The Influence of Biological Rhythms on Host-Parasite Interactions

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Abstract

Biological rhythms—from circadian control of cellular processes to annual cycles in life history—are a main structural element of biology. Biological rhythms are considered adaptive because they allow organisms to partition activities to cope with, and take advantage of, predictable fluctuations in environmental conditions. A flourishing area of immunology is uncovering rhythms in the immune system of animals, including humans. Given the temporal structure of immunity, and rhythms in parasite activity and disease incidence, we propose that the intersection of Chronobiology, Disease Ecology and Evolutionary Biology holds the key to understanding host-parasite interactions. We review host-parasite interactions while explicitly considering biological rhythms, and propose that (1) rhythms influence within-host infection dynamics and transmission between hosts, (2) rhythms might account for diel and annual periodicity in host-parasite systems, and (3) rhythms can lead to a host-parasite arms race in the temporal domain.

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Biological Timekeeping

Environmental rhythms are a ubiquitous feature of our planet. Many rhythms are caused by geophysical cycles, including diel, tidal, lunar, and annual rhythms. These rhythms are highly predictable and have resulted in the evolution of biological clocks throughout the tree of life [1]. Most biological activities have rhythmic time structure, which scales from gene expression to life history events such as breeding and hibernation. Rhythmic time structure allows organisms to partition and prioritize life history activities—whether they are molecular or behavioral—relative to predictable fluctuations in environmental conditions. For example, for cyanobacteria, which are an ancient lineage, sunlight provides both energy and risk. Cyanobacteria have adapted to this challenge by temporally partitioning photosynthesis from UV-sensitive DNA replication [2]. Likewise, throughout the year, organisms must meet survival needs, while seasonally requiring further resources for reproduction and other activities. This leads to annual cycles of life history, when animals alternate between reproductively active states and inactive states such as dormancy, hibernation, or migration, a retreat to wintering grounds that buffer against resource scarcity [1].

Over evolutionary time, organisms have adapted to environmental fluctuations by an internal representation of time—endogenous biological clocks—that perpetuate biological rhythms even when environmental conditions are kept constant. These rhythms are characteristically innate, evidenced by

the observation that individuals who have never experienced environmental fluctuations display rhythmicity [1]. Endogenous biological rhythms oscillate with period lengths that approximate those of geophysical cycles, and are accordingly called circadian, circatidal, circalunar, and circannual. Circadian rhythms, which are most heavily studied, are driven by cell-specific transcription-translation feedback loops that are integrated across the organism. The evolutionary origin of internal clocks is ancient, with circadian clocks being a unifying feature of eukaryotes and cyanobacteria [3], and a new area of research in other bacterial lineages [4]. The endogenous circannual clock underlying seasonal rhythms is also thought to be evolutionarily conserved, since circannual clocks are found in organisms ranging from dinoflagellates [5] to mammals and birds [6, 7].

An internal representation of time enables the anticipation of favorable environmental conditions, ensuring that activities are initiated in advance to match the opportune time. For example, to rear offspring at the time of maximal food abundance, many species activate their reproductive system and copulate far in advance, potentially under harsh conditions. If individuals initiated breeding activities when food abundance was maximal, offspring would be reared outside the optimal environmental window [6]. Endogenous biological clocks function in concert with the geophysical cycles to which they synchronize [8, 9]. Synchronizing cues (also called *zeitgebers*) include diel and annual changes in light, temperature, and other factors. Jetlag, the overturning of rhythms resulting from changing time zones, and the subsequent re-synchronization of the circadian clock, is familiar to many of us. Species and even populations vary greatly in the way their clocks interact with the environment. They assume different phases, e.g., of activity or reproduction, relative to the environmental cycle, and also differ in the use of synchronizing cues. To varying degrees, organisms retain the ability to adjust their rhythms to respond to current, less predictable, conditions. While some species' rhythms show considerable phenotypic plasticity (e.g., the reproductive rhythm of Great tits, *Parus major*), other species have rigid rhythms that impose fitness costs under rapid environmental change (e.g., the seasonal phenology of Snowshoe hare coat color, *Lepus americanus*) [8, 10, 11]. In addition to phenotypic plasticity, evolutionary malleability of biological rhythms is supported by directional evolution of time adjustments in multiple species, which include heritable shifts in the seasonal timing of life history events such as reproduction, dormancy, and migration [12, 13].

Biological rhythms are observed across biological processes. In addition to substantial diel and annual fluctuations in activity, reproduction, and metabolism, there is also overwhelming evidence for temporal structuring of immunity. Importantly, such fluctuations cannot be comprehensively characterized as changes in overall immunity; rather, they are a selective re-organization of structural and functional aspects of the immune system [14–16]. Differentiated temporal structuring of immune defenses can arise from heterogeneous requirements and costs of specific defenses, investment in self-maintenance versus immunity, or the integration of immunity with other aspects of physiology [17, 18]. In light of this, we review biological rhythms pertinent to host-parasite interactions, and propose that rhythms of hosts, parasites, and the environment impose temporal structure on epidemiological and evolutionary dynamics.

Timekeeping in the Host-Parasite Context

Interactions between hosts and parasites (i.e., microparasites and macroparasites) are embedded within environmental rhythms (Figure 1A). In addition to the environment, host immunity imposes selective pressure on parasites, whilst parasite-driven morbidity and mortality reduces host fitness. These multiple selective forces make optimal timing of allocation of limited resources to survival and reproduction

particularly tricky. For hosts, massive investment into parasite resistance, for instance, might only be energetically feasible during a resource pulse (i.e., opportunity) also favorable for reproduction, resulting in an optimization problem for resource allocation to survival versus reproduction [19]. Yet hosts also undoubtedly face the challenge of mitigating the deleterious effects of parasites when resources are scarce, a situation that might favor investment into parasite tolerance versus resistance. For parasites, not only does the host immune response impose risk, additional risks can be introduced by environmental regimes during transmission [20] or environmental life stages [21]; which has led to parasite risk avoidance strategies such as climate-driven arrested development [22]. For both hosts and parasites, therefore, external environmental conditions impose selective pressure by providing fluctuating opportunity for reproduction and risk of mortality. These exogenous factors need not be identical for hosts and parasites, although they co-occur in the same physical environment. For example, we need not expect that rhythms in parasite reproduction, host reproduction, and host immune investment be synchronized. An empirical case of this is the seasonal influence of temperature and humidity on development of the free-living nematode parasite (*Trichostrongylus*) of rabbits, which results in an autumn peak in the force of infection; whereas, the rhythm in host immunocompetence has a peak in the springtime [23].

