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Epidemiology, Game Theory, and Evolutionary Rescue: Understanding How Outbreaks Impact Population Viability

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ABSTRACT

Evolutionary game theory (EGT) analyzes the stability of competing strategies for withstanding selective pressures within a population over generations. Under rapid shifts in selective pressures (e.g., introduction of a novel pathogen), evolutionary rescue may preserve a population, but how it may re-stabilize over generations is also critical for estimations of population persistence. Here, we present a simple model that couples EGT with epidemiology to investigate evolutionary rescue under a novel and epidemiologically-driven dynamic selective pressure from an infectious outbreak. We consider a hypothetical population where payoffs from competing wild-type and mutant strategies reflect immune-reproductive trade-offs. Our study shows evolutionary rescue occurs under higher wild-type fecundity and a lower-bounded boost in mutant immunity prolongs the timescale of evolutionary rescue. Higher disease-induced mortality in the wild-type and a larger mutant immunity significantly reinforce the pattern. This model reveals transient synergies between epidemiological and evolutionary dynamics during evolutionary rescue during novel infectious outbreaks.

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conservation epidemiology, infectious selective pressure, evolutionary rescue, life-history-epidemiology trade-offs

1 Introduction

The theory of evolutionary games (Smith, 1982) has significantly aided analyses of species interactions and the effectiveness of wildlife conservation management strategies (Pintor et al., 2011; Tanimoto, 2015; Vincent, 1994). In an evolutionary game, players represent individuals within or across species, and each player plays (i.e., acts in each situation) by some strategy, whether genetically determined or learned (Akçay, 2020; Zomorrodi and Segrè, 2017; Robertson et al., 2018). Each strategy has an associated "payoff" quantifying its fitness that ultimately lays bare conditions for stable or unstable strategies and regime shifts, while imposing minimal assumptions on the interacting players themselves. As a result, evolutionary game theory can predict changes in the strategic makeup of the population of players over time. These changes become a proxy for evolution, where pressures come from different strategies and the population's environment.

In considering the possible trajectories for threatened populations, one likely source of increased viability over time comes from the potential for evolutionary rescue (Bell, 2013). Evolutionary rescue can occur when novel environmental factor(s) cause dramatic population decline and act as selective pressures favoring the proliferation of an existing (or recently arisen) beneficial trait (Bell and Gonzalez, 2011). The new shift to increased representation of that beneficial trait then increases population growth in the face of the novel environmental factors and "rescues" the overall population from extinction. This rescue pattern can happen in relatively few generations (Carlson et al., 2014), leading to a rapid evolution occurring on the same timescale as ecological phenomena (Gonzalez et al., 2013). This inherent eco-evolutionary nature of evolutionary rescue fits well to game theoretic methods, where players can have different strategies that reflect different genetically- and behaviorally- derived traits, ecological roles, and physiological processes impacting them (Hammerstein and Selten, 1994; Sigmund, 2017; Vickery and Poulin, 2010).

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There have been recent attempts to develop models combining SIR dynamics with game theory (Reluga, 2010), especially recently regarding social distancing and vaccination during the Covid-19 Pandemic (Wang et al., 2020). Additionally, there are studies regarding evolutionary rescue in the context of global warming and other changing environments using fitness gradients and other concepts adapted from evolutionary game theory (Osmond and de Mazancourt, 2013; Ferriere and Legendre, 2013). However, the feedback between multiple competing populations in the presence of a disease creates dynamics not captured by models of evolutionary rescue from other environmental threats. Thus our model, which combines the aspects of disease, game theory, and evolutionary rescue, is likely to find new dynamics not captured by models only considering two of these features.

Here, we introduce evolutionary game theory to a system in which a devastating infectious disease acts as the selective pressure that could drive evolutionary rescue. We assume that the host species can evolve, but for simplicity, that the pathogen does not. This system is likely to exist when a new pathogen or disease invades a naive host population (e.g., White Nose Syndrome, Ranavirus; see Echaubard et al., 2014; Maslo and Fefferman, 2015). To describe the epidemic that ensues, we use the susceptible-infected-recovered (SIR) compartmental epidemiological framework (see Keeling and Rohani, 2011). This involves explicitly quantifying strategies in terms of epidemiological parameters such as transmission, recovery, birth, and death rates, which govern the movement of individuals into or out of a class (Leigh, 1973; Restif and Koella, 2003). We thereby propose a model that can consider host evolution on the time scale of the epidemic.

In this paper, we focus on the evolutionary dynamics of a hypothetical iteroparous population of wild types (wt) and mutants (mt) with different genetically-based phenotypic strategies in response to a devastating infectious disease. We consider a scenario in which mutants exhibit stronger resistance to the infection (i.e., have both decreased susceptibility to catching the disease and more rapid recovery from it; see Roy and Kirchner, 2000) and higher tolerance (i.e., can better ameliorate damage caused by pathogen, including lower disease-induced mortality and less disease-induced decrease in fecundity; see Roy and Kirchner, 2000). However, in the absence of infection, they have lower fecundity than uninfected wild type individuals. This trade-off exists in many biological systems (e.g., a more sensitive immune system decreases reproductive output; see Robertson et al., 2018; Sheldon et al., 2014; Kerr et al., 2010). Payoffs from these two competing strategies come from assumed relative birth rates grouped by infection status. In this paper, we first verify the existence of evolutionary rescue under the chosen parameters for the system. We then use this model system to explore how immune-reproductive trade-offs can affect the expected likelihood/timescale of evolutionary rescue. Due to the complexity of the model structure, here, we rely on numerical simulation in MATLAB (2018) and R language (R Core Team, 2013) for model analyses.

2 Methods

2.1 Overview of model

Our deterministic model in MATLAB aims to heuristically capture disease-driven evolutionary dynamics of a hypothetical iteroparous host population with only two heritable strategies, wild type (wt) and mutant (mt), that differ in their response to a devastating disease. We assume that these strategies are heritable and constant throughout an individual's life. For simplicity, we also assume continuous disease transmission, life-long immunity upon recovery, no differences in susceptibility or recovery based on life history, and no vertical disease transmission.

