$egin{array}{c} oldsymbol{A} & \text{pproximate} \ oldsymbol{B} & \text{lockwise} \ oldsymbol{L} & \text{ikelihood} \ oldsymbol{E} & \text{stimation} \end{array}$ 

Version xyz November 12, 2016

Champak Beeravolu Reddy champak.br@gmail.com

# Contents

1	Intr	oductio	on	2	
2	Inst	allatior	n	2	
3	Configuration				
	3.1	Comm	nand line options	3	
		3.1.1	The tbi keyword	4	
	3.2		g file options		
		3.2.1	Syntax	4	
		3.2.2	Keywords	4 4 5	
	3.3	Data f	format	11	
		3.3.1	The pseudo_MS genotype format	12	
		3.3.2	The pseudo_MS binary format	13	
	3.4	Examı	ples	13	
		3.4.1	The exact bSFS	14	
		3.4.2	The conditional bSFS	14	
		3.4.3	Inference with the bSFS	15	
Ιn	dex o	of keyw	vords	17	

## 1 Introduction

ABLE is a program written in C/C++ for the joint inference of arbitrary population histories and the genome-wide recombination rate using data from multiple whole genome sequences or fragmented assemblies (e.g. UCE's, RADSeq, and targeted exomes). The inference results in a Maximum Likelihood Estimate (MLE) of the parameters corresponding to the demographic model of interest along with the recombination parameter. It makes use of the distribution of blockwise SFS (bSFS) patterns which retain information on the variation in genealogies or Ancestral Recombination Graphs (ARGs) spanning short-range linkage blocks across the genome. ABLE does not require phased data as the bSFS does not distinguish the sampled lineage in which a mutation has occurred. Like with the SFS, outgroup information can be also be ignored by folding the bSFS. ABLE takes advantage of openmp parallelization and is tailored for studying the population histories of model as well as non-model species.

This is the documentation accompanying ABLE and the current version of the project is freely available from https://github.com/champost/ABLE.

## 2 Installation

It is easiest to build an ABLE binary under all flavours of Linux. ABLE requires the GNU Compiler Collection (gcc) and GNU Make (make) for a smooth installation and has been tested using gcc 4.8.4 and make 3.81. If you don't have gcc or make, you can use your OS specific package handling utility.

Under Ubuntu this corresponds to the following in a terminal

```
sudo apt-get install build-essential
```

Other dependencies such as the GNU Scientific Library (GSL) and the Non-Linear Optimization (NLopt) library are automatically installed by following the instructions outlined below.

• Download the ABLE repository

```
\verb|wget| https://github.com/champost/ABLE/archive/master.tar.gz|
```

• Untar the archive and change directory

```
tar -xzf master.tar.gz && cd ABLE-master
```

 If you are installing ABLE for the <u>first time</u> you might have to install the GSL and NLopt libraries. This can take some time as the command below performs a **static installation** of the libraries. You can skip this step if you already have these libraries installed system-wide or if you are simply updating ABLE to the latest version.

```
make deps
```

• Finally, build an ABLE binary

```
make clean && make all
```

If you want ABLE to be accessible from everywhere, such as your data folder, you might want to

```
cp ABLE ~/bin
```

This ensures that you can execute the program by specifying ABLE ... instead of ./ABLE ... from the installation folder. This holds only if ~/bin exists and is part of your \$PATH environment variable.

# 3 Configuration

For ABLE to execute correctly, you need to specify a command line, some options in a config file and provide a data file.

## 3.1 Command line options

The command line needs to be in the *ms* format. Note that ABLE supports only a subset (shown below) of all the available *ms* command line options. Please refer to the full *ms* documentation for a better understanding of these options.

