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Does parental divergence predict reproductive compatibility?

Suzanne Edmands

Hybridization between populations or species can have either beneficial or detrimental effects on fitness. If these effects could be predicted based on the genetic or geographical distance between parents, this would be of great use to plant and animal breeders, managers and conservation biologists. The relationship between divergence and compatibility is also increasingly relevant to evolutionary biology, because recent work on the genetic architecture of reproductive isolation has fuelled a renewed interest in speciation rates and processes. Many studies have shown a correlation between parental divergence and both pre- and postzygotic isolation, but this relationship is clearly not strong enough to guide management decisions. Although it has been suggested that the speciation clock might tick at similar rates in different taxa, this appears to be far from true, because the divergence times resulting in hybrid vigor, outbreeding depression or partial reproductive compatibility vary widely both within and among taxonomic groups.

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Hybridization between divergent populations or species can result in increased fitness in some cases, but it is generally expected to result in reduced fitness [1]. Concern over these fitness effects is increasing as the rate of anthropogenically induced hybridizations increases [2–6]. Some of these mixing events are accidental; for example, when farmed salmon (e.g. *Salmo salar*) escape from pens and mate with wild salmon, or when domesticated crop plants (e.g. *Oryza sativa*) cross with their wild relatives. However, other crosses are intentional. Hybridization has been used to induce HYBRID VIGOR (see Glossary) in domesticated plants and animals since before Darwin, and translocation between natural populations is increasingly being proposed as a management tool with which to bolster dwindling population sizes and to prevent INBREEDING DEPRESSION [7–9]. However, enthusiasm for this management method is tempered by concerns about OUTBREEDING DEPRESSION [3–5].

Can the consequences of hybridization be predicted from the degree of divergence between parents? In addition to its importance for conservation biology, this question is central to our understanding of speciation. The relationship between divergence and compatibility might be expected to be stronger if

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Box 1. Genetic basis of outcrossing effects

Some crosses between divergent populations or species result in an increase in fitness known as hybrid vigor. This fitness increase is generally attributed to either OVERDOMINANCE (see Box Glossary) or the masking of deleterious recessive alleles. However, EPISTASIS can also be involved [a].

Other crosses result in a decrease in fitness known as outbreeding depression. This can occur in first generation (F1) hybrids, where it can be attributed to disruption of local adaptation (i.e. gene × environment interactions), UNDERDOMINANCE or epistatic interactions (heterozygote × heterozygote interactions or interactions involving sex chromosomes). Frequently, however, fitness declines do not occur until the second (F2) or backcross generations (i.e. hybrid breakdown). Here, the original parental gene combinations are broken up by recombination, creating the possibility for deleterious heterozygote × homozygote or homozygote × homozygote interactions [b].

Hybridization can create both extrinsic and intrinsic incompatibility [c,d]. Extrinsic incompatibility (also called environment-dependent postzygotic isolation) occurs when hybrids suffer a reduction in fitness because of an interaction between their phenotype and the environment. For example, a hybrid with a phenotype intermediate to the two parents might do poorly in both parental habitats. By contrast, intrinsic incompatibility occurs when reductions in hybrid fitness are largely independent of the environment. This incompatibility can be caused by underdominance, chromosomal rearrangements or deleterious epistatic interactions. The Dobzhansky–Muller model explains how epistatic incompatibilities can evolve without causing a radical breakdown in fitness by postulating that alleles that are neutral or beneficial on one genetic background encounter conflicts only when combined with alleles from an independently evolved lineage. A related model recently developed by Lynch and Force involves divergent resolution of duplicate genes in isolated populations [e].

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Box Glossary

Epistasis: phenotypic effect caused by the interaction of alleles at two or more loci.
Overdominance: heterozygote advantage.
Underdominance: heterozygote disadvantage.

incompatibility results from the slow accumulation of many genes of small effect, than if it results from a few genes of large effect or from chromosomal rearrangements. Interest in whether reproductive isolation is a gradual process has been enhanced by recent work on the genetic architecture of speciation, which points to >100 interacting genes in some cases [10] and chromosomal rearrangements in others [11,12]. The question is also topical because of the renewed interest in natural hybridization and its role in evolution [1,13].

