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PERSPECTIVE

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Extending phylogeography to account for lineage fusion

Abstract

Secondary contact between long isolated populations has several possible outcomes. These include the strengthening of preexisting reproductive isolating mechanisms via reinforcement, the emergence of a hybrid lineage that is distinct from its extant parental lineages and which occupies a spatially restricted zone between them, or complete merging of two populations such that parental lineages are no longer extant ("lineage fusion" herein). The latter scenario has rarely been explicitly considered in single-species and comparative phylogeographic studies, yet it has the potential to impact inferences about population history and levels of congruence. In this paper, we explore the idea that insights into past lineage fusion may now be possible, owing to the advent of next-generation sequencing. Using simulated DNA sequence haplotype datasets (i.e., loci with alleles comprised of a set of linked nucleotide polymorphisms), we examined basic requirements (number of loci and individuals sampled) for identifying cases when a present-day panmictic population is the product of lineage fusion, using an exemplar statistical framework—approximate Bayesian computation. We found that with approximately 100 phased haplotype loci (each 400 bp long) and modest sample sizes of individuals (10 per population), lineage fusion can be detected under rather challenging scenarios. This included some scenarios where reticulation was fully contained within a Last Glacial Maximum timeframe, provided that mixing was symmetrical, ancestral gene pools were moderately to deeply diverged, and the lag time between the fusion event and gene pool sampling was relatively short. However, the more realistic case of asymmetrical mixing is not prohibitive if additional genetic data (e.g., 400 loci) are available. Notwithstanding some simplifying assumptions of our simulations and the knowledge gaps that remain about the circumstances under which lineage fusion is potentially detectable, we suggest that the recent release from data limitation allows phylogeographers to expand the scope of inferences about long-term population history.

1 | INTRODUCTION

Phylogeography is in the midst of a transformation from a data-limited to data-rich field of research. It was once a sub-discipline of biogeography that relied almost exclusively on genetic data from animal mitochondrial DNA or plant chloroplast DNA (Avise, 2000), but now increasingly makes use of DNA sequence polymorphisms across tens to hundreds of informative nuclear autosomal loci (Edwards, Shultz, & Campbell-Staton, 2015; Garrick et al., 2015). These developments have pushed the field forward, as multi-locus datasets minimize the potential for inferences to be misled by stochastic phenomena (Kuo & Avise, 2005), and provide greater accuracy and precision in estimates of parameters that are important for understanding present-day population structure and reconstructing long-term history (e.g., the number of natural genetic groups, effective population sizes, population divergence times, and post-divergence gene flow dynamics; Edwards & Beerli, 2000; Carling & Brumfield, 2007; Lee & Edwards, 2008; Willing, Dreyer, & van Oosterhout, 2012). Indeed, the DNA sequence data revolution has eroded the distinction between population genetics, landscape genetics and phylogeography (Garrick et al., 2015; Rissler, 2016), and in the latter case, has enabled complex questions to be addressed (Bi et al., 2013; Carstens et al., 2013; Catchen et al., 2013; Prates et al., 2016). As such, it is timely to ask whether increased data availability allows phylogeographers to gain previously unattainable insights into the evolutionary history of natural populations (Edwards, Potter, Schmitt, Bragg, & Moritz, 2016).

Genetic estimates of the number of distinct populations, and neutral demographic parameters such as their effective sizes, divergence times and genetic connectivity, were all routinely used before the advent of next-generation sequencing (NGS; e.g., Kuhner, Yamato, & Felsenstein, 1998; Beerli & Felsenstein, 2001; Nielsen & Wakeley, 2001; Dupanloup, Schneider, & Excoffier, 2002). However, one component of population history that has received relatively little consideration is the complete merging of divergent population lineages, resulting in a single randomly mating group ("fusion" sensu Campbell et al., 2008). Whereas introgression often simply refers to the incorporation of alleles from one population or species into the new genetic background of another, lineage fusion is a special case of the broader phenomenon of secondary contact in which parental lineages are no longer extant (and therefore cannot be readily sampled) after they meet and collapse together (e.g., Jansson & Dynesius, 2002). Little or no selection against F1 hybrids and backcrosses that are formed upon initial fusion is an inherent feature of this process, given that hybrid disadvantage would maintain the integrity of the parental lineages. However, fitness benefits of hybridization can sometimes arise, facilitating the complete merging of formerly separate gene pools (Fitzpatrick & Shaffer, 2007; Grant & Grant, 2016 and references therein). Lineage fusion events may have been quite common as the glacial-interglacial cycles of the Quaternary repeatedly altered organismal distributions (Hewitt, 1999), and the resulting unstable range dynamics increased the propensity for lineages to merge on secondary contact (Phuong, Bi, & Moritz, 2017). As such, it stands to reason that lineage fusion events could have had major impacts on present-day distributions of intraspecific genetic diversity. Indeed, the importance of these events in shaping levels of spatial-genetic structure was highlighted when phylogeography was still

quite a young sub-discipline (Jansson & Dynesius, 2002). However, the ways in which lineage fusion may counteract—or perhaps even facilitate—speciation and diversification processes remains underappreciated (Alcala & Vuilleumier, 2014; Dynesius & Jansson, 2014; Emerson & Faria, 2014; Rosenblum et al., 2012).

