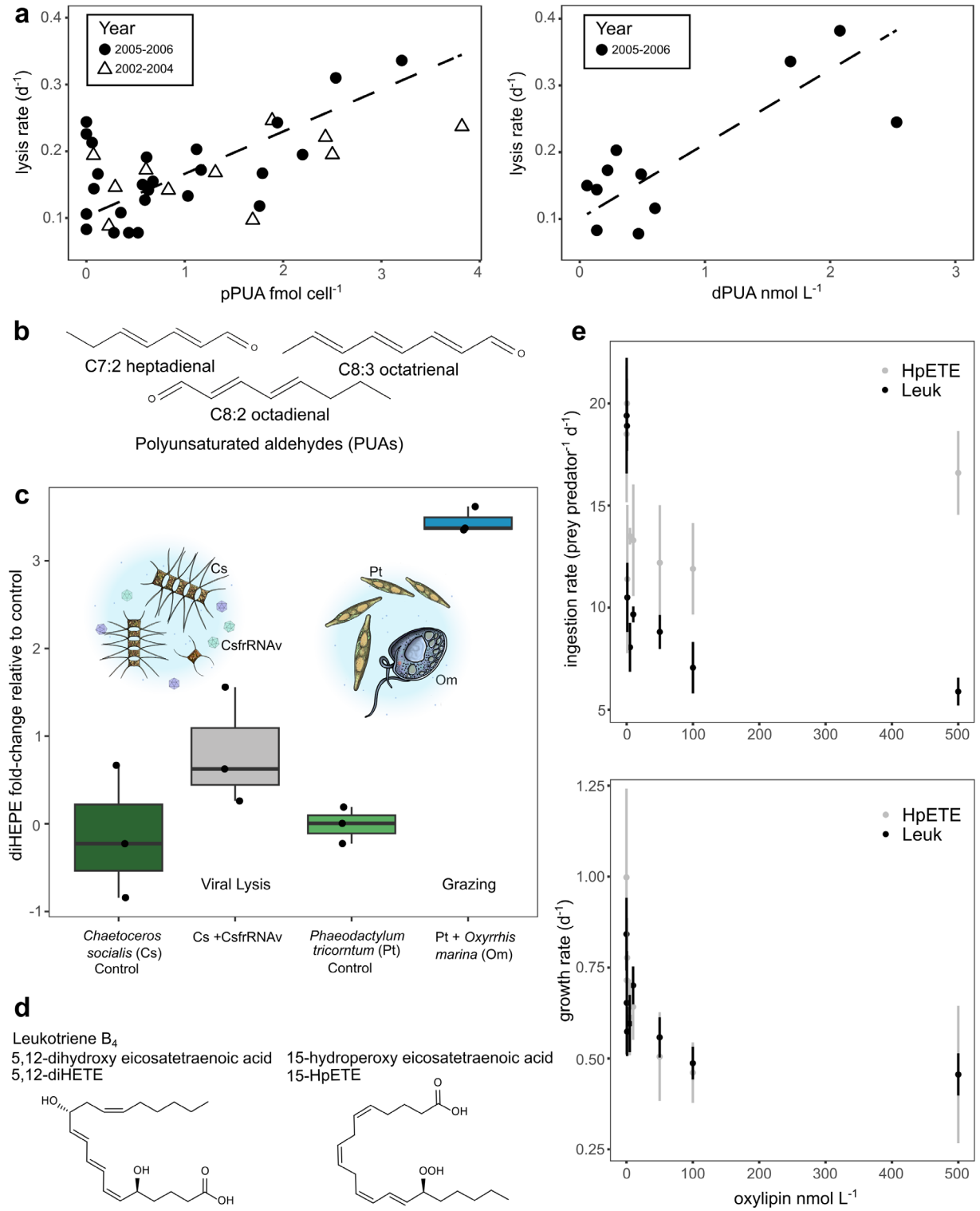
Indicator metabolites include compounds whose presence, absence, or change in abundance reveals the biological condition(s) or health of an ecosystem (Siddig et al. 2016; Fig. 1d). While there has been extensive work on metabolites as taxonomic indicators (Mackey et al. 1996), we focus on those that serve as indicators of community functions and ecosystem health. Such indicator metabolites may reveal stress induced by resource limitation or exposure to environmental factors beyond the acclimated range and pathogen infections (Supporting Information Table S4). We highlight metabolites that indicate microbial stress and nutritional status, as well as toxins that negatively impact ecosystem health, wherein a metabolite's abundance is linked to health status in natural marine ecosystems (Table 1; Supporting Information Tables S1, S4). We also leverage experimental evidence that demonstrates such relationships in laboratory studies to explore putative indicator metabolites.

