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Host-pathogen coevolution in the presence of predators: fluctuating selection and ecological feedbacks

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Abstract

Host-pathogen co-evolution is central to shaping natural communities and is the focus of much experimental and theoretical study. For tractability, the vast majority of studies assume the host and pathogen interact in isolation, yet in reality they will form one part of complex communities, with predation likely to be a particularly key interaction. Here I present the first theoretical study to assess the impact of predation on the coevolution of costly host resistance and pathogen transmission. I show that fluctuating selection is most likely when predators selectively prey upon infected hosts, but that saturating predation, due to large handling times, dramatically restricts the potential for fluctuations. I also show how host evolution may drive either enemy to extinction, and demonstrate that while predation selects for low host resistance and high pathogen infectivity, ecological feedbacks mean this results in lower infection rates when predators are present. I emphasise the importance of accounting for varying population sizes, and place the models in the context of recent experimental studies.

Keywords: Host-pathogen, coevolution, communities, fluctuating selection

Introduction

Antagonistic co-evolution between hosts and their pathogens is central to shaping the structure and function of biological communities [1,2]. A rich field of experiment and theory has been developed to understand the drivers of host-pathogen co-evolution and its impact on ecological dynamics [3-6]. However, for tractability the vast majority of studies assume that the host and pathogen exist in isolation. In reality host-pathogen interactions will be embedded within complex communities with an array of biological interactions. These community interactions will have significant impacts on the host-pathogen interaction, which will in turn feed back to the community dynamics [6]. Predation will be particularly significant due to the direct effects on host population size, as well as indirect links between infection and predation. Classic empirical work has shown that hosts with higher pathogen burdens are more likely to be predated [7,8], potentially altering selection pressure on both antagonists, and thus impacting the community structure itself.

Theoretical studies on the co-evolution of host resistance and pathogen infectivity have found a range of possible qualitative outcomes, including long-term stable investment (Continuously Stable Strategies), branching to polymorphism and co-evolutionary cycles (fluctuating selection dynamic), depending on the ecological and evolutionary context [9-20]. A particular focus has been on fluctuating selection (FSD) given its importance to the maintenance of diversity [21], evolution of sex [22] and local adaptation [23]. It is well known that highly specific, 'matching-allele', infection mechanisms give rise to FSD due to negative frequency-dependent selection [17,18], while gene-for-gene

mechanisms (variation between specialists and generalists) can lead to FSD if there are costs [19,20]. Recent work including explicit ecological dynamics found that cycles of host and pathogen investment could occur even without specificity [14]. However we have little understanding of how robust theoretical predictions are to including community interactions.

There is increasing awareness in experimental literature of the importance of community interactions to host-pathogen co-evolution [1,2,6], and there have been some direct experimental tests [24-26]. Friman & Buckling [24] found that the Arms Race Dynamic between a bacteria (*Pseudomonas flourescens*) and its phage (Φ2) appeared to break down when a predatory protist (*Tetrahymena thermophila*) was present, while Örmälä-Odegrip et al. [26] found that selection due to predatory protists led to lower susceptibility to phage infection in both *Serratia marcescens* and *Pseudomonas flourescens*. Alongside this experimental work, there is increasing theoretical focus on how the evolution of hosts and pathogens [27-32] are separately impacted by an immune predator (a predator that cannot be infected by the parasite). These studies have shown that pathogens invest in higher virulence and transmission when a predator is present [27], while hosts maximise defence to parasitism at intermediate predation rates [31]. In contrast to standard models, predation allows for evolutionary branching to coexistence in pathogens (if virulence and predation are linked; [28] v [33]) and the pathogen can be eradicated through host evolution ([30] v [34]). These studies provide a broad examination of the separate evolutionary properties of hosts and pathogens in the presence of a predator. However, given the importance of the co-evolutionary setting to the

potential for FSD [14,16-20], the differing predictions of the impact of predation on parasites [27] to hosts [31] and the importance of changing population sizes to host-parasite coevolution [5], it is vital that we investigate the full coevolutionary dynamics in the presence of a predator. Here I present a model of the co-evolution of host resistance (through reduced susceptibility) and pathogen transmission with non-specific infection, and respective costs to host birth rate and virulence.

