Environmental variability can promote parasite diversity within hosts and transmission among hosts

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1.0.0. Abstract

While the mechanisms that govern disease emergence and spread among hosts are increasingly well-described, the mechanisms that promote parasite diversity within-hosts, affecting host outcomes and spillover potential, have been comparatively understudied. Furthermore, while attention has been paid to the effects of increasing temperatures on disease systems, the effects of environmental variability have been left underexplored, despite rising climatic variability and internal temperature variability in a prolific reservoir for disease. To investigate the impacts of environmental variability on parasite diversity within-hosts, we analyzed a model of within-host population dynamics wherein two parasites indirectly compete through the host's immune response. We simulated the model under constant, demographically stochastic, environmentally stochastic, and demographically and environmentally stochastic conditions, and analysed the viability and longevity of non-equilibrium parasite co-occurrence. We found that environmental stochasticity increased the viability and longevity of parasite co-

occurrence, suggesting that thermal variability arising from climatic change and as a physiological trait may promote parasite diversity within ectotherms and help explain bats' propensity to support diverse communities of parasites. Further, we found that under certain conditions, the transmissibility of co-occurring parasites can surpass the transmissibility of single parasites, suggesting that thermal variability may increase the transmission potential of co-occurring parasites.

2.0.0. Introduction

In 2019, SARS-CoV-2 spilled into the human population, sparking a global pandemic from which we've yet to emerge. Worryingly, SARS-CoV-2 is not the first zoonotic disease we've encountered, nor is it predicted to be the last (Baker et al., 2022; Jones et al., 2008; Taylor et al., 2001). In recent years, it has become clear that climate and land-use change can facilitate novel species interactions and increase contact rates between wild populations and humans, resulting in devastating epidemics and enabling spillover events and disease emergence among wild and human hosts alike (Daszak et al., 2000, 2001; Patz et al., 2004; R. Plowright et al., 2020; R. K. Plowright et al., 2017). However, despite the consequential interplay between within- and among-host processes, the mechanisms that promote parasite diversity within hosts and create kindling for events observed among hosts have been understudied. In particular, while stabilizing mechanisms like niche differentiation have been employed to explain the maintenance of parasite diversity within hosts, the contributions of equalizing mechanisms, which decrease average fitness differences between competitors, have yet to be examined (Bashey, 2015; Chesson, 2000; Chesson & Huntly, 1997; Karvonen et al., 2006; Rynkiewicz et al., 2015).

An intermediate level of disturbance may promote species diversity by forestalling the competitive advantages allowed by low levels of disturbance, and the extinction risks brought on by high levels of disturbance (Chesson, 1994; Connell, 1978). Expanding on the work of Connell (1978) and Chesson (1994), Roxburgh et al. (2004) posited that because different species respond to disturbances in different ways, there are myriad ways in which diversity may be generated, thereby interpreting the intermediate disturbance hypothesis not as a mechanism unto itself, but as a collection of mechanisms through which intermediately sized or timed disturbances in resource availability or environmental conditions may promote diversity (Roxburgh et al., 2004). Though the applicability of the intermediate disturbance hypothesis has been debated, positive and negative effects of environmental variability on diversity have been well-documented across systems (Laprise & Dodson, 1994; Righetti et al., 2019; Shurin et al., 2010; Vega-Rodriguez et al., 2015).

When considering the effects of environmental variability on parasite diversity within hosts, there arise a number of ways to conceptualize environmental variability. First, one may consider rising environmental variability as a facet of climate change (Stocker et al., 2013). While much attention has been paid to the effects of rising temperatures on disease systems, far less has been invested in exploring the effects of rising temperature variability, despite evidence of its outsized impacts on species outcomes (Dobson & Carper, 1992; Lafferty, 2009; Lawson et al., 2015; Vasseur et al., 2014). In ectothermic hosts, increasingly erratic external conditions will affect the internal conditions of the host, thereby also affecting any parasites the host may harbour (Cizauskas et al., 2017). A relationship between thermal variability and within-

host parasite diversity may be of particular interest when considered alongside the long-debated relationship between climate change and widespread disease-mediated amphibian declines (Cohen et al., 2019; Daszak et al., 1999, 2003; Lips et al., 2008; Pounds et al., 1999; Rohr et al., 2008; Rohr & Raffel, 2010).

Second, one may consider environmental variability as a physiological trait of hosts. In particular, bats (order *Chiroptera*) have long been acknowledged as prolific reservoirs for disease and have oft been implicated in zoonotic spillover events (Brook & Dobson, 2015; Calisher et al., 2006; Irving et al., 2021). Bats are also unique among mammals in their ability to vary their internal temperature according to their activity level (e.g. torpor, flight) (Fumagalli et al., 2021). It has been theorized that these variations in internal temperature may aid bats' immune responses, allowing them to carry microparasites without suffering outsized morbidity (Fumagalli et al., 2021; Luo et al., 2021). Extending on that idea, it seems pertinent to question how internal temperature variation may contribute to bats' propensity to support diverse communities of parasites.

We used a model to investigate the impacts of environmental variability on the viability and maintenance of parasite diversity within hosts. We began by modifying Antia et al.'s (1994) model of within-host population dynamics to include two parasite species or strains that indirectly interact via the host's immune system. We analyzed a deterministic version of the model, a demographically stochastic version of the model, an environmentally stochastic version of the model, and a demographically and environmentally stochastic version of the model. Within the environmentally stochastic versions of the model, we varied the magnitude and frequency of thermal disturbance within the system. Between and among the deterministic and stochastic simulations of

the model, we compared the ability of the secondary parasite to invade a system containing the primary parasite and the host's immune system, and the duration of time for which the primary and secondary parasites co-occurred. Further, we compared the transmission potentials of co-occurring parasites with the transmission potential of a single parasite. We found that compared to a constant environment, a variable environment tended to increase the ability of the secondary parasite to invade the system, facilitated longer periods of co-occurrence between the primary and secondary parasites, and increased the transmissibility of co-occurring parasites. These results suggest that climatic changes may have significant effects on parasite diversity within ectothermic hosts, provide insight on bats' propensity to support diverse communities of parasites, and influence transmission dynamics at the among-host level.

3.0.0. Methods

3.1.0. Model Description

3.1.1. Within-Host Population Dynamics Model

We began with a model of within host population dynamics based on Antia et al., (1994) that represents the interaction between an infecting parasite and its host's immune system as analogous to the interaction between a prey item and its predator. The model assumes that the replication rate of the host's immune system is proportional to parasite density at low parasite densities, and saturates at high parasite densities, allowing the host's immune system to either extirpate or succumb to the infection (Antia et al., 1994). We adapted the model to include a second parasite that interacts indirectly with the primary parasite through the host's immune response (Eqns. 1-3, Table 1).

$$(1) \quad P_i(t+1) = (1 + r_i - \left(1 - e^{-kI(t)}\right))P_i(t)$$

$$(2)\quad P_j(t+1) = (1 + r_j - \left(1 - e^{-kI(t)}\right))P_j(t)$$

$$(3)\quad I(t+1) = (1 + \rho\left(\frac{P_i(t)}{P_i(t)+\phi} + \frac{P_j(t)}{P_j(t)+\phi}\right))I(t)$$

Table 1: Parameter definitions and values.

Symbol	Parameter	Value in Antia et al. (1994)	Value Used
P_i and P_j	Parasite abundance	1*	1*
I	Host immune cell abundance	1*	1*
r_i and r_j	Replication rates of parasites	0.1 – 10.0	0.1 – 2.0†
k	Rate at which parasites are destroyed by host's immune system	10^{-3}	10^{-2}
ρ	Maximum replication rate of host's immune system	1.0	1.0
ϕ	Parasite density at which replication rate of host's immune system is half its maximum	10^3	10^3
D	Lethal within-host parasite density	10^9	10^9

* Initial conditions.
† Dependent on the temperature of system in environmentally stochastic simulations.

