SelNeTime: a python package inferring effective population size and selection intensity from genomic time series data

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Summary

Genomic samples collected from a single population over several generations provide direct access to the genetic diversity changes occurring within a specific time period. This provides information about both demographic and adaptive processes acting on the population during that period. A common approach to analyze such data is to model observed allele counts in finite samples using a Hidden Markov Model (HMM) where hidden states are true allele frequencies over time (i.e. a trajectory). The HMM framework allows to compute the full likelihood of the data, while accounting both for the stochastic evolution of population allele frequencies along time and for the noise arising from sampling a limited number of individuals at possibly spread out generations. Several such HMM methods have been proposed so far, differing mainly in the way they model the transition probabilities of the Markov chain. Following Paris et al. (2019a), we consider here the Beta with Spikes approximation, which avoids the computational issues associated to the Wright-Fisher model while still including fixation probabilities, in contrast to other standard approximations of this model like the Gaussian or Beta distributions. To facilitate the analysis and exploitation of genomic time series data, we present an improved version of Paris et al. (2019a) 's approach, denoted SelNeTime, whose computation time is drastically reduced and which accurately estimates effective population size (assuming no selection) or the selection intensity at each locus (given a previously estimated value of N). This method is implemented in a user friendly python package, which also allows to easily simulate genomic time series data under a user-defined evolutionary model and sampling design.

Introduction

One limitation of most population genetic analyses is to use data from a single time point, the present. The genetic diversity observed in this single sample is very informative about past population history, but it integrates the effect of many evolutionary processes acting on a large time-scale, which may be hard to clearly separate. For instance, selection constraints acting on a given locus often fluctuate along time as a result of environmental changes, and such complex and changing processes are difficult to reconstruct from the observation of the resulting genetic diversity at a single recent time point. In contrast, the study of samples collected at several different generations allows to directly measure changes in the genetic diversity of populations, informing about the evolutionary processes acting on that specific time period. Such genomic time series arise in different contexts and time scales, such as the monitoring of wild or domestic populations (Boitard et al., 2023), experimental evolution (Long et al., 2015) or ancient DNA (Fages Antoine et al., 2019) studies.

A common approach to analyze genomic time series data is to model observed allele frequencies using a Hidden Markov Model (HMM); this approach allows computing the full likelihood of the data, while accounting both for the stochastic evolution of population allele frequencies along time, under the combined effects of demography and selection, and for the noise arising from sampling a limited number of individuals at different generations (Bollback et al., 2008). Several such HMM methods have been proposed so far, differing mainly in the way they model the transition probabilities of the Markov chain. Indeed, while the Wright-Fisher (WF) model appears as a natural choice to model these transitions, it leads to transition matrices whose dimension is equal to the population size so it is limited in practice to small populations. Among the various approximations of the allele frequency transition distribution that have been proposed to overcome this issue (e.g. Gaussian, Beta), the Beta with Spikes (BwS) distribution (Tataru et al., 2015) was pointed out by Paris et al. (2019a) as particularly promising, because it combines a continuous (Beta) density with discrete fixation probabilities at frequencies 0 and 1. These features allow accurate estimations for a large range of demographic and selective parameters (Paris et al., 2019a), while previous methods were either impossible to run in large populations or inaccurate for some parts of the parameter space (e.g. strong selection).

However, the current implementation of this method, compareHMM (Paris et al., 2019b), considers a fixed effective population size provided by the user, assuming that this parameter is known or has been previously estimated from another software. Besides, it was initially implemented as a test tool comparing different approximations of the Wright-Fisher model in the context of genomic time series analyses, not to be used by a large community. In particular, it was not optimized to analyze very large data sets such as those typically found in the genomics era.

With the objective of improving on these several limitations, the SelNeTime python package (Uhl et al., 2024) provides a user friendly and computationally efficient implementation of Paris et al. (2019a)'s method, allowing to estimate effective population size or selection from genomic time series and to simulate such data in order to easily test the expected

performance of the approach under custom sampling designs. This package is available on the python package index https://pypi.org/project/selnetime/ and on the project git repository https://forge.inrae.fr/simon.boitard/snt.

Materials and Methods

Modelling genomic time series through an HMM

Let us consider a population for which genomic data has been collected at n sampling times $t_1, \ldots, t_n$. For a given bi-allelic locus, we model the evolution of the (arbitrary) reference allele frequency along time using a Hidden Markov Model (HMM). We denote X_i the (hidden) population allele frequency at time t_i and Y_i the (observed) sample allele frequency at time t_i. As all HMMs, this stochastic process is fully determined by three components : the initial distribution of X_1, the transition distributions from X_{i-1} to X_i ($i \in 2, \ldots, n$) and the emission distributions of Y_i given X_i ($i \in 1, \ldots, n$). Here we assume that X_1 is distributed uniformly in $[0, 1]$ and that observed frequencies result from a binomial sampling within the population, i.e.

$$P(Y_i = y_i \mid X_i = x_i) = C_{n_i}^{y_i}(x_i)^{y_i}(1 - x_i)^{n_i - y_i}$$

where y_i is the number of reference allele copies observed at time t_i and n_i the haploid sample size (i.e. total number of allele copies) at this time. Transition distributions, which make the link between observed data and the parameters of interest, are described in the next two sections.

Modelling transitions through the Wright-Fisher model

Let us now assume that the studied population evolves under a Wright-Fisher (WF) model, i.e. with panmixia, non overlapping generations and a constant (haploid) size N. Under this model, allele frequencies X_i are discrete and take values in $\{0, \frac{1}{N}, \ldots, 1\}$. We ignore mutations due to the short time scale of interest, but model selection using a diploid codominant fitness function with selection coeficient s, i.e. the fitnesses of homozygote reference, heterozygote and homozygote alternative genotypes are respectively equal to 1, $1 + s/2$ and $1 + s$. For a single generation, this results in the transition probabilities

$$P(X_{t+1} = \frac{k}{N} | X_t = \frac{j}{N}) = C_N^k f_s(\frac{j}{N})^k (1 - f_s(\frac{j}{N}))^{N-k}, \quad j, k \in 0, 1, \ldots, N$$

where

$$f_s(x) = \frac{x(1 + s/2 + sx/2)}{1 + sx}$$

Denoting $Q_{s,N} = ((Q_{s,N})_{j,k})_{0 \leq j,k \leq N}$ the matrix of these single generation transition probabilities, the transition probabilities from t_{i-1} to t_i can be computed as

$$P(X_i = \frac{k}{N} | X_{i-1} = \frac{j}{N}) = (Q_{s,N,i})_{j,k} = (Q_{s,N}^{t_i - t_{i-1}})_{j,k}$$

The Beta with Spikes approximation

Because $Q_{s,N}$ has dimension $N \times N$, likelihood computations under the WF model described above are only possible for small values of N. Following Paris et al. (2019a), SelNeTime computes (by default) this transition matrix based on a Beta with Spikes (BwS) approximation of the WF model (Tataru et al., 2015). This model assumes that

$$X_i \sim p_{0,i}\delta_0 + p_{1,i}\delta_1 + (1 - p_{0,i} - p_{1,i})B(a_i, b_i)$$

where $p_{0,i}$ and $p_{1,i}$ are the fixation probabilities in 0 and 1 at time t_i and $B()$ is a beta distribution with parameters a_i and b_i. While the continuous part modelled by $B()$ allows to control the size of $Q_{s,N,i}$ using a discretization grid that is independent of N, accounting for the discrete fixation probabilities $p_{0,i}$ and $p_{1,i}$ was shown to provide better results compared to other standard continuous approximations of the WF (Paris et al., 2019a).