• -t θ	• -en <i>t i x</i>	
• -r ρ nsites	<ul> <li>-eM t x</li> </ul>	
• -G α	$\bullet$ -em $t i j x$	
• -I npop n1 n2 [4 <i>N</i> <sub>0</sub> <i>m</i> ]	a company M. M. M. M.	
• -eG t α	• -ema $t$ npop $M_{11} M_{12} M_{13} M_{21}$	
$ullet$ -eg $t$ $i$ $lpha_i$	• -es <i>t i p</i>	
<ul> <li>-eN t x</li> </ul>	• -ej <i>tij</i>	

## 3.1.1 The tbi keyword

While *ms* provides for the tbs option, we introduce the tbi keyword which stands for "to be inferred" as part of the ABLE command line. tbi keywords are to be used instead of the values of the parameters of a demographic model (*i.e.* some floating value) which need to be inferred. All tbi keywords need to be suffixed by a number (tbi1, tbi2,...). Thus, all occurrences on the command line of the same demographic parameter can be correctly identified.

Below is a typical example of an ABLE command line for a simple history describing a single discrete change in population size defined by three parameters (current and ancestral population sizes and the time of size change) which are to be inferred (see 3.4.1):

```
./ABLE 4 100000 -t tbi1 -eN tbi2 tbi3 -T config.txt
```

ABLE also requires the user to specify a \_-T towards the end of the command line indicating the start of the config filename (if any) specified by the user. If no filename is specified, by default ABLE looks for a file called config.txt.

## 3.2 Config file options

#### Note

- **All options** of the config file are **case sensitive**.
- Successive options can undo previous ones.

## **3.2.1** Syntax

Any line in the config file beginning with the hash symbol # will be considered as a comment by ABLE and ignored. Every keyword along with its corresponding options are to be specified on a separate line. Also, keywords and options are to be separated by a single space. All config file keywords introduced here will be of one or more of these types:

```
T1: Key

T2: Key val or Key val1 val2 val3 ...

T3: Key SubKey val or Key SubKey val1 val2 val3...
```

Here, the presence/absence of a T1 keyword respectively represents a binary true/false option whereas it is possible to specify a lot more with a T2/T3 keyword.

#### 3.2.2 Keywords

#### Note

**ABLE** expects entire lines to be commented. So, **unexpected behaviour** can result if you specify keywords and/or options along with a comment on the same line *e.g.* Key val # comment after keyword

#### ▶ datafile (T2)

Accepts a single value specifying the name and location (relative to the config file) of the file containing the data (see 3.3 for more on the data format).

#### datafile filename

► datafile\_format (T2)

Data can be specified in either of the two formats below.

#### Note

The **default** input file format is bSFS.

## - datafile\_format bSFS

Each line in this format contains a tag describing the bSFS configuration (joint bSFS if multiple population samples) and its respective frequency of occurrence in the data.

```
(tag1) : prob1
(tag2) : prob2
...
```

For an example of this format please refer to the accompanying Orangutan dataset in the /data folder. Further information on the general logic behind the bSFS/jbSFS tags will be provided here later.

#### datafile\_format pseudo\_MS

This format closely resembles that of simulated samples output by the *ms* software and will be the easiest for all users of ABLE to provide. A more detailed description of this format can be found in 3.3. A file named <code>block\_SNPs.txt</code> is created with the number of SNPs per sequence block providing for a manual cross-check that ABLE has correctly accounted for available polymorphism. While tri/quadri-allelic nucleotide positions are ignored they are however listed in <code>block\_SNPs.txt</code>.

## ► allele\_type (T2)

This option provides additional information to ABLE on how to read in the data when it is already in a pseudo\_MS format. See 3.3 for full examples of both the formats below.

- allele\_type genotype
   Valid characters are A, T, G or C and missing information is specified by using N (see 3.3.1).
- allele\_type binary
   Valid characters are 0 or 1 and missing information is specified by using N (see 3.3.2).

## ► task (T2)

This option defines any one of the three principal tasks (or modes) that **ABLE** is meant to undertake. More information can be found in the examples section (3.4).

#### task exact\_bSFS

ABLE attempts to calculate the **exact bSFS** for a given number of genealogies to be sampled and there is no requirement for a file containing data. Results obtained under this mode can be readily compared with analytical results. A fille named **expected\_bSFS.txt** is generated with the expected bSFS for a given number of genealogies and a point in parameter space (see 3.4.1).

#### - task conditional\_bSFS

This mode of ABLE (along with the bSFS keyword below) calculates the **conditional bSFS** (*i.e.* only configurations found in the data) at a given point in parameter space and for some number of genealogies (see 3.4.2).

