Towards evolutionary predictions: current promises and challenges

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Abstract

Evolution has traditionally been a historical and descriptive science and predicting future evolutionary processes has long been considered impossible. However, evolutionary predictions are increasingly being developed and used in medicine, agriculture, biotechnology and conservation biology. Evolutionary predictions may be used for different purposes, such as to prepare for the future, to try and change the course of evolution or to determine how well we understand evolutionary processes. Similarly, the exact aspect of the evolved population that we want to predict may also differ, for example we could try to predict which genotype will dominate, the fitness of the population, or the extinction probability of a population. In addition, there are many uses of evolutionary predictions that may not always be recognized as such. The main goal of this review is to increase awareness of methods and data that are used to make these predictions in different research fields by showing the breadth of situations in which evolutionary predictions are made. We describe how diverse evolutionary predictions share a common structure described by the predictive scope, time scale and precision. Then, by using examples ranging from SARS-CoV2 and influenza to CRISPR-based gene drives and sustainable product formation in biotechnology, we discuss the methods for predicting evolution, the factors that affect predictability, and how predictions can be used to prevent evolution in undesirable directions or to promote beneficial evolution (i.e. evolutionary control). We hope that this review will stimulate collaboration between fields by creating a common language for evolutionary predictions.

Keywords
Evolution, prediction, models, population genetics, disease modelling, evolutionary control, predictability

1. Introduction

Important questions for battling diseases, improving biotechnology and protecting biodiversity include the following: “Which pathogen strains will be most prevalent a month from now?”, “When and where will pathogenic mutants that escape vaccine-conferred immunity arise?”, “Which patient will be cured of cancer and which patient will see the tumour come back, but now resistant to chemotherapy?”, “Can we use gene drive systems to get rid of (vectors for) dangerous diseases or will they evolve resistance to the gene drive?”, “How fast will a strain engineered for ethanol production evolve and lose its efficiency during prolonged fermentation?” and “Which endangered species will go extinct and which will adapt successfully to their changing environment?”.

Answering these questions requires the ability to **predict the future course of evolution**. In addition, some of these situations would have us trying to **influence** the course of evolution. While some fields have been working for many years on predicting and influencing evolution, for other fields this is a new endeavour. We argue that predicting and trying to influence evolution is more common than one may think, but it is not always easy to recognize because the jargon used in different fields is varied. The main goal of this review is to show the breadth of situations in which evolutionary predictions are being made. In addition, we aim to provide a common language to improve information transfer between research communities. We discuss the study of predictability of evolution, we describe different methods for evolutionary forecasting and we discuss situations where the goal is to influence evolution (evolutionary control).

Note that throughout this paper, we focus on predictions of how populations will evolve, that is how the genetic and phenotypic makeup of populations will be different in the future (Nosil *et al.* 2020), rather than predictions about the evolution of new species, or predictions about the past. We thus generally take a more applied approach to predicting evolution compared to some of the existing literature (Gould 1990, Conway Morris 2003)**.**

The scientific basis of evolutionary predictions

What is the basis upon which we can make sound predictions about evolution? Evolving populations are complex dynamical systems and one has to take into account different forces (e.g., directional selection), including stochastic effects (mutation, environment) and non-linear dynamics (e.g., due to eco-evolutionary feedback loops). Evolutionary predictions are often based on Darwin’s theory of evolution by natural selection which states that if populations of entities manifest heritable variance in fitness, then these populations will adapt to their environment. For example, we can predict that if we treat bacteria with antibiotics, and if these bacteria harbour (or acquire) genetic variation for antibiotic susceptibility then the bacterial population will adapt to that challenge and become resistant. We can also recreate this scenario as an experiment in the lab and see whether our prediction holds true.

In addition to the basics of Darwin’s theory, there are many extensions that make this theory more precise and quantitative. For example, our understanding of the polygenic nature of

quantitative traits has aided in developing tools such as the “breeder’s equation” and “genomic selection”, facilitating selective breeding strategies in order to deliver particular (predicted) outcomes in animal husbandry and agriculture (Cooper *et al.* 2014, Masuka *et al.* 2017). For other situations we need more extensive population genetic models to include forces that can distort the expected impact of selection, such as random genetic drift, migration, recombination, and mutation, and the stochasticity associated with these forces.

An additional complicating factor is that populations impact their environment. In many situations, we therefore have to consider both evolutionary and ecological dynamics and these can feedback onto each other (eco-evolutionary feedback loops). For example, the fate of endangered species may critically rely on the abundance of pollinators, predators, and prey and other members of their ecological community, while these populations are in turn affected by the endangered species in question (Govaert *et al.* 2019).

Predicting evolution has long been considered challenging, or even impossible. Fundamental difficulties of predicting evolution include the inherent stochasticity of mutation, reproduction and environment, and the unknowns of the genotype-phenotype and phenotype-fitness maps which, together, determine the fitness landscape (Wright 1932, de Visser & Krug 2014, Fragata *et al.* 2019). In addition, eco-evolutionary feedback loops make long-term predictions challenging. These aspects of evolving populations will limit accuracy, and predictions will therefore always be probabilistic and provisional, especially for predictions further into the future. Thus, short-term and microevolutionary predictions may be most achievable (Lässig *et al.* 2017).

Why predict evolution?

There are different reasons why we are interested in predicting evolution, which we have organised in three main categories (Fig. 1). In the first category, although not the focus of this paper, are predictions that are used for experimental systems to develop fundamental knowledge on evolving systems and to test assumptions of models that are used to predict future evolution (Fig 1A). Most work in experimental evolution falls in this category. These experiments can focus on the speed of adaptation, the distribution of fitness effects of new and existing mutations, repeatability of evolutionary outcomes and causes of such repeatability. Several studies using experimental evolution with *E. coli* have revealed general rules of microbial adaptation. For instance, (i) fitness improvement is faster in maladapted genotypes (Couce & Tenaillon 2015), (ii) the beneficial mutation supply is large, such that often multiple beneficial mutations coexist and compete in a population (Lang *et al.* 2013), (iii) in most environments mutations with large fitness benefits are only found in a few genes (Tenaillon *et al.* 2012, Lind *et al.* 2017), which leads to high evolutionary convergence at the gene level, (iv) mutations with large fitness benefits typically occur at a low rate (Schenk *et al.* 2022), and (v) a change in mutation rate can easily be selected for in the course of adaptation (Sniegowski *et al.* 1997). These observations, while made mostly *in vitro*, were recovered in (experiments in) more natural conditions such as the mammalian gut (Barroso-Batista *et al.* 2014, Lescat *et al.* 2017, Zhao *et al.* 2019). Experiments to test fundamental knowledge and assumptions force us to

define the necessary information to predict evolution and determine reasons for failure, and they allow us to test the limits of the generality of predictions.

A second reason for making evolutionary predictions is to be prepared for the future. A key example here is seasonal influenza (Fig 1B). In the spring of any year, vaccines are produced for the next fall (for the Northern hemisphere). To make sure the vaccine is as effective as possible, it is necessary to predict which strains will be most common in the next influenza season.

A third reason to predict the course of evolution is to choose actions that influence the direction or speed of evolution – also referred to as evolutionary control (Fig 1C). Evolutionary control is the alteration of an evolutionary process with a specific purpose. Control can either suppress evolution, e.g., prevent pathogens evolving drug resistance, or facilitate evolution, e.g., increase the ecological range of a species to avoid extinction. As an example of the first, treatment regimes may be chosen with different combinations of antibiotics that, together, reduce the risk of resistance evolution or that guide evolution to low fitness types that are less likely to spread in antibiotic-free environments. There are general measures to achieve these goals, but measures can be more targeted if we can predict their effects on evolution. We devote a section of this review to evolutionary control.

For predictions in the second and third categories above, it might be enough to just predict the future without knowing why a prediction is correct, e.g., by using machine learning or other statistical methods. In other words, a useful prediction doesn't need to come from an understanding of the underlying mechanisms. However, precise predictions often come at the expense of generality, which means predictions cannot be applied in conditions that are even slightly different (Huneman 2014). This is related to Levins' triangle, following the 1966 paper in which Levins states that models cannot simultaneously achieve realism, precision and generality (Levins 1966).

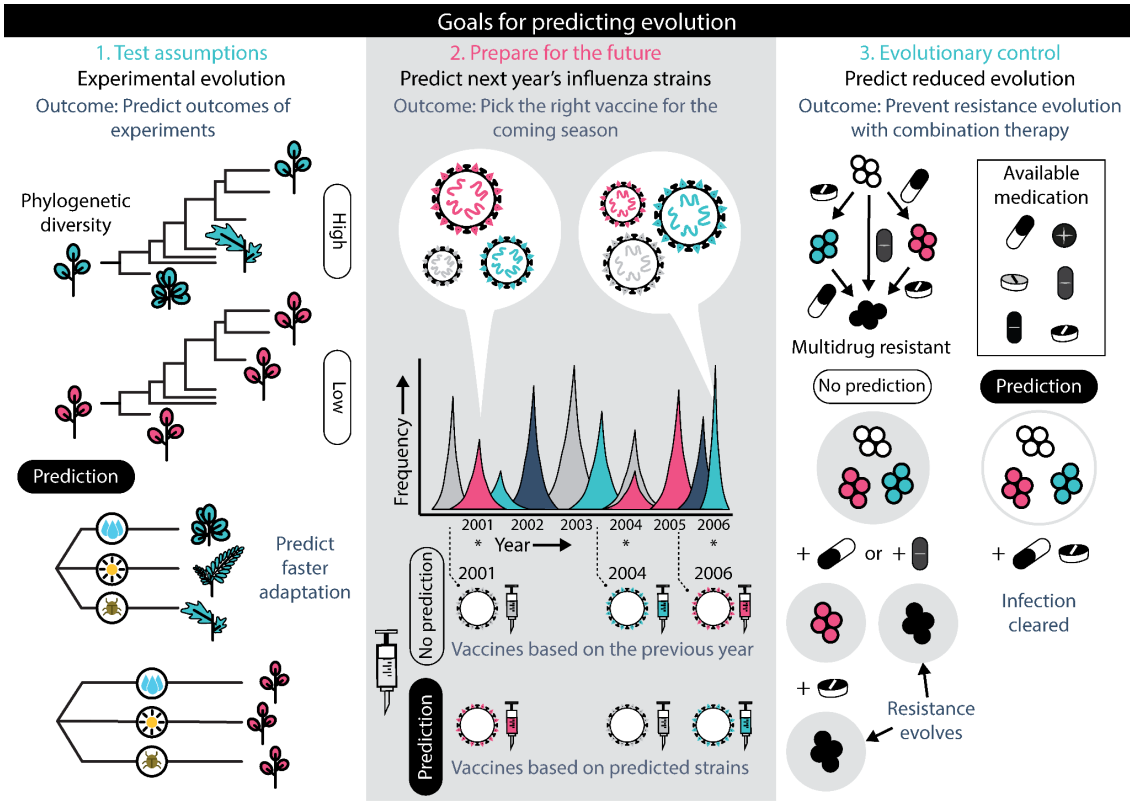


Figure 1. Why do we need predictions? *(1) To test hypotheses of evolution for a better fundamental understanding of evolving systems. Based on their phylogenetic history we can predict how species evolve when exposed to a given treatment. These predictions can be tested with experimental evolution approaches. (2) To be prepared for future outbreaks, we aim to match vaccines with the most common influenza strains each year. (3) To have control over evolutionary outcomes and design treatment strategies that prevent evolution of resistance from happening in pathogens. In this review we focus on predicting evolution for goals (2) and (3), while (1) plays a role in obtaining the information at the basis of these predictions.*

What do we want to predict?

