Ecological memory preserves phage resistance mechanisms in bacteria

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Bacterial defenses against phage, which include CRISPR-mediated immunity and other mechanisms, can carry substantial growth rate costs and can be rapidly lost when pathogens are eliminated. How bacteria preserve their molecular defenses despite their costs, in the face of variable pathogen levels and inter-strain competition, remains a major unsolved problem in evolutionary biology. Here, we present a multilevel model that incorporates biophysics of molecular binding, host-pathogen population dynamics, and ecological dynamics across a large number of independent territories. Using techniques of game theory and non-linear dynamical systems, we show that by maintaining a non-zero failure rate of defenses, hosts sustain sufficient levels of pathogen within an ecology to select against loss of the defense. This resistance switching strategy is evolutionarily stable, and provides a powerful evolutionary mechanism that maintains host-pathogen interactions, selects against cheater strains that avoid the costs of immunity, and enables co-evolutionary dynamics in a wide range of systems.
Survival of species in the presence of pathogens requires effective defense mechanisms, which exist in a wide range of biological systems1–4. Host-pathogen interactions are subject to the availability of susceptible hosts that sustain a viable pool of pathogens, while defense mechanisms are under evolutionary pressure to reduce or eliminate the ability of pathogens to proliferate. Once a threat is removed so is the pressure to preserve the relevant defense mechanism which may carry significant fitness costs5–7. In the absence of defenses, pathogens can reemerge and wipe out a host population. The selective forces that drive the defense mechanisms to become highly efficient may thus eventually lead the host to extinction. How species avoid this inherent fragility of their defenses is not presently understood8.

Bacteria and their pathogens, the bacteriophages, present a powerful system to study this question. A bacteriophage infects a bacterial cell by attaching to the cell surface and injecting its genetic material, then replicates and assembles phage particles, which are released upon cell lysis (Fig. 1a). Bacteriophage resistance mechanisms9,10 exhibit a great deal of variety across two major classes: (i) preventative defenses, which operate by loss, modification, or blocking of phage receptors11–12, and (ii) immune defenses, such as restriction-modification systems13 and CRISPR14 which cleave phage DNA after it enters the host. Costs of resistance mechanisms15 have been demonstrated in different preventative16–18 and immune19,20 defense systems. The diversity of phage-host systems in terms of routes of infection and modes of resistance points to strong evolutionary pressures favoring the emergence and maintenance of resistance21,22.

A well-studied example of a preventative defense is found in the host-pathogen interaction of Escherichia coli and the phage λ, which attaches to the host cell through the maltoporin LamB, an outer membrane protein. Preventative resistance is conferred on the bacterial cell by injecting its DNA. Reaction rates are shown on arrows; the phage receptor binding and unbinding rates q and q′ and phage absorption rate α are defined per receptor. (b) Population dynamics for a preventative defense model. The resistant phenotype R generates phage-sensitive cells S at rate s, on which the phage P grows. I labels cells infected by phage. Arrows indicate rate constants for each type of transition; the circular arrows indicate the growth rates of R and S cells (respectively, b and d) with d − b > 0 being the cost of resistance. For immune defenses, all phenotypes express receptors and absorb phage, but only sensitive cells transition to infection and lysis.

Fig. 1 Phage-host molecular interactions and population dynamics. (a) Molecular interactions. The phage diffuses onto a host that expresses phage receptors (solid circles), binds reversibly to a receptor and infects the cell by injecting its DNA. Reaction rates are shown on arrows; the phage receptor binding and unbinding rates q and q′ and phage absorption rate α are defined per receptor. (b) Population dynamics for a preventative defense model. The resistant phenotype R generates phage-sensitive cells S at rate s, on which the phage P grows. I labels cells infected by phage. Arrows indicate rate constants for each type of transition; the circular arrows indicate the growth rates of R and S cells (respectively, b and d) with d − b > 0 being the cost of resistance. For immune defenses, all phenotypes express receptors and absorb phage, but only sensitive cells transition to infection and lysis.

Results

Multilevel model: Molecular, cellular, population, and ecological levels. We introduce a multilevel model of bacteria and phage dynamics with: (i) molecular and cellular levels, which model the phage receptor kinetics and yield the functional form of the infection rate; (ii) population level, which uses the infection rate in a system of differential equations describing the population dynamics within a single patch; and (iii) ecological level, which models competitions among a set of bacterial strains across a large number of patches. Table 1 summarizes the key notation used at different levels of the model. The specific values of the molecular parameters (Fig. 1) determine the set of fixed points of the population dynamics equations (Figs. 2, 3). These fixed points in turn dictate the different kinds of migration and invasion dynamics that can occur in a single patch (Fig. 4). Analysis of fixed points for CRISPR systems is shown in Fig. 5. Modeling and analysis at the ecological level using game theory is shown schematically in Fig. 6.

