



The Rhythm of Many: Biological Rhythms in the Marine Environment, From Macro-Scale Planktonic Ecosystems to Micro-Scale Holobionts

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Daily environmental oscillations that follow Earth's rotation around the Sun set a metronome for life, under which all organisms have evolved. Entrainment to these cues allow organisms to rhythmically set the pace of their own endogenous biological clocks with which the timings of diverse cellular activities are coordinated. In recent years, our knowledge of biological rhythms has extended across all domains of life. This includes both free-living and symbiotic life forms. With the resurgence of metagenomic sequencing tools, the field of holobiont chronobiomics (encompassing chronobiology of host and its associated microbiota) has recently opened and gained significant traction. Here, we review current knowledge regarding free-living prokaryote rhythmic regulation before exploring active areas of research that consider the coordinated rhythmic regulatory activities of hosts and their symbionts as a single entity, i.e., holobiont, and even the extent to which rhythmicity influences virus–host interactions. We describe rhythmicity within non-photosynthetic bacteria, cyanobacteria, and archaea, before investigating the effect of light, and, thus, diel cycle, on viral life cycles and host–virus population dynamics in marine planktonic ecosystems along with their potential to influence host cyanobacterial circadian clocks. We then explore current evidence outlining coordinated rhythmic regulation within marine holobionts and the significance of this for holobiont health and adaptive fitness that, in turn, optimizes their success within their local environments. Finally, we assess the critical role of circadian regulation for holobiont innate immunity and metabolism within well-studied non-marine mammalian systems, and, thus, assess how this can guide us within understudied marine chronobiomics research.

Keywords: circadian clock, chronobiomics, microbiome, rhythmic regulation, marine plankton, viruses, symbioses, nested ecosystems

INTRODUCTION

The phrase “no man is an island” as put by the 17th-century metaphysical poet John Donne in his prose work ‘Devotions upon Emergent Occasions’ talks about how humans do not do well in isolation and require a community to thrive (Donne, 1987). Similarly, in light of current research, it is becoming increasingly evident that no organism can be considered in isolation. Beyond considering organisms simply within the ecological communities they reside in, it is imperative we also consider the ecological communities they harbor within—their microbiome.

Since the dawn of metagenomic sequencing, research into microbiome community composition has exponentially advanced, shedding light on the complexity of host–symbiont relationships (Huttenhower et al., 2014; Norman et al., 2014; Yoon et al., 2015; Jovel et al., 2016). Yet, much regarding the synchrony of these interactions remains elusive. Rhythmic regulations, including the **circadian (Supplementary Box 1)** rhythms (~24-h endogenous biological clocks; **Supplementary Box 2**) set a metronome for coordinated activity across all domains of life (Edgar et al., 2012), and not only warrant exploration of their critical role in mediating individual cellular activity but also for their role in mediating the rhythmically coordinated activities between host and their symbionts, ultimately facilitating successful adaptive optimization of the **holobiont (Supplementary Box 1)**.

In recent years, the significance of circadian clock regulation has become increasingly apparent. Entrained by external cues, circadian regulation mediates the rhythmic expression of numerous genes under the locally fluctuating environment, including those of innate immunity, metabolism, behavioral responses, cellular division, and global gene expression (Mori et al., 1996; Markson et al., 2013; Thaiss et al., 2016; Parkar et al., 2019). Indeed, the origins of circadian regulation are considered ancient, hypothesized to have first arisen under the strong selecting forces of high ultraviolet (UV-B and UV-C) radiation. Prior to the formation of the Earth’s protective ozone layer, light-vulnerable processes were entrained to the solar night, termed the ‘escape from light’ hypothesis (Pittendrigh, 1993; Nikaido and Johnson, 2000). However, despite these ancient origins, circadian clocks have independently evolved, multiple times across distinct lineages, but with convergent functions (Rosbash, 2009; Takahashi, 2017), and, thus, likely have wide-reaching functional roles in disparate organisms.

Within marine ecosystems, the rhythmic activities and regulation of diverse organisms pertain significantly on a macro-scale (Häfker et al., 2017). The open ocean of the earth’s marine ecosystems comprises vast planktonic communities, important globally for large-scale biogeochemical cycling. These communities comprise a wide variety of organisms from all domains including algae, bacteria, protists, and metazoans. Here, we consider the rhythmically aligned regulation of these communities, entrained to cyclically fluctuating external environmental stimuli. Viruses, though hardly considered living, form an important part of the marine planktonic community and play a huge role in (re)shaping the community

structure. Viruses are entirely dependent on their host for proliferation and in the process, often lyse their hosts. The spatiotemporal dynamics of virioplankton communities, like other subsections of the planktonic communities, depend on various direct and indirect biotic and abiotic factors (reviewed in Mojica and Brussaard, 2014). The natural spatiotemporal dynamics of virus–host communities in the marine environment becomes a topic of discussion on the biological rhythms of marine viruses.

Similarly, rhythmic regulation is also significant on a micro-scale, for the nested ecological communities comprising host–symbiont holobionts. Eukaryotic circadian clock mechanisms have been well-studied in diverse multicellular organisms including mammals, arthropods, sponges, and plants (McClung, 2001; Dibner et al., 2010; Jolma et al., 2010; Jindrich et al., 2017; Morioka et al., 2018). Within mammals, a hierarchical system comprises a host of individual circadian clocks that are all centrally aligned by a core circadian clock within the suprachiasmatic nucleus of the hypothalamic region of the brain (Dibner et al., 2010). This allows individual cells of different tissues to independently mediate rhythmic gene expression on diverse periods, appropriate for their cellular function (Dibner et al., 2010). Interestingly, a comparable system has been hypothesized to occur within animal–bacterial holobionts. Here, the central endogenous clock of the host coordinates rhythmic alignment amongst all independent clocks within the microbial symbionts of the microbiome (Lee et al., 2019). Elucidating host and symbiont rhythmic co-regulation could provide further key insights into the establishment of host–symbiont relationships. For instance, whether circadian clock alignment provides an important selection filter in host–symbiont compatibility (temporal mutualism), or whether prokaryotic symbionts first colonize, and later adapt their circadian cycle to match that of their host to stabilize the relationship.

Research into holobiont chronobiology, the dynamic interaction of host–microbe circadian clock regulation, has predominantly focused upon mammalian organisms and provides only tantalizing glimpses at applicable prospects within other holobiont systems. However, considering the global ubiquity and significance of prokaryotes within marine environments, either as symbiotic or free-living forms, and the scarcity of available studies (Sartor et al., 2019), we must extend circadian research to encompass a greater degree of prokaryotic diversity and their crucial functions within holobionts. Here, we outline the currently very limited data from marine holobionts, as well as from more extensively studied terrestrial/mammalian holobionts with the aim that such research can help accelerate that within organisms from marine ecosystems. Indeed, we propose that future **chronobiomics (Supplementary Box 1)** research should increase its focus upon globally diverse and dominant phyla that comprise basal marine metazoa, such as Porifera, Cnidaria, and Ctenophora. These organisms comprise considerably less complex body plans, making them tractable model systems for the investigation of molecular circadian holobiont regulation. Additionally, since these organisms comprise ancient lineages that were the

earliest to diverge from the rest of the animal kingdom (i.e., bilaterians), any shared mechanisms of rhythmic regulation identified may logically be traced back to the last common animal ancestor.

In this review, we first outline the mechanisms of circadian clock regulation within free-living prokaryotes, including non-photosynthetic bacteria, cyanobacteria, and archaea. Secondly, we consider the implication of biological rhythms on marine viruses. We explore the dynamics of host–virus populations and the effect of light in controlling planktonic community dynamics. We also delve into the understudied niche of viral influences upon host biological rhythms by discussing host photosynthesis take-over by the viruses. In the third part, we discuss the significance of circadian rhythm regulation for holobiont health and optimization (using well-studied terrestrial mammalian examples) and, thus, how such chronobiomics research must be considered in the marine environment. We present the currently limited evidence of circadian clocks within marine holobiont systems, demonstrating host–symbiont rhythmically aligned regulatory activity. We aim to provide a comprehensive review of holobiont rhythmic regulation, which promotes the consideration and extension of the universally significant field of chronobiomics research within marine environments.

BIOLOGICAL RHYTHMS IN PROKARYOTES

Current knowledge of prokaryotic circadian regulation is severely lacking. To date, prokaryotic circadian clocks have been formally described within the phylum Cyanobacteria only, of which *Synechococcus elongatus* serves as the current ‘model’ organism (Johnson et al., 2017). That said, evidence of prokaryotic rhythmicity has been around for some time.

Evidence of rhythmic regulation within prokaryotes (outside of Cyanobacteria) dates back as early as the 1930s. Despite early hypotheses that circadian rhythms would not be adaptive for single-celled organisms, for which generation times are shorter than the diel cycle (“circadian-infradian rule”; Ehret and Wille, 1970), studies did report rhythmic periods for bacteria that, remarkably, surpassed the duration of their cell cycles. Within *Escherichia coli* cultures, Rogers and Greenbank (1930) demonstrated a growth period indicative of long circadian-like rhythms that were later shown to be periods of 20.5 h (Halberg and Conner, 1961). However, later observations demonstrated this was not fully temperature compensated (**Supplementary Box 2**) and, thus, does not display a fully robust circadian clock (Sturtevant, 1973). Within Alphaproteobacteria *Rhodospirillum rubrum*, enzymatic activity of hydrogenase (Hup) uptake, which participates in redox metabolism during photosynthesis and nitrogen fixation, demonstrated circadian rhythmic oscillations of 12–15 h (Van Praag et al., 2000). Moreover, non-photosynthetic bacteria *Klebsiella pneumoniae* and *Klebsiella aerogenes* displayed rhythmic growth and activity, respectively (Sturtevant, 1973; Paulose et al., 2016); of which *K. aerogenes* demonstrated a

