OPINION

# Is evolvability evolvable?

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Abstract | In recent years, biologists have increasingly been asking whether the ability to evolve — the evolvability — of biological systems, itself evolves, and whether this phenomenon is the result of natural selection or a by-product of other evolutionary processes. The concept of evolvability, and the increasing theoretical and empirical literature that refers to it, may constitute one of several pillars on which an extended evolutionary synthesis will take shape during the next few years, although much work remains to be done on how evolvability comes about.

The Modern Synthesis is the current paradigm in evolutionary biology[1]; it is an expansion of Darwin's insights[2] that all organisms share common descent and are adapted to the environment through natural selection. Several authors have called for and attempted to outline an extended evolutionary synthesis (EES)[3–7], and most researchers who agree that such a synthesis is necessary regard evo–devo[8–13] as providing the major impetus for it; after all, one of the elements that is missing from the original synthesis is an integrated account of development. In particular, the EES must explicitly account for the evolution of phenotypic novelties[14–16] that are explained only in general terms by the Modern Synthesis. Although we know increasingly more about the molecular bases of such structures, we still do not have detailed scenarios about their evolutionary origin[11], including both the specific developmental changes that are involved and the ecological conditions that favoured them.

Notwithstanding evidence from fields such as phenotypic plasticity, epigenetic inheritance and evo–devo, however, the EES is not yet around the corner. Nonetheless, it is instructive to ask what new elements a new synthesis might contain that are neither part of nor implied by the Modern Synthesis. Here I concentrate on one such element — evolvability. Alberch[17] credited Dawkins[18] with the first usage of the term, although the actual concept is much older. Since then, hundreds of papers have included the word evolvability (364, according to a recent search on Web of Science), most of them conceptual or theoretical, but some based on empirical data. Given my contention that evolvability will be a cornerstone of the EES, it is appropriate to discuss how the idea of evolvability can be properly formulated, in what sense — if any — it differs from the concepts within the Modern Synthesis, such as heritability, and what exactly the EES can contribute to our understanding of evolution.

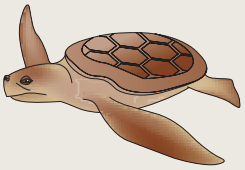
I begin with a discussion of the multiple meanings of evolvability that different authors have proposed. I then attempt to clear up some conceptual confusion and to show that, in fact, the term has been used to refer to different, if partly overlapping, phenomena. The middle portion of the paper will discuss the 'building blocks' of evolvability, such as robustness, modularity and the idea of a genotype→phenotype (G→P) mapping function. Finally, I discuss whether and under what conditions evolvability itself might evolve, and what all of this means for the prospect of an EES.

## The many meanings of evolvability

Although evolvability is a relative latecomer in the jargon of evolutionary biology, a remarkable number of people have attempted formal definitions of it[19], generating some conceptual confusion, or at least pluralism, about what exactly it is. I will consciously refrain from providing my own definition because I am convinced that we are actually dealing with a family of related concepts that are well characterized by the available definitions. Therefore, I will instead examine the existing meanings to illuminate the theoretical work that biologists want evolvability to do and the sorts of empirical data that promote our understanding of evolvability.

At one end of the spectrum, evolvability is either equated with or thought of as a refinement of the classic concept of heritability (TABLE 1). Fisher's fundamental theorem of natural selection[20] shows that the standing genetic variance in a population is a measure of the potential of that population to respond to natural selection. Accordingly, several authors explicitly treat heritability as a measure of evolvability: for example, Flatt[21] defines evolvability as "the ability of a population to respond to selection," whereas Griswold[22] thinks in terms of the rate of evolution of a given character (which depends on its heritability, among other things). Houle[23], however, has proposed that the genetic coefficient of variation, rather than heritability, is actually the appropriate quantification of evolvability (BOX 1). The genetic coefficient of variation allows the potential for evolution of different characters to be directly compared, regardless of type (for example, morphological characters or life history). Recently, this quantitative approach has been expanded into the multivariate concept of a genetic variance–covariance (G)-matrix[24,25], despite standing criticisms of its usefulness[26]. Adopting a different angle, from computational science, Quayle and Bullock[27] operationally measure evolvability as the time that it takes for a population to hit a given phenotypic target (although this makes the simplifying assumption that the target itself doesn't shift over time, as a result of environmental changes). However, all of these are restricted views of evolvability that are certainly not what Dawkins and Alberch intended. Evolvability in the sense related to heritability, or the G-matrix, resides well within the Modern Synthesis and offers no particular excitement to theoretical biologists.

