

The genomic consequences of hybridization

Benjamin M Moran^{1,2†*}, Cheyenne Payne^{1,2†*}, Quinn Langdon¹, Daniel L Powell^{1,2}, Yaniv Brandvain³, Molly Schumer^{1,2,4*}

¹Department of Biology, Stanford University, Stanford, United States; ²Centro de Investigaciones Científicas de las Huastecas “Aguazarca”, Hidalgo, Mexico; ³Department of Ecology, Evolution & Behavior and Plant and Microbial Biology, University of Minnesota, Minneapolis, United States; ⁴Hanna H. Gray Fellow, Howard Hughes Medical Institute, Stanford, United States

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 synthesize 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.

***For correspondence:**

benmoran@stanford.edu (BMM);
cypayne@stanford.edu (CP);
schumer@stanford.edu (MS)

†These authors contributed equally to this work

Competing interests: The authors declare that no competing interests exist.

Funding: See page 20

Received: 01 April 2021

Accepted: 09 July 2021

Published: 04 August 2021

Reviewing editor: Patricia J Wittkopp, University of Michigan, United States

© Copyright Moran et al. This article is distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use and redistribution provided that the original author and source are credited.

Introduction

Recent evidence has shown that hybridization between species is common. Hybridization is widespread across the tree of life, spanning both ancient and recent timescales and a broad range of divergence levels between taxa (*Dobzhansky, 1982; Payseur and Rieseberg, 2016; Sankararaman et al., 2014; Schumer et al., 2016; Rieseberg et al., 1995; Teeter et al., 2008; Turissini and Matute, 2017; Káldy et al., 2020; Chae et al., 2014; Bolnick, 2009; Eberlein et al., 2019; Langdon et al., 2020; Taylor et al., 2014; Delmore and Irwin, 2014; Steensels et al., 2021; Shen et al., 2018; Möller and Stukenbrock, 2017; Langdon et al., 2019; Gryganskyi et al., 2018*). This 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 hybridization shapes 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 (*Sankararaman et al., 2016*), including genes that contribute to adaptation and genetic diseases (*Dannemann et al., 2017; Dannemann and Kelso, 2017; Enard and Petrov, 2018; Zeberg and Pääbo, 2020*). In other taxa, such as swordtail fishes, *Heliconius* butterflies, Italian sparrows, sunflowers, and cichlid fishes, upwards of 10% of some species' genomes are derived from ancient hybridization (*Cui, 2013; Meier et al., 2017; Hermansen et al., 2011; Martin et al., 2013*). These findings have spurred interest in the genomic consequences of hybridization.

Some of this genetic exchange reflects the process of **adaptive introgression**, which has been well-documented in several species (*Marques et al., 2019; Hedrick, 2013; Racimo et al., 2015*). However, the introgression of adaptive and neutral variants occurs against the backdrop of broad, genome-wide selection against hybrids (*Orr, 1995; Arnegard et al., 2014; Svedin et al., 2008;*

Christie and Strauss, 2018) and hybridization-derived regions in the genome (*Sankararaman et al., 2014; Juric et al., 2016; Harris and Nielsen, 2016; Schumer et al., 2018; Calfee, 2021*). 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, widespread selection against foreign ancestry seems to conflict with evidence that hybridization is common. However, understanding the processes through which genomes resist ongoing introgression (in the case of **hybrid zones** or **tension zones**) or stabilize after pulses of hybridization 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 (*Sankararaman et al., 2014; Sankararaman et al., 2016; Schumer et al., 2018; Calfee, 2021; Edelman et al., 2019; Brandvain et al., 2014; Kulmuni et al., 2020; Runemark et al., 2018*). One common observation from these cases is that, on average, selection acts to remove ancestry from the **minor parent** (i.e., the species from which hybrids derive less of their genome) 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 on the many cases where hybridization appears to globally reduce fitness, even if adaptive introgression occurs locally in the genome (*Sankararaman et al., 2016; Song et al., 2011; Heliconius Genome Consortium, 2012*), rather than cases where hybridization appears to fuel diversification, as has been reported in some systems (*Meier et al., 2017; Marques et al., 2019; Meier et al., 2019; Grant and Grant, 2019; Marcet-Houben and Gabaldón, 2015*). We also focus our discussion throughout this article explicitly on ancestry variation across the genome (*Padhukasahasram, 2014; Schumer, 2019*) rather than on statistics summarizing population differentiation that can be correlated with ancestry (*Cruickshank and Hahn, 2014*).

One major challenge for researchers studying the genetic consequences of 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 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.

Models of hybridization and introgression

In this review, we synthesize research into the consequences of admixture spanning different time-scales and population histories of hybridization. The advent of inexpensive whole-genome sequencing has allowed for the detection of ancient hybridization events, adding to a rich literature of contemporary hybridization events (*Taylor et al., 2014; Salvatori et al., 2019; Grant et al., 2005; Chaturvedi et al., 2020; Arantes et al., 2020; Carling and Zuckerberg, 2011; Geraldès, 2014*) and stable zones where hybridization has been ongoing for thousands of generations (*Teeter et al., 2008; Smith et al., 2013; De La Torre et al., 2015; Ramsey, 2003; Szymura and Barton, 1986; Shaw and Wilkinson, 1980; Sage, 1986; Bert and Arnold, 1995; Ruegg, 2008*). The distinct

timescales of different admixture events allow us to ask questions about both the early and late stages of genome evolution and stabilization following hybridization.

Much of our discussion focuses on a pulse model of hybridization, where an admixed population arose from two diverged populations at some point in time in the past, and hybridization has since stopped. While this model is an oversimplification in most cases, many scenarios of introgression can be well approximated by a pulse model (*Taylor et al., 2014; Salvatori et al., 2019; Grant et al., 2005; Chaturvedi et al., 2020; Arantes et al., 2020*), which simplifies interpretation of the dynamics of genome stabilization following hybridization. For example, this model lends itself to evaluating how the genome stabilizes over time, which evolutionary processes occur shortly after initial gene exchange (*Schumer et al., 2018; Matute et al., 2020*), and which occur over a longer time period (*Schumer et al., 2016; Sankararaman et al., 2016; Chaturvedi et al., 2020; Gompert et al., 2006; Trier et al., 2014*).

While pulses of admixture are common, they are not the only mode of admixture. A rich theoretical tradition has examined ongoing gene flow between two distinct populations (a two-island model) and in spatially structured populations (ecotones and tension zones), and there are many empirical examples that are well approximated by these models (*Teeter et al., 2008; Smith et al., 2013; De La Torre et al., 2015; Bronson et al., 2005; Wang et al., 2019; Nolte, 2005*). Often the intuition and results developed from the pulse model can be effectively brought to bear on these more complex models. For example, some of the processes acting on recent migrants in tension zones approximate those occurring shortly after a pulse of admixture (*Sedghifar et al., 2015; Sedghifar et al., 2016*). In other cases, tension zones provide a complementary view of the architecture of selection on hybrids, such as which regions of the genome are intolerant of introgression (*Mallet et al., 1990; Hopkins et al., 2014; Payseur, 2004; Payseur, 2010; Yanchukov, 2006*). Throughout our discussion below, we reference both literatures and highlight cases where results from a pulse model can and cannot be extended to island and spatial models of ongoing introgression.

Emerging principles of hybridization

Why do some regions of the genome retain genetic material derived from hybridization while others are purged of 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 on average acts against hybridization, but may not apply to systems where hybridization is globally neutral or beneficial (*Meier et al., 2017; Meier et al., 2019; Grant and Grant, 2019; Mitchell et al., 2019*).

Principle 1: a combination of rapid and slower removal of foreign ancestry stabilizes admixed genomes

Variance in genome-wide ancestry in admixed populations is predicted to be 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 (*Harris and Nielsen, 2016; Veller, 2019*). This initial 'fast' period of purging lasts tens of generations (*Veller, 2019*), shifts ancestry genome-wide (*Schumer et al., 2018; Matute et al., 2020*), 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 (*Veller, 2019*), primarily as a function of the total recombination rate (see *Principle 3*). These predictions have been explored in a handful of systems to date (hominins, swordtails, *Drosophila*), but theory suggests they should be widespread. Similarly, research in this area has primarily focused on pulses of admixture but related patterns are expected for recent migrants in hybrid zone models (*Sedghifar et al., 2015; Sedghifar et al., 2016*).

Principle 2: functionally important regions of the genome experience reduced rates of introgression

Although the sources of selection on hybrids undoubtedly differ between species (*Juric et al., 2016; Schumer et al., 2018; Brandvain et al., 2014*), studies across diverse taxa have largely found that regions of the genome that are dense in coding or conserved elements tend to be particularly resistant to movement between species (*Sankararaman et al., 2014; Teeter et al., 2008; Turissini and Matute, 2017; Martin et al., 2013; Calfee, 2021; Brandvain et al., 2014; Masly and Presgraves, 2007; Maxwell et al., 2018*). In the case of conserved regulatory elements in humans, this pattern is stronger at enhancers that harbor derived mutations as opposed to ancestral variants (*Telis et al., 2020*). The consistency of the observation that introgression is depleted in functionally important regions implies that selection against minor parent ancestry generates barriers to introgression that are, in many cases, common, functionally broad, and **polygenic** (*Calfee et al., 2020*). These genome-scale observations echo classic work reporting depleted introgression on sex chromosomes (*Martin et al., 2013; Payseur, 2004; Presgraves, 2008*) and asymmetry in the effects of hybridization between the sexes (e.g., *Orr, 1997; Schilthuizen et al., 2011; Turelli, 1998*; Haldane's rule), well-accepted rules in the speciation literature (*Masly and Presgraves, 2007*) that have been thoroughly reviewed elsewhere (*Presgraves, 2008; Payseur and Rieseberg, 2016*).

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 (*Wu, 2001; Nachman and Payseur, 2012*). Data from diverse taxa, including swordtail fishes, humans, monkeyflowers, maize, and *Heliconius* butterflies (*Schumer et al., 2018; Calfee, 2021; Edelman et al., 2019; Brandvain et al., 2014; Martin et al., 2019*), support this theoretical prediction (but see *Corbett-Detig and Nielsen, 2017*). 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 (*Myers et al., 2005; Coop et al., 2008*), resulting in a tendency to purge introgressed DNA near genes driven by *both* Principles 2 and 3, while in swordtail fishes and birds, recombination rates are elevated near genes (*Baker et al., 2017; Singhal et al., 2015*), pitting these rules against one another. In fact, the rapid evolution of the recombination landscape in some taxa (*Auton et al., 2012; Baker et al., 2015*) 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 are a mosaic of regions with little to no minor parent ancestry and regions where such ancestry is much more common. The observed ancestry variation in these modern genomes is likely driven in part by each of the principles described above, which are expected to act whenever there is global selection against hybrid ancestry. 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, which has been at the heart of research in evolutionary genetics for decades (*Turner et al., 2005*), by leveraging data from both ancient and recent hybridization events across diverse groups of species.

Because hybridization combines two diverged genomes into a single organism, hybrids can face a suite of challenges, from reconciling protein interactions at the cellular level (*Sloan et al., 2017; Dandage et al., 2021; Piatkowska et al., 2013*) to targeting the appropriate ecological niche at the organismal level (*Arnegard et al., 2014*). 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 cause of reduced fitness in hybrids. However, recent work has revealed that other forms of selection, such as hybridization load, can generate similar patterns in hybrid genomes (*Simon et al., 2018*). 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 (**Box 1**) and motivator for our work, we caution readers against drawing a strong line separating some of 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. As such, we approach these models as a source of biological inspiration for the types of mechanisms shaping hybrid genome evolution.

Hybrid incompatibilities

Dobzhansky–Muller hybrid incompatibilities (DMIs) occur when mutations that have arisen in each parental species' genome interact negatively in hybrids (*Dobzhansky, 1982*). 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 (*Barbash, 2010*). In addition to incompatible substitutions that arise in directly interacting proteins, DMIs can take the form of reciprocal losses following gene duplication or modifications in co-evolving regulatory elements, among other mechanisms (*Mack and Nachman, 2017; Dion-Côté and Barbash, 2017; Nguyen et al., 2017; Brucker and Bordenstein, 2013*). The DMI model has also been explored in the context of developmental pathways (commonly referred to as 'developmental systems drift'), where compensatory changes in gene interaction networks can lead to divergent molecular pathways that are incompatible in hybrids, despite resulting in the same phenotypes in both parent species (*Schiffman and Ralph, 2018; Tulchinsky et al., 2014; Porter and Johnson, 2002*). The loci involved in DMIs identified to date are functionally diverse (*Presgraves, 2010a; Maheshwari and Barbash, 2011; Atanasov et al., 2018; Dujon and Louis, 2017*), 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 (*Teeter et al., 2008; Zuellig and Sweigart, 2018; Macholán et al., 2008; Macholán et al., 2008; Carling and Brumfield, 2009*), but can also favor the adaptive introgression of pairs of compatible alleles (*Bank et al., 2012*). Thus, the genomic location of DMIs and the forces that drive their evolution will directly impact where introgression can occur in the genome. One well-established example is the observation that introgression is reduced on the sex chromosomes, presumably because DMIs are overrepresented on the sex chromosomes, due to factors such as faster X evolution, meiotic drive, and the importance of X chromosome genes in male fertility (*Trier et al., 2014; Presgraves, 2008; Maheshwari and Barbash, 2011; Qvarnström and Bailey, 2009; Storchová et al., 2010*). Beyond sex chromosomes, certain genes appear to be repeatedly involved in hybrid incompatibilities (**Figure 1**; *Trier et al., 2014; Atanasov et al., 2018; Barr and Fishman, 2010; Chase, 2007; Schartl, 2008; Arévalo, 2020; Smagulova et al., 2016; Davies et al., 2016*). While some of this overrepresentation may reflect sampling biases (*Chase, 2007*), as DMIs are characterized across more species it will become increasingly possible to test the hypothesis that certain genes act as 'hotspots' for the formation of hybrid incompatibilities. Looking forward, unanswered questions about the number of DMIs that distinguish recently diverged species, the strength of selection acting on them (*Schumer et al., 2014*), and the rate at which they evolve (*Presgraves, 2010b*) 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 (*Juric et al., 2016; Harris and Nielsen, 2016; Bierne et al., 2002*). 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

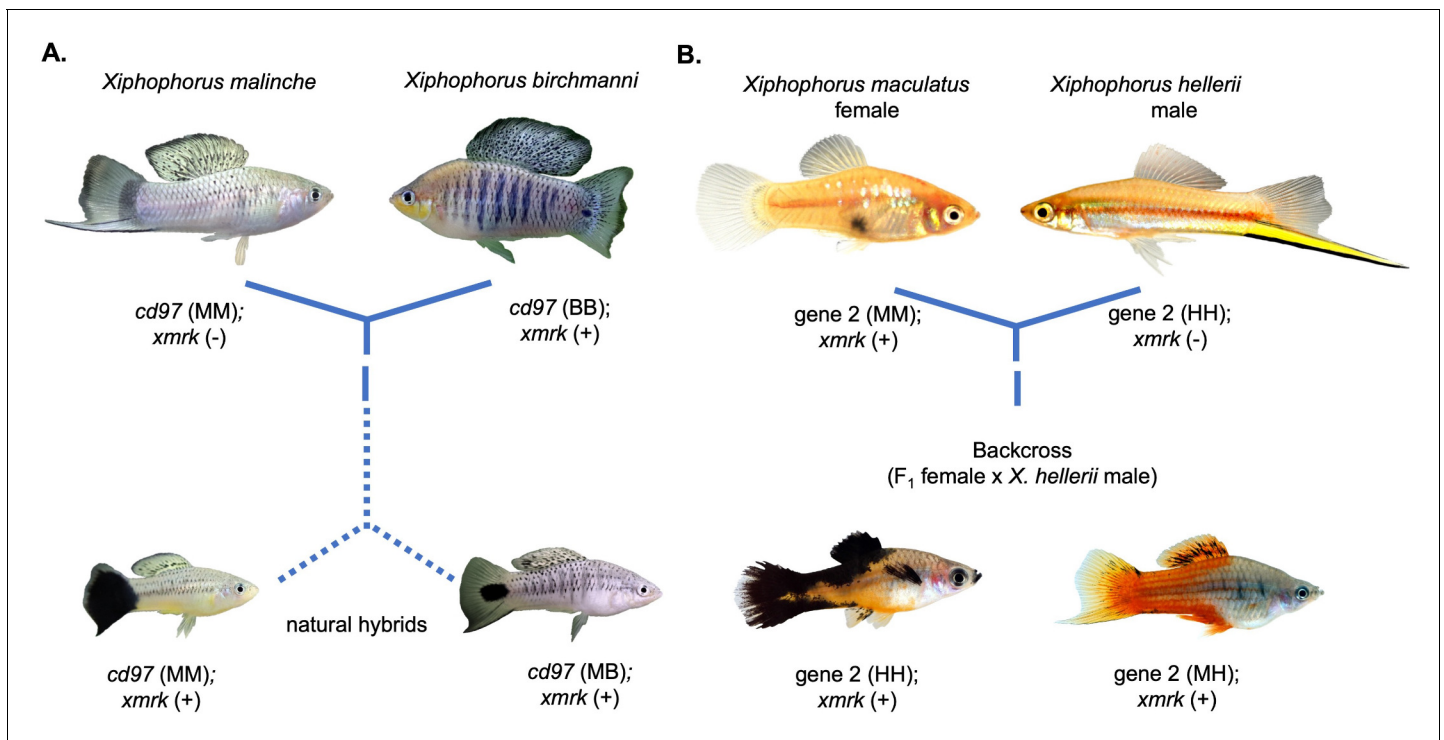


Figure 1. Repeated hybrid incompatibilities in *Xiphophorus*. Classic models in evolutionary biology predict that incompatibilities can arise between any pair of interacting genes. Recent empirical work has suggested that certain genes or pathways may be especially prone to becoming involved in hybrid incompatibilities. The gene *xmrk* independently causes melanoma in hybrids between different swordtail fish species. (A) In crosses between *Xiphophorus birchmanni* and *Xiphophorus malinche*, *xmrk* interacts with the gene *cd97* to generate melanoma in a subset of hybrids (Powell et al., 2020). (B) In crosses between distantly related species *Xiphophorus maculatus* and *Xiphophorus hellerii*, *xmrk* interacts with a different region, *rab3d*, to cause melanoma (Schartl et al., 2010; Kazianis et al., 1998; Lu et al., 2020). Phylogenetic analyses suggest that these incompatibilities with *xmrk* have arisen independently (Powell et al., 2020). Photos of hybrids in (B) were provided by Manfred Schartl.