Following Tataru et al. (2015), the transition matrix $Q_{s,N,i}$ from time t_{i-1} to time t_i is computed in three steps. 1) We compute $m_i(N, s, x) = E[X_i \mid X_{i-1} = x]$ and $z_i^2(N, s, x) = Var(X_i \mid X_{i-1} = x)$ under a Wright-Fisher process, using a recursion from $t = 1$ to $t = t_i - t_{i-1}$. For $s \neq 0$, this recursion relies on a large N Taylor expansion called Delta method (Lacerda & Seoighe, 2014). 2) Using another recursion from $t = 1$ to $t = t_i - t_{i-1}$, we set the values $p_{0,i}(N, s, x)$, $p_{1,i}(N, s, x)$, $a_i(N, s, x)$ and $b_i(N, s, x)$ ensuring that the mean and variance of the resulting BwS distribution match the values $m_i(N, s, x)$ and $z_i^2(N, s, x)$ obtained at step 1. 3) The line of $Q_{s,N,i}$ corresponding to a starting frequency of x is derived from the BwS distribution characterized at step 2. Detailed equations used at steps (1-2) can be found in Paris et al. (2019a).

For step 3, we introduced a technical difference with the approach of Paris et al. (2019a). In this original study, the quantities stored in $Q_{s,N,i}$ were a mixture of probability and density values: the first and last columns represented the discrete probabilities of arriving respectively in 0 and 1, but other columns represented probability densities at arriving frequencies, which were later (numerically) integrated during likelihood computation. While more elegant mathematically, this approach occasionnaly lead to numerical issues and implied that likelihood computations could not be fully vectorized, because different parts of the matrix were processed differently. In contrast, SelNeTime implementation considers that all coefficients in the matrix correspond to a discrete probability. More precisely, for a discretization grid of $(0, 1)$ into p bins $I_j = [m_j, M_j]$, $j \in 1, \ldots, p$, $Q_{s,N,i}$, has dimension $p + 2 \times p + 2$ where I_0 corresponds to an allele frequency of exactly 0 and I_{p+1} to an allele frequency exactly 1. Its coefficients are defined by

$$Q_{s,N,i}(j, k) = P(X_i \in I_k | X_{i-1} \in I_j)$$

For $j \in 1, \ldots, p$ (i.e. when starting from a discretization bin), this probability is approximated by $P(X_i \in I_k | X_{i-1} = \overline{I_j})$, where $\overline{I_j}$ is the middle of I_j. For $k \in 1, \ldots, p$ (i.e. when arriving into a discretization bin), the probability is derived as $g(M_k) - g(m_k)$, where $g()$ is the cumulative density function of the Beta distribution obtained at step (2).

Likelihood computation and optimization

For an initial distribution ν, transition matrices $Q = (Q_2, \ldots, Q_n)$ and emission probabilities $E = (E_1, \ldots, E_n)$, the likelihood of observed data in a HMM can be computed using the so-called forward algorithm. This algorithm focuses on the quantity

$$\alpha_i(x_i) = P(Y_1 = y_1, \ldots, Y_i = y_i, X_i = x_i)$$

which is initiated by

$$\alpha_1(x_1) = E(x_1, y_1)\nu(x_1)$$

for all possible values of x_1 and then updated recursively, for $i = 2, \ldots, n$, by

$$\alpha_i(x_i) = E(x_i, y_i) \sum_{x_{i-1}} Q(x_{i-1}, x_i)\alpha_{i-1}(x_{i-1})$$

for all possible values of x_i. The likelihood is finally obtained by summing over x_n:

$$L(y_1, \ldots, y_n; \nu, Q, E) = P(Y_1 = y_1, \ldots, Y_n = y_n \mid \nu, Q, E) = \sum_{x_n} \alpha_n(x_n)$$

In our application, the parameters of interest are N and s, which influence Q but not ν and E. Thus, the forward algorithm provides

$$L(y_1, \ldots, y_n; \nu, Q, E) = L(y_1, \ldots, y_n; \nu, Q_{s,N,2}, \ldots, Q_{s,N,n}, E) = L(y_1, \ldots, y_n; N, s)$$

In other words, we are able to evaluate numerically the likelihood of the data for any given values of N and s. Note that this likelihood function also implicitely depends on the time intervals $t_i - t_{i-1}$, because these affect the $Q_{s,N,i}$ matrices (see section 'Modelling transitions through the Wright-Fisher model'). We omit this dependence here because we consider these parameters as known fixed values, but this could in principle be relaxed in applications where sample age or generation time is unknown.

In the original study of Paris et al. (2019a), N was assumed to be known and the likelihood was optimized over s (see below) to get the Maximum Likelihood Estimator (MLE) of selection intensity at the studied locus. One novelty in SelNeTime is to also estimate N by cumulating data from L loci. Indeed, N reflects the demography of the population so a single value applies to the whole genome. Denoting $\mathbf{y}_l = (y_{l,1}, \ldots, y_{l,n})$ the sequence of observed reference allele counts at locus l, the likelihood of N is evaluated as

$$L(\mathbf{y}_1, \ldots, \mathbf{y}_L; N) = \prod_l P(\mathbf{Y}_l = \mathbf{y}_l | N, s_l = 0)$$

Two important assumptions here are that the loci are independent (which almost holds in practice if these loci are taken sufficiently far away from each other, but see the discussion) and that the effect of selection at each locus can be neglected in first approximation. To obtain the MLE in practice, we first evaluate the likelihood on a broad grid of candiate N values ranging from 10 to 1000000, and next perform a refined search on a second grid of candidate N values centered around the value maximizing the likelihood in the first grid.

Importantly, note that only integer values of N are explored during this two step search (besides the biological realism, several steps of the computations require integer N values, both for the WF and the BwS model).

