Theory and speciation

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The study of speciation has become one of the most active areas of evolutionary biology, and substantial progress has been made in documenting and understanding phenomena ranging from sympatric speciation and reinforcement to the evolutionary genetics of postzygotic isolation. This progress has been driven largely by empirical results, and most useful theoretical work has concentrated on making sense of empirical patterns. Given the complexity of speciation, mathematical theory is subordinate to verbal theory and generalizations about data. Nevertheless, mathematical theory can provide a useful classification of verbal theories; can help determine the biological plausibility of verbal theories; can determine whether alternative mechanisms of speciation are consistent with empirical patterns; and can occasionally provide predictions that go beyond empirical generalizations. We discuss recent examples of progress in each of these areas.

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This review covers both verbal and mathematical theories of SPECIATION (see Glossary) in sexually reproducing diploid organisms. Adopting the BIOLOGICAL SPECIES CONCEPT, we equate speciation to the evolution of reproductive isolating mechanisms that essentially prevent gene exchange between newly arising taxa. However, our use of this definition does not imply that we believe REPRODUCTIVE ISOLATION to be essential for morphological, ecological or genetic divergence, or that we regard other aspects of divergence between sympatric or allopatric groups as being less interesting than the evolution of reproductive isolation.

As with most areas of population biology, theories of speciation are generally verbal, describing conditions or mechanisms that are thought to cause reproductive isolation. Classic examples include Dobzhansky's suggestion[1] that evolution in ALLOPATRY leads to POSTZYGOTIC ISOLATION through the accumulation of incompatibilities between alleles in different LINEAGES, and Mayr's idea[2] that population BOTTLENECKS can produce rapid speciation through 'genetic revolutions'. Mathematical analyses serve mainly to test the plausibility of such conjectures. Recent treatments of SYMPATRIC SPECIATION and REINFORCEMENT are obvious examples.

Discussions of molecular evolution have been dominated by mathematically based theory. By contrast, speciation is dominated by verbal theories because the process involves so many complex mechanisms, including ecology, behavior and interactions between multilocus genotypes. Moreover, speciation focuses on a composite trait – reproductive isolation – that is a property of pairs of taxa and hence is inherently more complex than are traits evolving within a single lineage[3]. Because of this complexity, progress on major issues, including the biogeography of speciation, the frequency of reinforcement, the roles of sexual versus natural selection, and the relative rates of evolution of premating and postmating isolation, is more likely to emerge from empirical than from mathematical analyses[4–6]. However, some important questions are mathematically tractable, such as the plausibility of reinforcement[7,8] and the evolutionary consequences of genetic incompatibilities that cause postzygotic isolation[9,10].

We first discuss ALLOPATRIC SPECIATION, and then proceed to PARAPATRIC and sympatric speciation. Given the recent flurry of empirical and theoretical studies of sympatric speciation[11–13] (Via[14], this issue) and of rapid PHENOTYPIC DIVERGENCE driven by DISRUPTIVE SELECTION (Schluter[15], this issue), our traditional biogeographical approach requires some defense. We offer two rationales, one conceptual, the other empirical.

The conceptual rationale is simply that, given enough time, speciation is an inevitable consequence of populations evolving in allopatry. Because there are no forces acting to enforce reproductive compatibility between geographically isolated populations, they will eventually become reproductively incompatible. Thus, in contrast to the balance of forces required to produce sympatric or parapatric speciation, allopatric speciation requires only geographical isolation and time.

In addition, several lines of empirical evidence support the view that allopatric speciation is pervasive; whereas current data suggest that the opposite extreme, sympatric speciation, is far less common. First, we have many empirical examples of allopatric speciation (e.g. geminate sister pairs and island endemics). Second, despite recent data and theory indicating that sympatric speciation almost certainly occurs, few examples are unambiguous or widely accepted. Because it is harder to demonstrate sympatric than allopatric speciation, these first two lines of evidence are compromised by an ascertainment bias. However, recent comparative analyses[5] (Barraclough and Nee[16], this issue) show that, in several taxa, the most recently evolved species generally have allopatric ranges, supporting Mayr's view that allopatric speciation might be most common. These tests are conservative, because related sympatric species might falsely appear to be sister species because of genetic homogenization resulting from hybridization after divergence in allopatry. Third, if sympatric speciation were extremely common, we would expect to often see sister taxa of highly mobile species on islands, but the few existing studies[6,17] do not show such a pattern. An alternative review of speciation could be based on a

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Box 1. Evolution of prezygotic isolation via sexual selection

Sexual selection can produce sexual isolation between allopatric populations because female preferences can evolve for arbitrary male characteristics. In Lande's seminal model[a], both trait and preference are additive polygenic traits. The female preference is assumed to have no direct effect on fitness, evolving solely through its association with the male trait. When the mean trait value is plotted against the mean strength of female preference, this model produces a line of neutral equilibria, corresponding to the infinite number of ways that natural and sexual selection on the male trait can counterbalance. Isolated populations can move freely along the line, leading to sexual isolation.

Many models have built upon Lande's[a], invoking various mechanisms to drive populations to different points on the equilibrium line; these mechanisms include genetic drift, selection on the male trait, and changes in the intensity of female preferences[a–g]. In many of these models, however, the evolution of reproductive isolation is facilitated by the unrealistic assumption that female preferences are not subject to direct selection[a–d,h–j].

Lande's[a] invocation of drift as a possible mechanism for population divergence and sexual isolation seems implausible for two additional reasons. First, when divergent populations meet, incomplete sexual isolation will collapse[b,d]. This is a common problem for schemes in which divergence is not opposed by selection. However, reproductive isolation can persist if sexual isolation is complete. A more serious problem is that slight changes in the assumptions (e.g. a slight cost to female choice) reduce the neutral line to a single point, preventing divergence by drift alone. One must then invoke other forces to produce sexual isolation.

These other forces can include a cost of exercising preference[g], direct selection on female preferences through paternal care, and indirect genetic benefits accruing to females who mate with males possessing 'good genes'. There can often be multiple stable states that produce sexual isolation. Slight perturbations (e.g. the effect of environmental differences between isolated populations) might then lead to rapid evolutionary changes in trait and preference[c,f]. However, natural selection need not be involved in speciation via sexual selection: examples are changes in male genitalia or post-mating, prezygotic reproductive isolation (e.g. sperm–egg incompatibility), both of which can be driven by male–male competition or by female behavioral or biochemical 'preference'.

'Arms races' set off by a divergence between the reproductive interests of males and females can also cause non-ecological sexual selection that yields speciation[k,l]. However, other types of arms race (e.g. host–parasite coevolution) could also drive divergence, and if sexual selection is important in speciation, one must explain why it is especially likely to be involved in such coevolutionary arms races. One might argue that the arbitrary nature of sexual signals facilitates differences that lead to complete sexual isolation when allopatric populations meet[f,l]; however, it is not obvious that sexual signals are any less likely to be subject to direct selection than, say, the antigenic signals that trigger host immune response.

