Genotype imputation using the Positional Burrows Wheeler Transform

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Abstract

Genotype imputation is the process of predicting unobserved genotypes in a sample of individuals using a reference panel of haplotypes. Increasing reference panel size poses ever increasing computational challenges for imputation methods. Here we present IMPUTE5, a genotype imputation method that can scale to reference panels with millions of samples. It achieves fast and memory-efficient imputation by selecting haplotypes using the Positional Burrows Wheeler Transform (PBWT), which are used as conditioning states within the IMPUTE model. IMPUTE5 is 20x faster than MINIMAC4 and 3x faster than BEAGLE5, when using the HRC reference panel, and uses less memory than both these methods. IMPUTE5 scales sub-linearly with reference panel size. Keeping the number of imputed markers constant, a 100 fold increase in reference panel size requires less than twice the computation time.

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Introduction

Genotype imputation is a ubiquitous method in human genetic studies that infers unobserved genotypes in a sample of individuals. In a typical scenario, the study samples are genotyped on a SNP microarray with between 300,000 to 5 million markers. This data is then combined with a reference panel of haplotypes with many tens of millions of markers, and a statistical model is used to predict the genotypes at these markers in the study samples [1].

One of the main applications of genotype imputation is to increase the resolution of genome-wide association studies (GWAS). Imputed datasets increase the number of markers that can be tested for association. For example, in the UK Biobank dataset [2] imputation increased the number of testable markers from 825,927 to over 96 million. This increased number of SNPs can boost the power of the study. Genotype imputation also facilitates meta-analysis across cohorts that are often genotyped using different SNP microarrays. Imputatation on from the same reference panel standardizes the set of testable markers, allows simple integratation of data and/or results across studies [3]. Imputation can also be used to predict markers necessary to calculate polygenic risks scores (PRSs), which typically involve a weighted sum of genotypes across the genome.

Many different methods have been proposed over the years [4], however the most widely used and accurate methods are based on Hidden Markov Models (HMM). Typically the study samples will have been phased in advance using accurate methods [5–7], and this has become known as 'pre-phasing' [8]. The imputation HMM is then used to model the sharing of sequence between the haplotypes in the study sample (which we refer to as the *target haplotypes*) and the haplotypes in

the reference panel. The HMM models each study haplotype as an imperfect mosaic of haplotypes in the reference panel [1]. The output of the HMM at each position in the genome is a vector of copying probabilities for each haplotype in the reference panel. For each of the markers in the reference panel these are used to make a weighted prediction of the unobserved allele at the markers.

One of the most important factors that determines imputation quality is the number of haplotypes in the reference panel. As the number of haplotypes increases, each study sample haplotype is able to find fewer longer stretches of matching sequence in the reference panel, which increases the accuracy. Table 1 shows how reference panel size has increased over the years due to projects such as the International HapMap Project [9], the 1000 Genomes Project (1000G) [10], the UK10K Project [11], and the Haplotype Reference Consortium (HRC) [12]. Soon larger reference panels will become available from the Trans-Omics for Precision Medicine (TOPMed) program [13] and the 100,000 Genomes Project [14], both of which will exceed 100,000 high-coverage whole genome sequenced samples. Further ahead, as sequencing data on all 500,000 participants of the UK Biobank [2] becomes available, this will be used as an even larger reference panel.

In this paper we present IMPUTE5, a genotype imputation method designed to handle the new generation of reference panels. To achieve this, the method builds on three main components: (i) the use of a new reference panel file format, allowing fast access to data in specific chromosome regions (ii) the use of the PBWT [15] to select a subset of reference panel haplotypes and reduce the state space in the IMPUTE model [16] (iii) imputation during output directly into the BGEN [17] file

Reference panel	Released Year	Number of Samples	Number of Markers (Millions)
HapMap Project phase 3	2009	1,011	1.4
1000 Genomes phase 1	2012	1,092	29.0
1000 Genomes phase 3	2014	2,504	81.7
UK10K Project	2015	3,781	42.0
HRC	2016	32,470	40.4

Table 1. Evolution of commonly used imputation reference panels over time.

format that is specifically designed for imputation data.

To demonstrate the superior performance of IMPUTE5, we benchmark our imputation method against against IMPUTE4 [2], MINIMAC4 [18] and BEAGLE5 [19], using simulated reference panels up to 1,000,000 haplotypes in size, and real reference panels such as the 1000 Genomes project reference panel [10] and the Haplotype Reference Consortium [12].

Materials and Methods

PBWT The main methodological advance in this paper is the incorporation of the PBWT [15] into the IMPUTE model. This section provides some brief background on the PBWT needed to describe the IMPUTE5 method. The PBWT is a generic way to encode binary matrices, especially useful in the case of haplotypes at a set of binary markers, each with two alleles arbitrarily coded as 0 and 1. Let $H = \{h_0, h_1, \ldots, h_{N-1}\}$ be a set of N haplotypes genotyped at M markers, $h_n = \{h_{n,0}, h_{n,1}, \ldots, h_{n,M-1}\}$, where $h_{n,m} \in \{0, 1\}$, represents the nth haplotype. H can be

thought as a $N \times M$ binary matrix: each entry of the matrix is defined by the reference haplotype (row) and marker (column). For this reason, we refer to H using the usual matrix notation.

The PBWT of H, indicated as Y, is another $N \times M$ binary matrix, where the m-th column of Y is an invertible transformation of the m-th column of H. In its basic form, Y is complemented by another $N \times (M+1)$ matrix A, where every column $A_{:,m}$, called the *positional prefix array*, is a permutation of $\{0, \ldots, N-1\}$ which defines the reverse prefix order of the haplotypes in H up to marker $m-1$.

Using a similar notation as in [20], we define the binary string $h^r_{n,1:m}$ as the reverse prefix of the n-th haplotype ending at marker m:

$$h^r_{n,0:m} = h_{n,m} h_{n,m-1}, \ldots, h_{n,0} \tag{1}$$

and let be $\{h^r_{n,1:m}\}_n$ be the set of all the N reverse prefixes at marker m. We then define $A_{n,m}$ to be the index of the n-th lexicographically sorted reverse prefix along the set $\{h^r_{n,1:m}\}_n$. $A_{:,m}$ represents a bijection on $\{0, \ldots, N-1\}$ and thus is invertible. As a special case, we define $A_{n,-1} = n$, representing the order of empty reverse prefixes.

The PBWT of H is directly derivable from H and the prefix array A:

$$Y_{n,m} = H_{A_{n,m-1},m} \tag{2}$$

in other words, the PBWT at marker m is the vector of values of the haplotypes in H at marker m,

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$(H_{:,m})$, in the order defined by the reverse prefix array at marker $m-1$, $A_{:,m-1}$.

One use of $Y_{:,m}$ is to update $A_{:,m-1}$ to $A_{:,m}$. Suppose b is a symbol, $b \in \{0,1\}$. We can define a mapping between positional prefix array at markers $m-1$ and m:

$$\phi_m(n) = c_m(Y_{n,m}) + rank_m(Y_{n,m}, n) \tag{3}$$

where $c_m(b)$ gives the number of symbols in $Y_{:,m}$ that are lexicographically smaller than b and $rank_m(b,n)$ the number of b symbols in $Y_{:,m}$ before position n. The n-th haplotype in the positional prefix order at column $m-1$ is ranked $\phi_m(n)$ in column m. Thus

$$A_{\phi_m(n),m} = A_{n,m-1} \tag{4}$$

Eq. (2) and (4) give a procedural algorithm to compute $A_{:,m}$ and $Y_{:,m}$ from $H_{:,m}$ and $A_{:,m-1}$. Since there is strong correlation between adjacent markers in H due to linkage disequilibrium, there are long runs of the same symbol in the columns of Y. This makes columns of Y much more compressible than the columns of H.

Y and A represent only the basic form of the PBWT. It is possible to complement them by storing additional information such as the rank indices U, V (usually called FM index [21]). Each column m of these two matrices store information about the $rank_m(b,n)$ for symbol $b = 0$ and $b = 1$ respectively. It is also important to notice that there is no need to store both these matrices because it is possible to derive one from the other: $rank_m(1-b,n) = n + 1 - rank_m(b,n)$ since

$$rank_m(0, n) + rank_m(1, n) = n + 1.$$

Another important information that can be added is the divergence matrix D. Columns of D contain the position of the last (reverse prefix) mismatch between adjacent haplotypes in the order A. The value of $D_{n,m}$ is defined to be the smallest value m' such that $h^r_{n,0:m-1}$ matches $h^r_{n-1,0:m-1}$. In the case of a mismatch, the value of $D_{n,m}$ is set to m. An important property is that the start of any maximal match ending at m between any $\{h^r_{i,1:m}, h^r_{j,1:m}\}, (i < j)$ is given by:

$$max_{i<n\leq j}D_{n,m} \tag{5}$$

The cost of building a PBWT Y from H is $O(NM)$, including all the complementary matrices described above. Using the PBWT indices, it is possible to find maximal matchings within H in linear time and find maximal matchings of a new sequence z in H in $O(M)$, independently from the number of haplotypes in H.

