Title: The genetic consequences of hybridization

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Abstract

In the past decade, advances in genome sequencing have allowed researchers to uncover the history of hybridization in diverse groups of species, including our own. Although the field has made impressive progress in documenting the extent of natural hybridization, both historical and recent, there are still many unanswered questions about its genetic and evolutionary consequences. Recent work has suggested that the outcomes of hybridization in the genome may be in part predictable, but many open questions about the nature of selection on hybrids and the biological variables that shape such selection have hampered progress in this area. We discuss what is known about the mechanisms that drive changes in ancestry in the genome after hybridization, highlight major unresolved questions, and discuss their implications for the predictability of genome evolution after hybridization.

Introduction

It is becoming clear that interspecific hybridization is much more common than previously thought [1,2]. Contrary to historical perspectives, hybridization is now known to be widespread across life’s diversity, spanning both ancient and recent timescales and a broad range of divergence levels between taxa [3–9]. Appreciation of the prevalence of hybridization has renewed interest among researchers in understanding its consequences.

Perhaps one of the most surprising outcomes of this recent research is the extent to which ancient hybridization has contributed to the genomes of extant species (see Glossary). In humans, ~2–5% of the genomes of some populations are derived from ancient admixture with our extinct relatives, the Neanderthals and Denisovans [10], including genes that contribute to adaptation and genetic diseases [11–14]. In other taxa, such as swordtail fishes, as much as 10% of some species’ genomes are derived from ancient hybridization [15]. In addition to raising questions about the nature of species (see Box 1) these findings have spurred interest in the genomic consequences of hybridization.

Observations of hybridization across diverse groups are surprising not only because they reveal previously unknown genetic exchange between species, but also because hybrids typically have a reduced ability to survive and reproduce compared to their parental species. A few notable exceptions of adaptive introgression [16–18] notwithstanding, the overwhelming majority of studies find evidence for selection against hybrids [19–22] and hybridization-derived regions in the genome [3,23–25]. The mechanisms resulting in lower fitness of hybrids are diverse, ranging from ecological selection against hybrids, to differences in the number of deleterious variants harbored by the hybridizing species (known as hybridization load), to negative interactions between genes derived from the two parental species’ genomes (hybrid incompatibilities). Superficially, the observation of widespread hybridization in spite of selection against foreign ancestry seems to conflict with evidence that hybridization is common. However, understanding the processes through which genomes stabilize after hybridization and retain or purge introgressed DNA can help us reconcile both observations.
Because many factors interact simultaneously in hybrids, genome evolution is unusually dynamic after hybridization. In the last several years, the community has shifted from describing the presence of admixture in the genomes of diverse species to documenting patterns of local variation in ancestry along the genome [3,10,25–27]. One common observation from these cases is that selection acts on average to remove ancestry from the minor parent (i.e., the species that contributed less to the genome in admixed populations) in the most functionally important regions of the genome. However, we still lack a basic understanding of the different forces driving variation in local ancestry, how they interact, and how predictable the ultimate outcomes of hybridization are.

Here, we synthesize the emerging “principles” of hybridization – that is, repeated outcomes observed across species – and outline outstanding questions. In doing so, we focus exclusively on a “pulse model” of hybridization, rather than cases in which gene flow is ongoing and strongly spatially structured, as these scenarios often require different analytical methods (e.g [28,29]) and raise distinct questions [30–32]. We also focus our discussion throughout the manuscript explicitly on ancestry variation across a genome [33,34] rather than on statistics summarizing population differentiation that are often correlated with ancestry [35].

One major challenge for researchers studying genome evolution after hybridization is reconciling how different genetic and evolutionary processes may interact in hybrids to shape variation in ancestry along the genome. Most current models consider sources of selection in isolation, but in nature, multiple selective and demographic processes operate simultaneously, potentially interfering with or amplifying each other. We propose that a key priority for future work should be developing predictions about how particular combinations of selective pressures will impact local and global ancestry patterns after hybridization.

With better models for how selection operates in admixed genomes, we can begin to ask whether outcomes of hybridization between species are in part predictable and where we expect these predictions to break down. In addition to leading to a clearer understanding of the architecture of modern genomes, pursuing these questions will allow us to move from describing patterns of local ancestry variation along the genome to pinpointing the evolutionary and genetic processes driving this variation.

**Emerging principles of hybridization**

Why do some regions of the genome retain genetic material derived from hybridization while others have completely purged foreign DNA? We begin here by outlining emerging principles associated with variation in ancestry in admixed genomes, regardless of the evolutionary process driving this variation (see next section). We note that these principles apply to the large number of cases in which selection acts against hybridization, but may not apply to systems where hybridization appears to be neutral or globally beneficial [36–39].
Principle 1: A combination of rapid and slower purging of foreign ancestry stabilizes admixed genomes

Variance in genome-wide ancestry in admixed populations is highest just after hybridization, and decreases over time as recombination breaks down long ancestry tracts. When foreign ancestry is deleterious, selection during this initial period rapidly reduces the population's admixture proportion [24,40]. This initial “fast” period of purging lasts tens of generations [40], shifts ancestry genome-wide [25,41], and begins to generate broad scale differences in ancestry within and among chromosomes. Populations then enter a “slow” period of purging, where selection on individual hybridization-derived haplotypes only subtly shifts genome-wide ancestry proportions. The shape and rate of this change in ancestry can vary from species to species [40], primarily as a function of the total recombination rate (see Principle 3).

