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A community perspective on the concept of marine holobionts: current status, challenges, and future directions

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^{*} This working group gathers 31 scientists from ten different countries, with expertise covering different scientific disciplines including philosophy, evolution, computer sciences, marine biology, ecology, chemistry, and microbiology, who participated in a workshop on marine holobionts, organized at the Roscoff Biological Station in March 2018. Their aim was to exchange ideas regarding key concepts and opportunities in marine holobiont research, to start structuring the community, and to identify and tackle key challenges in the field.

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ABSTRACT

Host-microbe interactions play crucial roles in marine ecosystems. However, we still have very little understanding of the mechanisms that govern these relationships, the evolutionary processes that shape them, and their ecological consequences. The holobiont concept is a renewed paradigm in biology that can help to describe and understand these complex systems. It posits that a host and its associated microbiota, living together in a stable relationship, form a holobiont, and have to be studied together as a coherent biological and functional unit to understand its biology, ecology, and evolution. Here we discuss critical concepts and opportunities in marine holobiont research and identify key challenges in the field. We highlight the potential economic, sociological, and environmental impacts of the holobiont concept in marine biological, evolutionary, and environmental sciences. Given the connectivity and the unexplored biodiversity specific to marine ecosystems, a deeper understanding of such complex systems requires further technological and conceptual advances, e.g. the development of controlled experimental model systems for holobionts from all major lineages and the modeling of (info)chemical-mediated interactions between organisms. Here we propose that one significant challenge is to bridge cross-disciplinary research on tractable model systems in order to address key ecological and evolutionary questions. This first step is crucial to decipher the main drivers of the dynamics and evolution of holobionts and to account for the holobiont concept in applied areas, such as the conservation, management, and exploitation of marine ecosystems and resources.



Glossary*

* If no other examples of the use of each term are cited below, the definition was based on the online version of the Merriam-Webster dictionary (2019, <https://www.merriam-webster.com/>) or the Oxford dictionary (2020, <https://www.lexico.com/>)

Anna Karenina principle – a number of factors can cause a system to fail, but only a narrow range of parameters characterizes a working system; based on the first sentence of Leo Tolstoy’s “Anna Karenina” (1878): “Happy families are all alike; every unhappy family is unhappy in its own way” (Zaneveld *et al.* 2017).

Aposymbiotic culture – a culture of a host or a symbiont without its main symbiotic partner(s) (*e.g.* Kelty and Cook 1976). In contrast to gnotobiotic cultures, aposymbiotic cultures are usually not germ-free.

Biological control (biocontrol) – methods for controlling diseases or pests by introducing or supporting natural enemies of the former (see *e.g.* Hoitink and Boehm 1999).

Biomonitoring – the use of living organisms as quantitative indicator for the health of an environment or ecosystem (Holt and Miller 2010).

Community assembly process – the processes that shape community composition in a given habitat, according to Nemergut *et al.* (2013) the four main forces relevant for community assembly are evolutionary diversification, dispersal, selection, and ecological drift.

Dysbiosis – microbial imbalance in a symbiotic community that affects the health of the host (Egan and Gardiner 2016).

Ecological process – the processes responsible for the functioning and dynamics of ecosystems including biogeochemical cycles, community assembly processes, interactions between organisms, and climatic processes (see *e.g.* Bennett *et al.* 2009).

Ecosystem services – any direct or indirect benefits that humans can draw from an ecosystem; they include provisioning services (*e.g.* food), regulating services (*e.g.* climate), cultural services (*e.g.* recreation), and supporting services (*e.g.* habitat formation) (Millennium Ecosystem Assessment Panel 2005).

Ectosymbiosis – a symbiotic relationship in which symbionts live on the surface of a host. This includes, for instance, algal biofilms or the skin microbiome (Nardon and Charles 2001).

Emergent property – a property of complex systems (*e.g.* holobionts), which arises from interactions between the components and that is not the sum of the component properties (see *e.g.* Theis 2018).

Endosymbiosis (sometimes also referred to more precisely as endocytobiosis; Nardon and Charles 2001) – a symbiotic relationship in which a symbiont lives inside the host cells; prominent examples are mitochondria, plastids/photosymbionts, or nitrogen fixing bacteria in plant root nodules. See also **ectosymbiosis**.

Gnotobiosis – the condition in which all organisms present in a culture can be controlled, *i.e.* germ-free (axenic) organisms or organisms with a controlled community of

symbionts. Gnotobiotic individuals may be obtained *e.g.* by surgical removal from the mother (vertebrates) or by surface sterilization of seeds (plants) and subsequent handling in a sterile environment and possible inoculation with selected microbes (Hale *et al.* 1973; Williams 2014).

Holism – the theory that parts of a whole are in intimate interconnection, such that they cannot exist independently of the whole, or cannot be understood without reference to the whole, which is thus regarded as greater than the sum of its parts.

Holobiont – an ecological unit of different species living together in symbiosis. The term is frequently used for the unit of a host and its associated microbiota but can be extended to larger scales. Whether or to what extent holobionts are also a unit of evolution is still a matter of debate (Douglas and Werren 2016).

Hologenome – the combined genomes of the host and all members of its microbiota; Rosenberg *et al.* 2007a; Zilber-Rosenberg and Rosenberg 2008)

Horizontal transmission – acquisition of the associated microbiome from the environment (*e.g.* Myers and Rothman 1995; Roughgarden 2019, preprint).

Host – the largest or dominant partner in a holobiont.

Infochemical – a chemical compound, usually diffusible, that carries information on the environment, such as the presence of other organisms, and can be used to mediate inter- and intraspecific communication (Dicke and Sabelis 1988).

Microbial gardening – the act of frequently releasing growth-enhancing or inhibiting chemicals or metabolites that favor the development of a microbial community beneficial to the host (see *e.g.* Saha and Weinberger 2019).

Microbiome – the combined genetic information encoded by the microbiota; may also refer to the microbiota itself or the microbiota and its environment (see Marchesi and Ravel 2015).

Microbiota – all microorganisms present in a particular environment or associated with a particular host (see Marchesi and Ravel 2015).

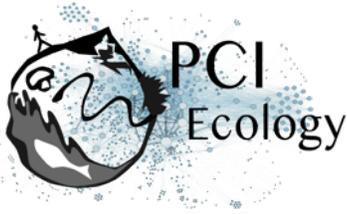
Nested ecosystems – a view of ecosystems where each individual system, like a “Russian doll”, can be decomposed into smaller systems and/or considered part of a larger system (Figure 2), all of which still qualify as ecosystems (*e.g.* McFall-Ngai *et al.* 2013).

