# Supplementary Material: Dating Ancient Splits in Phylogenetic Trees, with Application to the Human-Neanderthal Split

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# 1 Theoretical Details

## 1.1 Proof of Lemma 1

Let $Y \sim \text{Pois}(\lambda)$ and $Z$ be the parity of $Y$. Then $Z \sim Ber(\frac{1}{2}(1-e^{-2\lambda}))$.

*Proof.*

$$P(Z_i = 1) = \sum_{n=0}^{\infty} P\left(Y_i = 2n+1\right) = \sum_{n=0}^{\infty} e^{-\lambda} \frac{\lambda^{2n+1}}{(2n+1)!} =$$
$$= e^{-\lambda}\frac{1}{2}\left(\sum_{n=0}^{\infty}\frac{\lambda^n}{n!} - \sum_{n=0}^{\infty}\frac{(-\lambda)^n}{n!}\right) = \frac{e^{-\lambda}}{2}\left(e^{\lambda} - e^{-\lambda}\right) = \frac{1}{2}\left(1 - e^{-2\lambda}\right).$$

□

## 1.2 Proof of Theorem 1

Denote the Fisher information matrix for the estimation problem above by $I \in \mathbb{R}^{(n+1,n+1)}$, where the first $n$ indexes correspond to $\{\lambda_i\}_{i=1}^{n}$ and the last index $(n+1)$ corresponds to $p$. For clarity denote $I_{p,p} \doteq I_{n+1,n+1}, I_{i,p} \doteq I_{i,n+1}, I_{p,i} \doteq I_{n+1,i}$. Then:

$$I_{i,j} = 0, \quad I_{i,i} = \frac{1}{\lambda_i} + \frac{4p^2}{e^{4\lambda_i p} - 1}, \quad I_{i,p} = I_{p,i} = \frac{4p\lambda_i}{e^{4\lambda_i p} - 1}, \quad I_{p,p} = 4\sum_{i=1}^{n}\frac{\lambda_i^2}{e^{4\lambda_i p} - 1}. \tag{9}$$

Consequently, an unbiased estimator $\hat{p}$ holds:

$$\mathbb{E}\left[(p-\hat{p})^2\right] \geq \left[4\sum_{i=1}^{n}\frac{\lambda_i^2}{e^{4\lambda_i p} - 1 + 4p^2\lambda_i}\right]^{-1}. \tag{10}$$

If $\forall i = 1..n : \lambda_i = \lambda$, we can further simplify the expression:

$$\mathbb{E}\left[(p-\hat{p})^2\right] \geq \frac{e^{4\lambda p} - 1 + 4p^2\lambda}{4n\lambda^2}. \tag{11}$$

*Proof.* We calculate the second derivative of the log-likelihood. Denote:

$$\beta_i = -2\lambda_i p + j\pi Z_i, \quad \sigma(t) = \frac{e^t}{1+e^t},$$

then the first derivatives are given by:

$$\begin{aligned}
\frac{\partial l}{\partial \lambda_i} &= -1 + \frac{X_i}{\lambda_i} + \frac{(-2p)\left(-1\right)^{Z_i}\exp\left(-2\lambda_i p\right)}{1+\left(-1\right)^{Z_i}\exp\left(-2\lambda_i p\right)} \\
&= -1 + \frac{X_i}{\lambda_i} - 2p\sigma\left(-2\lambda_i p + j\pi Z_i\right) \\
&= -1 + \frac{X_i}{\lambda_i} - 2p\sigma\left(\beta_i\right),
\end{aligned} \tag{12}$$

and

$$\frac{\partial l}{\partial p} = \sum_{i=1}^{n} \frac{(-2\lambda_i)\left(-1\right)^{Z_i}\exp\left(-2\lambda_i p\right)}{1+\left(-1\right)^{Z_i}\exp\left(-2\lambda_i p\right)} = -2\sum_{i=1}^{n}\lambda_i\sigma\left(\beta_i\right). \tag{13}$$

The second derivatives are now given by:

$$\begin{aligned}
\frac{\partial^2 l}{\partial \lambda_i \lambda_j} &= 0 \\
\frac{\partial^2 l}{\partial {\lambda_i}^2} &= -\frac{X_i}{\lambda_i^2} - 2p\left(-2p\right)\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right) = -\frac{X_i}{\lambda_i^2} + 4p^2\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right) \\
\frac{\partial^2 l}{\partial \lambda_i \partial p} &= -2p\left(-2\lambda_i\right)\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right) - 2\sigma\left(\beta_i\right) = 4p\lambda_i\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right) - 2\sigma\left(\beta_i\right) \\
\frac{\partial^2 l}{\partial p^2} &= \sum_{i=1}^{n} 4\lambda_i^2\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right)
\end{aligned}$$

