Hapl-o-Mat - Getting Started Linux

Please also see the README.

Hapl-o-Mat

Hapl-o-Mat is software for HLA haplotype inference coded in C++. Besides estimating haplotype frequencies via an expectation-maximization algorithm, it is capable of processing HLA genotype population data. This includes translation of alleles between various typing resolutions and resolving allelic and genotypic ambiguities. Both common formats for recording HLA genotypes, multiple allele codes (MAC) and genotype list strings (GLS), are supported.

For more information refer to our publications on Hapl-o-Mat:

Journal article to come

C. Schäfer, A.H. Schmidt, J. Sauter: Hapl-O-mat: A Versatile Software for Haplotype Frequency Estimation. HLA (2016), 87, 236-320

If you use Hapl-o-Mat for your research, please cite preferably the journal article.

Getting Started

This guide is an introduction on how to use Hapl-o-Mat under Linux. In order to follow this guide, you need a Linux system, a C++ compiler supporting C++11, and Python. In this tutorial, we use Ubuntu 14.04.4 LTS and GNU compiler collection (GCC) version 4.8.4. This Ubuntu version comes with Python. We process every step from the terminal. Of course, you can use some tool with a graphic interface to move files, create folders, and so on. If you are a seasoned Linux-User, feel free to refer to the shorter version of this guide, "Hapl-o-Mat/gettingStarted".

After successfully downloading Hapl-o-Mat, start a terminal and browse to the location where Hapl-o-Mat is stored. Enter the folder Hapl-o-Mat by typing "cd Hapl-o-Mat". Check what is inside by typing "ls". You should see the following files, where we mark important files for using Hapl-o-Mat as bold.

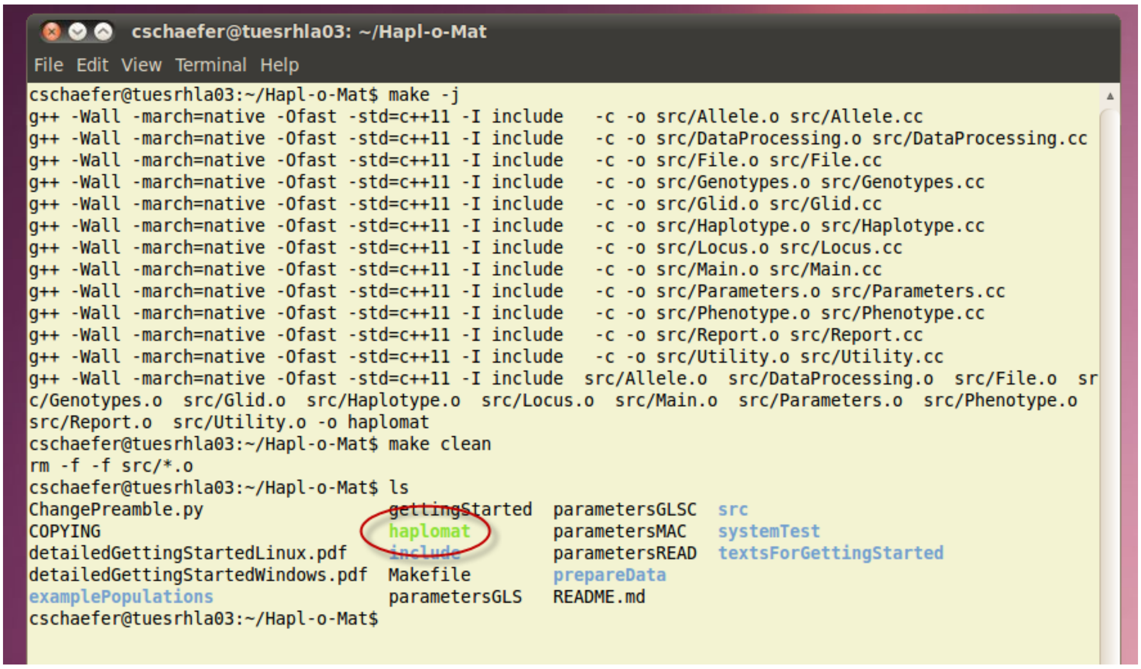
File name	Description
ChangePreamble.py	A python-script to adapt the preamble in all files; You are not going to use it.
COPYING	The GNU General Public License
detailedGettingStartedLinux	Guide for using Hapl-o-Mat under Linux
detailedGettingStartedWindows	Guide for using Hapl-o-Mat under Windows
examplePopulations	Some genotype population data we are going to work with in the section Tutorials.
gettingStarted	A shorter form of this tutorial
include	A part of Hapl-o-Mat's source code; If you do not want to change code, do not touch it.
Makefile	Instructions for building Hapl-o-Mat; You might need to adapt it, if you use another compiler than GCC.
parametersGLS, parametersGLSC, parametersMAC, parametersREAD	Parameter files for Hapl-O-mat; We are going to discuss these in section Parameters.

