Coinfection interactions systematically influence parasite diversity estimates in simulated host populations

July Pilowsky[1*], Gregory F Albery[3], Barbara Han[1], Amy Sweeny[2]

[1]Cary Institute of Ecosystem Studies, PO AB, Millbrook, New York 12545, USA

[2]Institute of Ecology & Evolution, University of Edinburgh, Edinburgh EH9 3JT, UK

[3]School of Natural Sciences, Trinity College Dublin, College Green, Dublin 2, D02 PN40, Ireland

*Corresponding author: pilowskyj@caryinstitute.org

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

All authors conceptualized the paper and experimental design, wrote the manuscript jointly, and interpreted data. JP wrote the software, ran the simulations, conducted statistical analysis, and created the figures.

Abstract

Parasite diversity is a central component of epidemiological dynamics. Parasite diversity is commonly studied across animal populations and species using metrics like parasite species richness; although these metrics generally assume no interactions among parasite species within a community, such interactions are common and important, and could affect parasite diversity estimates in ways that are currently difficult to account for. Nevertheless, the strength of these effects are currently unclear due to a relative rarity of community-level parasite interaction data. To address this gap, we use theoretical models to explore how interactions among pathogen strains might influence estimates of pathogen diversity, using parasite species richness as an example. We simulate interactions among co-infecting pathogens and assess their impact on strain detectability, informing population-level pathogen richness estimates. We find that such interactions introduce bias and uncertainty into richness measurements which is as yet unaccounted for, possibly impacting a wide range of studies. The magnitude of this bias is dependent on the frequency and the nature (competitive or facilitative) of interactions among coinfecting pathogens. Until more is known about the structure of these pathogen communities, we cannot fully gauge the extent of this bias. Coinfection studies may benefit from approaches developed in microbial ecology to quantify networked interactions among pathogens within hosts.

Keywords: coinfection, community ecology, parasite ecology, competition, facilitation, parasite diversity

Introduction

A broad diversity of different parasites infect wild animals. Understanding this diversity is important for identifying the causes and consequences of infection as well as being crucial for conservation interventions and understanding spillover into human populations (Albery et al., 2021; Olival et al., 2017). Parasite species richness (PSR), or the number of distinct parasite species infecting a host population or species, is commonly used to understand disease dynamics and macroecological patterns of parasite diversity (Poulin, 2004). PSR helps to identify potential reservoirs (Albery et al., 2021), biogeographic patterns of parasite diversity (Nunn et al., 2005), and effects of host traits such as social behavior, geographic range size, and longevity (Bordes et al., 2007; Deere et al., 2021; Lindenfors et al., 2007; Nunn & Altizer, 2006). However, PSR can be biased substantially by factors like uneven sampling and phylogenetic influence (Poulin, 1997). Because these approaches and measures are so commonly used in disease ecology and related fields, it is important to understand the potential influence of these sources of bias when considering the causes and consequences of parasite diversity.

Interactions among parasites are a potentially crucial but unexplored source of bias in parasite diversity estimates. Coinfections are commonplace in wildlife, and parasites often interact (Cox, 2001; Pedersen & Fenton, 2007; Petney & Andrews, 1998). These interactions fall broadly into competitive or facilitative interaction types: for example, parasites may compete directly for space within their niche in the host (Knowles et al., 2013; Rynkiewicz et al., 2015), compete for resources such as red blood cells (Graham, 2008), or interact via immune responses (Fenton et al., 2008; Graham, 2008; Pedersen & Fenton, 2007). Empirically, these interactions can result in various outcomes for the hosts. In laboratory mice for example, helminths exert competitive and facilitative interactions on malaria parasitemia dependent on *Plasmodium* species *(Knowles, 2011).* In wildlife, coinfection interactions have been shown to predict risk and prevalence of other circulating pathogens (Clark et al., 2016; Glidden et al., 2021; Johnson & Hoverman, 2012; Telfer et al., 2010). To date, these investigations have focussed largely on consequences for individual hosts. Where the population-level consequences of coinfection have been investigated, they have focussed on the impact of individual-level coinfections for transmission and health of the population. For example, increased mortality at the individual level due to coinfection of brucellosis and bovine tuberculosis (bTB) ultimately reduces the population-level prevalence of bTB (Gorsich et al., 2018). Because these processes could determine who is observed with a given infection and when, they could magnify to influence our observations of parasite diversity (i.e., PSR) through a variety of mechanisms. Nevertheless, the impact of such interactions on parasite diversity remains unexplored, particularly in comparison to other sampling parameters and processes.