#### task infer

This is the standard mode for inferring demographic parameters and will be the most used feature of ABLE. This mode typically consists of a global search followed by a local search and finally a refined log-likelihood (*lnL*) at the MLE (see 3.4.3).

#### ► bSFS (T1)/(T2)

Accepts a single value specifying the name and location (relative to the config file) of the output file for the "pseudo-expected bSFS" of a given demographic model, at a point in parameter space and for a specified number of genealogies (see task conditional\_bSFS above).

#### bSFS filename

The default name of the output file is bSFS.txt if no filename has been specified.

#### ► kmax (T2)

A single argument following this keyword specifies the maximum number of mutation classes at single nucleotide sites (*i.e.* singletons, doubletons, *etc.*) to be explicitly accounted for in the bSFS. Mutations appearing more frequently in your data than the specified kmax are not ignored but rather grouped into a marginal probability class. A maximum of 3 is specified as follows

#### kmax 3

Thus, when sampling genealogies/ARGs, ABLE will account for 0, 1, 2 and 3 SNPs in all blocks and bundle the probability of observing more the 3 SNPs into a marginal probability.

#### ► folded (T1)

The presence of this keyword instructs ABLE to consider the "polarity" *i.e.* account for the ancestral/derived states of alleles with respect to an outgroup and thus use the folded bSFS. If the data is not in a binary format (see Pg. 12) then the first allele at every nucleotide position in the first population is taken to be of the ancestral type.

#### ► pops (T3)

This option takes as a first argument the number of population samples that will be analysed followed by the number of samples per population in the order that they have been specified on the *ms* command line

```
pops npops n1 n2 n3 ...
```

For a single population example with 5 genomes it should be

```
pops 1 5
```

whereas for a 3 population example with 1, 4 and 2 genomes respectively it should be specified as

```
pops 3 1 4 2
```

#### convert\_data\_to\_bSFS (T2)

With this option ABLE simply converts a pseudo\_MS format file into the bSFS format. It is advised for users to store data in the bSFS format (especially for large samples) as it is quicker to load and because internally ABLE works

with the bSFS. When asked to convert data, ABLE performs the task, creates a block\_SNPs.txt file like in the case of datafile\_format pseudo\_MS (see Pg. 5) and terminates. For the conversion you can run ./ABLE config.txt in the terminal with the contents of config.txt as below

```
# (modify the "pops" option according to your sampling)
pops 2 4 4
datafile input_filename
convert_data_to_bSFS output_filename
```

#### ► start (T2)/(T3)

This applies only when this keywords have been specified as part of the command line (see 3.1) and need to be initialized with numeric values from within the config file.

- start all val1 val2 ...

When all parameters need to be initialized at once with respect to the "tbi order". Let us assume that your demographic model contains three free parameters, tbi2, tbi3 and tbi7. If you want to initialize these parameters with tbi7 = 10, tbi2 = 5.2 and tbi3 = 1, then

```
start all 5.2 1 10
```

#### start random

Initializes all tbi keywords with uniformly drawn random values over the respective bounds of each demographic parameter. The default lower and upper bounds for all parameters are  $10^{-3}$  and 5 respectively.

- start tbi val

If a single tbi parameter needs to be initialized (e.g. tbi4 = 3), then

## ► global\_search (T2)

start tbi4 3

This option sets the global search strategy for the MLE and makes use of the algorithms implemented in the NLopt library.

- global\_search DIRECT
   Uses the DIviding RECTangles (DIRECT) algorithm for global optimization.
- global\_search CRS
   Uses the Controlled Random Search with local mutation (CRS) algorithm for global optimization.

## - global\_search ISRES

Uses the Improved Stochastic Ranking Evolution Strategy (ISRES) algorithm for global optimization.

## global\_search ESCH

Uses the Evolutionary Strategies algorithm by Carlos Henrique da Silva Santos (ESCH) for global optimization.

## ▶ global\_search\_trees (T2)

Accepts a single value which specifies the number of genealogies/ARGs to be sampled during the **global search** of the MLE. The default number of genealogies is 1000 times the number of tbi parameters.