Our model takes as parameters the initial wild-type and mutant population sizes and birth and death rates grouped by strategy and progress of infection, as well as disease transmission and recovery rates grouped by strategy and carrying capacity. We also specify the frequency of discrete breeding periods for the host. Based on these inputs, the epidemiological component of the model determines population dynamics whenever breeding does not occur, while the evolutionary game theoretic aspect of the model determines the number of offspring produced per breeding event, according to the latest host population demographics (i.e., the relative representation of the different strategies). The number of infected individuals and the disease-induced mortality rate in the host population serve as measures of the pathogen's fitness. As the model runs, it transitions from the epidemiological framework to the game theoretical framework and back again as each breeding cycle passes. For simplicity, we assume that deaths, transmission, and recovery controlled by the epidemiological framework do not occur during breeding and vice versa.

For the purposes of our research, we consider a population that has one breeding bout per annual cycle, $t_{cycle} = 365$ (Table 1). As such, birth rates operate on an annual time scale (Table 1) while all other rates operate on a daily time scale. All simulations start with an initial population, $N(0)$, of 14500 individuals with a carrying capacity, K, of 15000. Simulations in the presence of an epidemic begin with no recovered (i.e., immune) individuals, no infected mutants, and 10 infected and 1000 uninfected wild type individuals. The remaining 1500 individuals are mutants. The basic reproductive ratio ($R_0 = \beta/\gamma$) exceeds 1 for both wild type and mutant.

Table 1: Quantity, description, units and default values for all model variables and parameters.

Quantity	Description	Unit	Value
$S_{wt}(t)$	susceptible density at time t for wild type	indiv.	variable
$S_{mt}(t)$	susceptible density at time t for mutant	indiv.	variable
$I_{wt}(t)$	density of infected individuals at time t in wild type	indiv.	variable
$I_{mt}(t)$	density of infected individuals at time t in mutant	indiv.	variable
$R_{wt}(t)$	recovered density at time t for wild type	indiv.	variable
$R_{mt}(t)$	recovered density at time t for mutant	indiv.	variable
r_{wt_-}	growth rate of wild type without disease	1/time	variable
r_{mt_-}	growth rate of mutant without disease	1/time	variable
r_{wt_+}	growth rate of wild type with disease	1/time	variable
r_{mt_+}	growth rate of mutant with disease	1/time	variable
β_{wt}	transmission in wild type	1/indiv./time	0.008
β_{mt}	transmission in mutant	1/indiv./time	0.005
γ_{wt}	recovery rate for wild type	1/indiv./time	0.00001
γ_{mt}	recovery rate for mutant	1/indiv./time	0.003
μ_{wt_-}	natural mortality rate of wild type without disease	1/time	0.001
μ_{mt_-}	natural mortality rate of mutant without disease	1/time	0.001
μ_{wt_+}	mortality rate of wild type with disease	1/time	0.002
μ_{mt_-}	mortality rate of mutant with disease	1/time	0.0011
α_{wt_-}	assigned growth rate of wild type without disease	1/time	0.6
α_{mt_-}	assigned growth rate of mutant without disease	1/time	0.55
α_{wt_+}	assigned growth rate of wild type with disease	1/time	0.35
α_{mt_+}	assigned growth rate of mutant with disease	1/time	0.4
K	carrying capacity	indiv.	15000

Simulation time is from 1 day to 19 years. Parameter values are consistent with our previous study (Jiao and Fefferman, 2021).

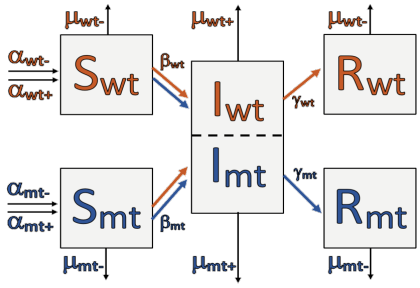

Figure 1: Boxes represent susceptible (S), infected (I), and recovered (R) groups of wild type (wt) and mutant (mt) individuals. Arrows show the direction of movement of a portion of the host population into or out of a disease class, and their corresponding symbols refer to the rate of this movement. The two pairs of color-coded arrows coming out of the separate boxes for susceptible wild type and mutants into the single box for the infected class refer to whether the source of infection came from the wild types or mutant. We assume that the source of infection does not alter the transmission rate, β. The dotted line dividing the box for the infected class conveys that wild types and mutants can transmit the disease to each other while reiterating that infected mutants cannot become infected wild types and vice versa. Symbols with a "−" or "+" in the subscript following "wt" and "mt" refer to uninfected or infected groups respectively. β, transmission rate; γ, recovery rate; μ, death rate; α, birth rate.

Table 2: Initial values of population variables.

Quantity	Description	Initial value
$S_{wt}(t)$	susceptible density at time t for wild type	1000
$S_{mt}(t)$	susceptible density at time t for mutant	1500
$I_{wt}(t)$	density of infected individuals at time t in wild type	0 or 10
$I_{mt}(t)$	density of infected individuals at time t in mutant	0
$R_{wt}(t)$	recovered density at time t for wild type	0
$R_{mt}(t)$	recovered density at time t for mutant	0

2.2 Epidemiological modeling

Applying traditional epidemiological modelling approaches, we created a coupled SIR paradigm for a host population with wild-type (wt) and mutant (mt) strategies that respond differently to the pathogen and can transmit the pathogen to each other (Figure 1). We assumed the target's strategy, rather than that of the source, determines transmission rate. In the presence of a transmissible pathogen in the host population, the portion of the population called the susceptibles has not yet been infected by the pathogen. Another portion of the population, known as the infectious, have caught the infection and shed enough pathogen to potentially spread it to the susceptibles. Once the pathogen has cleared from an infectious individual's system, that individual moves into the recovered class, and we assume that the individual is no longer susceptible to the same type of pathogen. In other words, this movement of individuals to the recovered class assumes that recovery confers lifelong immunity. Susceptibles move to the infectious class according to β, the transmission rate (including the probability of rates of contact), and infected individuals into the recovered class according to γ, the recovery rate. We treated the infected class as one category, regardless of strategy, to better reflect the fact that, oftentimes, individuals regardless of their strategy can transmit the pathogen to each other. All offspring fed into the susceptible wild type or mutant population based on the birth rates for the four parental types, $\alpha_{wt_-}, \alpha_{wt_+}, \alpha_{mt_-}, \alpha_{mt_+}$. For simplicity, we assume that only maternal type influences reproductive outcome; this assumption is easily relaxed in future studies. Uninfected individuals from the susceptible and recovered groups die at the natural background death rate (μ_{wt_-} or μ_{mt_-}) and at rate μ_{wt_+} or μ_{mt_+} in the infectious group to account for disease-induced mortality. Note, this framework may not reflect diseases where hosts experience differential susceptibility and recovery based on life history stage or current body condition.