Once N has been estimated, SelNeTime estimates the selection intensity at each locus l based on this value using the same approach as Paris et al. (2019a), i.e. optimizing $P(\mathbf{Y}_l|\hat{N}, s_l)$ over different values of s_l in order to find the MLE of this parameter at each locus. As indicated in the notation, s_l is a locus specific parameter, because selective contraints typically differ between loci.

Important features

Estimation of effective population size

Using computer simulations, we checked the accuracy of SelNeTime estimation of N, a task that has not been investigated by Paris et al. (2019a). We first considered simulation scenarios without selection, in order to evaluate the method in the favorable situation where its assumptions are met (except that simulations were performed under the true WF model, not the BwS approximation). As a comparison, we also estimated N for the same data with the method of Hui & Burt (2015), implemented in the NB package (Hui, 2014), which is based on a continuous Beta approximation of allele frequency transitions. Interestingly, both methods performed equally well for short sampling time intervals ($\Delta t = 1$) but the accuracy of NB was reduced for larger time intervals ($\Delta t = 10$) (Figure 1); this is consistent with the higher probability of fixation events, which are not accounted for in the method of Hui & Burt (2015), when Δt increases, illustrating the advantage of the BwS approximation.

We also explored (neutral) scenarios with different values of N and of the initial allele frequencies, in order to evaluate the influence of these parameters on SelNeTime estimations. SelNeTime performed almost equally well for all choices of the initial allele frequencies, with a slight advantage for trajectories starting from $x_0 = 0.5$ (Figure 2). This can be explained by the higher probability of fixation events when the initial allele frequency is close to 0 or 1. Indeed, while these events are accounted for in our method, the effect of approximating the true (simulated) WF distribution by the BwS distribution is stronger when the probability of fixation events increases. Estimations of N were also less accurate (in particular they showed a higher variance) for large populations, as expected given the more subtle effect of genetic drift in such scenarios. However, results obtained with $N = 10,000$ (the largest value tested here) remain very good. They could also be improved by increasing the sample size at each time point, which would reduce the sampling variance and thus make the drift variance easier to capture.

Finally, we included selection in the simulated datasets. In order to evaluate the influence of unaccounted selection on N estimations, we first considered datasets simulated with different selection intensities and various proportions of loci under selection while running SelNeTime with its original assumption that selection can be neglected (Figure 3). As expected, this generally lead to a negative bias in N estimations, which increased with selection intensity

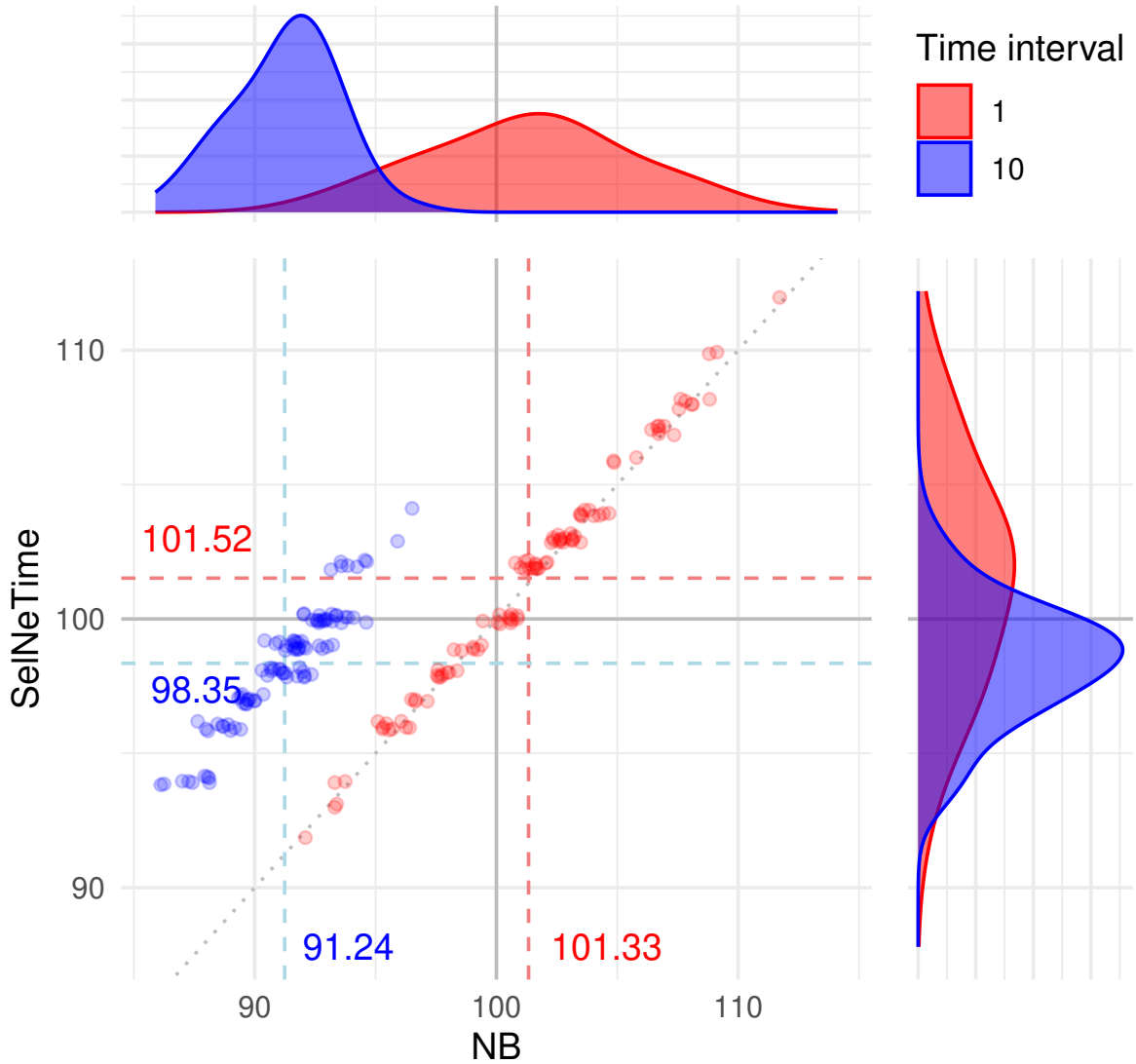


Figure 1: Estimation of the effective population size for 100 datasets, using SelNeTime or NB (Hui, 2014). Each dataset includes 1000 loci and 10 sampling times $t = 1 \ldots 10$ (red) or $t = 10, \ldots, 100$ (blue). Allele frequency trajectories at each locus were simulated under the Wright-Fisher model with $N = 100$, $s = 0$ and an initial allele frequency $x_0 = 0.5$. At each time point t_i, sample size is $n_i = 30$.