The degree to which parasite community interactions impact observed parasite diversity will depend on the degree to which parasites compete with or facilitate one another within their hosts. Although there is a rich and expanding literature investigating coinfection within wildlife populations (e.g. (Clark et al., 2016; Glidden et al., 2021; Jones et al., 2023; Knowles et al., 2013; Telfer et al., 2010)), quantifying the specific nature of the interactions and the proportion

of parasites that are interacting remains difficult. This is partly due to logistical difficulties in sampling and quantifying entire parasite communities, where many parasites are likely to be very low prevalence, not quantifiable from non-destructive sampling, as-yet-unknown, or expensive to diagnose. There is also a lack of longitudinal datasets that sample pathogen community dynamics in the same populations over time (Fenton et al., 2014). Even as our ability to identify parasites is advancing, the coinfection experiments necessary to parse ecological interactions prioritize tractability, selecting strains that impose the strongest fitness costs or those that are most prevalent in the host population (Hammoud et al., 2022). The sheer complexity of interactions among parasites, combined with the limitations of imperfect and sparse surveillance, makes it challenging to formulate robust hypotheses about expected patterns in natural communities. Consequently, we are likely far from accurately understanding how these interactions deviate from what we might consider baseline expectations.

While coinfection data are becoming more widely available, monitoring of entire communities and demonstration of interactions within the community is still lacking. This is primarily due to the difficulty in sampling wild hosts, the high genetic and species diversity of pathogenic microbes, and the sensitivity and availability of diagnostic tests. Consequently, while some coinfection data do exist, they are selective and incomplete; in particular, they are often missing rare or hard-to-detect pathogens that may nevertheless strongly influence observed patterns at the population level. Additionally, they frequently lack the longitudinal resolution to resolve interactions. This lack of comprehensive data makes it difficult not only to estimate pathogen richness but also to understand how interactions among unobserved parasite species might shape community dynamics.

Here, we use epidemiological simulations to understand how parasite interactions could influence observed parasite species estimates. Using general models of host and parasite populations, we explore how interactions among parasites might bias parasite species richness as an estimate of parasite diversity. Our model represents a null hypothesis: a simple model of pathogen interactions, mostly centered around an expectation of few to no interactions, with conservative deviations from the center. We examine a wide variety of potential community interaction strengths among pathogens infecting individual hosts, summarising our findings to understand how these interactions impact the detectability of pathogen strains at the population level.

Methods

To explore how ecological interactions among coinfecting pathogens affect their detectability, we created a process-explicit model of coinfection and disease surveillance in a single-host-multi-pathogen system (https://zenodo.org/records/13840790). The model was coded using a mix of C++ and R Version 4.3.3 (R Core Team 2023). We ran 10,000 simulations with different parameter settings and analyzed the results with a generalized additive model (GAM) and a generalized linear model (GLM).

The model

The process-explicit model is a stochastic SI model with constant host numbers (i.e., no births or deaths) and pathogen interactions governed by a P × P matrix, where P is the number of pathogens, with a multiplier value in each cell describing facilitation (>1) or competition (<1) between unique pathogen pairs. Interactions of pathogens with themselves were not relevant because hosts could not be multiply infected with the same pathogen. We tested priority effects (asymmetric interaction matrices where interactions could differ depending on which pathogen infected the host first) early on and found they did not affect disease dynamics or detectability. Therefore, all interaction matrices investigated here are symmetric (though the code repository contains options to make them asymmetric for further investigation).

Each simulation featured a population of 1000 identical hosts. The system had anywhere from 5 to 100 pathogens, and the simulations started with one host infected with each pathogen and no coinfection. The pathogens had identical base transmission rates; the only difference was their set of interactions in the interaction matrix.

Each simulation ran for 100 timesteps. At each timestep, all individuals were exposed to all other individuals. The probability of infection with each strain to which a host was susceptible was drawn from a binomial distribution with size equal to the number of hosts infected with the strain, and probability equal to the base transmission rate multiplied by all the interaction multipliers exerted upon that strain by the strains that already infect the host, if any. Competing strains multiplied the transmission rate by a factor less than 1, reducing it, while facilitating strains did the opposite.

Once the disease simulations were complete, we simulated a disease surveillance process in each population using a subsampling regime. Sampling ranged from 10 - 100% of the host population. Assays were error-free and could detect all strains. We sampled independently at all timesteps and noted whether each strain was detected or not.

Parameter space

Across 10,000 simulations, we varied interaction strength (0-0.3), competition-facilitation ratio (0.7-1.3), strain number (5-100), and sampling proportion (0.1-1) while keeping host number, simulation length, and base transmission rate constant (Figure 1).. We were conservative in our range of interaction strengths and competition to facilitation ratio, under the null expectation that most interactions would be neutral. We tested more extreme interaction strength values and found that they either caused so much suppression that no outbreaks occurred, or so much facilitation that the entire outbreak played out in less than 5 time steps. We varied the number of strains across a range spanning the number of parasites that have been empirically observed to coinfect hosts and much higher numbers postulated to coinfect hosts.

