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Opinion

# Capturing the facets of evolvability in a mechanistic framework

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**'Evolvability' – the ability to undergo adaptive evolution – is a key concept for understanding and predicting the response of biological systems to environmental change. Evolvability has various facets and is applied in many ways, easily leading to misunderstandings among researchers. To clarify matters, we first categorize the mechanisms and organismal features underlying evolvability into determinants providing variation, determinants shaping the effect of variation on fitness, and determinants shaping the selection process. Second, we stress the importance of timescale when studying evolvability. Third, we distinguish between evolvability determinants with a broad and a narrow scope. Finally, we highlight two contrasting perspectives on evolvability: general evolvability and specific evolvability. We hope that this framework facilitates communication and guides future research.**

## Highlights

Evolvability, the capability to undergo adaptive evolution, is determined by a staggering diversity of mechanisms and organismal features. When discussing evolvability, it is useful to distinguish three categories of determinants: those providing variation, those shaping the effect of variation on fitness, and those shaping the selection process.

Some determinants of evolvability have a broad scope in that they affect adaptive evolution across many different environments; others have a narrower scope in that they impact evolvability only with respect to particular challenges. Being explicit about the scope of evolvability determinants would largely facilitate communication across disciplines.

On different timescales, the comparison of organisms regarding their evolvability and the comparison of mechanisms regarding their effects on evolvability can lead to very different conclusions.

## Evolvability is an important yet elusive concept

Understanding adaptation to changing environments is more important than ever. Climate change, antibiotic resistance, and viral vaccine evasion represent major societal challenges. Is an endangered species able to adapt to environmental change? Will a bacterial pathogen evolve antibiotic resistance? Can a virus evade vaccine-based immunization? At the core of these issues lies a common element: the capability of organisms to adapt – evolvability [1]. Evolvability research sheds new light on genomic architecture [2], the structure of regulatory networks [3,4], and many other features of **biological systems** (see Glossary). It has yielded surprising new insights, such as: adaptive evolution can proceed at a pace similar to ecological change, resulting in intricate and unexpected ecoevolutionary dynamics [5,6]; evolvability and **robustness** do not conflict but mutually reinforce each other [3,7,8]; and organisms with high evolvability can 'generalize' over environments [9,10]. Furthermore, evolvability research may add new perspectives to the formulation of a predictive theory of evolution (Box 1 and see Outstanding questions).

Evolvability is studied by diverse approaches; for instance: Johansson *et al.* [11] inspect the genetic variance–covariance matrix; Woods *et al.* [12] compare the speed of adaptation of bacterial strains; and Martín-Serra *et al.* [13] focus on morphological integration and **modularity**. These approaches, although all valid, are widely disparate: all aim to understand evolvability, yet each focuses on a different facet. This plurality is also reflected in the fact that evolvability has been defined in many different ways (Box 1). We aim to highlight the different facets of evolvability and how they relate to each other, to facilitate a more nuanced and cohesive discourse on the topic. Throughout, we define evolvability as the capability of a biological system to undergo adaptive evolution (see Box 1 for a justification).

## Toward a mechanistic approach to evolvability

Evolvability is often viewed in terms of outcomes (e.g., speed of adaptation). As the same outcome can be achieved in many ways, it is useful to study evolvability by a mechanistic approach

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### Box 1. Definitions of evolvability

Here we briefly discuss some definitions of evolvability, as they provide a good overview of the diversity of approaches in the field of evolvability research [63,72,73]. One important early definition revolves around the additive genetic coefficient of variation. It defines evolvability as the ability to respond to selection as governed by the presence or absence of standing genetic variation (often assessed in the G matrix) [38,58,74]. Another important perspective was given by Wagner and Altenberg [59], who made a distinction between variation and variability (i.e., the propensity of characters to vary). Evolvability is then considered not as the currently present variation but instead as the ability to generate new variation. A third, different perspective on evolvability considers the ability to generate major innovations [75,76]. For a comprehensive review of these developments, the reader is referred to [1]. Note that these definitions of evolvability are reflected in our first category of determinants, as they all view evolvability as determined by the presence or provisioning of variation.