The expectation of these are given by:

$$\mathbb{E}\left[\sigma\left(\beta_i\right)\right] = \frac{1}{2}\left(1+\exp\left(-2\lambda_i p\right)\right)\frac{\exp\left(-2\lambda_i p\right)}{1+\exp\left(-2\lambda_i p\right)} + \frac{1}{2}\left(1-\exp\left(-2\lambda_i p\right)\right)\frac{(-1)\cdot\exp\left(-2\lambda_i p\right)}{1-\exp\left(-2\lambda_i p\right)} = 0$$

$$\begin{aligned}
\mathbb{E}\left[\sigma^2\left(\beta_i\right)\right] &= \frac{1}{2}\left(1+\exp\left(-2\lambda_i p\right)\right)\frac{\exp\left(-4\lambda_i p\right)}{\left(1+\exp\left(-2\lambda_i p\right)\right)^2} + \frac{1}{2}\left(1-\exp\left(-2\lambda_i p\right)\right)\frac{\exp\left(-4\lambda_i p\right)}{\left(1-\exp\left(-2\lambda_i p\right)\right)^2} = \\
&= \frac{1}{2}\exp\left(-4\lambda_i p\right)\left[\frac{1}{1+\exp\left(-2\lambda_i p\right)} + \frac{1}{1-\exp\left(-2\lambda_i p\right)}\right] = \frac{1}{e^{4\lambda_i p}-1}
\end{aligned}$$

$$\mathbb{E}\left[\frac{\partial^2 l}{\left(\partial\lambda_i\right)^2}\right] = E\left[-\frac{X_i}{\lambda_i^2} + 4p^2\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right)\right] = -\frac{1}{\lambda_i} - \frac{4p^2}{e^{4\lambda_i p}-1} = -I_{i,i}$$

$$\mathbb{E}\left[\frac{\partial^2 l}{\partial\lambda_i\partial p}\right] = E\left[4p\lambda_i\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right) - 2\sigma\left(\beta_i\right)\right] = -\frac{4p\lambda_i}{e^{4\lambda_i p}-1} = -I_{i,p}$$

$$\mathbb{E}\left[\frac{\partial^2 l}{\left(\partial p\right)^2}\right] = E\left[\sum_{i=1}^{n} 4\lambda_i^2\sigma\left(\beta_i\right)\left(1-\sigma\left(\beta_i\right)\right)\right] = -\sum_{i=1}^{n}\frac{4\lambda_i^2}{e^{4\lambda_i p}-1} = -I_{p,p}.$$

By CRB, for an unbiased estimator:

$$\begin{aligned}
\mathbb{E}\left[(p-\hat{p})^2\right] \geq [I^{-1}]_{p,p} &= \frac{1}{I_{p,p} - I_{p,i}I_{i,i}^{-1}I_{i,p}} \\
&= \left[\sum_{i=1}^{n}\frac{4\lambda_i^2}{e^{4\lambda_i p}-1} - \sum_{i=1}^{n}\frac{\frac{16p^2\lambda_i^2}{\left[e^{4\lambda_i p}-1\right]^2}}{\frac{1}{\lambda_i} + \frac{4p^2}{e^{4\lambda_i p}-1}}\right]^{-1} \\
&= \left[\sum_{i=1}^{n} 4\lambda_i^2\frac{\left(e^{4\lambda_i p}-1\right)\left(\frac{1}{\lambda_i} + \frac{4p^2}{e^{4\lambda_i p}-1}\right) - 4p^2}{\left[e^{4\lambda_i p}-1\right]^2\left(\frac{1}{\lambda_i} + \frac{4p^2}{e^{4\lambda_i p}-1}\right)}\right]^{-1} \\
&= \left[4\sum_{i=1}^{n}\frac{\lambda_i^2}{e^{4\lambda_i p}-1+4p^2\lambda_i}\right]^{-1}
\end{aligned}$$

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## 1.3 Proof of Proposition 1

