Controversy persists regarding the contributions of climate change to biodiversity losses, through its effects on the spread and emergence of infectious diseases. One of the reasons for this controversy is that there are few mechanistic studies that explore the links among climate change, infectious disease, and declines of host populations. Given that host–parasite interactions are generally mediated by physiological responses, we submit that physiological models could facilitate the prediction of how host–parasite interactions will respond to climate change, and might offer theoretical and terminological cohesion that has been lacking in the climate change–disease literature. We stress that much of the work on how climate influences host–parasite interactions has emphasized changes in climatic means, despite a hallmark of climate change being changes in climatic variability and extremes. Owing to this gap, we highlight how temporal variability in weather, coupled with non-linearities in responses to mean climate, can be used to predict the effects of climate on host–parasite interactions. We also discuss the climate variability hypothesis for disease-related declines, which posits that increased unpredictable temperature variability might provide a temporary advantage to pathogens because they are smaller and have faster metabolisms than their hosts, allowing more rapid acclimatization following a temperature shift. In support of these hypotheses, we provide case studies on the role of climatic variability in host population declines associated with the emergence of the infectious diseases chytridiomycosis, withering syndrome, and malaria. Finally, we present a mathematical model that provides the scaffolding to integrate metabolic theory, physiological mechanisms, and large-scale spatiotemporal processes to predict how simultaneous changes in climatic means, variances, and extremes will affect host–parasite interactions. However, several outstanding questions remain to be answered before investigators can accurately predict how changes in climatic means and variances will affect infectious diseases and the conservation status of host populations.

Key words: Acclimatization, amphibian, chytridiomycosis, climate change, host–parasite interaction, metabolic theory of ecology

Editor: Steven Cooke

Received 1 May 2013; revised 17 July 2013; accepted 17 July 2013

Introduction

Over the past 50 years, scientists have documented significant anthropogenic climate change and extraordinary biodiversity losses (Walther et al., 2002; Stuart et al., 2004; Thomas et al., 2004; Parmesan, 2006). Anthropogenic greenhouse gas emissions are affecting several components of climate, including temperature and precipitation means, variance, and extremes (Easterling et al., 2000; Meehl et al., 2000, 2009; Raisanen, 2002; Kunkel et al., 2003). Both paleontological and contemporary data suggest that such changes in temperature and precipitation can contribute to declines in biodiversity (Walther et al., 2002; Stuart et al., 2004; Thomas et al., 2004; Parmesan, 2006). Indeed, there is evidence that recent climate changes have already caused population declines or extirpations of lizards, corals, butterflies, and polar bears (Stirling et al., 1999; Bruno et al., 2007; Sinervo et al., 2010; Breed et al., 2013). Moreover, projected climate-induced faunal changes suggest profound changes in populations of numerous species (Lawler et al., 2009).

Alongside changes in climate, scientists have also documented unprecedented rates of emerging infectious diseases over the last 50 years (Daszak et al., 2000; Stuart et al., 2004; Thomas et al., 2004; Jones et al., 2008; Lafferty, 2009; Rohr et al., 2011a). Although it was traditionally assumed that parasites did not cause extinctions of their host populations because parasites themselves require a threshold host population size to persist, we know now that there are several conditions in which parasites can cause host population extinctions, such as when the parasite can persist in alternative hosts or environmental reservoirs (de Castro and Bolker, 2005). Even if these conditions do not occur, parasites can drive host populations to low levels and, coupled with demographic stochasticity, can contribute to host extinctions (de Castro and Bolker, 2005). For example, emerging infections have been linked to population declines of chestnut, elm, pine, and oak trees (Anagnostakis, 1987; Mamiya, 1988; Brasier, 2001; Rizzo and Garbelotto, 2003; Anderson et al., 2004; Rohr et al., 2011a). Emerging fungal infections are driving losses of amphibians, snakes, bees, crayfish, and bats (McCallum et al., 2009; Rohr et al., 2011a; Fisher et al., 2012). Malaria is believed to have caused declines in the diversity of Hawaiian birds (Vanriper et al., 1986; Garamszegi, 2011), and an infectious cancer has caused the near extinction of the Tasmanian devil (McCallum et al., 2009; Rohr et al., 2011a; Fisher et al., 2012). Consequently, increases in infectious diseases often threaten biodiversity.

Several researchers have suggested that climate change is indirectly contributing to biodiversity losses by increasing the spread and emergence of infectious diseases (Epstein, 2000; Harvell et al., 2002; Lafferty, 2009; Rohr et al., 2011a). Nonetheless, the extent to which climate change causes increases in some diseases but declines in others is an area of active debate, and more studies are required to identify the diseases that will be likely to pose the greatest risk in the event of future climate change (Lafferty, 2009; Rohr et al., 2011a). Mechanistic studies of how climate change influences disease will help clarify this debate for several reasons. First, mechanisms provide concrete evidence of a cause-and-effect relationship between a change in climate and an increase in infectious disease. Such evidence is urgently needed to enable identification of the diseases, regions, and species most likely to face increased disease threats with climate change (Rohr et al., 2011a). Second, our predictions for how host–parasite interactions will respond to shifts in climate should improve if we understand the underlying mechanisms linking these factors. Finally, understanding the mechanistic links between climate and disease should allow us to develop more effective measures targeted at mitigating the threats posed to species by pathogens.

