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Environmental refuges from disease in host–parasite interactions under global change

Alena S. Gsell[1,2] | **Arjen Biere**[3] | **Wietse de Boer**[4,5] | **Irene de Bruijn**[4,6] | **Götz Eichhorn**[7,8] | **Thijs Frenken**[1,9] | **Stefan Geisen**[3,10] | **Henk van der Jeugd**[7,8] | **Kyle Mason-Jones**[3] | **Annelein Meisner**[4,11,12] | **Madhav P. Thakur**[3,13] | **Ellen van Donk**[1] | **Mark P. Zwart**[4] | **Dedmer B. Van de Waal**[1,14]

[1]Department of Aquatic Ecology, Netherlands Institute of Ecology (NIOO-KNAW), Wageningen, The Netherlands

[2]Ecosystem Research Department, Leibniz Institute of Freshwater Ecology and Inland Fisheries (IGB), Berlin, Germany

[3]Department of Terrestrial Ecology, Netherlands Institute of Ecology (NIOO-KNAW), Wageningen, The Netherlands

[4]Department of Microbial Ecology, Netherlands Institute of Ecology (NIOO-KNAW), Wageningen, The Netherlands

[5]Soil Biology Group, Wageningen University & Research, Wageningen, The Netherlands

[6]Koppert, Berkel en Rodenrijs, The Netherlands

[7]Department of Animal Ecology, Netherlands Institute of Ecology (NIOO-KNAW), Wageningen, The Netherlands

[8]Centre for Avian Migration and Demography, Netherlands Institute of Ecology (NIOO-KNAW), Wageningen, The Netherlands

[9]Great Lakes Institute for Environmental Research (GLIER), University of Windsor, Windsor, Ontario, Canada

[10]Department of Nematology, Wageningen University and Research, Wageningen, The Netherlands

[11]Wageningen University & Research, Wageningen Research, Wageningen, The Netherlands

[12]Microbial Ecology Group, Department of Biology, Lund University, Lund, Sweden

[13]Terrestrial Ecology Group, Institute of Ecology and Evolution, University of Bern, Bern, Switzerland

[14]Department of Freshwater and Marine Ecology, Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
Alena S. Gsell
Email: a.gsell@nioo.knaw.nl

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Abstract

The physiological performance of organisms depends on their environmental context, resulting in performance–response curves along environmental gradients. Parasite performance–response curves are generally expected to be broader than those of their hosts due to shorter generation times and hence faster adaptation. However, certain environmental conditions may limit parasite performance more than that of the host, thereby providing an environmental refuge from disease. Thermal disease refuges have been extensively studied in response to climate warming, but other environmental factors may also provide environmental disease refuges which, in turn, respond to global change. Here, we (1) showcase laboratory and natural examples of refuges from parasites along various environmental gradients, and (2) provide

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hypotheses on how global environmental change may affect these refuges. We strive to synthesize knowledge on potential environmental disease refuges along different environmental gradients including salinity and nutrients, in both natural and food-production systems. Although scaling up from single host–parasite relationships along one environmental gradient to their interaction outcome in the full complexity of natural environments remains difficult, integrating host and parasite performance–response can serve to formulate testable hypotheses about the variability in parasitism outcomes and the occurrence of environmental disease refuges under current and future environmental conditions.

KEYWORDS
ectotherm, mismatch, nutrients, parasitism, performance–response curves, reaction norms, salinity, temperature, tolerance range

INTRODUCTION

Phantoms, castrators, and body snatchers; it is not surprising that parasites have reputation issues. Here, we define parasites broadly as organisms that live in or on another organism, derive all nutrition at the cost of their host, and therefore clearly are detrimental to the performance of their host. However, through their impacts on individual hosts, parasites affect all levels of organization, including populations, communities, and entire ecosystems. Parasites have been shown to increase food-web complexity through added diversity and network connectance (Lafferty et al., 2006), and to modify community dynamics by altering species interactions (Hatcher & Dunn, 2011). Moreover, parasites can increase community diversity (e.g., kill-the-winner hypothesis; Thingstad, 2000) as well as genetic diversity of host populations (e.g., Red Queen hypothesis; Brockhurst et al., 2014; Gsell, de Senerpont Domis, Verhoeven, et al., 2013) and hence play a key role in evolutionary and eco-evolutionary dynamics (Barrett & Heil, 2012). Parasites force hosts to evolve elaborate and costly defense mechanisms, such as their immune system, at the expense of other functions, and this trade-off is an important driver in evolution (Sheldon & Verhulst, 1996). The outcome of parasite infections often seems arbitrary and remains difficult to predict, particularly so under seasonal and global change variations in environmental conditions.

All organisms experience variation in their abiotic environment, both seasonal fluctuations in, for example, temperature or precipitation, and variation resulting from global environmental change (Altizer et al., 2013). Such environmental variation not only affects hosts or parasites directly but can also alter the intensity and outcome of their interaction (McNew, 1960; Wolinska & King, 2009). Moreover, host–parasite interactions are not just influenced by one single environmental factor at a time, but rather by several, often interacting, environmental factors. Understanding the impacts of environmental variation on parasites in natural systems therefore is not trivial, as it involves a complex interplay between the effects of these changes on parasites, their hosts, and other food-web components. One way to address this complexity is gaining an understanding of how individual genotypes or populations respond to variation in a single environmental variable, which subsequently can serve as a null model when studying responses of host–parasite interactions in natural and therefore more complex systems. Aware of the shortcomings of this simplistic approach, we here provide several examples from laboratory experiments and natural systems showing how mismatches in host and parasite performance curves based on gradients of a single environmental variable might be used to explain the outcome of host and parasite interactions.