The temporal structure of host immunity and parasite success suggests that constraints (1) preclude hosts from maintaining high levels of parasite resistance, and (2) prevent parasites from sustaining high reproductive output (fitness). Such constraints would result in trade-offs between investments in opportunity versus risk avoidance [19, 24]. Consequently, we hypothesize that both hosts and parasites time their biological processes with reference to both the external environment and each other, and that therefore in many cases periodic incidence of infectious disease is a consequence of biological rhythms, as has been suggested elsewhere (e.g., [25]). Below, we first lay out empirical evidence for the role of rhythms in host-parasite interactions. In order to inspire quantitative study of biological rhythms in host-parasite systems, we utilize a transmission model to illustrate the epidemiological consequences of rhythms. We then formulate a conceptual evolutionary model for understanding host-parasite dynamics embedded within the rhythmic context in which they are evolving.

Biological Rhythms in Host and Parasite Traits

The incidence of many infectious diseases displays substantial seasonality [26–28]. Seasonally structured disease incidence can be discussed from the viewpoint of hosts or parasites. From a host's perspective, parasite exposure can be influenced by host behavior, such as seasonal aggregation; a contemporary example being epidemic seasonality of mycoplasmal conjunctivitis in house finches [29]. However, physiological factors influencing host susceptibility to infection and symptomatic disease, such as seasonal changes in immunity, can also drive disease seasonality [23, 28, 30]. Table 1 summarizes some known diel and annual rhythms in host immunity and parasite traits (see [16, 31–34] for extensive reviews). Although rhythms in immunity are observed across a broad array of taxa, including plants [35, 36] and animals, we focus on mammalian and avian hosts to enhance the link to human health. A very active area of biomedical research is characterizing temporal structure in both innate and adaptive immunity, and correspondingly, in disease susceptibility [32, 33]. For now, biomedical studies use model organisms; but in the future should include non-model organisms [37], which are either directly relevant for understanding natural host-parasite systems, or enable a broader understanding of within-host dynamics of infection. Longitudinal studies of wild or captive animals compare immune parameters during active versus resting phases and are typically combined with experimental approaches. In the wild these may include repeated immune challenges [38–40], and in captivity may involve constant conditions, shifted environmental rhythmicity, or biological clock disruption. Studies of rhythms in immunity under natural

conditions—wild immunology—are important for understanding how non-model organisms deal with exposure to multiple co-occurring parasites [41]. Studies of wild systems allow us to test, for instance, how seasonal allocation into defense against one parasite can result in enhanced susceptibility to another [42], and whether temporal variation in immune status covaries with other physiological traits and is influenced by nutritional status and parasite exposure [18, 43, 44]. Laboratory studies, in turn, are necessary for distinguishing between endogenous rhythms in immunity versus variation that occurs as a result of patterns of infection or other biotic factors.

By profiling the response to infection across time, much progress has been made in characterizing biological rhythms in immunity. For example, in mice, the circadian rhythmicity of a receptor that recognizes pathogens substantially influences the inflammatory response and survival prospects (for details, see Box 1). The health implications of circadian rhythms in immunity have also been demonstrated using hosts entrained to different light-dark cycles, and mice with genetically modified circadian clocks. Such recent studies have revealed that the immune system is fundamentally circadian in nature [33, 45–49], which is highlighted by the local circadian clock of macrophages [46], and the feedback between immunity and molecular, cellular, and behavioral rhythms. The emerging picture is that the immune system is an active component of integrated whole-body circadian rhythms in animals [50] and plants [35, 36], lending support to the idea that sophisticated mechanisms of immune defense were also present in their common ancestor [51].

Annual cycles in immunity are not as well characterized as circadian cycles because of the time scale of experimentation [16, 31] but are epidemiologically relevant [28]. Longitudinal studies under controlled captive conditions have revealed substantial annual changes in immune parameters (Table 1). These included a down-regulation of key aspects of immunity during the time of reproductive activation, induced solely by photoperiodic simulation [14, 16, 34, 52]. Such rhythms might have evolved from a trade-off between immune defense and demanding life-cycle stages, and can underlie annual patterns of disease incidence, as suggested, for example, by rhythms of bactericidal capacity of whole blood (Box 1; Figure 1D [53]). It is important to note, however, based on the existing evidence for both circadian and annual immunomodulation, that temporal patterns can differ between innate and adaptive immunity and among traits even within the same immune cell subset [16, 33].

In addition to immunomodulation, several other aspects of host rhythmicity can have population-scale consequences for host-parasite dynamics. Relevant host annual cycles include aggregation [29, 54, 55], sexual contacts (with regard to STDs), habitat use, migration [56–58], and birth pulses that (1) act to replenish the pool of susceptible individuals, (2) can influence the critical community size required for parasite persistence, and (3) can determine the geographic synchrony of outbreaks [59–63]. The sweeping effects of annual cycles in host physiology on disease incidence are exemplified by White-Nose Syndrome (WNS), which is drawing many North American bat species near extinction. A new longitudinal study indicated that neither birth pulses nor social behavior affected transmission and intensity of WNS. Instead, WNS is associated with hibernation [30], which in mammals that have been studied in captivity, is a programmed circannual rhythm [6]. We speculate the link between WNS and hibernation is mediated by hibernation-associated changes in immunity. Evidence thus far suggests that there are large adjustments in immunity in hibernating mammals, including a 90% decrease in circulating white blood cells [64], down-regulation of the acute-phase response to LPS [65], and modifications of intestinal immunity [64, 66].

Migration is another host rhythmicity receiving attention in infectious disease ecology. In monarch butterflies, the protozoan parasite *Ophryocystis elektroscirrha* displays a seasonal pattern of prevalence and a spatial gradient along the monarchs' migratory flyway. Parasite prevalence declines as monarchs migrate, which is likely due to migratory culling [57]. In migratory culling, the coupled energetic demands of migration and fighting infection result in increased mortality of infected individuals during fall and spring migrations. The uninfected are most likely to survive the journey to the breeding or wintering grounds, allowing the destination to be relatively parasite-free. Thus, migratory culling is a direct intersection of host seasonal rhythms and disease prevalence [56], and anthropogenically-driven disruption of this rhythm results in elevated disease burden [58].