(as seen in 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, which would generate a strong selective force after hybridization with a species that harbors fewer such mutations. In such cases, hybridization can introduce deleterious mutations at much higher frequencies in the recipient population than expected from mutation-selection balance in the species with higher historical effective population size. Although each mutation is weakly selected against 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 relatively small (Schumer et al., 2018). In the case of a pulse model of admixture, after genome-wide admixture proportions have 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 of the genome (Juric et al., 2016; Harris and Nielsen, 2016).

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 and some empirical data predict that selection will favor an excess of foreign ancestry (Box 2; Harris and Nielsen, 2016; Kim, 2017), especially in the species with lower historical population sizes. 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

Box 1. Predicted outcomes under different sources of selection on hybrids.

Here, we discuss cases in which different mechanisms of selection on hybrids can and cannot be distinguished based on genome-wide ancestry patterns.

Selection against minor parent ancestry – Under the Dobzhansky–Muller hybrid incompatibility (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 (**Schumer et al., 2018**). 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 in hybrid swarms or a lower probability of survival of individuals with higher minor parent ancestry in the case of hybrid zones or tension zones.

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 (**Juric et al., 2016; Harris and Nielsen, 2016; Schumer et al., 2018**). 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 the minor parent, selection is expected to favor ancestry from the minor parent, and if hybrids occur in a habitat most similar to that of the major parent, selection is expected to favor ancestry from the major parent.

Signals that are indicative of a specific mechanism of selection – 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 lower N_e parental species are not consistent with the predictions of this model (**Juric et al., 2016; Harris and Nielsen, 2016**). Ecological selection is dependent on the environment, and thus changing the relevant environmental parameters should change the direction of selection (**Bjerkan et al., 2020**). Though technically challenging, 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 **Figure 4**; Ways forward).

expected to be broadly distributed throughout the genome and fall within a particular range of selection coefficients (**Box 1; Juric et al., 2016; Harris and Nielsen, 2016**).

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., **Hermansen et al., 2011; Hayden et al., 2011**) or express ‘phenotypically mismatched’ traits (**Thompson, 2019a** and **Box 2**). In such cases, ecological selection will disfavor hybrids (**Delmore and Irwin, 2014; Linn et al., 2003; Gow et al., 2007; Melo et al., 2014; Soria-Carrasco et al., 2014; Nosil et al., 2005; Scordato et al., 2020**), unless hybrids exist in an intermediate ecological niche or an environment favoring these mismatched phenotypes (**Schluter, 2000; Stelkens et al., 2009; Rieseberg et al., 1999; Selz and Seehausen, 2019; Hesnauer et al., 2020**). 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 1**).

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 (**Thibert-Plante and Hendry, 2009; Zhang et al., 2020; Comeault, 2018; Lindtke et al., 2013**). While it is straightforward to make predictions about the outcome of ecological selection on 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

Box 2. Complexity introduced by asymmetry in selection, transgressive traits, recessive load, and sexual selection on hybrids.

Asymmetry in selection on Dobzhansky–Muller hybrid incompatibilities (DMIs) – An open question about the impact of DMIs on introgression relates to their genetic architecture. The original DMI model proposed that only one hybrid genotype combination should be under selection, the haplotype that combines two derived mutations (**Figure 4—figure supplement 1A**). Under this model, selection on hybrid haplotypes is strongly asymmetric, and minor parent ancestry is only expected to be purged at one of the two interacting loci (**Figure 4—figure supplement 1A**). Other researchers have proposed variants of the DMI model where selection ranges from less asymmetric (**Gavrilets, 1997; Blanckaert and Bank, 2018**) to completely symmetric (**Schumer et al., 2015; Lindtke and Buerkle, 2015**). In such cases, both hybrid haplotypes would suffer from reduced fitness, leading to purging of minor parent ancestry at both interacting loci (**Schumer et al., 2015**). While there is little data on the architecture of DMIs in general, examples of both types of architecture can be found in the empirical literature, with asymmetric DMIs appearing to be more common (**Maheshwari and Barbash, 2011; Rawson and Burton, 2002; Presgraves, 2010c**).

Ecological selection and transgressive traits – 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; **Thompson, 2019a**). Though we might generally expect such traits to be selected against (**Figure 2**), transgressive phenotypes are sometimes better suited to novel environments than parental phenotypes, and as a result can promote ecological speciation (**Marques et al., 2019; Selz and Seehausen, 2019; Lewontin and Birch, 1966; McCarthy et al., 1995; Buerkle et al., 2000; Rieseberg, 1997; Martin and Richards, 2019; Pereira et al., 2014**). 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 (**Comeault and Matute, 2018; Stelkens and Seehausen, 2009**). However, 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 in admixture between species with similar historical effective population sizes. This is because each diverged population accumulates its own private set of deleterious variants, which will be reciprocally masked by heterozygous ancestry tracts (**Harris and Nielsen, 2016; Bierne et al., 2002**). These heterosis dynamics can even mimic the signal of adaptive introgression (**Kim, 2017; MacPherson, 2020**).

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 signal and preference loci in the population (**Rosenthal, 2013**). Furthermore, mating preferences are often multivariate, and recombination can break up trait correlations as well as multimodal preferences (**Barton and Hewitt, 1989; Brooks, 2005; Chenoweth and Blows, 2006; Gerhardt and Brooks, 2009; Hohenlohe and Arnold, 2010; Seehausen, 2004**), 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 (or males in systems with sex-role reversal), and whether preferences are fundamentally different in hybrid populations.

polygenic genetic architecture respond to different types of selection within a species (**Barghi et al., 2020; Hayward and Sella, 2019**), but these models do not capture the increased trait variance and **ancestry linkage disequilibrium** expected in hybrids (see next section).

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 (**Rieseberg et al., 1999**). We discuss the possible interaction of ecological selection and transgressive segregation in **Box 2**.

Polygenic selection on hybrids

Given that populations evolve independently before admixture, hybridization has the potential to decouple suites of co-adapted alleles originally linked within the parental species. In hybrids, selection on polygenic traits has been frequently modeled using **Fisher’s geometric model** (**Fisher, 1930**), a simple mathematical description of the distance of an individual from its phenotypic optimum, that predicts many of the dynamics of selection against hybrids (**Simon et al., 2018; Schiffman and Ralph, 2018; Tulchinsky et al., 2014; Porter and Johnson, 2002; Tenaillon, 2014; Schneemann, 2019; Yamaguchi and Otto, 2020; Fraïsse et al., 2016**). We note that because of its

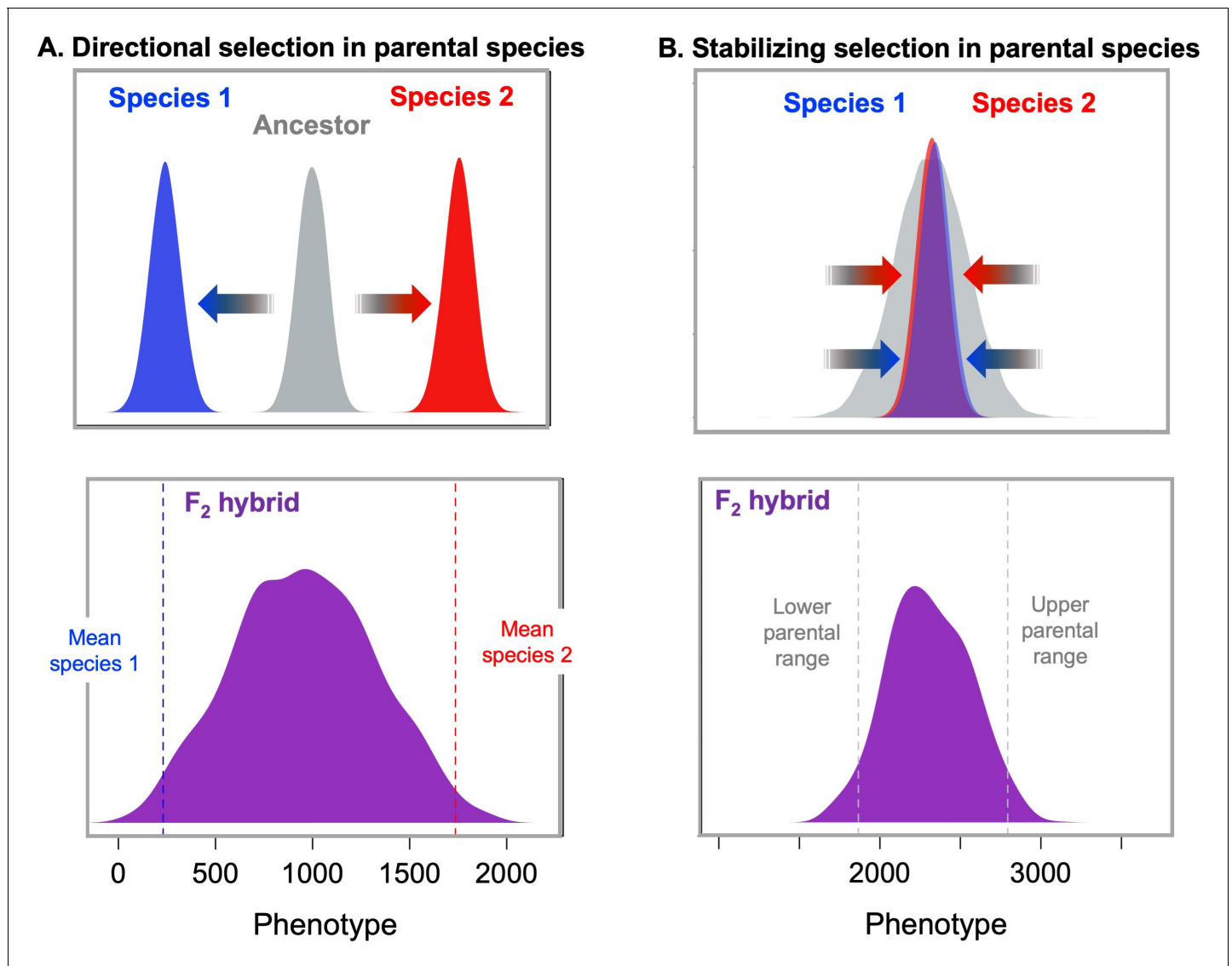


Figure 2. Models of selection on polygenic traits in parental species and their implications for hybrids. (A, top) If two species have adapted from the ancestral state (gray) towards two different phenotypic optima (blue and red respectively), hybrids between those two species (purple, bottom) are predicted to fall far from the phenotypic optimum of either parental species (Barton, 2001; Thompson et al., 2019b; Thompson, 2020). The distribution shown for F₂ hybrids was generated by 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 1 (dashed blue line), a mean trait value of 1750 for parent species 2 (dashed red line), and additive effects at each locus on the phenotype. Simulations were performed in admix'em (Cui et al., 2016). (B, top) Similar principles apply in the case of a polygenic trait that does not differ between the parental species because it has been under stabilizing selection (Slatkin and Lande, 1994; Barton, 2001). In this case, different combinations of trait increasing and trait decreasing alleles are expected to have fixed over time in the two parental species without changing the average trait value across species. As a result, this will generate increased phenotypic variance in F₂ and later generation hybrids compared to the parental species (Slatkin and Lande, 1994; Barton, 2001). These higher variance phenotypes in hybrids should be selected against via stabilizing selection. Simulations shown here illustrate this principle; F₂ hybrids (purple bottom) have increased trait variance relative to the parental species. Simulations were performed as above but the average trait value was the same in the two parental species (2200). The underlying alleles and their effect sizes for this simulation were drawn from a random exponential distribution. Simulation code can be accessed on GitHub (https://github.com/Schumerlab/hybridization_review, copy archived at [swh:1:rev:69a398b89365cc069c6856d990c2b74293b52486](https://www.swh.io/rev/69a398b89365cc069c6856d990c2b74293b52486) . Schumerlab, 2021).

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 (*Tenaillon, 2014*). 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 (*Slatkin and Lande, 1994; Barton, 2001*). 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** (*Barton, 1989; Slatkin and Lande, 1994*). 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 (*Figure 2*). 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 (*Melo, 2019*) or distinct (*Walter et al., 2020*) phenotypic optima (*Figure 2*), and when genotypic effects are non-additive (*Schneemann, 2019; Fierst and Hansen, 2010*).

Adaptive introgression

There is no doubt that haplotypes introduced by hybridization can confer an adaptive advantage (*Hedrick, 2013; Racimo et al., 2015; Song et al., 2011; Heliconius Genome Consortium, 2012; Norris et al., 2015; Feurtey et al., 2019; Corcoran et al., 2016*). Along with hybrid incompatibilities, adaptive introgression is among the best studied consequences of hybridization and has been thoroughly discussed in many previous reviews (*Marques et al., 2019; Hedrick, 2013; Racimo et al., 2015; Suarez-Gonzalez et al., 2018; Mallet, 2005*). Here, we briefly summarize what is known about the impact of adaptive introgression on ancestry in the genome. Intuitively, adaptive introgression increases minor parent ancestry locally around the adaptive allele. The footprint of these peaks in minor parent ancestry is expected to be positively correlated with the selection coefficient in the absence of negative selection on linked sites (see below). However, adaptive haplotypes can actually be shorter in certain demographic scenarios, since they persist longer in hybrid populations, leaving more time for them to be broken up by recombination (*Sedghifar et al., 2016; Shchur et al., 2020*).

Recent work has also highlighted how adaptive introgression can generate unique signatures of ancestry heterozygosity at neighboring sites (*Setter et al., 2019*). As an adaptive haplotype sweeps to fixation, it drives minor parent ancestry to intermediate frequency in large flanking regions, creating a ‘volcano-shaped’ signature of genetic diversity approaching the site under positive selection (*Setter et al., 2019*). This shape is generated because recombination events that shorten the haplotype but still contain the adaptive allele are retained during the sweep, resulting in a concentration of ancestry heterozygosity at the edges of a fixed adaptive haplotype (*Setter et al., 2019; Moest et al., 2020*).

Adaptive introgression against the genomic background

Given broad selection against minor parent ancestry, adaptive introgression is often occurring against a background of genome-wide purging (*Calfee, 2021; Edelman et al., 2019; Turner and Harr, 2014*). In some cases, this has made adaptively introgressed haplotypes easy to identify empirically since they form peaks of high minor parent ancestry against a background of low minor parent ancestry (*Sankararaman et al., 2014; Vernot and Akey, 2014*). This also means that several factors will impact the probability that a globally adaptive allele will introgress between species. These include the locations of potentially adaptive alleles relative to deleterious neighbors, the relative selection coefficients on adaptive and deleterious sites, and other features of genome organization (*Veller, 2019*). Although there is little empirical or theoretical work in this area to date, some predictions can be made from first principles. For example, an adaptive haplotype in a region of the genome with a very low recombination rate would have a lower probability of introgressing than a haplotype with the same advantage in a higher recombination rate region (*Principle 3*).

These factors highlight that beyond distinguishing between sources of selection on hybrids (*Box 1*), 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. As discussed above, in the admixture event between humans and Neanderthals, both hybridization load and adaptive introgression have shaped

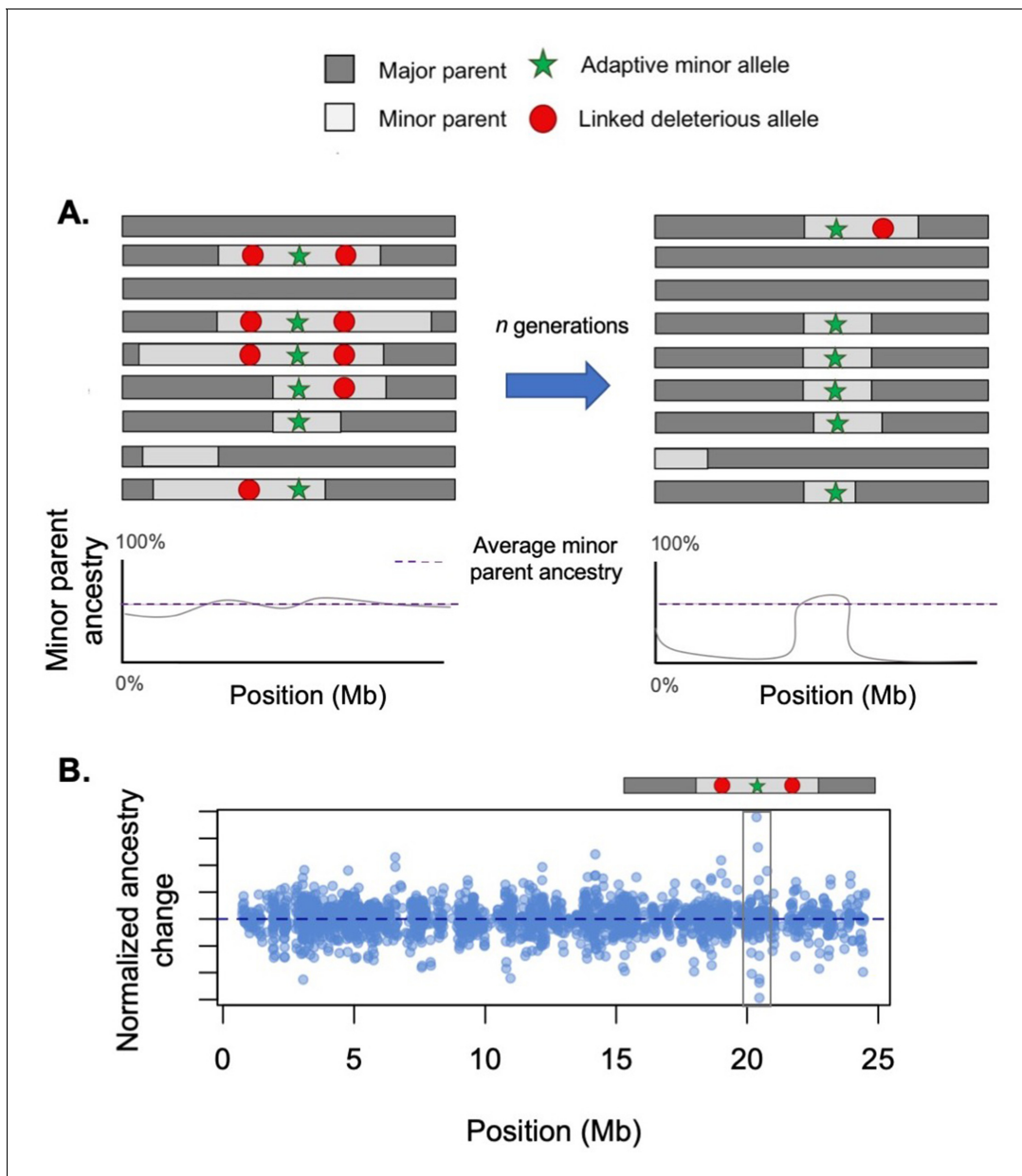


Figure 3. Conflicting selection between linked alleles. Hybridization-derived haplotypes can be deleterious, neutral, or adaptive. In some cases, selection on deleterious and adaptive sites may interfere with each other. (A) Here, we illustrate a case in which there is tight physical linkage between sites that are deleterious in hybrids (such as Dobzhansky–Muller hybrid incompatibilities [DMIs]) and a site that is beneficial. Left – When positively and negatively selected sites are linked on the same haplotype, selection will act on the average of their selection coefficients. In this case, due to interference between positive and negative selection, ancestry is relatively stable in this region when selected sites are linked on the same haplotype. (Right) After a recombination event occurs and breaks apart this linkage, the positively selected haplotype will begin to rapidly increase in frequency. (B) Although not easily detectable using existing methods, such interference effects are potentially detectable using sharp transitions in ancestry over a short distance. Here, we illustrate the results of a simulation using the hybrid population simulator admix'em (Cui et al., 2016) 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 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 (gray box) is detectable due to the sharp ancestry change surrounding it.