When making evolutionary predictions, we can focus on many different aspects of the future state of a population. Here it may be useful to briefly compare evolutionary predictions to weather and climate predictions, which have many dimensions as well. Sometimes we care about *whether or not* it will rain tomorrow; whereas other times, when we worry about flooding, we care about exactly *how much* rain will fall in the next 24 hours. Also, on most days, wind speeds may not be mentioned in a weather forecast, but when a hurricane is arriving, wind speeds are suddenly crucial to prepare for the impact of the hurricane. Evolutionary predictions are similarly diverse. Evolutionary predictions can be about different population variables (e.g., majority phenotype or genotype, average fitness, identity of fixed mutations, allele frequencies, population size) and include a time component (from a few hours to many years).

In this paper we focus on evolutionary predictions that are forward-looking in the sense that they concern future events. Predictions can be focused on either the genotypic or the phenotypic level. For instance, at the genotypic level we can predict the frequency of influenza variants in the next influenza season and *which strains* will be most common (Łuksza & Lässig 2014), or we can predict the mutational targets of *E. coli* responding to various environmental pressures (Wang *et al.* 2018). At the phenotypic level, we can predict the shape of Darwin's finches' beaks after a drought (Grant & Grant 2002). Other times, we want to predict *whether* or *after how long* drug resistance will evolve in a virus or bacterial infection in a patient. In experimental evolution, the goal may be to predict a certain *phenotype* (e.g. cell size) or the *average fitness* of a population after some amount of time, or we may want to predict *which genes* will acquire new mutations or confer increased fitness. With increasing interest in engineering microbial communities, interest turns to predicting the evolution of *interacting populations*. In conservation biology, the focus may be on predicting future *population sizes*. For all of these cases, besides predicting the most likely outcome, sometimes the *probability* of a *certain outcome* (e.g., extinction) is most important.

A conceptual model of evolutionary predictions

Although the objects of evolutionary predictions are highly diverse, at an abstract level, they nevertheless share a common structure (Supp Fig. 1). All evolutionary predictions result from a model — including conceptual, verbal, mechanistic, statistical, computational or mathematical models — that allows for a projection of the state of the evolving system beyond the input that is provided.

The model for all evolutionary predictions starts from describing the current state of the evolving system, and incorporates prior scientific knowledge of relevance (e.g., facts and mechanisms, evolutionary processes, etc.). This is the input of the model. The assumptions that are made, and that have not (yet) been proven to be true can also form input or constraints for the model. The output of the model describes the state of the evolving system in the future.

When we describe predictions, we can consider various attributes. First, we should consider which attributes of a population we want to predict, or what is the **predictive scope**: Is the prediction about genotypes, phenotypes, fitness or population sizes? Are we trying to predict the average feature of a population, or the distribution of a trait? Are we predicting the evolutionary path or the outcome?

Second, we need to consider the temporal scope of a prediction, the **predictive horizon**: We can predict the state of a population at a given time point (in the near or far future), or we can predict the time point at which a given state is reached. Generally, predictions of a system's trajectory are more precise for the near future. This is relevant especially when predictions are needed to decide on actions, such as which vaccine to manufacture. For example, when predicting influenza strain frequencies it seems that predictions are useful for up to one year into the future but not after that (Lassig et al. 2017).

Third, we can consider the level of detail of a prediction or **predictive precision**. A prediction about the direction of an effect is less detailed than one that also includes its magnitude, rate or trajectory. For instance, predicting that microbes will evolve to consume a novel food source is less detailed than predicting that the evolution will occur via a given sequence of mutations (trajectory) (Lind *et al.* 2019). In a sense, predictions are a type of hypothesis and if they are too general they cannot be falsified.

A fourth attribute of a prediction may be the *a priori* likelihood (absence of 'surprisingness') of the prediction, the **predictive risk**. All else being equal, predicting something which is *a priori* unlikely, given background knowledge, is harder but possibly more interesting.

2. What makes evolution more or less predictable?

Most of this paper focuses on studies that *make* evolutionary predictions, but to predict evolution it has to be predictable in the first place. The study of predictability and repeatability of evolution is of wide interest and we'll provide a short discussion of main issues here (Imhof & Schlötterer 2006, Szendro *et al.* 2013, de Visser & Krug 2014, Miton & Tokuriki 2016, Rego-Costa *et al.* 2018, Chevin *et al.* 2022). It is known that many deterministic and stochastic factors influence the predictability of evolution. In a highly predictable scenario, the efficiency of selection is high, relative to the stochasticity of genetic drift, mutation, recombination and unpredictable environmental changes. In such a situation, the fitness increase of the population, and possibly the increase in population size, can be accurately predicted with deterministic models. In addition, predictability is high when very few strongly beneficial mutations are available to a population. For example, (Feder, Pennings, *et al.* 2021) show that in 19 of 20 patients infected with HIV and treated with a single drug (3TC), viral drug resistance fixed within 3 months through exactly the same mutation (M184V) in the reverse transcriptase gene.

There are many reasons why predictability is usually much lower: the mutation supply may be low (leading to stochastic waiting times for a successful beneficial mutation), multiple mutations with different beneficial effects may occur (wider distribution of fitness effects), fitness effects may be influenced by interactions with other mutations (linkage, epistasis and pleiotropic effects), the population may be small (allele frequencies affected by drift), and the environment may change in unpredictable ways. Predictability may also be affected by mating system, recombination (or lack thereof), species interactions, feedback loops and historical contingency. We will not discuss all of these in detail, but address a selection of the genetic and ecological factors that affect the predictability of evolution.

Genetic factors

Many genetic factors can influence the predictability of evolution, and here we discuss three of them, namely mutation bias, mutational supply and epistasis.

We first consider the influence of mutation bias and the distribution of fitness effects on predictability of evolution. **Mutation bias** describes the variability in mutation rates of different

mutation classes (e.g., transitions vs. transversions) or genomic sites. The **distribution of fitness effects (DFE)** of new mutations tells us what percentage of mutations have what fitness effect. Variation in mutation rate (mutation bias) and fitness effects of mutations (selection bias, DFE) can both enhance parallel evolution (and hence predictability) by reducing the number of "successful" mutations that achieve fixation or high frequency (Stoltzfus & Yampolsky 2009, Storz 2016, Storz *et al.* 2019). These successful mutations are either favoured by the existing mutation bias (i.e. they occur at a higher rate than other mutational classes), or they provide the largest benefits (Gerrish & Lenski 1998, Schenk *et al.* 2022).

Theory predicts that in the absence of selection (i.e., under neutrality), mutation bias is the only driver of parallel evolution (Kimura 1983). But even when selection occurs, a strong mutational bias reduces the spectrum of mutations available for selection, and should therefore increase predictability. Somewhat counter-intuitively, when selection is very strong for multiple possible mutations, mutation bias is again as important as it is under neutrality (Stoltzfus 2021). In a wide range of taxa, mutation bias explains a non-negligible proportion of cases of parallel genetic evolution (Stern & Orgogozo 2008, Bailey *et al.* 2017, 2018, Stoltzfus & McCandlish 2017). For instance, an elegant study on adaptation to high altitudes in birds found parallel evolution, in part due to mutation bias at CpG sites (Storz *et al.* 2019). When highly beneficial mutations are under-sampled due to the existing mutational bias, other smaller-effect but more frequent mutations may fix instead. Such a pattern was observed in replicated evolving populations of bacteriophage (Sackman *et al.* 2017) where the mutation with the largest fitness effect was not the one that reached fixation most often, because its mutation rate was lower than that of other mutations with smaller fitness effects.

The impact of selection bias (i.e. fitness effect of different mutations) can be analysed via the distribution of fitness effects (DFE). The above mentioned bacteriophage study (Sackman *et al.* 2017) experimentally quantified the fitness effects of new mutations and then used the shape of the quantified DFE and number of beneficial mutations to predict the probability of parallel evolution (eqn 37 in (Joyce *et al.* 2008)), comparing those estimates to observed measures of parallel evolution within the same system. These authors found that including the shape parameters of the DFE in a model improved estimates of the probability of parallel evolution, providing support for the idea that DFEs are important drivers of evolutionary predictability.
On the other hand, theoretical work using extreme value theory has shown that regardless of the specific shape of the entire DFE (i.e. including deleterious, neutral, and beneficial mutations), there will always be many more small than large-effect mutations. This reduces predictability because the more numerous small-effect mutations may collectively have a similar fixation probability compared to the small set of large-effect mutations (Joyce *et al.* 2008, Sackman *et al.* 2017).

Mutational supply is the total number of mutations that occur in a generation (or other unit of time) within a population, and hence, is determined by the population size and the mutation rate. If mutational supply is low (e.g. in small populations), having only a few large-effect beneficial mutations means that the waiting time for one of these mutations may be long, making the timing of their appearance unpredictable (Orr 2005). With increase in the mutation supply rate,

selection bias becomes the dominant driver of adaptive trajectories, though mutation bias still has an impact on the identity of successful mutations. For instance, in larger populations where mutational supply is high, multiple beneficial alleles are present simultaneously (i.e., the clonal interference regime). Here, selection bias is expected to dominate over mutation bias and genetic drift, and fix the most beneficial mutations largely independent of their mutation rate (Szendro *et al.* 2013, Bailey *et al.* 2017, Pinheiro *et al.* 2021, Pennings *et al.* 2022).

