Population genomics: Background, tools and programming

Gene-genealogy methods for demographic inferences

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Outline

1. Genetic Diversity and Population Demography
2. Demographic Reconstruction
3. Coalescent Simulations
4. Approximate Bayesian Computation (ABC)
5. Practicals

1. Genetic Diversity and Population Demography

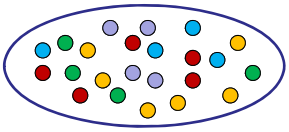
Effect of demography on genetic diversity

Evolutionary forces

Mutation, recombination

Selection

Observed genetic diversity



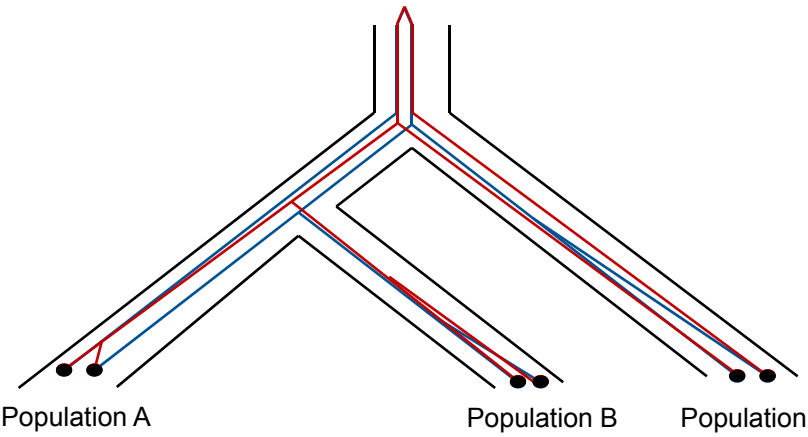
Demography & migration

- Low population size → More genetic drift
- Large population size → Less genetic drift
- Few migrations among populations → High genetic differentiation
- Many migrations among populations → Genetic homogenisation
- Temporal dynamics (growth, bottleneck, etc...) → ...
- Spatial dynamics (population expansion or contraction) → ...

It is possible to make inferences on population demography from genetic data using appropriate tools

Course example: coalescent simulations and ABC

Gene genealogy ≠ Population genealogy

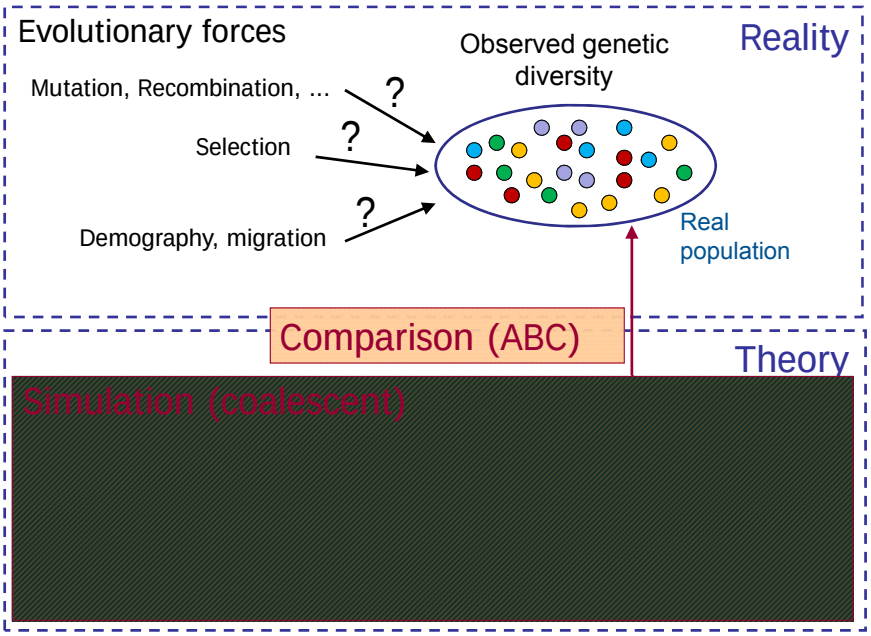


The reconstruction of population demographic history requires to overlap the information from a maximum of genetic loci (portions of DNA).