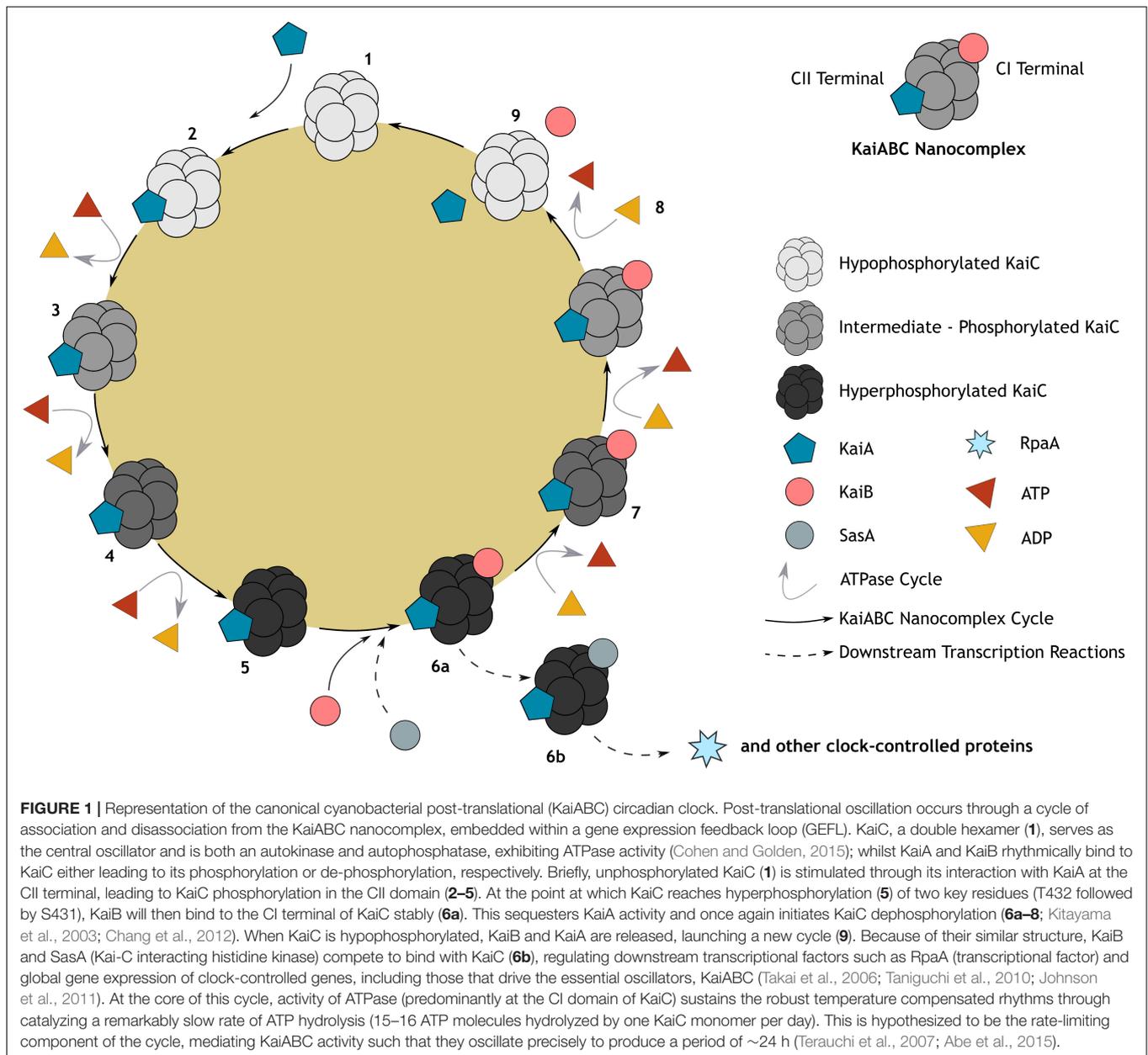
fully temperature-compensated rhythm. Thus, diverse bacteria from multiple phyla, likely, rhythmically regulate their cellular activities on either a **circadian-like** or **ultradian** (**Supplementary Box 1**) period.

Prokaryotic Clock Molecular Mechanisms

Molecular mechanisms of the prokaryotic circadian clock were first described for *S. elongatus* in 1997, which has since become one of the best-studied circadian systems from all domains (Sartor et al., 2019). Remarkably, the prokaryotic circadian clock is a post-translational system (as opposed to the transcription-translation feedback loop (TTFL), see **Supplementary Box 3**), which relies solely on the phosphorylation cycles of three proteins (KaiA, KaiB, and KaiC) causing rhythmic oscillations throughout the day (**Figure 1**; Ishiura et al., 1998). This system has since been more generally classified as a gene expression feedback loop (GEFL).

The cyanobacterial KaiABC system supports a fully robust, self-entrained, temperature-compensated circadian clock (Morrow et al., 2006). Notably, as the only circadian system to have been demonstrated both *in vitro* and *in situ*, it has been possible to demonstrate the adaptive benefit of circadian-mediated cellular activity. *In vitro* growth competition experiments demonstrated that wild-type cyanobacteria outcompeted their arrhythmic counterparts whilst exposed to variable environmental conditions (Ouyang et al., 1998; Woelfle et al., 2004). Indeed, within Cyanobacteria, the circadian clock provides a critical regulatory function for numerous cellular processes. For instance, circadian regulation can mediate cell division (Mori et al., 1996; Mori, 2009), global gene expression (Liu et al., 1995; Markson et al., 2013), chromosome compaction (Smith and Williams, 2006), nitrogen fixation (Grobelaar et al., 1986; Mitsui et al., 1986), amino acid uptake (Chen et al., 1991), and metabolism (Diamond et al., 2015). Given the importance of such activities to the functions that symbionts perform for their hosts, the circadian regulation of such must also be considered within the context of the holobiont.

However, outside of Cyanobacteria, evidence of fully robust self-entrained endogenous rhythms has yet to be molecularly described within other prokaryotes. Currently, the gammaproteobacterium *Enterobacter aerogenes*, housed within human gut microbiota, is considered to be the only observation of a fully robust clock outside of Cyanobacteria (Paulose et al., 2016). Specifically, *E. aerogenes* display robust, temperature-compensated circadian rhythms of luciferase activity that synchronize on daily 24-h cycles with the secretion of the gastrointestinal hormone melatonin (Paulose et al., 2016). Thus, true ~24-h period rhythms are likely more prevalent amongst prokaryotes, and indeed bacterial symbionts than our current observations suggest. Interestingly, Cyanobacteria are the only bacterial phyla to possess KaiA (Schmelling et al., 2017). Subsequently, it is hypothesized that the evolution of KaiA facilitates fully robust circadian rhythms to sustain regardless of the external environment, and even in the absence of any environmental stimuli (Ouyang et al., 1998; Ma et al., 2016).



Indeed, members of the cyanobacterial genus *Prochlorococcus*, from which KaiA was evolutionarily lost, cannot sustain free-running rhythms under conditions of constant light or dark (Holtzendorff et al., 2008).

Nonetheless, several other key prokaryotic circadian clock components have been identified in diverse bacteria. Several circadian gene homolog searches based on *S. elongatus* sequences have identified the presence of KaiBC homologs, as well as circadian associated input and output factors amongst diverse prokaryotes (Loza-Correa et al., 2010; Schmelling et al., 2017). Additionally, orthologs of KaiB and KaiC are observed within alphaproteobacteria *Rhodobacter sphaeroides* and *Rhodospirillum rubrum*, both considered to entrain “proto” circadian clocks (Min et al., 2005; Ma et al., 2016),

since their rhythmicity is lost under exposure to constant environmental conditions. To encompass the anticipated broad spectrum of rhythmic regulatory mechanisms represented within diverse prokaryotic organisms, a revised, simplified criterion for circadian clock regulation has recently been proposed (Loza-Correa et al., 2010; Johnson et al., 2017; Schmelling et al., 2017). Although we may draw comparisons with the *S. elongatus* clock model, it is likely that circadian regulation of Proteobacteria (or other bacterial phyla) evolved through distinct environmentally mediated processes (Johnson et al., 2011). As observed in eukaryotes, the core proteins involved in circadian regulatory mechanisms evolved independently several times, despite demonstrating a conserved general mechanism (Rosbash, 2009; Takahashi, 2017).

Redox Clock: An Ancient and Universal Mechanism for Circadian Rhythm Regulation

Recently, it was demonstrated that the cellular redox cycle, which prevents the build-up of reactive oxygen species (ROS), also serves as a circadian oscillator within all domains of life (O'Neill et al., 2011; O'Neill and Reddy, 2011; Edgar et al., 2012). Maintenance of ROS homeostasis is critical to survival since oxidative stress caused from the build-up of toxic ROS (e.g., hydrogen peroxide, superoxide anion radical) can cause a variety of damaging effects, including protein oxidation, lipoprotein modification, lipid peroxidation, and DNA damage (Dalle-Donne et al., 2003; Karlenius and Tonissen, 2010; Hanschmann et al., 2013). Peroxiredoxin (PRX) proteins maintain redox homeostasis by reducing ROS such as hydrogen peroxide to water. In turn, PRXs are reduced themselves, usually consuming a reducing equivalent from nicotinamide adenine dinucleotide phosphate (NADPH). The cyclical activity of peroxiredoxin oxidation-reduction reactions occur rhythmically, overlain by circadian oscillations in the redox state (O'Neill et al., 2011; O'Neill and Reddy, 2011), although the underlying molecular mechanisms for this are not yet fully understood (Xia et al., 2018). ROS is produced as a by-product of metabolic reactions, including respiration and photosynthesis (Turens, 2003; Pospíšil, 2016), thus, the timing of ROS production, aligned with environmental stimuli may provide an additional circadian *zeitgeber* (Supplementary Box 1).

The discovery of the redox clock suggests an intricate link between innate immunity (to which ROS contributes) and circadian regulation. Peroxiredoxin proteins protect against stress; for instance, Peroxiredoxin 6 (PRX6) protects supercoiled DNA damage by oxidative stress and negatively regulates toll signaling transduction in red swamp crayfish *Procambarus clarkii* (Chu et al., 2019). Thus, PRX circadian cycling may maximize efficiency in maintaining ROS cellular homeostasis by aligning PRX activity in anticipation of daily, fluctuating environmental conditions, that may signal innate immune responses. For instance, it has been demonstrated that redox rhythms can be aligned to multiple periods, including both circadian and *circatidal* (Supplementary Box 1), within the intertidal isopod *Eurydice pulchra* (O'Neill et al., 2015). Subsequently, an unprecedented environmental stimulus could lead to circadian disturbance and the onset of a ROS-induced stress response/signal.

