1 **Coalescent models at small effective population sizes and population declines**
2 **are positively misleading**

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Abstract

Population genetics employs two major models for conceptualizing genetic relationships among individuals – outcome-driven (coalescent) and process-driven (forward). These models are complementary, but the basic Kingman coalescent and its extensions make fundamental assumptions to allow analytical approximations: a constant effective population size much larger than the sample size. These make the probability of multiple coalescent events per generation negligible. Although these assumptions are often violated in species of conservation concern, conservation genetics often uses coalescent models of effective population sizes and trajectories in endangered species. Despite this, the effect of very small effective population sizes, and their interaction with bottlenecks and sample sizes, on such analyses of genetic diversity remains unexplored. Here, I use simulations to analyze the influence of small effective population size, population decline, and their relationship with sample size, on coalescent-based estimates of genetic diversity. Compared to forward process-based estimates, coalescent models significantly overestimate genetic diversity in oversampled populations with very small effective sizes. When sampled soon after a decline, coalescent models overestimate genetic diversity in small populations regardless of sample size. Such overestimates artificially inflate estimates of both bottleneck and population split times. For conservation applications with small effective population sizes, forward simulations that do not make population size assumptions are computationally tractable and should be considered instead of coalescent-based models. These findings underscore the importance of the theoretical basis of analytical techniques as applied to conservation questions.

41 Introduction

42 Inferring how a population evolves or has evolved under circumstances of interest is a
 43 key goal of population genetics. To understand the dynamics of real-world populations,
 44 we often turn to analytically and computationally tractable coalescent models of Wright-
 45 Fisher population genetics, with the standard being the Kingman coalescent (1982a,
 46 1982b). These models allow the estimation and simulation of current and past
 47 population genetic parameters of interest, perhaps foremost among them, genetic
 48 diversity or $\theta = 4N_e\mu$ (Fu and Li 1993; Fu and Li 1999).

49 Coalescent theory in its standard form (Kingman 1982a, 1982b) both makes certain
 50 simplifying assumptions that allow its analytical elegance, and remains the typical model
 51 used to interpret genetic variation. These include a stable effective population size large
 52 enough to be effectively infinite, that is much larger than the sample size. This is
 53 because of the fundamental simplifying assumption that only two lineages coalesce per
 54 generation. However when the effective population size is very small ($N_e < 1000$),
 55 and/or the sample size approaches or exceeds the effective population size, the
 56 probability of more than two lineages coalescing in a single generation (multiple
 57 mergers) increases exponentially (figure 1) (Wakeley 2016).

Figure 1. Effective population size and multiple merger probability. The probability that more than two lineages coalesce per generation (multiple mergers) as a function of sample size (n) and effective population size from $N_e = 0$ to 1000.

In species of conservation concern, as well as widely-sampled species such as humans, one or more of these assumptions (large N_e , $N_e \gg n$, stable N_e) are often unmet. For example, in a sample of 138 studies of species with genetically estimated effective population sizes, Palstra and Ruzzante (2008) found 120 species to have estimated effective population sizes of less than 1000, and 27 to have effective

population sizes of less than 100. Included among these are a population North Sea cod (*Gadus morhua*) off the Yorkshire coast of England, with an effective population size of 70 - 120 depending on sampling period (Hutchinson et al. 2003); Brazilian water hyacinth (*Eichhornia paniculata*) in northeastern Brazil, with an effective population size of < 5 - 70 depending on the population sampled (Husband and Barrett 1992); and the Siberian tiger (*Panthera tigris altaica*) with an effective population size of approximately 14 (Alasaad et al. 2011).

Given these small N_e , some species and populations may be oversampled relative to effective population size. For example, the hihi (*Notiomystis cincta*) of New Zealand was estimated to have an effective population size of 10 and a census size of 30 after reintroduction to Mokoia island (Castro et al. 2004). In this case, because of banding and monitoring, it was possible to sample the entire population, and thus have a sample size three times that of the effective population size. Estimates of human effective population sizes vary depending on population(s) and method of estimation, but are generally in the range of a few thousand to ~15,000 (Tenesa et al. 2007; Mezzavilla 2015; The 1000 Genomes Project Consortium 2015). This means that current human research involving samples of tens or even hundreds of thousands of individuals (eg. Mazet et al. 2016; Martin et al. 2017) is also likely to be oversampled relative to effective population size.

