# Deep learning for population size history inference: design, comparison and combination with approximate Bayesian computation

**Théophile Sanchez**[1*], **Jean Cury**[1], **Guillaume Charpiat**[1], **Flora Jay**[1*]

1. Laboratoire de Recherche en Informatique, CNRS UMR 8623, Université Paris-Sud, Université Paris-Saclay, Inria, Orsay, France

∗ Correspondence: `theophile.sanchez@inria.fr` and `flora.jay@lri.fr`

## Abstract

For the past decades, simulation-based likelihood-free inference methods have enabled to address numerous population genetics problems. As the richness and amount of simulated and real genetic data keep increasing, the field has a strong opportunity to tackle tasks that current methods hardly solve. However, high data dimensionality forces most methods to summarize large genomic datasets into a relatively small number of handcrafted features (summary statistics). Here we propose an alternative to summary statistics, based on the automatic extraction of relevant information using deep learning techniques. Specifically, we design artificial neural networks (ANNs) that take as input single nucleotide polymorphic sites (SNPs) found in individuals sampled from a single population and infer the past effective population size history. First, we provide guidelines to construct artificial neural networks that comply with the intrinsic properties of SNP data such as invariance to permutation of haplotypes, long scale interactions between SNPs and variable genomic length. Thanks to a Bayesian hyperparameter optimization procedure, we evaluate the performances of multiple networks and compare them to well established methods like Approximate Bayesian Computation (ABC). Even without the expert knowledge of summary statistics, our approach compares fairly well to an ABC based on handcrafted features. Furthermore we show that combining deep learning and ABC can improve performances while taking advantage of both frameworks. Finally, we apply our approach to reconstruct the effective population size history of cattle breed populations.

## 1 Introduction

In the past years, fields such as computer vision and natural language processing have shown impressive results thanks to the rise of deep learning methods. What makes these methods so powerful is not fully understood yet, but one key element is their ability to handle and exploit high dimensional structured data. Therefore, deep learning seems particularly suited to extract relevant information from genomic data, and has indeed been used for many tasks outside population genetics at first, such as prediction of protein binding sites, of phenotypes or of alternative splicing sites (Alipanahi et al., 2015, Jaganathan et al., 2019, Ma et al., 2018).

As genomic data becomes more and more available, it is possible to study the genetic variations within species or populations and investigate complex demographic histories including admixture events, population structure or size fluctuation through time, and this for many species. In fact, initiatives like the 1000 Genomes Project for human populations (Consortium et al., 2010) have been extended for better world coverage and data quality (Bergström et al., 2019, Consortium et al., 2015, Leitsalu et al., 2014, Mallick et al., 2016, Pagani et al., 2016) and opened up to many other species such as *Bos taurus* with the 1000 Bull Genomes Project (Daetwyler et al., 2014) or chimpanzees and gorillas with the Great Apes Genome Project (Prado-Martinez et al., 2013). Even for smaller scale studies, researchers have access to the whole genomes or high-density SNP data of numerous samples. These data collections can only be treated with inference methods able to scale to dozens or hundreds of individuals and large amount of genetic markers.

In this study, we propose several deep learning approaches for reconstructing the detailed histories of past effective population sizes from genetic polymorphism within a single population, a task considered difficult for various reasons. First, a present-day population, and even more so a sample of it, is one among many possible outcomes of a stochastic process depending on population sizes, mutation and recombination. Second, many other factors such as selective pressure, admixture events or population structure also shape the contemporary genetic diversity, which can blur the link between population size history and genetic data. As a result, the accuracy of the reconstruction and its level of resolution depend on the number of individuals available, the quality of the data and the methodology used. Nonetheless, in practice and under some simplifying assumptions, previous methods such as Bayesian skyline plots and their derivatives (Ho and Shapiro, 2011), sequential Markov coalescent (SMC) (PSMC, diCal and their derivatives (Li and Durbin, 2011, Sheehan et al., 2013)), Approximate Bayesian Computation (Boitard et al., 2016, Navascués et al., 2017) and SFS-based approaches (Bhaskar et al., 2015, Liu and Fu, 2015) have shown great results, supporting archaeological evidence and helping to understand species decline or expansion.

The study of genetic variation relies primarily on genotyping and sequencing data of very high dimensionality, which is a major difficulty for most inference methods. Some approaches, such as coalescent-HMMs methods (Spence et al., 2018), enable parameter inference using the full dataset by making simplifying assumptions on the underlying models. Despite impressive recent improvements, they still suffer some limitations: if a few of them can now process unphased data (Terhorst et al., 2017), scale to large sample size (Terhorst et al., 2017) or to complex models (Steinrücken et al., 2019), no method simultaneously address the three, and handling arbitrarily complex models remains untested (e.g.

models with more than three populations) or intractable (e.g. complex spatial models) (Spence et al., 2018). Hence, most frameworks solving complex population genetic tasks do not rely on coalescent-HMMs and reduce the data dimension with a pre-processing step during which the dataset is converted into a smaller set of statistics called summary statistics. These statistics can then be used in likelihood and composite likelihood inference frameworks, when the model or statistics are simple enough, or in simulation-based approaches. Among the latter, the widely used Approximate Bayesian Computation (ABC) framework as well as several machine-learning algorithms, including SVM and random forests, were able to tackle a variety of tasks such as demographic model selection and parameter inference (Excoffier et al., 2013, Jay et al., 2019), detection of selection (Sugden et al., 2018, Tournebize et al., 2019) and introgression (Schrider et al., 2018). The current trend when addressing complex tasks is to include a large number of summary statistics inspired by population genetic theory in order to minimize the information loss. Summary statistics commonly used are the site frequency spectrum (SFS) and its summaries (e.g. Tajima D), linkage disequilibrium (LD) and statistics based on shared segments that are identical-by-state (IBS) or identical-by-descent (IBD) (Jay et al., 2019, Sheehan and Song, 2016, Smith and Flaxman, 2019). However, they are not guaranteed to be sufficient and the inclusion of numerous statistics can impact the performances of standard ABC, a problem known as curse of dimensionality (Blum, 2010). An active research topic in the ABC community is thus the development of methods addressing this curse of dimensionality by (i) selecting the best subset of summary statistics according to some information-based criteria, or (ii) integrating machine learning steps into ABC to handle a larger number of summary statistics (e.g. kernel methods, random forests), or (iii) constructing summary statistics using linear and non-linear models based on candidate statistics or on the original data when feasible (Aeschbacher et al., 2012, Blum et al., 2013, Fearnhead and Prangle, 2012, Jiang et al., 2017, Nakagome et al., 2013, Raynal et al., 2018). In our study, we chose to use deep learning to bypass summary statistics computation. The artificial neural network not only automatically computes its own summary statistics, also called features in the deep learning community, directly from the genomic dataset, but also performs the inference task to output effective population size predictions.

Deep learning, i.e. the use of artificial neural networks (ANN), has only very recently been used to tackle population genetics questions. First, multilayer perceptron (MLP) were used to process large sets of summary statistics and to predict jointly selective sweeps and simple demographic changes (Sheehan and Song, 2016), or to disentangle between multiple scenarios of archaic introgression thanks to an additional ABC step (Lorente-Galdos et al., 2019, Mondal et al., 2019). A second type of ANN, convolutional neural networks (CNN), were then applied to summary statistics computed over 5Kb genomic regions in order to predict selective sweeps (Xue et al., 2019). A considerable shift occurred when several studies applied ANN directly on genomic data instead of using summary statistic. Various CNN architectures processing SNP matrices were proposed to infer recombination rates along the genome (Chan et al., 2018, Flagel et al., 2018), selection (Flagel et al., 2018, Torada et al., 2019), introgression (Flagel et al., 2018) and three-step population size histories (Flagel et al., 2018). The CNN implemented by Chan et al. (2018) and based on Deep Sets (Zaheer et al., 2017) is invariant to haplotype permutation (i.e to the permutation of lines in the SNP matrix) thanks to convolution filters that treat each haplotype in an identical way. The other approaches proposed instead to sort haplotypes by similarity before processing them with filters sensitive to the haplotype order (Flagel et al., 2018, Torada et al., 2019). More recently, Recurrent Neural Networks (RNN) were applied to estimate the recombination rate (Adrion et al., 2019), and Generative Adversarial Networks (GAN) to learn the distribution of genomic datasets and to generate artificial genomes (Yelmen et al., 2019).