Oxylipin indicators of stress

Oxylipins are enzymatically produced from PUFAs when cells are stressed and their lipid membranes are disrupted. Dissolved and particulate concentrations of volatile oxylipins called polyunsaturated aldehydes (PUAs) were associated with an increase in diatom cell lysis during spring bloom decline in the Adriatic Sea (Ribalet et al. 2014; Fig. 4a,b; Supporting Information Table S8a,b). In culture experiments, virus-infected *Chaetoceros* diatoms release oxylipins that are analogs of the eicosatetraenoic acid-derived oxylipins shown to inhibit grazing and growth of the dinoflagellate *Oxyrrhis marina* in a dose-dependent manner (Johnson et al. 2020; Edwards et al. 2024; Fig. 4c–e; Supporting Information Table S8c,d). Grazing also induces the production of oxylipin compounds in simulated grazing experiments with both natural communities and diatom cultures (Pohnert 2000; Ribalet et al. 2014), as well as feeding experiments with *O. marina* and the diatom prey *Phaeodactylum tricornutum* (Johnson et al. 2020; Fig. 4a,c). A study in the Mediterranean found that oxylipin concentrations tracked diatom cell concentrations, thus acting as a general biomarker of diatoms, albeit per-cell values decreased with increasing diatom density (Russo et al. 2020). Further investigation of transcripts for the first gene in oxylipin biosynthesis, lipoxygenase (LOX), demonstrated an inverse relationship between LOX transcripts and relative abundance of diatoms, concluding that diatoms upregulate LOX when cell abundance is low to essentially "shout" via chemical communication. Current evidence demonstrates oxylipins as phytoplankton stress indicators with dose-dependent effects on grazer predation (Fig. 4e) necessitating further quantitative studies.

Lipid indicators of nutrient scarcity

Lipid membrane composition is somewhat flexible, and there is strong evidence that marine microbes alter their lipid



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structure to alleviate nutrient scarcity. This is particularly acute for phosphorus limitation since lipids are a major allocation of phosphorus within cells. Evidence for lipid substitution is observed along phosphorus gradients in the oligotrophic upper ocean (Van Mooy et al. 2006, Van Mooy et al. 2009; Supporting Information Table S4). Under phosphorus limitation, cyanobacteria increase the production of sulfur-containing sulfoquinovosyl diacylglycerol (SQDG) lipids relative to phosphorus-containing phospholipids (Van Mooy et al. 2006). Similarly, certain eukaryotic phytoplankton and heterotrophic bacteria increase the production of nitrogen-containing lipids like betaine lipids diacylglyceryl hydroxymethyl-trimethyl-β-alanine (DGTA) and diacylglyceryl carboxyhydroxymethylcholine (DGCC) relative to phospholipids under phosphorus scarcity (Van Mooy et al. 2009; Sebastián et al. 2016), and similar remodeling of membrane lipids has been observed seasonally in response to changing nutrient conditions in the Mediterranean Sea (Sebastián et al. 2016). Notably, membrane remodeling may impair bacterial resistance toward bacteriophages and thus bear ecological trade-offs (Stirrup et al. 2023).

Phytoplankton toxins

Toxins produced by harmful algal bloom (HAB)-forming phytoplankton can have severely negative health and economic impacts. Given the predicted increase in the frequency, duration, and severity of HABs due to climate change and anthropogenic impact, for example, increased temperature, eutrophication, and weather-related disturbances, it is critical to monitor HABs and associated toxins to assess water quality and improve predictions of HABs (Anderson et al. 2021). We briefly highlight a few HAB toxins (Supporting Information Table S4), while others have published more extensive reviews on their chemical diversity, geographic ranges, and health impacts (Pinto et al. 2023).

Brevetoxins (BTXs) are fat-soluble neurotoxins produced by *Karenia brevis* and other dinoflagellates (Beasley 2020). Brevetoxin production tends to increase when conditions are nitrogen- or phosphorus-limited (Hardison et al. 2013), at low (< 25 psu) or high (> 37.5 psu) salinity levels, and when cells are in the stationary growth phase (Maier Brown et al. 2006). Also produced primarily in dinoflagellates are neurotoxic saxitoxins (STXs; Beasley 2020; Pinto et al. 2023). Production of STXs increases with temperature, light intensity, salinity, and low nitrogen concentrations (Pinto et al. 2023). For example, limited inflow of the Atlantic Ocean in the Indian River Lagoon estuarine system along US Florida's coast creates long water residence times, poor water quality, and subsequent favorable conditions for STX-producing species (Laureano-Rosario et al. 2021). Domoic acid (DA) is a non-proteinogenic amino acid and excitotoxin primarily produced by diatoms in the cosmopolitan genus *Pseudo-nitzschia* during certain life cycle stages, in response to environmental changes, and during stress from grazing (Beasley 2020). Discovery of the DA biosynthetic gene cluster (*dab*) has opened avenues for rapid forecasting of HABs and DA monitoring (Brunson et al. 2018). Indeed, researchers have detected increased *dab* gene transcription by *Pseudo-nitzschia* in advance of DA production and linked elevated DA production to iron and silica co-limitation (Brunson et al. 2023).