The most straightforward explanation of female preferences for extreme and arbitrary male traits is that these preferences are pleiotropic side effects of alleles selected for other reasons[f,g,m], for instance, selection for finding prey or mates, or for mating with conspecifics. In this scenario, females can evolve strong preferences even for traits that do not exist in the population. This 'sensory drive' mechanism can lead naturally to prezygotic isolation between isolated populations.

In all these models, it is easy to evolve population differences that produce prezygotic isolation. As in other 'quasi-neutral' models, many combinations of trait and preference are compatible, and transitions between them can be produced by natural and/or sexual selection. Paths of high fitness that connect incompatible genotypes also occur in the Dobzhansky–Muller model of epistasis[n] and in Gavrilets' 'holey landscapes'[o].

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classification of evolutionary forces; however, even then the conditions required for speciation would involve considering biogeography (e.g. SEXUAL SELECTION by itself is unlikely to lead to speciation in SYMPATRY but can easily produce species in allopatry; Box 1).

Allopatric speciation

Both pre- and postzygotic isolating mechanisms arise as inevitable by-products of genetic divergence in allopatry, and their evolution can be accelerated by DIVERGENT SELECTION[18] (Schluter[15], this volume). The main problem with understanding the origin of

isolating mechanisms during allopatric speciation is not theoretical but empirical: in most cases, we do not know which forms of reproductive isolation evolved first, and which forms evolved only after other forms had already prevented gene flow.

When examining a pair of species isolated by both pre- and postzygotic isolation, one often finds that factors acting earliest in the life cycle of the organism (e.g. sexual or habitat isolation) restrict gene flow more than those acting after hybridization (e.g. hybrid sterility and inviability). But the current importance of isolating mechanisms need not reflect their importance during speciation: as taxa continue to diverge over time, PREZYGOTIC ISOLATION, which acts first, will always restrict current gene flow more than does postzygotic isolation. New species of polyploid plants, for example, originate entirely through postzygotic isolation (chromosomally based hybrid sterility), but can later develop prezygotic mechanisms that prevent the formation of hybrids. Moreover, reinforcement operates when pre-existing postzygotic isolation accelerates the later evolution of prezygotic isolation. We are almost completely ignorant of which isolating mechanisms are involved in the origin of species. Comparative studies of allopatric taxa in different stages of evolutionary divergence can address this problem[19].

Verbal theory usually suffices to explain or describe the origin of reproductive isolation in allopatry. Unlike sympatric or parapatric speciation, in which the probability of divergence depends on the precise nature and strength of selection, the lack of gene flow between allopatric populations allows them to diverge by any evolutionary force, regardless of its nature or strength. Reproductive isolation might be functionally related to adaptive divergence (e.g. the presence of different pollinators can lead to floral isolation, or adaptation to different prey can cause hybrids to be less efficient predators). Alternatively, isolation might result not from the adaptive traits themselves, but from the pleiotropic byproducts of those traits that can cause incompatibilities in hybrids (e.g. the developmental breakdown of hybrids discussed in Box 2).

Prezygotic isolation and sexual selection

Under natural selection, prezygotic isolation can evolve directly via ecological forces acting differently in different places (e.g. isolation via habitat or host-plant use). Natural selection can also cause sexual isolation if selection-driven changes in phenotype are accompanied by selection to prefer the new high-fitness phenotypes as potential mates. Evidence connecting prezygotic isolation to selection response comes from several sources: (1) laboratory experiments showing that such isolation can be a by-product of artificial selection[18]; (2) observations that closely related, sympatric species can be isolated by characters that clearly evolved in response to different local environments[20]; and (3) observations of incipient reproductive isolation between allopatric populations adapting to different physical and biotic habitats[21,22], such evidence is especially compelling when parallel divergence is seen in naturally occurring 'replicates' (Schluter[15], this issue). Mathematical theory is hardly needed to understand such cases. Similarly, mathematical demonstrations that selectively driven substitutions can accelerate reproductive isolation[23] simply restate the obvious unless they yield novel and testable predictions.

There is substantial evidence that sexual selection has caused speciation. It is often noted that ADAPTIVE RADIATIONS, such as Hawaiian *Drosophila* or the New Guinea birds of paradise, are accompanied by spectacular divergence of male SECONDARY SEXUAL TRAITS. This does not prove that sexual selection caused speciation, for we do not know whether those traits are actually involved in reproductive isolation, or whether they evolved before or after other isolating mechanisms. Better evidence comes from comparative studies showing a correlation between the species richness of taxa and various proxies for the intensity of sexual selection[24,25], and from species in which traits demonstrably subject to *intraspecific* sexual selection also produce interspecific sexual isolation[26].

Although there are many verbal and mathematical theories of sexual selection[27], understanding how this process causes behavioral isolation, mechanical isolation based on male genitalia, and postmating, prezygotic isolation (such as sperm–egg incompatibility) is, in principle, straightforward. If two geographically isolated lineages diverge in male traits and female preferences, they are likely to be sexually isolated when their ranges subsequently overlap. With sexual selection, as with some forms of natural selection (e.g. adaptation to a particular habitat or resource also used as a mating site), there can be a direct and intuitive connection between changes within a lineage and reproductive isolation between lineages.

Allopatric populations can diverge via sexual isolation for many reasons: for example, ecological differences between habitats can affect either male traits (e.g. through differential selection by predators) or female preferences (e.g. different habitats that affect the ability to perceive sights or sounds), different mutations occurring in different places, and random GENETIC DRIFT in small populations. Some mathematical studies of allopatric SPECIATION BY SEXUAL SELECTION[28,29] are simply analyses of pure anagenic change, followed by the verbal assertion that if different lineages evolve in different directions, sexual isolation will occur (Box 1). [However, divergent sexual selection need not cause substantial reproductive isolation. For example, divergence of male traits with open-ended (i.e. psychophysical[30]) female preferences for extreme phenotypes will lead only to asymmetric isolation.] Mathematical models of sexual selection become more important when

Box 2. Evolution of intrinsic postzygotic isolation

Incompatibilities of the type postulated by Dobzhansky and Muller, especially those involving only two loci, provide a simple framework for modeling both the decline of hybrid fitness through time[a,b] and the patterns of postzygotic isolation seen among hybrids[c,d]. In this model, allopatric lineages diverge without opposition from selection, and a small fraction of hybrid gene combinations reduce fitness. This contrasts with models, such as those involving 'peak shifts', in which the divergence is directly opposed by selection (for instance, under a fixed regime of stabilizing selection) and a large proportion of intraspecific substitutions lead to selection against hybrids[e,f].

Orr[a] modeled the accumulation of Dobzhansky–Muller (D–M) incompatibilities by assuming that each substitution differentiating two taxa has a small chance of causing fitness problems in their hybrids. A fundamental prediction emerges: if genetic divergence between taxa increases linearly with time, the number of incompatibilities contributing to postzygotic isolation should increase at least as fast as the square of the divergence time between the two groups[a,b] – the 'snowball effect'. This effect implies that analyses of long-separated species pairs will seriously overestimate the number of incompatibilities contributing to the *initial* postzygotic isolation[a]. Testing this prediction will require analyzing the genetics of postzygotic isolation between recently diverged sister taxa, as well as between more distantly related pairs. Such data are only beginning to emerge, and are confined to the genus *Drosophila*.