Convolution layers have been particularly efficient for large size data with spatial coherence such as images, exploiting the geometric structure of the image pixel grid. Instead of requiring as many weights as the input data size (like fully-connected layers in MLP), convolution layers take advantage of the spatial structure of the data, by defining spatially-small filters and applying them at each location along the input dimension (here, the SNP sequence). The result of each operation is ordered spatially according to the corresponding location in the input, to keep spatial coherence throughout the network. The filters of the first convolution layers have a small scope over the data input of the network, but adding layers on top of each other gives a larger scope to the last layers, allowing to handle long range interactions, in particular when combined with max-pooling layers. These interactions are important for demographic inference, e.g. they can allow the network to measure linkage disequilibrium and thus, the level of recombination.

Among the variety of developed ANN architectures, it is not straightforward to know which one is the most adapted to genomic data for a given population genetic task. In particular, this study aims at reconstructing detailed step-wise effective population size histories with 21 size parameters under an unknown recombination rate, a complex model with a fairly high dimensional parameter space compared to the population genetic task previously addressed with ANN. Hence we propose multiple networks, some of which are new and designed specifically for population genomics, and others that are more basic. We then apply a hyperparameter optimisation procedure (BOHB (Falkner et al., 2018)) to select the best architecture and hyperparameters. We investigate the performance of two MLPs, one using summary statistics and one using SNPs data of fixed length. We also compare two novel CNN based architectures, one with mixed convolution filter sizes over multiple individuals and another CNN that is adaptive to the genomic input size and invariant to the permutation of individuals or haplotypes. Both networks incorporate SNP data and their relative positions, a concept also developed in a different fashion by Flagel et al. (2018). In our last setup, we combine ABC and ANN by using the ANN predictions as summary statistics with the aim to benefit from both method advantages. Because no end-to-end deep learning approach for demographic inference had yet been compared to ABC or other traditional methods, we carefully benchmarked all these networks against variations of PopSizeABC, one of the highly performing methods for step-wise size inference that is based on ABC (Boitard et al., 2016). We also compare our architecture with CNNs developed for a related demographic task (Flagel et al., 2018). Finally we apply our approach to real genomes in order to reconstruct the size history of three cattle breeds.

## 2 Results

In this study, we introduce the first deep learning approaches for inferring detailed histories of effective population sizes using genomic data. Based on whole sequences of SNP data of multiple individuals from a single population, we aimed to predict 21 population size parameters, each corresponding to a time step. Our method and the baseline frameworks all relied on large-scale simulated datasets for which the true demographic parameters are known and drawn from prior distributions of population sizes and recombination rates. For each drawn parameter set, we simulated 100 2Mb-long genomic regions using msprime (Kelleher et al., 2016). Using this reference panel, we then trained methods based on ABC, deep learning or a combination of both, to predict the demographic parameters (Figure 1). In this section, we will give an overview of these methods as well as the hyperparameter optimisation procedure, followed by the evaluation of their performance and the inference of the demographic history of three cattle breeds.

## 2.1 Baselines

We compare our approach to 5 baselines: an ABC approach and a MLP both using linkage disequilibrium and site frequency spectrum as summary statistics, and another MLP, a "custom CNN" and a CNN from (Flagel et al., 2018), all using genomic data directly. We evaluate four ABC methods (rejection, local linear regression, local ridge regression and a single-hidden-layer neural network) with six tolerance rates (0.05, 0.1, 0.15, 0.2, 0.25 and 0.3). Their performances represent a baseline for state-of-the-art methods. The second framework, a MLP processing the same summary statistics as ABC, is similar in spirit to the one previously proposed for predicting 3 demographic parameters alongside selection (Sheehan and Song, 2016). It is the baseline for methods using deep learning based on summary statistics. The third and fourth baselines consist in a MLP and a CNN processing directly the first 400 SNPs of a 2Mb-long genomic region instead of summary statistics. The MLP takes as input SNP data and locations flattened into a single vector. In this configuration, the spatial information between SNPs, the link between the SNPs and their location, and the link between alleles of the same individual are lost. The fourth baseline is a newly design CNN with rectangular shaped filters that cover more than one haplotype (see Methods). This "custom CNN" is a first step towards an architecture tailored to raw genomic data, because spatial information is preserved as for recent ANNs applied to population genetics (Chan et al., 2018, Flagel et al., 2018, Torada et al., 2019), but also because asymmetrical filters of various sizes account for the heterogeneous entities of axes (haplotype versus SNP, rather than pixel versus pixel). Finally we adapted and re-trained four networks among the top-ranked CNNs proposed by Flagel et al. (2018) so that they could reconstruct a 21-epoch model of instantaneous effective population size rather than the three-epoch model initially investigated by the authors, and for practicability we called them *Flagel* CNNs.

## 2.2 Sequence Position Informed Deep Neural Architecture

We called our architecture SPIDNA, for Sequence Position Informed Deep Neural Architecture, and designed it to comply to the principal features of SNP data: data heterogeneity (data includes genetic markers and their positions), haplotype permutation invariance, long range dependencies between SNPs and variable number of SNPs.

### 2.2.1 Permutation invariance

One of the SNP matrix properties is its invariance to the permutation of haplotypes or genotypes. The same matrix with permuted rows contain the exact same information and should lead to the same predictions. Most summary statistics are already invariant to the haplotype order by definition. On the other hand, typical operations used in ANN such as rectangular filters and fully connected layers are not invariant, and consequently our two baseline ANNs do not respect this data feature. Here we implemented an architecture invariant by design, that stacks functions equivariant and invariant to row permutations (Lucas et al., 2018). It is a modification of the Deep Sets scheme (Zaheer et al., 2017) used for population genetics under the name "exchangeable networks" (Chan et al., 2018). In our study, the equivariant function is a convolutional layer with filters of size $1 \times a$, that treats each haplotype (row) independently and computes equivariant features, while the invariant function computes the mean of these features over the row dimension. The invariant function reduces the dimension of the data to one row, which is then concatenated to each equivariant row (Figure 2). Therefore the correlation between rows increases at each layer, which progressively transforms the equivariant input to an invariant output. However, the correlation increase should be moderate and progressive to avoid immediate loss of the information at the haplotype level. To promote this, we perform two independent normalizations, one over the output of the equivariant function and one over the input of the invariant function, and associate a correlation control parameter $\alpha$ that quantifies the contribution of the invariant function to the next layer, thus controlling the speed at which the correlation increases between rows.

### 2.2.2 Convolution networks to handle data with variable size

A major difficulty that arises with genomic data is that the number of SNP varies from one dataset to another, or from one genomic region to another, due to the stochasticity of biological and demographic processes (and of their corresponding genetic simulator). Therefore, we use convolution layers as they can handle data with variable size while keeping the number of network weights constant. A filter can be repeated more or fewer times to cover the whole input entering each layer, letting the network adapts itself to the data. Consequently, the output size of each convolution layer will vary depending on the input size. This prevents the use of fully connected layers directly after a convolution layer as it is often the case with CNNs. Instead, we use fully-connected layers only after operations independent of the input size and with a fixed output size, namely mean functions over the column and row dimensions (Figure 2).

Overall, we carefully designed an architecture accounting for invariance and adaptive specificities by stacking multiple equivariant blocks consisting in convolution layers with filters of size $1 \times 3$, invariant average pooling layers that are also adaptive to the number of SNPs and fully-connected layers that predict demographic parameters at each block (Figure 2). Contrary to our previous networks that include batch normalization of neuron activities, adaptive SPIDNA networks include instance normalization (see Methods).

### 2.3 Hyperparameter optimization

Compared to other machine learning methods, ANNs have a potentially infinite amount of hyperparameters when including for instance the number of layers, the number of neurons in each of them, the learning rate, weight decay or the batch size. Moreover, a run over a full dataset with enough epochs to reach convergence is time consuming for networks with a complex architecture defined by many learnable parameters. Therefore, the development of deep learning architectures often relies on the experience and intuition of the practitioner in a try-and-repeat process. Grid search and random search are two strategies for exploring the hyperparameter space uniformly. They are commonly used but are limited by the computing resources available. In our study, we used HpBandSter, a package that implements the HyperBand (Li et al., 2016) algorithm to run many hyperparameter trials on a smaller resource budget (i.e. few epochs) and runs the most promising trials on a greater budget. Combined with BOHB (Falkner et al., 2018), a Bayesian optimisation procedure that models the expected improvement of the joint hyperparameters, this method provides more guided and faster search of the hyperparameter space. At each step, BOHB draws a new combination of hyperparameter values to be tested according to the expected improvement and to a predefined prior. Here, we performed a search in a 5-dimensional space defined by: the type of architecture (architectures from our baselines and variations of SPIDNA architecture, based on 400 SNPs or the full number of SNPs), the learning rate, the weight decay, the batch size and the correlation control parameter $\alpha$. The search was performed for 3 budget steps and replicated 5 times, leading to a total of 83 successfully trained networks.

