Introgression makes waves in inferred histories of effective population size

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Abstract

Human populations have a complex history of introgression and of changing population size. Human genetic variation has been affected by both these processes, so that inference of past population size depends upon the pattern of gene flow and introgression among past populations. One remarkable aspect of human population history as inferred from genetics is a consistent "wave" of larger effective population size, prior to the bottlenecks and expansions of the last 100,000 years. Here I carry out a series of simulations to investigate how introgression and gene flow from genetically divergent ancestral populations affect the inference of ancestral effective population size. Both introgression and gene flow from an extinct, genetically divergent population consistently produce a wave in the history of inferred effective population size. The time and amplitude of the wave reflect the time of origin of the genetically divergent ancestral populations and the strength of introgression or gene flow. These results demonstrate that even small fractions of introgression or gene flow from ancient populations may have large effects on the inference of effective population size.

Introduction

The origins of today's modern human populations included introgression or gene flow from genetically divergent ancestral populations of archaic humans. Direct evidence of this ancient introgression comes from the ancient DNA of Neandertals, which contributed between 1 and 4 percent of the genetic makeup of today's populations outside Africa (Green et al., 2010; Prüfer et al., 2013) and from the Denisova 3 genome, which represents an archaic population that contributed up to 5 percent of the genetic makeup of today's Melanesian and Australian populations (Reich et al., 2010; Reich et al., 2011; Meyer et al., 2012; Prüfer et al., 2013). No ancient DNA evidence from any archaic human skeletal remains within Africa has yet been recovered. However, abundant indirect evidence exists of introgression from genetically divergent populations into the ancestral populations of living Africans. Genetic comparisons extending to whole genomes now show the signature of archaic human introgression in samples of various populations within Africa (Lachance et al., 2012; Hsieh et al., 2016b; Beltrame et al., 2016).

At the same time, whole-genome analyses have added a longer-term dimension to our understanding of human population size over time (Li and Durbin, 2011; Mallick et al., 2016). But the inference of changes in effective population size depends in part upon the same features of genetic data that allow the inference of introgression. The genetic variation within a population is a product not only of its size but also its structure, and many aspects of human population history may complicate the understanding of

53 effective population size (Hawks, 2008). While it is possible to explicitly employ complex
54 population history models to generate estimates of past population size and structure
55 (e.g., Schaffner et al., 2005), our ability to probe evidence of extinct "ghost" populations
56 that contributed introgression or gene flow into living people is extremely limited.
57
58 Some studies have examined how demic expansion may have interacted with archaic
59 human introgression during the expansion of modern human populations into Eurasia
60 (Currat and Excoffier, 2011; Sugden and Ramachandran, 2016). However, the effects of
61 introgression upon signatures of ancient population growth that predate the dispersal
62 of modern humans into Eurasia have not previously been subject to close examination.
63 Hence, it is valuable to look directly at how a history of introgression or gene flow
64 between populations may affect the inference of ancestral effective population size.
65
66 **History of human effective population size.** Statistical methods such as the pairwise
67 sequential Markovian coalescent (PSMC) (Li and Durbin, 2011) make it possible to infer
68 changes in effective population size over time based upon the time to most recent
69 common ancestor (TMRCA) of alleles of single genetic loci, extended across many loci up
70 to whole genomes. The TMRCA indirectly reflects the genealogical coalescence of
71 alleles, conditioned on the probability of mutations and recombination in each
72 generation. Under a Wright-Fisher population model, the probability of coalescence of
73 two alleles in a single generation is $1/2N_e$, and if the effective size in such a population
74 changed in the past, different intervals of time will have different probabilities of

coalescence. Li and Durbin (2011) showed the effectiveness of this approach to inferring changes in past population size as applied to single diploid genomes. They found that although the recent population history of human groups differs, for the time intervals prior to 100,000 years ago, different human genomes give repeatable and consistent estimates of effective population size.

These approaches have been applied to many samples of living humans as well as to ancient human genomes (e.g., Li and Durbin, 2011; Prüfer et al., 2013; Mallick et al., 2016). Several aspects of human population histories as inferred from the PSMC approach are notable. Non-African population samples reflect a bottlenecked history in which the ancestral effective size was rather strongly reduced between 100,000 and 50,000 years ago. Some sub-Saharan African populations also show a moderate reduction in effective size across that time interval, which may reflect either their own population history or admixture from populations of Eurasian origin, possibly via North Africa (Mallick et al., 2016). Sub-Saharan hunter-gatherer populations do not present any evidence of such a population bottleneck prior to 50,000 years ago, although their current population sizes are relatively small. All living human population samples in the period before 100,000 years ago show a similar inferred pattern of changes in effective population size. In broad terms looking backward into the past, this population history resembles a “wave” in which the effective size was large around 100,000—200,000 years ago, gradually smaller further back in time, with a minimum between 500,000 and 1 million years ago, and then gradually larger in the period before a million years ago

(Figure 1). The inference of larger ancestral effective population size prior to 1 million years ago is repeated across different populations. It is also evident when considering genomes from archaic humans, specifically high-coverage Neandertal and Denisovan genomes from Denisova Cave, Russia (Prüfer et al., 2013). These genomes reflect an extremely small ancestral effective size through most of the evolutionary history of these groups back to their differentiation from other human populations before 500,000 years ago. But in the interval preceding their divergence, both samples share an inferred history of effective population size similar to that of living human populations. The inference of higher effective population size in the earliest part of human origins is also evident from rare genomic insertions (Huff et al., 2010). Both the replication in ancient genomes with very different recent population histories, and the evidence for a similar expansion from non-SNP datasets providing corroborating evidence that the appearance of a "wave" in effective population size is not merely an artifact of the PSMC method.