Taking the parasite's perspective, rhythmic patterns in parasite dissemination can be influenced by fluctuating abiotic and biotic conditions that affect parasite survival and transmission. Clear examples of abiotic influences are (1) the role of temperature and humidity in transmission of influenza [67], which might be responsible for latitudinal clines observed in influenza incidence [68, 69], and (2) the UV sensitivity of sporulation in *Isospora*, which might have driven the remarkably robust diel pattern of oocyst outputs [21]. In addition to abiotic effects, biotic influences can stem from rhythms of vectors [70] and other parasites [71]. Effects of vector circadian rhythmicity have been studied in the malaria vector *Anopheles gambiae*, whose rhythmic gene expression persists under constant conditions. Rhythmically expressed genes include those implicated in the melanization immune response, which encapsulates the Plasmodium parasites, and can thereby affect mosquito to human transmission. Vectors can also temporally structure parasite transmission via their diel patterns of feeding [72] and their phenology [73]. Interspecific influence of parasites on one another's rhythm, to our knowledge, has only been described for *Drosophila* parasitoids, which gain a fitness advantage by temporally segregating circadian rhythms in egg oviposition [71], hypothesized to alleviate competition.

Perhaps then unsurprisingly, parasites—faced with rhythms in their abiotic environment, hosts, and vectors—display what seem to be biological rhythms. Documentation of parasite rhythms dates back over 100 years, long before the discovery of biological clocks. In fact, the early observation that both malaria parasites and microfilariae are abundant in the blood of hosts at night was instrumental to the discovery of mosquitoes as the malaria vector [74]. Experimental studies of parasites report diel and annual rhythms, as measured by fluctuations in parasite burden and infectivity (Table 1), but disentangling the contributions of host and parasite to these rhythms is difficult [75]. To our knowledge, the only described example of a parasite life history event that depends on a host rhythm is reproduction in the ectoparasitic rabbit flea, a vector of myxoma virus. To reproduce, rabbit fleas must undergo maturation on a pregnant or newborn nestling host, and flea maturation is controlled by host hormone cues associated with pregnancy and parturition, thereby synchronizing parasite and host life cycles [76–78]. There is solid evidence for adjustment of diel parasite rhythms to those of the host, for example from trematodes like *Schistosoma mansoni*—an agent of schistosomiasis in humans—whose emergence from snail hosts is initiated by light [79, 80]. These parasites display diel cycles that shift to match perturbations in their hosts' circadian rhythm [81]. Similar results were found in rodent-infecting *Trypanosomes*. Rats infected with *T. lewisi* and housed under a normal light-dark cycle (LD 12:12 h) experienced a peak in circulating *T. lewisi* during the early part of night and a trough in the early morning. However, when the host photoperiod was inverted, the parasite rhythm was also reversed [82]. In *Isospora*, the characteristic diel pattern of oocyst output persisted under continuous light in the high Arctic, although feeding and activity rhythmicity of their avian hosts was greatly diminished, suggesting synchronization to subtle host rhythms or possibly self-sustained parasite rhythms [21].

Experimental studies give clear evidence that synchronization to host rhythms impacts parasite fitness. For example, murine host rhythms were experimentally mismatched to that of their malaria parasite (*Plasmodium chabaudi*). This mismatch resulted in a 50 per cent reduction in both parasite replication and production of transmissible life-stages [83]. Follow up experiments have now revealed additional complexities, with the effect of mismatch manifesting differently between parasite life stages, and downstream effects on host disease severity. Mismatch can confer a substantial cost to the parasite, and this cost is experienced at the onset of infection, rather than acquired throughout infection [84, 85]. This suggests there can be intense selective pressure on parasites to maintain a specific phase position relative to their host rhythms, or to vector rhythms, since parasite ability to infect vectors is also time-of-day dependent [72]. Fortunately, the amassing knowledge of biological clocks might help identify host cues used for entrainment of parasite rhythms. For example, the nocturnally-peaking hormone melatonin is a core circadian feature of many vertebrates, and applying this knowledge produced indication that parasites might be using melatonin to synchronize their circadian cell cycle [21, 86].

While we still lack unambiguous evidence for endogenous circadian or circannual rhythms of parasites, recent research suggests the intriguing possibility that parasites can actively manipulate host and vector rhythms to their advantage. For example, various parasites interrupt host diel activity at specific times of day to enhance transmission [87, 88]. The diel timing and synchrony of host behavioral manipulation, along with candidate molecular mechanisms of manipulation, strongly implicate circadian clock pathways [87, 89]. By integrating chronobiology with infectious disease ecology, we might be able to identify, for example, the mechanism by which the trematode *Dicrocoelium* manipulates diel host behavior, inducing suicide, and facilitating trophic transmission [90], and how the notoriously manipulative fungus (*Ophiocordyceps unilateralis s.l.*) seemingly breaks the host circadian clock to perpetuate transmission [87]. Transkingdom cross-regulation between prokaryotic and eukaryotic rhythms is plausible because it has already been documented for other systems (e.g., in bioluminescent squid light organ symbionts and in mammalian gut microbiota) [4, 91].

Despite our knowledge of (1) rhythmic host immunity and physiology, (2) rhythms in parasite reproduction and transmission, and (3) enticing evidence that host rhythms can impact parasite fitness and be exploited by parasites, the effects of biological rhythms on host-parasite dynamical processes remain poorly understood. We surmise that careful consideration of biological rhythms in infectious disease ecology and evolution will provide a better understanding of (1) daily and annual patterns of diseases, (2) within-host parasite dynamics, and (3) parasite transmission.

Models for Investigating Host-Parasite Contributions to Rhythms in Infectious Disease

In order to determine how biological rhythms impose temporal structure on host-parasite dynamical processes, we can integrate empirical data on host and/or parasite rhythms into epidemiological and evolutionary models. Biological rhythms research has great potential for feedback between laboratory studies, field ecology, and dynamical systems modeling. First, rhythms in immunity characterized under laboratory or field conditions can be used in transmission models to make predictions about the epidemiological consequences of those rhythms in nature. Second, observations of diel and annual cycles in infection—characterized via disease incidence, parasite abundance, or host serological markers of infection history—can be used to make predictions regarding rhythms generating such patterns. A new study of the first type [92] explores the effect of annual and biannual rhythms in births (in bats) on the persistence of filoviruses (i.e., Marburgvirus and Ebolavirus). Transmission models predict that filoviruses

can persist in species with biannual birth pulses—making them potential reservoirs of infection—and this prediction is supported by serology data showing that species with biannual birth pulses are more likely to be seropositive for filoviruses; demonstrating that explicit consideration of host rhythms can inform targeted surveillance and control of emerging zoonotic diseases. A study of the second type is that of [23], in which long-term field data on nematode infections in European rabbits were used to discriminate among multiple potential seasonal rhythms in the host-parasite system. This led to identification of epidemiologically relevant seasonality in host immunity; the endogenous nature of which can be tested in the lab.