Both pre- and postzygotic isolation might be expected to evolve more rapidly if they are driven by direct selection, than by neutral drift or indirect selection via pleiotropy. Predicting the evolution of postzygotic isolation is particularly difficult because of the complex gene action occurring in hybrids (Box 1). Hybridization can simultaneously create both beneficial and detrimental gene interactions, and these can change substantially between generations because of recombination. Similarly, hybridization can simultaneously create both INTRINSIC INCOMPATIBILITIES and EXTRINSIC INCOMPATABILITIES. Intrinsic incompatibilities that are neutral within populations might be expected to accumulate in a clock-like fashion. By contrast, extrinsic incompatibilities might be driven by selection to evolve rapidly [14] and might therefore be more important for the success of intraspecific hybridizations [3,5]. However, the contrast between the evolution of intrinsic and extrinsic incompatibilities is not so clear cut. There is some evidence that intrinsic coadaption can be disrupted by intraspecific crosses [15,16] and extrinsic incompatibilities might be expected to evolve in a linear fashion along an environmental cline [17].

Here, I review the relationship between reproductive compatibility and divergence for a variety of taxa. I focus largely on experimental rather than natural hybridization, because this allows a more straightforward distinction between pre- and postzygotic barriers to be made, as well as better estimates of the mean effect of hybridization. Examples include both intra- and interspecific hybridization. However, I do not include crosses at the smallest levels of divergence that can be distinguished only from a pedigree, because the deleterious effects of such high parental relatedness are well established [18]. Also, I focus heavily on postzygotic isolation, because postzygotic isolation is often thought to evolve at a more regular rate than does prezygotic isolation [19,20]. Although this is far from an exhaustive review of the hybridization literature, the selected examples support the conclusion that the acquisition of reproductive isolation is not sufficiently clock-like to make parental divergence a reliable predictor of reproductive compatibility.

Methods for assessing the relationship between divergence and compatibility

Measurements of parental divergence

There are many methods for estimating parental divergence, including geographical, environmental, phenotypic and genetic measures (Box 2), and each has advantages and disadvantages. Here, I focus primarily on geographical and genetic divergence, because these measures are most easily compared between studies.

Measurements of reproductive compatibility

Prezygotic isolation can include differences in behavior, ecology, reproductive timing, gametic compatibility or pollinators. In practice, prezygotic compatibility is most frequently measured by the

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Box 2. Methods for estimating parental divergence

Geographical divergence
Physical distance between parents is by far the most prevalent and easiest means of measuring divergence. However, it is a very indirect measure of parental relatedness. It can serve as a proxy for evolutionary divergence in cases of isolation-by-distance or as a proxy for adaptive divergence when there are environmental clines.

Environmental divergence
This is a composite measure of ecological factors (climate, elevation, soil type, etc.) that might be an appropriate surrogate for adaptive divergence. Although such measures should be particularly useful for predicting extrinsic incompatibilities, they have been used only rarely [a].

Phenotypic divergence
A variety of morphological and behavioral traits can be summarized by measures of phenotypic divergence, which are often expressed as euclidian distance. This can serve as an indicator of adaptive divergence if the traits are under selection [b] or evolutionary divergence if the traits are sufficiently numerous, neutral and independent [c].

