OPINION

Revising the human mutation rate: implications for understanding human evolution

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Abstract | It is now possible to make direct measurements of the mutation rate in modern humans using next-generation sequencing. These measurements reveal a value that is approximately half of that previously derived from fossil calibration, and this has implications for our understanding of demographic events in human evolution and other aspects of population genetics. Here, we discuss the implications of a lower-than-expected mutation rate in relation to the timescale of human evolution.

Differences between the genomes of any two individuals correspond to mutations accumulated on both lineages since their common ancestor. Therefore, if we know the rate or rates at which such mutations have accumulated, we can calculate the time since divergence. Genomic mutation rates can be estimated in two ways: either by calibrating genetic divergence against fossil evidence for a past separation (the phylogenetic rate) or by direct observation of mutations in present-day individuals (BOX 1).

For human and great ape evolution, comparison of the sequence divergence between humans and macaques with fossil evidence for the split between apes and Old World monkeys[1] gives a phylogenetic rate estimate of approximately 10^{-9} bp^{-1} year^{-1}, and a similar calibration is obtained from the divergence between humans and orang-utans[2] (FIG. 1). Estimates around this value (or equivalent scalings) have been used in studies of recent human evolution and demography to date key events, such as the divergence from Neanderthals and the exodus from Africa of modern humans.

However, recent analyses of *de novo* mutations in modern humans, some facilitated by developments in genome-sequencing technology, have produced genome-wide estimates of the per-generation mutation rate averaging at $\sim 1.2 \times 10^{-8}$ bp^{-1} generation^{-1} (REFS 3–5) (FIG. 1; Supplementary information S1 (table)). Similar analyses focusing on mutations in exomes and dominant disease loci have produced an average rate of 1.38×10^{-8} bp^{-1} generation^{-1} (Supplementary information S1 (table); REFS 6–8), and a study of genes sequenced in more than 14,000 individuals estimates an identical value[9]. A slightly elevated rate around genes is consistent with sequences at these locations having a higher GC content than the genome average[6] (BOX 1).

To convert per-generation rates to yearly rates requires dividing by the average generation time (BOX 1). Studies of the modern human generation time[10,11] suggest a value of around 30 years, and scaling the whole-genome per-generation average by this results in a yearly mutation rate of 0.4×10^{-9} bp^{-1} year^{-1}. However, given that chimpanzees and gorillas have generation times of around 20 years[11,12], it may be that the longer generation time in modern humans is a recent development that is associated with changes in life history within the past few millennia. A plausible range of generation times between 20 and 30 years would correspond to a range of mutation rates between 0.4×10^{-9} and 0.6×10^{-9} bp^{-1} year^{-1}. A much lower value of 10–15 years, which is needed for the *de novo* and phylogenetic rates to match, would be shorter than any other living great ape and less than half of the value measured in present-day humans. Below, for demonstrative purposes, we propose a value of 0.5×10^{-9} bp^{-1} year^{-1} — which is half of the phylogenetic rate — as a revised mutation rate for humans within the past million years.

We expect precision to increase in the near future on the basis of further measurements in pedigree studies and perhaps alternative approaches combining genetic data from ancient samples with radiometric dating. However, the case for revision is established, and it is appropriate to examine the implications. In this article, we discuss some of the ways in which this lower value, by revising the chronology for nuclear genomic divergence, has implications for our understanding of human evolution. We begin by considering evolution within the great apes and in particular why a lower rate in modern humans is compatible with higher phylogenetic rate estimates based on longer timescales. Then we focus on evolution since the divergence of modern humans from Neanderthals and consider how a lower rate might affect the timing of key demographic events and the interpretation of relevant genetic and palaeoanthropological evidence.

Mutation rates within great apes

The revision in human mutation rate could be regarded as doubly unexpected because previous studies of mutations accumulated in pedigrees have estimated rates that are higher, not lower, than those inferred from phylogenetic analysis[13] (BOX 1). However, the mutation rates considered in these studies have either been those of mitochondrial DNA in humans and other animals or nuclear DNA from organisms such as *Drosophila melanogaster*[14] and *Caenorhabditis elegans*[15]. In each of these genomes, the influence of selection, which suppresses the rate estimated by phylogenetic analysis (BOX 1), is expected to be substantially greater than in the human nuclear genome owing to their much greater gene density and, in the cases of *D. melanogaster* and *C. elegans*, their much larger effective population sizes (N_e). Under neutrality, it

would be expected that *de novo* and phylogenetic rates would be similar, so the fact that *de novo* rates are lower in humans suggests that factors other than selection dominate.

A plausible explanation, given that the phylogenetic estimates average over lineages extending back tens of millions of years, is that there has been a decrease in mutation rate per year within the great apes since their divergence from other primates (FIG. 1). Evidence has previously been seen for shorter phylogenetic branch lengths within the apes (corresponding to lower mutation rates) relative to other primate lineages; this is referred to as the hominoid slowdown. For example, humans have accumulated 30% fewer mutations than baboons since their common ancestor[16]. Given a correlation across the primates between body size and generation time[17], such a decrease is consistent with an increase in the body size of all four great apes since the early Miocene epoch (which was 15–20 million years ago)[18] and a consequent increase in generation time. Considering genetic and fossil evidence for more recent splits within the African apes[19], a picture emerges of a progressive decrease in the yearly mutation rate within the great ape family: a finding that is consistent with the lower mutation rate estimate of 0.5×10^{-9} bp^{-1} year^{-1} for modern humans.