Statistical analysis

For analysis, we tested whether strain- and population-level factors determined detectability, combining all strains from all simulations. First, we analyzed strain detectability (i.e., whether or not a given strain was detected) as the outcome variable using a binomial GAM. The explanatory variables were number of strains in the simulation, proportion of the population sampled, mean competition, and mean facilitation. Mean competition was calculated as the mean strength of competitive interactions acting upon the focal strain across the simulation, while mean facilitation was the mean strength of facilitative interactions acting upon the focal strain.

Contingent upon a lack of significant nonlinearity in the GAM, we used a binomial GLM to analyze the impact of model settings on detectability. The GLM included the number of strains in the simulation, the proportion of the population sampled, the time step in the simulation, and the interactions of time with mean competition and mean facilitation.

Results

We simulated 523,222 strains across 10,000 simulations. Of these strains, 34.5% never reached 50% prevalence at any point in the simulation, indicating that they never reached the full saturation expected of a standard SI model with $R_0 > 1$. Of the strains that did reach 50% prevalence, the mean timestep of 50% prevalence was 36.33 (95% CI: 36.28 - 36.39).

The GAM ($R^2 = 0.0289$) only explained 8% of the deviance in detectability due to demographic stochasticity and randomness in the interaction matrices; however, it identified several strong and significant patterns. The largest effect size came from the proportion of the population sampled, followed by the tensor interaction between competition and facilitation. We did not include time because the GAM was computationally intensive, and the timesteps were precisely the same for each simulation and could be safely factored out. As the GAM did not present significant nonlinearities in the smooths (Figure 2), we proceeded with a GLM, which did explore detectability over time.

In the binomial GLM ($R^2 = 0.481$), as in the GAM, the largest increase in detectability came from the proportion of the population sampled (4.7302; 95% CI: 4.7223 - 4.7381), followed by time (0.1668; 95% CI: 0.1664 - 0.1672; Figure 3). Mean competition decreased the positive slope of detectability over time (-0.2080; 95% CI: -0.2096 - -0.2065), while facilitation increased it (0.1072; 95% CI: 0.1051 - 0.1093; Figure 4). For example, in the absence of competition or facilitation, the detectability of strains started at 10.47%, and increased by 1.6% with each timestep. If the mean facilitation was 0.5 and competition was 0, detectability increased by 2.26% with each time step. If the mean competition was 0.5 and facilitation was 0, detectability increased by 0.6% with each time step. The effect of the number of strains on detectability was negative and statistically significant, but the effect size was so small as to be negligible (-0.0007; 95% CI: -0.0008 - -0.0006).

Discussion

This study demonstrates that coinfection interactions significantly influence population- and species-level PSR estimates. Facilitative interactions greatly increased pathogen detectability compared to competitive interactions. The magnitude of this effect was surprisingly large (e.g., at the highest levels of facilitation, detectability increased by 2.26% per timestep, while at the highest levels of competition, detectability decreased by 0.6% per timestep). This finding is important because it influences (for example) how likely we are to discover a specific pathogen in a given sample of a host or our conclusions regarding how many pathogens a host species maintains in general. Coinfection is the norm in wild animal populations (Cox, 2001; Petney & Andrews, 1998), and it is commonly acknowledged that interactions between pairs of pathogens can exacerbate or inhibit symptoms at the individual level (Gorsich et al., 2018; Johnson & Hoverman, 2012) and cause non-linear “syndemic” dynamics at the population level (Sweeny et al., 2021). Building on this bank of coinfection theory, our findings imply that large numbers of small interactions between even relatively small communities of pathogens can drive surprisingly large fluctuations in PSR across multiple scales. These simulations reveal a surprising gap in integrating coinfection into host-level community ecology theory. Coinfection studies typically focus on organismal contexts with small datasets, making it challenging to extrapolate findings to broader ecological scales. We propose bridging this gap by integrating coinfection research with related fields to elevate our understanding of coinfection impacts on higher levels of biological organisation.