Principle 2: Functionally important regions of the genome experience reduced introgression

Although the sources of selection on hybrids undoubtedly differ between species [23,25,27], studies across diverse taxa have largely found that regions of the genome that are dense in coding or conserved elements are particularly resistant to movement between species [3,6,7,27,42–44]. In the case of conserved regulatory elements in humans, this pattern is stronger at enhancers that harbor derived mutations as opposed to ancestral variants [45]. The consistency of the observation that introgression is depleted in functionally important regions implies that barriers to introgression are, in many cases, common, functionally broad, and polygenic [46]. These genome-scale observations echo classic work reporting depleted introgression on sex-chromosomes [42,47,48], a well-accepted rule in the speciation literature [43].

Principle 3: The recombination landscape plays a key role in genome stabilization

Selection acts to remove many introgressed haplotypes after hybridization. Because haplotypes derived from the minor parent species are longer in regions of the genome where recombination events are rare, minor parent haplotypes in low recombination rate regions are more likely to harbor variants that will be harmful in hybrids. This is conceptually similar to the reason why ancestry proportions shift drastically in the early generations after hybridization when ancestry tracts are long (i.e. Principle 1). Even after genome-wide admixture proportions have stabilized, theory predicts that minor-parent ancestry will be more fully removed from regions of the genome with low recombination rates [49,50]. Data from diverse species, including swordtail fish, humans, monkeyflowers, and Heliconius butterflies [25–27,51], support this theoretical prediction (but see [52]). However, differing correlations between recombination rate and gene density can lead to local differences in minor parent ancestry, depending on where in the genome recombination primarily occurs. For example, in humans, recombination rates tend to be locally reduced near genes [53,54], resulting in a tendency to purge introgressed DNA near genes driven by both Principles 2 & 3, while in swordtail fish and birds, recombination rates are elevated near genes [55,56], pitting these rules against one another. In fact, the rapid
evolution of the recombination landscape [57,58] may be another factor contributing to variation in the landscape of introgression across species groups.

**From pattern to process: Genome evolution after hybridization is shaped by diverse evolutionary forces**

Admixed genomes, such as those of modern-day Europeans, are a mosaic of regions with little to no minor parent ancestry (e.g. Neanderthal ancestry) and regions where such ancestry is much more common. The observed ancestry variation in these modern genomes is likely driven by each of the principles described above, which are expected to act whenever there is selection against hybrid ancestry regardless of the underlying source of selection. The next key question is what demographic processes and mechanisms of selection have generated the rugged ancestry landscape we observe many generations after initial hybridization? We are now poised to address this question across species groups, which has been at the heart of research in evolutionary genetics for decades [59].

Because hybridization combines two diverged genomes into a single organism, hybrids face a host of challenges, from reconciling protein interactions at the cellular level [60,61] to targeting the appropriate ecological niche at the organismal level [20]. Although we know that reconciling these challenges often involves changes in ancestry at genes and regulatory regions (Principle 2), we rarely know the mechanisms that act to drive these changes. Historically, researchers have focused on the possible role of hybrid incompatibilities as a major source of selection against hybridization. However, recent work has revealed that other forms of selection, such as hybridization load, can generate similar patterns in hybrid genomes [62]. As such, determining what different patterns of ancestry can tell us about the sources of selection acting after hybridization is a key challenge for this field.

Although, disentangling the causes of selection against introgression is a major goal of the field, and motivator for our work, we caution readers against drawing a bright line separating the models discussed below. This is particularly true for Fisher’s Geometric model (see below), which was proposed as a synthetic framework to interpret and predict many patterns and processes underlying hybrid fitness. However, even the distinction between a simple hybrid incompatibility model and ecological selection against mismatched parental phenotypes is unclear. As such, we approach these models as a source of biological inspiration for the types of mechanisms shaping hybrid genome evolution while noting that edge cases exist that can arguably be placed in several categories.

**Hybrid Incompatibilities**

Dobzhansky-Muller hybrid incompatibilities (DMIs) occur when mutations that have arisen in each parental species’ genome interact negatively in hybrids. DMIs are the best documented and best understood mechanism of selection on hybrids. Indeed, the search for DMIs predates the recognition of the ubiquity of hybridization [63]. In addition to incompatible
substitutions in directly interacting proteins, DMIs can also take the form of reciprocal losses following gene duplication or modifications in co-evolving regulatory elements, among other mechanisms [64–66]. The DMI model is conceptually similar to models of ‘developmental systems drift’, where neutral changes in protein-protein interaction networks can lead to molecular pathways that are incompatible without changing the function of the pathway in either species [67–69]. The loci involved in DMIs identified to date are functionally diverse [70–72], but existing theory and data have hinted at broader evolutionary forces that drive the emergence of hybrid incompatibilities.

DMIs are largely expected to locally restrict gene flow by preventing introgression at the incompatible loci and regions linked to them [73], but can also favor the adaptive introgression of pairs of compatible alleles [74]. Thus, the genomic location of DMIs and the forces that drive their evolution will directly impact where in the genome introgression can occur. One well-established example is overrepresentation of DMIs and reduced levels of introgression on the sex chromosomes [48,71,75–77]. Beyond sex chromosomes, certain genes appear to be repeatedly involved in hybrid incompatibilities (Fig. 3; [72,76,78–81]). While some of this overrepresentation may reflect sampling biases [79], it will become increasingly possible to test the hypothesis that some genes act as “hotspots” for the formation of hybrid incompatibilities as DMIs are characterized across more species. Looking forward, unanswered questions about the number of DMIs that distinguish recently diverged species, the strength of selection acting on them [82], and the rate at which they evolve [83] will be crucial in distinguishing signatures of selection against DMIs from other forms of selection on hybrids.