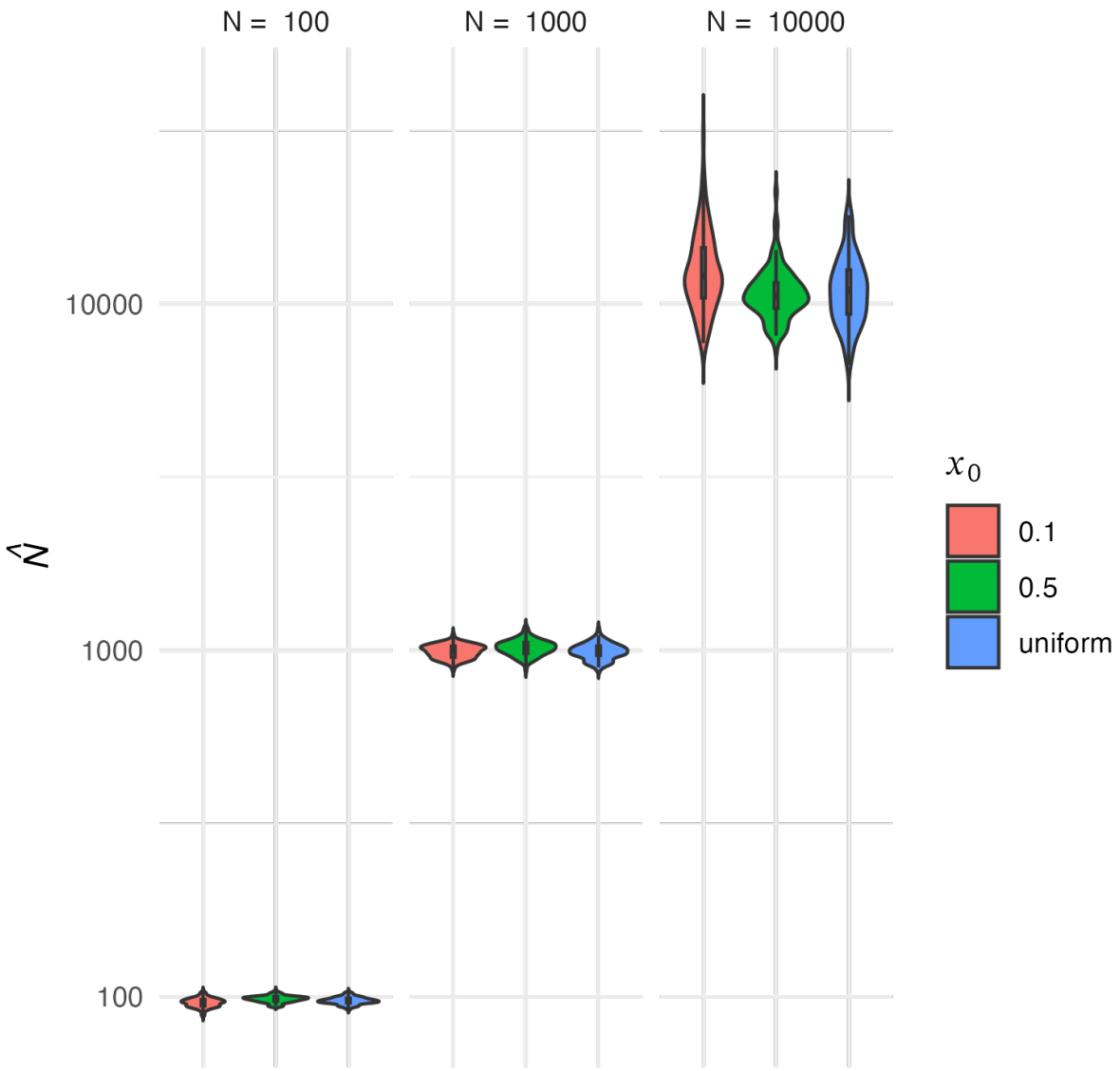


Figure 2: Estimation of the effective population size using SelNeTime, for different values of N (panels) and different values / distributions of the initial allele frequency x_0 (colors). For each combination of these two parameters, 100 datasets of 1000 (independent) loci were considered. Allele frequency trajectories at each locus were simulated under the Wright-Fisher model, with $n = 30$ at each of 10 sampling times $t = 10, \ldots, 100$.

and the proportion of the genome under selection. The effect was also more pronounced for larger populations, for instance in the worst case where all loci were selected with $s = 0.1$ the relative bias was about 25% for $N = 100$ and 75% for $N = 1000$. This last observation likely results from the fact that selection is more efficient in large populations; to phrase it in a different way, the effect of selection on genetic diversity is known to be better captured by the product Ns than by s alone (Paris et al., 2019a).

To test whether the bias observed in (Figure 3) can be avoided by accounting for the presence of selection, we also estimated N on datasets where all loci were simulated under selection with the same intensity s_T, but this time providing this true value to SelNeTime (i.e. computing the likelihood given $s = s_T$ instead of $s = 0$). Results were much more accurate, as shown in Figure 4. Mean estimated values with and without the $s = 0$ assumption are summarized in Table 1.

Table 1: Mean estimated values of N over 100 replicates, for datasets simulated with different combinations of N and s_T and a sampling time interval $\Delta t = 10$. Estimations assuming either $s = 0$ or $s = s_T$ are compared.

	$N_T = 100$ $s = 0$	$N_T = 100$ $s = s_T$	$N_T = 1000$ $s = 0$	$N_T = 1000$ $s = s_T$
$s_T = 0$	98.4	–	1018	–
$s_T = 0.01$	97.8	98.4	805	1014
$s_T = 0.1$	73.5	98.5	199	1002

Estimation of selection intensity at a given locus

We next evaluated the accuracy of SelNeTime to estimate s_l at each locus, assuming that N is known (i.e. that it has been correctly estimated). As this method is essentially a re-implementation of the BwS approach described by Paris et al. (2019a), we first compared it with the inital implementation published by these authors on a limited number of scenarios (Paris et al., 2019b). As expected, we found very similar results between the two implementations (Figure 5), which both lead to almost unbiased estimations of the selection intensity.

To provide a first hint of SelNeTime performance in more diverse scenarios, we then ran it on datasets simulated with various population sizes, selection coefficients and sampling times, with the true value of N still provided (Figure 6). Results showed a larger estimation variance for lower values of N and Δt, but the median of estimated values was always close to the true value of s. A more detailed study of the estimation accuracy and of the power to detect selection can be found in the study of Paris et al. (2019a), which explored these questions for a large range of parameter values and sampling designs.