*Proof.* Following Equations 12, 13, we compare the first order derivatives to 0:

$$\frac{\partial l}{\partial \lambda_i} = -1 + \frac{X_i}{\lambda_i} - 2\hat{p}\frac{(-1)^{Z_i} e^{-2\lambda_i \hat{p}}}{\left(1 + (-1)^{Z_i} e^{-2\lambda_i \hat{p}}\right)} = 0 \Rightarrow X_i = \hat{\lambda}_i + 2\hat{p}\hat{\lambda}_i \frac{(-1)^{Z_i} e^{-2\hat{\lambda}_i \hat{p}}}{\left(1 + (-1)^{Z_i} e^{-2\hat{\lambda}_i \hat{p}}\right)}$$

$$\frac{\partial l}{\partial p} = -\sum_{i=1}^{n} 2\lambda_i \frac{(-1)^{Z_i} e^{-2\lambda_i \hat{p}}}{\left(1 + (-1)^{Z_i} e^{-2\lambda_i \hat{p}}\right)} = -\sum_{i=1}^{n} \frac{\lambda_i}{\hat{p}} \left[-1 + \frac{X_i}{\lambda_i}\right] = 0 \Rightarrow \sum_{i=1}^{n} \hat{\lambda}_i = \sum_{i=1}^{n} X_i.$$

Summing the first equation for every $i$ and substituting the second equation results in the last part in Equation 6. □

## 1.4 Proof of Proposition 2

If $Y_i | X_i \sim Bin(X_i, p)$, then:

1. $Y_i \sim \text{Pois}(\lambda_i \cdot p)$, which justifies this approach.

2. $Z_i | X_i \sim Ber\left(\frac{1}{2}\left(1 - (1-2p)^{X_i}\right)\right)$, so we can compute the likelihood of $p$ without considering $\lambda_i$.

3. The maximum likelihood estimate of $p$ given $Z_i$ holds:

$$\sum_{i=1}^{n} \frac{X_i}{1 + (-1)^{Z_i} (1-2p)^{-X_i}} = 0 \tag{14}$$

   and the maximum likelihood estimate of $p$ given $\sum_{i=1}^{n} Z_i$ holds:

$$\sum_{i=1}^{n} (1-2\hat{p})^{X_i} = n - 2\sum_{i=1}^{n} Z_i \tag{15}$$

*Proof.* Denote $q \equiv 1-p$. For item 1:

$$\begin{aligned}
\Pr(Y_i = k) &= \sum_{n=k}^{\infty} \Pr(X_i = n) \cdot \Pr(Bin(n,p) = k) \\
&= \sum_{n=k}^{\infty} \frac{\lambda_i^n \cdot e^{-\lambda_i}}{n!} \cdot \Pr(\binom{n}{k})p^k q^{n-k} \\
&= \frac{(\lambda_i \cdot p)^k \cdot e^{-\lambda_i p}}{k!} \sum_{n=k}^{\infty} \frac{\lambda_i^{n-k} \cdot e^{-\lambda_i q}}{(n-k)!} \cdot q^{n-k} \\
&= \frac{(\lambda_i \cdot p)^k \cdot e^{-\lambda_i p}}{k!} \sum_{n=0}^{\infty} \frac{\lambda_i^{n} \cdot e^{-\lambda_i q}}{n!} \cdot q^{n} = \frac{(\lambda_i \cdot p)^k \cdot e^{-\lambda_i p}}{k!}.
\end{aligned}$$

Now moving on to item 2:

$$\begin{aligned}
\Pr(Z_i = 1|X_i) = \Pr(Y_i \text{ is odd}|X_i), &\quad Y_i|X_i \sim Bin(n = X_i, p) \\
(q+p)^n = \Sigma_{k=0}^n \binom{n}{k} p^k q^{(n-k)} &= P(Y_i \text{ is even}) + P(Y_i \text{ is odd}) \\
(q-p)^n = \Sigma_{k=0}^n \binom{n}{k} (-p)^k q^{(n-k)} &= P(Y_i \text{ is even}) - P(Y_i \text{ is odd})
\end{aligned}$$

And summing up these two equations leads to:

$$P(Y_i \text{ is even}) = \frac{1}{2}\left((q+p)^n + (q-p)^n\right) = \frac{1}{2}\left(1 + (1-2p)^n\right).$$