Although our simulations strongly support the notion that coinfection may be important to consider when sampling wildlife populations for pathogens, the literature and available data fall far short of being able to test these ideas. A vital next step is empirically identifying coinfection interactions in systems with known interactions among parasite species or strains. Most pathogen datasets sampled from wild animals focus on a few different species or strains – or, more often, higher taxa – in numbers far lower than our simulated data. For example, a well-used dataset of 713 individuals spanning 11 rodent species identifies 36 genera of pathogenic bacteria (Abbate et al., 2024), but some of the best examples for pathogen interactions influencing infection risk focus on only four species (Telfer et al., 2010). Indeed, in most of these systems, coinfection interactions are quantified in a maximum of perhaps 3-4 pairs of strains. Our simulations included 5-100 strains, yet the effect of strain number on detectability was exceedingly small. The number of strains produced in our simulations ranged from 10 to 4,950 possible interactions. Most systems have orders of magnitude too little data to inform or parameterise such models.

Fortunately, microbial interactions extend beyond infectious organisms, offering opportunities to test and parameterize coinfection models in diverse systems. These include soil or gut microbial communities where understanding interaction types and their consequences is a key focus. For

example, recent efforts in mammalian microbiome studies have sought to characterise the nature of interaction types that comprise the complex gut bacterial communities of wild baboons (Roche et al., 2023). Understanding interaction types and their contribution to community assembly and stability is an increasing focus for microbial systems across free-living and host-associated microbiomes (Coyte et al., 2015; Debray et al., 2022). Expanding microbial community datasets and ecological network repositories like Mangal (Poisot et al., 2016) offer valuable opportunities to explore how interactions among community members broadly impact detectability and richness estimates across diverse ecosystems.

Here, we provide a theoretical demonstration of coinfection interactions influencing the interpretation of parasite species richness. These results build on a rich history of coinfection investigations demonstrating that such interactions have measurable individual and population level effects, highlighting the importance of accounting for their net effects to understand parasite community dynamics at macroecological scales. While our simple theoretical approach illuminates how coinfection processes influence efforts to quantify parasite diversity, there are practical hurdles to scaling up within-host interactions to the population level. Surveillance is patchy due to focus on high-risk areas or pathogens, the high costs of monitoring entire parasite communities, especially rare or benign members, and the practical and economical challenges of conducting long-term fieldwork with sufficient data density. Despite these limitations, empirical studies support our theoretical findings. A meta-analysis of human coinfections revealed that coinfection affects overall parasite abundance (Griffiths et al., 2011). Similarly, research on wild rodents demonstrated that coinfection can substantially alter infection risk and detectability of co-circulating parasites (Telfer et al., 2010), and in non-mammalian hosts, experimental co-infection inoculations of the flowering plant *Plantago lanceolata* result in population-level impacts of more severe epidemics (Susi et al. 2015). Determining causality between parasites remains challenging for wildlife studies dominated by observational, cross-sectional data (Fenton et al., 2014). Encouragingly, long-term studies to understand inter-specific parasite relationships (e.g., (Ezenwa & Jolles, 2011; Gorsich et al., 2018; Knowles et al., 2013)) provide a wealth of *a priori* hypotheses for how specific groups of parasites may interact (e.g. (Graham, 2008; Pedersen & Fenton, 2007)). Concurrently, a boom in within-host community data afforded by metabarcoding approaches is increasing the resolution of information available on entire communities of bacteria and viruses in wildlife (Raghwani et al., 2023). Insights from focused parasite interaction studies alongside large-scale microorganism data offer unprecedented opportunities to build on the conceptual ideas presented here to better understand and account for the impact of within-host parasite community dynamics on disease patterns across broader ecological scales.