As in humans, small effective population sizes are often the result of population bottlenecks. Bottlenecks are characteristic of populations of conservation concern as

well as the founding of new populations. Immediately after a bottleneck, genetic diversity, as measured by descriptive statistics involving the number of alleles, such as Watterson's θ_w , drops precipitously (Maruyama and Fuerst 1985; Leberg 1992). This is because of the immediate loss of rare alleles, particularly singletons. In contrast, heterozygosity is reduced less immediately after a bottleneck, but continues to fall if the bottleneck is prolonged (Allendorf 1986).

The robustness of coalescent theory to violations of theoretical assumptions has been relatively well-studied with respect to sample size, migration, population size fluctuations, and variation in reproductive success, among others. For example, Wakeley and Takahashi (2003) and Bhaskar et al. (2014) found that large sample sizes, relative to the effective population size, increase the proportion of singleton polymorphisms relative to standard coalescent expectations. Bhaskar et al. (2014) were able to attribute this directly to multiple mergers in oversampled genealogies. In addition, variance in reproductive success can also result in multiple coalescent events per generation, and increases the complexity of the relationship between effective population size and the per-locus neutral mutation rate (Eldon and Wakeley 2005). Migration and recolonization in metapopulations also causes skew in the site frequency spectrum (Wakeley and Aliacar 2001). In these cases, deviations are attributable to multiple mergers.

Intuition might suggest that very small effective population sizes could have the same effects on parameter inference as do other violations resulting in multiple mergers, but

the exact nature of the consequences and how they interact with population bottlenecks remains unexplored. As previously suggested, application of multiple merger coalescent models could resolve erroneous estimates of population genetic parameters in populations that violate assumptions of the standard coalescent (Schweinsberg 2000; Mohle and Sagitov 2003; Eldon and Wakeley 2005; Birkner and Blath 2008; Tellier and Lemaire 2014; Koskela, Jenkins, and Spano 2015; Montano 2016). However, if and how this applies to populations with very small effective population sizes ($N_e < 1000$) and bottlenecks has so far been neglected.

Here, I use simulations to examine the effect of small effective population sizes and population declines, and their interaction with sample size, on coalescent estimates of genetic diversity. I compare coalescent estimates of genetic diversity to genetic diversity generated by forward simulations for a range of constant effective population sizes between $N_e = 10$ and 1000, and a range of sample sizes between $n = 2$ and 1000. This includes scenarios of oversampling: parameter spaces in which the sample size approaches and even exceeds the effective population size ($n > N_e$). Because small effective population sizes are often the result of more or less recent bottlenecks, I extend the simulations to include bottlenecks of severity ranging from 0% to 99% and sampling times (without recovery) between $T = 1$ and 1000 generations post-bottleneck. These comparisons show that coalescent models tend to incorrectly estimate genetic diversity when effective population sizes are very small and when sample size exceeds effective population size. These effects are especially pronounced after a recent bottleneck.

130 Materials and Methods

131 To ascertain the reliability of coalescent-based estimates of genetic diversity at low
 132 effective population sizes ($N_e < 1000$) and sample sizes (n) approaching N_e , both with
 133 and without bottleneck at varying times (T), I used forward, process-based simulations
 134 to ground-truth coalescent simulations (table 1). Unlike coalescent simulations, which
 135 probabilistically model the history of a sample backward in time, Wright-Fisher forward
 136 simulations follow the entire population of individuals generation by generation from the
 137 beginning of the simulation until it ends and individuals are sampled (eg. Hernandez
 138 2008; Haller and Messer 2017, 2019).

139 Table 1. Explored parameter space of N_e and n , with approximate relationship between
 140 N_e and n in the cells.

$n \mid N_e$	10	20	50	100	200	500	1000
2	$n < N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$
5	$n < N_e$	$n < N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$
10	$n = N_e$	$n < N_e$	$n < N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$
20	$n > N_e$	$n = N_e$	$n < N_e$	$n < N_e$	$n \ll N_e$	$n \ll N_e$	$n \ll N_e$
50	$n > N_e$	$n > N_e$	$n = N_e$	$n < N_e$	$n < N_e$	$n \ll N_e$	$n \ll N_e$
100	$n \gg N_e$	$n > N_e$	$n > N_e$	$n = N_e$	$n < N_e$	$n < N_e$	$n \ll N_e$
200	$n \gg N_e$	$n \gg N_e$	$n > N_e$	$n > N_e$	$n = N_e$	$n < N_e$	$n < N_e$
500	$n \gg N_e$	$n \gg N_e$	$n \gg N_e$	$n > N_e$	$n > N_e$	$n = N_e$	$n < N_e$
1000	$n \gg N_e$	$n \gg N_e$	$n \gg N_e$	$n \gg N_e$	$n > N_e$	$n > N_e$	$n = N_e$