The configuration with the lowest loss generated by the hyperparameter optimization procedure used 400 SNPs with SPIDNA, batch normalization, a weight decay of $2.069 \cdot 10^{-2}$, a learning rate of $1.416 \cdot 10^{-2}$ and a batch size of 78 (Figure S1). Configurations with large batch sizes tended to have lower losses (Figure S1), which is expected as large batches provide a better approximation of the full training set gradient. However, a batch size too close to the training set size can lead to overfitting the training set. Here, we did not observe overfitting for any run when monitoring training and validation losses. The best configurations also tended to have low learning rates and weight decays (Figure S1). These low values slow down the convergence, but usually decrease the final prediction error if the budget is high enough for the network to reach convergence.

### 2.4 Comparison of the optimized architectures

For each architecture, we selected the best configuration obtained with the hyperparameter optimization procedure and trained it for a greater budget (i.e. 10 epochs), allowing an in-depth comparison. We found no strong decrease of prediction errors after this longer training compared to their counterparts with a $10^7$ budget ($10^7$ training SNP matrix, i.e. 5.57 epochs) (Figures 3 and S1).

We first compared the optimized neural networks to optimized ABC approaches based on predefined summary statistics. The prediction errors achieved by ABC using summary statistics ranged from 0.490 (ABC rejection, i.e. without correction) to 0.352 (ABC neural networks). The MLP network based on summary statistics performed comparatively well (0.388). On the contrary the MLP based on raw data performed very poorly (0.690). All other networks based on raw data outperformed this MLP, and most of them (all except SPIDNA instance normalization and SPIDNA instance normalization adaptive) outperformed the ABC rejection (SPIDNA batch normalization, 0.453) or led to similar errors (ranging from 0.485 to 0.489). The *Flagel* CNNs adapted from Flagel et al. (2018) that were not using dropout had extreme overfitting issues (average training losses of 0.004 and 0.006 versus validation losses of 0.719 and 0.984). The two other *Flagel* networks achieved prediction errors similar to SPIDNA (network based on the first 400 SNPs: 0.447; network based on 1784 downsampled SNPs: 0.437), however they had 8 to 34 times more parameters than SPIDNA and despite the dropout procedure they still suffered from overfitting (validation over training loss ratio of 2.50 and 1.39 for *Flagel* CNNs versus 0.89, 1.01 and 0.97 for SPIDNA which indeed sometimes performed better on the validation set).

Lastly, we evaluated two methods that combine deep learning and ABC, by considering the features automatically computed by a network as summary statistics for ABC (Jiang et al., 2017). When using only the predictions of SPIDNA as input to ABC with correction (linear regression, ridge regression or neural network), we improved greatly SPIDNA's performances and obtained errors similar to the ABC based on predefined summary statistics (0.363 compared to 0.352). When using both SPIDNA predictions and predefined summary statistics as input to the ABC algorithm we decreased further the prediction errors (0.335).

We further illustrated the performances of SPIDNA on a subset of demographic scenarios that were previously investigated (Boitard et al., 2016) (Figure 4). The method correctly reconstructed histories of constant size, expansion and decline, as SPIDNA predictions from 100 independent genomic regions (black boxplots) approximately followed the real population size trend and magnitude. The true parameters were always included in the 90% credible intervals (light blue envelopes) predicted by SPIDNA combined with ABC without predefined summary statistics and, for most cases, in the 50% credible intervals (dark blue). Both methods also correctly reconstructed a complex history encompassing an expansion interrupted by a bottleneck and followed by a constant size (see Figure 4 'Bottleneck'). However, they were unable to correctly estimate the parameters of a very complex 'Zigzag' history except for its initial growth period and instead reconstructed a smoother history with values intermediate to the lower and higher population sizes (see Figure 4 'Zigzag'). This confirmed the smoothing behavior identified previously for ABC and MSMC (Boitard et al., 2016). Finally, similarly to ABC on predefined summary statistics (Boitard et al., 2016), SPIDNA predictions of very recent population sizes were slightly biased toward the center of the prior distribution, however combining SPIDNA with ABC tended to correct this bias in most cases.

### 2.5 SPIDNA infers the decline of effective population size of cattle

We inferred the effective population size history of three breeds of cattle (Angus, Fleckvieh and Holstein) based on the same 75 individuals studied by Boitard et al. (2016) and sampled by the 1000 Bull Genomes Project (Figure 5). The best ABC and SPIDNA configurations both infer a large ancestral effective population size and a decline for the past 70,000 years. However, SPIDNA reports higher recent population size (Angus:11,334, Holstein:12,311, Fleckvieh:13,579) than ABC (Angus:361, Holstein:552, Fleckvieh:1,329). Interestingly, SPIDNA infers the same population sizes for all three breeds before 10 thousand years ago. This is in agreement with the estimation of the beginning of the domestication (Zeder, 2008). SPIDNA combined with ABC also reconstructed a decline after domestication but estimated larger population sizes for the last 30,000 years than SPIDNA alone. In addition Angus had the largest recent population and Fleckvieh the smallest in contrary to the two previous methods. Finally SPIDNA combined with ABC identified an episode of smooth decline and recovery of the population size preceding the domestication in the putative ancestral species (between  400,000 and 30,000 years ago).

## 3 Methods

### 3.1 Simulated data and summary statistics

All methods compared in this study are trained in a supervised fashion, and thus require genetic data of numerous populations under various demographic scenarios. We defined the demographic parameters by following similar rules as Boitard et al. (2016): $I = 21$ time windows $[t_i, t_{i+1}]$ were defined from present to ancient periods with $t_i = (exp(log(1 + aT)i/(I - 1)) - 1)/a$ generations, $i$ going from 0 to $I - 1$, $T = 130,000$, $a = 0.06$ and $t_I = +\infty$. By increasing exponentially the time windows as we go further in the past, we obtain more detailed scenarios for recent times. The time windows are identical for all scenarios to focus on the population size parameters. Each demographic scenario is generated by drawing a first population size $N_0$ between 10 and 100,000 from a uniform distribution and corresponds to the most recent time window $t_0$. The population sizes of the next time windows follow $N_i = N_{i-1} \times 10^{\beta}$ with $\beta$ sampled uniformly between -1 and 1. $\beta$ is redrawn if it gives a population size out of $]10, 100000[$. 50000 scenarios are drawn from this prior distribution and are passed to the msprime coalescent simulator version 0.6.1 (Kelleher et al., 2016) to simulate 100 independent 2Mb-long segments of 50 haploid individuals. Each simulation gives a SNP matrix $X$ of size $M$ haplotypes $\times$ $S$ SNP sites and a location vector of size $S$ that features the relative locations between SNPs in the corresponding DNA sequence. Ancestral and derived alleles are encoded with 0 and 1. The mutation rate is set to $10^{-8}$ and the recombination rate is sampled uniformly between $10^{-9}$ and $10^{-8}$ for each scenario. The real cattle dataset has 4357 SNPs on average, thus we remove the scenarios with lower than 400 SNPs as we consider them outside of our prior. That reduced the dataset to 18461 scenarios, with 100 examples each, that we split into a validation set of 500 scenarios and a training set with the remaining 17961 scenarios.

For each group of 100 segments corresponding to one scenario, we computed the site frequency spectrum and the linkage disequilibrium as a function of the distance between SNPs averaged over 19 distance bins for a total of 87 summary statistics. Our python script is partly based on the scikit-allel python module (Miles et al., 2019).

### 3.2 Baseline specifications

**Approximate Bayesian Computation** We compared ABC with the simple rejection procedure (i.e. no correction) and three correction methods implemented in the R package 'abc' (Csilléry et al., 2012): local linear regression, ridge regression and non-linear regression based on a single-hidden-layer neural network. Settings were set to default except for the tolerance rate. ABC was run on (a) Predefined summary statistics, (b) SPIDNA outputs (i.e. automatically computed summary statistics), or (c) a combination of predefined summary statistics and SPIDNA outputs.