Virtually all host–parasite interactions are mediated by physiological responses, and climate can have profound effects on these responses, especially for ectothermic species, which comprise 99.9% of all species (Daufresne et al., 2009). Therefore, understanding physiology is essential for attaining a mechanistic understanding of how climate change affects infectious disease (Fig. 1). Physiology has a rich history of quantifying both the response of biological and chemical systems to mean climatic conditions ($Q_{10}$ coefficients) and the response of organisms to climatic variability through quantification of acclimatization effects (Hutchison, 1961; Brattstrom, 1963; Spotila, 1972; Nadel et al., 1974; Atkin and Tjoelker, 2003; Hoffmann et al., 2003). Hence, physiological models should facilitate the prediction of how host–parasite interactions respond to simultaneous changes in climatic means, variances, and extremes, and might offer theoretical and terminological cohesion that has been lacking in the climate change–disease literature (Martin et al., 2010; Blaustein et al., 2012).

The goal of this paper is to explore how physiology and disease ecology can be better integrated to understand the outcome of climate–disease interactions, especially those that involve species of conservation concern. We first offer background on the physiology and thermal biology of host–parasite interactions. We stress that much of the work on how climate influences host–parasite interactions has emphasized changes in climate means, despite a hallmark of climate change being alterations in climate variability and extremes (Easterling et al., 2000; Meehl et al., 2000, 2009; Raisanen, 2002; Kunkel et al., 2003). Owing to this gap in the literature, we highlight the role of climatic variability in driving host–parasite interactions. Specifically, we discuss how nonlinearities in response to mean climate, coupled with temporal

![Figure 1: Flowchart highlighting the importance of physiology in understanding the influence of climate on host–parasite interactions and changes in host population densities.](http://conphys.oxfordjournals.org/Downloadedfrom/278721312)
variability in weather and organismal acclimatization responses, can be used to predict the effects of climate on host–parasite interactions. We propose that the metabolic theory of ecology (MTE) offers an instrument to integrate physiological mechanisms and large-scale spatiotemporal processes to enable successful prediction of how changes to climatic means, variances, and extremes will affect host–parasite interactions. We then provide a quantitative example for how metabolic theory can be used to derive models of host–parasite interactions in a changing temperature environment. Finally, we end with conclusions and outstanding questions.

**Thermal biology and disease**

In this section, we explore the application of approaches from thermal biology to host–parasite interactions. We begin by defining performance curves and show how they can be used to predict host–parasite interactions, highlighting differences in the temperature-dependent defense strategies of ecto- and endothermic hosts. We then discuss the importance of phenotypic plasticity of hosts and parasites to temporal variability in temperature, emphasizing likely differences in the acclimatization rates of hosts and parasites.

**Thermal performance curves of parasites and ecto- and endothermic hosts**

Performance curves depict the ability of an organism to perform a physiological function (e.g. muscle strength) across a range of temperatures (Angilletta et al., 2002; Angilletta, 2009). In host–parasite interactions, the physiological parameters of most interest are the rate of growth or replication of the parasite within or on the host (referred to here as ‘parasite infectivity’) and the capacity of the host to reduce parasite growth (referred to here as ‘host resistance’; Raffel et al., 2013). We can conceptualize these two processes as separate thermal performance curves, the combination of which describes the ability of the parasite to infect the host at a particular temperature (Fig. 2A and B). Both parasite infectivity and host resistance may be temperature dependent, so both must be accounted for when predicting the effects of temperature on infection (Raffel et al., 2013).

There might also be fundamental differences in the thermal biology of parasitism in ectothermic vs. endothermic hosts, the latter of which has received more attention by ecological immunologists (Martin et al., 2008). The thermal environment of a parasite should be essentially constant within an endothermic host, which expends energy heating or cooling itself to maintain a constant internal temperature. Thus, effects of external temperature on the parasites of an endotherm might be indirect and driven primarily by energetic trade-offs between host thermoregulation and investment in immune responses (Nelson and Demas, 1996). This leads to a general prediction of decreased host resistance to infection when external temperatures are far from the host’s optimal temperature, because an endotherm would need to invest more in maintaining its internal temperature, thereby leaving less energy available to invest in anti-parasite defenses. However, many endothermic hosts have parasites transmitted by ectothermic vectors, thus making many of the concepts discussed below regarding ectothermic hosts relevant to the transmission of vector-borne parasites to endothermic hosts.

