Using chemical language to shape future marine health

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"Infochemicals" (information-conveying chemicals) dominate much of the underwater communication in biological systems. They influence the movement and behavior of organisms, the ecological interactions between and across populations, and the trophic structure of marine food webs. However, relative to their terrestrial equivalents, the wider ecological and economic importance of marine infochemicals remains understudied and a concerted, cross-disciplinary effort is needed to reveal the full potential of marine chemical ecology. We highlight current challenges with specific examples and suggest how research on the chemical ecology of marine organisms could provide opportunities for implementing new management solutions for future "blue growth" (the sustainable use of ocean resources) and maintaining healthy marine ecosystems.

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Approximately 1500 different spoken languages currently exist, with ~100 of the most commonly used ones making up the great majority of global human conversation. Language is not only an important part of one's identity and cultural background, but is also a prerequisite for social interactions, social behavior, and a functioning society. However, species other than humans also "talk", and this chatter is not limited to the terrestrial world. Underwater communication is bountiful although somewhat alien to us because it relies on means of communication that extend well beyond the audible clicking sounds produced by dolphins or the "singing" of whales. For example, glows and flashes from the light-producing organs of deep-sea fishes attract prey and mates or stun and confuse prey and predators (Haddock *et al.* 2010). Although sharks employ a range of sensory systems that include vision, touch, electroreception, and specialized organs (lateral lines) that detect water turbulence (Gardiner 2012), they also exploit chemical cues to locate prey over distances of several hundred meters (see Panel 1 for a glossary of terms; Gardiner *et al.* 2014). In the marine realm, use of such cues is not limited to top predators but is also very common among organisms at the microscopic scale. For instance, plankton rely on chemicals to deter enemies or synchronize mutual as well as inhibitory or "allelopathic" interactions that critically affect marine community structure and ecosystem function (reviewed by Hay [2009]). The study of such chemical interactions among organisms and their environment is referred to as "chemical ecology", which aims to translate this chemical "language" so as to interpret behaviors, processes, and functions (Hay 2014). Over the past 50 years, research on chemical ecology in marine ecosystems has improved our understanding of ecological functionality and aided in the development of tools required for the conservation and management of marine systems (Hay 2014).

The enormous diversity of very small organisms (submillimeter sizes) that form the basis of the marine food web strongly influences carbon and nutrient cycling, and provides the scaffold for stable, healthy ecosystems and fisheries. Despite harboring an immense gene pool, microscopic marine biota lack many of the sensory organelles or organs found in larger organisms, including auditory and acoustic sensors and complex vision. Instead, their communication is dominated by "infochemicals": multifaceted compounds (both volatile and non-volatile, as well as polar and non-polar [Mollo *et al.* 2017]) that convey information (Figure 1). A variety of compounds influence organismal interactions either positively or

In a nutshell:

- In marine environments, species interactions that form the basis of food webs and shape ecosystem functioning are dependent on chemical communication
- "Infochemistry" is already used to manage agricultural processes in terrestrial contexts, but applications in marine systems are underexplored
- We highlight two distinct challenges to sustainable growth in marine aquaculture and maritime operations, and propose solutions that require major interdisciplinary efforts, the development of a strengthened knowledge base, improved innovation and predictive capacity, and adaptive management plans for sustainable use of marine resources

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Panel 1. Glossary of terms

Biofilms: surface-associated microbial (including bacteria, archaea, and microalgae among others) communities encased in a self-secreted matrix of extracellular polymeric substances (natural polymers of high molecular weight).

Chemical cues: unintentionally released compounds that supply information.

Chemical ecology: a cross-disciplinary field of research that investigates chemically mediated interactions among organisms and their environment.

Chemical signals: intentionally released compounds that supply specific information.

Epibiosis: the spatial association between a substrate organism ("basibiont") and a sessile organism ("epibiont") attached to the basibiont's outer surface without being trophically dependent on it.

Fouling: colonization process of a solid surface (living or non-living).