Subsequently, the likelihood of $Z_i$ is given by:

$$\begin{aligned}
l(\vec{Z}; p) &= \prod_{i=1}^{n} \frac{1}{2}\left(1 + (-1)^{Z_i}(1-2p)^{X_i}\right) \\
L(\vec{Z}; p) &= \sum_{i=1}^{n} \log\left(1 + (-1)^{Z_i}(1-2p)^{X_i}\right) + Const
\end{aligned}$$

34 Taking the derivative to 0:

$$\frac{\partial L}{\partial p} = \sum_{i=1}^{n} \frac{-2(-1)^{Z_i} X_i (1-2p)^{X_i - 1}}{(1 + (-1)^{Z_i}(1-2p)^{X_i})} = \sum_{i=1}^{n} \frac{-2X_i}{((-1)^{Z_i}(1-2p)^{1-X_i} + 1 - 2p)} = 0, \tag{16}$$

35 and division by $\frac{-2}{1-2p}$ yields the solution.

Now, according to Le Cam's theorem[1] [1], $\sum_{i=1}^{n} Z_i \sim \text{Pois}\left(\lambda = \sum_{i=1}^{n} \frac{1}{2}\left(1-(1-2p)^{X_i}\right)\right)$, and the likelihood is therefore:

$$L\left(\sum_{i=1}^{n} Z_i = m|\vec{X};p\right) = \lambda^m \frac{e^{-\lambda}}{m!}.$$

Now we look at the log-likelihood and take the derivative with respect to $p$ to zero:

$$\begin{aligned}
l\left(\sum_{i=1}^{n} Z_i = m|\vec{X};p\right) &= m\log\lambda - \lambda + Const \\
&= m\log\left(\sum_{i=1}^{n}\frac{1}{2}\left(1-(1-2p)^{X_i}\right)\right) - \sum_{i=1}^{n}\frac{1}{2}\left(1-(1-2p)^{X_i}\right) + Const \\
\frac{\partial l}{\partial p} &= m\frac{\sum_{i=1}^{n} X_i(1-2p)^{X_i-1}}{\sum_{i=1}^{n}\frac{1}{2}\left(1-(1-2p)^{X_i}\right)} - \sum_{i=1}^{n} X_i(1-2p)^{X_i-1} \\
&= \left(\frac{m}{\sum_{i=1}^{n}\frac{1}{2}\left(1-(1-2p)^{X_i}\right)} - 1\right)\sum_{i=1}^{n} X_i(1-2p)^{X_i-1} = 0
\end{aligned}$$

Leading to the solution:

$$\sum_{i=1}^{n}(1-2\hat{p})^{X_i} = n - 2m = n - 2\sum_{i=1}^{n} Z_i$$

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[1] More precisely:
$\sum_{k=0}^{\infty} |P(\sum_{i=1}^{n} Z_i = k) - \frac{1}{k!}(\sum_{i=1}^{n}\frac{1}{2}(1-(1-2p)^{X_i}))^k e^{-\sum_{i=1}^{n}\frac{1}{2}(1-(1-2p)^{X_i}}| < 2\sum_{i=1}^{n}\left(\frac{1}{2}(1-(1-2p)^{X_i})\right)^2$ .

## 1.5 Proof of Proposition 3

Let $\lambda_i \sim \Gamma(\alpha,\beta)$, then the maximum a posteriori estimator of $p$ holds:

$$\frac{\partial l}{\partial p} = \sum_{i=1}^{n} \frac{X_i+\alpha}{(-1)^{Z_i}\left(1+\frac{2p}{\beta+1}\right)^{X_i+\alpha}+1} = 0 \tag{17}$$

Subsequently, estimated values for $\alpha, \beta$ can be substituted for a numerical estimator for $p$.

*Proof.* We first compute the probability for each observation:

$$\begin{aligned}
\Pr\left(X_i=k, Y_i\, is\, even\right) &= \int_0^\infty P\left(\lambda_i=\lambda\right)P\left(X_i=k|\lambda_i=\lambda\right)P\left(Y_i\, is\, even|\lambda_i=\lambda\right)d\lambda \\
&= \int_0^\infty \lambda^{\alpha-1}e^{-\lambda\beta}\frac{\beta^\alpha}{\Gamma\left(\alpha\right)}e^{-\lambda}\frac{\lambda^k}{k!}\frac{1}{2}\left(1+e^{-2\lambda p}\right)d\lambda \\
&= \frac{\beta^\alpha}{2k!\Gamma\left(\alpha\right)}\left[\int_0^\infty \lambda^{\alpha-1+k}e^{-\lambda(\beta+1)}d\lambda + \int_0^\infty \lambda^{\alpha-1+k}e^{-\lambda(\beta+1+2p)}d\lambda\right] \\
&= \frac{\beta^\alpha}{2k!\Gamma\left(\alpha\right)}\Big[\frac{\Gamma\left(\alpha+k\right)}{\left(\beta+1\right)^{\alpha+k}}\underbrace{\int_0^\infty \lambda^{\alpha-1+k}e^{-\lambda(\beta+1)}\frac{\left(\beta+1\right)^{\alpha+k}}{\Gamma\left(\alpha+k\right)}d\lambda}_{=1} + \\
&\qquad \frac{\Gamma\left(\alpha+k\right)}{\left(\beta+1+2p\right)^{\alpha+k}}\underbrace{\int_0^\infty \lambda^{\alpha-1+k}e^{-\lambda(\beta+1+2p)}\frac{\left(\beta+1+2p\right)^{\alpha+k}}{\Gamma\left(\alpha+k\right)}d\lambda}_{=1}\Big] \\
&= \frac{\beta^\alpha\Gamma\left(\alpha+k\right)}{2k!\Gamma\left(\alpha\right)}\left[\frac{1}{\left(\beta+1\right)^{\alpha+k}}+\frac{1}{\left(\beta+1+2p\right)^{\alpha+k}}\right] \\
&= \frac{\Gamma\left(\alpha+k\right)}{2k!\Gamma\left(\alpha\right)}\left[\left(\frac{\beta}{\beta+1}\right)^\alpha\left(\frac{1}{\beta+1}\right)^k+\left(\frac{\beta}{\beta+1+2p}\right)^\alpha\left(\frac{1}{\beta+1+2p}\right)^k\right]
\end{aligned}$$

Hence, the likelihood is given by:

$$\begin{aligned}
&L\left(\vec{X},\vec{Z};p,\alpha,\beta\right) = \\
&= \prod_{i=1}^{n}\frac{\Gamma\left(\alpha+k\right)}{2k!\Gamma\left(\alpha\right)}\left[\left(\frac{\beta}{\beta+1}\right)^\alpha\left(\frac{1}{\beta+1}\right)^{X_i}+(-1)^{Z_i}\left(\frac{\beta}{\beta+1+2p}\right)^\alpha\left(\frac{1}{\beta+1+2p}\right)^{X_i}\right]
\end{aligned}$$

and the log-likelihood:

$$l\left(\vec{X},\vec{Z};p,\alpha,\beta\right)=\sum_{i=1}^{n}\log\frac{\Gamma\left(\alpha+X_i\right)}{X_i!\Gamma\left(\alpha\right)}+\alpha log\beta-(X_i+\alpha)\log(\beta+1)+\log\left[1+(-1)^{Z_i}\left(\frac{\beta+1}{\beta+1+2p}\right)^{X_i+\alpha}\right]$$

Now comparing the derivative with respect to $p$ to zero:

$$\frac{\partial l}{\partial p}=\sum_{i=1}^{n}\frac{-\frac{2}{\beta+1}\left(-1\right)^{Z_i}\left(X_i+\alpha\right)\left(1+\frac{2p}{\beta+1}\right)^{-X_i-\alpha-1}}{1+\left(-1\right)^{Z_i}\left(1+\frac{2p}{\beta+1}\right)^{-X_i-\alpha}}=0$$

□

# 2 Simulation details

## 2.1 Phylogenetic tree simulations

The rate parameter for sites with no transitions along the tree is denoted as $\epsilon$, and we estimate it using the following simulation-based method. To generate $\vec{\lambda}$, we use the following equation:

$$\min D=\sup_x|F(\vec{X}_{\text{mtDNA}})-F(\vec{X})|\quad s.t.\quad \lambda_i=\begin{cases}X_{\text{mtDNA},i} & X_{\text{mtDNA},i}\neq 0\\ \epsilon & X_{\text{mtDNA},i}=0\end{cases}\tag{18}$$

The value of $\epsilon$ is chosen to minimize the Kolmogorov–Smirnov statistic. Figure 1 shows a simulation of $D(\epsilon)$, with the mean of 1,000 runs for each $\epsilon$ value. The minimum value of $D$ is obtained for $\epsilon=0.0913$ (marked in red).