IMPUTE model IMPUTE5 is a haploid imputation method, assuming that both the reference and study samples are phased. In what follows we will refer to the phased study samples as the *target panel* of haplotypes. IMPUTE5 uses the same HMM used in previous versions of the IMPUTE software [16] that is based on the Li and Stephens model [22]. Each reference haplotype represents a hidden state of the HMM. The model assumes that each target haplotype is an imperfect mosaic of haplotypes emitted from the sequence of hidden states representing the reference panel haplotypes. The changes from one state to another are modelled as recombination events and the observed target allele may differ from the alleles on the underlying true haplotypes to allow for mutation

and genotype error.

HMM definition Let H be the set of N haplotypes genotyped at M markers, that have been selected as a subset from a reference panel of haplotypes. The way in which the N haplotypes are chosen in each window is described in a later section. We also have a set of K study sample (target) haplotypes, defined only at a subset of the M markers. We refer to the set of T markers that are genotyped in both the panels as *target markers* ($\mathcal{T}$), and the others, present only in the reference panel, as *reference markers* ($\mathcal{R}$). Consecutive pairs of haplotypes represent the diplotype of each study individual. We define the HMM model only at target markers. Therefore, we use the symbol $H^{\mathcal{T}}$ to indicate the restriction of the reference panel H to target markers and we use the symbol m to indicate a marker in $\mathcal{T}$.

Given a target haplotype t the probability of observing t from $H^{\mathcal{T}}$ can be then written as:

$$Pr(t|H^{\mathcal{T}}, \rho) = \sum_{Z} Pr(t|Z)Pr(Z|H^{\mathcal{T}}, \rho) \tag{6}$$

where Z is a sequence of unobserved copying labels, one for each target marker, $Z_m \in \{0, 1, \ldots, N-$

1} and the term $Pr(Z|H^\mathcal{T}, \rho)$ models sequence of transitions of the HMM and is defined by

$$Pr(Z|H^\mathcal{T}, \rho) = Pr(Z_1) \prod_{m=1}^{T} P(Z_{m+1}|Z_m) \tag{7}$$

$$Pr(Z_1 = n) = \frac{1}{N}; \tag{8}$$

$$Pr(Z_{m+1} = i|Z_m = j) = \begin{cases} (1 - \rho_m) + \frac{\rho_m}{N} & \text{if } i = j, \\[2ex] \frac{\rho_m}{N} & \text{otherwise.} \end{cases} \tag{9}$$

where ρ_m is a locus specific parameter modelling genetic recombination events, defined as $\rho_m = 1 - e^{\frac{-4Ne(r_{m+1} - r_m)}{N}}$, where N_e is the effective diploid population size and $r_{m+1} - r_m$ is the average rate of crossover per unit physical distance per meiosis between target markers $m + 1$ and m multiplied by their physical distance. Eq. 9 is motivated by the fact that recombination events can be described as a Poisson process having rate $4N_e(r_{m+1} - r_m)$.

We model the emission probability $Pr(t|Z)$ in Eq. 6 differently to the standard IMPUTE model, and we adopt a simpler version as in the SHAPEIT4 model [6], reducing the equation to:

$$Pr(t|Z) = \prod_{m=1}^{T} Pr(t_m = a|Z_m = n) \tag{10}$$

$$Pr(t_m = a|Z_m = n) = \begin{cases} 0.9999 & \text{if } h_{n,m} = a \\[2ex] 0.0001 & \text{otherwise.} \end{cases} \tag{11}$$

where $a \in \{0, 1\}$ is a haplotype value. It has been shown that imputation is relatively insensible to the mutation parameter [23], and we tested that the new emission probability slightly increases both accuracy and speed, especially in the case of big reference panels.

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Imputation The posterior probability of the hidden states is computed using the forward-backward algorithm [24]. IMPUTE5 calculates and stores these quantities at each target marker. The imputation step is performed after the marginal posterior distribution of the copying states has been computed. The state probabilities at reference markers $\mathcal{R}$ can be linearly interpolated from the probability at the two bounding target markers. The motivation of using linear interpolation is, that over short genetic distance, the change in state probabilities can be approximated by a straight line [2,23]. The imputed probability for a particular allele is then just the sum of all the state probabilities at that marker in which the correspondent reference haplotypes carry the allele.

As performed by BEAGLE5 [19], we store state probabilities at consecutive markers for a reference haplotype only if one of the state probabilities is greater than the inverse of the number of HMM states. Since only a small subset of the state probabilities at consecutive markers needs to be stored, imputation can be delayed during output, saving the memory required to store imputed probabilities at reference markers.

State Selection Using the PBWT IMPUTE5 uses the PBWT of the reference panel at target markers to identify a subset of states that share long identity by state (IBS) sequences with target haplotypes. Using just a subset of haplotypes saves computation time memory usage. The copying state selection is performed upfront before the HMM calculations and determines the set of N haplotypes in $H^{\mathcal{T}}$. This set will be different for each target haplotype.

The PBWT of the reference panel at the target markers is calculated sequentially from left to right across the region being imputed, and the state selection occurs at the same time. So after one

pass through the full dataset the state selection has been performed for *all* the target haplotypes. This means that there is no need to store the full PBWT of the reference panel in memory.

The selection procedure occurs in two steps. First, each target haplotpes is inserted (or located) in the PBWT. Second, haplotypes 'close' to the target haplotype in the PBWT are identified. This selection only occurs at a relatively sparse set of target markers. Moving left to right through the PBWT the set of 'close' haplotypes are added to a list, and this list is then used as the copying set of states in the HMM. Figure 1 illustrates the method on a small example dataset.

Inserting each target haplotype into the PBWT involves searching the prefix array of the reference panel using Eq. 3 and the FM-index. For a target t at marker m, this search finds the location of the reference haplotype in the PBWT that shares the longest reverse prefix with t up to marker m.

The updated matched position f of the target t at marker m is given by:

$$f = \begin{cases} U_{f,m}, & \text{if } t_m = 0 \\ \\ c_m + V_{f,m}, & \text{otherwise} \end{cases} \tag{12}$$

where c_m, $U_{:,m}$ and $V_{:,m}$ are respectively the number of 0s in each marker m, and the rank matrices for the reference panel at marker m. The search itself costs $O(1)$ at each marker using the FM-index of the PBWT, and it is therefore independent of the number of haplotypes in the reference panel.

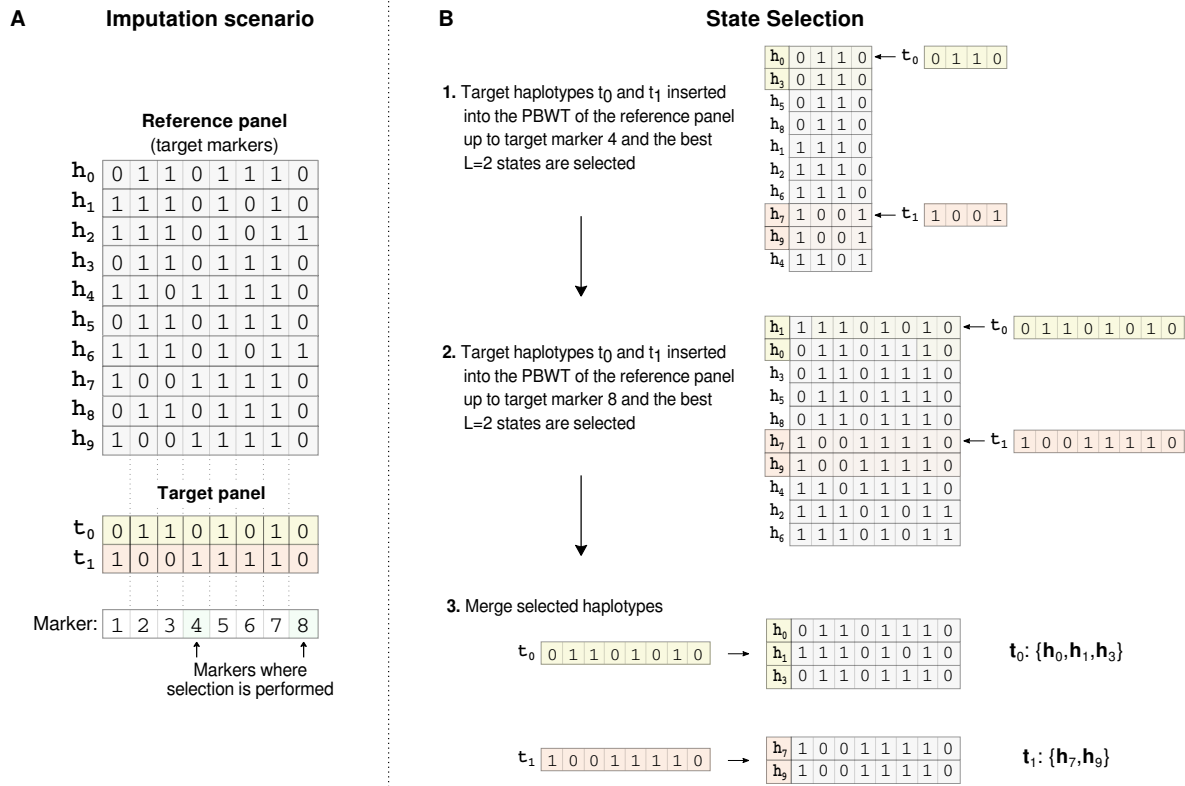We keep the list of locations for each target haplotype. At each marker, we first update the