Phagocytosis – a process by which a eukaryotic cell ingests other cells or solid particles, *e.g.* the uptake of bacteria by sponges (Leys *et al.* 2018).

Phycosphere – the physical envelope surrounding a phytoplankton cell; usually rich in organic matter (see Amin *et al.* 2012).

Phylosymbiosis – congruence in the phylogeny of different hosts and the composition of their associated microbiota (Brooks *et al.* 2016).

Rasputin effect – the phenomenon that commensals and mutualists can become parasitic in certain conditions (Overstreet and Lotz 2016); after the Russian monk Rasputin who became the confidant of the Tsar of Russia, but later helped bring down the Tsar’s empire during the Russian revolution.



Sponge loop – sponges efficiently recycle dissolved organic matter turning it into detritus that becomes food for other consumers (de Goeij *et al.* 2013).

Symbiont – an organism living in symbiosis; usually refers to the smaller/microbial partners living in mutualistic relationships (see also host), but also includes organisms in commensalistic and parasitic relationships.

Symbiosis – a close and lasting or recurrent (*e.g.* over generations) relationship between organisms living together; usually refers to mutualistic relationships, but also includes commensalism and parasitism.

Vertical transmission – acquisition of the associated microbiome by a new generation of hosts from the parents (as opposed to horizontal transmission; *e.g.* Roughgarden 2019, preprint).

Marine holobionts from their origins to the present

The history of the holobiont concept

Holism is a philosophical notion first proposed by Aristotle in the 4th century BC. It states that systems should be studied in their entirety, with a focus on the interconnections between their various components rather than on the individual parts (Met. Z.17, 1041b11–33). Such systems have **emergent properties** that result from the behavior of a system that is ‘larger than the sum of its parts’. However, a major shift away from holism occurred during the Age of "Enlightenment" when the dominant thought summarized as “dissection science” was to focus on the smallest component of a system as a means of understanding it.

The idea of holism started to regain popularity in biology when the endosymbiosis theory was first proposed by Mereschkowski (1905) and further developed by Wallin (1925). Still accepted today, this theory posits a single origin for eukaryotic cells through the **symbiotic** assimilation of prokaryotes to form first mitochondria and later plastids (the latter through several independent symbiotic events) via **phagocytosis** (reviewed in Archibald 2015). These ancestral and founding symbiotic events, which prompted the metabolic and cellular complexity of eukaryotic life, most likely occurred in the ocean (Martin *et al.* 2008).

Despite the general acceptance of the endosymbiosis theory, the term ‘**holobiont**’ did not immediately enter the scientific vernacular. It was coined by Lynn Margulis in 1990, who proposed that evolution has worked mainly through symbiosis-driven leaps that merged organisms into new forms, referred to as ‘holobionts’, and only secondarily

through gradual mutational changes (Margulis and Fester 1991; O'Malley 2017). However, the concept was not widely used until it was co-opted by coral biologists over a decade later. Corals and dinoflagellate algae of the family Symbiodiniaceae are one of the most iconic examples of symbioses found in nature; most corals are incapable of long-term survival without the products of photosynthesis provided by their endosymbiotic algae. Rohwer *et al.* (2002) were the first to use the word “holobiont” to describe a unit of selection *sensu* Margulis (Rosenberg *et al.* 2007b) for corals, where the holobiont comprised the cnidarian polyp (**host**), algae of the family Symbiodiniaceae, various ectosymbionts (endolithic algae, prokaryotes, fungi, other unicellular eukaryotes), and viruses.

Although initially driven by studies of marine organisms, much of the research on the emerging properties and significance of holobionts has since been carried out in other fields of research: the **microbiota** of the rhizosphere of plants or the animal gut became predominant models and have led to an ongoing paradigm shift in agronomy and medical sciences (Bulgarelli *et al.* 2013; Shreiner *et al.* 2015; Faure *et al.* 2018). Holobionts occur in terrestrial and aquatic habitats alike, and several analogies between these ecosystems can be made. For example, in all of these habitats, interactions within and across holobionts such as induction of chemical defenses, nutrient acquisition, or biofilm formation are mediated by chemical cues and signals in the environment, dubbed **infochemicals** (Loh *et al.* 2002; Harder *et al.* 2012; Rolland *et al.* 2016; Saha *et al.* 2019). Nevertheless, we can identify two major differences between terrestrial and aquatic systems. First, the physicochemical properties of water result in higher chemical connectivity and signaling between macro- and micro-organisms in aquatic or moist environments. In marine ecosystems, carbon fluxes also appear to be swifter and trophic modes more flexible, leading to higher plasticity of functional interactions across holobionts (Mitra *et al.* 2013). Moreover, dispersal barriers are usually lower, allowing for faster microbial community shifts in marine holobionts (Kinlan and Gaines 2003; Martin-Platero *et al.* 2018). Secondly, phylogenetic diversity at broad taxonomic scales (*i.e.* supra-kingdom, kingdom and phylum levels), is higher in aquatic realms compared to land, with much of the aquatic diversity yet to be uncovered (de Vargas *et al.* 2015; Thompson *et al.* 2017), especially marine viruses (Middelboe and Brussaard 2017; Gregory *et al.* 2019). The recent discovery of such astonishing marine microbial diversity in parallel with the scarcity of marine holobiont research suggest a high potential for complex cross-lineage interactions yet to be explored in marine holobionts (Figure 1).