At the molecular and cellular levels, we consider the coarse-grained mechanism of infection by a phage freely diffusing onto a host cell20–28 (Fig. 1a). We consider a phage-receptor binding
Table 1 Notation Guide. Key symbols and their meaning for each stage of the multi-level model.

| Symbol | Definition |
|--------|------------|
| $r_a$ | Receptor concentration (free, bound) |
| $n_a$ | Number of receptors per cell (average) |
| $q$, $q'$ | Receptor-phage binding, unbinding rates |
| $\alpha$ | Phage absorption (injection) rate |
| $K_m$ | Michaels constant for receptor-phage binding |
| $k_i(t)$ | Infection rate of sensitive cell |
| $R(t)$, $S(t)$, $I(t)$ | Phenotype concentration (resistant, sensitive, infected) |
| $A(t)$ | Total concentration of phage-absorbing phenotypes |
| $P(t)$ | Phage concentration |
| $\lambda(t)$ | Dilution rate |
| $d$, $b$ | Growth rate of sensitive, resistant cells |
| $s$ | Switching rate from resistant to sensitive phenotype |
| $\beta_i$ | Phage burst size (average) |
| $k_i$ | Lysis rate of infected cell |
| $S$ | Sensitive strain (phenotypes: $S_i$) |
| $R_0$ | Resistant strain (phenotype: $R$) |
| $R_i(t)$ | Resistance switching strain (phenotypes: $R$, $S_i$) |
| $x_i(t)$ | Frequency of strain $i$ |
| $f_{ij}$ | Fitness difference between strains $i$ and $j$ |
| $c$ | Patch clearing rate |

At the population level, we model a single population of phage ($P$) and bacteria that express a resistant phenotype ($R$) or a sensitive phenotype ($S$) (see Fig. 1b), according to the following equations:

$$
\begin{align*}
\dot{R}(t) &= (b - \lambda)R(t) - \lambda R(t), \\
\dot{S}(t) &= d S(t) + \lambda R(t) - k_i(t) S(t) (S(t) - \lambda(t) S(t)), \\
\dot{I}(t) &= k_i(t) S(t) (S(t) - \lambda(t) U(t)) - \lambda(t) I(t), \\
\dot{P}(t) &= -k_i(t) A(t) + \beta k_i(t) I(t) (S(t) - \lambda(t) U(t)),
\end{align*}
$$

(3)

where $R$, $S$, $I$, and $P$ are expressed in concentration units. Phage infect sensitive cells at rate $k_i(t)$ determined above (Eq. (2)) generating infected cells ($I$), and these lyse at rate $k_i$ to produce new phage particles; $\beta k_i$ is the phage burst rate, the overall rate at which phage particles are released into the environment. Resistance switching is modeled as spontaneous conversion of $R$ cells into $S$ cells at rate $s$, and the cost of resistance, $d - b > 0$, is given by the difference in growth rates of sensitive and resistant cells. $A$ is the total number of phage-absorbing hosts: for preventative defenses $A = S + I$, as only sensitive and infected cells absorb phage, while for immune defense systems $A = R + S + I$. The model can also include phage decay by adding a term $-\delta P$ to the last equation (see Methods, `Phage decay`). The dilution rate $\lambda(t)$ is chosen to implement different types of population growth control. We present results for growth in rich media with feedback dilution (turbidostat growth) in the main text, or in a nutrient-limited environment with constant dilution (chemostat growth) in Supplementary Note 1; the specific growth modality does not impact the major outcomes. We analyze Eq. (3) to determine fixed points, which correspond to steady-state population compositions, and their stability to perturbations (see Methods, `Linear stability analysis`).

At the ecological level, we model the dynamics of migration and invasion that take place in the setting of a large number of patches, each of which consists of a single population as modeled above. Each patch is taken to correspond to a fixed point (or more generally to any invariant set, e.g. a periodic orbit) of the single population dynamics equations. We index the possible patch types by $i$, which corresponds to all possible fixed points, stable or unstable, for a given choice of model parameters, and denote by $x_i$ the frequency of each patch type, where $0 \leq x_i \leq 1$ and $\sum x_i = 1$. Patch clearing events, which occur with rate $c$ per patch per unit time, clear a patch of its inhabitants and enable invasion by strains from other patches. We assume that cleared patches are rapidly invaded at rate $m$, such that patch clearing is the rate limiting step to initial patch invasion, i.e. $c \ll m$. When invasions occur, they bring in a small inoculum from a patch of type $i$ with probability $x_i$. Patch clearing and migration mimic natural turnover events that occur e.g. in the gut due to peristalsis, in soil microenvironments due to physical perturbations, or during host-to-host transmission in epidemiology.

In the initial stages of patch invasion, we postulate that it takes a time $\tau_{est}$ for an invading type to establish on the patch and thereafter exclude other invaders. If no further migration events occur during time $\tau_{est}$ after the initial invasion, the patch will become type $i$. However, since the patch clearing rate is independent of patch type, and invading types are chosen randomly according to the distribution $x_i$, there will be no net change of $x_i$ due to single invasion events. Thus, the dynamics of $x_i$ are determined by multiple invasion events, which occur with total rate $c(1 - e^{-mt_{est}}) \approx c m \tau_{est} + c O(m \tau_{est})$. We can therefore disregard invasion events from three or more patches if $m \tau_{est} \ll 1$, e.g. for short establishment time and/or rare migration, and consider the dynamics due to co-invasion events, i.e. competitions between invaders from exactly two
patches. We note that co-invasion does not require simultaneous arrival of competitors, as two strains can arrive within time \( \tau \) of each other.

Co-invasion events from patch types \( i \) and \( j \) occur with rate \( 2c \cdot m \tau_{est} x_i x_j \), for \( i \neq j \), and rate \( c \cdot m \tau_{est} x_i^2 \) for \( i = j \). If \( i = j \), the types are identical resulting in a patch of type \( i \). If \( i \neq j \), competition occurs and resolves itself over a timescale that is determined by the fitness difference \( f_i - f_j \) between the two types, where \( f_i \) is the fitness of type \( i \). When \( f_i > f_j \), the competition will resolve in favor of type \( i \), provided that the competition is over before the