To implement the conceptual framework above, we used ordinary differential equations to approximate the number of individuals in each class:

$$\frac{dS_{wt}}{dt} = -\beta_{wt}S_{wt}(I_{wt}+I_{mt}) - \mu_{wt_-}S_{wt} \qquad \frac{dS_{mt}}{dt} = -\beta_{mt}S_{mt}(I_{wt}+I_{mt}) - \mu_{mt_-}S_{mt}$$

$$\frac{dI_{wt}}{dt} = \beta_{wt}S_{wt}(I_{wt}+I_{mt}) - \gamma_{wt}I_{wt} - \mu_{wt_+}I_{wt} \qquad \frac{dI_{mt}}{dt} = \beta_{mt}S_{mt}(I_{wt}+I_{mt}) - \gamma_{mt}I_{mt} - \mu_{mt_+}I_{mt}$$

$$\frac{dR_{wt}}{dt} = \gamma_{wt}I_{wt} - \mu_{wt_-}R_{wt} \qquad \frac{dR_{mt}}{dt} = \gamma_{mt}I_{mt} - \mu_{mt_-}R_{mt}$$

Given wild-type and mutant strategies in the host population, the model runs two systems of SIR equations, one for each strategy, using the appropriate corresponding rates. To couple these systems so that wild type and mutant individuals can transmit the disease to each other, the number of infected individuals obtained from $\beta S(I_{wt}+I_{mt})$ pools the number of infected wild types and mutants. We computed the number of individuals from each class using MATLAB's `ode45` function. In reality, disease transmission may not always be continuous, especially for animals that do not spend the majority of their time in close proximity to other members of their species. In these cases, the transmission rate can be considered an average.

2.3 Evolutionary game theoretic modeling

For each breeding cycle, our model accounts for competition from different strategies by using a zero-sum game matrix P:

1 \ 2	W_-	W_+	M_-	M_+
W_-	0	0	a	b
W_+	0	0	$-c$	$-d$
M_-	$-a$	c	0	0
M_+	$-b$	d	0	0

where W and M represent wild and mutant types respectively, and the subscripts − and + represent uninfected and infected. This matrix represents the change in fitness an individual in group 1 receives when interacting with others of the corresponding type in group 2 (Cressman and Tao, 2014). For example, when W_- in group 1 interacts with M_- in group 2, then W_- receives a fitness increase as "a". Without loss of generality, we assume that all interactions within a species type have zero change in fitness. This is because individuals for one type give birth to individuals of the same type, so any fitness gained by one is cancelled by a corresponding loss in the other, leading to no net effect on births for that type. Here we constrain $0 < a, b, c, d < 1$ (here we used $a = b = c = d = 0.001$ in all simulations) to fit the assumptions that uninfected hosts have an advantage in fitness against infected hosts, wild-type hosts having an advantage compared to mutant when both are uninfected, and mutant-type hosts having an advantage versus wild type when both are infected. In addition, the values being less than 1 prevents negative birthrates in the following replicator equation.

If we assume that x is the vector (length 4) of current population frequencies, for type i within the four groups (uninfected wild type, infected wild type, uninfected mutant, and infected mutant), the average fitness of individuals in that type (i.e., $f_i(x)$) is the i^{th} coordinate of the vector resulting from P multiplied by x, in particular:

$$f_i(x) = [P \cdot x]_i$$

where P is the above zero-sum fitness matrix. We further modify to get the relative birth rate for type i : r_i:

$$r_i = [1 + f_i(x)]\alpha_i$$

where α_i is the user-defined natural birthrate of type i in the absence of competition (when in a population of only their own species). This relative birth rate corresponds to the average number of births each individual of type i will have. The results from the replicator equations then replenish the susceptible populations after each round of the game. The number of recovered and infectious individuals of both strategies remain constant during the game phase, reflecting the "no vertical transmission" assumption of the model; individuals are born only into the susceptible class. Whenever the number of offspring would cause the total population size to exceed carrying capacity, the model caps the population size at carrying capacity by uniformly scaling with c the number of offspring produced from each group.

$$\begin{aligned}
S_{wt}(t+1) &= S_{wt}(t) + c\Delta S_{wt} & S_{mt}(t+1) &= S_{mt}(t) + c\Delta S_{mt}\\
I_{wt}(t+1) &= I_{wt}(t) & I_{mt}(t+1) &= I_{mt}(t)\\
R_{wt}(t+1) &= R_{wt}(t) & R_{mt}(t+1) &= R_{mt}(t)\\
\Delta S_{wt} &= r_{wt_-}(S_{wt}(t) + R_{wt}(t)) + r_{wt_+} I_{wt}(t) & \Delta S_{mt} &= r_{mt_-}(S_{mt}(t) + R_{mt}(t)) + r_{mt_+} I_{mt}(t)
\end{aligned}$$

$$c = \begin{cases} \frac{K - N(t)}{z - N(t)} & \text{if } z > K \\ 1 & \text{if } z < K \end{cases}$$

$$z = S(t) + \Delta S_{wt} + \Delta S_{mt} + I(t+1) + R(t+1)$$

$$N(t) = S(t) + I(t) + R(t)$$

Since our model assumes iteroparous (rather than semelparous) hosts, the mothers do not die directly after producing offspring. Both they and their offspring get passed back into the SIR part of the model.