Holobiont: a collective biological entity including the host, its microbiome, and other associated symbionts.

Infochemicals: information-conveying chemicals (semiochemicals) including allelochemicals and pheromones that mediate interspecific and intraspecific communication, and population- and ecosystem-level interactions.

Metabolic fingerprinting: qualitative description of an internal or external metabolome.

Metabolic footprinting: characterization of metabolites excreted/secreted by and/or consumed by a biological system.

Metabolome: the complete set of typically low-molecular-weight molecules found within a biological sample.

Volatolome: the volatile subset of metabolites produced by the collective metabolism(s) of organism(s), communities, or entire ecosystems.

negatively at intra- and interspecific levels (eg John *et al.* 2015). Notably, these compounds may function as intentional "signals" (eg a sexual attractant released by a sender) or as unintentionally released "cues" (eg prey-specific chemicals that attract predators [Steiger *et al.* 2011] or warn prey of predator presence [Selander *et al.* 2015, 2019]).

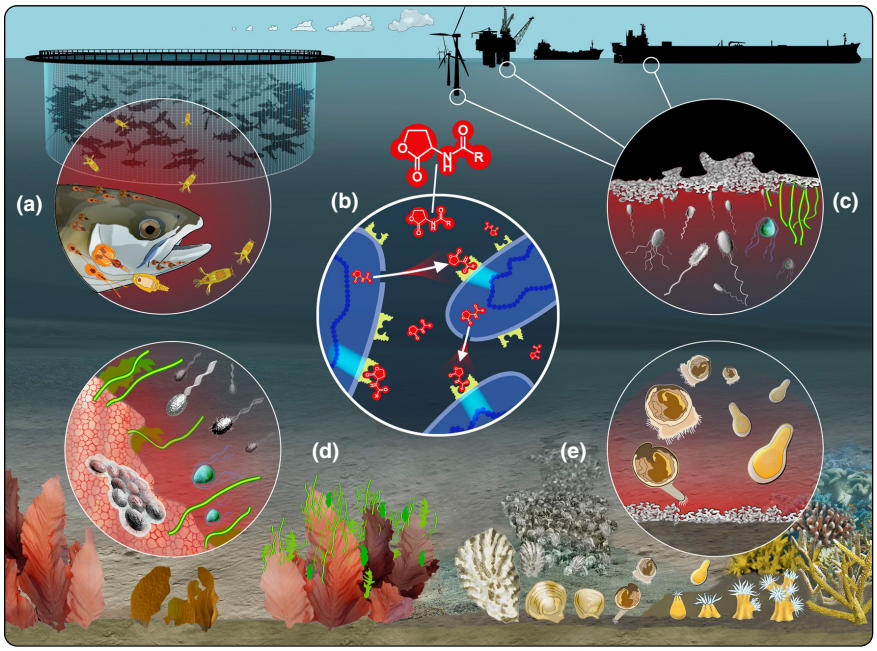

Figure 1. The role of infochemical gradients (indicated by the diffused red shading emanating from the point sources) in guiding marine interactions among living organisms and with non-living substrates. (a) Parasites on farmed salmon: salmon release infochemicals that enable host finding in parasitic sea lice. (b) Cell-to-cell communication: quorum sensing using, for example, *N*-acyl homoserine lactone (AHL) in bacteria, results in settlement and biofilm formation. (c) Biofouling: ship hulls, oil rigs, and wind farm turbine foundations are prone to fouling that can cause detrimental biocorrosion. (d) Epibiosis on farmed seaweeds: micro- and macrofouling by bacteria and filamentous green algae is triggered by infochemicals. (e) Larval settlement: larvae of oysters, mussels, and corals are attracted to infochemicals from conspecifics, as well as specific flora and fauna living on the seafloor surface, leading to gregarious larval settlement. Persistent chemical gradients act as a directional cue to these colonizing organisms. Graphics prepared by G Gorick.