Hybridization load

Historically researchers have considered selection against introgression to reflect interactions between diverged genomes. However, processes occurring within populations can also generate barriers (or thoroughfares) to introgression [23,24,84]. In other words, selection on introgressed ancestry might reflect the unconditional deleterious effect of a mutation, rather than its poor interaction with other sites in the genome (i.e. DMIs). Such mildly deleterious alleles will preferentially reach fixation in populations with weaker purifying selection, such as those with smaller effective population sizes. With sufficient time, a large number of weakly deleterious mutations can accumulate within a species, generating a strong selective force after hybridization with a species that harbors fewer such mutations. Although each mutation is weakly selected individually, in aggregate these mutations strongly reduce hybrid fitness relative to populations with fewer deleterious mutations, because they are linked to the same haplotypes after hybridization. Interestingly, this prediction holds even if the census population size of the admixed population is also relatively small [25]. Even after genome-wide admixture proportions have largely equilibrated, selection against specific deleterious sites may still drive long-term ancestry purging (see Effects of hybrid demography). Empirical studies support this prediction, showing that ancestry from the species with less effective purifying selection can be depleted
over many generations of selection, particularly in coding and conserved non-coding regions [23,24].

In contrast to other models, which predict widespread selection against minor parent ancestry, the additive hybridization load model predicts selection for directional introgression from the species that harbors fewer deleterious mutations. Alternatively, if deleterious mutations are recessive, theory predicts that selection will favor an excess of foreign ancestry (Box 3), although this dynamic has yet to be identified in empirical data [24,85]. In principle, selection against hybridization load could produce patterns that are distinguishable from other models of selection on hybrids because these weakly deleterious mutations are expected to be broadly distributed throughout the genome and fall within a particular range of selection coefficients (Box 2; [23,24]).

Ecological selection

Ecological selection is a potentially important but poorly understood source of selection on hybrids. This is in part because less is known about both the genetic architecture of ecological adaptation and the ways in which ecological traits can become decoupled in hybrids. Moreover, this source of selection is sensitive to the environments in which hybrids find themselves.

Hybrids may express ecological traits that are intermediate to those of their parent populations (e.g. [86]) or express “phenotypically mismatched” traits ([87] and Box 3). In such cases, ecological selection will disfavor hybrids [88,89], unless hybrids exist in an intermediate ecological niche or an environment favoring these mismatched phenotypes [90–92]. Like the DMI and hybridization load models, ecological selection is predicted to result in biased ancestry around functionally relevant genomic regions, though the expected direction of bias depends on the environment (Box 2).

What patterns of ancestry can indicate the presence of ecological selection on hybrids? The answer to this question depends largely on the architecture of ecological traits [93–96]. While it is straightforward to make predictions about the outcome of ecological selection in hybrids when the trait in question is controlled by a handful of genes, we know less about ancestry shifts after hybridization in ecologically relevant traits with a highly polygenic basis. Theory has explored how traits with a polygenic genetic architecture respond to different types of selection within a species [97,98], but these models do not capture the increased trait variance and ancestry linkage disequilibrium expected in hybrids (see below).

Our discussion of ecological selection on hybrids above ignores “transgressive” segregation – where hybrid trait values fall outside of the range of phenotypes observed in either parent [62,63]. We discuss the possible interaction of ecological selection and transgressive segregation in Box 3.
Polygenic selection on hybrids

Given that populations evolve independently before admixture, hybridization has the potential to decouple suites of adaptive alleles originally linked within the parental species. In hybrids, selection on polygenic traits has been frequently modeled using Fisher’s geometric model [99], a simple mathematical description of the distance of an individual from its phenotypic optimum in quantitative trait space that predicts many of the dynamics of selection against hybrids [62,67–69,100–103]. We note that because of its generality, Fisher’s geometric model has also been used to model selection on DMIs among other phenomena, but focus on its application to polygenic traits here.

In a Fisherian model of polygenic adaptation, individual fitness in the parental species can be described as a function of distance from a phenotypic optimum in quantitative trait space, and isolated populations maintain their respective optima through the independent fixation of sets of trait-increasing and trait-decreasing alleles [100]. Crucially, given enough time, the sets of loci underlying the trait and the sign of their phenotypic effects are likely to differ across populations, even between populations with identical phenotypic optima. In hybrids, recombination decouples these sets of parental alleles. This can result in hybrid phenotypes that fall outside of the phenotypic optima of either parental species, reducing fitness through a phenomenon known as segregation load [104,105]. More precisely, when parental alleles are mixed into different genetic backgrounds, hybrids can show greater variance in a trait than observed in either of the parental species (Fig. 1). If the trait is also under stabilizing selection in hybrids, this increased variance could drive purging of minor parent ancestry over time. Notably, these predictions should hold when parental species are adapting to similar [106] or distinct [107] phenotypic optima (Fig. 1), and when genotypic effects are non-additive [101,108].

Multiple sources of selection

In Box 2, we discuss approaches for distinguishing between sources of selection on hybrids. Another difficult hurdle is characterizing how they may interact. Although research to date has largely focused on each mechanism in isolation, most hybridization events likely involve the interplay between several modes of selection. For example, in the admixture event between humans and Neanderthals, both hybridization load and adaptive introgression have shaped Neanderthal ancestry in modern human genomes [3,23,24] (Fig. 2). Moreover, certain forms of selection can interfere with each other, especially in the early generations following hybridization when long haplotypes of each ancestry type are common (Fig. 2). Simulations hint that it may be possible to disentangle different signals of selection on hybrids using local ancestry variation and changes in ancestry over time (Fig. 2, 4) [109].

Overlooked complexities of selection on hybrids

The mechanisms discussed above likely represent an incomplete picture of the breadth of forms of selection after hybridization. For example, weak but pervasive epistatic interactions (e.g. of interacting genes in pathways) could select for similar shifts in ancestry as expected from
selection on polygenic traits, but whether such weak epistatic interactions are common is unknown. There are also emerging examples of hybrid dysfunction that do not fit cleanly into the sources of selection described above. These cases raise the question of whether these mechanisms are truly distinct or more often represent a combination of selective forces.

