# Demographic inference using the SFS with `moments` and `demes`

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**Abstract**

Placeholder

## Introduction

The genetic composition of a sample of individuals is shaped by their genome biology and evolutionary history. Variation resulting from this history can be fully represented by the ancestral relationships among samples at each locus in the genome and how those gene-genealogical relationships change along a chromosome due to recombination (that is, information stored in the Ancestral Recombination Graph (Nielsen et al., 2025)). However, the ARG can be large and unwieldy, and methods for reconstructing history directly from the ARG, while showing promise (e.g., YC Brandt et al., 2022; Fan et al., 2023; Brandt et al., 2024), are in their infancy and so far limited in application and scalability. Instead, evolutionary inference using informative summaries of genetic variation remains a tractable and powerful alternative for learning parameters of population history, natural selection and genome biology.

One such summary that has seen wide use is the site frequency spectrum (SFS), which stores the counts (observed or expected) of alleles carried by a given number of genomes in a set of samples. Like any summary of the data, the SFS discards some information stored in the ARG – in this case, loci are treated independently so that haplotypic information is lost. Even so, the relative densities of allele frequencies and the overall scale of the SFS are both sensitive to demographic and non-demographic processes.

This chapter focuses on multi-population demographic inference from the SFS using `moments` (Jouganous et al., 2017). Past population processes, including changes in population size, splits, gene flow and population structure, impact the SFS in predictable ways. A population size expansion (or contraction) leads to a relative excess (or deficit) of low-frequency variants, for example, and commonly used statistics measuring population divergence, such as $F_{ST}$, are themselves summaries of the SFS. Thus, the development of methods to learn demographic history from the SFS came soon after the publication of whole-genome sequencing from multiple individuals (Marth et al., 2004; Williamson et al., 2005). More recent methodological advances allow for increased sample sizes and numbers of populations, providing a rich ecosystem of software for SFS-based demographic inference (Gutenkunst et al., 2009; Excoffier and Foll, 2011; Gravel et al., 2011; Jouganous et al., 2017; Ragsdale et al., 2018; Kamm et al., 2020; Dilber and Terhorst, 2024). We return to this in the final section: Considerations and Caveats.

Other evolutionary mechanisms are known to affect allele frequency dynamics and the SFS. This presents a challenge for demographic inference, as the observed SFS may be distorted by non-demographic processes. However, this also presents an opportunity to learn about different evolutionary processes, if demographic history can be controlled for. The SFS has been used to infer the distribution of fitness effects of new mutations, primarily for nonsynonymous variation in coding regions (e.g., Eyre-Walker et al., 2006; Boyko et al., 2008; Kim et al., 2017); to scan for historical selective sweeps (e.g., Kim and Stephan, 2002; Nielsen et al.,

2005); and to understand how selection on quantitative traits impacts the genetic architecture underlying those traits (eg., Patel et al., 2024; Ragsdale, 2024). The SFS has also been used to infer relative mutation rates and how they have changed over time (DeWitt et al., 2021). Each of these analyses typically requires partitioning the data in some way – by functional annotation, mutation context, local recombination rate, etc – so that comparisons can be made across SFS from different classes of mutations.

## Interfacing `moments` with `demes`

Specifying demographic models requires defining populations (or "demes") and their relationships via splits and gene flow. `demes` provides a standardized and accessible format for defining demographic models (Gower et al., 2022), and has been adopted by widely used software for population genetics simulation and inference (including `msprime` (Baumdicker et al., 2022), `momi` (Dilber and Terhorst, 2024), `fwdpy11` (Thornton, 2019), `GADMA` (Noskova et al., 2023)). `demes` encourages interoperability and reuse of code across software, and ease of model implementation and reduction of errors.