Methods

I use a standard model of the population dynamics of susceptible (S) and infected hosts (I), adding an immune predator (P), as given by the following ordinary differential equations,

$$(1)\ \frac{dS}{dt} = (b - qH)S - dS - \beta SI + \gamma I - c\rho(S,I)SP$$

$$(2)\ \frac{dI}{dt} = \beta SI - (d + \alpha + \gamma)I - c\phi\rho(S,I)IP$$

$$(3)\ \frac{dP}{dt} = ecP(S + \phi I)\rho(S,I) - \mu P$$

Susceptible hosts reproduce at birth rate b which is reduced due to crowding by a factor q (H=S+I). All hosts die at natural death rate d. Transmission is a density-dependent term with coefficient β. As well as the natural death rate, infected hosts suffer an additional mortality, which I define as virulence, at rate α, and can recover back to susceptibility at rate γ. Both susceptible and infected hosts are at risk of predation with coefficient c, with a functional response given by $\rho(S,I) = 1/(1 + ch(S + \phi I))$ (see ESM and figure S1). If h=0 (i.e. there is no 'handling time'), the functional response is linearly dependent on the effective

host density, $S + \phi I$ (type I). If $h>0$ then the response is saturating at higher effective host densities (type II). In what follows I assume the type I response unless otherwise stated. I also allow the predator to selectively predate infected hosts by the inclusion of the parameter $\phi > 1$. Predators convert energy from eating hosts in to births through parameter e, and die at rate μ. Note that I do not assume any link between virulence and predation, as in [28].

When there is linear (type I) predation, the full host-pathogen-predator equilibrium (where it exists) is always stable. However, for a type II response population cycles can occur. In the type I case, the resident equilibrium for $\hat{S}$ and $\hat{I}$ can be found as,

$$(4)\hat{S} = \frac{\alpha + d + \gamma}{\beta} + \frac{c\phi}{\beta}\hat{P}$$

$$(5)\hat{I} = \frac{\mu}{ec\phi} - \frac{\alpha + d + \gamma}{\beta\phi} - \frac{c}{\beta}\hat{P}$$

Therefore the susceptible density will always increase as the predator is introduced, while the infected density will always decrease (the total host density, $\widehat{H}$, also decreases with increasing $\hat{P}$). Note that this relationship is independent of whether ϕ is greater than or less than unity. This is because, as in classic host-parasite models, the susceptible density is regulated by the parasite [35]. Therefore the increase in predation ultimately benefits susceptible hosts by reducing the density of infecteds. Models with different underlying assumptions, such as an explicit carrying capacity in the host [36], may yield different feedbacks.

I assume that the host can evolve its susceptibility to infection, and the pathogen its infectivity. As such I need to determine how the two jointly control transmission. Here I use a multiplicative function, $\beta(\sigma,\tau) = \sigma\tau + k$, where σ is the host's susceptibility and τ the pathogen's transmission. Such a 'universal' infection function has been commonly used in theoretical studies [11,12,15,17], and is representative of systems where infection is not specific to certain combinations of host and parasite strains [37-39]. I assume that investment in lower susceptibility and higher transmission incur respective costs for the host (lowered birth rate) and pathogen (increased virulence). Examples of the trade-offs are plotted in figure S2; see ESM and figure legends for the form of the trade-off functions. I model co-evolution using the evolutionary invasion analysis framework of adaptive dynamics [40-42], assuming that small, rare mutants (σ_m, τ_m) arise and attempt to invade a resident equilibrium. The success of the mutant is given by its invasion fitness, which is defined as its growth rate whilst rare. As described in the online ESM, assuming a type I functional response, this is given for the host by,

$$(7) s(\sigma_m;\sigma,\tau) = (T + \sqrt{T^2 - 4D})/2$$

where,

$$\begin{aligned} T = &\quad b(\sigma_m) - q\widehat{H} - 2b - \beta(\sigma_m,\tau)\hat{I} - c(1+\phi)\hat{P} - \alpha(\tau) - \gamma \\ D = &\quad -\left(b(\sigma_m) - q\widehat{H} - b - \beta(\sigma_m,\tau)\hat{I} - c\hat{P}\right)\left(b + \alpha(\tau) + \gamma\beta + c\phi\hat{P}\right) - \gamma\beta(\sigma_m,\tau)\hat{I} \end{aligned}$$

and for the pathogen,

$$(8) r(\tau_m;\sigma,\tau) = \beta(\sigma,\tau_m)\hat{S} - (d + \alpha(\tau_m) + \gamma) - c\phi\hat{P}$$

where all population densities are evaluated at the resident equilibrium (denoted by hats).