Building upon the examples above, as well as other transmission models that incorporate reproductive rhythms [59–61, 93, 94], here we provide a Susceptible-Infected-Recovered (SIR) model of a directly transmitted hypothetical bacterial infection in the Siberian stonechat to illustrate the numerous entry points for biological rhythms into epidemiological processes (Figure 1B). We narrate our model with seasonal rhythms in mind; however, this can be extended to circadian rhythms. The model incorporates ambient temperature as a covariate influencing parasite transmission as well as empirical data on host circannual cycles in reproduction, immunity and migration (Figure 1CD; cf. Box 1) [53, 95]. For migration, the timing is defined empirically, while the model assumes migratory culling of infected individuals only during the autumn migration, when host bacterial killing activity is lowest [53]. Importantly, we propose that circannual cycles in host immunity can influence (1) the transmission rate, (2) the recovery rate, and (3) the pathological consequences of infection, which manifests as symptomatology and enters the model as the report rate. The multiple rhythms: temperature, births, bacterial killing activity, and migratory culling act collectively to shape the observed incidence of disease, which is the model output shown in Figure 1E. We define the resulting seasonal window of elevated disease incidence as the parasite's temporal niche. The seasonal incidence that arises from this model matches the expectations from the underlying data. However, in contrast to most models of seasonal infectious diseases, which only place sinusoidal seasonality in the transmission rate, it contains multiple axes of seasonal forcing. Thus, we provide this model to encourage the inclusion of empirically characterized rhythms into models as covariates. Such models can be used to explore the epidemiological consequences of host and parasite rhythms, although for simplicity the parasite is not explicitly modeled here. Host-parasite systems where modeling parasite rhythms is particularly compelling include nematodes with seasonal arrested development [22, 96], microfilariae which display both circadian and seasonal cycles [97], and *Plasmodium* within-host circadian cycles [75]. Major challenges of incorporating biological rhythms into epidemiological or within-host models, will be (1) recognizing which host and/or parasite rhythms are epidemiologically relevant, and (2) identifying the functional relationships between rhythms and epidemiological parameters, including: transmission, recovery, and symptomatology.

In addition to the epidemiological consequences of rhythms, we can benefit from understanding the feedback between host and parasite rhythms and the multiple axes that shape their temporal structure. Thus, we provide a conceptual evolutionary model for understanding how hosts and parasites time their biological processes with reference to each other while being embedded in environments with temporally structured risk and opportunity. We pose this model in evolutionary terms, but depending on the varying degrees of plasticity of biological rhythms, individuals may also adjust their rhythms during their life.

Our evolutionary model illustrates three idealized scenarios of how host immune defense varies seasonally, relative to fluctuating environmental conditions (Figure 2A–C). These scenarios are motivated by life history theory and by empirical observations of seasonal immunity in mammals and birds (Table 1). The scenarios assume that immune defense, specifically, parasite resistance, either parallels the

availability of resources (A, "resource-driven"), or is reduced when resources are used for reproduction (B, "traded-off"). The third is an extension of the "resource-driven" scenario with modulation related to life history events that can lead to complicated, but potentially important, annual patterns. In our example of migration (C) we assume down-regulation of immune defense during migration (see Figure 1; this could also occur during other vulnerable times such as molting or hibernation [65]), and a shallow trough under favorable conditions in the wintering grounds. We then (D) switch to the parasite's perspective and illustrate how parasites are subject to two axes of seasonal fluctuations: (i) seasonal environmental conditions outside the host and, (ii) seasonal immune defense of the host. We propose that together the two seasonal axes shape parasite transmission (i.e., parasite fitness; which is captured by the basic reproductive number).

The last and crucial component of our model is the evolutionary feedback between host and parasite rhythms. We propose that due to parasite-induced host morbidity and mortality, selection can drive changes in host seasonal immune defense. Subsequently, since host immune defense is one of the seasonal axes influencing parasites, selection will favor changes in the parasite rhythm. This interplay can continue, driving hosts and parasites to sequentially alter their seasonal rhythms while working within the constraints of environmental conditions. Figure 2E shows these steps.

We suggest that under certain conditions this can escalate into an evolutionary arms race. In this framework, the prerequisite for an arms race is that parasite fitness is sufficiently impacted by the temporal structure of the host immune response, and that the host immune response is predictably rhythmic. To be clear, when considering the temporal structure of immune defense, reference to "low" host immune defense pertains to the parasite in question. However, it must be appreciated that a time of diminished resistance to one parasite (e.g., a helminth) can be a time of high investment into fighting another (e.g., a virus). Furthermore, infection with one parasite can seasonally elevate host susceptibility to another, as is exemplified by concomitant infections of myxoma virus and nematodes [98] and increased susceptibility to bovine TB resulting from helminth coinfection [18]. The arms race itself has two requirements. First, hosts must be able to shift their immune defense to counter exploitation by parasites (host changes in Figure 2E). Changes in host rhythms then translate into a new landscape of time-structured risk and opportunity for parasites. Upon experiencing a new temporal landscape, a dynamic host-parasite arms race can arise only if the second requirement is met: parasites shift their rhythm by changing reproduction within hosts, or release from hosts (parasite changes in Figure 2E). As with other host-parasite arms races, an arms race in the temporal domain is subject to tradeoffs for both the host and the parasite that might constrain the extent to which their rhythms can be altered. Host tradeoffs can include an immunity-reproduction tradeoff [99]; whereas, tradeoffs for the parasite can include a transmission-virulence or transmission-recovery tradeoff [99–101]. Also, due to the rapid generation time of parasites, relative to hosts, evolution of host rhythm shifts might be slow relative to the evolution of parasite rhythms, but this would not preclude an arms race from occurring.