One additional aspect of the definitions of evolvability (also called 'evolutionary potential' or 'adaptive capacity') is the relationship between variation and adaptation. While earlier treatments (as discussed in [1]) define evolvability as the ability of a biological system to evolve, irrespective of whether evolution is adaptive or not, recent definitions tend to restrict the concept to adaptive processes. For example, Payne and Wagner [14] combine the aspects of variation and adaptation when they define evolvability as '...the ability of a biological system to produce phenotypic variation that is both heritable and adaptive'. Other definitions in this vein have been provided in [7,38,60,77–81].

Following the general trend in the field, we here focus on adaptive evolution as well. When defining evolvability as the 'capability of a biological system to undergo adaptive evolution' we do not mean the presence or absence of this capability, but rather we consider its degree in a continuous fashion. Adopting an adaptive perspective does by no means imply that nonadaptive processes (e.g., genetic drift) are irrelevant; many of the determinants of evolvability reflect such processes (e.g., mutation). However, there are at least two reasons for focussing on adaptive evolution. First, many applications of evolvability (e.g., evolution of antibiotic resistance, adaptation to anthropogenic change) consider the adaptation to environmental challenges. Second, relating the rate and outcome of evolution to underlying selection pressures provides a yardstick, making it possible to differentiate between organismal and environmental features [38] and allowing comparisons across organisms. Both features are important first steps toward a predictive theory of evolution [82].

[14]: viewing evolvability not as a phenomenon *per se* but as a product of the mechanisms and organismal features that underlie it. A mechanistic perspective also clarifies discussions on the evolution of evolvability [1,14]: while questions regarding the evolution of 'the capability to undergo adaptive evolution' easily turn abstract, they become more obvious and transparent when translated into questions regarding the evolution of concrete mechanisms (e.g., the mutation rate).

## Categorizing the determinants of evolvability

We refer to the mechanisms and organismal features that govern evolvability as determinants of evolvability. These affect different aspects of adaptive evolution and consequently shape evolvability in different ways. We here identify three ways in which determinants can shape evolvability, based on what aspect of adaptive evolution they affect, and categorize them accordingly (Figure 1). First, determinants may affect evolvability by providing variation. The mutation rate is the most obvious example of such a determinant [2,15–17]. Second, determinants may affect evolvability by influencing the effect of variation on fitness. For example, **developmental biases** may predispose mutations toward being beneficial [18–21]. Third, determinants may affect evolvability by shaping the selection process; shorter generation times, for example, may accelerate adaptation [22,23].

### Category 1: providing variation

Heritable variation serves as the raw material for evolution. Hence, our first category refers to those mechanisms that generate and maintain variation. For example, mutations generate variation in many ways, ranging from point mutations to genome rearrangements. Interestingly, mutation rates vary widely between organisms as well as within genomes [24–26] and they can be regulated based on the environment (e.g., stress-induced mutagenesis, [27]), indicating that evolvability can evolve through the evolution of the mutation rate. Examples of determinants maintaining variation include **evolutionary capacitors** such as heat shock proteins. HSP-90 in *Saccharomyces*

## Glossary

**Biological system:** we here define a biological system to be any biological entity that can be subject to evolution by natural selection.

**Cryptic genetic variation:** standing genetic variation that has little effect on phenotypic variation under normal conditions but generates variation under changed conditions. The release of this variation can facilitate (or hamper) adaptation and thus impact evolvability.

**Developmental bias:** the developmental mechanisms underlying a trait can introduce biases in the variation in the phenotype, even if the underlying mutations are unbiased. These biases can be (but need not be) aligned with the direction of selection, in which case they facilitate adaptive evolution.

**Developmental canalization:** robustness to genetic or environmental perturbations frequently exhibited by developmental systems, leading to a stable phenotypic outcome.

**Evolutionary capacitor:** mechanism that prevents the expression of genetic variation under some conditions, thus allowing the accumulation of cryptic genetic variation, and 'releases' this variation under other conditions, thus exposing it to selection.