Variations in environmental gradients elicit the expression of different phenotypes in organisms, resulting in reaction norms at the genotype level, or performance–response curves at the population level (Angilletta Jr, 2006; Sultan & Stearns, 2005). Reaction norms and performance–response curves typically show unimodal patterns with an optimum at which a given trait reaches a maximum, and with a tolerance range delimited by a lower and an upper critical limit at which the trait value becomes zero due to inactivity (for example resting or dormancy stages) or death (Figure 1A). The width and shape of these curves often differ depending on the performance trait under observation (Vale & Little, 2009) and is determined by the sensitivity of physiological processes to environmental conditions, such as temperature-driven changes in metabolic rates (Brown et al., 2004; Molnár et al., 2017). Moreover, the shape of performance–response curves itself is subject to

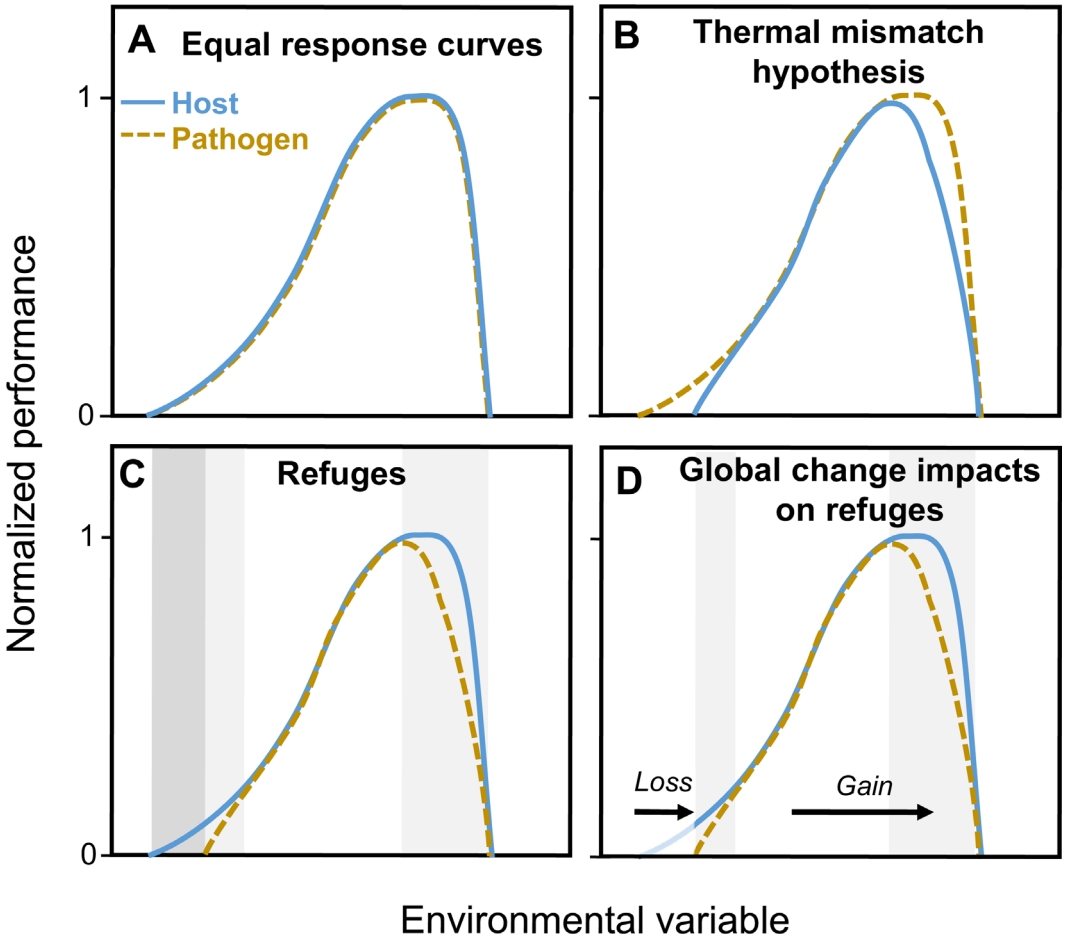

FIGURE 1 Conceptual diagram of absence or presence of hypothetical disease refuges, and the potential impacts of global environmental change on the occurrence and position of such refuges using host and parasite performance normalized to their own maximum value. (A) If tolerance range and shape of performance–response curves are equal for host (solid blue lines) and parasite (dashed orange lines), then the host can physiologically be infected across its own entire environmental tolerance range and no definite disease refuge exists. (B) The thermal-mismatch hypothesis proposes that hosts become more susceptible to infection as they move farther from their own thermal optimum (Cohen et al., 2017) and no disease refuges exist. (C) Disease-reduced environmental refuges (light gray) occur when the host outperforms the parasite, while disease-free environmental refuges (dark gray) occur when the tolerance range of the host is broader than that of the parasite. (D) Global environmental change may lead to shifts in refuges, for example due to loss of low temperatures in warmer winters (loss of refuge) or a shift toward warmer mean temperatures (vertical black dashed lines) in warmer summers (gain of refuge).

evolutionary change in response to abiotic stress (Rohr et al., 2018) or interacting organisms including parasites (Agrawal, 2001; González et al., 2020).

Free-living organisms, such as most hosts but also many parasite transmission stages, are directly exposed to abiotic environments, and their performance–response curves are generally evaluated individually. Attached parasites differ here, as they experience both the host environment as well as the abiotic environment. The latter can either be experienced directly (e.g., in free-living transmission stages or externally attached ectoparasites) or indirectly through host-mediated effects (e.g., in endoparasites). Their observed performance–response curves are therefore a composite function of host and parasite physiology, and hence of direct and host-mediated effects (Vale & Little, 2009; Van den Wyngaert et al., 2014). In vector-borne and multihost parasites, the performance–response curve can additionally be modified by indirect vector- or various host-mediated effects. The outcome of parasite infections, therefore, relies on the performance–response curves of the parasite, one or multiple hosts and potential parasite vectors. If the tolerance range of a parasite is equal to that of a host, the host can be infected across its entire environmental tolerance range if it encounters a parasite (Figure 1A). However, other factors, such as host densities below parasite transmission thresholds, will, in real systems, lower encounter rates, hamper parasite maintenance in the host population, and thereby also change the observed pattern.