In the context of understanding human evolutionary history, methods for determining the extent of archaic admixture between modern humans and Neanderthals or other members of the *Homo* genus have received considerable attention (Schraiber & Akey, 2015 and references therein). Since the scenarios that have been investigated involve a present-day gene pool that is comprised of genetic contributions from at least one other divergent lineage that is no longer extant, these archaic admixture scenarios are generally relevant here. However, methods that use patterns of linkage disequilibrium in nuclear DNA sequences to detect archaic admixture rely on very long DNA sequence haplotypes (e.g., 25-kb, Plagnol & Wall, 2006; Wall, Lohmueller, & Plagnol, 2009) which are not yet attainable for most organisms. Furthermore, while methods based on phylogenetic thinking do not require long sequence reads, they do depend on sampling archaic gene pools (Durand, Patterson, Reich, & Slatkin, 2011; Green et al., 2010). Given that identifiable macrofossils containing useable DNA are typically unavailable, the transferability of analytical approaches developed for reconstructing human history to other systems remains limited for now.

In the absence of explicit assessment of evidence for lineage fusion in phylogeographic studies, effects of these events could potentially be attributed to other processes. One immediate impact of a fusion event is an abrupt increase in locally co-occurring allelic and genotypic diversity. For example, the effects of cyclic isolation followed by complete merging of divergent populations has been shown to produce an initial spike in diversity, and although this increase may be transient owing to subsequent erosion by drift, it can take many generations to eventually return to equilibrium (Alcala & Vuilleumier, 2014). Accordingly, if the lag time between a fusion event and gene pool sampling is short relative to the number of generations required for equilibrium to re-establish, then genetic estimates of effective population size—which are critical components of most statistical phylogeographic analyses—would be upwardly biased (Jesus, Wilkins, Solferini, & Wakeley, 2006). Given that elevated levels of genetic diversity can be mistakenly interpreted as an indicator of long-term stability (Petit et al., 2003), unrecognized lineage fusion is a potential source of error that may affect inferences about the number and locations of past habitat refuges.

In comparative phylogeographic studies, a common goal is to distinguish between species-specific versus shared responses to past environmental change (Arbogast & Kenagy, 2001; Avise, 2000; Bermingham & Moritz, 1998). However, unrecognized fusion events may alter interpretations about the levels of congruence in several ways. For instance, if two species exhibit very similar present-day geographic range boundaries of genetically distinct populations, but these similarities are underpinned by a lineage fusion event in one species but not the other, then despite initial appearances, this would actually represent a case of weak congruence (Figure 1). Likewise, if the evolution of post-zygotic isolating mechanisms among allopatric populations [e.g., due to cytonuclear incompatibilities (Burton, Pereira, & Barreto, 2013), or Dobzhansky-Muller incompatibilities (Fitzpatrick, 2008)] is stochastic, then a situation where a co-vicariance event was preserved in one species but overwritten by lineage fusion in the other would represent a case of weak incongruence, even though the present-day number and distribution of genetically distinct populations are now very different (Figure 1). Indeed, the role of stochasticity in preserving versus overwriting past vicariance may be considerable, given that a relatively broad range of DNA sequence divergences lie in the "grey zone" where it is unclear whether between-lineage differences are governed by species-level versus population-level processes (Roux et al., 2016). Ultimately, conclusions about the extent to which species have responded to past climatic changes in a lock-step manner (e.g., host plants and their arthropod mutualists, parasites or commensals; DeChaine & Martin, 2006; Smith et al., 2011; Garrick, Nason, Fernández-Manjarrés, & Dyer, 2013; Satler & Carstens, 2016, 2017) could be impacted by unrecognized lineage fusion.

Our goal is to stimulate discussion about broadening the scope of phylogeographic studies to explicitly consider lineage fusion. To understand the circumstances under which detecting such events is achievable, simulations were used to explore basic data requirements (number of loci and individuals sampled) for identifying cases where a present-day panmictic population is the product of past lineage fusion. To assess whether NGS data are a fundamental prerequisite for detecting lineage fusion, simulations were conditioned on phased DNA sequence haplotype datasets, and the number of loci were chosen to span what is typically generated by Sanger sequencing and targeted capture-based NGS. We also investigated how some aspects of fusion scenarios (duration of drift-induced divergence between two ancestral sister populations, symmetry of mixing at the time of fusion, and lag time between the fusion event and gene pool sampling) contribute to difficulty in distinguishing them from competing hypotheses such as long-term panmixia or population expansion-contraction.