Parasites of ectothermic hosts might often experience different thermal environments from parasites of endothermic hosts, because the internal temperature of ectothermic hosts varies with external temperature (Angilletta, 2009). Thus, both the host and the parasite must adapt to temperature at the tissue level (Raffel et al., 2013). Furthermore, lower temperatures will not necessarily drive energetic trade-offs...
between thermoregulation and the host immune response; indeed, many ectotherms expend less energy at lower temperatures because their metabolic rates are reduced (Gillooly et al., 2001). Depending on their specific thermal optima relative to hosts, pathogen and parasite growth rates might also decrease at lower temperatures (Ratkowsky et al., 1982), such that a slower immune response might be sufficient to control infection (Raffel et al., 2006, 2013; Murdock et al., 2012). Thus, the effects of temperature on the parasites of ectothermic hosts should depend on the thermal performance curves of both parasite growth (Fig. 2) and host resistance and might be driven less by energetic trade-offs with host thermoregulation than they are for endothermic hosts. Importantly, much of the work in thermal biology has been conducted on organismal responses to mean temperature, despite climate change also affecting temporal variability in temperature (Easterling et al., 2000; Benedetti-Cecchi, 2003).

**Host and parasite phenotypic plasticity in response to temporal variability in temperature**

Thermal biology also provides insights into potential effects of sudden shifts in temperature on host–parasite interactions. Biologists have long known that organisms can respond to a temperature shift by adjusting their physiological systems to operate more effectively at the new temperature (Angilletta, 2009). Such plastic responses to temperature shifts are referred to as physiological acclimatization, which can be thought of as the organism shifting its performance curve to optimize performance at the new temperature (Angilletta, 2009). Acclimatization responses are usually assumed to be adaptive, but they are energetically costly and take time (Deere and Chown, 2006). Therefore, acclimatization responses are effective only if an organism can expect to be at the new temperature for an extended period of time, or if it can anticipate when the next temperature shift will occur. Thus, the frequency and predictability of temperature variation are likely to determine the effectiveness of acclimatization responses in both free-living and parasitic organisms (Raffel et al., 2013).

Thermal acclimatization responses are potentially important for understanding the effects of temperature variability on infectious disease, because parasites and hosts are likely to have differential responses to temperature variability. For example, metabolic theory predicts that smaller organisms will have faster metabolisms and correspondingly shorter times to complete physiological processes, including thermal acclimatization (Pörtner, 2002); therefore, parasites, which are almost universally smaller than their hosts, would be expected to acclimatize to new temperatures more rapidly than their hosts (Raffel et al., 2013). Indeed, it can take weeks for ectothermic vertebrates to acclimatize their immune systems to a new temperature (Bly and Clem, 1991), whereas one of the few parasites investigated so far acclimatized to comparable temperature shifts in a matter of hours (Terblanche and Chown, 2006). Therefore, parasites might become more infectious in conditions of frequent and unpredictable shifts in temperature, because of lags in host acclimatization following temperature shifts (Raffel et al., 2006). This hypothesis has potentially important implications for responses of host–parasite systems to climate change, which is altering temperature variability over various time scales (Easterling et al., 2000; Meehl et al., 2000, 2009; Raisanen, 2002; Kunkel et al., 2003).

Hosts can also use plastic responses, such as behaviours, to track temperatures ideally suited for resisting infections, a process called behavioural thermoregulation (Angilletta, 2009; Kearney et al., 2009). Ectothermic hosts often use behaviour to increase body temperature in response to infectious diseases (‘behavioural fever’; Lefcort and Blaustein, 1993; Thomas and Blanford, 2003; Elliot et al., 2005) and might also use behavioural thermoregulation to modulate temporal shifts in temperature (e.g. to move to a relatively warm place if the temperature drops). Spatial variation in temperature can also assist endothermic hosts in responding to pathogens by allowing them to reduce the energetic costs of physiological thermoregulation. For example, bats that gather in warmer parts of caves during winter are better able to survive infection by the fungus that causes white-nose syndrome, because they expend less energy heating their bodies in response to the pathogen (Boyles and Willis, 2010). Behavioural thermoregulation also poses an empirical challenge, however, because it suggests that coarse-scale temperature projections might sometimes fail to capture the local temperatures experienced by particular hosts or pathogens (Boyles and Willis, 2010). The extent to which such behavioural effects might diminish the predictive power of models based on coarse-scale temperatures is unclear, however, because large-scale temperature shifts might cause losses of suitable habitat or overwhelm the capacity of organisms to thermoregulate, even in heterogeneous environments. Thus, further study is needed to determine the extent to which behavioural thermoregulation can help hosts mitigate effects of climate shifts on infection.

**Effects of climate change on host–parasite interactions**

Climate change involves changes to both the mean and the variability of climatic conditions. Here, we discuss evidence in support of the hypothesis that shifts to both temperature means and variances affect host–parasite interactions and that these altered interactions are facilitating some host population declines. We argue for development of models that integrate the effects of changes to both temperature means and variances on host–parasite interactions to distribute limited conservation funds effectively.

