

Mitochondrial DNA replacement versus nuclear DNA persistence

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Abstract. In this paper we consider two populations whose generations are not overlapping and whose size is large. The number of males and females in both populations is constant. Any generation is replaced by a new one and any individual has two parents concerning nuclear DNA and a single one (the mother) concerning mtDNA. Moreover, at any generation some individuals migrate from the first population to the second.

In a finite random time T , the mtDNA of the second population is completely replaced by the mtDNA of the first. In the same time, the nuclear DNA is not completely replaced and a fraction F of the ancient nuclear DNA persists. We compute both T and F . Since this study shows that complete replacement of mtDNA in a population is compatible with the persistence of a large fraction of nuclear DNA, it may have some relevance for the 'out of Africa'/multiregional debate in palaeoanthropology.

Keywords: models for evolution (theory), population dynamics (theory)

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1. Introduction

Mitochondrial DNA (mtDNA) is inherited in a haploid manner through females. Since its mutation rate is high and can be easily measured, mtDNA is a powerful tool for tracking matrilineages and it has been widely used in this role by molecular biologists. In contrast, nuclear DNA is inherited from both parents and it recombines at any generation. We show in this paper that haploid reproduction allows for a complete replacement of the mtDNA of a population by the mtDNA of immigrants. In contrast, diploid reproduction allows for some of the ancient nuclear DNA to persist.

We consider two interbreeding populations whose generations are not overlapping and whose size is large and constant in time. The number of males and females is the same and constant both in the first and in the second population. Any generation is replaced by a new one and any individual has two parents concerning nuclear DNA and a single one (the mother) concerning mtDNA. One of the two populations, that we call the African population, produces some emigrants at any generation ($2p$ on average). The second population, that we call the Asian population, receives these people as immigrants. The sizes of the two populations are not necessarily the same and we assume that the number of African females is M while the number of Asian females is N , so that the total number of individuals in the two populations is $2N + 2M$.

Let us now explain how reproduction and migration are modelled. We assume that any individual in the new generation chooses independently the two parents at random in the previous one (see [2, 3, 7]). The choice of an individual is independent of the choice of the others. Moreover, the Africans always choose among Africans while Asians choose with probability $1 - p/N$ among Asians and with probability p/N among Africans. The choice is neutral, i.e. there is no preferred choice among African individuals and there is no preferred choice among Asian ones. The choice of an African parent with probability p/N is equivalent to a migration of $2p$ Africans on average, one half of which, still on average, are females. Remark that the number of emigrants remains finite even if the population becomes very large ($N \rightarrow \infty$). To be clearer, we assume that Africans can migrate even if they have one or more African children. The reason of our choice is that the resulting model is the simplest. Other choices are possible; for example one may assume that if

Africans migrate they become Asian, that is, they cannot have children in the African population. Nevertheless, it turns out that the exact migration mechanism is irrelevant for large populations.

If the migration rate p vanishes, the mtDNA of a population cannot be transmitted to the other. In this case, both the African mtDNA and the Asian one separately undergo standard coalescence (see [4, 5] and more recently [6, 8] for dynamical aspects). In contrast, if migration is allowed, we show that in a finite random time T the mtDNA of the Asian population is completely replaced by the mtDNA of immigrants (time is the number of generations divided by N). We also show that, in the same time, a fraction F of the nuclear DNA persists in the Asian population. In other words, the mtDNA of the Asian population living at a time T before the present completely disappeared in the present population while a fraction F of the ancient nuclear DNA still persists (hereafter the ‘ancient nuclear DNA’ is the nuclear DNA of the Asian population living TN generations before the present). Complete mtDNA replacement together with nuclear DNA persistence occurs even if the migration rate is very low.

We find the random replacement time T in the second section and the fraction F of ancient nuclear DNA in the third. In the last section we discuss the eventual relevance of our results for the debate about ‘out of Africa’ and multiregional models in palaeoanthropology. The mathematical core of the paper is the appendix where we show that the fraction of ancient nuclear DNA is a deterministic quantity which decreases exponentially in time. This is why the ancient nuclear DNA can be diluted by the nuclear DNA of immigrants but it cannot be totally replaced.

