

Steering and controlling evolution – from bioengineering to fighting pathogens

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Abstract

Control interventions steer the evolution of molecules, viruses, microorganisms or other cells towards a desired outcome. Applications range from engineering biomolecules and synthetic organisms to drug, therapy and vaccine design against pathogens and cancer. In all these instances, a control system alters the eco-evolutionary trajectory of a target system, inducing new functions or suppressing escape evolution. Here, we synthesize the objectives, mechanisms and dynamics of eco-evolutionary control in different biological systems. We discuss how the control system learns and processes information about the target system by sensing or measuring, through adaptive evolution or computational prediction of future trajectories. This information flow distinguishes pre-emptive control strategies by humans from feedback control in biotic systems. We establish a cost–benefit calculus to gauge and optimize control protocols, highlighting the fundamental link between predictability of evolution and efficacy of pre-emptive control.

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Introduction

For thousands of years, humans have steered the evolution of animals and plants by selective breeding. Such interventions are a form of eco-evolutionary control: they alter the ecological or evolutionary trajectory of a target system towards a predefined objective. Modern eco-evolutionary control still fits this definition but has broader objectives and a wider range of applications in bioengineering, ecology, medicine and public health¹. In many cases, the targets of control are fast-evolving systems, such as microbial and viral pathogens or cancer cell populations.

Control of living systems is challenging because of their inherent complexity. An intended change is inevitably coupled to other molecular traits and functions. For example, a controlled metabolic change may increase the output of a target pathway but, at the same time, decrease the overall fitness of the target organism^{2,3}. Or an induced immune response may target cancer cells but also affect healthy cells⁴. The interactions between controller and target system are often modulated by the ecological context of both systems. Hence, control is a multi-dimensional problem: desired and collateral changes, which generate benefits and costs of control, have to be weighed and managed simultaneously. In particular, evolution of the target system can be an intended or a collateral effect of control^{5,6}. Fast-evolving pathogens respond rapidly to an intervention; for example, bacteria acquire resistance to antibiotics and viruses escape from vaccination. The challenge of controlling such systems is to develop pre-emptive strategies that factor in the likely evolution of the target.

In this Review, we first present examples of eco-evolutionary control that highlight recent experimental and modelling advances. In the second part, we distil common aspects and differences between these systems in the mechanisms of control and in the dynamics of target and controller. The target system may change by regulation and by evolution, and the controller may be a biotic system co-evolving with the target or a human applying rational control strategies, often implemented by computation. These dynamics determine central issues of control: how does the control system acquire and process information about the target system? What makes computational control different from co-evolution? Specifically, we discuss the roles of target monitoring, adaptive learning and computational prediction⁷ in successful control strategies. In the third part, we outline elements of an emerging eco-evolutionary control theory and highlight challenges for future research with a focus on biomedical questions. We argue that theory-based optimization of control is important for further development of the field. We close with a discussion of ethical issues in eco-evolutionary control.

Examples of evolutionary control

Control of biological systems has a diverse set of goals, from enhancing productivity and sustainability of biosynthetic processes to controlling the spread of disease. Here, we introduce several examples of recent research that shows the extraordinary breadth of evolutionary control problems. In all these systems, the objective of control includes inducing or suppressing evolution of the target system.

Directed evolution for molecular design

Directed evolution experiments with artificial selection have been used to improve the activity and selectivity of molecules and enzymes, qualities that are often desirable in industrial or pharmaceutical applications (Fig. 1a). Recently developed in vivo directed evolution systems leverage the replication machinery of a host organism to perform autonomous

hypermutation and selection steps without active external intervention⁸. In these systems, the artificial selection protocol couples the desired output of the target gene to the reproductive fitness of a carrier cell or organism. This happens, for example, when the target gene acts to increase the metabolism of new resources or the tolerance of new environmental conditions. Directed evolution experiments implement feedback control mechanisms to monitor fitness and protein functions of interest and tune the strength of artificial selection accordingly^{9–13}. The resulting protocols can steer the evolutionary trajectories of the target gene or pathway, subject to constraints imposed by the natural fitness landscape of the carrier organism.

Directed evolution of microorganisms

In biotechnology, inducing adaptive evolution under controlled laboratory conditions is highly effective in generating organisms with specific traits, such as heat tolerance¹⁴ or resistance to stressors¹⁵ (Fig. 1b). This approach is advantageous when the target organism is difficult to engineer or the genetic basis of the desired phenotype is complex and poorly understood. However, molecular traits lacking fitness benefit cannot be directly selected by adaptive evolution. This limitation can be circumvented by exploiting environment-dependent trait correlations. For example, a recent study used environment switching, guided by metabolic modelling, to evolve fitness-neutral or costly traits in *Saccharomyces cerevisiae*³. Controlled evolution takes place in a transient environment, by adaptive evolution of a secondary trait that is coupled to the target trait via a metabolic network. After the controlled evolution phase, the target environment is switched on and the enhanced target trait becomes effective. This method allows the directed evolution of features such as metabolite secretion, which are currently inaccessible to direct adaptive evolution protocols.

Engineering of microbial communities

A new frontier in synthetic biology is to use genetic engineering in assembling microbial communities with designed functions. This allows division of labour and specialization of subpopulations towards a given objective, for example, the secretion of compounds. However, engineered functions consume resources and put stress on the community, which can lead to loss-of-function mutations and make these communities unstable^{16,17}. Recent work has achieved the stabilization of a model community by adding a bacterial strain with an engineered toxin production mechanism¹⁸. This strain senses and controls the population size of competing species. Its toxin production can operate autonomously or by an externally set protocol, which manipulates the density of the underlying quorum sensing molecules. Such stabilization in variable environments can be achieved by various mechanisms, based on insights from engineering control theory^{19,20}.

Control by gene drive

A gene drive is a genetic engineering technique that allows a specific allele of a diploid gene to spread rapidly through a population of sexually reproducing organisms so that the allele is inherited more than 50% of the time, that is, more than expected under Mendelian inheritance. Such systematic biasing of inheritance can drive chosen, even deleterious, alleles to prevalence in a target population. It serves, for example, to introduce new traits into a population or to reduce the prevalence of harmful traits or diseases²¹. However, gene drive systems, similar to control by drugs, can be affected by resistance evolution²². A showcase application of this method will be to combat malaria by introducing a