Here, we explore the socioeconomic potential of marine chemical ecology. We focus on two distinct research challenges that illustrate the utility of chemical ecology within a "blue growth" framework for the future (the sustainable use of ocean resources for economic growth, improved livelihoods, and jobs [ie for human health and well-being], while preserving the health of ocean ecosystems). We illustrate the power of chemical communication that, in contrast to the spoken words of humans, readily transmits across taxonomic lineages and even kingdoms of life, including communication between the simplest unicellular organisms (Figure 1b) and more complex multicellular plants (Figure 1d) and animals (Figure 1, a and e; eg Joint *et al.* 2007). For instance, corals use chemical cues to attract mutualistic fishes to assist them with the removal of nuisance algae (Dixson and Hay 2012); a better understanding of this language would provide crucial insights into the evolutionary history of this chemically mediated communication that underpins critical ecological interactions. We emphasize that deciphering at least part of the multitude of chemical "words" will substantially enhance our understanding and so provide potential avenues to facilitate novel management strategies to improve food safety and security, mitigate harmful impacts on humans and the environment, and enhance blue growth.

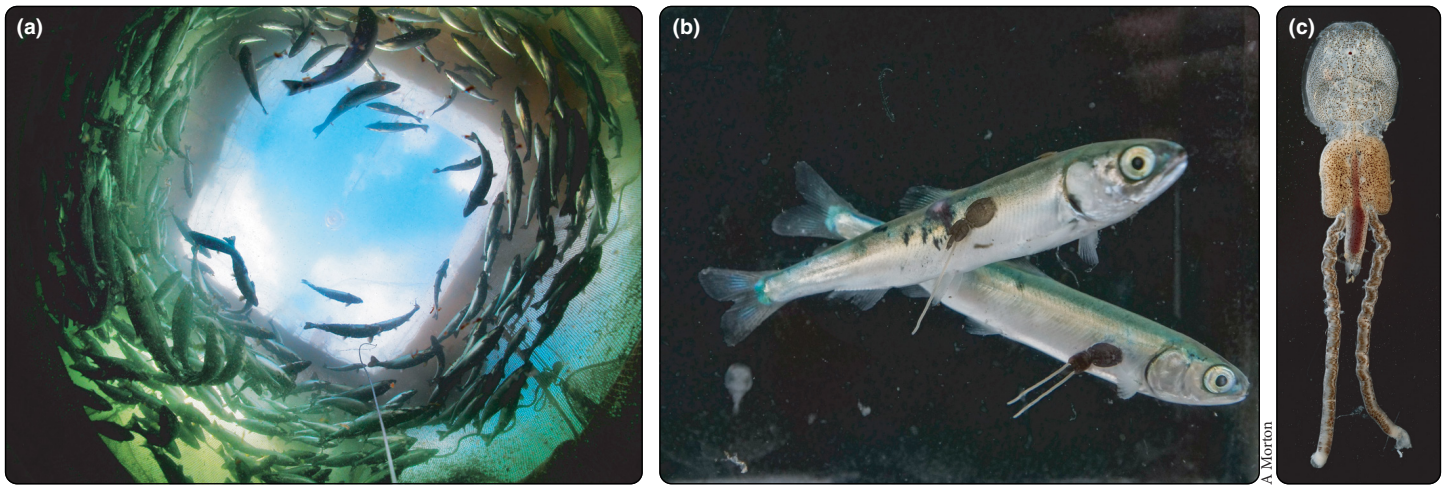

Figure 2. (a) High stocking density of caged salmon in an aquaculture farm. (b) Salmon infested with sea lice. (c) Female sea louse (*Lepeophtheirus salmonis*) with egg sacs.