Neanderthal ancestry in modern human genomes (Sankararaman et al., 2014; Juric et al., 2016; Harris and Nielsen, 2016). This combination of positive and negative selection on hybridization-derived haplotypes can generate interference, especially in the early generations following

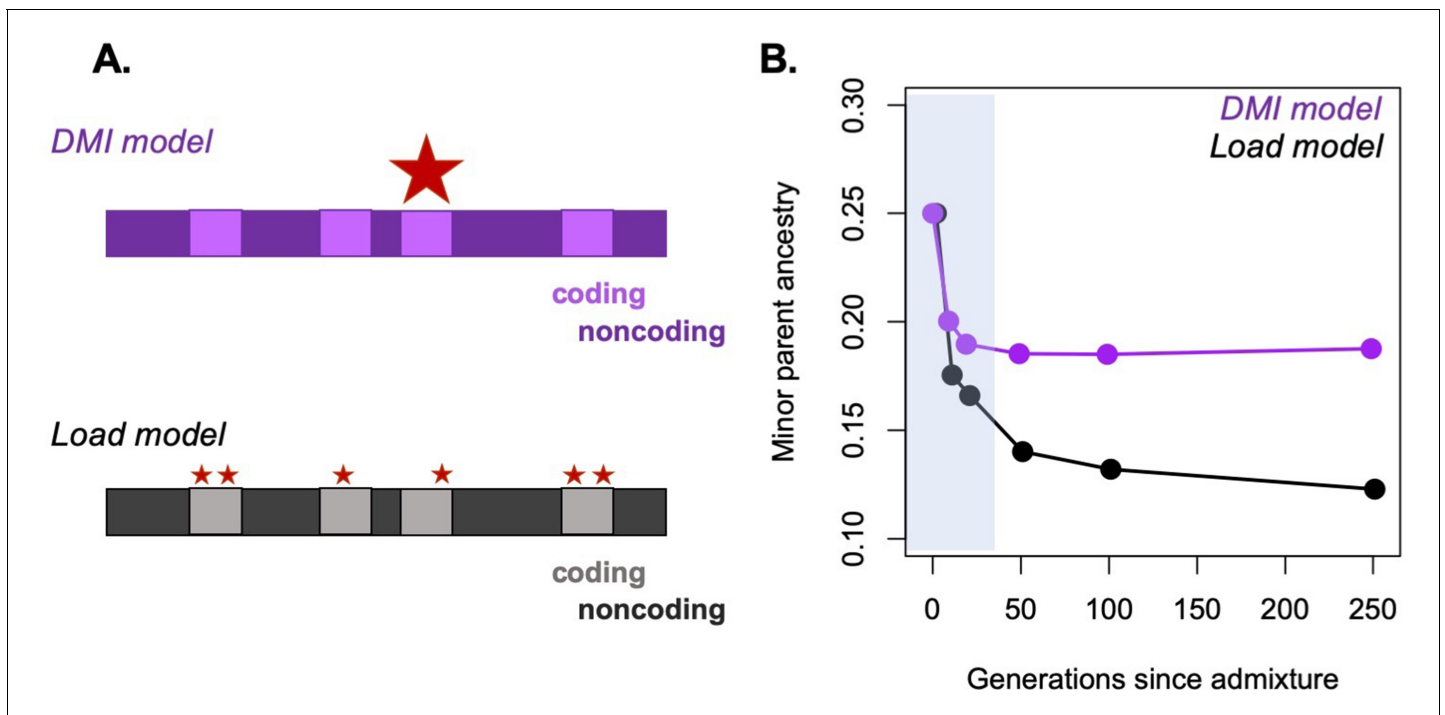


Figure 4. Possible approaches to differentiating between selective forces in simulations. A major challenge in the field is distinguishing between possible sources of selection driving particular patterns of ancestry in hybrids. One promising approach is to use simulations to begin to distinguish between these possibilities. (A) As an example, we simulate ancestry change under two models, the Dobzhansky–Muller hybrid incompatibility (DMI) model and the hybridization load model after a pulse of admixture. 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. (B) We performed simulations using SLiM under these two models of selection on hybrids (Haller and Messer, 2019). Admixture proportions for both simulations were set at 75% parent 1 and 25% parent 2, and F_1 fitness was 0.85. Ancestry was tracked on a 25 Mb chromosome in a diploid hybrid population ($N = 2000$). 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 under selection along the chromosome. In this case, the selected sites are deleterious in all genetic backgrounds. 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. Although differences in the dynamics of purging between the two models are partly driven by the number of loci under selection in hybrids, the DMI model differs from other models of selection because not all minor parent alleles are disfavored (see Figure 4—figure supplement 1). Simulation code can be accessed on GitHub (https://github.com/Schumerlab/hybridization_review). The online version of this article includes the following figure supplement(s) for figure 4:

Figure supplement 1. The Dobzhansky–Muller hybrid incompatibility (DMI) model and model of selection against hybridization load differ not just in assumptions about the number of sites under selection and strength of selection coefficients but also in the types of genotypes under selection.

hybridization when long haplotypes of each ancestry type are common (Figure 3). Simulations hint that it may be possible to disentangle different signals of selection on hybrids using local ancestry variation (Figure 3) or changes in ancestry over time (Figure 4; Uecker et al., 2015), presenting exciting opportunities for future work.

Overlooked complexities of selection on hybrids

The mechanisms discussed above likely represent an incomplete picture of the breadth of forms of selection on hybrids. 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. It is also important to also note that, to some extent, the distinctions made above between different sources of selection can be arbitrary and not biologically meaningful. In some cases, two or more of the selective frameworks may be simultaneously applied – such as a DMI caused by genes underlying an ecologically relevant trait (Arnegard et al., 2014; Thompson, 2019a).

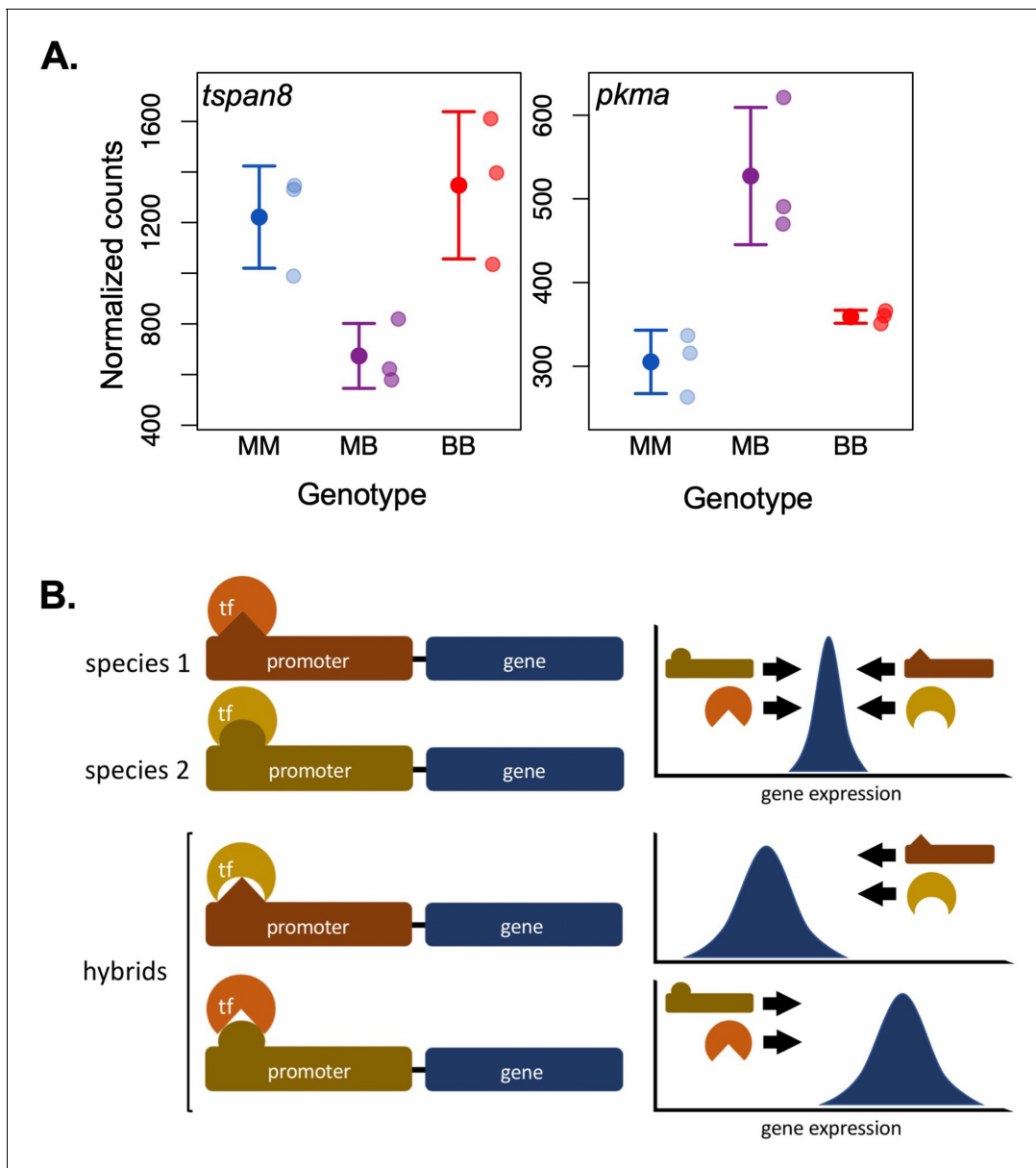


Figure 5. Selection on gene expression in hybrids. Hybridization can generate mismatches between *cis*- and *trans*-acting regulatory factors that have co-evolved within the parental lineages to regulate expression of target genes around an expression optimum (i.e., through stabilizing selection). This can result in an incompatibility generated by misregulation and transgressive expression of such genes in hybrids. (A) *tspan8* (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 Powell et al., 2021). (B) This simplified diagram illustrates how mismatches in co-evolved regulatory elements can cause misexpression. Promoters and transcription 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 underexpression of target genes, leading to misexpression (bottom).

In other cases, multiple selective frameworks may best describe different aspects of the same empirical case. For example, in the case of hybrid gene regulation two frameworks of selection may be 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 (Mack and Nachman, 2017; Mack et al., 2016; Sánchez-Ramírez et al., 2021). As a result, mismatches in these interacting factors in hybrids can lead to dramatic under- or overexpression of the genes they regulate (Figure 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, via 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 (**Figure 5**) can lead to strong selection on this non-functional genotype combination. After the misexpression is resolved, additional *smaller effect* variants from the two parental species may still have an impact on variance in expression (e.g., **Figure 2B**). Changes in ancestry at these variants would then be driven by stabilizing selection on the overall expression of the gene.

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, are reminiscent of the fast versus slow purging of ancestry tracts after initial hybridization (*Principle 1*). While in many cases there is no strong 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.

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 whether evolution is predictable (**Blount et al., 2018**). 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 consistent effects on ancestry in many species (e.g., *Principles 2 and 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 between the same species, the same genetic interactions and selective forces are predicted to drive concordant changes in ancestry along the genome. Indeed, this has been observed in experimental hybrid populations, natural hybrid populations (**Schumer et al., 2018; Chaturvedi et al., 2020; Matute et al., 2020; Calfee et al., 2020; Kovach et al., 2016; Bay et al., 2019; Hufford et al., 2013; Riquet et al., 2019; Smukowski Heil et al., 2019**), and in replicated cline studies (**Westram et al., 2021**; but see **Nolte et al., 2009**).

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 (**Orr, 1995**). Studies in *Arabidopsis* and *Xiphophorus* have repeatedly uncovered some of the same genes underlying hybrid incompatibilities (**Figure 1; Chae et al., 2014; Alcázar et al., 2014; Powell et al., 2020; Schartl et al., 2010**), and certain genetic interactions, such as cytonuclear incompatibilities, are common across the tree of life (**Chase, 2007; Hill, 2017; Bar-Yaacov et al., 2015; Beresford et al., 2017; Bolnick et al., 2008; Burton and Barreto, 2012; He et al., 2020; McDaniel et al., 2007; Giordano et al., 2018**). 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.

Similarly, comparisons of dynamics of adaptive introgression across species have identified possible hotspots in terms of gene families that appear to confer advantages when introgressed. This process could also generate fine-scale repeatability in local ancestry. The best documented examples include immune-related genes (**Sankararaman et al., 2014; Enard and Petrov, 2018**;

Fijarczyk et al., 2018), pigmentation genes (Moest et al., 2020; Vickrey et al., 2018; Giska et al., 2019; Jones et al., 2018; Rotival and Quintana-Murci, 2020; Stryjewski and Sorenson, 2017; Wallbank et al., 2016), and genes that underlie resistance (Song et al., 2011; Lindtke et al., 2013; Norris et al., 2015; Bechsgaard et al., 2017; Whitney et al., 2006; Ford et al., 2015), but many other functional categories of genes or selfish elements could have similar behavior (Staubach et al., 2012; Meiklejohn et al., 2018).

Compared to incompatibilities and adaptive introgression, we know much less about how other forms of selection on hybrids might lead to predictable outcomes at the local scale. Although this 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_e (i.e., due to variation in the effects of background selection; McVicker et al., 2009; Elyashiv et al., 2016) 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, 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., Jones et al., 2012). Without selection on the same underlying regions of the genome, any repeatability in local ancestry patterns in hybrids should not exceed what is expected due to broad-scale features such as gene density (Principles 2 and 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 fishes and humans, likely due to differences in the underlying recombination maps (Schumer et al., 2018). 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 fishes (Baker et al., 2017), and tends to occur away from such regions in humans (Myers et al., 2005; Coop et al., 2008). This results in distinct patterns of local ancestry, with swordtail fishes retaining more minor parent ancestry than humans in and around genes (presumably due to differing outcomes of the action of Principles 2 and 3 in the two species groups). As data from more diverse systems accumulates, comparative analyses of patterns of introgression as a function of these features of genome structure, combined with theoretical analyses, will further develop our understanding of how selection acts in admixed genomes.

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 (Veller, 2019). 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 (Veller, 2019; Stapley et al., 2017). Notably, these factors together may be important in explaining the variation in admixture proportions observed in the genomes of different species that are known to commonly hybridize, from cases where retention of minor parent ancestry after hybridization is rare, such as *Drosophila* (Coyne and Orr, 2004), to those where extensive introgression is common, such as swordtail fishes (Cui, 2013).

Effects of hybrid demography

As is the case in non-admixed populations, we expect that certain features of genome evolution will be sensitive to the demographic history of hybrid populations themselves. The importance of demography has long been appreciated in the theoretical literature on tension zones (though less frequently incorporated into empirical analyses), where dynamics of dispersal and population density at the contact zone (Pierce et al., 2017; Larson et al., 2019) play a key role in the outcomes of hybridization and interpretation of cline analysis (Payseur, 2004; Barton, 2001; Barton and Hewitt, 1989; Bierne et al., 2011). The impacts of demography on hybridization have been less thoroughly explored in the context of pulses of admixture. However, there are multiple reasons to predict that

Box 3. 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 that will likely take years of further study to address.

Are there additional undiscovered variables that contribute to tolerance of introgression? It has been recently shown 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 frequent hybridization in nature, including classic models such as *Drosophila* (Turissini and Matute, 2017). 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, reproductive system) 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 Dobzhansky–Muller hybrid incompatibilities (DMIs) and stabilizing selection on gene expression. These predictions become even more complicated with conflicting sources of selection acting on hybrids (e.g., Figure 3) and disentangling them may not always be tractable.

pulses of hybridization may coincide with strong bottlenecks since they are often driven by ecological disturbance (Fisher et al., 2006; Chunco, 2014) and because selection on hybrids can be so strong that it essentially drives population collapse (Shorter et al., 2017).

Intuitively, the long-term size of hybrid populations and the proportion of parental genetic diversity retained in hybrids should have important 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 a small effective size will be less efficient at purging weakly deleterious variants that occur in short ancestry tracts.

Another important consideration is the number of parental individuals from each species that contributed 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 fishes. Notably, this tail pigmentation spot is polymorphic in one of the parental species (~30% frequency; Powell et al., 2020). 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 (Powell et al., 2020). 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. Studies in other systems such as *Drosophila*, *Mimulus*, *Mus*, and *Caenorhabditis elegans* have identified polymorphic hybrid incompatibilities, suggesting that these founder dynamics could have important impacts on hybrid populations (Zuellig and Sweigart, 2018; Corbett-Detig et al., 2013; Cutter, 2012; Larson et al., 2018; Turner et al., 2012; Good, 2008).

These factors will also impact the repeatability and predictability of genome evolution after hybridization. Distinct demographic histories in hybrid populations or variation in genetic contributions from the parental species could drive differences in local ancestry between populations by shaping features such as the distribution of ancestry tract lengths and the efficacy of selection. These factors could in turn impact the inferences researchers make about the extent of repeatability of local ancestry patterns in studies of replicate hybrid populations (Schumer et al., 2017). Whether demographic differences will substantially limit repeatability in local ancestry in replicate hybrid populations will depend in part on the strength of selection relative to demographic forces such as genetic drift. Simulations matching the inferred demographic histories of independently formed hybrid populations can help researchers begin to tease apart differences due to distinct sources of selection versus demography.