Putative indicator metabolites of infection and senescence

Additional putative indicator metabolites require further observation to understand their broader community significance. For example, several metabolites can indicate phytoplankton infection. Glycosphingolipid (GSL) markers can reveal viral infection in coccolithophore blooms (Laber et al. 2018) and allow identification of susceptible and resistant cells within the population (Schleyer et al. 2023). Further, induction of algal blooms in mesocosms in combination with comparative untargeted metabolomics allowed mapping of temporal changes in dissolved metabolites throughout community succession to link unique chlorine-iodine-containing metabolites with viral infection of coccolithophores (Kuhlisch et al. 2021). In diatoms, oomycete infection elicits synthesis of specific alkaloids β-carboline and 2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid that arrest host cell division and induce plasmolysis to support proliferation of the oomycete, though this metabolite marker has yet to be validated in the field (Vallet et al. 2019). As for additional infochemicals,

Fig. 4. Oxylipins are indicator metabolites of phytoplankton stress. Oxylipins are associated with cell lysis during grazing and viral infection. (**a**) Correlation between polyunsaturated aldehyde (PUA) concentrations in the Mediterranean Sea and phytoplankton lysis as assessed by an esterase assay in both particulate (pPUA) and dissolved (dPUA) pools. Data replotted from Ribalet et al. 2014. (**b**) Chemical structures of three PUA compounds heptadienal, octadienal, and octatrienal that were summed together in panel a. (**c**) Fold change in the abundance of the dissolved oxylipin dihydroxy eicosapentaenoic acid (diHEPE) relative to the control in laboratory culture experiments infecting the diatom *Chaetoceros socialis* (Cs; dark green; $n = 3$) with CsfrRNAv virus (gray; $n = 3$) and in experiments feeding the diatom prey *Phaeodactylum tricornutum* (Pt; green; $n = 3$) to the dinoflagellate grazer *Oxyrrhis marina* (Pt + Om; light blue; $n = 3$; Johnson et al. 2020; Edwards et al. 2024). Inset drawings depict the relevant organisms to the two studies. (**d**) Chemical structure of leukotriene B_4 or 5,12-dihydroxy eicosatetraenoic acid (5,12-diHETE), the C20:4 analog of the C20:5 diHEPE produced by diatoms in (c) and 15-HpETE, an isomer of leukotriene B_4. (**e**) Oxylipins deter grazers in a dose-dependent response. Ingestion rates and growth rates of grazer *O. marina* fed *P. tricornutum* prey in the presence of various concentrations of oxylipins 15-HpETE and leukotriene B_4. All points are means, ± SD of $n = 3$ biological replicates (Johnson et al. 2020). *See* Supporting Information Summary and Tables S8a–d for details on compiled data. Data from Ribalet et al. 2014 and Edwards et al. 2024 were replotted under the terms of the Creative Commons Attribution License. Data from Johnson et al. 2020 were replotted under Wiley journal author permission to reproduce. Figure illustrations by Rebecca S. Key.

phenolic compounds like *p*-coumaric acid are building blocks of cell wall lignin, and their biosynthesis seems preserved among marine microalgae lineages (Goiris et al. 2014). Environmental stress can lead to an increase in phenolic compounds in algae, as shown in diatoms (Rico et al. 2013). Interestingly, *p*-coumaric acid acts as a chemical cue of senescent phytoplankton cells for marine bacteria, with responses ranging from the incorporation of *p*-coumaric acid into the QS molecule *p*-coumaroyl-HSL to the biosynthesis and release of algicides and siderophores (Schaefer et al. 2008; Seyedsayamdost et al. 2011; Wang et al. 2022). Interpretation of their dynamics in the field requires further assessment.