History of introgression. Statistical evidence for introgression comes from joint consideration of local heterozygosity and recombination in genetic samples. Recombination and mutation are both random processes that occur over time, leading to the expectation that regions of high local heterozygosity (because of a long history of mutations) should tend to be relatively short (because of an equally long history of recombination). If a population contains two long alleles that differ by a relatively large number of mutations, this suggests that some process may have suppressed recombination during the evolution of the locus. Relatively long, strongly linked

119 divergent haplotypes can occur within a random-mixing population for several reasons,
120 including balancing selection or structural variation such as chromosomal inversion
121 (Evans et al., 2006; Hawks et al., 2008). However, if such loci are statistically common
122 including across regions without notable selective or structural constraints,
123 introgression of alleles from a genetically divergent population is a likely explanation.
124
125 Plagnol and Wall (2006) developed an approach to test the hypothesis of introgression
126 of DNA into a population from a genetically diverged ancestral population, using the
127 statistic *S**. This method relies upon the idea that for a genetic locus with some
128 proportion of introgressed DNA sequences, these sequences will tend to be
129 distinguished by a relatively large number of single nucleotide variants that tend to be in
130 linkage disequilibrium. Such a pattern repeated at many loci will appear inconsistent
131 with random mating and therefore suggest some proportion of descent from one or
132 more genetically divergent populations. Using this approach, Plagnol and Wall (2006)
133 found evidence for introgression at a level of approximately 5% in multilocus data from
134 European and from Yoruba samples, suggesting for the first time that intermixture with
135 extinct populations had contributed substantially to the ancestry of African peoples as
136 well as Eurasians. Significantly, the result preceded the recovery of ancient
137 chromosomal DNA from Neandertal, Denisovan and early modern human specimens,
138 which would demonstrate introgression based on direct genome comparisons (Green et
139 al., 2010; Reich et al., 2010; Prüfer et al., 2013; Fu et al., 2015).
140

141 In adapted form, the *S** approach has been applied by a series of investigators to African
142 population samples. Hammer and colleagues (2011) found evidence for ancient
143 introgression within samples of Biaka and San peoples, consistent with a model of 2%
144 admixture from a genetically divergent population 35,000 years ago. They further found
145 some candidate loci for introgression had widespread geographic distributions across
146 Africa. Using whole-genome data from Western Pygmy, Hadza, and Sandawe
147 individuals, Lachance et al. (2012) supported the hypothesis of introgression from an
148 extinct population or populations with genetic divergence as great as the Neandertals.
149 Some candidate loci for introgression were private within each population; others were
150 shared across all three populations. Hsieh et al. (2016b) examined whole genome
151 sequences from Baka and Biaka individuals, finding evidence for introgression from one
152 or more genetically diverged populations extending over a possibly long period of time,
153 with a pulse as recently as 9000 years ago.
154
155 Statistical modeling of introgression as applied to African population samples suggests
156 an origin of some genetically divergent source populations for introgression around the
157 time that Neandertals diverged from the ancestors of living African populations
158 (Lachance et al., 2012), which we now think was prior to 700,000 years ago (Meyer et
159 al., 2016). If these genetically divergent archaic populations originated from a common
160 ancestral population around this time, then the probability of coalescence should have
161 been relatively low during the time period immediately following the divergence of
162 these populations, and higher during the time interval that immediately preceded this

163 original divergence. In other words, the scenario of introgression from genetically
164 divergent ancestral populations appears to predict a low coalescence rate during much
165 of the last 700,000 years, and a high coalescence rate earlier in time. Inferences from
166 the genomes of living Africans, from PSMC and other approaches, appear to show a
167 contrasting pattern: a "wave" of effective population size over time, with an increasingly
168 low effective population size (increased probability of coalescence) in the period leading
169 from 300,000 back to 700,000 years ago, and an increasingly large estimated effective
170 size (lower probability of coalescence) going further back in time.
171
172 Here I investigate whether the evidence from effective population size is consonant with
173 evidence of introgression in human ancestral populations in Africa. I carry out numerical
174 simulations to investigate how introgression and gene flow among genetically divergent
175 populations affect the probability of coalescence at different times in the populations'
176 histories. I also examine how the mutation process may affect data that emerge from a
177 population history with introgression or migration between genetically divergent
178 populations. The question is how much, if any, of the apparent evidence for population
179 size changes in the prehistory of African populations may be explained by gene flow or
180 introgression from genetically divergent ancestors.
181

182 ## Methods

183 I consider here the case of independent, non-recombining genetic loci sampled from a
184 single diploid genome in a population. This is convenient because of the relative

simplicity of the simulation model and the comparability to PSMC approaches that examine evidence from single diploid genomes (Li and Durbin, 2011; Prüfer et al., 2013; Mallick et al., 2016). The purpose of the model is to examine in what way introgression and gene flow may affect the probability of coalescence in specific time intervals related to known simulated population histories. This question is of interest even in cases where gene flow was common enough that recombination may not have been substantially suppressed (in other words, where gene flow among genetically divergent populations might not be characterized as "introgression"), and therefore might not reject the hypothesis of random mating under common statistical approaches for detecting introgression (Plagnol and Wall, 2006). The model applied here is not sufficient to investigate the ancestral recombination graph of a population or to examine the power of inferences about gene flow or introgression.

The probability of coalescence in a random-mating population is expected to be a function of the population size. Here I deal only with constant population sizes, to specifically examine the effect of population structure. The assumption of constant population size is of course unrealistic as applied to African populations of ancestral humans; many of these populations have grown substantially during the last 50,000 years and possibly during much earlier time periods (Beltrame et al., 2016; Hsieh et al., 2016a; Mallick et al., 2016). These populations have also recently diversified in structure, with cross-coalescence among living African populations suggesting the existence of some aspects of today's population structure going back to as much as

200,000 years (Mallick et al., 2016). Recent population expansions would have reduced the probability of coalescence during the last interval of African population evolution, but aside from increasing the proportion of loci that coalesce prior to these expansions, these recent events would not change the relative probabilities of coalescence before any proposed archaic introgression. The issue of structure versus size as influences on the probability of coalescence is taken up in the Discussion.