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, across taxa and timescales, we can begin 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 patterns of introgression across species. Although there are outstanding questions that may require years to disentangle (see **Box 3**), we conclude our discussion by proposing a way forward to tackle a subset of these questions.

Repeatability in the evolution of hybrid incompatibilities

In previous sections, we discussed the uncertainties surrounding how hybrid incompatibilities arise and the degree to which we expect incompatibilities to arise repeatedly (**Figure 1**), either in the same genes (*Powell et al., 2020; Schartl et al., 2010*) or in the same regions of the genome (*Schumer et al., 2018; Brandvain et al., 2014; Martin et al., 2019*). Such repeatability in the evolution of hybrid incompatibilities could undermine assumptions of the **snowball effect**, which posits that because newly arising mutations in one species can interact with any derived mutations in the second species, the number of incompatibilities between two species should increase exponentially over time (*Orr and Turelli, 2001*). Data consistent with this phenomenon has been documented in several systems (*Matute et al., 2010; Moyle and Nakazato, 2010; Wang et al., 2015*). However, if the mutations that cause DMIs are enriched in the same genes or genomic regions, the rate of this accumulation should slow (*Kalirad and Azevedo, 2017; Maya-Lastra and Eaton, 2021*). 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 (*Yang and Scarpino, 2020; Satokangas, 2020*). Systematic differences in gene network connectivity between species could drive differences in the distribution of DMIs across the tree of life (*Cutter and Bundus, 2020*). Though limited by the experimental and statistical challenges inherent in identifying DMIs, both evidence for DMI 'hotspots' 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 1**; but empirical evidence is lacking, see *Fierst and Hansen, 2010* 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 (**Figure 4**). Moreover, under a DMI model ancestral and transitional genotypes can be favored by selection, which will actually act to increase minor parent ancestry in some regions of the genome (**Figure 4—figure supplement 1**). Together these factors will lead to greater purging of minor parent ancestry over time under polygenic models of selection against minor parent ancestry, as opposed to classic DMI models (**Figure 4**). Comparing the predictions of these different architectures of selection on hybrids using modeling or simulations could serve as a powerful tool to allow researchers to distinguish between them, at least on a genome-wide scale (as in *Juric et al., 2016*).

Empirical studies of hybrid evolution

Studies of selection in contemporary hybridizing populations offer another route to merge pattern and process, and to tease apart forms of selection acting in admixed populations. For example, *Chen et al., 2019; Chen et al., 2016* and *Fitzpatrick, 2019* 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 that hybridization load shapes genome-wide ancestry in hybrid swordtail populations formed between species with substantial differences in historical effective population size (*Schumer et al., 2018*). 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 (*Smukowski Heil et al., 2019*). 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.

Complex roles of the recombination landscape

Several studies have highlighted the key role of local and global recombination rates in mediating the retention and purging of minor parent ancestry in the presence of selection on hybrids. It is also possible that hybrids will have different recombination landscapes than their parental species due to features such as structural differences between species that suppress recombination (*Kirkpatrick, 2010*), dysfunction in the recombination process (*Davies et al., 2016*), recombination modifiers (*Brand et al., 2018*), or different hotspot usage in hybrids compared to the parental species (*Li et al., 2019*). While historically the difficulty of constructing accurate recombination maps for non-model species would have made understanding these complexities infeasible, the dropping costs of sequencing in combination with new methods for directly mapping double-strand breaks in meiotic cells (*Canela et al., 2016*) may soon put the answers to these questions within reach for a number of hybridizing species.

Predicting differences between species after hybridization

Examples of hybridization across the tree of life pose 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 (*Veller, 2019*, e.g., in species such as *Arabidopsis*, *Drosophila*, mosquitoes). 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 (*Nouhaud et al., 2020*). 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 (*Pickup et al., 2019; Hamlin et al., 2020*). Similarly, some data suggest that systems with facultative asexual reproduction can retain larger minor parent contributions (*Langdon et al., 2019; Marcet-Houben and Gabaldón, 2015; Gallone et al., 2019*), and tolerance of genome duplication and aneuploidy will interplay with retention or loss of parental genomic material (*Steensels et al., 2021*).

Variation in the structure and function of the genome between species may also play a key role. Decades of work have established an important role for inversions in locally restricting (or promoting; *Edelman et al., 2019; Jay et al., 2018; Todesco et al., 2020*) gene flow (*Noor et al., 2001; Wellenreuther and Bernatchez, 2018; Kirkpatrick and Barton, 2006; Faria et al., 2019*). Beyond inversions, 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 (*Smukowski Heil et al., 2021; Castillo and Moyle, 2020; Dion-Côté et al., 2014*). 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 (*Telis et al., 2020*). 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. Other features of genome organization that differ widely across species groups such as the presence of micro-chromosomes, polyploidy, and recombination mechanism will all be rich areas to study in this regard (*Singhal et al., 2015; Nouhaud et al., 2020; Marcet-Houben and Gabaldón, 2015; D'Angiolo et al., 2020; Bozdogan et al., 2021; Lamichhaney et al., 2020; Elgvin et al., 2017; Soltis, 2004; Lafont-Placette et al., 2018; Backström et al., 2008*).

Conclusions

Though there are major challenges ahead, we have made significant progress in the past decade characterizing the diversity of hybridization events across the tree of life. Here, we hope to have illustrated that our knowledge of the basic processes at play and theoretical predictions about hybrid genome evolution has grown greatly as a product of this work. On a broad scale, genome stabilization after admixture is now known to be a multi-stage process affected by the distribution of functional elements and the recombination landscape. Several 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 the recipient population.

Admixture

A more general term than hybridization that encompasses all gene flow 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 a 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; *Figure 2*), ecological selection on hybrids, and hybrid incompatibilities.

Genetic architecture

The number, effect size, and location in the genome of loci contributing to a phenotype.

Haplotype

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

Hybrid incompatibilities

Mutations that 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 that 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. Fitness in hybrids is not reduced relative to the parental species with lower historical effective population size.

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 hybrids between them have reduced viability or fertility. This can range from moderate impacts on viability or fertility to complete inviability or infertility.

Hybrid zone

Spatial zone where hybrids form between the geographic regions occupied by two parental species.

Tension zone

A stable zone where hybrids are found in a narrow geographical region as a result of balance between ongoing dispersal of individuals from parental populations and strong selection against hybrids.

Acknowledgements

We thank Nico Bierne, Erin Calfee, Kelley Harris, Bernard Kim, Erica Larson, Pavitra Muralidhar, Greg Owens, Yuval Simons, Scott Taylor, Ken Thompson, Carl Veller, and members of the Schumer, Brandvain, and Matute labs for helpful discussion or feedback on earlier versions of this work. Stanford University and the Stanford Research Computing Center provided computational support for this project.

Additional information

Funding

Funder	Grant reference number	Author
National Science Foundation	2019273798	Benjamin M Moran
National Science Foundation	2010950	Quinn Langdon
National Science Foundation	1753632	Yaniv Brandvain
National Science Foundation	1754246	Yaniv Brandvain

National Institutes of Health	1R35GM133774	Molly Schumer
Center for Computational, Evolutionary and Human Genomics, Stanford University		Quinn Langdon
Stanford University	Knight-Hennessy Scholars Fellowship	Benjamin M Moran
Howard Hughes Medical Institute	Hanna H. Gray Fellow	Molly Schumer
Human Frontier Science Program	Human Frontiers in Science Young Investigator Award	Molly Schumer

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Author contributions

Benjamin M Moran, Conceptualization, Formal analysis, Visualization, Writing - original draft, Writing - review and editing; Cheyenne Payne, Conceptualization, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review and editing; Quinn Langdon, Conceptualization, Writing - original draft, Writing - review and editing; Daniel L Powell, Conceptualization, Visualization, Writing - original draft, Writing - review and editing; Yaniv Brandvain, Conceptualization, Supervision, Writing - original draft, Writing - review and editing; Molly Schumer, Conceptualization, Resources, Data curation, Software, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Visualization, Methodology, Writing - original draft, Project administration, Writing - review and editing

Author ORCIDs

Benjamin M Moran  <https://orcid.org/0000-0001-5230-0863>

Cheyenne Payne  <https://orcid.org/0000-0003-4651-3824>

Daniel L Powell  <https://orcid.org/0000-0001-9204-645X>

Molly Schumer  <https://orcid.org/0000-0002-2075-5668>

References

- Alcázar R**, von Reth M, Bautor J, Chae E, Weigel D, Koornneef M, Parker JE. 2014. Analysis of a plant complex resistance gene locus underlying immune-related hybrid incompatibility and its occurrence in nature. *PLOS Genetics* **10**:e1004848. DOI: <https://doi.org/10.1371/journal.pgen.1004848>, PMID: 25503786
- Arantes LS**, Ferreira LCL, Driller M, Repinaldo Filho FPM, Mazzoni CJ, Santos FR. 2020. Genomic evidence of recent hybridization between sea turtles at Abrolhos Archipelago and its association to low reproductive output. *Scientific Reports* **10**:12847. DOI: <https://doi.org/10.1038/s41598-020-69613-8>, PMID: 32733067
- Arévalo L**. 2020. Haldane's rule in the placenta: sex-biased misregulation of the *Kcnq1* imprinting cluster in hybrid mice. *International Journal of Organic Evolution* **75**:86–100. DOI: <https://doi.org/10.1111/evo.14132>
- Arnegard ME**, McGee MD, Matthews B, Marchinko KB, Conte GL, Kabir S, Bedford N, Berges S, Chan YF, Jones FC, Kingsley DM, Peichel CL, Schluter D. 2014. Genetics of ecological divergence during speciation. *Nature* **511**:307–311. DOI: <https://doi.org/10.1038/nature13301>, PMID: 24909991
- Atanasov KE**, Liu C, Erban A, Kopka J, Parker JE, Alcázar R. 2018. *NLR* mutations suppressing immune hybrid incompatibility and their effects on disease resistance. *Plant Physiology* **177**:1152–1169. DOI: <https://doi.org/10.1104/pp.18.00462>, PMID: 29794019
- Auton A**, Fledel-Alon A, Pfeifer S, Venn O, Ségurel L, Street T, Leffler EM, Bowden R, Aneas I, Broxholme J, Humburg P, Iqbal Z, Lunter G, Maller J, Hernandez RD, Melton C, Venkat A, Nobrega MA, Bontrop R, Myers S, et al. 2012. A fine-scale chimpanzee genetic map from population sequencing. *Science* **336**:193–198. DOI: <https://doi.org/10.1126/science.1216872>, PMID: 22422862
- Backström N**, Karaiskou N, Leder EH, Gustafsson L, Primmer CR, Qvarnström A, Ellegren H. 2008. A gene-based genetic linkage map of the collared flycatcher (*Ficedula albicollis*) reveals extensive synteny and gene-order conservation during 100 million years of avian evolution. *Genetics* **179**:1479–1495. DOI: <https://doi.org/10.1534/genetics.108.088195>, PMID: 18562642
- Baker CL**, Kajita S, Walker M, Saxl RL, Raghupathy N, Choi K, Petkov PM, Paigen K. 2015. PRDM9 drives evolutionary erosion of hotspots in *Mus musculus* through haplotype-specific initiation of meiotic recombination. *PLOS Genetics* **11**:e1004916. DOI: <https://doi.org/10.1371/journal.pgen.1004916>, PMID: 25568937

- Baker Z**, Schumer M, Haba Y, Bashkirova L, Holland C, Rosenthal GG, Przeworski M. 2017. Repeated losses of PRDM9-directed recombination despite the conservation of PRDM9 across vertebrates. *eLife* **6**:e24133. DOI: <https://doi.org/10.7554/eLife.24133>, PMID: 28590247
- Bank C**, Bürger R, Hermisson J. 2012. The limits to Parapatric speciation: Dobzhansky–Muller Incompatibilities in a Continent–Island Model. *Genetics* **191**:845–863. DOI: <https://doi.org/10.1534/genetics.111.137513>
- Bar-Yaacov D**, Hadjivasiliou Z, Levin L, Barshad G, Zarivach R, Bouskila A, Mishmar D. 2015. Mitochondrial involvement in vertebrate speciation? the case of Mito-nuclear genetic divergence in chameleons. *Genome Biology and Evolution* **7**:3322–3336. DOI: <https://doi.org/10.1093/gbe/ewv226>, PMID: 26590214
- Barbash DA**. 2010. Ninety years of *Drosophila melanogaster* hybrids. *Genetics* **186**:1–8. DOI: <https://doi.org/10.1534/genetics.110.121459>, PMID: 20855573
- Barghi N**, Hermisson J, Schlötterer C. 2020. Polygenic adaptation: a unifying framework to understand positive selection. *Nature Reviews Genetics* **21**:769–781. DOI: <https://doi.org/10.1038/s41576-020-0250-z>, PMID: 32601318
- Barr CM**, Fishman L. 2010. The nuclear component of a cytonuclear hybrid incompatibility in *Mimulus* maps to a cluster of pentatricopeptide repeat genes. *Genetics* **184**:455–465. DOI: <https://doi.org/10.1534/genetics.109.108175>
- Barton N**. 1989. The divergence of a polygenic system subject to stabilizing selection, mutation and drift. *Genetical Research* **54**:59–78. DOI: <https://doi.org/10.1017/S0016672300028378>
- Barton NH**. 2001. The role of hybridization in evolution. *Molecular Ecology* **10**:551–568. DOI: <https://doi.org/10.1046/j.1365-294x.2001.01216.x>, PMID: 11298968
- Barton NH**, Hewitt GM. 1989. Adaptation, speciation and hybrid zones. *Nature* **341**:497–503. DOI: <https://doi.org/10.1038/341497a0>, PMID: 2677747
- Bay RA**, Taylor EB, Schluter D. 2019. Parallel introgression and selection on introduced alleles in a native species. *Molecular Ecology* **28**:2802–2813. DOI: <https://doi.org/10.1111/mec.15097>
- Bechsgaard J**, Jorgensen TH, Schierup MH. 2017. Evidence for Adaptive Introgression of Disease Resistance Genes Among Closely Related *Arabidopsis* Species. *G3: Genes, Genomes, Genetics* **7**:2677–2683. DOI: <https://doi.org/10.1534/g3.117.043984>
- Beresford J**, Elias M, Pluckrose L, Sundström L, Butlin RK, Pamilo P, Kulmuni J. 2017. Widespread hybridization within mound-building wood ants in southern Finland results in Cytonuclear mismatches and potential for sex-specific hybrid breakdown. *Molecular Ecology* **26**:4013–4026. DOI: <https://doi.org/10.1111/mec.14183>, PMID: 28503905
- Bert TM**, Arnold WS. 1995. An empirical test of predictions of two competing models for the maintenance and fate of hybrid zones: both models are supported in a Hard-Clam hybrid zone. *Evolution* **49**:276–289. DOI: <https://doi.org/10.1111/j.1558-5646.1995.tb02240.x>
- Bierne N**, Lenormand T, Bonhomme F, David P. 2002. Deleterious mutations in a hybrid zone: can mutational load decrease the barrier to gene flow? *Genetical Research* **80**:197–204. DOI: <https://doi.org/10.1017/S001667230200592X>, PMID: 12688658
- Bierne N**, Welch J, Loire E, Bonhomme F, David P. 2011. The coupling hypothesis: why genome scans may fail to map local adaptation genes. *Molecular Ecology* **20**:2044–2072. DOI: <https://doi.org/10.1111/j.1365-294X.2011.05080.x>, PMID: 21476991
- Bjerkkan KN**, Hornslien KS, Johannessen IM, Krabberød AK, van Ekelenburg YS, Kalantarian M, Shirzadi R, Comai L, Brysting AK, Bramsiepe J, Grini PE. 2020. Genetic variation and temperature affects hybrid barriers during interspecific hybridization. *The Plant Journal* **101**:122–140. DOI: <https://doi.org/10.1111/tpj.14523>, PMID: 31487093
- Blanckaert A**, Bank C. 2018. In search of the goldilocks zone for hybrid speciation. *PLOS Genetics* **14**:e1007613. DOI: <https://doi.org/10.1371/journal.pgen.1007613>, PMID: 30192761
- Blount ZD**, Lenski RE, Losos JB. 2018. Contingency and determinism in evolution: replaying life's tape. *Science* **362**:eaam5979. DOI: <https://doi.org/10.1126/science.aam5979>, PMID: 30409860
- Bolnick DI**, Turelli M, López-Fernández H, Wainwright PC, Near TJ. 2008. Accelerated mitochondrial evolution and "Darwin's corollary": asymmetric viability of reciprocal F1 hybrids in Centrarchid fishes. *Genetics* **178**:1037–1048. DOI: <https://doi.org/10.1534/genetics.107.081364>, PMID: 18245356
- Bolnick DI**. 2009. Hybridization and speciation in centrarchids. In: Cooke S, Philipp D. P (Eds). *Centrarchid Fishes: Biology, and Conservation*. Hoboken, New Jersey, USA: Wiley-Blackwell. p. 39–69. DOI: <https://doi.org/10.1002/9781444316032>
- Bozdag GO**, Ono J, Denton JA, Karakoc E, Hunter N, Leu JY, Greig D. 2021. Breaking a species barrier by enabling hybrid recombination. *Current Biology* **31**:R180–R181. DOI: <https://doi.org/10.1016/j.cub.2020.12.038>, PMID: 33621502
- Brand CL**, Cattani MV, Kingan SB, Landeen EL, Presgraves DC. 2018. Molecular evolution at a meiosis gene mediates species differences in the rate and patterning of recombination. *Current Biology* **28**:1289–1295. DOI: <https://doi.org/10.1016/j.cub.2018.02.056>, PMID: 29606420
- Brandvain Y**, Kenney AM, Flagel L, Coop G, Sweigart AL. 2014. Speciation and introgression between *mimulus nasutus* and *mimulus guttatus*. *PLOS Genetics* **10**:e1004410. DOI: <https://doi.org/10.1371/journal.pgen.1004410>, PMID: 24967630
- Bronson CL**, Grubb TC, Sattler GD, Braun MJ. 2005. Reproductive success across the Black-Capped chickadee (*Poecile atricapillus*) and carolina chickadee (*P. carolinensis*) Hybrid zone in Ohio. *The Auk* **122**:759–772. DOI: <https://doi.org/10.1093/auk/122.3.759>