→ Demography affects the whole genome while selection affects a limited number of loci

2. Demographic reconstruction from genetic/genomic data

Main principles



Modeling/Simulation part

- A model is not a reproduction of the reality but a simplified theoritical representation of the main processes and elements that one wants to better understand
- Many genetic simulation resources available, choose carefully the most adapted to your question.

  A (non-exhaustive) list:
  https://popmodels.cancercontrol.cancer.gov/gsr/packages/
- Two main kinds of genetic simulation approaches:
  1. Forward-in-time: i.e. Wright-Fisher, …
  2. Coalescent: i.e. Fastsimcoal, SPLATCHE, …

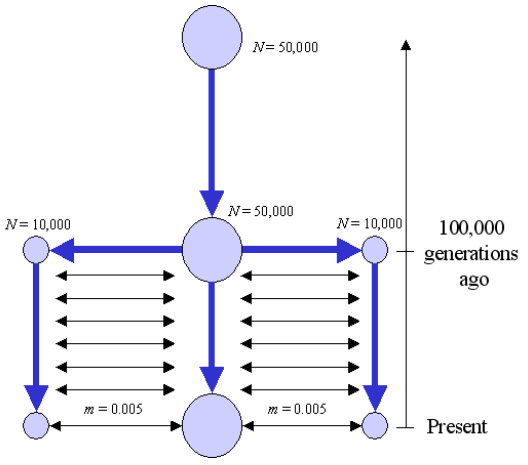
3 – Coalescent simulation

fastSimcoal2: example of demographic scenario

Example of input file

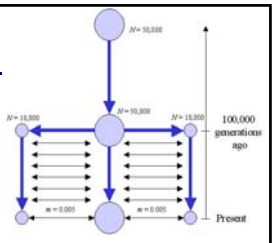
```
3 samples to simulate
//Deme sizes (haploid number of genes)
10000
50000
10000
//Sample sizes
2
0
3
//Growth rates
0
0
0
//Number of migration matrices
2
//Migration rates matrix 0 :
0.000 0.005 0.000
0.005 0.000 0.005
0.000 0.005 0.000
//Migration rates matrix 1 :
0 0 0
0 0 0
0 0 0
//Historical event: time, source, sink, migrants, new deme size, new growth rate, new migration matrix
2 historical events
100000 0 1 1 1 0 1
100000 2 1 1 1 0 1
```

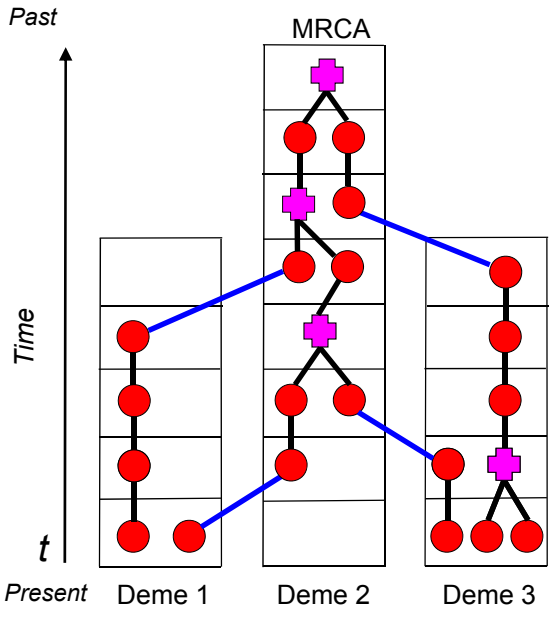
fastSimcoal2: A general coalescent program for the simulation of molecular data in interconnected populations with arbitrary demography.