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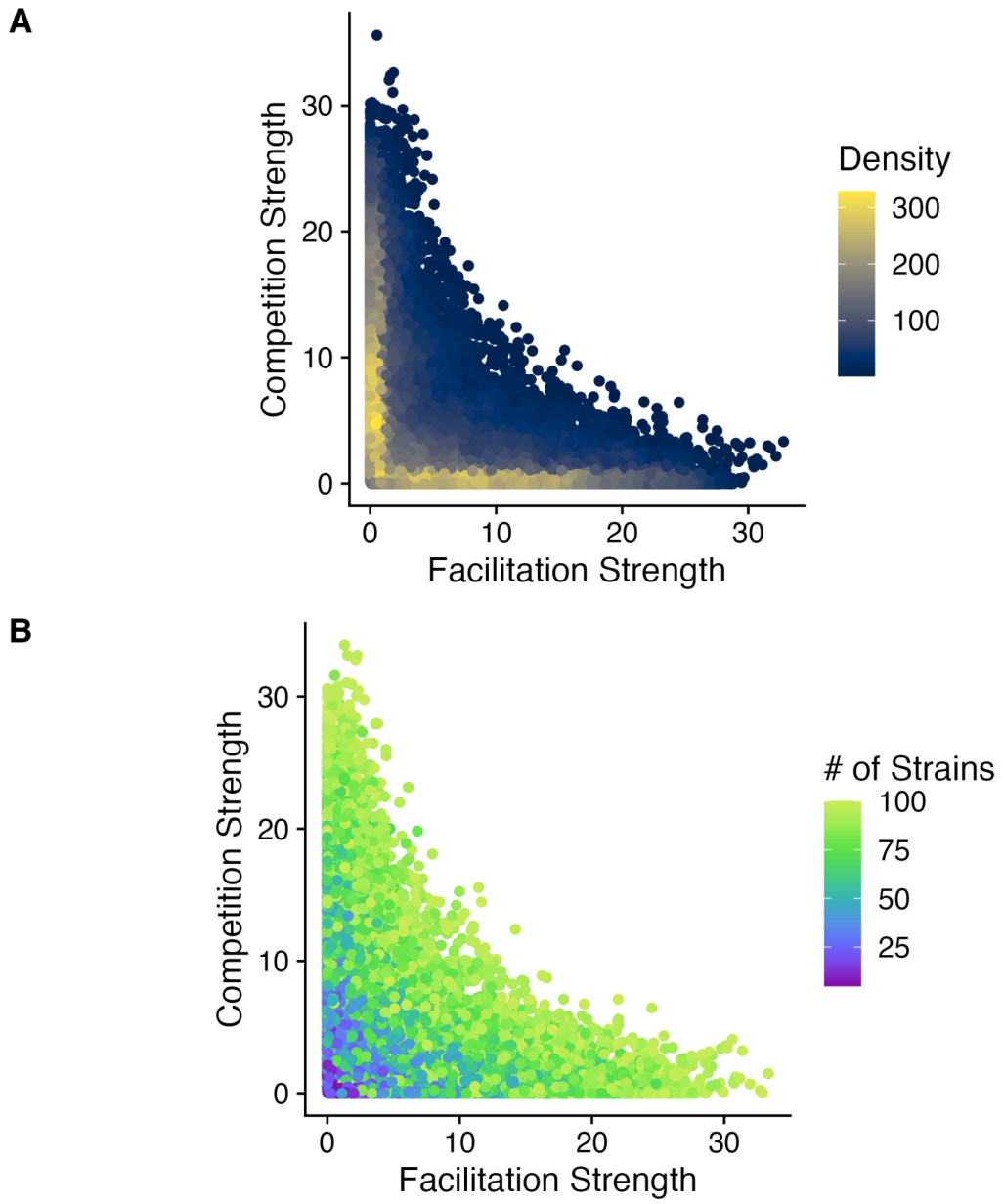


Figure 1: Parameter distribution of simulated strains. In our simulations, we explored the parameter space using stratified sampling to simulate many possible interaction patterns for infectious strains. Facilitation strength is the sum of all facilitative interactions that act upon a strain, while competition strength is the sum of all competitive interactions that act on a strain. The number of strains indicates how many other strains are present in the population in a strain's particular simulation. Simulations with low numbers of strains are clustered at low competition and facilitation strength because fewer strains means that there can be fewer total interactions, limiting the strength of competition and facilitation.