Many species differ in their tolerance range and sensitivity to environmental factors, affecting the outcome of their interaction with other species, including those with parasites (Stenseth & Mysterud, 2002; Wolinska & King, 2009). The thermal-mismatch hypothesis postulates that hosts should be more susceptible to parasites when temperature conditions shift away from the thermal optimum of the host (Figure 1B; for details, see Cohen et al., 2017). This is based on the observation that many ectotherm parasites have broader thermal tolerance ranges than their hosts, following the hypothesis that parasites, given their generally smaller body size, have shorter generation times and therefore can adapt faster to change than their larger-bodied hosts (Cohen et al., 2017). Endotherm hosts, however, have been shown to withstand more extreme climates than either their parasites or disease transmission vectors (e.g., Paaijmans et al., 2009) which elicits a different response curve pattern. Whether parasites of ectotherms can exploit their theoretically broader tolerance range depends on their ability to survive (temporally) without a host or to infect several species, that is, facultative and generalist parasites, and parasites with free-living life stages or resting stages. In contrast with faster adaptation rates in smaller organisms, the acclimatization capacity (i.e., how much the tolerance range can shift or change) increases with body size, as recently shown in a meta-analysis on individual thermal optima and tolerances (Rohr et al., 2018). Such a higher acclimatization capacity may allow ectotherm hosts (as generally larger-bodied organisms) to exploit a broader thermal tolerance range than their parasites. Indeed, in some cases, thermal windows of opportunity for disease-free growth have been observed in both natural and laboratory environments, which suggests that ectotherm hosts can exhibit a broader or a shifted tolerance range relative to their parasite (Figure 1C; Altizer et al., 2013; González et al., 2020; Thomas & Blanford, 2003). In addition to seasonal variation in environmental conditions, global environmental change modifies long-term environmental conditions, altering the mean and variance in temperature, nutrient load, salinity, and water availability (IPCC, 2013). Such changes may shift conditions into or out of a refuge for a given host–parasite system. The loss of cold winters with lake ice cover (Sharma et al., 2019), for instance, may lead to the loss of a low-temperature refuge at a given location (Figure 1D) as the conditions for the refuge simply do not occur anymore at that specific location. These conditions may still occur elsewhere by shifting in latitudinal space, in elevation/depth or even in small-scale differences in microhabitats (e.g., Ben-Horin et al., 2013; Dawson et al., 2005). Similarly, longer-lasting and warmer summers may lead to the gain of a warm-temperature refuge (Figure 1D) if the parasite has a lower maximum critical thermal limit than its host (Altizer et al., 2013). While temperature reaction norms typically show unimodal, left-skewed curves, other environmental factors may elicit different reaction norm shapes. However, all performance–response curves are bound by lower and upper limits, which can give rise to mismatches between any two performance–response curves, and thereby potential windows of opportunity for disease-free host growth. For ease of illustration, we plotted the potential occurrence, gains, and losses of environmental disease refuges due to changes in the congruence of host and parasite response curves using a generic unimodal curve focusing on hypothesized shifts in host and parasite ranges, and not in their optima performance (i.e., the curves depict relative responses, normalized to the individual host or parasite optima; Figure 1).

Here, we define environmental disease refuges as a set of environmental conditions that potentially provide a window of opportunity for hosts, where parasites either cannot withstand the prevailing conditions (i.e., disease-free refuge), or show lower performance than their host (i.e., disease-reduced refuge). Thus, even though a disease refuge will likely occur close to the tolerance limits of the host (and hence be suboptimal for the host, e.g., Ben-Horin et al., 2013), it may still be beneficial for the survival and reproduction of the host if its parasite cannot withstand these conditions or shows a relatively stronger decline in performance. It remains unclear how commonly these environmental refuges driven by single environmental variables occur, whether they also exist for environmental variables other than temperature, and to what extent we can use host and parasite performance curves as null models to understand host–parasite interactions in natural systems in which hosts and parasites are exposed to multiple, interacting environmental factors. We showcase several field observations and laboratory examples for disease refuges in ectotherm host–parasite systems along temperature gradients, and afterward explore evidence of potential refuges for other environmental variables. Subsequently, we discuss how global environmental change may lead to gains or losses of disease refuges, and we highlight the potential role of evolutionary adaptation for the presence or absence of refuges. Because our single environmental reaction norm-based approach is reductionistic, we last discuss how host and parasite performance curves can be used as null models to predict how environmental changes will affect host–parasite interactions in complex natural systems.

GAINS AND LOSSES IN THERMAL REFUGES

Temperature has profound effects on all physiological processes in organisms and affects performance traits

such as growth rates, metabolism or infectivity (Brown et al., 2004; Dell et al., 2011; Thomas & Blanford, 2003). Differences in thermal performance curves between organisms may alter ecological interactions, including competition, grazing, and predation (Dell et al., 2014; Gilbert et al., 2014; Kordas et al., 2011). Mismatches in thermal performance curves of hosts and their parasites may also explain patterns in disease occurrence and severity (Altizer et al., 2013; Nowakowski et al., 2016; Thomas & Blanford, 2003) as has been described by the thermal-mismatch hypothesis (Cohen et al., 2017). Global environmental change includes an overall increase in temperature means and extremes as well as increasing variability in most regions of the world (IPCC, 2013). The effects of warming on parasite transmission potential and outcome of infections are variable (Lafferty & Mordecai, 2016; Mordecai et al., 2019) with observed gains and losses of disease refuges (Altizer et al., 2013) hindering effective prediction of the effect of climate warming on parasitism outcomes.

Climate warming may lead to the loss or gain of disease refuges when assuming no adaptation of the host and parasite. Disease refuges may be lost if the underlying environmental conditions cease to occur, as with the predicted loss of cold winters (Sharma et al., 2019) and therefore of cold-temperature refuges for ectotherm hosts. This has been described for several host–parasite systems (Table 1). In a diatom host–fungal parasite system, for example, the loss of cold winters and thereby ice cover of Lake Maarsseveen (the Netherlands) has led to

TABLE 1 Examples of refuges along environmental gradients in aquatic (freshwater, F; marine, M) and terrestrial habitats.

Environmental variable	Habitat	Host group	Host species	Parasite type	Parasite species	Refuge location	References
Temperature	Aquatic^{F}	Phytoplankton	*Asterionella formosa*	Fungus	*Zygorhizidium planktonicum*	Low	Ibelings et al. (2011)
	Aquatic^{F}	Phytoplankton	*Planktothrix* sp.	Fungus	*Rhizophydium megarrhizum*	Low	Kyle et al. (2015)
	Aquatic^{F}	Fish	*Cyprinus carpio koi*	Virus	KHV	Low	Gilad et al. (2003)
	Aquatic^{M}	Phytoplankton	*Micromonas* sp.	Virus	MicV	High	Demory et al. (2017)
	Aquatic^{M}	Crustacean	*Eurypanopeus depressus*	Crustacean	*Loxothylacus panopaei*	High	Gehman et al. (2018)
Salinity	Aquatic^{F}	Fish	*Cyprinodon tularosa*	Trematode	N/A	High	Rogowski and Stockwell (2006)
	Aquatic^{M}	Mollusk	*Crassostrea virginica*	Alveolate	*Perkinsus marinus*	Low	Levinton et al. (2011)
	Aquatic^{M}	Crustacean	*Rhithropanopeus harrisii*	Crustacean	*Loxothylacus panopaei*	Low	Reisser and Forward (1991)
	Aquatic^{M}	Fish	*Salmo trutta*, *Rutilus rutilus*	Oomycete	*Saprolegnia parasitica*	High	Harrison and Jones (1971)
	Terrestrial	Angiosperm	*Hesperolinon californicum*	Fungus	*Melampsora lini*	High	Springer et al. (2007)
	Terrestrial	Amphibia	*Litoria aurea*	Fungus	*Batrachochytrium dendrobatidis*	Low	Stockwell et al. (2015)
Nutrients	Aquatic^{F}	Phytoplankton	*Phormidium* sp.	Virus	Cyanophage PP	Low (P)	Cheng et al. (2019)
	Aquatic^{F}	Phytoplankton	*Planktothrix rubescens*	Fungus	*Rhizophydium megarrhizum*	Low (N)	Frenken et al. (2017a)
	Aquatic^{M}	Phytoplankton	*Micromonas pusilla*, *Phaeocystis globosa*	Virus	MpV-08T, PgV-07T	Low (N and P)	Maat and Brussaard (2016)