Simulations

Forward simulations were performed using SFS_CODE (Hernandez 2008) and SLiM v2 (Haller and Messer 2017), and coalescent simulations were performed with Hudson's ms (Hudson 2002). I performed 10,000 simulations of each parameter combination $\{N_e, n, T\}$ with SFS_CODE and Hudson's ms. SLiM v2 was used to verify the SFS_CODE results by performing 10,000 simulations of each parameter combination $\{N_e, n\}$ to mutation-drift equilibrium. Effective population size N_e could take the values $\{10, 20, 50, 100, 200, 500, 1000\}$, and sample size n the values $\{2, 5, 10, 20, 50, 100, 200, 500, 1000\}$, chosen to reflect plausible effective population sizes of populations of conservation concern. For the forward simulations, when sample size exceeded effective population size, individuals were resampled until the sample size was reached. The non-bottleneck simulations were run with constant $N_e = \{10, 20, 50, 100, 200, 500, 1000\}$, and forward simulations were run with a burn-in of $10 * 2N_e$.

For the bottleneck simulations, pre-bottleneck $N_e = 1000$, since preliminary simulations showed no significant differences between forward and coalescent diversity estimates at $N_e = 1000$, and because forward simulations were computationally impractical at $N_e > 1000$. The bottleneck reduced the population to one of the above set of possible N_e values at $T = \{1, 10, 100, 1000\}$ generations, resulting in sampling times ranging from 1 to 1000 generations after the bottleneck event. There was no post-bottleneck recovery of N_e . For both non-bottleneck and bottleneck scenarios, a 5,000-base-pair locus was simulated with mutation rate $= 4N_e * 10^{-6}$ and recombination rate $= 4N_e * 10^{-8}$ per bp. See table 1 for $\{N_e, n\}$ parameter space.

Since rare variants are lost first during a bottleneck, which reduces the number of segregating sites, Watterson's θ (θ_w) is an appropriate and sensitive summary statistic for comparing genetic diversity estimated by each type of simulation (Allendorf 1986). It is also commonly used in studies of genetic diversity both within and among populations. I compared θ_w estimated by each type of simulation at each parameter combination $\{N_e, n, T\}$.

Statistical comparisons

Each set of 10,000 simulations per parameter combination $\{N_e, n, T\}$ and simulation type (forward, coalescent) created a distribution of estimated θ_w values. At small N_e , the distributions of the number of segregating sites, thus θ_w , is zero-inflated, and parametric tests are inappropriate. To compare mean θ_w among coalescent and both forward simulators for each set of simulations with the same parameter combination (without a bottleneck), I used Kruskal-Wallis tests followed by a post-hoc Dunn's test for each significant case. For the bottleneck scenarios, I used Kolmogorov-Smirnov tests to compare the distributions, and Mann-Whitney U tests to determine if the coalescent and forward samples could have come from a distribution with the same mean θ_w , between pairs of forward-coalescent distributions created with the same parameter combination. All p-values were converted to false discovery rate (FDR) with a threshold of 0.001 to control for multiple comparisons.

Data Availability

Supplementary tables have been uploaded to figshare, and code and data for analyses have

184 been uploaded to <https://github.com/lauterbur/Ne>.

Results

Constant small effective population size

There were few differences between genetic diversity (as measured by Watterson's θ) calculated from both forward simulators, SFS_CODE and SLiM v2. The post-hoc Dunn's test showed false discovery rates (FDR) under the 0.001 threshold only occurred for 4 out of 63 comparisons (6%). Thus, only comparisons between SFS_CODE (forward) and Hudson's ms (coalescent) are shown and used for subsequent bottleneck analyses (Table S1).

For those scenarios in which significant differences between θ_w calculated from SFS_CODE and SLiM simulations were found, these differences were 16-30% the magnitude of differences between the coalescent estimate and either forward θ_w . All such scenarios had sample sizes approximately double the effective population size ($\{N_e = 100, n = 200\}, \{N_e = 200, n = 500\}, \{N_e = 500, n = 1000\}$). Hence, the discrepancy could be an effect of the resampling of individuals performed when sample size exceeds effective population size.