- Brooks R.** 2005. Experimental evidence for multivariate stabilizing sexual selection. *Evolution* **59**:871–880. DOI: <https://doi.org/10.1111/j.0014-3820.2005.tb01760.x>
- Brucker RM**, Bordenstein SR. 2013. The hologenomic basis of speciation: gut Bacteria cause hybrid lethality in the genus *Nasonia*. *Science* **341**:667–669. DOI: <https://doi.org/10.1126/science.1240659>, PMID: 23868918
- Buerkle CA**, Morris RJ, Asmussen MA, Rieseberg LH. 2000. The likelihood of homoploid hybrid speciation. *Heredity* **84**:441–451. DOI: <https://doi.org/10.1046/j.1365-2540.2000.00680.x>, PMID: 10849068
- Burton RS**, Barreto FS. 2012. A disproportionate role for mtDNA in Dobzhansky-Muller incompatibilities? *Molecular Ecology* **21**:4942–4957. DOI: <https://doi.org/10.1111/mec.12006>, PMID: 22994153
- Calfee E**, Agra MN, Palacio MA, Ramírez SR, Coop G. 2020. Selection and hybridization shaped the rapid spread of african honey bee ancestry in the americas. *PLOS Genetics* **16**:e1009038. DOI: <https://doi.org/10.1371/journal.pgen.1009038>
- Calfee E.** 2021. Selective sorting of ancestral introgression in maize and teosinte along an elevational cline. *bioRxiv*. DOI: <https://doi.org/10.1101/2021.03.05.434040>
- Canela A**, Sridharan S, Sciascia N, Tubbs A, Meltzer P, Sleckman BP, Nussenzweig A. 2016. DNA breaks and end resection measured Genome-wide by end sequencing. *Molecular Cell* **63**:898–911. DOI: <https://doi.org/10.1016/j.molcel.2016.06.034>, PMID: 27477910
- Carling MD**, Brumfield RT. 2009. Speciation in *Passerina* buntings: introgression patterns of sex-linked loci identify a candidate gene region for reproductive isolation. *Molecular Ecology* **18**:834–847. DOI: <https://doi.org/10.1111/j.1365-294X.2008.04038.x>, PMID: 19207259
- Carling MD**, Zuckerberg B. 2011. Spatio-temporal changes in the genetic structure of the passerina bunting hybrid zone. *Molecular Ecology* **20**:1166–1175. DOI: <https://doi.org/10.1111/j.1365-294X.2010.04987.x>
- Castillo DM**, Moyle LC. 2020. Genetic analysis of hybrid incompatibility suggests transposable elements increase reproductive isolation in the *D. virilis* clade. *bioRxiv*. DOI: <https://doi.org/10.1101/753814>
- Chae E**, Bombliis K, Kim ST, Karelina D, Zaidem M, Ossowski S, Martín-Pizarro C, Laitinen RA, Rowan BA, Tenenboim H, Lechner S, Demar M, Habring-Müller A, Lanz C, Rättsch G, Weigel D. 2014. Species-wide genetic incompatibility analysis identifies immune genes as hot spots of deleterious epistasis. *Cell* **159**:1341–1351. DOI: <https://doi.org/10.1016/j.cell.2014.10.049>, PMID: 25467443
- Chase CD.** 2007. Cytoplasmic male sterility: a window to the world of plant mitochondrial-nuclear interactions. *Trends in Genetics* **23**:81–90. DOI: <https://doi.org/10.1016/j.tig.2006.12.004>, PMID: 17188396
- Chaturvedi S**, Lucas LK, Buerkle CA, Fordyce JA, Forister ML, Nice CC, Gompert Z. 2020. Recent hybrids recapitulate ancient hybrid outcomes. *Nature Communications* **11**:2179. DOI: <https://doi.org/10.1038/s41467-020-15641-x>, PMID: 32358487
- Chen N**, Cosgrove EJ, Bowman R, Fitzpatrick JW, Clark AG. 2016. Genomic consequences of population decline in the endangered Florida Scrub-Jay. *Current Biology* **26**:2974–2979. DOI: <https://doi.org/10.1016/j.cub.2016.08.062>, PMID: 27746026
- Chen N**, Juric I, Cosgrove EJ, Bowman R, Fitzpatrick JW, Schoech SJ, Clark AG, Coop G. 2019. Allele frequency dynamics in a pedigreed natural population. *PNAS* **116**:2158–2164. DOI: <https://doi.org/10.1073/pnas.1813852116>, PMID: 30598449
- Chenoweth SF**, Blows MW. 2006. Dissecting the complex genetic basis of mate choice. *Nature Reviews Genetics* **7**:681–692. DOI: <https://doi.org/10.1038/nrg1924>, PMID: 16921346
- Christie K**, Strauss SY. 2018. Along the speciation continuum: quantifying intrinsic and extrinsic isolating barriers across five million years of evolutionary divergence in California jewelflowers. *Evolution* **72**:1063–1079. DOI: <https://doi.org/10.1111/evo.13477>
- Chunco AJ.** 2014. Hybridization in a warmer world. *Ecology and Evolution* **4**:2019–2031. DOI: <https://doi.org/10.1002/ece3.1052>, PMID: 24963394
- Comeault AA.** 2018. The genomic and ecological context of hybridization affects the probability that symmetrical incompatibilities drive hybrid speciation. *Ecology and Evolution* **8**:2926–2937. DOI: <https://doi.org/10.1002/ece3.3872>, PMID: 29531706
- Comeault AA**, Matute DR. 2018. Genetic divergence and the number of hybridizing species affect the path to homoploid hybrid speciation. *PNAS* **115**:9761–9766. DOI: <https://doi.org/10.1073/pnas.1809685115>, PMID: 30209213
- Coop G**, Wen X, Ober C, Pritchard JK, Przeworski M. 2008. High-resolution mapping of crossovers reveals extensive variation in fine-scale recombination patterns among humans. *Science* **319**:1395–1398. DOI: <https://doi.org/10.1126/science.1151851>, PMID: 18239090
- Corbett-Detig RB**, Zhou J, Clark AG, Hartl DL, Ayroles JF. 2013. Genetic incompatibilities are widespread within species. *Nature* **504**:135–137. DOI: <https://doi.org/10.1038/nature12678>, PMID: 24196712
- Corbett-Detig R**, Nielsen R. 2017. A hidden markov model approach for simultaneously estimating local ancestry and admixture time using next generation sequence data in samples of arbitrary ploidy. *PLOS Genetics* **13**:e1006529. DOI: <https://doi.org/10.1371/journal.pgen.1006529>, PMID: 28045893
- Corcoran P**, Anderson JL, Jacobson DJ, Sun Y, Ni P, Lascoux M, Johannesson H. 2016. Introgression maintains the genetic integrity of the mating-type determining chromosome of the fungus *Neurospora tetrasperma*. *Genome Research* **26**:486–498. DOI: <https://doi.org/10.1101/gr.197244.115>, PMID: 26893460
- Coyne JA**, Orr HA. 2004. *Speciation*. Sunderland, MA: Sinauer Associates.
- Cruickshank TE**, Hahn MW. 2014. Reanalysis suggests that genomic islands of speciation are due to reduced diversity, not reduced gene flow. *Molecular Ecology* **23**:3133–3157. DOI: <https://doi.org/10.1111/mec.12796>, PMID: 24845075

- Cui R. 2013. Phylogenomics reveals extensive reticulate evolution in Xiphophorus fishes. *Evolution* **67**:2166–2179. DOI: <https://doi.org/10.1111/evo.12099>
- Cui R, Schumer M, Rosenthal GG. 2016. Admix'em: a flexible framework for forward-time simulations of hybrid populations with selection and mate choice. *Bioinformatics* **32**:1103–1105. DOI: <https://doi.org/10.1093/bioinformatics/btv700>, PMID: 26615212
- Cutter AD. 2012. The polymorphic prelude to Bateson-Dobzhansky-Muller incompatibilities. *Trends in Ecology & Evolution* **27**:209–218. DOI: <https://doi.org/10.1016/j.tree.2011.11.004>, PMID: 22154508
- Cutter AD, Bundus JD. 2020. Speciation and the developmental alarm clock. *eLife* **9**:e56276. DOI: <https://doi.org/10.7554/eLife.56276>, PMID: 32902377
- D'Angiolo M, De Chiara M, Yue JX, Irizar A, Stenberg S, Persson K, Llored A, Barré B, Schacherer J, Marangoni R, Gilson E, Warringer J, Liti G. 2020. A yeast living ancestor reveals the origin of genomic introgressions. *Nature* **587**:420–425. DOI: <https://doi.org/10.1038/s41586-020-2889-1>, PMID: 33177709
- Dandage R, Berger CM, Gagnon-Arsenault I, Moon K-M, Stacey RG, Foster LJ, Landry CR. 2021. Frequent assembly of chimeric complexes in the protein interaction network of an interspecies yeast hybrid. *Molecular Biology and Evolution* **38**:1384–1401. DOI: <https://doi.org/10.1093/molbev/msaa298>
- Dannemann M, Prüfer K, Kelso J. 2017. Functional implications of neandertal introgression in modern humans. *Genome Biology* **18**:61. DOI: <https://doi.org/10.1186/s13059-017-1181-7>, PMID: 28366169
- Dannemann M, Kelso J. 2017. The contribution of neandertals to phenotypic variation in modern humans. *The American Journal of Human Genetics* **101**:578–589. DOI: <https://doi.org/10.1016/j.ajhg.2017.09.010>, PMID: 28985494
- Davies B, Hatton E, Altemose N, Hussin JG, Pratto F, Zhang G, Hinch AG, Moralli D, Biggs D, Diaz R, Preece C, Li R, Bitoun E, Brick K, Green CM, Camerini-Otero RD, Myers SR, Donnelly P. 2016. Re-engineering the zinc fingers of PRDM9 reverses hybrid sterility in mice. *Nature* **530**:171–176. DOI: <https://doi.org/10.1038/nature16931>, PMID: 26840484
- De La Torre A, Ingvarsson PK, Aitken SN. 2015. Genetic architecture and genomic patterns of gene flow between hybridizing species of *Picea*. *Heredity* **115**:153–164. DOI: <https://doi.org/10.1038/hdy.2015.19>, PMID: 25806545
- Delmore KE, Irwin DE. 2014. Hybrid songbirds employ intermediate routes in a migratory divide. *Ecology Letters* **17**:1211–1218. DOI: <https://doi.org/10.1111/ele.12326>, PMID: 25040456
- Dion-Côté AM, Renaut S, Normandeau E, Bernatchez L. 2014. RNA-seq reveals transcriptomic shock involving transposable elements reactivation in hybrids of young lake whitefish species. *Molecular Biology and Evolution* **31**:1188–1199. DOI: <https://doi.org/10.1093/molbev/msu069>, PMID: 24505119
- Dion-Côté AM, Barbash DA. 2017. Beyond speciation genes: an overview of genome stability in evolution and speciation. *Current Opinion in Genetics & Development* **47**:17–23. DOI: <https://doi.org/10.1016/j.gde.2017.07.014>, PMID: 28830007
- Dobzhansky T. 1982. *Genetics and the Origin of Species*. New York, NY: Columbia University Press.
- Dujon BA, Louis EJ. 2017. Genome diversity and evolution in the budding yeasts (Saccharomycotina). *Genetics* **206**:717–750. DOI: <https://doi.org/10.1534/genetics.116.199216>, PMID: 28592505
- Eberlein C, Hénault M, Fijarczyk A, Charron G, Bouvier M, Kohn LM, Anderson JB, Landry CR. 2019. Hybridization is a recurrent evolutionary stimulus in wild yeast speciation. *Nature Communications* **10**:923. DOI: <https://doi.org/10.1038/s41467-019-08809-7>, PMID: 30804385
- Edelman NB, Frandsen PB, Miyagi M, Clavijo B, Davey J, Dikow RB, García-Accinelli G, Van Belleghem SM, Patterson N, Neafsey DE, Challis R, Kumar S, Moreira GRP, Salazar C, Chouteau M, Counterman BA, Papa R, Blaxter M, Reed RD, Dasmahapatra KK, et al. 2019. Genomic architecture and introgression shape a butterfly radiation. *Science* **366**:594–599. DOI: <https://doi.org/10.1126/science.aaw2090>, PMID: 31672890
- Elgvin TO, Trier CN, Tørresen OK, Hagen IJ, Lien S, Nederbragt AJ, Ravinet M, Jensen H, Sætre GP. 2017. The genomic mosaicism of hybrid speciation. *Science Advances* **3**:e1602996. DOI: <https://doi.org/10.1126/sciadv.1602996>, PMID: 28630911
- Elyashiv E, Sattath S, Hu TT, Strutsovsky A, McVicker G, Andolfatto P, Coop G, Sella G. 2016. A genomic map of the effects of linked selection in *Drosophila*. *PLOS Genetics* **12**:e1006130. DOI: <https://doi.org/10.1371/journal.pgen.1006130>, PMID: 27536991
- Enard D, Petrov DA. 2018. Evidence that RNA viruses drove adaptive introgression between neanderthals and modern humans. *Cell* **175**:360–371. DOI: <https://doi.org/10.1016/j.cell.2018.08.034>, PMID: 30290142
- Faria R, Chaube P, Morales HE, Larsson T, Lemmon AR, Lemmon EM, Rafajlović M, Panova M, Ravinet M, Johannesson K, Westram AM, Butlin RK. 2019. Multiple chromosomal rearrangements in a hybrid zone between *Littorina saxatilis* ecotypes. *Molecular Ecology* **28**:1375–1393. DOI: <https://doi.org/10.1111/mec.14972>, PMID: 30537056
- Feurtey A, Stevens DM, Stephan W, Stukenbrock EH. 2019. Interspecific gene exchange introduces high genetic variability in crop pathogen. *Genome Biology and Evolution* **11**:3095–3105. DOI: <https://doi.org/10.1093/gbe/evz224>, PMID: 31603209
- Fierst JL, Hansen TF. 2010. Genetic architecture and postzygotic reproductive isolation: evolution of bateson-dobzhansky-muller incompatibilities in a polygenic model. *Evolution* **64**:675–693. DOI: <https://doi.org/10.1111/j.1558-5646.2009.00861.x>
- Fijarczyk A, Dudek K, Niedzicka M, Babik W. 2018. Balancing selection and introgression of new immune-response genes. *PNAS* **285**:20180819. DOI: <https://doi.org/10.1098/rspb.2018.0819>
- Fisher RA. 1930. *The Genetical Theory of Natural Selection*. Oxford, United Kingdom: The Clarendon Press.

- Fisher HS, Wong BBM, Rosenthal GG. 2006. Alteration of the chemical environment disrupts communication in a freshwater fish. *PNAS* **273**:1187–1193. DOI: <https://doi.org/10.1098/rspb.2005.3406>
- Fitzpatrick SW. 2019. Genetic rescue without genomic swamping in wild populations. *bioRxiv*. DOI: <https://doi.org/10.1101/701706>
- Ford CB, Funt JM, Abbey D, Issi L, Guiducci C, Martinez DA, Delorey T, Li BY, White TC, Cuomo C, Rao RP, Berman J, Thompson DA, Regev A. 2015. The evolution of drug resistance in clinical isolates of *Candida albicans*. *eLife* **4**:e00662. DOI: <https://doi.org/10.7554/eLife.00662>, PMID: 25646566
- Fraïsse C, Gunnarsson PA, Roze D, Bierne N, Welch JJ. 2016. The genetics of speciation: insights from Fisher's geometric model. *Evolution* **70**:1450–1464. DOI: <https://doi.org/10.1111/evo.12968>
- Gallone B, Steensels J, Mertens S, Dzialo MC, Gordon JL, Wauters R, Theßeling FA, Bellinazzo F, Saels V, Herrera-Malaver B, Prah T, White C, Hutzler M, Meußdoerffer F, Malcorps P, Souffriau B, Daenen L, Baele G, Maere S, Verstrepen KJ. 2019. Interspecific hybridization facilitates niche adaptation in beer yeast. *Nature Ecology & Evolution* **3**:1562–1575. DOI: <https://doi.org/10.1038/s41559-019-0997-9>, PMID: 31636425
- Gavrilets S. 1997. Hybrid zones with Dobzhansky-type epistatic selection. *Evolution* **51**:1027–1035. DOI: <https://doi.org/10.1111/j.1558-5646.1997.tb03949.x>
- Geraldes A. 2014. Landscape genomics of *Populus trichocarpa*: the role of hybridization, limited gene flow, and natural selection in shaping patterns of population structure. *Evolution* **68**:3260–3280. DOI: <https://doi.org/10.1111/evo.12497>
- Gerhardt HC, Brooks R. 2009. Experimental analysis of multivariate female choice in gray treefrogs (*Hyla versicolor*): evidence for directional and stabilizing selection. *Evolution* **63**:2504–2512. DOI: <https://doi.org/10.1111/j.1558-5646.2009.00746.x>
- Giordano L, Sillo F, Garbelotto M, Gonthier P. 2018. Mitonuclear interactions may contribute to fitness of fungal hybrids. *Scientific Reports* **8**:1706. DOI: <https://doi.org/10.1038/s41598-018-19922-w>, PMID: 29374209
- Giska I, Farelo L, Pimenta J, Seixas FA, Ferreira MS, Marques JP, Miranda I, Letty J, Jenny H, Hackländer K, Magnussen E, Melo-Ferreira J. 2019. Introgression drives repeated evolution of winter coat color polymorphism in hares. *PNAS* **116**:24150–24156. DOI: <https://doi.org/10.1073/pnas.1910471116>, PMID: 31712446
- Gompert Z, Fordyce JA, Forister ML, Shapiro AM, Nice CC. 2006. Homoploid hybrid speciation in an extreme habitat. *Science* **314**:1923–1925. DOI: <https://doi.org/10.1126/science.1135875>, PMID: 17138866
- Good JM. 2008. Asymmetry and polymorphism of hybrid male sterility during the early stages of speciation in house mice. *Evolution* **62**:50–65. DOI: <https://doi.org/10.1111/j.1558-5646.2007.00257.x>
- Gow JL, Peichel CL, Taylor EB. 2007. Ecological selection against hybrids in natural populations of sympatric threespine sticklebacks. *Journal of Evolutionary Biology* **20**:2173–2180. DOI: <https://doi.org/10.1111/j.1420-9101.2007.01427.x>, PMID: 17887972
- Grant PR, Grant BR, Petren K. 2005. Hybridization in the recent past. *The American Naturalist* **166**:56–67. DOI: <https://doi.org/10.1086/430331>, PMID: 15937789
- Grant PR, Grant BR. 2019. Hybridization increases population variation during adaptive radiation. *PNAS* **116**:23216–23224. DOI: <https://doi.org/10.1073/pnas.1913534116>, PMID: 31659024
- Gryganskyi AP, Golan J, Dolatabadi S, Mondo S, Robb S, Idnurm A, Muszewska A, Steczkiewicz K, Masonjones S, Liao HL, Gajdeczka MT, Anike F, Vuck A, Anishchenko IM, Voigt K, de Hoog GS, Smith ME, Heitman J, Vilgalys R, Stajich JE. 2018. Phylogenetic and phylogenomic definition of *Rhizopus* Species. *G3: Genes, Genomes, Genetics* **8**:2007–2018. DOI: <https://doi.org/10.1534/g3.118.200235>, PMID: 29674435
- Haller BC, Messer PW. 2019. SLiM 3: forward genetic simulations beyond the Wright-Fisher model. *Molecular Biology and Evolution* **36**:632–637. DOI: <https://doi.org/10.1093/molbev/msy228>, PMID: 30517680
- Hamlin JAP, Hibbins MS, Moyle LC. 2020. Assessing biological factors affecting postspeciation introgression. *Evolution Letters* **4**:137–154. DOI: <https://doi.org/10.1002/evl3.159>, PMID: 32313689
- Harris K, Nielsen R. 2016. The genetic cost of Neanderthal introgression. *Genetics* **203**:881–891. DOI: <https://doi.org/10.1534/genetics.116.186890>, PMID: 27038113
- Hayden B, Massa-Gallucci A, Caffrey JOE, Harrod C, Mariani S, O'Grady M, Kelly-Quinn M. 2011. Trophic dynamics within a hybrid zone - interactions between an abundant cyprinid hybrid and sympatric parental species. *Freshwater Biology* **56**:1723–1735. DOI: <https://doi.org/10.1111/j.1365-2427.2011.02604.x>
- Hayward LK, Sella G. 2019. Polygenic adaptation after a sudden change in environment. *bioRxiv*. DOI: <https://doi.org/10.1101/792952>
- He S, Mork J, Larsen WB, Møller PR, Berumen ML. 2020. Morphology and genetic investigation of flatfish interspecies hybrids (*Pleuronectes platessa* X *Platichthys flesus*) from the Baltic Sea. *Fisheries Research* **225**:105498. DOI: <https://doi.org/10.1016/j.fishres.2020.105498>
- Hedrick PW. 2013. Adaptive introgression in animals: examples and comparison to new mutation and standing variation as sources of adaptive variation. *Molecular Ecology* **22**:4606–4618. DOI: <https://doi.org/10.1111/mec.12415>, PMID: 23906376
- Heliconius Genome Consortium. 2012. Butterfly genome reveals promiscuous exchange of mimicry adaptations among species. *Nature* **487**:94–98. DOI: <https://doi.org/10.1038/nature11041>, PMID: 22722851
- Hermansen JS, Saether SA, Elgvin TO, Borge T, Hjelle E, Saetre GP. 2011. Hybrid speciation in sparrows I: phenotypic intermediacy, genetic admixture and barriers to gene flow. *Molecular Ecology* **20**:3812–3822. DOI: <https://doi.org/10.1111/j.1365-294X.2011.05183.x>, PMID: 21771138
- Hessenaue P, Fijarczyk A, Martin H, Prunier J, Charron G, Chapis J, Bernier L, Tanguay P, Hamelin RC, Landry CR. 2020. Hybridization and introgression drive genome evolution of Dutch elm disease pathogens. *Nature Ecology & Evolution* **4**:626–638. DOI: <https://doi.org/10.1038/s41559-020-1133-6>, PMID: 32123324