Table 1 | **The 'conceptual spectrum' of evolvability**

| Suggested term | Scale | Description | Effects | Example |
|---|---|---|---|---|
| Heritability (*sensu* Houle) | Within populations | Standing pool of genetic variation and covariation | Determines the response to natural selection within populations |  |
| Evolvability (*sensu* Wagner & Altenberg) | Within species | Includes variability (*sensu* Wagner & Altenberg), depends on genetic architecture and developmental constraints | Affects long-term adaptation, channels evolution along non-random trajectories, allows mid-term exploration of phenotypic space |  |
| Innovation (*sensu* Maynard-Smith & Szathmary) | Within clades | As for within species, but includes the capacity to overcome standing genetic and developmental constraints, opening new areas of phenotypic space for further evolution | Generates major phenotypic (morphological, behavioural or physiological) breakthroughs (novelties) |  |

Wagner and Altenberg[28] moved significantly from this 'classical' concept of evolvability with their groundbreaking articulation of the distinction between variation and variability as determining evolvability. Variation is a measure of the realized differences within a population, whereas variability is the propensity of characters to vary (whether or not they actually do) and depends on the input of new genetic variation through mutation or recombination. Variation is measured by heritability and the G-matrix (or, better, by evolvability *sensu* Houle), whereas variability is an entirely new property that is not considered within the Modern Synthesis. Wagner and Altenberg argue that variability depends on the structure of the G→P mapping function; that is, how the genetic architecture of an organism produces its phenotype through developmental interactions with the external environment[4]. Variability — a property of the so-called 'M-matrix' (analogous to the G-matrix, but extending beyond standing variation to the variance that is induced by new mutations) — has been studied empirically, through mutagenesis experiments, mutation accumulation lines and artificial selection under laboratory conditions, to explore the phenotypes that are producible by genetic variants of reference genotypes[29–30]. One problem is that the M-matrix is a statistical summary of the variability-based relationships among traits, and therefore suffers from the same limitations as the G-matrix[26]. Moreover, it is not clear how one can go from the study of mostly deleterious mutations (which affect the M-matrix) to a theory of mutations that underlie phenotypic innovations.

Despite these caveats, the Wagner and Altenberg paper has unleashed a barrage of new definitions of evolvability, most of which turn out to be variations of Wagner and Altenberg's own proposal. For example, West-Eberhard[30] maintains that evolvability is "the ability of particular features of systems to facilitate change." Dichtel-Danjoy and Felix[31] say it is "the capacity to evolve at the phenotypic level, irrespective of the action of natural selection," a point (that of the possibility of neutral evolution) that is agreed to by Schlichting and Murren[19], for whom evolvability is "the tendency of a genotype or lineage to generate genetic variability and produce or maintain phenotypic variation over evolutionary time, enabling it to pursue diverse [not necessarily adaptive] evolutionary trajectories." Hansen[32], however, although he adopts a definition similar to that of Schlichting and Murren, returns to Wagner and Altenberg's contention that evolvability is interesting if it tells us about adaptation, as it represents "the ability of the genetic system to produce and maintain potentially adaptive genetic variants." These definitions tend to be focused on phenotypes — a significant departure from the gene-centric view that is typical of the Modern Synthesis. The important point that distinguishes the Houle type from the Wagner and Altenberg type of evolvability is that the first depends on standing genetic variation whereas the second accounts for potential variation that is as yet unrealized in the population.

The last category of concepts includes the bold claim that evolvability is the propensity to evolve novel structures, as in Brookfield's proposal[33], "the proportion of radically different designs created by mutation that are viable and fertile." Of course, it is hard to get biologists to agree on what counts as a "radically different design," but the idea actually arches back to Alberch's[17] contention that evolvability is facilitated by major transitions in evolution[34], such as the invention of multicellularity or the sequestration of the germ line.