2. Replacement time

Let us start with the following remark: since Africans always choose among Africans, African mtDNA undergoes standard coalescence. The average coalescence time for African females is $2M/N$ which means $2M$ generations (the probability density for the coalescence time can be found, for example, in [6]). In contrast, the present Asian female population may have mtDNA ancestors both in the Asian and in the African population. Assume that at a given time in the past the number of Asian mtDNA female ancestors is n . Going backward for one generation, the probability that this number decreases to $n - 1$ is $b(n)/N$ where $b(n) = pn + n(n - 1)/2$. The term pn/N is due to the probability that one of the female ancestors chose an African mother and the term $(n(n - 1)/2)/N$ is due to the probability that two of the female ancestors chose the same Asian mother (the celebrated coalescence phenomenon). Then, the probability that the number of ancestors remains the same going backward for tN generations is $[1 - b(n)/N]^{tN}$ which, for large N , becomes $\exp(-b(n)t)$. Therefore, the time t_n needed for reducing from n to $n - 1$ the number of Asian female ancestors is exponentially distributed with average $[pn + n(n - 1)/2]^{-1}$. Finally, the time needed for complete replacement, i.e. for the present Asian population to have not Asian mtDNA ancestors, is

$$T = \sum_{j=1}^{\infty} t_j \quad (1)$$

which is a sum of independent random times exponentially distributed and with parameters $[b(j)]^{-1}$. Remark that the above sum starts from one (not from two as in

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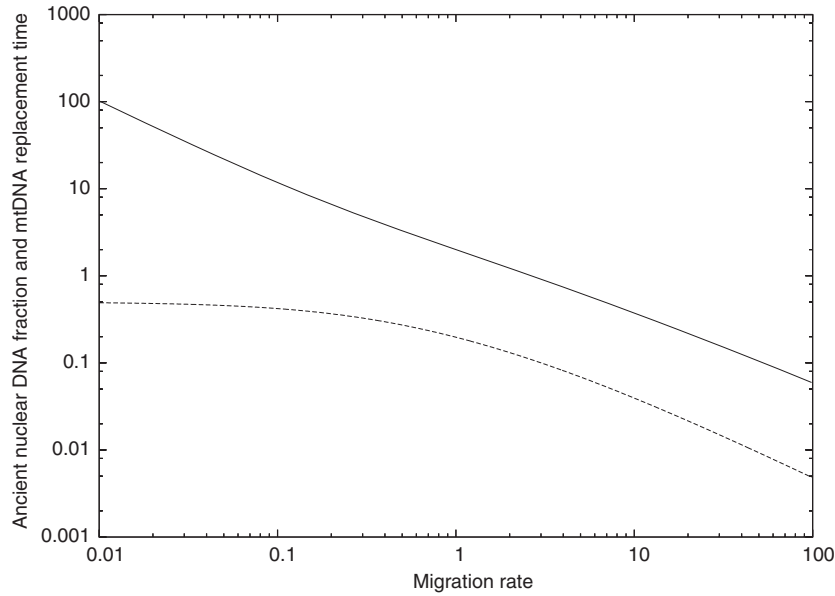


Figure 1. Average of mtDNA replacement time (full line) and average of ancient nuclear DNA fraction (dashed line) versus emigration rate p .

the coalescence) since complete replacement occurs when the number of Asian ancestors vanishes.

The average replacement time is then

$$\langle T \rangle = \sum_{j=1}^{\infty} \left[jp + \frac{j(j-1)}{2} \right]^{-1} \quad (2)$$

which is plotted in figure 1.

It should be remarked that the number of emigrants which is required for the rapid replacement of mtDNA is very small. A couple of immigrants at any generation ($p = 1$) in a large population of size N allows for a complete replacement of the Asian mtDNA in about $2N$ generations, while, if the couples are two ($p = 2$), it is sufficient 60% of the time.

3. Ancient nuclear DNA

We have shown that the mtDNA of the Asian generation at a time T in the past (the ancient generation) completely disappeared in present Asian population. We want to see now what happened to the nuclear DNA of that generation (the ancient DNA).