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Fig 1. IMPUTE5 copying state selection Small example to illustrate IMPUTE5 copying state selection. (A) A reference panel of haplotypes $H = \{h_0, \ldots, h_9\}$ is restricted to the set of target markers and is shown together with a target panel of two haplotypes $T = \{t_0, t_1\}$. The copying state selection is only performed at a subset of target markers. In this example, these are the 4th and 8th markers, and are shaded green. (B) The target haplotypes are inserted into the PBWT, using the rank operations (FM-index). In (B1) target haplotypes $\{t_0, t_1\}$ are searched in the positional prefix array of the reference panel up to marker 4 and $L = 2$ reference haplotypes are selected for each target haplotype. In (B2) t_0 and t_1 are searched in the positional prefix array of the reference panel up to marker 8 and again L reference haplotypes are selected. (B3) The selected haplotypes are then merged to form a list of copying states for each target haplotype. The list may not necessarily be the same length. These states will be used in the HMM to perform imputation.

PBWT of the reference marker, and then we update the list of target locations. The selection is performed every interval of length I (0.1 cM by default). We call *selection markers* the markers where the selection is performed. The cost of the search is $O((N + K)M)$, where K is the number of target haplotypes.

Selection algorithms IMPUTE5 has two algorithms that select the 'closest' L haplotypes to the target haplotype within the PBWT. Both selection methods have $O(LK)$ computational cost. The first one, which we call *divergence selection*, and first proposed in the software package SHAPEIT4 [6], selects the best L states in the neighbourhood of the current match position f by using the divergence matrix, exploiting Eq. 5.

By design the PBWT encapsulates a large amount of local linkage disequilibrium information. The longest reverse prefixes are by definition in the neighbourhood of the best matching haplotype found during the search. In order to take only the best haplotypes, the divergence matrix is used.

Starting from an optimal position f at marker m, it checks the values of the divergence array at $i = f - 1$ and $j = f + 1$. If $D_{i,m} <= D_{j,m}$ then i is decreased and positional prefix $A_{i,m}$ is added to the list of selected states, otherwise j is increased and $A_{j,m}$ is added to the list. The algorithm continues until L states are selected. A pseudo algorithm of the copying state selection is shown in Algorithm S1.

The second selection algorithm, which we call *neighbour selection*, does not use the diver-

gence matrix. At every selection marker, it simply takes the L neighbouring states ($L/2$ in both the directions) of the current best match position. This algorithm only guarantees to select the best $L/2$ reverse prefixes, but it requires less operations than the divergence selection, because it does not need to compute and interrogate the divergence array for that marker. The only checks needed are when the target haplotype occurs close to a border (start or end of the positional prefix array), and to avoid copying a mismatch position. In the case that the target haplotype is close to a border, less than L states are selected for that marker. A pseudo algorithm of the copying state selection is shown in Algorithm S2.

Durbin et al. [15] proposed an algorithm to find the set of set maximal matches with the target haplotypes. The set of set maximal matching is the set of states that share the longest stretches with the target haplotype. We tested the use of the set maximal matches as a selection algorithm and we found that these contain a lot, but not all of the relevant information, and there is a small but evident loss in accuracy when we use only those matches.

IMP5 File Format We developed a new file format, called imp5 to read the reference panel quickly into memory. Each marker is stored independently in one of two different ways: if the alternative allele is rare (MAF $< 1/256$), the indices of the haplotypes that carry the alternative allele are stored, otherwise the sequence of alleles is stored using one bit per allele. Imp5 files are compact in memory and do not require other compression algorithms like gzip. This makes reading from a file an efficient operation, similar to bref3 [19].

This data structure is also used internally within IMPUTE5 to store the reference panel in

memory. When imputing each target haplotype, at each target marker, the set of selected reference haplotypes that carry the alternate allele are needed. If the target site is stored as a bitset in the reference panel then the lookup is straightforward. If the site is stored as a list of indices of alternate alleles then either the list of reference panel indices is searched for the selected state index, or vice versa, depending upon which search is likely to be quicker.

Another feature of the imp5 files is that they are indexed, so that regions can be extracted efficiently. The indexing was developed along the same lines as *bgenix* [17], using sqlite3. The indexing is an important feature for imputation, especially when imputing different windows on the same chromosome independently. Other file formats like bref3 [19] and m3vcf [18] do not provide an index and therefore cannot directly interrogate arbitrary regions in constant time. In addition to this, IMPUTE5 can also read VCF/BCF reference panels.

IMPUTE5 requires that the reference and the target panel files are indexed, using the native imp5 index or tabix in the case of VCF/BCF files. In this way, several independent imputation jobs can be run at the same time, using a multi-process parallelization approach. A comparison of the memory required to store m3vcf, bref3 and imp5 file formats is given in Table 2.

Parallelization A typical IMPUTE5 job runs multiple 5Mb regions in parallel. Each region is completely independent from the others and can be run on different machines. The use of the indexing of the IMP5 files allows each process to read the reference panel efficiently.

Output is written in GEN, VCF or BGEN v2 file format [17], all explicitly designed to store

Reference panel	vcf.gz	bcf	m3vcf.gz	bref v3	imp5
Sim10K	0.06	0.04	0.02	0.02	0.04
Sim100K	0.83	0.56	0.15	0.11	0.42
Sim1M	18	10	1.90	0.75	4.06

Table 2. Memory (GB) required by reference file formats. Memory usage in Gigabytes required to store 10 Mb of reference sample data for 10K, 100K, and 1M simulated UK European reference samples stored in vcf.gz, bcf, m3vcf.gz, bref3 and imp5 file formats. For the imp5 file format, the value reported is the sum of the memory required by the imp5 file plus the index file. Imp5 has been optimised to provide random access and fast reading time for a region of the chromosome, and not for data compression.

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imputed data. Merging GEN and BGEN files at the end of imputation is an efficient process and allows to impute each window independently (*cat* or *cat-bgen* commands are used to merge output files).

IMPUTE5 can also multi-thread each process. We developed multi-threading using a shared memory approach. Each thread is responsible for a single target haplotype when running the HMM, or an imputation region between two target markers. The data sharing approach is crucial for reducing the memory required by each computational thread.

Real and simulated data experiments We compared IMPUTE5 to other existing imputation methods using real reference panels from the 1000 Genomes Project [10] and the Haplotype Reference Consortium [12]. We used data from both chromosome 10 and chromosome 20. For both panels we extracted a subset of samples, thinned down to a subset of sites, that are uses as the target

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haplotype panel, and used the remaining samples as reference panel. We also use a UK-European reference panel of simulated data for 10K, 100K, and 1M samples generated using MSPRIME [25]. Details of the real and simulated datasets are summarised in Table 3.

Reference Panel	Length (Mb)	Number of Reference Samples	Number of Reference Markers	Target Marker Description	Number of Target Markers
1000 Genomes chr 20	62.9	2,452	1,569,377	Illumina Omni2.5	53,183
1000 Genomes chr 20	62.9	2,452	1,569,377	Infinium OmniExpress-24	17,806
1000 Genomes chr 10	135.5	2,452	3,431,035	Illumina Omni2.5	111,570
1000 Genomes chr 10	135.5	2,452	3,431,035	Infinium OmniExpress-24	37,798
HRC chr 20	62.9	31,470	884,983	Illumina Omni2.5	53,600
HRC chr 20	62.9	31,470	884,983	Infinium OmniExpress-24	18,002
HRC chr 10	135.5	31,470	1,927,503	Illumina Omni2.5	111,657
HRC chr 10	135.5	31,470	1,927,503	Infinium OmniExpress-24	38,206
Panel A Sim10K	10.0	10,000	223,116	> 5% MAF	3,333
Panel A Sim100K	10.0	100,000	747,162	> 5% MAF	3,333
Panel A Sim1M	10.0	1,000,000	2,274,530	> 5% MAF	3,333
Panel B Sim10K	10.0	10,000	223,116	> 0.05% MAF in Panel B Sim1M	33,333
Panel B Sim100K	10.0	100,000	223,116	> 0.05% MAF in Panel B Sim1M	33,333
Panel B Sim1M	10.0	1,000,000	223,116	> 0.05% MAF in Panel B Sim1M	33,333

Table 3. Summary of the real and simulated datasets used in comparing methods.