Genetic divergence
Notwithstanding molecular clock issues (Box 3), measures of genetic divergence often provide the best-available surrogate for evolutionary time and the best common currency for comparing studies of different taxa. In the past, allozymes were the most common markers using Nei's D [d] or other similar measures that assess differences in allele frequencies. More recently, allozyme distances have largely been supplanted by DNA-based estimates, such as percent nucleotide divergence, average percent difference for minisatellite loci or distance measures based on microsatellite loci. In spite of the declining popularity of allozymes, a reanalysis of published *Drosophila* data shows both pre- and post-mating isolation to be more tightly correlated with allozyme divergence than silent DNA divergence, suggesting that natural selection influences reproductive isolation [e]. For very closely related populations, divergence estimates become unreliable, because within-population variation is confounded with between-population variation. At this finer scale, fitness might be more related to divergence between parental individuals. This can be estimated by individual heterozygosity, or by d^2, a measure of the squared difference in microsatellite allele size within an individual. Recent work suggests that individual fitness is more tightly correlated with microsatellite heterozygosity than with mean d^2 in all but a few situations [f].

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strength of sexual isolation in the laboratory. This includes measures of a wide variety of surrogates, such as pollen tube growth [21], clasping behavior [22], egg cleavage [23], copulation [24], insemination [24] and the absence of attack behavior [25].

Postzygotic isolation is defined as a reduction in fertility or viability in hybrid offspring. This also involves a range of surrogates, such as hatching [26], growth [27], survival [28], seed set [27], metamorphosis [29] and cumulative fitness [30]. Because of the diversity of methods used to measure postzygotic isolation and the frequent differences between reciprocal crosses [31,32], some authors [24,26,33] have defined postzygotic isolation as a discrete character (0 = both sexes viable and fertile in both reciprocal crosses; 0.25 = at least one sex sterile or inviable in one cross, etc.) to maximize the size of the data set. In spite of the observation that F1 hybrid vigor is often followed by HYBRID BREAKDOWN in later generations [34] (Box 1), studies of the relationship between divergence and mean fitness in known generations have focused on the F1, with a few exceptions extending to the F2 or F3 [28,35,36]. Most of the studies cited here therefore include only the F1 generation.

Tests of correlation

The relationship between parental divergence and reproductive compatibility is typically measured by simple regression analysis. Because each species (or population) is often involved in multiple hybridizations, and because the taxa might be related evolutionarily, the analyses should be restricted to an appropriate set of phylogenetically independent contrasts [37]. When phylogenies are available, some studies [24,26,33] have therefore corrected the data by averaging all comparisons between pairs of taxa spanning a node to produce a single estimate of genetic distance and reproductive isolation.

General patterns in the relationship between divergence and reproductive isolation

Prezygotic isolation

At the smallest scales of parental relatedness, there are many examples of negative relationships between divergence and prezygotic isolation (i.e. inbreeding avoidance) [18]. However, at divergence scales that are distinguishable by genetic or geographical measures (Table 1a), prezygotic barriers often increase with divergence [22,24,25,33,38]. In at least one case [39], prezygotic compatibility is highest at intermediate geographical distances, a phenomenon known as optimal outbreeding, which is presumably driven by mate choice avoiding both inbreeding and outbreeding. In spite of these examples of a rough correlation with divergence, prezygotic isolation is generally believed to evolve more rapidly and erratically than does postzygotic isolation. In Coyne and Orr's classic compilation of *Drosophila* studies [24,33], accelerated prezygotic isolation was found only in sympatric taxa, and was taken as support for the theory of reinforcement. However, in their studies of the sea urchin *Echinometra* on either side of the Isthmus of Panama, Lessios and Cunningham [23] found greater gametic incompatibility between allopatric than between sympatric species, suggesting that isolation occurred as an incidental byproduct of processes