Another important factor influencing predictability is interactions between mutations (**epistasis**), which introduce ruggedness in fitness landscapes. Generally speaking, epistasis reduces predictability, because even if fitness effects are measured in one genetic background we do not know the effects in another background (Miton & Tokuriki 2016). Additionally, the complexity and redundancy in genotype-phenotype maps decreases the predictability of evolution: if many different genotypes map to the same phenotype, the observation of any particular genotype is just one of many, equally probable evolutionary outcomes (Zheng *et al.* 2019). However, there are interesting nuances; e.g., when epistatic interactions change the sign of mutational effects from beneficial to deleterious or *vice versa*, a condition referred to as sign epistasis (Weinreich *et al.* 2005). Sign epistasis can both increase and decrease predictability. A seminal study on the antibiotic resistance enzyme TEM-1 β-lactamase showed that sign epistasis can strongly reduce the number of mutational pathways along which a population can evolve towards higher fitness (Weinreich *et al.* 2006), which increases the predictability of evolutionary trajectories. On the other hand, sign epistasis can also lead to fitness landscapes with multiple peaks (Poelwijk *et al.* 2011), which means that populations can end up moving towards different fitness peaks depending on which mutation fixes first, thus decreasing the predictability of evolution.

How the combined knowledge on these genetic factors aids us towards forecasting organisms' responses to changing conditions in the future is illustrated in the predictability of the mutational routes for adaptive "wrinkly spreader" phenotypes of *Pseudomonas* (Lind *et al.* 2019). *Pseudomonas* can evolve to grow flattened or wrinkled colonies that compete for access to oxygen. Three mutational routes have commonly been found to underlie the convergent evolution of the wrinkly spreader phenotype (McDonald *et al.* 2009). However, a study that eliminated these three mutational routes revealed 13 other routes that also led to the wrinkly spreader phenotype. These other paths had similar fitness, but much lower mutation rates (e.g., because of smaller mutational target size), which explained why they were not observed in the original studies (Lind *et al.* 2015). This detailed information on mutational biases that affect the genotype-phenotype map could then be used to forecast genetic evolution for wrinkly spreader phenotypes in other *Pseudomonas* species (Pentz & Lind 2021). Detailed knowledge of the genotype-phenotype map may seem superfluous when phenotypic evolution can be forecasted without this knowledge, as in the case for the wrinkly spreader phenotype in *Pseudomonas*. However, knowledge of the genetics constraining evolutionary responses is relevant when we want to use evolutionary forecasting to control populations.

Ecological factors

Experimental evolution studies are typically performed in a laboratory environment where most environmental and ecological conditions are controlled. However, predictability of evolution in the wild will depend on characteristics of populations and their habitat as well as interactions with the biotic and abiotic environment (here jointly referred to as 'ecological factors'). Ecological factors affect the predictability of evolution both through their effect on the amount and distribution of genetic variation and on the fitness effects of variants. To illustrate this, below, we briefly outline the effect of the **rate of environmental change**, the characteristics and complexity of the **habitat**, and the ecological **interactions** within a community on the predictability of evolution.

Firstly, the speed of environmental change may affect predictability by setting the strength and variability of selection pressures. Overall, adaptation is more likely under gradually changing environments compared to rapid or saltational environmental shifts (Bell & Gonzalez 2011, Radchuk *et al.* 2019). Empirical evidence for the higher predictability during gradual change was provided with a yeast laboratory system exposed to different gradients of salt stress (Bell & Gonzalez 2011). Also, a recent study emphasised that current global climate change causes imperfect adaptive responses due to the high speed of environmental change (Radchuk *et al.* 2019). An exception is when the change is so fast that populations cannot cope, in which case the predictability of the evolutionary outcome – local extinction – is high. Fast environmental changes impose large selection pressures, which can increase predictability (Gorter *et al.* 2017), but when the environmental change exceeds the limits of extant spatio-temporal variation in the habitat, the new fitness landscape becomes largely unexplored. This indicates that fast changing environments can limit the ability to predict evolution. Moreover, when environmental change is accompanied by the erratic occurrences of extreme conditions that dramatically alter the fitness landscape, either temporally or spatially, it introduces high stochasticity, further reducing predictability.

Secondly, characteristics of a species' habitat can also affect predictability, including the complexity or heterogeneity of the habitat, patch size, and connectedness. The more complex a habitat, the more selective pressures act, which may reduce the predictability of evolution. This can arise through trade-offs between traits for adaptation to multiple selection pressures (Roff & Fairbairn 2012, Armbruster *et al.* 2014, Stuart *et al.* 2017, Svensson *et al.* 2021), as well as by decreases in population size. Patch size strongly influences population size, and connectedness of habitat patches will influence the flow of individuals and, as a consequence, the influx of genetic variation. Dispersal between populations has a dual influence on adaptation: (1) Local dispersal may provide a genetic and/or demographic rescue effect, by effectively increasing the population size resulting in less drift and a higher absolute input of mutations (but see (Szendro *et al.* 2013)). (2) High dispersal rates may however induce a migration load between populations adapting to different stressors (Bisschop *et al.* 2019).

Finally, feedbacks between ecological and evolutionary dynamics (eco-evo dynamics) will influence evolutionary predictability. We know that higher ecological complexity (more diversity, more interactions) promotes ecological stability in some cases (Ives & Carpenter 2007, Pennekamp *et al.* 2018, Xu *et al.* 2021). Can we expect evolutionary dynamics in more complex communities also to be more predictable? One may expect that it is more straightforward to

predict evolutionary outcomes in simple communities, because there are fewer parameters to take into account. However, this argument is based on data constraints and not on fundamental constraints to evolutionary predictions in complex communities, where feedbacks might stabilise communities resulting in more stable short and long-term dynamics. Ecological feedback may lead to frequency dependent selection in various ecological interactions. In particular, negative frequency dependent selection (NFDS) can lead to predictable frequency fluctuations and stable equilibria of polymorphisms within a population. The strength of NFDS, and the (un)predictability of environmental changes then determines whether this leads to unpredictable chaos or whether it can increase predictability of evolution (Chevin *et al.* 2022). Moreover, when environmental variability strongly affects population growth and natural selection, as is commonly observed in natural systems, this "environmental forcing" tends to render the evolutionary responses and tracking of the environment less chaotic and more predictable (Rego-Costa *et al.* 2018). Therefore, although the complexity of the real world and the inherent stochastic nature of some core ecological processes (such as priority effects (Fukami 2015)) suggest limits to our ability to predict evolutionary change, exploring the effect of eco-evo dynamics on the stability of dynamics across timescales can shed new light on the potential for evolutionary forecasting.

Empirical support for the effect of ecological factors on the predictability of evolution exists. For example, in a microcosm experiment with *Escherichia coli*, the spread of beneficial genotypes was mostly stochastic in communities with low complexity, but deterministic in high complexity communities (Imhof & Schlötterer 2006), suggesting a positive relationship between ecosystem complexity and predictability of evolution. Similarly, communities of bacteria that were experimentally evolved for several hundred generations followed repeatable trajectories towards a final, stable community structure (Celiker & Gore 2014). Natural 'laboratories' also offer insight into the role of ecology on evolutionary predictability, for example in the form of parallel evolution in replicated habitats where organisms respond similarly to similar changes in their environments. Urbanisation provides a unique setting where similar environmental changes are replicated amongst cities, such as the selection of a behavioural gene in the common blackbird (*Turdus merula*) (Mueller *et al.* 2013, Donihue & Lambert 2015). Other examples are the convergent evolution of colour morphs in Hawaiian spiders caused by their surrounding environment (Gillespie *et al.* 2018), and reduced armour when marine three spine sticklebacks (*Gasterosteus aculeatus*) colonised freshwater, which is explained by both abiotic and biotic changes (differences in salinity and predation pressure respectively) (Jones *et al.* 2012). Based on these patterns of repeated evolution, we can potentially forecast how other populations would respond to similar ecological or environmental factors.

3. Methods for predicting evolution

If we establish that we want to predict evolution, and what such a prediction entails, the next question is how we can predict evolution. Predictions can be data-driven, e.g., based on observations of repeatability that we would expect to observe again under similar conditions, or based on theory and mechanistic understanding of the evolutionary processes which we can model. Sometimes a combination of the two is used. There are many different approaches and

methods to predict evolution. We mention some of those here and in figure 2. For more details we refer readers to the supplementary text. Note that phylogenetic models are not described here but feature in box 1.

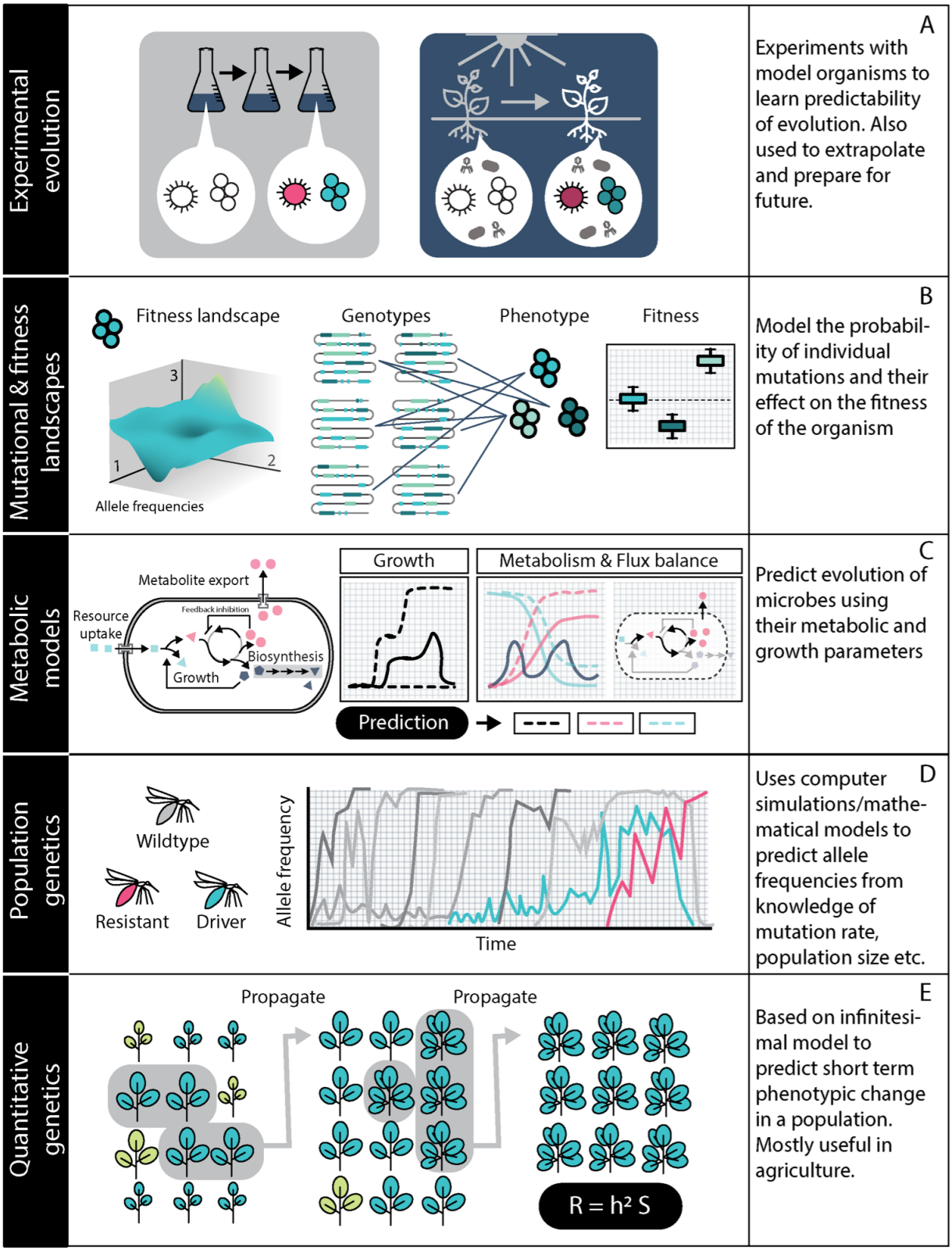
Experimental evolution. A straightforward method for evolutionary predictions is creating the conditions of interest (in the lab or in a natural environment), observe (a lack of) evolution and identify which conditions lead to which outcomes (Kawecki *et al.* 2012, Jagdish & Nguyen Ba 2022).

