Diversity of immune strategies explained by adaptation to pathogen statistics

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Biological organisms have evolved a wide range of immune mechanisms to defend themselves against pathogens. Beyond molecular details, these mechanisms differ in how protection is acquired, processed, and passed on to subsequent generations—differences that may be essential to long-term survival. Here, we introduce a mathematical framework to compare the long-term adaptation of populations as a function of the pathogen dynamics that they experience and of the immune strategy that they adopt. We find that the two key determinants of an optimal immune strategy are the frequency and the characteristic timescale of the pathogens. Depending on these two parameters, our framework identifies distinct modes of immunity, including adaptive, innate, bet-hedging, and CRISPR-like immunities, which recapitulate the diversity of natural immune systems.

immune systems | CRISPR immunity | adaptive immunity | bet hedging | evolution of immunity

Immune systems have evolved to protect organisms against large and unpredictable pathogenic environments. However, immunity always comes at a cost (metabolic and maintenance costs, autoimmune disorders, etc. (1), and this cost must be balanced by the benefits that protection confers (2, 3). Faced with the problem of evolving a suitable defense, different organisms, from archaea to humans, have developed different strategies to identify and target pathogens, which have given rise to a diversity of mechanisms of immunity.

A large effort has been made to elucidate these mechanisms down to their molecular details in a variety of species (4–9). Beyond many differences, these studies have revealed many commonalities (10, 11), which hint at a possible general understanding of the trade-offs that shape their design (1, 2). For instance, independently of the well-known adaptive immune systems of jawed vertebrates, jawless vertebrates (e.g., lampreys) have developed an alternative adaptive system that uses a distinct molecular family of receptors, but both systems function largely in the same way, relying on the generation of a large number of diverse receptors expressed by two types of lymphocytes (B- or T-like cells). Likewise, the innate immune systems of invertebrates and vertebrates share many similarities, relying on the selected expression of germ-line Toll-like receptors upon infection. Some of the features of vertebrate immunity are even shared with bacteria, who have developed their own targeted immunity based on the CRISPR/Cas system (9, 12), which itself bears strong resemblance to genome protection through interfering RNAs in eukaryotes (13).

Independently of how they evolved and their particular molecular implementation, we may classify these diverse mechanisms into a few broad modes of immunity: heritable but not adaptable within an individual's lifetime, as innate immune systems; heritable and adaptable within a lifetime but with the benefits of adaptation being nonheritable, as adaptive immune systems; acquired from the environment and heritable, as the CRISPR/Cas system; and mixed strategies combining several of these elements. These broad distinctions call for general principles to characterize the conditions under which one or another mode of immunity may be expected to evolve (1, 10, 11). The diversity and variability of threats from the pathogenic environment suggest that different modes of immunity may offer better protection, depending on the patterns of occurrence and virulence of pathogens or the effective population size of the protected population. Here we apply a general theoretical framework for analyzing populations in a varying environment (14) to predict the emergence of the basic forms of observed immunity.

Model

Individuals reproduce in the presence of pathogens, which randomly appear and may persist for several generations and disappear before possibly reappearing at a later time (Fig. 1*A*). In our framework, a given pathogen has a probability α to appear and a probability β to disappear from one generation to the next (Fig. 1*B*). The pathogenic dynamics are quantified both by the pathogen frequency $\pi_{\text{env}} = \alpha/(\alpha+\beta)$, which is the probability that it is present at any given generation, and by the characteristic timescale $\tau_{\text{env}} = -1/\ln(1-\alpha-\beta)$, which sets how fast pathogens appear and disappear. Although other parameterizations may be considered, this choice for τ_{env} preserves the symmetry between the presence and absence of the pathogen (*SI Appendix A: Parameterizing a Two-State Markov Chain*).

Pathogens reduce the fitness of the individuals in the population and the immune system is designed to mitigate this effect. An individual's fecundity, defined as its expected number of descendants in the next generation $\bar{\xi}$, depends on the pathogenic environment and its ability to protect itself against it. Each pathogen independently lowers the fecundity of an unprotected

Significance

Organisms possess many mechanisms for protecting themselves from pathogens. In addition to the well-studied innate and adaptive immune systems of vertebrates, recently discovered mechanisms such as CRISPR immunity in prokaryotes diversify the known modes of information processing used in immune protection. By classifying these different systems in terms of their rules of heritability and response to the environment, we propose a mathematical framework that recapitulates the observed natural diversity of immune systems. We show how the basic modes of immunity emerge as optimal strategies of a population adapting to a changing pathogenic environment. The proposed framework offers a unified view of immunity across species and helps rationalize the diversity of observed mechanisms.