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**Fig. 2 Stable phases for preventative defenses.** (a–d) Flow diagrams of Eq. (3), plotting frequencies of the resistant (R) phenotype along the bottom edge, sensitive (S) phenotype along the left edge and phage and infected (as \( P + I \)) along the right edge in a ternary plot. Empty (filled) circles - unstable (stable) fixed points. Color of the fixed point matches the phase displayed in the phase diagram below. Host extinction at the top corner is represented with a black empty circle. (e) Phase diagram for preventative defenses. The S phase (gray region) carries only the S phenotype, the SP phase (pink region) carries the S phenotype and phage, the RSP phase (blue region) carries all phenotypes and phage, the S&E phase (dark gray region) corresponds to bistability between phase S or host extinction E. The curves \( \gamma \) (gray), \( \gamma' \) (dark red) and \( \gamma'' \) (black) denote locations of bifurcations. Letters a-d indicate the locations corresponding to the flow diagrams above. Rates are expressed in units of per cell division time (1/div), with \( d = 1, b = 0.9, k_L = 1 \) and \( s = 10^{-4} \). Results are shown for high phage-receptor binding affinity (\( K_m \to 0 \)) and minimal sensitivity (\( n_r = 1 \)). See Methods, ‘Stability analysis at low binding affinity’ for \( K_m > 0 \) and Supplementary Figs. 7–9 for dependence on \( n_r, b \) and \( k_L \).
next patch clearing event. If patch clearing occurs before resolution, then neither type makes any gains. The probability of successful resolution in favor of type \(i\) is thus \(p_{ij} \equiv f_{ij}/(f_{ij} + c)\), if \(f_i > f_j\), or \(p_{ij} = 0\) if \(f_i < f_j\). The total rate of co-invasions of \(i \neq j\) successfully resolving in favor of \(i\) is \(2c \tau_{est} p_{ij} x_i x_j\). This yields the patch frequency dynamics

\[
\dot{x}_i = c \tau_{est} x_i \left( x_i + 2 \sum_{j \neq i} p_{ij} x_j - F \right)
\]

where \(F \equiv \sum_i x_i^2 + 2 \sum_{i,j \neq i} p_{ij} x_i x_j\). The above equation takes the form known in game theory as the replicator equation,

\[
\dot{x}_i = x_i \left[ (\phi x^T)_i - x^T \cdot \phi x \right],
\]

where the payoff matrix \(\phi\) is given by \(\phi_{ij} \equiv c \tau_{est} (\delta_{ij} + (1 - \delta_{ij})2p_{ij}\). Since the prefactor \(c \tau_{est}\) sets the overall timescale but does not otherwise impact the dynamics, we set it equal to 1 by rescaling the time unit. The equilibria of patch frequency dynamics can therefore be analyzed using game theory, i.e. through the identification of Nash equilibria and evolutionarily stable strategies.

**Stable phases of a phage and host population.** The state of a single population of phage and bacteria can be visualized as a ternary plot in which each corner corresponds to a monomorphic population composed entirely of sensitive cells, resistant cells, or phage particles (Fig. 2a and Supplementary Fig. 1). Flow lines within the diagram show the solutions of the model starting from different initial conditions. Points in the interior of the triangle represent different number compositions of host cell phenotypes and phage, using total counts of cells and phage for normalization; one can alternatively plot the composition as biomass fractions, which is a one-to-one transformation of the ternary plot that preserves all topological features including fixed points, trajectory structure, and stability (see Methods, ‘Population structure and control of total biomass’). We present results separately for the preventative and immune defense models below.

**Representative flow diagrams for the preventative defense model, in which resistant cells do not absorb the phage, are shown in Fig. 2a–d, where each panel corresponds to a different phage absorption rate \(\alpha\) and burst rate \(\beta k\). Across all possible combinations of phage parameters, there are four possible long-term outcomes of the dynamics which correspond to fixed points..."
of the model equations: (i) fixation of S [S phase], (ii) coexistence of S and P [SP phase], (iii) coexistence of R, S, and P [RSP phase] and (iv) host extinction [E phase].

Depending on the phage parameters, one or more of these phases may be stable to small perturbations of the population composition. The stable phases are shown as distinct regions in the space of phage parameters (Fig. 2e), separated by curves $\gamma$ and $\gamma'$, which correspond to transcritical bifurcations of the dynamical system (see Methods, ‘Linear stability analysis’, and Supplementary Fig. 2). Curve $\gamma''$ where the RSP fixed point becomes unstable is obtained numerically. There also exist regions where two phases are stable (for $\alpha > d/n_r$), and which phase is observed depends on initial conditions; these include the S&E bistable region and a narrow region of RSP&S bistability (Supplementary Fig. 3). The phase diagram for a model that lacks the resistance phenotype is shown in Supplementary Fig. 4 and analyzed in Supplementary Note 2.

In the S phase, which is the unique stable phase for $\alpha < d/n_r$ and $\beta k_1 < \gamma$, the resistant phenotype and phage will be outgrown by the sensitive phenotype (Fig. 2a). As $\alpha$ increases along the thin black horizontal line in Fig. 2e, it crosses the curve $\gamma$, where the phage can coexist with the host in the SP phase (Fig. 2b). In this phase, the growth rate of S, while reduced by the phage, is still larger than the growth rate of R, and resistance cannot establish.

With further increase in $\alpha$, the growth rate of S cells decreases until it equals the growth rate of R at the location of $\gamma'$, where the system transitions to the RSP phase (Fig. 2c). Beyond $\gamma'$, the frequency of R at the RSP stable fixed point increases with $\alpha$, while the frequencies of S, I and P decrease (Fig. 2d).