Putative indicator metabolites of nutrient scarcity

Another molecule implicated in nutrient limitation is methylthioadenosine (MTA), a derivative of adenosine and intermediate in the methionine salvage pathway. Methylthioadenosine demonstrates both diel and seasonal variability in the field (Boysen et al. 2021; Liu et al. 2022; Longnecker et al. 2024), and over a latitudinal transect of the Atlantic Ocean, particulate MTA concentrations followed biomass, while dissolved concentrations were significantly greater in the Northern Atlantic relative to the Southern Atlantic (Johnson et al. 2023). Culture work with *Prochlorococcus* suggests this pattern could be due to phosphorus limitation wherein MTA is excreted relative to its phosphorus-containing counterpart, methylthioribose-phosphate (MTRP), to conserve intracellular phosphorus (Kujawinski et al. 2023). Methylthioadenosine is further linked to B_{12} limitation, showing increased intracellular concentrations in diatoms during B_{12} deprivation (Heal et al. 2019). Methylthioadenosine is a distinguishing metabolite feature across coral reefs, with MTA cycling gene abundances in reef seawater microbial communities correlated to dissolved MTA concentrations (Weber et al. 2022; Becker et al. 2023). Additionally, sponges can be net sinks for compounds including MTA with concurrent release of amino acids and nucleosides (Fiore et al. 2017), further implicating MTA in microbe–macroorganism interactions.

Intersection of ecological metabolite categories

In our ecological categorization of marine microbial metabolites, we propose that some metabolites may fit into more than one of the three categories discussed above. When considering functional role(s) and community-scale impact(s) at the metabolite level, it may be appropriate to consider ecological categories as non-mutually exclusive. Of course, our ability to categorize a metabolite into more than one category is further biased to metabolites with a wealth of available data.

Dimethylsulfoniopropionate was formerly proposed as a keystone metabolite (Ferrer and Zimmer 2013), and here, we suggest that it harbors characteristics of both a dominant and keystone metabolite. Dimethylsulfoniopropionate is an abundant, widespread organosulfur metabolite with high environmental flux. It acts as a compatible solute in many microbes and thus helps in their osmoadaptation (Gebser and Pohnert 2013). Furthermore, DMSP mediates algae–bacteria interactions by chemoattraction of heterotrophic prokaryotes (Seymour et al. 2010) and modulation of bacterial virulence, physiology, and metabolite release (Johnson et al. 2016; Barak-Gavish et al. 2018). Beyond the biogeochemical impact of DMSP on carbon and sulfur cycling within marine microbial communities (Simó et al. 2009), its cleavage product dimethyl sulfide (DMS) is emitted from the ocean to the atmosphere, transferring $\sim$13 to 37 teragrams (Tg) of sulfur annually, where it plays a critical role in climate regulation (Kettle and Andreae 2000). Furthermore, DMS acts as an infochemical, mediating chemoattraction of single-cell plankton, activation of parasitoids, and foraging in megafauna like birds (Seymour et al. 2010; Garcés et al. 2013; Savoca and Nevitt 2014). Thus, DMSP is a dominant metabolite that plays additional ecosystem support roles as a keystone metabolite. Because it has been studied for decades, DMSP demonstrates how focused work on a metabolite can unlock understanding of ecosystem dynamics. Looking forward, the PUFA arachidonic acid has both keystone and dominant metabolite characteristics, and its high flux in North Pacific metabolomes (Fig. 2) warrants further study.

Oxylipins are indicators of stress, and they further act as chemical signals within diatom communities, impact the growth of other plankton, and deter grazers (Miralto et al. 1999; Johnson et al. 2020). Growing observational evidence demonstrates that oxylipins impact community function, characteristic of keystone metabolites. Oxylipins not only deter microzooplankton grazing (Johnson et al. 2020; Fig. 4e), but they impair the reproductive success of copepod grazers (Wolfram et al. 2014), decreasing the hatching success rate of copepod eggs by 80% (Miralto et al. 1999) and causing teratogenic effects on resulting nauplii (Ianora et al. 2004). In the Chesapeake Bay, the addition of exogenous PUAs resulted in a trophic cascade shifting copepod grazing from diatoms to ciliates and ciliate grazing from diatoms to cyanobacteria (Franzè et al. 2018). Thus, a negative feedback loop exists where grazing induces oxylipin production by the prey and deters further grazing, altering trophic transfer. Further, the PUA decadienal can also mediate cell death in neighboring diatom cells and is thought to play a role in a stress surveillance system for diatom populations (Vardi et al. 2006). In sinking particles, PUAs cause bacteria community compositional changes and stimulate respiration with implications for carbon export efficiency (Edwards et al. 2015). Given their roles in community structure and function, oxylipins demonstrate overlap between ecological indicator and keystone categories.