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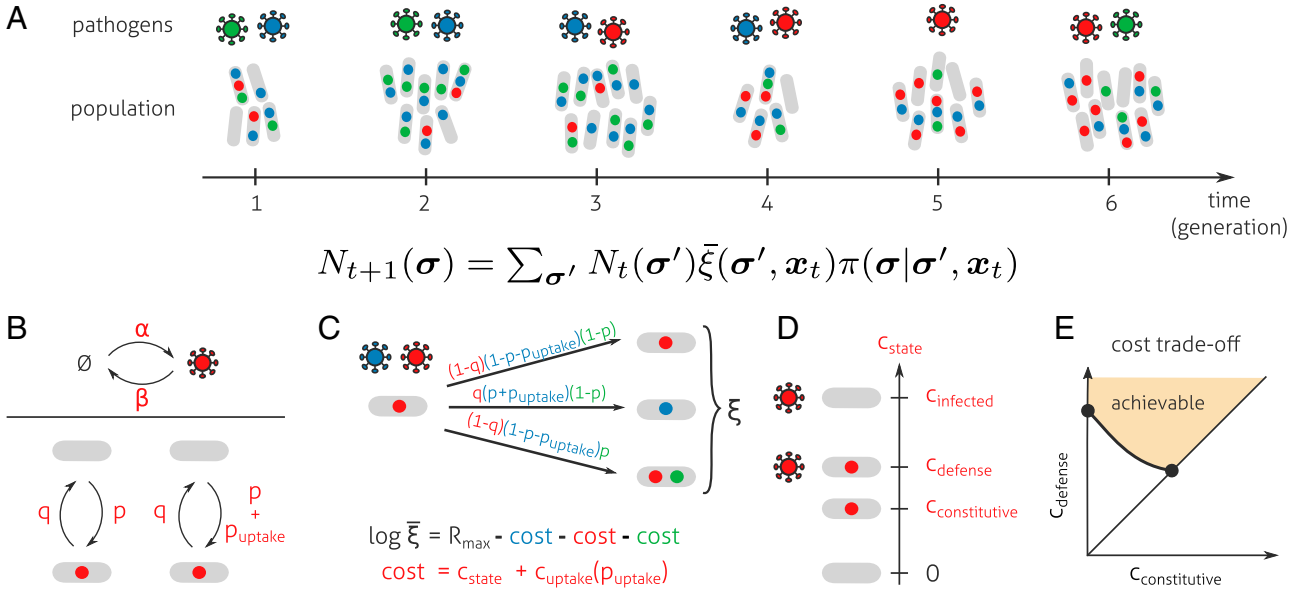

Fig. 1. A model to explore the incidence of different modes of immunity on the long-term growth of populations. (*A*) A population of organisms, each possibly protected against no, one, or several pathogens (no, one, or several colored circles), evolves in the presence of a pathogenic environment that varies from generation to generation. The mean number of individuals with protection σ at generation t, $N_t(\sigma)$, is given by a recursion equation involving the mean number of offspring $\bar{\xi}(\sigma', x_t)$ for individuals with protection σ' and the probability $\pi(\sigma|\sigma', x_t)$ that each of their offspring inherits a protection σ; both of these quantities may depend on the current pathogenic environment x_t. The long-term growth rate of the population is given by $(1/t)\ln N_t$ at large t, with $N_t = \sum_\sigma N_t(\sigma)$ the total population size. (*B*) Dynamics of appearance and disappearance of pathogens x_t and immune protection σ. A pathogen appears with rate α and disappears with rate β; these rates define the frequency $\pi_{env} = \alpha/(\alpha+\beta)$ and characteristic time $\tau_{env} = -1/\ln(1-\alpha-\beta)$ of the pathogen. Protection against a given pathogen is acquired spontaneously with rate p and lost from one generation to the next with rate q. Additionally, the presence of the pathogen can increase the rate of acquisition of protection by p_{uptake}, as, e.g., in the CRISPR-Cas system of prokaryotes. (*C*) The ξ offspring produced by an individual inherit the immune protections of their parent with rules specified in *B*. Each pathogen reduces the mean number of offspring $\bar{\xi}(\sigma, x_t)$ by a cost c_{state} that depends on whether the individual is in state "infected," "defense," or "constitutive" relative to the pathogen and by a cost $c_{uptake}(p_{uptake})$ that depends on the rate p_{uptake} at which protection is directly induced by the presence of the pathogen. (*D*) An unprotected organism pays a cost of infection $c_{infected}$ if the pathogen is encountered, which is reduced to $c_{defense}$ if it is protected. A protected organism must, however, pay a constitutive cost $c_{constitutive}$ even in the absence of the pathogen, whereas an unprotected organism pays no cost. (*E*) We assume a trade-off between the constitutive and defense costs: A more efficient defense (lower $c_{defense}$) requires more resources (higher $c_{constitutive}$).

individual by a relatively large cost factor $c_{infected} > 0$ (Fig. 1*D*). This cost is reduced to a lower cost $c_{defense} < c_{infected}$ when the individual is protected by its immune system; however, this protection comes at a basal cost $c_{constitutive} < c_{defense}$ of maintaining the immune defense in absence of the pathogen (Fig. 1*E*).