Mitochondrial mutation rates

Mitochondrial DNA (mtDNA), which is present at a much higher copy number per cell than nuclear DNA and hence is more readily sampled, is also widely used to estimate divergence times. For each of the demographic events discussed below, we compare timing estimates based on the revised nuclear rate with those from mtDNA, and here we review some of the issues involved in such comparisons. Because it is transmitted down the female line and is haploid in each individual, the N_e of mtDNA would be smaller than at autosomal loci by a factor of four if the locus were neutral, and in practice the difference is even greater as it is under selection. This has the advantage of substantially reducing the relative importance of ancestral demography (BOX 2). However, there are also disadvantages. Because mtDNA is a single locus, sampling the ancestry in mtDNA is far more susceptible to stochastic variation than taking a genome-wide average, and it may be discordant with most ancestry across the nuclear genome. Such discordance may correspond to a more recent common ancestor at the mtDNA locus or even to a different phylogenetic tree owing to incomplete lineage sorting or introgression, examples of which have been widely observed in other species[20]. Because the mtDNA sequence is subject to selection, different regions of the sequence accumulate mutations at different rates, and these may vary between species or even populations. Finally, the mtDNA mutation rate is high (estimates are around 200×10^{-9} bp^{-1} year^{-1} in hypervariable region 1 (HVR1) and HVR2, which are typically used for dating), so the incidence of recurrent mutations needs to be accounted for in calculations. Various approaches have been proposed to handle these problems in dating mtDNA divergences[21–23], and differences between them correspond to different estimates of the time to the most recent common ancestor (TMRCA) at the mtDNA locus. The main branches of the mitochondrial phylogeny are named haplogroups; below, we refer to the M and N haplogroups, which are common in out-of-Africa populations, and to their parent L3 haplogroup[24].

Modern humans and Neanderthals

We first consider the consequences of a lower nuclear mutation rate for estimates of divergence between modern humans, Neanderthals and Denisovans. Neanderthals and Denisovans are closer to each other than they are to modern humans, and the sequence divergence from both of these to modern humans is approximately 12% of that between humans and chimpanzees[25]. On the basis of demographic modelling to account for coalescence within the ancestral population (BOX 2), a population split between modern humans and Neanderthals has been estimated to have occurred 272,000–435,000 years ago, assuming a human–chimpanzee sequence divergence time of 5.6–8.3 million years ago[2]. Taking the human–chimpanzee sequence divergence as 1.35 kbp^{-1} (REF. 19), this range of human–chimpanzee divergence times corresponds to average mutation rates of $(0.81–1.20) \times 10^{-9}$ bp^{-1} year^{-1} over that time. Accounting for lower mutation rates in recent great ape evolution (specifically, assuming the rate

Box 1 | **Estimating mutation rates**

DNA sequences evolve in various ways, the most straightforward of which is to accumulate changes or mutations in individual nucleotides, resulting in single-base differences when genomes are aligned against each other. Most estimates of divergence and speciation time are based on such alignments, and the rate at which mutations accumulate is therefore a key scaling parameter.

Two approaches are used to estimate mutation rates. The direct approach is to count mutations that occur between generations in present-day individuals. Older studies taking this approach used data for disease cases associated with autosomal-dominant or X-linked loci in which a child is affected but neither parent is[8,56,57]. More recently, several studies have used next-generation sequencing technology to collect whole-genome or exome sequence data and directly to identify *de novo* mutations in parent–child trios[3–7]. In both cases, the resulting estimate μ_g is a mutation rate per generation, so a further estimate of the mean generation time t_g is needed to convert to a rate per year: $\mu = \mu_g / t_g$. Another important issue for sequencing studies, owing to the low number of mutations involved in any one transmission, is correction for false-positive and false-negative counts[58].

The other less-direct approach is to use an independent estimate of the time t since the common ancestor of two present-day genomes that have been derived, for example, from fossil dating of the speciation event in which their ancestors diverged. Given this estimate, the average mutation rate on the lineage that connects the genomes (via their common ancestor) is calculated as $\mu = 2d / t$, where d is the sequence divergence (that is, the number of substitutions per base pair) between them. The latter is straightforwardly obtained from genome sequence alignments, but there are many uncertainties associated with the estimate of t, such as the phylogenetic placing of fossil taxa[59] and the impact of ancestral polymorphism (BOX 2). The mutation rate estimated in this way is sometimes referred to as the phylogenetic rate.

Mutation rates vary between genomic regions[60] as they are affected by sequence content and other factors, meaning that estimates based on different subsets of the genome may differ in value. More problematic for some analyses is that rates can also vary between and along evolutionary lineages, breaking the assumption of a molecular clock[61]. This means that rates estimated on one part of a phylogenetic tree or in certain species may not be valid elsewhere.

Selection also contributes to differences between the two approaches, as weakly deleterious mutations may be detected in a pedigree but will tend not to survive on timescales measured by interspecies comparison. Hence, a distinction is made between the *de novo* mutation rate and the rate at which fixed inter-species differences or substitutions accumulate. The latter, estimated by the phylogenetic rate, is also referred to as the substitution rate. At neutral sites (and discounting other factors) the two should be equal, but in loci under selection, such as mitochrondrial DNA (mtDNA), the *de novo* rate is expected (and is generally found) to be higher[13].

averaged over the human–chimpanzee lineage is intermediate between the present day human rate and the rate averaged over more distant lineages (FIG. 1)) revises the modern human–Neanderthal population split estimate upwards to 400,000–600,000 years ago (FIG. 2). This is consistent with mtDNA estimates of modern humans and Neanderthals, shown in FIG. 2, that are centred around 500,000–600,000 years ago, although these vary, possibly for the technical reasons described above. (The much older modern human–Denisovan mtDNA sequence divergence has been ascribed either to variance in ancestry sampling or to potential admixture with some other archaic hominin group[25].)