Population model. The population model is illustrated in Figure 2. In the model, a single Wright-Fisher population P_1 of constant size is assumed to have existed from an indefinite time in the past up to the present day. At time T_0, this population instantaneously gave rise to a second population P_2. In each generation from T_0 up to a second time, T_i, a proportion m of alleles in each population transferred to the other population, a symmetric island model of migration. At T_i, a fraction q of the alleles in P_1 are derived by introgression from P_2. The model assumes this introgression did not change the population size of P_1, which is unrealistic but not too poor for small q. Time is scaled in terms of $2N$ generations, where N is the population size of P_1 (which equals the population size of P_2). This is a similar model to that considered by Plagnol and Wall (2006) and later authors (Hammer et al., 2011; Hsieh et al., 2016b), with the differences that it does not incorporate any recent population expansions and it adds the possibility of migration between the genetically diverged populations prior to the time of introgression, instead of assuming complete reproductive isolation.

The model was implemented on Mathematica version 11.0, using the coalescent probabilities for a two-allele case with migration as described by Hudson (1990). The two alleles have a probability $1/2N$ of coalescing in each generation that they are in the same population, each has a probability q of transferring to P_2 at time T_i, each has a probability m of transferring from its population into the other population between T_0 and T_I, and any allele in P_2 at T_0 will transfer to P_1. Source code is available from Figshare. Each parameter was allowed to vary over a range of values in simulations. For each combination of parameter values, 50,000 genealogies were obtained, and the coalescence time (TMRCA) for the two alleles was recorded, in generations scaled to a factor of $2N$. While the probability of coalescence within a single population is given by $2N$, in the population model there are time increments where the effective probability of coalescence is less because of population structure. The effective probability of coalescence in a given time increment in the population model can be estimated as the ratio of the observed number of coalescence events in the time interval (c_i) relative to all genealogies that coalesce in this and earlier time intervals ($\sum_{j=i}^{\infty} c_j$). The effective population size in this time increment is then the reciprocal of the effective probability of coalescence.

Mutation. Genetic differences between alleles sampled in diploid humans reflect not only the genealogy of the alleles (modeled by the coalescent) but also the random process of mutation. Because mutations are rare events, the mutational process exerts substantial "noise" upon any attempt to estimate the TMRCA of a given locus. Sharp

changes in the probability of coalescence will likely appear to be smeared across a relatively long period of time (Li and Durbin, 2011), and slight or short-term fluctuations might not be evident by examining the distribution of mutations. To examine the effects of the mutation process on the apparent TMRCA distribution, neutral mutations were added to the genealogies in a selected number of simulations. Under a constant rate of random neutral mutations, the expected number of mutations separating two alleles, E(*H*), is a product of the neutral rate of mutations per site per generation, *mu*, the length of the locus in nucleotides, *L*, and 2 times the TMRCA in generations. In these simulations, the number of mutations for a given genealogy was modeled as a Poisson-distributed random variable with mean E(*H*). The mutation rate, *mu*, was assumed to equal 3.5 times 10^{-8} per site per generation, and the length of each sampled locus was assumed to be 50,000 base pairs. Across 50,000 replicates, this roughly approximates the total length of a human genome.

Results

A population model with introgression or migration between genetically divergent ancestral populations affects the distribution of TMRCA between two alleles by suppressing the effective probability of coalescence in the period when alleles may be resident in different genetically divergent populations. Figure 3 shows the TMRCA distribution in a population history with no introgression or migration, in which the effective probability of coalescence (Figure 3a) and the inferred effective population size (Figure 3b) are constant over time, with fluctuation only due to sampling. By

273 comparison, a population history with introgression shows a sharp discontinuity in the
274 effective probability of coalescence (Figure 3c) and inferred effective population size
275 (Figure 3d) at the time of initial divergence of the genetically divergent ancestral
276 populations.
277
278 Adding mutations to the genealogies results in a substantial smoothing of the history of
279 inferred effective population size. Figure 4 contrasts the inferred effective population
280 size based upon the distribution of TMRCA from the coalescent (Figure 4a) with the
281 inferred effective population size as estimated based on pairwise mutational differences
282 between simulated 50-kb segments (Figure 4b). The sharp change in the effective
283 probability of coalescence produced by the population model is smoothed substantially
284 into a wave when mutations are added. Without modeling recombination, these results
285 are not formally compatible with the history of effective population size for human
286 genomes as inferred by PSMC. But the "wave" appearance of the population history as
287 inferred from independent simulated loci is very similar in form to the wave that
288 appears in PSMC-generated human population histories.
289
290 The results show very little difference when comparing sudden introgression versus
291 slow, long-term gene flow. Both these processes result in a wave of similar form in the
292 inferred history of effective population size (Figure 5). The key feature of the data in
293 both cases is the initial divergence of populations at T_0 in the model. The transition from
294 a random-mating ancestral population to two partially isolated populations separates

two intervals with respectively high and low probabilities of coalescence, and the sharp transition is smoothed by adding mutations to the resulting genealogies. Whether subsequent migration between the populations is sudden or continuous, it has broadly similar results on the inferred history of effective population size.

The amount of introgression or gene flow from the genetically divergent ancestral population (P_2 in the population model considered here) determines the height of the wave of inferred effective population size. Figure 6 demonstrates the effect of different levels of introgression on the inferred population history. Human data are consistent with a 1.5 to 3-fold change in effective population size from the trough to the crest of the wave. This level of change in population size would require a rather large contribution of the genetically divergent ancestral population, for example, a level of introgression of 10% at 50,000 years ago combined with 0.2 migrants per generation (= $2Nm$) between T_0 and T_i in the model. Alternatively, it is possible that populations involving introgression from multiple genetically divergent ancestors might explain the height of the wave in inferred effective population size.

The time intervals affected by the wave of effective population size are determined by the time T_0 in the population model considered here. Figure 7 shows the effect of this time of population divergence upon the wave, with successively older times of divergence giving rise to both older waves and waves of greater amplitude, all other

parameters being held constant. Evidence of introgression from populations that diverged earlier in time is stronger than for populations that diverged more recently.

