Source-sink migration of natural enemies drives local maladaptation of victim populations in edge habitats

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Abstract

Natural enemies are critical drivers of species biogeography. Local adaptation of victim populations in edge habitats is particularly likely to be limited by enemies. We experimentally tested this hypothesis using a model microbial system, bacterium *Pseudomonas fluorescens* (victim) and a lytic bacteriophage (enemy). When evolving alone, bacterial populations in a low temperature environment (10°C) showed obvious abiotic adaptation in terms of increased growth performance; and immigration of bacteria from an optimal environment (28°C) reduced such evolutionary adaptation. However, when phages were present, no significant abiotic adaptation was observed. Crucially, phage immigrants from source populations even caused maladaptation (decreased growth performance relative to the ancestral genotype), and bacterial adaptation was less affected when both bacteria and phages had joint migration. Our results demonstrate intraspecific apparent competition mediated by enemies with which prosperity in core habitats can exacerbate hardship in edge habitats.

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Abstract

Natural enemies are critical drivers of species biogeography. Local adaptation of victim populations in edge habitats is particularly likely to be limited by enemies. We experimentally tested this hypothesis using a model microbial system, bacterium *Pseudomonas fluorescens*(victim) and a lytic bacteriophage (enemy). When evolving alone, bacterial populations in a low temperature environment (10°C) showed obvious abiotic adaptation in terms of increased growth performance; and immigration of bacteria from an optimal environment (28°C) reduced such evolutionary adaptation. However, when phages were present, no significant abiotic adaptation was observed. Crucially, phage immigrants from source populations even caused maladaptation (decreased growth performance relative to the ancestral genotype), and bacterial adaptation was less affected when both bacteria and phages had joint migration. Our results demonstrate intraspecific apparent competition mediated by enemies with which prosperity in core habitats can exacerbate hardship in edge habitats.

INTRODUCTION

Local adaptation of populations to low-quality habitats, such as species range edges, is crucial for within-species genetic diversity and range expansion/contraction dynamics, with consequences for long-term species persistence (Wright 1943; Pulliam 1988; Venail *et al.* 2008; Edelaar & Bolnick 2012). The typically asymmetric migration between core and edge habitats (source-sink dynamics) can play a crucial role in local adaptation to the latter. Immigrants into the edge populations may fuel local adaptation by supplementing genetic variation (Holt *et al.* 2004; Perron *et al.* 2007), or retard it by competing with the locally adapted genotypes or disrupting locally adaptive alleles via recombination (Figure 1a, 1b) (García-Ramos & Kirkpatrick 1997; Fedorka*et al.* 2012; Eriksson & Rafajlović 2021). Theory suggests that the net effect of immigration on local adaptation will depend on a number of factors including migration rate; and both positive and negative effects have been reported in previous empirical studies (Perron *et al.* 2007, 2010; Tigano & Friesen 2016; Mirrahimi & Gandon 2020).

Coevolving natural enemy species have recently been recognized as important players for population diversification and species biogeography (Engelkes *et al.* 2008; Ricklefs 2010; Ricklefs & Jenkins 2011; Betts *et al.* 2018). Here we investigate how the presence of enemy species may limit abiotic adaptation in edge habitats with and without source-sink dynamics. In an isolated edge habitat, enemy species can reduce victim population sizes and thus the supply of genetic variation and the efficiency of natural selection (Hudson*et al.* 1998; Bohannan & Lenski 2000); and may also drive the evolution of defenses that trade-off with growth traits underlying abiotic adaptation (Figure 1c) (Kraaijeveld & Godfray 1997; Webster & Woolhouse 1999; Brockhurst *et al.* 2004; Agrawal *et al.*2010).

When the enemy species are far more mobile than the victim (as in many predator-prey and plant-herbivore systems), immigration of the enemy individuals from the core habitats would further reduce victim population size, particularly when the core habitats also function as evolutionary hotspots that promote enemy-victim arms race coevolution (Figure 1d) (Hochberg & Van Baalen 1998; Lopez Pascua *et al.*2012; Gorter *et al.* 2016). This negative effect of the source populations on the sink populations is an example of enemy-

mediated intraspecific apparent competition (Holt 1977; Morris *et al.*2004; Ricklefs 2010; Allen *et al.* 2018). Enemy migration may also coincide with victim migration, particularly in host-parasite systems. Here, the net effect for abiotic local adaptation is less predictable: Immigration of victim species itself may promote local adaptation by increasing genetic variation, but it is equally possible that the co-occurring enemy-victim migration leads to repeated sweeps of sink populations by immigrants and thus prevents local adaptation (Figure 1e) (Zhang & Buckling 2016; Poulin & de Angeli Dutra 2021). Some more complex but less realistic scenarios are not considered here, e.g. enemy species being present in the core, but not edge habitats; or enemy species having much lower migration rate than victim species.