**Mean temperature effects**

The outcomes of host–parasite interactions in different constant-temperature conditions in the laboratory are generally
for pathogens causing species extinctions (Box 1). Moreover, assumptions of linearity alter the predictions for how climate change would affect disease and thus extinction risk, illustrating the conservation importance of integrating the non-linear physiological responses of both host and parasite to temperature (Box 1).

**The importance of temperature variability**

The incorporation of non-linearities in disease risk into climate-driven disease models becomes even more important in the context of temperature variability (Scherm and van Bruggen, 1994; Raffel et al., 2013). This is because when a response to temperature is purely linear, then the only information required to predict the average response accurately is the average temperature. However, when responses to temperature are non-linear, as is almost always the case if a wide enough thermal range is considered, it is necessary to know how much time was spent at each temperature to predict the response accurately, because estimates based on mean temperature will yield erroneous results. Scherm and van Bruggen (1994) illustrated this phenomenon using simulated performance curves for growth of a hypothetical pest species with a thermal optimum between 25 and −30°C (Fig. 4A). Using performance curves to calculate growth rates at a variety of simulated temperatures and levels of fluctuation, the authors show that the greater the amplitude of the temperature fluctuation, the more the growth predicted by the mean temperature deviates from that predicted by the performance curve at a given temperature (Fig. 4B). For instance, a temperature fluctuation of 15°C around a mean temperature of 25°C yields a predicted growth rate for the pest that is less than half that expected from constant temperatures, because the organism is regularly exposed to suboptimal temperatures as the temperature fluctuates above and below its thermal optimum (Fig. 4B). A similar pattern has been demonstrated experimentally for mosquito vectors (Paaijmans et al., 2013) and several parameters associated with both *Plasmodium* and chytrid fungal transmission (Box 1). This suggests that models for the risk of malaria and chytridiomycosis (the disease caused by the amphibian chytrid fungus) based on mean temperatures might substantially under- or over-estimate transmission at particular temperatures (Paaijmans et al., 2009).

![Figure 3](http://conphys.oxfordjournals.org/)

Figure 3: Hypothetical diagram showing that increases in parasite infectivity that are approximately linear over a small range of temperatures combined with linear declines in parasite virulence or host susceptibility (potentially caused, for example, by faster host growth out of vulnerable stages of development) can yield non-linear changes to host pathology.
Box 1. Climate-driven non-linearities, disease, and biodiversity losses

Non-linear responses of host and/or parasite to temperature can complicate predictions of the effects of climate change on disease risk and thereby threaten conservation efforts. Non-linearities in disease risk arise in at least two ways. First, they arise as a result of integration across generally linear portions of host and parasite temperature performance curves that have opposite slopes (Fig. 3). For example, Paull et al. (2012) found a mid-temperature peak in the risk of trematode-induced deformities in the amphibian *Pseudacris regilla*. Fewer deformities at the warmest temperature appear to have been the result of faster host development, and a consequent reduction in the time that hosts spent in early developmental stages where they are vulnerable to deformities. Reduced deformities in the coldest treatment were consistent with an observed decline in parasite infectivity at that temperature. Thus, the combined positive effect of temperature on parasite infectivity and negative effect on host vulnerability may have been responsible for the observed non-linear temperature–disease risk function in this system (Fig. 3). These trematode infections have been associated with mass malformations and reduced survival in amphibians (Johnson et al., 2004), again illustrating the conservation importance of integrating the non-linear physiological responses of both host and parasite to temperature (Rohr et al., 2011a; Mordecai et al., 2013).

Non-linearities can also arise if host, vector, and/or parasite performances across temperature are inherently non-linear, as was shown for the amphibian chytrid fungus, *Batrachochytrium dendrobatidis* (Raffel et al., 2013), which has been implicated in hundreds of amphibian extinctions (Stuart et al., 2004; Wake and Vredenburg, 2008), and the performance of *Plasmodium* spp. and their vector (Paaijmans et al., 2009, 2010, 2013; Mordecai et al., 2013). While the studies on *Plasmodium* focused on human malaria, similar patterns are likely to hold for the ecologically similar avian malaria, which has been implicated in extinctions of several Hawaiian birds (Vanriper et al., 1986; Garamszegi, 2011). Importantly, Mordecai et al. (2013) showed that the incorporation of empirically demonstrated non-linearities in parasite development and mosquito performance (e.g. development, reproduction, survival, and bite rate) into a model of malaria transmission yielded an optimal transmission temperature of 25°C, which is considerably lower than the 31°C predicted by previous studies. Given the role of malaria in the declines of bird species (Vanriper et al., 1986; Garamszegi, 2011), this example illustrates how non-linearities might affect predictions for how climate change will affect disease risk for hosts of conservation concern.

2009, 2010; Mordecai et al., 2013; Raffel et al., 2013), with potential consequences for disease-driven host declines (Box 1).