At constant effective population size, statistically significant differences between θ_w estimated by coalescent models and calculated from forward models were most pronounced when sample size was much different from effective population size (Kruskal Wallis FDR < 0.001 and Dunn's FDR < 0.001). When $N_e \geq n$, the coalescent overestimated genetic diversity, and when $N_e < n$, the coalescent underestimated

204 genetic diversity (figure 3).

205 Figure 2. Significant differences between θ_w values for SLiM and SFS_CODE. Grey
 206 indicates no significant difference, colors indicate significant differences with darker
 207 oranges associated with larger mean percent differences.

Figure 3. Significant differences between θ_w values for forward (SFS_CODE) and coalescent (ms) simulations. Grey indicates no significant difference, colors indicate significant differences with darker oranges associated with larger mean positive percent differences and darker blues associated with larger mean negative percent differences.

The relationship between sample size (n) and effective population size (N_e) influenced the result of forward to coalescent comparisons of genetic diversity. At small n/N_e ratios (≤ 0.1), coalescent simulations were more likely to underestimate θ_w by up to 13%, especially at small N_e , while at large n/N_e ratios (≥ 2.0) coalescent

216 simulations were more likely to overestimate θ_w by up to 60% (figure 4)

217 Figure 4. The effect of the relationship between sample size and effective population
218 size (n/N_e) on coalescent estimates of θ_w relative to forward calculations of θ_w . When
219 the percent difference is positive, the coalescent estimate is larger and thus
220 overestimating θ_w , and when the percent difference is negative, the coalescent estimate
221 is smaller and thus underestimating θ_w .

222 *Bottlenecks to small effective population size*

223 The time between sampling and a population bottleneck in small populations had a
 224 greater effect on the accuracy of coalescent estimates of θ_w than effective population
 225 size and its relationship with sample size in populations of constant size (Table S2).
 226 Immediately after a bottleneck ($T = \{1, 10\}$), coalescent estimates of θ_w overestimate
 227 genetic diversity at all effective population sizes except $N_e = 1000$, though not all
 228 comparisons at $N_e = 200$ and $N_e = 500$ are significant. At $N_e = 1000$, coalescent
 229 estimates underestimate genetic diversity (figure 5, figure 6). There was no effect of the
 230 relationship between sample size and effective population size at $T = 1$. At $T = 10$ there
 231 was an effect only at the smallest effective population sizes ($N_e = \{10, 20\}$, figure 7a, b).

232 As the time since the bottleneck increases, coalescent estimates of θ_w approach
 233 forward calculations of θ_w . Despite this, there are still statistically significant differences
 234 between distributions and means of coalescent and forward θ_w s (Kruskal Wallis and
 235 Mann-Whitney U tests FDR for most scenarios < 0.001 , figure 5). For most scenarios at
 236 $T = 100$ and $T = 1000$, coalescent estimates overestimate θ_w (figure 5, figure 8). At
 237 these longer times since the bottleneck, the relationship between sample size and
 238 effective population size becomes important (figure 7c, d). Since all bottlenecks were
 239 from a starting $N_e = 1000$, these comparisons do not distinguish between percent
 240 population size reduction during the bottleneck and final effective population size.

241 Figure 5. Significant differences between θ_w values for forward (SFS_CODE) and
 242 coalescent (ms) simulations, by time since bottleneck (T). Grey indicates no significant
 243 difference, colors indicate significant differences with darker oranges associated with
 244 larger mean positive percent differences and darker blues associated with larger mean
 245 negative percent differences.

246 Figure 6. Distributions of θ_w (log transformed for visibility) estimated from coalescent
 247 simulations (grey) compared to θ_w calculated from forward simulations (black), across

247 sample size (x axis) and effective population size (vertical facets) for $T = 1$ (left) and $T =$
248 10 (right).

250 Figure 7. The effect of the relationship between sample size and effective population
 251 size (n/N_e) on coalescent estimates of θ_w relative to forward calculations of θ_w at
 252 different sampling times after a bottleneck ($T = \{1, 10, 100, 1000\}$). When the percent
 253 difference is positive, the coalescent estimate is larger and thus overestimating θ_w , and
 254 when the percent difference is negative, the coalescent estimate is smaller and thus
 255 underestimating θ_w . Note the scales of the y-axes of each panel are different for
 256 readability.

257 Figure 8. Distributions of θ_w (log transformed for visibility) estimated from coalescent

258 simulations (grey) compared to θ_w calculated from forward simulations (black), across
 259 sample size (x axis) and effective population size (vertical facets) for $T = 100$ (left) and
 260 $T = 1000$ (right). Note the scales of the y-axes of each panel are different for readability.

