Simulation Based Inference of the Evolutionary History of Wildcats (Felis silvestris): Machine Learning for Population Genomics

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**Abstract**

Software for simulating the evolution of genomes has become increasingly widespread in the field of population genomics due to its numerous applications. One such application is for simulation-based inference, where simulated data are compared with observed data to draw conclusions about a system. A popular implementation of this is Approximate Bayesian Computation (ABC), but recently machine learning approaches to this inference have been developed and offer a more flexible and efficient option. The Scottish wildcat is a sub-population of the European wildcat (*Felis silvestris*) under threat of eradication by genetic swamping due to hybridisation with wildcat Cats (*F. catus*). Previous studies have used ABC with population genomics simulators to explore the extent of this hybridisation for a three-population model of wildcats, Scottish *F. silvestris*, and a captive population of *F. silvestris*. This study expands the previously studied model to include European *F. silvestris* and African wildcats (*F. lybica*), and to use Sequential Neural Posterior Estimation to infer parameter distributions based on whole-genome data. Initial rounds of inference indicated some model misspecification, so we implemented a number of techniques for pruning summary statistics to improve model fit. This improved our posterior estimates of wildcat demography, however, estimation of some parameters, particularly those describing ancient demography, remained intractable. Despite this, our approach provides a valuable and flexible template for inferring models of evolution and demography based on whole genome sequence data, and we describe novel tools for tackling model misspecification.

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**Keywords**

Population Genomics, Machine Learning, Simulation, wildcats, Bayesian Inference.

**Author’s declaration**

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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**Contents**

1. Introduction
2. Methods
   1. Model of wildcat demography
   2. Prior distributions
   3. Genomic data
   4. Coupling forward-time and coalescent simulators
   5. Summary statistics
   6. SNPE procedure
   7. Addressing model misspecification
3. Results
   1. Posterior distributions
   2. *Maximum a posteriori* model
4. Discussion
   1. Conclusions for demography
   2. Choice of summary statistics
   3. Possible model improvements
   4. Genomic data
   5. Simulation approach limitations
   6. Final conclusions

**1. Introduction**

In genetic data, patterns of mutation and inheritance give us clues as to the demographic history of the species. However, in isolation, it is hard to unpiece exactly what these patterns indicate, so if one wants to infer a detailed account of the species’ demographic history, a more comprehensive approach is often needed. A common method of inference in population genomics is Bayesian Inference, for which the main aim is to find the posterior *P(θ|D)* - the probability distribution of model parameter values given some observed data. According to Bayes’ theorem (below), this distribution can be obtained by evaluating the joint distribution between the prior probability distribution (the prior belief of the probability distribution of *θ*) and the likelihood, which describes how likely each particular set of parameters is to produce the observed sample. In this way, previous estimates for parameters can be incorporated into the analysis and ‘updated’ with observed empirical data (M. A. Beaumont et al., 2002).

However, models in population genomics often possess a complexity that renders the likelihood intractable, meaning the explicit evaluation of the likelihood function is impossible. Approximate Bayesian Computation, or ABC, presents an elegant solution to this problem by simulating, according to a mathematical model which implicitly defines the likelihood, an approximation of this likelihood using model parameters sampled from the prior, thereby generating the joint distribution between the likelihood and the prior and side-stepping the mathematically intensive step of explicit likelihood evaluation (M. A. Beaumont & Rannala, 2004). As highly dimensional data are hard to handle computationally, summary statistics describing the simulated data are calculated and compared with that of observed data, and an algorithm that accepts models that are consistent with the observed data is implemented to obtain the posterior distribution.

For models of population genomics, simulation tools that can generate this likelihood have been in constant development for many years and are becoming widespread within the field. The ‘Wright-Fisher model’ and ‘Coalescent theory’ are mechanistic models describing the genealogy of a population of individuals, and underpin all simulators of this nature (Barroso et al., 2020; Hudson, 2002; Kingman, 1982). The main applications of these simulations are in evaluating population genomics methods, investigating scenarios of evolution, and simulation-based inference (Hoban, 2014). Since their arrival, these simulators have improved massively in their efficiency and scope of possible models, which has allowed for increasingly complex analyses (Peng et al., 2015).