Here we experimentally test the above hypotheses using a model bacterium-phage system, *Pseudomonas fluorescens* SBW25 and its lytic phage SBW25Φ2 (Buckling & Rainey 2002). This is a host-parasitoid system as the phages both develop within the bacterial cells and kill the bacterial cells after replication (Lenski 1984; Buckling & Rainey 2002; Forde *et al.* 2004). Therefore, the bacterium and the phage are victim and enemy species, respectively. Due to the experimental amenability of this system, we are able to study all the five scenarios illustrated above (Figure 1). We considered a low temperature environment as an edge habitat for the bacterium and an optimal temperature its core habitat.

MATERIAL AND METHODS

Strains and culture conditions

We used the bacterial strain *Pseudomonas fluorescens* SBW25 (Rainey & Bailey 1996) and the lytic bacteriophage SBW25Φ2 (Buckling & Rainey 2002). Cultures were grown statically in microcosms of 6 mL of KB medium in 25 mL glass vials with loosened lids (glycerol 10 g L^{-1}, proteose peptone no.3 20 g L^{-1}, $K_2HPO_4{\cdot}3H_2O$ 1.5 g L^{-1}, and $MgSO_4{\cdot}7H_2O$ 1.5 g L^{-1}). The optimal growth temperature for this bacterium is 28°C. When grown in batch cultures with a dilution rate of 0.01 every 48 h at a low temperature, 10°C, the bacterium can maintain a viable population with an average population sizes 0.15-fold of that at 28°C (Figure S1; density of the ancestral strain at 10°C was approximately 6.2×10^8 cells mL^{-1}).

The evolution experiment

Thirty low-temperature (10°C) microcosms were set up as edge-habitat populations, six replicates for each of the following treatments: bacterial populations (B), bacterial populations with immigration (B+IB), bacteria/phage populations (BP), bacteria/phage populations with immigration of phages (BP+IP) and bacteria/phage with immigration of bacteria and phages (BP+IBP). Immigrants to B+IB were from six source bacterial microcosms grown at 28°C (SB); and those to BP+IP and BP+IBP were from six source bacteria/phage microcosms grown at 28°C (SBP). Therefore, we set up a total of 42 microcosms.

Each microcosm was initially inoculated with 60 μL of bacterial culture that had been acclimated at an appropriate temperature, and about 10^3 phage particles for the microcosm designed to include phages. The bacterial acclimation procedure involved transferring 60 μL of cultures reconditioned overnight at 28°C to fresh medium and grown at relevant temperatures (10 or 28°C) for 48 h. Cultures were then propagated for 20 serial transfers (one transfer every 48 h). At each transfer, 60 μL of culture from each microcosm was transferred to fresh media. Microcosms with immigration received a further 3 μL of proper cultures from the source microcosms. To obtain phage populations from the source bacteria/phage microcosms, samples of the cultures were mixed with chloroform (10:1 volume ratio), vortexed and centrifuged at 13000 g, with phages remaining in the supernatant (Buckling & Rainey 2002). Optical density at 600 nm wavelength (mOD_{600}) of each culture (200 μL of sample) was measured using a plate reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) before each transfer, as a proxy for the density of *P. fluorescens* . Samples of cultures at transfer 8 and 20 were frozen at -80°C with glycerol (final glycerol concentration 25%).

Measurement of abiotic adaptation of bacterial populations

The abiotic adaptation of bacteria from each low-temperature microcosm was determined by measuring growth performance in the absence of phages. To do so, bacterial populations in coevolution microcosms (that included both bacteria and phages) were first isolated by Virkon treatment. Specifically, KB medium

with 0.375% of the disinfectant Virkon (Antec International, Sudbury, England) was prepared; and 60 μL of each culture was added to 6 mL of the Virkon-supplemented medium and left for 24 h at 28°C. This procedure left bacterial viable and completely phage free; then 60 μL of each Virkon-treated culture was added to 6 mL of fresh KB and grown for 24 h to give a phage-free and Virkon-free culture (Morgan *et al.* 2005). The potential presence of phages in Virkon-treated cultures was tested for by spotting cultures onto semi-solid agar seeded with ancestral *P. fluorescens* strain and incubated at 28°C for 24 h; plaques would indicate the presence of phages. Bacteria from all except one coevolution lines were successfully rescued from phages; and the one exception was a BP+IBP microcosm where bacterial population failed to revive and thus was excluded in the measurement of abiotic adaptation.