Table 1. Examples of the relationship between parental divergence and isolation

Relationship	Taxa	Range of divergence		No. of hybrid crosses[a]	Refs
		Geographical (km)	Genetic (time estimate)		
(a) Prezygotic					
i. Intraspecific crosses					
Positive	Crustaceans (*Scottolana canadensis*)	~200–2000		13	[22]
Positive[b]	Amphibians (*Desmognathus ochrophaeus*)	~0–250	0.04–0.64 D (0.2–3.2 my)[c]	28	[38]
Intermediate optimum[d]	Angiosperms (*Delphinium nelsonii*)	0.001–0.1		3	[39]
None	Angiosperms (*Chamaecrista fasciculata*)	~0.001–0.1		3	[21]
ii. Interspecific crosses					
Positive	Crustaceans (*Alpheus* spp.)		0.03–0.27 D (0.2–1.4 my)[c] 7.7–19.2% mtDNA (3.2–8.0 my)[e]	7	[25]
Positive	Insects (*Drosophila* spp.)		0.02–1.95 D (0.1–9.8 my)[c]	171	[24,33]
None	Echinoderms (*Echinometra* spp.)		0.11–0.64 D (0.6–3.2 my)[c]	3	[23,66]
(b) Postzygotic					
i. Intraspecific crosses					
Positive	Ascidians (*Botryllus schlosseri*)	~0–0.005		10	[29]
Positive	Crustaceans (*Scottolana canadensis*)	~200–2000		13	[22]
Positive[f]	Crustaceans (*Tigriopus californicus*)	0.005–2007	0.20–22.30% mtDNA (0.1–9.3 my)[e]	12	[28]
Positive[g]	Angiosperms (*Lotus scoparius*)	~30–350	0.00–0.13 D (0.0–0.7 my)[c]	15	[30]
Intermediate optimum	Angiosperms (*Zea mays*)	~0–3800		8	[35]
Intermediate optimum	Angiosperms (*Delphinium nelsonii*)	0.001–0.03		4	[42,67]
Intermediate optimum	Angiosperms (*Agave schottii*)	0–2.5		4	[41]
None	Angiosperms (*Chamaecrista fasciculata*)	0.1–2000		6	[36]
ii. Intra- and interspecific crosses					
None	Angiosperms (*Gilia* spp.)	~20–500		>170	[43]
None	Angiosperms (*Oryza* spp.)		0–0.06% cpDNA (0–0.4my)[h]	13	[68–70]
None	Chlorophytes (*Chara* spp.)	2–15 000		>150	[71]
iii. Interspecific crosses					
Positive	Insects (*Drosophila* spp.)		0.02–1.95 D (0.1–9.8 my)[c]	171	[24,33]
Positive	Amphibians (multiple frog families)		0.08–2.21 D (0.4–11.1 my)[c]	116	[26]

[a]Excluding reciprocals and replicates.
[b]Significant correlation with geographical distance when genetic distance is held constant; however, with geographical distance held constant, the correlation with genetic distance is positive but nonsignificant.
[c]Nei's genetic distance (D); time estimate assumes 0.2 D million years^{-1} (my) [48].
[d]Minimum reproductive isolation at intermediate parental divergence.
[e]Percent sequence divergence for cytochrome oxidase I mitochondrial DNA (mtDNA); time estimate assumes 2.4% my^{-1} [25].
[f]Positive correlation in F1, no correlation in F2.
[g]Significant correlation with genetic distance; positive but nonsignificant correlation with geographical distance.
[h]Percent sequence divergence for maturase K chloroplast DNA (cpDNA); time estimate assumes 1.7×10^{-3} synonymous substitutions site^{-1} my^{-1} [70].

occurring in different oceans. In some cases, prezygotic isolation shows no correlation with parental divergence [21,23] (Table 1a). The rapid and erratic evolution of sexual isolation might be related to the strength of environmental selection and the lability of behaviors and sexual signals [19,20]. However, even in free-spawning invertebrates, such as sea urchins, where mating behaviors are largely absent, strong sexual isolation can still evolve rapidly [23], possibly because of the involvement of a few key loci [40].