By assuming that postzygotic isolation is attributable to numerous D–M incompatibilities between loci scattered throughout the genome, one can make simple predictions about the relative fitness of all possible hybrid genotypes by considering the relative effects of different genetic classes of D–M incompatibilities[d].

When two loci are involved, there are three classes of incompatibilities to consider: between heterozygous loci, between a heterozygous and a homozygous (or hemizygous) locus, and between homozygous loci. Both Haldane's rule and the large-X effect will result if making an incompatible allele homozygous (or hemizygous) reduces fitness significantly more than does making such an allele heterozygous at one of the interacting loci (Muller's 'dominance theory')[c,d]. However, to explain Haldane's rule for sterility, one must also take into account the fact that different sets of genes affect fecundity in males and females, so that incompatibilities causing sterility in hybrids of each sex can accumulate at different rates[g]. In particular, if male-sterilizing incompatibilities accumulate faster (possibly because they are driven by sexual selection via male–male competition[h]), this will tend to produce Haldane's rule for sterility in male-heterogametic species and, at the same time, reduce the frequency of cases of Haldane's rule for sterility versus inviability in female-heterogametic species. Data from male-heterogametic and female-heterogametic species support both predictions[i,j].

Gavrilets[k] proposed an alternative class of models that makes explicit assumptions about the forces driving the substitutions that cause reproductive isolation. These models explore the development of pre- and postzygotic isolation within a single theoretical framework. His model involves sexually reproducing haploids, and assigns fitnesses to (diploid) mating pairs based only on the number of heterozygous loci. This assumption seems implausible for postzygotic isolation, which is expected to be mediated by specific deleterious epistatic interactions rather than selection against heterozygosity *per se*. Gavrilets treats both the causes and consequences of sister-group divergence in a single mechanistic framework. However, there is no empirical basis for assuming a connection between the intraspecific and interspecific effects of alleles that cause intrinsic reductions in hybrid viability and fertility[l].

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dealing with reinforcement or sympatric speciation. In such cases, the exact form of the model and its biological assumptions become crucial in assessing the likelihood of reproductive isolation[7,8].

One potential role of theory, then, is to determine which of the various forms of sexual selection can lead to patterns observed in nature. This task is difficult. There are many competing theories of sexual selection that can produce reproductive isolation[27], and the behavior of these theories depends crucially on many parameters whose values are difficult to measure, such as the intensity of natural selection acting on female preferences. The unfortunate result is that well-known cases of interpopulation divergence in male traits and female preferences are often compatible with virtually every theory of sexual selection[31].

Postzygotic isolation

Postzygotic isolation can be characterized as either EXTRINSIC or INTRINSIC. In extrinsic isolation, the relative viability and fertility of hybrids varies with

the environment in which organisms are tested, whereas intrinsic isolation depends on developmental problems that are relatively independent of the environment. These categories are not sharply demarcated. For instance, even in the laboratory, reduced viability of young hybrids might reflect higher frequency of developmental abnormalities, reduced feeding efficiency of hybrid phenotypes, or both. Conversely, behavioral dysfunction of hybrids can stem from either intermediate phenotypes being unable to find mates, or from reduced vigor caused by intrinsic incompatibilities[19].

Laboratory studies of the genetics of postzygotic isolation have concentrated on intrinsic incompatibilities expressed under even 'optimal' conditions, simply because these incompatibilities are genetically most tractable. Recently, however, field studies have concentrated on how niche differences produce extrinsic 'ecological' selection against hybrids[20] (Schluter[15], this issue). These two broad classes of hybrid dysfunction differ both in their genetic basis and in the way that selection producing evolutionary divergence is related to the selection against hybrids [selection during divergence and selection against hybrids are often expected to be directly (i.e. functionally) connected in extrinsic isolation but indirectly (i.e. pleiotropically) connected in intrinsic isolation].

Specifying the fitness of hybrid genotypes is central to models of both intrinsic and extrinsic selection. Models of intrinsic selection are constrained – and hence simplified – by two widespread genetic patterns (HALDANE'S RULE and the LARGE X EFFECT, Box 2) and by empirical evidence for epistatic incompatibilities that accumulate between lineages. By contrast, the genetics of phenotypic differences between taxa that contribute to extrinsic postzygotic isolation do not generally display either disproportionate X-chromosome effects or sex-specific effects analogous to Haldane's rule (Orr[32], this issue).

Intrinsic postzygotic reproductive isolation arises because alleles that increase fitness (or are neutral) in one genetic background can decrease fitness in hybrid backgrounds. The potential origin of such epistatic interactions, which are expected to accumulate as a result of favorable (or, less likely, neutral) substitutions within lineages, was first described by Bateson, but is usually associated with Dobzhansky and Muller[33]. The key point is that deleterious epistatic interactions [including DOBZHANSKY–MULLER (D–M) INCOMPATIBILITIES] in hybrids might occur between alleles that never appeared together in a single lineage. Thus, the fitness loss experienced by hybrids does not imply that any 'unfit' alleles were fixed within a lineage, or that lineages passed through adaptive valleys[34].

This view does not deny the existence of epistasis within populations, but simply postulates that complex genomes provide many potential routes to adaptation that do not traverse maladaptive intermediates. This idea becomes more compelling when we appreciate how many substitutions separate lineages that remain isolated for, say, half a million years – a reasonable timescale for the development of appreciable postzygotic isolation[4,35]. With non-synonymous substitution rates of about 10^{-9} bp^{-1} year^{-1}, after one million years, each non-synonymous site will experience a substitution with probability about 10^{-3}. For genomes having roughly 10^4 loci, with each locus containing approximately 10^3 non-synonymous sites, the number of non-synonymous sites differing between allopatric populations after half a million years of separation can easily be around 10^4. Thus, on average, every locus could have undergone about one non-synonymous substitution[36].

The many potentially novel interactions among loci that differ between species supports the view that substantial postzygotic isolation can result from only a tiny fraction of these interactions – which might still number in the tens or hundreds. We know that some loci maintain the same basic function over hundreds of millions of years, even after having evolved different regulatory and amino acid sequences[37,38]. Thus, the breakdown of viability and fertility seen in hybrids between lineages separated for hundreds of thousands rather than hundreds of millions of years must arise either because some parts of the genome evolve functionally much faster than do conserved aspects of development and metabolism, or because many slight incompatibilities (possibly including those that result from pleiotropic effects of genes whose 'basic' function is conserved) have a large cumulative effect.