We explore the choices and trade-offs underlying various modes of immunity along three axes: adaptability, heritability, and mode of acquisition. The first one, adaptability axis, concerns how much resources are invested in the protection for the return of an efficient response. This trade-off imposes a relationship between $c_{defense}$ and $c_{constitutive}$ (Fig. 1*E*): The more effective the defense is (the lower $c_{defense}$), the higher the maintenance cost (the higher $c_{constitutive}$). For example, having a large number of immune cells specialized against a specific pathogen allows for a quick and efficient response in the case of invasion, but this enhanced protection comes at the cost of producing and maintaining these cells in the absence of the pathogen. This strategy is adopted, for example, by much of the innate immune systems of plants and animals (4). On the contrary, the adaptive immune system keeps a very small specialized pool of lymphocytes for each potential antigen and makes them proliferate only in the case of infection (10). Having the machinery of adaptive immunity comes at some upfront investment cost, but the huge diversity of adaptive immune repertoires then allows for a response against many pathogens at essentially no marginal constitutive cost. It is this marginal constitutive cost that determines when to use a mode of defense once an organism has the machinery (*SI Appendix D: Nonindependent Pathogen–Protection Pairs*). We assume that the cost of defense grows faster at small constitutive costs than at large ones (reflected in the convexity in Fig. 1*E*). The second one, heritability axis, is defined by the probability q that the protection is not transmitted to the offspring (Fig. 1*B*). Finally, the third one, acquisition axis, specifies how individuals may acquire the protection without inheriting it from their parent. This acquisition may occur randomly independently of the environment, with probability p, for instance by mutation or phenotypic switching, as is the case for antibiotic resistance in bacteria (15); or it can be induced by the presence of the pathogen with probability p_{uptake}, as in CRISPR-Cas immunity (Fig. 1*B*) (9). This mechanism comes at an extra cost $c_{uptake}(p_{uptake})$ due to maintenance and the risks of uptaking foreign genetic material (Fig. 1*C*), in addition to the state-dependent cost c_{state} (Fig. 1*D*). To account for the dangers associated with taking up foreign DNA we assume that c_{uptake} increases superlinearly with p_{uptake}.

Results

Each choice of the parameters $c_{constitutive}$, q, p, and p_{uptake} defines a specific immune strategy. This strategy is optimal if a population that adopts it outgrows in the long run any other population following a different strategy. Our goal is to characterize this optimal strategy, in particular its dependency on the two key properties of the pathogen, its frequency π_{env} and its characteristic time τ_{env}. We achieve this goal by maximizing the long-term growth rate of populations, defined by $(1/t)\ln N(t)$, where $N(t)$ is the total population size at generation t (Fig. 1*A*) (16). Conveniently, because the fecundity is affected independently by the different pathogens, each pathogen contributes additively to the

growth rate and can be studied separately (Fig. 1*C* and *Materials and Methods*).

Remarkably, we obtain qualitatively different optimal solutions for different values of π_{env}, τ_{env}, with sharp transitions between these strategies as we vary the parameters of the pathogen statistics, allowing us to define distinct immune regimes (Fig. 2*A*). The emergence of these very distinct regimes is not an assumption, but the result of the optimization itself.

Fig. 2*B* describes these optimal strategies along the three axes of variation outlined earlier. Along the first axis of variation, adaptability, we find that frequent or persistent pathogens are best dealt with by constitutively expressed immunity ($c_{constitutive} = c_{defense}$) and rare and transient pathogens by investing minimally in the defense ($c_{constitutive} = 0$, in blue); between these two extremes, only a limited form of adaptation is required ($c_{constitutive} < c_{defense}$, in green). Along the second axis, heritability, we find that carrying the protection at all times ($q = 0$) is beneficial against fast pathogens but that losing the protection with probability $q > 0$ is more advantageous for slow ones. Finally, along the third axis, acquisition, we verify that there is no need to pay the price of informed acquisition ($p_{uptake} = 0$) whenever protection is systematically inherited ($q = 0$); when it is not the case ($q > 0$), we find that uptake is advantageous for sufficiently infrequent pathogens (yellow and orange regions in Fig. 2*B*) but that only for very infrequent pathogens does it becomes the exclusive mode of acquisition of protection ($p = 0$, $p_{uptake} > 0$, in yellow).