Postzygotic isolation

In contrast to sexual isolation, postzygotic isolation might be expected to evolve at a more regular rate, particularly if it is driven by the accumulation of small differences that are nearly neutral within populations. Many studies report a positive relationship between parental divergence and postzygotic isolation (Table 1b). This includes work using different metrics of divergence and spanning vastly different scales, from intraspecific to interspecific, meters to thousands of kilometers, and thousands to millions of years. A few studies, however, have found patterns other than a positive correlation, particularly when they focus on a fine geographical scale, as has frequently been done within plant populations. In Waser's 1993 review of angiosperms [27], he lists seven examples in which fitness was highest for crosses at the widest geographical distance (60–3000 m), presumably because of relief from inbreeding depression. He also cites 15 examples where fitness was highest at intermediate distances (typically ~3–5 m), where the combined dangers of inbreeding and outbreeding depression were apparently minimized. More recent

Box 3. Estimating evolutionary divergence times

Allozymes are commonly used to resolve relationships at the level of populations and closely related species. Allozyme distances cited in this review are Nei's genetic distances (D), although not all the studies cited specified which form of Nei's D. The accuracy of D is highly dependent on the number of loci assayed, and whether monomorphic loci are included. For this review, I assume a divergence rate of 0.2 D my^{-1} (million years) [a]. This is an average based on several organisms and might be inaccurate for any particular taxon. Furthermore, at genetic distances >1, D is expected to become less reliable, because of multiple substitutions [a].

The highest divergence times cited in Table 2 (main text) are based on immunological distance (ID) in proteins, specifically the albumin protein. This was one of the earliest techniques of estimating molecular distance and involves measuring the strength of antigen-antibody reaction by quantitative complement fixation. This method was once extremely popular for divergence estimates above the species level [a,b], although it has more recently been supplanted by DNA-based methods. Calibrations in this review assume a rate of 1.7 ID my^{-1} in mammals and frogs and 0.6 ID my^{-1} in birds, which are well known to have slow divergence rates[b].

The remaining divergence times in Tables 1 and 2 (main text) are based on DNA. Animal mitochondrial DNA (mtDNA), which diverges at an average rate of ~2% my^{-1} is generally useful for lineages separated by <10 my [c]. In plants, mtDNA sequence evolution is much slower and chloroplast nucleotide substitutions give better resolution at lower taxonomic levels [d]. Finally, one of the divergence times for mammals in Table 2 is based on microsatellites [e]. Mutation rates at these loci are sufficiently high that they can be calibrated by direct observation over a few generations.

It should be noted that all of the divergence times used here are in terms of absolute time, not number of generations. This is because long-lived organisms, such as elephants, typically have relatively small populations compared with short-lived organisms, such as mice. A central, although controversial, tenet of the molecular clock hypothesis is that generation time and population size cancel each other out, causing molecules to reflect the absolute time since divergence [f].

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work on plants [41,42] continues to find intermediate optima at similar scales and, in one older study of *Zea mays* [35], the optimum fitness level was found to be at the much greater distance of thousands of kilometers (Table 1b). Finally, several studies have found no clear relationship between postzygotic isolation and geographical divergence (Table 1b). In some of these cases, reproductive isolation was extremely idiosyncratic, showing no apparent relationship even with morphology, ploidy or systematic position [43].

Which is the best metric for predicting compatibility?

Very few studies have looked at how reproductive compatibility correlates with different divergence measures, such as geographical, environmental, phenotypic and genetic distance. The ideal metric is likely to differ between taxa depending on the relative importance of selection and genetic drift, the strength of ecological gradients, and the environmental grain size (the scale of spatial heterogeneity relative to the mobility of a particular organism) [44]. One study of the salamander *Desmognathus ochrophaeus* found that genetic and geographical distance between populations together accounted for ~50% of the variance in sexual isolation [38]. However, when geographical distance was held constant, the remaining relationship with genetic distance became insignificant. This might be because drift plays a relatively minor role in ethological isolation in these salamanders, or because genetic distance is more vulnerable to measurement error than is geographical distance. A more recent study of postzygotic isolation among plant populations found a very different pattern. In the subshrub *Lotus scoparius*, both genetic and environmental distance were significantly correlated with isolation, whereas geographical distance was not [30]. This might be because sites were distributed among a mosaic of environments, instead of along a cline. Finally, a study of the copepod *Tigriopus californicus* found that neither genetic nor geographical distance predicted F1 hybrid fitness, whereas both measures were significantly correlated with F2 fitness [28]. However, the geographical distances were fairly evenly distributed, whereas the genetic distance formed two clusters, precluding any strong conclusions about the predictive powers of the two divergence measures.