Note: Refuge location indicates where the refuge is located on the environmental gradient (i.e., at low or high temperature, salinity, or nutrients nitrogen [N] and phosphorus [P]).

the subsequent loss of the cold-temperature refuge, a permanent low infection prevalence and an overall lower host density after infections by the fungal parasite *Zygorhizidium planktonicum* (Figure 2A; Gsell, de Senerpont Domis, Van Donk, & Ibelings, 2013; Ibelings et al., 2011). Comparably, a cyanobacterium host profited

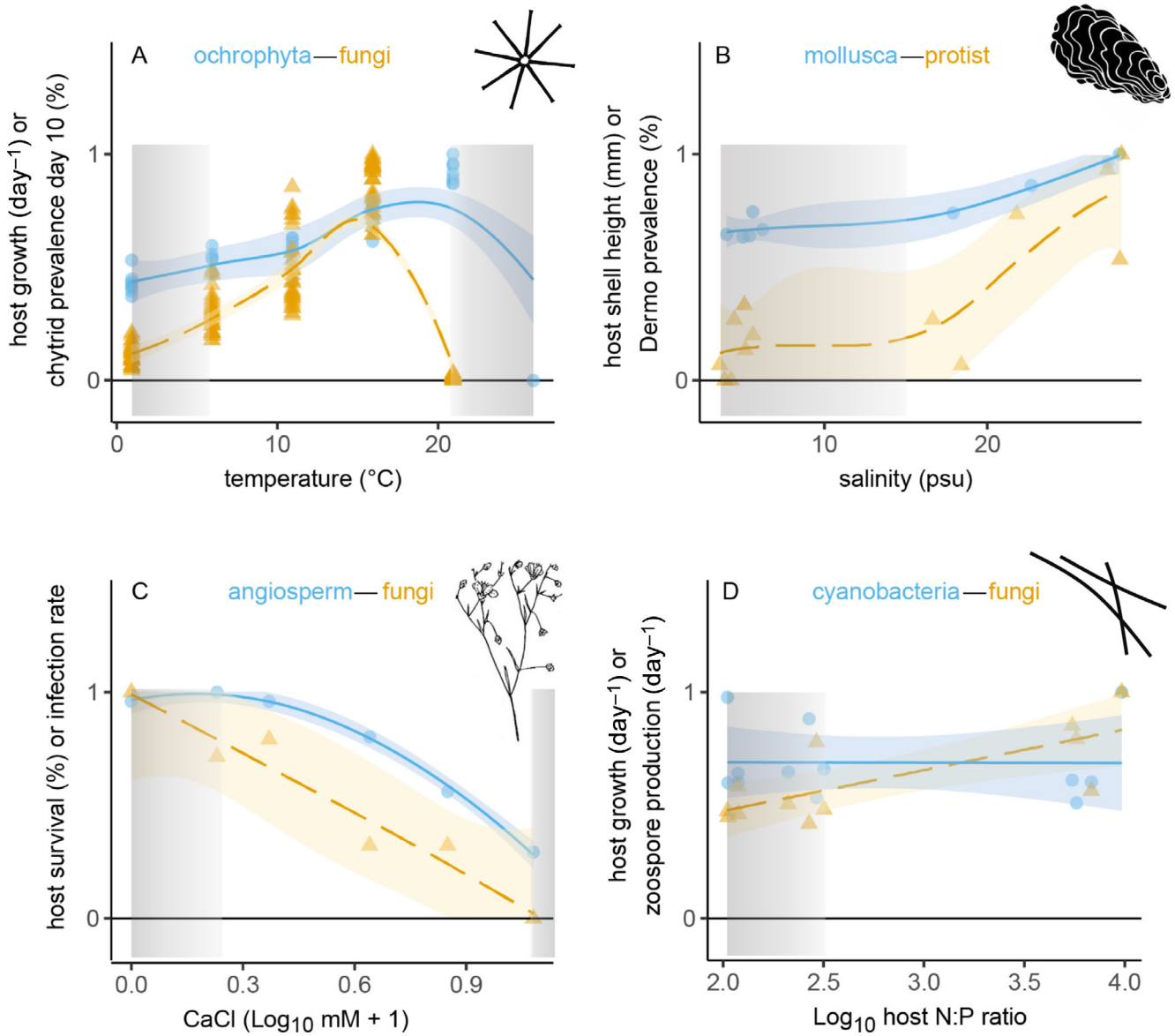

FIGURE 2 Examples of environmental performance–response curves with host (blue solid lines) and pathogen response (orange dashed lines). When not available from a repository, data were extracted from published figures using WebPlotDigitizer v.4.1, and values for each performance–response curve were normalized to their own maximum value. Performance–response curves are shown as loess-smoothed conditional means with 95% confidence intervals to aid pattern recognition; no underlying curve shapes were assumed. The locations of disease refuges are indicated by gradient bars, the darker grays indicating disease-free refuges. (A) A cold- and warm-temperature disease refuge for a diatom host (*Asterionella formosa*) from infection by a chytrid fungus parasite (*Zygorhizidium planktonicum*) as the parasite formed noninfective resting spores below 3°C and died above 18°C, here measured as host growth rate (day^{-1}) and chytrid infection prevalence at day 10 (Gsell, de Senerpont Domis, Van Donk, & Ibelings, 2013, data from Gsell et al., 2022). (B) A low-salinity refuge for the mollusk host (*Crassostrea virginica*) from infection by a protist parasite (*Perkinsus marinus* [Dermo]) as measured in host growth (shell height in millimeters) and the proportion of Dermo infection prevalence (Levinton et al., 2011). (C) A potential high calcium chloride refuge for the dwarf flax host (*Hesperolinon californicum*) from its mildew parasite (*Melampsora lini*) as measured in host proportion of survival until mildew exposure and proportion parasite infection prevalence (Springer et al., 2007). (D) A low nitrogen-to-phosphorus ratio refuge for the freshwater cyanobacteria host (*Planktothrix rubescens*) from infection by its chytrid parasite (*Rhizophydium megarrhizum*) as measured in host growth rate and parasite zoospore production rate (both day^{-1}) across host nitrogen-to-phosphorus ratio (Frenken et al., 2017a, data from Frenken et al., 2017b). psu, practical salinity unit.