In ABC, the posterior is traditionally estimated by use of a rejection algorithm, which involves rejecting data that is not within a tolerance of the observed data and then weighting or adjusting this approximate posterior towards the observed data (M. A. Beaumont & Rannala, 2004). Sequential Neural Posterior Estimation (SNPE) harnesses the flexibility of neural networks to carry out this step in the analysis and makes inferences based on all the simulated data without the need for rejection (Ward, 2024). In this study we use normalising flows, one of the multiple variants of SNPE, to handle density estimation and sampling. Normalising flows learn a bijective transformation between our target distribution and a simple, known distribution such as a multivariate normal distribution. This way they can sample from the complex target distribution by sampling from a normal distribution and then applying the transformation to those samples (Papamakarios et al., 2021). These learned transformations can be conditioned using observed data to obtain samples from the posterior distribution that are consistent with our observed data. If carried out sequentially, SNPE can make robust inferences using relatively little simulated data when compared to ABC, as sequential simulations are sampled from the previous rounds posterior, providing a narrower posterior distribution with each round. For studies of large populations over a long time, which often have very long simulation runtimes, this is extremely important. The principal aim of this project was to develop a versatile and flexible inference framework using SNPE with simulated data, that can be applied to a range of population genetics scenarios.

*Felis silvestris*, the European wildcat, is a species of wildcat native to many parts of continental Europe and Scotland. Due to decreased habitat range and population size, these wildcats can hybridize with feral domestic cats (*F. catus*) which has resulted in high levels of domestic cat genetic material in some populations (Yamaguchi et al., 2015). Hybridisation can be beneficial, as in the case of genetic rescue in small populations of highly inbred individuals. However, it is often a driver of species extinction due to genetic swamping, where rare genetic material is replaced by hybrid material, which is especially severe if the population size of the species at risk is far smaller than the other . One population which suffers from extensive hybridization with domestic cats is the Scottish wildcat, which some have described as unviable and on the verge of eradication (Breitenmoser et al., 2019). This hybridisation has been driven by years of anthropogenic persecution and habitat destruction, and forces of selection such as disease have increased the rate of introgression (M. Beaumont et al., 2001; Howard-McCombe et al., 2023). To conserve the species and protect genetically pure individuals, a captive population of *F. silvestris* was founded with the aim of breeding and releasing pure individuals into the wild. However, even individuals in captivity have high levels of hybridisation and the rescue of this species remains a challenge. The second aim of this project is to use SNPE to infer a demographic model describing the flow of genetic material from *F. catus* to *F. silvestris* and wildcat evolution more broadly. Successfully inferring the extent of this hybridisation would provide useful information to assist in conservation efforts and the model would support our wider understanding of wildcats.

Previous studies similar to ours have used an ABC framework with a three-population model and reduced-representation sequencing data to investigate Scottish wildcat hybridisation, using the forward-time simulator SLiM to simulate 500 generations of recent demography for wildcat cats, Scottish wildcats and a captive population (Haller & Messer, 2019; Howard-McCombe et al., 2021). A subsequent study optimized this ABC framework for a more detailed form of the same three-population model, this time using a combination of SLiM and a coalescent simulator, msprime (Baumdicker et al., 2022), to model the demographic history of the three populations from the divergence of wildcats and European wildcats to the present (Ward, 2021). This coupled simulation approach was used in our study and will be covered in more detail in the methods section. SNPE is a relatively recently developed tool in the field of statistics and is not yet widely used in scientific disciplines such as population genomics. Most studies that have used this method so far have investigated topics within subjects such as neuroscience (Gonçalves et al., 2020; Groschner et al., 2022) and physics (Akhmetzhanova et al., 2023; Furia & Churchill, 2022). However, very few studies, if any, have tried to use this approach sequentially to infer a model of evolution in population genomics.