Is there a speciation clock?

Not surprisingly, most studies report a positive relationship between parental divergence and reproductive isolation (Table 1). However, these studies span a vast range of scales. It would be both interesting and useful to know whether there were common patterns in the amount of time that is necessary for partial or complete reproductive isolation to evolve. That is, does the SPECIATION CLOCK [24] tick at similar rates in different taxa? Here, I focus primarily on postzygotic isolation, because prezygotic isolation appears to evolve in a more erratic fashion, and total prezygotic isolation has been reported in the complete absence of detectable genetic divergence [19].

Molecular clock calibrations

In some cases, divergence times can be estimated based on the fossil record, but most cases require invoking a MOLECULAR CLOCK. Considerable debate has focused on examples of rate variation among molecules and among taxa, particularly those that differ in generation time, thermal habit, metabolic rate or population size [45,46]. Still, there is substantial evidence that nucleic acids and proteins often evolve in a roughly clock-like fashion [47,48] and, in many cases, they provide our only means of estimating evolutionary timing. Box 3 describes the methods used for estimating divergence times in Tables 1 and 2, and also discusses some of the complexities of making these estimates.

Taxonomic comparisons

Taxonomic patterns in the evolution of reproductive isolation are difficult to discern, because the most

Table 2. Examples of the range of divergence times resulting in various outcrossing effects

Taxa	Parental divergence (time estimate/ basis)			Refs
	Maximum for heterosis	Minimum for outbreeding depression	Maximum for partial reproductive compatibility	
Crustaceans (*Tigriopus californicus*, *Eurytemora affinis*)	8.3 my / 20% mtDNA[a]	0.06 my / 0.15% mtDNA[a]	9.6 my / 23% mtDNA[a]	[28,72–74]
Insects (*Drosophila* spp.)	3.0–4.3 my / 5.9–8.5% mtDNA[b]	0.35 my / 0.07 D[c]	9.8 my / 1.95 D[c]	[24,33,53,54]
Amphibians (multiple frog families)	6.7–9.5 my / 1.33–1.90 D[c]	0.25 my / 0.05 D[c]	56 my / 95.2 ID[d]	[26,52,55]
Fish (*Oncorhynchus gorbuscha*)		0.01 my / fossil record[e]		[16]
Birds (multiple orders)	0.05 my / 0.01 D[c]	0.20 my / 0.04 D[c]	60 my / 36 ID[c]	[52,75–77]
Mammals (multiple orders)	0.5 –1.4 my / 23.36 $[(\delta\mu)^2]$[f]		8 my / 13.6 ID[d]	[52,78]

[a]Percent sequence divergence for cytochrome oxidase I mitochondrial DNA (mtDNA); time estimate assumes 2.4% million years^{-1}(my) [25].
[b]Percent sequence divergence for the gene encoding mitochondrial NADH dehydrogenase subunit 5 (ND5); time estimate assumes 2% my^{-1} [45].
[c]Nei's genetic distance (D); time estimate assumes 0.2 D my^{-1} [48].
[d]Immunological distance (ID) based on albumin; time estimate assumes 1.7 ID my^{-1} in mammals and frogs and 0.6 ID my^{-1} in birds [52].
[e]Estimated date of glacial retreat allowing even- and odd-year pink salmon *Oncorhynchus gorbuscha* runs to become established [79].
[f]Microsatellite-based distance measure calibrated by direct observation of ovine mutation rates [80].