Each bacterial population from the low-temperature microcosms, as well as the ancestral strain, was acclimated at 10°C for 48 h, 1% of which was transferred into fresh medium and incubated for another 48 h. Optical densities of resultant cultures were measured (mOD_{600}), as a surrogate of bacterial density (three replicates for each assay and the mean value used in subsequent analyses).

Measurement of bacterial resistance

The resistance of bacteria to phages was measured for the coevolution lines (BP, BP+IP, and BP+IBP) from transfer 8 and 20. Bacterial resistance to within-microcosm phages was determined by streaking 20 independent bacterial colonies across a line of 20 μL phages pre-streaked on agar plates. Specifically, bacterial colonies were isolated by plating dilutions on KB agar plate and incubating for 48 h, grown in 96-well plates at 28°C for 48 h, and then reconditioned at 10°C for 48 h before streaking. Phage samples were extracted using chloroform as described above. A bacterial colony was scored as resistant if there was no inhibition of growth after incubated at 10°C for 72 h and population-level bacterial resistance was calculated as proportions of resistant bacterial colonies. We also measured resistance of bacterial populations from those microcosms against phages from the source habitats (SBP), where each source-habitat phage population was paired with one bacterial population from each of the following evolution regime: BP, BP+IP, BP+IBP.

Statistical analysis

All analysis was performed in R (version 4.0.5; R Core Team 2018) and plots were made using the R package 'ggplot2' (Wickham 2016). Population density data were log-transformed and bacteria resistance data were arcsine-transformed before analysis. Bacterial population size (density) during the evolution experiment was analysed using mixed-effect linear model in the 'nlme' package (Pinheiro *et al.* 2021). Treatment and time (transfer number) were included as categorical and continuous explanatory variables respectively, with microcosm ID as a random effect. Significance of each explanatory variable was estimated using the 'Anova' function provided by the 'car' package (Fox *et al.*2021). Pairwise multiple comparison between treatments was performed using Tukey's HSD with the 'glht' function in 'multcomp' package (Bretz *et al.* 2022). To further estimate population dynamics, separate analyses were conducted for each treatment using linear models with time as an explanatory variable.

One-tailed t-tests were used to analyse the growth performance (density data) measured at 10°C and the top-down effect by phages. Wilcoxon rank tests were used when data were not normally distributed. The effects of treatment and transfer time on bacteria resistance were estimated using mixed-effect linear models.

RESULTS

Population dynamics during the evolution experiment

Overall, bacterial density increased through time and differed among evolution treatments (linear mixed effect model, time, χ^2_1= 360.563, $P < 0.001$; treatment, $\chi^2_4 = 2533.771$, $P < 0.001$; time × treatment, χ^2_4= 74.013, $P < 0.001$; Figure 2). There was a significant difference in mean population density between all pairs of treatments (multiple comparisons, Table S1). The clearest effect was that evolution lines with phages had lower bacterial population sizes than those without (Figure 2). Among the three types of microcosms with phages, those with bacteria/phage immigration (BP+IBP) had the greatest bacterial densities, and those with phage-only immigration (BP+IP) had the lowest bacterial densities. For the evolution lines without

phages, immigration of bacteria led to higher bacterial densities (B+IB versus B). An increase of population sizes over time was found for every treatment (separate analysis for each treatment, Table S2). While the increase in population size over time in B microcosms indicates abiotic adaptation of bacteria, that in the other evolution treatments may also have been affected by changes in the immigrant populations, or changes in the top-down control effect due to the evolution of bacterial resistance.

Abiotic adaptation of bacterial populations

Growth performance of bacterial populations from the end of the evolution experiment was measured in the absence of phages, without immigration (Figure 3). The bacteria evolution lines (B) showed the most pronounced increase in growth performance compared with the ancestral strain (one-tailed t -test: $t_{5} = 17.831, P < 0.001$), followed by bacterial lines with immigration (B+IB) (one-tailed t -test: $t_{5} = 8.120$, $P < 0.001$). Growth performance of bacteria from bacteria/phage lines (BP) was not different from the ancestral strain (one-tailed t -test: $t_{5} = 0.681, P = 0.737$). Bacteria from bacteria/phage lines with phage immigration (BP+IP) showed the poorest growth performance, significantly lower than that of the ancestral strain (one-tailed Wilcoxon test: $V = 2$, $P = 0.047$); and those from bacteria/phage lines with bacteria/phage immigration (BP+IBP) did not significantly differ from the ancestral strain (one-tailed t -test: $t_{4} = -0.605$, $P = 0.290$).