prepareData	Here is everything to create the data required by Hapl-o-Mat.
README.md	Read me
src	Another part of Hapl-o-Mat's source code; If you do not want to change code, do not touch it.
systemTest	Run the system test after changing code to check, if you broke something. Refer to its README.
textsForGettingStarted	Raw files for the guides including this guide

To estimate haplotype frequencies we only need to consider the folder prepareData and the files Makefile, parametersGLS, parametersGLSC, parametersMAC, and parametersREAD. To finish the tutorials we need the folder examplePopluations, too.

Install Hapl-o-Mat

We compile Hapl-o-Mat with GCC using a Makefile. Just enter the folder "Hapl-o-Mat" and type "make" to create the executable "haplomat" (Run "make -j" to use more than one core for compiling). Type "make clean" to clean up. Use the command "ls" to find a new file, haplomat.


cschaefer@tuesrhla03: ~/Hapl-o-Mat
File Edit View Terminal Help

```
cschaefer@tuesrhla03:~/Hapl-o-Mat$ make -j
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Allele.o src/Allele.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/DataProcessing.o src/DataProcessing.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/File.o src/File.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Genotypes.o src/Genotypes.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Glid.o src/Glid.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Haplotype.o src/Haplotype.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Locus.o src/Locus.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Main.o src/Main.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Parameters.o src/Parameters.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Phenotype.o src/Phenotype.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Report.o src/Report.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include   -c -o src/Utility.o src/Utility.cc
g++ -Wall -march=native -Ofast -std=c++11 -I include  src/Allele.o  src/DataProcessing.o  src/File.o  sr
c/Genotypes.o  src/Glid.o  src/Haplotype.o  src/Locus.o  src/Main.o  src/Parameters.o  src/Phenotype.o
src/Report.o  src/Utility.o -o haplomat
cschaefer@tuesrhla03:~/Hapl-o-Mat$ make clean
rm -f -f src/*.o
cschaefer@tuesrhla03:~/Hapl-o-Mat$ ls
ChangePreamble.py                 gettingStarted  parametersGLSC  src
COPYING                           haplomat        parametersMAC   systemTest
detailedGettingStartedLinux.pdf   include         parametersREAD  textsForGettingStarted
detailedGettingStartedWindows.pdf Makefile        prepareData
examplePopulations                parametersGLS   README.md
cschaefer@tuesrhla03:~/Hapl-o-Mat$
```

Data Preparation

Hapl-o-Mat relies on information on the HLA nomenclature. This information is provided by data files, which we are going to create. As the HLA nomenclature evolves over time, e.g. by finding new alleles or adding new multiple allele codes, it is important to update data from time to time. Hapl-o-Mat relies on the following files, which must be placed in the folder "Hapl-o-Mat/data" for Hapl-o-Mat to work:

File name	**Description**
AllAllelesExpanded.txt	A list of relevant existing HLA alleles with their enclosed more-digit typing resolutions
AlleleList.txt	If your input data in GLS format includes a missing single-locus genotype, it can be replaced by combining all alleles of the same

	locus from this file. You only must create it in this case.
Ambiguity.txt	Data for the ambiguity filter
LargeG.txt	A list of G-groups with their enclosed alleles in 8-digit resolution
MultipleAlleleCodes.txt	A list of multiple allele codes and their translation to alleles in 4-digit resolution
P.txt	A list of P-groups with their enclosed alleles in 8-digit resolution
Smallg.txt	A list of g-groups with their enclosed alleles in 8-digit resolution

In the following we are going to create these data files. As the data-processing is a little bit tedious, we provide you with an automated script. If you want to build the data manually, follow the short instructions in “Hapl-o-Mat/prepareData/README” or the detailed version in “Hapl-o-Mat/prepareData/detailedExplanationManuallyPrepareData.pdf”.

To build data automatically, enter the folder “Hapl-o-Mat/prepareData” und just run

```
python BuildData.py
```

to download all relevant data, process them, and move the created files to folder “Hapl-o-Mat/data”.

If the script terminates due to a connection time out, a proxy or a firewall issue, you can still use the command “python BuildData.py” but you have to download certain files manually. Please see the document “detailedExplanationPrepareData.doc” for a detailed description; refer there to the section “Semi-Automated Way”.

Run Hapl-o-Mat

Now, you are able to run Hapl-o-Mat for the first time. Enter the folder “Hapl-o-Mat” and run

```
./haplomat MAC
```

We explain the output and the meaning of “MAC” in the following sections.

Input Genotype Data

Hapl-o-Mat infers haplotypes from population genotype data. It supports different formats of recording genotype data. To use Hapl-o-Mat, your data should be in one of the following data formats:

Data format	**Description**
MAC	**M**ultiple **A**llele **C**odes: ambiguities are encoded by multiple allele codes (MAC). Except for the first line, input files hold an individual's identification number and genotype per line. Genotypes are saved allele by allele without locus name. Identification number and alleles are TAB-separated. The first line of the file is a header line indicating the name of the first column and the loci of the other columns. Same loci must be placed next to each other. For an example refer to “Hapl-o-Mat/examplePopulations/populationData_a.dat”.
GLSC	**G**enotype **L**ist **S**trings **C**olumn-wise: genotypes with or without ambiguities are saved by genotype list strings (GLS). Input files hold an individual's identification number and genotype per line. Identification number and single-locus genotypes are TAB-separated. For an example refer to “Hapl-o-Mat/examplePopulations/populationData_b.dat”.

GLS	**G**enotype **L**ist **S**trings: genotypes with or without ambiguities are saved by genotype list strings (GLS). Population data is saved in two files. The pull-file contains an individual's identification number and a list of integer numbers, GLS-ids, referring to its single-locus genotype. The GLS-ids are separated from the identification number via ";" and from each other via ":". The second file, the glid-file, contains a translation from GLS-ids starting with "1" to actual single-locus genotypes. GLS-id and genotype are separated via ";". A GLS-id of "0" is interpreted as a missing typing at the corresponding locus and does not require a translation in the glid-file. For an example refer to "Hapl-o-Mat/examplePopulations/populationData_c.pull" and "Hapl-o-Mat/examplePopulations/populationData_c.glid".
READ	**READ**: ambiguities are completely resolved and alleles are already translated to the wanted typing resolutions. The input data is of the format as Hapl-o-Mat records processed genotype data. This allows for easily repeating a run without the need to resolve genotype data again.