**2. Methods**

*2.1. Model of wildcat demography*

The model outline was derived from a previous study on Scottish wildcat introgression by Howard-McCombe *et al.* in 2021 which defined a three-population model including domestic cats, Scottish *F. silvestris*, and a captive population of Scottish *F. silvestris*. Our model (*Fig. 1*) is an expansion of this and features two more populations: A European population of *F. silvestris* and African wildcats (*F. lybica*) which are ancestral to domestic cats. For purposes of simulation, there are parameters for:

* 5 modern population sizes: *F. lybica* (N5), Scottish *F. catus* (N4), and European (N3), Scottish (N2), and captive Scottish (N1) populations of *F. silvestris*.
* 2 ancestral populations: *F. lybica* (N7) and *F. silvestris* (N6).
* 4 population divergence times representing the divergence of: *F. lybica* (T1), *F. catus* (T2), Scottish *F. silvestris* (T3), and captive Scottish *F. silvestris* (T4) populations.
* Migration between Scottish wildcats and wildcat Scottish cats. Including the migration rate (M1) and duration (t) from wildcats to wild-living *F. silvestris* and the rate from wild-living *F. silvestris* to the captive population (M2) to model the introduction of progressively more hybridized individuals to the captive population.
* Mutation rate (m) and recombination rate (r) for all individuals.

All population sizes, divergence times, and rates should be thought of as effective sizes, effective times, and effective rates as our model is a simplified version of wildcat demography and does not exhaustively parametrize all the forces acting on the wildcat genome.

*2.2. Prior distributions*

To generate the genomic data to be used in training the neural network, we simulated genomes according to parameters sampled from prior probability distributions, i.e. a previous belief of the parameter values. Sampling from these distributions generates a range of genomic data that describes all the possible demographic models supported by our prior beliefs. Table 1 specifies the prior probability distributions for each parameter and the source or justification for each prior. Many of the priors are based upon the posterior distributions obtained from a previous study of simulation based inference using ABC on RADSeq wildcat data (Howard-McCombe et al., 2021). In general, priors were chosen to be reasonably wide, i.e. conservative estimates of current belief, causing some initial simulations, modelling a combination of large parameters, to take a long time to compute. Regression of runtimes was conducted on a sample set of 5000 simulations to determine the causes of simulation time, and it was found that most population sizes and the divergence time of *F. lybica* significantly affected simulation time; In general terms, simulations took longer to compute the more individuals are modelled and the further back in time modelled. After simulating the first round of data points (~10,000) the narrower posterior from this round will be used as the prior for the next, meaning fewer models with large populations and early divergences would be simulated. Thus, long simulation times caused by wide priors may only be present for the first round.

*2.3. Genomic data*

We used the whole genome SNP data for the E3 wildcat chromosome of 112 individuals from 5 different populations. These individuals included: 65 captive Scottish *F. silvestris*, 22 Scottish *F. silvestris*, 15 European *F. Silvestris*, 6 Scottish wildcats, and 4 *F. lybica*. The E3 chromosome was used as it is the smallest of the cat chromosomes (~45Mb) and chromosomes larger than this would drastically increase simulation times and therefore reduce the efficiency of our inference framework. Using VCFtools (v0.1.16), the genomic data was filtered to remove sites with missing data and sites with a minor allele count (MAC) of two or less (removing singletons and doubletons) to remove potential sequencing errors or sites with low statistical power (Danecek et al., 2011). As our simulation software only simulates mutations with one alternate allele (variants 0 and 1), we also removed sites in the genomic data with more than one alternate allele. This left approximately 370k SNPs. The WGS data was generously provided by authors of recent studies on wildcats who used BGISEQ and Illumina methods to sequence samples from a variety of sources (Howard-McCombe et al., 2023; Jamieson et al., 2023).