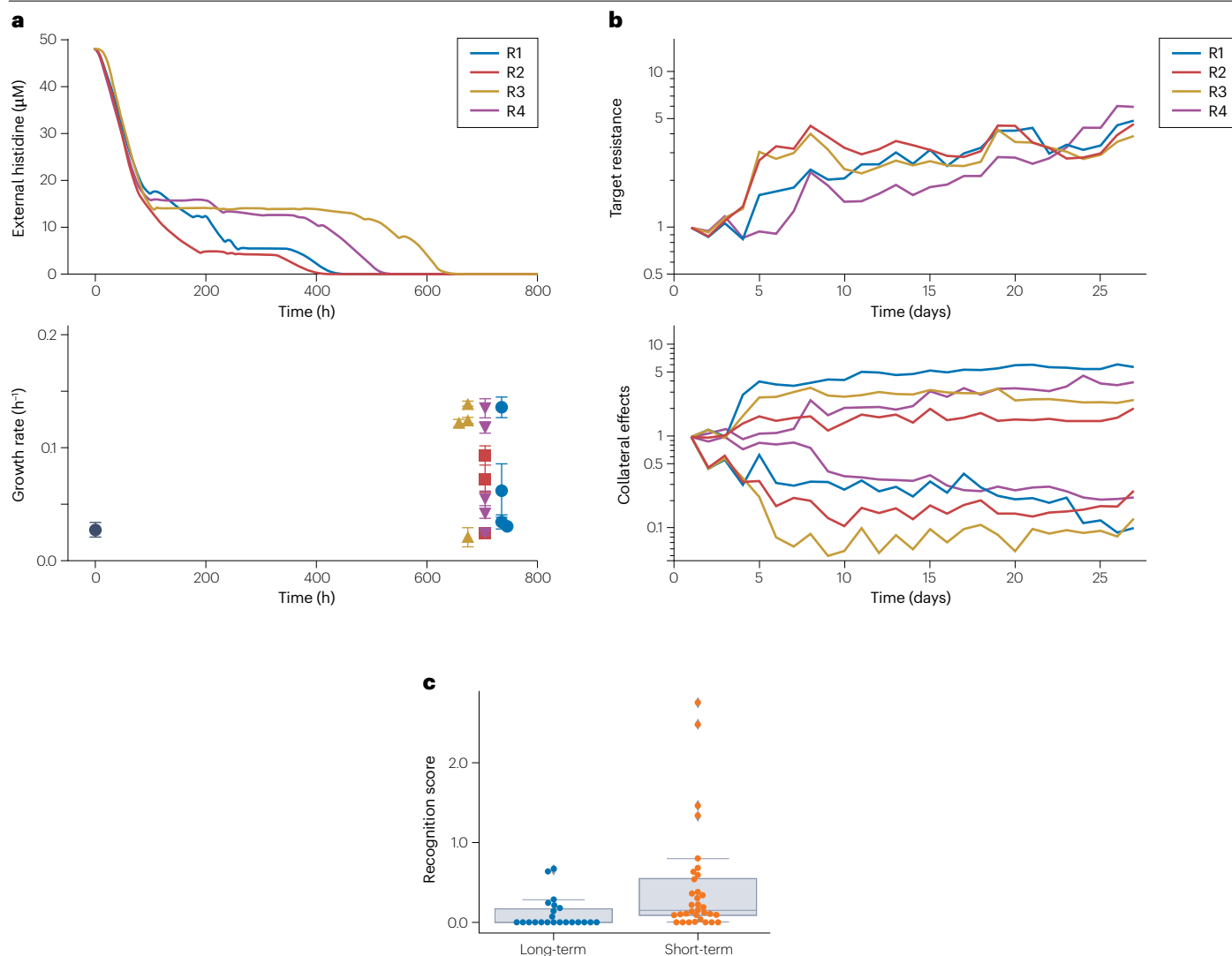


Fig. 1 | Examples of evolutionary control. a, Directed evolution of an enzyme. The TmHisA enzyme, which is part of a histidine production pathway, is evolved to function in a new species, *Saccharomyces cerevisiae*. Top: the control protocol gradually decreases the supply of external histidine, using a feedback mechanism to maintain an approximately constant growth rate in four replicate populations (R1–R4 in different colours). By evolution of TmHisA, the yeast cells gradually adapt to function in environments without external histidine. Bottom: fitness in a histidine-free environment for the wild type (black circle) and for evolved TmHisA variants sampled from each replicate population after 700 h (~100 generations, R1–R4 in different colours). Successful TmHisA variants acquired 6–15 mutations. Part **a** adapted with permission from ref. 13. **b**, Directed evolution of antibiotic resistance. Top: controlled evolution of tetracycline resistance in four replicate *Escherichia coli* populations (R1–R4); resistance

is measured by the half-inhibitory drug concentration (IC50) relative to the wild type. Feedback control maintains stable growth by keeping the actual drug concentration close to the IC50 value. Bottom: collateral trait evolution, measured against seven other drugs, can increase or decrease sensitivity; lines show the drug with maximum and minimum IC50 in each population. Part **b** re-plotted using data from ref. 15. **c**, Control of cancers by the immune system. Evolving cancers accumulate new mutations and new neoantigens. The resulting change in immune recognition during the evolution from a primary to a recurrent tumour is computed from a neoantigen fitness model and compared between cohorts of long-term (blue) and short-term (orange) survivors. These dynamics are shaped by immune interactions: recognition increases less in long-term survivors, indicating the stronger suppression of clones with high-affinity neoantigens. Part **c** re-plotted using data from ref. 43.

gene drive in mosquitoes that reduces transmission of the pathogen *Plasmodium falciparum*. Although many technological challenges of gene drives have been mastered, controlling resistance evolution and collateral effects as well as securing regulatory and community approval to test these systems in natural contexts remain major hurdles for this application²¹.

Antimicrobial interventions

Antibiotics control bacterial pathogens by interfering in cellular functions and metabolic pathways. Targets of these drugs include bacterial ribosomes, as well as cell wall and DNA synthesis pathways²³. Most clinically relevant antibiotics are derived from natural compounds that are part of the inter-microbial weaponry²⁴. Immune systems mount similar

antimicrobial forces, including antimicrobial peptides^{25,26}, which are also involved in the immune response to tumours²⁷.

Bacteria acquire resistance to drugs by physiological adaptation or by evolution. The failure of antibiotic treatments due to resistance evolution generates an accelerating global health crisis²⁸. Under antibiotic pressure, bacteria can mutate the molecules targeted by the drug, import resistance genes by horizontal gene transfer, activate specific defence pathways such as efflux pumps or globally re-allocate their proteome resources^{29,30}. Diverse resistance mechanisms have also been described for antimicrobial peptides³¹. In some cases, metabolic fitness models can predict dosage-dependent trajectories of resistance evolution³² based on metabolic models of drug action³³. Successful control protocols should limit resistance evolution, for example, by using judiciously chosen drug combinations³⁴ or by exploiting ecological interactions³⁵. However, we currently lack a general modelling framework to pre-empt resistance evolution and to optimize antimicrobial interventions.

Immunotherapy

A patient's immune system can be activated to treat diseases. Such therapies trigger an adaptive immune response against an antigen, based on the binding of immune receptors to antigenic epitopes. In an immune response against cancer, T cell receptors recognize so-called neoantigens, short peptides presented on the surface of cancerous cells that contain information on cancer-specific genome mutations³⁶. Thus, the primary objective of immunotherapy is to activate T cells with strong binding to a cancer neoantigen.

Collateral effects include autoimmune reactions caused by spurious binding to peptides presented by healthy cells³⁷. Additionally, tumours can develop resistance to immunotherapy by regulatory changes or escape evolution^{38–42}. The evolutionary feedback of cancers to immunotherapy includes immune editing^{39,43}, that is, the dynamics of cancer clones and their associated neoantigens changes towards reduced immune recognition (Fig. 1c). These dynamics are similar to the clade turnover of viral pathogens (discussed below). Recently, tumour–immune interactions have been combined into quantitative fitness models for cancer and used for computational prediction of neoantigens and their effects on cancer evolution^{38,43–45}. Such models can serve as a basis for the optimized selection of cancer vaccines^{40,46,47}.

Immunotherapy can also be used to treat autoimmune diseases by modulating the overall immune response in a host. Autoimmunity is caused by dysregulated inflammation against antigens from the host, so-called self-antigens. Targeted immunotherapy against autoimmune diseases selectively inhibits inflammatory signals but affects other immune functions only minimally. A successful control approach is to induce appropriate combinations of signalling molecules⁴⁸, while avoiding toxicity caused by high dosage of these molecules⁴⁹. Modulation of signalling molecules can also be used to establish robust immune responses in cancer immunotherapy, improving the efficacy of these treatments^{50,51}.

Vaccination

Active vaccines produce an adaptive immune response against a specific pathogen to reduce the risk of future infections and to mitigate their effects. This type of intervention combines multiple aspects of control: a human intervention triggers directed evolution in a biotic system, producing a control mechanism to combat the pathogen and to constrain its escape evolution. Vaccines against influenza or SARS-CoV-2 are raised against a circulating viral strain; they provide

protection against infection by that strain and by closely related strains. However, viral populations are often highly heterogeneous, and some strains are not covered by the vaccine. Subsequent escape evolution of the virus from existing population immunity further degrades vaccine cross-protection against future strains. Therefore, the selection of vaccine strains for influenza has a pre-emptive objective: to generate optimal protection against circulating strains in the next winter season. Antigenic fitness models have been developed in recent years to predict viral evolution and to compare the expected performance of candidate vaccines against future strains^{52–54}.

The evolutionary feedback of vaccination on viral evolution seems to be small for influenza⁵⁵. By contrast, recent work for SARS-CoV-2 suggests that vaccination can significantly contribute to immune selection, shaping global evolution⁵⁶. This is a prerequisite for using vaccination as evolutionary control, specifically to reduce the rate of escape evolution or to increase the collateral cost of escape for the virus.