Discussion

To determine if and how standard coalescent models influence estimates of genetic diversity in populations with small effective population sizes, this analysis compares genetic diversity estimates based on coalescent models to genetic diversity calculated in forward simulation ground-truths at a range of effective population sizes, sample sizes, and sampling times since a bottleneck. Coalescent models give unreliable estimates of genetic diversity, as measured by Watterson's θ , regardless of the relationship between sample size and effective population size. This occurs particularly when the population is oversampled with respect to effective population size (sample size exceeds effective population size), and when sampled soon after a bottleneck.

The profound differences between coalescent estimates of θ_w and forward calculations of θ_w soon after a bottleneck show that applying standard coalescent models to bottlenecked populations can give misleading results. Overestimates would have the effect of fitting null coalescent models with incorrectly long times to the most recent common ancestor to estimates of θ_w from real data, thus artificially extending estimates of both bottleneck times and population split times into the past. Underestimates of θ_w that occur after prolonged small effective population sizes would artificially shorten estimates of bottleneck times or population split times.

Bottlenecks are very common, both in species of conservation concern and others, including humans (Hey and Harris 1999). There have been suggestions that standard coalescent models would be inappropriate for bottlenecked populations because a

population bottleneck does not merely shorten branches (thus necessitating the rescaling of coalescent time), it increases the likelihood of multiple mergers (Wakeley and Aliacar 2001; Wakeley and Takahashi 2003). However, previous analyses have been restricted to metapopulations, which include migration and extinction/recolonization dynamics (Wakeley and Aliacar 2001), and the results herein show that coalescent models are inappropriate even for the simplest of bottlenecked populations.

The result that coalescent models overestimate θ_w when $n > N_e$ is corroborated by previous observations that when $n > N_e$ the proportion of singleton polymorphisms increases relative to standard coalescent expectations (Wakeley and Takahashi 2003; Bhaskar, Clark, and Song 2014). Wakeley and Takahashi attribute this excess of singletons to mutations in the generation immediately previous to sampling, at a rate $(\theta * n/N_e)/2$. These mutations account for most of the singletons expected in the entire tree ($E[S] = \theta$) (Watterson 1975).

Multiple merger coalescent models, which are more general than the Kingman coalescent, include the Ξ -, Ψ -, and Λ -coalescent (Irwin et al. 2016). These have been developed since the early 2000s, and vary in how they handle multiple merger events as well as the number of descendants per lineage (Árnason and Halldórsdóttir 2015). Though most of the development has so far been theoretical, potential applications to real-world multiple merger scenarios are clear (Schweinsberg 2000; Mohle and Sagitov 2003; Eldon and Wakeley 2005; Birkner and Blath 2008; Tellier and Lemaire 2014;

Koskela, Jenkins, and Spano 2015; Montano 2016). At least one software package, Hybrid-Lambda, has been developed to allow the simulation of multiple merger trees, including conversion of the resulting branch lengths to coalescent estimates (Zhu et al. 2015).

When applied to the limpet *Cellana ornata*, which has high reproductive skew, Zhu et al. (2015) showed that multiple merger coalescent models using the Hybrid-Lambda package estimated a population split time of approximately 9,000 generations with a multiple merger model vs. approximately 48,000 generations with the standard Kingman coalescent. Similarly, Árnason and Halldórsdóttir (2015) applied Ξ - and Λ -coalescent null models (Eldon et al. 2015) to another species, Atlantic cod (*Gadus morhua*), whose high reproductive skew may have contributed to its small effective population size (Hutchinson et al. 2003). They found that previous population divergence time estimates may be too high because of inappropriate applications of the standard coalescent, and that multiple merger models may provide better null hypotheses for testing both split times and natural selection.

Despite the importance of exploring and applying multiple merger coalescent models for species with small effective population sizes and those subject to bottlenecks, a more expedient alternative when simulating null expectations is to use forward instead of coalescent simulations. Forward simulators require more computational resources than coalescent simulators, but effective population sizes of $N_e = 1000$ and even larger can be manageable, even for tens of thousands of iterations. There are many forward

simulation options to choose from, including SFS_CODE (Hernandez 2008), SLiM (Haller and Messer 2017, 2019), and fwdpp (Thornton 2014). SLiM v3 in particular supports non-Wright-Fisher models, which has the potential to extend our understanding of the dynamics of natural populations even further.