from the metalimnion (the layer separating upper, warm-water and lower, cold-water layers) as a cold-temperature refuge from its fungal parasite *Rhizophydium megarrhizum* (Kyle et al., 2015). Under climate warming, these cold-water layers in lakes have already become warmer and shallower, which may lead to a decline in the occurrence of this cold-temperature refuge and thus promote infections in cyanobacteria. Analogously, the increase in summer duration due to global warming may lead to shorter periods of cool-water refuges, as was shown for carp hosts that became more sensitive to infections by a herpes virus during extended warm summer periods (Gilad et al., 2003). In temperate regions, climate warming can also cause a gain in high-temperature refuges when temperature conditions exceeding the parasite's upper critical limit become more frequent or long-lasting (Table 1; Altizer et al., 2013; Demory et al., 2017; Gehman et al., 2018). In parasitic diseases with latency periods or with resting stages, however, this pattern may differ as the temperature at infection may not equal the temperature at which the disease shows clinical symptoms (e.g., Ben-Horin et al., 2013).

Thermal conditions vary not only across time, but also across local elevational and geographic spatial scales. Hence, hosts can choose to move toward places with conditions that are beneficial to them and may provide a thermal disease refuge. The small-scale movement to warmer sites can allow ectotherms to increase their body temperature to reduce the health impact of parasites (Elliot et al., 2002). Such behavioral fever has been documented in many different ectotherms, including invertebrates and vertebrates (Covert & Reynolds, 1977; Elliot et al., 2002; Sauer et al., 2019). For example, insects infected with parasites may prefer higher temperatures than noninfected individuals, coinciding with increased immune responses partly through decreased expression costs (Catalán et al., 2012). Moving to places with higher solar radiation can increase the body temperature of infected hosts and leads to both, faster maturation of the host and parasite kill-off. This has been observed in grasshoppers when infected by the fungal pathogen *Entomophaga grylli* (Carruthers et al., 1992). Some insects such as the grasshopper *Chorthippus parallelus*, can actively thermoregulate and use behavioral fever in response to different types of pathogens which differ in their thermal susceptibility (Springate & Thomas, 2005). Humans themselves have taken advantage of refuges from parasites and their vectors over spatial environmental gradients for the benefit of their crops and their own health. In the tropics, humans have long recognized the protective effect of elevation against diseases, including human malaria (Lindsay & Martens, 1998), an example of endotherm hosts having a broader thermal tolerance range than their parasite or disease transmission vector. The development of *Plasmodium* and its ectothermic insect vectors depends on specific climatic conditions, most notably temperature and rainfall, which vary along latitudinal and elevational clines, and which are now changing due to human influences. It is feared that climate change will increasingly allow malaria and other diseases to invade tropical highland populations that have no or little immunity against malaria and therefore suffer higher morbidity compared with lowland populations that have been in regular contact with the pathogen (Siraj et al., 2014). Similarly, based on forecasted changes in climate and land use, Hawaiian honeycreepers stand to lose their refuge from avian malaria and its mosquito vector (Benning et al., 2002) as cooler habitats at higher altitudes restricting parasite transmission are disappearing (IPCC, 2013). At the same time, management actions interact with these climate-driven shifts in disease outbreaks, and risks may be mitigated through improved disease preparedness (Dye-Braumuller & Kanyangarara, 2021).

GAINS AND LOSSES IN OTHER ENVIRONMENTAL REFUGES

Thermal disease refuges have received considerable attention in the literature (e.g., Altizer et al., 2013; Cohen et al., 2017; Gilbert et al., 2014; Molnár et al., 2013; Nowakowski et al., 2016; Thomas & Blanford, 2003). However, other environmental factors can also show considerable gradients and may therefore allow similar mismatches in host and parasite tolerance ranges. In aquatic systems, for instance, nutrient concentrations often shift from replete in spring to depleted in summer (Sommer et al., 1986), while estuarine and terrestrial systems can experience substantial changes in salinity due to changes in seasonal precipitation patterns (Cloern et al., 2017; Nedjimi, 2012). Analogously to thermal refuges, mismatches in performance–response curves of hosts and parasites along gradients of salinity or absolute as well as relative nutrient availability (i.e., nutrient ratios) may also alter the outcome of host–parasite interactions and govern the occurrence of refuges (Figure 2B,C,D; Table 1). The exact shape of these curves may differ from the typical left-skewed optimum curve of thermal reaction norms.

Mismatches in host and parasite performance–response curves along salinity gradients have been documented in several cases. For example, oysters are less infected by a protist parasite under low-salinity conditions (Figure 2B; Levinton et al., 2011), while dwarf flax suffers less from mildew infections under high-salinity (i.e., calcium chloride) conditions (Figure 2C; Springer et al., 2007). Salinity is expected to be affected by global environmental change, although the direction of change strongly depends on local

and regional conditions (IPCC, 2013). Climate change may lead to higher salinities in oceanic regions where evaporation dominates, while it may also result in reduced salinities in regions where precipitation dominates (IPCC, 2013). With projected increases in precipitation for the United States northeast coast and stronger freshening events, estuarine areas with (temporarily) low salinity are expected to increase and may thereby provide oysters with low-salinity refuges and support oyster production (Levinton et al., 2011), although extreme freshening events, in turn, also increase host mortality independent of disease (Du et al., 2021). In contrast, sea level rise may lead to increased salinity levels in estuaries, as was projected for the Chesapeake Bay (Hilton et al., 2008), which consequently may lead to enhanced infections and threaten oyster production. Arid and semiarid regions are expected to experience declines in precipitation with extended periods of droughts, which may lead to soil salinization and subsequently increased salinity stress in plants (Ahmad et al., 2013), in turn enhancing infections (Chojak-Koźniewska et al., 2018). In contrast, drought may also reduce parasite invasion and/or performance, particularly for fungal and fungal-like parasites that rely on wet conditions for transmission (Ramegowda & Senthil-Kumar, 2015). High-salinity refuges are shown for various host–parasite systems (Table 1; Harrison & Jones, 1971; Reisser & Forward, 1991; Rogowski & Stockwell, 2006; Stockwell et al., 2015). Whether climate-driven changes in salinity will lead to losses or gains of these refuges will strongly depend on the specific shape of host and parasite performance–response curves, but also on the complexity of the system and the occurrence of other interactions that may counteract the potential benefits of an environmental disease refuge. However, whatever environmental disease refuges are gained or lost, they are likely to occur at the edges of the tolerance ranges of hosts and parasites.