Induced evolution of broadly neutralizing antibodies

Whereas antibodies generated by standard vaccines generate limited cross-protection against other strains, broadly neutralizing antibodies (bNAbs) bind to conserved protein regions and cover a diverse set of viruses. Vaccines that direct the immune system to evolve bNAbs can substantially improve the breadth and duration of protection against rapidly evolving viral pathogens. This topic has been extensively studied in HIV^{57–63} and influenza^{64–69}. Previous computational work shows that bNAbs against HIV may be induced by successive vaccination in a healthy individual^{70–72}. However, directing the immune system to evolve bNAbs against HIV has proved difficult. The main reason is that bNAbs require many mutations to acquire breadth, making their somatic evolutionary trajectories long and difficult to drive^{63,73–75}. Moreover, under any given antigen challenge, bNAbs compete with many available target-specific antibodies of higher affinity^{70–72,76,77}. For influenza, bNAbs targeting conserved regions of viral proteins have been elicited in animal systems^{64,66,68}. Broad neutralization has also been achieved by simultaneous application of multiple antigens⁶⁹. The immune interactions of conserved protein regions are often weak, but presentation on nanoparticles and repeated applications have improved the immune response to these vaccines^{65,67}. A population-level broadening of neutralization has also been observed against SARS-CoV-2, where repeat (booster) vaccinations are cross-protective against more viral variants than initial vaccinations^{78–82} and can even elicit bNAbs against the virus⁸³.

The evolutionary feedback of broadly protective vaccines is currently unknown. Broader protection can be argued to decrease escape evolution. On the other hand, larger vaccination coverage and long-lived vaccine-induced immunity in the human population can increase selection pressure for viral escape compared with current vaccinations.

Key concepts of evolutionary control

The examples above show a common structure of eco-evolutionary control problems: a control system defines a control objective and sets up a control mechanism to interact with an evolving target system, following a control protocol (Fig. 2). Such interactions couple the eco-evolutionary dynamics of both systems and generate multiple feedback loops. We now discuss these building blocks and their role in successful control of evolving systems.

Objectives and collateral effects

Directed evolution. A new biological feature in a target system can be elicited by a controlled evolution process. The control force is

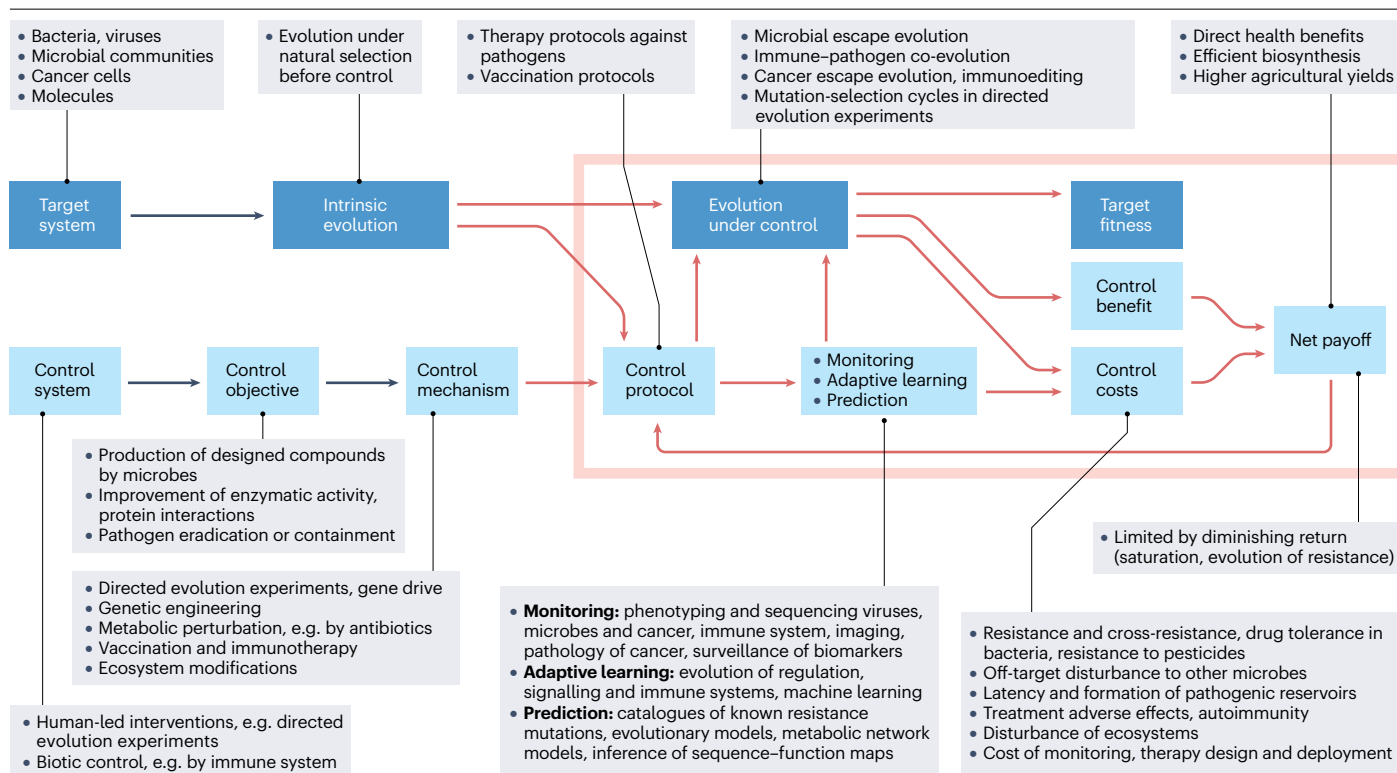


Fig. 2 | Concepts and key steps of evolutionary control. All instances of evolutionary control discussed involve a fast-evolving target system and a biotic or computational control system. The controller establishes a control objective and sets up a mechanism and protocol for control interaction with the target system. Control mechanisms include directed evolution experiments^{8–10,12,192–196}, gene drive²¹, genetic engineering^{197–199}, vaccination and immunotherapy^{4,40,46,200,201}, and metabolic perturbations, for example by antibiotics³³. The mechanisms of control determine the control protocols that can be realized, for example, in therapies^{158,202–206} and vaccination^{58,70–72,74,98,207–210}. Red frame and arrows highlight the key feedback loop of control and the underlying interactions. Control alters fitness and evolution of the target system towards the control objective; evolution under control includes microbial escape^{158,159,211,212}, tumour escape in cancer^{38,39,41,213}, immune–pathogen

co-evolution^{77,122,146,214} and mutation-selection cycles in directed evolution experiments^{9,12,13,189,215–221}. The controlled dynamics generates benefit and costs of control, which determine the net payoff for the controller. Control cost is system specific and includes the cost associated with the emergence of resistance^{213,222–227}, cross-resistance^{39,228,229} or tolerance^{230,231} in microbes targeted by a therapy (for example, antibiotics), off-target disturbance to other microbes in the same ecological environment^{232–236}, resistance to pesticides in agriculture^{237–242}, latency and formation of pathogenic reservoirs^{243–247}, treatment side effects^{248–250} and disturbance of ecosystems^{251,252}. Monitoring^{253–262}, adaptive learning^{176,177} and prediction of the target dynamics based, for example, on a catalogue of resistance mutations²⁶³, evolutionary models^{38,43,52,53}, metabolic models^{32,264–266} or statistical inference of sequence–function maps^{168,171,176,177,267,268} serve to evaluate the net payoff and to update and improve control protocols.

artificial selection superimposed onto the natural selection governing the unperturbed system. Directed evolution is often synergistic: control induces positive selection, increasing the controller's payoff as well as the absolute fitness, or growth rate, of the target system in the presence of control (Fig. 3a). In parallel, the controlled target system often deviates from its intrinsic fitness peak, which defines the evolutionary optimum under natural selection. This marks a key problem of control: the gain of target features is coupled to deleterious changes of other functions^{15,84} (Fig. 1b). In other words, control is likely to come with collateral effects on the target and the control system⁶. A ubiquitous source of collateral effects are co-varying secondary traits. An example is the directed evolution of PbrR, a multi-target transcription factor, to improve its affinity to a primary target. This process can reduce binding to other functional targets or induce spurious binding to off-target locations in the genome⁸⁵ (Fig. 3a). Collateral effects will often reduce the payoff for the controller, but they can also be neutral or reinforce the primary objective (Fig. 1b).

Hence, successful control requires navigating a multi-dimensional space, by monitoring and processing of multiple target interactions to optimize their combined payoff^{85,86}.