2.4 Immune-reproductive trade-offs and boundary conditions

To implement the scenario where a more sensitive immune system acts counterproductive to reproduction (as described at the end of the Introduction), we defined the following bounds on parameter values in our model:

$$\beta_{wt} > \beta_{mt} \tag{1}$$

$$\gamma_{wt} < \gamma_{mt} \tag{2}$$

$$\mu_{wt_-} = \mu_{mt_-} < \mu_{mt_+} < \mu_{wt_+} \tag{3}$$

$$\alpha_{wt_-} > \alpha_{mt_-} > \alpha_{mt_+} > \alpha_{wt_+} \tag{4}$$

Bounds (1) and (2) are assumed trade-offs due to stronger immune function in mutants that allows for the stronger resistance and higher tolerance to the pathogen as compared to wild type individuals. Death rates (3) for uninfected mutants and wild types were assumed to be equivalent in the absence of disease.

Wild types and mutants both experience decreases in birth rate (4) when infected. However, since wild types exhibit weaker tolerance to the pathogen than mutants, we assumed that infected mutants are better at reproducing than infected wild types. The enhanced immune system acts as a trade-off trait: mutants can better protect themselves from the pathogen but produce fewer offspring under normal circumstances as a result.

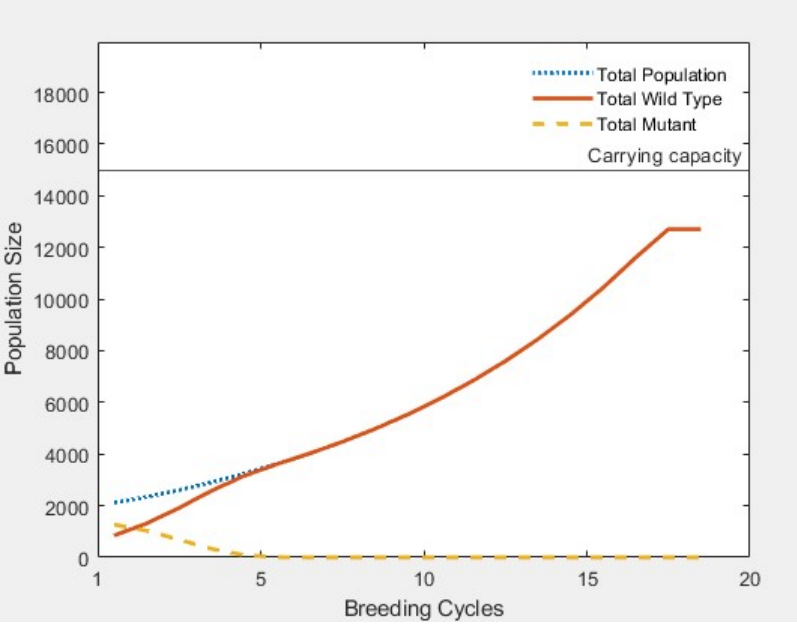

Figure 2: Dynamics of the total host population, mutant and wild type, over 19 breeding cycles in the absence of an epidemic and interpolated by midpoint. The corresponding parameters and initial values are in Tables 1 and 2. The black horizontal line indicates carrying capacity.

3 Results

In the case in which mutants exhibit stronger resistance and higher tolerance but have lower fecundity than wild types in the absence of disease, we chose the following parameter values and initial values of variables (Tables 1 and 2; see also the parameters of Edmunds et al., 2016; Maslo and Fefferman, 2015). We first verified that these parameter values can produce evolutionary rescue in our model. We then investigated the combined effects of three pairs of example trade-off traits to analyze how they can change the timescale of observed rescue patterns.

3.1 Verifying evolutionary rescue in the model

To confirm that the parameter values shown above create conditions for evolutionary rescue in our model, we first observed the dynamics of the hypothetical host population in the absence of the epidemic by running the model with the same parameter values shown in Table 1 and initial value in Table 2 without infected individuals. Under this scenario, we expect the wild type to dominate, and the model supports this (Figure 2).

In the presence of an epidemic starting with 10 infected wild types, evolutionary rescue occurs (Figure 3) (Note that all graphs in this section show interpolation using the midpoint of each year). As a result, the curves seem to approach a limit below carrying capacity, when in actuality, the population oscillates with carrying capacity as the upper bound (within the Supplemental Materials see Figure S1 in Appendix 1 for raw simulation dynamics and see Figure S2 in Appendix 2 for a heatmap showing the sharp transition in outcome from no infection to infection).

3.2 Investigating the timescale of evolutionary rescue

Given the capacity for evolutionary rescue, we also explored the timescale for population decline and recovery. A high ratio of mutants to wild types early after the introduction of the disease would correspond to a rescue pattern occurring over a short time span, while a low ratio over that same time horizon would reflect a prolonged rescue pattern, which could leave the population vulnerable to stochastic die-out for longer (i.e., faster selection on mutant when mutant has higher proportion than wild type; see Jiao et al., 2020). Therefore, to conduct our analyses, we used heat maps showing the ratio of mutants to wild types 20 years (19 breeding cycles) after the introduction of infection into the population, across three pairs of trade-off traits relative to the wild-type and mutant populations: recovery rate and disease-induced mortality (Figure 4), recovery rate and uninfected (natural) birth rate (Figure 5), and disease-induced mortality and uninfected birth rate (Figure 6).