Taken as a whole, the evidence from mtDNA and nuclear DNA (with its lower mutation rate) suggests a separation of Neanderthals and modern humans around 500,000 years ago. This is consistent with the proposal that the ancestral population from which they diverged was *Homo heidelbergensis*[26], but given the widespread classification of fossils within that taxon across Europe and Africa[27], it seems likely that substantial population structure would have existed around the time of separation. Indeed the divergence of these populations may have been an extended process, complicating the inference from genetic and fossil data (BOX 2). Further analysis based on more extensive genomic data from Neanderthal and Denisovan samples may shed more light on this.

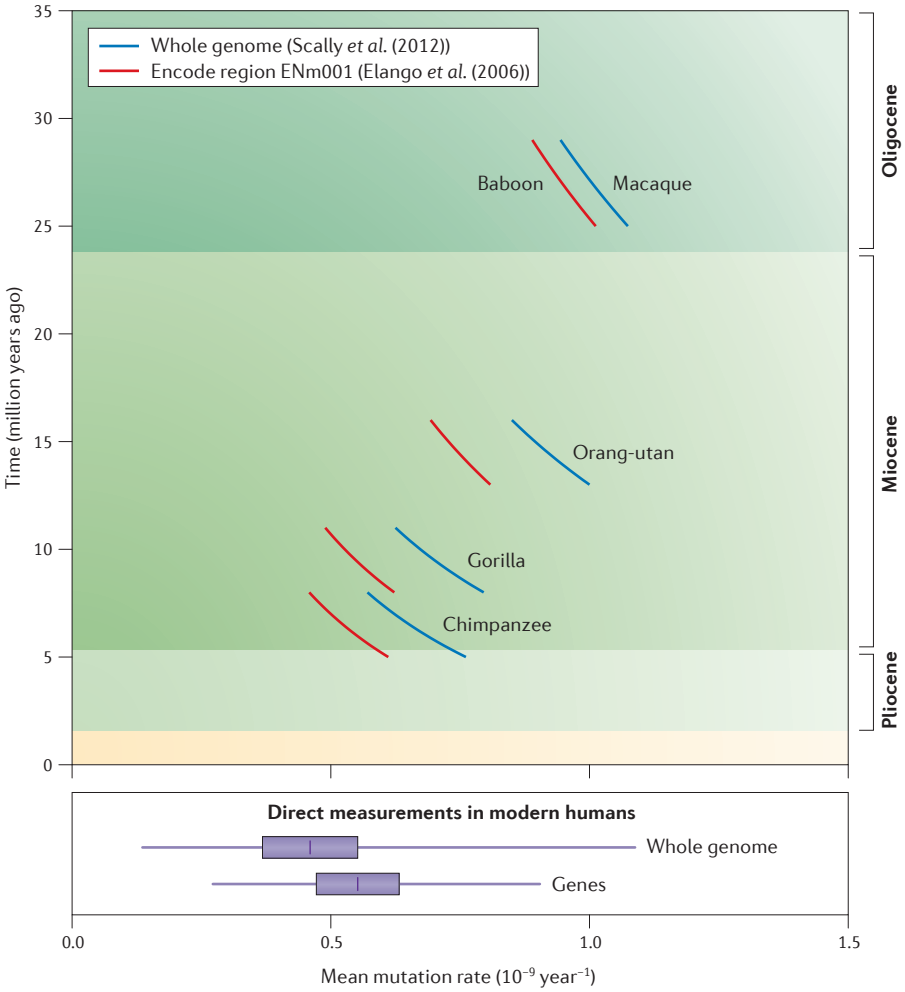

Figure 1 | **Decreasing mutation rates during great ape evolution.** This figure illustrates how the sequence divergences from humans to other primates, in combination with speciation dates derived from fossil evidence, suggest a slowdown in mutation rate throughout great ape evolution. Sequence divergence calculations for humans compared to chimpanzees, gorillas, orang-utans, macaques and baboons were taken from Scally *et al.*[19] and Elango *et al.*[68]. For each species pair, we consider a range of speciation dates consistent with available fossil evidence[69] and calculate a corresponding range of implied average mutation rates on the lineage between the two species using the equation in BOX 2. (We assume an ancestral coalescent time of 3 million years for the human–gorilla comparison[19] and 4 million years elsewhere.) Differences between the red and blue lines for each species pair are due to different calculated sequence divergences and correspond to differences in methodology as well as mutation rate between the regions studied, but both studies exhibit the same trend of lower average mutation rate when calculated on more recently diverged lineages. (Note that divergence data for human–macaque comparison were only available from REF. 19, and data for human–baboon comparison were only available from REF. 68.) Below the main panel is the range of yearly mutation rates in modern humans, across the whole genome and around genes, estimated from direct observation of *de novo* mutations[3–8] (Supplementary information S1 (table)), assuming a 25-year generation time. These data show that the rate slowdown appears to have continued until the present day. In both cases, the horizontal line represents the full range, the filled bar represents a combined 95% confidence interval, and the black line marks the mean.