In the RSP phase, any amount of non-zero switching ($s > 0$) will generate S on which phage can grow, and promote phage presence in the host population. Interestingly, in this phase a phage that infects at a higher rate will be present at lower frequency, because resistance will have a higher selective advantage in the presence of a stronger pathogen (Supplementary Fig. 2). In the absence of switching ($s = 0$), the RSP phase reduces to a pure resistant population. We note that the model does not distinguish between mechanisms underlying resistance switching, e.g. if both mutations and epigenetic switching are present, these would both contribute to the effective value of $s$ in the model. We additionally show that resistance switching allows distinct phage strains with different parameters to coexist within the same host population (Supplementary Fig. 5 & Supplementary Note 3).

Representative flows and the phase diagram for immune defenses, in which all phenotypes absorb the phage, are shown in Fig. 3a–c. Absorption of phage by the resistant cells directly couples phage and resistant subpopulations in Eq. (3) and generates a region where none of the four possible fixed points are
stable. In this region, stable limit cycles are possible in which $R$, $S$, and $P$ levels oscillate periodically (Fig. 3c, white region); this region is therefore part of the RSP phase. In Fig. 3a and b we show two such orbits, one for the dynamics located near the edge of that region and one located further inside the region. The limiting orbit in Fig. 3b passes extremely close to the $P = 0$ boundary, a behavior that in finite systems would eventually lead to loss of phage and collapse to a stable $S$ fixed point. For higher switching rates, such orbits are pulled away from the boundary and toward the interior of the simplex (Supplementary Fig. 6).

A Hopf bifurcation curve $\gamma''$ separates the stable and unstable fixed points of the RSP phase, and is shown in Fig. 3c for different values of $s > 0$ (solid and dotted black curves) or for $s = 0$ (dashed black curve). As $s$ increases from zero, $\gamma''$ confines the region of periodic dynamics to lower phage burst rates, while the $\gamma'$ curve shifts (slightly) to higher $\beta k_i$ across the thickness of the dark red curve in Fig. 3c.

**Invasion dynamics in a single patch.** We now examine invasions in a single patch or territory occupied by distinct host strain genotypes, corresponding to fixed points of Eq. (3), including a resistance switching strain $R_i$ (phenotype $R$ switches to $S$ at rate $s > 0$), a non-switching resistant strain $R_0$ (phenotype $R$), and a sensitive strain $S$ (phenotype $S$). We consider a single phage type with parameters in the RSP phase for $s > d/n_s$, hence only the $R_i$ strain carries the phage, while the $R_0$ and $S$ strains do not. We note that simple coexistence of $S$ and $P$ is not possible in this part of the phase diagram, as phage with such parameters would drive $S$ to extinction. We analyze dynamics within a patch dominated by one strain when a second strain is introduced initially at low frequency.

For preventative defenses, Fig. 4a shows that $S$ is replaced by $R_0$, as $R_i$ brings phage into the patch together with infected cells that carry and release phage, which infect the $S$ strain and drive it to extinction. However, switching to the sensitive phenotype reduces the growth rate of $R_i$ in the presence of phage, which allows an $R_0$ strain to invade over a timescale $1/s$, and eventually drive both the $R_i$ strain and phage to extinction. Subsequently, an $S$ strain could invade the patch, replacing $R_0$ in the absence of phage. It is therefore crucial to consider how invasion trajectories such as $S \rightarrow R_i \rightarrow R_0 \rightarrow S \ldots$, may impact the preservation of resistance at the level of inter-patch dynamics, which we analyze in the next section below.

For immune defenses, the $S \rightarrow R_i \rightarrow R_0$ invasion proceeds in a similar way, but the critical difference is that competitions between $R_0$ and $R_i$ resolve in a surprising manner: the non-switching $R$ phenotype of the $R_i$ strain drives the switching $R$ phenotype of the $R_0$ strain to extinction at rate $s$, but the patch reaches a coexistence of $R_0$, $S$ and $P$, either as a fixed point or limit cycle. The coexistence persists despite the fact that there is no new generation of $S$. Instead, $R_0$ cells act as a phage sink and alleviate the phage pressure on $S$ so that its growth rate matches that of $R_0$, enabling true coexistence.

The stable coexistence of sensitive and immune resistant cells in the presence of phage suggests the possibility that unrelated ‘cheater’ strains could enjoy the benefit of coexistence with immune strains without paying the cost of resistance. Analysis of the stable phases in that scenario (Fig. 5) indicates that resistance switching can prevent the establishment of such immune defense cheaters. For higher values of $s$, as can be achieved in the mechanism of CRISPR spacer loss, higher levels of phage are present, and an $R_i$ strain generates selection pressure against invaders that is proportional to $\beta s$. Invaders whose growth advantage is below that threshold will be driven to extinction (see Methods, ‘Model of CRISPR spacer loss’).

**Evolutionary stability of the resistance switching strategy.** To analyze the long-term outcomes of competition among a set of
strains across many patches, we apply the ecological model. Each patch is dominated by a single strain, corresponding to a fixed point of the population dynamics equations (3). Patch clearing events occur at rate \( c \), and co-invasions of two strains into a cleared patch drive the dynamics of strain frequencies across the ecology, which depend on the set of rates \( f_{ij} \) at which strain \( i \) competes with strain \( j \) (Fig. 6a). If a patch is cleared before a competition is resolved, no change in strain frequency will occur. The frequency of strain across the ecology is denoted by \( x_i \) and evolves in time according to the replicator equation of game theory (Eq. (5)), where each strain is a pure strategy in a two-player game with a payoff matrix whose entries depend on \( f_{ij} \) and \( c \).

We apply the model to the set of strains \( i \in \{R_0, R_s, S\} \) in the RSP phase for \( \alpha > 1 \) (Fig. 6b). For a preventative defense, the competition between \( R_0 \) and \( R_s \) will result in the former driving both the latter strain and the phage to extinction, at rate \( f_{R_0R} = s \).