## ► local\_search\_trees (T2)

Accepts a single value which specifies the number of genealogies/ARGs to be sampled during the **local search** of the MLE. The default number of genealogies is 1000 times the number of tbi parameters.

#### ▶ global\_search\_evals (T2)

Accepts a single value which specifies the number of points in parameter space that should be explored before concluding the **global search** for the MLE. The default number of evaluations is 5000 times the number of tbi parameters.

#### Warning issued!

## ► local\_search\_evals (T2)

Accepts a single value which specifies the number of points in parameter space that should be explored before concluding the **local search** for the MLE. The default number of evaluations is one fifth of the specified value for <code>global\_search\_evals</code>. If this wasn't specified then it is set to 1000 times the number of <code>tbi</code> parameters.

#### Warning issued!

## ▶ global\_upper\_bound (T2)

Accepts a single value which defines the **upper bound** for all **tbi** parameters though this can be undone for certain by specifying individual bounds (see the **bounds** keyword). The default upper bound for all parameters is 5.

# ► global\_lower\_bound (T2)

Accepts a single value which defines the **lower bound** for all **tbi** parameters though this can be undone for certain by specifying individual bounds (see the **bounds** keyword). The default lower bound for all parameters is  $10^{-3}$ .

## ▶ skip\_global\_search (T1)

This keyword skips the global search and starts the local search with the user-specified start point in parameter space with the help of the start keyword (see Pg. 8).

#### ▶ bounds (T3)

Individual parameter bounds during the MLE search can be set with this keyword. The tbi parameter needs to be specified as the second keyword and followed by the minimum and maximum bounds respectively. So if you want to impose 0.5 < tbi2 < 4.2, then

#### bounds tbi2 0.5 4.2

The default lower and upper bounds for all parameters are  $10^{-3}$  and 5 respectively.

#### ► constrain (T2)

Presently in ABLE, it is possible to specify simple parameter constraints to enforce biological coherence between two demographic events *e.g.* gene flow is necessarily a more recent event than divergence in a two population model. Multiple constraints can be specified (each on a separate line) and each constraint only accepts two tbi parameters. For example, in order to impose the constraint tbi4 < tbi2, specify

#### constrain tbi4 tbi2

and in this very order.

#### ► seed\_PRNG (T2)

Accepts a single value which acts as the starting seed for the Pseudo random Number Generator (PRNG) which follows the Mersenne Twister algorithm (as implemented in the GNU Scientific Library). By default, ABLE uses all available threads on a system for computation (see also set\_threads option), and automatically attributes a different seed to each thread by successively incrementing the user-specified start value by 1. If no value was specified, ABLE uses the state of the system clock to generate a seed and then attributes a seed by successive incrementation to each thread.

## ► refine\_likelihoods (T2)

Accepts a single value which specifies the number of genealogies to be sampled for a further refinement of the Monte Carlo *lnL* at the MLE found after a global/local search.

## ► report\_likelihoods (T2)

Accepts a single value which asks ABLE to report the parameter point with

the best MLE during the (global or local) search after the specified number of likelihood evaluations.

## ► start\_likelihood (T2)

Accepts single value which is a user-specified *lnL* and **ABLE** is asked to check if it can improve over this value. This option applies only when the global search is skipped altogether.

#### ► no\_bSFS\_file (T1)

This asks ABLE not to output a bSFS file. Only standard information such as the *lnL* and computation time are written to the console.

## ▶ print\_correction\_factor (T1)

This option asks ABLE to print the correction factor ( $\geq 1$ ) which penalizes the likelihood at a point in parameter space. These situations can arise when the number of genealogies specified by the user are insufficient for explaining all the bSFS configurations present in the data. Or when you are attempting to fit the data without recombination when the data bSFS contains configurations which violate the four gamete test. The printing is only activate when task conditional\_bSFS (see Pg. 6) and a value greater than 1 indicates that the penalization is in effect.