Future outlook

Advances in metabolite extraction techniques and analytical tools have certainly broadened the chemical space of

measurable metabolites. Yet, additional metabolites of importance remain poorly quantified. For example, small organic acids like acetate act as a major carbon source exchanged among microbes in laboratory-based studies of marine polysaccharide degrading communities (Pontrelli et al. 2022; Amarnath et al. 2023) but are often not detected by untargeted LC–MS approaches, particularly under environmentally relevant concentrations. Further, high molecular weight compounds like polysaccharides are secreted by algae and consumed by heterotrophic bacteria (Mühlenbruch et al. 2018); however, they are often too large for detection using standard mass spectrometry methods and can contain complex linkages and modifications that make characterization challenging. Indeed, the development of analytical methods remains critical for the metabolomics community.

Experimental validation and spatiotemporal observations continue to be crucial for resolving the ecological and biogeochemical impact of metabolites, especially for putative ecological metabolites that lack community-scale observations and/or lack reproducibility of lab measurements. Such measurements are essential for identifying indicator metabolites whose abundance correlates with nutrient availability or cell lysis over time and/or space (Fig. 4) and dominant metabolites that have both high abundance and temporal dynamics (Fig. 2). For dominant metabolites, flux measurements are needed to disentangle the balance between the sources of dissolved metabolites and their sinks through assimilation by neighboring cells. Rates are crucial to the inclusion of metabolite processes in computational models and to resolve the biogeochemical impact of metabolites in a changing ocean, with isotope-based tracers as important tools moving forward (Obata et al. 2013; Boysen et al. 2022). Spatial information for metabolites at the micron scale is another research frontier (Martínez-Pérez et al. 2024). While our observations typically come from filtration and homogenization of milliliter- to liter-sized samples, we know that metabolites are heterogeneously distributed in microzones of particles, cell surfaces, and in animal excretions. Metabolites can also be exchanged during cell-to-cell attachment, which would be missed with traditional bulk seawater measurements (Arandia-Gorostidi et al. 2017). Emerging single-cell mass spectrometry imaging and microscopy techniques now allow resolution of metabolites exchanged in microbial consortia and physicochemical interactions between cells and their environment for investigation of such micron-scale dynamics.

Quantitative measurements alongside ecosystem monitoring (e.g., community composition, primary production) and experimental manipulations are also necessary to understand the ecological impact of (groups of) metabolites (Fig. 3). For example, in reef systems, diverse metabolites support the growth of micro- and macroorganisms within the complex ecosystem (Fiore et al. 2017; Weber et al. 2022). Preliminary experiments using holobiont exudates from corals vs. singular metabolites demonstrate conflicting impacts on microbial growth. Studies with mixed exudates result in the enrichment of diverse microbial taxa (Weber et al. 2022), whereas the impact of singular exudates does not document a consistent growth or community composition change. These results suggest that a combination of metabolites may be necessitated for ecological impact. More extensive coral holobiont metabolomics surveys, for example, Tara Pacific (Reddy et al. 2023), will help disentangle the interplay among metabolites at the community level.

Untargeted metabolomics approaches continue to aid in identifying metabolites of interest. For example, untargeted exometabolomes of microalgae have pointed to the enrichment of extracellular lumichrome, dipeptides, and prostaglandin-like compounds, several of which act as effector metabolites to impact algal growth (Brisson et al. 2021). Combining genetic tools alongside mass spectrometry has also proven powerful for elucidating novel metabolites. In *Prochlorococcus*, relaxed substrate specificity in a single biosynthetic enzyme leads to the production of 29 different cyclic peptide metabolites, called prochlorosins, yet their ecological impact remains unknown (Li et al. 2010). As more marine metabolites are chemically and functionally annotated, the framework presented herein can aid their broader ecological categorization. To help navigate the complexity that exists in the ocean metabolome, this ecological framework establishes a set of rules that define key characteristics and relationships of important metabolites within the ocean microbiome over space and time.

Author Contributions

Bryndan P. Durham and Winifred M. Johnson co-led and co-managed all aspects of the research and manuscript preparation. Elizabeth B. Kujawinski led the C-CoMP 2022 Labile DOM Workshop where group members conceived ideas for the manuscript. Bryndan P. Durham, Winifred M. Johnson, Catherine C. Bannon, Erin M. Bertrand, Anitra E. Ingalls, and Elizabeth B. Kujawinski conceptualized and developed the framework for the manuscript. Bryndan P. Durham, Winifred M. Johnson, Catherine C. Bannon, Erin M. Bertrand, and Bethanie R. Edwards curated and visualized data. All authors contributed to compiling and organizing existing data and writing and revising the manuscript.

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Conflicts of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

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