- Hill GE. 2017. The mitonuclear compatibility species concept. *The Auk* **134**:393–409. DOI: <https://doi.org/10.1642/AUK-16-201.1>
- Hohenlohe PA, Arnold SJ. 2010. Dimensionality of mate choice, sexual isolation, and speciation. *PNAS* **107**:16583–16588. DOI: <https://doi.org/10.1073/pnas.1003537107>, PMID: 20823250
- Hopkins R, Guerrero RF, Rausher MD, Kirkpatrick M. 2014. Strong reinforcing selection in a Texas wildflower. *Current Biology* **24**:1995–1999. DOI: <https://doi.org/10.1016/j.cub.2014.07.027>, PMID: 25155503
- Hufford MB, Lubinsky P, Pyhäjärvi T, Devengeno MT, Ellstrand NC, Ross-Ibarra J. 2013. The genomic signature of crop-wild introgression in maize. *PLOS Genetics* **9**:e1003477. DOI: <https://doi.org/10.1371/journal.pgen.1003477>, PMID: 23671421
- Jay P, Whibley A, Frézal L, Rodríguez de Cara MÁ, Nowell RW, Mallet J, Dasmahapatra KK, Joron M. 2018. Supergene evolution triggered by the introgression of a chromosomal inversion. *Current Biology* **28**:1839–1845. DOI: <https://doi.org/10.1016/j.cub.2018.04.072>, PMID: 29804810
- Jones FC, Grabherr MG, Chan YF, Russell P, Mauceci E, Johnson J, Swofford R, Pirun M, Zody MC, White S, Birney E, Searle S, Schmutz J, Grimwood J, Dickson MC, Myers RM, Miller CT, Summers BR, Knecht AK, Brady SD, et al. 2012. The genomic basis of adaptive evolution in threespine sticklebacks. *Nature* **484**:55–61. DOI: <https://doi.org/10.1038/nature10944>, PMID: 22481358
- Jones MR, Mills LS, Alves PC, Callahan CM, Alves JM, Lafferty DJR, Jiggins FM, Jensen JD, Melo-Ferreira J, Good JM. 2018. Adaptive introgression underlies polymorphic seasonal camouflage in snowshoe hares. *Science* **360**:1355–1358. DOI: <https://doi.org/10.1126/science.aar5273>, PMID: 29930138
- Juric I, Aeschbacher S, Coop G. 2016. The strength of selection against neanderthal introgression. *PLOS Genetics* **12**:e1006340. DOI: <https://doi.org/10.1371/journal.pgen.1006340>, PMID: 27824859
- Káldy J, Mozsár A, Fazekas G, Farkas M, Fazekas DL, Fazekas GL, Goda K, Gyöngy Z, Kovács B, Semmens K, Bercsényi M, Molnár M, Patakiné Várkonyi E. 2020. Hybridization of russian sturgeon (*Acipenser gueldenstaedtii*, Brandt and ratzeburg, 1833) and american paddlefish (*Polyodon spathula*, walbaum 1792) and evaluation of their progeny. *Genes* **11**:753. DOI: <https://doi.org/10.3390/genes11070753>
- Kalirad A, Azevedo RBR. 2017. Spiraling complexity: a test of the snowball effect in a computational model of RNA folding. *Genetics* **206**:377–388. DOI: <https://doi.org/10.1534/genetics.116.196030>, PMID: 28007889
- Kazianis S, Gutbrod H, Nairn RS, McEntire BB, Coletta LD, Walter RB, Borowsky RL, Woodhead AD, Setlow RB, Schartl M, Morizot DC. 1998. Localization of aCDKN2 gene in linkage group V of *Xiphophorus* fishes defines it as a candidate for theDIFF tumor suppressor. *Genes, Chromosomes and Cancer* **22**:210–220. DOI: [https://doi.org/10.1002/\(SICI\)1098-2264\(199807\)22:3<210::AID-GCC6>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1098-2264(199807)22:3<210::AID-GCC6>3.0.CO;2-Z)
- Kim BY. 2017. Deleterious variation mimics signatures of genomic incompatibility and adaptive introgression. *bioRxiv*. DOI: <https://doi.org/10.1101/221705>
- Kirkpatrick M. 2010. How and why chromosome inversions evolve. *PLOS Biology* **8**:e1000501. DOI: <https://doi.org/10.1371/journal.pbio.1000501>, PMID: 20927412
- Kirkpatrick M, Barton N. 2006. Chromosome inversions, local adaptation and speciation. *Genetics* **173**:419–434. DOI: <https://doi.org/10.1534/genetics.105.047985>, PMID: 16204214
- Kovach RP, Hand BK, Hohenlohe PA, Cosart TF, Boyer MC, Neville HH, Muhlfeld CC, Amish SJ, Carim K, Narum SR, Lowe WH, Allendorf FW, Luikart G. 2016. Vive la résistance: genome-wide selection against introduced alleles in invasive hybrid zones. *PNAS* **283**:20161380. DOI: <https://doi.org/10.1098/rspb.2016.1380>
- Kulmuni J, Nouhau P, Pluckrose L, Satokangas I, Dhaygude K, Butlin RK. 2020. Instability of natural selection at candidate barrier loci underlying speciation in wood ants. *Molecular Ecology* **29**:3988–3999. DOI: <https://doi.org/10.1111/mec.15606>, PMID: 32854139
- Lafon-Placette C, Hatorangan MR, Steige KA, Cornille A, Lascoux M, Slotte T, Köhler C. 2018. Paternally expressed imprinted genes associate with hybridization barriers in capsella. *Nature Plants* **4**:352–357. DOI: <https://doi.org/10.1038/s41477-018-0161-6>
- Lamichhaney S, Han F, Webster MT, Grant BR, Grant PR, Andersson L. 2020. Female-biased gene flow between two species of Darwin's finches. *Nature Ecology & Evolution* **4**:979–986. DOI: <https://doi.org/10.1038/s41559-020-1183-9>, PMID: 32367030
- Langdon QK, Peris D, Baker EP, Opulente DA, Nguyen HV, Bond U, Gonçalves P, Sampaio JP, Libkind D, Hittinger CT. 2019. Fermentation innovation through complex hybridization of wild and domesticated yeasts. *Nature Ecology & Evolution* **3**:1576–1586. DOI: <https://doi.org/10.1038/s41559-019-0998-8>, PMID: 31636426
- Langdon QK, Peris D, Eizaguirre JI, Opulente DA, Buh KV, Sylvester K, Jarzyna M, Rodríguez ME, Lopes CA, Libkind D, Hittinger CT. 2020. Postglacial migration shaped the genomic diversity and global distribution of the wild ancestor of lager-brewing hybrids. *PLOS Genetics* **16**:e1008680. DOI: <https://doi.org/10.1371/journal.pgen.1008680>, PMID: 32251477
- Larson EL, Vanderpool D, Sarver BAJ, Callahan C, Keeble S, Provencio LL, Kessler MD, Stewart V, Nordquist E, Dean MD, Good JM. 2018. The evolution of polymorphic hybrid incompatibilities in house mice. *Genetics* **209**:845–859. DOI: <https://doi.org/10.1534/genetics.118.300840>, PMID: 29692350
- Larson EL, Tinghitella RM, Taylor SA. 2019. Insect hybridization and climate change. *Frontiers in Ecology and Evolution* **7**:348. DOI: <https://doi.org/10.3389/fevo.2019.00348>
- Lewontin RC, Birch LC. 1966. Hybridization as a source of variation for adaptation to new environments. *Evolution* **20**:315–336. DOI: <https://doi.org/10.1111/j.1558-5646.1966.tb03369.x>
- Lewontin RC, Kojima K. 1960. The evolutionary dynamics of complex polymorphisms. *Evolution* **14**:458–472. DOI: <https://doi.org/10.1111/j.1558-5646.1960.tb03113.x>

- Li R, Bitoun E, Altemose N, Davies RW, Davies B, Myers SR. 2019. A high-resolution map of non-crossover events reveals impacts of genetic diversity on mammalian meiotic recombination. *Nature Communications* **10**:3900. DOI: <https://doi.org/10.1038/s41467-019-11675-y>, PMID: 31467277
- Lindtke D, González-Martínez SC, Macaya-Sanz D, Lexer C. 2013. Admixture mapping of quantitative traits in *Populus* hybrid zones: power and limitations. *Heredity* **111**:474–485. DOI: <https://doi.org/10.1038/hdy.2013.69>, PMID: 23860234
- Lindtke D, Buerkle CA. 2015. The genetic architecture of hybrid incompatibilities and their effect on barriers to introgression in secondary contact. *Evolution* **69**:1987–2004. DOI: <https://doi.org/10.1111/evo.12725>
- Linn C, Feder JL, Nojima S, Dambroski HR, Berlocher SH, Roelofs W. 2003. Fruit odor discrimination and sympatric host race formation in *Rhagoletis*. *PNAS* **100**:11490–11493. DOI: <https://doi.org/10.1073/pnas.1635049100>, PMID: 14504399
- Lu Y, Sandoval A, Voss S, Lai Z, Kneitz S, Boswell W, Boswell M, Savage M, Walter C, Warren W, Schartl M, Walter R. 2020. Oncogenic allelic interaction in *Xiphophorus* highlights hybrid incompatibility. *PNAS* **117**:29786–29794. DOI: <https://doi.org/10.1073/pnas.2010133117>, PMID: 33168740
- Macholán M, Baird SJ, Munclinger P, Dufková P, Bímová B, Piálek J. 2008. Genetic conflict outweighs heterogametic incompatibility in the mouse hybrid zone? *BMC Evolutionary Biology* **8**:271. DOI: <https://doi.org/10.1186/1471-2148-8-271>, PMID: 18834509
- Mack KL, Campbell P, Nachman MW. 2016. Gene regulation and speciation in house mice. *Genome Research* **26**:451–461. DOI: <https://doi.org/10.1101/gr.195743.115>, PMID: 26833790
- Mack KL, Nachman MW. 2017. Gene regulation and speciation. *Trends in Genetics* **33**:68–80. DOI: <https://doi.org/10.1016/j.tig.2016.11.003>, PMID: 27914620
- MacPherson A. 2020. Parental population range expansion before secondary contact promotes heterosis. *bioRxiv*. DOI: <https://doi.org/10.1101/2020.04.28.066308>
- Maheshwari S, Barbash DA. 2011. The genetics of hybrid incompatibilities. *Annual Review of Genetics* **45**:331–355. DOI: <https://doi.org/10.1146/annurev-genet-110410-132514>, PMID: 21910629
- Mallet J, Barton N, Lamas G, Santisteban J, Muedas M, Eeley H. 1990. Estimates of selection and gene flow from measures of Cline width and linkage disequilibrium in *Heliconius* hybrid zones. *Genetics* **124**:921–936. DOI: <https://doi.org/10.1093/genetics/124.4.921>, PMID: 2323556
- Mallet J. 2005. Hybridization as an invasion of the genome. *Trends in Ecology & Evolution* **20**:229–237. DOI: <https://doi.org/10.1016/j.tree.2005.02.010>, PMID: 16701374
- Marcet-Houben M, Gabaldón T. 2015. Beyond the Whole-Genome duplication: phylogenetic evidence for an ancient interspecies hybridization in the Baker's Yeast Lineage. *PLOS Biology* **13**:e1002220. DOI: <https://doi.org/10.1371/journal.pbio.1002220>, PMID: 26252497
- Marques DA, Meier JI, Seehausen O. 2019. A combinatorial view on speciation and adaptive radiation. *Trends in Ecology & Evolution* **34**:531–544. DOI: <https://doi.org/10.1016/j.tree.2019.02.008>, PMID: 30885412
- Martin SH, Dasmahapatra KK, Nadeau NJ, Salazar C, Walters JR, Simpson F, Blaxter M, Manica A, Mallet J, Jiggins CD. 2013. Genome-wide evidence for speciation with gene flow in *Heliconius* butterflies. *Genome Research* **23**:1817–1828. DOI: <https://doi.org/10.1101/gr.159426.113>, PMID: 24045163
- Martin SH, Davey JW, Salazar C, Jiggins CD. 2019. Recombination rate variation shapes barriers to introgression across butterfly genomes. *PLOS Biology* **17**:e2006288. DOI: <https://doi.org/10.1371/journal.pbio.2006288>, PMID: 30730876
- Martin CH, Richards EJ. 2019. The paradox behind the pattern of rapid adaptive radiation: how can the speciation process sustain itself through an early burst? *Annual Review of Ecology, Evolution, and Systematics* **50**:569–593. DOI: <https://doi.org/10.1146/annurev-ecolsys-110617-062443>
- Masly JP, Presgraves DC. 2007. High-resolution genome-wide dissection of the two rules of speciation in *Drosophila*. *PLOS Biology* **5**:e243. DOI: <https://doi.org/10.1371/journal.pbio.0050243>, PMID: 17850182
- Matute DR, Butler IA, Turissini DA, Coyne JA. 2010. A test of the snowball theory for the rate of evolution of hybrid incompatibilities. *Science* **329**:1518–1521. DOI: <https://doi.org/10.1126/science.1193440>, PMID: 20847270
- Matute DR, Comeault AA, Earley E, Serrato-Capuchina A, Peede D, Monroy-Eklund A, Huang W, Jones CD, Mackay TFC, Coyne JA. 2020. Rapid and predictable evolution of admixed populations between two *Drosophila* Species Pairs. *Genetics* **214**:211–230. DOI: <https://doi.org/10.1534/genetics.119.302685>, PMID: 31767631
- Maxwell CS, Sepulveda VE, Turissini DA, Goldman WE, Matute DR. 2018. Recent admixture between species of the fungal pathogen *Histoplasma*. *Evolution Letters* **2**:210–220. DOI: <https://doi.org/10.1002/evl3.59>, PMID: 30283677
- Maya-Lastra CA, Eaton DAR. 2021. Genetic incompatibilities do not snowball in a demographic model of speciation. *bioRxiv*. DOI: <https://doi.org/10.1101/2021.02.23.432472>
- McCarthy EM, Asmussen MA, Anderson WW. 1995. A theoretical assessment of recombinational speciation. *Heredity* **74**:502–509. DOI: <https://doi.org/10.1038/hdy.1995.71>
- McDaniel SF, Willis JH, Shaw AJ. 2007. A linkage map reveals a complex basis for segregation distortion in an interpopulation cross in the moss *Ceratodon purpureus*. *Genetics* **176**:2489–2500. DOI: <https://doi.org/10.1534/genetics.107.075424>, PMID: 17603096
- McVicker G, Gordon D, Davis C, Green P. 2009. Widespread genomic signatures of natural selection in hominid evolution. *PLOS Genetics* **5**:e1000471. DOI: <https://doi.org/10.1371/journal.pgen.1000471>, PMID: 19424416