The boundaries of holobionts are usually delimited by a physical gradient, which corresponds to the area of local influence of the host, *e.g.* in unicellular algae the so-called **phycosphere** (Seymour *et al.* 2017). However, they may also be defined in a context-

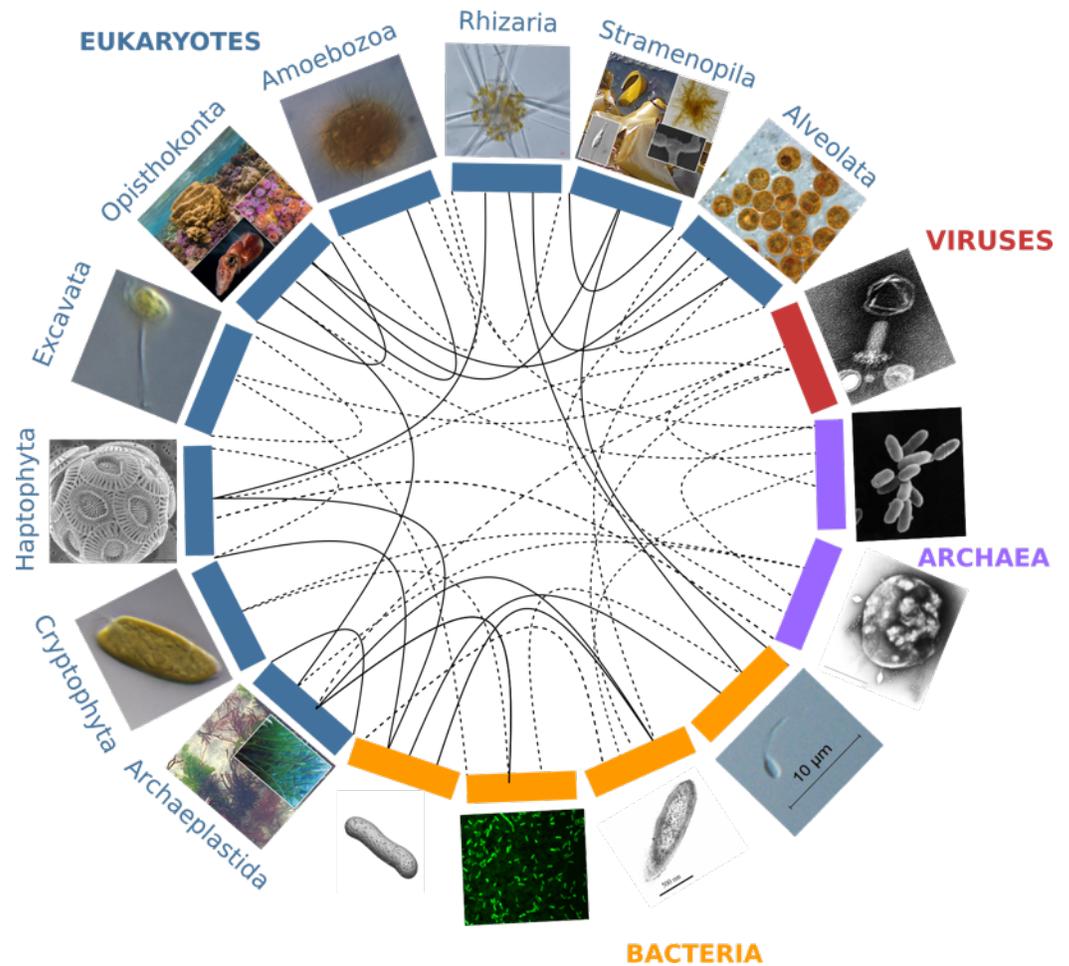


Figure 1. Partners forming marine holobionts are widespread across the tree of life including all kingdoms (eukaryotes, bacteria, archaea, viruses), and represent a large diversity of potential models for exploring complex biotic interactions across lineages. Plain lines correspond to holobionts referred to in the present manuscript. Dashed lines are examples of potential interactions. Photo credits: Archaeplastida – C. Leblanc, U Cardini; Cryptophyta, Excavata, Amoebozoa – Roscoff Culture Collection; Stramenopila – C. Leblanc, S. M. Dittami, H. KleinJan; Alveolata – A. M. Lewis; Rhizaria – F. Not; Haptophyta – A. R. Taylor; Opisthokonta – C. Frazee, M. McFall-Ngai, W. Thomas, L. Thiault; Bacteria – E Nelson, L Sycuro, S. M. Dittami, S. Le Panse, Planktomania; Archaea – National Space Science Data Center, Xiaoyu Xiang; Viruses – M. B. Sullivan et al..

dependent way as a ‘Russian Matryoshka doll’, setting the boundaries of the holobiont depending on the interactions and biological functions that are being considered. Thus

holobionts may encompass all levels of host-symbiont associations from intimate **endosymbiosis** with a high degree of co-evolution up to the community and ecosystem level; a concept referred to as “**nested ecosystems**” (Figure 2; McFall-Ngai *et al.* 2013; Pita *et al.* 2018).