Let us first remark that the fraction of ancient DNA for the ancient generation equals 1, while, at any following generation, this fraction is less than 1. In fact, at any generation replacement, both the father and the mother are independently chosen with probability p/N among Africans and with probability $1 - p/N$ among Asians. Since nuclear DNA of an individual comes one half from the father and one half from the mother, at any generation replacement, the fraction of ancient nuclear DNA in the entire Asian population is reduced, on average, by a factor $(1 - (p/N))$. The non-averaged factor, indeed, randomly fluctuates

around this value. Fluctuations are due to the fact that the number of immigrants is random and are also due to the Wright–Fisher diffusion associated with generation replacement. Fluctuations of both origins are of order $1/N$ as is shown in the appendix.

Fluctuations are small because diploid reproduction is able to rapidly span ancient and new genes in all population. This self-averaging behaviour is very much at variance with haploid reproduction where a single individual only may have new mtDNA or ancient.

After a time T from the ancient generation (i.e. in the present population), the average fraction of ancient nuclear DNA reduces to $(1 - (p/N))^{TN}$, which, for large N , becomes $\exp(-pT)$.

For each generation replacement, random fluctuations are of the order $1/N$ and, since they are uncorrelated, after TN generations they are of order $1/\sqrt{TN}$ (see the appendix). Therefore, the fraction of ancient DNA in the present generation is exactly $F = \exp(-pT)$ when the population is large and randomness is only due to the randomness of the time T . It must be remarked that F is never vanishing, since the random time T is finite with probability one. This implies that nuclear DNA is never completely replaced, unlike with mtDNA.

As already remarked, this self-averaging behaviour in the large N limit is typical of diploid reproduction (see [2, 3, 7]). Indeed, self-averaging, which is proved in the appendix, is the key point of our results since the persistence of a fraction of ancient nuclear DNA, when the mtDNA is totally replaced, is a direct consequence of it.

In order to see how F depends on p we take now the average of F with respect to T and we obtain

$$\langle F \rangle = \langle \exp(-pT) \rangle = \prod_{n=1}^{\infty} \frac{2np + n(n-1)}{2(n+1)p + n(n-1)} \quad (3)$$

which is also plotted in the figure.

As already remarked, $p = 1$ allows for a complete replacement of the Asian mtDNA in about $2N$ generations, while for $p = 2$ a number $1.2N$ of generations is sufficient. In the first case the average fraction of ancient nuclear DNA is 0.2 while in the second it is 0.12. The point is to compare the average replacement time $\langle T \rangle$ with the African average coalescence time $2M/N$. Assuming that the African population size is equal to or larger than the Asian population size ($2M \geq 2N$) one finds that in both the above examples $\langle T \rangle$ is equal to or smaller than $2M/N$. In other words, one or two couples of immigrants at any generation allow for a replacement of Asian mtDNA in a time smaller than the African coalescence time. Furthermore, they allow for the persistence of a significant fraction of ancient nuclear DNA.

4. Discussion

In our model we assume panmixia in both populations; however, there is actually a delay in the spreading of genetic material when space is considered. A more realistic approach should be able to estimate both the timescale involved in the process and the gradient of African nuclear DNA in the Asian population. We leave open this much more difficult problem and, in our simplified framework, we now discuss some possible consequences of our results concerning palaeoanthropology.

Assume that $N = M = 5000$ (number of African and Asian women); in this case, the average number of generations required for coalescence of African mtDNA is $2M = 10\,000$ which, assuming generations of 20 years, corresponds to 200 000 years. A couple of immigrants at any generation ($p = 1$) induces complete replacement of the Asian mtDNA in the same time, while, for two couples ($p = 2$), the time required is 120 000 years. As already discussed, the fraction of ancient nuclear DNA ranges between 0.12 and 0.2. Moreover, if N is smaller than $M = 5000$, the migration rate p required for having $\langle T \rangle \leq 2M/N$ can be smaller than 1 and, therefore, the fraction of ancient nuclear DNA can be higher, up to a maximum of 0.5.

In conclusion, mtDNA argument cannot be used to prove the ‘out of Africa’ theory (see [1] for a review) or to disprove the multiregional model (see [10] for a review) since a very small migration flux is compatible both with pre-African nuclear DNA persistence and complete pre-African mtDNA replacement in Asia and Europe. Indeed, the picture in this paper is compatible with [9], where a study of worldwide human nuclear DNA seems to show repeated migrations from Africa to Europe and Asia.