The PRX active site is highly conserved across all domains of life, representing an ancient, ancestral circadian mechanism that likely predates the canonical circadian clock (Edgar et al., 2012; Hoyle and O'Neill, 2015). Edgar et al. (2012) hypothesize that the redox clock evolved under strong selecting forces during the great oxidation event (~2.5 billion years ago) when organisms were first exposed to toxic ROS concentrations. They further speculate that, in the absence of such pressure, organisms inhabiting anoxic environments would lack a circadian redox clock (Edgar et al., 2012). Interestingly, the redox clock functions in tandem with, but independently of the GEFL/TTFL canonical circadian clock (Supplementary Box 3). Organisms lacking either

endogenously or experimentally (pharmacologically abrogated) canonical circadian clocks can sustain rhythmic cycles of redox regulation, albeit with an altered rhythm (O'Neill et al., 2011; Edgar et al., 2012). This supports the hypothesis that both clock mechanisms evolved independently, but under common selecting pressures, enabling rhythmic synchrony. Since PRXs are present in most organisms (Rosbash, 2009), the redox clock could provide a universal, conserved indicator of non-canonical, post-translational circadian cycling (Edgar et al., 2012).

Circadian Rhythms in Archaea

Archaea are one of the oldest domains of life (Gribaldo and Brochier-Armanet, 2006) and contribute an integral part to the symbiotic community of holobionts globally (Bang and Schmitz, 2018). For instance, they may dominate the microbiomes of organisms from environmental extremes, such as highly acidic temperate waters (Korzhenkov et al., 2019). Thus, for a holistic understanding of circadian clock evolution and its role within holobiont systems, rhythmic regulation within archaea must also be explored. To date, archaeon rhythmic activity and circadian clock components have only been identified within the halophilic, aerobic genus *Halobacteria* (Whitehead et al., 2009; Edgar et al., 2012; Maniscalco et al., 2014; Johnson et al., 2017). Whitehead et al. (2009) first reported diurnal oscillatory transcription (either ultradian or circadian) within *Halobacterium salinarum* NRC-1, demonstrating rhythmic control for ~12% of global gene expression under constant conditions after 3 days entrainment in light-dark. Furthermore, Maniscalco et al. (2014) characterized four cyanobacterial circadian clock *kaiC* homologs (*cirA*, *cirB*, *cirC*, and *cirD*) within the halophilic, mesophilic archaeon *Haloferax volcanii* that display rhythmic transcriptional regulation under diel conditions. However, the potential mechanisms underlying archaeal circadian regulatory systems are still far from clear. Although homologs for *S. elongatus KaiC* are widespread amongst all three archaeal phyla (Maniscalco et al., 2014), they are also much more diversified, with their potential functions mostly unknown. Indeed, Makarova et al. (2017) alternatively demonstrated a proposed central role for archaeal *KaiC* homologs within signal transduction mechanisms. The largely expanded family of *KaiC* homologs within archaea lends support to the hypothesis that *KaiC* first originated within archaea (Makarova et al., 2017) but not necessarily as a circadian oscillator, since to date, this has only been observed within the genus *Halobacteria*. Considering archaeal and bacterial lineages diverge over distances even greater than that with Eukaryota, it would not be surprising to discover an archaeon circadian mechanism distinct from that observed within bacteria. Thus, considering also the comparatively limited research within this area, it remains feasible that the archaeal canonical circadian oscillators have yet to be identified. That said, evidence of the post-translational, circadian redox clock has recently been observed within archaea and is likely widespread amongst species inhabiting oxygenated environments. This opens new directions to explore rhythmic regulation within this less studied but equally important, prokaryotic domain (Edgar et al., 2012; Hoyle and O'Neill, 2015).

BIOLOGICAL RHYTHMS AND MARINE VIRUSES

Sufficient literature indicates that the cellular regulation of most, if not all, bacterial lineages are rhythmically influenced, albeit with likely diverse periods, but can these rhythms also influence viruses, that are hardly considered living? This is an area of research that has received little attention to date. Thus, we will explore the intriguing subject of biological rhythms concerning viruses in the marine environment. Typically, viruses are considered highly infectious, disease-causing lethal entities that wreak havoc. Indeed, considering the COVID-19 pandemic and its societal impact (Heymann and Shindo, 2020), this view is not entirely wrong. However, knowledge of marine and other aquatic viruses, along with their roles in ecosystem functioning have barely been valorized and are deserving of a more prominent focus.

In 1989, it was discovered that viral abundance within marine environments may be as high as millions within a cubic milliliter (Bergh et al., 1989). Subsequently, this led to the recognition of viruses as the most abundant biological entity within our oceans; totaling up to 10^{30} virus-like particles (Wommack and Colwell, 2000; Breitbart, 2012). Viruses form the ocean's second-largest biomass, second only to the prokaryotes (Suttle, 2005). With the capacity to infect all forms of life, viruses lyse considerable volumes of daily prokaryotic production in the marine environment. Thereby, facilitating the flow of nutrients from higher trophic levels back to the lower levels, in what is known as the 'viral shunt' (Fuhrman, 1999; Wommack and Colwell, 2000; Koonin et al., 2006; Suttle, 2007; Miranda et al., 2016). Subsequently, one cannot stress enough the ecological importance of viruses for the functioning of marine ecosystems.

To better understand the influence of biological rhythms, we must consider the spatiotemporal community dynamics of viruses within marine planktonic assemblages. In this section, we will discuss the importance of light as a crucial abiotic factor affecting community dynamics through the viral life cycle, focusing specifically on the intensity, duration, and quality of light in determining viral activity and burst size. Lastly, we will discuss the influence of viruses on their cyanobacterial hosts' biological rhythm through redirecting photosynthesis to enhance viral replication.

Variables Influencing Host–Virus Population Dynamics Within the Marine Environment

Viruses heavily influence the planktonic ecosystems through (re)shaping, and hence mediating, planktonic community dynamics. Two major hypotheses have been proposed to explain the dynamics of marine viral ecology- 'Kill the Winner' (KtW) and 'Piggyback the Winner' (PtW) (discussed in **Supplementary Box 4**).

When assessing marine planktonic communities, the significance of cyanobacterial abundance and their role in carbon fixation must not be overlooked (Falkowski, 1994). Marine phytoplankton communities are heavily dominated by

photosynthetic cyanobacteria, of which the estimated absolute annual mean cellular abundances of *Synechococcus* spp. and *Prochlorococcus* spp. are as high as $7.0 \pm 0.3 \times 10^{26}$ and $2.9 \pm 0.1 \times 10^{27}$ cells across the world's oceans, respectively (Flombaum et al., 2013). The population dynamics of these cyanobacteria have been studied in a wide range of environments and at different spatial and temporal scales (Flombaum et al., 2013). Brunet et al. (2007) reported a 24 h oscillation in the cell cycle profile for both *Synechococcus* and *Prochlorococcus* genera. They observed a peak in the percentage of cells in the G2 phase of the cell cycle at the end of the night for *Synechococcus* and at the end of the light period for *Prochlorococcus* at the Strait of Sicily in the Mediterranean Sea (Brunet et al., 2007). Diel dynamics of cyanophage (i.e., phages that infect cyanobacteria) abundance was found to be synchronized with light-dark cycles (Suttle and Chen, 1992). Short-term temporal sampling was conducted at 1 m depth every 3 h for 3 days in the Northwest Mediterranean Sea to explore the activity of various microbial groups including cyanobacteria *Synechococcus* spp., heterotrophic bacteria, nanoflagellates, and viruses (Bettarel et al., 2002). *Synechococcus* spp. was observed to reach an abundance peak at midnight and a trough at 9:00 p.m., although the highest number of *Synechococcus* spp. dividing cells were observed at 9:00 p.m. This diel pattern was consistent throughout the 3-day sampling effort. Viral abundance also showed diel oscillation with a peak at 6:00 p.m. and trough at midnight. Although the authors did not measure *Synechococcus*-specific viruses, they concluded that the observed decrease in *Synechococcus* abundance at the time of viral peak was due to viral production (Bettarel et al., 2002).

It is important to note that the abundance and infectivity of marine viruses are also dependent on the loss of viruses via various means of decay, including, but not limited to, removal through adhesion on particulate matters, consumption by heterotrophs such as bacteria and flagellates, and destruction of infectivity by solar radiation (Suttle and Chen, 1992). In the absence of solar radiation, viral decay rates range from 0.009 to 0.028 h^{-1} , but in full sunlight may be as high as 0.4 to 0.8 h^{-1} . Decay rates in full sunlight were demonstrated to be 2 to 10 times higher than those in the absence of sunlight, even when wavelengths of $<320 \text{ nm}$ were removed, or 80% of the incident irradiance was excluded (Suttle and Chen, 1992). Specifically, UV-B radiation has been shown to have a significant effect in reducing viral infectivity, though a strong link between UV-A radiation and viral infectivity is yet to be described (reviewed by Mojica and Brussaard, 2014). The average decay rate due to flagellate consumption was around 0.15 h^{-1} (Suttle and Chen, 1992). It is important to note, that viral infectivity is reduced by the solar radiation at a greater rate than the removal of viruses from the water column due to grazing by heteroflagellates, and, thus, a large proportion of viral abundance measured (by electron microscopy, epifluorescence microscopy, and flow cytometry) are at a state of decay and rendered non-infective (Suttle and Chen, 1992). Subsequently, any direct inferences made on viral activity from viral enumeration methods (mentioned above) may not be representative; as they cannot differentiate between infectious viruses, non-infective viruses, and **virus-like particles** (**Supplementary Box 1**, Suttle and Chen, 1992). Here, we

emphasize the importance of performing viral activity assays in addition to the abundance counts to estimate true proportions of plankton host losses due to viruses (Winget et al., 2005; Baudoux et al., 2006; Evans et al., 2009).

Recently, Kolody et al. (2019) described the expression of viral and host transcripts with a focus on transcripts that exhibited diel oscillatory patterns. Co-expression of host and viral transcripts were observed for diverse reference taxa, including heterotrophic bacteria, cyanobacteria, photosynthetic eukaryotes, and predatory heterotrophic eukaryotes. Interestingly, this opposed Thingstad's (2000) 'Kill-the-Winner' hypothesis. As per the KtW, Kolody et al. (2019) hypothesized an increase in host transcript in the planktonic community should have been preceded by an increase in viral transcripts. An exception to this was the aggregated gene expression of algae *Phaeocystis globosa*, which peaked during day hours, compared to a synchronized increase in expression of the giant *Phaeocystis globosa* virus and virophages (Supplementary Box 1). This pattern was not observed for the ssRNA viruses on which viral RNA molecules lagged host transcription (Kolody et al., 2019). Therefore, the KtW hypothesis holds for RNA viruses and viruses of *Phaeocystis*, whilst the PtW for the other measured groups.