Conclusion

There is enticing evidence that biological rhythms are structuring elements of host-parasite interactions, both in within-host processes and in epidemiological dynamics. Host circadian rhythms in the immune system influence the progression of infection and parasite burden, and annual rhythms might have similar effects [23, 30]. The existing evidence leads us to conclude that the effects of biological rhythms on the perpetuation of parasites, and on host reactions during infection, can generate

population-level rhythms in infectious disease incidence [25], which we here define as the parasite's temporal niche. To formalize temporal niches across parasite taxa and life history strategies, we will need novel integration of epidemiological, immunological, and life history data of both hosts and parasites.

Importantly, circadian rhythms in immunity have direct implications for transmission, and practical application for (i) timing of antibiotic, antiviral, and anthelmintic treatment, and (ii) managing immunopathology, such as cytokine storms. The rhythms of parasites themselves can drive patterns of exposure and illness, as is evident in malaria and filarial infections. Similarly, rhythms in parasitemia and parasite release from hosts can impose temporal structure on transmission, which can be leveraged for interventions such as deworming campaigns.

We believe that a multi-disciplinary approach at the intersection of Chronobiology, Disease Ecology and Evolutionary Biology holds the key to understanding how biological rhythms influence host-parasite interactions. We have outlined open questions that will bring us closer to understanding the underlying biological interactions in the temporal domain (refer to Outstanding Questions Box). We hope that this Opinion will generate discussion on how to leverage rhythms for translational medicine, for instance to counter the evolution of resistance; and we hope the insights provided here inspire new avenues for interrogating transmission models with host-parasite data from the laboratory and the field, ultimately, to better understand the forces structuring disease incidence and the immunology of non-model organisms.

Finally, although it is beyond the scope of this Opinion, the importance of accounting for biological rhythms is accentuated by the accumulating data on anthropogenically-driven disruptions and mismatches of biological rhythms that are occurring across taxa. Circadian disruption due to light-at-night [102] and altered environmental seasonality due to climate change [13] are challenging the plasticity of rhythms and modifying the fitness advantages of their endogenous basis. For example, the adverse effects of circadian disruption have already been seen in human health and gut microbiota [91]. Given the pervasiveness of rhythms in host immunity, vectors and parasites, we might soon be faced with palpable effects of rhythm disruptions on infectious diseases [73, 103, 104].