When the infected death rate in wild type (indicated by μ_{wt+}/μ_{mt+} with μ_{mt+} fixed) increases, the mutant population grew faster than the infected wild type, leading to a larger ratio of mutant vs. wild type individuals (see the color progression along

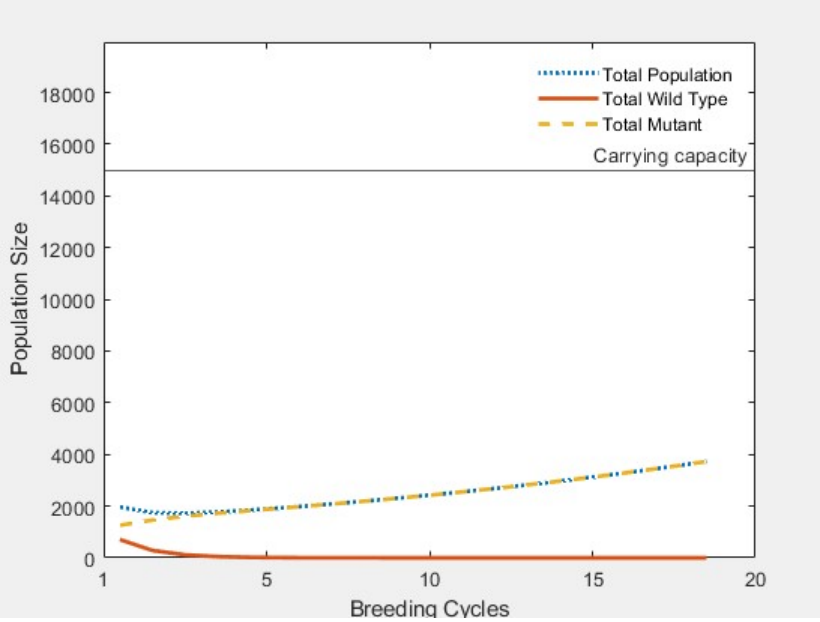

Figure 3: Dynamics of the total host population, mutant and wild type, over 19 breeding cycles in the presence of an epidemic and interpolated by midpoint. The corresponding parameters and initial values are in Tables 1 and 2. The black horizontal line indicates carrying capacity.

the y-axis in Figure 4 and x-axis in Figure 6). Conversely, when the relative uninfected birth rate of the wild type ($\alpha_{wt-}/\alpha_{mt-}$ with α_{mt-} fixed) increased, the wild type showed faster growth, thereby slowing down the rescue pattern (see the decrease in the ratio of mutant vs. wild type along y-axis in Figures 5 and 6). Overall, these changes in timescale reveal varying how sensitive evolutionary rescue outcomes might be to the specific demographic and etiological traits represented in the population.

We also found an interesting unimodal pattern in outcomes when varying the infected recovery ratio (within the Supplemental Materials see Appendix 3 and its Figure S3).

4 Discussion

By incorporating evolutionary game theory into an existing epidemiological framework, we have demonstrated how the combined dynamics of epidemiological and evolutionary forces, can shape the viability of populations over the course of days, months, and decades following the introduction of a novel pathogen (see Maslo and Fefferman, 2015; Saunders et al., 2018). In addition, this model also provides a flexible framework to incorporate the ecological factors of population dynamics and persistence, leading to further exploration of the combined effects of epidemiological and ecological effects on host conservation. This adds to the growing literature quantifying eco-evol interactions (Lambrinos, 2004; Brown and Hastings, 2003; Schreiber et al., 2018; Lion and Gandon, 2015; Best et al., 2011). Specifically, we found in our model that evolutionary rescue can occur under immune-reproductive trade-offs (Table 1; Figures 2 and 3) and that the timescale of evolutionary rescue is highly sensitive to the magnitude of these trade-offs.

An increase in disease-induced mortality of wild types relative to that of mutants (indicated by μ_{wt+}/μ_{mt+} with μ_{mt+} fixed) increased the ratio of mutants to wild types (see the color intensity increase along the y-axis in Figure 4 and from left to right along the x-axis in Figure 6). This result occurs due to the reduction in competition (Gause, 1970; Tilman, 1990) for mutants in the population, allowing them to quickly overtake the wild-type as part of an evolutionary rescue pattern. In contrast, an increase in the uninfected wild-type birth rate relative to that of the mutants ($\alpha_{wt-}/\alpha_{mt-}$ with α_{mt-} fixed) increases competition against mutants, thus decreasing the proportion of mutants in the population (see color fade along y-axis in Figures 5 and 6) and potentially prolonging or delaying evolutionary rescue. The cascading impacts of these dynamics mean that a short-term increase in the mutant population (due to high mortality rates in infected wild-type individuals) would then also weaken the increase in the wild-type population. This is because the birth rate will shift due to the increasing reliance on uninfected reproductives (Figure 6).

Due to the complexity of analytical solutions, we have relied on the outcomes of simulations in this first effort. It is possible that bifurcation points determining evolutionary rescue exist, but analytical results stemming directly from the model are difficult to achieve due to the nature of a continuous epidemiological system tied to a discrete, evolutionary game theoretic one, and

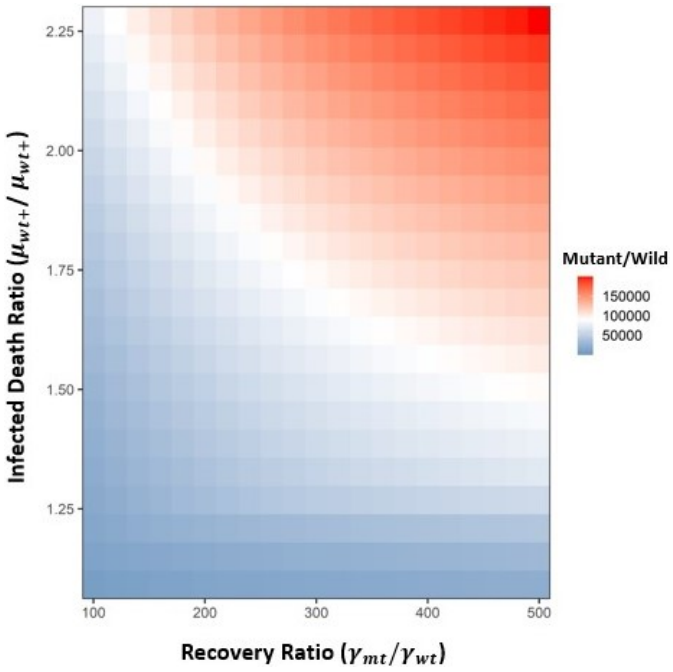

Figure 4: The effects of the recovery ratio (γ_{mt}/γ_{wt}) and infected death ratio (μ_{wt+}/μ_{mt+}) on the mutant to wild-type population ratio after 19 breeding cycles of post-disease introduction. On the x-axis, the wild-type recovery rate stays fixed while the mutant recovery rate varies. On the y-axis, the infected death rate of the mutant stays fixed while the wild-type infected death rate varies.