2 | APPROACH

2.1 | Hypothetical study system

Oceanic islands are considered natural laboratories for studying evolution, and they provide a setting where near-instantaneous merging of two or more genetically divergent lineages could occur. For example, mega-landslide events brought about by volcanic flank collapse can create large volumes of floating organic material that enable synchronous rafting of many individuals from one island to another (García-Olivares et al., 2017), and subsequent volcanic events could drive extinction of the remaining source population on its island of origin. Even within an island, new connections between long isolated populations can establish rapidly via geologically-driven changes (Garrick et al., 2014; Waters, Craw, Youngson, & Wallis, 2001). Indeed, long-term isolation followed by gene flow upon secondary

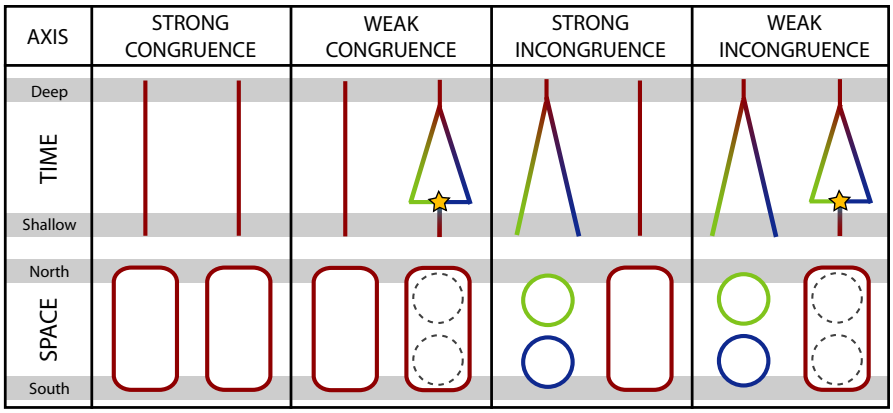

FIGURE 1 The potential impacts of unrecognized lineage fusion upon interpretation of phylogeographic congruence between two co-distributed species. The time axis represents evolutionary divergence (or lack thereof), where colour transitions indicate accumulated effects of genetic drift on isolated gene pools derived from a common ancestral population (stars are fusion events). The space axis shows the present-day number and geographic distribution of distinct gene pools, where solid lines circumscribe panmictic populations. Dashed grey lines are pre-fusion geographic distributions of gene pools that are no longer distinct

contact between divergent lineages—including those below the species level—is more common than previously thought (Mallet, Beltrán, Neukirchen, & Linares, 2007; Wallis et al., 2017). Here we performed simulations to generate pseudo-observed datasets (PODs) under the simplifying assumptions of instantaneous fusion between two well-defined and genetically distinct sister populations, and that only genetic drift was operating.

2.2 | Lineage fusion scenarios with contrasting divergence and sampling lag times

Fusion scenarios were designed to reflect the timing of palaeoclimatic events frequently cited in the phylogeographic literature. Four representations of present-day populations that have a history of past fusion were constructed, with divergence between ancestral sister populations originating either at the Penultimate Glacial Maximum (PGM) or the Last Glacial Maximum (LGM), and subsequent fusion occurring either very soon after the LGM, or at the end of the mid-Holocene (Figure 2 upper panel). In all cases, gene pools were sampled in the present-day only (i.e., from a randomly mating population with a history of fusion), as this reflects constraints that apply to many studies.

2.3 | Model parameters and pseudo-observed datasets

Three classes of model parameters characterized lineage fusion scenarios: effective population size (N_e), timing (t) and mixing. To simulate PODs, values of N_e = 10,000 were specified for the present-day population, the two ancestral sister populations that fused in the past, and their ultimate ancestral population. Given that N_e of each population was constant over time yet the number of populations temporarily doubled, this would be analogous to a phylogeographic scenario where habitat availability (and cumulative N_e of the species as a whole) changed through time. Two timing parameters were used: the number of generations since the initial divergence of ancestral sister populations (t_{div}), and number of generations since the fusion event (t_{fuse}). Depending on the scenario, values of t_{div} were set at either 140,000 or 20,000 (PGM vs. LGM origin, respectively), and values of t_{fuse} were set at 15,000 or 5,000 (pre-Holocene vs. mid-Holocene fusion, respectively). Mixing was set at 0.5, such that each ancestral sister population contributed equally to a fusion event. Because the impact of population sampling on phylogeographic inferences was also of interest, PODs contained sequence data from either 10 or 50 diploid individuals (see Appendix S1 in Supporting Information for rationale).

Pseudo-observed datasets reflected characteristics of empirical genetic datasets typically produced via Sanger sequencing of nuclear loci, as well as reduced representation NGS approaches that yield haplotype data (Appendix S1). We assumed that phased haplotypes (cf. phase-unknown diplotypes) are available. The length of alleles was set at 400 bp, consistent with nuclear DNA alignments reported in the literature (Garrick et al., 2015) and with the length of flanking region sequence obtained using NGS capture methods (A.R. Lemmon, pers. comm.). To assess the impact of the number of sampled loci on inferences about past lineage fusion, PODs contained 1, 5, 25 or 100 polymorphic diploid autosomal loci. The first three values encompass the range of loci attainable using Sanger sequencing (Lee & Edwards, 2008). Conversely, the latter value is representative of the number of loci obtained via NGS capture methods that can be simultaneously analyzed using sophisticated methods for phylogeographic inference (Carstens et al., 2013; Jackson, Morales, Carstens, & O'Mera, 2017; O'Neill et al., 2013). All PODs were simulated in DIY-ABC 2.1.0 (Cornuet et al., 2014) using the HKY model of nucleotide sequence evolution (Hasegawa, Kishino, & Yano, 1985) with proportion of invariant sites = 10%, gamma = 2.0, and a mutation rate (μ) of 1×10^{-7} substitutions per site per generation assuming a one year generation time. Ten replicate PODs were simulated