For example, hybrid gene regulation presents a case where two frameworks of selection may be simultaneously applied to the same genes. Often under stabilizing selection within the parental species, it is common for cis- and trans-acting regulatory factors to show evidence of compensatory evolution within species [64,110]. As a result, mismatches in these interacting factors in hybrids can lead to dramatic under or overexpression of the genes they regulate (Fig. 5). We speculate that this type of misexpression could result in two forms of selection on hybrids. Large-effect expression aberrations would be selected against as a DMI, with selection acting against heterospecific allelic combinations at cis- or trans-acting loci. For example, allelic combinations that reduce or eliminate expression of a given gene (Fig. 5) can lead to strong selection on this non-functional genotype combination. After the misexpression is resolved, additional smaller effect variants may still have an impact on variance in expression. There may then be a shift to stabilizing selection on overall expression of the gene, with the major selective pressure being increased variance in expression.

Such “priority” effects of selection on hybrids, with rapid purging of interactions in response to strong selective pressures and slower purging associated with weaker selective pressures is reminiscent of the fast versus slow purging of ancestry tracts after initial hybridization (Principle 1). While in many cases there is no bright line between the mechanisms of selection discussed in this section, we propose that this approach of considering phases of selection on hybrids may be a fruitful way of understanding the complexity of several intertwined selective forces acting on hybrid genomes.

Because of this complexity, it is important to also note that to some extent the distinctions made between different sources of selection can be arbitrary and not biologically meaningful. Some types of selection on hybrids may be best described by multiple nested mechanisms, as discussed above, whereas others may be innately coupled – such as a DMI that involves genes underlying an ecologically relevant trait [20,87].

**Predicting the landscape of introgression within and between species**

In the previous sections we discussed what is known about the outcomes of hybridization across diverse species (Principles 1-3) as well as the challenges and prospects for understanding how different evolutionary processes lead to changes in ancestry after hybridization. Armed with these tools, we can begin to explore the directions that these advances will allow geneticists and evolutionary biologists to pursue.
Causes of convergent patterns of introgression across taxa

Biologists have long been fascinated with the question of the predictability of evolution [111]. A key unanswered question is the extent to which we can predict outcomes of hybridization within and between pairs of species. At a broad scale, some predictions can be made due to the interplay between selection and features of genomic organization such as recombination rate and the locations of coding and conserved basepairs, which appear to have predictable effects on ancestry in many species (e.g. Principles 2 & 3). Moving beyond these broad scale features, there are good reasons to expect that replicated hybridization events between the same species will lead to predictable outcomes at the genomic level. In repeated hybridization events, the same genetic interactions and selective forces are predicted to drive concordant changes in ancestry along the genome. Indeed, this has been observed in both replicated experimental and natural hybrid populations [25,41,46,112–115].

While it seems sensible to expect that replicated hybridization events should lead to similar patterns of local ancestry, recent work has suggested that in some cases we may expect more repeatability across taxa than predicted by classic evolutionary theory [19]. Mapping results in Arabidopsis and Xiphophorus have unexpectedly uncovered repeated use of the same genes in hybrid incompatibilities (Fig. 3; [9,116–118]), and certain genetic interactions, such as cytonuclear incompatibilities, are common across the tree of life [119]. These results suggest that some types of genetic interactions are more prone to breaking down in hybrids, perhaps due to their function, the rate at which they accumulate substitutions, or their position in a gene network. Whether incompatibilities frequently evolve in the same genes or pathways has important implications for whether we expect regions resistant to introgression to be shared across species.

Compared to incompatibilities, we know much less about how other forms of selection on hybrids might lead to predictable outcomes at the local scale. Although it has not been directly studied, selection against hybridization load could lead to partially predictable outcomes across replicated hybridization events. Regions of the genome with lower local \( N_c \) should accumulate more weakly deleterious mutations within populations and thus be more likely to be purged after hybridization. Additionally, gene dense regions provide a larger target for functionally relevant mutations to occur and may therefore experience stronger selection in the early generations after hybridization when ancestry tracts are long.

For other mechanisms of selection on hybrids, we expect much lower predictability across systems. For example, if species have independently adapted to distinct ecological conditions, we would not expect the genetic architecture of such traits to be shared except in rare cases (e.g. [120]). Without selection on the same underlying regions of the genome, any repeatability in local ancestry patterns should not exceed what is expected due to broad scale features such as gene density (Principles 2 & 3).
Predicting differences in local and global ancestry between species

Conserved mechanisms that shape ancestry after hybridization can also point to cases where we predict to see differences between species. We recently found differences in the extent to which introgressed haplotypes were retained in coding regions in the genomes of swordtail fish and humans, likely due to differences in the underlying recombination maps [25]. Both species share a strong positive correlation between introgression and the local recombination rate. However, recombination is concentrated in promoters and other functional regions in swordtail fish [55], and tends to occur away from such regions in humans [53,54]. This results in distinct patterns of local ancestry, with swordtail fish retaining more minor parent ancestry than humans in and around genes (presumably due to differing outcomes of the action of Principles 2 & 3 in the two species groups).

Similarly, as discussed in Principle 1, the speed of initial purging of minor parent ancestry is sensitive to the aggregate recombination rate, which differs widely between species [40]. This is because the aggregate recombination rate is strongly influenced by the total number of chromosomes and whether recombination occurs in both sexes - properties that vary widely across the tree of life [40,121]. Notably, these factors together may be important in explaining the extent of introgression observed in the genomes of different species, from cases where retention of minor parent ancestry after admixture is rare, such as Drosophila [122], to those where extensive introgression is common, such as swordtail fish [15].