- Meier JI, Marques DA, Mwaiko S, Wagner CE, Excoffier L, Seehausen O. 2017. Ancient hybridization fuels rapid cichlid fish adaptive radiations. *Nature Communications* **8**:14363. DOI: <https://doi.org/10.1038/ncomms14363>, PMID: 28186104
- Meier JI, Stelkens RB, Joyce DA, Mwaiko S, Phiri N, Schliwen UK, Selz OM, Wagner CE, Katongo C, Seehausen O. 2019. The coincidence of ecological opportunity with hybridization explains rapid adaptive radiation in lake mweru cichlid fishes. *Nature Communications* **10**:5391. DOI: <https://doi.org/10.1038/s41467-019-13278-z>, PMID: 31796733
- Meiklejohn CD, Landeen EL, Gordon KE, Rzatkiewicz T, Kingan SB, Geneva AJ, Vedanayagam JP, Muirhead CA, Garrigan D, Stern DL, Presgraves DC. 2018. Gene flow mediates the role of sex chromosome meiotic drive during complex speciation. *eLife* **7**:e35468. DOI: <https://doi.org/10.7554/eLife.35468>, PMID: 30543325
- Melo MC, Grealy A, Brittain B, Walter GM, Ortiz-Barrientos D. 2014. Strong extrinsic reproductive isolation between parapatric populations of an australian groundsel. *New Phytologist* **203**:323–334. DOI: <https://doi.org/10.1111/nph.12779>
- Melo MC. 2019. Evidence for mutation-order speciation in australian wildflower. *bioRxiv*. DOI: <https://doi.org/10.1101/692673>
- Mitchell N, Owens GL, Hovick SM, Rieseberg LH, Whitney KD. 2019. Hybridization speeds adaptive evolution in an eight-year field experiment. *Scientific Reports* **9**:6746. DOI: <https://doi.org/10.1038/s41598-019-43119-4>, PMID: 31043692
- Moest M, Van Belleghem SM, James JE, Salazar C, Martin SH, Barker SL, Moreira GRP, Mérot C, Joron M, Nadeau NJ, Steiner FM, Jiggins CD. 2020. Selective sweeps on novel and introgressed variation shape mimicry loci in a butterfly adaptive radiation. *PLOS Biology* **18**:e3000597. DOI: <https://doi.org/10.1371/journal.pbio.3000597>, PMID: 32027643
- Möller M, Stukenbrock EH. 2017. Evolution and genome architecture in fungal plant pathogens. *Nature Reviews Microbiology* **15**:756–771. DOI: <https://doi.org/10.1038/nrmicro.2017.76>
- Moyle LC, Nakazato T. 2010. Hybrid incompatibility "snowballs" between *Solanum* species. *Science* **329**:1521–1523. DOI: <https://doi.org/10.1126/science.1193063>, PMID: 20847271
- Myers S, Bottolo L, Freeman C, McVean G, Donnelly P. 2005. A fine-scale map of recombination rates and hotspots across the human genome. *Science* **310**:321–324. DOI: <https://doi.org/10.1126/science.1117196>, PMID: 16224025
- Nachman MW, Payseur BA. 2012. Recombination rate variation and speciation: theoretical predictions and empirical results from rabbits and mice. *Philosophical Transactions of the Royal Society B: Biological Sciences* **367**:409–421. DOI: <https://doi.org/10.1098/rstb.2011.0249>, PMID: 22201170
- Nguyen GN, Yamagata Y, Shigematsu Y, Watanabe M, Miyazaki Y, Doi K, Tashiro K, Kuhara S, Kanamori H, Wu J, Matsumoto T, Yasui H, Yoshimura A. 2017. Duplication and loss of function of genes encoding RNA polymerase III subunit C4 causes hybrid incompatibility in rice. *G3: Genes, Genomes, Genetics* **7**:2565–2575. DOI: <https://doi.org/10.1534/g3.117.043943>
- Nolte AW. 2005. Evolutionary genetic analysis of an invasive population of sculpins in the Lower Rhine. PhD thesis. Germany, Universität zu Köln.
- Nolte AW, Gompert Z, Buerkle CA. 2009. Variable patterns of introgression in two sculpin hybrid zones suggest that genomic isolation differs among populations. *Molecular Ecology* **18**:2615–2627. DOI: <https://doi.org/10.1111/j.1365-294X.2009.04208.x>, PMID: 19457191
- Noor MA, Grams KL, Bertucci LA, Reiland J. 2001. Chromosomal inversions and the reproductive isolation of species. *PNAS* **98**:12084–12088. DOI: <https://doi.org/10.1073/pnas.221274498>, PMID: 11593019
- Norris LC, Main BJ, Lee Y, Collier TC, Fofana A, Cornel AJ, Lanzaro GC. 2015. Adaptive introgression in an african malaria mosquito coincident with the increased usage of insecticide-treated bed nets. *PNAS* **112**:815–820. DOI: <https://doi.org/10.1073/pnas.1418892112>, PMID: 25561525
- Nosil P, Vines TH, Funk DJ. 2005. Perspective: reproductive isolation caused by natural selection against immigrants from divergent habitats. *Evolution* **59**:705–719. DOI: <https://doi.org/10.1554/04-428>
- Nouhaud P, Blanckaert A, Bank C, Kulmuni J. 2020. Understanding admixture: haplodiploidy to the rescue. *Trends in Ecology & Evolution* **35**:34–42. DOI: <https://doi.org/10.1016/j.tree.2019.08.013>
- Orr HA. 1995. The population genetics of speciation: the evolution of hybrid incompatibilities. *Genetics* **139**:1805–1813. DOI: <https://doi.org/10.1093/genetics/139.4.1805>, PMID: 7789779
- Orr HA. 1997. Haldane'S RULE. *Annual Review of Ecology and Systematics* **28**:195–218. DOI: <https://doi.org/10.1146/annurev.ecolsys.28.1.195>
- Orr HA, Turelli M. 2001. The evolution of postzygotic isolation: accumulating Dobzhansky-Muller incompatibilities. *Evolution* **55**:1085–1094. DOI: <https://doi.org/10.1111/j.0014-3820.2001.tb00628.x>
- Padhukasahasram B. 2014. Inferring ancestry from population genomic data and its applications. *Frontiers in Genetics* **5**:204. DOI: <https://doi.org/10.3389/fgene.2014.00204>, PMID: 25071832
- Payseur BA. 2004. Differential patterns of introgression across the X chromosome in a hybrid zone between two species of house mice. *Evolution* **58**:2064–2078. DOI: <https://doi.org/10.1111/j.0014-3820.2004.tb00490.x>
- Payseur BA. 2010. Using differential introgression in hybrid zones to identify genomic regions involved in speciation. *Molecular Ecology Resources* **10**:806–820. DOI: <https://doi.org/10.1111/j.1755-0998.2010.02883.x>, PMID: 21565092
- Payseur BA, Rieseberg LH. 2016. A genomic perspective on hybridization and speciation. *Molecular Ecology* **25**:2337–2360. DOI: <https://doi.org/10.1111/mec.13557>, PMID: 26836441

- Pereira RJ, Barreto FS, Burton RS. 2014. Ecological novelty by hybridization: experimental evidence for increased thermal tolerance by transgressive segregation in *Tigriopus californicus*. *Evolution* **68**:204–215. DOI: <https://doi.org/10.1111/evo.12254>
- Piatkowska EM, Naseeb S, Knight D, Delneri D. 2013. Chimeric protein complexes in hybrid species generate novel phenotypes. *PLOS Genetics* **9**:e1003836. DOI: <https://doi.org/10.1371/journal.pgen.1003836>, PMID: 24137105
- Pickup M, Brandvain Y, Fraïsse C, Yakimowski S, Barton NH, Dixit T, Lexer C, Cereghetti E, Field DL. 2019. Mating system variation in hybrid zones: facilitation, barriers and asymmetries to gene flow. *New Phytologist* **224**:1035–1047. DOI: <https://doi.org/10.1111/nph.16180>
- Pierce AA, Gutierrez R, Rice AM, Pfennig KS. 2017. Genetic variation during range expansion: effects of habitat novelty and hybridization. *PNAS* **284**:20170007. DOI: <https://doi.org/10.1098/rspb.2017.0007>, PMID: 28381622
- Porter AH, Johnson NA. 2002. Speciation despite gene flow when developmental pathways evolve. *Evolution* **56**:2103–2111. DOI: <https://doi.org/10.1111/j.0014-3820.2002.tb00136.x>
- Powell DL, García-Olazábal M, Keegan M, Reilly P, Du K, Díaz-Loyo AP, Banerjee S, Blakkan D, Reich D, Andolfatto P, Rosenthal GG, Schartl M, Schumer M. 2020. Natural hybridization reveals incompatible alleles that cause melanoma in swordtail fish. *Science* **368**:731–736. DOI: <https://doi.org/10.1126/science.aba5216>, PMID: 32409469
- Powell DL, Payne C, Banerjee SM, Keegan M, Bashkirova E, Cui R, Andolfatto P, Rosenthal GG, Schumer M. 2021. The genetic architecture of the sexually selected sword ornament and its evolution in hybrid populations. *Current Biology* **3**:923–935. DOI: <https://doi.org/10.1101/2020.07.23.218164>
- Presgraves DC. 2008. Sex chromosomes and speciation in *Drosophila*. *Trends in Genetics* **24**:336–343. DOI: <https://doi.org/10.1016/j.tig.2008.04.007>, PMID: 18514967
- Presgraves DC. 2010a. Darwin and the origin of interspecific genetic incompatibilities. *The American Naturalist* **176**:S45–S60. DOI: <https://doi.org/10.1086/657058>, PMID: 21043780
- Presgraves DC. 2010b. Speciation genetics: search for the missing snowball. *Current Biology* **20**:R1073–R1074. DOI: <https://doi.org/10.1016/j.cub.2010.10.056>, PMID: 21172625
- Presgraves DC. 2010c. The molecular evolutionary basis of species formation. *Nature Reviews Genetics* **11**:175–180. DOI: <https://doi.org/10.1038/nrg2718>, PMID: 20051985
- Qvarnström A, Bailey RI. 2009. Speciation through evolution of sex-linked genes. *Heredity* **102**:4–15. DOI: <https://doi.org/10.1038/hdy.2008.93>, PMID: 18781167
- Racimo F, Sankararaman S, Nielsen R, Huerta-Sánchez E. 2015. Evidence for archaic adaptive introgression in humans. *Nature Reviews Genetics* **16**:359–371. DOI: <https://doi.org/10.1038/nrg3936>, PMID: 25963373
- Ramsey J. 2003. Components of reproductive isolation between the monkeyflowers *mimulus lewisii* and *M. cardinalis* (phrymaceae). *Evolution* **57**:1520–1534. DOI: <https://doi.org/10.1111/j.0014-3820.2003.tb00360.x>
- Rawson PD, Burton RS. 2002. Functional coadaptation between cytochrome c and cytochrome c oxidase within allopatric populations of a marine copepod. *PNAS* **99**:12955–12958. DOI: <https://doi.org/10.1073/pnas.202335899>, PMID: 12271133
- Rieseberg LH, Van Fossen C, Desrochers AM. 1995. Hybrid speciation accompanied by genomic reorganization in wild sunflowers. *Nature* **375**:313–316. DOI: <https://doi.org/10.1038/375313a0>
- Rieseberg LH. 1997. Hybrid origins of plant species. *Annual Review of Ecology and Systematics* **28**:359–389. DOI: <https://doi.org/10.1146/annurev.ecolsys.28.1.359>
- Rieseberg LH, Archer MA, Wayne RK. 1999. Transgressive segregation, adaptation and speciation. *Heredity* **83**:363–372. DOI: <https://doi.org/10.1038/sj.hdy.6886170>, PMID: 10583537
- Riquet F, Liautard-Haag C, Woodall L, Bouza C, Louisy P, Hamer B, Otero-Ferrer F, Aublanc P, Béduneau V, Briard O, El Ayari T, Hochscheid S, Belkhir K, Arnaud-Haond S, Gagnaire PA, Bierne N. 2019. Parallel pattern of differentiation at a genomic island shared between clinal and mosaic hybrid zones in a complex of cryptic seahorse lineages. *Evolution* **73**:817–835. DOI: <https://doi.org/10.1111/evo.13696>
- Rosenthal GG. 2013. Individual mating decisions and hybridization. *Journal of Evolutionary Biology* **26**:252–255. DOI: <https://doi.org/10.1111/jeb.12004>, PMID: 23323999
- Rotival M, Quintana-Murci L. 2020. Functional consequences of archaic introgression and their impact on fitness. *Genome Biology* **21**:3. DOI: <https://doi.org/10.1186/s13059-019-1920-z>, PMID: 31898502
- Ruegg K. 2008. Genetic, morphological, and ecological characterization of a hybrid zone that spans a migratory divide. *Evolution* **62**:452–466. DOI: <https://doi.org/10.1111/j.1558-5646.2007.00263.x>
- Runemark A, Trier CN, Eroukhanoff F, Hermansen JS, Matschiner M, Ravinet M, Elgvin TO, Sætre GP. 2018. Variation and constraints in hybrid genome formation. *Nature Ecology & Evolution* **2**:549–556. DOI: <https://doi.org/10.1038/s41559-017-0437-7>, PMID: 29335572
- Sage RD. 1986. Genetic Analysis of a Hybrid Zone Between *Domesticus* and *Musculus* Mice (*Mus musculus* Complex): Hemoglobin Polymorphisms. In: Potter M, Nadeau J. H, Cancro M. P (Eds). *The Wild Mouse in Immunology*. Berlin, Heidelberg: Springer. p. 75–85. DOI: https://doi.org/10.1007/978-3-642-71304-0_9
- Salvatori V, Godinho R, Braschi C, Boitani L, Ciucci P. 2019. High levels of recent wolf × dog introgressive hybridization in agricultural landscapes of central Italy. *European Journal of Wildlife Research* **65**:73. DOI: <https://doi.org/10.1007/s10344-019-1313-3>
- Sánchez-Ramírez S, Weiss JG, Thomas CG, Cutter AD. 2021. Widespread misregulation of inter-species hybrid transcriptomes due to sex-specific and sex-chromosome regulatory evolution. *PLOS Genetics* **17**:e1009409. DOI: <https://doi.org/10.1371/journal.pgen.1009409>, PMID: 33667233

- Sankararaman S**, Mallick S, Dannemann M, Prüfer K, Kelso J, Pääbo S, Patterson N, Reich D. 2014. The genomic landscape of neanderthal ancestry in present-day humans. *Nature* **507**:354–357. DOI: <https://doi.org/10.1038/nature12961>, PMID: 24476815
- Sankararaman S**, Mallick S, Patterson N, Reich D. 2016. The combined landscape of denisovan and neanderthal ancestry in Present-Day humans. *Current Biology* **26**:1241–1247. DOI: <https://doi.org/10.1016/j.cub.2016.03.037>, PMID: 27032491
- Satokangas I**. 2020. Multi-locus interactions and the build-up of reproductive isolation. *arXiv*. <http://arxiv.org/abs/2005.13790>.
- Schartl M**. 2008. Evolution of *xmrk*: an oncogene, but also a speciation gene? *BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology* **30**:822–832. DOI: <https://doi.org/10.1002/bies.20807>, PMID: 18693261
- Schartl M**, Wilde B, Laisney JA, Taniguchi Y, Takeda S, Meierjohann S. 2010. A mutated EGFR is sufficient to induce malignant melanoma with genetic background-dependent histopathologies. *Journal of Investigative Dermatology* **130**:249–258. DOI: <https://doi.org/10.1038/jid.2009.213>, PMID: 19609310
- Schiffman JS**, Ralph PL. 2018. System drift and speciation. *bioRxiv*. DOI: <https://doi.org/10.1101/231209>
- Schilthuizen M**, Giesbers MC, Beukeboom LW. 2011. Haldane's rule in the 21st century. *Heredity* **107**:95–102. DOI: <https://doi.org/10.1038/hdy.2010.170>, PMID: 21224879
- Schluter D**. 2000. *Ecological Character Displacement in Adaptive Radiation*. Chicago, IL: The American Naturalist. DOI: <https://doi.org/10.1086/303412>
- Schneemann H**. 2019. The geometry and genetics of hybridization. *bioRxiv*. DOI: <https://doi.org/10.1101/862235>
- Schumer M**, Cui R, Powell DL, Dresner R, Rosenthal GG, Andolfatto P. 2014. High-resolution mapping reveals hundreds of genetic incompatibilities in hybridizing fish species. *eLife* **3**:e02535. DOI: <https://doi.org/10.7554/eLife.02535>
- Schumer M**, Cui R, Rosenthal GG, Andolfatto P. 2015. Reproductive isolation of hybrid populations driven by genetic incompatibilities. *PLOS Genetics* **11**:e1005041. DOI: <https://doi.org/10.1371/journal.pgen.1005041>, PMID: 25768654
- Schumer M**, Cui R, Powell DL, Rosenthal GG, Andolfatto P. 2016. Ancient hybridization and genomic stabilization in a swordtail fish. *Molecular Ecology* **25**:2661–2679. DOI: <https://doi.org/10.1111/mec.13602>
- Schumer M**, Powell DL, Delclós PJ, Squire M, Cui R, Andolfatto P, Rosenthal GG. 2017. Assortative mating and persistent reproductive isolation in hybrids. *PNAS* **114**:10936–10941. DOI: <https://doi.org/10.1073/pnas.1711238114>, PMID: 28973863
- Schumer M**, Xu C, Powell DL, Durvasula A, Skov L, Holland C, Blazier JC, Sankararaman S, Andolfatto P, Rosenthal GG, Przeworski M. 2018. Natural selection interacts with recombination to shape the evolution of hybrid genomes. *Science* **360**:656–660. DOI: <https://doi.org/10.1126/science.aar3684>, PMID: 29674434
- Schumer M**. 2019. Versatile simulations of admixture and accurate local ancestry inference with mixnmatch and ancestryinfer. *Molecular Ecology Resources* **20**:1141–1151. DOI: <https://doi.org/10.1111/1755-0998.13175>
- Schumerlab**. 2021. hybridization_review. *Software Heritage*. swh:1:rev:69a398b89365cc069c6856d990c2b74293b52486. [https://archive.softwareheritage.org/swh:1:rev:69a398b89365cc069c6856d990c2b74293b52486](https://archive.softwareheritage.org/swh:1:dir:a969a8f859e3f13c5bcfc5f7392da85b2e225bfa;origin=https://github.com/Schumerlab/hybridization_review;visit=swh:1:snp:4977d95d93c451e20c212227887334bb17457f6f;anchor=swh:1:rev:69a398b89365cc069c6856d990c2b74293b52486). https://github.com/Schumerlab/hybridization_review;visit=swh:1:snp:4977d95d93c451e20c212227887334bb17457f6f;anchor=swh:1:rev:69a398b89365cc069c6856d990c2b74293b52486
- Scordato ESC**, Smith CCR, Semenov GA, Liu Y, Wilkins MR, Liang W, Rubtsov A, Sundev G, Koyama K, Turbek SP, Wunder MB, Stricker CA, Safran RJ. 2020. Migratory divides coincide with reproductive barriers across replicated avian hybrid zones above the tibetan plateau. *Ecology Letters* **23**:231–241. DOI: <https://doi.org/10.1111/ele.13420>, PMID: 31746098
- Sedghifar A**, Brandvain Y, Ralph P, Coop G. 2015. The spatial mixing of genomes in secondary contact zones. *Genetics* **201**:243–261. DOI: <https://doi.org/10.1534/genetics.115.179838>, PMID: 26205988
- Sedghifar A**, Brandvain Y, Ralph P. 2016. Beyond clines: lineages and haplotype blocks in hybrid zones. *Molecular Ecology* **25**:2559–2576. DOI: <https://doi.org/10.1111/mec.13677>, PMID: 27148805
- Seehausen O**. 2004. Hybridization and adaptive radiation. *Trends in Ecology & Evolution* **19**:198–207. DOI: <https://doi.org/10.1016/j.tree.2004.01.003>, PMID: 16701254
- Selz OM**, Seehausen O. 2019. Interspecific hybridization can generate functional novelty in cichlid fish. *PNAS* **286**:20191621. DOI: <https://doi.org/10.1098/rspb.2019.1621>
- Setter D**, Mousset S, Cheng X, Nielsen R, DeGiorgio M, Hermisson J. 2019. VolcanoFinder: genomic scans for adaptive introgression. *PLOS Genetics* **16**:e1008867. DOI: <https://doi.org/10.1371/journal.pgen.1008867>
- Shaw DD**, Wilkinson P. 1980. Chromosome differentiation, hybrid breakdown and the maintenance of a narrow hybrid zone in *Caledia*. *Chromosoma* **80**:1–31. DOI: <https://doi.org/10.1007/BF00327563>
- Shchur V**, Svedberg J, Medina P, Corbett-Detig R, Nielsen R. 2020. On the distribution of tract lengths during adaptive introgression. *G3: Genes, Genomes, Genetics* **10**:3663–3673. DOI: <https://doi.org/10.1534/g3.120.401616>
- Shen XX**, Oplente DA, Kominek J, Zhou X, Steenwyk JL, Buh KV, Haase MAB, Wisecaver JH, Wang M, Doering DT, Boudouris JT, Schneider RM, Langdon QK, Ohkuma M, Endoh R, Takashima M, Manabe RI, Čadež N, Libkind D, Rosa CA, et al. 2018. Tempo and mode of genome evolution in the budding yeast subphylum. *Cell* **175**:1533–1545. DOI: <https://doi.org/10.1016/j.cell.2018.10.023>, PMID: 30415838
- Shorter JR**, Odet F, Aylor DL, Pan W, Kao CY, Fu CP, Morgan AP, Greenstein S, Bell TA, Stevans AM, Feathers RW, Patel S, Cates SE, Shaw GD, Miller DR, Chesler EJ, McMillian L, O'Brien DA, Villena FP. 2017. Male