To compare the impacts of different types of stochasticity on parasite diversity, we wrote a demographically stochastic version of the model (S_D), an environmentally stochastic version of the model (S_E), and a demographically and environmentally stochastic version of the model (S_{DE}). For the demographically stochastic version of the model, we wrote the model's growth terms as Poisson processes, and mortality term as a binomial process (Eqns. 4-6).

$$(4)\quad P_i(t+1) = P_i(t) + P_{i,B}(t) - P_{i,D}(t)$$

$$(5)\quad P_j(t+1) = P_j(t) + P_{j,B}(t) - P_{j,D}(t)$$

$$(6)\quad I(t+1) = I(t) + I_B(t)$$

In Eqns. (4) and (5), $P_{i,B}(t)$ and $P_{j,B}(t)$ are Poisson random variables such that $P_{i,B}(t) \sim Poisson(1, \lambda_i)$, where $\lambda_i = r_i \cdot P_i(t)$, and $P_{j,B}(t) \sim Poisson(1, \lambda_j)$, where $\lambda_j = r_j \cdot P_j(t)$. In Eqn. (6), $I_B(t)$ is a Poisson random variable such that $I_B(t) \sim Poisson(1, \lambda)$, where $\lambda = \rho\left(\frac{P_i(t)}{P_i(t)+\phi} + \frac{P_j(t)}{P_j(t)+\phi}\right) I(t)$. In Eqns. (4) and (5), $P_{i,D}(t)$ and $P_{j,D}(t)$ are binomial random variables such that $P_{i,D}(t) \sim Binomial(1, P_i(t), p)$, where $p = 1 - e^{-kI(t)}$, and $P_{j,D}(t) \sim Binomial(1, P_j(t), p)$. To write the environmentally stochastic version of the model, we generated a stochastic temperature series and allowed the replication rates of each parasite to vary in response to the temperature of the system (Eqns. 7-9).

(7) $$P_i(t+1) = (1 + r_i(T(t+1)) - \left(1 - e^{-kI(t)}\right))P_i(t)$$

(8) $$P_j(t+1) = (1 + r_j(T(t+1)) - \left(1 - e^{-kI(t)}\right))P_j(t)$$

(9) $$I(t+1) = (1 + \rho\left(\frac{P_i(t)}{P_i(t)+\phi} + \frac{P_j(t)}{P_j(t)+\phi}\right))I(t)$$

We used first-order autocorrelated Gaussian noise to generate stochastic temperature series. We began with a value of 0, and generated the next value, $T(t+1)$, by multiplying the previous value by the coefficient of autocorrelation (AC = 0.25), and summing the resulting value with a value drawn from a normal random variable with a mean of zero. When considering the effects of rising and frequent environmental variability and variations, we varied and held constant the standard deviation of the normal random variable, respectively. We then added the average temperature of the system to each value in the series. Values outside the thermal range of the system were re-drawn. We then converted the stochastic temperature series into series of replication rates using various parameterizations of the Sharpe-Schoolfield sub-model, as detailed below (Eqns. 7.1, 8.1; Table 2, Table A1).

$$(7.1) \quad r_i(T(t+1)) = r_{i,0} e^{\frac{-E_{r_i}}{k}\left(\frac{1}{T(t+1)} - \frac{1}{T_0}\right)} \cdot \left(1 + e^{\frac{E_{r_i}^L}{k}\left(\frac{1}{T_{r_i}^L} - \frac{1}{T(t+1)}\right)} + e^{\frac{E_{r_i}^H}{k}\left(\frac{1}{T_{r_i}^H} - \frac{1}{T(t+1)}\right)}\right)^{-1}$$

$$(8.1) \quad r_j(T(t+1)) = r_{j,0} e^{\frac{-E_{r_j}}{k}\left(\frac{1}{T(t+1)} - \frac{1}{T_0}\right)} \cdot \left(1 + e^{\frac{E_{r_j}^L}{k}\left(\frac{1}{T_{r_j}^L} - \frac{1}{T(t+1)}\right)} + e^{\frac{E_{r_j}^H}{k}\left(\frac{1}{T_{r_j}^H} - \frac{1}{T(t+1)}\right)}\right)^{-1}$$

Table 2: Parameter definitions. See Table A1 for parameter values.

Symbol	Unit	Parameter
T	K	Temperature of the system at time t
r_0		Baseline values of r_i or r_j at a reference temperature T_0
T_0	K	Reference temperature (set arbitrarily such that $T^L << T_0 << T^L$)
E_r	eV	Activation energy of r_i or r_j
E_r^L, E_r^H	eV	Low- and high-temperature inactivation energies of r_i or r_j
T_r^L, T_r^H	K	Low- and high-temperature inactivation thresholds for r_i or r_j
k		Boltzmann's constant

3.1.2. Sharpe-Schoolfield Sub-Model

The Metabolic Theory of Ecology (MTE) predicts how metabolic rates control ecological processes across levels of organization, and explains how metabolic rates vary with body size and temperature (Brown et al., 2004). Building off the MTE, the Boltzmann-Arrhenius (BA) relation describes metabolism as a function of temperature. As an extension of the BA relation, the Sharpe-Schoolfield model characterizes the performance of a trait as a function of temperature through a thermal performance curve (TPC) (Dell et al., 2011; Molnár et al., 2017; Schoolfield et al., 1981). When applied to disease systems, the Sharpe-Schoolfield model has been shown to accurately describe the relationships between temperature and species traits, and has proven useful in investigating the relationship between rising temperatures and disease transmission (Kirk et al., 2018; Molnár et al., 2013).

We used various parameterizations of the Sharpe-Schoolfield model to generate a suite of paired thermal performance curves relating the temperature of the system to the replication rates of two parasites (r_i and r_j) (see Figure 1 for a schematic of the experimental design). We generated two sets of four paired thermal performance curves, representing two thermal environments, and four thermal scenarios per environment (Table S1). The first thermal environment exhibits a lower average temperature (min. = 0°C, mean = 18 to 20.8°C, max. = 30°C), while the second exhibits a higher average temperature (min. = 0°C, mean = 25.5 to 28°C, max. = 40°C), representing the thermal conditions within ectotherms and bats, respectively (Fumagalli et al., 2021). Each thermal scenario describes a different relationship between the temperature of the system and the parasites' replication rates. Within the first scenario, r_i and r_j respond identically to the temperature of the system (Fig. 1A, 2A). Within the second scenario, r_i and r_j peak on opposite sides of the average temperature of the system (Fig. 1B, 2B). To develop the third scenario, we shifted the average temperature of the system to give the first parasite, P_i, a thermal advantage (Fig. 1C, 2C). We considered two versions of the fourth scenario, each of which give the secondary parasite a thermal advantage. To develop the first version, (A), we shifted the average temperature of the system to give the secondary parasite a quantitatively comparable thermal advantage (Fig. 1D, 2D). For the second version, (B), we reversed the curves resulting from the third scenario to give the secondary parasite the same thermal advantage given to the primary parasite and isolate the effect of asymmetrical thermal performance curves (Fig. 1E, 2E). Given that versions (A) and (B) produced qualitatively comparable results, we will only discuss version (A) moving forward (see supplement

for complete results). Within each scenario, the average temperature of the system was chosen to maintain quantitatively comparable (1) parasite replication rates between scenarios and (2) differences between parasite replication rates at the average temperature of the system between the third and fourth scenarios.