Challenge 1: sustainable aquaculture

Understanding infochemical communication provides opportunities for targeted manipulation of behaviors benefiting sustainable aquaculture. Marine aquaculture is dominated by the salmon industry in Europe and the Americas (Figure 1a; Figure 2a). Ectoparasitic "sea lice", including copepod crustaceans such as *Caligus elongatus* and *Lepeophtheirus salmonis*, infect salmon (Figure 2, b and c) and cause annual economic losses of approximately €300 (~US$330) million worldwide. Infectious stages spread from farms and threaten wild populations of salmon and trout, and may also be pathogenic to wild fishes under natural conditions (Costello 2009). Current treatment of sea lice infection relies on a combination of mechanical cleaning, use of the often wild-caught cleaner wrasse (Labridae) fish that feed on the parasites, and application of chemotherapeutic agents (eg macrocyclic lactones) that are toxic to many invertebrates and that can be damaging to aquatic food webs. Meanwhile, sea lice have developed resistance to three of the five compound groups used in chemical remedies (Aaen *et al.* 2015) and, with more than 18 million cleaner fish used annually in Norwegian salmon farms alone, wild populations of cleaner fish cannot support the industry, and wrasse stocks are now in decline in many fished areas (Halvorsen *et al.* 2017). As such, there is an urgent need for new, sustainable methods for sea lice control.

Tapping into infochemical cues of terrestrial predator–prey interactions has provided useful strategies for integrated pest management (Atsatt and O'Dowd 1976; Pickett and Khan 2016). Such proven management strategies offer a blueprint for transfer to an aquatic setting. Sea lice are highly evolved to locate and attach to salmonid fishes using chemical cues (Mordue and Birkett 2009); stimuli-guided diversionary strategies based on sexual pheromone traps or push–pull strategies (strategies for controlling agricultural pests by using repellent "push" plants and attractive "pull" plants) initially developed for herbivore management in agriculture (Pickett *et al.* 2014) could therefore be complementary tools for integrated sea lice management. For example, sea lice avoid turbot (*Scophthalmus maximus*), and host-finding success has been found to decrease in the presence of the turbot-derived compound 2-aminoacetophenone, which eliminates activation and directional responses in sea lice (Hastie *et al.* 2013). By harnessing one or more species' parasite-deterrent properties, chemical communication could be exploited to help manage multiple aquaculture species in a communal setting. In addition, cues that mediate parasite attraction can (once identified) be used to develop decoy traps to monitor parasite abundance or disrupt recognition of host cues, thereby reducing parasite infection. Thus, improving our understanding of the chemical ecology between hosts and their parasites can substantially benefit marine-based industries and enhance blue economic growth.

Protection of seaweed crops against pests, including overgrowth with epibionts (organisms that live on the surface of other living organisms, a process called epibiosis) that compete for nutrients and/or light (Figure 1d) and colonization by pathogens, is a major challenge faced by the intensive monocrop mariculture in East and Southeast Asia (Gachon *et al.* 2010). Perennial brown seaweeds (Phaeophyceae) such as *Sargassum* spp release chemicals that act as grazing deterrents, which protect crops from herbivores and improve growth (Yun *et al.* 2012). In the Philippines, natural aqueous extracts of *Ascophyllum* sp previously used as plant biostimulants (Sangha *et al.* 2014) were successfully introduced as a pre-treatment to alleviate the epiphytic growth of the alga *Neosiphonia* in farming the highly valuable red seaweed crop *Kappaphycus* sp (Borlongan *et al.* 2011). This example suggests that "companion cropping" of brown seaweed lines with tropical red seaweeds may be of mutual benefit to both types of seaweeds. Release of inhibitory infochemicals by brown seaweeds may provide seaweed farmers with a useful strategy for protecting their commercially important crops, one that is analogous to the push–pull strategies used in agriculture (Pickett and Khan 2016).