Each of these distinct regimes, or phases, is instantiated by natural immune systems (Table 1). For transient and rare pathogens (blue phase in Fig. 2*A*), the optimal strategy is to inherit a defense with minimal constitutive cost. This strategy is characteristic of the adaptive immune system in vertebrates, where an effective immune response is mounted from a small number of precursor cells, the marginal cost of which is negligible (10). For transient but frequent pathogens (purple phase in Fig. 2*A*), the optimal strategy consists instead of inheriting a maximally efficient protection that makes the individuals effectively insensitive to the presence of the pathogen at the expense, however, of a large constitutive cost. The recognition of pathogen-associated molecular patterns by pattern recognition receptors, for instance the recognition of lipopolysaccharide by Toll-like receptors, is an example of such an innate strategy (4). An intermediate phase (green in Fig. 2*A*) separates these two extremes, where adaptation is present with a nonzero constitutive cost. This strategy, which we call proto-adaptive, is represented by certain specialized cells of the innate immune system, such as natural killer cells (17), whose abundance can vary as a

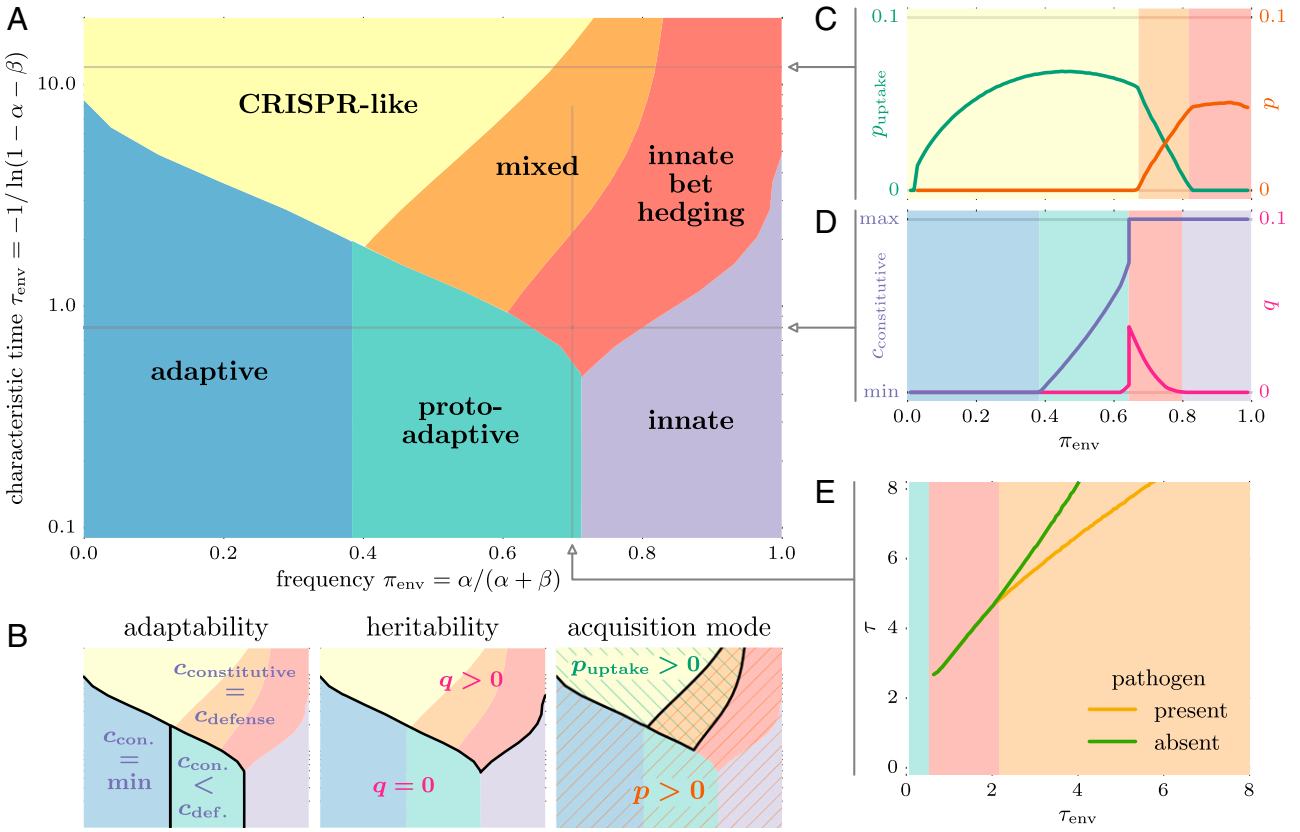

Fig. 2. Optimal immune strategies as a function of the frequency and characteristic time of pathogens. (*A*) Distinct optimal immune strategies emerge for different statistics of appearance of the pathogens. Each phase is characterized by the value of parameters indicated in *B* and named after a known immune system that has similar characteristics (the term "adaptive" refers to the vertebrate immune system). (*B*) The different phases of immunity are defined by the values of parameters along three main axes: adaptability (constitutive cost $c_{constitutive}$), heritability ($1-q$), and mode of acquisition (p and p_{uptake}). (*C* and *D*) Optimal parameters as a function of π_{env} for $\tau_{env} = 12$ (*C*) and $\tau_{env} = 0.8$ (*D*). For slowly varying environments (*C*), rare pathogens are best targeted by CRISPR-like uptake of protection, whereas frequent pathogens are best dealt with by spontaneous acquisition of protection, with a crossover in between where both coexist. For faster varying environments (*D*), the constitutive cost invested in the protection goes from negligible to maximal as the pathogen frequency increases. When it is maximal, the best strategy transitions from bet hedging ($q > 0$) to a full protection of the population ($q = 0$). (*E*) The correlation times of protection in absence of the pathogen, $\tau = -1/\ln(1-p-q)$, and in its presence, $\tau = -1/\ln(1-p-p_{uptake}-q)$, are shown for $\pi_{env} = 0.7$ as a function of τ_{env}. Both times increase with the correlation time of the pathogen. Here, an infinite population size is assumed and the following parameters are used: $c_{infection} = 3$; $c_{constitutive} = (1.8 - c_{defense})/(c_{defense} - 0.2)$; $c_{uptake}(p_{uptake}) = 0.1 \times p_{uptake} + p_{uptake}^2$ (see Fig. S3 for other choices).