**Gene regulatory network (GRN) model:** model that explicitly represents the genotype-to-phenotype map as a complex network of regulatory interactions between genes. GRN models have been studied extensively in the context of evolutionary developmental biology and evolvability.

**Modularity:** the ability of subsets of a system ('modules') to function independently of other parts of the system (see [51]). Modularity can impact evolvability in various ways – for example, independent modules can be easily combined in different ways and furthermore do not interfere with each other's functioning.

**Phenotypic plasticity:** the expression of different phenotypes by the same genotype in response to environmental conditions. The impact of phenotypic plasticity on evolvability is subject to much debate (e.g., [10,47–50]); their relationship is complex and not yet well understood.

**Robustness:** the capability of the state of a biological system to persist under (environmental or genetic) perturbation. For example, robustness may refer to *cerevisiae*, for instance, acts as a chaperone protein aiding correct protein folding. Chaperoning can shield sequence mutations from selection, thus maintaining variation. This can later be released under stressful conditions [28,29]. **Developmental canalization** can affect evolvability in a similar manner, in that it allows the accumulation of **cryptic genetic variation** [30]. Furthermore, capacitors may also be behavioural in nature, as parental care and thermoregulatory behaviour also allow cryptic genetic variation to accumulate [31,32]. Horizontal gene transfer may also be viewed as a category 1 determinant, as it allows variants to be maintained that would otherwise be lost from the population; for instance, by establishing an 'accessory genome' [33,34] or through the so-called rescuable gene hypothesis [35]. Not all heritable variation is genetic: epigenetic inheritance, inheritance of environmental features, and cultural inheritance can also affect adaptive evolution [36,37]. Hence, category 1 also includes mechanisms providing non-genetic heritable variation.

the ability to maintain a certain phenotype in the face of environmental fluctuations or genetic mutations. Intuitively, one might consider evolvability (the ability to change) and robustness (the ability to withstand change) to be opposed; however, it has been shown that they can be two sides of the same coin [3,7].