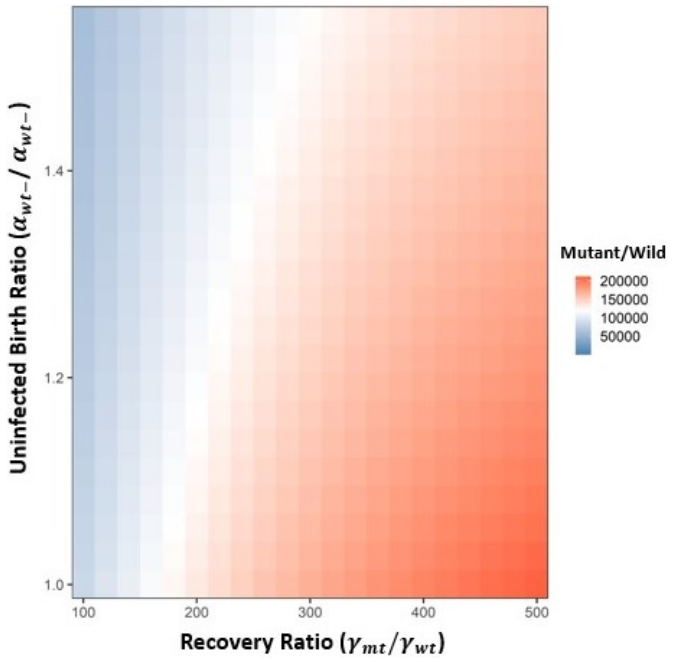

Figure 5: The effects of the recovery ratio (γ_{mt}/γ_{wt}) and uninfected (natural) birth ratio ($\alpha_{wt-}/\alpha_{mt-}$) on the mutant to wild-type population ratio after 19 breeding cycles of post-disease introduction. On the x-axis, the wild-type recovery rate stays fixed while the mutant recovery rate varies. On the y-axis, the mutant uninfected birth rate stays fixed while the wild-type uninfected birth rate varies.

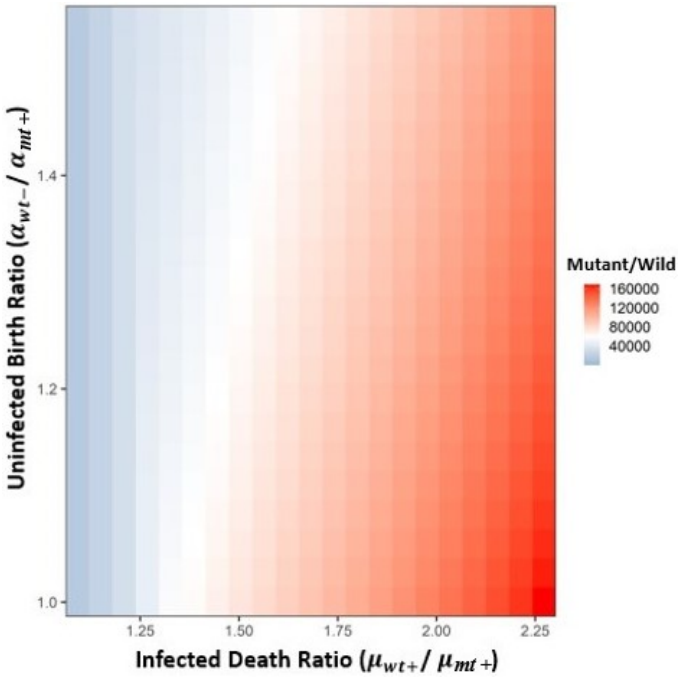

Figure 6: The effects of the infected death ratio (μ_{wt+}/μ_{mt+}) and uninfected (natural) birth ratio ($\alpha_{wt-}/\alpha_{mt-}$) on the mutant to wild-type population ratio after 19 breeding cycles of post-disease introduction. On the x-axis, the mutant infected death rate stays fixed while the wild-type infected death rate varies. On the y-axis, the mutant uninfected birth rate stays fixed while the wild-type uninfected birth rate varies.

are outside of the scope of this paper. Future work to more seamlessly integrate these models and allow for such analysis is under way. However, even simulations can yield notable findings applicable to wildlife conservation. Unlike the inevitable recovery in our simulations, factors delaying or prolonging the timescale of evolutionary rescue in a species can lower the chance of species recovery in the real world (i.e., the "small population paradigm"; see Caughley, 1994; Mattsson et al., 2008; Ouborg et al., 2006; Weeks et al., 2016).

Moving forward, models such as this should explore additional scenarios to characterize the potential influence of epi-evolutionary dynamics, starting with the case where the mutant population can stably coexist with the wild type population in the absence of an epidemic (Note that parameters in Figure 2 only consider the situation where mutants would die out without the epidemic). Simple next-step additions to our model include relaxing the breeding assumptions to include semelparous hosts, exploring dynamic/seasonal carrying capacity, and considering different types of infections via different compartmental epidemiological frameworks (e.g., SI, SIS, SIRS, and intermittent outbreaks where we might analyze the Red Queen hypothesis; see Leigh, 1973; MacPherson and Otto, 2018). Together, this understanding will lay the groundwork for more detailed biological models to understand the full spectrum of coevolutionary dynamics through nonlinear functions for epidemiological parameters (Restif and Koella, 2003), involve more players and strategies that might incorporate ecological interactions between host populations (Best, 2018), and disease vectors (North and Godfray, 2017); and creating migration within metapopulations (Jiao et al., 2016, 2018; Diffendorfer et al., 1995; Revilla and Wiegand, 2008). Alternatively, we could reimplement the evolutionary game to operate more strictly on genotypic strategies (Hashimoto and Aihara, 2009; Rowe, 1988), which would open the possibility for modeling mutations, genetic drift, and gene flow and understanding their contribution to evolutionary rescue (Carlson et al., 2014; Mills et al., 2018; Orr and Unckless, 2014; Oziolor et al., 2019).