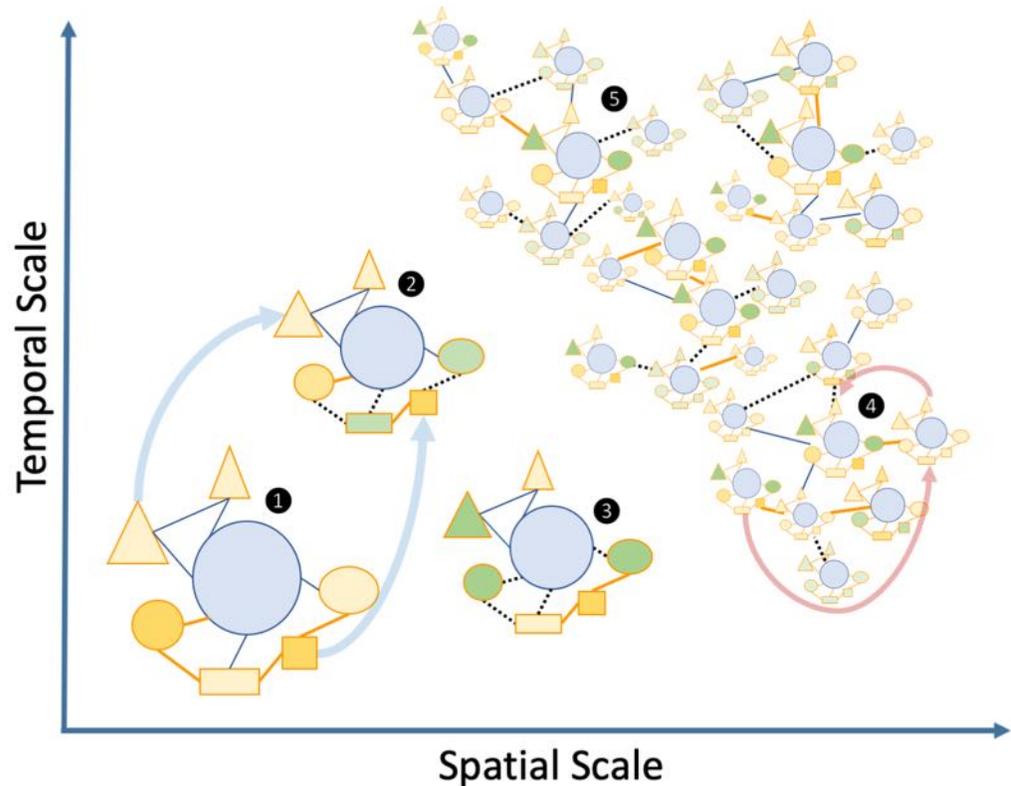


Figure 2. Schematic view of the “Russian Doll” complexity and dynamics of holobionts, according to diverse spatiotemporal scales. The host (blue circles), and associated microbes (all other shapes) including bacteria and eukaryotes that may be inside (*i.e.* endosymbiotic or outside the host, *i.e.* ectosymbiotic), are connected by either beneficial (solid orange lines), neutral (solid blue lines) or pathogenic (dashed black lines) interactions respectively. Changes from beneficial or neutral to pathogenic interactions are typical cases of dysbiosis. The different clusters can be illustrated by the following examples: 1, a model holobiont in a stable physiological condition (*e.g.* in controlled laboratory condition); 2 and 3, holobionts changing during their life cycle or submitted to stress conditions – examples of vertically transmitted microbes are indicated by light blue arrows; 4 and 5, marine holobionts in the context of global sampling campaigns or long-term time series – examples of horizontal transmission of microbes and holobionts are illustrated by pink arrows.

Such a conceptual perspective raises fundamental questions not only regarding the interaction between the different components of holobionts and processes governing their dynamics, but also of the relevant units of selection and the role of co-evolution. For instance, plant and animal evolution involves new functions co-constructed by members of the holobiont or elimination of functions redundant among them (Selosse *et al.* 2014), and it is likely that these processes are also relevant in marine holobionts. Rosenberg *et al.* (2010) and Rosenberg and Zilber-Rosenberg (2018) argued that all animals and plants can be considered holobionts, and thus advocate the **hologenome** theory of evolution, suggesting that natural selection acts at the level of the holobiont and its hologenome. This interpretation of Margulis' definition of a 'holobiont' considerably broadened fundamental concepts in evolution and speciation and has not been free of criticism (Douglas and Werren 2016), especially when applied at the community or ecosystem level (Moran and Sloan 2015). More recently, it has been shown that species that interact indirectly with the host can also be important in shaping coevolution within mutualistic multi-partner assemblages (Guimarães *et al.* 2017). Thus, the holobiont concept and the underlying complexity of holobiont systems should be better defined and further considered when addressing evolutionary and ecological questions.

Marine holobiont models

Today, an increasing number of marine model organisms, both unicellular and multicellular, are being used in holobiont research (Figure 1), often with different emphasis and levels of experimental control, but altogether covering a large range of scientific topics. Here, we provide several illustrative examples of this diversity and some of the insights they have provided.

Environmental or "semi-controlled" models, *i.e.* holobiont systems in which microbiome composition is not or only partially controlled: radiolarians and foraminiferans (both heterotrophic protist dwellers harboring endosymbiotic microalgae) are emerging as ecological models for unicellular photosymbiosis due to their ubiquitous presence in the world's oceans (Decelle *et al.* 2015; Not *et al.* 2016). The siphonous green alga *Bryopsis* is an example of a model that harbors heterotrophic endosymbiotic bacteria, some of which exhibit patterns of co-evolution with their hosts (Hollants *et al.* 2013). The discovery of deep-sea hydrothermal vents revealed symbioses of animals with chemosynthetic bacteria that have later been found in many other marine ecosystems (Dubilier *et al.* 2008; Rubin-Blum *et al.* 2019) and frequently exhibit high levels of metabolic and taxonomic diversity (Duperron *et al.* 2008; Petersen *et al.* 2016; Ponnudurai *et al.* 2017). The

cosmopolitan haptophyte *Emiliana huxleyi*, promoted by associated bacteria (Seyedsayamdost *et al.* 2011; Segev *et al.* 2016), produces key intermediates in the carbon and sulfur biogeochemical cycles, making it an important model phytoplankton species.

Controlled bi- or trilateral associations: Only a few models, covering a small part of the overall marine biodiversity, are currently being cultivated *ex-situ* and can be used in fully controlled experiments, where they can be cultured **aposymbiotically**. The flatworm *Symsagittifera* (= *Convoluta*) *roscoffensis* (Arboleda *et al.* 2018), the sea anemone *Exaiptasia* (Baumgarten *et al.* 2015; Wolfowicz *et al.* 2016), the upside-down jellyfish *Cassiopea* (Ohdera *et al.* 2018), and their respective intracellular green and dinoflagellate algae have, in addition to corals, become models for fundamental research on evolution of metazoan-algal photosymbiosis. In particular, *Exaiptasia* has been used to explore photobiology disruption and restoration of cnidarian symbioses (Lehnert *et al.* 2012). The *Vibrio*-squid model provides insights into the effect of microbiota on animal development, circadian rhythms, and immune systems (McFall-Ngai 2014). The unicellular green alga *Ostreococcus*, an important marine primary producer, has been shown to exchange vitamins with specific associated bacteria (Cooper *et al.* 2019). The green macroalga *Ulva mutabilis* has enabled the exploration of bacteria-mediated growth and morphogenesis including the identification of original chemical interactions in the holobiont (Wichard 2015; Kessler *et al.* 2018). Although the culture conditions in these highly-controlled model systems differ from the natural environment, these systems are essential to gain elementary mechanistic understanding of the functioning, the roles, and the evolution of marine holobionts.

The influence of marine holobionts on ecological processes

Work on model systems has demonstrated that motile and macroscopic marine holobionts can act as dissemination vectors for geographically restricted microbial taxa. Pelagic mollusks or vertebrates are textbook examples of high dispersal capacity organisms (*e.g.* against currents and through stratified water layers). It has been estimated that fish and marine mammals may enhance the original dispersion rate of their microbiota by a factor of 200 to 200,000 (Troussellier *et al.* 2017) and marine birds may even act as bio-vectors across ecosystem boundaries (Bouchard Marmen *et al.* 2017). This host-driven dispersal of microbes can include non-native or invasive species as well as pathogens (Troussellier *et al.* 2017).

A related ecological function of holobionts is their potential to sustain rare species. Hosts provide an environment that favors the growth of specific microbial communities distinct from the surrounding environment (including rare microbes). They may, for

instance, provide a nutrient-rich niche in the otherwise nutrient-poor surroundings (Smriga *et al.* 2010; Webster *et al.* 2010; Burke, Thomas, *et al.* 2011; Chiarello *et al.* 2018).