Loci from natural populations are typically sampled with ascertainment bias toward polymorphic sites. This would reduce or eliminate sites without polymorphisms, which account for most sites at small effective population sizes, and also accounts for some of the differences in mean θ_w between coalescent and forward simulations. The resulting distributions of both coalescent and forward θ_w would be biased upward, with reduced right skew. This has the potential to reduce apparent differences between coalescent and forward θ_w . In addition, θ_w is expected to be more sensitive to the immediate loss of rare variants (and thus segregating sites) caused by a bottleneck than some other commonly used summary statistics such as heterozygosity (Allendorf 1986). Like loci chosen with ascertainment bias, heterozygosity might also reduce the apparent differences between coalescent and forward θ_w .

Since natural selection has the effect of reducing effective population sizes at (and near) loci under selection, these results have implications for tests for selection using coalescent-based null models. A similar effect has recently been suggested of the influence of sample size on tests for selection under exponential population growth (Subramanian 2016). The effect of small effective population size and bottlenecks could be easily tested using similar methods as were applied in this study.

This study shows limits in the accuracy of coalescent models with respect to small effective population sizes and bottlenecked populations, including in combination with oversampling. Under these population conditions, standard coalescent models have the potential to produce misleading results and generate incorrect conclusions about population history and structure. In applications to empirical data, it is thus imperative to take into account how robust coalescent models may or may not be to violations of their assumptions.

Thus, standard coalescent models are inappropriate for developing null expectations of genetic diversity for many scenarios with small effective population sizes, especially soon after a bottleneck. This is particularly relevant to studies of species of conservation concern, in which small effective population sizes and bottlenecks are common (Allendorf 1986; Palstra and Ruzzante 2008), but may also be relevant to other species subject to oversampling or bottlenecks. This has implications for studies of species of conservation concern, because coalescent models that profoundly mischaracterize the timings of bottlenecks, population splits, and other demographic events could detrimentally influence management actions. In addition, these mischaracterizations are potentially pernicious in studies of disease population genetics, because repeated bottlenecks and intense selection are classic aspects of disease agent ecology.

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References

- Alasaad, Samer, Ramón C. Soriguer, Galina Chelomina, Yury Petrovich Sushitsky, and Joerns Fickel. 2011. "Siberian Tiger's Recent Population Bottleneck in the Russian Far East Revealed by Microsatellite Markers." *Mammalian Biology* 76 (6): 722–26. <https://doi.org/10.1016/j.mambio.2011.01.011>.
- Allendorf, Fred W. 1986. "Genetic Drift and the Loss of Alleles versus Heterozygosity." *Zoo Biology* 5 (2): 181–90. <https://doi.org/10.1002/zoo.1430050212>.
- Árnason, Einar, and Katrín Halldórsdóttir. 2015. "Nucleotide Variation and Balancing Selection at the *Ckma* Gene in Atlantic Cod: Analysis with Multiple Merger Coalescent Models." *PeerJ* 3 (February): e786. <https://doi.org/10.7717/peerj.786>.
- Bhaskar, Anand, Andrew G. Clark, and Yun S. Song. 2014. "Distortion of Genealogical Properties When the Sample Is Very Large." *Proceedings of the National Academy of Sciences* 111 (6): 2385–90. <https://doi.org/10.1073/pnas.1322709111>.
- Birkner, Matthias, and Jochen Blath. 2008. "Computing Likelihoods for Coalescents with Multiple Collisions in the Infinitely Many Sites Model." *Journal of Mathematical Biology* 57 (3): 435–65. <https://doi.org/10.1007/s00285-008-0170-6>.
- Castro, Isabel, Karen M. Mason, Doug P. Armstrong, and David M. Lambert. 2004. "Effect of Extra-Pair Paternity on Effective Population Size in a Reintroduced Population of the Endangered Hihi, and Potential for Behavioural Management." *Conservation Genetics* 5 (3): 381–93. <https://doi.org/10.1023/B:COGE.0000031146.51681.b0>.
- Eldon, Bjarki, Matthias Birkner, Jochen Blath, and Fabian Freund. 2015. "Can the Site-

392 Frequency Spectrum Distinguish Exponential Population Growth from Multiple-
393 Merger Coalescents?" *Genetics* 199: 841–56.

394 Eldon, Bjarki, and John Wakeley. 2005. "Coalescent Processes When the Distribution of
395 Offspring Number Among Individuals Is Highly Skewed." *Genetics* 172 (4): 2621–
396 33. <https://doi.org/10.1534/genetics.105.052175>.