**Multi-Layer-Perceptron Networks** Our MLP based on summary statistics has 3 hidden layers, ReLU activation functions, and uses batch normalisation and the adam optimizer. As in Sheehan and Song (2016), the hidden layers have respectively 25, 25, and 10 neurons. It takes 35 summary statistics as input. This network and all the following ones output 21 demographic parameters and are trained with a regular L2 loss function unless stated otherwise. This MLP has a total of 2,986 trainable parameters. Our second MLP is based on 'raw' genomic data and takes a matrix of 50 haplotypes (rows) for 400 SNPs (columns) and its associated position vector as input. Its hidden layers respectively have 20, 20, and 10 neurons, which gives it 408,981 trainable parameters.

**Custom CNN** Our convolutional neural network takes as input the same matrix of 400 SNPs and has 2-dimension filters of various shapes. The first layer consists of 5 kernels with rectangular shape ($2\times2,\ 5\times4,\ 3\times8,\ 2\times10,\ 20\times1$) applied to the SNP matrix $X$. Each kernel creates 50 filters, which amounts to 250 feature maps after the first layer. The position vector $d$ is treated by the 5 associated kernel shapes ($1\times2,\ 1\times4,\ 1\times8,\ 1\times10,\ 1\times1$) with 20 filters each, making 100 filters in total. The results of the first convolutional layer are then concatenated so that the second convolutional layer will couple information from $X$ and $d$ in a way that emphasizes the original location of the SNPs along the genome. The outputs of this second layer are then combined and go through 5 convolutional layers and 2 fully connected layers. Adding convolutional layers one after each other allows our network to combine patterns and reduce the size of the data without adding too many weights to our model. This network has a total of 131,731 trainable parameters.

***Flagel* network** We reused the code associated with the repository of the first paper using a CNN for demographic inference (Flagel et al., 2018) and adapted it to our dataset and task. We trained the network with the exact same architecture as the one published, except that we changed the last layer to allow the prediction of our 21 population size parameters. We parametrized the network with the set of hyperparameters leading to the best performance in the previous work for two different types of SNP encoding (0/255 or -1/1). It is noteworthy that the actual encoding in their code is 0/-1 and not 0/255, thus we kept the same encoding to be able to compare the performances. The networks were trained with the same procedure of 10 epochs with early stopping in case of no progression of the loss after 3 epochs. The batch size is 200. The input data had 50 haplotypes and either 400 SNPs as processed by our custom CNN or we downsampled the data to one every ten SNPs as done in the original work, leading to 1784 wide input SNP matrices. This size corresponds to the tenth of the biggest SNP matrix in our dataset. Smaller simulations are padded with zeros. All parameters can be found in table S1.

## 3.3 SPIDNA architecture

For our permutation invariant architecture, we designed three variations. The first one uses batch normalization, after each convolution layer, and therefore takes as input a fixed number of 400 SNPs, similarly to two of the baselines.

The second one is invariant to the number of SNPs and uses instance normalization, after each convolution layer, to normalize layer inputs per-data instead of per-batch (for the batch normalization). The last variation is also invariant to the number of SNPs, but uses two separate instance normalization steps, as well as the correlation control parameter $\alpha$.

Except for these differences, these three variations have the same architecture, represented in Figure 2. At each step $i$ of the network, we consider that the data has four dimensions $B_i \times M_i \times S_i \times F_i$, $B$ being the batch dimension, $M$ the row dimension (also the haplotype/genotype dimension before the first layer), $S$ the column dimension (also the SNP dimension before the first layer) and $F$ the feature dimension (only one feature before the first layer). A first convolution layer of 50 $1 \times 3$ filters is applied to the SNP matrix, and another convolution layer of 50 $1 \times 3$ filters is applied to the position vector and repeated $M$ times. The results of the two convolutions have now the same dimensions and are concatenated along the feature dimension. The resulting tensor is then passed to seven blocks put end to end, each one involving an equivariant function and an invariant function. The equivariant function $\psi$ is a convolutional layer of 50 $1 \times 3$ filters that outputs a tensor of size $B_{i-1} \times M_{i-1} \times (S_{i-1} - 2) \times F_{i-1}/2$. The result of the equivariant function is then passed to the invariant function $\rho$, which is the mean over the dimension $M$. Thus $\rho(\phi(X_{i-1}))$ has size $B_{i-1} \times (S_{i-1} - 2) \times F_{i-1}/2$, which is repeated $M$ times to maintain the same dimension as $\phi(X_{i-1})$. Then $\rho(\phi(X_{i-1}))$ and $\phi(X_{i-1})$ are concatenated over the feature dimension. Finally, max-pooling filters of dimension $1 \times 2$ are applied, and the result is passed to the next block. In parallel, each block computes the average over the column dimension $S$ of the 21 first features of $\rho(\phi(X_{i-1}))$ that are then passed to a fully-connected layer with 21 outputs. The predictions of each block are summed.

## 3.4 From batch normalization to instance normalization

Network weight initialization is a difficult task that can lead to vanishing or exploding gradient when not carefully done and associated with a poor learning rate (Bengio et al., 1994, Glorot and Bengio, 2010). Most initialization schemes try to force the outputs of each layer to follow some distribution assuming normalized input data. Batch normalization solves this problem by normalizing layer outputs over the whole batch during training and computing a running mean and variance for the evaluation steps. We used this type of normalization for our networks that take as input a fixed number of SNPs. For the networks invariant to the number of SNPs, we could not concatenate all batch data into the same tensor because of their varying sizes. Therefore, we use instance normalization, which computes both mean and variance over the feature dimension.

## 3.5 Hyperparameter optimization

**ABC** The tolerance rates ranged from 0.05 to 0.3 by step of 0.5 and were optimized for 12 ABC algorithms independently (4 correction methods $\times$ 3 types of inputs: predefined summary statistics, SPIDNA outputs or both).

**MLP using summary statistics** As the training time for this algorithm was short, we optimized its hyperparameters with a random search by drawing 27 configurations from uniform distributions and trained a network for each configuration during 6 epochs. The batch size was drawn between 10 and 100, learning rate between $5 \cdot 10^{-5}$ and $1 \cdot 10^{-2}$ and weight decay between $5 \cdot 10^{-5}$ and $1 \cdot 10^{-2}$.

**ANNs over SNP matrices** Batch size, learning rate, weight decay and the architecture choice were optimized using the Bayesian optimization procedure BOHB (Falkner et al., 2018) with the same hyperparameter prior distributions than the MLP using summary statistics, and with a uniform distribution over the architecture choices. For SPIDNA architectures that controlled correlation, we added the control parameter $\alpha$ to the Bayesian optimization procedure with a log-uniform prior between 0.5 and 1.

### 3.6 Cattle breed data

We inferred the demographic history of Angus, Fleckvieh and Holstein cattle breeds using the data set of 25 sequenced individuals from the 1,000 genome bull project (Daetwyler et al., 2014) that was analysed by (Boitard et al., 2016). As the data of real cattle sequence is prone to phasing and sequencing errors, we converted the real data from haplotype to genotype with a minimum allele frequency (maf) of 0.2, as suggested by Boitard et al. (2016) and applied the same treatment to the simulated training set. We split the real data of each breed into 1213 segments of 2Mb and removed segments comprising centromeres. Then we trained ABC and SPIDNA with the best hyperparameter configurations on the modified simulated data and performed the inference.

## 4 Discussion

In this paper, we introduced a deep learning approach to infer the detailed size history of a single population directly from genomic data given an unknown recombination rate. This consisted in inferring jointly 21 population size parameters. We not only increased the complexity of the demographic model with respect to previous works such as Flagel et al. (2018), but also compared the performances of our architecture to other methods including ABC, and applied our approach to real data sets. We found that our approach compared competitively with one of the best to date approaches, with the added advantage of not relying on summary statistics. Finally, we reconstructed the effective population size fluctuations of three cattle breeds and confirmed that they all had similar sizes when they were part of the same ancestral species *Bos taurus* and underwent a decline likely linked to their domestication, although the estimated strength of this decline depended on the inference method.