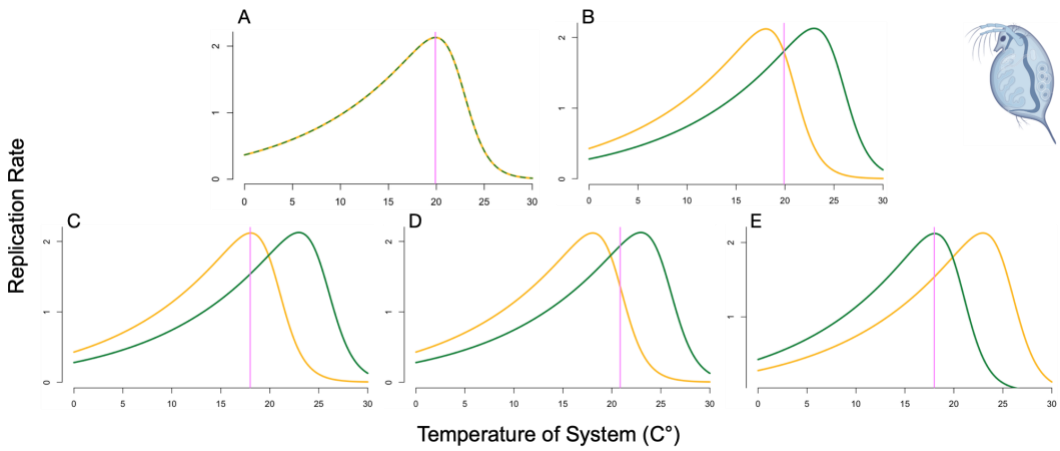

Figure 1: Sharpe-Schoolfield thermal performance curves relating the temperature of the system to the replication rates (r_i and r_j) of two parasites (P_i and P_j) in the low-average temperature environment, representing the conditions within ectotherms. Yellow lines show the relationship between the temperature of the system and the replication rate (r_i) of P_i. Green lines show the relationship between the temperature of the system and the replication rate (r_j) of P_j. Pink lines denote the average temperature of the system. Each panel (A-E) shows a different thermal scenario. Panels A, B, and C show the first, second, and third thermal scenarios. Panels D and E show versions A and B of the fourth thermal scenario.

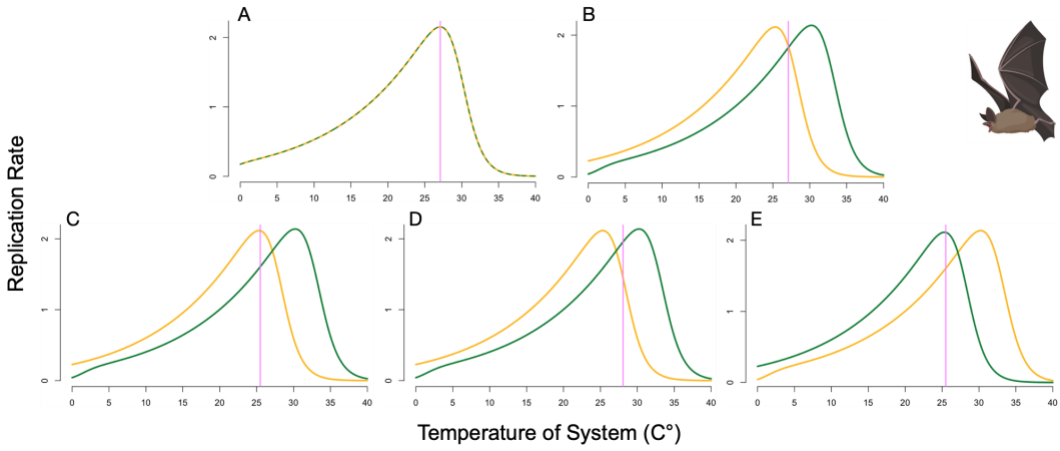

Figure 2: Sharpe-Schoolfield thermal performance curves relating the temperature of the system to the replication rates (r_i and r_j) of two parasites (P_i and P_j) in the low-average temperature environment, representing the conditions within ectotherms. Yellow lines show the relationship between the temperature of the system and the replication rate (r_i) of P_i. Green lines show the relationship between the temperature of the system and the replication rate (r_j) of P_j. Pink lines denote the average temperature of the system. Each panel (A-E) shows a different thermal scenario. Panels A, B, and C show the first, second, and third thermal scenarios. Panels D and E show versions A and B of the fourth thermal scenario.

3.2.0. Model Simulations

Within each thermal environment and scenario, we simulated the deterministic model (D), and each of the three stochastic models (S_D, S_E, S_{DE}) for fifty days with a discretization time step of 0.1, which was sufficient to capture the full course of parasite infection and clearance across all simulations. We began each set of simulations with the primary parasite, P_i, and the host's immune system in the system, at initial abundances of 1 as the initial condition. We then considered all cases for the introduction time of the secondary parasite, P_j, from its introduction at the onset of infection, to its introduction on the 49th day of infection.

For each environmentally stochastic model (S_E, S_{DE}) simulation, we generated a new stochastic temperature series and the corresponding series of replication rates for each parasite. When determining the ways in which new temperatures would be selected, we considered two axes of thermal disturbance: magnitude and frequency. To vary the magnitude of disturbance, we varied the standard deviation of the normal random variable in the temperature autocorrelation function, starting from zero (no thermal disturbance) and increasing by two until the effect of magnitude on co-occurrence plateaued (where SD ≈ 30-40), resulting in 15 and 20 magnitudes of disturbance in the low and high average temperature environments, respectively. To vary the frequency of thermal disturbance, we ran the model with one temperature change every 10, 9, 8, 7, 6, 5, 4, 3, 2, and 1 days, and 2, 5, and 10 temperature changes per day (preliminary simulations indicated this was sufficient to characterize the results), resulting in thirteen frequencies of disturbance. We ran each permutation of each stochastic simulation one thousand times (Fig. 3).