Additionally, the trophic status of water leads to variation in viral production and decay rates. High nutrient conditions can increase bacterioplankton growth rate and viral burst size (number of viruses released per cell due to viral lysis). Bongiorno et al. (2005) investigated the viral dynamics of production and decay along a trophic gradient in the North Adriatic basin. A decrease in burst size was observed down the trophic gradient, attributable to decreased nutrient availability and smaller cell sizes (Bongiorno et al., 2005). Indeed, a 1.3 to 10.7% viral decay rate of the total viral production was observed in oligotrophic waters, compared with 40% in the eutrophic waters of the Adriatic Sea. But the production rates in Adriatic eutrophic waters were also three to four times higher than that of oligotrophic waters; pointing toward higher viral production and decay rates in eutrophic versus oligotrophic waters (Bongiorno et al., 2005). Grazing by nanoflagellates, dissolved-colloidal substances, and lysogenic infections was responsible for the removal of ca. 66% of viral production in eutrophic waters as compared to 17% in oligotrophic waters (Bongiorno et al., 2005).

Oscillations in marine viral populations are dependent on various direct and indirect factors including, but not limited to, viral inactivation by light, trophic status of the water, abundances of their host, grazing by nanoflagellates, and the latency period (Suttle and Chen, 1992; Bongiorno et al., 2005; Mojica and Brussaard, 2014). These variables pose a significant challenge in the field of marine viral ecology, particularly in the study of spatiotemporal community dynamics of viruses and their host and hence must be meticulously considered.

The Effect of Light on Proliferation of Marine Viruses

Environmental light can significantly influence the viral life cycle, and, thus, is likely the most important factor when considering marine viral chronobiomics. Variation in the duration, intensity,

and wavelength of light may all influence various stages of the viral life cycle. In short, a typical life cycle of a lytic virus begins with adsorption on a competent host followed by entry of the viral particle or the genetic material, transcription of the genes required for viral replication, replication of the viral genome, assembly of virions, and finally release through host lysis (Dimmock et al., 2009). Temperate viruses are known to incorporate themselves into the host genome as prophages and proliferate with the host (Dimmock et al., 2009). The effect of light on the adsorption of the virus and replication has been a predominant focus of current research in the field of marine viral ecology.

Viral-Host Adsorption

Host susceptibility to a virus is determined by specific interactions between the receptors present on the host and either the viral-encoded envelope (enveloped viruses), capsid protein (non-enveloped viruses), or proteins present on the tail (bacteriophages) (Rakhuba et al., 2010; Thorley et al., 2010).

Although light is well known to influence downstream viral replication, there is currently no consensus for the dependence of viral adsorption on light (Ni and Zeng, 2016). Assessing the diurnal rhythms of infection by certain cyanophages, Liu et al. (2019) observed three different diel-dependent life-history traits of phages when infecting cultured *Prochlorococcus* and *Synechococcus* in the continuous dark. These include the absence of adsorption, presence of adsorption but not viral replication, and presence of both adsorption and viral replication. Specifically, P-HM2 and P-SSM2 cyanomyophages exhibited a diurnal rhythm in adsorption on *Prochlorococcus* strains MED4 and NATL2A, respectively, with maxima during the day (Liu et al., 2019). On the other hand, cyanomyophage P-SSP7 adsorption on the *Prochlorococcus* strain MED4 was independent of the light-dark cycle (Liu et al., 2019). Alternatively, Cséke and Farkas (1979), demonstrated that adsorption of AS-1 cyanomyophage on *Anacystis nidulans* (synonym *S. elongatus* PCC 6301) does have a light-dependent adsorption pattern that is independent of photosynthesis and host circadian rhythm (discussed later) (Ni and Zeng, 2016). Around 70% of the cyanomyophage AS-1 inoculate titer adsorbed to *S. elongatus* PCC 6301 in the presence of light. This figure was dropped to 40% when the cultures were moved to the dark right after addition of viruses (Cséke and Farkas, 1979; Ni and Zeng, 2016). A similar pattern was also observed for *S. elongatus* PCC 7942 and AS-1 phage (Kao et al., 2005). It was long believed that the presence of light always facilitated viral adsorption, however, Jia et al. (2010) disproved this in their study comparing the adsorption patterns of nine cyanophages on unsynchronized *Synechococcus* WH7803 cells. They demonstrated that the cyanomyophages, S-PWM1, S-BM3, S-MM4, S-MM1, and S-MM5 were not affected by light and adsorbed to unsynchronized WH7803 cells to the same extent (~90%), regardless of light presence; thereby displaying a light-independent adsorption pattern. Conversely, the cyanomyophage S-BNM1, S-PWM3, S-PM2, and cyanopodophage S-BP3 exhibited significantly lower adsorption of ~10% in the dark as opposed to adsorption of ~90% in the presence of light (Jia et al., 2010). To test for an influence

of host circadian rhythm on phage adsorption, synchronized *Synechococcus* WH7803 cells (with known circadian rhythm), maintained in 12:12 light-dark (LD), were infected with the light-dependent cyanomyophage S-PM2. Host cultures were sampled at six different timepoints throughout the 24-h LD cycle from two sets (three in the light period, three in the dark period); one incubated with S-PM2 under constant light, and the other under constant dark, for 45 min before measuring the free phage titer. A similar pattern of ~90% adsorption in the light and ~10% adsorption in dark was observed for S-PM2 and synchronized WH7803 cells, indicating adsorption of S-PM2 is independent of the host circadian rhythm (Jia et al., 2010; Ni and Zeng, 2016). However, to conclusively demonstrate the independence of viral adsorption from host circadian rhythm, this experiment should also be conducted on light-independent phages (Ni and Zeng, 2016).

Failure of viruses to adsorb in the dark is immediately reversed upon reillumination, indicating a light-dependent temporary change (Jia et al., 2010). This may either be a function of host receptor protein conformational changes or be associated with long-tail fibers (LTFs) of the phages (Jia et al., 2010). In T4 myovirus, protein whiskers (encoded by the *wac* gene) extending outward from the collar region (Conley and Wood, 1975) control retraction and extension of LTFs and determine the competency of adsorption with respect to environmental abiotic factors, including temperature, ionic strength, pH, and biotic cofactors such as tryptophan (Conley and Wood, 1975). It is hypothesized that the cyanomyovirus S-PM2 possesses an environment sensing mechanism that prevents phage adsorption in the dark by maintaining LTFs in a retracted position (Jia et al., 2010). However, yet no homolog of *wac* has been found within the genome of S-PM2 (Mann et al., 2005; Clokie et al., 2008). When comparing T4 orthologs of the *wac* gene, only a short, conserved segment was identified at the N-terminus (Letarov et al., 2005). Subsequently, this leaves the possibility of the discovery of a *wac* homolog in S-PM2 cyanophage open (Jia et al., 2010). Additionally, Clokie et al. (2010) described the presence of distinct whiskers on a newly isolated cyanomyovirus, strongly suspected to be a potential product from a *wac* gene homolog. To conclude, it can be noted that though certain wavelengths of the electromagnetic spectrum differentially promote viral decay, light is proven to be essential for adsorption for many viruses. However, to the best of our knowledge, the diel nature of host and viral receptors has not been explored and/or documented.

Viral Replication

Post initial infection, viruses must replicate using their hosts' replication machinery which, in turn, may be regulated in a rhythmic manner (i.e., circadian or diurnal). A strong dependence of cyanophage replication upon light presence and intensity has been demonstrated in various cyanobacterial hosts (Lindell et al., 2005; Dimmock et al., 2009). For instance, Kao et al. (2005) demonstrated a strong positive correlation in burst size with increasing intensity of light. A two-log fold increase was observed in AS-1 cyanomyophage production in *S. elongatus* PCC 7982 when light intensity increased from 5 to 25 $\mu\text{Mol m}^{-2} \text{ s}^{-1}$. Indeed, the effect of light on viral replication has

been shown for various cyanobacteria including, *Prochlorococcus* spp. (Lindell et al., 2005; Thompson et al., 2011), *Nostoc muscorum* (Adolph and Haselkorn, 1972), and *Plectonema boryanum* (Padan et al., 1970). Notably, a minimum exposure time was also required for successful infections and subsequent viral replication; with a 10 times higher viral production rate observed when the host cultures were incubated with viruses for at least 3 h as compared to 1 and 0.5 h, during a 10-h cycle. Notably, a decreased transcript abundance was reported when the T4-like myovirus P-HM2 was incubated under complete darkness with *Prochlorococcus* MED4 (Thompson et al., 2011). Such observations demonstrate a clear reliance on light for cyanophage replication. However, it must be considered, that this could alternatively be due to the direct influence of light on the photosynthetic capacity of the cyanobacterial host, in turn, influencing host replication machinery, or through the activity of the auxiliary photosynthetic genes brought in by the viruses (discussed below), or indeed a mixture of both.

To confirm the reliance of viral replication on photosynthesis, photosynthetic inhibitors, DCMU (3-(3,4-dichlorophenyl)-1,1-dimethylurea) and CCCP ([3-(3-chlorophenyl)hydrazono]malononitrile) were used. A reduction in phage genomic DNA copies was observed by Lindell et al. (2005) when the phage-infected bacterial samples were incubated with DCMU. Moreover, Mackenzie and Haselkorn (1972) found a complete suppression in viral production when cyanosiphophage SM-1 was incubated with *Synechococcus* strain NRC-1 in the presence of DCMU and CCCP. Subsequently, it can be concluded that cyanophages acquire their energy by exploiting host photosynthetic mechanisms.