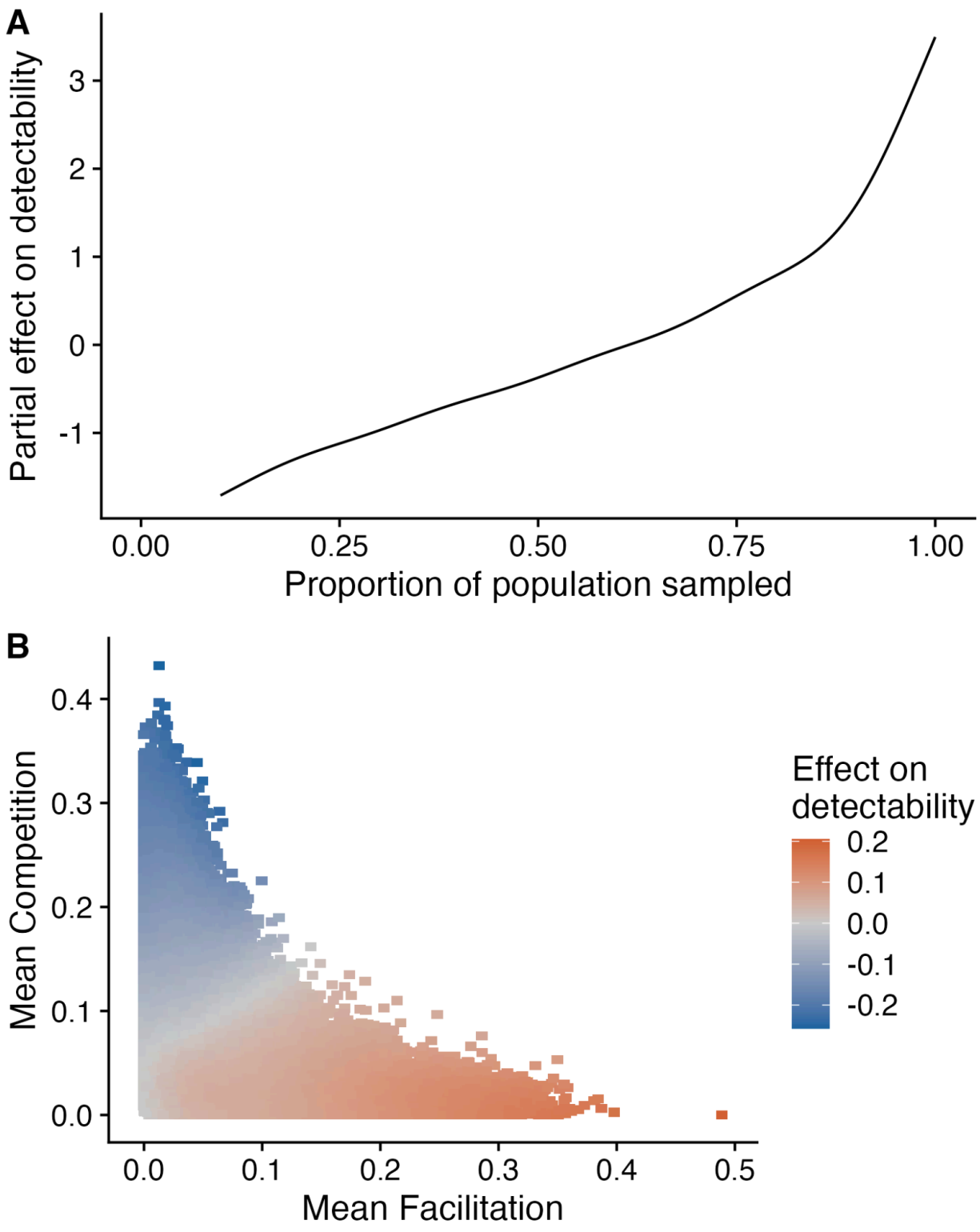


Figure 2: Partial effects of coinfection and sampling scheme on strain detectability. We analyzed our simulation results using a general additive model with a binomial response (strain detected vs. strain not detected). The proportion of the population sampled had the strongest effect on strain detectability. The second strongest effect came from a tensor of mean

competition (average negative effects of other strains on the focal strain) and mean facilitation (average positive effects of other strains on the focal strain). Stronger competition reduced detectability and stronger facilitation increased detectability.