Temperature variability might also influence the outcome of host–parasite interactions through differences in the acclimatization rates of hosts and parasites to shifts in temperature (Raffel et al., 2006, 2013; Rohr and Raffel, 2010). Relative to the historical variability to which hosts evolved, global change has modified and is projected to modify climate variability, including changes to monthly variability, diurnal temperature range, and the frequency of El Niño events (Easterling et al., 2000; Raisanen, 2002; Yeh et al., 2009). These changes to climate could theoretically be detrimental to parasites if their hosts or vectors drop to low density during these periods, if their short lifespans make it difficult to persist through unfavourable weather conditions, or if their free-living stages are sensitive to unfavourable conditions. However, the climate variability hypothesis for disease-related declines posits that increased unpredictable climatic variability and extreme events might provide a temporary advantage to pathogens, because they are smaller (fewer cells and processes) and have faster metabolisms than their hosts, thereby allowing them to acclimatize more quickly following a temperature shift (Raffel et al., 2006, 2013; Rohr and Raffel, 2010).

Support for the climate variability hypothesis in driving disease-related declines of amphibians and abalone is growing (Box 2), but several underlying assumptions and the generality of the hypothesis remain to be tested thoroughly (Box 3). Nevertheless, the hypothesis holds great promise for enhancing predictions about how disease risk will be modified by simultaneous changes to both the mean and the variance of climatic conditions and thus how and where conservation efforts related to disease should be targeted. Moreover, most proposed mechanisms for how climate change can generally increase infectious disease are highly controversial, because increases in temperature are expected to cause parasite range shifts rather than expansions (Lafferty, 2009) and possibly just as many scenarios where optimal temperatures of organisms are exceeded as approached (Rohr et al., 2011a). The climate variability hypothesis, however, might offer a plausible mechanism by which global climate change could, on average, cause general increases in infectious diseases, because temperature variability is becoming less predictable, acclimatization of physiological parameters (e.g. cold hardiness) to temperature shifts is a widespread phenomenon observed across ectothermic taxa (Angilletta, 2009), and all parasites are smaller than their hosts and thus should acclimatize more quickly than hosts to temperature shifts. Consequently, climatic variability and predictability...
remains unclear how accurate it will be for predictions. Pursuit of both approaches in tandem may ultimately represent the most effective path forward.

We submit that the metabolic theory of ecology offers a general modelling framework for predicting how changes to climatic means, variances, and extremes will affect disease risk. The MTE relates an individual organism’s metabolic rate (I), or its rate of energy uptake and allocation, to its body size (M) and the ambient temperature (T, in kelvin) using the expression $I = \frac{ME^{\frac{1}{k}}e^{\frac{k}{MT}}}{M}$, where $E$ is the average activation energy of respiration and $k$ is Boltzmann’s constant (Brown et al., 2004). For temperature, total metabolism increases exponentially over a ‘normal’ range of temperatures owing to the influence of temperature on chemical reaction rates (although note that, above a critical threshold temperature, enzymes denature and halt reaction rates). There are also extensions of this theory that predict unimodal impacts of temperature on physiological processes, such as the Van’t Hoff–Arrhenius and Sharpe–Schoolfield models (see modelling section below; Hechinger, 2013; Molnár et al., 2013). For body size, the increase in metabolic rate is allometric (i.e. $M$ raised to the $\frac{1}{3}$ power rather than unity, which would be isometric). This means that the mass-specific metabolic rate (or $I$ divided by $M$) decreases to the $-\frac{1}{3}$ power with increases in body size. Stated another way, larger-bodied organisms expend less energy per unit mass relative to smaller-bodied ones, typically owing to increases in heat retention and metabolic efficiency with size. Owing to the importance of metabolic rate in determining both resource uptake and resource allocation, MTE has successfully predicted life history, demographic patterns, and ecosystem processes in taxa ranging from protists to mammals (Brown et al., 2004; Price et al., 2012).