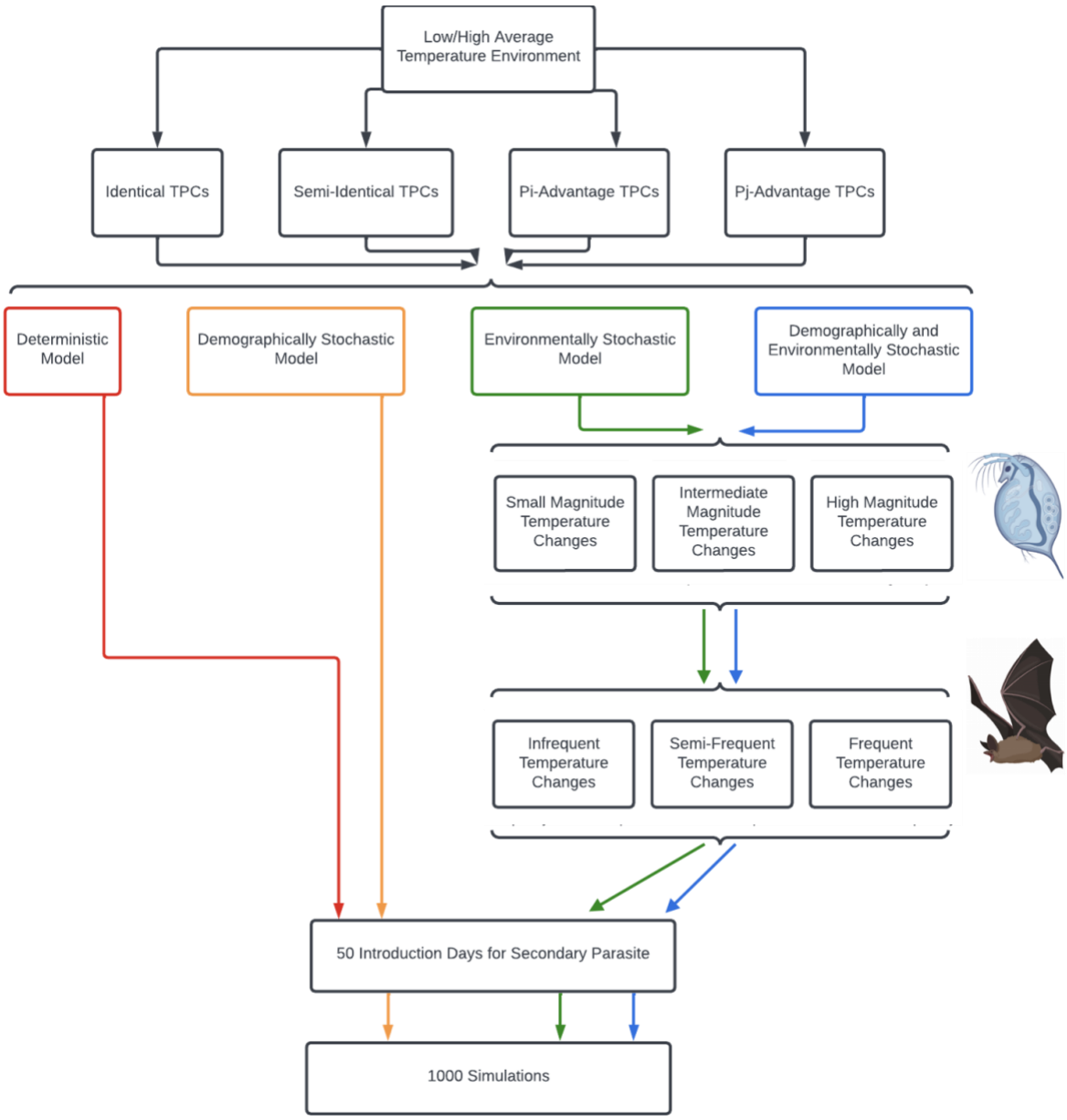

Figure 3: Schematic detailing simulations. Within the low- and high- average temperature environments, we considered four thermal scenarios. We then considered four models (deterministic, demographically stochastic, environmentally stochastic, and demographically and environmentally stochastic). When simulating the environmentally stochastic models, we considered a range of magnitudes and frequencies of disturbance. When simulating each of the four models, we considered 50 introduction days. When simulating the stochastic models, we conducted 1000 simulation per permutation.

3.3.0. Co-Occurrence Analyses

For each simulation, we evaluated the duration of time for which the primary and secondary parasites co-occurred (i.e. the number of time steps for which P_i and P_j had population abundances greater than one). We then summarised these outputs to

quantify distributions of co-occurrence for each stochastic treatment. Using the deterministic simulation outputs as a baseline, we investigated the effects of environmental variability on the viability and maintenance of parasite diversity by comparing the ability of the secondary parasite to invade a single-parasite system, and the duration of time for which the primary and secondary parasites co-occurred across stochastic treatments. Additionally, we analysed (1) the proportion of stochastic simulations per treatment that resulted in longer periods of co-occurrence than the deterministic simulation to quantify rarity of outcome, and (2) competitive outcomes of each treatment to gain insight on the biological drivers of said outcomes.

3.4.0. Transmissibility Analyses

To explore the impacts of co-infection on transmission potential, we compared the transmission potentials of co-occurring parasites with the transmission potential of a single parasite in constant and variable environments. As per Antia et al., (1994), we determined the total transmission (q_i, q_j, q, where q is the total transmission of the single parasite) of a parasite (P_i, P_j, P, where P is the single parasite) from an infected host by taking the integral of the rate of transmission (u) of each parasite from the host over the duration of infection (Eqns. 10.1-10.3). For simplicity, we set the rate of transmission to one.

$$(10.1) \quad q_i = \int_0^\infty uP_i(t)dt$$

$$(10.2) \quad q_j = \int_0^\infty uP_j(t)dt$$

$$(10.3) \quad q = \int_0^\infty uP(t)dt$$

To compare constant and variable environments, we analysed multi-parasite and single-parasite versions of the S_D and S_{DE} models. When analysing outputs from the multi-parasite and single-parasite versions of the S_{DE} model, we considered both thermal environments, and all four thermal scenarios. Within each thermal environment and scenario, we considered a fully factorial design with regards to the magnitude and frequency of disturbance.

4.0.0. Results

Within the deterministic model, the secondary parasite could invade ($P_{j(t+1)} > P_{j(t)}$) when $I(t) < \frac{-\ln(1-r_j)}{k}$. Our parameterization of the model allowed the secondary parasite to invade when introduced before the tenth to twelfth day of infection, resulting in 8.4 to 9.2 days of co-occurrence, depending on thermal environment and scenario (Fig. 4, Supplementary Datafile 1-1:10).

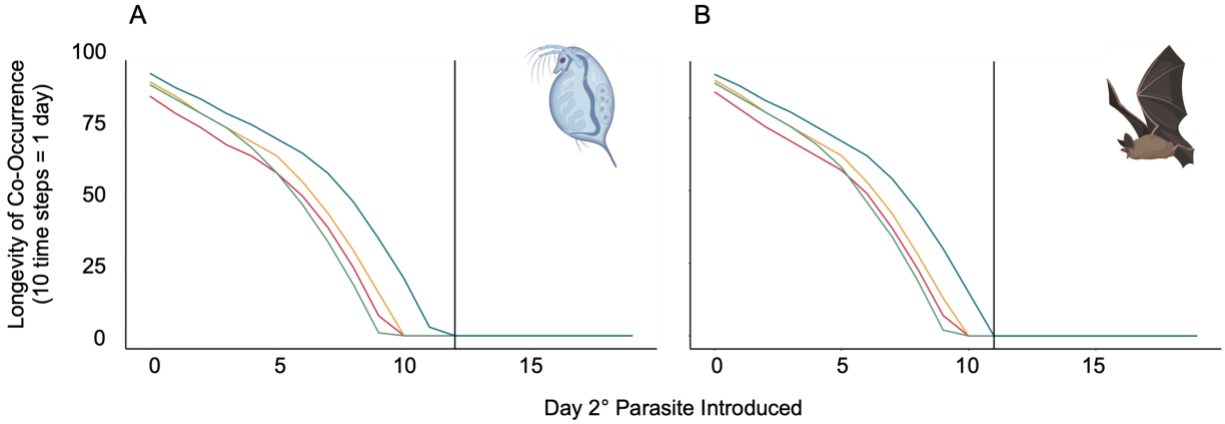

Figure 4: Longevity of co-occurrence as per the deterministic model. Both panels show the number of time steps for which P_i and P_j have population abundances greater than one, by introduction day, as per the deterministic model. The red, yellow, green, and blue lines show results from the first, second, third, and fourth thermal scenarios, respectively. The black line denotes the first day on which the introduction of the secondary parasite, P_j, does not result in any co-occurrence between the two parasites. Panel A shows the results from the low-average temperature environment. Panel B shows the results from the high-average temperature environment.

Within both thermal environments, simulation outputs show that compared to deterministic conditions, the introduction of demographic stochasticity has little effect on

co-occurrence (Supplementary Datafile 2-1:10), while a thermally variable environment increases the ability of the secondary parasite to invade the system and facilitates longer periods of co-occurrence between the primary and secondary parasites. More specifically, the parasites co-occur for longer when the secondary parasite is introduced earlier (Figs. 5, S1A-S1E).