Divergence of modern humans

Whereas comparatively few genetic data are currently available for Neanderthals and Denisovans, a wealth of data from nuclear genome and mtDNA sequences has been collected from modern human populations worldwide. These data, along with extensive fossil and archaeological evidence, have provided strong support for the recent African origin model (RAO model) of modern human evolution[28], wherein modern humans appeared first within Africa and subsequently spread from there to other continents, even though there is a low level of interbreeding with other hominin populations[2,25], and this has led to, for example, some Neanderthal admixture in modern European and Asian genomes. FIGURE 3 shows the effect of the revised mutation rate on genetic estimates for the timing of three key divergences in this process: between Europeans and Asians, between Africans and non-Africans, and between the Khoe–San of southern Africa and other modern humans.

Khoe–San divergence. Phylogenies constructed from mtDNA and Y-chromosomal data have shown the Khoe–San divergence to be the deepest split within the modern human tree[24,29]: a finding that is also reflected in analyses of nuclear DNA (FIG. 3). However, in the revised chronology for nuclear DNA, population split estimates between the Khoe–San and other Africans of 250,000–300,000 years ago are substantially older than mtDNA estimates (which are estimates of the TMRCA for modern humans as a whole) of 120,000–250,000 years ago. This seems inconsistent,

but as discussed above it may be that ancestry at the mtDNA locus does not fully represent the depth of the human tree. Indeed, the issue of gradual population divergence discussed in BOX 2 is particularly relevant here, given that it is not clear to what extent the Khoe–San have been genetically separated from other African populations, so estimates of a split time may correspond to something other than a genuine separation. It is possible that the population structure of human ancestors 150,000–300,000 years ago was more complex than is represented in the models that underlie these estimates and that are based on limited sampling of African genetic diversity. Such structure would also be consistent with the reduction in coalescence observed in this period between all modern human chromosomes[30].

African and non-African split. Turning to the separation between Africans and non-Africans, FIG. 3 shows that, as originally presented, nuclear genomic estimates for the separation between non-African populations and Yoruba Africans (from Nigeria) cluster around 50,000 years ago. Previous interpretations have therefore taken these to support a model in which the exodus from Africa was essentially contemporaneous with the spread of modern humans across Eurasia and into Australia. Under this model, fossil evidence for modern humans in the Middle East before 100,000 years ago (such as at Skhul in Israel[31]) has been interpreted as a temporary excursion that is unrelated to the later event, and possible archaeological evidence for modern human presence in the Arabian peninsula dating to the same period[32,33] or 74,000 years ago in India[34] has been disputed[35].

However, when rescaled with the revised lower rate, nuclear genomic estimates of the split between non-Africans and the Yoruba range from 90,000 to 130,000 years ago. In this revised chronology, there is a gap of 50,000 years or more between this and the subsequent colonization of Eurasia. A possible interpretation might be that the early split represents a separation within Africa and that the revised scaling suggests a modified RAO model in which the exodus from Africa occurred via an intermediate population in East Africa, perhaps extending into the Middle East, 60,000–120,000 years ago. This interpretation is interesting in light of the suggestion[30,36] that there was continued genetic exchange or migration between the ancestors of Yoruba and non-Africans for a prolonged period after their main separation (FIG. 3). It would have been more feasible for such an intermediate population to remain in partial genetic contact with other African populations for at least some of this period (FIG. 4) than for populations spread distantly across Europe and Asia. The putative intermediate population would also have had a small N_e corresponding to the well-established genetic bottleneck associated with lower genetic diversity outside Africa, now re-dated as starting 100,000–120,000 years ago and potentially continuing until 40,000–60,000 years ago. Palaeoanthropological evidence for modern humans in the Middle East during the period 60,000–120,000 years ago may then represent either permanent or repeated temporary occupation by this intermediate population, perhaps driven by or facilitated by changes in regional climatic and environmental conditions[37–39].

Other aspects of non-African ancestry also fit with a picture of earlier modern human presence in the Middle East. For

Box 2 | **Inference of population separation times from genetic divergence**

In considering the divergence of two populations, allowance needs to be made for the difference between population separation time (the time at which the two populations became reproductively isolated) and mean sequence divergence time (the average time at which genomes from the two populations find a common ancestor; see panel **a** of the figure). Mean sequence divergence time is older than population separation time by an amount that depends on the diversity and demography of the ancestral population before separation. In population genetic models, this difference is expressed as the mean coalescent time t_c and is proportional to the effective population size (N_e): larger populations are more genetically diverse and correspond to greater values of t_c. In a simple case in which no interbreeding occurs between the separated populations, and given an estimate of t_c, the separation time t_s can then be estimated as $t_s = d/(2\mu) - t_c$, where d is the mean sequence divergence and μ is the mutation rate. Estimates averaged over many loci genome-wide are more accurate than those based on a few loci or on a single locus.

However, more complex modes of speciation are common in nature. For example, separation may involve an intermediate period of partial gene exchange (panel **b** of the figure) with potentially ambiguous start and end points and in which both the strength and the direction of exchange may vary with time. Even long after the onset of isolation, there may be further incidents of admixture between separated populations. Indeed, such complex speciation processes have been suggested in all four extant great ape genera[2,19,25,62–65].

More sophisticated analyses incorporate model parameters representing gene exchange and migration, and clearly it is of interest to identify as much structure as possible. However, the parameter space is potentially large, and it remains the case that where divergence is an extended and complex process, the values of inferred parameters depend on details of the demographic model, the method of inference used and the data available[66,67]. It may be preferable to consider the separation time in simple models as an effective separation time, representing a weighted average of last common ancestry between populations and analogous as a parameter to effective population size (N_e).