**Metabolic theory of ecology and disease ecology**

Although the MTE shows great potential for predicting climate change–disease interactions, thus far, the relatively few studies that have examined components of the MTE in relationships to parasites and body mass have yielded mixed results. In a study of fish parasites, Poulin and George-Nasciemento (2007) reported that parasites within hosts violated the ‘energetic equivalency rule’, which states that the energy use of a population is independent of body size (Damuth, 1987). In a survey of free-living and parasite biomass within estuarine systems, Hechinger et al. (2011) reported that including parasites alongside free-living taxa required incorporation of a correction term (which they ascribed to ‘trophic position’). Finally, Hoverman et al. (Johnson PTJ, Paull SHP. Unpublished observations) found that parasites within hosts had much lower metabolic rates than expected based on relationships developed for free-living organisms, such that they operated functionally as part of the host rather than as separate organisms. Collectively, these studies suggest that the body size–metabolic rate linkage may be different for parasites than for free-living organisms and emphasize the need for more comparative work incorporating parasitic life histories.
One of the reasons why the body size–metabolic rate relationship might appear to be different for parasites compared with free-living organisms is because it is not entirely clear what mass (M) term to use for parasites. There are reasonable arguments for using the following parameters: (i) the mass of individual parasites; (ii) the mass of the entire parasite population within a host; (iii) the mass of the host, which could control parasite metabolism; or (iv) some relationship between host and parasite biomass that might depend on whether the host is an endo- or ectotherm. Cable et al. (2007) found that, across a range of pathogen and host types, the time to pathology scaled with the mass of the host multiplied by a scaling term, or $cM^{1/4}$. How $c$ related to pathogen mass was not explored, however, and in general, more empirical data and syntheses examining the influence of temperature, body size (host and pathogen), and pathogen transmission mode are sorely needed to evaluate these issues thoroughly (Box 3). Through a series of models validated with data, Hechinger (2013) emphasized the importance of energy constraints (rather than space constraints) in affecting parasite-carrying
capacity and maximal energy flux within hosts. According to Hechinger (2013), incorporation of both host and per capita parasite mass into an MTE theoretical framework allows a more direct prediction of total parasite biomass within hosts. Owing to an overall shortage of empirical data, however, there remain few opportunities to test these principles and evaluate whether the metabolic relationships for parasites differ from those for non-parasitic species, which is an important prerequisite before climate change predictions could be used to promote conservation.

One of the most exciting potentials for applying the MTE to host–pathogen interactions involves more deeply exploring the temperature-dependency component of vital rates, which thus far has received surprisingly little attention in disease research. A groundbreaking new study by Molnár...
et al. (2013) linked MTE host–macroparasite models to understand the ‘fundamental thermal niche’ of parasites and how their fitness (e.g. \( R_0 \), or the basic reproductive number of parasites) varies with changes in temperature. Using arctic nematodes and their mammalian hosts as their empirical foundation, the authors developed temperature-dependent values for parasite mortality and development rate during their free-living periods (which is when they are infectious to roaming mammals). They then developed a temperature-dependent value of \( R_0 \), a focal parameter of epidemiologists and studies of disease dynamics, that accounted for trade-offs between development and mortality expected to occur with changing temperatures (i.e. to identify the net effects). This model offered both general predictions about how infection patterns will shift in different warming scenarios and, when parameterized to the nematode system, specific predictions that corresponded well with available empirical data. It also drew attention to the central importance of identifying the threshold temperatures at which parasite development ceases or mortality occurs; values that are either not measured in many empirical studies or are often presented in an unstandardized way.

### Using the metabolic theory of ecology to model host–parasite interactions in a changing temperature environment

To illustrate how a host–parasite interaction could be described using thermal biology theory, we focus on the simple case of a directly transmitted microparasite infecting an ectothermic host and build upon the MTE-based models of DeLeo and Dobson (1998), Morand and Poulin (2002), Molnár et al. (2013), and Hechinger (2013). Once a host is exposed to the parasite, we assume that the parasite’s replication rate within the host, \( \lambda_T \), is a function of the temperature-dependent infectivity of the parasite, \( i_T \), and resistance of the host to infection, \( r_T \), such that:

\[
\lambda_T = e^{i_T - r_T}
\]

(1)

Infectivity here represents the within-host parasite population growth rate in ideal conditions (i.e. in the absence of a host immune response), and resistance is the ability of the host to reduce this population growth rate. The parasite population grows (\( \lambda > 1 \)) if \( i_T > r_T \), and declines (\( \lambda < 1 \)) if \( r_T > i_T \). To derive equations for infectivity and resistance as a function of temperature, we used the Sharpe–Schofield model for temperature-dependent performance of a physiological parameter, which assumes that performance scales with the Boltzmann factor, \( e^{-E_r/kT} \) and that irreversible deactivation of rate-controlling enzymes occurs at high and low temperatures, \( T^H \) and \( T^L \) (Molnár et al., 2013). This approach gives us:

\[
\begin{align*}
  r_T &= r_T e^{(i_T/k)(1/T - 1/T_0^L)} \cdot (1 + e^{(E^L/kT^L - 1/T_0^L)}) \\
  &\quad + e^{(E^H/kT^H - 1/T_0^H)})}^{-1} \\
  \end{align*}
\]

(2a)

where \( i_T \) and \( r_T \) are infectivity and resistance measured at the standardization temperature \( T_0 \), \( E_r \) and \( E_r \) are the activation energies for infectivity and resistance, \( E^H \) and \( E^L \) are the low- and high-temperature deactivation energies for infectivity and resistance, \( T^H \) and \( T^L \) are the low- and high-temperature thresholds for infectivity and resistance (in kelvin), and \( k = 8.62 \times 10^{-5} \) is Boltzmann’s constant. Metabolic theory and empirical measurements indicate that activation energies are similar across different physiological processes and organism taxa, allowing us to simplify the model (\( E_r = E_r = 0.65 \); Molnár et al., 2013). Metabolic theory is less informative regarding deactivation energies, but we assumed that \( E_r = E_r = E_r = E_r = 5E_r \approx 3.25 \), after Molnár et al. (2013). For parasites that can be cultured, the replication rate of the parasite in culture at the standardization temperature \( T_0 \) (any temperature within the normal range for infection) could be used as a proxy for \( r_T \), with resistance \( r_T \) estimated as the decrease in parasite replication at \( T_0 \) while growing in or on the host, relative to growth in culture. Note that temperature is modelled in kelvin, but is described hereafter in degrees celsius for clarity.