Fastsimcoal:Excoffier et al, PLoS genetics 2013
http://cmpg.unibe.ch/software/fastsimcoal2/

Coalescent implementation





At each generation, 2 kinds of events are possible

- Migration

with $\mathbf{Prob_m} = \boldsymbol{m}$

where m = migration rate

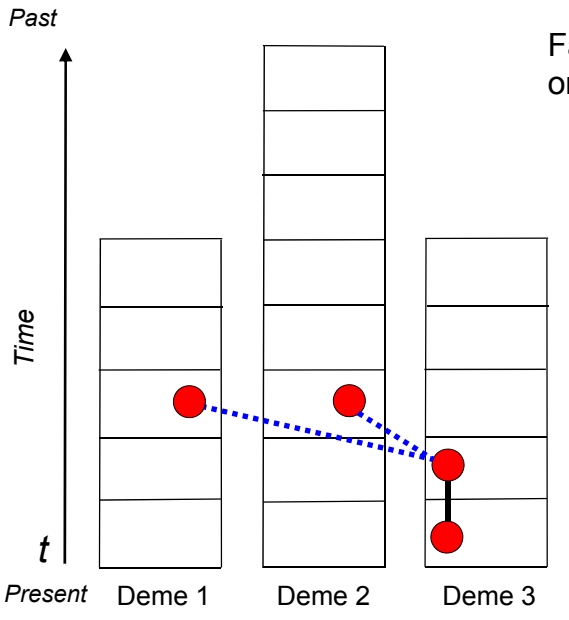
- Coalescent event

with $\mathbf{Prob_c} = \boldsymbol{n(n-1)/N}$

where n = gene number
N = deme (population) size

= neutral gene

Coalescent implementation

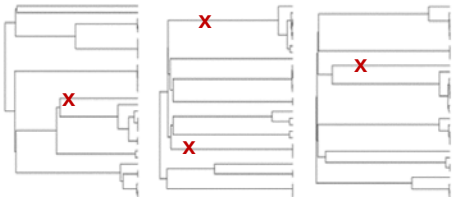


Fastsimcoal is based on an island model

= neutral gene

Simulation of genetic diversity

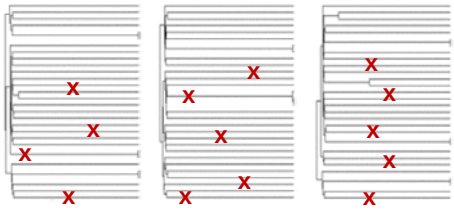
Small size
Expanding
population



DNA, STR, SNP

ATTATCGATATAT
....
ATAATCGATATAT
....
....

Large size
Expanding
Population



....
....
....
....

μ = mutation rate **X = mutation**

Arlsumstat: computation of summary statistics

Arlsumstat is a Linux version of Arlequin 3.5 which compute summary statistics from arlequin projects in a very efficient way, specifically designed for ABC.

Excoffier & Lischer, Mol Ecol Res 2010
http://cmpg.unibe.ch/software/arlequin35/

Executable name:

arlsumstat3522_64bit

Input data file: *.arp

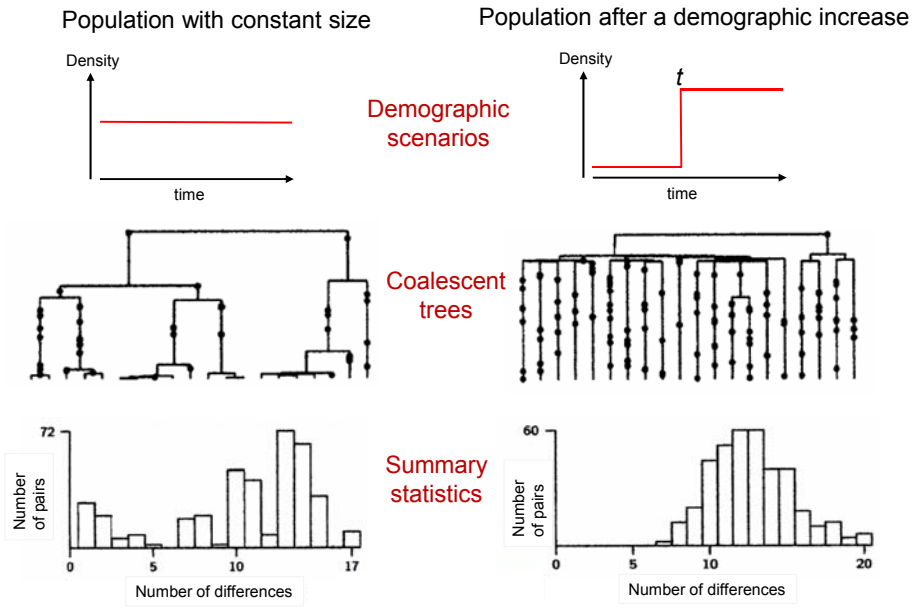
Input settings files:
arl_run.ars, ssdefs.txt