Lastly, biological processes regulated by microbes are important drivers of global biogeochemical cycles (Falkowski *et al.* 2008; Madsen 2011; Anantharaman *et al.* 2016). In the open ocean, it is estimated that symbioses with the cyanobacterium UCYN-A contribute ~20% to total N₂ fixation (Thompson *et al.* 2012; Martínez-Pérez *et al.* 2016). In benthic systems, sponges and corals may support entire ecosystems *via* their involvement in nutrient cycling thanks to their microbial partners (Raina *et al.* 2009; Fiore *et al.* 2010; Cardini *et al.* 2015; Pita *et al.* 2018), functioning as sinks and sources of nutrients. In particular the “**sponge loop**” recycles dissolved organic matter and makes it available to higher trophic levels in the form of detritus (de Goeij *et al.* 2013; Rix *et al.* 2017). In coastal sediments, bivalves hosting methanogenic archaea have been shown to increase the benthic methane efflux by a factor of up to eight, potentially accounting for 9.5% of total methane emissions from the Baltic Sea (Bonaglia *et al.* 2017). Such impressive metabolic versatility is accomplished because of the simultaneous occurrence of disparate biochemical machineries (*e.g.* aerobic and anaerobic pathways) in individual symbionts, providing new metabolic abilities to the holobiont, such as the synthesis of specific essential amino acids, photosynthesis, or chemosynthesis (Venn *et al.* 2008; Dubilier *et al.* 2008). Furthermore, the interaction between host and microbiota can potentially extend the metabolic capabilities of a holobiont in a way that augments its resilience to environmental changes (Berkelmans and van Oppen 2006; Gilbert *et al.* 2010; Dittami *et al.* 2016; Shapira 2016; Godoy *et al.* 2018), or allow it to cross biotope boundaries (*e.g.* Woyke 2006) and colonize extreme environments (Bang *et al.* 2018). Holobionts thus contribute to marine microbial diversity and possibly resilience in the context of global environmental changes (Troussellier *et al.* 2017) and it is paramount to include the holobiont concept in predictive models that investigate the consequences of human impacts on the marine realm and its biogeochemical cycles.

Challenges and opportunities in marine holobiont research

Marine holobiont assembly and regulation

Two critical challenges partially addressed by using model systems are 1) to decipher the factors determining holobiont composition and 2) to elucidate the impacts and roles of the different partners in these complex systems over time. Some marine organisms such as bivalves transmit part of the microbiota maternally (Bright and

Bulgheresi 2010; Funkhouser and Bordenstein 2013). In other marine holobionts, vertical transmission may be weak and inconsistent, whereas mixed **modes of transmission (vertical and horizontal)** or intermediate modes (pseudo-vertical, where horizontal acquisition frequently involves symbionts of parental origin) are more common (Björk *et al.* 2019). Identifying the factors shaping holobiont composition and understanding their evolution is highly relevant for marine organisms given that most marine hosts display a high specificity for their microbiota and even patterns of **phylosymbiosis** (Kazamia *et al.* 2016; Brooks *et al.* 2016; Pollock *et al.* 2018), despite a highly connected and microbe-rich environment.

During microbiota transmission (whether vertical or horizontal), *selection* by the host and/or by other components of the microbiome, is a key process in establishing or maintaining a holobiont microbial community that is distinct from the environment. The immune system of the host is one way of performing this selection in both marine and terrestrial holobionts. Perturbations in the transmission or the recruitment of the microbiota can lead to **dysbiosis**, and eventually microbial infections (Selosse *et al.* 2014; de Lorgeril *et al.* 2018). Dysbiotic individuals frequently display higher variability in their microbial community composition than healthy individuals, an observation in line with the “**Anna Karenina principle**” (Zaneveld *et al.* 2017), although there are exceptions to this rule (*e.g.* Marzinelli *et al.* 2015). A specific case of dysbiosis is the so-called “**Rasputin effect**” where benign endosymbionts opportunistically become detrimental to the host due to processes such as reduction in immune response under food deprivation, coinfections, or environmental pressure (Overstreet and Lotz 2016). Many diseases are now interpreted as the result of a microbial imbalance and the rise of opportunistic or polymicrobial infections upon host stress (Egan and Gardiner 2016). For instance in reef-building corals, warming destabilizes cnidarian-dinoflagellate associations, and some beneficial *Symbiodiniacea* strains switch their physiology and sequester more resources for their own growth at the expense of the coral host, leading to coral bleaching and even death (Baker *et al.* 2018).

Another way of selecting a holobiont microbial community is by chemically mediated **microbial gardening**. This concept has been demonstrated for land plants, where root exudates manipulate **microbiome** composition (Lebeis *et al.* 2015). In marine environments, the phylogenetic diversity of hosts and symbionts suggests both conserved and marine-specific chemical interactions, but studies are still in their infancy. For instance, seaweeds can chemically garden beneficial microbes, facilitating normal morphogenesis and increasing disease resistance (Kessler *et al.* 2018; Saha and Weinberger 2019), and seaweeds and corals structure their surface-associated microbiome by producing chemo-attractants and anti-bacterial compounds (Harder *et al.*

2012; Ochsenkühn *et al.* 2018). There are fewer examples of chemical gardening in unicellular hosts, but it seems highly likely that similar processes are in place (Gribben *et al.* 2017; Cirri and Pohnert 2019).

In addition to selection, ecological drift, dispersal and evolutionary diversification have been proposed as key processes in community assembly, but are difficult to estimate in microbial communities (Nemergut *et al.* 2013). The only data currently at our disposal to quantify these processes are the diversity and distribution of microbes. Considering the high connectivity of aquatic environments, differences in marine microbial communities are frequently attributed to a combination of selection and drift, rather than limited dispersal (e.g. Burke, Steinberg, *et al.* 2011), a conclusion which, in the future, could be refined by conceptual models developed for instance for soil microbial communities (Stegen *et al.* 2013; Dini-Andreote *et al.* 2015). Diversification is mainly considered in the sense of coevolution or adaptation to host selection, which may also be driven by the horizontal acquisition of genes. However, co-speciation is challenging to prove (de Vienne *et al.* 2013; Moran and Sloan 2015) and only few studies have examined this process in marine holobionts to date, each focused on a restricted number of actors (e.g. Peek *et al.* 1998; Lanterbecq *et al.* 2010).

