CANN ONE HEAR THE SHAPE OF A POPULATION HISTORY?

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Abstract

Reconstructing past population size from present day genetic data is a major goal of population genetics. Recent empirical studies infer population size history using coalescent-based models applied to a small number of individuals. While it is known that the allelic spectrum is not sufficient to infer the population size history, the distribution of coalescence times is. Here we provide tight bounds on the amount of information needed to recover the population size history at a certain level of accuracy assuming data given either by exact coalescence times, or given blocks of non-recombinant DNA sequences whose loci have approximately equal times to coalescence. Importantly, we prove lower bounds showing that it is impossible to accurately deduce population histories given limited data.

1 INTRODUCTION

The recent availability of whole-genome data has spurred interest in reconstructing both recent and ancient human population size history. Accurate inference of the history of the population size has widespread applications, e.g., due to it having confounding effects in association studies. Recent work uses a coalescent hidden Markov model to infer population size history from a diploid whole-genome sequence [10, 17]. A different approach is to use the spectrum of shared haplotype lengths, such as identity-by-descent [13] and identity-by-state [7] tract lengths. Yet another, earlier approach tries to infer population histories from allele frequencies. While it is known that allele frequencies are not sufficient statistics for the population size history in general [12], such data is often used to infer population history, see, e.g., [5, 1].

The distribution of coalescence times is sufficient to infer the population size history of a mixing population. Here we study how much information is needed to recover population history from coalescence data. In particular, we present a simple inference algorithm and analyze the number of samples needed for the algorithm to recover the history within a certain level of accuracy. Furthermore, we provide almost matching information-theoretic lower bounds showing that no procedure can accurately recover the population history given less data.

1.1 Model

We consider Kingman’s coalescent with a single panmictic population with varying population size and we study inverse problems (see, e.g., [20] for background on the coalescent). Let $N(t)$ be the
population size at time $t$ “generations” in the past, and let the rate of coalescence of two arbitrary individuals/lineages be $1/N(t)$ at time $t$. We call $N = \{N(t)\}_{t \geq 0}$ the shape of the population size history, or simply the population shape. The population shape $N = \{N(t)\}_{t \geq 0}$ determines a distribution $\mathbb{P}_N$ over coalescent trees; in particular, $\mathbb{P}_N$ determines the distribution of coalescent trees of any finite number of individuals, at any number of loci. The main question we study is: given information about $\mathbb{P}_N$, can we recover $N$?

A first step is to ensure that the distribution over coalescent trees uniquely determines the shape of a population history, i.e., that $N \neq N'$ implies that $\mathbb{P}_N \neq \mathbb{P}_{N'}$. This is indeed true: if we know $\mathbb{P}_N$, then we also know the rate of coalescence of two arbitrary individuals at any time $t$, which is just $1/N(t)$. Thus with an infinite amount of data, we can reconstruct the population shape.

Our main interest is to estimate the population shape given a finite amount of data. We assume that we have coalescence time data from a diploid genome sequence. More precisely, we assume that there are $L$ independent blocks along the genome, and for each block we know the coalescence time of loci in that block. Thus the data $t_L = \{t_1, \ldots, t_L\}$ are assumed to be i.i.d. with distribution

$$\mathbb{P}(t_1 < T) = 1 - \exp \left( - \int_0^T \frac{1}{N(t)} \, dt \right).$$

Later on we also address the situation when the coalescence times need to be estimated from genetic data.

### 1.2 Our results

Consider the following simple estimation procedure (analyzed in detail in Section 2) that, given the data $t_L$, returns a piecewise constant estimate $\hat{N} = \{\hat{N}(t)\}_{t \geq 0}$ for the population shape. The procedure involves a single parameter, $\varepsilon$, which controls the length of the time intervals where our estimate is constant, and which then also affects the accuracy of our estimate in each time interval. Assume that there are $N_0$ individuals initially, at time 0.

1. Partition time backwards in time into intervals of length $\varepsilon N_0$, i.e., let $I_1 = [0, \varepsilon N_0]$, $I_2 = [\varepsilon N_0, 2\varepsilon N_0], \ldots, I_K = [(K - 1)\varepsilon N_0, K\varepsilon N_0]$. ($K$ is the minimum integer such that the interval $[0, K\varepsilon N_0]$ covers the data and we do not provide estimates past time $K\varepsilon N_0$.)

2. For $k = 1, \ldots, K$, denote the fraction of data points lying in the time interval $I_k$ by

$$\hat{X}_k := \frac{1}{L} \# \{i : t_i \in I_k\},$$

and furthermore let $\hat{S}_0 = 0$ and $\hat{S}_k = \sum_{i=1}^{k} \hat{X}_i$, the fraction of data points lying in the time interval $[0, k\varepsilon N_0]$.

3. Our estimate $\hat{N}_k$ in the time interval $I_k$ is

$$\hat{N}_k := \frac{\varepsilon N_0}{-\log \left( 1 - \frac{\hat{X}_k}{1 - \hat{S}_{k-1}} \right)},$$

provided that $\hat{X}_k > 0$, i.e., we have at least one data point in the time interval $I_k$. If $\hat{X}_k = 0$, then we do not give an estimate.
Remark 1.1. The estimate (1.1) is motivated by the fact that
\[ \frac{ \mathbb{P}(t_1 \in I_k) }{ \mathbb{P}(t_1 \notin [0, (k-1)\varepsilon N_0]) } = 1 - \exp \left( - \int_{(k-1)\varepsilon N_0}^{k\varepsilon N_0} \frac{1}{N(t)} \, dt \right). \]

Remark 1.2. In Step 1 above, we partition time into intervals of equal length. This is done solely to make the subsequent analysis and discussion as simple as possible. Depending on the specific application, it might be of interest to consider other choices of partitions, for instance, choosing intervals whose lengths grow exponentially backwards in time. Our estimation procedure (and also the subsequent analysis) works in an analogous way: \( \hat{X}_k \) and \( \hat{S}_k \) can be defined in the same way in Step 2, and the only change in the estimate (1.1) is to replace \( \varepsilon N_0 \) in the numerator of the fraction with the length of the appropriate interval, \( |I_k| \).