rigorous studies are restricted to *Drosophila*. Nevertheless, there are hints of interesting patterns. In *Drosophila*, outbreeding depression (defined here as one or both sexes being inviable or sterile in the F1) begins at a genetic distance (D) as low as 0.07 [~0.35 my (million years)] [24], and partial reproductive compatibility (one or both sexes being viable and fertile in the F1) extends to a maximum of 1.95 D (~9.8 my) [33]. When both sympatric and allopatric taxa are combined, complete reproductive isolation (scored by Coyne and Orr as anything >90.3%, the degree of total isolation that is sufficient to prevent fusion of sympatric taxa) occurred at an average distance of 0.18 D (~0.9 my) [33]. Other than *Drosophila*, the largest study of reproductive isolation patterns is arguably Sasa *et al.*'s compilation of frog data [26], which also looks at F1 viability and fertility. Here, outbreeding depression begins as early as 0.05 D (~0.25 my) and partial compatibility extends to a maximum of 1.90 D (~9 my). The striking similarity between the data for *Drosophila* and frogs led Sasa *et al.* to suggest there might be a general pattern in the acquisition of reproductive isolation in animals. Indeed, others have suggested speciation clocks on similar scales. The minimum allozyme distance between nominal species for a variety of invertebrate taxa is reported by Thorpe and Solé-Cava [49] to be 0.15 D (~0.75 my), which is curiously similar to Coyne and Orr's mean of 0.18 D (~0.9 my). Avise *et al.* [50] report a somewhat slower rate, with speciation in vertebrates requiring an average of 2 my.

In spite of these very broad patterns, even a limited taxonomic survey (Table 2) reveals so much variation that divergence time is clearly an unreliable predictor of the consequences of hybridization. Across broad taxonomic groups (crustaceans, insects, amphibians, etc.), the divergence times that result in particular outcrossing effects (maximum for heterosis, minimum for outbreeding depression and maximum for partial reproductive compatibility) span at least an order of magnitude. For example, large surveys using similar techniques find that birds and frogs maintain the capacity for hybridization for up to 55–60 my, whereas mammals lose compatibility after only 8 my [51,52]. Within taxonomic groups, the divergence time resulting in partial or complete isolation between one pair of taxa can result in hybrid vigor for a different pair. For example, some pairs of *Drosophila* spp. exhibit reduced F1 viability or fertility as early as ~0.35 my (0.07 D) [24], whereas other *Drosophila* pairs up to 3–4.3 my apart (5.9–8.5% mitochondrial DNA) show F2 fecundity heterosis [53,54].

Why is the speciation clock so inconstant?

There are several reasons why the same divergence time can cause wildly different effects in different parental pairs. The first is that Table 2 specifically includes extreme examples, and these might not be representative. For example, the heterosis produced by crossing highly divergent (6.7–9.5 my) frog species involves an unusual case of hemiclonal reproduction [55]. A second cause of the variation might be poor estimates of the rate of divergence. For example, pairs of shrimp species assayed for both mtDNA and allozymes by Knowlton *et al.* [25] yielded between six and 16-fold higher divergence estimates when using a mitochondrial clock (2.4% my^{-1}) than when using a standard allozyme clock (0.2 D my^{-1}). Finally, a third reason why similar divergence times yield different outcrossing effects is that real biological differences exist between organisms. One obvious difference is generation time. The inverse correlation between generation time and population size is the justification for expecting the molecular clock, and the speciation clock, to tick in terms of absolute time instead of number of generations [56] (Box 3). However, this simplistic assumption clearly does not apply to all situations and there appears to be a strong correlation between generation time and speciation rate in some groups [57]. Another important biological variable is sex chromosome differentiation [11,58]. HALDANE'S RULE predicts that genic incompatibility will evolve fastest in organisms with a large X chromosome and a very degenerate Y chromosome. Incompatibility