Associated Script:

LlaunchArlSumStatModified.sh

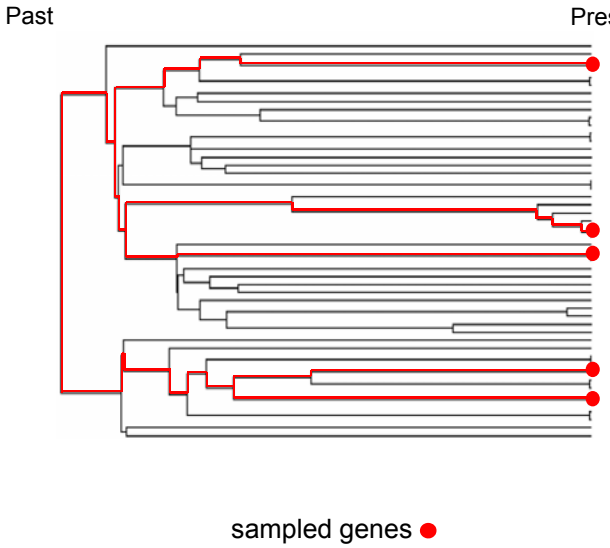
```
[Profile]
        Title="A series of simulated samples"
        NbSamples=1
        GenotypicData=1
        GameticPhase=0
        RecessiveData=0
        DataType=DNA
        LocusSeparator=NONE
        MissingData='?'

[Data]
        [[Samples]]
                SampleName="Sample 1"
                SampleSize=25
                SampleData= {
1_1     1       TATTCTAATTCAGCTTCTGAACGTAAGG
                TAGTAGTCTGCATAGCGGCGTTGTGCGA
1_2     1       TAGTCGTCTGCGTATTGGGGTTGTGCAG
                TAGTCGTCTGCGTATTGGGGTTGTGCAG
1_3     1       TATGCTAATTCAGCTTCTGATCGTAAGG
                TAGTCGTCTGCATAGTGGCGTTGTGCGA
1_4     1       AATGCTAATTCAGCTTCTGATCGTAAGG
                TAGTCGTCTGCATAGTGGCGTTGTGCGA
1_5     1       TATGCTAATTCAGCTTCTGATCGTAAGG
                TATTCTAATTCAGCTTCTGAACGTAAGG
```

Translation of demography to genetics

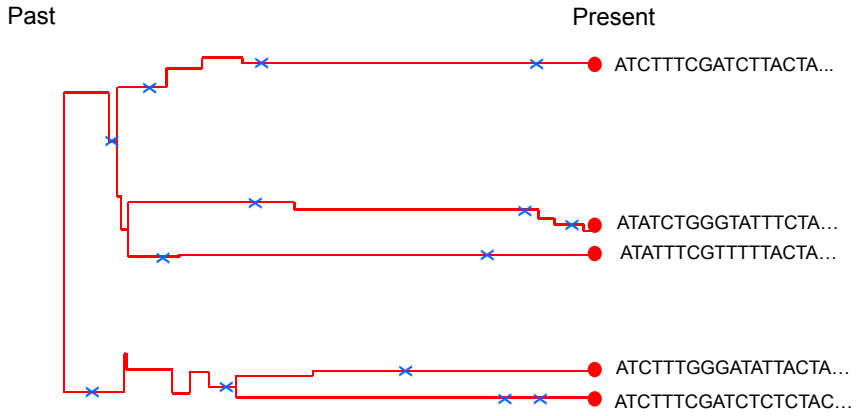


Modified from Harpending et al (1998)