Demographic models are specified in YAML format (see Gower et al. (2022) and the associated documentation). The two-population split-with-migration model depicted in Figure 1A is specified as below:

```yaml
description: split-with-migration model, loosely based on example 2
generation_time: 29
time_units: years
demes:
- name: ancestral
  epochs:
  - {start_size: 15000, end_time: 300000}
  - {start_size: 25000, end_time: 75000}
- name: popA
  ancestors: [ancestral]
  epochs:
  - {start_size: 30000}
- name: popB
  ancestors: [ancestral]
  epochs:
  - {start_size: 1200, end_size: 14000}
migrations:
- demes: [popA, popB]
  rate: 5e-5
```

In `moments`, a `demes`-specified demographic model can be directly used to compute either the SFS or multi-population LD statistics (Ragsdale and Gravel, 2019, 2020). For the SFS, we simply need to load the demographic model using `demes` and specify the number of haploid samples to draw and from which populations.

```python
import demes, moments
g = demes.load('model.yaml')
samples = {'popA': 60, 'popB': 60}
fs = moments.Demes.SFS(g, samples=samples)
```

Here, we have not specified a mutation rate. The default behavior sets $u = 1$, so that $\theta = 4N_e u = 4N_e$, where $N_e$ is the ancestral population's initial size. With a known mutation rate, the SFS will be properly scaled by passing the mutation rate as a keyword argument: `moments.Demes.SFS(g, samples=samples, u=u)`. This is equivalent to scaling the output SFS above by multiplying by `u`, as `u*fs`.