Effects of hybrid demography

As is the case in non-admixed populations, we expect that certain features of genome evolution after hybridization will be sensitive to the demographic history of hybrid populations themselves. There are multiple reasons to predict that in some contexts hybridization itself may coincide with strong bottlenecks, since hybridization is often driven by ecological disturbance [123,124] and because selection on hybrids can be so strong that it essentially drives population collapse [125]. In addition, hybrid populations tend to form at the edges of parental ranges, where life is challenging for both parental species [126,127].

Intuitively, the long-term size of hybrid populations and the proportion of parental genetic diversity retained in hybrids will have major impacts on genome evolution. In many cases selection on hybrids will be strong enough to overcome the effects of genetic drift, even in small populations, especially in early generation hybrids when many selected sites are linked. Over long time periods, however, populations with small effective size will be less efficient at purging short ancestry tracts that harbor weakly deleterious variants.

Another important consideration is the number of parental individuals from each species that contribute to a hybridization event, which will shape the raw material on which selection can act. We recently mapped the genetic basis of a hybrid melanoma that develops from a tail pigmentation spot in swordtail fish. Notably, this tail pigmentation spot is polymorphic in one of the parental species (~30% frequency; [118]). Presumably due to differences in the founding parental populations, some hybrid populations have both a high frequency of the tail spot and of
melanoma, whereas others have a low frequency of both [118]. Though just one example, this highlights how the genetic contribution of the parental species can be an important element influencing how selection will act within hybrid populations and impact variation between populations.

**Ways forward**

Hybridization often leads to unusually dynamic genome evolution and reorganization, which we are just beginning to understand. As more data become available from diverse hybridization events, we can leverage patterns of ancestry variation to distinguish between the different processes that shape ancestry in the genome after hybridization. Ultimately, we hope such research will lead to an understanding of how different sources of selection interact with each other and with variables such as genome structure, to drive similarities and differences in introgression across species. Although there are outstanding questions that may require years to disentangle (see Box 4), to conclude our discussion, we propose a way forward to tackle a subset of these questions.

**Repeatability in the evolution of hybrid incompatibilities**

In previous sections we discuss the uncertainties surrounding how hybrid incompatibilities arise and the degree to which we expect incompatibilities to arise repeatedly (Fig. 3), either in the same genes [117,118] or in the same regions of the genome [25,27,51]. Such repeatability in the evolution of hybrid incompatibilities would undermine key assumptions of the snowball effect, which posits that each newly arising mutation will have an increasing number of partners with which it may interact negatively, resulting in faster-than-linear accumulation of incompatibilities over time [128]. However, if the mutations that cause DMIs occur repeatedly in the same genes or genomic regions, the rate of this accumulation should slow [129]. Similar predictions emerge from theoretical studies of gene regulatory network evolution, where the likelihood of a gene’s involvement in DMIs is directly related to the density of the gene network [130,131]. Systematic differences in gene network connectivity between species could drive differences in the distribution of DMIs across the tree of life [132]. Though limited by the experimental and statistical challenges inherent in identifying DMIs, both patterns of DMI sharing and a slowed snowball effect should be detectable from empirical data, in experiments with sufficient power.

**Distinguishing between selective forces**

The differences in genetic architecture assumed by each model of selection on hybrids is one promising route to inferring their role in shaping local ancestry after hybridization. Selection on DMIs is generally thought to be stronger and less polygenic than hybridization load models (Box 2; but see [108] for an exploration of polygenic epistatic selection). Higher levels of polygenicity will increase the proportion of neutral basepairs that are linked to sites that are
deleterious in hybrids. Simulations suggest that this should lead to greater purging of minor parent ancestry over time under hybridization load and likely under any polygenic model of selection on hybrids (Fig. 4). Assuming the same total strength of selection on hybrids, the greater relative importance of initial purging under a DMI model and long-term purging in cases of polygenic selection also suggests that there may be systematic differences in the size of deserts of minor parent ancestry in these different scenarios. Comparing the predictions of these different architectures of selection on hybrids using modeling or simulations could allow researchers to begin to distinguish between them, at least on a genome-wide scale (as in [23]).

**Empirical studies of hybrid evolution**

Studies of selection in hybridizing populations offer another route to merge pattern and process, and to tease apart forms of selection acting in hybridizing populations. For example, Chen [133,134] and Fitzpatrick [135] studied weakly differentiated populations and found that genome-wide selection broadly favored ancestry derived from migrants in small populations, consistent with the idea that in small populations foreign ancestry can be favored to lighten the genetic load. In contrast, we recently found little evidence for hybridization load relative to DMIs in shaping genome-wide ancestry in hybrid swordtail populations formed between species with substantial genetic divergence [25]. While these studies used genomic tracking in natural populations, other researchers have leveraged laboratory crosses and systematically varied environmental conditions to explore how ecological selection shapes genome evolution [136]. Combining such observational and manipulative approaches with comparisons across diverse species may reveal the relative importance of the forces shaping evolution after hybridization along the speciation continuum.

**Predicting differences between species after hybridization**

Examples of hybridization across the tree of life poise the field for a broader analysis of what genetic and biological features are associated with variation in rates of introgression. For one, theory predicts that species with fewer chromosomes will undergo faster and stronger purging of minor parent ancestry in their genomes, due to a low aggregate recombination rate [40]. In addition to empirical analyses to address key theoretical predictions, the wealth of newly available data opens up a large number of possible studies of underexplored features of organismal biology that could influence retention of minor parent ancestry after hybridization, which we discuss briefly here.