#### ► set\_ftol\_abs (T2)

Accepts a single value which sets the tolerance in terms of the difference in absolute value between successive evaluations at points in parameter space during the local search. Let  $\epsilon$  be the user provided value and assume that the local search has evaluated the likelihood function, f(x), at points  $x_1$  and then  $x_2$ . If the condition  $|f(x_2) - f(x_2)| < \epsilon$  is satisfied, the search is terminated and the MLE is reported by ABLE.

#### ► set\_threads (T2)

Accepts a single value indicating the number of threads that ABLE needs to spawn for a parallel computation of the bSFS likelihoods.

#### 3.3 Data format

pseudo\_MS or bSFS (see Pg. 5). If you have your data in other formats (e.g. VCF,...), then converting it into the pseudo\_MS should be very easy. The order in which population samples need to be input closely resembles the *ms* format. Briefly, the samples from each population for which you will have attributed an *a priori* order (pops keyword, see Pg. 7) should be listed.

By default, the pseudo\_MS format expects sequence blocks using only the genotype information (i.e. A/T/G/C/N). If you have prior information regarding

the ancestral/derived states at each segregating site you can specify the blocks in a binary format (using the allele\_type option, see Pg. 6), in which case all sequences must be in this format. Nucleotide positions containing a N (e.g. due to missing information) will be completely ignored as are tri/quadri-allelic SNPs.

## 3.3.1 The pseudo\_MS genotype format

Each block begins with a // followed by an optional header which can span any number of lines. Below is an example of three sequence blocks – a Chr7 block, a fictional monomorphic block and from Chr4 respectively – from the accompanying 2kb Orangutan dataset (/data folder). The first four samples (2 diploids) are from the Bornean population and the rest are from Sumatran individuals. The corresponding population order is pops 2 4 4 (see Pg. 7).

Headers may not begin with either of A, T, G, C or N characters! Use a # to start a line if necessary.

```
//
7_41030400-41032000
TCATCTG
TCATCTG
GCATTGT
GCATTGT
GCAGCGG
TCTTCTG
GTATCGG
GTATCGG
//
7_xxxxxxxx-xxxxxxx (monomorphic_block_example)
4_179188400-179190000
ATGGAGT
ATGGAGT
ACAGAGC
GTGGGGC
ATGGAAT
GTGGGGT
ATGAGGT
ATGAGGT
```

## 3.3.2 The pseudo\_MS binary format

Now assume that the ancestral states in the previous example (3.3.1) were given by the genotypes of the first sequence of each block. The binary equivalent is obtained by replacing the ancestral allele with 0 and derived allele with 1 and should look like the following.

```
Headers may not begin with either of 0, 1 or N characters! Use a # to start a line if necessary.
```

```
//
7_41030400-41032000
0000000
0000000
1000111
1000111
1001010
0010000
1100010
1100010
//
7_xxxxxxxx-xxxxxxx (monomorphic_block_example)
//
4_179188400-179190000
0000000
0000000
0110001
1000101
0000010
1000100
0001100
0001100
```

# 3.4 Examples

In this section we shall refer to three demographic models (Fig. 1), also considered in the accompanying bioRxiv draft (although some details may vary) for illustrating the different tasks performed of ABLE (see Pg. 6). Note however that the following assumes a good working knowledge of the *ms* command line options.

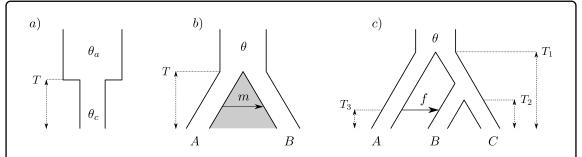


Figure 1: Demographic models previously considered in the accompanying bioRxiv draft. (a) a single population with a sudden reduction in  $N_e$ , (b) isolation between populations A and B followed by continuous unidirectional migration (from A to B) at rate M migrants per generation and (c) isolation between three populations A, B and C followed by unidirectional admixture of a fraction f from A to B.