Making predictions about the consequences of D–M incompatibilities that arise in allopatry is relatively simple because, to a reasonable first approximation, one can ignore the evolutionary forces driving the underlying substitutions. The relative fitness of different hybrid genotypes (F_1s, backcrosses, and introgressions of particular segments) can be predicted by assuming that the fitness loss caused by individual D–M incompatibilities in hybrids is far greater than are the fitness gains produced by the individual substitutions within the evolving lineages[10]. Similarly, the accumulation of incompatibilities can be studied with a simple stochastic model of the substitution process that assumes that each genetic difference between lineages has a small chance of producing a D–M incompatibility. Such models show that the number of D–M incompatibilities must rapidly 'snowball' through time, increasing at least as fast as the square of divergence time (Box 2). No comparable simplification is possible when studying extrinsic hybrid fitness loss or many forms of prezygotic isolation in which the fitness of both parental species and their hybrids are affected by identical factors (e.g. resource use or mate choice). Similarly, the specific evolutionary forces driving divergence between lineages cannot be ignored when trying to understand how gene flow inhibits the accumulation

of D–M incompatibilities in parapatry or sympatry, because the nature of selection driving substitutions determines how rapidly alleles spread within subpopulations and how readily they will spread past barriers to dispersal. Box 2 compares models that do and do not assume specific mechanisms of evolutionary divergence.

Mechanisms driving allopatric speciation: drift versus selection

One of the first mathematical models for the evolution of reproductive isolation was Wright's analysis[39] of the probability of fixation of UNDERDOMINANT chromosome rearrangements by random drift. He showed that the probability of such fixation is $\sim exp(-Ns)$, where s represents selection against heterozygotes, and N is the effective population size. Later analyses have shown that this is a very general result. Whenever a single population drifts through an adaptive valley, the rate of shifts between adaptive peaks is proportional to $\overline{W}^{2N}$, where $\overline{W}$ is the mean fitness of a population in the valley relative to the original peak[40]. Because the strength of reproductive isolation depends primarily on the mean fitness of a hybrid population, this result shows that divergence by drift is unlikely to yield strong reproductive isolation in a single step[41]. In a sudden population bottleneck, the dynamics of peak shifts are rather different: selection is negligible, and all that matters is whether the population will drift into the domain of a new equilibrium. This is feasible only if there is substantial segregating variation for alleles that can produce reproductive isolation. Because it is unlikely that populations can maintain levels of fitness variation associated with such epistatic variation, strong reproductive isolation (especially postzygotic isolation) via bottlenecks seems improbable.

These considerations suggest that if drift is to be responsible for reproductive isolation, there must be little or no opposition from selection[30,42–44]. We call such models 'quasi-neutral'. Several such models (including the D–M model[33]) invoke a specific genetic basis for reproductive isolation[23,30,42–45], but all behave in a similar way. The genetic differences causing reproductive isolation might be established by random drift; because the valley is shallow or nonexistent, divergence can occur in large populations. Alternatively, the origin of novel favorable mutations in specific populations is a powerful cause of divergence that can be effective in very large populations ($N \sim 1/\mu$, where μ, the mutation rate to favorable alleles, is likely to be very small – probably $\leq 10^{-7}$ locus^{-1}). However, fluctuating selection might be at least as effective as drift or mutation[34,46] in producing interpopulation genetic differences. The important feature of these models is that the absence of any substantial selective barrier allows ready divergence – and consequent reproductive isolation – between populations.

Models of speciation by random drift have received much attention because they offer a tractable theory with few parameters, and because some researchers have been strong proponents of chromosomal and founder-effect speciation. However, the verbal and mathematical theories have developed independently. The result is that verbal theories have invoked several factors that do not appear in the mathematical models, including general relaxation of selection during population flushes, changes of fitness effects of alleles in alternative genetic backgrounds, and modifiers of major genes. Unless verbal theories are modeled mathematically, it is hard to determine whether such phenomena can actually facilitate speciation. Although Wright claimed that his shifting balance process was ubiquitous in adaptive evolution[34], Templeton[47,48] – the major advocate of drift-associated speciation – has always conceded that drift very rarely affects speciation. Nevertheless, Templeton has proposed from circumstantial evidence that the process could produce a significant fraction of all morphological innovations and adaptive radiations in certain groups, such as the Hawaiian *Drosophila*[47].

Although the existence of adaptive radiations supports the view that speciation is accelerated when a limited number of individuals colonize a new habitat, there is little evidence that drift is as important as novel selection pressures in producing reproductive isolation. Indeed, much experimental and theoretical evidence shows that isolated populations under intense, novel selection can undergo rapid and substantial changes in morphology and mating behavior[18,49–51]. Conversely, experiments using repeated bottlenecks[52] have failed to produce substantial reproductive isolation in the laboratory, and such extreme bottlenecks might not even have occurred in some of the classic examples of speciation on islands[40,53]. The continuing experimental and theoretical interest in drift-based models of speciation is curious in view of the very weak empirical support[44,45,52–55].

A question separate from, but related to, the evolution of reproductive isolation is why evolution produces morphologically distinct species rather than a multivariate continuum of phenotypes and genotypes (Box 3).

Parapatric and sympatric speciation

Hybrid speciation and polyploidy

Many botanists have argued that hybridization provides variation that facilitates adaptation and that hybrids might even evolve into new species[56–59]. Such 'hybrid speciation' must, by necessity, begin in sympatry. We expect recombinant hybrid genotypes to be, on average, less fit than individuals from the parental species, simply because most have never been tested by natural selection. However, some hybrid genotypes might be fitter than the parentals: given some degree of gene interaction, it is unlikely that the fittest possible gene combination would occur

Box 3. Why species?

As Dobzhansky noted[a], 'the living world is not a single array of individuals in which any two variants are connected by unbroken series of intergrades, but an array of more or less distinctly separate arrays, intermediates between which are absent or usually rare'. The most distinct arrays are species. This raises a question: what properties of sexually reproducing organisms and their environments inevitably lead to the evolution of discrete species? In some ways, this topic is more difficult than understanding how species arise because it is more abstract, addressing not just the natural history of species differentiation but trying to understand whether and why such differences must occur.

The clustering of organisms into groups is evident not only in morphology, but also in gene sequence and reproductive compatibility, with these factors usually coinciding. (We do not deal with clustering in asexual taxa, because it is not clear whether they form clumps as discrete as those seen in sexual species[b–d]. Various theoretical explanations of clumping in asexuals have been suggested, based on distinct ecological niches, phylogenetic history, and the consequences of selection on organisms that rarely exchange genes[e].)

Many explanations have been offered for such co-incident clusters in sexually reproducing taxa, the two most common being the supposition that ecological niches are discrete, and that adaptation to the environment (or simple divergence by drift) inevitably produces the reproductive isolation necessary to keep species discrete in sympatry[b]. The ecological explanation sees clusters as resulting from intrinsic discreteness in ways of exploiting physical resources (e.g. the mechanisms by which microbes use alternative carbon sources or capture energy might impose distinct phenotypic 'solutions' in the same way that different jaw morphologies are needed to efficiently handle different prey). This effect cascades as clumps at one trophic level foster clumps at higher levels. The ecological explanation also rests on the inevitability of tradeoffs that create disruptive selection, with hybrids who fall 'between niches' being less fit.