Pathogen escape control. In infection or cancer therapy, interventions are aimed at containing, weakening or eradicating the disease agent. In this case, the primary objective is antagonistic: the controller's payoff increase is coupled to a decline in absolute fitness and population size of the target system. Again, successful control navigates a complex space of primary and collateral effects, which requires a careful choice of the control objective^{87,88}. In pathogen control, a detrimental collateral effect is the evolution of resistant variants that escape control and carry a rebound of the pathogen population. In some cases, the target system can even hijack the control mechanism for its own benefit (as discussed below)⁸⁹. Escape evolution is common in antibiotic treatment, immune therapy and vaccination. Many successful protocols suppress or delay the rise of

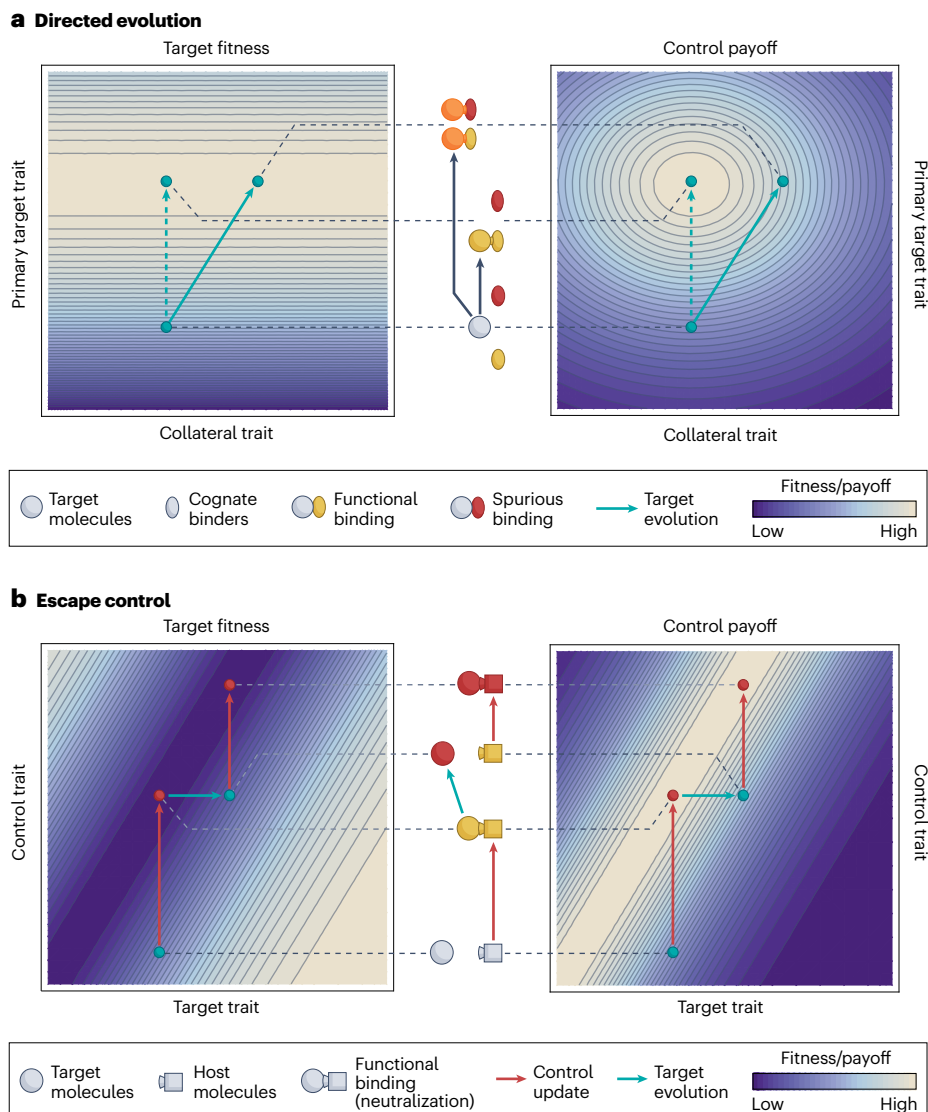


Fig. 3 | Directed evolution versus escape control. Control dynamics on target fitness (left) and control payoff landscapes (right) for two modes of evolutionary control. **a**, Directed evolution. Control is to elicit a primary trait of the target system, here molecular binding. The evolution of this trait is driven by a fitness increase of the target system, which goes along with a payoff increase for the control system (dashed arrows). The simultaneous evolution of collateral traits,

here spurious binding, can reduce the payoff gain (solid arrows). **b**, Escape control. Control is to suppress the target pathogen by neutralization, that is, functional binding to control molecules of the host system. Binding increases by updates of a control trait (red arrows) and decreases by escape evolution that affects a cognate pathogen trait (cyan arrows). Target fitness and control payoff evolve in opposite ways.

escape variants by reducing positive selection for escape (Fig. 3b). For example, evolutionarily informed adaptive cancer therapy⁹⁰, which aims to contain rather than eradicate the cancer cell population, has shown success in patients with prostate cancer by limiting escape evolution⁹¹. In other cases, a decline in absolute fitness of the target system can be achieved by inducing positive selection for a costly trait⁹². Escape evolution can also generate collateral effects in the target system that act to strengthen control. For example, immune escape mutations of the influenza virus are often coupled to a loss in protein fold stability, which reduces the available evolutionary paths and the speed of escape evolution^{93–95}.

The ecology of control

Primary and collateral interactions and their synergistic or antagonistic effects define what can be called the ecosystem of control and target systems (Fig. 2). As in any ecosystem, the strength of these interactions is modulated by feedback mechanisms in both components. Unlike in many ecological models, control interactions are not constants but can rapidly change by target evolution and control updates; we discuss these eco-evolutionary dynamics below. Control and target systems are often embedded in larger ecosystems, such as microbial communities. These ecological conditions can shape the efficacy of control. For example, the microenvironment of a cancer affects immunotherapy

by modulating the density of T cells available for neoantigen recognition in a specific tissue⁹⁶. In some cases, control protocols can exploit ecological complexity by steering the target system along environment-dependent fitness landscapes. An example is the directed evolution protocol discussed above, which bridges a fitness valley by switching environments³. Similarly, switching antigen environments may be a promising avenue to elicit bNAbs^{70–72,97–99}.

Mechanisms and leverage of control

How are control interactions realized in biological systems? The biotic and computational control mechanisms discussed here are ultimately based on molecular interactions, including specific binding and biochemical reactions of host and target molecules. Understanding control interactions at the molecular level is often a prerequisite for tuning them towards a specific system-level objective. A prominent example is antibiotics that bind to specific proteins in a bacterial target system, thereby interfering in its metabolism or regulation. Many biotic control mechanisms are based on molecular interactions as well. For example, bacteria living in communities have co-evolved a broad control weaponry, including phages and tailocins²⁴, as well as cognate response mechanisms. These interactions serve to control other microorganisms^{100–103} and to stabilize ecosystems against invasions¹⁰⁴. Immune interactions involve an array of molecular mechanisms, including antimicrobial peptides produced by the innate immune system^{31,105,106}, as well as T cells, B cells and antibodies of the adaptive immune system. These immune mechanisms have co-evolved with pathogens over millions of years, resulting in a biotic control machinery that can mount specific and effective responses against a multitude of infecting pathogens.

By modifying the balance of births and deaths, all of these mechanisms can alter selection in the target system. This is the most common form of evolutionary control. The selective force specified by a control protocol is often time dependent: control induces a fitness seascape for the target system (Fig. 4). Time-dependent selection can be tuned by real-time feedback from the growth of the target population^{10,13,15} (Fig. 1a,b). Similarly, spatial selection gradients induce effectively time-dependent selection on moving populations¹⁰⁷.

Besides selection, mechanisms that facilitate exploration of the trait space and the associated fitness landscape can be leveraged for control. In directed evolution, these mechanisms include changing the rate and types of mutations¹⁰⁸, as well as the population size of the target population. Control protocols for microbial communities can broadly manipulate species interactions, for example, through resource competition, species density manipulation or predation^{18,109}.

Regardless of the precise mechanism, successful control depends on sufficient leverage to change the target system's evolutionary trajectory. Limitations of control leverage observed ubiquitously across biology are a diminishing return and time-dependent degradation. For example, in control by molecular interactions, saturation of binding leads to a diminishing return per control molecule; thus, an intermediate level of control molecules often yields an optimal cost–benefit ratio¹¹⁰. Similarly, evolution of the target or the control system can curb control leverage over time. Both factors are present in the controlled microbial community discussed above¹⁸. First, the bacteria targeted by toxins can evolve resistance and overcome control. Second, in a microbial species performing autonomous control, the control mechanism of toxin production reduces growth, and adaptive evolution can lead to loss of this function.

These examples underscore that efficient control requires understanding the action pathway and the specific limitations of a given

control mechanism. As it stands, such knowledge is often incomplete. For instance, many cancer drugs undergoing clinical trials do not act via the mechanism that was originally proposed. Instead, the reported preclinical efficacy results from off-target toxicity as a mechanism of action¹¹¹. Off-target toxicity can lead to dangerous adverse effects and is a major cause of clinical trial failure^{112,113}.