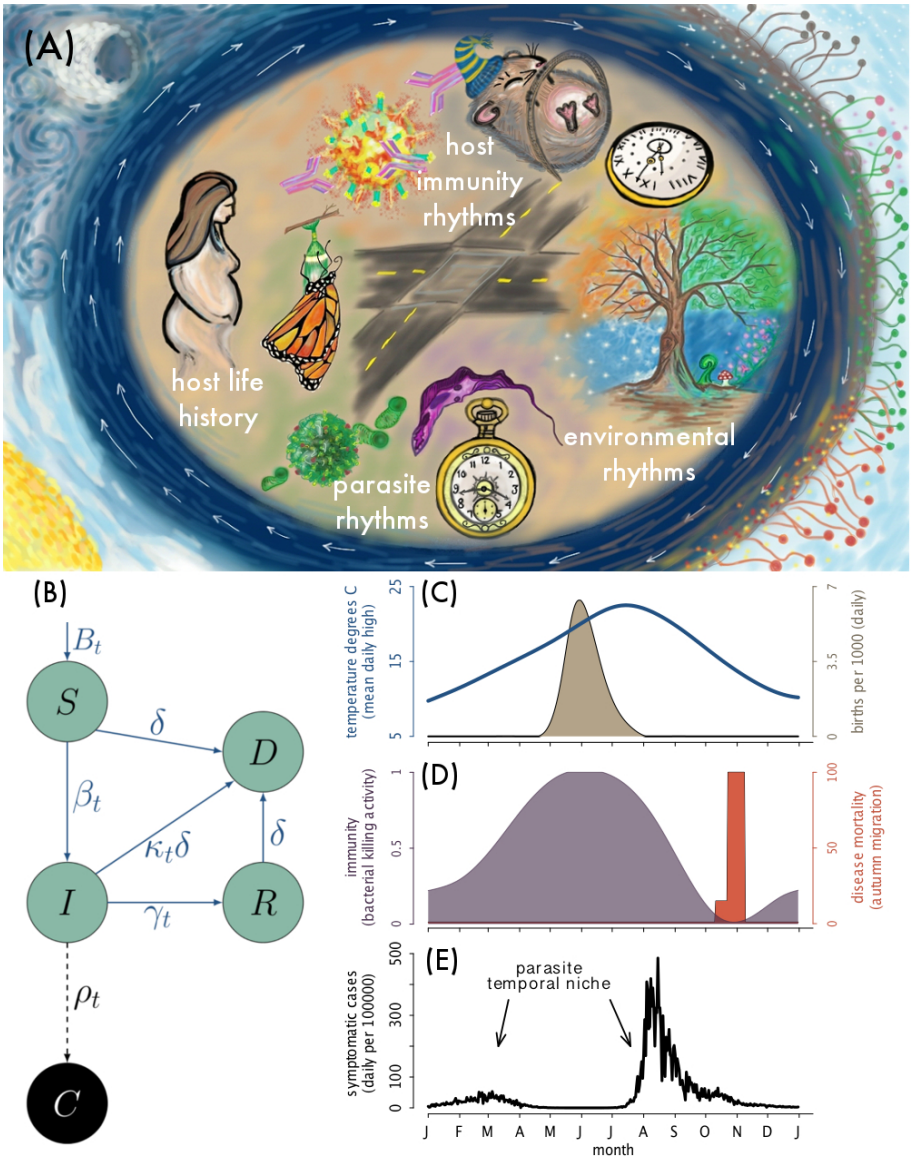

Figure 1: Rhythms and Temporal Niche. (A) The timing of host and parasite activities falls in the intersection of environmental rhythms, host life history, host immunity rhythms, and parasite rhythms. This intersection is embedded within geophysical rhythms, diel and annual cycles. (B) Biological and environmental rhythms can enter into epidemiological models in multiple ways. The schematic shows a Susceptible-Infected-Recovered model, SIR, with natural and disease-induced deaths, D. The model distinguishes between infections, I, and the subset of infections that are observed as symptomatic cases, C. The model is parameterized using the life history of Siberian stonechats. Four seasonal rhythms enter into the model (births, temperature, immunity, and migration). Host births, B_t, are seasonal. The transmission rate, β_t, is a function of (1) an environmental rhythm (i.e., temperature) that influences parasite transmissibility, and (2) the seasonal immune status of hosts. We assume seasonal immunity also influences the recovery rate, γ_t, and the probability of symptoms, ρ_t. We also assume infected individuals suffer disease-induced mortality, κ_t, associated with the autumn migration (i.e., migratory culling), which multiplies the (here constant) rate of natural mortality δ. (C) Annual fluctuations in temperature and birth seasonality in Siberian stonechats [95]. (D) Annual host immunity is based on bacterial killing activity [53], elevated mortality during autumn migration is inferred from natural migratory timing. (E) Incidence of symptomatic cases assuming: temperature has a positive correlation with transmission, bacterial killing activity reduces transmission, reduces the probability of symptoms, and increases the recovery rate. The four seasonal rhythms act collectively to determine the parasite's temporal niche, the time of year when the parasite is abundant and disease outbreaks occur.

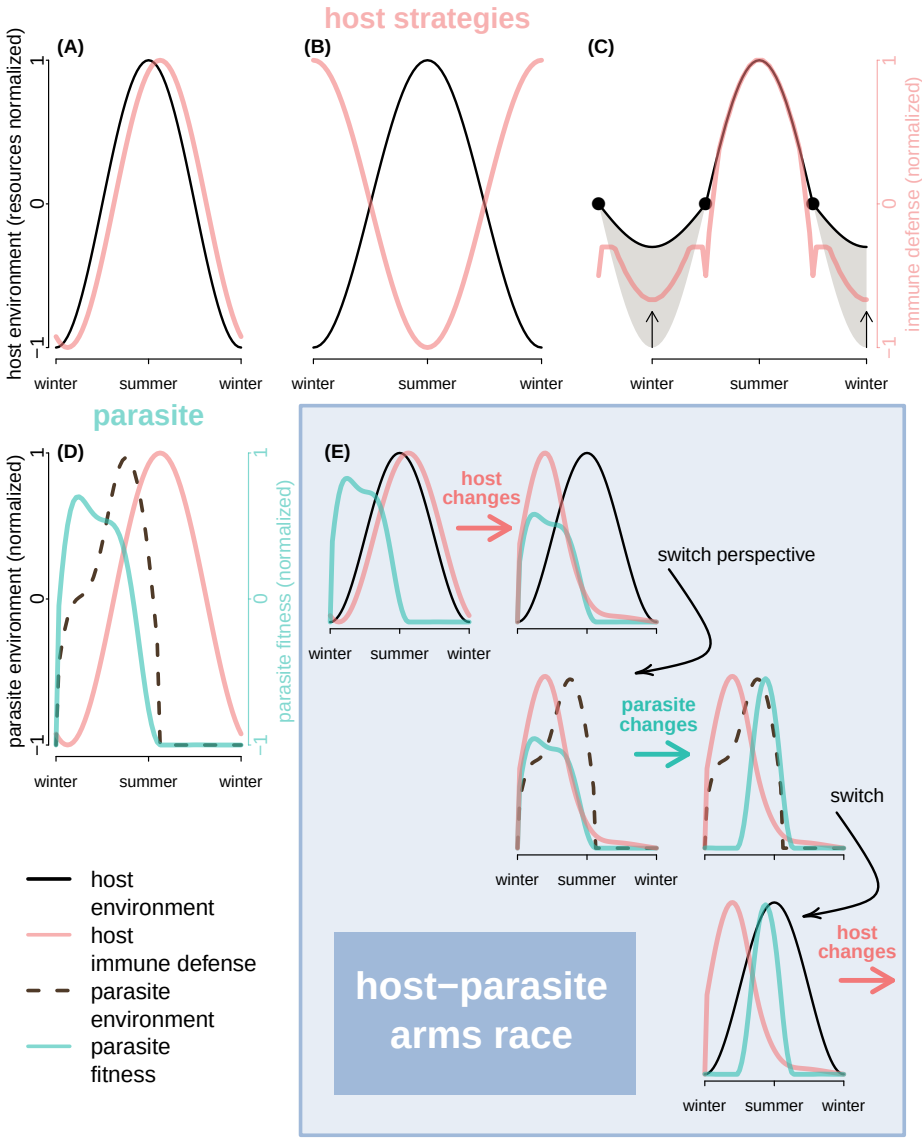

Figure 2: Conceptual model for investigating host-parasite contributions to rhythms in infectious disease. (A) Host immune defense is resource-driven and tracks the host's environmental conditions (i.e., host resource availability). (B) Host immune defense has an inverse relationship with environmental conditions; this could occur due to a trade-off against investment into reproduction during high resource availability. (C) Resource-driven immune defense in a migrating species that has reduced immune defense during migration. Migrations (indicated by black points) result in shallower environmental troughs since individuals migrate to regions with higher resource availability. For all scenarios, we consider immune defense to be resistance to the parasite in question, although we acknowledge that this simplifies the complexity of the immune system (e.g., independent immunomodulation of innate or adaptive immune parameters). For the resource-driven host immune defense strategy, in (D) we show seasonal parasite fitness shaped by both environmental conditions and seasonal host immune defense. Although host and parasite co-occur in the same physical environment, the environmental rhythms pertinent to the parasite need not be identical to the environmental rhythms pertinent to the host, which is why we distinguish host versus parasite environmental rhythms. (E) Arms race between host and parasite. For illustrative purposes, the arms race is initiated with resource-driven host immune defense and parasite seasonality. The host changes the seasonal timing of peak immune defense to coincide with peak parasite fitness. We then switch to the parasite perspective to consider the parasite's environment. In response to the new host seasonality, the parasite changes its timing of peak reproductive output. These cycles can continue, with both host and parasite seasonality shifting within the bounds of their respective environmental constraints.

Table 1: Rhythms in Hosts and Parasites. Diel (circadian) and annual (circannual/seasonal) rhythms in host immunity, parasite reproduction, and parasite release.