function of experienced infections, effectively implementing an adaptive memory within a single generation.

For slow and frequent pathogens (red phase), protection is acquired with probability $p > 0$ and lost with probability $q > 0$ independently of the presence of the pathogen. This bet-hedging strategy is implemented in bacteria that can switch on or off the expression of phage receptors (8). For slow but infrequent pathogens (yellow phase in Fig. 2*A*), a form of bet hedging is again present, but this time with a nonzero probability to acquire protection only in presence of the pathogen. An example of such a Lamarckian strategy is the CRISPR-Cas immune system in bacteria (9). Finally, a mixed phase (orange in Fig. 2*A*) is also possible where protection is randomly acquired at a rate that is increased by the presence of the pathogen.

We can gain insight into the transitions between the different phases by considering three analytically solvable simplifications of the model, detailed in *SI Appendix C: Analytical Insight into the Transitions Between Strategies*. In the first of these simplified models, we can calculate the transitions from a purely constitutive to a proto-adaptive to a purely adaptive strategy as the pathogen frequency π_{env} decreases. The second model highlights the transition from a bet-hedging to a deterministic protection, whereas the third one focuses on the transitions from a purely passive to a purely active acquisition of the protection, with a mixed phase in between.

It is instructive to examine how the parameters of immunity vary within the phases (Fig. 2 *C* and *D* and Fig. S1). As one may expect, the statistical properties of the protection tend to track the pathogen statistics (18). The more frequent the pathogen is, the more prevalent the protection in the population (Fig. 2*C*). Likewise, the characteristic time of the protection, τ, grows with that of the pathogen, τ_{env} (Fig. 2*E*).

The assumptions that we made allow us to treat each pathogen–protection pair independently of each other. However, there are a number of ways in which this assumption may be questioned. We discuss several in *SI Appendix D: Nonindependent Pathogen–Protection Pairs* and we find that these generalizations do not qualitatively affect our conclusions. For example, infections could interact by inflicting more harm together than the sum of each one alone, e.g., HIV in conjunction with other diseases (Fig. S2). This case can be incorporated into our approach by considering a modified effective cost including the extra cost of coinfection. Another way in which pathogen–protection pairs could be correlated is through a nonadditive cost of protection, if the marginal cost of protection increases or decreases with the number of protections. For example, if having protection against two pathogens is much more costly than twice the cost of having protection against just one, then the optimal strategy may be to hedge bets by keeping a subpopulation protected against one pathogen and another subpopulation protected against the other. Finally, cross-reactivity, the widespread ability of protections to recognize several pathogens, is another departure from independence, which can be partly overcome by grouping together pathogens recognized by a common protection.

Discussion

The phase portrait in Fig. 2*A* rationalizes the salient differences between the immune systems of prokaryotes and vertebrates. Bacterial and archaeal organisms evolve on timescales that are much closer to those of their pathogens than vertebrates. From the viewpoint of microbes, the pathogenic environment is relatively constant ($\tau_{env} > 1$), whereas for vertebrates a particular pathogenic strain is unlikely to survive a single generation ($\tau_{env} \ll 1$). Consistent with our results, vertebrates use fully heritable modes of immunity and do not rely on bet hedging. To deal with infrequent and fast-evolving pathogens such as viruses, they recourse to adaptive mechanisms by which they can up-regulate their protection in case of an invasion. The three predicted strategies—adaptive, proto-adaptive, and innate—correspond to the known modes of immunity in vertebrates (19). Prokaryotes, on the other hand, almost systematically use bet-hedging strategies. They recourse both to the CRISPR-Cas system of acquired immunity (9) and to innate immunity through, e.g., restriction endonucleases (8), which correspond to the predicted Lamarckian and innate bet-hedging strategies of the diagram, respectively. These results are robust to changes of parameters, although increasing costs can make bet hedging beneficial even at short characteristic times (Fig. S3).

Bacteria and vertebrates also have very different population sizes, which influence their overall survival probability. To evaluate this impact, we ran stochastic simulations, competing different strategies for increasing population sizes (*Materials and Methods* and Fig. S4). The phase diagram in Fig. 2*A* is recovered for population sizes as small as 1,000, whereas for smaller population sizes the boundaries between regimes are smeared. In small populations, adaptive strategies are generally favored over CRISPR-like strategies, and the amount of bet hedging increases. In fact, for finite populations it is always beneficial to recourse to some degree of bet hedging to react quickly to environmental changes and avoid extinction.