Advantage of the coalescent approach



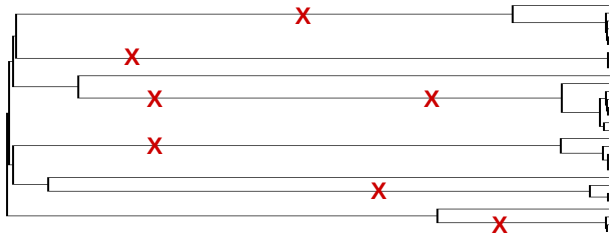
Advantage of the coalescent approach



Simulation of only the sampled genes ● and their ancestors, not the whole population → huge gain in computational efficiency !

Comparison between simulated and empirical data

Scenario A



Scenario B

DNA, STR, SNP

Real data

DNA, STR, SNP

X = mutation

4 – Approximate Bayesian Computation (ABC)

ABC main principles

Bayesian framework: *D* → Data (genetic/genomic) θ → Model Parameter (demographic/biological/…)
M → Model (evolutionary scenario)

$$P(\theta|D) \propto f_M(D|\theta)\ P(\theta)$$

Posterior distribution	**Likelihood** function	**Prior** distribution
Probability distribution of θ knowing *D*	Probability distribution of *D* given θ, based on model *M*	Probability distribution of θ before knowing *D*

Problem: for realistic evolutionary models, analytical solutions of the likelihood function are usually very hard and often impossible to obtain.

Solution: The ABC approach has been designed to bypass the computation of the likelihood function by approximating it using stochastic simulation of the model.

- Using summary statistics S instead of the full data D, with the assumption that $P(D|\theta)$ is proportional to $P(S|\theta)$.
- Using simulations to approximate the likelihood function $P(S|\theta)$.

Tavaré *et al*, Genetics (1997), Beaumont *et al*, Genetics (2002)

Tools: many recent developements and several packages to run ABC (DiyABC, PopABC, ABC R package, etc…)

For the practicals, you will use ABCtoolbox, Wegmann *et al*, Bioinformatics 2010

Parameter estimation through ABC

Observation

Empirical genetic data *D*

Computation of *k* summary statistics S_{obs}

Estimation

Euclidian distances

Parameters estimation $P(\theta|D)$

δ best simulations

Comparison

$$\sqrt{\sum_{i=1}^{k}(S_{sim} - S_{obs})^2}$$

Simulation

Input Parameters $P(\theta)$

Simulation of evolutionary scenario M_1

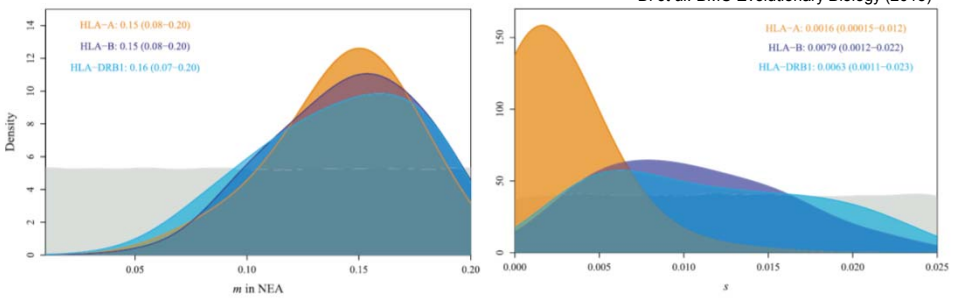
Virtual genetic Data

Computation of *k* summary statistics S_{sim}

Examples of parameter estimation outputs

Prior and posterior distributions

Di *et al.* BMC Evolutionary Biology (2015)



Point estimates and confidence intervals

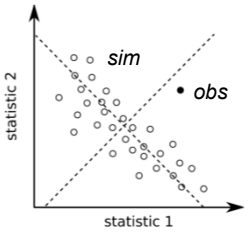
Alves *et al.* Mol. Biol. Evol. (2016)

Table 1. Demographic Parameters Estimated under the Best Fitting Model (*LDDRCop*).