Type	Period	Host Trait or Parasite Description	Organism/ Species	Rhythm	Citation
Immunity	Diel	Macrophages (detection and restriction of parasite invasion)	Mice	8% of transcripts are circadian; autonomous macrophage circadian clock controls rhythm	[46]
Immunity	Diel	Natural Killer Cells (early defense against viruses and intracellular bacteria)	Humans	Circadian trafficking between the blood and organ compartments; inverse trafficking compared to T-lymphocytes	[105]
Immunity	Diel	Toll-like receptor 9 (evolutionarily conserved receptor that recognizes bacteria and viruses)	Mice	Expression and function controlled by circadian clock	[47]
Immunity	Diel	T-lymphocytes (surveillance for infected cells)	Humans	Cytokine production	[106, 107]
Immunity	Diel	Leukocytes	Humans	Abundance in the blood follows a circadian rhythm for neutrophils, lymphocytes, monocytes, and eosinophils	[108]
Immunity	Diel	Whole blood response to LPS stimulation	Humans	Cytokine and chemokine production is circadian in an environment free of time cues	[109]
Immunity	Diel	*Salmonella* colonization and host cytokine response to infection	Mice	Mice have a different immunological response to infection depending on whether infection challenge occurs at day or night; infection during the day results in more inflammation; this effect is due to clock-controlled gene expression	[49]
Immunity	Diel	Clock genes and pro-inflammatory cytokines in spleen; inflammatory response	Birds (captive)	mRNA of cytokines and clock genes are rhythmic under LD cycles and constant conditions; inflammation is rhythmic under LD cycles	[110]
Immunity	Diel	Cellular (PHA) and humoral immune response	Birds (captive)	PHA response and antibody production depend on time of challenge, but their peaks are phase-inversed	[17]
Immunity	Annual	Bacterial killing activity	Birds (captive), turtles (wild), humans	Lower bactericidal activity during migration, especially in autumn (birds); Higher bactericidal activity during breeding season (turtles); Higher bacterial killing by neutrophils in summer (humans)	[53, 111–113]
Immunity	Annual	Leukocytes	Birds (captive)	Annual cycles in several immune traits, no effect of Coccidia on annual cycle of immune measures	[114]
Immunity	Annual	Lysis	Birds (wild)	Lower ability of plasma to lyse foreign cells during migration and winter	[38]
Immunity	Annual	Sickness behavior in response to LPS	Birds (captive and wild), hamsters	Repression of sickness behavior during reproduction in summer (birds); repression of sickness behavior during winter (hamsters)	[39, 115]
Immunity	Annual	Acquired Immunity	Rabbits (wild)	Resistance against nematodes	[23]
Immunity	Annual	Spleen size (spleen is important for both innate and adaptive immunity)	Birds (wild)	Regression of spleen during migration	[116]

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Type	Period	Host Trait or Parasite Description	Organism/ Species	Rhythm	Citation
Immunity	Annual	Cytokine production stimulated by bacterial endotoxin	Humans, rats, hamsters	Seasonal differences in pro- and anti-inflammatory cytokine production (humans); Summertime photoperiod increases production of pro-inflammatory cytokine TNF-α and extends (rats) or elevates (hamsters) disease symptoms	[117–119]
Immunity	Annual	Vaccine response	Humans	Seasonal variation in symptoms following live influenza vaccine	[120]
Immunity	Annual	Intestinal immunity	Ground squirrels (captive)	Increase in intestinal leukocytes, pro- and anti-inflammatory cytokines during hibernation	[66]
Susceptibility	Diel	Bacterial burden, pathogenesis, and/or virulence of infection	Mice	Timing of infection can affect: (a) bacterial burden due to circadian variation in monocyte trafficking and/or gene expression at site of infection, (b) disease severity from sepsis due to circadian TLR9 expression, and (c) virulence	[45, 47, 49, 121, 122]
Susceptibility	Annual	Susceptibility to fungal growth	Bats (wild)	Hibernating bats have temperatures that match that of hibernacula, allowing explosive growth of WNS fungal pathogen *Pseudogymnoascus destructans*	[30]
Parasite reproduction	Diel	*Plasmodium* species (Malaria parasite) asexual reproduction	Various mammalian hosts	Parasite cohorts of millions of individuals synchronously burst from red blood cells at a particular time in LD cycle	[75]
Parasite reproduction	Annual	Microfilariae (heartworm)	Dogs	Strong seasonal rhythm in microfilaria abundance in dogs infected in the lab	[97]
Parasite development	Annual	Nematodes (parasitic roundworms)	Domestic mammals	Parasites engage in seasonal hypobiosis, arrested development within hosts that allows for persistence when environmental conditions are unfavorable for transmission between hosts	[96]
Parasite discharge	Diel	Coccidia	Birds (wild and captive)	Oocyte release is strictly circadian; although parasites are vulnerable to sun exposure the rhythmic pattern persists under continuous light during the Arctic summer	[21, 123]
Parasite discharge	Diel	*Echinostoma* (parasitic flatworms), Pinworms, *Schistosoma*	*Echinostoma* in mice, Pinworms and Schistosomes in humans	The release of *Echinostoma* eggs by hosts occurs during night when mice are active. Human pinworms migrate out of anus during the night to lay eggs. In contrast, *Schistosoma* eggs are discharged in urine during the day.	[74, 124]
Parasite discharge	Annual	Nematodes (roundworms)	Dall's Sheep (wild)	Seasonal variation in intensity of parasite larvae shed in feces	[125]

Continued on next page

Type	Period	Host Trait or Parasite Description	Organism/ Species	Rhythm	Citation
Parasite manipulation of host behavior	Diel	*Dicrocoelium* trematode	Ants (intermediate host)	In the evening infected ants affix themselves to the top of blades of grass and enter torpor until the next morning, allowing them to be eaten by grazing mammals (definitive hosts)	[90]
Parasite manipulation of host behavior	Diel	Manipulating fungus *Ophiocordyceps*	Ants	*Ophiocordyceps* manipulates host behavior and causes host death at characteristic times of day	[87]