Using the mutational and fitness landscape. Though currently still out of reach, one day, it may be possible to predict the next evolutionary step for a population using detailed knowledge of the mutation and fitness landscape for a population in a given environment (Salverda *et al.* 2011, Fragata *et al.* 2019).

Metabolic and growth models. When selection on microorganisms is due to differential population growth of alternative genotypes, we can use genome-scale metabolic and growth models to predict how these populations will evolve (Schuetz *et al.* 2007, Wortel *et al.* 2016). Metabolic models have been used to predict de novo, dosage-dependent antibiotic resistance mutations in *E. Coli* (Pinheiro *et al.* 2021).

Population genetic models. Population genetic models are models that keep track of the genetic status (often at one or a few loci) of an entire population (Hartl 2020). These models are either mathematical in nature or use computer simulations and can include mutation, fitness, reproduction, recombination and other parameters, with both deterministic and stochastic forces. They are used to predict the success of gene drive systems (Noble *et al.* 2017, Champer *et al.* 2020).

Quantitative genetics and the breeder's equation. In situations where the focus is on altering one or a few phenotypes, over short timescales and in relatively controlled environments, quantitative genetics has achieved great success in predicting phenotypic changes (Walsh & Lynch 2018). Such models are used, for example, in maize breeding programs (Masuka *et al.* 2017).


Experimental evolution
A
Experiments with model organisms to learn predictability of evolution. Also used to extrapolate and prepare for future.
Mutational & fitness landscapes
Fitness landscape
Genotypes
Phenotype
Fitness
3
1
2
Allele frequencies
B
Model the probability of individual mutations and their effect on the fitness of the organism
Metabolic models
Metabolite export
Feedback inhibition
Resource uptake
Biosynthesis
Growth
Growth
Metabolism & Flux balance
Prediction
C
Predict evolution of microbes using their metabolic and growth parameters
Population genetics
Wildtype
Resistant
Driver
Allele frequency
Time
D
Uses computer simulations/mathematical models to predict allele frequencies from knowledge of mutation rate, population size etc.
Quantitative genetics
Propagate
Propagate
R = h² S
E
Based on infinitesimal model to predict short term phenotypic change in a population. Mostly useful in agriculture.

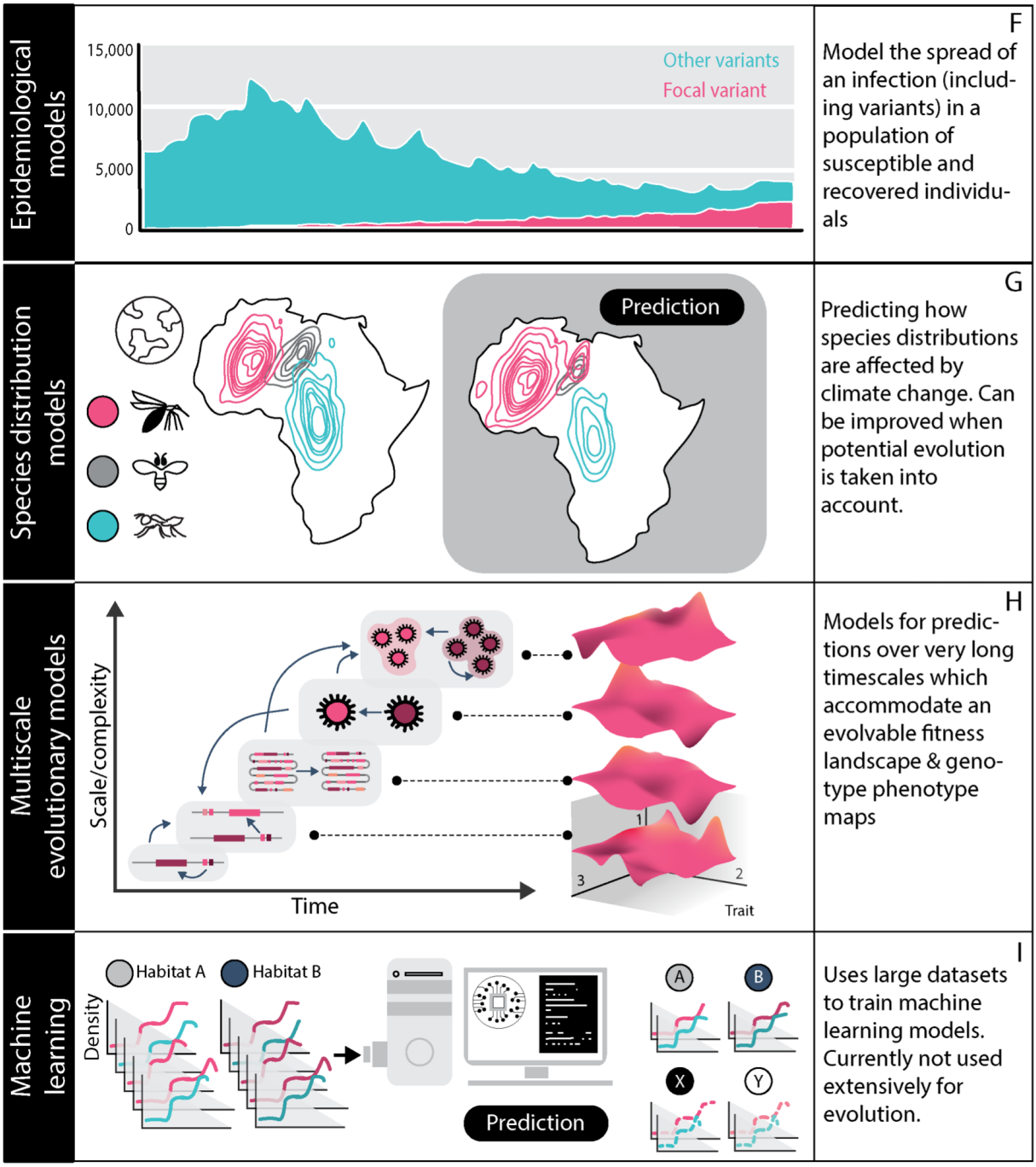


Figure 2. Selection of methods that are used to predict evolution.

Epidemiological models (SIR models). SIR models are compartment models where individuals can move from a susceptible to an infectious state and from an infectious to a recovered state. When classical SIR models are combined with the possibility of the pathogen to evolve (e.g., changing virulence or infection probabilities), we can predict the spread of an evolving infectious agent (Gordo *et al.* 2009)**.**

Species distributions across space and environmental conditions. Forecasting biodiversity responses to climate change are generally done through species distribution models. Such models can be combined with genomic data and evolutionary responses to predict adaptation (Bay *et al.* 2017) and range expansion (Kearney *et al.* 2009)**.**

Multi-scale evolutionary modelling. Studying long-term evolution requires models in which the genotype-phenotype map itself can evolve. Such models can be used to study genome evolution and evolution of communities. One example of a multi-scale model is combination of within-host and epidemiological levels in a model to study the effect of the HIV latent reservoir (Doekes *et al.* 2017)

Machine learning. In cases where large amounts of data on repeated evolutionary trajectories in the past are available, machine learning approaches are likely to become increasingly important for predicting evolution (Hayati *et al.* 2020, Schenk *et al.* 2022).

4. Evolutionary control

Evolutionary control needs predictions

Using predictions for control requires an extension of the scope of the prediction: we have to predict not only the evolutionary process under natural conditions, but also its response to specific control interventions. Important applications of evolutionary control are medical interventions against evolving human pathogens such as HIV (Lässig & Mustonen 2020). The case of HIV shows that predictions don't have to be very precise in order to allow some control. When triple-drug therapy became available for HIV patients in the 1990s, the prediction – based on a mathematical model – was that it would slow down the evolution of drug resistance, reducing the progression to AIDS and saving lives. Even though the model that was used wasn't entirely correct, the high level predictions held, and many lives were saved (Perelson & Nelson 1999, Rocheleau *et al.* 2018, Feder, Harper, *et al.* 2021). In this section we will describe several examples of evolutionary control, where predictions are used or could prove beneficial to improve control measures.

Preventing or reversing antibiotic resistance in bacterial pathogens

Increasing rates of antibiotic resistance threaten the efficacy of this mainstay of treatment for bacterial disease. Because the discovery and development of novel antimicrobial agents lags behind the rate of resistance evolution, newer approaches that focus on antimicrobial stewardship have emerged whose aim is to reverse or prevent resistance evolution to existing drugs (Read & Woods 2014, Nichol *et al.* 2015, Perron *et al.* 2015, Andersson *et al.* 2020).

These ideas, which can be implemented for individuals or at the population level in a hospital or agricultural setting, fundamentally rely on an accurate, empirical understanding of antimicrobial resistance evolution and spread. Two broad categories of evolutionary predictions to inform therapeutic decisions can be envisioned: one to avoid a specific outcome and another to promote one.

For example, several models and experiments have supported the intuitive predictions that combination therapies decrease the likelihood of resistance evolution compared to monotherapy. First, combination therapies increase the rate of pathogen decline, limiting the time window for *de novo* resistance mutations to occur. Second, they require resistance mutations in multiple targets, decreasing the probability that completely resistant mutants will arise (though see (Feder, Harper, *et al.* 2021)). Combination therapies encompass a wide range of approaches: using multiple antimicrobial agents simultaneously (e.g. antibiotic-antibiotic, antibiotic-adjuvant, antibiotic-phage or phage cocktails); antibiotic mixing, that is, random allocation of different antibiotics for different patients in the same hospital ward; and implementing temporally alternating therapies including antibiotic cycling (population level) and sequential therapy (individual level) (Sarraf-Yazdi *et al.* 2012, Abel zur Wiesch *et al.* 2014, Nichol *et al.* 2015, Yen & Papin 2017, Tyers & Wright 2019).