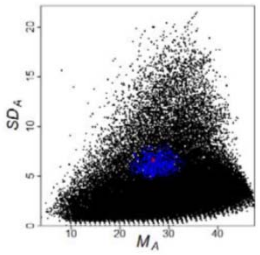
Parameters	Mode	Mean	Median	95% HPDI[a]
Start of the initial expansion in Africa ($T_{STARTEXP}$)[b]	80,704	94,903	91,777	80,000–120,916
Out of sub-Saharan Africa expansion time (T_{OOA})[b]	73,568	65,924	67,477	48,276–80,000
Ancestral size (Ne_{ANC})[c]	10,327	11,795	11,386	5,000–19,098
Carrying capacity (K)[c]	826	1,036	992	50–1,992
LDD proportion (LDD_{PROP})	0.044	0.038	0.040	0.021–0.050
Growth rate (r)	0.429	0.561	0.545	0.200–0.919
Average number of demes travelled by LDD migrants (μ)	5.357	4.780	4.946	3.074–6.000
Gamma shape parameter – LDD distance (α)	1.209	1.251	1.249	0.567–1.943
Migration rate (m)	0.110	0.155	0.148	0.050–0.268
Number of migrants (Nm)[c]	3	93	76	3–241
Number of LDD migrants ($LDDNm$)[c]	8	8	8	0–15
Mutation rate ($STR_{MUTRATE}$)	1.74E-04	1.72E-04	1.72E-04	1.07E-04–2.36E-04

Validation techniques: model fit

Is the model plausible ? Is it capable to reproduced adequately empirical statistics ?



ABCtoolbox user manual



Di *et al.* BMC Evolutionary Biology (2015)

ABCtoolbox provides model fit statistics:
Marginal p-value
Tukey p-value.
→ Low p-value indicates poor fit.

Validation techniques: accuracy of estimates

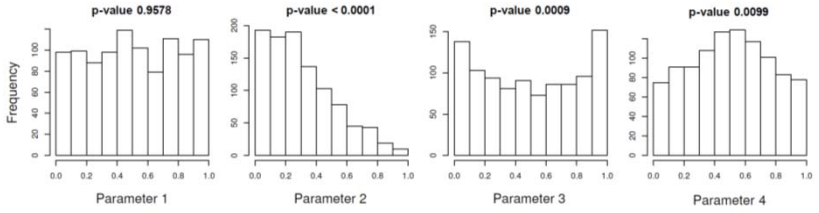
How accurate is the estimation of a parameter ?

The **cross-validation** procedure repeats the estimation with the output of one simulation considered as empirical values (pseudo-observed data, *pods*).

TRUE	Estimated			
Pop. Size	Pop. Size Mode	Pop. Size Mean	Pop. Size Quantile	Pop. Size HDI
10070	11987	16920	0	0.75
14386	23494	24055	0.067487	0.749736
46270	29248	31159	0.874571	0.868895
11806	10070	14996	0.001913	0.105752
24072	17741	20153	0.666673	0.689085

Checking for **biased posteriors**

Kolmogorov-Smirnov test of quantile distribution against an uniform distribution.