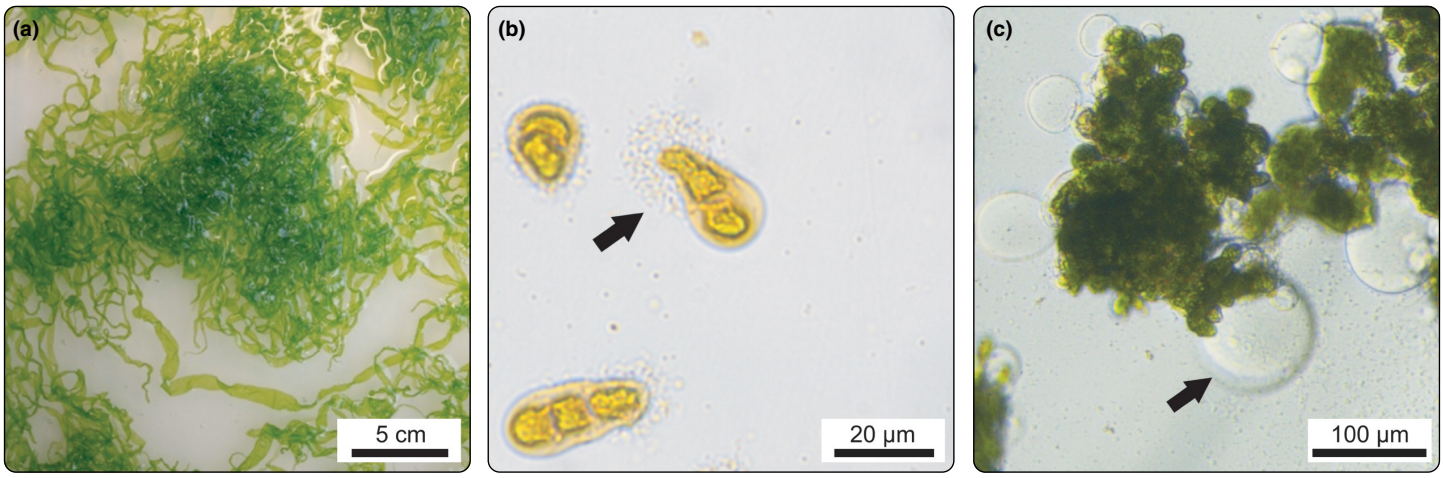

Figure 3. *Ulva mutabilis* (Chlorophyta, slender morphotype) and its cross-kingdom interactions with associated bacteria. (a) Adult specimens of a 5-week-old culture. (b) Two-cell stage of the macroalga, with a settlement of *Roseovarius* sp (arrow) on the pole of the nearby germling. (c) Bacteria-free 5-week-old culture with typical cell wall protrusions (arrow) indicating the lack of morphogen-producing bacteria. The photo in panel (a) was adapted from Wichard (2015) and is available under the terms of the Creative Commons Attribution License (CC BY 4.0).

Sustainable aquaculture of the green seaweed *Ulva* spp for the production of food additives or bioethanol is jeopardized by a switch in the seaweed's life cycle from vegetative to sexual growth phases. This switch is characterized by the production of unicellular spores and their dispersal into the environment (ie sporulation), which results in a rapid reduction in seaweed biomass. Young individuals of this seaweed chemically suppress sporulation via the release of sporulation inhibitors, including low-molecular-weight compounds and glycoproteins and their degradation products (Vesty *et al.* 2015; Kessler *et al.* 2018a); these compounds synchronize sporulation within a population and effectively control the vegetative status in conspecifics and closely related species. Applying knowledge about seaweed chemical communication – for instance by integrating seaweeds of different ages in the production process, breeding of seaweed stock cultures with increased levels and/or continued release of inhibitors, or supplementing the aquaculture with an externally supplied inhibitor – would prolong the vegetative growth phase, thereby increasing biomass yields and reducing economic risks for aquaculturists.