The sexual-isolation explanation relies on the fact that divergent evolution, in either sympatry or allopatry, is likely (and, given enough time, almost certain) to lead directly or indirectly to the evolution of reproductive isolation. Such isolation can allow both permanent coexistence between taxa in sympatry and future evolutionary divergence without the impediment of gene flow[f]. This explanation is also related to the existence of ecological niches, because divergent adaptation to such niches could impede gene flow by producing either prezygotic or extrinsic postzygotic isolation (e.g. adaptation in plants to discrete soil types or pollinators). In addition, there are 'developmental niches' that arise because development requires the joint action of many coadapted genes. Sufficiently diverged developmental systems cannot work properly within hybrids, leading to intrinsic hybrid sterility or inviability. Finally, sexual reproduction itself leads to the evolution of anisogamy, which, in turn, creates the possibility for sexual selection. Such selection operating in isolated populations leads almost inevitably to behavioral or gametic isolation.

According to recent theoretical models, the 'distinct niche' explanation seems necessary for the existence of species arising sympatrically, or those arising allopatrically whose later distinctness in sympatry is based on ecological or extrinsic postzygotic isolation. However, although discrete niches might be necessary to explain species coexistence in sympatry, they are sometimes unnecessary to explain species distinctness. Full species can arise in allopatry via non-ecological processes causing intrinsic postzygotic isolation (e.g. polyploidy or antagonistic coevolution of males and females). Such species, although completely genetically isolated, might not be able to coexist in sympatry.

The few mathematical analyses of why sexual reproduction might produce morphological clusters have dealt largely with the evolution of clusters in sympatry. Hopf and Hopf[g] showed that, given the pre-existence of reproductive isolation between species, 'Allee effects' (specifically, reduced fitness of rare phenotypes caused by difficulty in finding a mate) will produce distinct clusters on a resource gradient. However, their paper does not address the question of whether an initial continuum of sexually reproducing organisms inevitably breaks up into discrete clusters. When put into the context of resource competition without geographical isolation, this question is closely related to understanding sympatric speciation. Noest[h] addresses this with a simple model incorporating competition between phenotypes, assortative mating, outbreeding depression, genetic variability and an Allee effect. The Allee effect, outbreeding depression and assortative mating all tend to produce clusters (i.e. make the sexual continuum unstable). This process is facilitated by geographical isolation[i,j], by the intrinsic heterogeneity of the global environment and by the evolutionary pressures towards specialization and range limits (which lead to distinct taxa in different geographic regions)[k–m].

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in the lineage of either parental species. Yet, without a specific model of selection, it is impossible to predict the distribution of hybrid fitnesses or the potential gain in fitness that might be realized by selection on hybrids. A simple but highly idealized possibility is Orr's elaboration of Fisher's model of multidimensional selection[60]. Hybridization between populations that accumulate different favorable alleles can yield small fitness gains as a result of both introgression of single genes and fixation of recombinant genotypes[61]. However, given the model-dependence of predictions about this process, the potential contribution of hybridization to adaptation and speciation is best treated as an empirical question.

The key difficulties for hybrid speciation are singling out a particularly fit recombinant genotype after the parental species hybridize, and then keeping this genotype intact. The simplest solution is immediate reproductive isolation of the genotype, which can be attained through asexual reproduction, selfing, or allopolyploidy. In flowering plants, polyploidy (usually, allopolyploidy) is a frequent mode of speciation (2–4% of speciation events[62]); similarly, many parthenogenetic animal species are derived from interspecific hybrids[62]. The novel phenotypes attendant on combining two disparate genomes might also provide sufficient ecological divergence to allow polyploids to coexist with their ancestors[63].

In contrast to polyploidy, diploid hybrid speciation (the origination of a new species through selection acting on a diploid interspecific hybrid) is rare[64]. Because most putative diploid hybrid species outcross[65], the question arises of how such species are established despite the possibility of backcrossing to the parental species. One explanation is that mixed pollen stimulates selfing of the new recombinant, but the single existing study did not show this effect[65]. Alternatively, divergence in a new ecological niche, or colonization of a novel habitat, might lead to parapatric or allopatric isolation after initial hybridization. Indeed, diploid hybrid species are usually associated with novel habitats[66].

Even with random mating, fit recombinants can be established by selection, and this might lead to some reproductive isolation. The simplest case is a single population segregating for several underdominant chromosome rearrangements[58,67,68]. Under weak selection, any homozygous combination of chromosome arrangements is equally likely to be fixed and will show a degree of postzygotic isolation from the polymorphic parental species. With stronger selection, LINKAGE DISEQUILIBRIA tend to favor recovery of parental combinations. In their analysis of this model, Buerkle *et al.*[68] show that, even with multiple rearrangements, gene flow between populations remains high at NEUTRAL LOCI. Although new adaptive gene combinations can be established, especially if favored in a novel environment, there is little immediate reproductive isolation. This is simply because rearrangements are unlikely to be established if they cause enough sterility to significantly reduce gene flow. These models are based on chromosomal rearrangements, but the same considerations apply to genic incompatibilities.

The time taken to fix a hybrid genotype can be estimated from the extent of recombination; in sunflowers, it is roughly 20–60 generations, assuming a single isolated population[69]. This scenario can be seen as a special kind of founder-effect speciation triggered when a novel combination of alleles, produced by hybridization, allows a new adaptive peak to be reached. Similarly, a novel highly fit recombinant genotype can also be established at high frequency in a narrow hybrid zone, when clines at different loci are out of phase, producing different combinations of alleles at different points in the hybrid zone[70,71]. However, further divergence is required if a new species is to form: for example, reinforcement of prezygotic isolation between the recombinant and parents, or ecological divergence that allows the recombinant to spread into a new, widely distributed niche. The immediate effect of an increased fitness of the hybrid population is to weaken reproductive isolation between the parental populations[70].

Parapatric speciation

There has been much argument about whether speciation can occur between adjacent populations occupying a broadly continuous habitat – that is, populations in parapatry. Darwin's observations in South America, together with his gradualist view of evolution, convinced him that new species could evolve in this way, an assertion that later led to much dispute[72]. Population genetics, however, supports Darwin's view. Given a sufficiently broad geographical range, any mechanism that can produce divergence among allopatric populations can also cause divergence in parapatry. Indeed, even if most genetic divergence occurs in allopatry, the diverging populations are likely to be spatially extended, and each genetic difference that contributes to isolation is likely to originate in a local region within a broader range, either as a single mutation or as a localized adaptation. If different alleles arise in different places, and if these prove incompatible with each other when they meet, then they will contribute to the build up of reproductive isolation in parapatry – just as they would in allopatry.

The 'isolation by distance' necessary for parapatric speciation depends on the strength of selection acting during population divergence. If strong selection is involved (either causing adaptation to local conditions, or maintaining alternative adaptive peaks), then divergence of traits leading to reproductive isolation can occur over small spatial scales ($\sigma/\sqrt{2s}$, where σ measures average per-generation dispersal distance and s measures selection); this is true whether divergence is driven by

drift or by selection[73]. If divergence is 'quasi-neutral', then larger spatial scales might be involved, although they might still be small compared with the range of the species. Parapatric divergence of reproductive compatibility seems most difficult when it is based on alleles that are favorable everywhere against the ancestral genetic background but incompatible with each other. Such divergence requires that two or more alleles be established in different parts of the range before any one allele has spread over the whole range[74].