unbiased

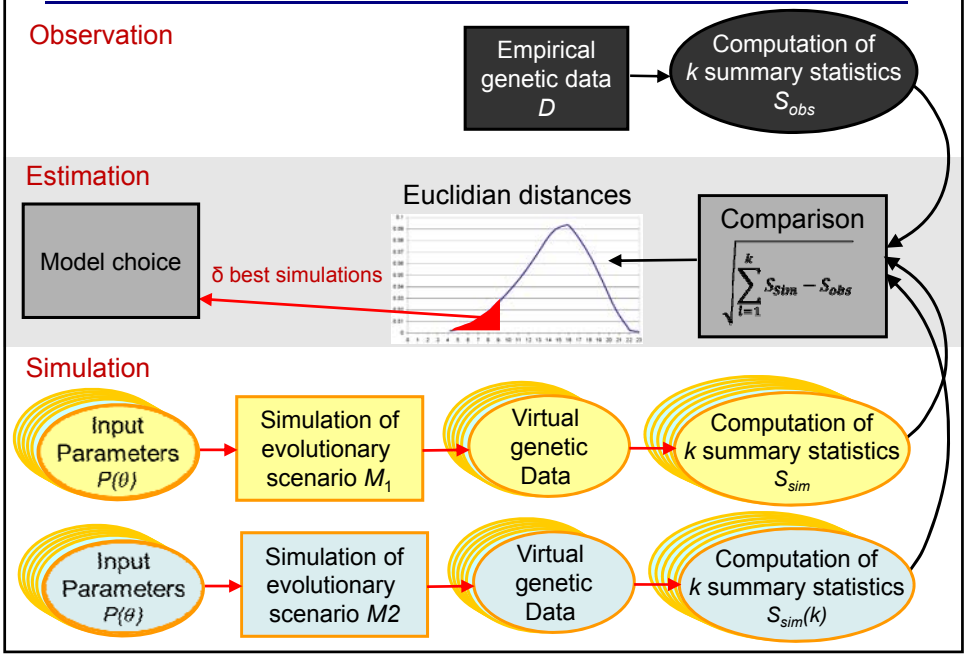
Biased → too large values

Biased → too narrow prior

Biased → too large prior

ABCtoolbox user manual

Model choice through ABC



Examples of model choice outputs

Table 3 Model comparison using retained simulations. Proportions of simulations (%) under each of the three models among 750, 1,500 and 3,000 best simulations retained from 300,000 simulations (100,000 for each model)

Number of retained simulations	Locus	Southern-origin model	Pincer model	Overlapping model
750	A	2.4	31.2	66.4
	B	0.5	26.3	73.2
	DRB1	0.2	37.5	62.3
1,500	A	3.8	33.1	63.1
	B	0.7	27.3	71.9
	DRB1	0.3	48.1	51.6
3,000	A	5.4	47.0	47.6
	B	1.4	40.4	58.2
	DRB1	1.0	48.8	50.2

Di *et al.* BMC Evolutionary Biology (2015)

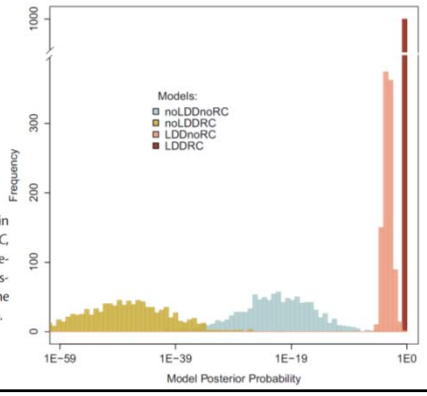
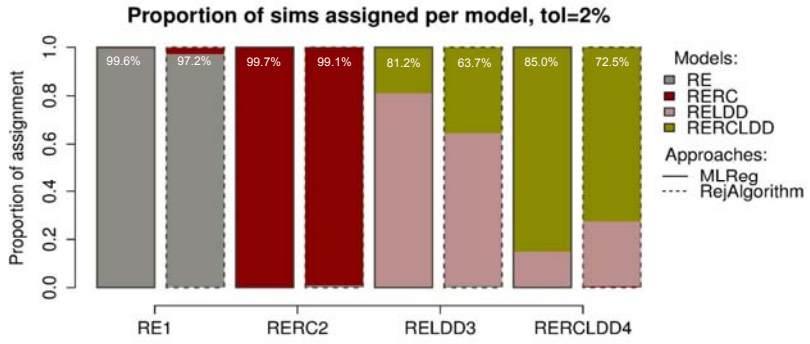


Fig. 2. Distributions of the posterior probabilities of the four main scenarios of human expansions (*noLDDnoRC*, *noLDDRC*, *LDDnoRC*, and*LDDRC*) obtained over the 1,000 bootstrap data sets. Model posterior probabilities were computed using the multivariate logistic regression (Beaumont 2008) on the 2% best simulations (closest to the empirical data) among 100,000 simulations per evolutionary scenario.