Life history traits may play an important role in variation in introgression across the tree of life. For example, the extent of selfing or asexual reproduction impacts the genetic diversity of the parent populations, their genetic load, and the frequency with which recombination reshuffles parental haplotypes, and therefore can shape the extent and direction of introgression [137,138]. Similarly, some data suggests that systems with facultative asexually reproduction often retain larger minor parent contributions [139–141], and tolerance of genome duplication and aneuploidy will interplay with retention or loss of parental genomic material.
Variation in the structure and function of the genome between species may also play a key role. The frequency and activity of transposable elements in the genome is a classic mediator of selection against hybrids, but mixed evidence for its generality necessitates broader study [142,143]. Gene expression (or misexpression) that is specific to life cycle stage or tissue type could lead to temporal or tissue-specific fitness effects in hybrids. Notably, recent work has demonstrated that there is weaker selection against Neanderthal ancestry in enhancers that are tissue specific in modern humans [45]. This highlights the potential for such context dependence, which would certainly vary across species groups (e.g. fungi versus plants and animals), and shape how admixed genomes are exposed to the varied forms of selection discussed above.

Conclusions

Though there are major challenges ahead, we have made significant progress in the past decade characterizing the diversity of hybridization events and understanding the processes generating them. Here, we hope to have illustrated that our knowledge of the basic processes at play and theoretical predictions about hybrid genome evolution have grown greatly as a product of this work. On a broad scale, hybrid genome stabilization is now known to be a multi-stage process affected by the distribution of functional elements and the recombination landscape. Multiple selective forces may affect genome evolution after hybridization, and the intersection of these forces is ripe for empirical and theoretical investigation. While many outstanding questions remain, we are now, more than ever, poised to disentangle the factors impacting genome evolution in hybrids and build new models of how they interact. Research in these areas will lead to a better understanding of the nature of reproductive barriers between species and the genetic and evolutionary impacts of hybridization across the tree of life.
Glossary

Adaptive introgression: the hybridization-mediated transfer of parental alleles that increase fitness in either one or both parental species.

Admixture: a more general term than hybridization that encompasses all mating between distinct populations, which may or may not be diverged enough to be considered species.

Ancestry linkage disequilibrium (ancestry LD): statistical association between haplotypes of the same ancestry, that can be caused by physical linkage of sites, selection, or population structure; in the case of linkage disequilibrium due to physical linkage, ancestry LD extends over much greater physical distances than is typical for non-admixed populations.

Ecological selection: Selection driven by the fitness of an organism’s traits in the context of its environment.

Fisher’s geometric model: a general model of selection where fitness is determined by distance from a phenotypic optimum, which has been applied in the hybridization literature to describe selection on polygenic traits (either stabilizing or directional), ecological selection on hybrids, and hybrid incompatibilities (Fig. 1).

Genetic architecture: the number, effect size, and location of loci contributing to a phenotype.

Haplotype: a physically contiguous tract of DNA inherited from a single parent unbroken by recombination.

Hybrid incompatibilities: mutations which arise in interacting genes after two lineages diverge such that when individuals from these populations hybridize a previously “untested” combination of alleles reduces hybrid viability or fertility.

Hybridization load: The burden of mildly deleterious mutations which preferentially accumulated in the parental lineage with less effective selection, leading to reduced fitness of hybrids that harbor more of that species’ genome and selection against ancestry derived from that species.

Introgression: Transfer of a region of the genome between species due to hybridization.

Major parent: the species that contributed a majority of the genome of an admixed population.

Minor parent: the species that contributed a minority of the genome of an admixed population.

Polygenic trait: a trait where phenotypic variation is explained by the combined effects of many, sometimes thousands, of variants spread throughout the genome.

Segregation load: the decrease in average fitness of hybrids expected due to the disruption of co-adapted sets of alleles inherited from the parental species that are broken apart by recombination and independent assortment.

Sexual selection: selection driven by mate choice and competition for mates.

Snowball effect: the faster-than-linear increase in the number of DMIs with increasing numbers of substitutions between two species that is predicted by evolutionary theory.

Species: Two groups of organisms where selection against reproduction between them ranges from strong impacts on viability or fertility to complete inviability or infertility (but see Box 1).
Box 1 – Broader Implications of the Prevalence and Outcomes of Hybridization

The working definition of hybridization as “mating between species” depends on the definition of a species, a perennial problem in evolutionary biology [144]. The idea that a species is a group of individuals that interbreed in nature or could do so in theory (the biological species concept) is largely incompatible with the observation of frequent natural hybridization. Definitions that depend on unique derived traits or monophyly are equally problematic in cases of introgression, where a subset of traits and the genes underlying them may move between species. This philosophical problem has real consequences for the concept of biological diversity and the legal frameworks built to protect that diversity. Major environmental laws are largely species-centric, and the discovery of hybrid ancestry in protected taxa may call their conservation status into question [145,146]. A conservation framework adjusted to the true frequency of hybridization is even more important given rising interest in the potential for artificial hybridization as a conservation tool [147,148].

We suggest that research regarding the genomic outcomes of hybridization may be complementary to conservation frameworks that account for admixture. Selection against introgression in functionally important regions of the genome suggest that even substantial admixture fractions may not homogenize the genomes of the taxa in question to the point of rendering them biologically or ecologically interchangeable. In taxa where hybridization makes traditional species concepts inadequate, a focus on other biological or ecological properties may be more appropriate [146,149].
Box 2 – Predicted outcomes under different sources of selection on hybrids

Here, we discuss ancestry patterns that are consistent with, though not necessarily diagnostic of, different modes of selection on hybrids.