1000 Genomes Project The 1000 Genomes Project phase 3 dataset contains phased sequenced data of 2,504 individuals sampled from 26 different populations. As performed in the BEA-GLE5 paper [19], we selected two random individuals from each population for the imputation target and used the remaining data as a reference panel. We restricted the 1000 Genomes reference data to markers having at least one copy of the minor allele in the reference panel, get-

ting 3,431,035 markers on chromosome 10 and 1,569,377 markers on chromosome 20. In the 52 target samples, we masked markers that were not on the Illumina Omni2.5 array and the less dense Infinium OmniExpress-24 v1.2, resulting in 111,570 (Omni 2.5) or 37,798 (Infinium OmniExpress-24) target markers on chromosome 10 and 53,183 (Omni 2.5) or 17,806 (Infinium OmniExpress-24) target markers on chromosome 20. The list of markers was obtained from `https://www.well.ox.ac.uk/~wrayner/strand/`.

The Haplotype Reference Consortium Haplotype Reference Consortium (HRC) [12] reference panel combines sequence data across 32,470 individuals from 20 sequencing studies. We randomly selected 1,000 target individuals from the HRC panel, and used the other 31,470 as a reference panel.

We removed monomorphic markers in the reference samples. In the target samples, we masked markers that were not on the Omni2.5 array and Infinium OmniExpress-24 v1.2, resulting in 111,657 (Omni2.5) or 38,206 (Infinium OmniExpress-24) target markers on chromosome 10 and 53,600 (Omni 2.5) or 18,002 (Infinium OmniExpress-24) target markers on chromosome 20.

Simulated Reference Panels As performed in the BEAGLE5 paper [19], we used MSPRIME [25] to simulate a 10Mb region of sequence data of UK-European samples. We simulated 11,000, 101,000 and 1,001,000 samples and extracted 1,000 samples from each of the three dataset, in order to have three reference panels of size 10K, 100K and 1M samples. We split each of the 1,000 target samples into three different target panels of size 10, 100 and 1,000.

In the target panels, we masked all but 3,333 markers, randomly selected between the markers having MAF $> 5\%$, to simulate chip sites. The reference panels have 223,116, 747,162 and 2,271,530 markers respectively. We refer to this setting (reference panel + target panels) as Panel A.

We created 3 other simulated datasets (called Panel B), with 1 million, 100,000 and 10,000 samples, and each with the same number of 223,116 markers. We created 3 target panels of size 10, 100 and 1,000 samples at a subset of 33,333 markers by randomly selecting markers having MAF $> 0,05\%$ in the 1M reference panel. Panel B is used to benchmark imputation on the same set of markers, varying the size of the reference panels.

Results

Comparison of Methods We compared IMPUTE5 to IMPUTE4, MINIMAC4 (v.1.0.0) [18] and BEAGLE5 (v.16May19.351) [19]. We used default parameters for each program. IMPUTE4 and IMPUTE5 require specification of an imputation region, and we used windows of 5Mb for 1000 Genomes and the HRC reference panels. A single window is enough for the 10Mb simulated reference panels. For both programs, we used a buffer region of 500 kb for each imputed window.

We used the HapMap2 [9] genetic map for BEAGLE5 and IMPUTE5 for real data imputation, and the true genetic map for analyses with simulated data. MINIMAC does not require a genetic map, as recombination parameters are estimated and stored when producing the m3vcf format input file for the reference data.

BEAGLE5, MINIMAC4 and IMPUTE5 use their specialized formats for reference panel data: bref3 for BEAGLE5, m3vcf 4 for MINIMAC4 and imp5 for IMPUTE5. IMPUTE5 has two different haplotype selection algorithms that we call *divergence selection* and *neighbour selection* (see Methods), both of which have a parameter L that controls the number of selected haplotypes. We tested both selection algorithms using $L = 8$. IMPUTE4 was run with all reference panels except on the simulated reference panels, mainly beceause IMPUTE4 is limited to 65,536 reference haplotypes and does not run on the two largest reference panels (100K, 1M).

As in previous papers [10,12,19], we measured performance by comparing the imputed allele probabilities to the true (masked) alleles. Markers were binned into frequency bins according to the minor allele count of the marker in the reference panel. In each bin we report the squared correlation (r^2) between the vector of all the true (masked) alleles, and the vector of all posterior imputed allele probabilities.

All imputation analyses were run on a 16-core computer with Intel Xeon CPU E5-2667 3.20GHz processors and 512 GB of memory.

Imputation accuracy Fig 2 shows the performance of all the methods on the Panel A simulated reference panels of size 10K, 100K, and 1M samples using $L = 8$ setting for IMPUTE5. Results using $L = 4$ are shown in Fig S3. These results illustrate the very close agreement between the methods. All the methods compared use the same Li and Stephens probabilistic model [22] so this is not surprising. The imputation performance of the three reference panels look visually similar, and this can be explained by the use of minor allele count (MAC) rather than minor allele frequency

(MAF), on the x-axis of each of the plots. For example, the performance of the 100K and 1M reference panels both have an $r^2 \approx 0.6$ at MAC=2, but these are a factor of 10 difference in terms of MAF.
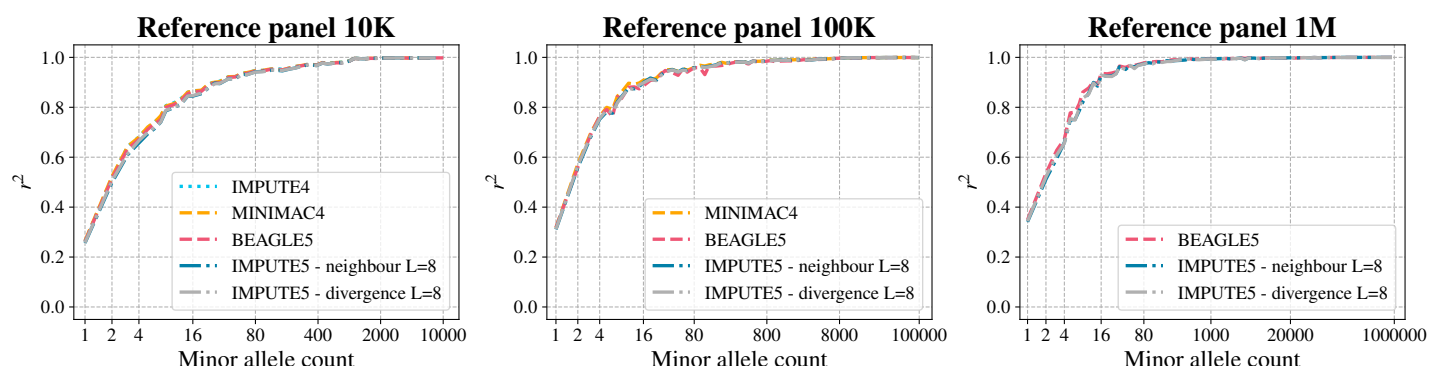

Fig 2. Imputation accuracy using Panel A dataset Genotype imputation accuracy when imputing genotypes from a simulated reference panel of 10K, 100K and 1M UK-European reference samples (Panel A). Imputed alleles are binned according to their minor allele count in each reference panel. The squared correlation (r^2) between the true number of alleles on a haplotype (0 or 1) and the imputed posterior allele probability is reported for each minor allele count bin. The horizontal axis in each panel is on a log scale.

Supporting Information shows the performance of IMPUTE5 for a range of values of $L \in \{1, 2, 4, 8, 16\}$) for both the selection algorithms proposed. As expected, increasing the value of L also accuracy increases, however, for values of $L >= 8$ imputation accuracy is almost indistinguishable. Both the selection algorithms perform well for values of $L \geq 8$, however neighbour selection algorithm seems to perform better for values of $L < 4$. This is probably explained by the fact that neighbour selection algorithm tends to select more states than divergence selection algorithm, making it more robust even with smaller values of L.