Parameters

Each input format for genotype data requires a different set of parameters. The parameters are saved in the corresponding files "parametersMAC", "parametersGLSC", "parametersGLS", and "parametersREAD". All input formats have the following parameters in common:

Parameter	Description
FILENAME_HAPLOTYPES	Name of the file which temporarily saves haplotype names
FILENAME_GENOTYPES	Name of the file which saves resolved genotypes
FILENAME_HAPLOTYPEFREQUENCIES	Name of the file which saves haplotypes and estimated haplotype frequencies
FILENAME_EPSILON_LOGL	Name of the file which saves stopping criterion and log-likelihood per iteration
INITIALIZATION_HAPLOTYPEFREQUENCIES	Initialization routine for haplotype frequencies. It takes the following values: • "equal": All haplotype frequencies are initialized with the same frequency, the inverse number of haplotypes. • "numberOccurrence": Haplotype frequencies are initialized according to the initial number of occurrence of haplotypes. • "random": Haplotype frequencies are initialized randomly. • "perturbation": Haplotype frequencies are initialized as in numberOccurrence and then randomly modified by a small (<10%) positive or negative offset.
EPSILON	Value for the stopping criterion, i.e. the maximal change between consecutive haplotype frequency estimations is smaller than the assigned value
CUT_HAPLOTYPEFREQUENCIES	Estimated haplotype frequencies smaller than this value are removed from the output.
RENORMALIZE_HAPLOTYPEFREQUENCIES	Takes values "true" and "false". If "true",

	normalize estimated haplotype frequencies to sum to one. Within machine precision, this becomes necessary, if estimated haplotypes are removed, e.g. via the option CUT_HAPLOTYPEFREQUENCIES.
SEED	Set the seed of the used pseudo random number generator. If set to "0", the seed is initialized by the system time.

Depending on the input format, additional parameters are:

Parameter	**Input format**	**Description**
FILENAME_INPUT	MAC, GLSC, READ	The file name of the input population data
FILENAME_PULL	GLS	The file name of the pull-file
FILENAME_GLID	GLS	The file name of the glid-file
LOCI_AND_ RESOLUTIONS	MAC, GLS, GLSC	Loci included into analysis and desired typing resolution per locus; The list is separated by "," and contains the locus name followed by ":" and the desired typing resolution, e.g. A:g,B:4d,C:g. Supported typing resolutions and their abbreviations are g-groups (g), P-groups (P), G-groups (G), 2-digit fields (2d), 4-digit fields (4d), 6-digit fields (6d), and 8-digit fields (8d). Alleles are not translated via the option asItIs (applying the ambiguity filter includes an intrinsic translation to G-groups).
LOCIORDER	GLS	Specify the order of loci the individual's GL-ids correspond to. Loci are separated via ",".
RESOLVE_MISSING_ GENOTYPES	GLS	Takes values "true" and "false". If set to true, a missing typing is replaced by a combination of all alleles from AlleleList.txt at the locus. Else, individuals with a missing typing are discarded from analysis.
MINIMAL_FREQUENCY_ GENOTYPES	MAC, GLS, GLSC	Genotypes which split into more genotypes than the inverse of this number are discarded from analysis.
DO_AMBIGUITYFILTER	MAC, GLS, GLSC	Takes values "true" and "false". The option "true" activates the ambiguity filter.
EXPAND_LINES_ AMBIGUITYFILTER	MAC, GLS, GLSC	Takes values "true" and "false". If set to "true", matching lines with additional genotype pairs in the ambiguity filter are considered.
WRITE_GENOTYPES	MAC, GLS, GLSC	Takes values "true" and "false". If "false", no file which saves resolved genotypes (FILENAME_GENOTYPES) will be written out.

Whenever specifying a file name including folders, you have to create the folders before running Hapl-o-Mat.

Quick Guide

The following overview gives you a small reminder on how to use Hapl-o-Mat:

1) Build the executable "haplomat" via make.

2) Update or build the data comprising information on the HLA nomenclature using the python-script “Hapl-o-Mat/prepareData/BuildData.py”.

3) Prepare the genotype population data you want to study. Identify how genotyping ambiguities are recorded (MAC or GLS) and choose the input format accordingly. Adapt the format of your data, e.g. include the header line or make alleles TAB separated.