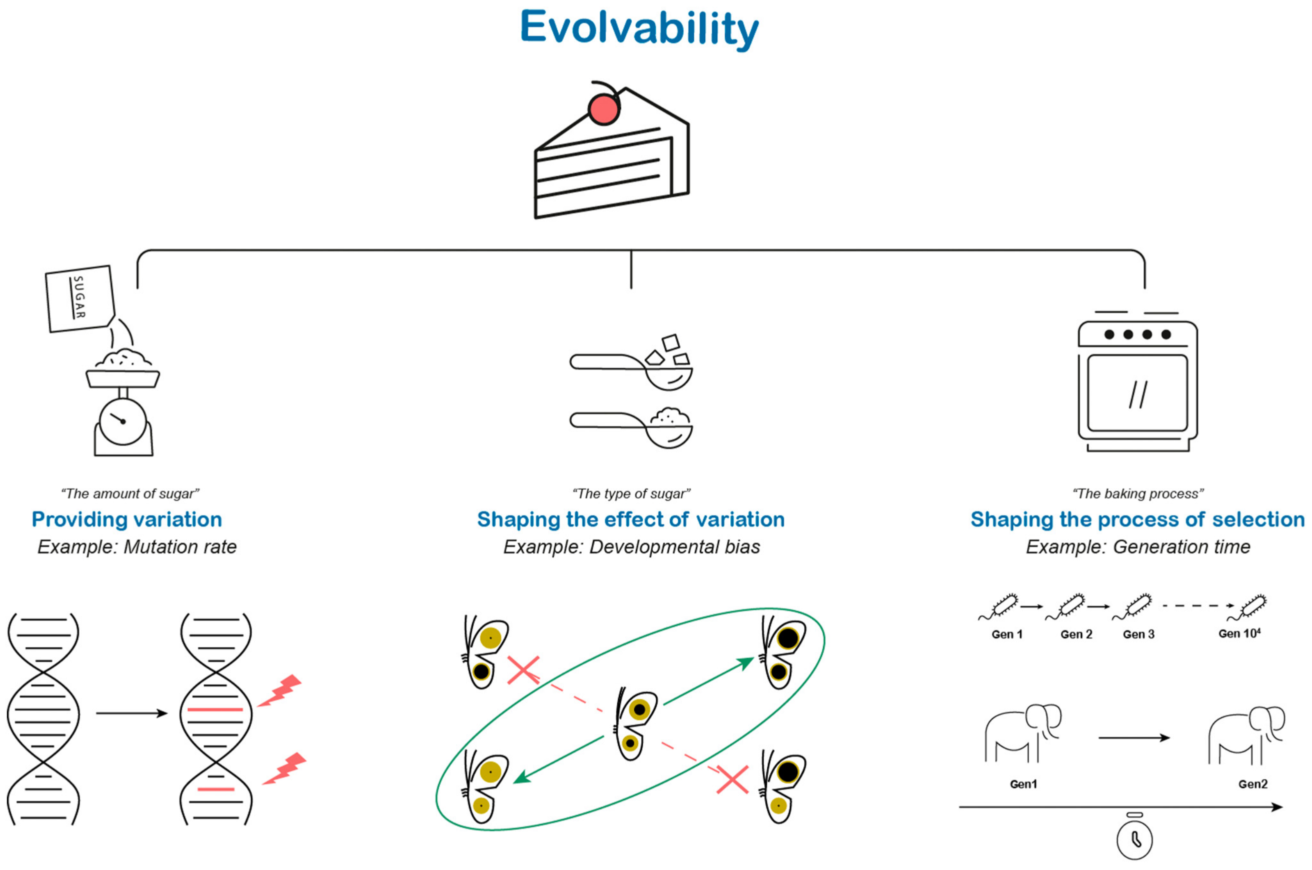

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Figure 1. The way that mechanisms and organismal features affect evolvability can be classified into three categories. Each one contributes to evolvability in a different way. This can be compared with the process of baking a cake: the end result depends on several fundamentally different aspects – the amount of ingredients, the quality of ingredients, and the baking process. We suggest that evolvability is analogously affected by three different classes of determinants: those providing variation ('the amount of sugar'), those shaping the effect of variation on fitness ('the type of sugar'), and those shaping the selection process ('the baking process'). An example of a determinant providing variation is the mutation rate, where mutation encapsulates a wide variety of phenomena ranging from point mutations to genome rearrangements. Developmental biases are examples of determinants that shape the effect of variation on fitness. Consider, for instance, the developmental system underlying the eyespot pattern on the wings of the butterfly *Bicyclus anynana*. This system is organized in such a manner that mutations can easily change the colour composition of the two wing eyespots in the same direction, while mutations changing the colour composition in opposite directions are extremely rare (depiction based on [40]). Depending on whether the selective pressure favours eyespots with the same colour composition or not, this bias may facilitate or impede evolvability. Finally, an example of a determinant that shapes the selection process is generation time: a shorter generation time allows faster adaptation – in absolute time, bacteria evolve faster than elephants.

### Category 2: shaping the effect of variation on fitness

The mapping from mutation to fitness is affected by a variety of mechanisms: mutations may be random with respect to the genotype, but their effects on the phenotype and consequently fitness are often not [8]. Through features such as genomic, developmental, and regulatory architecture, the genotype-to-phenotype-to-fitness map can bias the fitness effects of mutations [19,38]. Category 2 thus contains determinants that influence the effect of variation on fitness. Examples can be found in the evo-devo literature [19,21,39,40], which describes various biases introduced through the developmental process (developmental bias; for an example see the butterfly *Bicyclus anynana* in Figure 1). The effect of variation on fitness can also be biased by the genomic and regulatory architecture [4,41]. In yeast, for example, genes for which upregulation is selectively favoured in a higher-temperature environment are grouped on the same chromosome. Therefore, a duplication of this chromosome suffices to achieve upregulation of all relevant genes; without such genome organisation, many independent mutations would be required to obtain an equivalent high-temperature adaptation [42].