Dynamics of control

The eco-evolutionary dynamics of control can be described as a sequence of actions by the control system, which mounts and updates control pressure, and responses to such pressure by the target system. The fastest response takes place at the physiological level, by gene regulation and metabolic changes. For example, bacteria rearrange their cell metabolism in response to antibiotic pressure³³. Control also changes the population dynamics of the target system, as well as the frequency of genetically or phenotypically distinct variants, thereby affecting its ecological interactions. Finally, de novo mutations lead to evolutionary adaptation of the target population. The speed of evolution depends on the strength of selection and on the mutational target generated by the control interaction. In rapidly evolving bacterial and viral systems, ecological and evolutionary changes are often linked and take place on overlapping timescales^{114,115}. A prominent example is the dynamics of the SARS-CoV-2 pandemic, where most of the recent epidemic waves coincided with genetic turnover, leading to the rise of new variants with partial escape from population immunity within time intervals of a few months. Successful control protocols have to be tuned to the speed of the target system. Thus, many of the systems discussed in this Review show tightly coupled target dynamics and control updates on a common timescale – a hallmark of eco-evolutionary control.

Information flow and modes of control

The control system continuously gathers information about the target system and processes that information into a control force acting on the target. This feedback loop is central to control dynamics (Fig. 2). We can distinguish different modes of information gain and processing. First, all evolutionary control protocols require repeated monitoring of the target system in its instantaneous state. This information is then processed into control updates, resulting in a fitness seascape for the target system (Fig. 4). In biotic systems, control updates based on monitoring can be realized by regulation or by co-evolution with the target system. For example, bacteria in communities ubiquitously update their ecological interactions based on monitoring of environmental parameters and of other species^{24,116}. The adaptive immune system in vertebrates has a copious reservoir of naïve immune cells that enable monitoring and primary responses to novel pathogens¹¹⁷. Importantly, control dynamics based on monitoring alone can act against the current state of the target system but cannot pre-empt its future evolutionary changes (Fig. 4a).

In a second mode, the control system can gain leverage by learning broad features of the target's evolutionary dynamics. Computational and biotic controllers can learn sufficiently simple and repeatable dynamical patterns by adaptive evolution of their control machinery – we refer to such processes as adaptive learning (Fig. 4b). For example, the human immune system reduces the prevalence of memory B cells with high-affinity receptors by negative feedback regulation, introducing a bias towards moderate-affinity, more cross-reactive memory^{118,119}. As shown by recent theoretical work, this bias can reflect a response of the immune system to the speed of evolution of typical antigens^{120–124}. A high-affinity and highly specific memory repertoire is optimal against

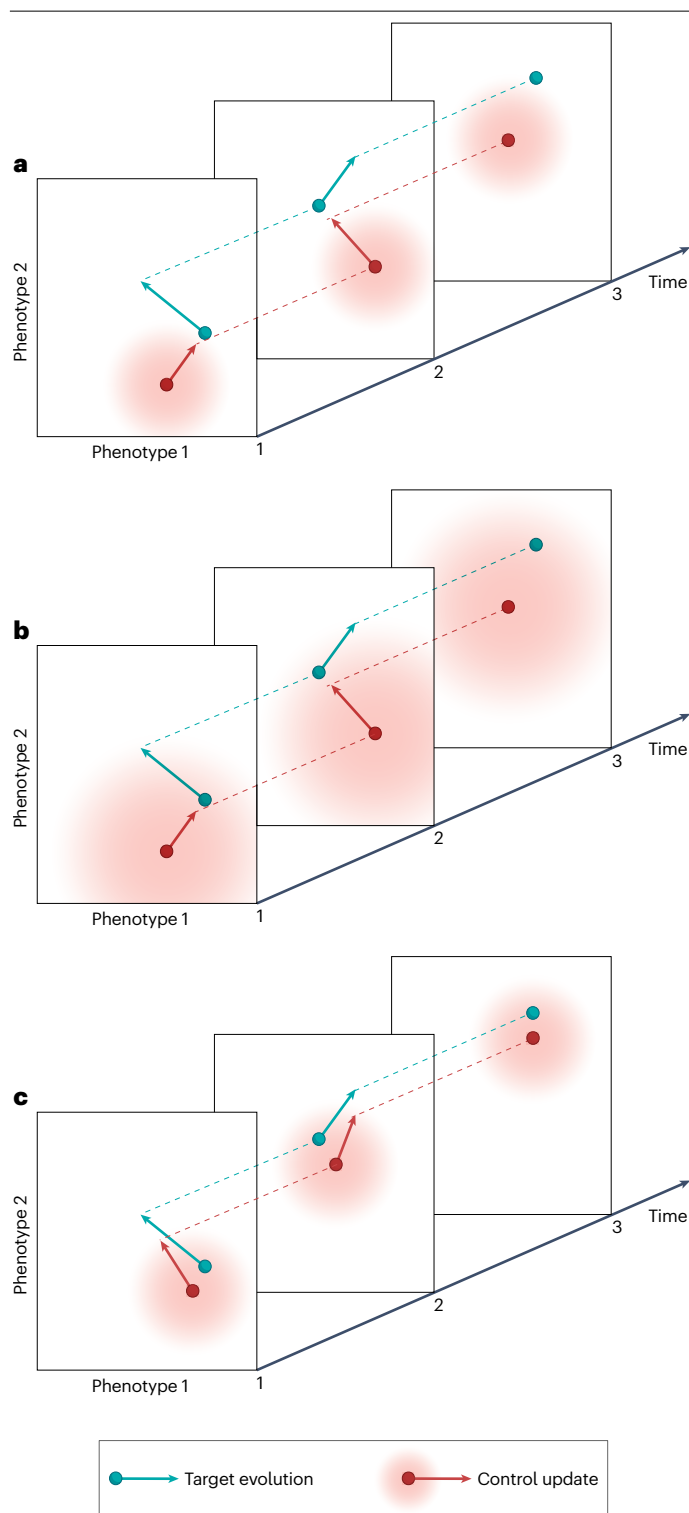


Fig. 4 | Monitoring, adaptive learning and prediction shape control protocols. In the control of a pathogen, control is a moving fitness trough for the target population (red, darker shading indicates lower fitness). Control partially suppresses growth in the target system and induces escape evolution away from the fitness trough (cyan arrows). In response, the control seascape is updated (red arrows); control updated at time t acts on the target system in the next time interval $(t, t + 1)$. The update dynamics of control protocols are shown for a given evolutionary trajectory of the pathogen in three different control modes. **a**, Control based on monitoring. Protocols are informed only by monitoring of past and present states and lag behind the evolution of the target system. **b**, Control based on adaptive learning. Protocols can adapt to broad dynamical features of target evolution (here, the breadth of the fitness trough is tuned to the speed of target evolution). **c**, Computational control leverages short-term predictions of target evolutionary trajectories to generate pre-emptive protocols.

cross-protective over periods of 3–5 years, curbing the number and burden of infections over a human's lifetime.

Human controllers can employ a third, rational control mode based on computational prediction of specific evolutionary trajectories in the target system^{38,43–45,52–54}. This method processes not only broad features of the target dynamics but also real-time information about the target trajectory up to the starting point of predictions (Fig. 4c). In some systems and over limited periods, predictions capture a priori unlikely trajectories and previously unseen mutations³², provided the underlying evolutionary rules are sufficiently simple to be learned from the available training data. Most importantly, control protocols based on computational predictions can factor in the evolutionary response of the target system to the control pressure⁵⁶ – we refer to this mode as pre-emptive control. Mathematical definitions of predictive information and pre-emptive control are given in Box 1. In the following sections, we describe how to construct such protocols.

Towards quantitative control of evolving systems

As the discussion so far shows, eco-evolutionary control contains the full complexity of living systems, including regulation, metabolism, ecology and evolution. This challenge is epitomized by the collateral effects of control, which can couple the target trait to a vast number of a priori unrelated biological functions. Biological insight is required to compress this complexity into a manageable set of key phenotypes, mechanisms and dynamical modes relevant for the problem at hand. Quantitative control can then build on high-throughput evolutionary monitoring of target systems and on computational models for the control dynamics. Such models establish a quantitative cost–benefit tally of control, which serves two main purposes. First, it allows a judicious decision on when to apply control: a given protocol should be used only when its benefit exceeds its cost. Second, computation can rapidly screen large numbers of alternative control protocols and filter out candidates for in-depth comparison. In particular, control models rationalize how the information gathered by monitoring, adaptive learning and predictions shape control protocols (Fig. 5 and Box 1). These are key elements of a developing eco-evolutionary control theory that will provide overarching principles for a diverse set of applications.