### 4.1 On the practicability and importance of architecture design

When applying deep learning techniques, the design of the neural network architecture is critical, as poor design can lead to a lack of expressive power, information loss, underfitting, overfitting, or unnecessary complications that slow down the training process. The recent history of successes in Computer Vision consists in architecture improvements, leading to performance gaps (e.g. from MLP to LeNet, AlexNet, VGG, Inception and ResNet (He et al., 2016, Krizhevsky et al., 2012, LeCun et al., 1998, Simonyan and Zisserman, 2014, Szegedy et al., 2017)). But these successes have been built incrementally by relatively small changes over the last years, involving a large number of studies, researchers and challenges. Indeed finding the best architecture suited for a task is hard and time-consuming given the wide range of possibilities. Therefore, automating architecture and hyperparameter choice is an important challenge that can yield benefit to smaller fields such as population genetics. In our study, the Bayesian hyperparmeter optimisation procedure allowed to test multiple networks thanks to a better usage of the computational power available by giving more budget to the most promising ANN architectures and hyperparameters. This procedure could be extended to hyperparameters that further describe the architecture of the network such as the number and type of layers, of neurons, the type of non-linearity or the topology. Thanks to this procedure we investigated a series of architectures, starting from the simple multi-layer fully-connected network (MLP) and moving on to more complex architectures, and exhibited the link between design and performances.

To interpret the results and compare them, let us first note that in Figure 3, a 0 error means perfect prediction, while an error of 1 means that no information is extracted from the input. Indeed, a function outputting always the same value, for all samples, can at best predict the average target value over the dataset, in which case the error is the standard deviation over the dataset of the value to predict, which is normalized to 1 in our setup.

Processing the SNP and position matrices with a MLP led to high prediction errors, especially for recent population sizes. This is not surprising, since genomic information is encoded as a simple list of values, where the order has no meaning from the MLP point of view, which then cannot exploit information given by the data structure. In summary, an MLP configuration has several drawbacks: (i) the number of network parameters to estimate is high; (ii) the MLP can only retrieve the geometry of the data through training, with no guarantee that it will learn the spatial structure of the genome (i.e. the column order and distance between SNPs) or distinguish from which individual comes each SNP. In spite of all these hindrances, the MLP still performed far better than random guesses or constant prediction (31% better).

On the contrary, CNN layers process input elements by groups, allowing close SNPs to be processed together. This feature, combined with the stacking of layers in CNN, helps the network to construct features dependent of the SNPs proximity. Important summary statistics used in ABC or other inference methods such as linkage disequilibrium can potentially be easily expressed by such CNN. Illustrating the difficulty of undertaking the resolution of a new task with previously designed networks, the adapted *Flagel* CNNs (Flagel et al., 2018) suffered overfitting. Hence we proposed several novel convolutional architectures, tailored to genetic data. We first developed a CNN with 2D filters that could have different shapes, i.e. mixed kernel sizes but also non symmetrical masks. There is indeed no rational behind considering square masks only as is usually done in computer vision to describe pixel neighborhoods, as rows and columns in our case correspond to different entities (individual or phased haplotype versus markers). Using varied mask shapes (e.g., $2\times2$, $5\times4$ or $3\times8$) helps our custom CNN to learn features of various patterns, potentially mimicking different types of summary statistics ("vertical" masks integrate over individuals, enabling the computation of allele frequencies at a SNP, while "horizontal" ones integrate over SNPs, as IBS or IBD sharing tract length does). Such mixed size filters have proved useful in the Computer Vision literature also, under the name of Inception architectures

(Szegedy et al., 2017); they allow to extract and mix different kinds of information from multiple scales within the same layer. The large gap in performance between a simple MLP and this custom CNN confirms the importance of such considerations. A natural extension would be to integrate this feature into SPIDNA, our permutation-invariant architecture.

## 4.2 Novel architectures tailored to genomic data

### 4.2.1 Invariance to haplotype permutation

The order in which simulated haplotypes are arranged in a SNP matrix has no meaning. Although the custom CNN network above cannot be guaranteed to be exactly invariant to the haplotype order, it can approximately learn this specificity. To avoid wasting training time to learn that there is no information in the row order, it has been proposed to systematically sort the haplotypes according to a predefined rule (Flagel et al., 2018, Torada et al., 2019). Because there is no ordering in high dimensional space that is stable with respect to perturbations (Qi et al., 2017), we chose yet another alternative and enforced our network to be permutation-invariant by design. Permutation-invariant networks, or exchangeable networks, were successfully applied in population genetics by Chan et al. (2018) for inferring local recombination, but our architecture is different in that the invariant operations are performed at each block, enabling both individual equivariant features and global invariant features to contribute to the next layer. It has been proven that this type of architecture provides universal approximation of permutation-invariant functions (**?**). Among our permutation-invariant architectures, the best one (SPIDNA using batch normalization) had a smaller prediction error than our custom CNN. However, it is not clear whether this improvement is directly linked to its built-in permutation-invariance property, or to other differences between the two networks. Controlling the speed to invariance thanks to the parameter $\alpha$ improved the performance of the instance normalization SPIDNA, but not significantly the performance of the instance normalization adaptive SPIDNA (see table S2).

Importantly, SPIDNA adapts to the number of individuals, which is an advantageous property compared to many methods relying on summary statistics. SPIDNA can be trained on data sets having similar or varying sample sizes, and, once trained, it can be directly applied to a dataset of sample size unobserved during training.

### 4.2.2 Automatic adaptation to the number of SNPs

The two networks designed to be adaptive to the number of SNPs have the advantage to be applicable to genetic data of any length, to the opposite of networks specific to a particular number of SNPs, which transform the data with padding or compression, or are retrained for different lengths, or take as input portions of larger sequences. Our two SPIDNA adaptive networks show results close to the best of non-adaptive versions, though slightly worse (0.487 versus 0.453, see table S2), although the difference disappears when SPIDNA is combined with ABC (0.363 versus 0.363). This small performance drop is likely due to differences in normalization rather than to the adaptive feature. Indeed, the best non-adaptive SPIDNA uses batch normalization while the adaptive versions use instance normalization, because of implementation limitations, as there is currently no implementation of batch normalization for batches with inputs of mixed sizes. Nonetheless, SPIDNA networks with instance normalization had much better performances when using all SNPs rather than the 400 first SNPs only, which suggests that adaptability is a useful feature (see table S2).

Our adaptive architecture provides an alternative to data compression based on computer vision algorithms: since compression is not optimized for the task of interest, it could induce information loss by reducing data prematurely. Note indeed that the success of deep learning in computer vision lies precisely in the replacement of ad-hoc data encoding (e.g. bag of words or SIFT (Lowe, 2004)) by ones that can be optimized. It is also an alternative to padding, a technique that consists in completing the SNP and position data at the edges so that they all match the biggest simulated SNP matrix; it is left to the neural network to guess where the real genetic data stops and where padding starts. As such it may make the task more difficult, given that the SNP matrix size is highly variable between different demographic histories and some examples would contain more padding values that actual genetic information. RNN are also a natural alternative, though they induce an unequal contribution of SNPs to the final result, depending on their ordering along the sequence. They were very recently proven to be useful to predict local recombination rate along the genome (Adrion et al., 2019) and future works should investigate whether this scales up to a global characteristic and to a different task.

### 4.3 Advantages and challenges of deep learning

Alongside the quality of deep learning to automatically extract informative features from high dimensional data, artificial neural networks are also very flexible. For instance, they can be used for transfer learning, that is, a network trained for a specific task can be reused for another one by only modifying the last layers (e.g. a network trained for population size history inference could be reused for classification between demographic scenarios) (Pan and Yang, 2009). The new network will benefit from the embedding already learned for the previous task, improving error and learning time. We also highlight that, as for most ABC methods, the parameters are inferred jointly, a major point as the common population genetics model parameters almost never have an independent impact on shaping genetic diversity. We noted that for highly fluctuating population sizes, SPIDNA estimated smooth histories. Smoothing can be seen as a good byproduct and was for example achieved by SMC++ using a spline regularization scheme (Terhorst et al., 2017).

#### 4.3.1 Combining deep learning and Approximate Bayesian Computation to approximate the posterior distribution

We found that adding an ABC step to the deep learning approach increased its performance. This ABC step takes as input the demographic parameters predicted by SPIDNA instead of the usual summary statistics. This strategy was proposed by Jiang et al. (2017) that showed that a deep neural network could approximate the parameter posterior means, which are desirable summary statistics for ABC. It was applied under the name of ABC-DL in two population genetics studies for performing model selection, however both papers relied on the joint SFS as predefined candidate summary statistics (Lorente-Galdos et al., 2019, Mondal et al., 2019). Here, we are taking advantage of both the deep architecture to bypass summary statistics and the Bayesian framework to refine the prediction and approximate the posterior distribution. Additionally, we showed that applying ABC to SPIDNA predictions combined with precomputed summary statistics led to an error 3.6% smaller than the one of a regular ABC and 6.7% smaller than SPIDNA. This indicates that the information retrieved by SPIDNA does not completely overlap the one encoded into the predefined summary statistics but is not completely orthogonal either. It is a first step towards understanding and interpreting the artificial neural networks currently used in population genetics, a major challenge that the deep learning field currently faces for many of its applications (Gilpin et al., 2018) and that has not yet been investigated in our community.