As an example of how this model could be implemented for a real parasite–host system, we estimated parameters for temperature dependence of the pathogenic fungus \( B. dendrobatidis \) growing on a susceptible Cuban treefrog (\( Osteopilus septentrionalis \)). We calculated low- and high-temperature thresholds (\( T^L \) and \( T^H \) ) based on estimates of the critical thermal maximum and minimum for \( B. dendrobatidis \) growth (\( CT_{min} = 0°C \); \( CT_{max} = 30°C \)) and Cuban treefrog survival (\( CT_{min} = 6.4°C \); \( CT_{max} = 39.0°C \); John-Alder et al., 1988; Rohr et al., 2008). The range of temperatures over which an organism can perform a particular physiological function (e.g. development) is generally narrower than the range over which an organism can survive (Molnár et al., 2013), so we assumed that \( T^L \) and \( T^H \) for infectivity and resistance were 5°C higher and lower than \( CT_{min} \) and \( CT_{max} \), respectively (\( T^L = 5°C; T^H = 25°C; T^H = 11.4°C \); and \( T^H = 34°C \)). We estimated \( i_T \approx 0.78 \), based on the average growth rate of \( B. dendrobatidis \) in culture at \( T_0 = 20°C \), as measured by Potrowski et al. (2004) and Woodhams et al. (2008) and analysed for population growth rates by Rohr et al. (2008). Model predictions were generated using the program R (R Development Core Team, 2010). Predicted values for \( i_T \) and \( \lambda_T \) were consistent with published patterns of temperature dependence for this parasite in culture and on Cuban treefrogs (Fig. 2A and B; Rohr et al., 2008; Raffel et al., 2013).

To show how this model could be incorporated into a dynamic model of a simple microparasite system, we started with a standard SI (susceptible–infected) model assuming density-independent growth of the host population, and that infected hosts become susceptible again following recovery. In this model, \( \Delta S / \Delta t \) and \( \Delta I / \Delta t \) represent the rates of change.
in the sizes of the susceptible and infected host populations, respectively. We then added our temperature-dependent parameter \( \lambda_T \) to this model, assuming that parasite transmission and virulence are both directly proportional to \( \lambda_T \) and that host recovery is inversely proportional to \( \lambda_T \), such that:

\[
\frac{\delta S}{\delta t} = (b - d)S - \lambda_T \beta SI + \frac{\gamma' T}{\lambda_T} \tag{3a}
\]

\[
\frac{\delta I}{\delta t} = \lambda_T \beta SI - \lambda_T \alpha' I - dI - \frac{\gamma' T}{\lambda_T}, \tag{3b}
\]

where \( b \) and \( d \) are the background birth and death rates, and \( \beta', \alpha', \gamma' \) are constants controlling the effects of \( \lambda_T \) on transmission, virulence, and recovery, respectively. From this model we can set \( \delta I / \delta t = 0 \) to derive the basic reproductive ratio \( R_0 \), a critical parameter indicating the expected number of new infections resulting from one infected individual in a population of susceptible individuals, as a function of temperature, as follows:

\[
R_0(T) = \frac{\lambda_T \beta S}{\lambda_T \alpha' + d + (\gamma' / \lambda_T)} \tag{4}
\]

To illustrate the relationship between \( \lambda_T \) and \( R_0(T) \), we selected arbitrary parameter values of \( \beta' = 0.001, \alpha' = 0.2, \gamma' = 0.2, d = 0.1, \) and \( S = 500 \) (Fig. 2B). This set of parameters predicts that \( R_0(T) \) will be >1 for temperatures below 25°C (Fig. 2B), consistent with laboratory and field data on frog strains (Raffel et al., 2013). Note that this model formulation constrains \( R_0(T) \) to be positively related to \( \lambda_T \) over the entire range of possible parameter values.