We now give a perspective on modelling and data input that will become important for the control of complex evolutionary systems.

Biological interactions of control

Cell metabolism. Successful control often relies on a quantitative understanding of metabolic processes, including their response to

slowly evolving antigens, where a subsequent infection is likely to involve a strain similar to the primary infection. By contrast, a more diverse and cross-reactive repertoire can protect against a secondary infection by an evolved strain at some evolutionary distance from the primary strain. For example, our B cell defence against influenza is

Box 1

Optimizing control by monitoring, learning and predictions

Here we describe the dynamics of information gathering by the controller and the resulting optimization of protocols in a minimal model for the control of escape evolution (Fig. 4). The maximum-impact protocol x_{\max} closely follows a moving target y , which requires full, posterior knowledge of its stochastic evolutionary path in the presence of the control force. In any practical application, the best available (forward) protocol x^* follows a projection of the target path informed only by data from the past (Fig. 5). To compare and optimize forward protocols, we use a payoff function $\Psi(t) = \psi_{\max}(t) - \Delta\Psi(t) - C$, where $\psi_{\max}(t) = \Psi(x_{\max}(t))$ is the direct benefit at the maximum-impact point, $\Delta\Psi(t) = c(x^*(t) - x_{\max}(t))^2$ is the payoff cost generated by the mismatch $x^*(t) - x_{\max}(t)$ and C is the sum of control costs.

Monitoring

Measurements provide information about the instantaneous state of the target. In between measurements, x^* deviates from x_{\max} , reflecting the increase of uncertainty on the target's evolutionary path (cones in Fig. 5). In the minimal model, the time-dependent mismatch $x^*(t) - x_{\max}(t)$ follows a random walk with diffusion constant D_0 . Each control update by measurement resets the mismatch to a small value determined by the measurement error and generates a measurement cost C_m , caused by the physiological process of signal processing. Over a time interval $(t, t + \tau)$ between consecutive updates, the optimal monitoring-based forward protocol maintains the action coordinate $x_{\max}(t)$ set by the last measurement (Fig. 5a). This produces an expected average payoff $\psi^* = \psi_{\max} - \Delta\psi - c_m - c_0$ with mismatch cost $\Delta\psi = cD_0\tau/2$, a measurement cost $c_m = C_m/\tau$, and other costs c_0 . More frequent updates reduce the mismatch but increase the measurement cost per unit of time⁶ (Fig. 5a,b). Hence, there is an optimal time interval between updates, $\tau^* = [2C_m/(cD_0)]^{1/2}$. We can express the information gain, or loss of uncertainty, by measurements as a Kullback–Leibler divergence (D_{KL}):

$$I_m(t, t + \tau) = D_{KL}(\hat{Q}_{t,t+\tau}, |, Q_{t,t+\tau}^0).$$

Here $Q_{t,t+\tau}^0$ is the prior distribution generated by the diffusion of the target's evolutionary path up to time $t + \tau$, following a measurement at time t , and $\hat{Q}_{t,t+\tau}$ is the posterior distribution of paths after the measurement at time $t + \tau$. The Kullback–Leibler divergence between these probability distributions indicates how likely random draws from the prior distribution look as if drawn from the posterior distribution; this probability decreases exponentially with increasing D_{KL} . Intuitively, I_m counts the (inverse, log) fraction of paths in the uncertainty cone that are compatible with the next measurement (Fig. 5a).

Adaptive learning

Long-term evolution of the control machinery can increase its efficacy. For example, a larger control range increases the payoff and

reduces the target fitness at a given mismatch $x^* - x_{\max}$. This reduces the mismatch cost (c decreases) and can slow down target evolution (D_0 decreases). Hence, adaptive learning increases the net payoff gain of monitoring-based protocols, but the more complex control machinery generates an additional control cost (Fig. 5c).

Evolutionary predictions

Computational predictions use dynamical rules inferred from past data to reduce the uncertainty about future path segments²⁶⁹. Here we define the predictive information⁷⁵² of evolutionary models as a difference between Kullback–Leibler divergences:

$$I_p(t, t + \tau) = D_{KL}(\hat{Q}_{t,t+\tau}, |, Q_{t,t+\tau}^0) - D_{KL}(\hat{Q}_{t,t+\tau}, |, Q_{t,t+\tau}^p),$$

where $Q_{t,t+\tau}^p$ is the predicted distribution of the target evolutionary path up to time $t + \tau$ based on data up to time t . Intuitively, I_p counts the density of paths compatible with the next measurement in the prediction-informed uncertainty cone (Fig. 5d), relative to the corresponding density in the naïve cone (Fig. 5a). The information measures I_m and I_p show the complementary roles of monitoring and computational predictions: measurements constrain the starting point of future evolutionary paths at time t , and predictions explain a part of the evolutionary change from t to $t + \tau$. The power of predictions is limited by incomplete knowledge of the past and by the intrinsic stochasticity of the future dynamics.

Pre-emptive control protocols, by definition, generate predictive information ($I_p > 0$) and harvest it to increase payoff. In the minimal model, pre-emptive control results in a reduced diffusion constant of the control path, $D < D_0$ for time intervals of order τ_p after each update (Fig. 5d). This timescale, called the prediction horizon, determines the added value of prediction for computational control⁶⁷. Given limited measurement information ($\tau_p < \tau$), successful pre-emptive protocols follow the predicted path after each update and are phased out to a constant action coordinate after a characteristic time τ_c (Fig. 5d). This crossover sets the pre-emptive control horizon, the period for which we bank on computational predictions for control. In protocols with $\tau_c < \tau_p$, the control path undershoots the prediction horizon (at a time Δt after the last update, its mismatch cost increases with diffusion constant D for $\Delta t < \tau_c$ and with D_0 for $\Delta t > \tau_c$). Conversely, in protocols with $\tau_c > \tau_p$, the path overshoots into a wrong direction (the cost increases with diffusion constant D for $\Delta t < \tau_p$ and with $D' > D_0$ for $\Delta t > \tau_p$). This suggests a general relationship: pre-emptive control becomes optimal if the control horizon matches the prediction horizon ($\tau_c \approx \tau_p$). That is, pre-emptive control is effective for as long as the target evolution can be successfully predicted⁶. Beyond this scale, control relies again on monitoring. Notably, control itself can generate or reduce predictive information, for example, by restricting the accessible trajectories or by accelerating escape evolution.