Note also that genetic and fossil evidence may be sensitive to different aspects of speciation. For example, it is possible that morphological characteristics that are evident in fossils and that are ultimately fixed by speciation (and hence considered to be derived) could pre-exist in an interbreeding population or within two populations in partial genetic contact.

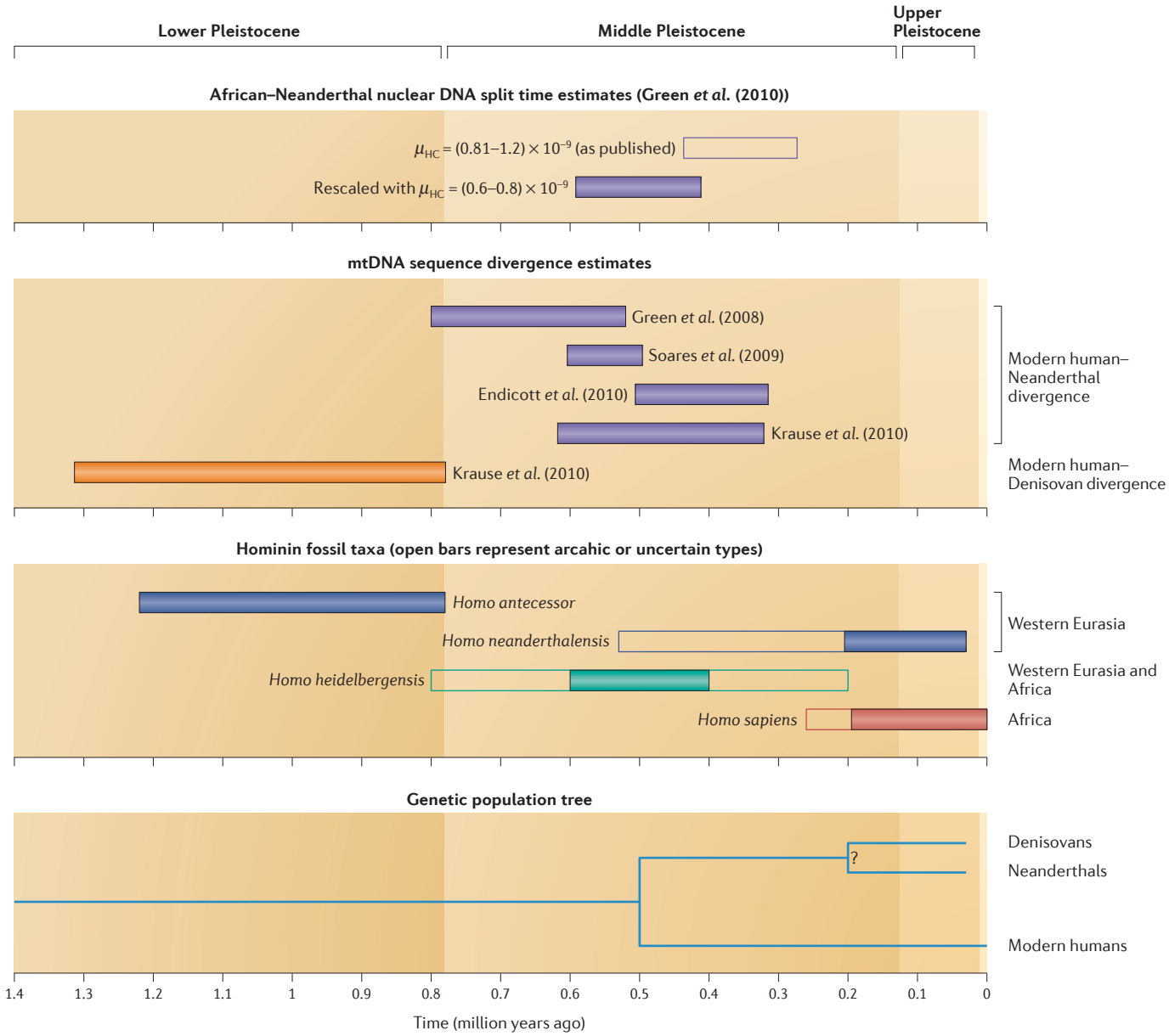

Figure 2 | **Timeline of evidence for modern human divergence from Neanderthals and Denisovans.** Nuclear DNA split time estimates are shown as published by Green *et al.* (2010)[2] and are rescaled with a lower range of possible values for the mutation rate averaged along the human–chimpanzee lineage (μ_{HC}). In each case, the length of the bar represents both the range of mutation rates assumed and additional spread from the estimation procedure. Estimates of the time to most recent common ancestor for mitochondrial DNA (mtDNA) are reported (with 95% confidence) from Green *et al.* (2008)[70], Soares *et al.*[21], Endicott *et al.*[26], and Krause *et al.*[71]. Hominin fossil taxa are represented by bars spanning the dates of fossils classified within them[27,31,45]. Open bars represent putatively archaic forms or uncertain classifications. At the bottom of the tree, the phylogenetic relationship between hominins[25] is shown and reflects the revised nuclear genomic chronology for the human–Neanderthal split. The timing of the Neanderthal–Denisovan split is uncertain.

example, interbreeding between modern humans and Neanderthals, as reflected in the evidence of Neanderthal admixture found in both modern European and Asian genomes[2], could have occurred in regions of overlapping or neighbouring occupation there. In western Eurasia at least, Neanderthals appear not to have survived beyond 40,000 years ago[40]. Note also that as no such admixture is detected in the Yoruba, any gene flow between the ancestors of the Yoruba and non-Africans in this period must have predominantly been from the former to the latter, which is again consistent with a much smaller N_e in the East African and Middle Eastern population.