**Selection against minor parent ancestry** – Under the DMI model, loci derived from the minor parent are more likely to uncover incompatibilities elsewhere in the genome, leading to global selection against minor parent ancestry [25]. Similarly, under a model of polygenic selection against hybrids as a function of the disruption of co-adapted parental alleles, loci derived from the minor parent will, on average, result in hybrids whose genotype combinations are further from phenotypic optima. This may result in a genome-wide shift towards major parent ancestry.

**Selection is context dependent** – In the case of hybridization load, selection is expected to act against ancestry derived from the parental species with lower historical effective population size, whether that is the major or minor parent [23–25]. Likewise, in the case of ecological selection, expected patterns are driven by the ecological environment. If hybrids occur in a habitat most similar to that of minor parent, selection is expected to favor ancestry from the minor parent, and if hybrids occur in a habitat most similar to that of major parent, selection is expected to favor ancestry from the major parent.

**Unique signals** – Unlike other models, hybridization load is explicitly limited to weak selection: selection coefficients that are much greater than the reciprocal of the historical effective population size of the parental species are not consistent with the predictions of this model [23,24]. Ecological selection is dependent on the environment, and thus changing the relevant environmental parameters should change the direction of selection [150]. Empirical studies evaluating the phenotypes of surviving hybrids compared to parentals could predict the traits and ancestry selected by specific environmental conditions.

**Genetic architecture** – Models of hybridization load and polygenic selection on hybrids tend to envision a scenario in which numerous loci are under weak selection, while DMIs are generally assumed to be stronger and less polygenic. While the validity of some of these assumptions awaits more empirical data, these models should generate distinct predictions about the extent and patterns of purging of minor parent ancestry after hybridization, which have yet to be rigorously characterized (see Fig. 4; Ways Forward).
Box 3 – Complexity introduced by transgressive traits, recessive load, and sexual selection on hybrids

**Ecological selection and transgressive traits** – Later generation hybrids will harbor novel allelic combinations as a result of recombination. While hybrids often have phenotypes that fall within the parental ranges, transgressive traits, or those outside of the distribution observed in either parental species, are also common (approximately 20% of traits in F$_1$s in some studies [61]). Though we might generally expect such traits to be selected against (Fig. 1), transgressive phenotypes are sometimes better suited to novel environments than parental phenotypes, and as a result can promote ecological speciation [151–154]. Because the genetic divergence between species appears to predict the frequency of transgressive traits, we may also expect to see variation in the frequency of hybrid speciation as a function of parental divergence [155,156]. However, measuring this is complicated by the fact that mechanisms driving selection against hybrids, such as hybrid incompatibilities, are also expected to scale with divergence.

**Recessive Load favoring Introgression** – If deleterious mutations segregating in populations are largely recessive, selection could broadly favor foreign ancestry. This is because each diverged population accumulates its own private set of deleterious variants, which will be reciprocally masked by heterozygous ancestry tracts [24,84]. These heterosis dynamics can even mimic the signal of adaptive introgression [85,157].

**Sexual selection** – Often overlooked as a force impacting genome evolution in hybrids, sexual selection acts on hybrids in complex ways that depend on the frequency of both preference and mate choice trait loci in the population [158]. Furthermore, mating preferences are often multivariate [159–162], and recombination can break up trait correlations as well as multimodal preferences [160,163,164], resulting in a variable landscape of sexually selected traits and preferences. The impacts of these recombinant trait and preference phenotypes on ancestry will be largely dependent on the strength and nature of selection exerted by both parental and hybrid females, and whether preferences are fundamentally different in hybrid populations.
Box 4 – Outstanding Questions

The near-term goals discussed in Ways Forward present tractable problems toward which preliminary efforts can be or have been made. Here, we highlight more open-ended questions which will likely take years of further study to address.

**How do we reconcile the evidence of frequent historical gene flow across the tree of life with the evidence for reduced hybrid fitness?** Widespread evidence of historical hybridization in the genomes of modern species suggests that despite strong selection on hybrids (on top of strong prezygotic barriers in many systems), hybrids do persist and contribute to subsequent generations. While this apparent conundrum could be explained in part by the rapid purging of regions of the genome that are deleterious in hybrids, the overall observation remains puzzling, as does the fact that premating barriers which prevent maladaptive hybridization are fragile in so many systems (e.g. [123,165]).

**Are there additional undiscovered variables which contribute to tolerance of introgression?** It has been recently discovered that aggregate recombination rate is a key variable impacting permeability of a genome to introgression, providing a novel explanation for the observation that some species have extremely low rates of introgression despite ongoing hybridization, including classic models such as Drosophila [7]. The observation that fitness of hybrids between pairs of species of a given genetic divergence varies widely across study systems suggests the presence of other, as of yet unknown factors, affecting the strength of selection against hybrids. Whether those factors are the true architecture of selection, the nature of genetic networks, or systematic differences between species (i.e. such as in recombination mechanisms, cell-cycle checkpoints, or organismal complexity) remains to be seen.

**Which theoretical model(s) best represent selection on hybrids?** Established models of selection provide tractable predictions about introgression patterns but may poorly describe the complexity of biological systems. For example, selection against gene misexpression in hybrids may reflect aspects of both DMI s and stabilizing selection on gene expression, depending on the architecture of the trait in question and the strength of selection on variance in expression versus misexpression. These predictions become even more complicated with conflicting sources of selection acting on hybrids and disentangling them may not always be tractable.
Figures

**Fig. 1: Models of selection on polygenic traits in parental species and their implications for hybrids.**

**A. Top** - If two species have adapted from the ancestral state (gray) towards two different phenotypic optima (blue and red respectively), hybrids between those two species are predicted to fall far from the phenotypic optimum of either parental species (purple, bottom). The distribution shown for F2 hybrids was generated simulating a phenotype controlled by 10 loci in each of the parental species with an exponential distribution of effect sizes, a mean trait value of 250 for parent species one (dashed blue line), a mean trait value of 1750 for parent species two (dashed red line), and additive effects at each locus on the phenotype. Simulations were performed in admix‘em [166]. In a case of unequal admixture between the parental species, hybrids will be closer to the phenotypic optimum of the major parental species. This may result in selection against minor parent ancestry at loci underlying the selected trait. 