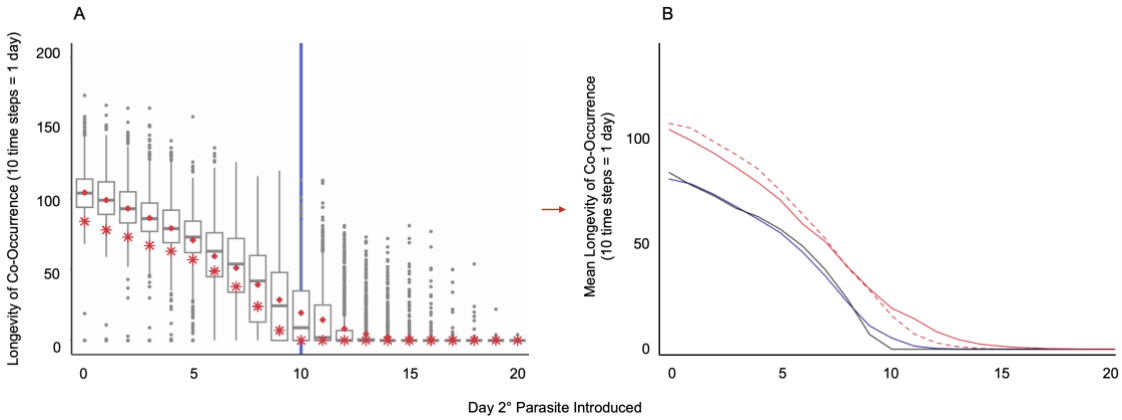

Figure 5: Simulation results and summary. Panel A shows the number of time steps for which P_i and P_j have population abundances greater than one, by introduction day, as per the demographically and environmentally stochastic model (in the low-average temperature environment, under the first thermal scenario, when the magnitude and frequency of disturbance are intermediate). Each dot shows the result of a single simulation. The grey lines represent medians, and red diamonds represent means. Red stars show the number of time steps for which P_i and P_j have population abundances greater than one as per the deterministic model. The blue line denotes the first day on which the introduction of the secondary parasite, P_j, does not result in any co-occurrence between the two parasites. Panel B shows a summarised version of Panel A, where each line represents mean longevities of co-occurrence by introduction day. The black and blue lines show results from the deterministic and demographically stochastic model simulations, respectively. The solid and dashed red lines show results from the environmentally stochastic and demographically and environmentally stochastic model simulations, respectively.

Additionally, while duration of co-occurrence is maximised under the fourth thermal scenario (P_j has a thermal advantage over P_i), the difference between the deterministic and environmentally stochastic models is not consistently maximised by any one thermal scenario. With respect to the combined effects of magnitude and frequency of thermal disturbance on the longevity of co-occurrence between the primary and secondary parasites, while higher magnitudes and frequencies of disturbance tend to promote longer periods of co-occurrence, increasing magnitudes of disturbance

produce a less steep effect than do increasing frequencies of disturbance. These findings are common among thermal environments and scenarios.

4.1.0. Ectotherms: Low Average Temperature Environment (LATE)

When the frequency of thermal disturbance is fixed and the magnitude of thermal disturbance varies, environmental variation can allow for co-occurrence beyond the deterministically simulated threshold (DST) and can promote longer periods of co-occurrence compared with the deterministic and demographically stochastic environments. More specifically, when the frequency of thermal disturbance is fixed at an intermediate value of ten (once per day) and the magnitude of thermal disturbance varies, environmental variation allows for some amount of co-occurrence when the secondary parasite is introduced 10 to 25 (S_E) and 17 to 20 days (S_{DE}) after the DST (9 to 11 days, depending on thermal scenario), and allows parasites to co-occur for a maximum average of 2.95 to 3.84 days (S_E) and 2.56 to 3.66 days (S_{DE}) past the deterministic maximum (8.4 to 9.2 days) and an absolute maximum of 17.5 to 22.8 days (S_E) and 18.1 to 22.4 days (S_{DE}), depending on thermal scenario. Further, as the size of thermal disturbances increases, periods of co-occurrence increase in length to a saturation point (standard deviation of the normal random variable in the temperature autocorrelation function ≈ 24-30, depending on thermal environment and scenario) (Figs. 6, S2, S4A-S4E, Supplementary Datafiles 3-1:5, 4-1:5).

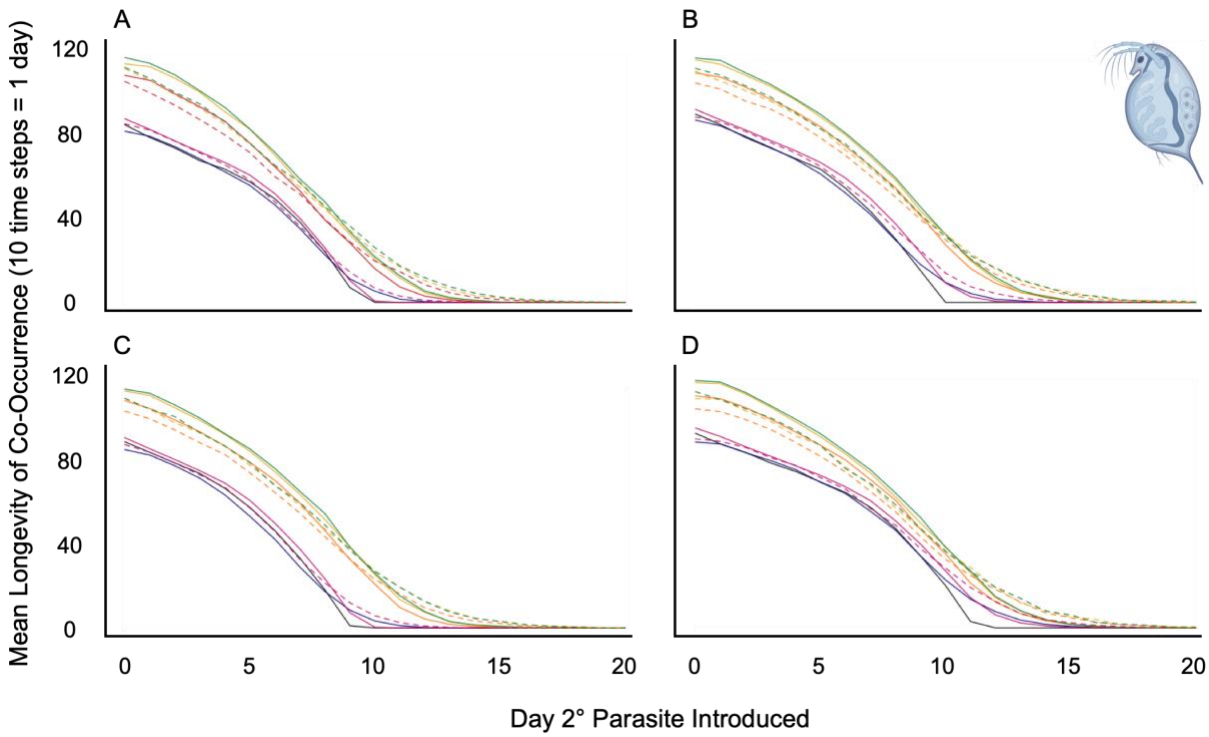

Figure 6: The impacts of varying magnitudes of disturbance on longevity of co-occurrence in the low-average temperature environment. Each panel shows the mean number of time steps for which P_i and P_j have population abundances greater than one, by introduction day, when the magnitude of disturbance varies, and the frequency of disturbance is intermediate (once per day). The black and blue lines show results from the deterministic and demographically stochastic model simulations. Solid and dashed lines show results from the environmentally and demographically and environmentally model simulations. Pink, orange, yellow, and green lines show results when magnitudes of disturbance are low (SD = 2), low-intermediate (SD = 10), intermediate-high (SD = 20), and high (SD = 30), respectively. Panels A-D show results from the first, second, third, and fourth thermal scenarios.