More interesting are approaches that would be used to drive a particular outcome. These are based largely on known epistatic or pleiotropic effects of resistance mutations. Resistance mutations are typically associated with fitness costs, and several authors have promoted treatment strategies designed to maximise these costs, thus maximising the probability that these strains are replaced once antibiotic selection is relaxed (Andersson & Hughes 2010). Interactions between resistance mutations can also be used to exploit drug synergies, thereby driving faster rates of population decline in the pathogen. Finally, a recent strategy is based on the idea that resistance to a given drug pleiotropically increases susceptibility (i.e. causes collateral sensitivity) to a second drug (Sommer *et al.* 2017). Knowledge of collateral sensitivity could help choose drugs to be used sequentially: if resistance to one drug evolves, it concomitantly increases the efficacy of the other one. Note however that epistatic effects (when a mutation's effect depends on the genetic background) can make it harder to predict, and thus use, collateral sensitivity (Barbosa *et al.* 2019, Hernando-Amado *et al.* 2020).

Insect resistance to transgenic plants

Evolutionary predictions have been used to guide the deployment of the most successful transgenic plants designed to protect crops against insect damage. Cotton, maize, and other crops have been transformed with the genes for insecticidal protein toxins from the bacterium *Bacillus thuringiensis* (Bt) and have been remarkably successful as an alternative to sprays with chemical insecticides (Tabashnik *et al.* 2013). From the beginning, the evolution of insect resistance to Bt toxins was anticipated and deployment strategies were deliberately designed to minimise its spread. For example, toxins were chosen for which resistance was known to be recessive, and for which standing genetic variation for resistance was shown to be low. This was done because population genetic models predict that evolution will proceed more slowly for

recessive alleles or when alleles are rare. Population genetic models of natural selection were also used to predict how soon resistance would evolve, based on assumptions about the genetics of resistance, the strength of selection, pest dispersal among Bt and non-Bt crops, and other genetic and ecological factors (Roush *et al.* 1998). Strategies based on these predictions, especially high dose/refuge strategies, were mandated by governmental regulatory agencies (Meihls *et al.* 2008). The high dose/refuge strategy means that (1) there is a refuge (crop that doesn't express the Bt toxin) which means that even if resistance evolves, very few homozygotes for the resistance allele will be produced, while (2) the dose of the toxin is so high that heterozygotes for the resistance allele will die. Retrospective analysis of the efficacy of these strategies has shown that they were more successful when more of the underlying assumptions were valid in the field, and when grower compliance was high (Tabashnik *et al.* 2013). This is probably the most successful test of the performance of evolutionary predictions in modern agriculture.

Prevention of resistance to gene drives

Gene drive systems use genetic constructs (currently often CRISPR/Cas9-based) to force the spread of a trait into a population (see Box 1). These systems are being developed to, one day, change wild populations (e.g., make mosquitoes resistant to malaria), but the target species can evolve to become resistant to the drive allele. Population genetic methods are used to predict how fast resistance would evolve against such a system and to design resistance-proof systems. One gene drive system is a so-called homing drive, in which the gene drive constructs cleave target sequences that are then repaired by copying the gene drive construct (using homologous recombination), which leads to an increase in the frequency of the gene drive construct in the population. Resistance to such gene drive systems can evolve when the cut that is made by the gene drive construct is repaired by the non-homologous end-joining pathway. This is because end-joining often leads to changes in the target sequence, which means that the drive construct can no longer cleave that sequence (Champer *et al.* 2020, Gomulkiewicz *et al.* 2021). When resistance has thus evolved, a drive construct can no longer spread and may go down in frequency if it comes with a fitness cost.

Because the evolution of resistance to a gene drive element is a key obstacle to deploying gene drive systems, research is focused on evolutionary control by reducing the rate of evolution of resistance (Unckless *et al.* 2017). The susceptibility of a gene drive construct to resistance can be reduced by (a) increasing the number of sites at which the gene drive construct can cut (Champer *et al.* 2020) or by (b) introducing a cost to resistance by targeting the gene drive to an essential gene (Noble *et al.* 2017). Predictions have been validated by laboratory experiments: several groups have shown that gene drives with multiple guide RNAs (which target multiple sites), or that target an essential gene, can spread in a population for much longer before resistance evolves (Kyrou *et al.* 2018, Champer *et al.* 2020, Kandul *et al.* 2021). In an important example of successful evolutionary control – at least in the lab – researchers from Imperial College London were able to create a gene drive system that targeted an important fertility gene (*doublesex*) in 2018. With this gene drive system no resistance evolved and the experimental mosquito populations all went extinct as hoped and predicted (Kyrou *et al.* 2018).

Preventing extinction by promoting evolution

One case where we want to promote evolution is to rescue a species from extinction. It is widely thought that lack of genetic variation increases extinction risk. For example, the Tasmanian devil had very low genetic variation and its population size was severely reduced by an infectious cancer (Hendricks *et al.* 2017). At the same time, loss of habitat, loss of dispersal opportunities and decrease in population size can lead to lower genetic variation in a species leading to an "extinction vortex" (Olivieri *et al.* 2015). The main method of promoting adaptation to a changed environment is therefore by increasing genetic diversity, as genetic diversity has shown to be beneficial for adaptation and rescue (Hughes *et al.* 2008, Agashe 2009, Agashe *et al.* 2011). Maintaining genetic variation also plays a role when breeding programs are used to rescue a population (Ebenhard 1995). Increasing genetic diversity in endangered populations, termed genetic rescue, often used to avoid inbreeding depression, is a promising intervention, but whether it predictably leads to increases in population sizes to prevent extinction remains to be seen (Bell 2017).

Box 1: Examples of evolutionary predictions

Evolutionary predictions and control are a guide in the SARS-CoV-2 pandemic

SARS-CoV-2, the coronavirus that started a pandemic in late 2019, is a focus of evolutionary predictions at the phenotypic and genetic level. The extremely high global prevalence of this virus as well as the recent host change and change in selective pressures (such as with vaccines) as well as the unprecedented scale of data that is available, make it possible to quickly test the accuracy of many predictions. It is common for viruses to adapt further after a host switch. At first, the main aim of predictions by public health agencies was to predict total case numbers using epidemiological or statistical models with no evolutionary dynamics included (Bertozzi *et al.* 2020, Watson *et al.* 2021). Next, there was interest in predicting the dynamics of different strains (Davies *et al.* 2021). And when vaccines became widespread, the big question was whether and when immune escape would happen (Kustin *et al.* 2021).
In the absence of herd immunity (due to infections or vaccines) the strongest selection is expected to be on increased transmission, whereas weaker selection is predicted on other disease life-history traits, such as the lengthening of the pre-symptomatic phase and decreased virulence. When large parts of the population become immune due to infection or vaccination, selection for immune escape is expected to become more important (Cobey *et al.* 2021, Grubaugh & Cobey 2021).

There is a strong interest in predicting specific genetic changes that will occur in the SARS-Cov 2 virus (Maher *et al.* 2022). Different methods have been used to try and predict which mutations are likely to arise and increase in frequency. These methods use existing genomic surveillance data (Harvey *et al.* 2021), deep mutational scanning (Starr *et al.* 2020) and by analysing different coronaviruses, (Armijos-Jaramillo *et al.* 2020).

Public health measures like physical distancing and vaccination not only reduce the number of infections, but can also reduce the evolutionary potential of the virus due to a reduced population size which could lower the rate at which new strains emerge. At the same time, wide-spread vaccination will increase selection for immune escape mutants. This means that vaccination campaigns and physical distancing rules can be seen, at least in part, as evolutionary control measures. A particularly interesting discussion about the effects of vaccination roll-out on viral evolution have been discussed in the context of dose-sparing strategies (e.g., getting more people a single dose or a half dose of a vaccine as opposed to vaccinating fewer people with two doses). Different epidemiological-evolutionary

models predict that dose-sparing strategies could speed up or slow down evolution of immune escape (Cobey *et al.* 2021, Saad-Roy *et al.* 2021).

Sustainable product formation by microorganisms

The chemical industry poses a high environmental burden and a sustainable alternative is (bio)chemical compound production by microorganisms. The major challenge for bio-based production of chemicals is the evolution of reduced product formation. This evolution happens because compound production diverts resources from growth, therefore inducing a fitness cost. We can use mathematical models of microbial metabolism to predict the evolutionary stability of production strains. For example, we can predict that for mutants where product formation is coupled to biomass production, evolutionary loss is least likely. Computational techniques that use genome-scale metabolic models can then predict which gene knock-outs couple product formation to biomass, which should lead to increased stability of product formation (Du *et al.* 2018). These predictions were applied for formate production by cyanobacteria and experimental validation showed that under growth coupling, indeed no decrease of product formation occurred within a month, whereas without growth coupling formate production decreased after days (Du *et al.* 2019).

Adaptation of natural populations to changing environments

To plan conservation efforts most efficiently we need to predict which species or populations can adapt to changing conditions and which will be threatened with extinction. These types of predictions are difficult to make, but several approaches are taken to enable forecasting of future population states. (1) We can apply a certain selection pressure in the lab and observe the adaptive potential (e.g. under size selective harvesting (Uusi-Heikkilä *et al.* 2015) or higher temperatures (Kellermann *et al.* 2009, Morgan *et al.* 2020)). (2) Similarly, species can be transplanted to different habitats and their adaptation monitored ((Colautti & Barrett 2013) and see (Edwards 2015) for a review). (3) We can determine if ongoing evolution has already led to adaptive change (e.g. a recent metaanalysis of evolutionary adaptation of birds to climate change showed that it is unlikely that adaptation will rescue populations (Radchuk *et al.* 2019); and contrary to predictions it does not seem that Atlantic Cod has adapted to fishing (Pinsky *et al.* 2021)). (4) We can use species distribution models along with genomic information (Hoffmann *et al.* 2015). Predictions for the last type have been made for the dwarf birch (Borrell *et al.* 2020), oaks (Rellstab *et al.* 2016) and the yellow warbler (Bay *et al.* 2018).
Approach (1) is difficult or impossible and time-consuming for many species and it remains to be seen how well these predictions can be extrapolated to natural systems. The latter problem is reduced in approach (2). Approach (3) can only be applied for changes that are already happening and needs a large amount of long-term data on individuals. Finally, approach (4) has usually yielded very weak correlations. Therefore, predicting which species may adapt to novel environmental conditions (e.g. rapid climate change) remains a big challenge.