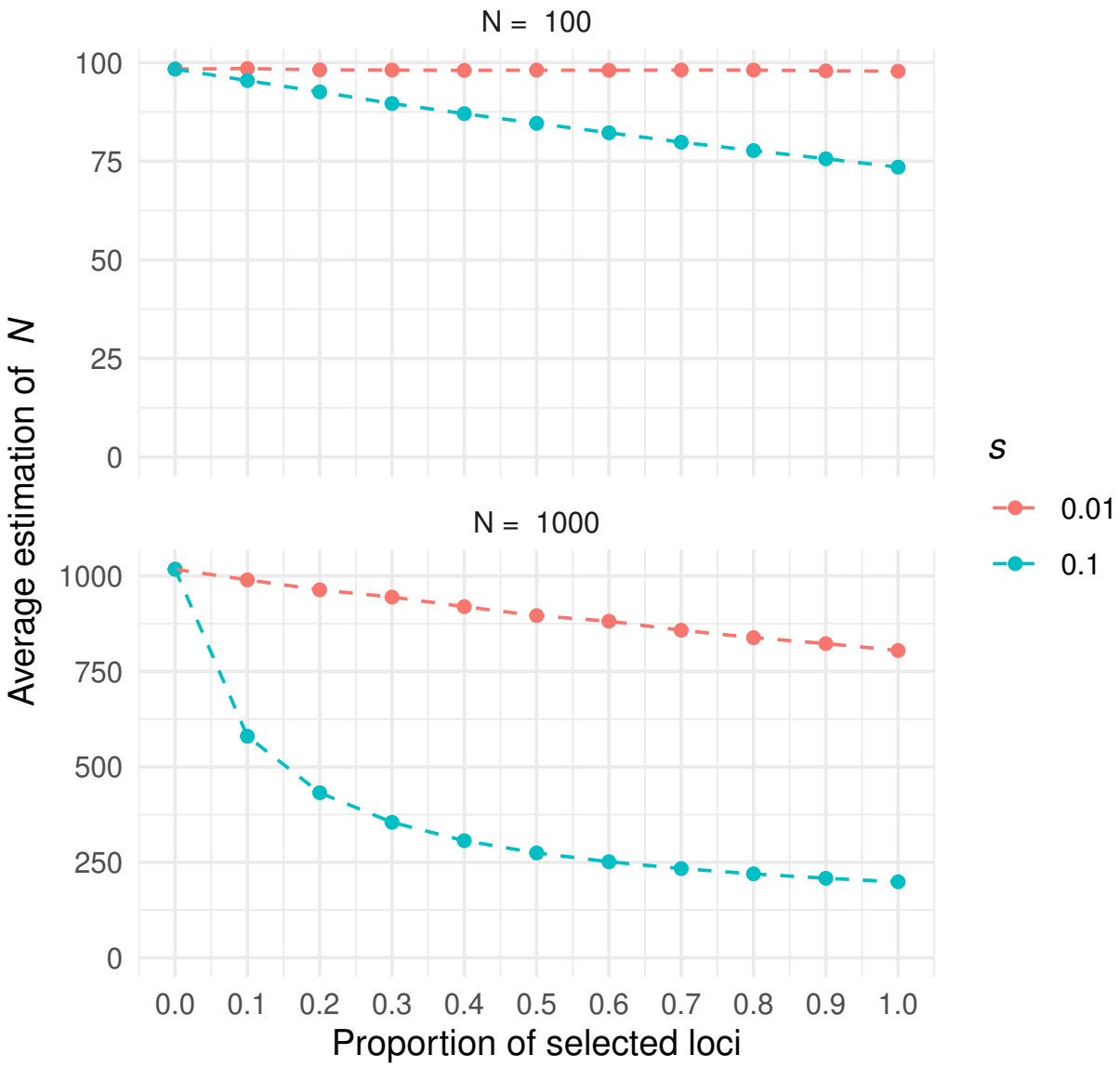


Figure 3: Estimation of the effective population size using SelNeTime, for simulated datasets with various proportions of loci actually under selection (x axis). For a given proportion p, 100 datasets of $1000 * p$ selected loci and $(1-p) * 1000$ neutral loci were considered. Allele frequency trajectories at each locus were simulated under the Wright-Fisher model, with $n = 30$ at each of 10 sampling times $t = 10, \ldots, 100$. Initial allele frequencies were set to $x_0 = 0.5$ and the true population size was $N = 100$ (top) or $N = 1000$ (bottom). The average estimated value over the 100 datasets is shown on the y-axis, for different selection intensities (colors)