This brief (and necessarily incomplete) survey demonstrates that biologists think of distinct, yet overlapping, concepts when they talk about evolvability, ranging from some variation of heritability to speculative claims about what made major evolutionary novelties possible, passing through an intermediate type of evolvability (the most highly populated class of definitions and authors) that is conceptualized as whatever property of the genetic architecture and developmental system facilitates (adaptive) phenotypic evolution. Interestingly, the continuum of definitions (TABLE 1) moves across timescales, from consecutive generations (within populations to within species) to mid-range phylogenetic events (within species to within clades), to rare events that might actually occur only once in the history of life (clade-level innovations, major transitions in evolution). This is not to imply that we are dealing with one conception of evolvability that can simply be scaled up (or down) at will. Rather, I see these concepts as a family of connected but partially distinct ideas under the general umbrella of evolvability.

The heritability end of the spectrum sits squarely within the Modern Synthesis. However, the end of the continuum that deals with major transitions is squarely in the territory that should be covered by the EES. This is not because the new ideas are incompatible with the Modern Synthesis (arguably, nothing in the EES is), but because they introduce new processes that enlarge the scope of the original synthesis and cannot reasonably be subsumed by it without resorting to anachronistic *post facto* reinterpretations of what that effort was historically about. The large middle ground of concepts (of the Wagner and Altenberg type) can be seen as a necessary building block of the EES. According to these definitions, evolvability is no longer seen as a matter of standing genetic variance but as a result of the propensity to vary that is afforded by the entire genetic architecture. This emphasizes the relevance of recent work on the properties of genetic networks (as opposed to individual genes or simple biochemical pathways)[27,35–38]. Moreover, the most sophisticated versions of evolvability invoke the ability of the developmental system to produce new adapted phenotypes, thereby pushing the frontier significantly beyond the genetic level and once again pointing to evo–devo as a key discipline for the EES.

**Robustness, modularity and the G→P map**

The related concepts of robustness, modularity, genetic architecture and the already mentioned G→P map can be seen as building blocks that mechanistically underpin evolvability. Most of these terms are new and will probably constitute the vocabulary of the EES. However, they find their roots in one of the early challenges to the almost exclusive focus of the Modern Synthesis on natural selection: the idea that constraints have a significant role not only in limiting adaptation, but also in positively channelling and even facilitating the action of natural selection itself[39–40].

A good example of this shift in focus from selective to non-selective features is A. Wagner's discussion of robustness and 'neutral spaces' in the G→P map[41]. Neutral spaces are broad genotypic regions in which mutations do not change the phenotype or fitness. Neutral spaces mean that developmental systems are 'robust', and can accumulate genetic variants that might be non-neutral in a different environmental context, thereby augmenting evolvability. This concept offers a wholly different take on the old selectionist–neutralist controversy[42].

Box 1 | **Heritability versus evolvability (*sensu* Houle)**

The standard measure of the potential of a natural (or artificial) population to evolve is the classic quantity of heritability, defined as:

$$h^2 = R/S \quad (1)$$

where $h^2$ is the heritability and R is the response of the population to a selective pressure S.

Heritability has been subject to much criticism because it is a local measure (it cannot be generalized beyond a specific trait, a given population and even a particular environment) and because its calculation is plagued by large confidence intervals that make the value of most applications dubious[96]. Houle also pointed out that heritability is not a good comparative measure for the propensity of various populations or traits to respond to selection, because of the high residual variance of many fitness-related traits, which tends to inflate the total phenotypic variance, artificially lowering estimates of $h^2$ (REF. 23).

Instead, Houle proposed to use a measure of the broader property of evolvability, quantified as:

$$CVa = 100\sqrt{(Va)}/X \quad (2)$$

where CVa is the additive coefficient of genetic variation, Va is the additive genetic variance (that is, the portion of total variance that responds to selection), and X is the mean of the character in question in the given population.

Houle combed the literature for papers that allowed a comparison of heritability and evolvability, and found with some surprise that traits that are closely associated with fitness — which typically have low heritabilities — actually have relatively high evolvabilities, an observation that may require a reformulation of our understanding of the evolution of quantitative characters in natural populations.