The existence of narrow clines and hybrid zones demonstrates that selection can dominate gene flow over quite small scales, allowing parapatric divergence. Reproductive isolation might arise as a pleiotropic by-product of locally selected alleles, just as in allopatric speciation. However, gene flow can alter the course of parapatric divergence in two ways. First, alleles that are favorable everywhere can readily spread across hybrid zones[75], slowing divergence and producing confusing genealogies. Such single-gene introgression might be much more widespread than is usually appreciated. Examples are known in sunflowers[76] and *Drosophila*[77], and seem especially common for cytoplasmically inherited genomes, which frequently show genealogies that differ from those of nuclear loci[66,78]. Nevertheless, such introgression might not prevent continuing divergence between populations. Second, gene flow might lead to increased prezygotic isolation through reinforcement.

Reinforcement

Noor[79] provides an excellent review of the empirical literature on reinforcement. As he emphasizes, there is no longer any question that the pattern of 'REPRODUCTIVE CHARACTER DISPLACEMENT' – greater interspecific mate discrimination between sympatric than between allopatric populations – is common. The question is whether this pattern is driven, as Dobzhansky claimed, by reinforcement, or by other mechanisms that do not involve direct selection against hybridization[80]. Following Coyne and Orr's[4] compilation of *Drosophila* data, many theoretical analyses, both numerical and analytical, have demonstrated that reinforcement can occur under biologically plausible conditions (Box 4). Although limited biogeographical data[5] suggest that reinforcement is not as common a route to speciation as is strictly allopatric divergence, reinforcement has spawned a much richer theoretical literature because its plausibility is less obvious, the process can be affected by many factors and it is appealing to believe that natural selection can play a direct role in creating new species. Sorting out the relative importance of different biological factors remains a major theoretical challenge.

From the diverse studies described in Box 4, we conclude that the evolution of reinforcement is theoretically plausible and becomes even more probable if substantial premating and/or postmating divergence have previously evolved[7]. However, the effects on reinforcement of alternative population structures, forms of selection against hybrids and mechanisms of nonrandom mating are difficult to disentangle. This is partly because many theoretical studies explore unique combinations of assumptions, making it difficult to sort out which factors are important. For example, Cain *et al.*[81] claim to have demonstrated that reinforcement occurs more readily in a MOSAIC HYBRID ZONE, in which fitnesses vary spatially across a patchy environment, than in a 'TENSION ZONE', in which two equally fit genotypes meet and produce less-fit hybrids. This claim is based on a comparison of their numerical results with those of a model by Sanderson[82]. However, Cain *et al.*'s model confounds the role of population structure (single zone of contact versus many zones) with that of the form of selection (hybrid dysfunction versus spatially varying selection on parentals). Moreover, the interaction between directional selection and ASSORTATIVE MATING in the model of Cain *et al.* provides an indirect force favoring the evolution of assortment, even if there is no hybrid dysfunction[8] (Box 4).

Theory has helped us to better understand the factors that can inhibit or prevent reinforcement, including: (1) lack of phenotypic differentiation on which mating discrimination can act[83]; (2) direct forces opposing the spread of 'reinforcement' alleles, such as migration from populations lacking the alleles[84] or natural selection acting directly to oppose their spread[85]; (3) restriction of hybrids to a narrow portion of the species range[7,82]; and (4) lack of sufficient ecological and/or mating differentiation to allow the taxa to coexist long enough for reinforcement to occur[7]. Factors (3) and (4) illustrate the difficulty of reaching unambiguous conclusions about which factors promote or inhibit reinforcement. If divergent populations compete and mate across a wide region, the rarer might go extinct (despite pervasive selection favoring reinforcement); yet, if they meet in a narrow hybrid zone, gene flow and lack of genetic variation can hinder reinforcement, even though each taxon has a 'refuge' that prevents its extinction in the region of sympatry[7]. Theoretical conclusions about such complex interactions are likely to be model dependent.

Although the pattern of reproductive character displacement has generally been interpreted as an evolutionary response to SECONDARY CONTACT (reinforcement), the same pattern can emerge even if there is no initial stage of allopatry, but there is continual gene flow across an environmental discontinuity[80,86]. In general, future theoretical analyses should aim at producing empirical predictions that can distinguish alternative evolutionary forces producing reproductive character displacement[83,85]. For instance, Kelly and Noor[85] show that reinforcement occurring with different types of change in female mate-choice criteria can

Box 4. Models of reinforcement

Over the past decade, at least seven theoretical studies[a–g] have supported the plausibility of reinforcement. These differ appreciably in assumptions about: (1) genetics (one locus per character[c,e,f] versus polygenic characters[a,d,g]); (2) population structures (a single mixed population[a,b,e] versus narrow contact zone[a,e,h] versus two islands[c,f] versus island–continent[d,g]); (3) the nature of selection against hybrids (e.g. all hybrids equally unfit[a] versus spatially varying selection favoring specific phenotypes[c,e]; hybrid inviability versus sterility[a]); (4) the potential basis for reinforcement (assortative mating[e,f,g] versus preference and trait coevolution[a,c,d] versus increasing discrimination[b]); (5) whether the 'reinforcement' alleles are under direct natural selection (yes[b,e] versus no[a,c,d,f,g]); and (6) density regulation of populations[a] (specifically, whether lineages can go extinct).

Because of the analytical complexities associated with strong selection acting on multiple loci in spatially distributed populations, most analyses are based on numerical calculations. By contrast, Kirkpatrick and Servedio[d,g] produced analytical, weak-selection results for polygenic models by allowing only small changes in mating patterns, assuming that selection against hybrids is weak, and positing limited one-way migration from a 'continent' to an 'island' population. They note, however, that their weak-selection predictions might not apply to more realistic levels of migration or selection or to the spread of alleles that induce large changes in mating discrimination[f,g]. Most other investigations have the typical weaknesses of numerical studies: only a limited range of parameters can be explored and the results can be difficult to interpret. These difficulties are compounded because alternative studies often modify several biological assumptions of previous analyses, making it difficult to know which individual assumptions are crucial in determining the outcomes. Furthermore, the effect of each assumption might vary depending on other assumptions[b,f], making a succinct summary of the results of alternative studies impossible. For instance, Kelly and Noor[b] explore several alternative genetic assumptions about the nature of postzygotic isolation, and find that a combination of factors can promote reinforcement even though numerical explorations suggest that each individual factor inhibits reinforcement.

One factor that affects the likelihood of reinforcement is the genetic basis of prezygotic isolation. Felsenstein[i] argued that speciation is generally facilitated if a single allele (or, more generally, a specific trait value) causes assortative mating in each INCIPIENT SPECIES (see Glossary; i.e. allele *A* causes its carrier to mate with phenotypically similar individuals). In contrast, speciation is opposed by recombination if hybridization is reduced only when sets of co-adapted genes become associated with different alleles (or traits). However, even this conclusion might depend on population structure[f]. In general, non-random mating can produce associations between mating-system alleles and alleles favored by local selection that either promote or inhibit reinforcement[f]. These indirect effects produced by linkage disequilibrium are analogous to Fisher's runaway effect for sexual selection, as both are driven by associations between male traits and female preferences[a,f].