#### 4.3.2 Application to real data

Applying a method trained on simulated data to a real dataset can be a difficult task. Here we show that the estimated effective population sizes of the three cattle breeds were qualitatively similar across the different methods used. All of them were able to recover the large ancestral population size shared by the three breeds, followed by its decline after domestication. However, the methods produced size estimates that were quantitatively different, notably in the strength of the decline and the recent population sizes. For quality reasons, inference was done using genotypes pruned of low frequency alleles rather than haplotypes. The architecture and hyperparameters were optimized based on simulated haplotypes, and the network was trained on simulated genotypes. It is possible that an architecture designed with a new hyperparameter optimization procedure calibrated for filtered genotypes would decrease SPIDNA error rate. However, the discrepancy between ABC and SPIDNA reconstructions in the last 10,000 years might also be due to the sensitivity of ANNs to overfitting and to mispecifications in the model generating training data. For example, decrease in performances due to demographic mispecification has already been shown for selection inference based on ANNs (Torada et al., 2019). In our case, model mispecification arises because cattle breeds are subjected to strong artificial selection pressures, with few males contributing to the next generations, which is a clear violation of the coalescent assumptions underlying our training simulated set. In addition, errors or missing information in real data were not modelled in the training set, a procedure that can improve ABC performances when using multiple summary statistics such as haplotype length statistics (Jay et al., 2019). When comparing performances on training and validation sets, we found that our architectures were not overfitting, contrary to the architectures directly adapted from Flagel et al. (2018). Yet it is possible that the features automatically constructed by ANNs are more sensitive to a gap between real and simulated data (e.g. unmodelled errors and artificial selection) than an ABC method based on SFS and LD statistics. Systematically testing and improving the robustness of ANNs trained on simulations is a great challenge for the coming years.

## Conclusion

We addressed a challenging task of population genetics, that is, reconstructing effective population size through time. We showed that this demographic inference could be done for unknown recombination rates. We are confident that a network exchangeable and adaptive to the input size is a promising architecture for future lines of works for other population genetics tasks, as it could prevent premature loss of information and favor learning new features rather than known haplotype invariance. As for now, co-estimating multiple processes remains a hard task, and inference is mostly done under a simplifying assumption, e.g. inferring selection or recombination under a fixed demographic scenario, or inferring step-wise population size for a single population (but see MSMC and MSMC-IM for an extension to two populations with interactions (Schiffels and Durbin, 2014, Wang et al., 2019)). The success of ABC and simulation-based methods are partly due to their convenience to include complex models via simulations. Here we showed, for the first time, that a well designed artificial neural network is capable of retrieving information about fluctuating effective population size and that it can also be combined with existing summary statistics. Additionally, recent studies demonstrated very good performances of other networks for solving tasks such as detecting introgression and selection. For the above reasons, and because extracting information automatically should lead to the identification of features that disentangle processes hardly distinguishable, we are hopeful that future robust networks trained on complex simulations could help solving jointly some of these tasks. Finally, we provided (i) a tool for users willing to infer population size history of any species that can be applied to phased or unphased genomes (available from `https://gitlab.inria.fr/ml_genetics/public/DNA_DNA`); (ii) new exchangeable network architectures, some of which have the promising feature of being adaptive to input size ; (iii) guidelines for future developers on building architectures and hyper-optimization to facilitate the development of new artificial neural networks for population genomics.

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## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## Figures and Tables

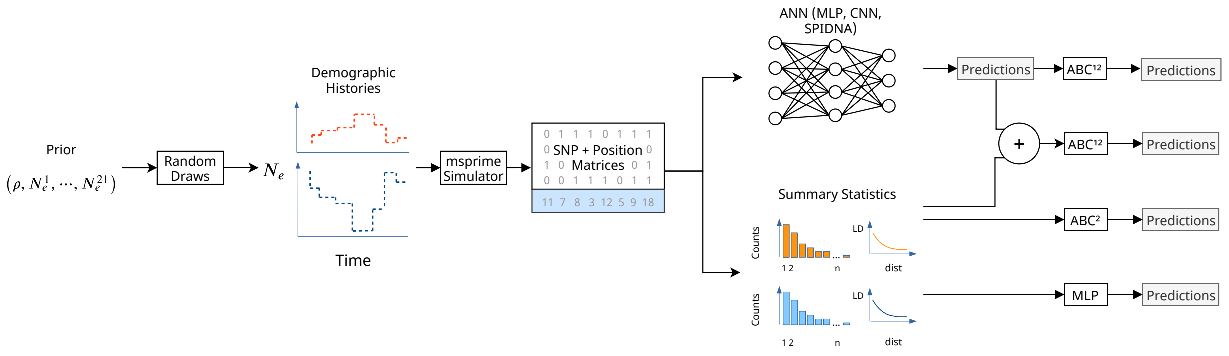

Figure 1: Overview of the methods compared in this study. Demographic histories are drawn from a prior distribution on 21 population sizes $N_e^i$ and one recombination rate $\rho$, and are used to generate SNP matrices with msprime. Two types of summary statistics are computed from these simulations (SFS and LD). The predictions (outputs) made by different kind of ANNs (MLP, custom CNN and SPIDNA architecture) are compared to an MLP using the summary statistics and to ABC using either the summary statistics, SPIDNA outputs or both. [1] ANN outputs used are the predictions made by the version of SPIDNA with the lowest prediction error. [2] ABC without correction, with linear regression, ridge regression or a single layer neural network are compared.

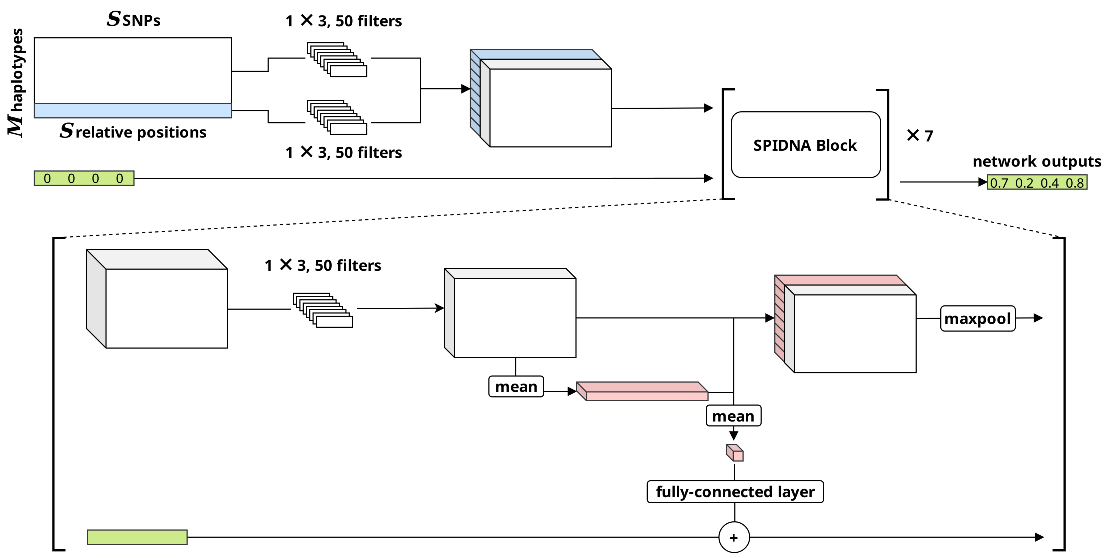

Figure 2: Schematic of SPIDNA architecture.