The time scale in all figures here is expressed in terms of $2N$ generations. If this scale were translated into terms of human population history, under the assumption that humans have a long-term N = 10,000 and a generation length of 25 years, then a value of "1" on the time axis of each chart would be equivalent to 500,000 years ago (=20,000 generations), "2" would be equivalent to 1 million years ago, and "5" at the rightmost side of each graph is equivalent to 2.5 million years ago. Based on this relationship, it is possible to find the best-fit value of T_0 in comparison with published inferences of human effective population size history. One such population history is illustrated in Figure 7b. Again, under the assumption that $N = 10^4$ in the ancestral African population, introgression or gene flow from a genetically divergent ancestral population that diverged between 400,000 and 800,000 years ago would provide an acceptable match to PSMC inferences of human effective population size.

Human effective population histories inferred by PSMC and other approaches consistently show a larger effective population size in periods earlier than a million years ago. The models considered here do not consistently produce this aspect of published inferences of prehistoric human effective sizes. There are instances in which the inferred effective population size does appear higher in the earliest phases of the population history, for example, Figure 5b and Figure 6c. These are deviations from the

338 expectation that the effective size will be 2*N* prior to the divergence of genetically
339 differentiated populations at T_0, which can be explained by random fluctuations among
340 the small sample of genealogies that have TMRCA earlier than around 3*N* generations.
341 However, even such examples do not really appear to match the consistently larger
342 effective size inferred for human populations prior to a million years ago.
343

344 ## Discussion

345 Human populations had varied histories in the last 100,000 years, but in time intervals
346 prior to 100,000 years ago, PSMC has generated very similar inferred histories of
347 effective population size for different present-day populations. The results of this study
348 suggest that some aspects of this consistent inferred population history can be
349 explained by gene flow or introgression from genetically divergent ancestral
350 populations. The wave of human population history during the period between 100,000
351 and 1 million years ago is best matched by introgression or gene flow from populations
352 that diverged between 500,000 and 1 million years ago. This is a similar range of values
353 as obtained by approaches that use other aspects of human genetic data to infer a
354 history of introgression, not only in the ancestry of non-African populations
355 (Sankararaman et al., 2014; Vernot and Akey et al., 2015), but in the ancestry of today's
356 African populations (Plagnol and Wall, 2006; Hammer et al., 2011; Lachance et al., 2012;
357 Hsieh et al., 2016b).
358

359 It is notable in the results that a very small fraction of introgression (on the order of 5%
360 or less, Figure 4b, 6b and 6c) still gives rise to a pronounced wave in the inferred history
361 of effective population size. Likewise, a very small amount of long-term gene flow also
362 gives rise to a pronounced wave. Figure 5a, with $2Nm = 0.2$, uses a rate of gene flow less
363 than one-twentieth the rate compatible with the current F_{ST} of human global
364 populations. How can a small fraction of introgression or gene flow have such a large
365 effect on inferred ancestral effective population sizes? This may seem paradoxical
366 considering that small amounts of introgression have a very small effect on genome-
367 wide heterozygosity, which is the primary evidence for long-term effective population
368 size. Introgression from Neandertals, for example, has not greatly increased the
369 heterozygosity of non-African populations despite the great genetic divergence between
370 Neandertal and modern genomes. But PSMC approaches go well beyond genome-wide
371 heterozygosity to examine the distribution of heterozygosity across regions of the
372 genome. It thus draws upon higher moments of a complex distribution, which is
373 affected by gene flow and introgression in complex ways. Introgression may slightly
374 decrease or increase the fraction of genetic loci that occur in a narrow window of
375 heterozygosity values, when under neutrality only a small fraction of loci occur in that
376 window to begin with. Hence, introgression or gene flow may have an outsized effect on
377 the inference of effective population size for the time intervals that correspond to these
378 differences.
379

Nothing about these results is inconsistent with the hypothesis that some large changes in actual population size may have occurred in the distant ancestry of human populations, irrespective of introgression or gene flow. In fact, under the population model considered here, the effective population size of the ancestral population *as a whole* is indeed larger during the time that ancestral lineages may exist within the genetically divergent second population. The inference of a larger effective size is accurate, it is simply explained by the presence of a ghost population. Ghost populations that are sources of introgression or gene flow are also ancestors of living human populations. The central point is that both population size and structure affect the relevant aspects of genetic variation, which means we cannot make progress understanding one demographic phenomenon without also considering the other.

PSMC examination of Neandertal and Denisovan genomes shows that their ancestral populations underwent a very different population history from the African ancestors of living human populations after they diverged (Prüfer et al., 2013). On the other hand, for the time intervals prior to the divergence of these archaic human populations, their inferred history of effective population size was congruent with the inferred history of living human populations (Figure 1b). The time that these histories come into congruence likely reflects the time of genetic divergence of these populations; it also approximates the minimum point in the wave of inferred human effective population size history. It is a good hypothesis that this minimum point in fact corresponds to the time immediately before the divergence of Neandertal and Denisovan from African

human populations, when the probability of coalescence was highest between introgressed alleles in living non-Africans and the alleles that had been resident in the African ancestors of living non-Africans. In this case, the later part of the wave, representing higher inferred effective population size in human ancestral populations, is what may be explained by introgression or gene flow with genetically divergent archaic human groups. For present-day populations of non-Africans, this introgression came in part from Neandertals. Inside Africa, it may have been from other archaic human groups, with approximately the same inferred divergence date as Neandertals, as suggested by Lachance et al. (2012).