In order to state the properties of this procedure, define for \( k \geq 1 \) the “effective constant population size in the time interval \( I_k \)” by
\[ \tilde{N}_k := \frac{\varepsilon N_0}{\int_{(k-1)\varepsilon N_0}^{k\varepsilon N_0} \frac{1}{N(t)} \, dt}; \]
the \( \tilde{N}_k \) give a natural piecewise constant approximation of the population shape \( N(t) \) that is directly comparable to the piecewise estimate \( \hat{N} \). Let
\[ E_k := \sup_{t \in I_k} \left| \log N(t) - \log \tilde{N}_k \right| \]
be the absolute error of our estimate \( \hat{N} \) on a logarithmic scale for each time interval. When estimating the error \( E_k \), there are two types of errors to consider. One is the inherent error coming from the fact that we are approximating the shape with a piecewise constant function; the other error comes from the finite sample size \( L \). By the triangle inequality we can bound the error \( E_k \) by the sum of these two errors:
\[ E_k \leq E_{k,1} + E_{k,2}, \]
where
\[ E_{k,1} := \sup_{t \in I_k} \left| \log N(t) - \log \tilde{N}_k \right| \]
is the error coming from approximating the shape in the time interval \( I_k \) with a constant, and
\[ E_{k,2} := \left| \log \tilde{N}_k - \log \hat{N}_k \right| \]
is the error coming from the finite sample size. Ignoring the error \( E_{k,1} \) for now, we can use concentration inequalities to derive the following finite sample estimate for the accuracy of our estimator:

**Proposition 1.3.** Given that \( \ell \) samples “survived” the first \( k-1 \) intervals, the probability that \( \log \hat{N}_k \), is in the interval
\[ \bigg[ \log (\varepsilon N_0) - \log \left( - \log \left( \left( 1 - \frac{L}{\ell} \hat{X}_k - c \right) \lor 0 \right) \right), \log (\varepsilon N_0) - \log \left( - \log \left( \left( 1 - \frac{L}{\ell} \hat{X}_k + c \right) \land 1 \right) \right) \bigg] \]
is at least
\[ 1 - 2 \exp \left( -2c^2 \ell \right) \]
for all \( c \geq 0 \).
Note that the interval in the proposition contains the estimate \( \hat{N}_k \). To complement this result, in Section 3 we provide matching lower bounds on the probability of inferring the history correctly given a certain amount of information. For example, we show that it is not even possible to distinguish between two hypotheses for a fixed population size at some interval of time back in history unless the interval is sufficiently long and the number of pairs that have not coalesced up to that time is sufficiently large.

**Proposition 1.4.** Consider the following hypothesis testing problem: \( H_1 \) states that the population size during the interval \([T_1, T_2]\) is constant \( N \), while \( H_2 \) states that the population size during the interval \([T_1, T_2]\) is the constant \((1 + \eta)N\), where \( \eta > 0 \) is fixed. Let \( \ell \) be the number of coalescence pairs that have not coalesced by time \( T_1 \). Assuming that the true history is given by either \( H_1 \) or \( H_2 \), each with prior probability \(1/2\), the probability of distinguishing between \( H_1 \) and \( H_2 \) is bounded by \((1 + \Delta)/2\), where \( \Delta \) satisfies:

\[
\Delta^2 \leq \frac{\ell \eta^2}{2} \min \left\{ \frac{(T_2 - T_1)}{N}, 1 \right\}.
\]

To understand in what sense Propositions 1.3 and 1.4 are matching bounds, note that for a fixed confidence

\[
1 - 2 \exp\left(-2c^2\ell\right) = \alpha,
\]

the constant \( c \) is of order \( \ell^{-1/2} \) as \( \ell \) becomes large, and thus the width of the interval in Proposition 1.3 is of order \( \log(1 + C\ell^{-1/2}) \) where \( C \) is some constant. Suppose we are in the setting of Proposition 1.4 with \( T_1 = (k-1)eN \) and \( T_2 = keN \). Then if \( \eta \gg \ell^{-1/2} \), then our method will distinguish between the histories with high probability; on the other hand, if \( \eta \ll \ell^{-1/2} \), Proposition 1.4 shows that no procedure will distinguish between the two histories with good probability.

While the results above concern the idealized setting of the availability of i.i.d. coalescence times, in Section 4 we extend these to the situation where coalescence times need to be estimated from blocks of DNA sequences. First, using concentration inequalities we show that if the block lengths are large enough, then we can estimate the coalescence times with good precision, and so we are again essentially in the i.i.d. setting. Second, we show that no procedure can distinguish between two hypotheses for a fixed population size unless the number of blocks is large and the block lengths are large as well.

Finally, to complement our theoretical results detailed above, we implement our estimation procedure and test it on simulated data in Section 5 where we find a good general performance. The remainder of the introduction is a discussion of results related to our methodology.

### 1.3 Additional related work

The fundamental question we address in Section 2 is given \( n \) i.i.d. copies of the first point of a Poisson point process on \([0, \infty)\) with intensity \( \varphi(t) \), what is a good estimate of \( \varphi(t)^{-1} \)? Poisson process intensity estimation has a large literature, see for example [2, 14, 24] and references therein, but the (natural) data assumed in this area is one realization of the point process, or the point process observed up to some fixed time, or i.i.d. copies of such data, which does not fit our framework.

For another perspective to this question, define the hazard rate for a positive random variable \( X \) with density \( f \) and distribution function \( F \) to be

\[
-\frac{d}{dt} \log(1 - F(t)) = \frac{f(t)}{1 - F(t)}.
\]

A simple calculation shows that the time of the first point of a Poisson process with intensity \( \varphi(t) \) has the same distribution as a positive random variable with hazard rate \( \varphi(t) \). Due largely to
their importance in applications in, e.g., insurance, medicine, and reliability theory [9, Section 1.1], hazard rate estimation is well studied; some seminal papers are [15, 16, 25] and see the recent [3] and references there. Without embellishments specific to lifetime data (such as censoring where some lifetimes are only known to be at least some value), the main technique to estimating (1.2) (which also applies to its inverse) is to adapt estimators of \( f \) and \( F \).