397 Fu, Yun-Xin, and Wen-Hsiung Li. 1993. "Maximum Likelihood Estimation of Population
398 Parameters." *Genetics* 134: 1261–70.

399 Fu, Yun-Xun, and Wen-Hsiung Li. 1999. "Coalescing into the 21st Century: An
400 Overview and Prospects of Coalescent Theory." *Theoretical Population Biology*
401 56 (1): 1–10. <https://doi.org/10.1006/tpbi.1999.1421>.

402 Haller, Benjamin C., and Philipp W. Messer. 2017. "SLiM 2: Flexible, Interactive
403 Forward Genetic Simulations." *Molecular Biology and Evolution* 34 (1): 230–40.
404 <https://doi.org/10.1093/molbev/msw211>.

405 Haller, Benjamin C, and Philipp W Messer. 2019. "SLiM 3: Forward Genetic Simulations
406 Beyond the Wright–Fisher Model." Edited by Ryan Hernandez. *Molecular Biology*
407 *and Evolution* 36 (3): 632–37. <https://doi.org/10.1093/molbev/msy228>.

408 Hernandez, R. D. 2008. "A Flexible Forward Simulator for Populations Subject to
409 Selection and Demography." *Bioinformatics* 24 (23): 2786–87.
410 <https://doi.org/10.1093/bioinformatics/btn522>.

411 Hey, J., and E. Harris. 1999. "Population Bottlenecks and Patterns of Human
412 Polymorphism." *Molecular Biology and Evolution* 16 (10): 1423–26.
413 <https://doi.org/10.1093/oxfordjournals.molbev.a026054>.

414 Hudson, R. R. 2002. "Generating Samples under a Wright-Fisher Neutral Model of

- Genetic Variation." *Bioinformatics* 18 (2): 337–38.
<https://doi.org/10.1093/bioinformatics/18.2.337>.
- Husband, Brian C., and Spencer C. H. Barrett. 1992. "Effective Population Size and Genetic Drift in Tristylous *Eichhornia Paniculata* (Pontederiaceae)." *Evolution* 46 (6): 1875–90. <https://doi.org/10.1111/j.1558-5646.1992.tb01175.x>.
- Hutchinson, William F., Cock van Oosterhout, Stuart I. Rogers, and Gary R. Carvalho. 2003. "Temporal Analysis of Archived Samples Indicates Marked Genetic Changes in Declining North Sea Cod (*Gadus Morhua*)." *Proceedings of the Royal Society of London. Series B: Biological Sciences* 270 (1529): 2125–32. <https://doi.org/10.1098/rspb.2003.2493>.
- Irwin, K K, S Laurent, S Matuszewski, S Vuilleumier, L Ormond, H Shim, C Bank, and J D Jensen. 2016. "On the Importance of Skewed Offspring Distributions and Background Selection in Virus Population Genetics." *Heredity* 117 (6): 393–99. <https://doi.org/10.1038/hdy.2016.58>.
- Kingman, J. F. C. 1982a. "On the Genealogy of Large Populations." *Journal of Applied Probability* 19: 27. <https://doi.org/10.2307/3213548>.
- . 1982b. "The Coalescent." *Stochastic Processes and Their Applications* 13: 235–48. [https://doi.org/10.1016/0304-4149\(82\)90011-4](https://doi.org/10.1016/0304-4149(82)90011-4).
- Koskela, Jere, Paul Jenkins, and Dario Spano. 2015. "Computational Inference beyond Kingman's Coalescent." *Journal of Applied Probability* 52 (2): 519–37.
- Leberg, Paul L. 1992. "Effects of Population Bottlenecks on Genetic Diversity as Measured by Allozyme Electrophoresis." *Evolution* 46 (2): 477–94. <https://doi.org/10.1111/j.1558-5646.1992.tb02053.x>.

438 Martin, Alicia R., Christopher R. Gignoux, Raymond K. Walters, Genevieve L. Wojcik,
439 Benjamin M. Neale, Simon Gravel, Mark J. Daly, Carlos D. Bustamante, and
440 Eimear E. Kenny. 2017. "Human Demographic History Impacts Genetic Risk
441 Prediction across Diverse Populations." *The American Journal of Human*
442 *Genetics* 100 (4): 635–49. <https://doi.org/10.1016/j.ajhg.2017.03.004>.

443 Maruyama, Takeo, and Paul A. Fuerst. 1985. "Population Bottlenecks and
444 Nonequilibrium Models in Population Genetics. II. Number of Alleles in a Small
445 Population That Was Formed by a Recent Bottleneck." *Genetics* 111: 675–89.