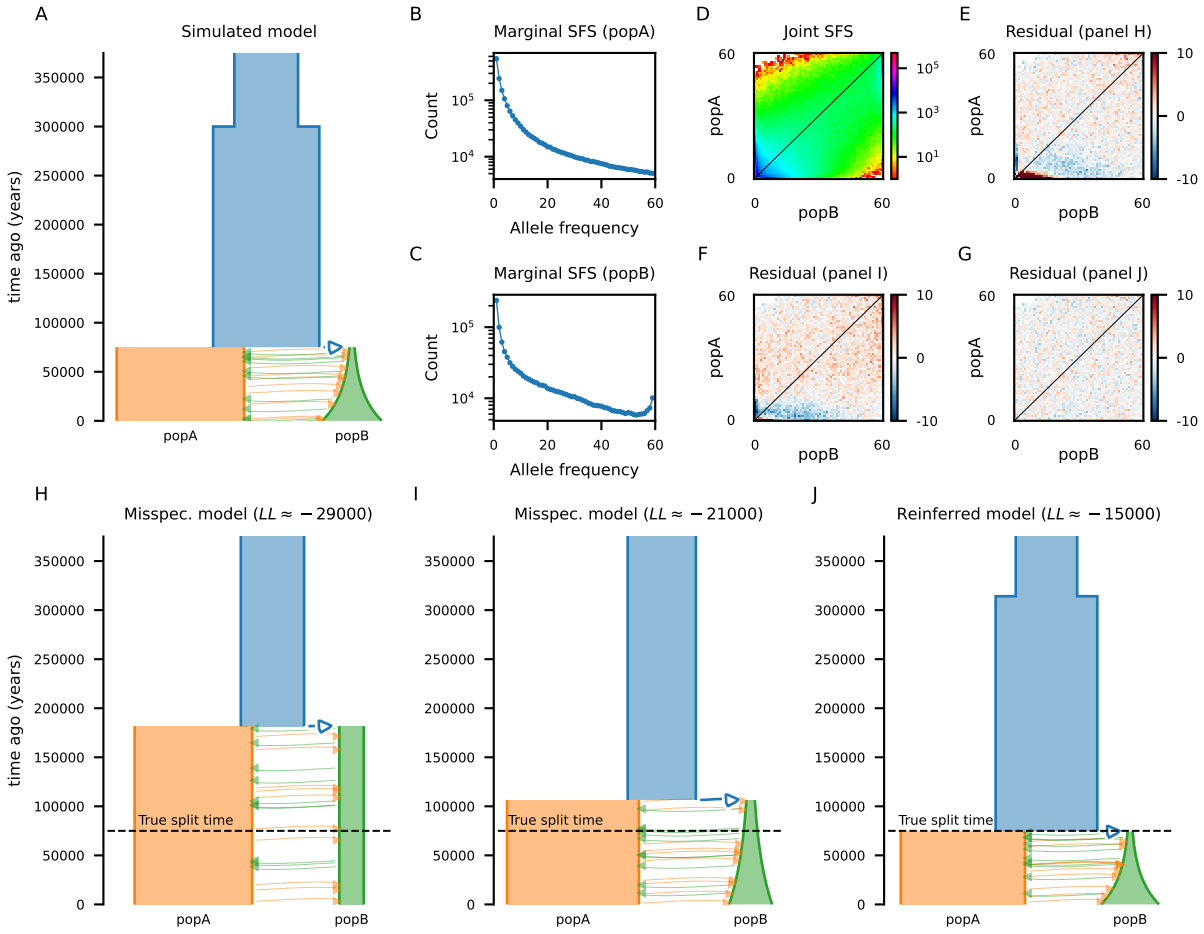


Figure 1: Caption placeholder

## Examples: inference in `moments` using `demes`

Below, we show two examples of multi-population demographic inference using the joint SFS. The first example simulates data with known demographic parameters, which we try to reinfer using the both the original and misspecified simpler models. In the second example, we infer a relatively simple human-Neanderthal history using data from two human populations and a high-coverage ancient sample from the Neanderthal lineage. For both of these examples, we briefly describe data processing and inference setup, highlighting the high-level components of the analyses. For detailed information for each example, including managing data, specifying models, performing inference, computing confidence intervals and visualizing fits, we refer readers to the accompanying GitHub repository (`https://github.com/StatisticalPopulationGenomics-2ndEd/moments`), which is maintained with up-to-date versioning.

In order to optimize parameters in a `demes` model, we need a way to specify which parameters should be fit. For this, we use a separate YAML-formatted file to define `parameters`, each of which points to the value(s) in the demographic model and sets lower and upper bounds. This file also specifies any relative `constraints` between pairs of parameters, to ensure the optimization routine only explores valid model space. Below, we have included a truncated parameters file – the full example is available on GitHub.

```
parameters:
```

```yaml
- name: T0
  values:
  - demes:
      ancestral:
        epochs:
          0: end_time
  lower_bound: 0
  upper_bound: 2e5
- name: T1
  values:
  - demes:
      ancestral:
        epochs:
          1: end_time
  lower_bound: 0
  upper_bound: 1e6
- name: Ne
  values:
  - demes:
      ancestral:
        epochs:
          0: start_size
  lower_bound: 1e2
  upper_bound: 1e6
...
constraints:
- params: [T0, T1]
  constraint: greater_than
```

Taking the demographic model, parameters file, and observed SFS together, we can perform inference using the `moments.Demes.Inference.optimize(...)` function. The initial parameter guesses are given by the input demographic model, which may be perturbed using a keyword argument. Any value in the demographic model that is not specified in the parameters file will remain unchanged, and is therefore treated as a fixed parameter. Here, we also assume we have an estimate for the total mutation rate, $U$.

```python
import moments

data = moments.Spectrum.from_file('data.fs')
U = 1e-8 * 5e8  # per-base mutation rate times the total length

model_file = 'model.yaml'
params_file = 'params.yaml'
output = 'model.fit.yaml'

ret = moments.Demes.Inference.optimize(
    model_file, params_file, data,
    perturb=1, uL=U, output=output
)
```

Confidence intervals may also be computed, once a (locally) optimal model has been found.

## Inferring parameters in a simulated split-with-migration model

Using the split-with-migration model defined above (illustrated in Figure 1A), we simulated data for 30 diploid individuals from both populations using `msprime` (Baumdicker et al., 2022). These simulations consided of 500 regions, each of length 1 Mb, with per-base recombination and mutation rates of $10^{-8}$. The joint SFS was computed using `tskit`'s `ts.allele_frequency_spectrum()` function separately on each replicate region and summing across regions to find the total SFS across 500 Mb of data (Figure 1B–D).