Indeed, our method is essentially an adaption of the histogram estimate of the density and distribution function to our setting. Other popular density estimation techniques such as those in the introduction of [18] can be adapted to our setting through the use of (1.2); for example see [23] for a survey of kernel smoothing methods for hazard function estimation. Our particular estimation procedure was chosen due to its simplicity and explicitness; in particular, we mention three points. The first is that we desire results like Proposition 1.3 with explicit non-asymptotic confidence intervals. Asymptotic confidence intervals can be obtained and used as estimates for smoothed density estimators, but with error depending on unknown quantities related to the underlying density which can lead to poor coverage accuracy [6]. Secondly, smoothed density estimators have improved performance only when the underlying density is itself smooth (expressed as differentiability and continuity conditions). A major purpose of estimating past population size is to discover drastic changes in population size such as bottlenecks [10, 13, 7, 17], when it is not clear such smoothness assumptions are appropriate. Finally, we want our method to be simple enough to be accessible to a wide variety of practitioners.

2 ESTIMATING THE POPULATION SHAPE

Recall that our goal is to estimate the population shape \( N = \{ N (t) \}_{t \geq 0} \) from the i.i.d. coalescence times \( tL = \{ t_1, \ldots, t_L \} \). In this section we analyze our piecewise constant population shape estimator \( \hat{N} = \{ \hat{N} (t) \}_{t \geq 0} \) introduced in Section 1.2.

Recall that we consider the absolute error of our estimate \( \hat{N} \) on a logarithmic scale for each time interval, i.e., for \( k \geq 1 \) we consider

\[
E_k := \sup_{t \in I_k} \left| \log N (t) - \log \hat{N}_k \right|.
\]

Recall also that \( E_k \leq E_{k,1} + E_{k,2} \), where \( E_{k,1} \) and \( E_{k,2} \) are also both defined in Section 1.2.

To bound the error \( E_{k,1} \) it is necessary to make an additional assumption on the population shape. We introduce an additional parameter, \( \delta \), which controls how much the population size can vary within a time interval, and we make the following assumption.

**Assumption 1.** We assume that in each time interval the population size can increase by a factor of at most \( e^{\delta \epsilon} \), and can decrease by a factor of at most \( e^{-\delta \epsilon} \).

Using this assumption, it is simple to bound the first type of error.

**Lemma 2.1.** Given Assumption 1, we have that \( E_{k,1} \leq 2 \delta \epsilon \).

**Proof.** Assumption 1 implies that

\[
\log N ((k - 1) \epsilon N_0) - \delta \epsilon \leq \log N (t) \leq \log N ((k - 1) \epsilon N_0) + \delta \epsilon
\]

for all \( t \in I_k \), and consequently also that

\[
\log N ((k - 1) \epsilon N_0) - \delta \epsilon \leq \log \hat{N}_k \leq \log N ((k - 1) \epsilon N_0) + \delta \epsilon.
\]

These inequalities then imply that \( E_{k,1} \leq 2 \delta \epsilon \). \( \square \)
To estimate the second type of error, $E_{k,2}$, it is not necessary to make any assumptions. We use concentration results for sums of i.i.d. random variables, and, in particular, we use the following simple corollary of the Chernoff bound.

**Theorem 2.2.** Let $Y_1, \ldots, Y_n$ be i.i.d. Bernoulli($p$) random variables, and let $Y = \sum_{i=1}^n Y_i$. Then for any $\lambda > 0$ we have

$$
\begin{align*}
\Pr(Y \leq np - \lambda) & \leq \exp\left(-\frac{2\lambda^2}{n}\right), \\
\Pr(Y \geq np + \lambda) & \leq \exp\left(-\frac{2\lambda^2}{n}\right).
\end{align*}
$$

The bounds in Theorem 2.2 imply the following concentration bound.

**Corollary 2.3.** For any $k \geq 1$ and $\lambda > 0$ we have

$$
\Pr\left(\left|\hat{X}_k - \mathbb{E}(\hat{X}_k)\right| \geq \lambda\right) \leq 2 \exp\left(-2\lambda^2L\right).
$$

In the following we present two bounds on the error $E_{k,2}$. We first present a bound for the first interval (i.e., when $k = 1$), which then also implies conditional bounds for general intervals, by conditioning on the number of data points that have not coalesced by a given time.

### 2.1 Bounds for the first interval

**Proposition 2.4.** For any $c \geq 0$, with probability at least $1 - 2 \exp\left(-2c^2L\right)$, the logarithm of the effective constant population size in $I_1$, $\log \tilde{N}_1$, is in the interval

$$
\left[\log (\varepsilon N_0) - \log \left(1 - \hat{X}_1 + c\right) \lor 0, \log (\varepsilon N_0) - \log \left(1 - \hat{X}_1 + c\right) \land 1\right].
$$

Note that the interval in (2.3) is an interval around our estimate $\log \tilde{N}_1$.

**Proof.** The inequality (2.2) for $k = 1$ can be rephrased as

$$
\Pr\left(\mathbb{E}\hat{X}_1 \in \left[\left(\hat{X}_1 - c\right) \lor 0, \left(\hat{X}_1 + c\right) \land 1\right]\right) \geq 1 - 2 \exp\left(-2c^2L\right).
$$

By algebraic manipulation, $\mathbb{E}\hat{X}_1 \in \left[\left(\hat{X}_1 - c\right) \lor 0, \left(\hat{X}_1 + c\right) \land 1\right]$ is equivalent to $\log \tilde{N}_1$ being contained in the interval in (2.3). \hfill \Box

This bound is useful because we can immediately determine a confidence interval for our estimate. To achieve a confidence level of $1 - \alpha$, we can choose $c = c(\alpha, L)$ to satisfy $2 \exp\left(-2c^2L\right) = \alpha$, i.e., choose

$$
c = \sqrt{\frac{\log (2/\alpha)}{2L}}.
$$

Then the interval in (2.3) with $c$ given by (2.4) has a confidence level of $1 - \alpha$.

### 2.2 Conditional bounds

Next, we present conditional bounds: given the number of samples that did not coalesce in the time interval $[0, (k - 1) \varepsilon N_0]$, what is the error we make when estimating the population size in the time interval $I_k$? The following result is the same as Proposition 1.3 just worded more precisely.
Proposition 2.5. For any $c \geq 0$, the probability conditioned on $L \left( 1 - \hat{S}_{k-1} \right) = \ell$ (i.e., that $\ell$ samples “survived” the first $k - 1$ intervals) that the logarithm of the effective constant population size, $\log \tilde{N}_k$, is in the interval
\[ \left[ \log (\varepsilon N_0) - \log \left( \left( 1 - \frac{L}{\ell} \hat{X}_k - c \right) \vee 0 \right), \log (\varepsilon N_0) - \log \left( \left( 1 - \frac{L}{\ell} \hat{X}_k + c \right) \wedge 1 \right) \right] \]
(2.5)
is at least $1 - 2 \exp \left( -2c^2 \ell \right)$.