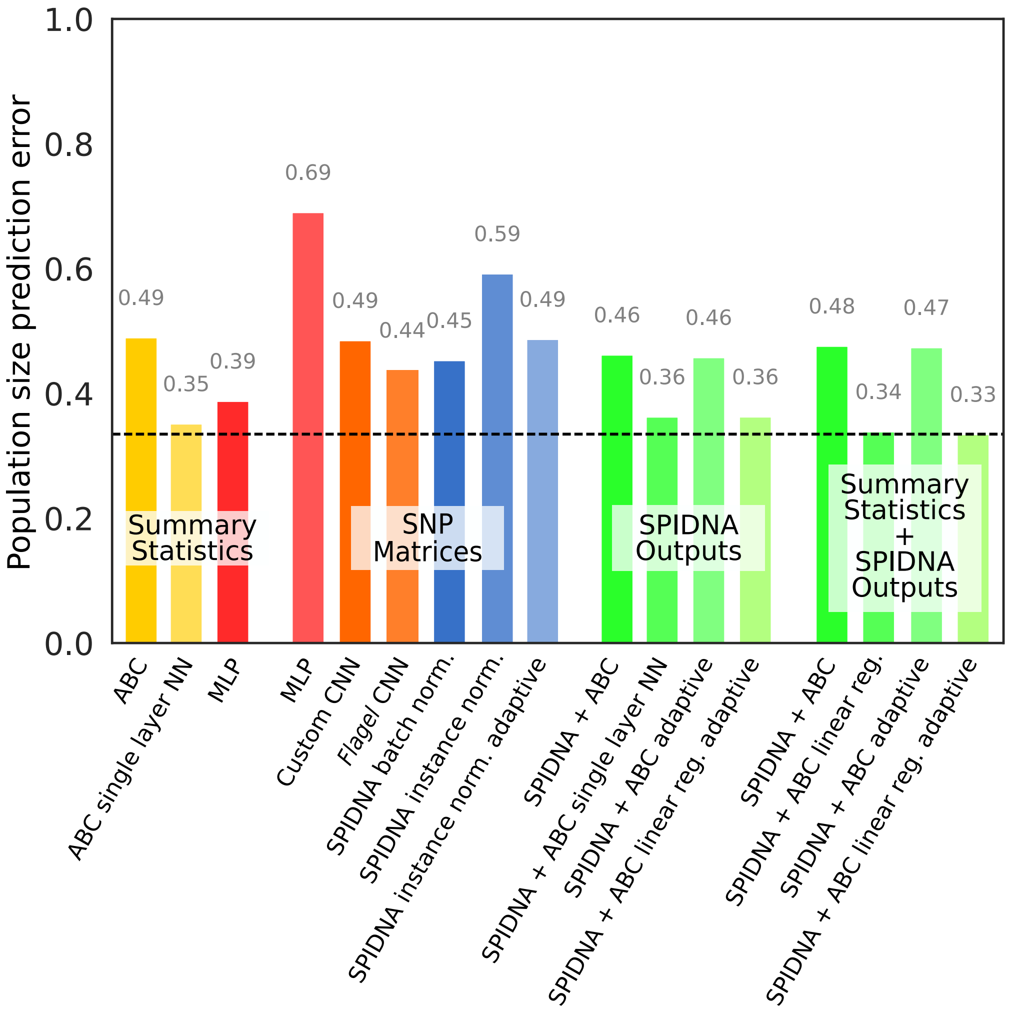

Figure 3: Prediction errors of the best run of each method after the hyperparameter optimization. The best configurations of each ANN (MLP, custom CNN and SPIDNA) have been retrained for 10 epochs. Traditional ABC methods are depicted in yellow, deep MLPs and CNNs in red and orange, SPIDNA ANNs in blue, combinations of ANNs and ABC in green. Methods are grouped into 4 families: "Summary statistics" (processed by ABC or ANN), "SNP matrices" (processed by ANN), "SPIDNA outputs" (processed by ABC, no summary statistic used), "Summary statistics and SPIDNA outputs" (processed by ABC).

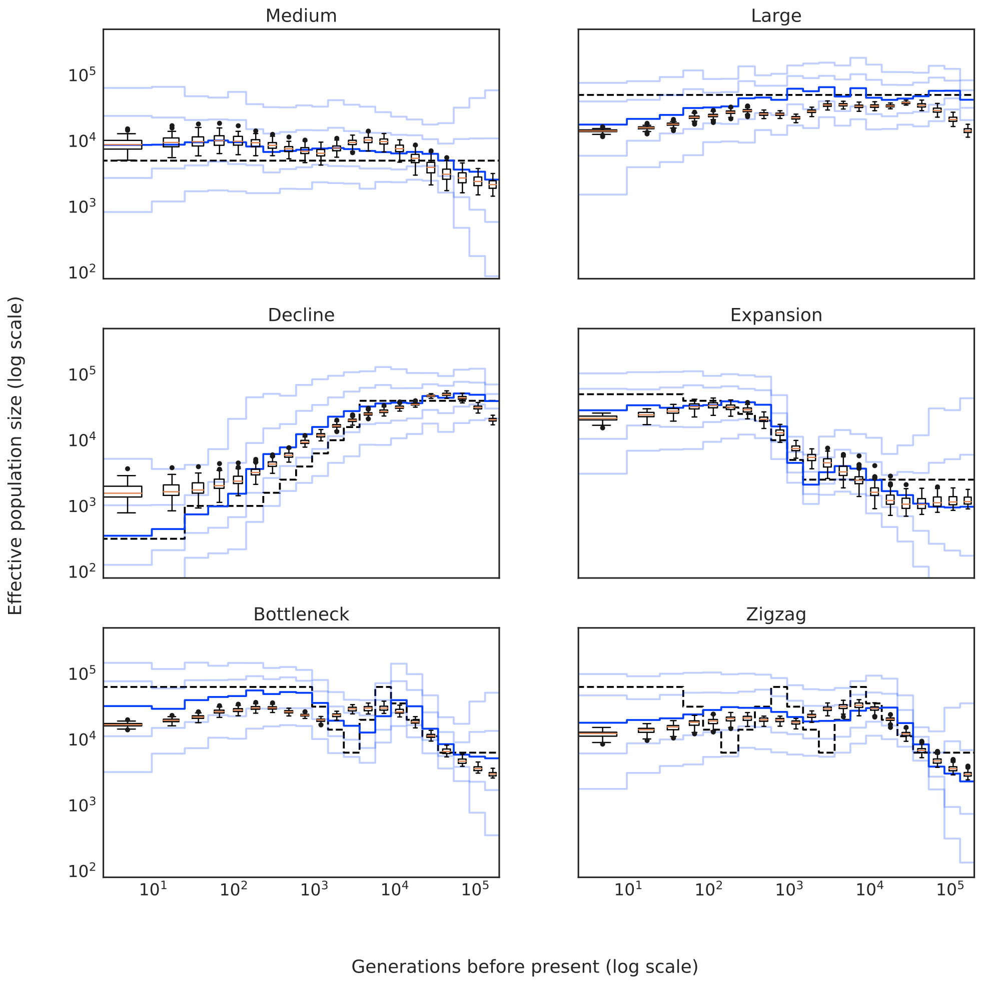

Figure 4: Predictions of SPIDNA and ABC using SPIDNA outputs, for six predefined scenarios (dashed black lines). 100 replicates were simulated for each scenario. Boxplots show the dispersion of SPIDNA predictions (over replicates). For each history inferred by SPIDNA combined with ABC, we display the posterior median (plain blue line), the 50% credible interval (dark blue) and the 90% credible interval (light blue).

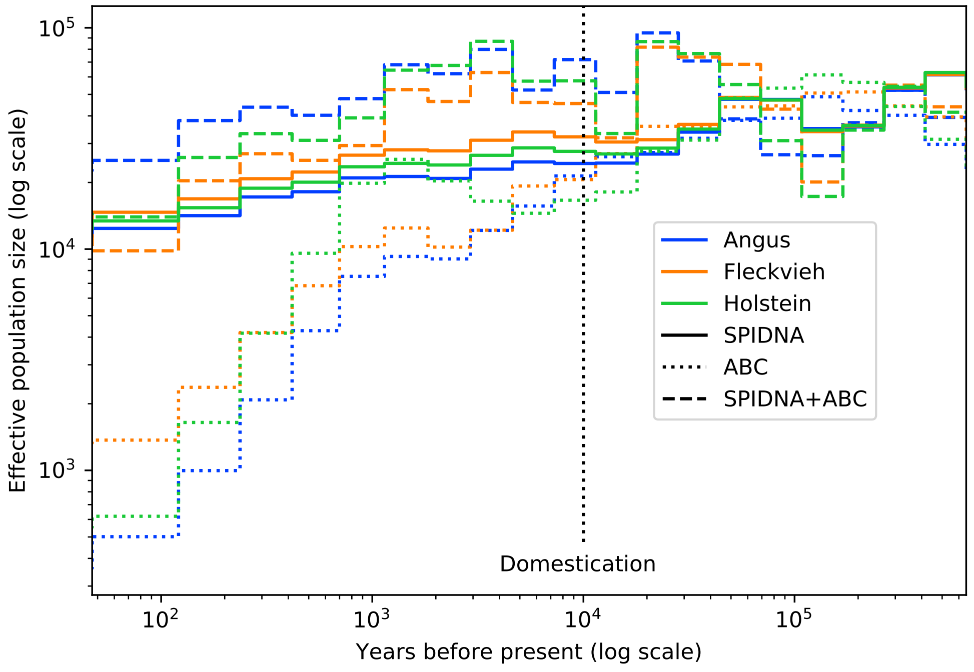

Figure 5: Effective population size of three cattle breeds inferred by ABC (dotted lines), by the best SPIDNA architecture, SPIDNA batch normalization (dashed lines), and by ABC based on SPIDNA outputs (dashed lines). Domestication is estimated to have occurred 10 000 years ago (vertical dotted line).