4.2.0. Bats: High Average Temperature Environment (HATE)

When the magnitude of thermal disturbance is fixed and the frequency of thermal disturbance varies, environmental variation can allow for co-occurrence beyond the deterministically simulated threshold and can promote longer periods of co-occurrence compared with the deterministic and demographically stochastic environments. More specifically, when the magnitude of thermal disturbance is fixed at an intermediate value (standard deviation of the normal random variable in the temperature autocorrelation function = 10) and the frequency of thermal disturbance varies, environmental variation allows for some amount of co-occurrence when the secondary parasite is introduced 23 to 35 (S_E) and 17 to 36 days (S_{DE}) after the DST (9 to 10 days, depending on thermal

scenario). When the frequency of disturbance is low (once every seven to ten days), periods of co-occurrence are similar in length to those resulting from deterministic simulations. Given that deterministically, P_i and P_j can co-occur for a maximum of nine days, environments subject to infrequent disturbances are functionally similar to a deterministic environment, making the outcome of a simulation reliant on the initial thermal conditions of the system. Interestingly, when the frequency of disturbance is intermediate (once every few days), periods of co-occurrence are routinely shorter than those resulting from deterministic simulations, to an average minimum of 0.96 to 1.53 (S_E) and 1.21 to 1.95 (S_{DE}) days fewer than the deterministic maximum (8.4 to 9.0 days). Periods of co-occurrence are longest when disturbances are very frequent (once every two days to ten times per day). When disturbances are very frequent, P_i and P_j co-occur for an average maximum of 2.63 to 4.57 (S_E) and 2.87 and 4.13 (S_{DE}) days past the deterministic maximum and an absolute maximum of 24.7 to 36.7 (S_E) and 23.5 to 28.5 (S_{DE}) days, depending on thermal scenario (see supplement for complete results) (Figs. 7, S3, S7A-S7E, Supplementary Datafiles 3-6:10, 4-6:10).

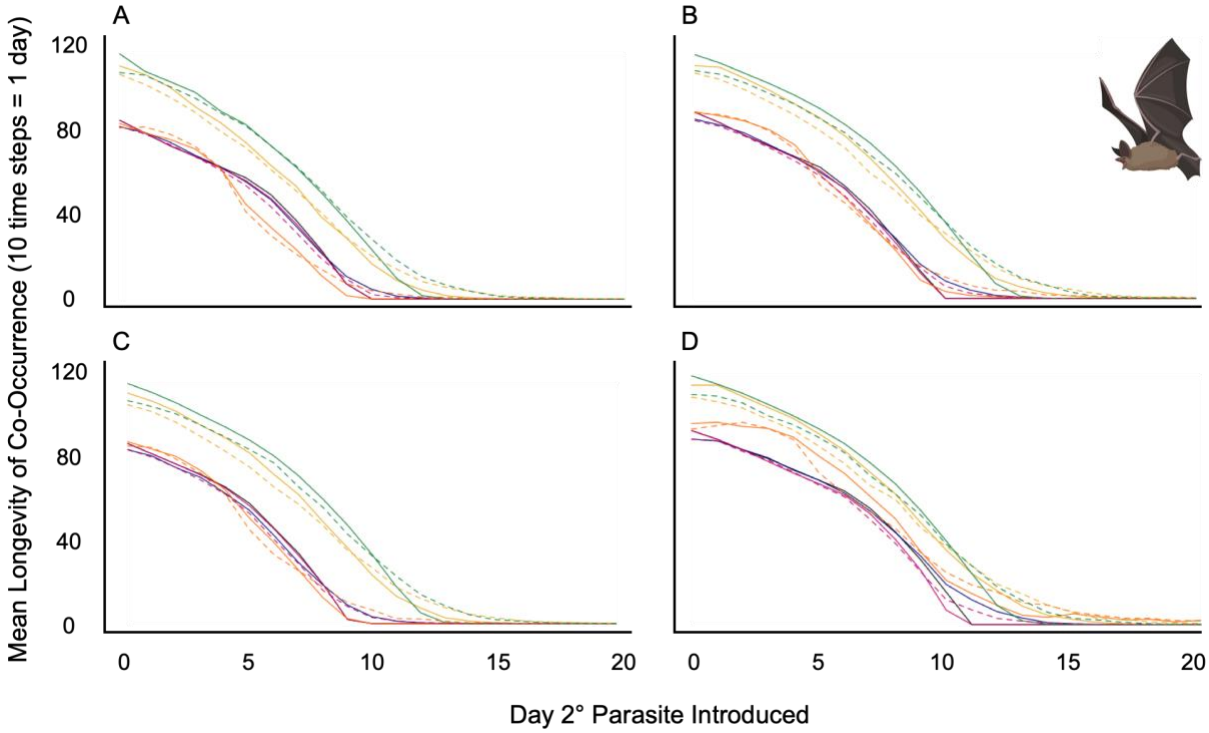

Figure 7: The impacts of varying frequencies of disturbance on longevity of co-occurrence in the high-average temperature environment. Each panel shows the mean number of time steps for which P_i and P_j have population abundances greater than one, by introduction day, when the frequency of disturbance varies, and the magnitude of disturbance is intermediate (SD = 10). The black and blue lines show results from the deterministic and demographically stochastic model simulations. Solid and dashed lines show results from the environmentally and demographically and environmentally model simulations. Pink, orange, yellow, and green lines show results when frequencies of disturbance are low (once every 10 days), low-intermediate (once every 5 days), intermediate-high (once per day), and high (ten times per day), respectively. Panels A-D show results from the first, second, third, and fourth thermal scenarios.

4.3.0. Rarity and Competitive Outcomes

Analyzing the number of simulations per treatment that resulted in a non-zero period of co-occurrence revealed that the effect of environmental variability on the viability and maintenance of parasite co-occurrence is not rare. When the secondary parasite is introduced early (before the 10th day of infection), $\gtrapprox$50% of environmentally stochastic simulations result in longer periods of co-occurrence than deterministic simulations. While the likelihood that an environmentally stochastic simulation will result in co-occurrence sharply declines when the secondary parasite is introduced after the deterministically simulated threshold, four to nine percent of environmentally stochastic

simulations result in some amount of co-occurrence four to six days after said threshold, depending on thermal scenario (Fig. S9).

Analyzing the competitive outcomes of each treatment revealed that under the second thermal scenario (r_i and r_j peak on opposite sides of the average temperature of the system), when P_i and P_j are introduced at the same time, P_j outlasts P_i 65.5% (LATE, S_E model) and 63.4% (LATE, S_{DE} model) of the time. Additionally, under the third thermal scenario (P_i has a thermal advantage), when P_i and P_j are introduced at the same time, P_i and P_j are equally likely to outlast each other (P_j outlasts P_i 49.9% (LATE, S_E model) and 51.0% (LATE, S_{DE} model) of the time), but under the fourth thermal scenario (P_j has a thermal advantage), P_j is much more likely to outlast P_i (P_j outlasts P_i 76.6% (LATE, S_E model) and 70.4% (LATE, S_{DE} model) of the time). Regardless of thermal environment or scenario, when the secondary parasite, P_j, is introduced later, P_i is more likely to outlast P_j, until the point at which P_j is introduced when P_i is about to be or has been extirpated (Fig. S11A-F). However, regardless of when P_j is introduced, simulations resulting in especially long periods of co-occurrence are equally likely to show either parasite outlasting the other (Fig. S10A-F).