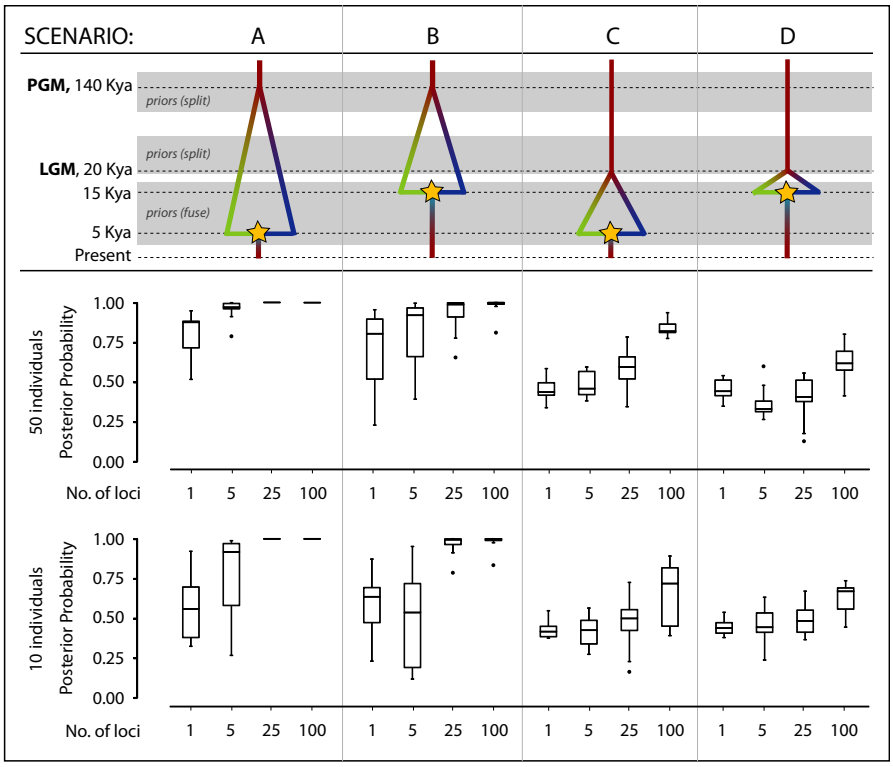

FIGURE 2 The influence of number of loci and number of sampled individuals on the power of ABC to correctly identify lineage fusion. Upper panels show four alternative fusion scenarios (A–D) that represent increasingly difficult cases (left to right). Dashed lines are time points of events used in simulations that generated PODs. ABC analyses used broad priors (exemplified by grey shading, not to scale) and considered two competing hypotheses: long-term panmixia and lineage fusion. Lower panels show outcomes of model selection, summarized as box-and-whisker plots, represented by posterior probabilities of the true lineage fusion model (for posterior probabilities of each competing hypothesis, and error associated with posterior probabilities, see Table S4.3)

for each combination of fusion scenario × population sample size × number of loci, giving a total of 320 PODs (genetic diversity summaries are given in Appendix S2, Table S2.1).

2.4 | Analyses

Approximate Bayesian computation (ABC; Beaumont, Zhang, & Balding, 2002) has been broadly applied in phylogeography (Bertorelle, Benazzo, & Mona, 2010; Hickerson, 2014), making it a suitable exemplar here. ABC was used to explore the circumstances under which a population with a history of lineage fusion carries signatures that are quantitatively different from long-term panmixia within a single isolated population (Appendix S1). To statistically distinguish between lineage fusion and the competing (false) hypothesis of long-term panmixia, PODs were characterized using seven summary statistics: number of haplotypes and segregating sites (averaged across loci for multi-locus datasets), mean and variance of pairwise differences, Tajima's (1989) *D*, and mean and variance of the rarest nucleotide at segregating sites. Together, these capture different aspects of within-population genetic variation. Uniform priors on model parameters were as follows: all N_e values = 5,000–15,000, t_{div} = 120,000–150,000 or 20,000–35,000 generations ago (PGM vs. LGM origin, respectively), and t_{fuse} = 2,500–17,500 (all hypotheses; Figure 2 upper panel). Notably, independent N_e parameters (albeit with the same priors) were used for all interior branches of the "population trees" that characterized competing hypotheses, and as such, both the lineage fusion and long-term panmixia hypotheses did permit some population size fluctuation over time (Appendix S3, Figure S3.1). Priors on DNA sequence evolution assumed a HKY model and $\mu = 1 \times 10^{-6}$ to 1×10^{-8}, with all other parameters fixed at true values. ABC runs consisted of 1×10^5 simulated datasets per competing hypothesis. Following Cornuet et al. (2014), model checking was performed via principal components analysis, and then posterior probabilities of competing hypotheses were determined via logistic regression on the 1% of simulated datasets closest to the POD, with a logit transformation. Following Robert, Cornuet, Marin, and Pillai (2011), confidence in choice of the best-fit model was evaluated using the recommended exploratory approach (i.e., Monte Carlo evaluation of false allocation rates) via computation of a global posterior error rate over all competing hypotheses, again using logistic regression on the 1% of simulated datasets closest to the POD, based on 1×10^5 simulated datasets.