Empirical support comes from studies showing that transcription factors in bacteria evolve much faster than their target sequences[35], an example of robustness-induced flexibility of regulatory networks. Further evidence comes from viruses, which experience stronger selection for robustness when the likelihood of co-infection is low[43], showing that robustness can be selected for. Also relevant is the finding that regulatory networks in yeast seem to evolve through neutral intermediates[36], and that robustness is one of three steady-state conditions uncovered by mathematical models of evolution in dynamic environments[44].

Robustness[41,45] has been studied using approaches varying from computer simulations of digital organisms, to the artificial evolvability of protein functions, to understanding the properties of gene regulatory networks[46]. Adami, for example, concludes that there is a trade-off between robustness and the speed of replication in the evolution of digital organisms: at low mutation rates, faster–replicating organisms outcompete those characterized by robustness; however, above a certain mutational threshold, the situation reverses[47]. Moreover, mutational robustness itself in these systems can evolve, in accordance with 'quasi-species' theory, which was originally developed to explain evolution immediately after the origin of life in terms of the self-organizing properties of biological systems[48]. Another example is the experimental study of Bloom *et al.* on robustness and its effects on the evolvability of proteins such as cytochrome P450 (REF. 49). An artificially produced thermostable version of P450 is more likely to evolve new or improved functionality because of an increased tolerance to new mutations (A. Wagner would call this an augmented neutral space).

The second keystone of evolvability is modularity[22,50]; that is, the degree to which groups of phenotypic characteristics are independent. For some authors, modularity depends on the level and pattern of pleiotropy and epistasis[51], although these two terms increasingly refer to a heterogeneous multitude of genomic phenomena. Moreover, too often the degree of modularity is empirically measured simply by phenotypic or genetic correlations, which are not reliable inferential tools for depicting the underlying genetic architecture[26].

The major point that authors do agree on is that there is some connection between the modularity of the genetic architecture and evolvability. But the agreement doesn't go much further, partly — I suggest — because of the heterogeneity in the conception of evolvability itself. For example, Budd[52] does not agree with Wagner and Altenberg's 'classical' view — that modularity facilitates evolvability because it uncouples groups of traits, thereby increasing the ability of some traits to evolve independently of other traits. Budd suggests instead that evolvability evolves because "it delivers the goods" — that is, it allows the evolution of whatever developmental system is suitable to a specific environment (and is, therefore, a direct target of natural selection), with modularity having a secondary role. Griswold[22] endorses a conception of evolvability as being

Box 2 | **Low- versus high-dimensional adaptive landscapes**

Conrad's[56] discussion of extra-dimensional bypasses that connect peaks across an adaptive landscape, thereby augmenting the evolvability of populations, anticipated Gavrilets'[57] work on the properties of high-dimensional landscapes by several years. To understand the significance of both Conrad's and Gavrilets' suggestions, we must realize that the so-called problem of 'peak shift' has been a major thorn for theoretical population biologists throughout most of the twentieth century, ever since Wright proposed the very idea of adaptive landscapes[97].

Wright's original 1932 paper aimed at presenting the mathematically complex idea of a relationship between fitness and the genetic architecture of an organism in a way that was digestible by most biologists, who were notoriously poorly versed in mathematics. Wright, following a suggestion by his mentor, presented his ideas graphically, as a diagram that related fitness to various dimensions of genetic differentiation, thereby producing a picture that resembled a rugged landscape. The metaphor was incredibly successful and was adopted by all the major architects of the Modern Synthesis, often with modifications and elaborations that had little direct connection with Wright's ideas (for example, the palaeontologist George Gaylord Simpson talked of phenotypic, not genotypic, landscapes[26], the two being related only through the anything but straightforward genotype→phenotype (G→P) map).