Finally, we would like to mention, that the Y chromosome is also inherited in an haploid manner; the only difference is that its reproduction is driven by males. The qualitative and quantitative arguments in the paper remain unchanged if the Y chromosome is considered in place of mtDNA.

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Appendix

Let us define $m_i(t)$ as the fraction of ancient nuclear DNA for the male individual i at tN generations after the ancient generation and let us also define the analogous $f_i(t)$ for the female individual i . By definition the fraction of ancient DNA for an individual of the ancient generation equals one; then we have $m_i(0) = f_i(0) = 1$. In the reproductive process an individual receives the nuclear DNA of both parents so that their fraction of ancient nuclear DNA will be an average of the fractions of the two parents. In fact, this holds exactly only for large genomes such as the human one. The link between two generations is then provided by the following stochastic equations:

$$m_i(t) = \frac{1}{2}[\mu_i(t) m_{j(i,t)}(t - \epsilon) + \phi_i(t) f_{k(i,t)}(t - \epsilon)] \quad (\text{A.1})$$

where $\epsilon \equiv 1/N$. The variables $j(i, t)$ and $k(i, t)$ take any integer value between 1 and N with equal probability $1/N$. The variables $\mu_i(t)$ and $\phi_i(t)$ take the values 0 with probability p/N and 1 with probability $1 - p/N$. With our choice the father’s contribution $\frac{1}{2}\mu_i(t) m_{j(i,t)}(t - \epsilon)$ to the fraction $m_i(t)$ vanishes with probability p/N (African father) and equals one half of the fraction of a given Asian father with probability $(1 - p/N)/N$. The same is true for the mother’s contribution. All variables $\mu_i(t)$, $\phi_i(t)$, $j(i, t)$, and $k(i, t)$ are mutually independent; furthermore, two variables of same type are independent whenever the individual indices or time indices are different (for example $j(i, t)$ and $j(k, s)$ are independent when $i \neq j$ and/or $t \neq s$).

An analogous stochastic equation holds for $f_i(t)$ with all variables in it independent from the mirror variables in (A.1).

Since $\langle \mu_i(t) \rangle = \langle \phi_i(t) \rangle = (1 - p/N)$ and since both $j(i, t)$ and $k(i, t)$ take any integer value between 1 and N with equal probability $1/N$, we obtain by averaging (A.1)

$$\langle m_i(t) \rangle = \frac{1}{2N} \left(1 - \frac{p}{N} \right) \sum_{l=1}^N (\langle m_l(t - \epsilon) \rangle + \langle f_l(t - \epsilon) \rangle). \quad (\text{A.2})$$

Since averages are independent of the individual index, and averages for females and males must coincide ($\langle m_i(t) \rangle = \langle f_i(t) \rangle$), we have

$$\langle m_i(t) \rangle = \left(1 - \frac{p}{N} \right) \langle m_i(t - \epsilon) \rangle = \left(1 - \frac{p}{N} \right)^{tN} \quad (\text{A.3})$$

where the second equality is obtained by iteration and using the initial condition $m_i(0) = 1$.

Analogously, $\langle [\mu_i(t)]^2 \rangle = \langle [\phi_i(t)]^2 \rangle = (1 - p/N)$ and $\langle m_i(t) f_i(t) \rangle = \langle m_i(t) f_j(t) \rangle = \langle m_i(t) m_j(t) \rangle$ when $i \neq j$, as can be easily verified using (A.1). Then we have

$$\langle [m_i(t)]^2 \rangle = \frac{1}{2} \left(1 - \frac{p}{N} \right) \langle [m_i(t - \epsilon)]^2 \rangle + \frac{1}{2} \left(1 - \frac{p}{N} \right)^2 \langle m_i(t - \epsilon) m_j(t - \epsilon) \rangle \quad (\text{A.4})$$

where it is intended that $i \neq j$ and where we have again made use of the averages' independence of the individual index, and of the fact that averages for females and males coincide ($\langle [m_i(t)]^2 \rangle = \langle [f_i(t)]^2 \rangle$).

Since $\epsilon = 1/N$, this equality can hold only if

$$\langle [m_i(t)]^2 \rangle = \langle m_i(t) m_j(t) \rangle + o\left(\frac{1}{N}\right) \quad (\text{A.5})$$

where $o(1/N)$ means 'of order $1/N$ '.