However, there are reasons to be skeptical of this scenario. The Neandertals and Denisovans share a common stem population, so the fact that they both have a similar history of divergence from the African ancestors of modern humans is not a chance coincidence. But it would be remarkable if one or more African archaic human populations mirrored precisely the same population history. Many different genetically divergent source populations for introgression may have existed within Africa, from archaic human populations as represented by the Kabwe, Florisbad, or Iwo Eleru crania, to "near-modern" human populations that nonetheless were strongly morphologically variable (reviewed by Stringer, 2016; Bräuer, 2008), possibly to highly-divergent hominin populations such as *Homo naledi* (Berger et al., 2015). Yet with all these candidates as possible sources for introgression, living populations in Africa have almost the same inferred history of effective population size as non-Africans across the period that these

424 source populations diverged from each other. The similarity of inferred population
425 histories for these different living groups of humans with different histories of
426 introgression deserves more critical examination.
427
428 Likewise deserving of investigation is the inference of larger effective population size of
429 human ancestral populations prior to 1 million years ago (Figure 1). The results from
430 PSMC that point to a larger effective size in these distant ancestors are paralleled by
431 approaches using rare insertion polymorphisms (Huff et al., 2010), suggesting a real
432 phenomenon. It may be that this larger effective size reflects different population
433 dynamics in the distant ancestors of humans, as may also be present in great ape
434 species like chimpanzees, gorillas, and orangutans, which each have larger inferred
435 effective population sizes than humans. Such dynamics may include introgression from
436 genetically divergent populations of earlier hominins prior to 1 million years ago. This
437 kind of introgression has already been documented for the Denisova 3 genome (Meyer
438 et al., 2012; Prüfer et al., 2013). A number of morphologically diverse hominin
439 populations inhabited Africa prior to 1 million years ago, and hybridization and
440 introgression among them may have been an important part of the evolution of the
441 genus *Homo*. This relatively remote interval of human population history is represented
442 by only a small fraction of genetic loci across the genome, but may illuminate a key time
443 in the origin of humans.
444

445 The discovery that introgression has contributed substantial variation into modern
446 human populations has had great significance for the understanding of human variation
447 (Hawks, 2013; Vattathil and Akey, 2015; Racimo et al., 2015). There is a growing
448 recognition that this process of introgression or gene flow from genetically divergent
449 ancestral populations played a role in the emergence of modern human populations in
450 Africa (Beltrame et al., 2016; Ackermann et al., 2016). Considering that introgression or
451 gene flow were widespread during human origins, the ancient divergence between
452 archaic and modern human populations that interacted with each other may be one of
453 the strongest influences on genetic diversity in humans today. The current study
454 suggests that the effective population size inferred for particular intervals of time in the
455 past is strongly influenced by the history of introgression or gene flow, even when the
456 proportion of genetic variation derived from such introgression amounts only to a few
457 percent of the ancestry of present-day people. This genetic contribution is very likely to
458 have given rise to adaptive genetic variants that were valuable for modern human
459 populations (Hawks and Cochran, 2006; Hawks et al., 2008; Vattathil and Akey, 2015;
460 Ackermann et al., 2016). To the extent that such introgression or gene flow may also
461 have occurred in earlier phases of human evolution, it was likely one of the key factors
462 contributing to the success of human ancestors.
463
464

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Figure 1. History of human effective population size based upon PSMC of whole genomes. In the top panel, the first PSMC inferences of human population history from Li and Durbin (2011) were based upon draft genomes from Yoruba, European ancestry, Korean, and Chinese individuals. The middle panel shows the results of PSMC analysis from Prüfer et al. (2013) including individuals from 11 diverse human populations and the Denisova and Altai Neandertal genomes. The bottom panel shows analyses from Mallick et al. (2016), including individuals from 3 African hunter-gatherer populations (Mbuti, Ju|'Hoan, and ‡Khomani San), 3 African agricultural and pastoral societies, and one French individual. The charts have different scales based on whether they leave data in a mutation time scale or attempt a conversion to years; all are presented with the *x*-axis (time dimension) as a logarithmic value. Mallick et al. (2016, bottom) did not report any inference for times earlier than 500,000 years. Despite the great variety evidenced in the inference of effective population size during the last 100,000 years of each population, every modern human genome gives substantially similar results for the time intervals prior to 100,000 years ago. All have a clear "wave" of larger inferred effective population size with a "crest" or maximum around 200,000 years ago, and a preceding "trough" or minimum around 500,000-800,000 years ago (beyond the timescale represented by Mallick et al., 2016).

560 **Figure 1 (continued).**

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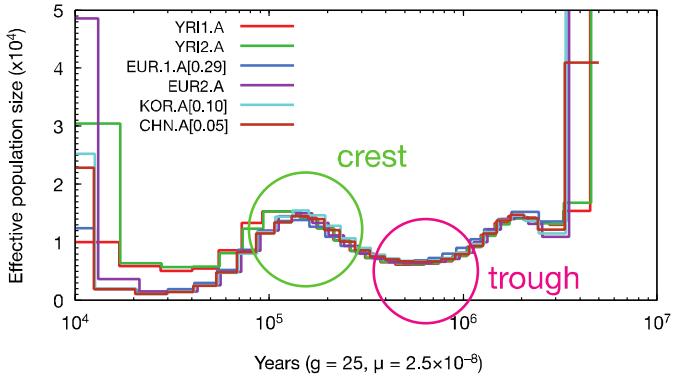

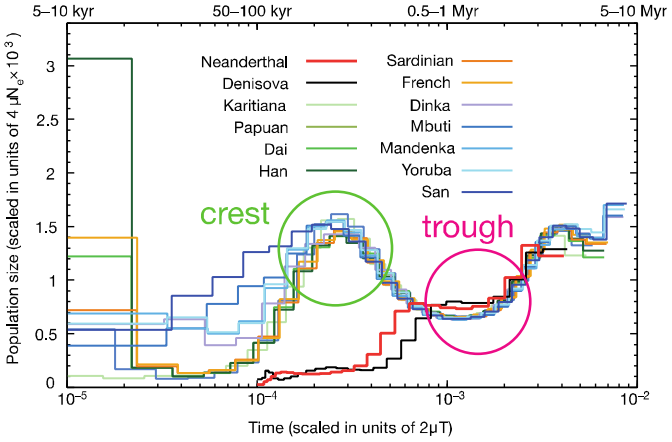

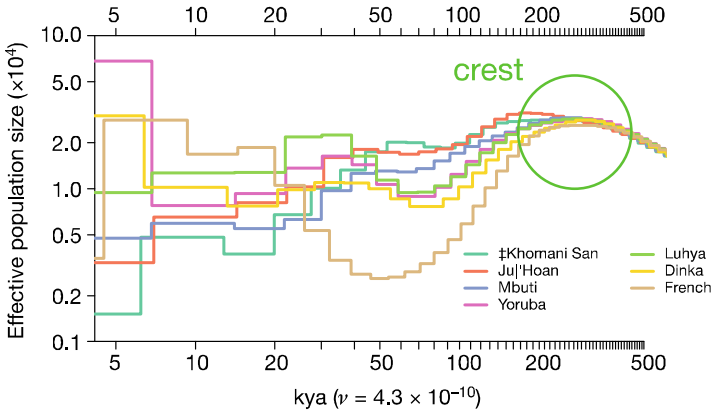

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563 **Figure 2: Population model used in this study.** P_1 is a Wright-Fisher population of size N