Indeed, one can argue that Wright's metaphor was too successful, as researchers implicitly assumed that the properties of highly dimensional landscapes (which, obviously, cannot be represented in two-dimensional diagrams) are similar to those of the sort of bi- or three-dimensional landscapes that Wright and others were drawing. This generated a large literature[57] that attempted to solve the resulting peak shift problem: if a population climbs a particular adaptive peak (because of selection), how does it then move to another — perhaps higher — peak, when it cannot be selected to evolve through an intermediate phase of lower fitness? Eventually, it became clear that Wright's own solution to the problem, his 'shifting balance' theory, would not work. Without entering into the details, shifting balance is a three-phase process that implies the action of both genetic drift and inter-population (that is, group) selection. Mathematical models as well as some experimental results have cast serious doubt on the likelihood of shifting balance occurring in natural populations[98], except under special circumstances.

A breakthrough came with the work of Gavrilets[57], who considered the possibility that high-dimensional landscapes do, in fact, behave qualitatively differently from low-dimensional ones. Using percolation theory from physics as well as the new generation of fast computer processors, Gavrilets was able to show that reasonably high-dimensional landscapes (that is, those characterized by hundreds or thousands of genetic axes of variation) allow for large areas of quasi-neutral genotypic space in which populations can 'slide' (that is, evolve neutrally) with no appreciable change in their mean fitness. Moreover, Gavrilets made rigorous the concept of extra-dimensional bypasses in genotypic space, landscape features that make it possible for a population to do (in high-dimensional space) the equivalent of a (low-dimensional) peak shift, without requiring the most controversial feature of the shifting balance mechanism — group selection.

We are only beginning to understand the properties of high-dimensional adaptive landscapes, but their logical connections to concepts such as robustness, modularity and G→P mapping will also necessitate their role in our understanding of evolvability.

dependent on pleiotropy (and therefore modularity) but, as we have seen earlier, this derives from thinking of evolvability in terms of genetic (co)variances. Misevic *et al.* take a different approach in simulating the evolution of sexual and asexual organisms, and conclude that sex yields a more modular genetic architecture, which in turn increases evolvability[53]. This opens up the intriguing possibility that evolvability is a by-product of the evolution of sex. However, given how little we understand about the evolution of sex[54], this is unlikely to be of huge comfort.

Inevitably, discussions of robustness and modularity come back to the G→P map. The problem is that this concept has itself been elusive. Dichtel-Danjoy and Felix[31] frame the issue in terms of the accessibility of the 'phenotypic neighbourhood' from a given starting genotype: what phenotypes are or are not 'accessible' (via mutation or recombination)? They give the specific example of the evolution of nematode vulva development, but other instances of what they refer to as anisotropy of phenotypic space are represented by the evolution of RNA folding, and by the genetic code itself. These authors suggest that evolvability can be assessed by genetic screening of induced mutants, and some work in that direction has in fact already appeared[29].

The G→P map does implicitly invoke development (and associated phenomena, such as phenotypic plasticity) as the link between genotype and phenotype, and evo–devo research is called on to fill in the details of this black box. This article is not a review of evo–devo, but it is likely that it will be from the evo–devo research programme that such understanding will be forthcoming. Indeed, Hendrikse *et al.* suggest that what sets evo–devo apart from developmental biology on the one hand and evolutionary biology on the other is precisely the focus on which characteristics of the developmental system allow for an explanation of evolvability[55].

Finally, evolvability can be linked to the G→P map through the idea of adaptive landscapes. In this respect, one of the most lucid discussions is an early work by Conrad[56]. Conrad argues that evolvability is made possible by what Gavrilets[57] more recently called "extra-dimensional bypasses," connectors between phenotypes that appear as a by-product of the characteristics of high-dimensional adaptive landscapes (BOX 2).

## How does evolvability evolve?

Kirschner and Gerhart[58] offered an early lucid discussion of the factors that might facilitate the evolution of evolvability, in particular the properties of regulatory processes that control development. It seems clear to me that evolvability — no matter how it is defined — does evolve. The evidence for this is beyond reasonable doubt. However, whether the evolution of evolvability is the result of natural selection or the by-product of other evolutionary mechanisms is very much up for discussion, and has profound implications for our understanding of evolution in general.