Glossary

Extrinsic incompatibility: reproductive isolation caused by deleterious interactions between a hybrid phenotype and a particular environment.
Haldane's rule: the observation than when hybrid sterility or inviability occurs in only one sex, that sex is usually the one with heterogametic sex chromosomes.
Hybrid breakdown: decreased fitness in the F2 or later generation progeny of a cross between genetically divergent parents.
Hybrid vigor: increased fitness in the progeny of a cross between genetically divergent parents.
Inbreeding depression: decreased fitness in the progeny of a cross between close relatives.
Intrinsic incompatibility: a form of reproductive isolation that is largely independent of the environment. Can be caused by deleterious epistatic interactions, chromosomal rearrangements or underdominance.
Molecular clock: hypothesis that base substitutions in a population accumulate as a linear function of time.
Outbreeding depression: decreased fitness in the progeny of a cross between genetically divergent parents.
Speciation clock: hypothesis that reproductive isolation results from a gradual process of uniform rate.

is thus predicted to evolve more slowly in organisms with few genes on the X chromosome, with homomorphic sex chromosomes or without sex chromosomes. A final biological variable is the tolerance for hybridization in different taxa. For example, it has long been known that mammals lose the capacity for hybridization far earlier than do birds or frogs. Some have suggested that this might be because mammals have more stringent regulatory controls of gene expression [51], whereas others have proposed that it might be related to accelerated evolution of mother–offspring conflicts in viviparous organisms relative to egg-laying organisms [52].

Conclusions and future directions

The data regarding divergence versus reproductive compatibility reveal several very broad patterns. Both pre- and postzygotic isolation are often roughly correlated with divergence, although prezygotic isolation tends to evolve faster and more erratically. The best metric for predicting compatibility (genetic, geographical or environmental divergence) clearly varies between systems depending, in part, on the role of selection versus drift in driving differentiation. Some of the largest studies show roughly similar patterns, with hybrid incompatibilities often beginning after hundreds of thousands of years, and partial compatibility persisting for up to 8 my or more.

In spite of these approximate patterns, the list of questions needing further study is daunting. To test for general patterns in the acquisition of reproductive isolation, we need to extend the sort of rigorous studies done with *Drosophila* [24,33] to a wide variety of taxa. We also need to extend this work beyond the laboratory. With few exceptions [30,36,59,60], experimental studies of the evolution of reproductive isolation have been done under benign laboratory conditions, and how these patterns might change in the wild is unknown. Particularly important are reciprocal transplant studies that can tease apart intrinsic and extrinsic forces driving incompatibility [61]. Such studies are relevant to determining which measures of divergence will best predict reproductive compatibility.

Another priority for future research is to extend experimental studies of hybridization beyond the F1. We know fairly little about how outbreeding effects change between generations. There are a few records of rapid recovery from hybrid breakdown in the laboratory [62], the greenhouse [63,64] and natural hybrid zones [65]. However, most studies quantifying mean hybrid fitness in known generations have stopped at the F1, with a few extending to the F2 [15,28,35] and one study showing that outbreeding depression was not apparent until the F3 [36]. Beyond this, hybrid fitness might continue to decline as recombination further disrupts tight linkages, or it might increase and possibly surpass parental fitness as selection promotes beneficial gene combinations. The likelihood of these alternative scenarios is related, in part, to the number and linkage relationships of genes underlying hybrid incompatibility; thus, a better understanding of the duration of outbreeding depression awaits both long-term hybridization experiments and further studies of the genetic architecture of speciation.

Studies of parental divergence versus reproductive isolation often show a rough positive relationship, and reveal several interesting patterns that are worthy of further investigation. However, the extent of variation precludes any simple guidelines for managers hoping to predict the consequences of a specific mixing event. There is still no good substitute for direct tests of the consequences of hybridization, preferably including observations beyond the first generation. When these tests are not possible (as is often the case in a conservation context) managers should: (1) strive to do no harm (i.e. resort to intentional hybridization only when significant inbreeding depression has been documented); and (2) choose populations that are as similar as possible in terms of molecular markers, adaptive traits and habitats.

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