365

366 Box 1. Circadian and Seasonal (circannual) Modulation of Host Immune 367 Defense.

368 **Circadian Immune Cycles.** In order for hosts to mount an immune response against an infecting
369 pathogen, the immune system must first detect the presence of the pathogen. One way that animals
370 detect pathogens is by immune surveillance for pathogen-associated molecular patterns (PAMPs), which
371 are shared across groups of pathogens. Host cells express pattern recognition receptors (PRRs) that
372 recognize PAMPs. Toll-Like Receptor 9 (TLR9) is an important PRR that can recognize both viruses
373 and bacteria, and is highly evolutionarily conserved. In 2012 Silver et al. discovered that the expression
374 of TLR9 by macrophages and B cells follows a circadian rhythm. Importantly, the circadian rhythm of
375 TLR9 has a significant effect on the immune response and disease severity because the rhythm of TLR9
376 also produces a rhythm in inflammatory cytokines. The implications were experimentally demonstrated
377 by inducing sepsis. Sepsis can occur during bacterial infections when a severe inflammatory immune
378 response causes damage to the host. Bacterial infection was induced in laboratory mice using a puncture
379 that allowed commensal bacteria to enter the body cavity from the intestine. Mice were entrained to a
380 light-dark cycle (LD 12:12 h), and infection was induced either at the midpoint of the light period or
381 of the dark period. Mice that were infected during the night, when the TLR9 inflammatory response
382 was elevated, had higher bacterial burdens, earlier mortality, and worse disease scores, hypothermia, and
383 tissue damage than mice that were infected during the day. This study demonstrated that the functional
384 response of the immune system varies according to a circadian rhythm, and this variation is biologically
385 relevant because it can have a significant effect on the dynamics of infection [47].

386 **Annual Immune Cycles.** Faced with stark annual fluctuations in environmental conditions and
387 resources, many avian and mammalian species partition life history events such as reproduction, growth,
388 and hibernation into distinct times of year, and their immune system also undergoes seasonal changes.
389 Versteegh et al. 2014 set out to investigate whether annual variation in immunity is due to seasonal
390 adjustments directly driven by environmental or physiological conditions, or originates from a genetically-
391 based circannual rhythm that allows organisms to prepare for changes in the environment. They looked at
392 5 different immune measures, including bactericidal competence of whole blood as a proxy for functional
393 implications.

394 To determine whether seasonal immunity is a genetically encoded circannual rhythm, genetically
395 distinct subgroups of a widespread songbird, the stonechat (Saxicola torquata), were bred and raised
396 in a common garden experiment. The subgroups chosen for this experiment differ in their seasonal life

history and traits. They included a (i) long-distance migrant, (ii) short-distance migrant, and (iii) a non-migrant, along with hybrids. The prediction was that if seasonal immunity is a direct response to seasonal environmental conditions and energy demands, then by raising birds in an environment where (a) they have ample food, (b) they are not allowed to migrate or breed, and (c) the only fluctuation to which they are exposed is changing day length, their annual rhythms in immunity would be lost.

The authors found that not only did the annual rhythm in immunity persist under these controlled conditions but also that the subgroups and hybrids of the birds showed specific patterns. The long-distance migrants displayed seasonality in 4 immunity parameters, which included bacterial killing ability (Figure 1D). The short-distance migrants displayed seasonality in only 3 immunity parameters, and the non-migrants displayed seasonality in only 2 parameters. Furthermore, the amplitude of the annual fluctuation was greatest in the long-distance migrants. The inheritance of the rhythm in hemolysis (the ability of antibodies and their compliment system to lyse foreign cells) was also quite striking. Both the long- and short-distance migrants showed reduced hemolysis during the time of the natural autumn migration. The reduction in hemolysis in the long-distance migrants was much more extreme than that of the short-distance migrant, and intermediate in F1- hybrids. Together, this work demonstrates that an inherited, biological clock controls seasonal immunity in stonechats, and these rhythms vary across groups that differ in their seasonal life history [53]. Related avian studies generally confirm annual cycles in immune parameters, and although species differ, there is a common tendency for greater seasonal immunomodulation with increasing migratory lifestyle.

Outstanding Questions.

1. Are rhythms in the immune system adaptive for fighting infection?
2. Are parasite rhythms adaptive for dealing with host rhythms or environmental conditions?
3. Are observed parasite rhythms truly endogenous?
4. If parasite rhythms are endogenous, are they entrained by host rhythms?
5. Are host circannual rhythms in immunity an adaptive response to (a) seasonal parasite exposure or (b) resource limitations and life history trade-offs?

Glossary.

Adaptive immune system - cells of the adaptive immune system include B cells and T cells. The initiation of the adaptive immune response occurs after the initiation of the innate immune response. Receptors of adaptive immune cells require genetic recombination and alteration to generate, resulting in antigen specificity and immunological memory [126, 127].

Annual cycle - cycle with a length of approximately 1 year, with phases occurring consistently at a particular time every year, on an annual/seasonal basis

Circadian - cycle that occurs with an approximate 24-hour period, used in reference to endogenous rhythms

Circannual - cycle that occurs with a period of approximately 1 year, used in reference to endogenous rhythms

Diel cycle - cycle with a length of approximately 1 day, with phases occurring consistently at a particular time during the day-night cycle

Immune defense - immune defense includes (1) resistance against the establishment of infection and the reproduction of parasites, and (2) parasite tolerance, in which the host mitigates the pathological consequences of infection, but tolerates infection

Innate immune system - cells of the innate immune system include macrophages and neutrophils. Innate immune cells are immediate responders to infection. A fundamental distinction between innate and adaptive immune cells is that innate immune cell receptors responsible for immune recognition are encoded in the germline; whereas, receptors of adaptive immune cells require genetic recombination and alteration to be generated. It was previously thought that the innate immune response is not parasite-specific and lacks memory, but that characterization is now considered incorrect [127].

LD-cycle - cycle in which light and darkness alternate, and each last for a given duration, for example in LD 12:12 h, light and darkness both last for 12 hours

LPS - Lipopolysaccharide is a component of the outer membrane of Gram-negative bacteria that is used in experiments to elicit an anti-bacterial immune response

Macroparasites - parasites that are large and typically metazoans (e.g., helminths)

Microparasites - parasites that are small and often unicellular (e.g., pathogenic viruses, bacteria, and fungi)

Macrophage - phagocytes, often referred to as big eaters because they engulf invading bacteria and are responsible for clearance of dead (apoptotic) cells. Macrophages are one of the cells responsible for detection and restriction of parasite invasion.

Parasite Resistance - The ability of the host's immune response to prevent infection from establishing or limit parasite replication. Parasite resistance has a negative impact on parasite fitness [128].

Parasite Tolerance - The ability of the host to mitigate the pathological consequences of infection, rather than mitigate infection itself. Parasite tolerance does not necessarily have a negative impact on parasite fitness [128].

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