We fit three demographic models to the simulated data. In addition to reinferring the parameters from the simulated model, we fit two simpler models to the same data. These had fewer parameters, both omitting the size change deeper in time in the ancestral population. This is meant to crudely mimic the scenario that we often face, in which the true history is more complicated than the parameterized model. It also highlights biases in inferences that can arise when features of the true history are not included.

When fitting the two misspecified models that do not allow for size changes in the ancestral population, this split time is inferred to be substantially deeper in the past than the true split time. This effect, as demonstrated by **?**, is due to the decreased coalescence rate within the ancestral population between the time of the expansion and divergence of the descendent populations. These two misspecified models (Figure 1H,I) also provide a worse fit to the data, as seen by the lower log-likelihoods and the large residuals between model predictions and data (Figure 1E-G).

## Inferring human-Neanderthal demographic parameters

We obtained modern human genome sequences from a recent resequencing of the 1000 Genomes Project cohort (Byrska-Bishop et al., 2022), and a high-coverage sequence of the Vindija Neandertal from Prüfer et al. (2017). From the 1000 Genomes cohort we took 85 MSL (Mende from Sierre Leone) and 91 GBR (British from England and Scotland) sequences as our modern human samples. After filtering out sites that lay outside the 1000 Genomes 'strict' mask, that were not genotyped in all four existing high-coverage archaic genome sequences, lacked high-confidence ancestral state assignments, or fell within 10 kb of exonic or promoter regions, we were left with approximately 960 Mb of well-characterized and putatively neutrally-evolving sequence. We estimated the genome-wide SFS using built-in `moments` parsing functions. Details concerning data processing (including our liftover of the Vindija sequence to a more recent genome build) can be found in the linked GitHub repository.

The model that we wished to fit is relatively simple but still has many parameters (11 in the example we present), so we constructed it in stages by first fitting simpler one- and two-population graphs. Throughout, we used $u = 1.5 \cdot 10^{-8}$ as an estimate of the mutation rate per generation and 29 years as the average generation time. We began by fitting one-population models with ancestral and recent size changes for MSL and GBR. For the MSL model, we allowed three epochs with constant effective size in each epoch. We attributed to GBR a sharp contraction ∼60 kya followed by exponential growth to represent the out-of-Africa bottleneck and subsequent rapid expansion. YAML files representing the models and parameters in this section can be found in the linked GitHub repository.

We next stitched these one-population models together and refitted the resulting graph to get a simple two-population out-of-Africa model, with continuous symmetric migration between MSL and GBR. Following this, we added a Neandertal branch and fit only the Neandertal-modern human divergence time, Neandertal effective size, and the Neandertal-to-GBR admixture proportion. We also fitted the divergence time between the sampled Vindija Neandertal and the lineage which admixed with modern humans, which we observed to be poorly constrained, likely in part due to the very small size of our Vindija sample. In a second round of optimization for the three-population model, we fixed the aforesaid divergence time to a value supported by literature (90 kya, Prüfer et al. (2017)) and refit all other parameters to refine the model.

After this refitting step, we were left with parameters in good agreement with prior authors, with a Neandertal-modern human divergence time of 547 kya, MSL-GBR split time of 77 kya, and Neandertal-GBR pulse proportion of 2.7 percent. We observe some large residuals in our best-fit model, suggesting ...