Table 1. Optimal strategies found in the phase diagram, their definition in terms of parameters of our framework, and biological examples

	Defining characteristics				
		Acquisition mode			
Strategy	Perfect heritability, $q = 0$	$p > 0$	$p_{uptake} > 0$	Adaptability, $c_{defense}$	Biological examples
Innate	Yes	Yes	No	Minimal	Innate defense by recognition of pathogen-associated molecular patterns by pattern recognition receptors (4)
Protoadaptive	Yes	Yes	No	Intermediate	"Trained" innate immunity (26), especially defense by natural killer cells (17); "systemic acquired resistance" in plants (20)
Adaptive	Yes	Yes	No	Maximal	Adaptive immune systems of jawed and jawless vertebrates (10)
Innate bet hedging	No	Yes	No	Minimal	Mutation of phage receptors by bacteria (8)
CRISPR-like	No	No	Yes	Minimal	CRISPR-Cas system in bacteria and archaea (9)
Mixed	No	Yes	Yes	Minimal	Concurrent use of CRISPR-Cas system and mutations of surface molecules by bacteria defending against phages (27)

Here, we consider the case of a common environment experienced by all individuals. Having different parts of the population experience different microenvironments that are not persistent over generations does not change the population dynamics on evolutionary timescales (*Materials and Methods*). These microenvironments can result from differing infection probabilities for different subsets of the population, e.g., arising from spatial niches, or other nonpathogenic factors such as nutrient availability that influence the capability of individuals to cope with pathogens. If there are microenvironments that persist over many generations, then our results hold in each microenvironment. An optimal strategy might then exploit the additional predictability stemming from knowing the statistical properties of the microenvironments and use the microenvironment diversity as a means of bet hedging.

Our results also suggest that plants and some invertebrates, which also have long generation times compared with the variation time of pathogens, should be endowed with adaptive and proto-adaptive immune systems, in addition to innate protection mechanisms (6). Consistent with this prediction, the innate branch of the plant immune system is able to increase protection in the entire plant following a local infection through "systemic acquired resistance" (20), providing the mechanistic basis of an inducible, proto-adaptive immune system. In addition, virus-derived small interfering RNAs, which accumulate during infections, are portrayed as likely candidates of adaptive immunity in plants and invertebrates—they are induced by the virus and keep a memory of past infections (21–23). Interestingly, small RNA-based immunity has been shown to be inheritable in *Caenorhabditis elegans* (24), an invertebrate with a short generation time of around 4 days, in agreement with our result that CRISPR-like immunity is desirable in this case.

By analyzing the long-term fate of populations under minimal assumptions concerning the rules governing adaptability, heritability, and acquisition of immune protections, we have recovered the basic known modes of immunity. Remarkably our results hold even for a single pathogen. The key determinants of optimal immune strategies are found to be the statistical features of pathogen occurrence: its frequency and its characteristic timescale. As an implication, a diverse pathogenic environment, with varying statistics, will favor mixed solutions, consistent with the observation of multiple immune systems within the same organism—such as adaptive and innate immune systems in vertebrates or CRISPR and innate defense in bacteria. Naturally, the molecular implementation of these general principles differs greatly even between organisms sharing the same type of immunity. However, an evolutionary perspective that accounts for the costs and benefits of protection is enough to explain the most salient features of immunity. It will be interesting to extend our framework to account for other essential features of immunity, e.g., the acquisition of protection by horizontal transfer or the coevolutionary dynamics between pathogens and their hosts. In view of our analysis, it is already less surprising that complex forms of immunity such as the adaptive immune system have evolved separately in jawed and nonjawed vertebrates, with the same general features but different molecular encodings.

Materials and Methods

Population Dynamics. The pathogenic environment is described by an L-dimensional vector $\boldsymbol{x}$ (symbols in boldface type refer to vectors), where $x_i = 1$ if pathogen i is present and 0 otherwise. Protection of an organism against these pathogens is also described by an L-dimensional vector $\boldsymbol{\sigma}$, where $\sigma_i = 1$ if the protection (antibody, T-cell receptor, CRISPR spacer) against pathogen i is present and 0 otherwise.