688 ## Supplementary materials

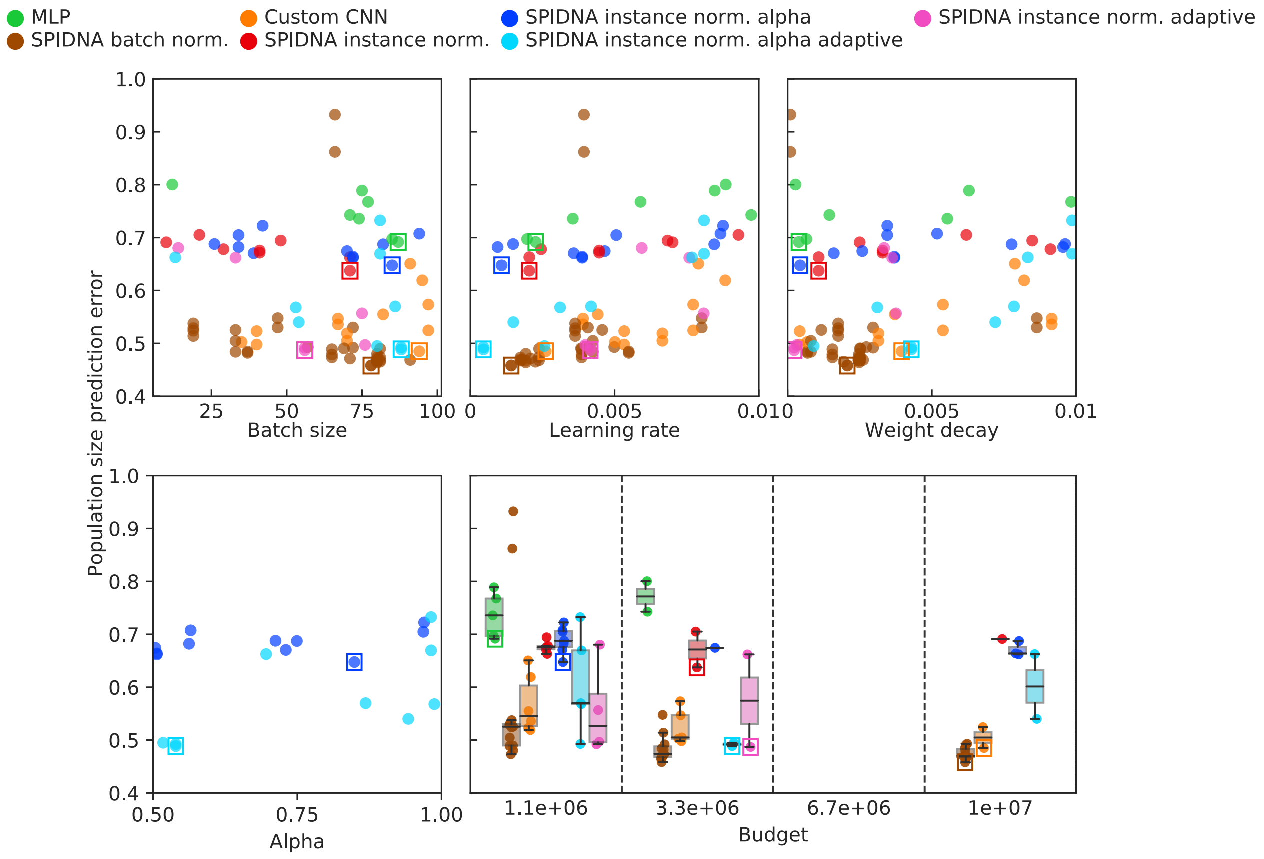

Figure S1: Population size prediction error for each run of the hyperparameter optimization procedure. X-axes indicate the hyperparameter (batch size, learning rate, weight decay and alpha) or budget values, and colors indicate the type of network used for the run (MLP, custom CNN and multiple SPIDNA architectures). For each network the best run is surrounded by a square.

| input dimension | SNP encoding | Convolution type | Kernel size | Pooling size | Log-scaled output? | Sort chromosomes? | Use dropout? |
|---|---|---|---|---|---|---|---|
| 50 × 400 | 0/-1 | 1D | 2 | 2 | Yes | Yes | Yes |
| 50 × 1784 | 0/-1 | 1D | 2 | 2 | Yes | Yes | Yes |
| 50 × 400 | -1/1 | 1D | 2 | 2 | Yes | Yes | No |
| 50 × 1784 | -1/1 | 1D | 2 | 2 | Yes | Yes | No |

Table S1: Parameters used for the *Flagel* CNN

| | Method | Adaptive | Summary statistics | ABC correction | Alpha | Prediction error |
|---|---|---|---|---|---|---|
| 0 | ABC | No | No | No | No | 0.490 |
| 1 | ABC | No | No | Linear reg. | No | 0.357 |
| 2 | ABC | No | No | Ridge reg. | No | 0.363 |
| 3 | ABC | No | No | Single layer NN | No | 0.352 |
| 4 | MLP | No | No | No | No | 0.690 |
| 5 | MLP | No | Yes | No | No | 0.388 |
| 6 | Custom CNN | No | No | No | No | 0.485 |
| 7 | *Flagel* CNN 0/1 encoding | No | No | No | No | 0.447 |
| 8 | *Flagel* CNN 0/1 encoding | Downsampling | No | No | No | 0.437 |
| 9 | *Flagel* CNN -1/1 encoding | No | No | No | No | 0.719 |
| 10 | *Flagel* CNN -1/1 encoding | Downsampling | No | No | No | 0.984 |
| 11 | SPIDNA | No | No | No | No | 0.453 |
| 12 | SPIDNA | No | No | No | No | 0.637 |
| 13 | SPIDNA | Yes | No | No | No | 0.487 |
| 14 | SPIDNA | No | No | No | 0.849 | 0.592 |
| 15 | SPIDNA | Yes | No | No | 0.539 | 0.489 |
| 16 | ABC + SPIDNA | No | No | No | No | 0.462 |
| 17 | ABC + SPIDNA | No | No | Linear reg. | No | 0.364 |
| 18 | ABC + SPIDNA | No | No | Ridge reg. | No | 0.371 |
| 19 | ABC + SPIDNA | No | No | Single layer NN | No | 0.363 |
| 20 | ABC + SPIDNA | Yes | No | No | No | 0.458 |
| 21 | ABC + SPIDNA | Yes | No | Linear reg. | No | 0.363 |
| 22 | ABC + SPIDNA | Yes | No | Ridge reg. | No | 0.382 |
| 23 | ABC + SPIDNA | Yes | No | Single layer NN | No | 0.374 |
| 24 | ABC + SPIDNA | No | Yes | No | No | 0.476 |
| 25 | ABC + SPIDNA | No | Yes | Linear reg. | No | 0.339 |
| 26 | ABC + SPIDNA | No | Yes | Ridge reg. | No | 0.341 |
| 27 | ABC + SPIDNA | No | Yes | Single layer NN | No | 0.345 |
| 28 | ABC + SPIDNA | Yes | Yes | No | No | 0.474 |
| **29** | **ABC + SPIDNA** | **Yes** | **Yes** | **Linear reg.** | **No** | **0.335** |
| 30 | ABC + SPIDNA | Yes | Yes | Ridge reg. | No | 0.339 |
| 31 | ABC + SPIDNA | Yes | Yes | Single layer NN | No | 0.347 |

Table S2: Prediction errors of the best configuration of each method after hyperparameter optimization