### Category 3: shaping the selection process

Starting from the same variation, evolution can still proceed at a very different pace and/or can lead to very different outcomes. Thus, category 3 contains determinants that impact evolvability not by shaping variation, but rather by shaping how the selective process acts on this variation. Examples are organismal features influencing population structure (e.g., dispersal tendency, mating patterns), as population structure may strongly affect adaptive evolution [43]. For instance, limited dispersal is hypothesized to have aided the rapid evolution of eusociality in diverse clades of insects [44]. Two other examples of category 3 determinants are generation time and the mode of reproduction. In coevolutionary host–pathogen arms races, the shorter generation time of pathogens provides them with an evolvability advantage, as they can evolve faster per time unit than their host [23]. Considering the Red Queen hypothesis, it becomes evident that hosts need other adaptations (e.g., sexual reproduction, a variation-generating immune system) to cope with pathogens on a longer-term perspective [45]. In the coevolution of hosts and their symbionts, the rapid evolution and/or diversification of the symbiont is often not in the interest of its host. Accordingly, the hosts of various symbiotic systems reduce the symbiont's evolvability by actively interfering with the symbiont's sexual reproduction [46].

## How a mechanistic categorisation aids our understanding of evolvability

Some determinants of evolvability can be classified into more than one category. This is a deliberate feature of the proposed categorisation, as it highlights that a determinant can affect evolvability in different ways. The categorisation prompts the researcher to critically consider how mechanisms and processes shape adaptive evolution. An illustrative example can be found in the literature on evolvability and **plasticity**. Some have argued that plasticity impedes evolvability: plastic responses shield organisms from selection, preventing genetic adaptation (category 3) [47]. Others have argued that plasticity allows the accumulation of cryptic genetic variation (category 1) [10,48], thus potentially enhancing evolvability, because plastic traits are expressed only under particular environmental conditions. Finally, arguments derived from **gene regulatory network (GRN) models** conclude that the evolution of plasticity can restructure the genotype–phenotype map in such a way that random mutations are more likely to produce adaptive phenotypes (category 2) [49,50]. Our categorisation of determinants thus showcases these often subtle but nevertheless crucial distinctions.

The effect of modularity on evolvability provides another example. Inspection of the underlying mechanisms reveals that modularity has not one but two impacts on evolvability. First, it facilitates innovation by allowing pre-existing modules to be combined in different configurations, thus providing variation (category 1) [51]. Second, it also allows individual modules to vary independently without affecting the functionality of the entire system (reducing antagonistic pleiotropy); this makes deleterious mutations less impactful, thus creating an adaptive bias that shapes the fitness effects of variation (category 2) [52]. This reduced impact of deleterious mutations (category 2) may also allow organisms to tolerate higher mutation rates (category 1), showing that determinants in different categories can interact in a reciprocal manner: the processes that provide variation (category 1), bias the fitness effects of variation (category 2), and shape the selection process (category 3) are not independent of each other.

Our view on the determinants of evolvability is suited to different approaches to evolution and evolvability. The first category (providing variation) contains not only mechanisms that provide new mutations, but also mechanisms that facilitate major innovations (however, the relationship between evolvability and major innovations is not yet well understood). Similarly, the second category not only considers instances of genotypic and developmental biases, but also includes broader ideas such as phenotypic accommodation and the theory of facilitated variation [20,53–55]. Finally, the third category considers not only genetic mechanisms (e.g., horizontal gene transfer, which also allows beneficial variants to spread more quickly [56]) but also – among others – niche construction, where organisms shape their own selective environment [57].

## Explicitly considering timescale resolves apparent incongruencies

Determinants differ in the timescale on which they act; thus, when comparing evolvability across biological systems, the outcome is crucially dependent on timescale (Figure 2). Considering the timescale can help to resolve several apparent discrepancies.

This is exemplified by comparing determinants that provide variation (category 1): consider the impact of standing genetic variation [58] and the impact of mechanisms generating variation [59] on evolvability ([1]; Box 1). In the short term, adaptation is more strongly influenced by standing genetic variation, whereas mechanisms generating and maintaining variation are of greater significance when considering longer-term evolutionary trajectories [60].