Population structure also affects the likelihood of reinforcement. Reinforcement seems to occur more readily when there is migration between two island populations, corresponding effectively to secondary contact occurring throughout the entire range of each incipient species[c]. This eliminates the problem of selection opposing the spread of 'reinforcement' alleles outside areas where hybridization occurs[h]. However, this model seems biologically unreasonable unless ecological divergence has already proceeded far enough to allow wide sympatry. Finally, explicit consideration of population dynamics, so that extinction is possible through maladaptive hybridization, seems to restrict the conditions for reinforcement[a,c]. Population structure can alter this conclusion[a,h]. If hybridization can produce local extinction, partial allopatry can aid[a] (rather than inhibit[h]) reinforcement by providing a 'refuge' from global extinction.

In summary, theoretical studies show that reinforcement is clearly plausible, which is reassuring given the growing evidence for its occurrence. However, the available studies provide few unambiguous predictions about when it is most probable.

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lead to qualitatively different outcomes of interpopulation mate-choice experiments.

Sympatric speciation

The emergence of strong empirical support for sympatric speciation in a study of Cameroon crater-lake cichlids[11] has generated a spate of models supporting the theoretical plausibility of sympatric speciation[12,13,87,88]. Many earlier sympatric speciation models (Via[14], this issue), motivated by the observation of host RACES in the tephritid fly *Rhagoletis pomonella*[89], involved ecologically driven reproductive isolation associated with adaptation to alternative discrete resources and/or habitats. A novel feature of more recent analyses is their emphasis on speciation driven by competition for continuously distributed resources (e.g. a continuum of prey-size categories versus alternative discrete

Box 5. Models of sympatric speciation

Sympatric speciation is driven by disruptive selection. Recent theoretical research has concentrated on three classes of models: ecological models based on competition for resources[a–c]; sexual-selection models based on competition for mates[d,e]; and models of habitat-race formation based on habitat-specific deleterious or beneficial alleles[f,g]. Of these, the sexual selection models are least convincing. Instead of invoking disruptive natural selection, they invoke disruptive sexual selection with different females preferring different extreme male phenotypes. This assumption might be plausible on its own, but the published analyses suggest that additional (and implausible) assumptions are required for such selection to sunder a population into reproductively isolated groups rather than to simply move the selected trait to one extreme phenotype throughout the entire species. For instance, the model of Higashi *et al.*[d] yields sympatric speciation using artificially symmetrical initial conditions (corresponding to females showing no preference on average for alternative values of the male trait) and invoking abrupt changes in parameter values governing the intensity of stabilizing selection on the male trait or the female preference. Their simulations suggest that relaxing this initial symmetry prevents speciation.

Kawecki[f,g] presents models of sympatric habitat- (or host-) race formation driven by the accumulation of mutations with habitat-specific beneficial or deleterious effects. By assuming mating within habitats, linkage disequilibrium develops between alleles beneficial in a habitat and alleles favoring behavioral selection of that habitat. This provides the indirect force that drives the evolution of habitat isolation and hence speciation. These models, which produce habitat races more easily than do models requiring balanced polymorphisms, can in principle be tested by determining the prevalence of alleles whose effects are limited to specific habitats.

Given the current interest in the ecology of speciation, most attention has been given to models in which competition for resources causes disruptive natural selection. The important lesson from these models is that sympatric speciation appears plausible even when it requires the evolution of genetic associations between ecologically important traits and 'neutral markers' that organisms use to discriminate among potential mates. The most convincing study is that of Dieckmann and Doebeli[b], in which disruptive selection emerges from an explicit model of competition for a continuum of resources. With a unimodal distribution of resources, disruptive selection results when the width of the resource distribution exceeds the average range of resources used by individuals.

For asexual haploids, this condition suffices to produce a bimodal distribution of phenotypes. For sexuals, roughly the same condition suffices to drive the evolution of assortative mating based directly on the ecologically important character, again leading to speciation. When mating is based instead on a neutral marker, the resource distribution must be significantly wider (for a fixed level of competition) for speciation to occur.

In contrast to this model, which allows the intensity of assortative mating to evolve, Kondrashov and Kondrashov[a] assume a fixed assortment rule, based on either the ecological character or a neutral marker. Their analysis incorporates a highly symmetric polygenic model (loci have equal effects and all alleles that increase a trait value have equal frequencies across these loci) and artificially imposes on the ecological trait a fixed level of disruptive selection that does not weaken as the incipient species diverge. (When disruptive selection is based on niche overlap, trait divergence should often lead to reduced competition and weaker disruptive selection.) Drossel and McKane[c] treat a simplified version of the Dieckmann and Doebeli model analytically, but they use several approximations whose validity cannot be assessed without explicit genetic simulations.

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prey types) and/or by sexual selection acting on a continuum of phenotypes. The central driving force in these newer models is selection against intermediate phenotypes. Such intermediates are deleterious because they accrue fewer resources as a result of density- and frequency-dependent selection or because they procure fewer mates as a result of preferences for extreme phenotypes[90]. The resulting disruptive selection can produce bimodal distributions of phenotypes for asexual taxa[13]; it can also drive the evolution of reproductive isolation for sexual taxa in sympatry. Box 5 discusses some recent models of sympatric speciation. The available data provide no basis for determining whether these new models have wider biological applicability than do earlier models that focused on assortative mating as a by-product of niche differences (Via[14], this issue).

The idea that disruptive selection can drive sympatric speciation was championed by Darwin in Chapter 4 of the *Origin of Species*. However, he used an explicitly phenotypic definition of species and focused only on the origin of distinguishable varieties under disruptive selection. Unlike recent models of sympatric speciation, Darwin's model failed to recognize the key role of reproductive isolation (usually via assortative mating) in maintaining sympatric species; niche differentiation alone does not necessarily impede gene flow between taxa. More convincing arguments for speciation in the face of (parapatric) gene flow were provided by Fisher[91]

(pp. 125–129), who did recognize the importance of assortative mating, and proposed that selection could plausibly achieve it through habitat selection or mate discrimination.

The quantitative predictions of the recent mathematical treatments are certainly sensitive to their genetic and ecological assumptions, but the qualitative conclusion that competition-driven sympatric speciation can occur seems secure. Superimposing disruptive sexual selection on selection mediated by competition for resources is likely to facilitate the process[92], but it is not clear whether disruptive sexual selection alone will produce new species in sympatry (Box 5). Models of reinforcement tell us that conditions for sympatric speciation are likely to depend on the criteria for non-random mating (e.g. assortative mating between males and females of similar phenotype versus matching male traits to female preferences[83]). Theoretical ecology tells us that the details of competition models can significantly alter their quantitative predictions[93]. Hence, although analytical treatments would be preferable to the numerical simulations that have dominated studies of sympatric speciation, predictions must surely depend on empirically elusive genetic, behavioral and ecological details. The challenge will be to uncover robust predictions that go beyond intuitive conjectures, such as the frequent claim that ecological sympatric speciation is most likely when competitor-free, resource-rich habitats are invaded. Until then, theory will take a back seat to empirical studies in revealing and understanding sympatric speciation.