Assuming small mutations, the co-evolutionary dynamics of the traits σ and τ over evolutionary time can then be approximated by a pair of ordinary differential equations [42] (see ESM),

$$(9)\ \frac{d\sigma}{dT} \propto \hat{S}\frac{\partial s}{\partial \sigma_m}\Big|_{\sigma_m=\sigma}$$

$$(10)\ \frac{d\tau}{dT} \propto \hat{I}\frac{\partial r}{\partial \tau_m}\Big|_{\tau_m=\tau}$$

The possible long-term outcomes are: (1) a Continuously Stable Strategy (CSS) in both antagonists where the host and pathogen both invest in a stable level of investment, (2) co-evolutionary cycles (FSD), (3) evolutionary branching in one or both species, (4) maximisation/minimisation to the imposed (physiological) limits of the trait by one or both species. In the latter two cases, one species may exhibit this outcome, while the other could exhibit any of behaviours 1, 3 or 4 [14]. Further details of the methods are given in the online ESM.

Results

Qualitative outcomes

In figure 1 I show the qualitative outcome from simulations as the host and pathogen trade-off curvatures (p_h and p_p) are varied, for (a) linear (type I), and (b)-(d) saturating (type II) predation (h=*0.4, 0.45, 0.5*). Note that accelerating (increasingly costly) trade-offs occur for p_h>0 but p_p<0 (marked *'(acc.)*' in figure 1; see also figure S2). A range of qualitatively different outcomes are possible (see sample outputs in figure S3). In all cases, while the pathogen's trade-off is accelerating, if the host's trade-off is also accelerating there is a coevolutionary CSS, while if the host's trade-off decelerates the host branches (and the parasite remains at its CSS). The potential for cycles (FSD) and pathogen branching

169 depend on the handling time. For type I predation (fig 1a), if both trade-offs
170 decelerate (marked *'(dec.)'*; $p_h < 0, p_p > 0$) then FSD is common. Initially
171 introducing a handling time (fig 1a vs 1b) shifts the region of FSD to higher
172 parasite trade-off curvatures but any host trade-off shape, suggesting the
173 parasite trade-off must be reasonably decelerating for selection to be
174 destabilised. This also introduces greater regions of pathogen branching, either
175 on its own or together with the host. However, figures 1(b)-(d) show that cycles
176 rapidly disappear once the handling time reaches a threshold value (here
177 between *h=0.4* and *h=0.*5). Comparing these figures the cycles are lost in two
178 ways. First, the dynamics can be stabilized towards an evolutionary branching
179 point, generally resulting in both species branching. Alternatively, the predator
180 can go extinct during the cycle (after this the host maximizes susceptibility and
181 the pathogen minimizes infectivity). The irregular nature of these transitions
182 (their 'scattered' nature) is due to small stochastic variations between
183 simulations –small amplitude cycles being close enough to a singular point to
184 branch, or low predator densities during a cycle being approximated to zero.
185 Why does saturating predation cause coevolution to stabilise towards a
186 branching point? When predation is linear, mortality is higher (figure S1). With
187 selective predation of infecteds, this will strengthen selection for host resistance,
188 pushing host investment, temporarily, to higher levels and continuing the cycles.
189 When predation saturates and mortality is lower, this effect is reduced and the
190 dynamics are stabilized.
191
192 Figure 2 shows how FSD depends on the predation rate, *c*, and selective
193 predation, ϕ. Here we see that FSD is most common when there is high selective

194 predation but low general predation. This means that infected hosts suffer much
195 higher mortality than susceptible hosts, fitting with the above argument that this
196 increases selection for host resistance, thus destabilizing selection. This region is
197 bounded on both sides by regions where one or both species branches. We also
198 see that when both selective and general predation are low, the predator dies out
199 and when both are high the pathogen dies out.
200
201 *Extinction of the predator or pathogen*
202 Invasion/exclusion thresholds exist for the pathogen and predator ([30]; see
203 ESM). This allows for one of the species to be driven to extinction. A particularly
204 interesting example of pathogen extinction can be seen in the phase portrait of
205 figure 3, highlighting regions where the pathogen (red) or predator (blue)
206 cannot persist (a case of predator extinction is in figure S4). The solid line shows
207 a trajectory that tends to intermediate host and high pathogen investment when
208 all three species coexist (blue dot). However, changing only the initial condition,
209 the dashed line crosses the threshold for pathogen persistence, at which point
210 the pathogen goes extinct. Note that this extinction occurs due to the host
211 increasing its susceptibility to infection, a rather unintuitive result. This occurs
212 because increasing susceptibility leads to a greater predator density, pushing the
213 infected host population to ever lower densities. Again, note that increased
214 predator density always leads to increased susceptible and decreased infected
215 densities, regardless of selective predation.
216
217 *Continuously Stable Strategies*