Interestingly, phages are also known to carry a myriad of host genes termed as 'auxiliary metabolic genes' (AMGs). Mann et al. (2005) reported the presence of *psbA* and *psbD* genes encoding proteins D1 and D2 of photosystem II, respectively, within cyanomyophage S-PM2. These two proteins are critical in curbing photoinhibition. Therefore, the presence of these genes in a phage infecting cyanobacteria might prevent the loss of photosynthetic activity due to photodamage. Notably, the D1 protein from S-PM2 is similar to that in *Synechococcus* sp. WH8102. This likely indicates a direct acquisition from the cyanobacteria through horizontal gene transfer. The *psbA* and *psbD* genes were interrupted by an unrelated non-photosynthetic gene in the S-PM2 genome, suggesting independent acquisitions of these two genes (Millard et al., 2004; Mann et al., 2005). In a comparison of genomes from three phages, myovirus P-SSM2, P-SSM4, and podovirus P-SSP7, Lindell et al. (2005) found that all three viral genomes possessed *psbA* which encodes for D1 as well as the *hli* gene encoding high light-inducible protein HLIP. Specifically, the myovirus contained *psbD*, whereas the podovirus contained photosynthetic electron transport proteins plastocyanin (*petE*) and ferredoxin (*petF*). In all cases, the identified genes were uninterrupted and conserved, thus, indicative of functional proteins. *Prochlorococcus* phage D1, D2, and HLIP cluster together with those from *Prochlorococcus*. Likewise, *Synechococcus* phage D1, D2, and HLIP clustered together with those from *Synechococcus*. This plays in line with the cyanobacterial origin of these cyanophage AMGs.

However, their widespread distribution amongst diverse clades also suggests multiple independent acquisition events throughout eons of coevolution (Lindell et al., 2005).

Light-dependent adsorption of P-HM2 and its inability to infect host cells at night is likely a result of the host's light-sensitive receptors and/or phage tail fibers (Thompson et al., 2011; Liu et al., 2019). Although adsorption itself does not rely on photosynthesis, as demonstrated using photosynthetic inhibitors in the cyanomyovirus S-PM2 and *Synechococcus* spp. system (Jia et al., 2010; Liu et al., 2019), cyanophage transcription may be regulated by the photosynthetic activity of host cells. Indeed, both photosynthesis inhibitors and the absence of light can reduce cyanophage transcript abundance. P-HM2-like cyanomyophages may only infect during the day, and when host cells are metabolically active (Liu et al., 2019). Conversely, P-SSP7-like cyanopodophages may infect during both day and night, though with a relatively slow replication rate considering the lower availability of cellular resources (Liu et al., 2019). This likely provides a competitive advantage when competing for a limited number of host cells. Interestingly, P-SSM2 cyanomyophages combine both phage strategies, infecting during day and night, but replicating only during the day (Liu et al., 2019). Although to date, no clear pattern in viral adsorption to light has been observed, we can conclude that a minimum threshold of photosynthetic activity is required for successful viral replication. As there are phages that display light-independent and light-dependent patterns of adsorption with adsorption maxima during the day or the night, no generalization can be made on the effect of light on viral adsorption. The certain minimum hours of light required for the viral transcripts to be abundant, the lowered transcript abundance due to the use of photosynthetic inhibitors, and the presence of AMGs in the phage genome point to a strong dependence on light for viral replication.

Viral Interaction With Host Circadian Clock Proteins

The field of marine chronobiomics is relatively new and, thus, research into the influence of host biological rhythms on the viral life cycle and viral community structure is scarce. Viruses completely rely on their host for proliferation. Studies on marine viruses suggest a role of host circadian rhythm in regulating viral infection and progression through the life cycle (Edgar et al., 2012). Research has also been conducted in outlining the role of viruses in influencing the host circadian rhythm (Edgar et al., 2012). In the final part of this section, we discuss the hypothesis on how marine cyanophages influence their host's circadian rhythm by redirecting host photosynthesis activity toward viral replication.

Previous descriptions that cyanomyophage S-PM2 adsorption patterns are independent of light and rhythmic synchronization are not considered conclusive since light-independent phages were not assessed (Jia et al., 2010). Kao et al. (2005) subjected the cyanomyophage AS-1 to *S. elongatus* PCC 7942 wild type and mutants ($\Delta kaiA$ and $\Delta kaiB$) under constant light to assess the effect of the mutation in the host circadian clock on cyanophage infection. Since no significant difference in burst

size was observed, they concluded that an absence of host circadian clock proteins does not influence cyanophage infection (Kao et al., 2005).

Currently, the specific details of the effect a cyanophage infection has on the host metabolism remains unknown. Thompson et al. (2011) explored the hypothesis that phages can influence host metabolism through bringing AMGs and directing the hosts' metabolic response toward nucleotide synthesis. The light reaction, within uninfected cyanobacteria, yields ATP and NADPH which is consumed by the Calvin cycle to fix CO₂ and produce glucose-6-phosphate, stored as glycogen. At night, the Calvin cycle is inhibited by CP12 (host regulatory protein which downregulates the activities of two Calvin cycle-associated enzymes) and the stored glycogen is utilized by the pentose phosphate pathway (PPP) to release further NADPH and ribose skeleton essential for nucleotide synthesis. In an assessment of 20 cyanophage genomes, PPP and light reaction-associated genes were commonly observed whilst those associated with the Calvin cycle were not (Lindell et al., 2005; Thompson et al., 2011). Subsequently, it is hypothesized that phages are responsible for redirecting the carbon flux toward PPP; supported by the discovery of the *cp12* gene in both wildtype and cultured cyanophages. An increased NADPH to NADP (electron-deficient NADPH) ratio in cyanobacteria infected with *cp12* containing cyanophages leads to the conclusion that cyanophages utilize CP12 to block the Calvin cycle and redirect this energy to the PPP pathway to promote ribose skeleton generation and, thus, nucleotide synthesis, therefore, increasing viral replication rate (Thompson et al., 2011). The glycogen metabolism rhythm (either in the Calvin cycle or PPP) is under host circadian clock regulation and can control the cellular ATP/ADP ratio (Pattanayak et al., 2014). Therefore, circadian clock outputs (glycogen) can feedback through metabolism to control the circadian clock inputs (ATP); as the production of ATP mediates the rhythm of the host circadian clock (as mentioned in section "Prokaryotic Clock Molecular Mechanisms"; Figure 1; Pattanayak et al., 2014; Ni and Zeng, 2016).

Additionally, genes encoding transaldolase, an enzyme required within the PPP and not shared with the Calvin cycle, have been identified within the cyanophage genome (Thompson et al., 2011). As with other PPP genes, the cyanobacterial host transaldolase gene has a maximal mRNA level in the evening, but transaldolase activity decreases to half of its maximum level at 10:00 a.m. the next day. Meanwhile, the activity of other PPP and Calvin cycle proteins remains relatively constant. Subsequently, a phage transaldolase may be critical in overcoming the host's low levels of this enzyme during the day to maximally exploit the host's photosynthetic light reactions (Waldbauer, 2010; Thompson et al., 2011). The cyanophage transaldolase (TalC) is significantly different from the host transaldolase (TalB) due to several deletions in the coding sequence, except for active site residues, essential for catalysis (Thompson et al., 2011). TalC resembles fructose-6-phosphate aldolase (FsaA) of *Escherichia coli* more closely than the host TalB (Thompson et al., 2011). First, the authors confirmed that the TalC had a transaldolase activity and not F6P aldolase activity, and subsequently hypothesized a higher phage transaldolase activity

to support the evolutionary selection of FsaA-like TalC over that of TalB. Surprisingly, they discovered a three times lower kinetic efficiency in TalC than that of TalB. Despite the acquisition of host metabolic genes by viruses contributing to more successful infections, there are fitness trade-offs/compromises involved such as the higher metabolic cost of replicating a larger genome (Bragg and Chisholm, 2008). Reduction in gene size can also be due to the partial limitation exhibited by the capsid size (Russell and Müller, 1984). The trend of shorter phage genes compared to their host orthologs was observed across most host-phage systems (Thompson et al., 2011). Albeit the generalization on kinetic differences cannot be made without performing *in vitro* studies (Thompson et al., 2011). With the presence of AMGs such as *psbA* and *psbD* for increased photosynthesis, *cp12* for blocking the Calvin cycle, and transaldolase to maintain the PPP, cyanophages have successfully adapted to exploit host metabolism to increase their fitness. Additionally, through the reversal of the host metabolic rhythm, cyanophages may affect the ATP/ADP ratio, and can, thus, mediate their host's circadian clock (Ni and Zeng, 2016).

APPLICATION OF CIRCADIAN RHYTHMS FROM MAMMALIAN MICROBIOME SYSTEMS

Research from mammalian gut microbial systems provides the backbone to our current understanding of microbiomes. Thus, it is tempting to draw upon mammalian microbiome studies when considering less well-studied species of marine metazoa but this must be done with caution. Mammalian microbiome studies can be extremely useful, considering many microbial symbiont genera are common across diverse host species, and that the mechanisms of both the eukaryote canonical TTFL and peroxiredoxin redox clocks are highly conserved (Jolma et al., 2010; Edgar et al., 2012). However, we must also be careful to consider the disparate influences on microbial communities within divergent host systems. Human gut microbiota is highly diverse and dense, containing up to 1000 horizontally acquired species, the abundances of which go through regular daily fluctuations (Turnbaugh et al., 2009). Thus, the nested ecosystem interactions of mammalian extracellular symbionts, and, hence, influences on their circadian cycling, will be diverse and varied from other host organisms. For instance, host nutrient uptake is known to be one of the most significant influences on human gut community composition and a circadian zeitgeber influencing prokaryotic circadian clocks of the microbiome (Rothschild et al., 2018; Murakami and Tognini, 2019; Perofsky et al., 2019), but whether this is consistent within other organisms remains unknown. Additionally, it was demonstrated that rhythmic cycling of microbial community composition differentiates with host sex (Liang et al., 2015). Ultimately, considering the increased complexity within mammalian study systems, it may prove productive to utilize comparatively less complex, and earlier diverged basal marine metazoa, which can also indicate how conserved the mechanism is.

The Significance of Mammalian Holobiont Rhythms for Innate Immune Response and Metabolic Activity

Circadian regulation has been well established for some time as a significant mediator of host viral, bacterial, and food pathogen responses (Silver et al., 2012; Curtis et al., 2014; Gibbs et al., 2014; Ehlers et al., 2018). However, only recently, it has become clear that holobiont health decline can specifically be induced by rhythmic disturbances to either the host or its symbionts. Mice and human hosts rely on the daily relative abundance fluctuations of around 20% of their total microbiome species (Thaiss et al., 2014). However, under circadian disruption, these delicate gut microbial community compositions are significantly altered, leading to weakened immune defenses and holobiont health decline (Voigt et al., 2016; Deaver et al., 2018; Leach et al., 2019). Specifically, in the absence of rhythmic bacterial abundance fluctuations, hosts exhibit increased susceptibility to disease and decreased metabolomic output (Leone et al., 2015; Montagner et al., 2016; Thaiss et al., 2016).