Fig 3 shows the results using the real reference panels, and shows a very slightly increase in
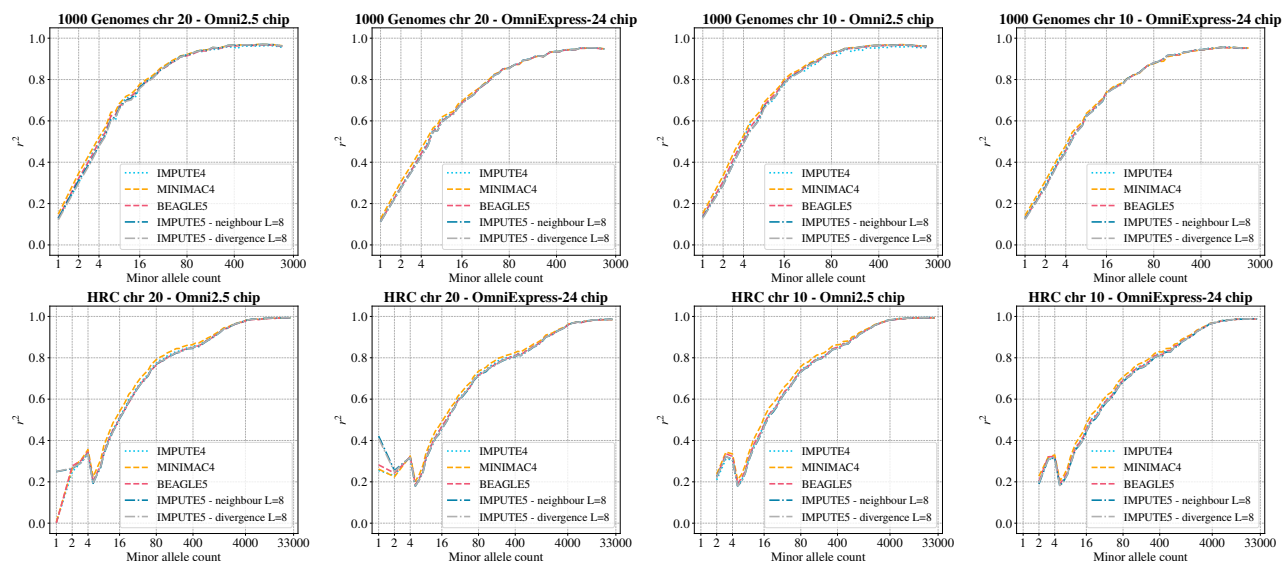
Fig 3. Imputation accuracy using 1000 Genomes and HRC datasets

Genotype imputation accuracy when imputing genotypes using the 1000 Genomes Project reference panel ($n = 2452$) and the Haplotype Reference Consortium reference panel ($n = 31470$). Imputed alleles are binned according to their minor allele count in each reference panel. The squared correlation (r^2) between the true number of alleles on a haplotype (0 or 1) and the imputed posterior allele probability is reported for each minor allele count bin. The horizontal axis in each panel is on a log scale.

accuracy when MINIMAC4 is used. The likely explanation is that MINIMAC4 performs an HMM parameter estimation step when m3vcf files are created, and this adds some adaption to genotyping errors and recombination rate variation. This explains also why we do not see differences between methods in Fig 2, because in that case the real recombination map in known and no genotyping errors are present for the MSPRIME simulations. Results using $L = 4$ are shown in Fig S4.

Computational efficiency Table 4 shows single core memory usage and time and parallel computation time of running MINIMAC4, BEAGLE5 and IMPUTE5 to impute the whole chromosome 20 and 10 for 1000 Genomes and HRC reference panels. MINIMAC4 and BEAGLE5 were run

using a single job on a single core,whereas IMPUTE5 was run on approximately 5 Mb chunks sequentially using a single core and $L = 8$. MINIMAC4 and BEAGLE5 were run using their default chunk size (20 Mb and 40 cM respectively). For both the 1000 Genomes and HRC reference panel, IMPUTE5 is at least 2 times faster than BEAGLE5, and on the HRC reference panel it is over 20 times faster than MINIMAC4. Results using $L = 4$ are shown in Table S1.

Fig 4 and Table 5 show the per-sample computation times for IMPUTE5, BEAGLE5 and MINIMAC4 for 10K, 100K and 1M simulated reference panels when imputing a set of 1,000 target samples on a 10Mb region. All methods were run using a single core on the same machine. The results are plotted on log-log scale, which illustrates that both BEAGLE5 and IMPUTE5 exhibit sub-linear scaling as reference panel size increases. For Panel A results, moving from 10K to 1M reference samples increases the number of reference samples by a factor of 100 and the number of reference markers by a factor of 10, but IMPUTE5s imputation time increases by only a factor of 7.5. Overall the results show that IMPUTE5 is consistently faster than all the alternative methods. Results using $L = 4$ are shown in Fig S5 and Table S2.

Dataset	Single core memory usage (MB)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	1,792	7,243	**308**	1,696	6,698	**437**
1000 Genomes chr 10	2,472	11,202	**367**	2,316	11,985	**522**
HRC chr 20	4,842	15,455	**2,368**	4,405	13,361	**936**
HRC chr 10	4,896	17,556	**2,428**	4,417	14,592	**1,001**

Dataset	Single core time (mm:ss)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	02:33	01:24	**00:32**	01:37	01:11	**00:26**
1000 Genomes chr 10	05:16	02:48	**01:04**	03:30	02:31	**00:52**
HRC chr 20	252:59	21:33	**09:13**	124:28	15:26	**05:52**
HRC chr 10	494:59	41:14	**18:26**	250:24	30:16	**12:01**

Dataset	Parallel time (mm:ss)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	01:08	00:15	**00:03**	01:08	00:12	**00:03**
1000 Genomes chr 10	02:25	00:28	**00:05**	01:56	00:24	**00:06**
HRC chr 20	27:13	02:12	**00:52**	15:07	01:20	**00:32**
HRC chr 10	56:08	06:07	**01:34**	30:54	02:41	**01:01**

Table 4. Memory usage and time to impute 1000 Genomes and HRC datasets. Memory usage and total time to impute a whole chromosome (chr 10 and chr 20) for 52 target samples when using the 1000 Genomes reference panel and 1000 target samples when using the HRC reference panel. IMPUTE5 was run on chunks of size 5 Mb, MINIMAC on chunks of size 20 Mb and BEAGLE5 on chunks of size 40 cM. Time is shown using the format mm:ss. Bold font is used to indicate the method with the lowest time. For the parallel computations, BEAGLE5 and MINIMAC4 were run using a single process with 16 threads; IMPUTE5 was run in 16 (chr 20) or 32 (chr 10) windows of size $\approx$ 5Mb, each of them run in parallel as a different process.

Dataset	Single core time (mm:ss)					
	Panel A			Panel B		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
10K reference panel	01:41	01:44	**00:48**	08:33	02:43	**02:41**
100K reference panel	09:20	03:50	**01:57**	65:15	04:10	**02:46**
1M reference panel	-	09:15	**06:22**	1690:50	18:08	**04:33**

Table 5. Single core time to impute Panel A and Panel B datasets. Total time to impute $1,000$ target samples in a 10Mb window using simulation data in Panel A and Panel B dataset. Time is shown using the format mm:ss. Bold font is used to indicate the method with the lowest time. Minimac4 was not able to run using the Panel A 1M reference panel due to time constraints in the construction of the m3vcf file.

Fig 4B and Table 5 show the imputation time for Panel B dataset. All the reference panels in Panel B have the same number of markers. In this case we have a very dense set target markers (33,333) and so more time is spent for the Li and Stephens calculations compared to Panel A scenario. The time spent by IMPUTE5 for the Li and Stephens HMM and imputation actually decreases when the number of reference haplotypes is increased. The increase in time shown in Fig 4B from 10K reference panel to 1M reference panel is only due to increased time to read the input and run the selection algorithm, the only linear components of IMPUTE5.

Fig 5A shows that the imputation time per sample decreases when the number of target haplotypes increases This is mainly explained by the fact that typically, for a small number of target haplotypes, the pbwt construction is the main part of the selection algorithm and the copying states selection is a small fraction of the time. Results using $L = 4$ are shown in Fig S6A.

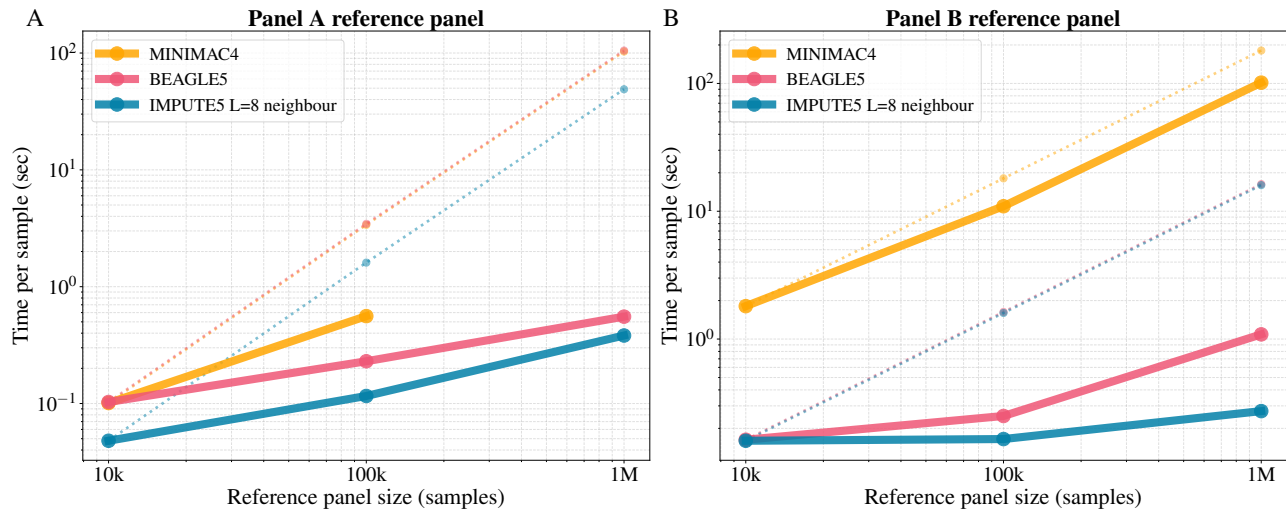Fig 5B shows the mean number of copying states selected across the 10Mb region for the