We can incorporate thermal acclimatization responses into this model by allowing the low- and high-temperature limits for infectivity and resistance \( (T_i^L, T_i^H, T_R^L, T_R^H) \) to vary according to the temperature to which the host or parasite is acclimatized \( (T_{accl}) \). If we assume that these parameters vary linearly with acclimatization temperature, the value of each parameter for a given acclimatization temperature can be estimated by measuring each parameter at two acclimatization temperatures, \( T_1 \) and \( T_2 \). For example, \( T_i^L \) as a function of the host’s acclimatization temperature would be determined using the following equation:

\[
T_i^L(T_{accl}) = \frac{T_i^L(T_1) - T_i^L(T_2)}{T_1 - T_2} \cdot (T_{accl} - T_1) + T_i^L(T_2) \tag{5}
\]

To model changes in host and parasite acclimatization status through time \( (t) \) in a changing temperature environment, we assumed that each organism is acclimatized to the weighted average of temperature \( (T) \) over the past \( \psi \) time units, with greater weight given to more-recent temperatures, as follows:

\[
T_{accl}^i(t) = \frac{2}{\psi_i} \int_{0}^{\psi_i} \left[ 1 - \frac{x}{\psi_i} \right] \cdot T(t - x) dx \tag{6a}
\]

where \( \psi \) and \( \psi_i \) represent the time it takes for the parasite and host to acclimatize, respectively. Here too, metabolic theory provides guidance for parameter estimation, because the time it takes for organisms to acclimatize following a temperature shift \( (\psi) \) is likely to scale with organism mass, with larger organisms taking longer to acclimatize than smaller organisms (Raffel et al., 2013). If we assume that \( \psi \) scales with mass in a similar manner to organism development times, then

\[
\psi \propto \text{Mass}^{1/14} \tag{7}
\]

As an example of how this model could be applied to predict parasite growth rates in or on hosts in a variable temperature environment, we applied the model parameters used to generate Fig. 2 (see above) to a model of parasite replication rates in a changing temperature environment. We generated time series of shifting temperatures (shifts between 10 and 25°C), ranging from shifts occurring every day to shifts occurring every 50 days. These time series were then converted to continuous functions using linear interpolation (function ‘connector’ from the ‘mosaic’ package; Pruim et al., 2012), which were then used to generate model predictions for infectivity \( (i_T) \), resistance \( (r_T) \), and parasite replication rate \( (\lambda_T) \) at each time point. The high and low deactivation temperatures used to generate Fig. 2 (see above) were assumed to be for warm-acclimatized parasites and hosts \( (T_{accl} = 25°C) \), whereas deactivation temperatures were 4 and 8°C lower for cold-acclimatized parasites and hosts, respectively \( (T_{accl} = 5°C) \). Hosts and parasites were assumed to take 20 and 2 days, respectively, to acclimatize fully to a new temperature \( (\psi_i = 20; \psi_r = 2) \), and were acclimatized to 25°C at the start of each time series. This temperature-explicit model predicted that infectivity and resistance would both increase with time following a temperature shift (Fig. 5A and B) and that parasite replication rates would be maximal with intermediate temperature shift frequencies (Fig. 5C), as postulated by Raffel et al. (2013).

Importantly, this modelling framework that builds upon the models of Molnár et al. (2013) should facilitate the prediction of the magnitude and direction of a change in disease risk in response to known or predicted changes in both
Conclusions

Here we argued for greater integration of physiology and disease ecology to provide better understanding of climate- and disease-associated host declines. We recommend the incorporation into predictive mathematical models both non-linear responses to climate and differences in the acclimatization responses of hosts and parasites to climatic shifts, because both have recently been shown to have important consequences for disease dynamics associated with host declines. In particular, rather than simply modelling climatic means, predictive models should move towards capturing changes in climatic variances and extremes, given that these changes are a hallmark of climate change (Easterling et al., 2000; Meehl et al., 2000, 2009; Raisanen, 2002; Kunkel et al., 2003). The metabolic theory of ecology offers intriguing promise for predicting host–parasite interactions within an environmental context. Given that parasites are always substantially smaller than their hosts and that body size is a reliable proxy of metabolic rate, the MTE should help to integrate physiological mechanisms and large-scale spatiotemporal processes to enable successful prediction of how changes in climatic means, variances, and extremes will affect host–parasite interactions. We hope that our mathematical model, based on the integration of metabolic theory and physiological mechanisms, provides the scaffolding to enable more successful prediction of how host–parasite interactions will respond to changes in climatic means, variances, and extremes. However, the success of these predictive models will depend on addressing many of the outstanding questions regarding the relationships between climate, physiology, and host–parasite interactions (Box 3). Addressing these pressing knowledge gaps and using this new information to improve climate–disease models should improve the capacity to predict how climate change will affect disease risk for species of conservation concern.

Acknowledgements

This work was supported by grants from the US Department of Agriculture (NRI 2006-01370, 2009-35102-05043 to J.R.R.), the US Environmental Protection Agency (STAR R833835, CAREER 83518801 to J.R.R.), and the National Science Foundation (EF-1241889 to J.R.R., IOS-1121529 to P.T.J.J. and T.R.R.), and the David and Lucile Packard Foundation (to P.T.J.J.).

References


Scherm H, van Bruggen AHC (1994) Global warming and nonlinear growth: how important are changes in average temperature? *Phytopathology* 84: 1380–1384.