564 that existed infinitely far back in time. P_2 came into existence instantaneously by

565 diverging from P_1 at time T_0 in the past. From that time the two populations exchanged

566 migrants at rate m, until time T_i, when a fraction q of P_1 is derived by introgression from

567 P_2.

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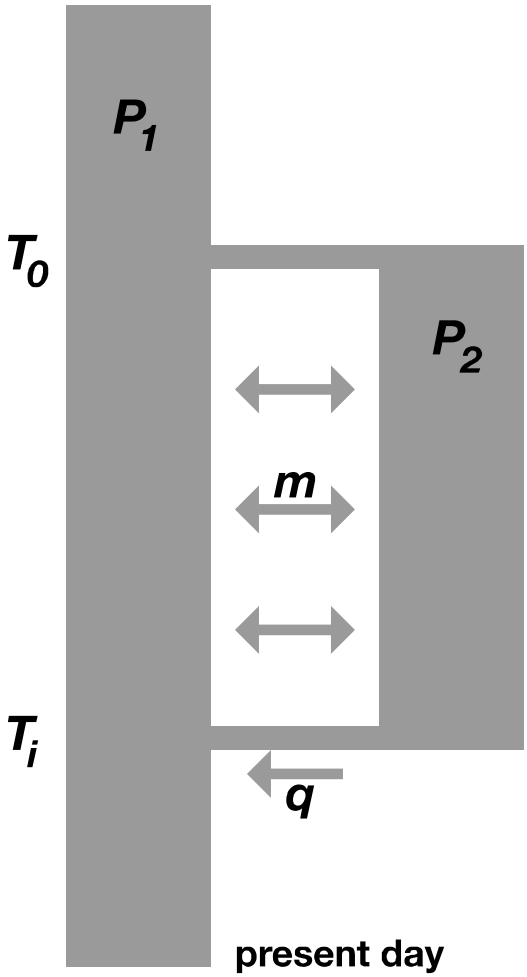

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571 **Figure 3. Comparing population histories with introgression to the null model.** Panes
572 (a) and (b) show the realized probability of coalescence and the inferred effective
573 population size in a Wright-Fisher population model with no introgression or migration.
574 Each data point represents the number of genealogies coalescing in a time increment of
575 0.05*N* generations. In (b), the effective size is estimated in each time increment, and the
576 blue line represents a moving average of 10 time increments. Panes (c) and (d) show the
577 same results for a population history in which 5% of the population derives from
578 introgression *N* generations in the past, from a second population that diverged 4*N*
579 generations ago. There is an abrupt shift in the realized probability of coalescence
580 corresponding to the divergence of the two populations 4*N* generations in the past.
581 Points become more scattered moving toward the right (more ancient times) because
582 the number of genealogies that coalesce in the most ancient time intervals is very small,
583 lending sampling noise to the data.
584
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586 **Figure 3 (continued).**

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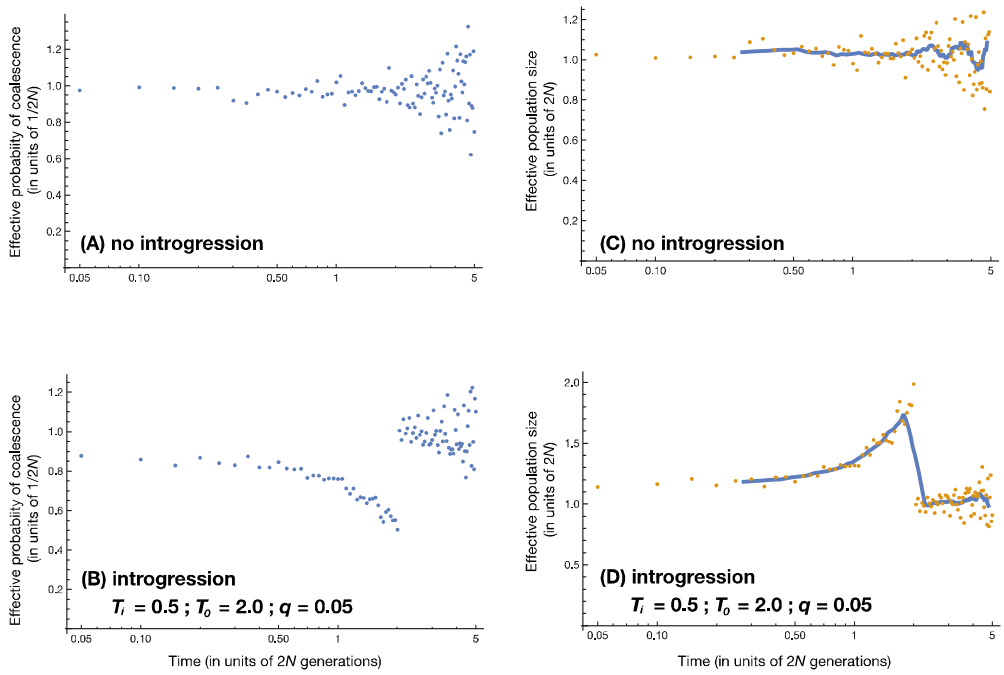