Increasing our knowledge on the contribution of these processes to holobiont community assembly in marine systems is a key challenge, which is of particular urgency today in the context of ongoing global change. Moreover, understanding how the community and functional structure of resident microbes are resilient to perturbations remains critical to predict and promote the health of their host and the ecosystem. Yet, the contribution of the microbiome is still missing in most quantitative models predicting the distribution of marine macro-organisms, or additional information on biological interactions would be required to make the former more accurate (Bell *et al.* 2018).

Integrating marine model systems with large-scale studies

By compiling a survey of the most important trends and challenges in the field of marine holobiont research (Figure 3), we identified two distinct opinion clusters: one focused on mechanistic understanding and work with model systems whereas another targets large-scale and heterogeneous data set analyses and predictive modeling. This illustrates that, on the one hand, the scientific community is interested in the establishment of models for the identification of specific molecular interactions between marine organisms at a given point in space and time, up to the point of synthesizing functional mutualistic communities *in vitro* (Kubo *et al.* 2013). On the other hand, another

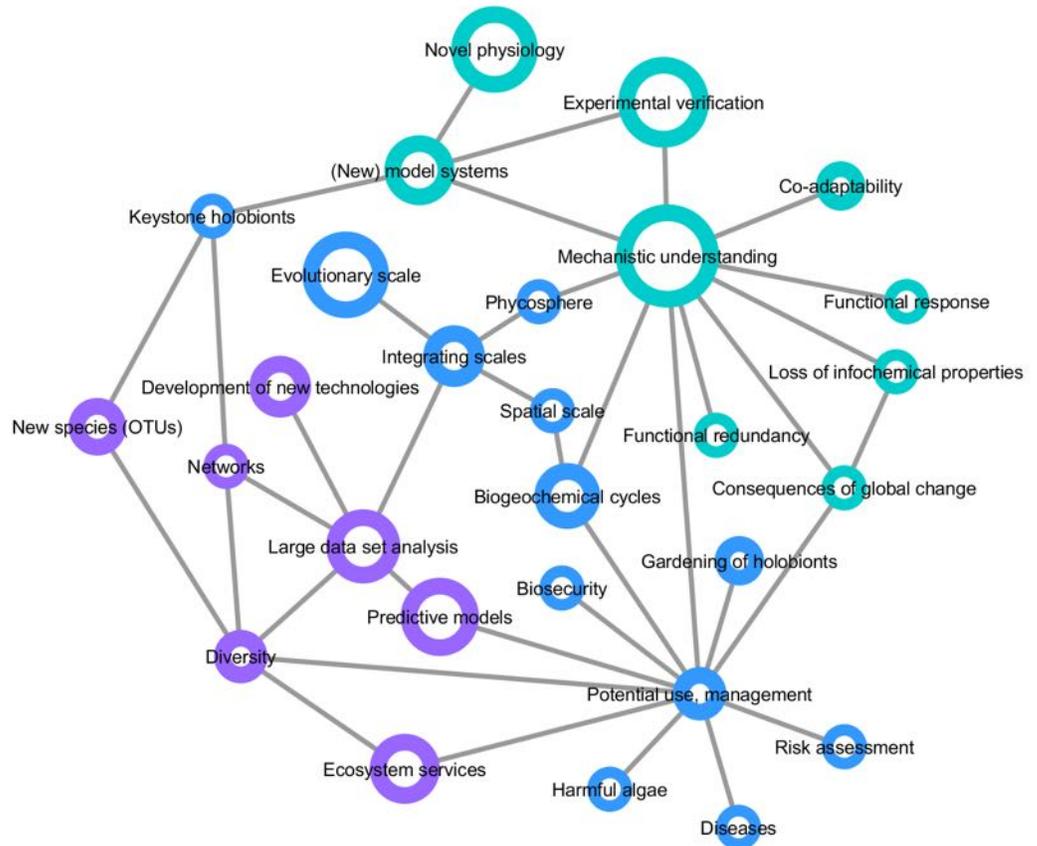


Figure 3: Mind map of key concepts, techniques, and challenges related to marine holobionts. The basis of this map was generated during the Holomarine workshop held in Roscoff in 2018 (<https://www.euomarinenetwork.eu/activities/HoloMarine>). The size of the nodes reflects the number of votes each keyword received from the participants of the workshop (total of 120 votes from 30 participants). The two main clusters corresponding to predictive modeling and mechanistic modeling, are displayed in purple and turquoise, respectively. Among the intermediate nodes linking these disciplines (blue) “potential use, management” was the most connected.

part of the community is moving towards global environmental sampling schemes such as the *TARA Oceans* expedition (Pesant *et al.* 2015) or the Ocean Sampling Day (Kopf *et al.* 2015), and towards long-term data series (*e.g.* Wiltshire *et al.* 2010; Harris 2010). What emerges as both lines of research progress is the understanding that small-scale functional studies in the laboratory are inconsequential unless made applicable to ecologically-relevant systems. At the same time, and despite the recent advances in community

modeling (Ovaskainen *et al.* 2017), hypotheses drawn from large scale-studies remain correlative and require experimental validation of the mechanisms driving the observed processes. We illustrate the importance of integrating both approaches in Figure 3, where the node related to potential applications was perceived as a central hub at the interface between mechanistic understanding and predictive modeling.

A successful example merging both functional and large-scale approaches, are the root nodules of legumes, which harbor nitrogen-fixing bacteria. In this system, the functioning, distribution, and to some extent the evolution of these nodules, are now well understood (Epihov *et al.* 2017). The integration of this knowledge into agricultural practices has led to substantial yield improvements (*e.g.* Kavimandan 1985; Alam *et al.* 2015). In the more diffuse and partner-rich system of mycorrhizal symbioses between plant roots and soil fungi, a better understanding of the interactions has also been achieved *via* the investigation of environmental diversity patterns in combination with experimental culture systems with reduced diversity (van der Heijden *et al.* 2015).

We advocate the implementation of comparable efforts in marine sciences through interdisciplinary research combining physiology, biochemistry, ecology, and computational modeling. A key factor will be the identification and development of tractable model systems for keystone holobionts that allow hypotheses generated by large-scale data sets to be tested in controlled experiments. Such approaches will enable the identification of organismal interaction patterns within holobionts and nested ecosystems. In addition to answering fundamental questions, they will help address the ecological, societal, and ethical issues that arise from attempting to actively manipulate holobionts (*e.g.* in aquaculture, conservation, and invasion) in order to enhance their resilience and protect them from the impacts of global change (Llewellyn *et al.* 2014).