However, the picture is complicated by evidence from mtDNA, in particular the L3 haplogroup, in which the TMRCA of 60,000–80,000 years ago[41] has been suggested as an upper bound for the exodus from Africa, as L3 is found within Africa but comprises a parent clade of haplogroups M and N (and hence all non-Africans). L3 shows the greatest diversity in East Africa and seems to have arisen there, judging by the placing of its deepest branches, but more

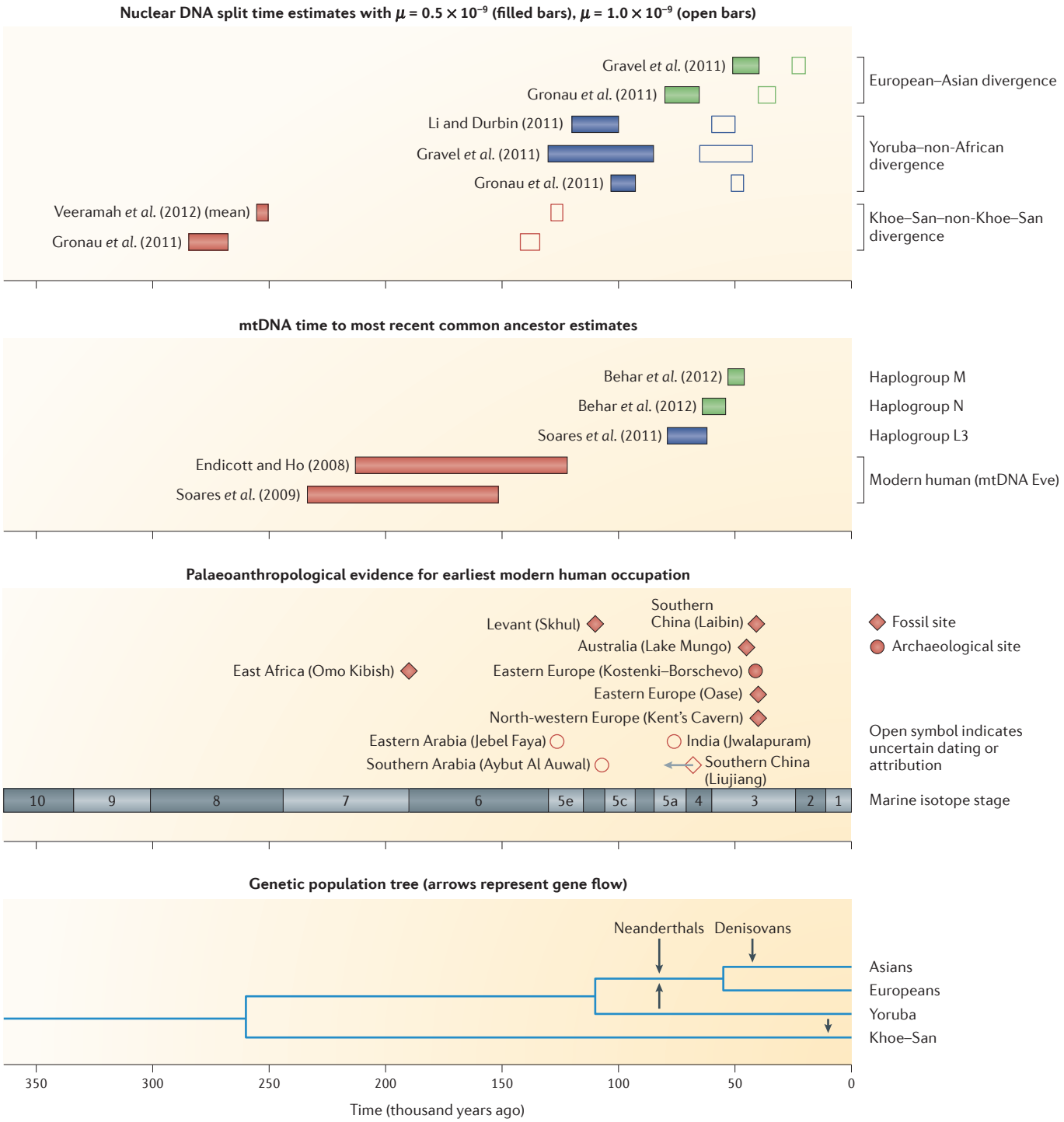

Figure 3 | **Timeline of evidence for the divergence of modern human populations.** Shown here are estimates from nuclear data published from Li *et al.*[30], Gravel *et al.*[36], Gronau *et al.*[44] and Veeramah *et al.*[72]. These studies implicitly or explicitly used mutation rates close to 1.0×10^{-9} bp^{-1} year^{-1} (typically by assuming a human–chimpanzee sequence divergence time of 6 million years). For comparison, here they are shown consistently rescaled to this rate (open bars) as well as to the revised lower rate for modern humans of 0.5×10^{-9} bp^{-1} year^{-1} (filled bars). Ranges for nuclear and mitochondrial DNA (mtDNA) estimates from Soares *et al.*[21], Endicott and Ho[22], Behar *et al.*[24] and Soares *et al.*[41] are reported for 95% confidence intervals, except for the estimate from Veeramah *et al.*[72], for which the reported ranges were so broad that only the mean is shown. Dates and locations of palaeoanthropological sites are drawn from REFS 31–34,45–51. The marine isotope stage scale is a widely used framework for dating palaeoanthropological and palaeoenvironmental data. The lower panel shows an indicative genetic population tree using separation times that are consistent with the revised nuclear estimates from the top panel. Arrows represent gene flows between populations after their initial separation, as inferred from genomic analyses[2,30,36]. The arrows are intended only to show that gene flow is thought to have occurred somewhere along these branches, not to indicate specific times; little is currently known about when, how many times or for how long these gene flows occurred. mtDNA Eve, Mitochondrial Eve (the maternal most recent common ancestor).

recently diverged subgroups are also found in central and West Africa, including in 40% of Yoruba HapMap samples[42].