- infertility is responsible for nearly half of the extinction observed in the mouse collaborative cross. *Genetics* **206**:557–572. DOI: <https://doi.org/10.1534/genetics.116.199596>, PMID: 28592496
- Simon A, Bierne N, Welch JJ. 2018. Coadapted genomes and selection on hybrids: fisher's geometric model explains a variety of empirical patterns. *Evolution Letters* **2**:472–498. DOI: <https://doi.org/10.1002/evl3.66>, PMID: 30283696
- Singhal S, Leffler EM, Sannareddy K, Turner I, Venn O, Hooper DM, Strand AI, Li Q, Raney B, Balakrishnan CN, Griffith SC, McVean G, Przeworski M. 2015. Stable recombination hotspots in birds. *Science* **350**:928–932. DOI: <https://doi.org/10.1126/science.aad0843>, PMID: 26586757
- Slatkin M, Lande R. 1994. Segregation variance after hybridization of isolated populations. *Genetical Research* **64**:51–56. DOI: <https://doi.org/10.1017/S0016672300032547>, PMID: 7958831
- Sloan DB, Havird JC, Sharbrough J. 2017. The on-again, off-again relationship between mitochondrial genomes and species boundaries. *Molecular Ecology* **26**:2212–2236. DOI: <https://doi.org/10.1111/mec.13959>, PMID: 27997046
- Smagulova F, Brick K, Pu Y, Camerini-Otero RD, Petukhova GV. 2016. The evolutionary turnover of recombination hot spots contributes to speciation in mice. *Genes & Development* **30**:266–280. DOI: <https://doi.org/10.1101/gad.270009.115>, PMID: 26833728
- Smith KL, Hale JM, Kearney MR, Austin JJ, Melville J. 2013. Molecular patterns of introgression in a classic hybrid zone between the australian tree frogs, *Litoria ewingii* and *L. Paraewingii*: evidence of a tension zone. *Molecular Ecology* **22**:1869–1883. DOI: <https://doi.org/10.1111/mec.12176>, PMID: 23294099
- Smukowski Heil CS, Large CRL, Patterson K, Hickey AS, Yeh CC, Dunham MJ. 2019. Temperature preference can bias parental genome retention during hybrid evolution. *PLOS Genetics* **15**:e1008383. DOI: <https://doi.org/10.1371/journal.pgen.1008383>, PMID: 31525194
- Smukowski Heil C, Patterson K, Hickey AS, Alcantara E, Dunham MJ. 2021. Transposable element mobilization in interspecific yeast hybrids. *Genome Biology and Evolution* **13**:evab033. DOI: <https://doi.org/10.1093/gbe/evab033>, PMID: 33595639
- Soltis DE. 2004. Advances in the study of polyploidy since plant speciation. *New Phytologist* **161**:173–191. DOI: <https://doi.org/10.1046/j.1469-8137.2003.00948.x>
- Song Y, Endepols S, Klemann N, Richter D, Matuschka FR, Shih CH, Nachman MW, Kohn MH. 2011. Adaptive introgression of anticoagulant rodent poison resistance by hybridization between old world mice. *Current Biology* **21**:1296–1301. DOI: <https://doi.org/10.1016/j.cub.2011.06.043>, PMID: 21782438
- Soria-Carrasco V, Gompert Z, Comeault AA, Farkas TE, Parchman TL, Johnston JS, Buerkle CA, Feder JL, Bast J, Schwander T, Egan SP, Crespi BJ, Nosil P. 2014. Stick insect genomes reveal natural selection's role in parallel speciation. *Science* **344**:738–742. DOI: <https://doi.org/10.1126/science.1252136>, PMID: 24833390
- Stapley J, Feulner PGD, Johnston SE, Santure AW, Smadja CM. 2017. Variation in recombination frequency and distribution across eukaryotes: patterns and processes. *Philosophical Transactions of the Royal Society B: Biological Sciences* **372**:20160455. DOI: <https://doi.org/10.1098/rstb.2016.0455>
- Staubach F, Lorenc A, Messer PW, Tang K, Petrov DA, Tautz D. 2012. Genome patterns of selection and introgression of haplotypes in natural populations of the house mouse (*Mus musculus*). *PLOS Genetics* **8**:e1002891. DOI: <https://doi.org/10.1371/journal.pgen.1002891>, PMID: 22956910
- Steensels J, Gallone B, Verstrepen KJ. 2021. Interspecific hybridization as a driver of fungal evolution and adaptation. *Nature Reviews Microbiology* **19**:485–500. DOI: <https://doi.org/10.1038/s41579-021-00537-4>, PMID: 33767366
- Stelkens RB, Schmid C, Selz O, Seehausen O. 2009. Phenotypic novelty in experimental hybrids is predicted by the genetic distance between species of cichlid fish. *BMC Evolutionary Biology* **9**:283. DOI: <https://doi.org/10.1186/1471-2148-9-283>, PMID: 19961584
- Stelkens R, Seehausen O. 2009. Genetic distance between species predicts novel trait expression in their hybrids. *Evolution* **63**:884–897. DOI: <https://doi.org/10.1111/j.1558-5646.2008.00599.x>
- Storchová R, Reif J, Nachman MW. 2010. Female heterogamety and speciation: reduced introgression of the z chromosome between two species of nightingales. *Evolution* **64**:456–471. DOI: <https://doi.org/10.1111/j.1558-5646.2009.00841.x>
- Stryjewski KF, Sorenson MD. 2017. Mosaic genome evolution in a recent and rapid avian radiation. *Nature Ecology & Evolution* **1**:1912–1922. DOI: <https://doi.org/10.1038/s41559-017-0364-7>, PMID: 29085063
- Suarez-Gonzalez A, Lexer C, Cronk QCB. 2018. Adaptive introgression: a plant perspective. *Biology Letters* **14**:20170688. DOI: <https://doi.org/10.1098/rsbl.2017.0688>, PMID: 29540564
- Svedin N, Wiley C, Veen T, Gustafsson L, Qvarnström A. 2008. Natural and sexual selection against hybrid flycatchers. *PNAS* **275**:735–744. DOI: <https://doi.org/10.1098/rspb.2007.0967>
- Szymura JM, Barton NH. 1986. Genetic analysis of a hybrid zone between the Fire-Bellied toads, *Bombina bombina* and *B. variegata*, near Cracow in southern Poland. *Evolution* **40**:1141–1159. DOI: <https://doi.org/10.1111/j.1558-5646.1986.tb05740.x>
- Taylor SA, White TA, Hochachka WM, Ferretti V, Curry RL, Lovette I. 2014. Climate-mediated movement of an avian hybrid zone. *Current Biology* **24**:671–676. DOI: <https://doi.org/10.1016/j.cub.2014.01.069>, PMID: 24613306
- Teeter KC, Payseur BA, Harris LW, Bakewell MA, Thibodeau LM, O'Brien JE, Krenz JG, Sans-Fuentes MA, Nachman MW, Tucker PK. 2008. Genome-wide patterns of gene flow across a house mouse hybrid zone. *Genome Research* **18**:67–76. DOI: <https://doi.org/10.1101/gr.6757907>, PMID: 18025268
- Telis N, Aguilar R, Harris K. 2020. Selection against archaic hominin genetic variation in regulatory regions. *Nature Ecology & Evolution* **4**:1558–1566. DOI: <https://doi.org/10.1038/s41559-020-01284-0>, PMID: 32839541

- Tenaillon O. 2014. The utility of Fisher's Geometric Model in Evolutionary Genetics. *Annual Review of Ecology, Evolution, and Systematics* **45**:179–201. DOI: <https://doi.org/10.1146/annurev-ecolsys-120213-091846>, PMID: 26740803
- Thibert-Plante X, Hendry AP. 2009. Five questions on ecological speciation addressed with individual-based simulations. *Journal of Evolutionary Biology* **22**:109–123. DOI: <https://doi.org/10.1111/j.1420-9101.2008.01627.x>, PMID: 19127610
- Thompson KA. 2019a. Patterns, predictors, and consequences of dominance in hybrids. *bioRxiv*. DOI: <https://doi.org/10.1101/818658>
- Thompson KA, Osmond MM, Schluter D. 2019b. Parallel genetic evolution and speciation from standing variation. *Evolution Letters* **3**:129–141. DOI: <https://doi.org/10.1002/evl3.106>, PMID: 31289688
- Thompson KA. 2020. Experimental hybridization studies suggest that pleiotropic alleles commonly underlie adaptive divergence between natural populations. *The American Naturalist* **196**:E16–E22. DOI: <https://doi.org/10.1086/708722>, PMID: 32552104
- Todesco M, Owens GL, Bercovich N, Légaré JS, Soudi S, Burge DO, Huang K, Ostevik KL, Drummond EBM, Imerovski I, Lande K, Pascual-Robles MA, Nanavati M, Jahani M, Cheung W, Staton SE, Muños S, Nielsen R, Donovan LA, Burke JM, et al. 2020. Massive haplotypes underlie ecotypic differentiation in sunflowers. *Nature* **584**:602–607. DOI: <https://doi.org/10.1038/s41586-020-2467-6>, PMID: 32641831
- Trier CN, Hermansen JS, Sætre GP, Bailey RI. 2014. Evidence for mito-nuclear and sex-linked reproductive barriers between the hybrid Italian sparrow and its parent species. *PLOS Genetics* **10**:e1004075. DOI: <https://doi.org/10.1371/journal.pgen.1004075>, PMID: 24415954
- Tulchinsky AY, Johnson NA, Watt WB, Porter AH. 2014. Hybrid incompatibility arises in a sequence-based bioenergetic model of transcription factor binding. *Genetics* **198**:1155–1166. DOI: <https://doi.org/10.1534/genetics.114.168112>, PMID: 25173845
- Turelli M. 1998. The causes of Haldane's rule. *Science* **282**:889–891. DOI: <https://doi.org/10.1126/science.282.5390.889>, PMID: 9841436
- Turissini DA, Matute DR. 2017. Fine scale mapping of genomic introgressions within the *Drosophila yakuba* clade. *PLOS Genetics* **13**:e1006971. DOI: <https://doi.org/10.1371/journal.pgen.1006971>, PMID: 28873409
- Turner TL, Hahn MW, Nuzhdin SV. 2005. Genomic islands of speciation in *Anopheles gambiae*. *PLOS Biology* **3**:e285. DOI: <https://doi.org/10.1371/journal.pbio.0030285>, PMID: 16076241
- Turner LM, Schwahn DJ, Harr B. 2012. Reduced male fertility is common but highly variable in form and severity in a natural house mouse hybrid zone. *Evolution* **66**:443–458. DOI: <https://doi.org/10.1111/j.1558-5646.2011.01445.x>
- Turner LM, Harr B. 2014. Genome-wide mapping in a house mouse hybrid zone reveals hybrid sterility loci and Dobzhansky-Muller interactions. *eLife* **3**:e02504. DOI: <https://doi.org/10.7554/eLife.02504>
- Uecker H, Setter D, Hermisson J. 2015. Adaptive gene introgression after secondary contact. *Journal of Mathematical Biology* **70**:1523–1580. DOI: <https://doi.org/10.1007/s00285-014-0802-y>, PMID: 24992884
- Veller C. 2019. Recombination, variance in genetic relatedness, and selection against introgressed DNA. *bioRxiv*. DOI: <https://doi.org/10.1101/846147>
- Vernot B, Akey JM. 2014. Resurrecting surviving Neandertal lineages from modern human genomes. *Science* **343**:1017–1021. DOI: <https://doi.org/10.1126/science.1245938>, PMID: 24476670
- Vickrey AI, Bruders R, Kronenberg Z, Mackey E, Bohlender RJ, Maclary ET, Maynez R, Osborne EJ, Johnson KP, Huff CD, Yandell M, Shapiro MD. 2018. Introgression of regulatory alleles and a missense coding mutation drive plumage pattern diversity in the rock pigeon. *eLife* **7**:e34803. DOI: <https://doi.org/10.7554/eLife.34803>, PMID: 30014848
- Wallbank RW, Baxter SW, Pardo-Díaz C, Hanly JJ, Martin SH, Mallet J, Dasmahapatra KK, Salazar C, Joron M, Nadeau N, McMillan WO, Jiggins CD. 2016. Evolutionary novelty in a butterfly wing pattern through enhancer shuffling. *PLOS Biology* **14**:e1002353. DOI: <https://doi.org/10.1371/journal.pbio.1002353>, PMID: 26771987
- Walter GM, Richards TJ, Wilkinson MJ, Blows MW, Aguirre JD, Ortiz-Barrientos D. 2020. Loss of ecologically important genetic variation in late generation hybrids reveals links between adaptation and speciation. *Evolution Letters* **4**:302–316. DOI: <https://doi.org/10.1002/evl3.187>, PMID: 32774880
- Wang RJ, White MA, Payseur BA. 2015. The pace of hybrid incompatibility evolution in house mice. *Genetics* **201**:229–242. DOI: <https://doi.org/10.1534/genetics.115.179499>, PMID: 26199234
- Wang S, Rohwer S, Delmore K, Irwin DE. 2019. Cross-decades stability of an avian hybrid zone. *Journal of Evolutionary Biology* **32**:1242–1251. DOI: <https://doi.org/10.1111/jeb.13524>, PMID: 31430391
- Wellenreuther M, Bernatchez L. 2018. Eco-Evolutionary genomics of chromosomal inversions. *Trends in Ecology & Evolution* **33**:427–440. DOI: <https://doi.org/10.1016/j.tree.2018.04.002>, PMID: 29731154
- Westram AM, Faria R, Johannesson K, Butlin R. 2021. Using replicate hybrid zones to understand the genomic basis of adaptive divergence. *Molecular Ecology* **30**:3797–3814. DOI: <https://doi.org/10.1111/mec.15861>, PMID: 33638231
- Whitney KD, Randell RA, Rieseberg LH. 2006. Adaptive introgression of herbivore resistance traits in the weedy sunflower *Helianthus annuus*. *The American Naturalist* **167**:794–807. DOI: <https://doi.org/10.1086/504606>, PMID: 16649157
- Wu C-I. 2001. The genic view of the process of speciation. *Journal of Evolutionary Biology* **14**:851–865. DOI: <https://doi.org/10.1046/j.1420-9101.2001.00335.x>
- Yamaguchi R, Otto SP. 2020. Insights from Fisher's geometric model on the likelihood of speciation under different histories of environmental change. *bioRxiv*. DOI: <https://doi.org/10.1101/596866>

- Yanchukov A.** 2006. Hybridization of *Bombina bombina* and *B. variegata* (anura, Discoglossidae) at a sharp ecotone in western Ukraine: comparisons across transects and over time. *Evolution* **60**:583–600. DOI: <https://doi.org/10.1111/j.0014-3820.2006.tb01139.x>
- Yang C-H, Scarpino SV.** 2020. Reproductive barriers as a byproduct of gene network evolution. *bioRxiv*. DOI: <https://doi.org/10.1101/2020.06.12.147322>
- Zeberg H, Pääbo S.** 2020. The major genetic risk factor for severe COVID-19 is inherited from neanderthals. *Nature* **587**:610–612. DOI: <https://doi.org/10.1038/s41586-020-2818-3>, PMID: 32998156
- Zhang Z, Bendixsen DP, Janzen T, Nolte AW, Greig D, Stelkens R.** 2020. Recombining your way out of trouble: the genetic architecture of hybrid fitness under environmental stress. *Molecular Biology and Evolution* **37**:167–182. DOI: <https://doi.org/10.1093/molbev/msz211>, PMID: 31518427
- Zuellig MP, Sweigart AL.** 2018. A two-locus hybrid incompatibility is widespread, polymorphic, and active in natural populations of *Mimulus* * . *Evolution* **72**:2394–2405. DOI: <https://doi.org/10.1111/evo.13596>