Figure 4 explores how predation impacts host and pathogen investment at a Continuously Stable Strategy (CSS). Figure 4a shows the host (solid) and pathogen (dashed) strategies as predation rate, c, is varied, with the overall transmission coefficient, β, in figure 4b and the resulting *per-capita* rates of infection, $\beta\hat{I}$, and predation, $c\hat{P}$, in figure 4c. For low predation the predator cannot persist and there is a fixed level of investment. Once the predator can persist, the pathogen increases its investment, while the host displays a 'U'-shaped curve (fig 4a), leading to an overall increase in the transmission coefficient (fig 4b). However, fig 4c shows that the negative feedback from predation to the infected density means that the *per-capita* rate of infection, $\beta\hat{I}$, is significantly reduced. Thus high rates of predation lead to high host susceptibility and high pathogen infectivity, yet relatively low rates of infection in the population. Similar patterns are found for varying other parameters (figure S5).

Evolutionary branching

Purely host-parasite models with ecological dynamics and universal transmission have found that branching can occur such that two hosts and one pathogen, or two of each antagonist, coexist [12,15]. Further work found that adding a predator means the pathogen can branch against a monomorphic host when there is a link between virulence and predation [28]. Here, I find the stronger result that the pathogen can branch (against a monomorphic host) even without this link when predation saturates (figures 1,2). This indicates the emergence of a negative feedback to pathogen selection once predation is saturating. Further branching is not possible and the maximum level of diversity

243 remains two hosts-two pathogens. After the pathogen has branched, the system
244 stabilizes. In particular, the predator cannot be driven to extinction without one
245 of the pathogen strains first being excluded (since standard host-parasite models
246 cannot support two pathogen strains [12]). Examining simulation results, after
247 host branching it seems there is never extinction of either the predator or
248 pathogen.
249
250 **Discussion**
251 There is increasing focus on understanding how community interactions impact
252 host-pathogen co-evolution [1,2,6]. I have examined the co-evolution of host
253 resistance (reduced susceptibility) and pathogen transmission, with respective
254 costs to birth rate and virulence, in the presence of a predator. Fluctuating
255 selection (FSD) is a particularly important co-evolutionary behaviour since it is
256 the only sustained dynamic outcome in a constant environment, and is the focus
257 of much theoretical study [14,16-20]. I have found that while FSD is common
258 when the predator's functional response is linear, if predation saturates at high
259 host densities FSD becomes an increasingly rare outcome, with evolutionary
260 branching of the pathogen occurring instead. FSD is also promoted when there is
261 strong selective predation of infected hosts. The driver of both results is that
262 mortality of infected hosts is higher when predation is selective and does not
263 saturate, destabilizing selection near an evolutionary attractor. Thus host-
264 pathogen FSD may be expected in communities with highly selective predators
265 with low handling times. In an experimental study of a microbial system the
266 addition of a predatory protist appeared to breakdown an Arms Race Dynamic,
267 but there was no conclusive evidence that the dynamics shifted to FSD [24]. It

268 would be interesting to conduct explicit experimental tests of how host-pathogen
269 systems that exhibit FSD behave when a predator is added.
270
271 In standard models hosts cannot cause pathogen extinction through the
272 evolution of costly resistance [34], but can when a predator is present [30]. Here
273 I have shown a particularly unintuitive example of pathogen extinction caused by
274 the host lowering its resistance. This drives an ecological feedback whereby the
275 predator density increases and pushes pathogen numbers to extinction. It is
276 notable that there is no evolutionary rescue of the pathogen. This is in fact
277 intuitive since as the pathogen numbers decrease the relative speed of mutation
278 also decreases. Host-driven pathogen extinction, in the absence of predation, has
279 been found in experimental studies when further pressures, for example,
280 population bottlenecks [43] or reduced resource availability [44], are placed on
281 the pathogen. This appears consistent with the result that extinction may occur
282 when a predator is introduced. Intriguingly, in their experimental study of
283 bacteria-phage co-evolution in the presence of a predatory protist, Friman &
284 Buckling [24] report a case of phage being driven to extinction, and it would be
285 fascinating to see whether such a result is repeated elsewhere.
286
287 I have shown that while the introduction of a predator may lead to lower host
288 resistance and higher pathogen infectivity at a co-evolutionary CSS compared to
289 when no predator is present, the negative feedback from predators to the
290 infected density means that there are in fact lower *per-capita* rates of infection
291 than when the predator is absent. This has important consequences for how
292 infection rates are measured in empirical studies, suggesting opposing patterns