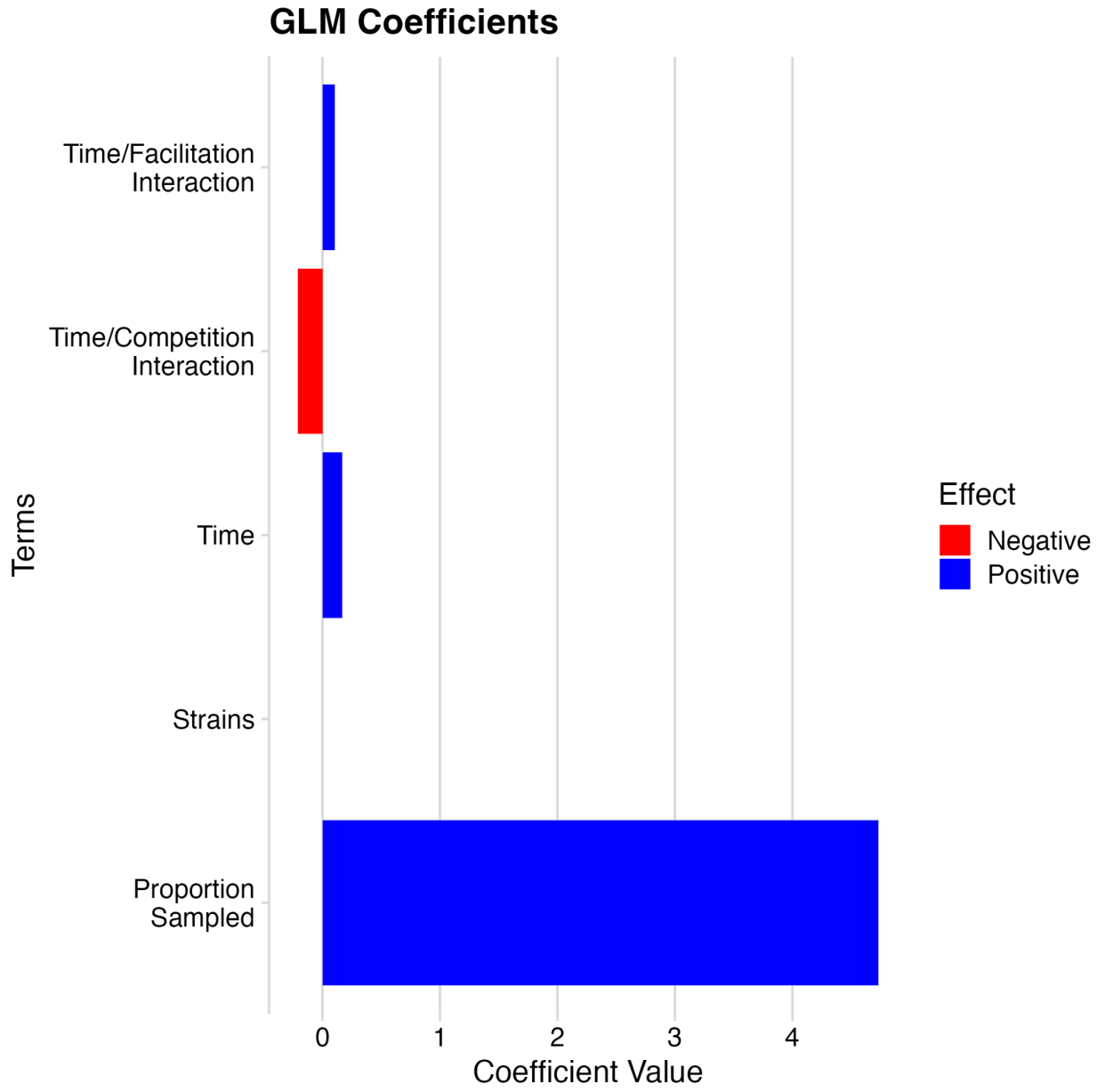


Figure 3: Effect sizes of simulation parameters. We analyzed simulation outputs using a generalized linear model with a binomial response (strain detected vs. strain not detected.) Proportion of the population sampled had a strong positive effect on strain detectability. Time had a weaker positive effect, with strains becoming more detectable as time passed in the simulation. Competition decreased the positive slope of detectability over time, while facilitation increased it. The number of strains in the simulation had no effect on detectability.