Note that the interval in (2.5) is an interval around our estimate $\log \tilde{N}_k$, given $L \left( 1 - \hat{S}_{k-1} \right) = \ell$.

Proof. Let $\hat{Y}_k := \frac{L}{\ell} \hat{X}_k$. Given $L \left( 1 - \hat{S}_{k-1} \right) = \ell$, $\hat{Y}_k$ is the average of $\ell$ i.i.d. indicator variables. Therefore Chernoff’s bound gives that
\[ P \left( \left| \hat{Y}_k - \mathbb{E} \hat{Y}_k \right| \geq c \left| L \left( 1 - \hat{S}_{k-1} \right) = \ell \right) \leq 2 \exp \left( -2c^2 \ell \right). \]
In other words,
\[ P \left( \mathbb{E} \hat{Y}_k \in \left[ \left( \hat{Y}_k - c \right) \vee 0, \left( \hat{Y}_k + c \right) \wedge 1 \right] \left| L \left( 1 - \hat{S}_{k-1} \right) = \ell \right) \geq 1 - 2 \exp \left( -2c^2 \ell \right). \]

Just as in the proof of Proposition 2.4, by algebraic manipulation, given $L \left( 1 - \hat{S}_{k-1} \right) = \ell$, $\mathbb{E} \hat{Y}_k \in \left[ \left( \hat{Y}_k - c \right) \vee 0, \left( \hat{Y}_k + c \right) \wedge 1 \right]$ is equivalent to $\log \tilde{N}_k$ being contained in the interval in (2.5). \hfill \Box

Again, this bound is useful because we can immediately determine a confidence interval for our estimate. To achieve a confidence level of $1 - \alpha$, we can choose $c = c (\alpha, \ell)$ to satisfy $2 \exp \left( -2c^2 \ell \right) = \alpha$, i.e., choose
\[ c = \sqrt{\log \left( \frac{2}{\alpha} \right)} \frac{2}{\ell}. \]
(2.6)
Then the interval in (2.5) with $c$ given by (2.6) has a confidence level of $1 - \alpha$.

3 LOWER BOUNDS

In this section we provide lower bounds for the amount of data needed for a given accuracy of estimating the population shape. This is done by formulating hypothesis tests deciding between two population shapes, and proving upper bounds on the probability of correctly inferring the population shape.

3.1 Background on probability metrics

We first recall a few metrics between probability distributions (see [4] for a survey). Let $P$ and $Q$ be two probability measures that are absolutely continuous with respect to a third probability measure $\lambda$. Write $f_P = \frac{dP}{d\lambda}$ and $f_Q = \frac{dQ}{d\lambda}$ for the respective Radon-Nikodym derivatives. The square of the Hellinger distance between $P$ and $Q$ is then defined as
\[ d_H^2 (P, Q) := \frac{1}{2} \int \left( \sqrt{f_P} - \sqrt{f_Q} \right)^2 d\lambda. \]
The definition does not depend on the choice of \( \lambda \). A nice property of the Hellinger distance is that for product measures \( P = P_1 \times P_2, Q = Q_1 \times Q_2 \), we have that

\[
1 - d_H^2 (P, Q) = (1 - d_H^2 (P_1, Q_1))(1 - d_H^2 (P_2, Q_2)),
\]

which immediately implies that

\[
d_H^2 (P, Q) \leq d_H^2 (P_1, Q_1) + d_H^2 (P_2, Q_2).
\]

Another commonly used metric is the total variation distance:

\[
d_{TV} (P, Q) := \sup_{A \in \mathcal{F}} |P(A) - Q(A)|,
\]

or, equivalently:

\[
d_{TV} (P, Q) = \frac{1}{2} \int |f_P - f_Q| d\lambda.
\]

We use the following well-known fact:

**Lemma 3.1.** With the notation above we have

\[
d_{TV} \leq \sqrt{2} d_H.
\]

**Proof.** This follows from the identity \( f_P - f_Q = (\sqrt{f_P} - \sqrt{f_Q})(\sqrt{f_P} + \sqrt{f_Q}) \), the Cauchy-Schwarz inequality, and the inequality \( (\sqrt{f_P} + \sqrt{f_Q})^2 \leq 2 (f_P + f_Q) \).

### 3.2 Testing between two histories

Consider the following hypothesis testing problem. Let \( \eta > 0 \), and let \( N_1 (\cdot) \equiv N \) and \( N_2 (\cdot) \equiv (1 + \eta) N \) be two population size histories. Let \( \kappa \) be uniform in \( \{1, 2\} \), and, given \( \kappa \), let \( t^{\kappa, L} = \{t_1^\kappa, \ldots, t_L^\kappa\} \) be a collection of \( L \) i.i.d. coalescence times drawn from the distribution induced by the population size history \( N_\kappa \). The problem is to infer \( \kappa \) from \( t^{\kappa, L} \).

The probability of correctly inferring \( \kappa \) using the optimal reconstruction strategy is clearly at least \( \frac{1}{2} \); denote this probability by \( (1 + \Delta) / 2 \) (here \( \Delta = \Delta (L, \eta) \)). The reconstruction algorithm from Section 2 gives us lower bounds on \( \Delta \), while in this section we give upper bounds on \( \Delta \), thus providing lower bounds on the amount of data needed to achieve a given accuracy of estimating the population size history.

The reconstruction method which gives the largest probability of correctly inferring \( \kappa \) is maximum likelihood: let \( \hat{\kappa} = 1 \) if \( P (\kappa = 1 \mid t^{\kappa, L}) \geq P (\kappa = 2 \mid t^{\kappa, L}) \) and \( \hat{\kappa} = 2 \) otherwise. Then we have

\[
\Delta = P (\hat{\kappa} = \kappa) - P (\hat{\kappa} \neq \kappa) = d_{TV} (t^{1, L}, t^{2, L}).
\]

The following result gives an upper bound on the reconstruction probability.