Mismatches in host and parasite performance–response curves along gradients of absolute or relative nutrient concentrations may also lead to refuges from disease at either the high or the low end of the host tolerance range. Nutrient concentrations in receiving waters, for instance, have generally been increasing due to the continued use of agricultural fertilizers, atmospheric nitrogen deposition, and run-off caused by extreme precipitation events (Zhang et al., 2009). Such anthropogenic eutrophication can have contrasting differing effects on the occurrence of parasite infections in receiving waters (Budria, 2017). It can increase host population densities and the nutritional condition of hosts and thereby benefit parasite infections (McKenzie & Townsend, 2007). However, it can also alter primary producer community composition or elicit ecosystem responses such as oxygen depletion, indirectly leading to a reduction in parasite performance (Budria, 2017). In soils, the role of nutrient enrichment on the occurrence of parasite infections is equally complex. For instance, nitrogen fertilization generally increases the disease severity of obligate plant pathogens but decreases that of facultative ones (Dordas, 2008). Just as for salinity, global change effects on nutrient concentrations will differ locally and regionally, depending on land use, precipitation, and deposition patterns (IPCC, 2013). Under climate warming, nutrient concentrations in the open oceans may decrease because of enhanced thermal stratification that will limit nutrient inputs from deepwater, leading to nutrient limitation of primary producers in the surface mixed layers (Boyce et al., 2010). Such nutrient limitation may provide hosts with a disease-reduced refuge if the nutrient content of the host does not fulfill the nutritional needs of the parasite, effectively starving the infection (Hite et al., 2020), or by lowering the host population density below the threshold necessary for maintaining positive parasite population growth even though infection would physiologically still be possible (Deredec & Courchamp, 2003). For instance, viral infections in several phytoplankton taxa were shown to decrease under nutrient limitation (Table 1; Cheng et al., 2019; Maat & Brussaard, 2016). In addition to the absolute amount of nutrients available, also the form in which a nutrient is present (e.g., nitrogen in NO_3^- vs. NH_4^+) and the balance in concentrations of different nutrients (i.e., ecological stoichiometry; Sterner & Elser, 2002) can play a role in the occurrence of parasite infections (Bernot & Poulin, 2018). The form in which nitrogen is available in the environment can qualitatively change its effect on plant disease severity (Wang et al., 2019). A mismatch in host and parasite stoichiometry due to their differential response to the environmental nutrient ratio can lead to a stoichiometric disease refuge. For example, a potential low nitrogen-to-phosphorus ratio disease-reduced refuge was observed in a freshwater cyanobacterial host–fungal infection model system (Figure 2D; Table 1; Frenken et al., 2017a). The balance in nutrients may shift with climate change, with consequences for host stoichiometry (Van de Waal et al., 2010) potentially further enhancing mismatches between hosts and parasites (Bernot & Poulin, 2018; Frenken et al., 2021).

EVOLUTIONARY ADAPTATION OF REFUGES

Hosts and parasites continuously have to adapt to new environmental conditions. One way for hosts and parasites to adapt is by enduring unfavorable environmental conditions as resting stages or in dormancy, which can have

implications for parasite transmission (Starkloff & Civitello, 2022). Another way to adapt is by shifting tolerance ranges accordingly. These shifts, however, may take place at different acclimatization rates (i.e., how fast acclimatization takes place) and cover different acclimatization capacities (i.e., how much the tolerance range shifts or changes Rohr et al., 2018) in hosts and parasites, thereby offering another opportunity for the gain or loss of refuges. For instance, hosts may have slower acclimatization rates but greater acclimatization capacities in response to warming than their relatively smaller-bodied parasites (Rohr et al., 2018). This greater acclimatization capacity may allow hosts to exploit environmental conditions that are detrimental to their parasites even if these conditions are suboptimal for the host. Thus, hosts with a greater acclimatization capacity benefit from this refuge and are under positive selection with the potential for the population to adapt.

Predicting the evolutionary trajectory of host and parasite response curves remains difficult, as adaptive phenotypic plasticity can slow the rate at which genotypic variation is selected (Fox et al., 2019) and as (potentially interacting) processes can exert differential selection pressures on disease-related traits at the same time (Wolinska & King, 2009). Moreover, differential evolutionary rates and capacities in hosts and parasites may lead to temporary gains or losses of refuges, for instance due to differences in their body size and, consequently, physiological rates and generation times (Brown et al., 2004; Rohr et al., 2018). The co-evolution of host and parasite will also depend on the level of host dependency of the parasite, for which facultative, generalist, or parasites with resting stages may show a more independent evolutionary response toward environmental changes that may even lead to broader tolerance ranges. Variations in spatial scales also affect the host–parasite co-evolution, with hosts and parasites showing divergent evolutionary trajectories and outcomes among locations (Penczykowski et al., 2016). Host populations that live in locations that continuously provide a refuge from disease, however, will remain relatively naïve to certain parasites. Emigration of such relatively naïve hosts to areas where parasites do occur would provide an influx of nonadapted, relatively susceptible host genotypes and thereby slow or even thwart the evolution of resistance in the host population (Lafferty et al., 2015).

Given that parasite performance responses can only rarely be measured independently from the host environment (except for parasites that can survive without a host for some time such as facultative parasites that can also grow on a nonliving substrate or parasites with free-living transmission stages), almost all available data report composite measures (e.g., disease prevalence), and it remains unclear how the underlying host–parasite interactions change along environmental gradients. Moreover, only a few studies have assessed the response curves of hosts and their parasites over their entire environmental tolerance range. Such full assessments of changes in the host–parasite interactions, however, can yield valuable insights into environmental conditions that particularly permit or hinder infection spread. For example, phage infection changed the shape of the thermal response curve and increased the optimum temperature of the host bacterium growth rate (Padfield et al., 2020). While temperatures above 30°C provided a disease-free refuge, the rapid evolution of resistance occurred at temperatures below the optimum temperature for the phage that came at a cost to the maximum growth rate of the host, thereby additionally altering the evolutionary trajectory of the host (Padfield et al., 2020). In variable environments, this may also result in hosts being intermittently subjected to selection pressures including or excluding parasite pressure depending on the occurrence of refuges.