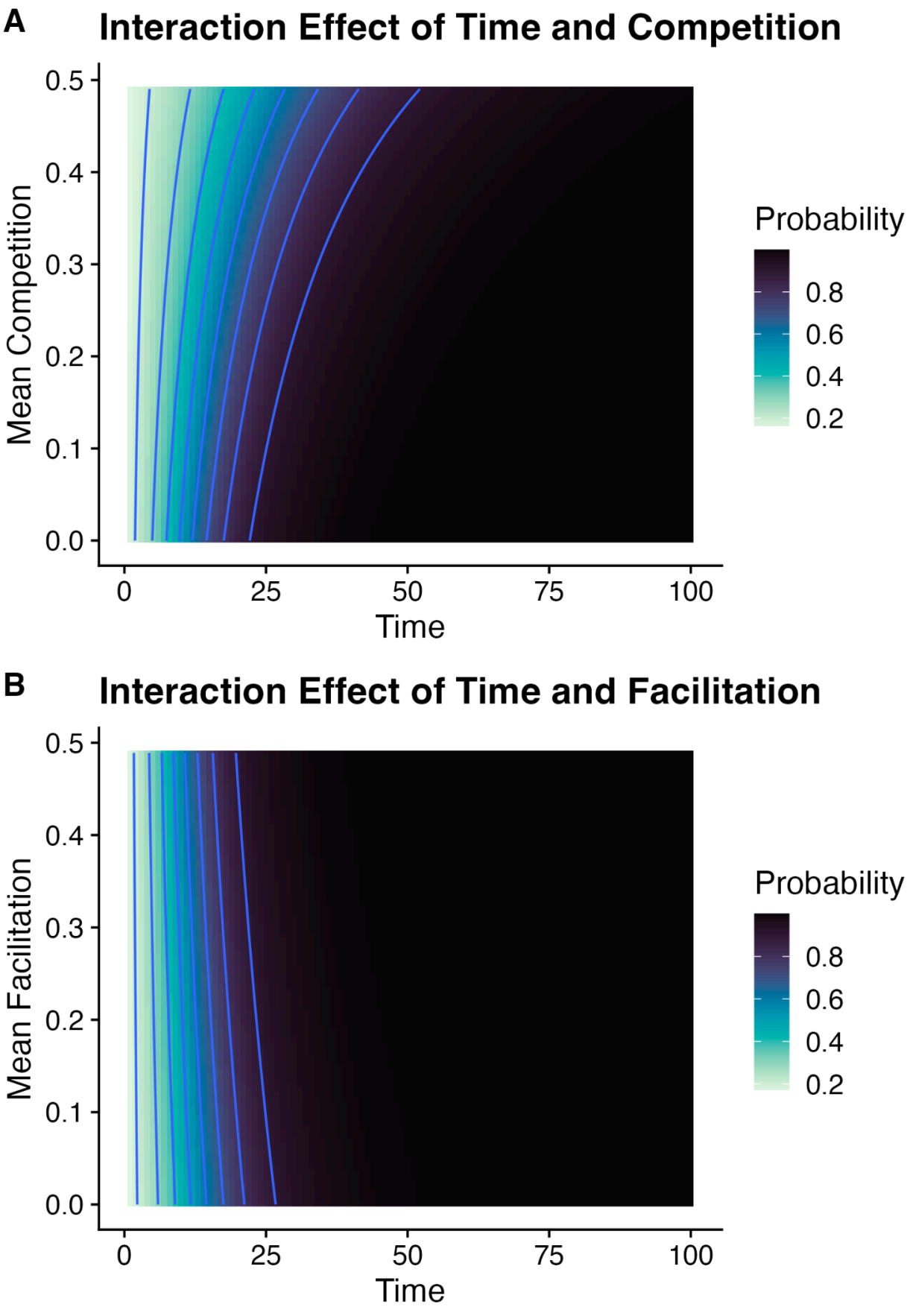
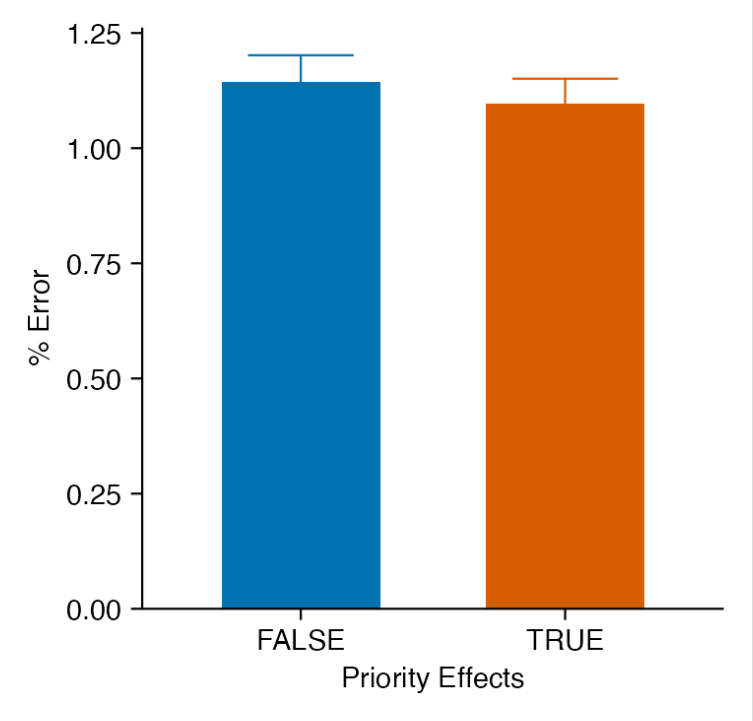

A
Interaction Effect of Time and Competition
Mean Competition
0.5
0.4
0.3
0.2
0.1
0.0
0
25
50
75
100
Time
Probability
0.8
0.6
0.4
0.2
B
Interaction Effect of Time and Facilitation
Mean Facilitation
0.5
0.4
0.3
0.2
0.1
0.0
0
25
50
75
100
Time
Probability
0.8
0.6
0.4
0.2

Figure 4: Probability of detection surfaces. The heatmaps show the mean probability that a strain will be detected when 10% of the host population is sampled. The facets show the interactions between time and mean facilitation or competition toward a focal strain. Strains always become more detectable over time, but high competition slows the increase in detectability (A) while high facilitation speeds it up (B).

Supplementary Information



Supplementary Figure 1: Priority effects and accuracy of parasite species richness estimates. We ran 5000 simulations of our process-explicit coinfection model in which pairwise interaction matrices were symmetric (no priority effects) and 5000 simulations in which pairwise interaction matrices were asymmetric (priority effects). We subsampled the resulting populations for parasites and used these samples as estimates of parasite species richness. We compared these estimates against the true species richness and calculated percent error. There was no difference in the accuracy of species richness estimates between simulations with and without priority effects ($t = 0.58835$, $df = 9935.7$, p-value = 0.5563).