*2.4. Coupling forward-time and coalescent simulators*

Simulations were carried out using a coupled framework of SLiM (v4.0.1) (Haller & Messer, 2023), in forward-time and msprime (v1.2.0) (Baumdicker et al., 2022) in the coalescent. An issue that arises with coalescent simulators is that, although more computationally efficient, these simulators can create unrealistic pedigree structures that are different at each locus, rather than treating the pedigree structure of a population as fixed (Wakeley et al., 2012). Therefore, similarly to a recent study using this coupling (Ward, 2021), our approach simulates the complex recent history of wildcat hybridisation in forward-time, and the simpler (under our model) ancient demography of wildcats in the coalescent.

Four starting populations were established and modelled by SLiM forwards in time from 100 generations in the past, with the captive population diverging after this. SLiM simulated a 45 Mb genome (length of the E3 wildcat genome) under our demographic model to the present-day generation. This ‘decapitated’ tree was then passed to msprime, which started at 100 generations in the past and simulated the genome in the coalescent according to our model backwards in time to the *F. lybica* divergence time, ‘recapitating’ the tree. Mutations were then generated and ‘overlaid’ onto the tree by msprime. The simulations were carried out in terms of generations, which are approximately 3 years for wildcats (M. Beaumont et al., 2001). During simulations, SLiM and msprime recorded ancestry using ‘succinct tree sequences’. This is a data model created by the authors of msprime which records local ancestry at SNPs along the genome, which reduces the memory requirement to handle and store data, and provides efficient calculation of descriptive statistics (Kelleher et al., 2018). After simulation, the tree sequence was simplified to include only the ancestry of a sample set matching our observed dataset and a MAC filter was applied to remove singletons and doubletons to match our observed data. To obtain simulated data and observed data in the same format for inference, tsinfer (v0.3.1) was used to infer the succinct tree sequence for the observed genomic data (Kelleher et al., 2019).

The simulations were carried out using the University of Bristol’s High-Performance Computing cluster, which allowed as many as ~400 simulations to run in parallel. (For the first round) 54Gb of memory was allocated for each simulation and a single processor was used. Simulations taking longer than 8 hours were aborted, as simulations exceeding this had combinations of very large populations and very early divergence times which were unlikely to be consistent with our observed data. Approximately 1% of simulations in the first round were discarded due to the time limit.

*2.5. Summary statistics*

To reduce the dimensionality of the data so it can be used by the neural network, descriptive summary stats were calculated for the tree sequences obtained from simulations and observed data. Overall, 135 summary statistics were calculated. These included:

* Diversity (Nei & Li, 1979), number of segregating sites, Tajima’s D (Tajima, 1989), divergence (Nei & Li, 1979), genetic relatedness (Speed & Balding, 2015), Patterson’s f statistics (Reich et al., 2009), Y statistics (Jaime et al., 2018), and Fst (Holsinger & Weir, 2009), all efficiently computed directly from the tree sequence by tskit (v0.5.5) (Kelleher et al., 2018).
* PCA median, inter-quartile range, and pairwise distance summary stats using scikit-learn (v1.2.2) (Pedregosa et al., 2011). For the calculation of PCA statistics, the 012 genotype matrix was generated from the tree sequence, which required a large amount of memory. Inference procedures like this, which are affected by simulation times, would be greatly benefitted if tskit possessed built-in features for calculating PCA statistics directly and efficiently from the tree sequence.

For each simulation, summary stats were calculated for all populations and collated along with the corresponding parameters into a reference table and used as input for SNPE.