Emerging methodologies to approach the complexity of holobiont partnerships

As our conceptual understanding of the different levels of holobiont organization evolves, so does the need for multidisciplinary approaches and the development of tools and technologies to handle the unprecedented amount of data and their integration into dedicated ecological and evolutionary models. Here, progress is often fast-paced and provides exciting opportunities to address some of the challenges in holobiont research.

A giant technological stride has been the explosion of affordable ‘-omics’ technologies allowing molecular ecologists to move from metabarcoding (*i.e.* sequencing of a taxonomic marker) to metagenomics or single-cell genomics, metatranscriptomics,

and metaproteomics, thus advancing our research from phylogenetic to functional analyses of the holobiont (Bowers *et al.* 2017; Meng *et al.* 2018; Figure 4). These approaches are equally useful in marine and in terrestrial environments, but the scarcity of well-studied lineages in the former makes the generation of good annotations and reference databases challenging for marine biologists. Metaproteomics combined with stable isotope fingerprinting can help study the metabolism of single lineages within the holobiont (Kleiner *et al.* 2018). In parallel, meta-metabolomics approaches have advanced over the last decades, and can be used to unravel the chemical interactions between partners. One limitation particularly relevant to marine systems is that many compounds are often not referenced in the mostly terrestrial-based databases, although recent technological advances such as molecular networking and meta-mass shift chemical profiling to identify relatives of known molecules may help to overcome this challenge (Hartmann *et al.* 2017).

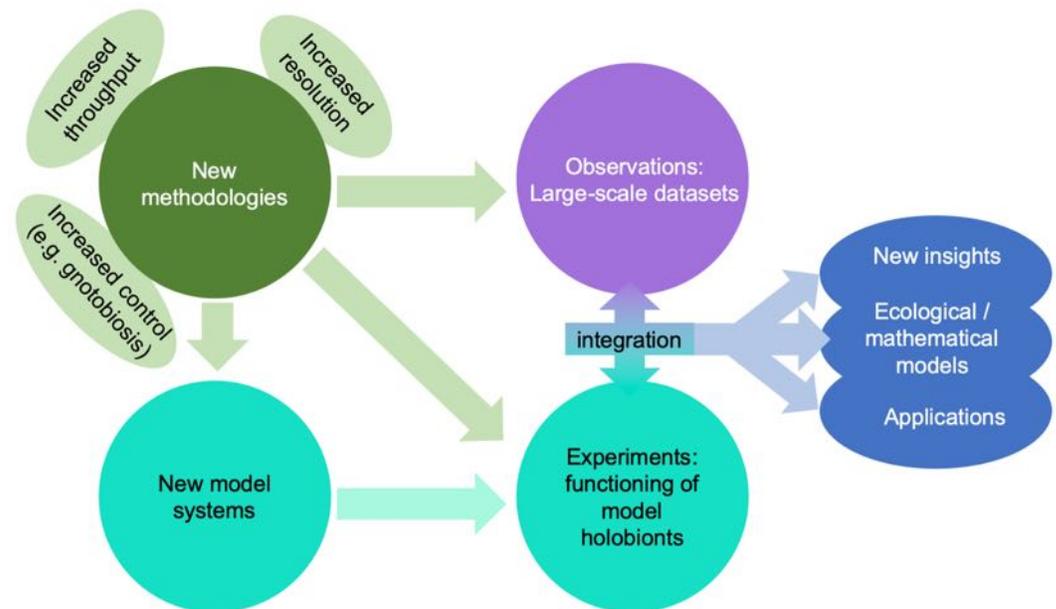


Figure 4: Impact of emerging methodologies (light green) on the main challenges in marine holobiont research identified in this paper (blue). Turquoise and purple correspond to the two main clusters of activity identified in Figure 3.

A further challenge in holobiont research is to identify the origin of compounds among the different partners of the holobionts and to determine their involvement in the maintenance and performance of the holobiont system. Well-designed experimental setups may help answer some of these questions (*e.g.* Quinn *et al.* 2016), but they will also

require high levels of replication in order to represent the extensive intra-species variability found in marine systems. Recently developed *in vivo* and *in situ* imaging techniques combined with ‘omics’ approaches can provide small-scale spatial and qualitative information (origin, distribution, and concentration of a molecule or nutrient), shedding new light on the contribution of each partner of the holobiont system at the molecular level (*e.g.* Geier *et al.* 2020). The combination of stable isotope labelling and chemical imaging (mass spectrometry imaging such as secondary ion mass spectrometry and matrix-assisted laser desorption ionization, and synchrotron X-ray fluorescence) is particularly valuable in this context, as it enables the investigation of metabolic exchange between the different compartments of a holobiont (Musat *et al.* 2016; Raina *et al.* 2017). Finally, three-dimensional electron microscopy may help evaluate to what extent different components of a holobiont are physically integrated (Colin *et al.* 2017; Decelle *et al.* 2019), where high integration is one indication of highly specific interactions. All of these techniques can be employed in both marine and terrestrial systems, but in marine systems the high phylogenetic diversity of organisms adds to the complexity of adapting and optimizing these techniques.

One consequence of the development of such new methods is the feedback they provide to improve existing models or to develop entirely new ones, *e.g.* by conceptualizing holobionts as the combination of the interactions between the host and its microbiota (Skillings 2016; Berry and Loy 2018), or by redefining boundaries between the holobiont and its environment (Zengler and Palsson 2012). Such models may incorporate metabolic complementarity between different components of the holobiont (Dittami *et al.* 2014; Bordron *et al.* 2016), or simulate microbial communities starting from different cohorts of randomly generated microbes for comparison with actual metatranscriptomics and/or metagenomics data (Coles *et al.* 2017).