This is the key point, since we will use it to prove that the ancient nuclear DNA fraction behaves deterministically in large populations. It is important to remark that the above equality is associated with diploid reproduction. In fact, (A.5) is a direct consequence of the fact that nuclear DNA is an average of those of the two parents as described by equation (A.1). For haploid reproduction an analogue of equation (A.1) holds, but the contribution comes only from a single parent and equality (A.5) cannot be stated.

Let us now define the fraction of ancient nuclear DNA in a population as the mean of the fractions of the component individuals:

$$x(t) = \frac{1}{2N} \sum_{i=1}^N [m_i(t) + f_i(t)]. \quad (\text{A.6})$$

Then, from (A.3) we immediately obtain

$$\langle x(t) \rangle = \left(1 - \frac{p}{N} \right)^{tN}. \quad (\text{A.7})$$

We will show now that $x(t)$ is a deterministic variable in a large population and, therefore, coincides with its average. Using again individual index symmetries and male/female symmetry we obtain from (A.1) and (A.6)

$$\langle [x(t)]^2 \rangle = \left(1 - \frac{p}{N}\right)^2 \langle [x(t - \epsilon)]^2 \rangle + R(t - \epsilon) \quad (\text{A.8})$$

where

$$R(t) = \frac{1}{2N} \left(1 - \frac{p}{N}\right) \left(\langle [m_i(t)]^2 \rangle - \left(1 - \frac{p}{N}\right) \langle m_i(t) m_j(t) \rangle \right). \quad (\text{A.9})$$

Using equality (A.5) we obtain $R(t) = o(1/N^2)$. Indeed this is the key of the proof; in fact, for haploid DNA transmission, we would obtain the same equation (A.8) but we would have $R(t) = o(1/N)$ in place of $R(t) = o(1/N^2)$.

From equation (A.8) together with the condition $R(t) = o(1/N^2)$ we obtain

$$\langle [x(t)]^2 \rangle = \left(1 - \frac{p}{N}\right)^{2tN} + o\left(\frac{1}{N}\right) \quad (\text{A.10})$$

which compared with (A.7) tells us that

$$x(t) = \left(1 - \frac{p}{N}\right)^{tN} \pm o\left(\frac{1}{\sqrt{(N)}}\right). \quad (\text{A.11})$$

We remark that for haploid reproduction, fluctuations are of order 1 ($o(1)$ in place of $o(1/\sqrt{(N)})$); that is why mtDNA disappears in a finite random time, even for large populations.

Finally, in the large N limit, we obtain from (A.10) $x(t) = \exp(-pt)$, which tells us that the ancient nuclear DNA fraction decreases exponentially. Moreover, since the random replacement time is finite with probability one, the fraction $F \equiv x(T) = \exp(-pT)$ is always finite.

References

- [1] Cann R L and Wilson A C, *The recent African genesis of humans*, 2003 *Sci. Am.* **13** 54
- [2] Derrida B and Jung-Muller B, *The genealogical tree of a chromosome*, 1999 *J. Stat. Phys.* **94** 277
- [3] Derrida B, Manrubia S C and Zanette D H, *Statistical properties of genealogical trees*, 1999 *Phys. Rev. Lett.* **82** 1987
- [4] Kingman J F C, *The coalescent*, 1982 *Stoch. Process. Appl.* **13** 235
- [5] Kingman J F C, *On the genealogy of large populations. Essays in statistical science*, 1982 *J. Appl. Probab. A* **19** 27
- [6] Serva M, *On the genealogy of populations: trees, branches and offspring*, 2005 *J. Stat. Mech.* **P07011**
- [7] Serva M and Peliti L, *A statistical model of an evolving population with sexual reproduction*, 1991 *J. Phys. A: Math. Gen.* **24** L705
- [8] Simon D and Derrida B, *Evolution of the most recent common ancestor of a population with no selection*, 2006 *J. Stat. Mech.* **P05002**
- [9] Templeton A, *Out of Africa: again and again*, 2002 *Nature* **416** 45
- [10] Thorne A G and Wolpoff M H, *The multiregional evolution of humans*, 2003 *Sci. Am.* **13** 46