446 Mazet, O, W Rodríguez, S Grusea, S Boitard, and L Chikhi. 2016. "On the Importance
447 of Being Structured: Instantaneous Coalescence Rates and Human Evolution—
448 Lessons for Ancestral Population Size Inference?" *Heredity* 116 (4): 362–71.
449 <https://doi.org/10.1038/hdy.2015.104>.

450 Mezzavilla, Massimo. 2015. "Neon: An R Package to Estimate Human Effective
451 Population Size and Divergence Time from Patterns of Linkage Disequilibrium
452 between SNPS." *Journal of Computer Science & Systems Biology* 8 (1).
453 <https://doi.org/10.4172/jcsb.1000168>.

454 Mohle, Martin, and Serik Sagitov. 2003. "Coalescent Patterns in Diploid Exchangeable
455 Population Models." *Journal of Mathematical Biology* 47 (4): 337–52.
456 <https://doi.org/10.1007/s00285-003-0218-6>.

457 Montano, Valeria. 2016. "Coalescent Inferences in Conservation Genetics: Should the
458 Exception Become the Rule?" *Biology Letters* 12 (6): 20160211.
459 <https://doi.org/10.1098/rsbl.2016.0211>.

460 Palstra, Friso P., and Daniel E. Ruzzante. 2008. "Genetic Estimates of Contemporary

Effective Population Size: What Can They Tell Us about the Importance of Genetic Stochasticity for Wild Population Persistence?" *Molecular Ecology* 17 (15): 3428–47. <https://doi.org/10.1111/j.1365-294X.2008.03842.x>.

Schweinsberg, Jason. 2000. "Coalescents with Simultaneous Multiple Collisions." *Electronic Journal of Probability* 5 (0). <https://doi.org/10.1214/EJP.v5-68>.

Subramanian, Sankar. 2016. "The Effects of Sample Size on Population Genomic Analyses – Implications for the Tests of Neutrality." *BMC Genomics* 17 (1). <https://doi.org/10.1186/s12864-016-2441-8>.

Tellier, Aurélien, and Christophe Lemaire. 2014. "Coalescence 2.0: A Multiple Branching of Recent Theoretical Developments and Their Applications." *Molecular Ecology* 23 (11): 2637–52. <https://doi.org/10.1111/mec.12755>.

Tenesa, A., P. Navarro, B. J. Hayes, D. L. Duffy, G. M. Clarke, M. E. Goddard, and P. M. Visscher. 2007. "Recent Human Effective Population Size Estimated from Linkage Disequilibrium." *Genome Research* 17 (4): 520–26. <https://doi.org/10.1101/gr.6023607>.

The 1000 Genomes Project Consortium, Richard A. Gibbs, Eric Boerwinkle, Harsha Doddapaneni, Yi Han, Viktoriya Korchina, Christie Kovar, et al. 2015. "A Global Reference for Human Genetic Variation." *Nature* 526 (7571): 68–74. <https://doi.org/10.1038/nature15393>.

Thornton, Kevin R. 2014. "A C++ Template Library for Efficient Forward-Time Population Genetic Simulation of Large Populations." *Genetics* 198 (1): 157–66. <https://doi.org/10.1534/genetics.114.165019>.

Wakeley, John. 2016. *Coalescent Theory: An Introduction*. Macmillan Learning.

- 484 Wakeley, John, and Nicolas Aliacar. 2001. "Gene Genealogies in a Metapopulation."
485 *Genetics* 159: 893–905.
- 486 Wakeley, John, and Tsoyoshi Takahashi. 2003. "Gene Genealogies When the Sample
487 Size Exceeds the Effective Size of the Population." *Molecular Biology and*
488 *Evolution* 20 (2): 208–13. <https://doi.org/10.1093/molbev/msg024>.
- 489 Watterson, G.A. 1975. "On the Number of Segregating Sites in Genetical Models
490 without Recombination." *Theoretical Population Biology* 7 (2): 256–76.
491 [https://doi.org/10.1016/0040-5809\(75\)90020-9](https://doi.org/10.1016/0040-5809(75)90020-9).
- 492 Zhu, Sha, James H. Degnan, Sharyn J. Goldstien, and Bjarki Eldon. 2015. "Hybrid-
493 Lambda: Simulation of Multiple Merger and Kingman Gene Genealogies in
494 Species Networks and Species Trees." *BMC Bioinformatics* 16 (1).
495 <https://doi.org/10.1186/s12859-015-0721-y>.