Clear evidence of the evolution of evolvability comes from the fact that both mutation[59] and recombination rates[60] vary across species or clades and are influenced by the genetic makeup of an organism — they are not just passive results of external factors such as the level of background mutagenic radiation. It is also hard to deny that the makeup of the developmental system of a species — say, having an exoskeleton versus an endoskeleton — affects what sort of phenotypic space the descendants of that species can occupy. For example, there are strict limits to the evolution of body size in insects[61] because of the allometric relationships that affect the shape of various organs, given the insect bauplan. The major transitions in evolution[34] clearly affected the evolvability of all descendant clades; consider, for instance, the enormous new areas of phenotypic space that were opened up by the transition from unicellularity to multicellularity.

Table 2 | **Evolvability as a by-product or a result of natural selection?**

| Mechanism | Class of phenomena | Evolvability: target or by-product? |
|---|---|---|
| Natural selection on linked effects | 'Mutator' alleles in asexual systems | Target, increases evolvability |
| Natural selection against signal degradation | Change in mutation frequency (towards reduction) | Target, but lowers evolvability |
| Natural selection against the breakage of adaptive gene complexes | Change in recombination frequency (usually suppression) | Target, but lowers evolvability |
| Natural selection on different genetic architectures (for example, dominance) | Slow decay in linkage disequilibrium | Selection? Increases evolvability |
| Natural selection on adaptive novelties (for example, multicellularity) | Novelties that open up new areas of phenotypic space for future exploration | By-product, increases evolvability |
| Homeostatic buffering | Hsp90-type capacitors | By-product? Increases evolvability |
| Natural selection on other functions | Prion-like capacitors | By-product, increases evolvability |
| Clade selection | Differential speciation or extinction | Selection? Increases evolvability and innovation |

Models of the evolution of evolvability are also clear in their verdict. Carter *et al.* showed that positive epistasis increases evolvability and negative epistasis leads to canalization[51]. Earl and Deem simulated the evolution of protein folding and concluded that randomly fluctuating environments lead to increased evolvability[62], although this can be seen as a by-product of selection for increased recombination.

The arguments and evidence become more equivocal when one moves from evolvability as a by-product of selection to evolvability as the result. Alberch invoked higher-level selection for evolvability when he said that "there must have been selection among pattern generating systems favouring the ones that exhibit the adequate balance between stability and potentiality,"[17] but of course it is not at all clear why selection "must" have facilitated evolvability.

Part of the problem is that such claims are vulnerable to Gould and Lewontin's[63,64] critique of "adaptationism," and for good reason. As Williams[65] put it, "adaptation is a special and onerous concept that should be used only where it is really necessary." The problem is the suggestion that natural selection could somehow favour properties that may prove useful to a given lineage in the future, but that have no present adaptive function. Philosophers of science[66] as well as biologists[67] have rightly cautioned against such a teleological fallacy.

There are some cases in which there is good evidence for a selective explanation for changes in evolvability. Several commentators[68,69] agree, for instance, that bacterial mutator genes[70] are perfectly good examples of systems in which the ability to evolve is selected because of its immediate beneficial consequences. In these systems, the mutator allele is favoured because it is linked to whatever newly adaptive mutant alleles it generates. However, the same authors point out that such systems are unlikely to evolve in sexually reproducing organisms, because recombination rapidly breaks down the linkage between the mutator allele and its beneficial consequences. Note, however, that population genetics theory tells us that linkage disequilibrium is often maintained for long periods of time, depending on the specific genetic architecture that is under consideration (for example, when there is dominance), so different genotypes might have different immediate fitnesses and distinct levels of evolvability. Such a transient direct link between the two would allow natural selection for evolvability in sexual populations[71].

Nonetheless, the conceptual terrain is treacherous (TABLE 2), as illustrated by the case of 'evolution capacitors'. Intriguing experimental work with systems such as the ubiquitous Hsp90 heat-shock proteins[72,73], a prion[74] and even heritable epigenetic markers[75] suggests that neutral genetic variation can accumulate in certain lineages, to be freed under stressful environmental conditions. This could accelerate the pace of adaptive evolution under the new conditions, and Hsp90-like systems would have acted as capacitors of phenotypic evolution. The authors of the original empirical papers[72–74] have presented the idea of 'capacitance' in a way that more or less suggests that natural selection could favour capacitance itself.