The seaweed *Ulva* serves as the eukaryotic host for associated bacteria (Figure 3b) in a mutualistic relationship, and research demonstrates that chemical communication between *Ulva* and these taxa can result in more productive and healthy holobionts (Figure 3a) (Egan *et al.* 2013). Under bacteria-free conditions, *Ulva* develops into a callus (ie a hard formation of tissue that is characterized by slow growth and lacks cell differentiation; Figure 3c). The release of the metabolite dimethylsulfoniopropionate in *Ulva* attracts associated microbes that induce normal seaweed morphogenesis by promoting its growth and stimulating the development of a holdfast (anchoring structure; reviewed in Wichard *et al.* [2015]). In turn, the growing seaweed provides carbon sources, such as polysaccharides and glycerol, that are needed for bacterial heterotrophic metabolism (Kessler *et al.* 2018b). This mutualistic relationship can also result in the "sharing" of bacterial compounds known as siderophores that can promote bacterial–algal interactions through enhanced iron acquisition (Amin *et al.* 2009; Wichard 2016). By understanding this cross-kingdom chemical language, seed stock and associated microbiome combinations can be optimized, which has the potential to substantially improve the sustainable production of food additives, nutraceuticals (pharmaceutical alternatives that claim physiological benefits such as polyunsaturated fatty acids [PUFAs]), and biofuels acquired through intensive aquaculture.

Challenge 2: marine biofilms

Many maritime operations are directly or indirectly affected by biofilms through detrimental biofouling and biocorrosion (Figure 1c; Dobretsov *et al.* 2009). Biofouling can be controlled through toxic antifouling coatings that include tributyl tin (TBT) or copper oxide, but these compounds can affect other marine organisms via direct toxicity, causing imposex (development of male sexual organs in females), and through transfer and bioaccumulation within the food web (Bellas 2006). In 2008, the International Maritime Organization introduced a complete ban on the use of TBT-based coatings, and a gradual phasing-out of all metal-containing antifouling agents is expected; these actions have stimulated research into approaches that rely on or are inspired by natural antifouling compounds produced by organisms that are largely free of epibionts. However, making these compounds durable, easy to use, cost effective in terms of production, and non-toxic to marine biota is an ongoing challenge (Saha *et al.* 2017), and as such the targeted prevention or detachment of marine biofilms via infochemicals has very high economic potential. A process known as "quorum sensing" (QS) often initiates the onset of biofilm formation (Figure 1b;

Figure 4a) and involves the density-dependent release of bacterial pheromones (Wirth *et al.* 1996), including *N*-acyl homoserine lactones (AHLs; reviewed in Dobretsov *et al.* [2009]). AHLs accumulate in the diffusion-limited environment surrounding bacterial cells and trigger the expression of settlement-related genes that induce the transition from a suspended to an attached bacterial phenotype (Waters and Bassler 2005). Several marine organisms, including the red seaweed *Delisea pulchra*, can counteract the formation of biofilms on their surface by actively interfering with QS (Figure 4b). For example, halogenated furanones produced by *D pulchra* interfere with a universal bacterial QS receptor, thereby disrupting bacterial cell-to-cell communication (Givskov *et al.* 1996; Manefield *et al.* 1999). In addition to furanones, seaweeds produce a multitude of chemical compounds with antibacterial, antifungal, antialgal, and antimacrofouling properties (reviewed in Saha *et al.* [2017]) that dynamically shape the seaweed's biofilm community. The translation of such infochemical research could facilitate the development of novel, natural strategies for suppressing biofilm growth. Furthermore, because unrestricted use of antibiotics often results in acquired antibiotic resistance that can be dangerous to human health, the development of nature-inspired strategies, including companion cropping, can potentially overcome current limitations in the control of pathogens.