We consider the dynamics of a population of organisms reproducing at discrete times t. At each generation, each individual produces a stochastic number ξ of offspring, whose distribution depends on the state $\boldsymbol{\sigma}$ of that individual and the environment $\boldsymbol{x}_t$. We denote its mean by $\bar{\xi}(\boldsymbol{\sigma}, \boldsymbol{x}_t)$. Let $N_t(\boldsymbol{\sigma}|\boldsymbol{x}_{t'<t+1})$ be the mean number of organisms in the population at time t with protection $\boldsymbol{\sigma}$, for a given environment history $(\boldsymbol{x}_{t'<t+1})$ (16). The change in population composition from one generation to the next is governed by the reproductive success of individuals in each state $\boldsymbol{s}$, modified by stochastic state switching from parents to offspring

$$N_{t+1}(\boldsymbol{\sigma}|\boldsymbol{x}_{t'<t+1}) = \sum_{\boldsymbol{\sigma}'} N_t(\boldsymbol{\sigma}'|\boldsymbol{x}_{t'<t})\bar{\xi}(\boldsymbol{\sigma}', \boldsymbol{x}_t)\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x}_t), \quad [1]$$

where $\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x}_t)$ is the switching probability from protection state $\boldsymbol{\sigma}'$ to state $\boldsymbol{\sigma}$. Note that the protection state switching probability, which represents to what extent protection is inherited, acquired, or lost, generally depends on the state $\boldsymbol{x}_t$ of the environment. For ease of notation, we omit in the following the condition on the environment $(\cdot\,|\boldsymbol{x}_{t'<t})$ when referring to conditional means.

A similar recursion to Eq. **1** can be written for the fraction of the population in each state, $n_t(\boldsymbol{\sigma}) = N_t(\boldsymbol{\sigma})/N_t$, with $N_t = \sum_{\boldsymbol{\sigma}} N_t(\boldsymbol{\sigma})$ the total population size

$$n_{t+1}(\boldsymbol{\sigma}) = \frac{1}{Z_t}\sum_{\boldsymbol{\sigma}'} n_t(\boldsymbol{\sigma}')\bar{\xi}(\boldsymbol{\sigma}', \boldsymbol{x}_t)\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x}_t), \quad [2]$$

where Z_t is a normalization constant enforcing $\sum_{\boldsymbol{\sigma}} n_t(\boldsymbol{\sigma}) = 1$. The population size is given by $N_t = N_0\prod_{t'=0}^{t-1} Z_{t'}$, so that the long-term growth rate, $\Lambda = \lim_{T\to\infty}(1/T)\ln N_T$, is given by

$$\Lambda = \lim_{T\to\infty}\frac{1}{T}\sum_{t=0}^{T}\ln(Z_t). \quad [3]$$

The strategy with maximal long-term population growth rate outperforms in the long run any other strategy for almost every sequence of environments in populations of infinite size. This rate thus provides a measure of long-term fitness (16).

We assume that the mutation and inheritance probabilities of different pathogen–protection pairs are independent of each other, i.e., that $\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x}_t)$ factorizes over the pathogens

$$\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x}_t) = \prod_i \pi_i(\sigma_i|\sigma'_i, x_{i;t}). \quad [4]$$

The entries of $\pi_i(\sigma_i|\sigma'_i, x_{i;t})$ are given in Fig. 1*B*: $\pi_i(1|0, x) = p + xp_{\text{uptake}}$ and $\pi_i(0|1, x) = q$.

In addition, the effects of different pathogen–protection pairs on the growth rate are taken to be additive (Fig. 1*C*), so that

$$\begin{aligned}\ln\bar{\xi} = R_{\max} - \sum_{i=1}^{L}\big[&c_{\text{infection},i}\,(1-\sigma_i)x_i \\ &+ c_{\text{constitutive},i}\,\sigma_i(1-x_i) + c_{\text{defense},i}\,\sigma_i x_i \\ &+ c_{\text{uptake}}\big(p_{\text{uptake},i}\big)\big],\end{aligned} \quad [5]$$

where $R_{\max}$ is the growth rate in the absence of any immune cost. With these assumptions, the distribution $n_t(\boldsymbol{\sigma})$ also factorizes over i

$$n_t(\boldsymbol{\sigma}) = \prod_{i=1}^{L}\big[r_i^t\sigma_i + (1-r_i^t)(1-\sigma_i)\big], \quad [6]$$

where r_i^t is the fraction of the population having protection i at time t. Plugging this ansatz into Eq. **2** with Eqs. **4** and **5** yields the following recursion for r_i^t:

$$\begin{aligned}r_i^{t+1} = \Big[(1-r_i^t)e^{-c_{\text{infection},i}x_i^t}\big(p_i + p_{\text{uptake},i}x_i^t\big) + r_i^t e^{-c_{\text{defense},i}x_i^t - c_{\text{constitutive},i}\left(1-x_i^t\right)}(1-q_i)\Big]\Big/ \\ \Big[(1-r_i^t)e^{-c_{\text{infection},i}x_i^t} + r_i^t e^{-c_{\text{defense},i}x_i^t - c_{\text{constitutive},i}\left(1-x_i^t\right)}\Big].\end{aligned} \quad [7]$$