Thorough investigation of epidemiological and evolutionary patterns requires a qualitative understanding of host, pathogen, (and potentially parasite and vector) evolution in changing environments. The model we present provides a first set of tools by which to understand and predict these dynamics. The scarcity of relevant data to detect evolutionary rescue (Carlson et al., 2014), the presence of potentially confounding environmental factors, as well as the effects of inter- and intra-species interactions in the host's environment can complicate interpretation of population dynamics even if they arose, in theory, from evolutionary rescue. As theoretical investigations into evolutionary rescue continue and await definitive confirmation from lab and field experiments, keeping evolutionary game theory in mind can bring us closer to understand the roles natural and human activities (e.g., Suarez et al., 2020) may play in evolutionary dynamics over short timescales and their long-term effects.

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References

Akçay, E. (2020). Deconstructing evolutionary game theory: coevolution of social behaviors with their evolutionary setting. *The American Naturalist 195*(2), 315–330. 75

Bell, G. (2013). Evolutionary rescue and the limits of adaptation. *Philosophical Transactions of the Royal Society B: Biological Sciences 368*(1610), 20120080. 75

Bell, G. and A. Gonzalez (2011). Adaptation and evolutionary rescue in metapopulations experiencing environmental deterioration. *Science 332*(6035), 1327–1330. 75

Best, A. (2018). Host-pathogen coevolution in the presence of predators: fluctuating selection and ecological feedbacks. *Proceedings of the Royal Society B: Biological Sciences 285*(1885), 20180928. 83

Best, A., S. Webb, A. White, and M. Boots (2011). Host resistance and coevolution in spatially structured populations. *Proceedings of the Royal Society B: Biological Sciences 278*(1715), 2216–2222. 81

Brown, D. H. and A. Hastings (2003). Resistance may be futile: dispersal scales and selection for disease resistance in competing plants. *Journal of Theoretical Biology 222*(3), 373–388. 81

Carlson, S. M., C. J. Cunningham, and P. A. Westley (2014). Evolutionary rescue in a changing world. *Trends in Ecology & Evolution 29*(9), 521–530. 75, 83

Caughley, G. (1994). Directions in conservation biology. *Journal of Animal Ecology 63*(2), 215–244. 83

Cressman, R. and Y. Tao (2014). The replicator equation and other game dynamics. *Proceedings of the National Academy of Sciences 111*(Supplement 3), 10810–10817. 79

Diffendorfer, J. E., M. S. Gaines, and R. D. Holt (1995). Habitat fragmentation and movements of three small mammals (sigmodon, microtus, and peromyscus) ecological archives e076-002. *Ecology 76*(3), 827–839. 83

Echaubard, P., J. Leduc, B. Pauli, V. G. Chinchar, J. Robert, and D. Lesbarreres (2014). Environmental dependency of amphibian–ranavirus genotypic interactions: evolutionary perspectives on infectious diseases. *Evolutionary Applications 7*(7), 723–733. 76

Edmunds, D. R., M. J. Kauffman, B. A. Schumaker, F. G. Lindzey, W. E. Cook, T. J. Kreeger, R. G. Grogan, and T. E. Cornish (2016). Chronic wasting disease drives population decline of white-tailed deer. *PloS One 11*(8), e0161127. 80

Ferriere, R. and S. Legendre (2013). Eco-evolutionary feedbacks, adaptive dynamics and evolutionary rescue theory. *Philosophical Transactions of the Royal Society B: Biological Sciences 368*(1610), 20120081. 76

Gause, G. (1970). Criticism of invalidation of principle of competitive exclusion. *Nature 227*(5253), 89–89. 81

Gonzalez, A., O. Ronce, R. Ferriere, and M. E. Hochberg (2013). Evolutionary rescue: an emerging focus at the intersection between ecology and evolution. *Philosophical Transactions of the Royal Society B: Biological Sciences 368*(1610), 20120404. 75

Hammerstein, P. and R. Selten (1994). Game theory and evolutionary biology. *Handbook of Game Theory with Economic Applications 2*, 929–993. 75

Hashimoto, K. and K. Aihara (2009). Fixation probabilities in evolutionary game dynamics with a two-strategy game in finite diploid populations. *Journal of Theoretical Biology 258*(4), 637–645. 83

Jiao, J. and N. Fefferman (2021). The dynamics of evolutionary rescue from a novel pathogen threat in a host metapopulation. *Scientific Reports 11*(1), 1–13. 77

Jiao, J., M. A. Gilchrist, and N. H. Fefferman (2020). The impact of host metapopulation structure on short-term evolutionary rescue in the face of a novel pathogenic threat. *Global Ecology and Conservation 23*, e01174. 80

Jiao, J., S. S. Pilyugin, and C. W. Osenberg (2016). Random movement of predators can eliminate trophic cascades in marine protected areas. *Ecosphere 7*(8), e01421. 83

Jiao, J., S. S. Pilyugin, L. Riotte-Lambert, and C. W. Osenberg (2018). Habitat-dependent movement rate can determine the efficacy of marine protected areas. *Ecology 99*(11), 2485–2495. 83

Keeling, M. J. and P. Rohani (2011). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press. 76

Kerr, A. M., S. N. Gershman, and S. K. Sakaluk (2010). Experimentally induced spermatophore production and immune responses reveal a trade-off in crickets. *Behavioral Ecology 21*(3), 647–654. 76

Lambrinos, J. G. (2004). How interactions between ecology and evolution influence contemporary invasion dynamics. *Ecology 85*(8), 2061–2070. 81

Leigh, V. V. (1973). A new evolutionary law. *Evolutionary Theory*, 1–30. 76, 83

Lion, S. and S. Gandon (2015). Evolution of spatially structured host–parasite interactions. *Journal of Evolutionary Biology 28*(1), 10–28. 81