Comparisons between evolution lines were also carried out (Figure 3). Immigration of bacteria from 28°C habitats reduced the extent of abiotic adaptation (B versus B+IB treatment, one-tailed Welch two-sample t -test: $t_{9.682} = 5.169$, $P < 0.001$). The presence of phages limited bacterial abiotic adaptation (B versus BP, one-tailed Welch two-sample t -test: $t_{5.500} = 3.230$, $P = 0.010$); and immigration of phages only further reduced bacterial abiotic adaptation (BP versus BP+IP, one-tailed Welch two-sample t -test: $t_{9.599} = 1.924$, $P = 0.042$), though joint bacteria and phage immigration did not significantly alter bacterial abiotic adaptation (BP versus BP+IBP, one-tailed Welch two-sample t -test: $t_{7.732} = 0.891$, $P = 0.200$).

Bacterial resistance to phages

For evolution lines with phages (BP, BP+IP and BP+IBP), population-level bacterial resistance against within-microcosm phages did not differ among treatments, and did not differ between transfer 8 and 20 (linear mixed effect model, time, $\chi^2_1 = 2.267$, $P = 0.132$; treatment, $\chi^2_2 = 4.712$, $P = 0.095$; time × treatment, $\chi^2_2 = 1.561$, $P = 0.458$; Figure 4a, 4b). Bacterial resistance against phages from the core habitat (SBP microcosms) increased from transfer 8 to 20, and did not differ among treatments (linear mixed effect model, time, $\chi^2_1 = 8.154$, $P = 0.004$; treatment, $\chi^2_2 = 1.257$, $P = 0.534$; time × treatment, $\chi^2_2 = 0.503$, $P = 0.778$; Figure 4c, 4d). Note that reciprocal challenges between the core and edge habitats (SBP versus BP microcosms) showed signals of more intense coevolution at transfer 8 but not at transfer 20 (Supplementary Text; Figure S2).

DISCUSSION

Migration of individuals from high- to low-quality habitats often help to maintain population sizes in the latter and may have varying effects on local adaptation. The high-quality habitats may also support greater abundances of natural enemies, and the effects of source-sink dynamics on local adaptation in low-quality habitats might fundamentally be altered by coevolving enemies. Our study suggests a negative effect of immigration of coevolving enemies on abiotic local adaptation of victims, particularly when enemies, but not victims themselves, migrate from source to sink habitats.

While bacterial evolution lines in a low temperature habitat showed obvious evolutionary adaptation in terms of population growth performance, bacterial immigration from an optimal temperature habitat reduced such adaptation (B versus B+IB microcosms, Figure 3), consistent with a "swamp by gene flow" view (Bennett & Lenski 2007; Rodríguez-Verdugo *et al.* 2014; Micheletti & Storfer 2020). It is likely that mutational supply was not, or only weakly, limited in our bacterial populations at 10°C (bottleneck population size $> 3 \times 10^7$), and immigration had little positive effect on mutation supply, but affected the fixation of beneficial mutations.

The presence of phages limited abiotic adaptation of bacterial populations. It is possible that fixation of phage-resistant mutations may constrain the acquisition of beneficial mutations for abiotic adaptation (Scanlan *et al.* 2015). Furthermore, the fact that our bacterial growth performance may become even poorer than the ancestral strain (in BP+IP coevolution lines) suggests fitness costs of bacterial resistance evolution, consistent with earlier studies (Buckling & Rainey 2002; Brockhurst *et al.* 2004; Buckling *et al.*2006). The bacterial growth performance from BP and BP+IBP coevolution lines was not poorer than the ancestral strain, though no difference in bacterial resistance to phages was found among the three types of coevolution lines. This suggests that bacterial adaptation that compensated for the fitness costs of resistance should have occurred; and such abiotic adaptation was less efficient in the BP+IP microcosms (probably due to the much lower bacterial population sizes and thus lower mutation supply). For the BP+IBP coevolution lines, the bacterial immigrants *per se* may have promoted bacteria abiotic adaptation, contrary to the effect of bacterial immigrants to the B+IB microcosms.