**B. Top** - Similar principles apply in the case of a polygenic trait under stabilizing selection within the parental species, since different combinations of trait increasing and trait decreasing alleles are expected to have fixed over time in the two parental species. As a result, this should generate increased phenotypic variance in F2 and later generation hybrids. These higher variance phenotypes in hybrids would presumably be selected against via stabilizing selection, since stabilizing selection on the trait is operating in the parental species. Simulations confirm this intuition, with increased trait variance relative to the parental species observed in F2 hybrids (purple bottom). Simulations were performed as above but the average trait value was the same in the two parental species (2200), although the underlying alleles and their effect sizes (drawn from a random exponential distribution) differed.
**Fig. 2: Conflicting selection between linked alleles.** Introgression derived-haplotypes are likely subject to several forms of selection and in some cases these distinct forms of selection may interfere with each other. **A.** Here, we illustrate a case in which there is tight physical linkage between sites that are deleterious in hybrids (such as DMIs) and a site that is beneficial. **Left** - Due to interference between positive and negative selection in early generations when selected sites are linked to the same haplotype, ancestry is relatively stable in this region. **Right** - After a recombination event occurs and breaks apart this linkage, the selected haplotype will begin to rapidly increase in frequency. **B.** Although not easily detectable in frequency scans before fixation, such loci are potentially detectable due to sharp transitions in ancestry over a short genetic distance. Here we illustrate the results of a simulation using the hybrid population simulator admix’em [166] where an adaptive locus \( s = 0.05 \) is flanked on either side with loci deleterious in hybrids (each \( s = -0.05 \), 50 kb away). The admixture proportions simulated here were 75% parent 1 and 25% parent 2 and the simulation was conducted for 200 generations. In this simulation a haplotype arises where recombination events have unlinked the adaptive and deleterious sites, allowing the haplotype harboring the adaptive allele to begin to sweep to fixation. Long before fixation has occurred, however, the adaptive haplotype is detectable due to the sharp ancestry change surrounding it (Left – shown chromosome wide, Right – shown locally in terms of minor parent ancestry).
Fig. 3: Repeated DMI in Xiphophorus. Classic models in evolutionary biology predict that incompatibilities can arise between any pair of interacting genes. Recent empirical work has suggested that certain genes or pathways may be especially prone to becoming involved in hybrid incompatibilities. The gene xmrk independently causes melanoma in hybrids between different swordtail fish species. A. In crosses between X. birchmanni and X. malinche, xmrk interacts with the gene cd97 to generate melanoma in a subset of hybrids [118]. B. In crosses between distantly related species X. maculatus and X. hellerii, xmrk interacts with a different region to cause melanoma [117,167]. Phylogenetic analyses suggest that these incompatibilities with xmrk have arisen independently [118]. Photos of hybrids in B were provided by Manfred Schartl.
**Fig. 4: Differentiating between selective forces in simulations.** A major challenge in the field is distinguishing between possible sources of selection driving particular patterns of local ancestry in hybrids. One promising approach is to use simulations with parameters inferred from the focal species to begin to distinguish between these possibilities. **A.** As an example, we simulate ancestry change under two models, the DMI model and the hybridization load model. Selected sites are shown as red stars, with the size of the star in the schematic corresponding to the strength of selection on individual sites. We note that although most DMIs detected to date are strongly selected against this does not preclude the possibility that weaker DMIs exist. **B.** We performed simulations using SLiM under these two models of selection on hybrids [168]. Admixture proportions for both simulations were set at 75% parent 1 and 25% parent 2, and F1 fitness in hybrids was 0.85. The chromosome simulated here is the length of chromosome 2 in *X. birchmanni* and uses the recombination map inferred for this species [25]. Ancestry was tracked from the time of admixture to 250 generations post admixture and the diploid hybrid population size was 2,000. In the simulation shown in purple, selection on hybrids is driven by selection on three hybrid incompatibilities with dominance of 0.5, randomly positioned along the chromosome. In the simulation shown in black, selection on hybrids mimics a load model, with a total of 160 sites derived from the minor parent under selection (randomly placed in exons) with dominance of 0.5. The shaded area indicates the period of “fast” initial purging (*Principle 1*) which is followed by a slower period of long-term purging in the hybridization load simulation.
Fig. 5: Selection on gene expression in hybrids. Hybridization can generate mismatch between cis- and trans-acting regulatory factors that have co-evolved within the parental lineages to regulate expression of target genes around an expression optimum (i.e. through stabilizing selection). This can result in an incompatibility generated by misregulation and transgressive expression of such genes in hybrids. A. ts pan8 (left) and pkma (right) are examples of genes for which swordtail hybrids exhibit low and high misexpression, respectively (MM – X. malinche, BB – X. birchmanni, MB – F1 hybrids; data from [169]). B. This simplified diagram illustrates how mismatches in co-evolved regulatory elements can cause misexpression. Promoters and transcripts factors (TFs) are a classic example of cis and trans regulatory elements that interact to promote or suppress expression of target genes. Promoters and TFs can evolve to have opposing regulatory effects on target genes to achieve optimal expression (top), leading to differences in structure, interacting residues, or binding affinity between diverged populations. In hybrids, divergent binding sites within the promoter and changes in binding affinity of the TF may result in over or under expression of target genes, leading to misexpression (bottom).
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Competing Interests
The authors declare no competing interests.
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