**Lemma 3.2.** With the notation above we have

\[
\Delta^2 \leq 2L \left( 1 - \frac{2 + 2\eta}{(2 + \eta) \sqrt{1 + \eta}} \right) \leq \frac{L\eta^2}{2}. \tag{3.1}
\]

**Proof.** By the facts in Section 3.1 we have

\[
\Delta^2 = d_{TV}^2 (t^{1, L}, t^{2, L}) \leq 2d_H^2 (t^{1, L}, t^{2, L}) \leq 2 \sum_{i=1}^L d_H^2 (t_i^1, t_i^2) = 2Ld_H^2 (t_1^1, t_1^2).
\]
We know that $t_1^1$ and $t_2^2$ are both exponentially distributed, with parameters $\frac{1}{N}$ and $\frac{1}{(\eta + 1)N}$, respectively. Hence a calculation shows that
\[
d_H^2 (t_1^1, t_2^2) = 1 - \frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}},
\] (3.2)
which gives the first inequality in (3.1). When $\eta > 0$, we can upper bound the right hand side of (3.2) by $\eta^2/4$ to get the simpler bound $\Delta^2 \leq L\eta^2/2$. □

This implies that $L = \Omega (1/\eta^2)$ samples are needed in order to differentiate between the two histories $N_1$ and $N_2$.

3.3 Testing between two histories on a finite interval

A natural modification of the hypothesis testing problem just studied is to consider only a finite interval $[0, T]$ back in time. We want to distinguish between the following two different population size histories on the interval $[0, T]$:
\[N_1 (t) = N \quad \text{and} \quad N_2 (t) = (1 + \eta)N \quad \text{for} \quad t \in [0, T], \] where $\eta > 0$.

We again assume a uniform prior on $\kappa \in \{1, 2\}$, but now our data is different. For a nonnegative random variable $X$ define
\[X^T := \begin{cases} X & \text{if} \ X \leq T, \\ \infty & \text{otherwise}. \end{cases} \]

We assume that we can only observe coalescence times if they happen in the time interval $[0, T]$; if they occur after time $T$, then all we know about them is that they occur after time $T$. Thus our data, given $\kappa$, is a collection of $L$ i.i.d. truncated coalescent times $t^{\kappa, L, T} = \{t^{\kappa, L, T}_1, \ldots, t^{\kappa, L, T}_L\}$ drawn from the distribution induced by the population size history $N_\kappa$. The problem is to infer $\kappa$ from $t^{\kappa, L, T}$. The hypothesis test considered previously in Section 3.2 is the special case when $T = \infty$.

The probability of correctly inferring $\kappa$ using the optimal reconstruction strategy is clearly at least $1/2$; denote this probability by $(1 + \Delta)/2$, where now $\Delta = \Delta (L, \eta, T)$. Again, the reconstruction method which gives the largest probability of correctly inferring $\kappa$ is maximum likelihood: let $\hat{\kappa} = 1$ if $\mathbb{P} (\kappa = 1 \mid t^{\kappa, L, T}) \geq \mathbb{P} (\kappa = 2 \mid t^{\kappa, L, T})$ and $\hat{\kappa} = 2$ otherwise. So we have
\[
\Delta = \mathbb{P} (\hat{\kappa} = \kappa) - \mathbb{P} (\hat{\kappa} \neq \kappa) = d_{TV} (t^{1, L, T}, t^{2, L, T}).
\]
The following result gives an upper bound on the reconstruction probability.

Lemma 3.3. With the notation above we have
\[
\Delta^2 \leq 2L \left( 1 - \frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}} \right) \left( 1 - e^{-\left(\frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}}\right) \frac{T}{N}} \right) \leq \frac{L\eta^2}{2} \min \left\{ \frac{T}{N}, 1 \right\}. \tag{3.3}
\]

Proof. Just as in the proof of Lemma 3.2 we have
\[
\Delta^2 = d_{TV}^2 (t^{1, L, T}, t^{2, L, T}) \leq 2d_H^2 (t^{1, L, T}, t^{0, L, T}) \leq 2 \sum_{i=1}^L d_H^2 (t^{1, i, T}_i, t^{2, i, T}_i) = 2Ld_H^2 (t^{1, 1, T}_1, t^{2, 1, T}_1).
\]

Now $t^{1, 1, T}_1$ and $t^{2, 1, T}_1$ are truncated exponential random variables, with parameters $\frac{1}{N}$ and $\frac{1}{(\eta + 1)N}$, respectively. A calculation then shows that
\[
d_H^2 (t^{1, 1, T}_1, t^{2, 1, T}_1) = \left( 1 - \frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}} \right) \left( 1 - e^{-\left(\frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}}\right) \frac{T}{N}} \right), \tag{3.4}
\]
which gives the first inequality in (3.3). In Lemma 3.2 we have seen that the first factor on the right hand side of (3.4) is at most $\eta^2/4$ when $\eta > 0$, while we can bound the second factor using the inequality $1 - e^{-x} \leq \min \{ x, 1 \}$ and the fact that $\frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}} \leq 1$ for $\eta > 0$. □
In particular, when \( T = \varepsilon N \), then the upper bound is \( L \varepsilon \eta^2 / 2 \), which implies that \( L = \Omega \left( 1 / (\varepsilon \eta^2) \right) \) samples are needed in order to differentiate between the two histories \( N_1 \) and \( N_2 \) on the finite interval \([0, \varepsilon N]\).

### 3.4 Testing between two histories on a finite interval long ago back in time

A further modification of the hypothesis testing problem is to consider a finite interval \([T_1, T_2]\), potentially long ago back in time. Our goal is to distinguish between two different population size histories, \( N_1 \) and \( N_2 \) on the interval \([T_1, T_2]\). We assume that the two population histories agree until time \( T_1 \): \( N_1(t) = N_2(t) = N \) for all \( t \in [0, T_1] \); however, they differ on the interval in question: \( N_1(t) = N \) and \( N_2(t) = (1 + \eta) N \) for \( t \in [T_1, T_2] \). Our prior on \( \kappa \in \{1, 2\} \) is still uniform, but our data is different. For a nonnegative random variable \( X \) define

\[
X^{[T_1, T_2]} := \begin{cases} 
0 & \text{if } X < T_1, \\
X & \text{if } T_1 \leq X \leq T_2, \\
\infty & \text{otherwise.}
\end{cases}
\]

Our data, given \( \kappa \), is now \( t^{\kappa, L, [T_1, T_2]} = \{ t^{\kappa, [T_1, T_2]}_1, \ldots, t^{\kappa, [T_1, T_2]}_L \} \), a collection of \( L \) i.i.d. coalescent times truncated from above and below, drawn from the distribution induced by the population size history \( N_{\kappa} \). Again, the problem is to infer \( \kappa \) from \( t^{\kappa, L, [T_1, T_2]} \). The hypothesis test considered previously in Section 3.3 is the special case when \( T_1 = 0 \).