In a competition of \( R_s \) versus \( S \), the phage will rapidly drive strain \( S \) to extinction, at rate \( f_{RS} = g_1 \), while competition of \( S \) versus \( R_0 \) results in the former outcompeting the latter at rate \( f_{SR} = g_2 \) due to the cost of defense in the absence of phage (Fig. 4a); we do not require the exact expressions of \( g_1 \) and \( g_2 \), and only assume that \( g_1, g_2 > c \). The payoff matrix for this game is given by

\[
\begin{pmatrix}
R_s & R_0 & S \\
1 & 0 & \frac{2c}{\epsilon} \\
R_0 & \frac{2c}{\epsilon} & 1 \\
S & \frac{2c}{\epsilon} & 1
\end{pmatrix}
\]

For \( s > c \) this is a rock-paper-scissors game with no stable Nash equilibria and a heteroclinic cycle on the boundary (Fig. 6c, blue curve). In this case, the system spends increasingly long times near each of the vertices, while continuing to transition from one to the next indefinitely. It is therefore expected that due to stochastic fluctuations, the ecology will end up in one of the vertices, however one is generally unpredictable, and could depend on details of the stochastic dynamics and the initial conditions. In contrast, for \( s < c \) a strict Nash equilibrium (i.e. an ESS) exists, which corresponds to the resistance switching strain \( R_s \) (Fig. 6c, pink curve). In this regime, the long-term outcome is deterministic, and the \( R_s \) strain is predicted to sweep across the ecology (see Supplementary Note 4).

We can further consider a set of \( R \) strains spanning a range of values of \( s \), either pre-existing or occurring by mutation (see Methods, ‘Game theory of the patch invasion model’). Competitions between strains \( R_0 \) and \( R_s \) will resolve in favor of the strain with a smaller switching rate, provided that \( |s - s'| > c \). Thus, the distribution of switching rates across the ecology will evolve toward lower values of \( s \) until all remaining \( R \) strains satisfy \( s < c \), rendering \( R_0 \) unable to invade. At that point, any remaining \( R_0 \) and \( S \) strains will be driven to extinction, and resistance will be preserved thereafter.

We note that the outcomes of patch invasion dynamics depend on the ability to transfer a representative inoculum between patches, which for the \( R \), strain includes the transfer of infected cells that release the phage. In practice, inter-patch migration may proceed through bottlenecks which select for large enough switching rates (but still smaller than \( c \)), so that the infected cells are stably represented in the founder population. A complete description of bottleneck effects and selection is beyond the scope of this work, and will be interesting to study in future work.

It is possible that phage could migrate through other routes, independent of their specific host bacteria. We therefore considered a generalization in which phage constitutes an independent pure strategy \( P \), which corresponds to the host extinction fixed point of Eq. (3). We analyzed the resulting four strategy game in Supplementary Note 5, and showed that \( R_s \) is the unique ESS for \( s < c \).

Finally, we comment on the patch invasion dynamics for immune defenses. The \( R_s \) strain can generate \( R_s \)-SP coexistence exclusively through co-invasions with the \( R_s \) strain, and can no longer be invaded by the \( S \) strain. The ecology for immune defenses could therefore contain patches with an \( R_s \)-SP coexistence, as well as patches occupied by \( R_s \) strains with \( s < c \).

**Discussion**

By analyzing host-pathogen dynamics within a single patch and modeling bacterial invasions on many patches, we determined the set of conditions in which resistance mechanisms are preserved. We showed that the resistance switching strategy, whereby pathogen-resistant hosts stochastically lose resistance, enables the ecology as a whole to maintain memory of the pathogen. Such ecological memory; an emergent property at the level of ecological dynamics, is the basic requirement for preserving resistance mechanisms over long timescales. Ecological memory has been considered in various contexts31–33 where it provides a mechanism by which ecosystems robustly adjust to change. In our work, ecological memory corresponds to an evolutionarily stable strategy that maintains a low level of pathogen across the ecology. Our analysis, which bridges from molecular and cellular to population and ecological levels, shows that a non-zero failure rate of defense mechanisms, which reduces host growth rate within a single patch, protects those same mechanisms from eventual loss within the ecology.

Spontaneous loss of a preventative defense was observed experimentally to enable persistence of phage at low frequencies24,25,34,35. Similarly, loss of immune defenses is known to occur in CRISPR systems25,36,37, and modeling has shown that this loss could be responsible for coexistence of phage and bacteria38, which was experimentally observed in39. Our work unifies these observations by providing the critical context of stochastic dynamics and memory, and thereby establishes a mathematical basis to analyze evolutionary maintenance of resistance mechanisms. We showed that the same resistance switching strategy that enables ecological memory can maintain multiple phage strains with different combinations of infection rates and burst sizes. Ecological memory can therefore involve a diverse collection of phage types that coexist stably with the host bacterium, which has implications for microbial ecosystem diversity and stability. Further extension of our modeling approach for immune defenses that accounts for CRISPR spacer acquisition and evasion by phage40–44 may be fruitful in identifying novel dynamics and strategies of generation and maintenance of ecological memory. Additional applications may be relevant in abortive immune systems, where spatial structure has been shown to promote evolution of altruistic resistance mechanisms45–47.