#### 3.4.1 The exact bSFS

Let us consider a single population sample of size 4 which doubled its effective population size at scaled time T=0.2 in the past with  $\theta_c=1$  and  $\theta_a=2$  (see Fig. 1a). We would like to calculate the exact *folded* bSFS (see Pg. 6) using 100K genealogies. The corresponding command line would look like

```
./ABLE 4 100000 -t 1 -eN 0.2 2 -T config_1pop_exact.txt
```

along with the contents of config\_1pop\_exact.txt as below

```
pops 1 4

kmax 4

folded

task exact_bSFS

bSFS exact_bSFS.txt

seed_PRNG 98368183
```

output file = expected bSFS.txt!!

The kmax 4 (see Pg. 7) is not a necessary option here and only serves to restrict the size of the bSFS by accounting explicitly for up to 3 SNPs per genealogy/block.

#### 3.4.2 The conditional bSFS

This example calculates the probabilities of observing only the bSFS configurations present in the data for a three population model. The parameter values used here

are  $f_{A\rightarrow B}=0.04$ , scaled population size  $\theta=2.432$ , scaled times  $T_3=0.0625$ ,  $T_2=0.075$  and  $T_1=0.3$  (see Fig. 1c).

```
./ABLE 3 1000000 -t 2.432 -I 3 1 1 1 -es 0.0625 1 0.96 -ej 0.0625 4 3 -ej 0.075 1 2 -ej 0.3 2 3 -T config_3pop_conditional.txt
```

And config\_3pop\_conditional.txt contains:

```
pops 3 1 1 1

task conditional_bSFS
datafile data_filename_to_be_specified_here.txt
bSFS conditional_bSFS.txt

seed_PRNG 12468192
```

Alternatively, in the conditional\_bSFS mode you can make use of this keywords in the command line and respectively specify the parameter values in the config file using the start thi ... options.

#### 3.4.3 Inference with the bSFS

We now consider a two population example with 3 genomes in population A and 2 genomes in B (*see* Fig. 1b) and blocks of size 500bp. This is a four parameter model with unidirectional gene flow at rate m after a split at time T, with all scaled populations size parameters equal to  $\theta$  and scaled intra-block recombination rate  $\rho$ . The parameters "to be inferred":  $\theta$ ,  $\rho$ , m and T have been respectively specified as tbi1, tbi2, tbi3 and tbi4 in the command line below. Note that the position corresponding to the number of genealogies to be sampled during inference (xxx below) is entirely ignored by ABLE and should only be specified in the config file.

```
./ABLE 5 xxx -t tbi1 -r tbi2 501 -I 2 3 2 -m 1 2 tbi3 -ej tbi4 1 2 -T config_2pop_infer.txt
```

The contents of config\_2pop\_infer.txt below starts a global search immediately followed by a local search with the resulting MLE form the former.

```
# general options
# -----
pops 2 3 2
task infer
datafile data_filename_to_be_specified_here.txt
```

```
seed_PRNG 29468147
# global search options
# -----
global_search CRS
global_search_trees 50000
global_search_evals 7000
report_likelihoods 1000
# parameter constraints
# -----
global_upper_bound 15
global_lower_bound 1e-2
bounds tbi1 1e-2 1
bounds tbi2 1e-2 1
# local search options
# -----
local_search_trees 50000
refine_likelihoods 1000000
```

# Index of keywords

# (commented line),4	kmax, 7
allele_type, 6 binary, 6, 13 genotype, 6, 12	<pre>local_search_evals, 9 local_search_trees, 9</pre>
bounds, 10	no_bSFS_file, 11 pops, 7
bSFS, 6	<pre>print_correction_factor, 11</pre>
constrain, 10 convert_data_to_bSFS, 7	refine_likelihoods, 10 report_likelihoods, 10
<pre>datafile,5 datafile_format,5 bSFS,5 pseudo_MS,5,12,13</pre>	<pre>seed_PRNG, 10 set_ftol_abs, 11 set_threads, 11 skip_global_search, 10</pre>
folded, 7	start,8
<pre>global_lower_bound, 9 global_search, 8     CRS, 8     DIRECT, 8     ESCH, 9     ISRES, 9 global_search_evals, 9 global_search_trees, 9 global_upper_bound, 9</pre>	all, 8 random, 8 tbi, 8 start_likelihood, 11  task, 6 conditional_bSFS, 6, 14 exact_bSFS, 6, 14 infer, 6, 15 tbi, 4