The recursion depends on the sequence of x_i^t, which is a stochastic binary process switching from 0 to 1 with probability α and from 1 to 0 with probability β (Fig. 1*B*). Note that the sequence x_i^t is the same for the whole population (a quenched variable in the statistical mechanics sense). We have $Z_t = e^{R_{\max}}\prod_{i=1}^{L} z_i^t$, with

$$z_i^t = e^{-c_{\text{uptake}}\left(p_{\text{uptake},i}\right)}\Big[(1-r_i^t)e^{-c_{\text{infection},i}x_i^t} + r_i^t e^{-c_{\text{defense},i}x_i^t - c_{\text{constitutive},i}\left(1-x_i^t\right)}\Big]. \quad [8]$$

From Eq. **3**, it then follows that

$$\Lambda = R_{\max} + \sum_{i=1}^{L}\left(\lim_{T\to\infty}\frac{1}{T}\sum_{t=1}^{T}\ln z_i^t\right). \quad [9]$$

The long-term growth rate is a sum of independent terms for each pathogen–protection pair, which allows us to treat the problem of maximizing the long-term growth rate one pathogen at a time.

Numerical Solution. The cost function of the optimization, Λ, can be approximated by solving the recursion equation describing the relative frequency of organisms with different protection states in the population for a large enough number of generations (we used at least 10^6 generations). Our goal is to optimize Λ over the four parameters $p, q, p_{\text{uptake}}, c_{\text{constitutive}}$ (or over the subset of free parameters for a given strategy) constrained to their domain of definition. For numerical purposes, all four parameters are first mapped onto the unit interval $[0,1]$. The noise in the evaluation of Λ arising from its approximation from finite time data makes the optimization challenging. Because the process is ergodic, averaging over very long periods is equivalent to repeating the process multiple times. The noise can therefore be reduced by both prolonged simulation or repeated sampling at the expense of a higher computational cost per function evaluation. To find the global optimum of this noisy function under the bound constraints on the parameters we use a two-phase algorithm. In the first phase the DIRECT algorithm (25) provides us with a rough, but global optimization for which we use a relatively low-quality approximation. The results of this first phase are then refined by a pattern-search algorithm with an adaptive sampling of the function (described in detail in *SI Appendix B: Pattern-Search–Based Optimization for Problems with Noisy Function Evaluations*), using the parameters $\Delta_{\text{tol}} = 0.0005$ (for Fig. S1 $\Delta_{\text{tol}} = 0.005$), $\alpha = 0.005$.

To obtain a phase diagram such as the one shown in Fig. 2*A* we first performed a global optimization over all four parameter values as described above, for every environment condition $(\pi_{\text{env}}, \tau_{\text{env}})$ (Fig. S1). Based on the optimal parameters found in this step, we defined the features of the emerging phases (Table 1). All phases are defined by a subset of the variables lying at a constraint boundary. To calculate precise phase boundaries, we find the frequency of pathogens π_{env} at a given characteristic time τ_{env} for which the difference in long-term growth rates between a given pair of strategies vanishes. To obtain the root of the difference function, we use a bisection algorithm. To decrease noise, the difference is calculated across pairs of simulations using the same sequence of pathogens $\{x_t\}$ and the function is sampled adaptively to ascertain statistical significance. The bisection algorithm is run up to a tolerance of 0.025 in π_{env} and then the precise position of the root is interpolated assuming linearity of the difference function within the interval. To prevent, e.g., the mixed strategy from reducing to a CRISPR-like strategy, we impose that the parameters that are not set to a fixed value in a particular strategy are not closer than a tolerance 0.005 (0.0005 for q) of the boundary.

All source code associated with this manuscript is available online at https://github.com/andim/evolimmune.

Simulations with Finite Populations Sizes. To study the influence of the effects of finite population size we perform direct agent-based simulations of a population of adapting individuals with strategies evolving on a slow timescale. The population has a finite size N that remains fixed over the course of the simulation. At every generation the parents of the N individuals are drawn from the individuals making up the previous generation with probabilities proportional to the mean number of offspring $\bar{\xi}$ of these individuals. The offspring's state $\boldsymbol{\sigma}$ is determined from the state of its parent $\boldsymbol{\sigma}'$ according to the switching rates $\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', x_t)$ defined previously. Along with the state $\boldsymbol{\sigma}$, the switching rates themselves, $\pi(\boldsymbol{\sigma}|\boldsymbol{\sigma}', \boldsymbol{x})$, as well as the degree of adaptability, $c_{\text{constitutive}}$—in other words, the parameters defining the immune strategy—are also transmitted to the offspring. They also change from parent to offspring, although at a much slower rate than the state to preserve a clear separation of timescales between short-term and long-term adaptations. In this setup, selection acts on the strategies. After an equilibration phase, we collect statistics on the strategies adopted by individuals in the population. To get rid of the effect of deleterious mutations that do not eventually fix in the populations the mutation rate and size were scaled down exponentially with time. As population size is finite deleterious mutations can fix in the population, which means that even in the limit of zero mutation rate there remains a spread in the distribution of strategies. Hence we represent not only the median as a measure of the central tendency of a parameter, but also the interquartile range as a measure of its spread.

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