MacPherson, A. and S. P. Otto (2018). Joint coevolutionary–epidemiological models dampen red queen cycles and alter conditions for epidemics. *Theoretical Population Biology 122*, 137–148. 83

Maslo, B. and N. H. Fefferman (2015). A case study of bats and white-nose syndrome demonstrating how to model population viability with evolutionary effects. *Conservation Biology 29*(4), 1176–1185. 76, 80, 81

MATLAB (2018). *9.7.0.1190202 (R2019b)*. Natick, Massachusetts: The MathWorks Inc. 76

Mattsson, B., R. Mordecai, M. Conroy, J. Peterson, R. Cooper, and H. Christensen (2008). Evaluating the small population paradigm for rare large-bodied woodpeckers, with implications for the ivory-billed woodpecker. *Avian Conservation and Ecology 3*(2). 83

Mills, L. S., E. V. Bragina, A. V. Kumar, M. Zimova, D. J. Lafferty, J. Feltner, B. M. Davis, K. Hackländer, P. C. Alves, J. M. Good, et al. (2018). Winter color polymorphisms identify global hot spots for evolutionary rescue from climate change. *Science 359*(6379), 1033–1036. 83

North, A. R. and H. C. J. Godfray (2017). The dynamics of disease in a metapopulation: The role of dispersal range. *Journal of Theoretical Biology 418*, 57–65. 83

Orr, H. A. and R. L. Unckless (2014). The population genetics of evolutionary rescue. *PLoS Genetics 10*(8). 83

Osmond, M. M. and C. de Mazancourt (2013). How competition affects evolutionary rescue. *Philosophical Transactions of the Royal Society B: Biological Sciences 368*(1610), 20120085. 76

Ouborg, N., P. Vergeer, and C. Mix (2006). The rough edges of the conservation genetics paradigm for plants. *Journal of Ecology 94*(6), 1233–1248. 83

Oziolor, E. M., N. M. Reid, S. Yair, K. M. Lee, S. G. VerPloeg, P. C. Bruns, J. R. Shaw, A. Whitehead, and C. W. Matson (2019). Adaptive introgression enables evolutionary rescue from extreme environmental pollution. *Science 364*(6439), 455–457. 83

Pintor, L. M., J. S. Brown, and T. L. Vincent (2011). Evolutionary game theory as a framework for studying biological invasions. *The American Naturalist 177*(4), 410–423. 75

R Core Team (2013). *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. 76

Reluga, T. C. (2010). Game theory of social distancing in response to an epidemic. *PLoS Computational Biology 6*(5), e1000793. 76

Restif, O. and J. C. Koella (2003). Shared control of epidemiological traits in a coevolutionary model of host-parasite interactions. *The American Naturalist 161*(6), 827–836. 76, 83

Revilla, E. and T. Wiegand (2008). Individual movement behavior, matrix heterogeneity, and the dynamics of spatially structured populations. *Proceedings of the National Academy of Sciences 105*(49), 19120–19125. 83

Robertson, S. A., A. S. Care, and L. M. Moldenhauer (2018). Regulatory T cells in embryo implantation and the immune response to pregnancy. *The Journal of Clinical Investigation 128*(10), 4224–4235. 75, 76

Rowe, G. W. (1988). To each genotype a separate strategy - a dynamic game theory model of a general diploid system. *Journal of Theoretical Biology 134*(1), 89–101. 83

Roy, B. and J. Kirchner (2000). Evolutionary dynamics of pathogen resistance and tolerance. *Evolution 54*(1), 51–63. 76

Saunders, S. P., F. J. Cuthbert, and E. F. Zipkin (2018). Evaluating population viability and efficacy of conservation management using integrated population models. *Journal of Applied Ecology 55*(3), 1380–1392. 81

Schreiber, S. J., S. Patel, and C. terHorst (2018). Evolution as a coexistence mechanism: Does genetic architecture matter? *The American Naturalist 191*(3), 407–420. 81

Sheldon, I. M., J. G. Cronin, G. D. Healey, C. Gabler, W. Heuwieser, D. Streyl, J. J. Bromfield, A. Miyamoto, C. Fergani, and H. Dobson (2014). Innate immunity and inflammation of the bovine female reproductive tract in health and disease. *Reproduction 148*(3), R41–R51. 76

Sigmund, K. (2017). *Games of Life: Explorations in Ecology, Evolution and Behavior*. Courier Dover Publications. 75

Smith, J. M. (1982). *Evolution and the Theory of Games*. Cambridge University Press. 75

Suarez, G. P., O. Udiani, B. F. Allan, C. Price, S. J. Ryan, E. Lofgren, A. Coman, C. M. Stone, L. K. Gallos, and N. H. Fefferman (2020). A generic arboviral model framework for exploring trade-offs between vector control and environmental concerns. *Journal of Theoretical Biology 490*, 110161. 83

Tanimoto, J. (2015). *Fundamentals of Evolutionary Game Theory and its Applications*. Springer. 75

Tilman, D. (1990). Constraints and tradeoffs: toward a predictive theory of competition and succession. *Oikos*, 3–15. 81

Vickery, W. L. and R. Poulin (2010). The evolution of host manipulation by parasites: a game theory analysis. *Evolutionary Ecology 24*(4), 773–788. 75

Vincent, T. L. (1994). An evolutionary game theory for differential equation models with reference to ecosystem management. In *Advances in Dynamic Games and Applications*, pp. 356–374. Springer. 75

Wang, X., D. Jia, S. Gao, C. Xia, X. Li, and Z. Wang (2020). Vaccination behavior by coupling the epidemic spreading with the human decision under the game theory. *Applied Mathematics and Computation 380*, 125232. 76

Weeks, A. R., J. Stoklosa, and A. A. Hoffmann (2016). Conservation of genetic uniqueness of populations may increase extinction likelihood of endangered species: the case of Australian mammals. *Frontiers in Zoology 13*(1), 31. 83

Zomorrodi, A. R. and D. Segrè (2017). Genome-driven evolutionary game theory helps understand the rise of metabolic interdependencies in microbial communities. *Nature Communications 8*(1), 1–12. 75