Rhythmic Regulation of Innate Immunity

A multitude of bilateral mechanisms likely mediates the observed reductions in holobiont health under circadian disruption. For instance, altered community composition may reduce colonization resistance, whereby distinct biological niches, usually occupied by commensal symbionts, are newly opened to potentially harmful pathogens (Mullineaux-Sanders et al., 2018). Reduced symbiont abundances can also lead to a loss of symbiont performed functions, critical to host health. This includes, for example, the onset of inflammation that creates less favorable pathogen colonization conditions (Mullineaux-Sanders et al., 2018), promotion of innate immune cells such as innate lymphoid cells (ILCs) (Mortha et al., 2014), or the production of beneficial metabolites that influence host circadian cycling through histone modification (Thaiss et al., 2016). Conversely, rhythmic disruption to symbionts may also increase symbiont production of harmful compounds, toxic in high concentrations. For example, bacterial production of Lipopolysaccharide (LPS) endotoxin, a key component within the outer membrane of nearly all Gram-negative bacteria (Baltrons and Garcia, 1999; Alexander and Rietschel, 2001), may increase under rhythmic disturbance (Deaver et al., 2018).

Rhythmic disruption to the endogenous rhythms of the holobiont clock can detrimentally moderate holobiont gene expression. Recently, several mammalian studies have demonstrated a connection between core circadian clock components and regulatory feedback of innate immune system pathways. The expression and function of mouse Toll-like receptor (TLR), TLR9, was demonstrated to be controlled by the host molecular circadian clock, in which disease severity varied with infection timing, per daily TLR9 oscillations of expression (Silver et al., 2012). In addition, a core circadian oscillatory protein CLOCK positively upregulates nuclear factor-kappa β (NF- κ β) transcription, whilst the activity of *BMAL1* results in down-regulation (Spengler et al., 2012). Moreover, *BMAL1* may mediate mRNA expression of NRF2 (basic leucine zipper

(bZIP) transcription factor) that reduces inflammation via suppression of ROS and direct inhibition of the proinflammatory cytokines, IL-1 β and IL-6. Indeed, under *BMAL1* deletion, cell responsiveness to LPS increased (Early et al., 2018).

Though documented to a lesser extent, microbial symbiont circadian rhythmicity feedback to mediate host gene expression has been an actively increasing focus of future research. Within mammalian gut microbial systems, microbe-associated molecular patterns (MAMPs) interact with and induce expression of intestinal epithelial cell wall Pattern Recognition Receptors (PRRs), including TLRs and NOD-like receptors (NLRs) (Abreu, 2010), which, in turn, induce downstream innate immune responses, such as proinflammatory cytokines and NF- κ B (Mukherji et al., 2013). The rhythmic cycling of bacterial abundance and activity, thus, results in oscillatory expression of these innate immune pathways within the host (Mukherji et al., 2013). Additionally, bacterial symbionts produce a range of metabolites to modulate host chromatin and transcriptional oscillations, locally within the large intestine, as well as further afield within the liver (Thaiss et al., 2014, 2016). Specifically, circadian gut microbial disturbance induced gain and loss of histone modifications such as H3K4me3 and H3K27 acetylation at active promoters, and H3K27 acetylation at enhancers, leading to disturbance of circadian regulation within the host (Thaiss et al., 2016). In mammals, the rhythmic oscillation of gut microbiota relative abundance is, at least in part, mediated through transcriptional regulation of the host's circadian clock (Thaiss et al., 2014); thus, demonstrating the tightly linked reciprocal feedbacks within this tripartite (i.e., host, symbiont, and circadian clock) regulatory system. Subsequently, it seems clear, disruption to any one of the three components is likely to induce detrimental responses within the other.

We also observe evidence of innate immune regulation by the redox circadian clock. Recently, it was shown that PRX6 can induce activation of NF- κ B in HEK293T cells via interaction with the C-terminal TRAF-C domain of TRAF6, which translocates PRX6 into the mitochondria; a significant pathway, in protecting supercoiled DNA from damage by oxidative stress (Chu et al., 2019). Furthermore, single-molecule experiments demonstrated the specific binding of PRDX5 to an innate immune PRR, namely TLR4 (Knoops et al., 2018). That said, specific evidence that demonstrates a link between innate immune responses with redox cycling is sparse, and to date has only been demonstrated within plant holobionts (Karapetyan and Dong, 2018). Zhang et al. (2019) review the independent roles of canonical circadian regulation and redox signaling in pre-empting environmental stressors and appropriate levels of defense, respectively, to facilitate an optimal balance between immune response and growth. They hypothesized the rhythmic activity of NPR1 (nuclear translocation of the non-expressor of PR genes 1), a protein involved with plant systemic acquired resistance (SAR)-mediated defense, to be the core element linking canonical molecular and redox clocks (Zhang et al., 2019). Research regarding the functions of peroxides as signaling molecules is a relatively new field. Only since recognizing that PRX activity is mediated through post-translational modifications, has their

involvement with vital cellular functions been hypothesized (Abbas et al., 2019). Indeed, considering the importance of PRX for maintaining cellular ROS homeostasis, rhythmic disturbances to PRX cycling will likely result in damage through oxidative stress. For instance, Khaper et al. (2018) demonstrated the significance of circadian cycling of oxidative stress pathways in contributing to heart disease and decreased brain functionality, especially following myocardial infarction. Considering the widespread significance of oxidative stress across all domains, elucidating the downstream signaling cascades from circadian redox rhythms could provide substantial benefits to understanding innate immune regulation.

Rhythmic Regulation of Metabolism

Host metabolic activity is tightly coupled with circadian regulation and microbiome functioning. Within humans, the connection between circadian disruption (e.g., through jet lag or night-shift workers) and increased levels of obesity, diabetes, or metabolic syndrome has been well documented (Shi et al., 2013; Depner et al., 2014). Similarly, circadian clocks themselves may be food-entrainable. Remarkably, time point restricted feeding was able to restore both transcriptional and behavioral rhythms within mice whose circadian clocks had been genetically impaired (Hughes et al., 2009, 2010; Vollmers et al., 2009). Notably, the timing of nutrient intake dominates over composition since time-restricted feeding restores the adverse metabolic effects from high-fat diets within the host (Chaix et al., 2014). Reciprocally, bacterial symbionts may also modulate host circadian gene expression (reviewed in Nobs et al., 2019). The production of bile salt hydrolase from bacterial symbionts stimulates a significant shift in circadian oscillators and CCGs regulating host lipid and cholesterol metabolism (Joyce et al., 2014). Remarkably, microbial transfer of circadian-disrupted dysbiotic communities from either mice or humans into germ-free mice recapitulates the metabolic derangements exhibited within the donor (Thaiss et al., 2014; Leone et al., 2015). However, the molecular mechanisms of such interactions have only recently been explored. Recently, Kuang et al. (2019) demonstrated that gut microbiota drive genome-wide rhythmic histone acetylation and gene expression within their host. Specifically, through binding with the nuclear receptor co-repressor (NCoR), the gut microbiota is required for diurnal rhythmic recruitment of the histone deacetylase Hdac3 to target gene promoters that regulate processes controlling host nutrient uptake and metabolism (Kuang et al., 2019). Such mechanisms are intricate and complex; thus, it will require extensive research of single pathways to uncover a holistic picture of circadian holobiont mediated activity.

To date, the rhythmic regulatory mechanisms linking host and symbiont activities have largely been demonstrated through correlative studies. Limited research has uncovered the specific molecular pathways by which rhythmic regulation mediates holobiont health (Lee et al., 2019). However, large-scale holobiont studies do not permit the observation of quantifiable cause and effect interactions on the molecular scale, since a multitude of interactions contributes to the intricate web of holobiont rhythmic regulatory pathways (Lee et al., 2019). Thus, the challenge for future chronobiomics research should be to identify

localized proteins/genes of interest that can facilitate molecular-level observations. We must demonstrate the environmental stimulus that initiates a primary response through to the resulting cyclical holobiont feedback. It is this reciprocal interaction between host and symbiont circadian rhythms that is most elusive but could prove most useful.

Influence of Viral Infection on Circadian Rhythm of Mice

The timing of infection can play a significant role in viral persistence and success. Recently, Edgar et al. (2016) demonstrated a time-dependent magnitude of response within mice infected with recombinant luciferase-expressing Murid Herpesvirus 4 (MuHV 4). They observed a 10-times higher MuHV 4 replication rate within mice infected intranasally just before their resting period, at subjective night (zeitgeber Time = 0 or ZT0), compared with those infected after the resting period, at the beginning of the subjective day (zeitgeber Time = 10 or ZT10). This indicates a likely dependence of viral infection success on the circadian rhythm of host mice. Within murine organisms, *BMAL1*, along with NPAS and CLOCK are the activating transcription factors that drive the transcription of repressor proteins CRY1/2 AND PER1/2 (**Supplementary Box 3**) which together sustain the molecular circadian rhythm. *BMAL1* activity reaches a maximum just before the subjective night, and within mutant mice, lacking *BMAL1* expression (*Bmal1*^{-/-}) circadian rhythmicity is disrupted. Notably, mutant mice infected with MuHV 4 virus at the above-mentioned time points (ZT10 and ZT0), demonstrated similar viral replication rates across all time points, thus, indicating an influence upon viral infection success. Interestingly, in an assessment of viral infection persistence, a higher replication rate was observed within mutant mice, showing a peak on day 5, in comparison to day 9 within wild-type mice infected at ZT0. Indeed, wild-type mice showed a significantly lower infection rate at ZT10, 10-times lower than that observed within the mutant mice, and only peaking on day 7. This demonstrates that the effects from variable timing of viral infection are relatively long-term.

However, it is also possible that the observed differences in replication rates at Z10 were a function of an increased host immune response. To test for this, the experiment was repeated using synchronized cell lines with a ~24-h rhythmic period. For both, MuHV 4 and Herpes Simplex Virus - 1 virus, an increased replication rate was observed in the *Bmal1*^{-/-} cell lines as compared to the wildtype (WT), indicating a direct influence of host circadian clock on viral replication and persistence. Furthermore, viral infection also affects the host's circadian rhythm. NIH 3T3 cells with *Bmal:luc* system, which expresses luciferase under the control of *Bmal1* promoter, were infected with MuHV 4 virus at different zeitgeber times. The herpes virus expressed *Bmal1* from ~6 h after infection, irrespective of the time of infection. If indeed, infection occurred at the point of endogenous *Bmal1* transcription fall, then a generated *Bmal1* peak disturbed the circadian rhythm. However, if infection occurred at another time, then it suggests a higher than usual peak in *Bmal1* expression was observed. This suggests that viral

infections can modulate host circadian rhythm, with the effect varying depending on the timing of infection.