A side-effect of these recent developments has been to move holobiont research away from laboratory culture-based experiments. We argue that maintaining or even extending cultivation efforts, possibly via the implementation of “culturomics” approaches as successfully carried out for the human gut microbiome (Lagier *et al.* 2012), remains essential to capture the maximum holobiont biodiversity possible and will facilitate the experimental testing of hypotheses and the investigation of physiological mechanisms. A striking example of the importance of laboratory experimentation is the way germ-free mice re-inoculated with cultivated bacteria (the so-called **gnotobiotic** mice) have contributed to the understanding of interactions within the holobiont in animal health, physiology, and behavior (*e.g.* Neufeld *et al.* 2011; Faith *et al.* 2014; Selosse *et al.* 2014). Innovations in cultivation techniques for axenic (or germ-free) hosts (*e.g.* Spoerner *et al.* 2012) or in microbial cultivation such as microfluidic systems (*e.g.* Pan *et al.* 2011) and

cultivation chips (Nichols *et al.* 2010) may provide a way to obtain pure cultures. Yet, bringing individual components of holobionts into cultivation can still be a daunting challenge due to the strong interdependencies between organisms as well as the existence of yet unknown metabolic processes that may have specific requirements. In this context, single-cell '-omics' analyses can provide critical information on some of the growth requirements of the organisms, and complement approaches of high-throughput culturing (Gutleben *et al.* 2018). Established cultures can then be developed into model systems, *e.g.* by genome sequencing and the development of genetic tools, in order to move towards mechanistic understanding and experimental testing of hypothetical processes within the holobiont derived from environmental meta'-omics' approaches. A few such model systems have already been mentioned above, but '-omics' techniques have the potential to broaden the range of available models, enabling a better understanding of the functioning of marine holobionts and their interactions in marine environments (Wichard and Beemelmanns 2018).

Ecosystem services and holobionts in natural and managed systems

A better understanding of marine holobionts will likely have direct socio-economic consequences for coastal marine ecosystems, estimated to provide services worth almost 50 trillion (10^{12}) US\$ per year (Costanza *et al.* 2014). Most of the management practices in marine systems have so far been based exclusively on the biology and ecology of macro-organisms. A multidisciplinary approach that provides mechanistic understanding of habitat-forming organisms as holobionts will ultimately improve the predictability and management of coastal ecosystems. For example, host-associated microbiota could be integrated in **biomonitoring** programs as proxies used to assess the health of ecosystems. Microbial shifts and dysbiosis constitute early warning signals that may allow managers to predict potential impacts and intervene more rapidly and effectively (van Oppen *et al.* 2017; Marzinelli *et al.* 2018).

One form of intervention could be to promote positive changes of host-associated microbiota, in ways analogous to the use of pre- and/or probiotics in humans (Singh *et al.* 2013) or inoculation of beneficial microbes in plant farming (Berruti *et al.* 2015; van der Heijden *et al.* 2015). In macroalgae, beneficial bacteria identified from healthy seaweed holobionts could be used as **biological control** agents and applied to diseased plantlets in order to suppress the growth of bacteria detrimental to the host and to prevent disease outbreaks in aquaculture settings. In addition to bacteria, these macroalgae frequently host endophytic fungi that may have protective functions for the algae (Porrás-Alfaro and

Bayman 2011; Vallet *et al.* 2018). Host-associated microbiota could also be manipulated to shape key phenotypes in cultured marine organisms. For example, specific bacteria associated with microalgae may enhance algal growth (Amin *et al.* 2009; Kazamia *et al.* 2012; Le Chevanton *et al.* 2013), increase lipid content (Cho *et al.* 2015), and participate in the bioprocessing of algal biomass (Lenneman *et al.* 2014). More recently, the active modification of the coral microbiota has even been advocated as a means to boost the resilience of the holobiont to climate change (van Oppen *et al.* 2015; Peixoto *et al.* 2017), an approach which would, however, bear a high risk of unanticipated and unintended side effects.

Also, holistic approaches could be implemented in the framework of fish farms. Recent developments including integrated multi-trophic aquaculture, recirculating aquaculture, offshore aquaculture, species selection, and breeding increase yields and reduce the resource constraints and environmental impacts of intensive aquaculture (Klinger and Naylor 2012). However, the intensification of aquaculture often goes hand in hand with increased amounts of disease outbreaks both in industry and wild stocks. A holistic microbial management approach, *e.g.* by reducing the use of sterilization procedures and favoring the selection of healthy and stable microbiota consisting of slow-growing K-strategists, may provide an efficient solution to these latter problems, reducing the sensitivity of host to opportunistic pathogens (De Schryver and Vadstein 2014).

Nevertheless, when considering their biotechnological potential, it should also be noted that marine microbiota are likely vulnerable to anthropogenic influences and that their deliberate engineering, introduction from exotic regions (often hidden in their hosts), or inadvertent perturbations may have profound, and yet entirely unknown, consequences for marine ecosystems. Terrestrial environments provide numerous examples of unwanted plant expansions or ecosystem perturbations linked to microbiota (*e.g.* Dickie *et al.* 2017), and cases where holobionts manipulated by human resulted in pests (*e.g.* Clay and Holah 1999) call for a cautious and ecologically-informed evaluation of holobiont-based technologies in marine systems.

Conclusions

Marine ecosystems represent highly connected reservoirs of largely unexplored biodiversity. They are of critical importance to feed the ever-growing world population, constitute significant players in global biogeochemical cycles but are also threatened by human activities and global change. In order to unravel some of the basic principles of life and its evolution, and to protect and sustainably exploit marine natural resources, it is



paramount to consider the complex biotic interactions that shape the marine communities and their environment. The scope of these interactions ranges from simple molecular signals between two partners, via complex assemblies of eukaryotes, prokaryotes, and viruses with one or several hosts, to entire ecosystems. Accordingly, current key questions in marine holobiont research cover a wide range of topics: What are the exchanges that occur between different partners of the holobiont, and how do they condition their survival, dynamics and evolution? What are the cues and signals driving these exchanges? What are the relevant units of selection and dispersal in marine holobionts? How do holobiont systems and the interactions within them change over time and in different conditions? How do such changes impact ecological processes? How can this knowledge be applied to our benefit and where do we need to draw limits? Identifying and consolidating key model systems while adapting emerging “-omics”, imaging, and culturing technologies to them will be critical to the development of “holobiont-aware” ecosystem models.

We believe that the concept of holobionts will be most useful and heuristic if used with a degree of malleability. It not only represents the fundamental understanding that all living organisms have intimate connections with their immediate neighbors, which may impact all aspects of their biology, but also enables us to define units of interacting organisms that are most suitable to answer specific scientific, societal, and economic questions. The consideration of the holobiont concept marks a paradigm shift in biological and environmental sciences, but only if scientists work together as an (inter)active and transdisciplinary community bringing together holistic and mechanistic views. This will result in tangible outcomes including a better understanding of evolutionary and adaptive processes, improved modeling of habitats and understanding of biogeochemical cycles, as well as application of the holobiont concept in aquaculture and ecosystem management projects.

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Conflict of interest disclosure

The authors of this preprint declare that they have no financial conflict of interest with the content of this article. FN is one of the PCI Ecology recommenders.

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