ENVIRONMENTAL DISEASE REFUGES AND MANAGEMENT PRACTICES

Pathogens cause major harvest losses and economic damage in a range of agri- and aquacultural farming practices. The disease refuges concept may be a useful starting point for the development of ecologically informed management practices in simple systems where performance–response curves of pathogen and host differ along an environmental gradient and where that particular environmental condition drives this interaction strongly. For example, seedlings experience a low-temperature refuge against beet necrotic yellow vein virus that causes rhizomania in sugar beet and is transmitted by the obligate protist root parasite, *Polymyxa betae* (McGrann et al., 2009; Figure 3A). The disease results in severe yield losses, especially when infection occurs early in plant growth (McGrann et al., 2009). Low soil temperatures suppress the development of the protist vector so that infection rates are low at soil temperatures below 15°C, while sugar beet germination can proceed already above 3°C (Blunt et al., 1992). Sowing sugar beet crops early in the year, when temperatures are still low, enables a head start against viral transmission and provides an important element of integrated pest management in the presence of the virus and its vector (Blunt et al., 1992).

In another example, low salinity may provide disease-reduced refuges for Eastern oysters (*Crassostrea virginica*) against the protist *Perkinsus marinus*, the agent of Dermo disease in Eastern oysters (Figure 3B). Dermo occurs along the eastern coast of the Americas where it can cause mass mortalities and thereby substantial economic losses

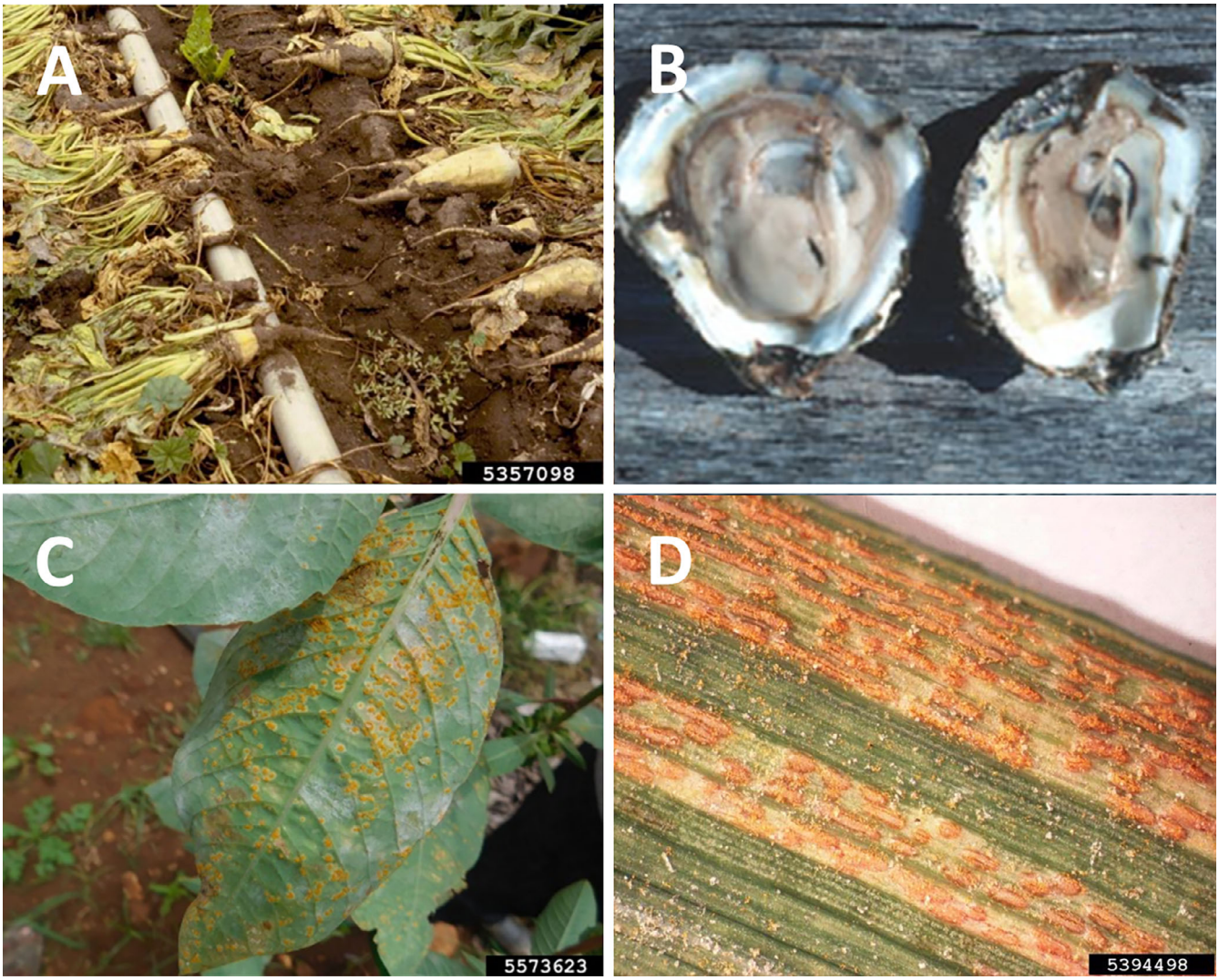

FIGURE 3 Examples of infections with (A) Beet necrotic yellow vein virus causing rhizomania in sugar beet in the left row, (B) the protist *Perkinsus marinus* on American oyster (*Crassostrea virginica*) on the right, (C) coffee rust *Hemileia vastatrix* on a leaf of the coffee plant, and (D) stripe rust *Puccinia striiformis* Westend on common wheat (*Triticum aestivum* L.) leaf. Image (A) by William M. Brown Jr., bugwood.org under CC BY 3.0 license; image (B) courtesy of Eugene Burreson, Virginia Institute of Marine Science, USA; image (C) by Parthasarathy Seethapathy, Tamil Nadu Agricultural University, India, bugwood.org under CC BY 3.0 license; image (D) by Mary Burrows, Montana State University, USA, bugwood.org under CC BY 3.0 license.

for oyster producers (Lafferty et al., 2015). Disease prevalence and disease-related host mortality are positively related to temperature and salinity, but negatively related to freshwater inflow (Bushek et al., 2012). Incidentally, management of the disease in wild and cultured Eastern oysters has included the relocation of oyster populations to low-salinity areas in estuarine areas (Bower, 2006) or establishing unfished oyster sanctuaries in low-salinity areas to restore degraded reefs. Such sanctuaries may have unintended detrimental effects, as they provide a source of relatively naïve hosts that emigrate to parasitized areas where they slow down the evolution of local disease resistance (Lafferty et al., 2015). Moreover, nondisease-related mortality in oysters also dramatically increases with extreme freshening events (Du et al., 2021), highlighting the necessity to consider the complexity of the host–parasite system and their interactions with their environment. Clearly, before the concept of environmental disease refuges can be made operational, we need to validate the generality and predictability of disease refuges derived from (often laboratory) studies of single host–parasite systems through observations of the outcome of the host–parasite interactions within the complexity of their entire ecological community (sensu Lee-Yaw et al., 2021).