4.4.0. Transmissibility

Comparing the transmission potentials (TPs) of co-occurring and single parasites revealed that under certain conditions, the transmissibility of co-occurring parasites can surpass the transmissibility of single parasites. Across thermal environments and scenarios, TPs from the multi-parasite version of the S_D model (median TP of P_i ranged between 1.49E+04 and 9.12E+05, median TP of P_j ranged between 2.59E+04 and 6.09E+05) were one to two orders of magnitude lower than TPs from the single-parasite

versions of the S_D model (median TP of P ranged between 3.62E+06 and 5.13E+07) (Supplementary Datafiles 5-1:16). Similarly, under the first three thermal scenarios, TPs from the multi-parasite version of the S_{DE} model (median TP of P_i ranged between 1.02E+04 and 1.05E+06, median TP of P_j ranged between 8.36E+03 and 3.00E+05) were one to two orders of magnitude lower than TPs from the single-parasite versions of the S_{DE} model (median TP of P ranged between 6.45E+04 and 3.41E+07). However, under the fourth thermal scenario, intermediate magnitudes and frequencies of disturbance often resulted in the TP of the secondary parasite, P_j (median TP ranged between 2.50E+04 and 7.76E+05), exceeding that of a single parasite (median TP ranged between 1.20E+05 and 1.07E+06. More specifically, in the low and high average temperature environments under the fourth thermal scenario, the TP of the secondary parasite, P_j, exceeded that of a single parasite in 62 of 195 and 60 of 260 disturbance regimes, or, in about 20-30% of disturbance regimes. In the low average temperature environment, the TP of P_j exceeded that of a single parasite by a maximum of 3.40E+05, when the magnitude of disturbance was equal to 20 and the frequency of disturbance was equal to 80 (Figs. 8A, S13A, Supplementary Datafiles 5-8). In the high average temperature environment, the TP of P_j exceeded that of a single parasite by a maximum of 2.55E+05, when the magnitude of disturbance was equal to 30 and the frequency of disturbance was equal to 80 (Figs. 8B, S13B, Supplementary Datafiles 5-16). Regardless of environment and scenario, the transmission potentials of co-occurring parasites peaked across a range of magnitudes of disturbance when the frequency of disturbance was low (once every ten days) to intermediate (once every six days) (Fig. S12A-H).

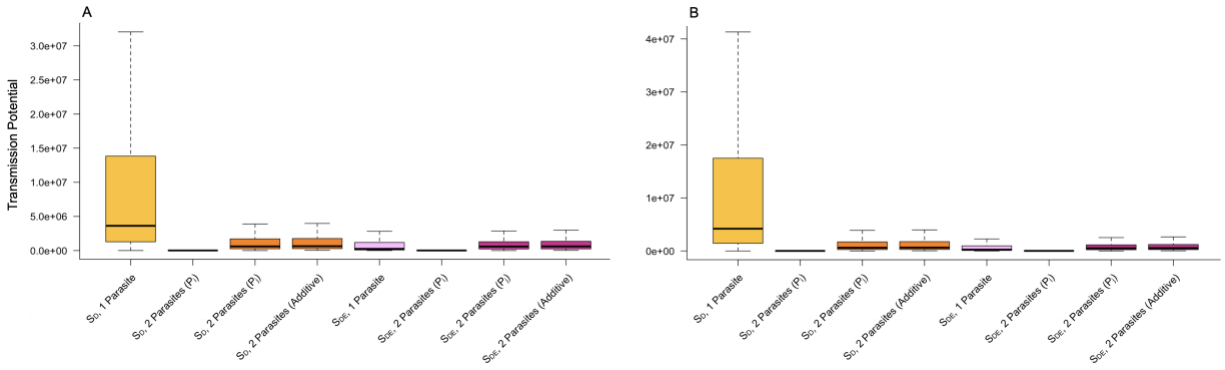

Figure 8: The impacts of environmental variability on the transmission potential of parasites. Panels A and B show the transmission potentials of parasites by model (S_D, S_{DE}) and formulation (1 Parasite, 2 Parasites). Further, Panels A and B show the two cases in which the inclusion of environmental variability resulted in the transmission potentials of co-occurring parasites exceeding that of a single parasite. Yellow (single parasite) and orange (co-occurring parasites) boxes show results from the demographically stochastic model simulations. Pink (single parasite) and magenta (co-occurring parasites) boxes show results from the demographically and environmentally stochastic model simulations. Panel A shows results from simulations in the low-average temperature environment, under the fourth thermal scenario when the magnitude of disturbance was intermediate (SD = 20), and disturbances occurred every eight days. Panel B shows results from simulations in the high-average temperature environment, under the fourth thermal scenario when the magnitude of disturbance was intermediate (SD = 30), and disturbances occurred every eight days.

5.0.0. Discussion

Despite increasing rates of disease emergence, the mechanisms that promote parasite diversity within hosts and create kindling for events observed among hosts, have been understudied (Baker et al., 2022; Jones et al., 2008; Taylor et al., 2001). It has been posited that by forestalling the competitive advantages allowed by low levels of disturbance, and the extinction risks brought on by high levels of disturbance, intermediately sized or timed disturbances in resource availability or environmental conditions may promote species diversity (Chesson, 1994; Connell, 1978; Roxburgh et al., 2004). Here, we investigated the potential for environmental variability, both as a facet of climate change and as a physiological trait unique to a prolific reservoir for disease, bats (order *Chiroptera*), to affect the viability and maintenance of within-host parasite diversity. The results of this work suggest that compared to a constant environment, demographic stochasticity has little impact on parasite co-occurrence, while the addition of environmental variability, and more specifically thermal variability,

can increase the ability of a secondary parasite to invade a single-parasite system, promote longer periods of co-occurrence between parasites, and increase the transmissibility of co-occurring parasites. The results of this work also indicate that the primary and secondary parasites were able to co-occur for longer when the secondary parasite was introduced earlier, and that the longevity of co-occurrence was maximised when the secondary parasite had a thermal advantage.

In the low average temperature environment, representing the thermal conditions within ectotherms subject to rising environmental variability, the relationship between the magnitude of thermal disturbance and the longevity of co-occurrence was initially positive and eventually saturating. It was determined that increasing magnitudes of disturbance produced a saturating response rather than the expected parabolic response due to the structure of the Sharpe-Schoolfield sub-model, which cannot generate negative replication rates. When we allowed for negative replication rates, larger disturbances began to have negative effects on parasite populations, resulting in the expected parabolic response, and implying that intermediate magnitudes of disturbance maximised the viability and longevity of parasite co-occurrence (Fig. S5A-D, Fig. S6A-D).

The relationship between climate change and disease-mediated amphibian declines has long been debated. While some argue that climatic changes may impede immune function or result in performance gaps between parasites and their hosts, and thus make amphibians more susceptible to infection, others argue that insufficient evidence should preclude a causal link (Cohen et al., 2019, 2019; Daszak et al., 1999, 2003; Lips et al., 2008; Pounds et al., 1999; Rohr et al., 2008). While much of the

literature proposes mean-climate hypotheses, some evidence suggests that intensifying El Niño events are increasing thermal variability, which may in turn affect amphibians' susceptibility to or ability to defend against infection (Rohr & Raffel, 2010). Similarly, emerging evidence suggests that in addition to rising mean temperatures, daily temperature fluctuations may affect the incubation period of malaria parasites and related vital rates, altering malaria transmission patterns (Paaijmans et al., 2010, 2013). Congruently, our findings provide theoretical evidence that thermal variability promotes the viability and maintenance of within-host parasite diversity, and thus suggest that as the climate continues to change, close attention should be paid to shifts in microparasite communities and their impacts on ectothermic hosts. In particular, well-documented climate-driven increases in disease incidence among a wide variety of marine organisms may constitute an important starting point for future work (Bates et al., 2009; Bruno et al., 2007; Carilli et al., 2012; Drinkwater et al., 2003; Harvell et al., 2001; Tracy et al., 2019).