Fig 4. Per sample imputation time for Panel A and Panel B datasets. Per-sample CPU time when imputing a 10 Mb region from 10K, 100K and 1M simulated UK-European reference samples into 1,000 target samples using one computational thread. (A) Imputation time when using Panel A dataset (3,333 target markers). (B) Imputation time when using Panel B dataset (33,333 target markers). Axes are on log scale. Hypothetical linear scaling of MINIMAC4, BEAGLE5 and IMPUTE5 are shown as dotted lines, generated by projecting the time using the 10K reference panel. Minimac4 was not able to run using the Panel A 1M reference panel due to time constraints in the construction of the m3vcf file.

imputation experiments using 10K, 100K and 1M simulated reference panels. It shows that IM-PUTE5 has the property that the number of copying states decreases as the number of reference haplotypes increases. This property is predicted from the Li and Stephens model Eq. 9, that is itself an approximation to the coalescent model, whereby the probability of switching between copying states decreases as the number of reference haplotypes increases. Results using $L = 4$ are shown in Fig S6B.
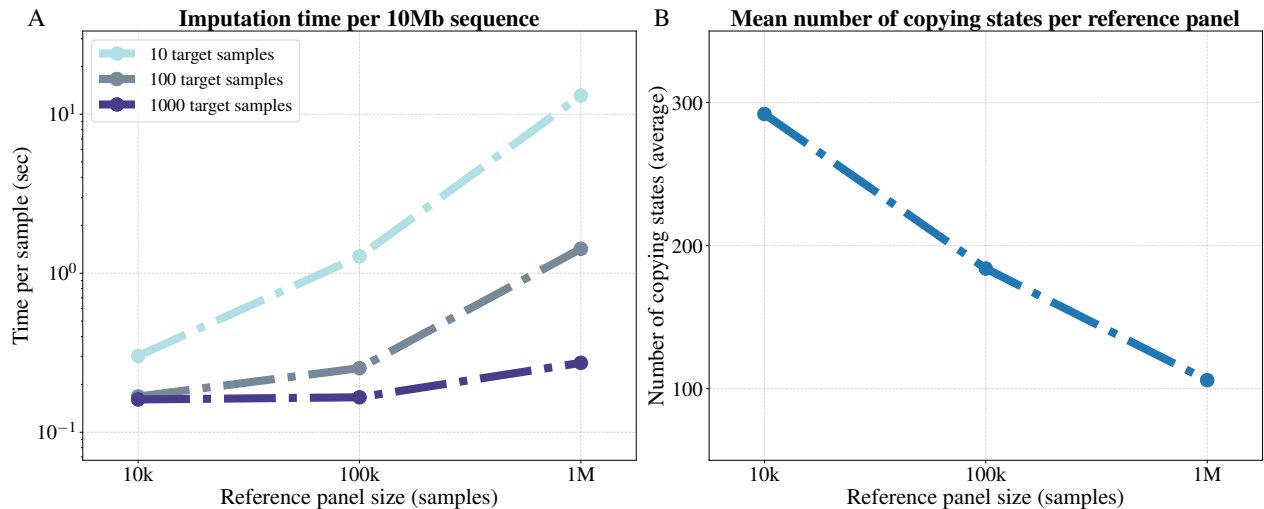
Fig 5. Sub-linear scaling. (A) Time per sample spent to impute a marker in a 10Mb region for reference panel size 10K, 100K, 1000K, when imputing 10, 100 and 1000 target samples. The vertical axis is on a log scale. Increasing the number of target samples, imputation time to impute a marker decreases. (B) Mean number of copying states selected for the simulated reference panels. The number of selected states decreases by increasing the size of the reference panel, showing sub-linear scaling. Time and number of conditioning states are obtained with neighbours select and $L = 8$ using Panel B reference panel (33,333 target markers).

Discussion

In this work we have developed a new genotype imputation method called IMPUTE5 that has the same accuracy and faster computation time compared to other currently available imputation methods. IMPUTE5 has the lowest computation time for all reference panel sizes and target sample sizes considered, both for small regions and for chromosome wide imputation.

IMPUTE5 shares the same model as IMPUTE4, but has several improvements, making IM-PUTE5 suitable for new generation reference panels. A new reference file format (imp5) and the ability to read indexed input files allows quick imputation on a small region of the genome. IM-

PUTE5's new copy states selection makes imputation more efficient when increasing the reference panel or target panel size. IMPUTE5 exhibits sub-linear scaling with reference panel sample size and provides highly accurate imputation for large scale data sets.

The flexibility, and the ability to impute quickly specific regions of the genome, make IMPUTE5 very suitable to be used as a part of an imputation server[18]. In addition, IMPUTE5 could be optimized to be used after the pre-phasing step. For example, using SHAPEIT4 [6] to pre-phase target haplotypes using a reference panel of haplotypes, it internally computes the PBWT of the reference panel at target markers to provide an accurate phase. Since the same data structure is used in a similar way by the two programs, IMPUTE5's selection algorithm could run as a last step of phasing.

We also believe that there is space for further improvements. For example, imp5 file format only provide a basic representation of the haplotypes and additional information can be added (i.e. PBWT divergence arrays). The ideas presented in this paper could be applied in other research areas, such as imputation for low coverage sequences, since the use of PBWT-based methods can improve speed and accuracy of imputation when imputing from a reference panel.

It seems likely that genotype imputation will continue to be an important part of most genome-wide association studies, since genotyping microarrays are relatively cheaper than whole-genome sequencing, and as reference panels continue to grow. Researchers will increasingly be able to impute a larger numbers of rarer variants, and they will be imputed to a higher quality.

The increased length of haplotype matching that occurs as reference panels grow in size (see Fig 5B) suggests that it could be interesting to investigate whether genotyping microarrays could reduce the number of variants they assay without losing accuracy.

Author contributions   S.R. and J.M. conceived the ideas for the model and methods development. S.R. implemented the methods, wrote the code and conducted all analyses. O.D. provided advice on aspects of the PBWT algorithm. J.M. supervised the project. S.R., O.D. and J.M. wrote the manuscript. J.M. carried out this work while affiliated with the University of Oxford.

Competing Interests   The authors declare that they have no competing financial interests.

Software availability   Software is available at `https://jmarchini.org/impute5/`

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Supporting Information

Algorithm S1 Divergence selection algorithm.

Divergence selection algorithm at selection marker m starting from match position f

1: copy $\leftarrow$ [ ]

2: copy.add($A_{f,m}$)

3: i $\leftarrow$ f-1

4: j $\leftarrow$ f+1

5: **for** $added \leftarrow 1$ to L **do**

6:     **if** $D_{i,m} <= D_{j,m}$ **then**

7:         copy.add($A_{i,m}$)

8:         $i \leftarrow i - 1$

9:     **else**

10:         copy.add($A_{j,m}$)

11:         $j \leftarrow j + 1$

12:     **end if**

13: **end for**

Algorithm S2 Neighbour selection algorithm.

Neighbour selection algorithm at selection marker m starting from position f

1: copy $\leftarrow$ [ ]

2: copy.add($A_{f,m}$)

3: **if** $t_m == 0$ **then**

4:      $s \leftarrow max\{f - L/2, 0\}$

5:      $e \leftarrow max\{min\{f + L/2 - 1, N - 1\}, c_k - 1\}$

6: **else**

7:      $s \leftarrow min\{max\{f - L/2, 0\}, c_m\}$

8:      $e \leftarrow min\{f + L/2 - 1, N - 1\}$

9: **end if**

10: **for** $i \leftarrow s$ to e **do**

11:      copy.add($A_{i,m}$)

12: **end for**

Dataset	Single core memory usage (MB)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	1,792	7,243	**294**	1,696	6,698	**420**
1000 Genomes chr 10	2,472	11,202	**352**	2,316	11,985	**506**
HRC chr 20	4,842	15,455	**2,015**	4,405	13,361	**809**
HRC chr 10	4,896	17,556	**2,086**	4,417	14,592	**873**

Dataset	Single core time (mm:ss)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	02:33	01:24	**00:24**	01:37	01:11	**00:20**
1000 Genomes chr 10	05:16	02:48	**00:50**	03:30	02:31	**00:41**
HRC chr 20	252:59	21:33	**06:58**	124:28	15:26	**04:45**
HRC chr 10	494:59	41:14	**14:26**	250:24	30:16	**10:01**

Dataset	Parallel time (mm:ss)					
	Omni 2.5 chip			OmniExpress-24 chip		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
1000 Genomes chr 20	01:08	00:15	**00:02**	01:08	00:12	**00:02**
1000 Genomes chr 10	02:25	00:28	**00:04**	01:56	00:24	**00:04**
HRC chr 20	27:13	02:12	**00:36**	15:07	01:20	**00:29**
HRC chr 10	56:08	06:07	**01:13**	30:54	02:41	**00:55**

Table S1. Memory usage and time to impute 1000 Genomes and HRC datasets using $L = 4$.
Memory usage and total time to impute a whole chromosome (chr 10 and chr 20) for 52 target samples when using the 1000 Genomes reference panel and 1000 target samples when using the HRC reference panel. IMPUTE5 was run on chunks of size 5 Mb, MINIMAC on chunks of size 20 Mb and BEAGLE5 on chunks of size 40 cM. Time is shown using the format mm:ss. Bold font is used to indicate the method with the lowest time. For the parallel computations, BEAGLE5 and MINIMAC4 were run using a single process with 16 threads; IMPUTE5 was run in 16 (chr 20) or 32 (chr 10) windows of size $\approx$ 5Mb, each of them run in parallel as a different process.