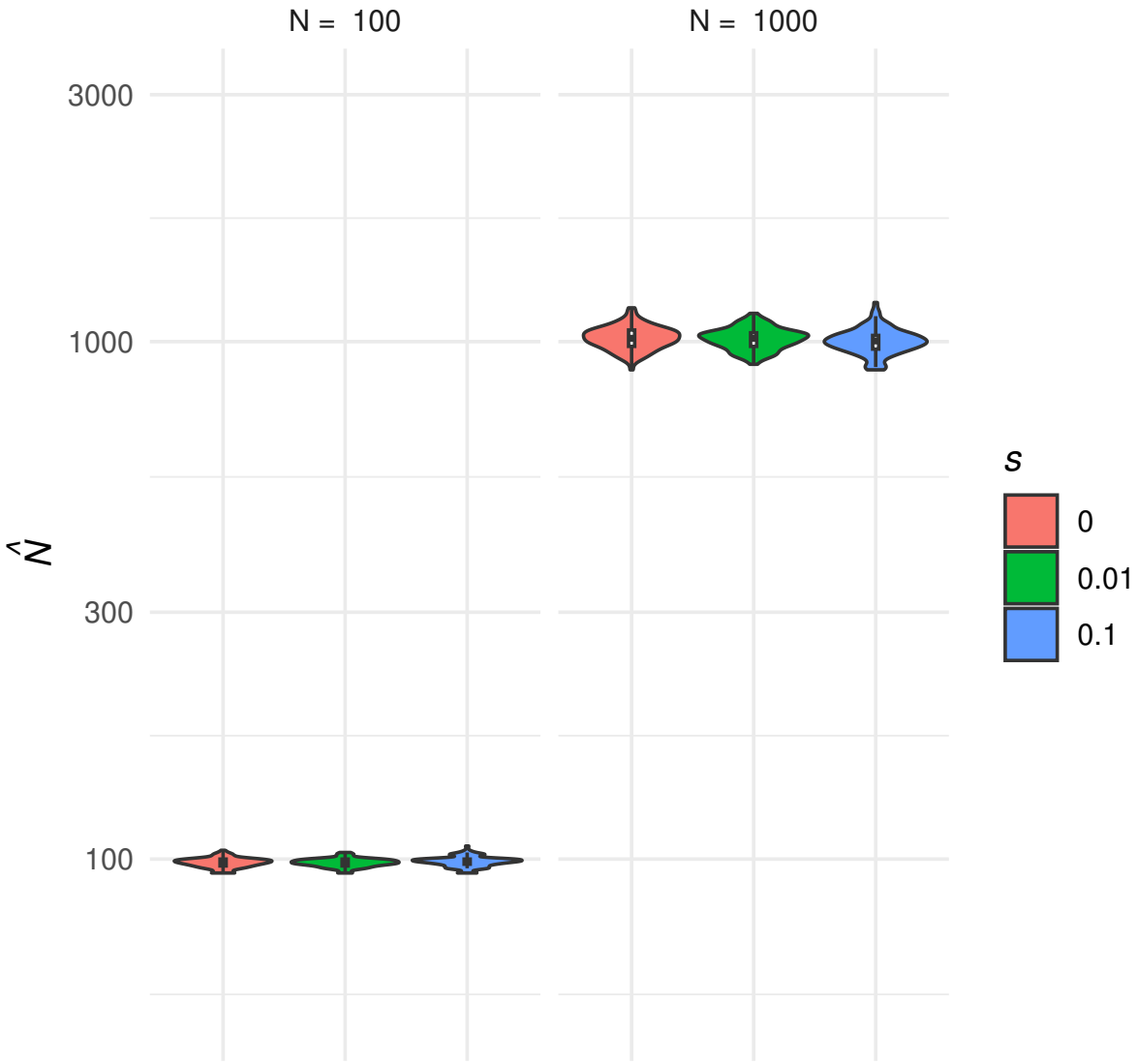


Figure 4: Estimation of the effective population size using SelNeTime with the true value of s provided, for simulated datasets where all loci are under selection with the same intensity. For given values of s (colors) and N (panels) 100 datasets of 1000 loci were considered. Allele frequency trajectories at each locus were simulated under the Wright-Fisher model, with $n = 30$ at each of 10 sampling times $t = 10, \ldots, 100$. Initial allele frequencies were set to $x_0 = 0.5$.

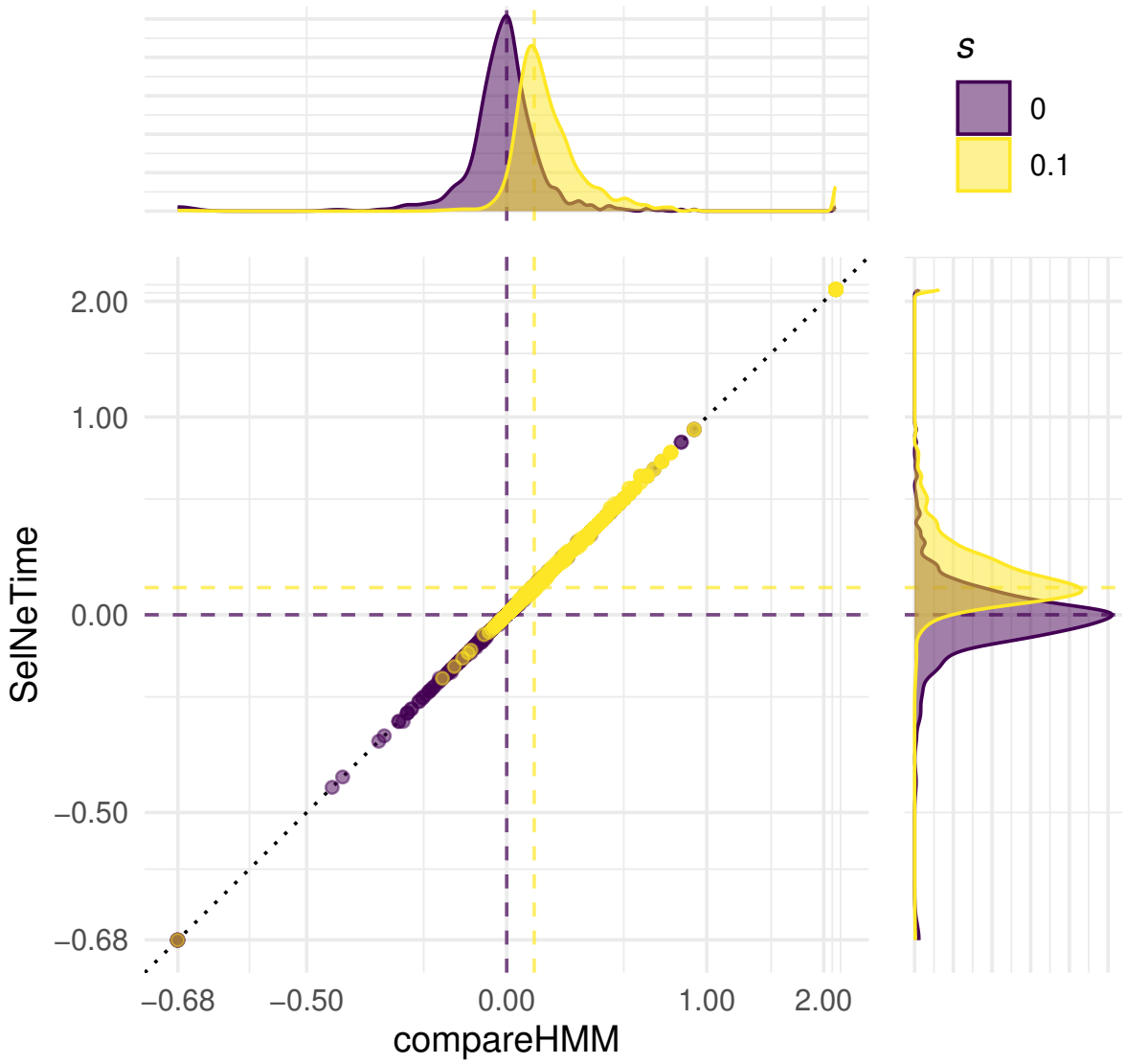


Figure 5: Estimation of the selection intensity for 1000 loci using SelNeTime and compareHMM. Allele frequency trajectories at each locus were simulated under the Wright-Fisher model with $N = 100$, $s = 0$ (purple) or $s = 0.1$ (yellow) and an initial allele frequency $x_0 = 0.5$. Allele frequencies were observed for $n = 30$ at 10 sampling times $t = 10 \ldots 100$. A $log_2(1 + x)$ transformation was applied to both axes, in order to have a qualitatively symmetrical scale around 0 (a selection of -0.5 is the opposite of $s = 1$, etc.)