Alves *et al.* Mol. Biol. Evol. (2016)

Validation techniques: cross-validation procedure



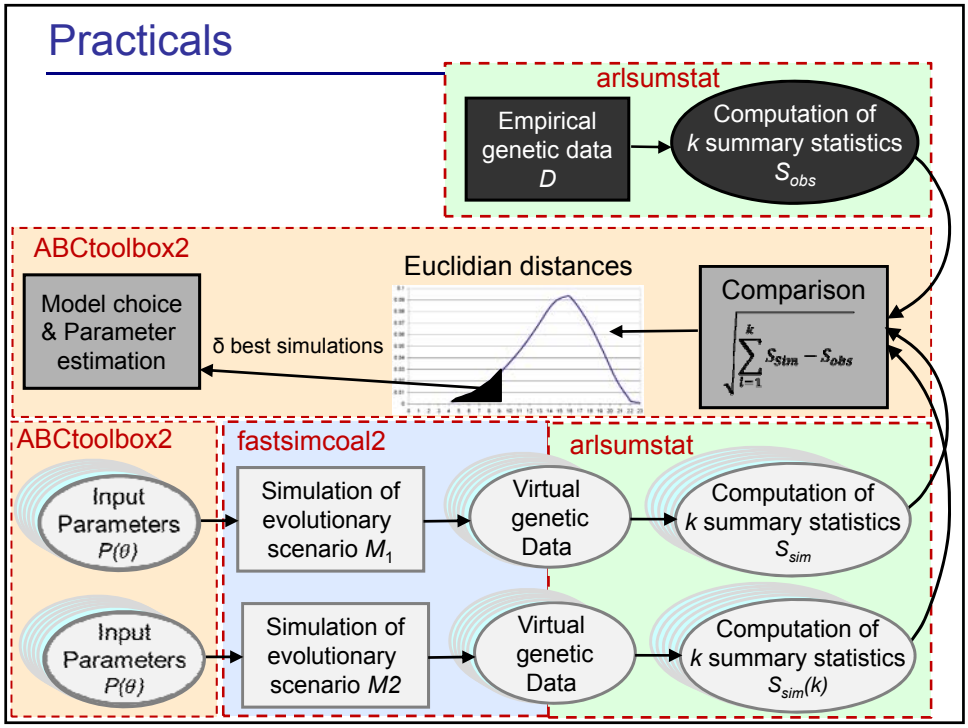
Alves *et al.* Mol. Biol. Evol. (2016)

Practical difficulties

1. Choice of the prior distribution(s)
   - Distribution shape and parameters (uniform, log uniform, normal, etc…)
2. Design of the model(s)
   - Reproduce the main elements but avoid unnecessary complexity
   - Model's output sufficiently different to be distinguished
3. Choice of the summary statistics
   - Enough to capture the main the characteristics of the model and have sufficient power for the estimation
   - Not too many to avoid random noise
4. Choice of the number of simulations to perform
   - Enough to explore the parameter space
5. Choice of the tolerance/retained parameter
   - Start between 1% and 5% and check that the results are robust across different values
6. Validation of the method
   - Check the capability of the model to reproduce real data and the accuracy of the parameter estimation

5. Practicals

Practicals



Practicals

STEP 1: SIMULATION OF DEMOGRAPHIC SCENARIO (fastsimcoal)

STEP 2: COMPUTATION OF SUMMARY STATISTICS (Arlsumstat)

STEP 3: USE A PARAMETER PRIOR DISTRIBUTION (ABCtoolbox)

STEP 4: GENERATE ABC SIMULATION DATASETS

(**OPTIONAL STEP 5**: GENERATE A NEW DATASET WITH TWO PARAMETERS)

STEP 6: MODEL CHOICE WITH ABC

STEP 7: PARAMETER ESTIMATION WITH ABC

(**OPTIONAL STEP 8**: EXPLORE AN ADDITIONAL SCENARIO)