Dataset	Single core time (mm:ss)					
	Panel A			Panel B		
	MINIMAC4	BEAGLE5	IMPUTE5	MINIMAC4	BEAGLE5	IMPUTE5
10k reference panel	01:41	01:44	**00:39**	08:33	02:43	**02:14**
100k reference panel	09:20	03:50	**01:40**	65:15	04:10	**02:22**
1M reference panel	-	09:15	**05:29**	1690:50	18:08	**03:47**

Table S2. Single core time to impute Panel A and Panel B datasets using $L = 4$.

Total time to impute $1,000$ target samples in a 10Mb window using simulation data in Panel A and Panel B dataset. Time is shown using the format mm:ss. Bold font is used to indicate the method with the lowest time. Minimac4 was not able to run using the Panel A 1M reference panel due to time constraints in the construction of the m3vcf file.
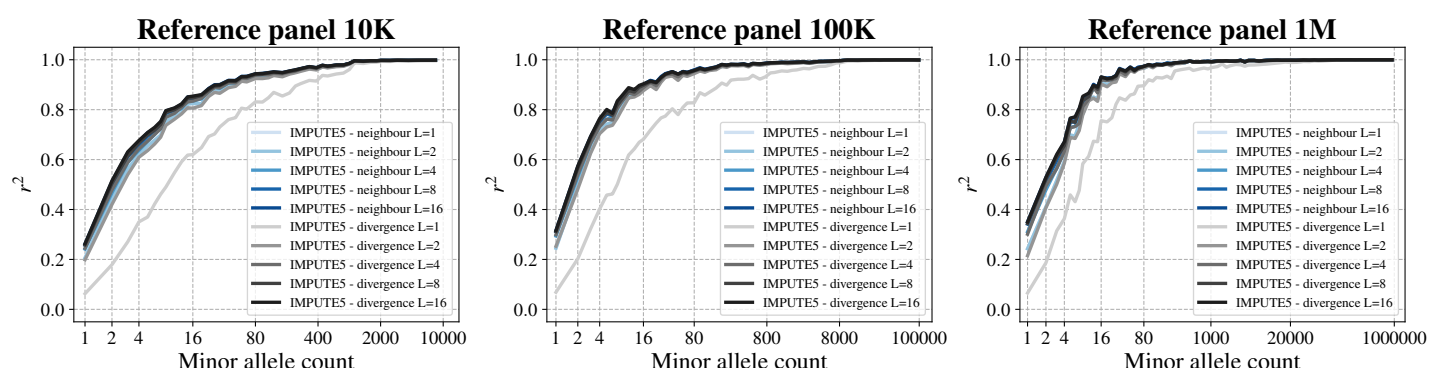
Fig S1. Imputation accuracy varying parameter L and the selection algorithm using Panel A dataset.
Genotype imputation accuracy when imputing genotypes using the 1000 Genomes Project reference panel ($n = 2452$) and the Haplotype Reference Consortium reference panel ($n = 31470$) for diffent values of the parameter L using the neighbour selection algorithm and the divergence selection algorithm. The horizontal axis in each panel is on a log scale.
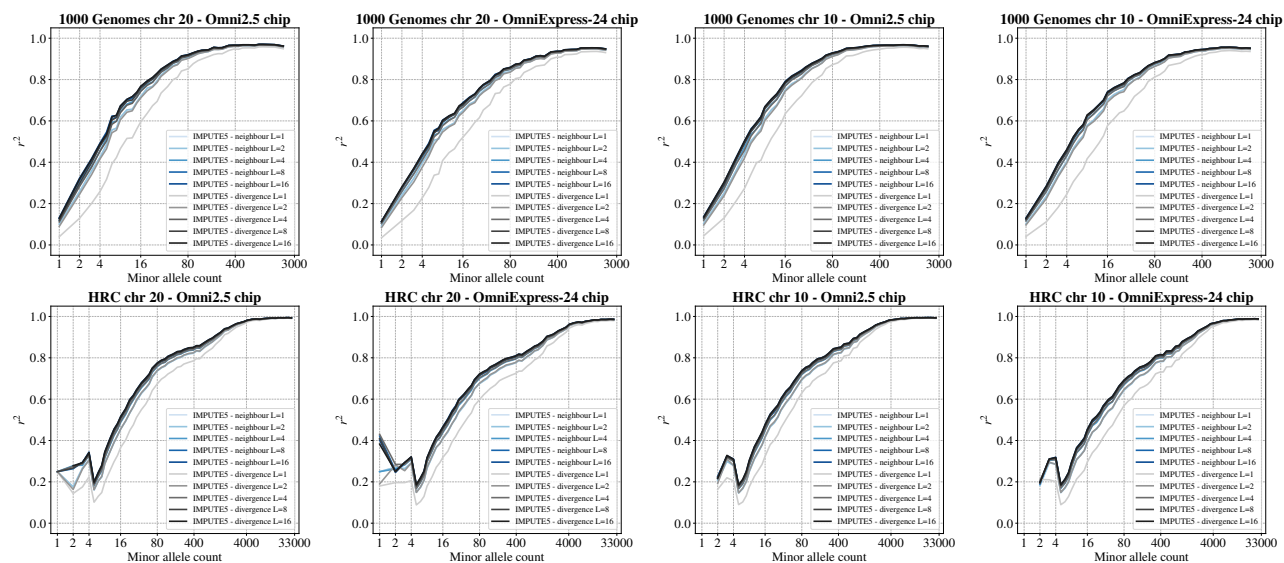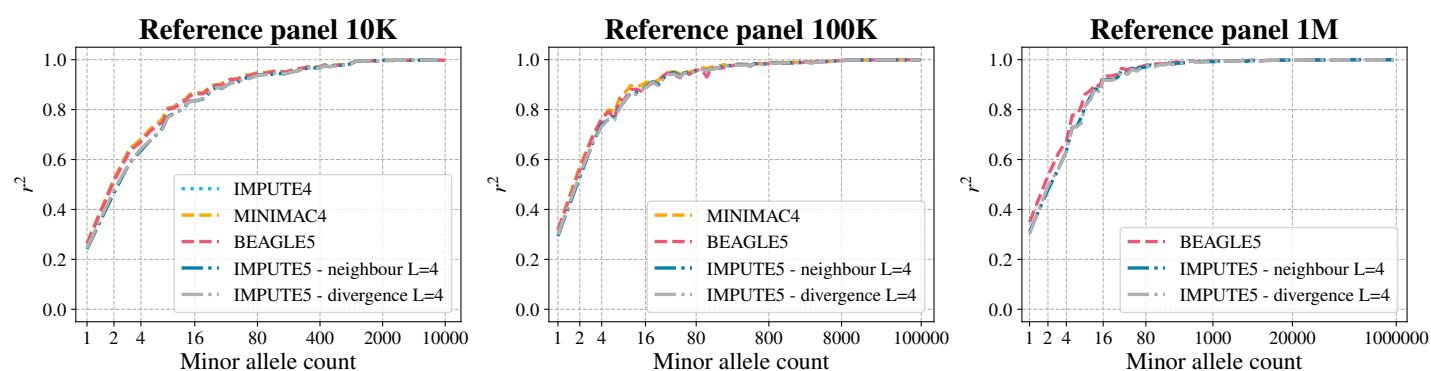
Fig S2.

Imputation accuracy varying parameter L and the selection algorithm using 1000 Genomes and HRC datasets. Genotype imputation accuracy when imputing genotypes using the 1000 Genomes Project reference panel ($n = 2452$) and the Haplotype Reference Consortium reference panel ($n = 31470$) for different values of the parameter L using the neighbour selection algorithm and the divergence selection algorithm. The horizontal axis in each panel is on a log scale.