Inferences From Other Model Organisms

Notably, significant insights may also be gained from other well-studied terrestrial model holobiont systems. Plant-mycorrhizal fungal relationships are one of the most well-known holobiont systems. Here, expression of circadian gene homologs (*wc-1*, *wc-2*, and *frq*) based on *Neurospora crassa*, the fungal circadian clock model (Grimaldi et al., 2006), were identified within the Arbuscular mycorrhizal fungus (AMF) *Rhizoglyphus irregularis* (Lee et al., 2018). This presents an interesting example, since AMF lives underground, unexposed to sunlight, yet the core circadian oscillator gene *frq* was still induced by brief light stimulation (Lee et al., 2018). This demonstrates that microbial symbionts may use a diverse range of environmental cues for rhythmic entrainment. Additionally, within the well-established model *Drosophila*, it was demonstrated that Alphaproteobacteria, *Wolbachia* endosymbionts support their hosts' peripheral clock oscillations and diurnal behavioral patterns (Morioka et al., 2018). We must consider these well-studied model organisms as they may provide useful experimental platforms toward understanding molecular mechanisms of circadian clocks within the less well studied, but ecologically significant species from vulnerable marine ecosystems.

RHYTHMS IN MARINE HOLOBIONTS

Current evidence demonstrating circadian regulation within microbial symbionts is largely limited to the mammalian gut microbiota, though a few marine systems have been explored. One of the best-studied examples includes luminous Gammaproteobacterium *Aliivibrio fischeri* (formerly, *Vibrio fischeri*) housed within the light organ of Hawaiian bobtail squid *Euprymna scolopes*. Horizontally acquired *A. fischeri* accumulate each day in the light organ of *E. scolopes* whereby nightfall, they reach a high enough density to produce bioluminescence through quorum sensing pathways (Miyashiro and Ruby, 2012). This is suggested to confer an advantage to the host by deterring predators through a mechanism known as counterillumination (Jones and Nishiguchi, 2004). Remarkably, each morning, the host then expels (known as "venting") 90% of these bacteria and the few remaining regrow throughout the day to again build up sufficient densities. This daily cycle forms the basis of their symbiotic relationship, of which host and symbiont demonstrate rhythmically aligned patterns of gene expression (Wier et al., 2010) underlying day/night activities (Heath-Heckman and McFall-Ngai, 2011). For instance, the transcriptional rhythms of *E. scolopes*' circadian associated cryptochrome *escry1* are upregulated through the temporal cycling of its symbiont *A. fischeri* (Heath-Heckman et al., 2013). Likewise, the cyclic provision of chitin by the host regulates symbiont metabolism resulting in the cyclic production of bioluminescence, essential to symbiosis (Schwartzman et al., 2015). Despite being one of the best-studied examples, gammaproteobacterial *A. fischeri* circadian oscillators have not yet been identified. Thus, indicative

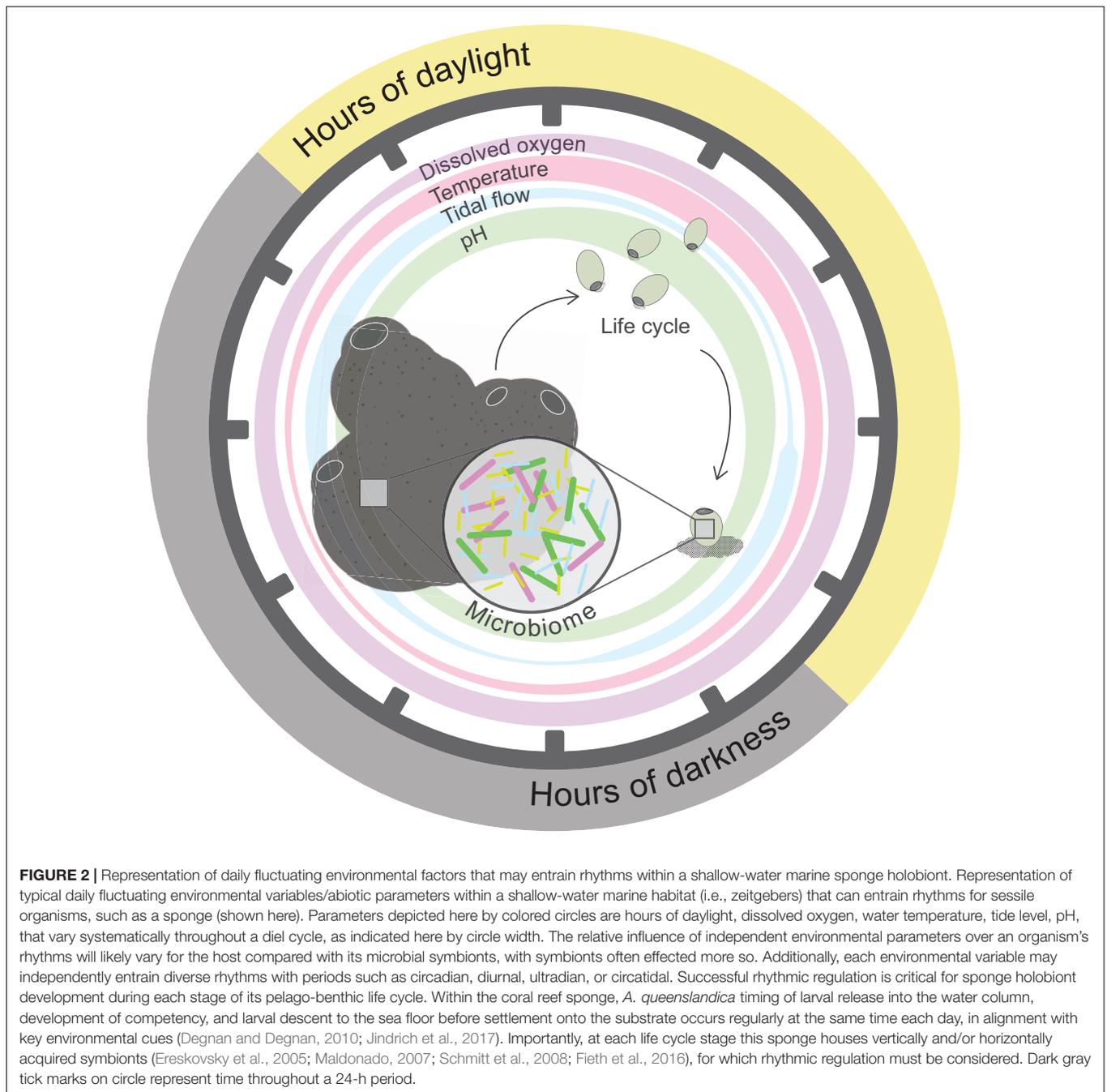
of the significant challenges in chronobiomics, limiting our current scope on the potentially widespread prevalence of rhythmic regulatory systems within marine ecosystems.

Circadian-like rhythmic activity has also been described within Cnidarian-Symbiodiniaceae holobionts. Diurnal rhythmic activity within corals has been observed since the 1930s and is perhaps unsurprising given that light, considered the major circadian zeitgeber (McClung, 2001), forms the basis of the coral-Symbiodiniaceae relationship through photosynthetic production of metabolites. Within both free-living Symbiodiniaceae and symbiotic Symbiodiniaceae, the rhythmic activity of photosynthetic processes including, oxygen evolution, PSII yield, and concentrations of pigments, is sustained under constant conditions (Sorek and Levy, 2012a; Sorek et al., 2013). This lends support to the hypothesis that an endogenous circadian clock mediates photosynthesis (Sorek et al., 2014). However, molecular evidence for circadian-driven regulation remains elusive, since uncoupling host-symbiont interactions and reciprocal regulation remains a significant challenge, particularly within vertically inherited intracellular endosymbionts (Sorek and Levy, 2012b). That said, molecular clock mechanisms have been demonstrated within several free-living algae, including *Lingulodinium polyedrum*, the dinoflagellate clock model (Hastings, 2007; Noordally and Millar, 2015). Additionally, considering the significance of ROS within the coral holobiont from Symbiodiniaceae photosynthesis, we predict an important role for the circadian redox clock in the maintenance of ROS homeostasis. Each day, coral tissue exhibits a significant day-night transition in oxidation state during the switch between daytime photosynthesis and evening respiration (Sorek et al., 2013). This could likely provide a dominant zeitgeber entraining peroxiredoxin circadian rhythms (Edgar et al., 2012). Indeed, evidence links the relationship between circadian regulation and several stress-related proteins. For instance, Heatshock protein 90 (HSP90), coupled to the circadian clock, demonstrates rhythmic expression under both constant and diurnal conditions and modulates the circadian period if inhibited (O'Neill et al., 2011; Hindle et al., 2014). Additionally, toxic stress driven by climate change-induced environmental perturbation results in disruption to host circadian genes, as well as an observed high prevalence of symbiont antioxidant genes (Kaniewska et al., 2015). Coral-Symbiodiniaceae symbioses are one of the best well-studied marine holobionts, yet we understand relatively little of their circadian mediated interactions, demonstrating both the current lack of research within this area and the significant challenge it presents. Given the ecological significance and vulnerability under anthropogenic and climate change-induced pressures, coral holobiont circadian activity ought to be a priority for research.

Closely related sea anemones can also provide tractable cnidarian holobiont study systems since, unlike coral, they exhibit both symbiotic and aposymbiotic morphs. In *Aiptasia diaphana*, Sorek et al. (2018) demonstrated symbiotic morphs display 24-h circadian rhythms of gene expression, whilst aposymbiotic morphs displayed only 12-h circatidal rhythms. Notably, when aposymbiotic morphs were repopulated with algae, they returned to a 24-h behavioral rhythm. This dramatic

rhythmic shift observed between symbiotic and aposymbiotic hosts indicates a strong influence from an endogenous symbiont circadian clock on photosynthesis and host rhythmicity through the transfer of metabolites (Sorek et al., 2018). Moreover, within the sea anemone *Nematostella vectensis*, significant shifts in the abundance of bacterial community members were observed under constant conditions (light-light LL or dark-dark DD). Under DD, bacterial community diversity increased, as well as upregulation of innate immunity genes, thus, indicative of a symbiont-driven circadian clock (Leach et al., 2019). Outside of Cnidaria, endogenous circadian regulation of Symbiodiniaceae symbionts has also been identified within the giant clam *Tridacna crocea*, where it was suggested that endogenous symbiont and/or host circadian rhythms, stimulated by light, mediate *T. crocea* daily trace element incorporation (Warter et al., 2018).