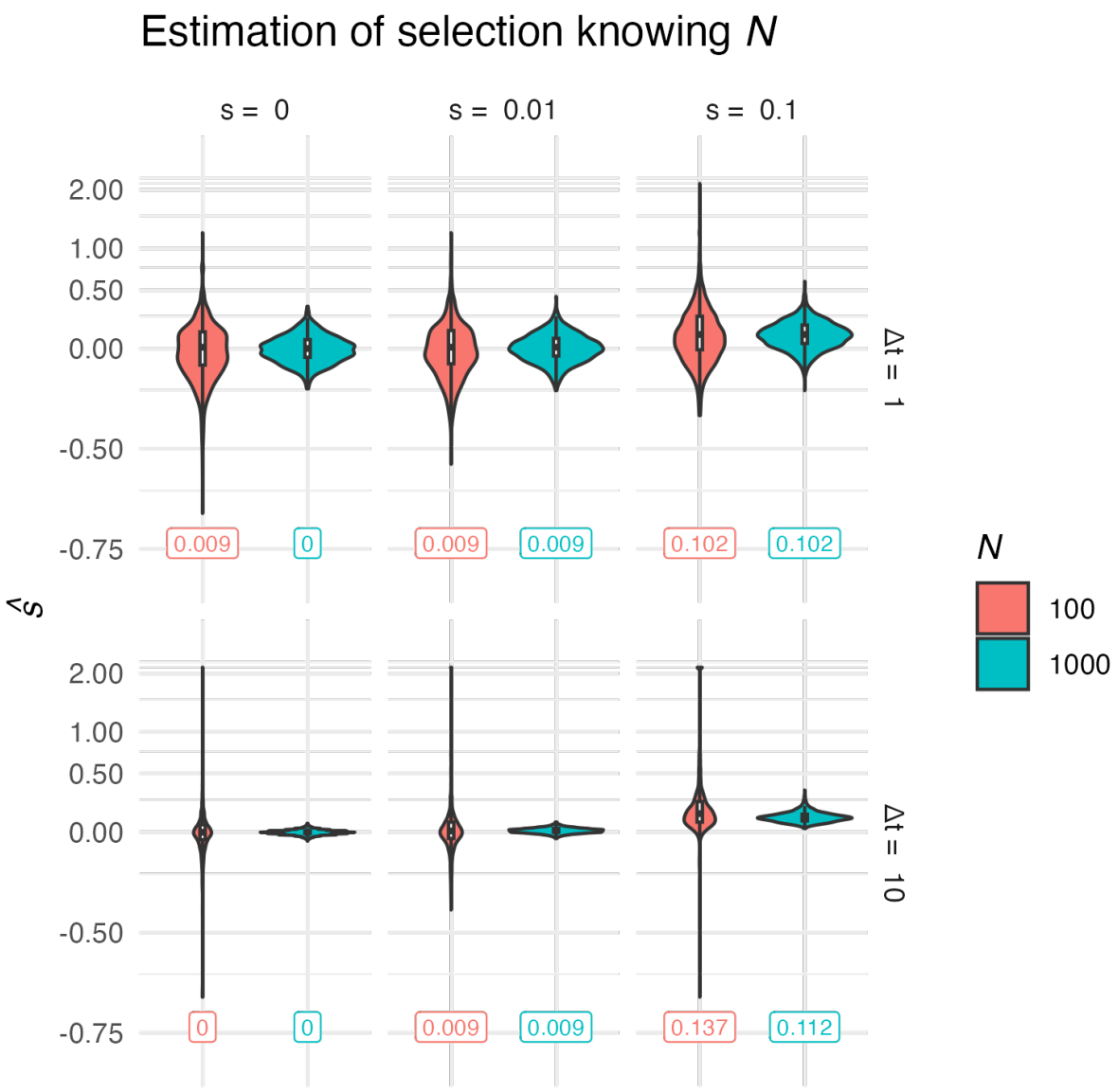


Figure 6: Estimation of the selection intensity using SelNeTime with the true value of N. For given values of s (columns) and N (colors), 1000 loci were considered. Allele frequency trajectories at each locus were simulated under the Wright-Fisher model, with $n = 30$ at each of 10 sampling times $t = 1, \ldots, 10$ or $t = 10, \ldots, 100$ (lines), and an initial allele frequency $x_0 = 0.5$. The median value for each simulation scenario is shown below the associated violin plot. A $log_2(1 + x)$ transformation was applied to the y axis

Improved computation time

One important improvement of SelNeTime compared to the inital implementation of the BwS approach in compareHMM (Paris et al., 2019b) concerns the computation time, which was reduced using two main actions. First, the continuous density of the distribution was discretized when building the transition matrices (with a controlled bin width), allowing this continuous part of the distribution to be analyzed exactly in the same way as the discrete probability mass points in 0 and 1 (see section 'The Beta with Spikes approximation'). Second, matrix computations performed at each iteration of the HMM forward algorithm were vectorized, taking advantage of the Numpy library (Harris et al., 2020) to efficiently handle different loci or parameter values in a single operation.

As an illustration, Table 2 shows the computation time required to analyze a time series of 10 samples of 30 observations each, with a sampling time interval of $\Delta t = 10$ generations and a number of loci varying from 100 to 10000.

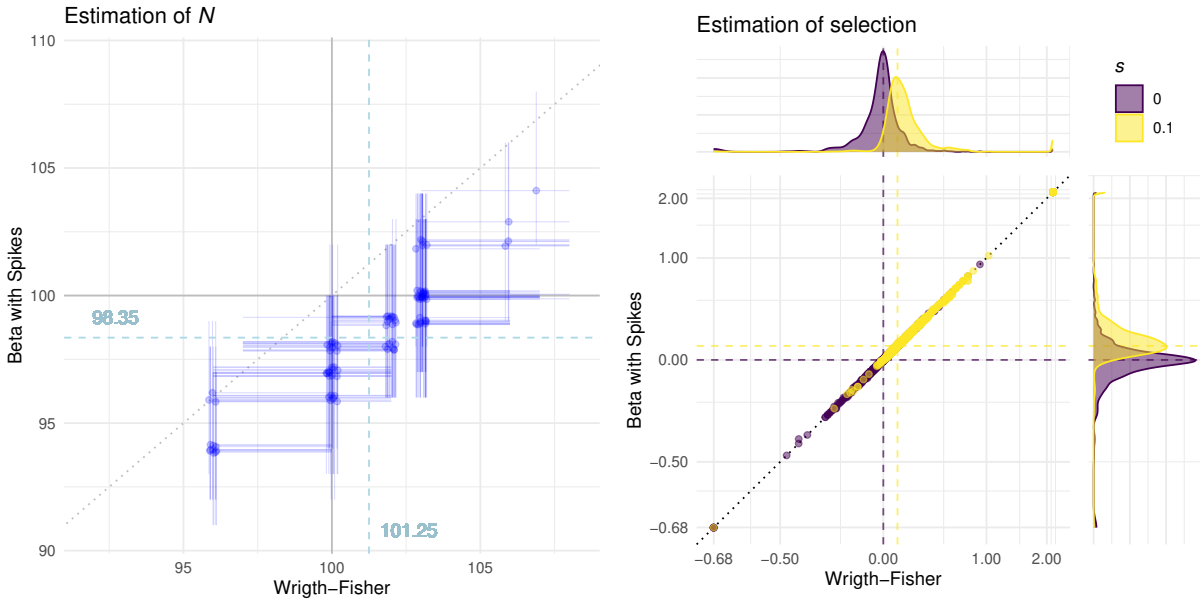
Table 2: Computation times of CompareHMM (Paris et al., 2019b) and SelNeTime, run on a single CPU of an Intel Xeon $16 * 2.60$ GHz processor with 32Gb of RAM