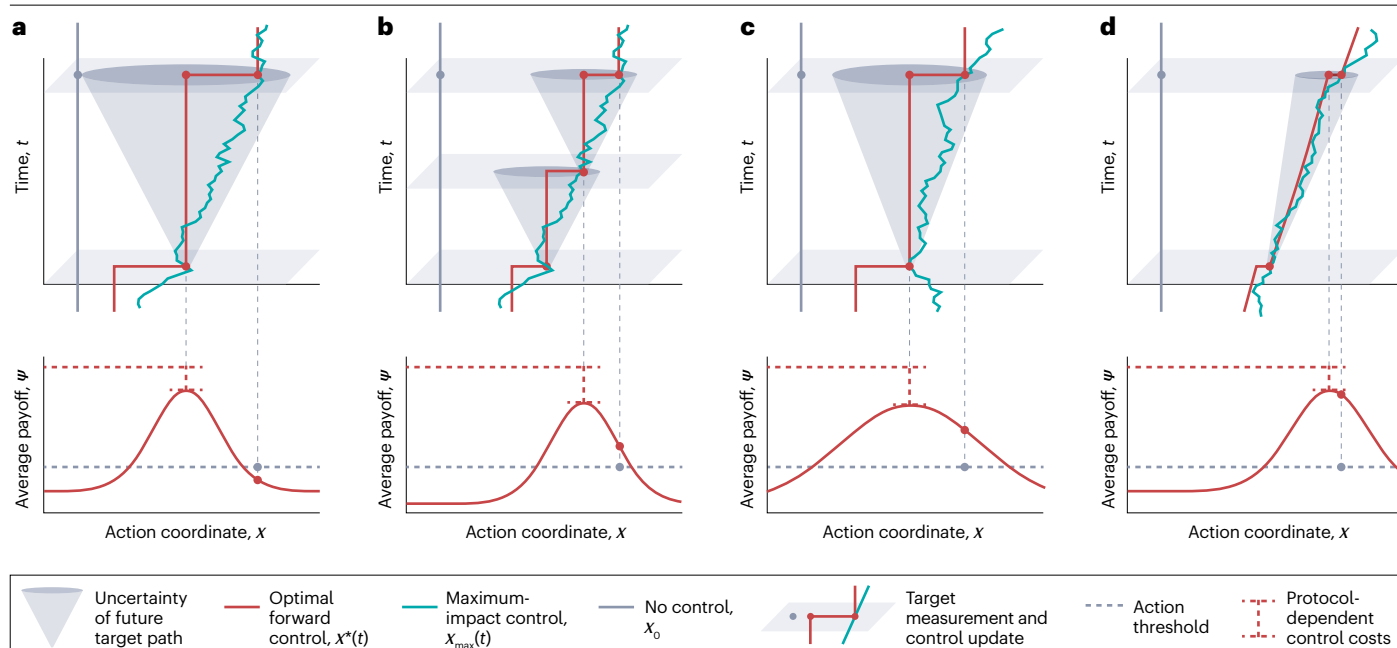


Fig. 5 | Computing and optimizing control. Upper panels: optimal control protocols available for different modes of information processing, $x^*(t)$ (red lines), compared with the maximum-impact protocol, $x_{\max}(t)$ (cyan lines), and the no-control protocol, x_0 (grey lines). Each protocol is characterized by a time-dependent action coordinate embedded in a high-dimensional space of a priori possible protocols (this space is indicated by planes). For control of escape evolution, the maximum-impact protocol closely follows the evolutionary trajectory of the target system (cf. Fig. 4). In all forward protocols $x^*(t)$, the action coordinate is periodically updated to the instantaneous maximum-impact point, which is inferred by monitoring the target system (updating times are marked by planes). In between updates, uncertainty about the target's future trajectory generates a mismatch $x^*(t) - x_{\max}(t)$ (expected uncertainty range indicated by cones). Lower panels: average payoff of conditionally optimal protocols, ψ^* (red lines), and of the no-control protocol, ψ_0 (grey lines), depending on the

maximum-impact action coordinate x_{\max} at the end of the displayed time interval (top planes). These payoffs include a mismatch cost, as well as costs for monitoring and mounting control (red dashed lines), that differ between control modes (see Box 1 for a minimal payoff model). **a, b**, Monitoring-based control. The action coordinate of each update is maintained for the subsequent time interval. A large mismatch cost can reduce the payoff below the action threshold (grey dashed line), that is, below the payoff of the no-control protocol (panel **a**). More frequent measurements of the target system reduce the mismatch, albeit at an additional monitoring cost (panel **b**). **c**, Adaptive learning. Here, adaptive increase of the control range reduces the mismatch cost and slows down target evolution (indicated by a narrower uncertainty cone), but generates an additional cost of the control machinery. **d**, Pre-emptive control. Using computational prediction of target evolutionary paths reduces the mismatch over limited periods (indicated by a tilted, narrower cone).

control pressure. Coarse-grained data on metabolic pathways and rates can be used to quantify the metabolic fluxes inside a cell¹²⁵. Metabolic models relate external parameters, including concentrations of nutrients and growth-limiting factors, to intracellular resource allocation and growth^{126,127}, providing a computable link between environment and eco-evolutionary dynamics. Recent models include explicit biochemical enzyme–substrate relationships¹²⁸. Metabolic models have been used to compute growth inhibition under antibiotic stress³³, to predict antibiotic resistance mutations³² and to design control protocols for adaptive evolution³. More broadly, such models can serve to rationalize metabolic shifts in target systems and biotic hosts under control and to compute the resulting fitness and payoff effects. These dynamics can be monitored by proteomics, metabolomics and fitness assays.

Ecological interactions. Developing a quantitative understanding of ecological feedback on control is important for successful strategies in complex environments. Abundance changes and emergent properties in multi-species communities can, in principle, be computed from basic reproductive rates of individual species and cross-species interaction parameters. In the context of control, ecological models can show how

pressure on a target species propagates through an ecosystem and generates collateral effects on the other species. Recent work has started to link ecological interactions to the metabolism of the constituent species¹²⁹ and to explore the implications for intra-species evolution^{104,130}. Such integrative models may have the power to capture the complex interactions of cancers and their microenvironment and of intracellular host–pathogen systems. For example, human cells remodel their mitochondria in response to pathogens, whereas the intracellular pathogen *Toxoplasma gondii* can hijack this metabolic shift for its own growth⁸⁹. Models of multi-species communities contain a large number of parameters. This challenge can be addressed by combining scalable high-throughput experimentation and computation¹³¹ and by choosing an appropriate level of modelling, for example, generalized Lotka–Volterra or resource–consumer dynamics¹³². Clearly, the optimal model choice depends on which parameters can be measured; for example, nutrient levels and uptake rates are the key input for resource–consumer models.

Immune interactions. Human immunity is a stunningly complex defence system, where biotic and planned control of pathogens play in concert. In recent years, the quantitative understanding of immune

systems has increased rapidly. Massively parallel sequencing of immune repertoires, combined with model-based analysis, has revealed patterns of global organization^{133,134} and molecular codes of antigen–receptor interactions^{135–143}. In parallel, statistical models have characterized how evolutionarily optimized repertoires should be organized^{144,145}, respond to pathogens¹⁴⁶ and store memory of past responses for cross-protection against re-infections by similar antigens^{120,122–124}. These advances will likely contribute to better vaccines and immunotherapies. Currently, however, it is still difficult to predict an individual's immune response to a given pathogen. Another challenge is to predict how the combined adaptive immunity of the human population constrains the evolution of globally circulating pathogens, such as influenza and Sars-CoV-2. Progress on these questions is paramount for the central goal of evolutionary control in biomedicine: to devise pre-emptive interventions that factor in and curb the future escape evolution of the pathogen.

Fitness and payoff components

Metabolic, ecological and immune models are examples of system interaction models that provide a key input of control: to quantify the relevant benefit and cost components for the target system and the control system (Fig. 2). The fitness of the target system under control includes the direct effect of control caused by the interaction with the control system, as well as intrinsic fitness costs of defence traits or escape from control. In many cases, such fitness functions contain a trade-off: systems that maximize fitness under control are suboptimal in the absence of control, and vice versa^{147,148}. The net payoff for the controller is the direct benefit of control, which is generated by the intended impact on the target system, discounted by the control costs. As shown by the preceding examples, evolutionary control often has a diminishing return of benefit relative to the control effort. This is for two main reasons: the saturation of control leverage (for example, through binding interaction), and resistance or escape evolution of the target population. Importantly, escape evolution introduces a decline of benefit over time, which has to be included appropriately into the payoff tally (Box 1).

Direct costs of mounting control include external resources, establishment and maintenance of a control repertoire (for example, the immune system), and protocol-dependent costs (for example, the immune response to a specific pathogen). Other costs arise from adverse interactions with the target system, such as collateral binding and off-target toxicity (Fig. 3) or the reduction of diversity in a microbial community¹⁴⁹. These cost factors, in particular collateral costs, arise from quite heterogeneous sources and may be difficult to quantify and compare in a given application. Nevertheless, plausible forms of all relevant cost terms should be included into the fitness and payoff tally, to test robustness and assess risks of control under variation of the corresponding model coefficients.

By accounting for cost and benefit factors, we can evaluate the total payoff for a given control protocol, ψ . Maximizing the total payoff defines the optimal protocol in a set of available protocols. In most cases, the optimal protocol differs substantially from the maximum-impact protocol, which maximizes only the direct benefit of control. Moreover, the payoff maximum, ψ^* , is often difficult to attain; realistic protocols have stochastically distributed payoffs $\psi < \psi^*$. We can also compare protocols with the payoff in the absence of control, ψ_0 . This sets an action threshold: control should be applied only if $\psi > \psi_0$.

Modelling control dynamics

Fitness and payoff terms enter the coupled dynamics of the controlled and the control systems. We can describe the control protocol by a

time-dependent action coordinate, $x(t)$, which maps the actual control in a high-dimensional space of possible protocols. Similarly, the target system is described by a time-dependent state variable, $y(t)$, which contains all traits that are affected by control and contribute to fitness. Recording these host and target variables over the entire period of control defines a specific control path (x, y) (Fig. 4).