293 of infection may be predicted depending on whether population sizes are
294 controlled or not. Previous theory has shown, when only one antagonist evolves,
295 that the pathogen should increase transmission when a predator is added [27]
296 but the host should maximise defence at intermediate predation rates [31].
297 These results remain broadly true here, but give a misleading impression of the
298 full co-evolutionary outcome when feedbacks to population sizes are not
299 included. Interestingly, experimental results from two bacteria-phage-protist
300 systems found hosts exhibited lower susceptibility to phage infection when a
301 predatory protist was present [26]. This host response is consistent with the
302 results here and earlier [31] assuming predation rates are not too high or co-
303 evolution and ecological feedbacks are not fully present. More generally, the
304 prediction here that overall infection rates may be lower when a predator is
305 present is consistent with two key experimental studies [24,26]. Interestingly,
306 Friman & Buckling [24] also reported that the introduction of the protist lowered
307 overall host numbers, as would be expected here. It would be interesting to see
308 whether direct experimental tests in the presence and absence of predators,
309 including measures of population sizes, confirm the findings here.
310
311 Almost all natural and managed populations are part of communities, and this
312 work is likely to have important implications to understanding a range of
313 empirical systems, not least in microbial communities [2,4,45,46]. However,
314 understanding antagonistic co-evolution in the context of complex communities
315 is still an emerging field, and many open questions remain. For example, here I
316 assumed no specificity in infection. Previous theory has shown that such
317 specificity has implications for both static and transient diversity [14,15], and

318 this may be more realistic for modelling certain systems. Further, I have assumed
319 that the additional interaction is with an immune predator, but other
320 interactions, such as mutualisms or competitors, may lead to different feedbacks.
321 A broader assessment of the impacts of community interactions on antagonistic
322 coevolution should be a long-term goal of both experiment and theory [6].
323
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326 feedback on earlier versions of this manuscript.
327
328 **Competing Interests**
329 I have no competing interests.
330
331 **Ethics**
332 No ethics approval was required.
333
334 **Data Accessibility**
335 C++ code for the simulations is available as ESM.
336
337 **Author Contributions**
338 AB is the sole contributor.
339
340 **References**
341

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458 **Figure Legends**

459

460 **Figure 1**: Qualitative output from numerical simulations of the co-evolutionary
461 dynamics for differing handling times, (a) *h=0*, (b) *h=0.4*, (c) *h=0.45,* (d) *h=0.5*, as
462 the shape of the host and parasite tradeoffs vary. Accelerating ('acc.') and
463 decelerating ('dec.') trade-offs are highlighted on the plots. The simulations were
464 run (see ESM) and the output analysed and classified. CSS=Continuously Stable
465 Strategy, BR=Branching, MX=Maximisation of trait, MN=Minimisation of trait,
466 FSD=Fluctuating Selection/Cycles. See colorbar for classifications.. Parameter
467 values: $q = 0.5, d = 0.2, \gamma = 0.2, \phi = 3, k = 0.5, \mu = 0.5, c = 0.15$. The trade-offs,
468 linking transmissibility and virulence in the pathogen, and susceptibility and
469 birth rate in the host, are given by $\alpha(\tau) = 1.06 - \frac{1-\tau}{1+p_p\tau}, b(\sigma) = 1.92 + \frac{0.16\sigma}{1+p_h(\sigma-1)}$
470 where p_p and p_h are varied along the x- and y-axes respectively.

471

472 **Figure 2:** Qualitative output from numerical simulations as the predation rate, *c*,
473 and selective predation, ϕ, are varied. Parameters are as of figure 1 with
474 $p_h = -0.5, p_p = 0.5$. See colorbar in figure 1 for classifications.

475

476 **Figure 3**: Phase portrait of co-evolution showing regions where the pathogen
477 (red) or predator (blue) cannot persist. Parameter values are as of figure 1a,
478 except $\phi = 2.25, k = 0.35$. The trade-offs are $\alpha(\tau) = 1.56 - \frac{1(1-\tau)}{1-0.23\tau}, b(\sigma) =$
479 $1.87 + \frac{0.21\sigma}{0.59+0.41\sigma}$.

480

Figure 4: How the co-CSS varies with predation, *c*. (a) Host, σ (solid) and pathogen, τ (dashed) strategies, (b) transmission coefficient, β, and (c) per-capita rate of infection, $\beta\hat{I}$ (solid) and predation, $c\hat{P}$ (dashed). Parameter values are as in figure 1a with $\mathrm{p_p} = -0.25, \mathrm{p_h} = 0.25$.