2.5 | Further exploration of parameter space

We assessed the impact of varying additional parameters upon the potential to identify when a population has a history of lineage fusion, focusing on one scenario that may be particularly relevant to real world landscape settings (i.e., divergence of ancestral sister populations originating at the PGM, with subsequent fusion occurring very soon after the LGM; scenario B in Figure 2 upper panel). Briefly, we (a) broadened the range of N_e values to include three categories (1,000, 10,000 or 100,000), (b) considered both symmetrical (1:1) and asymmetrical (1:3) mixing ratios during fusion, where the latter is expected to represent a more realistic case, and (c) extended the genetic sampling to include a fifth category (400 loci; Appendix S1). This exploration of parameter space was expanded further by simulating PODs in which PGM divergence was coupled

with bottlenecks that reduced each of the sister populations down to half the size of the ancestor, followed by recovery to the original size upon fusion. This latter set of PODs represents a case where cumulative N_e of the species as a whole is constant over time, and would be analogous to a phylogeographic scenario where a fixed amount of suitable habitat was fragmented then reconnected. For computational tractability, this suite of simulations generated PODs for 10 diploid individuals only, with five replicate datasets for each combination of N_e × mixing ratio × number of loci, giving a total of 300 PODs (genetic diversity summaries are given in Appendix S2, Table S2.2).

Pseudo-observed datasets were again analyzed via ABC. However, here we explored the impact of considering a third competing hypothesis that forced a compulsory and potentially strong expansion-contraction, given that this demographic history may produce genetic signatures that closely mimic those of lineage fusion, and thus could be analytically challenging. For the lineage fusion and long-term panmixia hypotheses, uniform priors on N_e were set at 0.5–1.5× the true value (e.g., 500–1,500 when analyzing PODs simulated with N_e = 1000; Appendix S3, Figure S3.1). For the expansion-contraction hypothesis, a transient population expansion event was modeled by upwardly adjusting priors on N_e to 2.0–4.0× the true value (i.e., that used to generate PODs being analyzed). This ensured a period of population growth, which was initiated 120,000–150,000 generations ago and ended 2,500–17,500 generations ago. Thus, this hypothesis postulated a fluctuating population size mimicking a contraction-expansion-contraction cycle, with the expansion event occurring during the last interglacial period (Appendix S3, Figure S3.1), as has been inferred for many plant and animal species (Jesus et al., 2006). For the lineage fusion hypothesis, priors for mixing were set at 0.25–0.50 (i.e., spanning a 1:3 to 1:1 ratio). All other priors were the same as those used to specify the lineage fusion hypothesis when analyzing PODs associated with "scenario B" in the earlier set of simulations, all ABC runs again consisted of 1×10^5 simulated datasets per competing hypothesis, and posterior probabilities of hypotheses were determined as before (see Lineage fusion scenarios with contrasting divergence and sampling lag times).

3 | OUTCOMES

Overall, our first set of simulations that focused on fusion scenarios with contrasting divergence and sampling lag times indicated that in many cases, sampling only 25 diploid autosomal loci is sufficient to recover signatures of past lineage fusion (Figure 2; Appendix S4, Table S4.3). However, to detect lineage fusion under more challenging scenarios (those with fewer generations between divergence and fusion, and/or longer lag times between lineage fusion and gene pool sampling) at least 100 loci are typically required. With a 100-locus dataset, in some cases it was even possible to correctly infer lineage fusion when the initial divergence of ancestral sister populations and their subsequent fusion was fully contained within a LGM timeframe (Figure 2 middle panel). Given that this period is thought to have had profound impacts on the spatial distribution of genetic variation within and among populations (Avise, 2000; Hewitt, 1999; Petit et al., 2003), the ability to identify a history of fusion using an attainable number of loci is encouraging (with the caveats that the simplifying assumption of symmetrical mixing was made, and long-term panmixia was the only competing hypothesis).