If the scenario of a divergence within Africa 100,000–120,000 years ago is correct, then L3 could have arisen within the intermediate population in East Africa (which is subsequently the source for the colonization of Eurasia), and the presence of L3 subgroups in West Africa must be due to later gene flow across the continent coupled with drift or selection to a higher frequency in the Yoruba at the mtDNA locus. As noted above, such phenomena are not uncommon at individual genetic loci, and episodes of continental-scale migration are a known feature of African demographic history[43]. Additionally, we note that a TMRCA of 60,000–80,000 years ago for L3, which is quite recent within the intermediate population period of 60,000–120,000 years ago, is consistent with the small N_e that was inferred for that population before the Eurasian expansion.

Alternatively, if L3 is more generally representative of Yoruba ancestry, then inferences from nuclear data of an older split between Yoruba and non-Africans must be incorrect. In this case, it may be that the latter studies are misled by more complex demographic factors, such as long-term population structure or admixture between the ancestors of the Yoruba and other older populations in West Africa.

European and Asian split. The most recent split considered here, between European and Asian populations, is difficult to date owing to the low number of mutations involved[44]. Nevertheless, when scaled with the revised rate, the estimates of this split range from 40,000–80,000 years ago and accord better with palaeoanthropological evidence than as originally reported, where they range from 20,000–40,000 years ago and thus postdate the earliest accepted fossil and archaeological evidence for modern humans in Europe and Asia 40,000–45,000 years ago[31–34,45–51].

Comparable estimates from mtDNA are obtained by dating the roots of haplogroups M and N, which are predominantly found outside Africa and comprise parent clades of all other non-African haplogroups. A recent study inferred TMRCAs of 46,000–53,000 years ago and 54,000–64,000 years ago for M and N, respectively[24], which is consistent with revised nuclear genomic estimates for the European–Asian split.

The oldest fossil evidence for modern human migration into Europe dates to approximately 45,000 years ago[45–47,51] (FIG. 3). However, there are indications that modern humans may have begun to expand eastwards into Asia at an earlier date and in more than one wave. From genetic data, there is the suggestion of a separate initial dispersal to Australia before a dispersal to East Asia, as inferred from differing proportions of Denisovan admixture[52], and a separation of 62,000–75,000 years ago between Aboriginal Australians and other Eurasians on the basis of sequencing an Aboriginal Australian genome[53]. Examples of palaeoanthropological evidence are the aforementioned attribution to modern humans of stone artefacts at Jwalapuram, India, 74,000 years ago[34] and the dating before 68,000 years ago of modern human remains at Liujiang, China[50]. Such findings are tentative or disputed at present, but they seem to be less improbable in the context of an earlier genetic separation from modern West Africans and an established presence in the Middle East during this period.

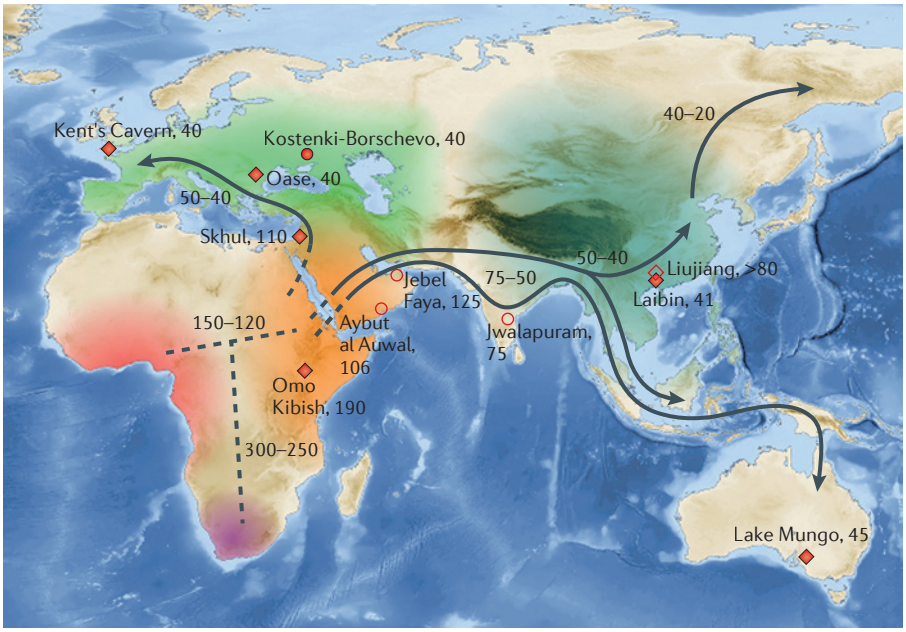

Figure 4 | **Populations and timescales involved in the origin of modern humans according to our revised model.** Shaded regions show possible distributions of Neanderthal (green; Europe), Denisovan (blue–green; Asia) and putative ancestral modern human populations. Arrows indicate some major human migrations into Eurasia and Australia (routes are figurative); palaeoanthropological sites are represented with symbols (diamonds are fossil sites, circles are archaeological sites, and open symbols represent uncertain dating or attribution). All numbers refer to dates in thousands of years ago. Within Africa, the dashed line running north to south represents the divergence between populations ancestral to Khoe–San (purple; South Africa) and other African populations; the dashed line running east to west represents divergence between populations ancestral to Yoruba (red; West Africa) and present-day non-Africans (orange; East Africa and the Middle East).