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590 **Figure 4. Adding mutations to the genealogies turns a sharp transition into a wave.** (A)
591 and (B) are based on the same simulation run, also illustrated in Figure 3c and 3d. (A)
592 shows the effective population size for each interval as estimated from the fraction of
593 loci with TMRCA in that interval; (B) shows the effective population size for each interval
594 based upon the pairwise counts of mutations. In both (A) and (B), the blue line
595 represents a moving average of the surrounding data points. Mutation adds a random
596 component that tends to smooth sharp transitions in the dataset.
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599 **Figure 4 (continued).**

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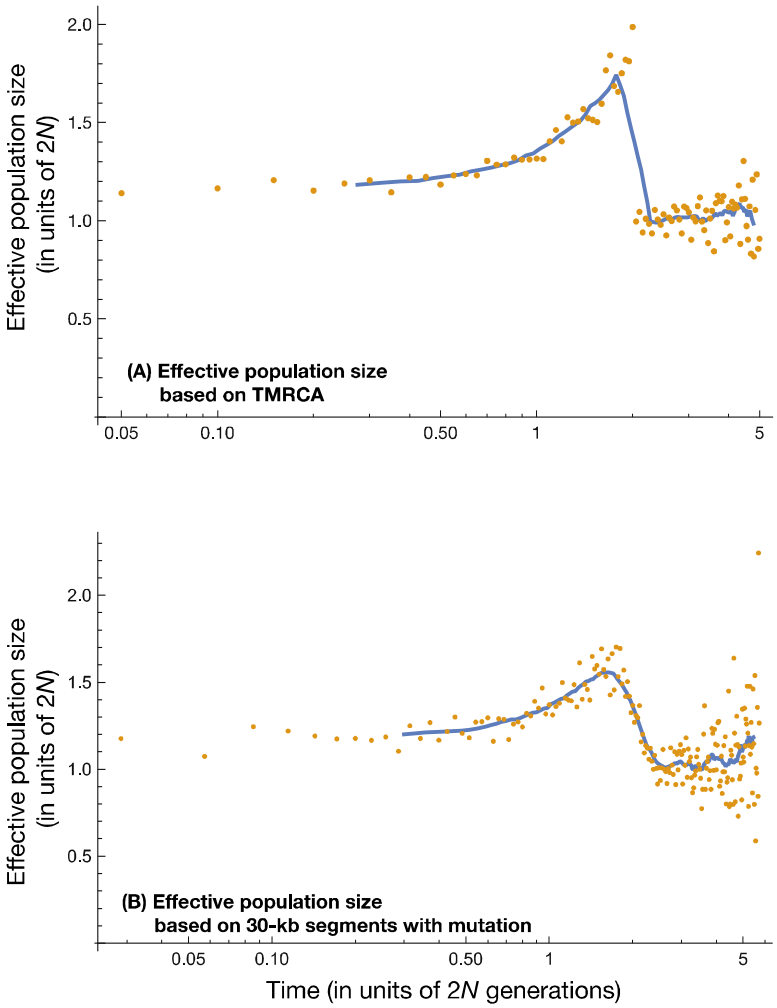

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603 **Figure 5. Sudden introgression versus long-term gene flow.** In (A), 0.2 individuals per
604 generation transfer between the two genetically divergent ancestral populations
605 between T_0 and T_i, and there is no sudden introgression at T_i. In (B), there is no gene
606 flow between the two populations, and 10% of population P_1 is the result of a sudden
607 introgression from P_2 at time T_i. Both these scenarios result in very similar outcomes,
608 with a wave of inferred effective population size at the same time and approximately
609 the same magnitude. The upturn of inferred effective size in the rightmost (oldest) time
610 intervals is not a reliable outcome of the simulations; this reflects the small sample of
611 genealogies with the oldest coalescence times.
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614 **Figure 5 (continued).**

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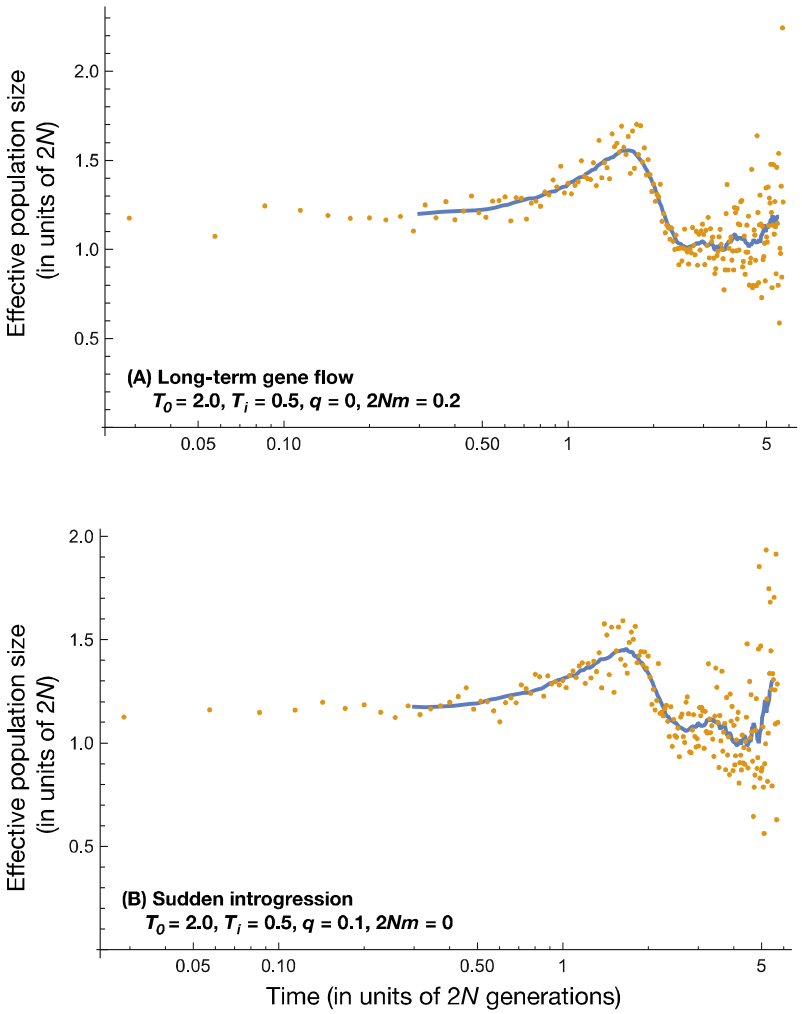