As described above, biotic systems update action coordinates and target variables by regulation or evolution. In the simplest case of a so-called greedy control dynamics, sequential updates of $x(t)$ and $y(t)$ follow the uphill gradient of the instantaneous payoff and fitness function, $\Psi(x(t), y(t))$ and $F(x(t), y(t))$, respectively. The structure of the fitness seascape and the supply of fitness-changing mutations determine the target's evolutionary dynamics and, hence, the outcome of control. In the case of directed evolution, successful control requires sufficient mutational supply and a navigable fitness seascape, where evolution along adaptive paths can generate new target features over realistic control periods. Mutational bottlenecks and intermediate fitness valleys, which are a characteristic of rugged fitness landscapes^{150–152}, slow down directed evolution and compromise the control objective. Escape control often works against a large number of potential escape mutations, because the loss of molecular binding interactions is favoured by entropy^{153–155}. However, co-varying traits can introduce intermediate fitness valleys and restrict the number of escape paths^{93–95}; building such constraints by control selection can be a viable strategy for escape control^{5,6}.

Mathematically, the evolutionarily stable fixed points of deterministic gradient dynamics in a time-independent landscape are Nash equilibria, which express a classic link between evolution and game theory¹⁵⁶. With additional stochastic terms generated by system-specific noise, this type of dynamics captures many cases of Darwinian evolution, as well as regulatory mechanisms evolved to maintain high fitness under recurrent stress. By contrast, computational protocols follow a long-term objective, for example, to maximize the average payoff over the entire control period. Importantly, the fixed points of computational protocols can be at higher payoff than Nash equilibria, by giving up short-term gain for long-term optimization^{5,157}. This mathematical framework quantifies a frequent characteristic of biomedical interventions: a drop in short-term payoff to ensure long-term success.

Learning and prediction

Pre-emptive control is based on predicting the evolution of the target system from fitness and payoff models and dynamical rules for the resulting evolutionary change. Specifically, fitness models informed by host–pathogen interaction data can be fed into population-genetic evolution equations to forecast specific evolutionary trajectories of pathogen populations over limited periods into the future. This approach has been applied successfully to the global evolution of influenza^{52–54} (with a prediction horizon of about 1 year⁷) and to the clonal evolution of cancer^{38,41,43}. Similar methods can predict the escape evolution of HIV from bNAbs^{158,159} and inform the design of combination therapies¹⁵⁸. Importantly, predictions for globally circulating pathogens depend on a worldwide concerted surveillance of genomic and antigenic evolution^{53,56}. Moreover, deep mutational scanning^{160–164} and laboratory evolution experiments with bar-coded strains^{165,166} can replay, and to some degree pre-play, evolutionary trajectories under controlled conditions. This may enable mechanistic fitness models to tackle a major challenge: to predict likely future mutations not yet seen in the wild.

Glossary

Action threshold

A boundary between parameter regimes of control protocols with higher/lower payoff than in the absence of control.

Adaptive evolution

The accumulation of heritable genetic changes that increase fitness in a given environment.

Adaptive learning

Evolutionary processes where the increase of information is coupled to a fitness benefit.

Artificial selection

Fitness effects in a target population induced by human intervention (in contrast to natural selection).

Co-evolution

The coupled evolution of two or more species interacting by natural selection, biological interactions and dependencies.

Directed evolution experiments

Laboratory protocols where organisms or biomolecules with desired traits are generated and amplified through iterative rounds of mutation and selection.

Eco-evolutionary dynamics

The coupled dynamics of population sizes, genetic changes and interactions between multiple species in an ecosystem.

Fitness seascape

A moving fitness landscape, generating selective forces that explicitly depend on time.

Greedy control

Algorithms with update rules that increase the instantaneous payoff.

Immunotherapy

The prevention or treatment of disease with substances that invoke immune responses.

Microbial communities

Multiple species of microorganisms that live together in a shared environment and interact with each other.

Molecular traits

Components of the molecular machinery of the cell relevant for a specific function. Examples include gene expression levels, binding affinities and activities of enzymes.

Nash equilibria

States of a game where no player can increase their payoff by unilaterally changing their strategy.

Prediction horizon

The timescale over which a computational model provides significant information about future evolutionary trajectories.

Pre-emptive control

Algorithms with update rules that increase payoff over future time periods.

Selecting control protocols

Successful predictions serve to rank the available control protocols by specific criteria, for example, maximizing the total expected payoff or the expected speed of target evolution. Importantly, this step requires probabilistic models that describe not only the observed target dynamics but also its likely perturbations under different control protocols to be compared. For example, predictive immune interaction models of viral evolution can directly integrate the effect of vaccinations on the subsequent dynamics⁵⁶.

The computation of optimal protocols can build on sophisticated mathematical methods developed in the engineering and physical sciences¹⁷⁹, as well as in finance^{180,181}. As in evolutionary control, the controller biases the stochastic process of a target system by applying a control force. Stochastic control theory provides powerful dynamic programming¹⁸² and path-integral techniques¹⁸³ to compute the time-dependent value of the control force that maximizes the future payoff for the controller. These methods have proven valuable for the solution of eco-evolutionary control problems in cases where a known model describes the underlying dynamics^{5,6,184,185}. However, multiple salient features of biological systems are beyond the focus of established control theory. These include strongly non-linear fitness and (diminishing return) payoff functions, limited information gathering and forecasting capabilities, and high-dimensional spaces of evolutionary and control force trajectories^{5,6}. Hence, the broader application to complex eco-evolutionary systems calls for major innovations in control theory.

Ethics of control

Eco-evolutionary control introduces genetic changes in pathogen systems outside laboratory environments, whether or not the evolution of the target system is the primary objective or a collateral effect of control. Development and application of control require stringent oversight by independent review panels following common ethical guidelines, in accordance with standard practice in the life sciences and medicine¹⁸⁶. This should ensure a transparent analysis of benefits, costs and risks for affected individuals, for communities and ecosystems, and at the global scale. Two broad classes of issues can arise in the application of control. First, self-replicating re-engineered cells may cause harm if they escape or overwhelm their intended environment¹⁸⁷. Similar issues arise in synthetic biology, where a bioethics framework already exists (for example, for the approval of novel gene therapies¹⁸⁸). When gene drive is used as a control mechanism, the drive machinery and driven traits can spread to populations beyond the target population or even to off-target species. Several safeguard systems have been engineered, including metabolic dependence on non-standard amino acids in synthetic cells¹⁸⁹ and kill switches¹⁹⁰. Second, ethical considerations arise in public health policies of control. For example, in the case of malaria or bacterial infections, pathogen-targeting drugs beneficial for an infected individual may have detrimental long-term effects at the population level, such as the emergence of resistance¹⁹¹. Hence, setting an appropriate objective for sustained control is challenging. Both kinds of issues call for cross-disciplinary studies in collaboration with bioethicists. Quantitative modelling, including an assessment of evolutionary predictability, can play an important role in pre-playing evolutionary scenarios of control.

Conclusions

In this Review, we have outlined the key concepts of eco-evolutionary control and discussed several important applications ranging from biotechnology to infection therapy. In this framework, control objectives,

As an alternative to mechanistic models, machine learning and artificial intelligence algorithms can learn evolutionary rules and inform control protocols. Recent work used machine learning-based selection of features to predict the success of emerging mutants¹⁶⁷. Artificial intelligence algorithms have been developed to infer sequence-to-function or structure-to-function maps for proteins^{168–173} and regulatory sequences¹⁷⁴, which can enter fitness models for evolution. Similar methods have been developed for evolutionary control of microbial co-cultures in bioreactors¹⁷⁵ and for directed evolution experiments^{176,177}. Specifically, artificial intelligence-trained genotype-phenotype maps from prior rounds of the experiment can improve the next selection cycle. Combining artificial intelligence techniques with emerging symbolic regression methods can guide the interpretation of the results and serve as a basis for follow-up mechanistic modelling¹⁷⁸.

mechanisms and leverages as well as the dynamics of target and control systems are intimately coupled (Fig. 2). All these determinants inform a calculus of eco-evolutionary control based on a quantitative cost–benefit tally. This provides an action threshold to decide whether control should be undertaken and allows systematic optimization of strategies and protocols.

In summary, evolutionary control approaches have shown remarkable success in numerous systems to date. At the same time, broader applications of evolutionary control face experimental challenges in monitoring target systems and delivering targeted control interactions, as well as theoretical questions of learning, prediction and optimization of control. Together, this field holds the promise of successful eco-evolutionary control interventions, guided by common principles, in multiple biomedicine and bioengineering systems.

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Competing interests

The authors declare no competing interests.

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