Conclusion

Mutation rates derived from phylogenetic analyses have been widely used to date events in recent human evolution, but doubts have also been raised about the validity of extrapolating such rate estimates over millions of years[54]. The *de novo* mutation rate measurements reviewed here allow us to consider the human evolutionary timescale from a different starting point. Assuming a generation time of around 25 years, they imply a yearly mutation rate that is half that obtained from phylogenetic analysis, and thus even if they are subject to further refinement, changes are required in our interpretation of genetic data.

In this brief Perspective, we have explored a possible reinterpretation of genetic and palaeontological evidence for key demographic events. Although the revised mutation rate increases many genetic dating estimates by approximately twofold, it seems possible to accommodate these older dates into a picture of evolution over the past million years that in most aspects is no less consistent with palaeoanthropological evidence than the previous consensus and in some aspects more so. The four key points may be summarized as follows. First, the divergence between modern humans and both Neanderthals and Denisovans,

which was originally estimated to be 272,000–435,000 years ago, is revised to 400,000–600,000 years ago. This is in better agreement with the range of estimated split times from mtDNA and also with the idea that the ancestral population of these groups may have been *H. heidelbergensis*. Second, for the split between the Khoe–San and other modern humans, revised estimates from nuclear genomic data suggest a divergence 250,000–300,000 years ago, older than single-locus estimates for the root of the human tree. Third, revised estimates of the separation time between Africans and non-Africans suggest that this predates the appearance of modern humans in Europe and Asia by up to 60,000 years. We have suggested a scenario of exodus from Africa via an intermediate population in East Africa and the Middle East, which may fit better with growing evidence for modern human occupation of the latter region before the wider colonization of Eurasia and may provide a longer interval for Neanderthal admixture with non-African populations. Finally, revised split times of 40,000–80,000 years ago for Europeans and Asians agree better with the palaeoanthropological record and with estimates from mtDNA.

In one or two cases, the revised nuclear chronology is older than the corresponding estimates from mtDNA. Factors such as sampling and introgression may lead to discordance in timing or ancestry between these loci, but it may also be that further investigation is warranted into the mtDNA timescale itself, which can be variously calibrated on external phylogenetic comparisons, on events within the human phylogeny or on both, depending on methodology.

Additionally, we note that the revision in mutation rate also doubles estimates of the population genetic parameter N_e as observed genetic diversity is proportional to the product of N_e and the mutation rate. This may have consequences for certain model-based interpretations.

Although the stochastic nature of genetic inheritance limits the resolution with which we can reconstruct ancestral demography, there are several important questions (which have been touched on in this discussion) that further sampling and novel methodological approaches may enable us to address. Furthest back in time, there is the timescale of divergence between humans and Neanderthals and how accurate our picture is of a split 500,000 years ago with limited admixture at a later date. Another question is the degree of ancestral population structure in modern humans around the time of their appearance in Africa and subsequently before the colonization of Eurasia. We note that a prediction under our scenario of an intermediate population in East Africa and the Middle East is that East African genomes associated with older L3 mtDNA haplotypes should contain sequence that is more similar to European and Asian genomes than Yoruba is while still predating the European–Asian split. Also, if there was admixture with other hominins[55] within Africa during this time — for example, in West Africa — we might expect to see this correlated with signals of ancestral population structure in present-day Africans. Outside Africa, there are questions around the timing of migrations into Asia and Australasia, which may have occurred gradually and in multiple waves rather than as a rapid event 50,000 years ago. Further study of genetic diversity across the whole genome, particularly in Africa, will be important in addressing these questions and clarifying our picture of recent human evolution.

Glossary

Effective population sizes
(N_e). Indicate how many individuals actually contribute alleles to the next generation, as opposed to the total number of individuals in a population. The expected time to the most recent common ancestor of two individual copies of a locus is proportional to N_e.

Hominoid slowdown
The phenomenon in which shorter phylogenetic branch lengths are found within apes relative to other primate lineages.

Haplogroups
Branches of the mitochondrial DNA phylogenetic tree that comprise a collection of related haplotypes. Each haplotype represents a unique pattern of DNA substitutions.

Coalescence
When two genetic lineages find a common ancestor.

Homo heidelbergensis
Fossil hominin predominantly found in Europe but also in Africa that typically dates to 400,000–600,000 years ago and a possible ancestor of both Neanderthals and modern *Homo sapiens*.

Recent African origin model
(RAO model). A model of human origins in which the transition from archaic forms to modern *Homo sapiens* occurred solely within Africa, followed later by migration out of Africa and dispersal across Eurasia.

Khoe–San
Indigenous people of the Kalahari desert in Southern Africa.

Molecular clock
The idea that nucleotide substitutions accumulate at a constant rate over time and that this rate can therefore be used to estimate divergence times between sequences.

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