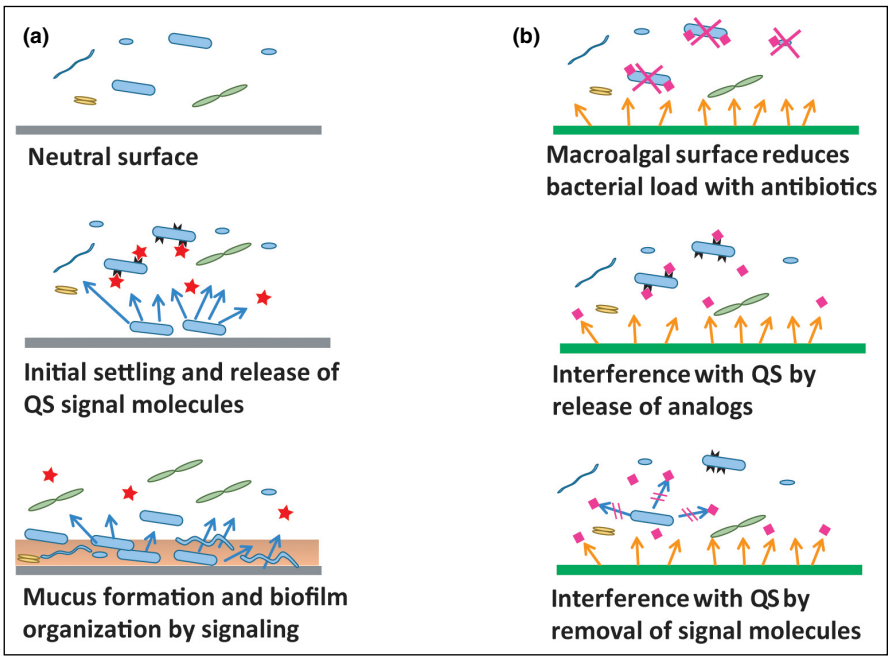

Figure 4. (a) Biofilm formation on neutral surface (gray) versus (b) processes interfering with biofilm formation on macroalgal surface (green). Blue arrows = release of quorum sensing (QS) molecules (red stars) that initiate settling in conspecifics; orange arrows = release of compounds (pink squares) that may have antibiotic properties, interfere with QS receptors, or remove QS molecules.

Scientists have only now begun to elucidate the molecular mechanisms controlling bacterial biofilm dispersal (Kaplan 2010), but the targeted delivery of the biogenic infochemical nitric oxide (NO) to such biofilms has been shown to stimulate the dispersal of bacteria from an existing biofilm matrix (Barraud *et al.* 2015); this suggests that NO may be useful for treating biofilms in a variety of medical and industrial applications (Barnes *et al.* 2015). NO also forms part of a stress-surveillance system in diatoms (Vardi *et al.* 2006), and recent results suggest that signaling interference might also be a strategy to control diatom biofilm formation. These unicellular algae respond to pheromones and inorganic nutrients with predictable movement patterns (Gillard *et al.* 2013; Bondoc *et al.* 2016); imprinting such molecular cues on surfaces through novel polymer technologies could be used to manipulate the behavior of biofilm-forming diatoms and thereby manage their settlement.

While the establishment of nuisance species may be deleterious or even eventually destructive, managed settlement of calcareous marine organisms (eg oysters, mussels, corals) may be both ecologically and economically desirable, as they may aid marine conservation, coastal protection, and fin- and shellfish husbandry. The larvae of most sessile invertebrates spend part of their life cycle as plankton before settling onto suitable substrates (Figure 1e). The suitability of these substrates is often determined by bacterial and algal metabolites (reviewed in Wahl *et al.* [2012]; Egan *et al.* 2013). Improved knowledge about these cues and their potential biotechnological applications provide opportunities for increasing the degree of targeted "spatfall" from the settlement of economically or ecologically valuable aquaculture species (eg commercially important bivalves) or reef-building hard corals in suitable habitats (Ladd *et al.* 2018). Infochemicals derived from crustose coralline algal holobionts – a common settlement substrate for many hard coral species (Heyward and Negri 1999) – have recently been shown to enhance coral recruitment on chemically imprinted artificial surfaces (Tebben *et al.* 2015). More information about marine invertebrate larval settlement cues would benefit bivalve husbandry and mariculture, as well as the seeding of new or rehabilitated reefs, which can provide structural complexity and help to restore areas of the seafloor subjected to dredging.