For the least challenging lineage fusion scenario (i.e., a long duration of divergence before fusion, coupled with a relatively short delay between fusion and gene pool sampling; scenario A), correct inferences were achieved with as few as five loci, provided that many (n = 50) individuals were sampled. However, little benefit was gained by sampling over 10 individuals when 25 or more loci were used (Figure 2 lower panel). More challenging scenarios could be resolved only with larger datasets. Although 25 loci generally provided enough power to handle a situation where fusion between two long-diverged sister populations was coupled with a considerable post-fusion time lag prior to sampling (scenario B), the reverse situation where shallow divergence was coupled with a short time lag (scenario C) required at least 100 loci. In the latter case, dense sampling of individuals was also necessary (Figure 2 middle panel). As expected, we saw a strong negative relationship (correlation coefficient, r = 0.924; slope = −1.331) between posterior probabilities of the true scenario versus the error associated with those posterior probabilities (assessment of correlation was performed on 32 data points, based on summaries reported in Table S4.3). This indicates that in cases with pronounced superior support for one hypothesis, ABC model choice outcomes may be more reliable, although it would be worthwhile to separately estimate type I and type II error for each competing scenario (Bertorelle et al., 2010) in order to understand risk of erroneous conclusions. Conversely, when support for the best-fit hypothesis is only moderately superior, inferences should be made very cautiously. Notably, compared to sampling larger numbers of individuals, adding loci appears to be a far more efficient way to reduce global error associated with posterior probabilities (Table S4.3).

The above findings may help understand the extent to which published datasets could be re-analyzed to assess evidence for lineage fusion. To explore this, we focused on Garrick et al.'s (2015) survey of phylogeographic datasets, and extracted additional information about population-level sampling of individuals from the original papers. Of the 35 datasets that included ≥5 diploid autosomal loci, 26 were generated via Sanger sequencing (range = 5–14 loci; mean = 7) and the remaining nine datasets were generated by NGS (range = 32–25,679 loci; mean = 4,537). For the Sanger datasets, all but one had sampled too few individuals per population (on average) to enable potentially reliable inferences even for the least challenging lineage fusion scenario to be made. Conversely, only one NGS dataset had sampled too few individuals per population to infer lineage fusion under the conditions modeled in our first set of simulations (Appendix S5, Table 5.5). Today, genotyping of several hundred haplotype-yielding nuclear loci is feasible for non-model organisms (Faircloth et al., 2012; Harvey, Smith, Glenn, Faircloth, & Brumfield, 2016; Lemmon, Emme, & Lemmon, 2012). While we do suggest that

this may allow signatures of lineage fusion to be recovered in some fairly difficult situations, it remains to be seen whether a very short time between divergence and fusion coupled with a long lag time before gene pool sampling (e.g., scenario D) is surmountable.

Our second set of simulations involved further exploration of parameter space using an exemplar fusion scenario (i.e., scenario B) to provide insights into the impact of mixing ratio, N_e, and the types of competing demographic hypotheses, on the potential to correctly infer past lineage fusion. This was done in two contexts: where cumulative N_e of the species as a whole doubled during the divergence phase versus where it remained constant over time (see Approach). Overall, compared to symmetrical mixing, asymmetrical mixing almost always negatively impacted the frequency with which the true hypothesis of lineage fusion was inferred (Figure 3; Appendix S4, Table S4.4). This is likely due to a weaker initial genetic signature of fusion under asymmetry, and thus a faster erosion of it. In nature, unequal contributions are likely to be common during fusion. Indeed, from an empirical standpoint, lack of clarity about recent human evolutionary history (Fagundes et al., 2007) may have persisted, even during the genomics era, due to highly asymmetrical mixing between modern humans and Neanderthals (Currat & Excoffier, 2011) and the analytical challenges that this creates. We also found that the N_e value used to generate PODs had a major impact on outcomes. When N_e was 10,000, the potential to correctly infer past fusion was consistently good with 400 loci across all variants of scenario B, except in the case of asymmetrical mixing coupled with divergence-associated bottlenecks that rendered cumulative N_e of the species constant over time (Figure 3). Fortunately, technical barriers associated with obtaining and screening over 400 DNA sequence haplotype loci for phylogeographic studies of non-model organisms are now being overcome (Smith, Harvey, Faircloth, Glenn, & Brumfield, 2014). Conversely, the potential to correctly infer past lineage fusion was generally quite poor when N_e was 1000, and it was almost always poor when N_e was 100,000 (except for two cases that we consider to be anomalies; i.e., when data from 100 or 400 loci were available, mixing was symmetrical, and there were divergence-associated bottlenecks; Figure 3).