CRISPR-based Gene drives

Gene drives or gene drive constructs are a special type of segregation distorter that use the CRISPR/Cas9 gene editing technology. Under Mendelian expectations, each gamete has a 50% chance to carry the allele that came from one parent and 50% chance to carry the allele that came from the other parent. One type of gene drives are called homing gene drives. They use a kind of copy-paste mechanism that distorts the 50-50 rule and can be present in many more gametes, which then leads to offspring that inherits the gene drive allele at a rate much greater than 50%. This works as follows: when the gene drive construct is initially present in the heterozygous state in a cell, it can cleave a genomic target site in the chromosome that doesn't carry the construct. This cut then induces the cell to repair the damage by copying the drive sequence into the damaged chromosome. The result is that the cell now has two copies of the gene drive allele. In this way, the gene drive construct can rapidly spread in the germline and therefore in the population. When the gene drive system is linked to an allele of interest (the "payload"), the transmission bias forces the spread of that allele. While CRISPR/Cas gene drives are not yet used outside the laboratory, there are plans to use this technology in mosquitoes and other species that cause harm to humans.

Evolutionary predictions at two different levels are of interest here: 1) how fast will the drive allele spread in the population, and 2) when will resistance to the gene drive evolve and spread? The first is a fairly straightforward

application of existing population genetic and population dynamic models, with an additional parameter for non-Mendelian segregation. However, in early experiments, the populations almost always became resistant to the gene drive element. The second level of prediction is therefore possibly more important: how fast will resistance evolve (Unckless *et al.* 2017, Dhole *et al.* 2020, Gomulkiewicz *et al.* 2021)?

Influenza vaccine development relies on evolutionary predictions

One of the best known examples of evolutionary predictions is predictions of which influenza strains will be common the next season, as a basis for vaccine development. Two main methods, that can also be combined, are used to make these predictions: genealogical trees and molecular properties of the virus (Morris *et al.* 2018). The first method uses data from recent clinical samples and makes a phylogenetic tree of these strains. The “bushy” parts that have a lot of recent diversification are the expected genotypes that will dominate next year (Neher *et al.* 2014). The second method uses specific molecular details of virus attachment to narrow down the entire genotype-fitness map to a short stretch of base pairs. From this short section of the HA protein, the physics of protein stability and binding to the human antibodies sum up to the fitness of the virus particle (Łuksza & Lässig 2014). Even though these methods are in use, success rates are still limited and further improvement would have a large impact on the effectiveness of influenza vaccines. Such improvement can come from a better understanding of the genotype-phenotype map for virus-antibody interactions, such that antigenic evolution can be predicted better from sequence data.

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5. Conclusion and outlook

Evolutionary predictions are used in many fields, including infectious disease, biotechnology and conservation biology. In some cases, the use of evolutionary models that include mutations, selection and drift is very explicit (such as in the gene-drive example or in the influenza vaccine predictions), whereas in other cases evolution may only be implicitly included in population size predictions (such as for predicting extinction risk for endangered species). In this review, we have shown how evolutionary predictions are used in many biological sub fields. Because researchers in different subfields use different languages, it is not always obvious that they are, in essence, doing the same thing: predicting the future state of an evolving population. Predictions can be improved when researchers can learn and be inspired by results from other subfields, but for this to happen, we need to use a common language. This review is meant as a start to bridge those research communities. We believe that those who work on preventing unwanted evolution (in biotechnology, agriculture and health) and also those who work on promoting or steering evolution (such as in conservation biology and biotechnology) could benefit from much more extensive communication.

Most of the theory we described in this review was featured in the paragraphs on predictability. This reflects the relative early stage of the field, where many researchers involved focus on understanding under which conditions evolution is more or less predictable, and which factors drive predictability. While this has led to many relevant insights, these theoretical insights are still far away from the applications where predictions are needed. We thus believe that the field could benefit from a stronger connection between theory and applications. Specifically, the efforts that are underway in the area of influenza research (using data and theory to predict influenza strains to design the best vaccine) could be replicated in other situations. For example, models could be made to predict drug resistance in a hospital over the next year,

given the current state and parameters such as antibiotic use. Also, evolutionary models could more explicitly be used in other situations, such as to predict which tumours will recur with resistance. By applying evolutionary methods to real life situations, we will discover the gaps in our knowledge and contribute to making evolutionary predictions more accurate and useful.

Finally, we expect that the increasing access to genome information and the use of modern statistical techniques, including machine learning, will improve evolutionary predictions in amenable taxa over the next few years. However, there will be a continued need to develop mechanistic models of evolution for various systems, for at least two fundamental reasons: (i) to extrapolate predictions to conditions other than those used to parameterize specific models, and (ii) to further our understanding of how evolution works. While the increasing access to high-resolution phenotype and genotype data make it tempting to include all these details in such models, more coarse-grained mechanistic models may allow more powerful predictions. We hope that together, improved collaboration, a shared language, and new combinations of methods will lead to further maturation of the field, leading to evolutionary predictions becoming mainstream in areas such as infectious disease, conservation biology and biotechnology.

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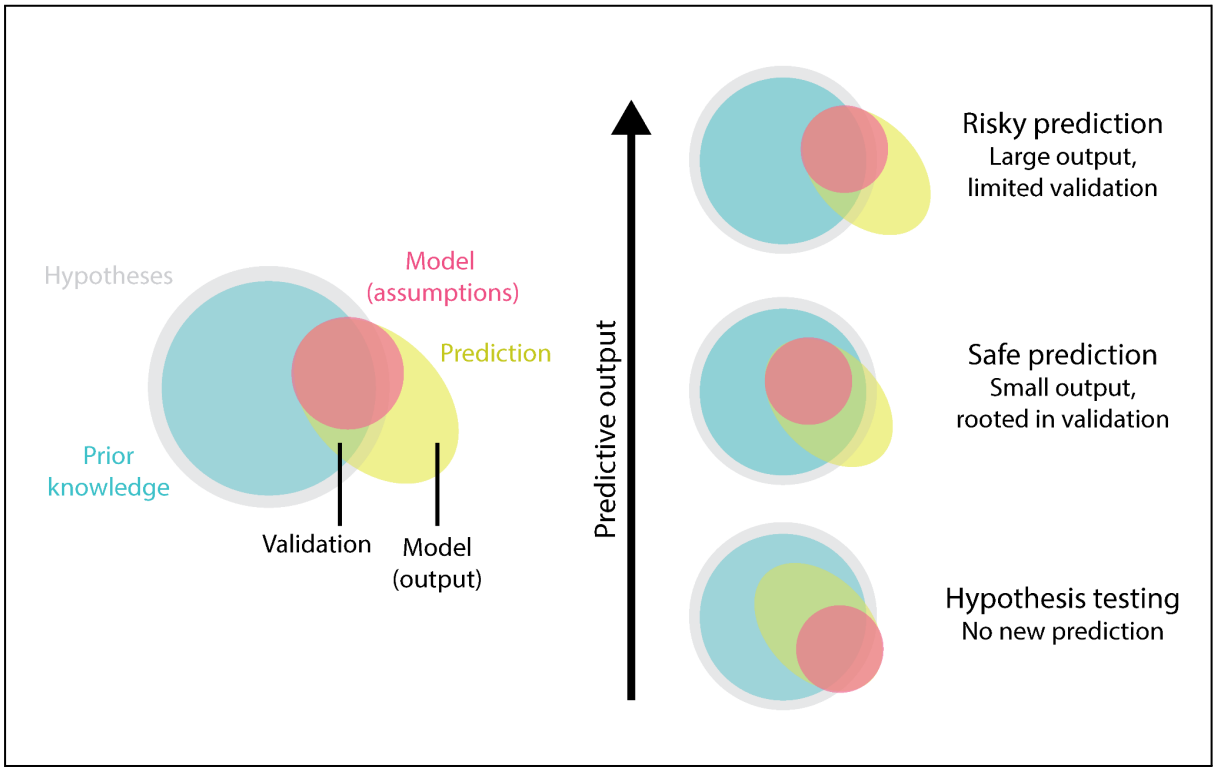
7. Supplementary material



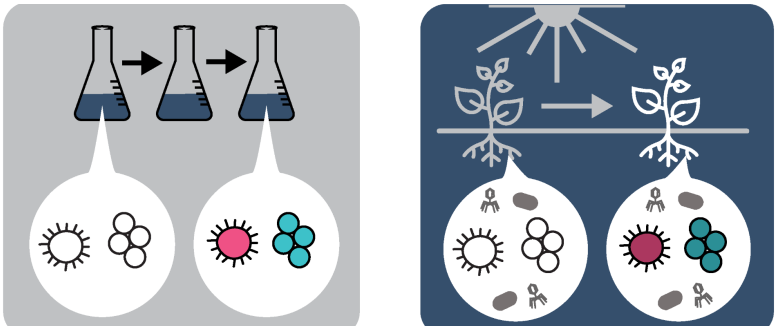
Supplementary Figure 1. Shared abstract structure of all (evolutionary) predictions. *Starting from prior knowledge (blue circle), models can be formalized (pink circle) which may project into the unknown (visualized by the yellow ellipse), using assumptions (grey aura). If pointing outwards, the yellow area of the ellipse constitutes a prediction, whereas the green area is used for validation of the model and its assumptions. The model assumptions and output will determine the orientation of the ellipse, and to what extent it projects into the unknown. The predictive output will range from the most risky predictions of more fundamental and serendipitous nature, to safer predictions which will be more suitable for predicting more practical matters such as potential pathogen escape mutants. Hypothesis testing here is the case where predictions are made about results that are known, to test if the model that we have of a process explains the observations.*

As an example we apply the conceptual model to the prediction about seasonal influenza strains in the next season, which is used to design the next vaccine. Prior knowledge (blue circle) is the current state of the population as inferred by observed frequencies of influenza strains in humans and other hosts, and the trajectory of these frequencies in the recent past. The model assumptions (grey) can include mathematical descriptions of how the frequency trajectories can be extrapolated into the future (taking into account mutation, drift and selection). The outcome of the model (yellow) is the predicted frequencies of the major strains during the next influenza season, only the list of the most prevalent clades, or the antigenic phenotypes of the future virus population.

In terms of the four attributes described in the main text, the predictive scope is the genetic or antigenic composition of the population, the predictive horizon is a time scale 6-12 months into the future. The predictive precision is high in terms of time (we need to know the common strains for the next season, not earlier or later than that) and genetics, as we are predicting the exact strains. The a priori likelihood is bounded when we consider only existing strains, as there may only be a small number of possible outcomes when only few strains currently exist in the population. However, the exact predictive risk depends on whether a common or uncommon strain is predicted to be prevalent the next season. Over longer time scales de novo mutations become important. De novo mutations are hard to predict, which is one reason why predictability is reduced over longer time scales.