Future challenge: learn and use the chemical language

An overarching challenge for marine chemical ecologists is to decipher the molecular signatures of the great pool of marine chemical signals and exploit this information to benefit blue growth. Such efforts should extend beyond the discovery of isolated active compounds that is often supported by metabolomic finger- and footprinting (Goulitquer

et al. 2012; Weber *et al.* 2013), and embrace the information included in complex infochemical mixtures that may elicit responses based on the mixing ratios (the abundance of one component of a mixture relative to that of all other components) of a large number of diverse components. For example, human behavior is affected by our ability to distinguish more than one trillion different tastes and smells using just several hundred types of olfactory receptors in the nasal cavity (Bushdid *et al.* 2014). This suggests that, in addition to the concentrations of individual chemical components, the mixing ratios of infochemicals may have a profound effect on the chemical ecology of recipients: a phenomenon that – to our knowledge – is not well understood and does not receive adequate attention in marine chemical ecology research.

Phytoplankton enrich the area surrounding their cells with organic substrates that structure the "phycosphere", or microscale physicochemical environment, which provides a setting characterized by intense interactions between phytoplankton and bacteria that controls nutrient cycling and biomass production in aquatic environments (Seymour *et al.* 2017). The resulting chemical gradients form a strong component of communication in marine systems, but scientists lack adequate micro- (and even nano-) scale sampling and analytical techniques to describe concentration gradients in the diffusion-limited phycosphere, and struggle to identify the microscopic sources of these gradients. Moreover, current methodological approaches frequently overlook volatile organic compounds that are well suited for bridging diffusion-limited communication gaps in the phycosphere (Pohnert *et al.* 2007). Gases are produced in response to numerous biological processes (Steinke *et al.* 2002; Fink 2007), and the volatile metabolomes (ie volatolomes; Achyuthan *et al.* 2017; Steinke *et al.* 2018) should be considered in future efforts to decipher the marine chemical language.

Advances in marine chemical ecology are also impeded by uncertainty about how future ocean conditions (eg elevated sea-surface temperature that affects the solubility and volatility of infochemicals, spread of invasive species, ocean acidification) will interfere with the perceptive abilities of receiver organisms: that is, how future ocean conditions will affect the functioning of sensors that "listen" to this chemical language. It is also possible that ongoing and projected environmental change and its effects on marine communities (eg Brodie *et al.* 2014) will disrupt – and thereby deprive organisms from receiving – information transmitted by infochemicals. For instance, under low pH conditions, peptide signaling molecules may undergo structural changes that affect the egg ventilation behavior of the green shore crab (*Carcinus maenas*; Roggatz *et al.* 2016); similarly, orange clownfish (*Amphiprion percula*) larvae reared under high pH conditions are incapable of distinguishing between chemical cues from suitable and unsuitable settlement sites and between kin and non-kin neighbors (Munday *et al.* 2009); and benthic and pelagic invertebrates exhibit altered behavior in response to volatile foraging cues under ocean acidification conditions (Zupo *et al.* 2016). It is therefore critical to address the degree to which ocean acidification and climate change will alter how species interact in the future environment.

Addressing these challenges requires an expanded knowledge base, improved innovation and predictive capacity, and the development of adaptive management plans for sustainable exploitation and use of marine resources. Future research in marine chemical ecology must be more interdisciplinary, involving natural product chemists, ecologists, and ecoinformaticians, among others. Blue growth industries, including seaweed, finfish, and shellfish aquaculturists, will have to provide access to facilities and assist with the collaborative development of funding streams. Prior to its implementation, the knowledge derived from chemical ecology must also include an assessment of socioeconomic benefits and potential drawbacks, and the application of relevant management strategies to address problems at the global scale will likely require input from lawyers and stakeholders in the maritime sector. Nevertheless, better understanding and utilization of the marine chemical language is critical for ensuring the future health of the marine realm.

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