At the molecular level, the phage-bacteria interaction has long been the subject of biophysical studies27,28,48,49, including a seminal work on chemoreception26. However, there has been a major gap in understanding how the molecular details of the phage-bacteria interaction impact processes at higher levels of organization, in particular at the population and ecological levels. For example, a change in the binding free energy of a phage receptor protein impacts the rate of infection and thus could have a direct fitness consequence which natural selection can act on. Here, by explicitly calculating the form of the infection rate \( k_1 \) in terms of biophysical parameters (Eq. (2)), we showed that the specific molecular mechanism of resistance has a large effect on host-pathogen dynamics.
In contrast to preventative defenses, immune mechanisms act as phage sinks, absorbing and removing phage from the environment. Phage-sensitive strains, which do not pay the cost of immunity, can act as ‘cheaters’ by exploiting immune strains to enable their own survival in the presence of phage. On the one hand, this means that immune defenses cannot be eliminated by faster-growing sensitive strains, as these depend on the mutualism for survival. On the other hand, cheating reduces the long-term growth potential of immune strains and may thus select for anti-cheating strategies. We found that resistance switching by immune strains increases the amount of phage in the environment and can be used to select against cheater strains.

The models introduced here enable testing and validation in laboratory experiments. Our single patch formulation corresponds to a well-mixed population of bacteria and phage growing in rich or limited media and maintained in a proliferating state by dilution. The host-pathogen interaction term, \( k(t) \), was constructed by considering phage-receptor binding interactions, yielding a general form applicable across different regimes of host and phage densities, spanning different experimental scenarios. A prediction of our single-patch models is that immune and sensitive strains can coexist stably with phage, which can be directly tested by growing mixtures of bacterial strains with and without a CRISPR system in the presence of the phage. Depending on the phage burst and infection rate parameters, our model predicts whether or not coexistence is possible. Our multi-patch ecological model can be tested in multi-well plate format experiments using the \( \lambda \)-phage system, where each well corresponds to a patch and is inoculated with one of three \( E. coli \) strains, \( R_0 \) (e.g. lamB deletion), \( S \) (e.g. constitutive lamB), and \( R_i \) (wild type) with phage, in media and grown to saturation. Daily dilution into fresh plates would be performed such that each well receives inocula from two randomly chosen wells of the saturated culture. Ecological dynamics are observed by tracking the prevalence of resistance across the plate.

While our modeling considered phage-bacteria interactions, the general principles that we identified are relevant in other systems, including epidemiological dynamics and host-parasite interactions. In particular, our formulation of patch invasion dynamics using game theory, together with the mechanism of ecological memory, may be applicable to the maintenance of pathogen resistance mechanisms in plants, as the costs of such resistance are well-known and patch dynamics models are widely used in plant ecology. As observed in Ref. 24, resistance switching in bacteria not only sustains the growth of phage but also allows the pathogen eventually to evolve to infect the host through a different pathway. Ecological memory, which allows sustained coexistence of hosts and pathogens, might thus be relevant for future studies of co-evolutionary dynamics in a range of systems.

**Methods**

**Phage-receptor binding and infection rate.** In the quasi-steady-state approximation of Eq. (1), \( \nu_0 \) is taken to be at steady-state,

\[
\frac{dr_{ab}}{dt} = q r_{ab} - (\alpha + q) \nu_0 = 0.
\]

By substituting \( r = r - r_0 \) and \( p = P - p_0 \) for free receptor and free phage concentrations, and solving the quadratic equation for \( \nu_0 \), we obtain

\[
\nu_0 = \frac{K_m + r + P}{2} - \sqrt{\left(\frac{1}{2} - \frac{4r_p}{K_m + r + P}\right)^2}.
\]

known as the Morrison equation, where \( K_m = (q + a)/q \) is the Michaelis constant. We expand in the small parameter \( c = 4r_p/(K_m + r + P) \) to the first order, noting that we always have \( c < 1 \),

\[
r_0 = -\frac{r_p}{K_m + r + P} + O(c^2).
\]

Using \( r = n_A \) above, we obtain the total phage absorption rate

\[
\frac{dP}{dt} = -\nu_0 = -\frac{an_A P}{K_m + n_A + P},
\]

which yields the per cell infection rate given in Eq. (2).

The value of \( K_m \) can be determined from experiments using \( E. coli \) and \( \lambda \) phage. In the Berg-Purcell limit of a perfectly absorbing host cell (\( n_A \rightarrow \infty \)), phage arrive at the cell surface rate at \( k_{inf} P \) (Ref. 25). For finite \( n_A \), the rate is given by

\[
k_{inf}(n_A, P) = k_{max}(n_A + n_i) \quad \text{in Eq. (1).}
\]

Measured values of \( k_{max} \) are on the order of \( 10^{-11} - 10^{-10} \text{ cm}^2 \text{ s}^{-1} \), while \( q' \) and \( a \) are \( 10^{-5} - 10^{-4} \text{ cm}^2 \text{ s}^{-1} \) (Ref. 27). From these, we find \( K_{max}/(n_i + n_l) \sim 10^{-10} \text{ cm}^2 \). This estimate shows that most prior experiments performed with \( E. coli \) and \( \lambda \) (e.g. Refs. 13,24,25,35) are consistent with the high binding affinity limit, \( n_i, A \geq K_m \). The low binding affinity limit, \( n_i, A > K_m \), yields a Lotka-Volterra interaction term \( A \cdot P \) in the population dynamics equations (3), and may be appropriate in other systems. We assume high binding affinity (\( K_m \rightarrow 0 \)) in the main text, and analyze the Lotka-Volterra interaction in Supplementary Note 1. We have \( k_{inf}(n_A, P) \) for or \( K_m \ll n_A, P \) if either \( P/(n_A A) \ll 1 \) or \( P/(n_i A) \ll 1 \), i.e. in the limits of low or high MOI per receptor.