The reason for N_e-dependent outcomes is likely related to how this parameter scales with time (measured in generations). In this study, simulations using N_e = 1,000 essentially modeled 125 N_e generations of drift-induced divergence between ancestral sister populations and a lag time between fusion and gene pool sampling of 15 N_e generations. Here, the effects of extensive post-fusion genetic mixing could be most influential in diminishing the potential to correctly infer past lineage fusion. Consistent with this idea, we found that long-term panmixia was most often erroneously identified as the best-fit model when N_e was 1,000, regardless of whether PODs were simulated based on a model of lineage fusion in which cumulative N_e of the species changed versus remained constant during the divergence phase (Table S4.4). In contrast, for N_e = 100,000 the values corresponding to scaled divergence and lag time were 1.15 and 0.15 N_e generations, respectively. Here, insufficient opportunity for accumulation of genetic differences between ancestral sister populations could be the main limiting factor (e.g., the formation of reciprocally monophyletic clades of nuclear allele haplotypes requires, on average, the $4N_e$ generations of divergence; Templeton, 2002). For PODs in which cumulative N_e of the species as a whole doubled during the divergence phase of lineage fusion modelled by scenario B, an inference of expansion-contraction was the most prominent error when N_e was 100,000, whereas for PODs simulated with divergence-associated bottlenecks, long-term panmixia was the common erroneous inference (Table S4.4). For empirical studies of natural populations, these findings broadly suggest that the complete merging of two populations will be easiest to detect if (1) they were deeply genetically divergent from one another owing to strong effects of drift (either due to small N_e or lengthy divergence times), (2) they were of similar effective sizes and thus made equal genetic contributions during fusion and (3) the fusion event occurred recently (in terms of N_e generations) relative to the time of gene pool sampling, so as to avoid the confounding effects of extensive post-fusion genetic mixing. Indeed, some of the clearest examples of lineage fusion in nature come from recently collapsed sympatric species (Seehausen, Takimoto, Roy, & Jokela, 2008). Also, compared to the first set of simulations, in our second set of simulations the relationship between posterior probabilities of the true scenario versus the error associated with those posterior probabilities was weaker (r = 0.558, slope = –0.627; assessment of correlation was performed on 30 data points, based on summaries reported in Table S4.4). Accordingly, increased model complexity (e.g., inclusion of additional parameters such as mixing ratio) and/or an increase in the number of competing hypotheses means that even when support for the best-fit hypothesis appears to be quite strong, inferences will still require caution. As above, estimation of scenario-specific of type I and type II error would be advised.

Unrecognized lineage fusion has the potential to impact inferences about population history and phylogeographic congruence among species, yet such events seem to be underappreciated. One reason could be that broadly suitable analytical frameworks for investigating signatures of lineage fusion are lacking (e.g., Strasburg & Rieseberg, 2013). Previously, Templeton (2001) developed test statistics to detect the complete merging of lineages on secondary contact, but these have not been widely applied, perhaps due to concerns about error rates of the broader analytical framework within which they were embedded (Nielsen & Beaumont, 2009). Subsequently, Nguyen, Spillner, Emerson, and Moulton (2010) proposed using a measure of haplotype connectivity to determine whether recent admixture has contributed to high levels of genetic diversity in a given geographic location. However, as with Templeton's (2001) test statistics, this network-based approach is not amenable to jointly analyzing multiple loci, and so may have limited applicability to NGS datasets. Notably, several popular multi-locus coalescent analyses do consider long-term gene flow dynamics (Beerli & Felsenstein, 2001; Hey, 2010), which are a component of lineage fusion. That said, the timing of discontinuous gene flow (a temporally constrained burst) has proven difficult to estimate (Muster, Maddison, Uhlmann, Berendonk, & Vogler, 2009; Sousa, Grelaud,

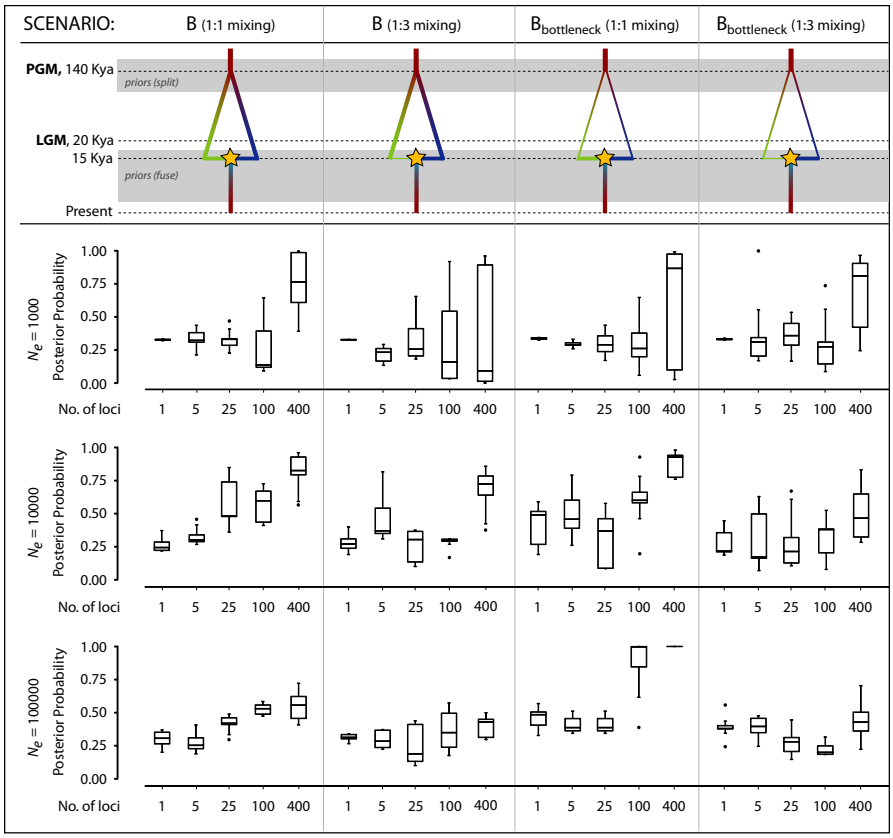

FIGURE 3 The influence of mixing symmetry, divergence-associated bottlenecks and N_e upon the power of ABC to correctly identify lineage fusion. Upper panels show four variants of lineage fusion scenario B (see Figure 2), where the initial divergences either are not versus are associated with bottlenecks (left vs. right), and mixing is either symmetric or asymmetric. Dashed lines are time points of events used in simulations that generated PODs. ABC analyses used broad priors (exemplified by grey shading, not to scale) and considered three competing hypotheses: long-term panmixia, expansion-contraction, and lineage fusion. Lower panels show outcomes of model selection, summarized as box-and-whisker plots, represented by posterior probabilities of the true lineage fusion model (for posterior probabilities of each competing hypothesis, and error associated with posterior probabilities, see Table S4.4)