There are several reasons for extreme caution about the link between evolvability and capacitance. Although Masel has produced a model that is analogous to a two-locus system in population genetics showing that evolvability through capacitance can evolve by natural selection[76], this again is true only in asexual populations. In sexual organisms, Bergman and Siegal show that functionally compromising most genes, not just heat-shock chaperones, can reveal previously hidden variation[38]. Although this might seem to make capacitance more

## Glossary

**Canalization**
A concept first introduced by C.H. Waddington in the 1940s to refer to the fact that development is often resistant to perturbation and seems to proceed along certain preferential directions (to be 'canalized' along certain channels).

**Epistasis**
A term that originated with quantitative genetic theory to describe a particular type of nonlinear statistical interaction of gene effects on quantitative traits. It is generally interpreted to be the population-level outcome of individual-level mechanistic effects due to the biochemical interaction between gene products. However, there is actually no simple relationship between individual-level, mechanistic epistasis and population-level, statistical epistasis.

**Negative epistasis**
Gene–gene interactions that decrease a given phenotypic effect. This usage of the term epistasis refers directly to population-level, statistical effects.

**Positive epistasis**
Gene–gene interactions that enhance a given phenotypic effect.

**Quasi-species**
A model for the evolution of replicating entities such as RNA and DNA, originally proposed by Eigen. The basic idea is that the early evolution of life was characterized by relatively high mutation rates, so that selection did not act on individual sequences but on clusters of closely related sequences, known as quasi-species.

**Teleology**
A philosophical approach, tracing back at least to Aristotle, that seeks explanations in terms of final causes. In evolutionary biology, teleology has often taken the form of some sort of vitalistic force that pushes evolution in a particular direction, for example, increased complexity.

Box 3 | **The 'levels of selection' debate**

Classical Darwinian theory is framed by the implicit assumption that natural (including sexual) selection occurs at the level of individual organisms. As introductory texts in evolutionary biology often put it, selection acts on individuals, and as a result populations evolve.

This simple view has repeatedly been challenged on different grounds[83,84,86,99]. On the one hand, some biologists and philosophers have suggested that selection can occur above the level of the individual: group selection can take the form of the rather uncontroversial kin selection, inter-deme (that is, inter-population) selection, or even species- and clade-level selection. Although this possibility is now accepted in principle, it is still difficult to find clear empirical examples under natural conditions (but this in turn might be because few people have embarked on the delicate observations and manipulations that are necessary to do so).

From the opposite side of the debate, the claim has been made that the real targets of selection are genes, not organisms[100], because genes are the long-term units of evolutionary change (they are the ones that are copied from one generation to the other, whereas organisms and their traits are 'reconstructed' through development, not inherited). Again, clear cases of gene-level selection have been convincingly demonstrated (for example, the non-Mendelian replication of transposons, repetitive DNA or genes that bias the meiotic process in their favour), but the broader idea that they are the 'real' target of selection can now be conclusively rejected[99].

Part of the debate hinges on conceptual confusions. For example, to claim that genes are 'replicators' (to use Dawkins's terminology) and can therefore be used as units to track the evolutionary process is not at all the same as claiming that they are the targets of natural selection. It is easy enough to conceive of selection at the organismal level (say, to increase photosynthetic capacity), indirectly changing the frequencies of whichever genes are causally connected with the physiological process that is under selection (in this example, photosynthesis). Changes in genetic units can be used to track change over time in populations of plants, without denying that selection is really targeting a higher-level physiological process.

Whereas defenders of higher-than-individual levels of selection face the challenge of providing good empirical examples, advocates of gene-level-only selection are often forced to engage in intellectually unsatisfactory somersaults. For example, a classic objection to the primacy of individual genes is the very uncontroversial observation that genes never affect fitness by themselves but always do so in concert with other genes. Consider the simple case of heterozygosity[101], whereby the net effect on fitness of allele *A* depends on what the other allele at the same locus happens to be (another *A*, or an alternative form, *a*). Because of this context-dependency, how can one possibly argue that it is the gene (*A* or *a*) that is under selection, rather than the genotypic complex that characterizes a given organism? Champions of gene selectionism respond that, from the 'point of view' of the *A* allele, the second allele is 'part of the environment', but to treat the rest of the genome as an environmental factor seems to be a logically forced move to defend the *a priori* idea that selection acts only on genes.