**Population structure and control of total biomass.** To analyze the dynamics of population structure, we compute the relative biomass fractions of each sub-population while holding the total biomass constant. The total biomass density is given by \( B = P_{R} (R + S + I) \) and \( P_{R} \), where \( P_{R} \) and \( P \) are the average mass of a host and a phage, respectively, and we define \( v \equiv v_{P} + v_{S} \). The biomass fractions are given by \( f_0 = v_{P} R/B, f_3 = v_{P} S/B, f_I = v_{P} I/B, \) and \( f_0 = v_{R} P/B \), and specify a point in the unit simplex. The host infection rate is expressed as

\[
k_f(t) = an_A K_m + n_i + P f_0 + P f_1 + f_3,
\]

where \( K_m = K_m/B \) and \( f_3 = v_{R} P/B \) is the biomass fraction of phage-absorbing hosts. The population dynamics equations on the simplex are given by

\[
f_S = f_S + f_0 - K_m + f_I - f_3 - f_S,
\]

\[
f_I = f_I - f_0 - f_S - f_3 - f_3 - f_I - f_S,
\]

where \( \lambda(t) = |f_0, f_3, f_I|^2 \) and \( \{f_0, f_3, f_I\} \) enforce the condition \( \sum f_i = 0 \) in Eq. (3). We analyze the high binding affinity limit (\( K_m \rightarrow 0 \)), and show that in this case the stability of the fixed points, which determines the phase structure, does not depend on the choice of \( v \). We then determine how inclusion of \( K_m \geq 0 \) modifies the stability of fixed points. We note that turbidostat control maintains constant host biomass, i.e. not including phage biomass, and yields equations that can be mapped by a smooth, 1-to-1 mapping to the equations above; the linear stability analysis in a turbidostat therefore matches that obtained at the corresponding fixed points on the simplex (Supplementary Note 1).

**Linear stability analysis.** We perform linear stability analysis of the fixed points of Eq. (12), by computing the eigenvalues of the Jacobian matrix, whose elements are given by

\[
L_{1} = -d - n_A, L_{2} = -k_1, L_{3} = b - s.
\]

Since \( L_{1} \geq 0 \), extinction is always unstable in the presence of resistant phenotype. Analysis of host extinction stability for a system with \( f_0 = 0 \) is presented in Supplementary Note 2.

The S phase fixed point corresponds to the solution \( f_0 = f_3 = f_I = 0 \), which exists in the whole phase diagram \( [a, \beta, \alpha] \) and \( b > 0 \). Eigenvalues of the Jacobian matrix are

\[
L_{1} = \gamma = (d + k_f) \frac{1 + \alpha}{\alpha} - b - s, \quad L_{2} = \lambda (q + 1) \frac{1}{\alpha} + \alpha \lambda, \quad L_{3} = -d - b - s,
\]

which are negative for \( d > b - s \) and \( \beta k_f < \gamma \), where

\[
\gamma = (d + k_f) \frac{1 + \alpha}{\alpha}.
\]

hence the S phase is stable in the region \( \{a, \beta, \gamma\} < \gamma \).
The SP phase fixed point corresponds to the solution \((f_3, f_5, f_I) = (0, 0, 0)\), which exists throughout the region \([\alpha, \beta] = a + d n, \beta a > y\) and within part of the region \([\alpha, \beta] = a + d n, \beta a < y\). One of the eigenvalues of the Jacobian evaluated at the SP fixed point is

\[
L_P^\dagger = b - s - (d - a) n_k(\beta a - d - k_h),
\]

while the other two eigenvalues are both negative in the region \([\alpha, \beta] = a + d n, \beta a > y\). Solving the \(L_P^\dagger < 0\) condition in this region yields the location of the stable SP phase as \([\alpha, \beta] = a + d n, \beta a < y\). Where one of the eigenvalues of the Jacobian evaluated at the SP fixed point is

\[
L_P^\dagger = b - s - (d - a) n_k(\beta a - d - k_h),
\]

while the other two eigenvalues are both negative in the region \([\alpha, \beta] = a + d n, \beta a > y\). Solving the \(L_P^\dagger < 0\) condition in this region yields the location of the stable SP phase as \([\alpha, \beta] = a + d n, \beta a < y\), where

\[
y' = (d + k_h)\left[1 + \frac{a}{n_k} (b - s)\right]
\]

\[
y'' = \frac{a}{n_k} (b - s) - d - \frac{a}{n_k} d
\]

The RSP phase fixed point corresponds to the solution \((f_3, f_5, f_I) = (0, 0, 0)\) satisfying \(f_3 \approx 0, f_5 \approx 0, f_I > 0\), which exists in the region \([\alpha, \beta] = a + d n, \beta a > y\). The RSP phase is determined by the eigenvalues of the Jacobian which were shown to be independent of \(n_k\) and \(d\). The locations of the RSP phase to the left, expanding the domain of the RSP phase (Supplementary Fig. 8). Phage burst sizes vary by orders of magnitude among different phages grown on similar hosts (e.g., \(\beta \approx 10^2\text{--}10^4\) in E. coli68) and a tradeoff in burst rate of the form \(\beta n_k = \text{constant}\)47–69 indicates that changes in \(k_h\) may be compensated by changes in \(\beta\). Likewise, changing the growth rate \(d\) does not impact the phage dynamics, as all rates are expressed in units of per cell division time. Phage are known to decay at rates that are several orders of magnitude lower than cell division rates60 and therefore phage decay does not impact the phase structure (Eq. (20)). To assess the importance of density-dependent growth on the results, we implemented the model using chemostat growth with a limiting resource, which displays a similar phase structure (Supplementary Note 1 & Supplementary Fig. 11).