In the high average temperature environment, intermediate and high frequencies of disturbance impeded and promoted the viability and longevity of parasite co-occurrence, respectively. Given the transient nature of infection specified by the underlying model, intermediate frequencies of disturbance (once every seven days, for example) resulted in the temperature of the system being disturbed towards the end of the infection period, when parasite populations were small and especially susceptible to unfavourable conditions. Conversely, high frequencies of disturbance resulted in the temperature of the system being disturbed throughout the duration of the infection period, and as such, neither favourable nor unfavorable conditions lasted long enough

for one parasite to gain a decisive advantage over and exclude the other. While it has been theorized that variations in internal temperature may aid bats' immune responses, allowing them to carry microparasites without suffering outsized morbidity (Fumagalli et al., 2021; Luo et al., 2021), these findings suggest that variations in internal temperature may also facilitate the co-occurrence of parasites within bats, and thus may help explain bats' propensity to support diverse communities of parasites. Further, these results, combined with the regularity with which bats are implicated in spillover events and epidemics, suggest that the observed effects of environmental variability on parasite diversity within hosts will scale up to have effects on between-host processes like transmission, as discussed below.

With regards to competitive outcomes, under the second thermal scenario (r_i and r_j peak on opposite sides of the average temperature of the system), P_j often outlasted P_i, while under the third scenario, P_i and P_j were equally likely to outlast each other, and under the fourth scenario, P_j was much more likely to outlast P_i. These outcomes are, in part, consequences of the asymmetrical structure of the thermal performance curves. Within the second thermal scenario, colder than average temperatures resulted in a slightly higher replication rate for P_i and a slightly lower replication rate for P_j, while warmer than average temperatures resulted in a much lower replication rate for P_i and a slightly higher replication rate for P_j. In short, P_i was more disadvantaged by unfavourable conditions than was P_j. Further, regardless of when P_j was introduced, simulations resulting in especially long periods of co-occurrence were equally likely to show either parasite outlasting the other. Taken together, these results suggest that to predict the competitive outcome of a multiple infection, one may need to consider the

interplay between how well adapted a parasite is to its host, priority effects, and environmental factors. While one might expect a specialist or well-adapted parasite (here, a thermally advantaged parasite) to exploit its host more efficiently than, and thus outcompete, a generalist or novel parasite, the results of this work suggest that environmental variability can even the scales, and allow a generalist or novel parasite to establish and persist, as predicted by the intermediate disturbance hypothesis (Chesson, 1994; Connell, 1978; Roxburgh et al., 2004). Similarly, while one might additionally expect a colonizing parasite (here, the primary parasite) to benefit from priority effects, the results of this work again suggest that environmental variability and disturbance may contribute to the structuring of communities by allowing latecomers to establish and persist more often and for longer than they otherwise would (Jiang & Patel, 2008; Munguia et al., 2010; Symons & Arnott, 2014). As anthropogenic changes alter host-parasite interaction networks, understanding how evolutionary and environmental factors combine to affect interactions between parasites will be essential in predicting and managing spillover and emergence in wildlife and human populations (Paull et al., 2012; Pedersen & Fenton, 2007).

From an array of parasites circulating among ectotherms to Hendra virus, emerging coronaviruses, and other parasites carried by bats, developing an understanding of how the impacts of environmental variability on parasite diversity within hosts may scale to affect among-host processes and events, including transmission, spillover, and emergence will be essential to the maintenance of wildlife, human, and ecosystem health (Allocati et al., 2016; Daszak et al., 2003; Halpin et al., 2000; Johnson, 2006). While increased within-host parasite diversity provides more

strains or species of a parasite or parasites an opportunity to transmit, within-host competition may result in decreased parasite loads, thus decreasing the transmission probability of any one strain or species, and altering expected transmission patterns (Johnson et al., 2013; Pedersen & Fenton, 2007). Similarly, our findings provide theoretical evidence that when environmental variations are very large and very frequent, within-host competition may decrease the transmission rates of coinfecting parasites, thereby decreasing transmission probability. However, our findings also suggest that when environmental variations are low to intermediately sized and timed, the transmission rates of coinfecting parasites are comparable to, or in excess of, the transmission rates of single parasites, indicating that the effects of environmental variability may not be limited to the promotion of within-host parasite diversity, but may also promote transmission between hosts. Additionally, we found that while large and frequent disturbances may maximally increase the amount of time for which two parasites co-occur, such infections do not result in particularly high transmission potentials, indicating that especially long periods of co-occurrence may be facilitated by lower replicative outputs that do not trigger a large immune response, and thus allow for more persistent infections. Conversely, low to intermediately sized and timed disturbances may constitute an anomalous region within which environmental variation can increase the amount of time for which two parasites co-occur, while allowing parasites to achieve high replicative outputs, resulting in longer and more transmissible infections.

Some studies have posited that high host diversity may decrease transmission risk via the dilution effect and increase parasite diversity among hosts by enhancing

colonization opportunities, while others have posited that high host diversity may increase transmission risk via the amplification effect (Hechinger & Lafferty, 2005; Johnson et al., 2015; Ostfeld & Keesing, 2012). Our findings suggest that by promoting transmission between hosts, low to intermediately sized and timed environmental variations may also increase parasite diversity among hosts. It is important to emphasize that while the impacts of global change on parasite diversity and of increasing or decreasing parasite diversity on wildlife and human global health remain disputed, parasites, like predators, are essential to the communities of which they are a part (Altizer et al., 2013; Anderson & May, 1979; Carlson et al., 2017; Cizauskas et al., 2017; Dobson & Hudson, 1986; Rohr et al., 2011). As such, the maintenance of parasite diversity should be, and increasingly is, recognized as an essential aspect of conservation ecology (Carlson et al., 2013; Dougherty et al., 2016).

While both Antia et al.'s (1994) model and our modified model should be broadly applicable to an array of within-host multi-parasite systems, including multi-strain or cross-species SARS-CoV-2 and influenza infections, both models are relatively simple as to remain generalizable, and thus cannot represent chronic infections, systems within which parasites exhibit more complex interactions with their host or their host's immune system (ex. malaria, HIV), nor systems within which parasites directly interact with one another, as is often observed in trematode coinfection and in hosts coinfected with multiple strains of the bacterium *Pseudomonas aeruginosa* (Al Khatib et al., 2020; Bashey, 2015; Kim et al., 2021; Saenz et al., 2010). As such, it may be interesting to validate the theoretical insights of this work in an empirical system. It may be of particular interest to explore the impacts of environmental variability on within-host

parasite diversity in amphibians, mosquitos, or marine organisms, as discussed above, in bats, given the risk posed to public health, or in rodents, another group of mammals that tends to host diverse communities of parasites (Bates et al., 2009; Bruno et al., 2007; Carilli et al., 2012; Drinkwater et al., 2003; Paaijmans et al., 2010; Rohr & Raffel, 2010; Tracy et al., 2019). This work is also limited by the scope with which thermal dependency was considered. Given the thermal sensitivity of immune function in ectotherms and endotherms, it will be worthwhile to consider the thermal dependency of immune processes like response time and replication rate in tandem with the thermal dependency of parasite replication rates (Butler et al., 2013; Wright & Cooper, 1981).

This work provides theoretical evidence that through climate change and as a physiological trait, environmental variability may promote parasite diversity within hosts and transmission among hosts, and thus create kindling for the spillover events, disease emergences, and epidemics we observe among wild and human hosts alike. Anthropogenic changes have allowed the next pandemic to leave the hypothetical and become a looming spectre. Camus wrote that plagues, despite their commonality, find us unprepared (Camus, Albert, 1991). Improving our understanding of how environmental variability will impact parasite diversity within- and between-hosts will allow us to expand our understanding of the mechanisms that can facilitate disease spread and emergence, which will allow us to make robust predictions, and develop and implement mitigation strategies as we move into an increasingly uncertain future. In brief, we will be found *less* unprepared.

6.0.0. Acknowledgements

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7.0.0. References

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