*2.6. SNPE procedure*

For inferring the posterior distribution, the Flowjax package (v12.0.1) was used to carry out SNPE (Ward, 2024). For stability during training, parameters were first log transformed and then normalised using affine transformations as outlined in the Flowjax documentation. Summary stats were also normalised using the same affine transformation method as carrying out inference without normalisation of the simulated data caused the neural network to fail to converge. The same affine transformation was used in subsequent rounds. The prior distribution provided to SNPE was a multivariate normal PyTorch (v2.0.1) distribution with mean 0 and standard deviation 1 (Paszke et al., 2019). The neural network was then trained with the first dataset of simulated data (10,000 simulations) to learn relationships between summary stats and parameters. The validation proportion was 0.1 (1000 out of 10,000 each round), the batch size was 100 and a learning rate of 1e-4 was used. After training, the estimated distribution of parameters was conditioned using the observed data, and then sampled from to obtain parameters consistent with our observed data. 10,000 sets of model parameters were sampled from this posterior, and inversely transformed and exponentiated to obtain the parameters for the next round of simulation. This simulation and inference procedure was repeated once more, serialising the previous round’s normalising flow and carrying this forward to be used in following rounds (Kidger & Garcia, 2021), which prevented SNPE from overconfidently estimating a new posterior based on resampled data. The basic outline of this approach is illustrated in Figure 2.

*2.7. Addressing model misspecification*

Initial rounds of inference using the full set of summary statistics yielded posteriors that had strong indications of model misspecification. These were characterized by overconfident first round posteriors followed by ‘exploded’ posteriors in subsequent rounds that were far wider than the prior. Prior and posterior predictive checks revealed that the observed data was far outside of the prior and posterior support for many summary statistics. For example, the observed Tajima’s D statistic for the European population of *F. silvestris* was negative (~-0.3), and well outside of the support of the simulated data, which ranged from 0.5 to 2.0. The negative value of Tajima’s D indicates a disproportionate level of rare alleles which can be a sign of population growth (Tajima, 1989), admixture (Stajich & Hahn, 2005), or a structured population (Wakeley, 1999). However, this demography is not consistent with current understanding (Langley & Yalden, 1977; Pierpaoli et al., 2003) and it would be difficult to replicate this statistic in the simulated data. To provide flexibility in the model, mutation and recombination rates, which were originally point values, were given prior distributions and included in the parameters to be inferred. This also has the added benefit of potentially providing a posterior estimate for these values, which do not currently have good estimates in the literature.

(should this bit be in Discussion?)

To address the clear misspecification in the initial set of 134 summary statistics, we implemented three methods to remove the statistics for which there was the largest discrepancy between the simulated and observed data.

1. **Removal of summary statistics with >0.99 correlation.** Pairwise correlations were calculated and one of the correlated stats were removed to limit the maximum correlation in the set of summary statistics to 0.99. 24 summary statistics were removed using this method
2. **Noise detection using normalising flows.** If we assume, in the misspecified case, that the observed data we are using has been generated according to our model plus some noise in the sample i.e. p(xobs) = p(x) + noise, we can attempt to infer a posterior over the noise to identify misspecified summary statistics. 10 summary statistics were removed using this method, with an absolute noise threshold of 0.8. (how to explain this/how much detail needed)
3. **Iterative improvement of percentile of observed data.** Previous studies have iteratively dropped summary statistics based on nearest neighbour distances, however, this method yielded inconsistent results with our data. Instead, we trained normalising flows on 10,000 simulations to approximate the joint distribution between all the summary statistics, and then evaluated the log probabilities of 5000 held-out simulations and the observed data. Thus, taking the rank of the observed data within these held-out simulations yielded the percentile of the observed data. To achieve consistent results in training the flows, we used a batch size of 25 and a learning rate of 5e-5. Using this method, we estimated observed percentiles for 100 sets of summary statistics (each with one stat dropped) and accepted the set with the lowest percentile i.e. the most specified set. This was repeated 7 times until an observed percentile of 0.78 was achieved (the best percentile achieved using this method). 7 summary statistics were removed in total.
4. **Posterior predictive checks.**  After the first round of inference, posterior predictive checks of the marginal distributions of summary statistics were carried out and statistics were removed if the observed data fell outside of the 0.99 percentile of the simulated data. 12 more summary statistics were removed this way.

This multi-faceted approach reduced our initial set of 134 summary statistics down to 81 of the most well-specified statistics. The statistics removed can be found in the supplementary materials (Table S1) – to be added.

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