### Model of CRISPR spacer invasion loss

We modify the immune defense model to account for a loss-of-spacer phenotype, \(S\), which is sensitive to phage but pays the cost of expressing the CRISPR system (i.e. it grows at the same rate as \(R\)), and which occurs by switching from \(R\) at a spacer loss rate \(\gamma\). We examine the coexistence of the resistant switching strain with a sensitive strain consisting of phenotype \(S\) which does not express CRISPR and grows at rate \(d\) - \(b\). The dynamics are given by

\[
\begin{align*}
\dot{R} &= (b - d - s)R - \lambda R I, \\
\dot{S} &= \delta S (1 + \rho R) - \lambda S I, \\
\dot{I} &= \lambda S I - k_1 S I - \lambda I (1 + \rho R), \\
\dot{P} &= -k_1 (a I + \beta n_k(1 - \rho R) - \lambda P I, \\
\end{align*}
\]

where \(\lambda = -R + S + S + I\). In this system there exist five stable fixed points that determine late-time population structure: the previously described \(S\), \(SP\) and \(E\) phases, and two new phases that carry resistance, the \(R\) and \(RSP\) phases in which all hosts coexist, and the \(RSP\) phase in which \(S\) is not present. Figure 5 shows the diagram of these phases separated by curves across which the system undergoes transcritical bifurcations (\(\gamma\), \(\gamma'\), \(\gamma''\) and Hopf \((\gamma''')\) bifurcations.

Starting from a point in the \(S\) phase and increasing phage burst rate, the frequency of \(S\) decreases until it becomes exactly zero at the location of the curve \(\gamma'\). The dynamics transitions to a stable fixed point which has \(S = 0\). Stability of the RSP phase implies that any transient increases of \(S\) frequency, e.g. through random mutations or immigration events, will decay exponentially. The location of this transition is controlled by the fitness difference between \(S\) and \(S\) which includes the cost of resistance, and the rate of spacer loss:

\[
\begin{align*}
\gamma' &= (b + k_h)\delta (a - d - b + s) (n_k a - d (b - s) (1 + n_k)) \\
\gamma'' &= (b + k_h)\delta (a - d - b - s) \\
\gamma''' &= (b + k_h)\delta (a - d - b - s)
\end{align*}
\]

For \(R \gg b\) we obtain the lower bound on burst size for which \(S\) is removed:

\[
\beta \approx (b + k_h)\delta (a - d - b - s)
\]

Therefore, for \(\beta \geq \delta\), where \((a - d - b - s)\) is the fitness difference between \(S\) and \(R\), resistance switching suppresses invasions by \(S\). Increasing the switching rate increases the selection against \(S\). For simplicity, in the above resistance switching strain we considered only spacer loss and did not include CRISPR loss. More generally, both spacer loss and CRISPR loss could occur in a resistance switching strain, further increasing the selection against strains that lack a CRISPR system. There also exist cases in which a CRISPR system exhibits no detectable constitutive costs64. In such cases, resistance switching via CRISPR loss corresponds to the above model in which both \(R\) and \(S\) grow at the same rate, and the above analysis shows that it would select against faster-growing sensitive strains whose growth advantage is unrelated to CRISPR.

### Game theory of patch invasion model

We analyzed the payoff matrix given in Eq. (6), where the pure strategies are \(R\), \(R_\text{s}\), and \(S\), given \(g_1, g_2 < c\). Each pure strategy is a fixed point of the replicator equation (Eq. (5)), and for \(s < c\) no pure strategy Nash equilibrium exists. For \(s < c\), \(R_\text{s}\), is a Nash equilibrium, and for \(s < c\) it is a strict Nash equilibrium, hence an ESS. For \(s = c\), \(R_\text{s}\) is an alternative best reply to \(R_\text{s}\), and since \(R\) does not beat \(R_\text{s}\), \(R\) is not an ESS. Depending on parameter values, two other fixed points can exist, one on the \(R_\text{s}\) axis edge for \(s < c\) and the other in the simplex interior, but neither one of these can be stable. See Supplementary Note 2 for derivation, Supplementary Note 3 for the case of independently dispersing phage, and Supplementary Fig. 12 for representative phase plots.
Next we considered a model with two switching strains, R₁ and R₂, with s' = s > c. In a similar fashion, we obtain the payoff matrix ϕ:

\[
\begin{pmatrix}
R₁ & R₂ & S \\
R₁ & 1 & 0 & \frac{R₁}{s+c} \\
R₂ & \frac{R₂}{s+c} & 1 & 0 \\
S & 0 & 0 & 1
\end{pmatrix}
\]

The stable fixed point corresponds to a pure R₁ strategy for s' < c. If both s and s' are larger than c, there is no interior equilibrium and the system will approach the boundary of the simplex \(\sum x_i = 1\) whose faces correspond to a reduction of the game theory model to a subset of three strains. The unstable fixed point on the (R₁, R₂, S) face repels interior orbits and the system transitions to a heteroclinic cycle on the (R₁, R₂, S) face. Equivalently, the strain with the highest switching rate is driven to extinction as it gets displaced by the strain with lower switching rate and the ecology reduces to the (R₁, R₂, S) patch invasion game.

We generalized to a large number of switching strains with s > s' > s'' > ... > c where the difference between each pair of switching rates is greater than c. The invasion diagram for three switching strains is:

![Diagram](image)

If all the strains have switching rates above c, the ecology will undergo a similar reduction where the strains with highest switching rates progressively go extinct until one of the rates evolves to become smaller than c, at which point it becomes an ESS.

Data availability
No datasets were generated or analyzed during the current study.

Code availability
Code used to produce figures is available at github.com/kussell-lab/ecological-memory.

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A.S. and E.K. performed the research and wrote the manuscript.

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