The probability of correctly inferring \( \kappa \) using the optimal reconstruction strategy is clearly at least \( 1/2 \); denote this probability by \( (1 + \Delta) / 2 \), where now \( \Delta = \Delta(L, \eta, [T_1, T_2]) \). Again, the reconstruction method which gives the largest probability of correctly inferring \( \kappa \) is maximum likelihood: let \( \hat{\kappa} = 1 \) if \( \mathbb{P}(\kappa = 1 \mid t^{\kappa, L, [T_1, T_2]}) \geq \mathbb{P}(\kappa = 2 \mid t^{\kappa, L, [T_1, T_2]}) \) and \( \hat{\kappa} = 2 \) otherwise. So we have

\[
\Delta = \mathbb{P}(\hat{\kappa} = \kappa) - \mathbb{P}(\hat{\kappa} \neq \kappa) = d_{TV} \left( t^{1, L, [T_1, T_2]}, t^{2, L, [T_1, T_2]} \right).
\]

The following result gives an upper bound on the reconstruction probability.

**Lemma 3.4.** *With the notation above we have*

\[
\Delta^2 \leq 2L \left( \frac{1}{2} e^{-\frac{T_1}{N}} \left( 1 + e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} \right) - \frac{4 + 4\eta}{(2 + \eta) \sqrt{1 + \eta}} e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} \right) - \frac{2 + 2\eta}{(2 + \eta) \sqrt{1 + \eta}} e^{-\left( \frac{2+\eta}{2+2\eta} \right) \frac{T_1}{N}}
\]

\[
\leq Le^{-\frac{T_1}{N}} \left( 1 + e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} - \frac{4 + 4\eta}{(2 + \eta) \sqrt{1 + \eta}} e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} \right).
\]

**Proof.** Just as in Lemmas 3.2 and 3.3 we have that

\[
\Delta^2 \leq 2L d_H^2 \left( t^{1, L, [T_1, T_2]}_1, t^{2, L, [T_1, T_2]}_1 \right).
\]

A calculation shows that

\[
dl H \left( t^{1, L, [T_1, T_2]}_1, t^{2, L, [T_1, T_2]}_1 \right)
= \frac{1}{2} e^{-\frac{T_1}{N}} \left( 1 + e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} - \frac{4 + 4\eta}{(2 + \eta) \sqrt{1 + \eta}} e^{\frac{\eta}{2+2\eta}} \frac{T_1}{N} \right) - \frac{2 + 2\eta}{(2 + \eta) \sqrt{1 + \eta}} e^{-\left( \frac{2+\eta}{2+2\eta} \right) \frac{T_1}{N}}
\]

from which [3.5] follows. \(\square\)
Suppose that $T_1 = k\varepsilon N$ for some $k$ such that $k\varepsilon$ is large and $\eta > 0$ is such that $\eta k\varepsilon$ is large (e.g., $\eta$ is constant). Then the upper bound in (3.6) is approximately $L e^{-(1-\eta)k\varepsilon}$, which implies that $L = \Omega \left(e^{(1-\eta)k\varepsilon}\right)$ samples are needed in order to differentiate between the two histories $N_1$ and $N_2$ on the interval $[k\varepsilon N, T_2]$. If the parameters are such that $k\varepsilon$ is large but $\eta k\varepsilon$ is small, then the upper bound in (3.6) is approximately $L = \Omega \left(\Omega \left(\eta k\varepsilon\right)^2 e^{k\varepsilon}\right)$ samples are needed in order to differentiate between the two histories.

3.5 Conditioning on the number of samples surviving

Finally, we can consider the same hypothesis testing problem as in Section 3.4, but now we condition on the number of samples that “survive” until time $T_1$, i.e., we condition on $\# \left\{ i : t^\varepsilon_i [T_1, T_2] \right\} = \ell$. The probability of correctly inferring $\kappa$ using the optimal reconstruction strategy is clearly at least $1/2$; denote this probability by $(1 + \Delta)/2$, where now $\Delta = \Delta (\ell, \eta, |T_1, T_2|)$.

This conditioning puts us back into the setting of Section 3.3, and therefore we have the following result giving an upper bound on the reconstruction probability.

**Lemma 3.5.** With the notation above we have

$$\Delta^2 \leq 2\ell \left(1 - \frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}}\right) \left(1 - e^{-\left(\frac{2 + 2\eta}{(2 + \eta)\sqrt{1 + \eta}}\right)\frac{T_2 - T_1}{N}}\right) \leq \frac{\ell \eta^2}{2} \min \left\{ \frac{T_2 - T_1}{N}, 1 \right\}. \quad (3.7)$$

4 ESTIMATING COALESCENCE TIMES

The estimates of Section 2 rely on having i.i.d. coalescence times between two loci which in practice will have to be estimated from sequences of DNA. In general these estimates come from the number of mutations that have occurred along the branches of the two loci until their MRCA. The mutations occur as an independent point process on top of the coalescent tree and in particular these numbers are independent with the same Poisson distribution having mean proportional to the branch length (the constant of proportionality is the mutation rate $\mu$ which we will assume to be known); see for example [11, 8, 19, 21, 22]. The methods of [11, 21] depend on the population shape and so are not useful for us here; the approach we describe below is similar in flavor to that of [22].

We imagine our data as two blocks of DNA having $m$ nucleotides such that the coalescence time $t$ between each pair of nucleotides is the same (we will discuss later about obtaining such data), and that for each pair of nucleotides, the mutations occur along the two branches to coalescence independently according to a Poisson process with rate $\mu$, and that the mutations occur in such a way so that we can write the probability $\pi(t)$ that two nucleotides at the same site will agree as

$$\pi(t) = p + (1 - p)e^{-2\mu t}. \quad (4.1)$$

For example, if the transitions between the nucleotides $A, C, G, T$ are uniform and Markovian between mutations (the Jukes-Cantor model), then $p = 1/4$, while in the so-called infinite sites model all mutations are unique and thus $p = 0$.