To make the simulated data closer to the real data, we also model transversions. We estimate the transversion rate per site in the same manner as the transition rate, using the Kolmogorov–Smirnov statistic to account for sites with no transversions. This results in

**Figure 1: Kolmogorov–Smirnov statistic as a function of $\epsilon$.**

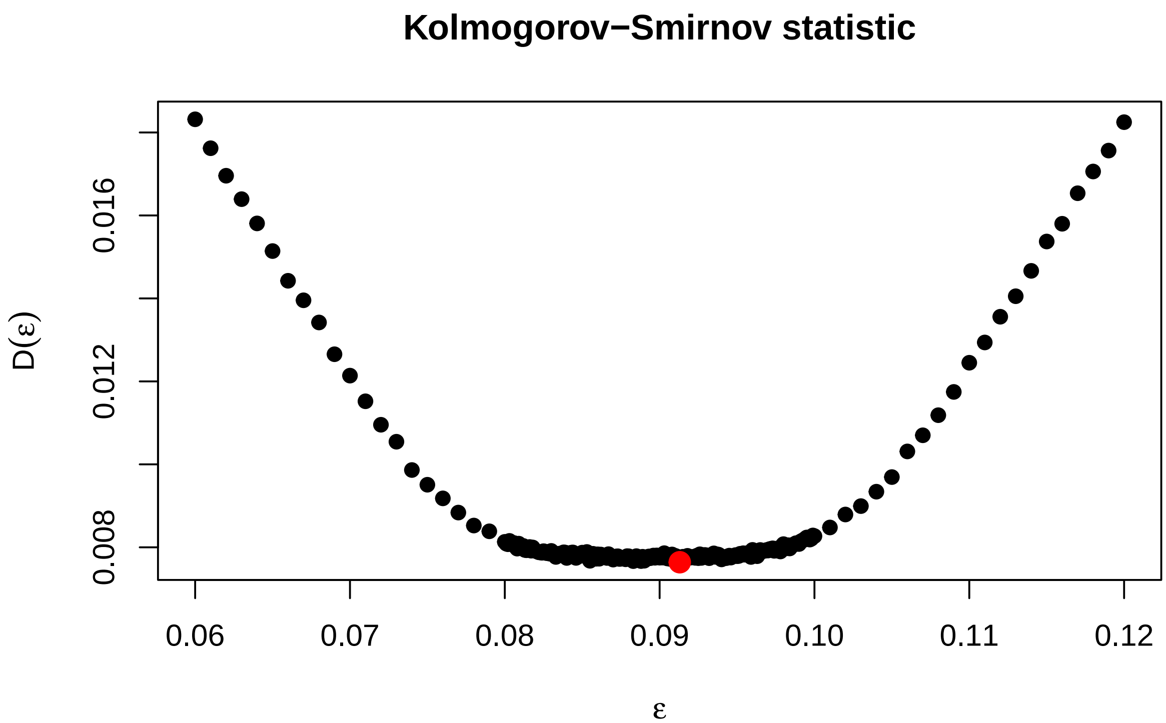


**Figure 3.** We performed 1,000 runs for each value of epsilon. The minimal $D(\epsilon)$ is marked red and equals $\epsilon = 0.0913$.

$\epsilon_{\text{transversion}} = 0.0149$. To determine the nucleotide at a given site, we sample whether an odd number of transversions have occurred. If so, a random nucleotide is sampled from the two available transversion options. The resulting sequence is then input into BEAST2, but our methods still use only the sites without observed transversions. Finally, the analysis is limited to the gene regions in the genome (11,341 sites).

## 2.2 BEAST2 run parameters

The sequences used in this work were aligned using mafft [2], and the 11.3 kb of protein-coding genes were extracted and used for the analysis. The analysis followed the approach described in [3], where the best fitting clock and tree model for the tree were identified using path sampling with the model selection package in BEAST2 [4, 5, 6]. Each model test was run with 40 path steps, a chain length of 25 million iterations, an alpha parameter of 0.3, a pre-burn-in of 75,000 iterations, and an 80% burn-in of the entire chain. The mutation rate was set to 1.57 x 10E-8 and a normal distribution (mean: mutation rate, sigma: 1.E-10) was used for a strict clock model [7]. The TN93 substitution model [8] was used for all models. The tree was calibrated with carbon dating data from ancient humans and Neanderthals, where available [9, 7, 10], and modern samples were set to a date of 0.

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