Some approach evolvability in terms of speed of evolution [61], while others approach it in terms of the attained level of adaptation [38,62]. Both aspects are relevant [63], but they are often two

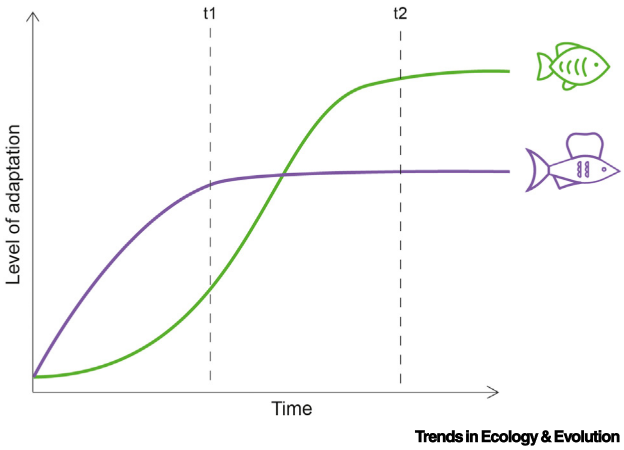

Figure 2. When studying evolvability, it is important to explicitly consider the timescale. Observing at different times can lead to different conclusions. Suppose that we observe the ability of two fish species to adapt to a new food source. Our conclusions on which of the two is more evolvable (is better able to adapt to the new selective challenge) will depend on the time at which we observe their level of adaptation. At time *t*1, the purple fish species is more adapted (and hence seems more evolvable), but at time *t*2 the green fish species is more adapted (and hence seems more evolvable). This occurs because rates of adaptation are not constant across time; thus, being explicit about the timescale of observation can resolve apparent discrepancies when comparing the evolvability of different organisms.

sides of the same coin, which becomes apparent when explicitly considering timescale. Consider, for example, different modes of inheritance. Epigenetically inherited traits can provide fast adaptation, yet this adaptation is often relatively inaccurate, given that the relative instability of epigenetic marks impedes the reliable maintenance of a certain optimal phenotype. By contrast, genetic adaptation proceeds more slowly, but in view of the high fidelity of genetic inheritance it may, in the long term, result in a higher level of adaptation. Therefore, epigenetic inheritance confers higher evolvability in the short term and genetic inheritance confers higher evolvability in the long term [36].

Another discrepancy that can be resolved by considering the timescale is the debate over the evolvability benefits of sexual reproduction, with both sexual and asexual reproduction being linked to increased evolvability [1,64]. All other things being equal, the response to selection (and hence the rate of adaptive evolution) is higher under asexual reproduction, as in the case of sexual reproduction, selection can act only on the additive component of genetic variation [65] (category 3). Therefore, asexual reproduction facilitates evolvability in the short term. In the longer term, sexual reproduction confers a higher evolvability, as the slower speed of evolution is outweighed by the ability to better explore the fitness landscape and reach global rather than local peaks. The claims that sexual reproduction increases evolvability and the claims that asexual reproduction increases evolvability can thus both be true, just at different timescales (Figure 2). Overall, the earlier examples show that the effects and relative importance of determinants vary over time. Therefore, explicit consideration of the timescale is crucial when studying evolvability.

## Accounting for environmental context shows that determinants differ in scope

Evolvability is the capability to undergo adaptive evolution; it is therefore necessary to consider in relation to which environmental challenge such adaptation arises. This reveals an additional property of determinants: their scope. Some determinants affect evolvability across many different environmental challenges; we consider these to have a broad scope. For example, mutation rates impact evolvability in virtually all environments. Other determinants have a narrow scope as they shape evolvability in only a restricted set of environments. For example, the grouping of temperature-relevant genes on one chromosome in yeast [42] enhances evolvability only to a change in temperature; it does not impact adaptation to other environmental challenges.