Under this model of data, we have similar results as detailed in Sections 2 and 3. For one, we have an estimation procedure that estimates a coalescence time given data from two blocks of length $m$, and we also have confidence intervals that show that if $m$ is large enough, the error of our estimate is small. On the other hand, we have an information-theoretic lower bound on the size of $m$ required for a given accuracy, no matter how the coalescence time is estimated from the data.
First, let us provide an estimation procedure for the coalescence time. If $\hat{k}$ denotes the number of homozygous sites between the two sequences of length $m$, then our estimate for $t$ is

$$\hat{t} = -\frac{1}{2\mu} \log \left( \frac{k/m - p}{1 - p} \right)$$

if $k/m > p$, and if $k/m \leq p$ then we give no estimate. We have the following confidence bounds for $\hat{t}$.

**Proposition 4.1.** For any $c \geq 0$, with probability at least $1 - 2 \exp(-2c^2m)$, the coalescence time $t$ is in the interval

$$\left[ -\frac{1}{2\mu} \log \left( \frac{\hat{k}/m - p + c}{1 - p} \right), -\frac{1}{2\mu} \log \left( \frac{\hat{k}/m - p - c}{1 - p} \right) \right].$$

(4.2)

Note that the interval in (4.2) is an interval around our estimate $\hat{t}$.

**Proof.** We apply Theorem 2.2 to obtain

$$P \left( p + (1 - p)e^{-2\mu t} \in \left[ \left( \frac{\hat{k}/m - c}{1 - p} \right) \lor 0, \left( \frac{\hat{k}/m + c}{1 - p} \right) \land 1 \right] \right) \geq 1 - 2 \exp(-2c^2m).$$

By algebraic manipulation, $p + (1 - p)e^{-2\mu t} \in \left[ \left( \frac{\hat{k}/m - c}{1 - p} \right) \lor 0, \left( \frac{\hat{k}/m + c}{1 - p} \right) \land 1 \right]$ is equivalent to $t$ being contained in the interval (4.2). \qed

On the other hand, no matter how one estimates the coalescence times from sequence data, we can study the following hypothesis testing problem. The setup is similar to those in Section 3: let $\eta > 0$ and define the two histories $N_1(\cdot) \equiv N$ and $N_2(\cdot) \equiv (1 + \eta)N$. Let $\kappa \in \{1, 2\}$ be uniform. The difference compared with Section 3 is that our data is not a collection of homozygous sites between the two sequences of length $m$, and instead a collection of Bernoulli random variables, $k^{\kappa,L,m} = \{k^{\kappa}_{i,j}, i = 1, \ldots, L, j = 1, \ldots, m\}$, where $k^{\kappa}_{i,j} = 1$ if the $j^{th}$ site in the $i^{th}$ block is homozygous, and $k^{\kappa}_{i,j} = 0$ if not. To generate $k^{\kappa,L,m}$ given $\kappa$, first generate $t^{\kappa} \equiv \{t^\kappa_1, \ldots, t^\kappa_L\}$ given $\kappa$, and then for each $i \in [L]$, $j \in [m]$ independently, let $k^{\kappa}_{i,j} = 1$ with probability $\pi(t^\kappa_i)$, and $k^{\kappa}_{i,j} = 0$ otherwise (recall the definition of $\pi(t)$ from (4.1)). The problem is thus to infer $\kappa$ from $k^{\kappa,L,m}$.

The probability of correctly inferring $\kappa$ using the optimal reconstruction strategy is clearly at least $1/2$; denote this probability by $(1 + \Delta)/2$, where now $\Delta = \Delta(N, L, m)$. Again, the reconstruction method which gives the largest probability of correctly inferring $\kappa$ is maximum likelihood, and it follows that $\Delta = d_{TV}(k^{1,L,m}, k^{2,L,m})$. The following result gives an upper bound on the reconstruction probability.

**Lemma 4.2.** With the notation above we have

$$\Delta^2 \leq cLmn^2 + O(\eta^3)$$

(4.3)

as $\eta \to 0$, where $c = c(p, N\mu)$ is given by

$$c(p, N\mu) = (1 - p) \int_0^1 (N\mu \log(u))^2 u^{2N\mu} \left( \frac{2 - u^{2N\mu}}{2 - 2u^{2N\mu}} - \frac{p + \frac{1}{2}(1 - p)u^{2N\mu}}{p + (1 - p)u^{2N\mu}} \right) du.\quad (4.4)$$

See Appendix A for a proof.
We examine the performance of our estimation procedure on simulated data for the following settings: (1) constant size population, (2) piecewise constant size population, and (3) a population experiencing recent exponential growth; the last setting being germane to recent human population history. In each case, we simulate $L$ independent coalescence times and apply our estimation procedure described in Section 2 with a given $\varepsilon$ to the data; the outcome is summarized in Figures 1–4 below. Each figure plots $\log (N(t)/N(0))$ versus $t/N(0)$, i.e., we scale time according to the coalescent timescale, and we plot the population size on a logarithmic scale.

The true history is the blue line, the estimates over each interval are the red lines, and the confidence intervals at the 95 percent level are given in pink. Recall that the logarithm of our estimate (1.1) is

$$\log \hat{N}_k = \log (\varepsilon N_0) - \log \left( - \log \left( 1 - \frac{\hat{X}_k}{1 - \hat{S}_{k-1}} \right) \right),$$

and our confidence interval for confidence level $1 - \alpha$ is given by (2.5):

$$\left[ \log (\varepsilon N_0) - \log \left( - \log \left( \left( 1 - \frac{\hat{X}_k}{1 - \hat{S}_{k-1}} - c \right) \lor 0 \right) \right), \log (\varepsilon N_0) - \log \left( - \log \left( \left( 1 - \frac{\hat{X}_k}{1 - \hat{S}_{k-1}} + c \right) \land 1 \right) \right) \right],$$

where

$$c = \frac{\log (2/\alpha)}{2L \left( 1 - \hat{S}_{k-1} \right)}.$$

In the case that $\hat{X}_k = 0$ we do not give an estimate but can sometimes still obtain a lower bound on the confidence interval. The intervals where the pink extends to the upper or lower margin of the graphing area represents a confidence bound that is infinite or zero, i.e., where the minimum or maximum are taken to be one or zero in the expressions for the confidence bounds above.