Conclusions and prospects

Because it often includes sophisticated mathematics, non-verbal theory has a special air of authority among biologists. Many experimentalists are unequipped to judge the limitations or weakness of such theory, which has occasionally been misleading. For example, the results of Spencer *et al.*[94] convinced many that reinforcement was nearly impossible to obtain, even under optimal conditions. Renewed empirical interest emerged only when new data indicated that reinforcement was plausible[4], and when subsequent theoretical treatment – using assumptions different from those of Spencer *et al.* – supported this plausibility[7]. With theory, as with architecture, God is in the details, and the conclusions of theories about speciation might be highly sensitive to only slight changes in their assumptions.

Because of this, we believe that significant understanding of speciation is more likely to be produced by new data than by new theory. Nevertheless, our review suggests several lines of useful theoretical research. We need convincing general models of sympatric speciation that delimit testable or observable conditions under which it can and cannot occur. Similarly, additional attention must be paid to models in which reproductive divergence occurs despite continual but limited gene flow. Existing models of sympatric speciation (Box 5) and the evolution of range limits[95] can be easily adapted to study parapatric speciation. We would like to understand how much gene flow is needed to inhibit the accumulation of D–M incompatibilities (in particular, under what conditions will interpopulation hybrids have lower fitness in a widely distributed organism with limited dispersal?). Most recent theoretical work on speciation consists of numerical analyses demonstrating the feasibility of some narrowly defined speciation scenario, often without sufficient exploration of the robustness of the conclusions or their relation to alternative published analyses (Boxes 4,5). To gain general insights, we need to explore the biologically plausible regions of parameter space more carefully. This demands more analytical treatments and fewer simulations.

When simple models seem reasonable, such as the evolution of hybrid inviability or sterility via D–M incompatibilities, one can derive testable quantitative predictions[9,10]. However, it might be unrealistic to expect quantitative predictions to emerge from complex models of sympatric speciation and reinforcement that involve ecology, behavior and multilocus genetic interactions. Nevertheless, we can expect testable qualitative predictions. For instance, we expect that reinforcement and sympatric speciation would be facilitated more by assortative mating based on characters subject to divergent ecological selection than by assortative mating based on secondary sexual characters[13,18]. Similarly, models of sympatric speciation mediated by disruptive selection lead to the prediction that speciation driven by 'extrinsic' selection against hybrids is likely to occur faster than does largely allopatric speciation associated with the gradual accumulation of D–M incompatibilities. In general, we expect that rapid speciation, e.g. 10^4 years or faster, is more likely to be associated with sexual selection and extrinsic selection against hybrids than with intrinsic selection against hybrids.

As well as providing testable predictions, mathematical theory can play at least two other roles in understanding speciation. First, it can help organize verbal theories, showing how they are interrelated and focusing research on the relative importance of different mechanisms (e.g. natural versus sexual selection, extrinsic versus intrinsic selection against hybrids, divergence in allopatry versus parapatry). Second, they can suggest new ways to think about evolution in the high-dimensional spaces defined by multilocus genotypes and multivariate phenotypes (Box 3). Such theory need not produce empirical predictions, nor lead directly to new observations or experiments. Two such cases are the influential papers on speciation of Maynard Smith[96] and Felsenstein[97], which clarified central biological issues about the origin of species.

Acknowledgements
We thank D. Bolnick, B. Fitzpatrick, S. Gavrilets, R. Haygood, C.D. Jones, M. Kirkpatrick, A. Kondrashov, J.B. Mullet, S.V. Nuzhdin, H.A. Orr, T.D. Price, T. Prout, D.W. Schemske, D. Schluter, M.R. Servedio and P.S. Ward for discussion and comments. Some of these reviewers disagree with our conclusions. This work was supported by US National Science Foundation grants DEB 9527808 and DEB 0089716 to MT, grants from the Darwin Trust of Edinburgh and the Biotechnology and Biological Sciences Research Council (GRJ/76057, GR/H/09928) to NHB, and National Institutes of Health grant R01 GM58260 to JAC.

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The genetics of species differences

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Species are separated by reproductive isolation as well as by more 'ordinary' differences in morphology and behavior that play no necessary role in blocking gene flow. Although a great deal is now known about the genetics of reproductive isolation, we are only beginning to understand the genetic basis of ordinary phenotypic differences between species. I review what is known about the number of genes involved in such differences, as well as about the role of major genes and epistasis in the evolution of these differences. I also compare and contrast these findings with those on the genetics of reproductive isolation.

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If we compare individuals from the same species with those from different species, we see two kinds of differences. First, members of separate species are reproductively isolated and, second, they often differ dramatically in morphology and behavior. According to the BIOLOGICAL SPECIES CONCEPT (see Glossary), these differences are themselves different. The first is a necessary part of what it means to be species whereas the second is not. Despite this, it is clear that REPRODUCTIVE ISOLATION and 'ordinary' phenotypic differences tend to go hand-in-hand, and there is good reason to think that this association is partly causal. In fact, there is good reason to think the causes run in both directions: phenotypic evolution might often give rise to reproductive isolation[1], whereas reproductive isolation might often preserve phenotypic differences when taxa come into contact with each other[2].

Although the genetics of reproductive isolation has been studied intensively, that of ordinary species differences (i.e. differences in traits expressed within pure species and that play no necessary role in blocking gene flow) has not. The reason does not seem primarily technical as the two kinds of study largely involve the same experimental approaches. Instead, the reason probably reflects the above difference in logical status: if species are things that are reproductively isolated, the genetic study of SPECIATION will sensibly start with such isolation. However, genetic studies of ordinary species differences have now progressed far enough to allow at least some preliminary conclusions.

The first survey of the genetics of species differences appeared in 1938, with J.B.S. Haldane's 'The nature of interspecific differences'[3]. Although the problem he discussed was largely dropped (little of much relevance appeared over the next 45 years; but see Ref. 4) two important developments occurred over the past 15 years. The first was the rise of QUANTITATIVE TRAIT LOCUS (QTL) and related association-mapping strategies. We now possess the polymorphic neutral molecular markers and the body of statistical theory required to map the genes underlying arbitrary trait differences in arbitrary species, at least roughly[5]. The second was the appearance of molecular tools (e.g. germline transformation) that allow us, in favorable cases, to confirm the identity of a particular gene underlying a phenotypic difference and, in especially favorable cases, to identify the actual nucleotide changes ('Quantitative Trait Nucleotides' or QTNs) involved.

Despite these technical advances, current questions about species differences largely remain the same as in Haldane's day. They are questions about genetic architecture: How many genes are involved? How large are their phenotypic effects? Where are these genes and what are their functions in development? And what are the roles, if any, of dominance and epistasis? This emphasis on numbers of genes and sizes of effects reflects one of the oldest problems in evolutionary biology – the complexity of

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