Nb. loci	compareHMM, estimation of s	SelNeTime, estimation of s	SelNeTime, estimation of N
100	39.27s	28.7s	6.12s
1000	360.01s	36.21s	14.23s
10000	3530.47s	96.95s	87.83s

For 100 loci, SelNeTime runs in approximately the same time as compareHMM, but the relative performance of SelNeTime improves quickly when the number of loci increases. Actually, the time to compute all transition matrices, which is the first step of both SelNeTime and compareHMM analyses, is independent of the number of loci (but it depends on the sampling design). This part of the analysis took approximately 28s for SelNeTime in this example, which was of the same order as compareHMM, but after this the time spent per locus was far lower with SelNeTime (approx. 0.007s) than with compareHMM (approx. 0.35s).

Comparison with the Wright-Fisher model

While SelNeTime computes by default HMM transitions using the BwS distribution, it might occasionally be useful to compute them based on the WF model, in particular to evaluate the impact of the BwS approximation on inference quality. Although this is numerically possible only for small population sizes (not more than a few hundreds), we included one option to do this in the program. For a true population size of $N = 100$, we could for instance check that using the BwS or the WF model had very limited impact on the inference of either effective population size or selection (Figure 7). A more detailed comparison between the estimations obtained by the BwS and WF distributions can be found in Paris et al. (2019a), but only for selection inference.



(a) (b)

Figure 7: Comparison of SelNeTime estimations based on the Beta with Spikes and the Wright-Fisher model. **(a)**: MLE and 95% confidence interval of effective population size for 100 datasets of 1000 loci each. **(b)** MLE of s for 1000 loci. The two panels show the estimations obtained using the WF (x axis) or the BwS (y axis) model on the same data, which were simulated under the Wright-Fisher model with $N = 100$ $s = 0$ (Left and Right, purple) or $s = 0.1$ (Right, yellow) and initial allele frequencies $x_0 = 0.5$. Allele frequencies were observed for $n = 30$ at 10 sampling times $t = 10 \ldots 100$. A $log_2(1 + x)$ transformation was applied to both axes of panel b in order to restore the symmetry between positive and negative values of s (for instance, $s = -0.5$ implies that the fitness of reference homozygote genotypes is twice that of alternative homozygote genotypes, the symmetric case of $s = 1$).

Simulation of datasets

As already observed in Paris et al. (2019a) and several other studies on the subject, the estimation accuracy of effective population size or selection depends on both the true evolutionary parameters of the population under study (N and s) and the sampling design of observed data (number and size of observed samples, time intervals between samples). In order to help researchers plan future experiments, or interpret the results obtained for a specific dataset, SelNeTime includes a simulator of observed allele frequency trajectories. Simulations can easily be tunned using either a yaml file or command line options and output data at a format that can directly be analyzed with other SelNeTime commands. Notably, this simulator was used to generate the data underlying the figures and tables of this study.

Discussion

The SelNeTime python package provides a re-implementation of the BwS approach proposed by Paris et al. (2019a) to analyse genomic time series data. Compared to the initial implementation of these authors (Paris et al., 2019b), SelNeTime (i) allows to estimate the effective population size during the temporal period covered by the samples, (ii) runs much faster, epecially for large SNP datasets, and (iii) provides a user-friendly interface with simple commands, including a simulation facility.

Simulation results reported in this study demonstrate that SelNeTime accurately infers effective population size in the absence of selection, or selection intensity at each locus assuming the true value of N is provided. Obviously, these two hypothetical conditions are almost never met in practice: populations are subject to selection constraints and their effective population size is generally unknown. A main objective of future research will be to extend the approach in order to co-estimate demography and selection. While this is clearly a challenging task, which very few population genetics studies tried to tackle so far, we point out that SelNeTime estimation of N is also accurate in the presence of selection, provided the true value of selection intensity is given as input (Figure 4). Encouragingly, this result suggests that optimization approaches accounting for the effects of both N and the s_l's on the likelihood, could perform well.

We note also that, in some circumstances, SelNeTime can already be considered as a good first approximation of the parameters of interest. Indeed, the influence of selection on N estimation can be very limited in some scenarios (Figure 3), and several recent studies using genomic time series suggested that accurate estimations of selection could be achieved despite demographic misspecification (Mathieson & Terhorst, 2022; Whitehouse & Schrider, 2023). Actually, the original compareHMM approach (Paris et al., 2019b) has already been applied to several empirical datasets and provided relevant biological insights (Paris et al., 2019a; Boitard et al., 2021, 2023).

Another strong assumption made by SelNeTime is to consider that allele frequency trajectories observed at distinct loci are independent, an assumption that does not hold in practice for at least two reasons: (i) linkage disequilibrium (LD) and (ii) the so-called Bulmer effect (Bulmer, 1971), i.e. the negative correlation of allele frequencies resulting from the polygenic selection

of quantitative traits. While the LD effect can easily be mitigated by sub-sampling SNPs, the Bulmer effect would be more tricky to model with our approach. One first step to explore this question could be to apply SelNeTime to genomic time series simulated under polygenic selection scenarios. In the longer term, we could also try to estimate temporal variations of s_l at each locus (see Mathieson & Terhorst (2022)), which would be more consistent with a model of selection on quantitative traits.

Finally, admixture might be another important counfouding effect for our approach, as recently outlined for another method analyzing genomic time series under the assumption of panmixia (Simon & Coop, 2024). The impact of admixture on SelNeTime performance will likely depend on the exact admixture scenario (admixture proportions, single versus recurrent events, overlap of these events with the sampling period, divergence with the source population, local versus global adaptation . . .) so a first step could again be to evaluate it using simulations. It should also be feasible to modify SelNeTime HMM transitions in order to account for specific well documented admixture scenarios, in a similar spirit of what was done in Simon & Coop (2024).

Data, script and code availability

SelNeTime is available on the python package index https://pypi.org/project/selnetime/ and on the project git repository https://forge.inrae.fr/simon.boitard/snt. All figures of this study can be reproduced using a snakemake pipeline available at https://forge.inrae.fr/genetic-time-series/these-paul-bunel/-/tree/main/simulations_snt

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Conflict of interest disclosure

The authors declare they have no conflict of interest relating to the content of this article. SB is a recommender for PCI Math Comp Biol; MN is a recommender for PCI Evol Biol.

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