The negative impact of immigrant phages on bacterial sink adaptation is presumably because the source phages evolved greater infectivity than sink phages and/or achieved higher densities. While the intensity of bacteria-phage coevolution, and hence the extent of phage infectivity evolution, did not differ between our 28 and 10°C microcosms at transfer 20, weak signals of more intense coevolution were detected for the core microcosms at transfer 8 (Supplementary text; Figure S2). This is consistent with previous studies: A previous short term (6-transfer) experiment showed that a modestly low temperature (15°C) could slow bacteria-phage coevolution compared with a higher temperature (25°C) (Zhang & Buckling 2016); and a 10-transfer coevolution study across 3 temperatures (8, 17, 28°C) found more intense coevolution at higher temperatures (Gorter *et al.* 2016). We suggest that the extremely low bacterial population sizes of BP+IP microcosms during the early stage of evolution experiment result from a "mass effect" of phage immigrations (and higher phage infectivity if coevolution was faster in 28°C microcosms at the early stages), and the low population sizes limited abiotic adaptation. The persistently lower bacterial population sizes of BP+IP microcosms compared with BP microcosms at the late stages of the evolution experiment, however, might be due to the poorer growth performance as a consequence of limited abiotic adaptation, but not greater top-down control effect by phages. The top-down control effect at the end of the evolution experiment could be estimated for BP and BP+IP microcosms by comparing their population sizes (in the presence of phages) and the abiotic adaptation measures (in the absence of phages); and this suggest that phages reduced bacterial population densities by 73% in BP and 62% in BP+IP microcosms (Figure S3).

Migration in coevolving systems often have asymmetric effects on victim and enemy populations (Gandon *et al.* 1996; Lion *et al.*2006). For instance, under homogeneous landscapes, phage Φ2 usually benefits from migration more than *P. fluorescens* on a global scale as phages are more genetically constrained and have a lower evolutionary potential (Brockhurst *et al.* 2003, 2007; Morgan*et al.* 2005, 2007). Under heterogeneous landscapes, mixed evidence was found for the effect of gene flow on the evolution of phage infectivity (Forde *et al.* 2004, 2007); and a net beneficial effect of bacterial immigrations on abiotic adaptation was inferred in the BP+IBP treatment here. Therefore, how migration affects the coevolving populations may depend on not only the heterogeneity between patches, but also the migration pattern of victims and enemies (Gandon & Michalakis 2002; Tigano & Friesen 2016; Zhang & Buckling 2016).

In summary, by (co)evolving bacteria and phage populations under various migration regimes across heterogenous environments (Figure 1), we found that abiotic adaptation of bacteria in sink environment was limited by the immigrated phages from the source environment. These results highlight that traditional thinking about source-sink dynamic should be interpreted with caution in antagonistic coevolution systems; immigrant victims and enemies may have opposing effects on the abiotic adaptation of victims in the edge habitats. Future work involving a variety of stress gradients would determine the generality of these findings, and therefore help to understand species' range expansion in nature with implications for conservation planning (Engelkes *et al.* 2008; Benning & Moeller 2021).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of the article at the publisher's website.

Figure legends

FIGURE 1 A schematic illustration about how natural enemies and migration from core habitats (in red color) may affect local adaptation in edge habitats (blue color). Populations of a focal species (victim) may evolve alone (a), or with immigrations from the core habitats (b). Victim/enemy populations in the edge habitats may coevolve without immigration (c), with immigration of enemy (d), or with joint immigration of enemy and victim (e) from the core habitats. Predicted strength of evolutionary driving forces (genetic variation and the efficiency of abiotic selection) in victim populations are indicated as the number of '+' signs.

FIGURE 2 Average bacterial population density (± se) for each treatment during the evolution experiment.

FIGURE 3 Growth performance of bacterial populations sampled from the (co)evolution lines, measured in the absence of phages and without immigration. Dashed line (mOD = 289) referred to the ancestral genotype. Scatter data points are shown together with boxplot summaries (the boxes covering the 25th

to 75th percentiles of the data, the middle lines being the medians, and the whiskers extended from the boxes hinging to the smallest or largest value no further than 1.5 times of interquartile range). Asterisks represent significant difference in bacterial density from the ancestor ($^{ns}P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$).

FIGURE 4 Resistance of bacteria from coevolution lines against phages from their own microcosms (top), or phages from the core habitats (bottom). Scatter data points are shown together with boxplot summaries.