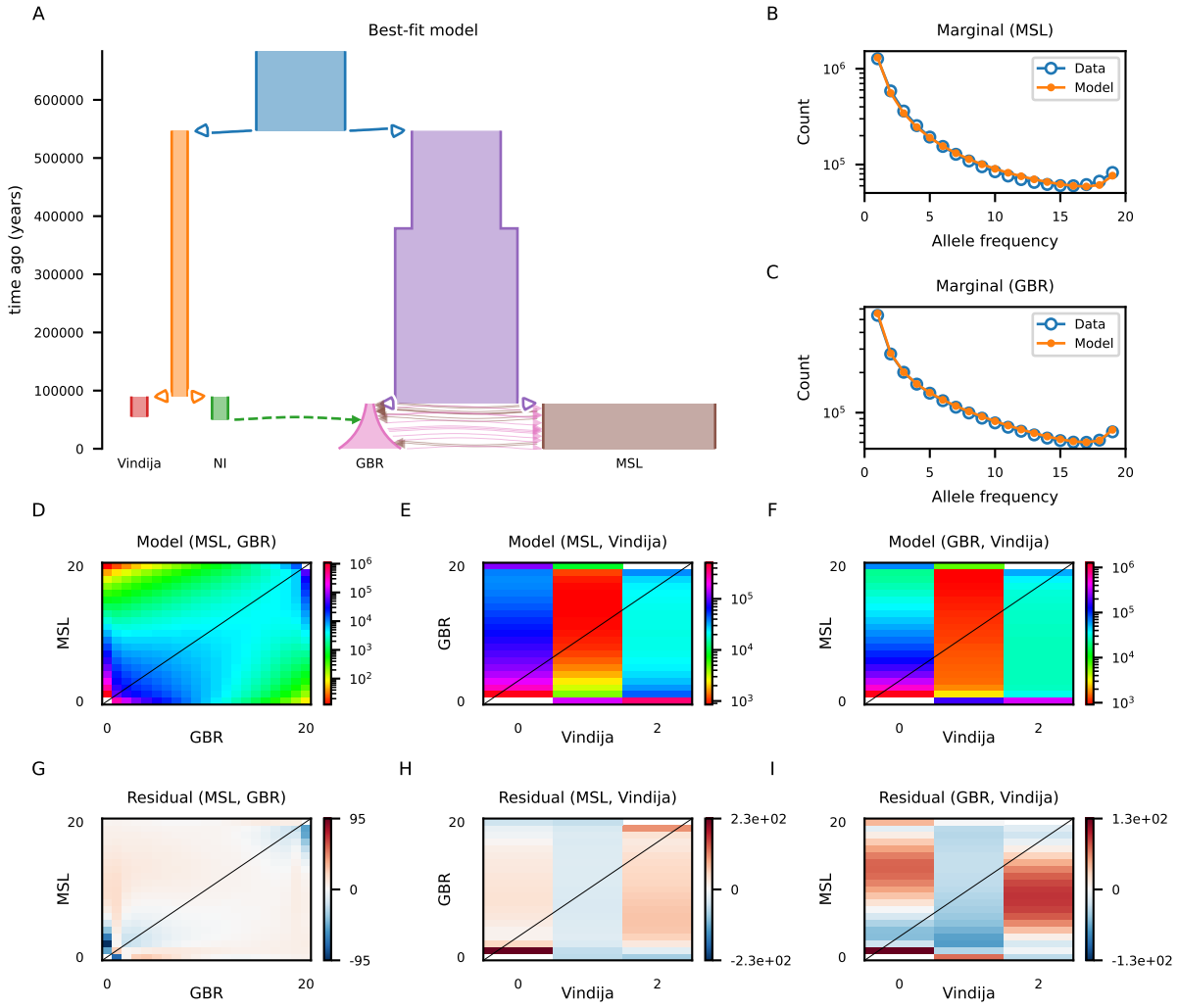


Figure 2: A plot of the best-fit model created using `demesdraw` is displayed in (A). Marginal SFS fits between the model and empirical data are shown for MSL (B) and GBR (C). Marginal two-way spectra predicted by the model and their residuals against the data are plotted for the three pairs of populations MSL, GBR (D and G), MSL, Vindija (E and H), and GBR, Vindija (F, I).

## Considerations and caveats

1. Include here general ideas about the strengths and weaknesses of various approaches in population genetic inference, including when using the SFS.
2. Challenges in finding local/global optima.
3. Challenges in exploring parameter space.
4. Background selection [Ewing, Johri]
5. Gene dense vs gene sparse genomic architectures among species.

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