& Hey, 2011; Strasburg & Rieseberg, 2011), limiting the utility of these analyses for detecting past fusion events. Some recent progress on this front has been made; for example, Morales, Jackson, Dewey, O'Meara, and Carstens (2017) estimated the timing of gene flow associated with admixture following recent secondary contact among species of *Myotis* bats using approximate likelihood. However, in the case of lineage fusion, all of these multi-locus coalescent methods are difficult to apply because after complete merging of genetically divergent lineages, only one extant population is available to sample. Indeed, this constraint also limits the use of gene tree-based approaches for making inferences about reticulated evolutionary histories within and among closely related species (Edwards et al., 2016).

In contrast to the analytical approaches mentioned above, ABC has the flexibility to model scenarios in which two or more genetically distinct populations have fully merged together, and it can take advantage of the NGS revolution in phylogeography by efficiently analyzing large multi-locus datasets (Robinson, Bunnefeld, Hearn, Stone, & Hickerson, 2014; Xue & Hickerson, 2015). That said, ABC analyses can suffer when a large number of candidate models are simultaneously considered, as the posterior probability of the true model is often reduced (Pelletier & Carstens, 2014; but see Stone et al., 2017). Fortunately, several other methods that address the challenges associated with detecting past lineage fusion have been developed. For example, signatures of such events can be recovered from patterns of linkage disequilibrium in nuclear DNA sequences (Plagnol & Wall, 2006; Wall et al., 2009), and summary statistics that characterize the site frequency spectrum or the modality of the distribution of pairwise nucleotide differences can also be informative (Alcala, Jensen, Telenti, & Vuilleumier, 2016). Geospatial information could also be leveraged to extend the scope of phylogeography to account for lineage fusion. In this context, forward-time simulations have been used to model range expansion in the lead up to secondary contact between Neanderthal and modern human populations, followed by progressive (cf. instantaneous) fusion that initially occurred only within a narrow zone (Currat & Excoffier, 2004). Although parameterizing such models is difficult for species with a poor fossil record, comparative phylogeographic studies may facilitate construction and testing of more realistic, spatially explicit, fusion scenarios. For example, if several species share a marked genetic break that another co-distributed species lacks, then not only is there clear value in assessing evidence for lineage fusion in the latter, but the set of species that do exhibit breaks could provide guidance on setting priors for the directionality of range expansion(s) and the location of initial contact between putative lineages that may have fused. Indeed, comparative studies have the unique ability to uncover cases of pseudo-congruence and pseudo-incongruence (Donoghue & Moore, 2003; Soltis, Morris, McLachlan, Manos, & Soltis, 2006 and references therein); here we advocate for expanding the view of these phenomena, beyond timing and pattern of lineage divergence, to include lineage fusion.

We aim to provoke deeper consideration of a special case of secondary contact that has been underappreciated in the phylogeographic literature. Further exploration is required, for example to: (a)

understand the impact of extant but unsampled populations on inferences, (b) determine the optimal balance between number of sites, sequences and loci for obtaining accurate inferences (Felsenstein, 2006), (c) assess the influence of the information content carried by different NGS data types that are relevant to phylogeography (Harvey et al., 2016) and (d) examine the power of different summary statistics and analytical methods to distinguish among a set of competing lineage fusion hypotheses, perhaps extending assessments to include repeated fission-fusion cycles (Alcala & Vuilleumier, 2014; Alcala et al., 2016). Notwithstanding these knowledge gaps and the need to integrate different approaches to deal with analytical challenges posed by asymmetrical mixing, we suggest that NGS data do indeed provide opportunities for fundamentally new insights into long-term demographic history. Furthermore, modest sample sizes of individuals seem to be sufficient, and so as NGS datasets accumulate, there should be opportunities for meta-analysis. Such studies can address broad questions in phylogeography (Pelletier & Carstens, 2018), and in this case could reveal how common lineage fusion is globally, and in which landscape settings or organismal groups it is most prevalent.

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DATA ACCESSIBILITY

All simulated datasets are available via DRYAD Repository entry https://doi.org/10.5061/dryad.q0b78b5.

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BIOSKETCH

Garrick's lab focuses on understanding processes that generate and maintain biodiversity within and among species, with an emphasis on montane forest biota.

Author contributions: R.C.G. conceived the study and simulated data; all authors analyzed data and developed the ideas; R.C.G. drafted the manuscript, and all authors contributed to revisions.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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