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Fig S3.

Imputation accuracy using Panel A dataset using $L = 4$.

Genotype imputation accuracy when imputing genotypes from a simulated reference panel of 10K, 100K and 1M UK-European reference samples (Panel A). Imputed alleles are binned according to their minor allele count in each reference panel. The squared correlation (r^2) between the true number of alleles on a haplotype (0 or 1) and the imputed posterior allele probability is reported for each minor allele count bin. The horizontal axis in each panel is on a log scale.
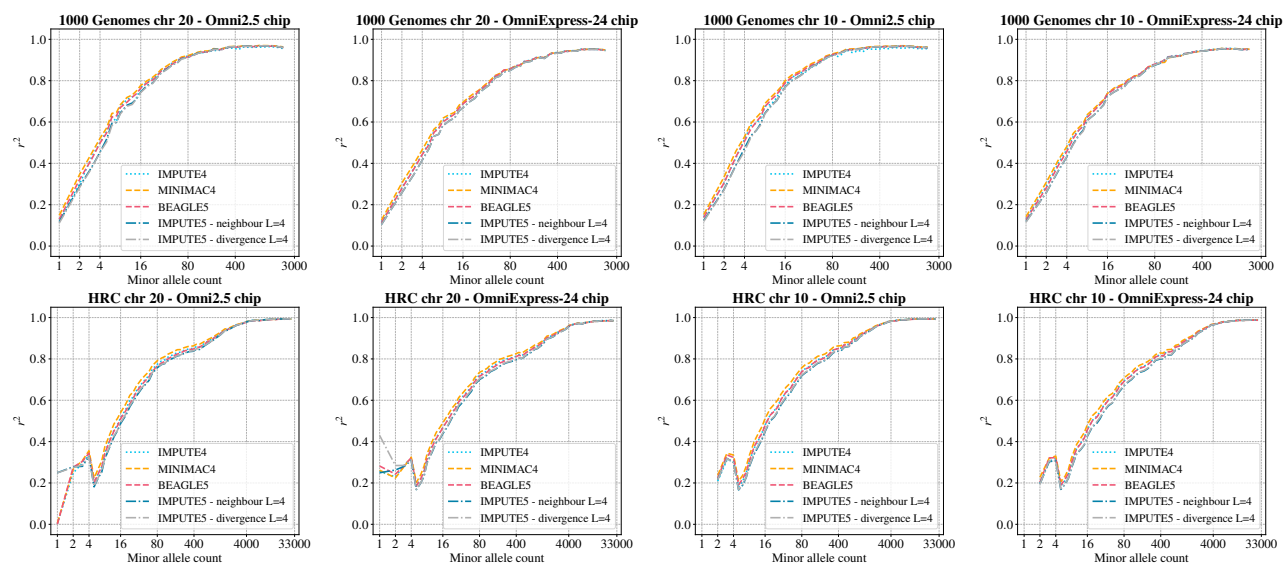
Fig S4.

Imputation accuracy using 1000 Genomes and HRC datasets using $L = 4$.

Genotype imputation accuracy when imputing genotypes using the 1000 Genomes Project reference panel ($n = 2452$) and the Haplotype Reference Consortium reference panel ($n = 31470$). Imputed alleles are binned according to their minor allele count in each reference panel. The squared correlation (r^2) between the true number of alleles on a haplotype (0 or 1) and the imputed posterior allele probability is reported for each minor allele count bin. The horizontal axis in each panel is on a log scale.
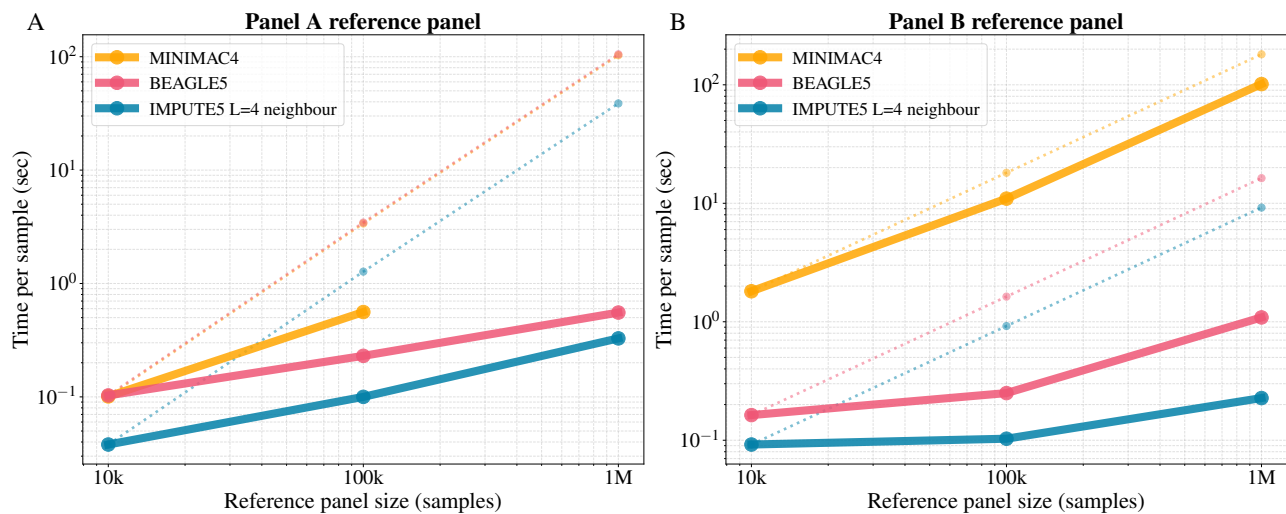
Fig S5.

Per sample imputation time for Panel A and Panel B datasets using $L = 4$.

Per-sample CPU time when imputing a 10 Mb region from 10K, 100K and 1M simulated UK-European reference samples into 1,000 target samples using one computational thread. (A) Imputation time when using Panel A dataset (3,333 target markers). (B) Imputation time when using Panel B dataset (33,333 target markers). Axes are on log scale. Hypothetical linear scaling of MINIMAC4, BEAGLE5 and IMPUTE5 are shown as dotted lines, generated by projecting the time using the 10K reference panel. Minimac4 was not able to run using the Panel A 1M reference panel due to time constraints in the construction of the m3vcf file.
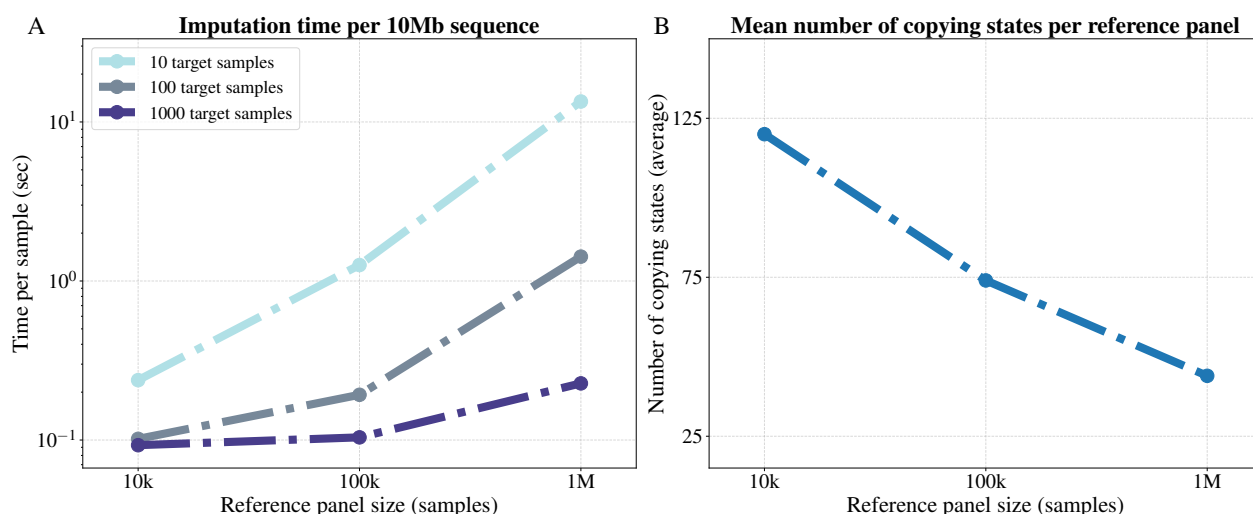
Fig S6.

Sub-linear scaling using $L = 4$.

(A) Time per sample spent to impute a marker in a 10Mb region for reference panel size 10K, 100K, 1000K, when imputing 10, 100 and 1000 target samples. The vertical axis is on a log scale. Increasing the number of target samples, imputation time to impute a marker decreases. (B) Mean number of copying states selected for the simulated reference panels. The number of selected states decreases by increasing the size of the reference panel, showing sub-linear scaling. Time and number of conditioning states are obtained with neighbours select and $L = 4$ using Panel B reference panel (33,333 target markers).