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621 **Figure 6. Amplitude of the wave is a function of the amount of introgression.** Each
622 panel represents an identical population model with introgression at 0.07 times 2*N*
623 generations and divergence of P_1 and P_2 at 1.2 times 2*N* generations. In (A) 2%
624 introgression; (B) 3% introgression; (C) 5% introgression; and (D) 8% introgression. The
625 amplitude of the wave increases with greater introgression. If *N* = 10000 individuals and
626 generations are 25 years long, then introgression in this model occurred approximately
627 35,000 years ago and the populations diverged approximately 600,000 years ago,
628 roughly corresponding to some values estimated for African ancestral introgression.
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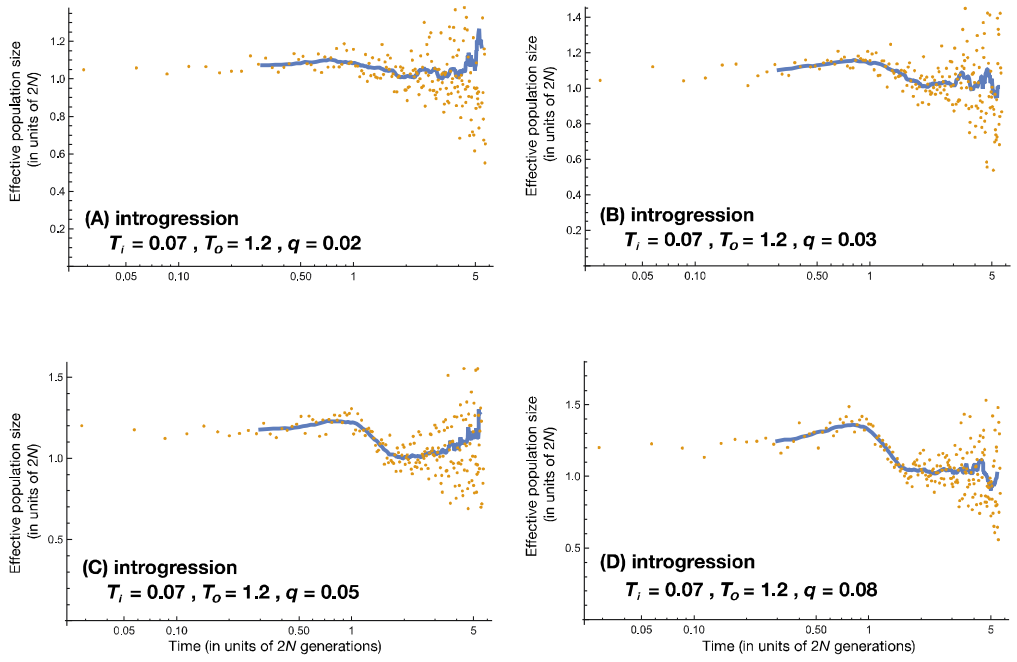

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633 **Figure 7. Leading edge of the wave reflects time of divergence of introgression source**
634 **population.** Each panel presents results with identical parameters except for the time of
635 origin of the genetically divergent source population for introgression (T_0), which is
636 indicated by the vertical red line. Migration ($2Nm$) in all panels is 0.1 individual per
637 generation; the fraction of introgression (q) is 10%. Older time of origin also
638 corresponds to greater wave amplitude, because the slight reduction in coalescence
639 probability is cumulative over time in its effect.
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642 **Figure 7 (continued).**

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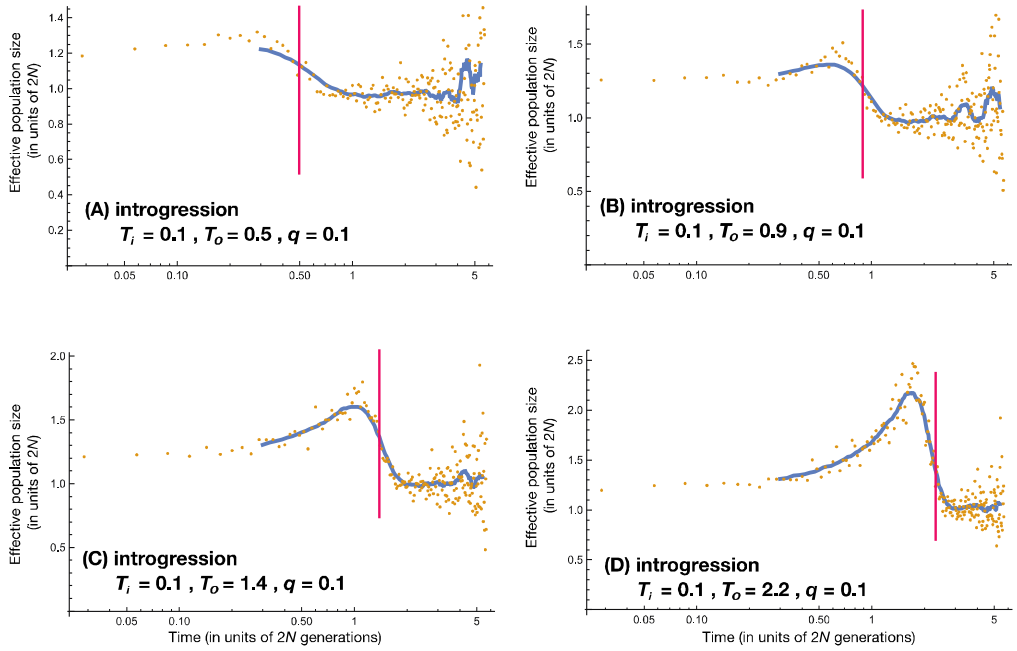

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