The scope of determinants pushes the researcher to consider the range of environments in which a determinant is relevant. Determinants relevant for adaptation to one environment may not be as relevant when considering adaptation to another. For example, in the radiation of Darwin's finches, developmental biases in beak development have been implicated in their adaptation to different seed sizes [66,67]. However, evolvability regarding beak shape will not be relevant with regard to other environmental challenges, such as temperature regulation or predator escape. By contrast, a higher mutation rate will affect evolutionary adaptation with regard to many different environmental challenges.

## Two perspectives on evolvability

A very different distinction does not refer to the determinants of evolvability, but to the scholars studying evolvability. Depending on their scientific discipline, research question, or model system, scholars differ in whether they view evolvability as 'general' or 'specific' with regard to environmental challenges (Figure 3). Scientists adopting a specific evolvability perspective refer to the capability of a biological system to undergo adaptive evolution to a specific environment or a specific challenge; the main focus therefore is on how well a biological system can meet a specific selective target. This perspective is useful when studying adaptation to a particular challenge; for example, when exploring the ability of bacteria to evolve resistance to a particular antibiotic,

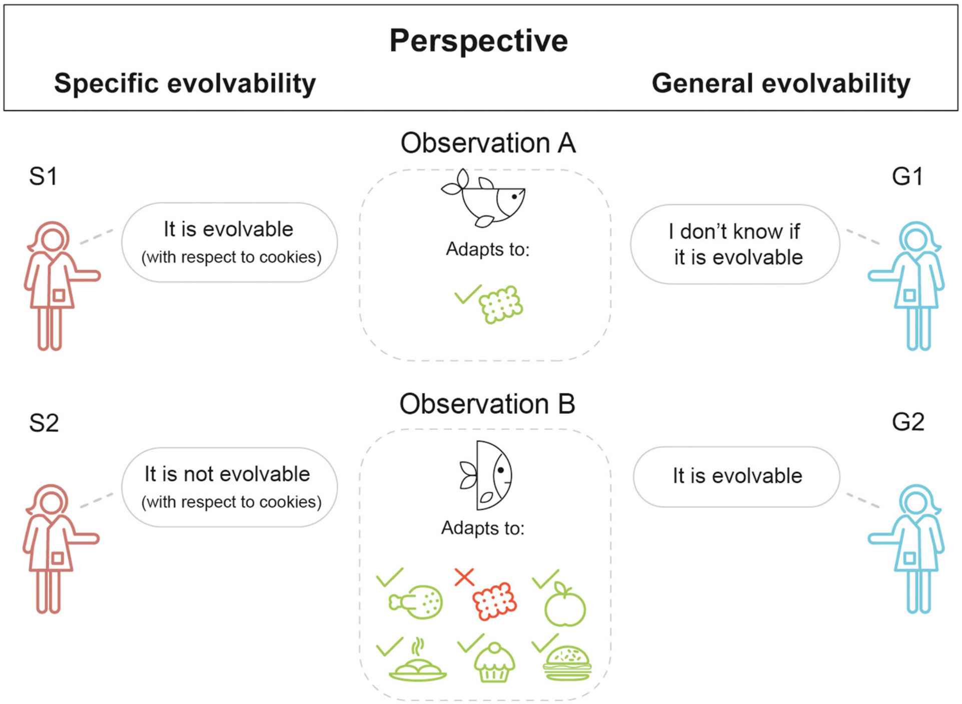

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Figure 3. Specific and general evolvability represent two different perspectives on evolvability. This influences questions and the interpretation of results in evolvability research. Different scientists can reach different conclusions from the same observations. This figure illustrates how scientists with different perspectives (on the left: specific evolvability; on the right: general evolvability) interpret the same observations regarding adaptation very differently. Observation A: a fish species can easily adapt to using cookies as a food source. From the specific evolvability perspective (S1), this is interpreted as high evolvability with respect to cookies. From the general evolvability perspective (G1), it is not possible to draw conclusions since no information is available regarding the ability to adapt to other food sources (environments). Observation B: a fish species cannot adapt to using cookies as food source, but (e.g., due to modular mouth parts) can undergo adaptation to a wide range of other food sources (environments). From a specific evolvability perspective (S2), this is interpreted as a lack of evolvability with regard to cookies. From a general evolvability perspective (G2), the ability to adapt to a wide range of different environments (ability to deal with dietary shifts) indicates high evolvability. Notice that the two perspectives characterise scholars of evolvability rather than the determinants of evolvability. The two perspectives should therefore not be confused with determinants acting at short versus long timescales or with determinants having narrow versus broad scope.