An increasingly popular position among both philosophers and biologists[83,99] is a pluralist one, which admits the theoretical possibility of multiple levels of selection but which treats every specific claim according to the empirical evidence that is available (or obtainable) to back it up. However, one important point that seems to have escaped most discussions on levels of selection is that there is no reason to ontologically favour the individual level (other than, historically, that was the level referred to by Darwin). Sceptics of group selection often claim that it should be considered only when individual-selection explanations are insufficient, essentially invoking Occam's razor. But this is a misunderstanding of the principle of parsimony: although it is surely heuristically sound to avoid introducing explanatory principles that are clearly redundant, there is no known metaphysical reason why nature ought to function on the basis of the simplest possible set of causes. On the contrary, multiple causality is well known in both biology and everyday life, and individual-level selective explanations should not win by default just because they are the ones that we are most used to invoking.

generally applicable, there is no need to invoke selection, as the finding is also compatible with the simpler hypothesis that these systems boost evolvability as a by-product of the way in which genetic networks and G→P mapping in general are structured[68,69,77]. Indeed, both capacitance systems — Hsp90 and the [PSI$^+$] prion-determining region of yeast — have other functions in the cell: Hsp90 is a chaperone molecule that stabilizes other proteins in response to stress[72], and there is indirect evidence that the prion-determining region of yeast is involved in other biological functions related to growth rate in the event of some types of chemical toxicity[74]. At the moment, caution is appropriate unless one is willing to bite the larger bullet and invoke the possibility of clade-level selection[78,79].

The debate on multiple levels of selection[80–82] (BOX 3) certainly cannot be addressed within the scope of this Review. However, the increasing consensus is that multiple levels of selection are in fact demonstrable empirically[83–85] whenever two levels conflict with each other, especially in the case of the individual versus the gene levels. It is certainly theoretically plausible to have selection at levels above the individual[86], and the issue is one of arguing for or against whether this actual happens in particular instances. This can be difficult, for the same reasons that species selection has always been controversial since Stanley[87] proposed the concept as a corollary to the theory of punctuated equilibria[88]. Ultimately, at least at the level of major transitions in evolution, we might simply have too few occurrences for a historically reliable analysis of causality and, for obvious reasons, it is not feasible to conduct experiments at that level of complexity. However, we might still be able to test ideas about evolvability and natural selection at smaller scales, within large clades in which the phylogenetic comparative method can be used at its maximum strength.

## Evolvability and the EES

Although evolvability represents one of the major conceptual novelties since the Modern Synthesis, there are two imminent problems facing the field, one theoretical and one empirical. The theoretical problem is to agree on a definition. I suggest that we should embrace the whole spectrum (TABLE 1), using the different overlapping concepts at different timescales and to address different questions. It follows that we should distinguish among three different meanings of the word, possibly actually using three distinct terms: concepts analogous to heritability (evolvability *sensu* Houle), phenomena such as capacitance and generative developmental constraints (evolvability *sensu* Wagner and Altenberg), and one that deals with the major evolutionary transitions (evolvability *sensu* Maynard-Smith and Szathmary).

The empirical problem is to determine how evolvability itself can evolve, and whether natural selection is responsible[89,90]. One potentially promising approach here is the application of well developed comparative phylogenetic methods[91] to studying evolvability. These methods have been successfully applied to similar problems, such as the comparative study of so-called adaptive constraints[92]; that is, constraints on phenotypic evolution that result from the past action of natural selection. Indeed, adaptive constraints can be seen as a particular instance of lineage-specific evolution of evolvability.

The broader context is that evolvability will constitute one of the foundational blocks for the much anticipated (or dreaded) EES in evolutionary biology[93], together with other concepts that are new to — and yet build upon the achievements of — the Modern Synthesis. This expansion will include the role of phenotypic and behavioural plasticity[4,7], a better understanding of the evolution of development[8–13], the role of epigenetic inheritance systems[94], the idea of genetic accommodation[7], the dynamics of evolution in highly dimensional adaptive landscapes[57], and of course the wealth of information provided by the post-genomic era[95]. It is an exciting moment to be an evolutionary biologist.

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