Many marine invertebrate organisms exhibit pelago-benthic life cycles that encompass a free-swimming larval stage, often particularly dependent on environmental cues (reviewed by Hodin et al., 2017). For instance, larvae of the coral reef sponge *Amphimedon queenslandica* inhabit a shallow-water reef flat where they are highly dependent on regularly oscillating environmental cues for the onset of development and timing of larval settlement to the substrate; occurring 4–6 h post-release, in the late afternoon each day (Degnan and Degnan, 2010; **Figure 2**). When maintained under conditions of constant environmental light, larvae do not settle, but when re-exposed to darkness, again exhibit settlement (Say and Degnan, 2019). Thus, environmentally entrained clocks can have a profound influence on behavior. As with other larval metazoa, *A. queenslandica* larvae house a vertically inherited microbiome dominated by proteobacteria (Fieth et al., 2016; Gauthier et al., 2016), which may also be rhythmically regulated. For instance, bacterial production of LPS endotoxin, a key component within the outer membrane of nearly all gram-negative bacteria (Baltrons and García, 1999; Alexander and Rietschel, 2001), may increase under rhythmic disturbance (Deaver et al., 2018). Significant upregulation of the export permease protein (*LptF*) and an LPS synthesis gene (*kdsB*) was observed within circadian disrupted gut microbiota (Deaver et al., 2018). As well as the direct toxic effects from LPS, increased production of such compounds may interfere with signaling pathways that sustain crucial holobiont molecular and behavioral activities. Indeed, LPS can interfere with chemosensory G-protein coupled receptors (GPCRs) (Baltrons and García, 1999; Alexander and Rietschel, 2001), which facilitate signaling cascades for an array of diverse host responses. The pelago-benthic life cycle, observed in many marine invertebrates, often relies on GPCR activation to induce settlement of larvae to the substrate (Schneider and Leitz, 1994; Strader et al., 2018; Say and Degnan, 2019), and, thus, may potentially be inhibited through GPCR circadian induced pathway disturbances. The successful development and establishment of free-swimming larvae is a crucial stage in the dispersal of many significant marine holobionts, functional as ecosystem engineers (e.g., coral, sponges, ascidians, bryozoans). Subsequently it is particularly important we understand



the rhythmically aligned regulation of these organisms that could likely be disrupted through climate change induced environmental perturbation.

PERSPECTIVES ON THE HOLOBIONT CLOCK

The bilaterally dependent feedback of host–symbiont rhythmic regulation is an intriguing area of research, presenting many significant challenges. For instance, does each individual within

the partnership contribute its own endogenous clock, or do they function cohesively, acting and reacting to rhythmic cues of the other? Regarding the canonical molecular clock within prokaryotic organisms, we observe a loss of features (Schmelling et al., 2017) and less robust rhythms within all non-cyanobacterial species, regardless of whether they are free-living or symbiotic. Thus, microbial symbiont clock features may feasibly have become redundant and led to a shift in reliance upon their hosts for entrainment cues, and even the expression of their clock-controlled genes via host oscillators. Indeed, this may be to a comparatively greater

extent within endosymbionts. Evidence indicates free-living ancestral mitochondria and chloroplasts once had their own endogenous clocks before becoming fully obligate within the eukaryotic cell. Likewise, within free-living Symbiodiniaceae, we observe longer-lasting, robust rhythms under constant conditions than within its symbiotic counterpart (Sorek et al., 2014). Robust clocks enable organisms to sustain rhythmic regulation for longer periods, despite variable environmental entrainment cues. Thus, for organisms housed within the relative stability of the microbiome, such a robust clock, that is likely more energetically costly, may not have been selected for. Conversely, considering the redox clock as a conserved and ancient mechanism, that likely predates the canonical clock (Edgar et al., 2012), we hypothesize individuals within the holobiont to each comprise their own endogenous redox clocks, that have optimally aligned through common/shared environmental stimuli. However, it is the interplay between the redox and canonical holobiont clocks that will be an important and challenging aspect of future chronobiomics research to address.

We must also consider the diversity and dominance of environmental cues that a holobiont may use for entrainment. An individual holobiont may each be exposed to a unique complexity of diverse environmental stimuli, specific to its local environment (Figure 1). Thus, as observed within the mantle of the giant clam *Tridacna squamosus*, multiple rhythms set on different periods (e.g., circadian, circatidal) may regulate specific activities (Hiong et al., 2018), such that the efficiency of each is optimized through oscillations under with the relevant environmental stimulus. Furthermore, the relative dominance of specific cues may vary for different members of the holobiont, in accordance with the often-disparate conditions experienced by the microbiome compared with its host. For instance, within human gut microbiota, symbiont rhythms are entrained most dominantly by host nutrient intake, whilst for the host, environmental light provides the dominant zeitgeber (Bass and Takahashi, 2010; Oosterman et al., 2015). In sponges, the ceasing of pumping activity can lead to internal anoxic conditions, which bacterial symbionts of the microbiome are hypothesized to mitigate (Hoffmann et al., 2008; Lavy et al., 2016). Circadian clock timing enables organisms to anticipate daily fluctuating environmental conditions and respond appropriately, thus, maximizing the efficiency of the holobiont; by maintaining an optimum balance in the energy requirements demanded from activities, such as ROS homeostasis, growth, or reproduction, and to help ward off viral infections at a cellular level.

It is widely observed that organisms exhibit thresholds of disturbance, beyond which they are unable to sustain homeostatic cellular functioning and, thus, exhibit, often irreversible, health decline. This can most commonly be observed under climate change-induced disturbances, such as coral holobionts during exposure to degree heating weeks (DHW), whereby different coral holobionts exhibit varying degrees of resistance to the number of DHWs (Sully et al., 2019). Here, we emphasize the importance of understanding circadian clock molecular mechanisms to elucidate the relationship between specific environmental cues and regulatory mechanisms that

nudge organisms past their tipping points beyond which they can cope. For instance, *in vitro* experiments have demonstrated the varied abilities of different organisms to sustain circadian regulation under conditions of prolonged circadian disturbance. We hypothesize that varying degrees of circadian clock robustness equate with longevity until disturbance thresholds are surpassed. That is, in the absence of appropriate environmental zeitgebers, a more robust clock may sustain rhythmic regulation of cellular activities for a longer duration, and, thus, be less likely to exhibit environmental disturbance-induced stress.

CONCLUSION

We have only just begun to touch the surface of understanding rhythmic regulations and the extent to which they can mediate cellular, organismal, or ecosystem-level functioning. Yet, circadian-driven regulatory systems, through both canonical molecular and redox clocks, have evolutionary ancient origins, of which the environmental zeitgebers entraining such rhythms are ubiquitous, although nuanced, for all organisms. Thus, we cannot stress enough the importance of elucidating the mechanisms by which organisms perceive entrainment cues and utilize them to optimize rhythmically coordinated regulation within their local environment.

The trophic interactions within large-scale planktonic systems, including the viral shunt, are extremely important for global biogeochemical cycling on a humungous scale, with numerous downstream effects for energy transfer within locally significant ecosystems, such as tropical coral reefs or deep-sea habitats. Dominant cues such as environmental light entrain the rhythms for free-living prokaryotes and viruses within large-scale planktonic communities. However, the molecular mechanisms by which these organisms coordinate such rhythms are less clear. To date, molecular evidence describing prokaryote circadian regulation is limited to Cyanobacteria and a few proteobacterial species. Though within the last decade, research has demonstrated that a circadian redox clock is ubiquitous across all domains, as well as less robust, simplified forms of the canonical molecular circadian clocks are also plentiful. Future research should expand our understanding of such mechanisms outside of Cyanobacteria to other important bacterial and archaeal phyla, which make up a significant part of these macro-scale ecosystems.

In parallel, rhythmically coordinated regulation of cellular activity is equally significant within micro-scale nested ecosystems of marine holobionts. Holobionts, which comprise a host and complex cohort of prokaryotic communities, interacting either competitively or beneficially with one another, are considered within an ecological context. Each member within this nested ecosystem will regulate activities on an independent endogenous clock. However, remarkably, the interdependent relationship between a host and its symbionts is also rhythmically coordinated, through both redox and canonical circadian clocks.

This association is complex, particularly as there are likely numerous entrainment cues, of which the relative importance of each will differ for host and symbiont. Untangling the links between host and symbiont-driven circadian regulation will require extensive research. Currently, the best models for this are from mammals and a few terrestrial organisms. Whilst studies from these models are insightful, they are not necessarily representative and we, therefore, encourage further research on marine metazoan, particularly from earlier diverged lineages such as Cnidaria, Porifera, and Ctenophora. This will facilitate greater evolutionary insight into the origins of such mechanisms since they provide the earliest sister group to all other bilaterians. Additionally, these organisms are very important parts of reef ecosystems in marine habitats currently facing climate change-induced stressors.

It is important to recognize the rhythmically interconnected nature of both micro- and macro-scale ecosystems. Indeed, many of the above-mentioned reef organisms (e.g., coral, sponges) help couple benthic and pelagic zones themselves through their filter-feeding, meroplanktonic life cycle, provision of larval settlement cues, and providing breeding grounds for a remarkably high number of species. Within each ecosystem, every organism is regulated by its endogenous rhythms, but crucially, those rhythms must also be aligned with both the abiotic cues and other clock-controlled biotic cues from within their local environment.

With this review, we have introduced the relatively new field of marine chronobiomics within both macro-scale planktonic ecosystems and micro-scale holobiont nested ecosystems. We highlighted the interplay of biological rhythms across the living domains, as well as the not-so-living viruses, both within and between micro- and macro-scale ecosystems. Our review

provides a baseline in which we emphasize the currently large gaps in knowledge and active research, to help guide future exploration and recognition of chronobiomics within the marine domain.

AUTHOR CONTRIBUTIONS

OH introduced the subject for this review. HS and OH drew **Figures 1, 2**, respectively, contributed equally toward the conception of this review, and provided essential and critical feedback throughout the writing process. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmars.2021.744169/full#supplementary-material>

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