Elevational gradients may also provide disease-reduced or even disease-free refuges. For instance, lower temperatures at higher elevations were shown to provide a refuge from the fungus *Hemileia vastatrix*, which

causes coffee leaf rust (CLR) in eight varieties of coffee that were planted at different elevations (Daba et al., 2019; Figure 3C). The CLR epidemics were most severe at the lowest elevation and decreased in intensity toward higher elevations where lower temperatures likely decreased rust spore germination. Moreover, CLR epidemics changed over seasons, and showed strongly reduced epidemics during the dry season (Daba et al., 2019). Likewise, the incidence of stripe rust disease on wheat (Figure 3D) decreased with elevation, which is attributed to the lower temperature limit of the overwintering stage of the fungal pathogen and the effects of wind chill (Ma et al., 2016). Similarly, increasing temperatures and less stable weather conditions led to an increase in the occurrence of brown rot at high elevations (Castillo & Plata, 2016). Understanding the role of the environment in promoting or suppressing disease in specific host–parasite systems is only one facet of many and can not fully explain the occurrence or absence of diseases in complex ecosystems. However, integrating the concept of environmental refuges from disease may serve as starting point for formulating novel hypotheses for ecologically informed approaches in disease-management strategies in nature conservation, agriculture, and aquaculture. These hypotheses then would need to be validated by observations of environmental disease refuges in natural or man-made complex systems as well as in experimental host–parasite systems along long environmental gradients.

APPLICATION OF PERFORMANCE–RESPONSE CURVES IN A COMPLEX WORLD

We have highlighted how mismatches in performance–response curves of hosts and parasites might lead to disease refuges along several environmental gradients, and we have discussed the potential consequences of global environmental change on gains and losses of such disease refuges. Whether disease refuges driven by single environmental factors are a general phenomenon and whether gains and losses of such potential refuges are suitable predictors for future shifts in host–parasite interactions remain to be tested against natural complexity. We argue that mismatches in host and parasite performance curves may be used as null models to predict potential host refuges and changes therein in response to environmental change. Obviously, the natural world is more complex, and involves a network of interactions with changes in many more abiotic factors than can often be reasonably tested. Consequently, potential refuges and their shifts may be masked by additional changes in the food web, host population dynamics, and confounding environmental conditions.

The occurrence of environmental disease-free refuges is based on physiological limits, and thus represents likely scenarios in which epidemics will not occur. Disease-reduced refuges, however, do not necessarily mean that no epidemic will occur, as this will also depend on the density and absolute growth and reproduction rates of both the host and parasite (Padfield et al., 2020). In other words, even when a parasite is more sensitive toward a certain environmental factor compared with its host, it may still cause an epidemic, although this is likely to be at a lower rate. Additionally, many parasites are generalists that can or even have to infect more than one host species to complete their life cycle. Hence, even if parasite performance was reduced on a specific host under certain environmental conditions, it may still perform well on another host species, and hence escape the effects of an environmental disease refuge. Moreover, many parasites are vector-borne, or have complex life cycles, and refuges may thus occur not only for the parasite, but also for its vector or any intermediate host (e.g., see Paull & Johnson, 2014). In serial-specialist parasites with complex life cycles or those with obligate transmission through a specific vector, the parasite transmission chain can be broken when one of the hosts or vectors encounters environmental conditions that prohibit infection or parasite development, leading to knock-on effects throughout all involved species (Rudolf & Lafferty, 2011). It remains difficult to scale up the actual impact and importance of environmental disease refuges from controlled laboratory studies of isolated host–parasite systems and a single environmental condition to complex natural communities exposed to many, often interacting environmental drivers (Aleuy & Kutz, 2020). However, despite these limitations, also in natural systems we can observe environmental refuges from disease recurrently and predictably (e.g., Ibelings et al., 2011). These mismatches can at least serve as a null hypothesis against which we can test the generality of environmental disease refuges.

Prediction of the effects of global environmental change on infectious disease occurrence and severity remains a challenge and no universal pattern has been observed for infectious disease occurrence with environmental change (Altizer et al., 2013). A better understanding of whether and how generally mismatches in performance–response curves of hosts and parasites occur depends on more case studies that cover wide environmental gradients and allows the evaluation of conditions that promote infections (sensu thermal-mismatch hypothesis) or, as we argue here, reduce parasite performance leading to disease refuges (Molnár et al., 2017). Additionally, gradients of environmental factors do not occur in isolation, but rather are a composite of several environmental factors acting together. In such a multivariate environment, time or space pockets may provide

hosts with temporally (e.g., seasonally) or spatially explicit, multienvironmental refuges.

CONCLUDING REMARKS

With our synthesis, we show how mismatches in performance–response curves of hosts and parasites may reveal putative environmental refuges and thereby improve our understanding of their interactions along current and future environmental gradients. However, the generality of such refuges remains to be tested across gradients of multiple environmental factors and across the spectrum of specialist to generalist parasites, including those that have complex life cycles. Therefore, we call for future host–parasite interaction studies to assess more than one performance trait and broader environmental gradients covering lower and upper critical limits of hosts and parasites. Moreover, the generality and predictability of environmental disease refuges need to be validated by observations of host–parasite systems in the complexity of their ecological community. The resulting insights will show where and how generally environmental disease refuges occur and whether they can ultimately benefit disease-management strategies for nature conservation, agriculture, and fisheries.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sets used for plotting Figure 2 were assembled from published literature (Levinton et al., 2011; Springer et al., 2007) or from archived datasets (Gsell et al., 2022; Frenken et al., 2017b).

ORCID

Alena S. Gsell https://orcid.org/0000-0001-7795-1996
Götz Eichhorn https://orcid.org/0000-0003-2151-8856
Thijs Frenken https://orcid.org/0000-0002-8989-2804
Stefan Geisen https://orcid.org/0000-0003-0734-727X
Madhav P. Thakur https://orcid.org/0000-0001-9426-1313

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