The error $E_{k,1}$ is not represented in the plots, but would add $\delta$ to each side of each confidence interval. Alternatively, we can view our statistic as an estimate of the average population size over the given interval.

The plots in Figure 4 also have black lines that are the 95 percent reconstruction intervals: in a given interval, populations outside of the black lines can be distinguished from the true blue line population with the data at hand at least 95 percent of the time. Thus if the red line is within the interval given by the black lines, then our estimate is in some sense the best that can be achieved.

These simulations allow us to make some general qualitative observations. The major determining factor of the performance of our procedure in an interval is the number of coalescence times that have survived to that interval. So having more data (i.e., larger $L$) leads to more accurate estimates, and the estimates lose accuracy moving back in time as the number of data points decrease. Moreover, there is a rare event effect when there are few coalescences in an interval—having no coalescences in an interval is not very informative—and this leads to the consistent underestimates in the deepest part of the histories. Possibly this effect would be lessened by lengthening the widths of the intervals as they go back in time. In general, the choice of $\varepsilon$ has a large effect on the estimates and the size of the confidence intervals; similar to bandwidth selection in density estimation, this is a thorny issue that does not have a tidy resolution in general. Another important feature to note is that in the presence of a so-called bottleneck, i.e., a time period where the population becomes small, there are many coalescences due to the increased rate. In turn this decreases the number of available data deeper in history. For example, compare the accuracy of the estimates at time $t/N(0) = 4$ in the constant population of Figure 3 to that of the piecewise constant population of
Figure 2 shows there is a bottleneck starting around time $t/N(0) = 1$. Our work provides understanding for the tolerance of our procedure as these crucial parameters ($L, \varepsilon$, and bottleneck sizes and locations) vary, which is important in determining the applicability of the procedure applied to genetic data.

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Figure 1: Estimating a constant population size.
Figure 2: Estimating a piecewise constant population size.
Figure 3: Estimating a population history with piecewise exponential change.
Figure 4: Constant and piecewise constant population histories with reconstruction intervals.
A PROOF OF LEMMA 4.2

We start with the following useful lemma.

Lemma A.1. If $X$, $Y$, and $T$ are random variables on the same probability space then

$$d_{TV}(X,Y) \leq \mathbb{E}[d_{TV}(\mathcal{L}(X|T), \mathcal{L}(Y|T))],$$

where $\mathcal{L}(X|T)$ denotes the law of $X$ conditioned on $T$. 

19
Proof. This follows from the following characterization of the total variation distance:

\[ d_{TV}(X,Y) = \frac{1}{2} \sup_{h: \|h\|_{\infty} \leq 1} |E[h(X)] - E[h(Y)]|. \]

Let \( t^L = \{(t^1_i, t^2_i)\}_{i=1}^L \) be i.i.d. bivariate vectors, with the marginal distributions of \( t^1_i \) and \( t^2_i \) being exponential, with parameters \( \frac{1}{N} \) and \( \frac{1}{(1+\eta)N} \), respectively, but with no restriction on the joint distribution of the bivariate vector. Let \( k^{1,L,m}_i \) and \( k^{2,L,m}_i \), respectively, be generated as described in Section 4 using \( t^{1,L}_i := \{(t^1_i)_{i=1}^L \) and \( t^{2,L}_i := \{t^2_i\}_{i=1}^L \), respectively. Then, using Lemma A.1, Jensen’s inequality, and the results of Section 3.1, we get that for any joint distribution of the vector \((t^1_1, t^2_1)\), we have

\[
\Delta^2 = d_{TV}^2(k^{1,L,m}_i, k^{2,L,m}_i) \leq (E[d_{TV}(\mathcal{L}(k^{1,L,m}_i | t^L), \mathcal{L}(k^{2,L,m}_i | t^L))]^2
\leq E[d_{TV}^2(\mathcal{L}(k^{1,L,m}_i | t^L), \mathcal{L}(k^{2,L,m}_i | t^L))] \leq 2E[d^2_H(\mathcal{L}(k^{1,L,m}_i | t^L), \mathcal{L}(k^{2,L,m}_i | t^L))]
\leq 2LmE[d^2_H(\text{Bernoulli}(\pi(t^1_i)), \text{Bernoulli}(\pi(t^2_i))))].
\]

Our goal now is to couple \( t^1_1 \) and \( t^2_1 \) so that the expectation

\[ E[d^2_H(\text{Bernoulli}(\pi(t^1_i)), \text{Bernoulli}(\pi(t^2_i))))] \]

is small. Let \( U \) be uniform in the interval \((0,1)\) and couple \( t^1_1 \) and \( t^2_1 \) by setting

\[ t^1_1 := -N \log(U), \quad t^2_1 := -(1+\eta) N \log(U). \]

With this coupling we have

\[
E[d^2_H(\text{Bernoulli}(\pi(t^1_i)), \text{Bernoulli}(\pi(t^2_i))))] = 1 - \int_0^1 \sqrt{(p+(1-p)u^{2N\mu}) \left(p+(1-p)u^{2N\mu(1+\eta)}\right)} du \\
- (1-p) \int_0^1 \sqrt{\left(1-u^{2N\mu}\right) \left(1-u^{2N\mu(1+\eta)}\right)} du.
\]

Taylor’s expansion in \( \eta \) around zero yields

\[
\sqrt{p+(1-p)u^{2N\mu(1+\eta)}} = \sqrt{p+(1-p)u^{2N\mu}} + \frac{(1-p)N\mu \log(u)u^{2N\mu}}{\sqrt{p+(1-p)u^{2N\mu}}} \eta
+ \frac{(1-p)(N\mu \log(u))^2u^{2N\mu}p + \frac{1}{2}(1-p)u^{2N\mu}}{p+(1-p)u^{2N\mu}} \eta^2 + O(\eta^3),
\]

\[
\sqrt{1-u^{2N\mu(1+\eta)}} = \sqrt{1-u^{2N\mu}} - \frac{N\mu \log(u)}{\sqrt{1-u^{2N\mu}}}u^{2N\mu} \eta
- \frac{(N\mu \log(u))^2u^{2N\mu}}{\sqrt{1-u^{2N\mu}}} \frac{2-u^{2N\mu}}{1-u^{2N\mu}} \eta^2 + O(\eta^3).
\]

Plugging these back in, the zeroth and first order terms cancel, leaving the second and higher order terms, which lead to the bound in Lemma 4.2.