Methods for making evolutionary predictions

1. Experimental evolution



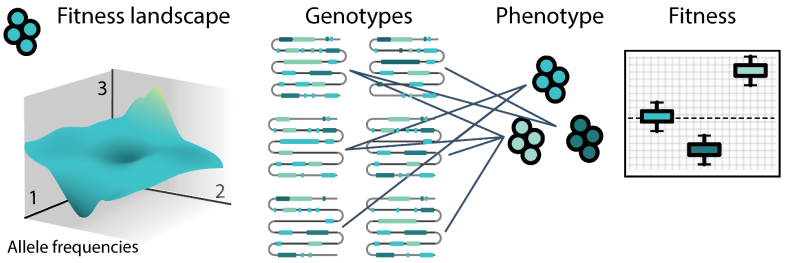
A straightforward method for evolutionary predictions is creating the conditions of interest (in the lab or a different natural environment), observe (a lack of) evolution, and extrapolate from these observations into the future.

Laboratory experimental evolution is diverse; it is commonly used for fast-evolving microbial systems (e.g. antibiotic resistance evolution (Kawecki *et al.* 2012, Remigi *et al.* 2019), but also larger organisms such as *Drosophila* (Burke & Rose 2009) and *Caenorhabditis* (Teotónio *et al.* 2017). Experimental evolution can also include interactions with the environment (i.e. eco-evolutionary interactions), such as the role of environmental spatial structure (Nadell *et al.* 2016) or the natural biotic context (Zandbergen *et al.* 2021).

Field studies are more appropriate for conditions or organisms that cannot be studied in the lab, for example because habitats are too large. In such cases, the effect of environmental conditions on evolution can be studied with reciprocal transplant experiments (Edwards 2015) or observations of “natural field experiments”, such as sticklebacks that have moved from marine environments to fresh water repeatedly (Jones *et al.* 2012).

Experimental evolution can also be used to study the predictability of evolution, and many such studies have indeed focused on the predictability (or repeatability) of evolution (e.g., (Bull & Molineux 2008, Sackman *et al.* 2017, Lind 2019, Schenk *et al.* 2022).

2. Using the mutational and fitness landscape



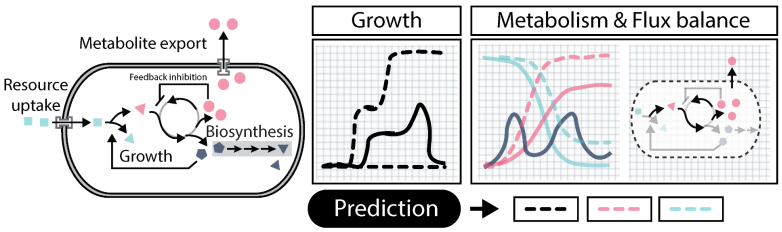
Though currently still out of reach, one day, it may be possible to predict the next evolutionary step for a population using detailed knowledge of the mutation and fitness landscape for the population in a given environment. To know what variation is available to a

population, we need to know the single step mutational landscape (the probability of each mutation to occur) and the effect of these mutations on the fitness of the organism (fitness landscape). Limited information on the mutational landscape might already inform evolutionary predictions (e.g., knowledge of epistasis for key mutations can predict evolutionary pathways (Salverda *et al.* 2011)).

Obtaining the single step mutational landscape with the accompanying fitness effects is a hard problem given the sheer scale of it. Even if we only focus on a single mutational step, and assume that the environment is stable, the number of possible mutations is very high (~>10^9 in eukaryotes) which makes it hard to determine the fitness effect for each mutation. Several approaches have been used to try and tackle parts of this problem, by focussing on small genome viruses (Tisthammer *et al.* 2020), mutational scanning of one gene (Lee *et al.* 2018), or on a small metabolic pathway (Kemble *et al.* 2020). Mutation accumulation experiments can also be used to understand the mutational landscape although they are unlikely to capture all mutations (Sane *et al.* 2018). For any prediction to be relevant, we need to take into account changing environments and multiple mutations and their interactions (epistasis), although there is some indication that environmental change does not change the fitness landscape completely (Vos *et al.* 2018).

Nevertheless, progress has been made through a combination of two approaches: the statistical approach where measured fitness effects are correlated with specific mutations (top-down) (Wang *et al.* 2018) and a mechanistic approach to predict by reconstructing the genotype-phenotype-fitness map (bottom-up) (de Vos *et al.* 2015). For instance, all the epistatic interactions between mutations affecting the expression of two genes in a linear metabolic pathway were resolved with a mechanistic perspective taking into account the flux in the pathway, the toxicity of the intermediate metabolite and the protein expression cost (Kemble *et al.* 2020). At a more integrated level, the well-established polarity network in budding yeast was predictive of mutation effects (Daalman & Laan 2020). Both approaches have their own advantages and disadvantages, and in most cases both approaches will need to be combined to make the best prediction.

3. (Microbial) metabolic and growth models

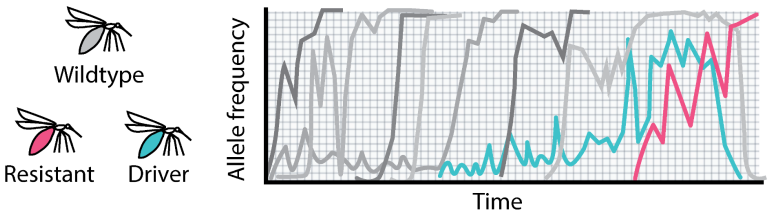


In many environments, selection on microorganisms is differential population growth of alternative genotypes, and therefore metabolism and growth are directly linked to fitness. This means we can use metabolic and growth models to predict evolution. The most well-known predictions are growth rates and metabolic adaptations in new environments (e.g. in *E. coli* (Schuetz *et al.* 2007) and *Lactobacillus plantarum* (Teusink *et al.* 2009)). These predictions use genome-scale metabolic models (Gu *et al.* 2019), which predict metabolic enzymes from genome information, constrain uptake fluxes with experimental data

and optimise for growth rate with flux balance analysis (Orth *et al.* 2010). Genome-scale metabolic models are also used for biotechnological applications, for example to predict how knock-outs of specific enzymes affect growth and product formation (see the Box in the main text)

Microbial growth and metabolism models come in different levels of detail. A simple phenomenological model can predict fitness increase (Wiser *et al.* 2013) and a more detailed model with intracellular 'macro'-reactions can be used to predict antibiotic resistance evolution (Pinheiro *et al.* 2021), or overflow metabolism (Molenaar *et al.* 2009, Wortel *et al.* 2016). Much more detailed models include genome-scale metabolic models (GEMs, current status in (Gu *et al.* 2019)), metabolism and expression models (ME models, (O'Brien *et al.* 2013)), resource balance analysis models (RBA models, (Goelzer *et al.* 2015)) and the most extensive whole cell models (Karr *et al.* 2012). Flux Balance analysis can be used to predict fluxes that lead to optimal growth, constrained by measured maximal fluxes, in GEMs, and therefore as a prediction of evolution . To improve predictions, proteome and kinetic constraints can be added (Sánchez *et al.* 2017, Chen & Nielsen 2021), or detailed descriptions of protein-metabolite dynamics can be incorporated at the expense of decreasing the model size (Wortel *et al.* 2018).

4. Population-genetic models



Population-genetic models are models that keep track of the genetic status (often at one or a few loci) of an entire population (Hartl 2020). Population genetic models can include mutation, fitness, reproduction, recombination and other parameters, with both deterministic and stochastic forces. These models are used widely to predict allele frequencies, e.g. incidence of deleterious recessive alleles in human populations (e.g. due to mutation/selection balance), or of conditionally beneficial alleles (e.g. sickle cell anaemia alleles in areas with Malaria parasites). Additionally, they can be used as a null model, to detect signatures of selection within population genomics, or deviations from panmixia (e.g. population differentiation).

Population-genetic models predict the evolutionary dynamics of allelic variants of genes. They use population-genetic theory, to describe the frequencies of alternative alleles (at one or multiple loci) over time. New alleles can be created from the wildtype allele by mutation, or may get introduced through immigration. Alleles at multiple sites can be recombined in following generations.

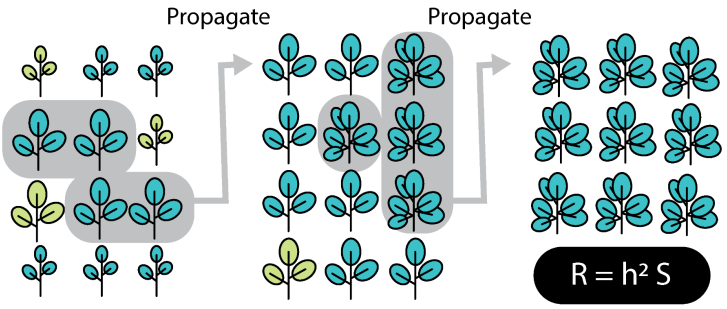
However, population genetic theory only works well for predicting changes in allele frequencies or population sizes if it is known which mutations have an effect on fitness and what these effects are (though see the extensive literature on adaptive walks (Gillespie

1983, Orr 1998)). Inferring the distribution of fitness effects of new mutations is difficult because of the sheer number of possible mutations and because this distribution may differ between genetic backgrounds and between different environments. Moreover, the mutations of interest, which are the beneficial ones, are only a small fraction of the possible mutations. Using population genetic theory to predict evolution relies either on the availability of large data sets capturing the genetic variation in natural populations (e.g. (Eyre-Walker & Keightley 2007, Tataru *et al.* 2017)) or on extensive measurements of fitness effects of selected mutations in the laboratory (e.g., (Fowler & Fields 2014, Cote-Hammarlof *et al.* 2021)).

Both Mendelian and non-Mendelian inheritance can be incorporated into the models. The models follow a population of individuals, to assess the separate or combined effects of mutation, selection, drift, non-random mating and migration, to calculate expectations for which allele(s) will spread, stabilise in frequency or disappear. In the absence of any of the evolutionary processes, allele frequencies are expected to remain largely constant and genotype frequencies can be accurately predicted, as described by the Hardy-Weinberg principle. If a beneficial allele is present in the population (from standing genetic variation, immigration or due to new mutations), it is expected to become more common in the population due to natural selection, and the models can predict the rate of change and the eventual equilibrium frequency to which the allele frequencies in the population will evolve. Ultimately, these models specify the particulars of the various deterministic and stochastic processes that operate concurrently, and how these processes contribute to the resulting evolutionary dynamics.