the ability of a virus to evolve resistance to a vaccine, or the ability of an endangered species to evolve adaptations to a specific anthropogenic threat [68,69]. By contrast, scientists adopting a general evolvability perspective view evolvability as the capability of a biological system to adapt to a wide spectrum of environments or of challenges, thus effectively considering evolvability irrespective of the environmental context. This perspective is useful when considering adaptation to unpredictable environments and is frequently used in studies exploring the link between evolvability and diversification [62,70,71].

While specific and general evolvability are both useful conceptualizations of evolvability, insights gained from one do not necessarily translate into insights about the other. Depending on the chosen perspective, the same observation can lead to different conclusions (Figure 3); it informs what questions are asked and affects how results are interpreted. Consider a population that is able to adapt rapidly to a specific challenge, such as a bacterial strain quickly evolving resistance to a particular antibiotic. From the perspective of specific evolvability, this strain has a high evolvability, while viewed from the perspective of general evolvability this single instance of rapid adaptation says nothing about the ability of the strain to adapt to other challenges (heat stress, pH stress, etc.). The distinction between general and specific evolvability should not be confused with the scope of a determinant: the latter is a property of a determinant, whereas the former concerns two different ways of viewing evolvability.

## Concluding remarks

Evolvability is an intricate concept with many facets. Different facets are at centre stage in different lines of research. Furthermore, evolvability is conceptualized in two different ways: specific and general evolvability. Being aware of these differences is crucial to foster an integrated and structured view on evolvability research.

Throughout we argue that evolvability should not be studied as a phenomenon *per se* but as a product of the mechanisms underlying it. Moreover, it is useful to clearly distinguish between determinants that provide variation, shape the effect of variation on fitness, and shape the selection process. A structured mechanistic approach clarifies debates in the literature and provides a sound basis for studying the evolution of evolvability.

Evolvability cannot be quantified by a single number. Both speed of evolution and level of adaptation are relevant, but they are not independent. Scholars should explicitly consider this when conducting evolvability research.

We hope that the proposed mechanistic approach facilitates communication across disciplines, helps to address major questions regarding evolvability (see Outstanding questions), and provides guidelines for the design of future studies on evolvability.

## Outstanding questions

What mechanisms are most important in determining evolvability?

While we are slowly gaining a better understanding of the mechanisms that underlie evolvability, the relative importance of these mechanisms is not always apparent. Which mechanisms are the key drivers of evolvability and its evolution? How does this depend on the ecoevolutionary context?

How do plasticity and evolvability interact?

The relationship between evolvability and plasticity is currently hotly debated and should remain a topic of future study. This discussion includes various questions and concepts, such as the ‘plasticity first hypothesis’, the ‘flexible stem hypothesis’, and the question of whether genes are ‘ leaders or followers’ in evolution.

Does evolvability evolve and if so how?

A mechanistic perspective may help in understanding the evolution of evolvability, as the mechanisms underlying evolvability can clearly evolve. Still, the question remains about whether and how organismal features that are mainly relevant on a long-term perspective (like the ability to adapt to novel environmental challenges) can be shaped by the myopic process of natural selection. Can evolvability be the target of selection or is it the by-product of other processes?

Can evolvability help in the formulation of a predictive theory of evolution?

The question of whether or to what extent evolution is predictable has fascinated evolutionary biologists for decades. Evolvability research may contribute new perspectives to this question: Understanding evolvability may be a first step toward a probabilistic prediction of evolutionary trajectories.

How can practical applications benefit from evolvability research?

While it is clear that evolvability is relevant for major societal problems, such as the evolution of antibiotic

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## Declaration of interests

No interests are declared.

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