One interesting case study of population genetic models for predicting evolution is the evolutionary dynamics of gene drive systems (Unckless *et al.* 2017). This is explained in more detail in Box 1. In this model the frequencies of three alleles are followed over time. The alleles are (1) the **wildtype allele** (which is susceptible to the gene drive system), (2) the **driver allele** (which can convert the wildtype allele into a driver allele and may come with a fitness cost, in particular when the gene drive is used to control a population) and (3) a **resistant allele**, which can be created from the wildtype allele by mutation, and cannot be converted to the driver allele. An additional layer of complexity that was included in the model by Unckless *et al.* is that the CRISPR/Cas9 gene drive system itself is mutagenic, because the cuts it makes in chromosomes are often repaired by the non-homologous end-joining pathway which leads to mutations. The population-genetic model showed that if we want gene drive systems to be successful, we need to either reduce the rate at which resistance alleles are created, or we need to drastically increase the cost of resistance. Both of these methods have now successfully been used in experimental populations (Noble *et al.* 2017, Champer *et al.* 2020).

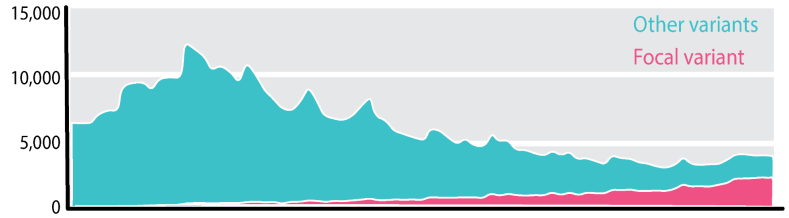
5. Quantitative genetics and the breeder's equation



The field of quantitative genetics was developed in close association with animal and plant breeders. In situations where the focus is on altering one or a few phenotypes, over short timescales and in relatively controlled environments, it has achieved great predictive success. For example, plant-breeding programs that are designed to improve crop yield focus on creating variable populations of hybrids and selecting for plants with the highest yield (under normal or stressed conditions) (Cooper *et al.* 2014, Gaffney *et al.* 2015, Masuka *et al.* 2017). Thanks to quantitative genetics, it is well understood that faster improvements will be attained when there is either more genetic variation to start with, or stronger selection. Specific predictions are achieved through the application of general statistical tools, often under simple assumptions of polygenicity and additivity (the infinitesimal model), to large sample sizes (Barton *et al.* 2017).

While application of the 'Breeder's equation' to predict the response of single traits, from their heritability and a defined selection differential, has yielded encouraging results (Walsh & Lynch 2018), p. 607), multivariate selection often fails, even in the controlled environment of the laboratory (Milocco & Salazar-Ciudad 2020, Rouzic *et al.* 2020) reviewed in (Roff 2007), though see (Beldade *et al.* 2002, Bolstad *et al.* 2015). In the wild, our aspirations must currently be limited to a number of exceptional, closely-studied systems such as the red deer on the Isle of Rum in Scotland (Bonnet *et al.* 2019), Soay sheep on St Kilda island (Clutton-Brock *et al.* 1991), and bird populations such as great and blue tits (Charmantier *et al.* 2008, 2014, 2016).

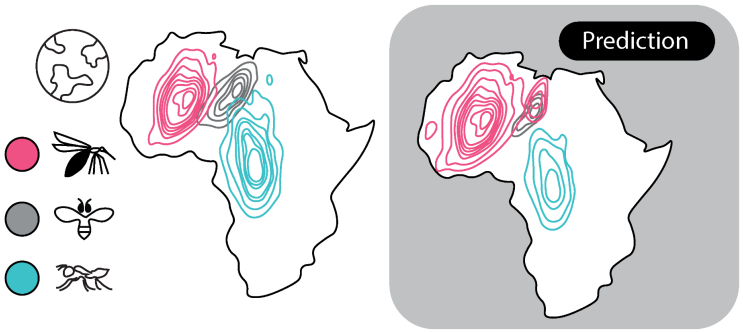
6. Epidemiological models (SIR models)



Classical SIR models are used to model the spread of an infectious agent in a population with susceptible, infected and recovered individuals. When we include the possibility of the pathogen to evolve (e.g., changing virulence or infection probabilities), we can predict the spread of an evolving infectious agent (Gordo *et al.* 2009). This type of model has been applied to modelling of influenza evolution (Boni *et al.* 2006).

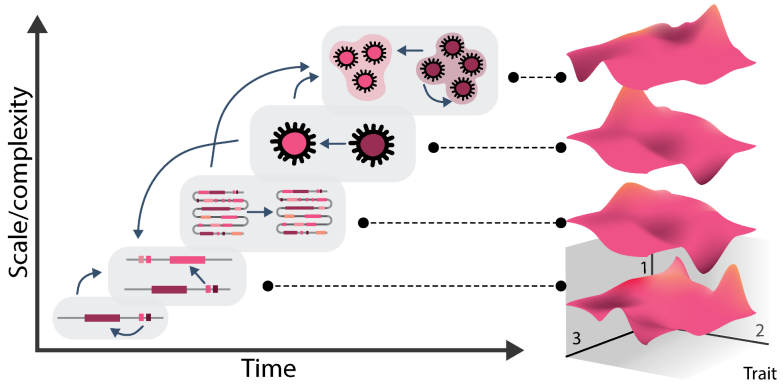
In the most simple case, evolution in SIR models can be modelled by including two or more versions of the pathogen with different parameters such as the replication number or transmission probability. Such models are used for the SARS-CoV-2 pandemic to predict case numbers in the near future and the spread of new variants. In early 2021, two main virus variants affected the predictions of cases in the near future in Europe: the “wildtype” strain and the alpha variant. In many locations, a simultaneous decline of the wildtype virus and increase of the alpha variant resulted in an initial reduction of total cases, followed by an increase (see figure). When enough sequencing data was available and R_0 was known for both variants, this U-shaped pattern of cases over time could accurately be predicted. When predictions are made further into the future, they need to account for the possibility that new, currently unknown, variants will emerge (Cobey 2020, Day *et al.* 2020, Kissler *et al.* 2020).

7. Species distributions across space and environmental conditions



Forecasting biodiversity responses to climate change are generally done through species distribution models, which include niche, envelope and bioclimatic models (Waldvogel *et al.* 2020). These models have been used in so-called rewilding, i.e. conservation efforts that include ecological restoration and reintroduction of predators and keystone species. However, species distribution models usually do not include intraspecific variation, adaptive plasticity and evolutionary potential (Jay *et al.* 2012, Fitzpatrick & Edelsparre 2018), and therefore greatly underestimate species range dynamics. Alternative models that include genomic data and evolutionary responses have been developed to predict the (potential) range expansion of *Aedes aegypti* mosquitoes transmitting dengue virus (Kearney *et al.* 2009), to predict coral adaptation to future ocean warming (Bay *et al.* 2017) and to predict future population declines of yellow warblers (*Setophaga petechia*) and to guide effective mitigation efforts for these birds (Bay *et al.* 2018). With models that include genomic data from a species, genomic variation can be related to environmental variables (Fitzpatrick & Keller 2015). This information can then be used to predict how vulnerable populations are to environmental change, such as climate change.

8. Multi-scale evolutionary modelling



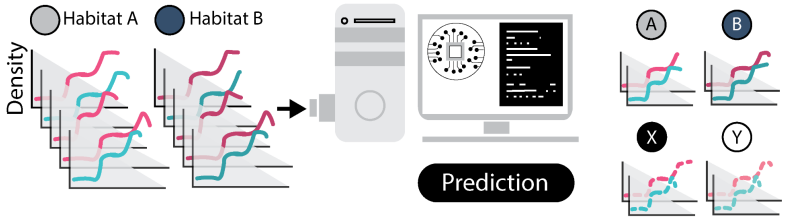
Predictions to test fundamental assumptions of evolving systems often require predictions over very long timescales. These predictions are complicated by the fact that the local mutational landscape changes with the accumulation of many new mutations, and the genotype-phenotype map changes as evolutionary innovations occur. Studying long-term evolution therefore requires models in which the genotype-phenotype map can evolve. An evolvable genotype-phenotype map can be achieved by including more than one level of organisation in a model and allowing for the evolution of traits at multiple spatiotemporal scales, leading to multi-scale evolutionary models.

Examples of multi-scale models are: the coupling of large gene regulatory networks to tissue-level patterning, which have been used for hindcasting the order of evolutionary innovations in bilateral animals (Vroomans *et al.* 2016), and estimating the likelihood that mutations increase morphological complexity (Hagolani *et al.* 2021); models of genome evolution (Cuypers & Hogeweg 2012), which predict that genomically complex ancestors primarily adapted through gene loss during major radiation events (Deutekom et al. 2019); and agent based models with rudimentary genomes, which predict emergent selective forces that can drive major evolutionary transitions (Colizzi *et al.* 2020). Multi-scale models can also generate predictions for clinically relevant evolutionary problems, such as HIV evolution (Doekes *et al.* 2017) or tumour progression (Szabó & Merks 2017).

A different scale on which selection can act, is at the level of the community (Doulcier *et al.* 2020, Chang *et al.* 2021). Predicting evolution at the level of communities is a newly emerging field with possible applications in medicine, biotechnology and agriculture. A promising application is for microbial communities that degrade hazardous compounds.

Multi-scale models are also used to study the predictability of evolution. This may either be done directly, e.g., to determine under what conditions evolution is predictable (Meijer *et al.* 2020), and show that although evolutionary paths and detailed characteristics can be hard to predict, in some cases population level traits are predictable (van Dijk *et al.* 2019). More indirectly, they can predict properties of the evolutionary landscape that affect predictability (see Section 2 of main text). E.g., common predictions of multi-scale models are that ruggedness and smoothness coexist in high dimensional fitness landscapes (e.g. arising from many-genes interactions), and the distribution of fitness effects is biased to high neutrality and high lethality, but with few intermediately deleterious mutants (Hogeweg 2012).

9. Machine learning



In cases where large amounts of data on repeated evolutionary trajectories in the past are available, machine learning approaches are likely to become increasingly important for predicting evolution. However, depending on the particular machine learning approach taken, these methods may or may not increase our understanding of the underlying evolutionary forces. An important limitation for using machine learning to make predictions is that it requires data from a very similar situation because the predictions can usually not be extended to novel situations beyond the data set used for training, in contrast to mechanistic models. One interesting example of machine learning for evolutionary predictions is a study on experimental evolution using the integration of numerous evolve and resequence experiments with *E. coli*. The researchers developed a predictor of the genes that will be modified in the course of adaptation, depending on the *E. coli* strain and the selection pressure (Wang *et al.* 2018). The model could predict around one third of the mutational targets in a new but similar evolve and resequence experiment.

Machine learning methods have also been used to predict the somatic evolution of cancer (Caravagna *et al.* 2018, Gerhauser *et al.* 2018) and success of influenza virus variants (Hayati *et al.* 2020). A particularly promising future direction is the ability for machine learning methods to combine increasingly complex cancer genomic data with data on transcriptome, epigenome and advanced imaging to guide precision medicine (Gerstung *et al.* 2020).

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