4) Set the parameters in the parameter file corresponding to your input format.

5) Copy the executable “haplomat”, the folder “data”, the parameter file, and your input population data into one folder. Create any folders you specified in the parameter file. You do not need all the other files to run Hapl-o-Mat. Run Hapl-o-Mat.

Tutorials

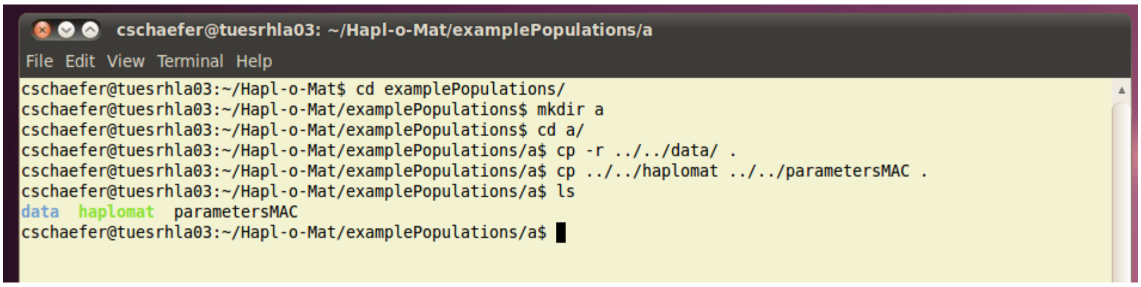
We have everything ready to use Hapl-o-Mat. In the following we estimate haplotype frequencies from some included genotype data recorded in different input formats. For all formats we are going to infer three locus (A, B, DRB1) haplotypes from this data. Alleles at loci A and B shall be translated to typing resolution g and alleles at locus DRB1 to 4-digits typing resolution.

Input Format MAC

You find the relevant population data in “Hapl-o-Mat/examplePopulations/populationData_a.dat”. As ambiguities are recorded as multiple allele codes, the input format is MAC.

Preparations

Enter the folder “Hapl-o-Mat/examplePopulations” by typing “cd examplePopulations”, create a folder named “a” by typing “mkdir a”, and enter the folder by typing “cd a”. Then provide the data required by Hapl-o-Mat by copying the folder “Hapl-o-Mat/data” to “a”, “cp -r ../../data .”. Additionally, copy the executable “haplomat” and the file “parametersMAC” to folder “a”, “cp ../../haplomat ../../parametersMAC .”. Check that everything is there by typing “ls”.



cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help

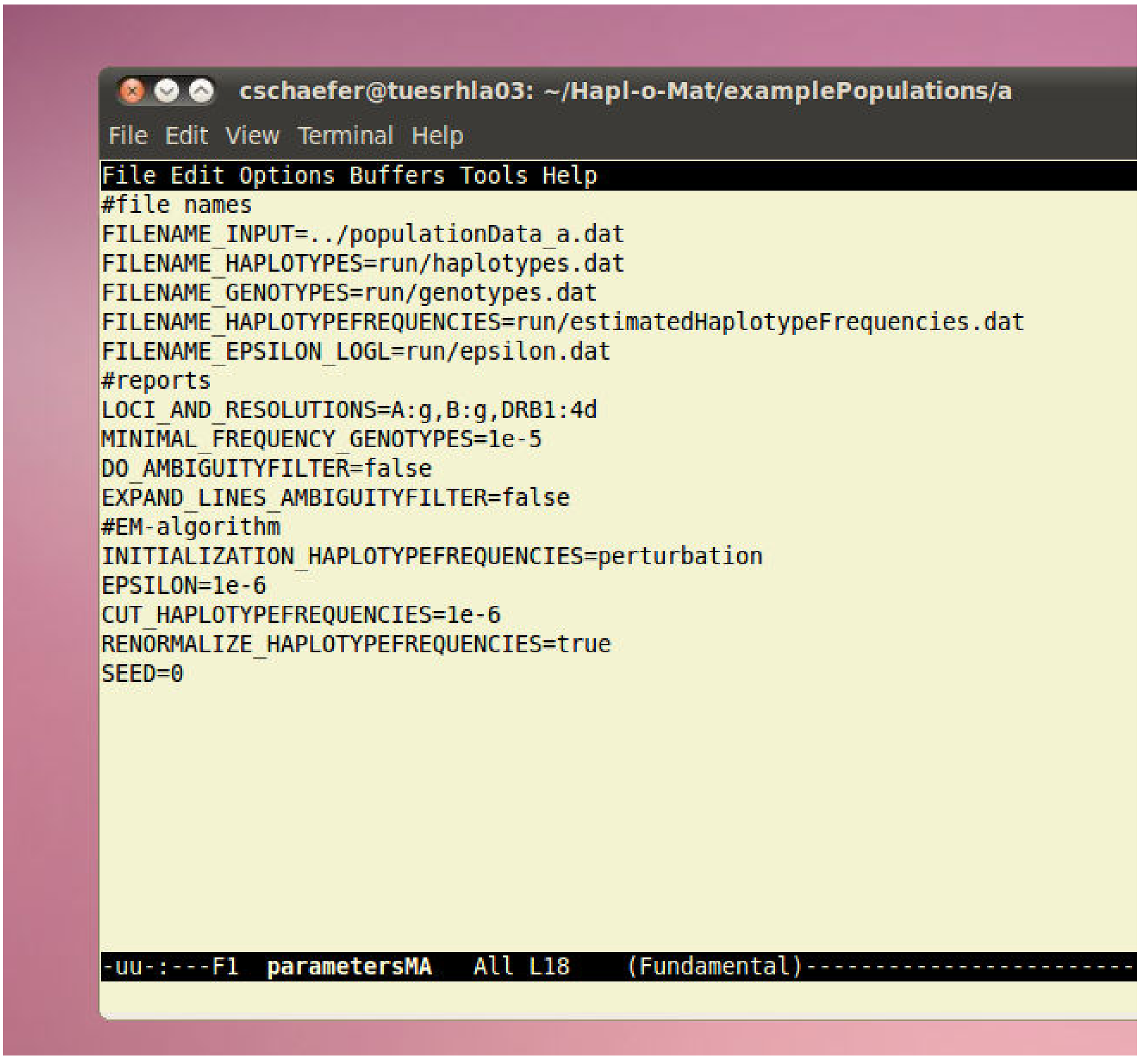
```
cschaefer@tuesrhla03:~/Hapl-o-Mat$ cd examplePopulations/
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ mkdir a
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ cd a/
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ cp -r ../../data/ .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ cp ../../haplomat ../../parametersMAC .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ ls
data  haplomat  parametersMAC
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ 
```

Parameters

According to the format of the input genotype data we use the parameter file “parametersMAC”. Open it in a text editor of your choice and set the following values:

```
#file names
FILENAME_INPUT=../populationData_a.dat
FILENAME_HAPLOTYPES=run/haplotypes.dat
FILENAME_GENOTYPES=run/genotypes.dat
FILENAME_HAPLOTYPEFREQUENCIES=run/hfs.dat
FILENAME_EPSILON_LOGL=run/epsilon.dat
```

```
#reports
LOCI_AND_RESOLUTIONS=A:g,B:g,DRB1:4d
MINIMAL_FREQUENCY_GENOTYPES=1e-5
DO_AMBIGUITYFILTER=false
EXPAND_LINES_AMBIGUITYFILTER=false
WRITE_GENOTYPES=true
#EM-algorithm
INITIALIZATION_HAPLOTYPEFREQUENCIES=perturbation
EPSILON=1e-6
CUT_HAPLOTYPEFREQUENCIES=1e-6
RENORMALIZE_HAPLOTYPEFREQUENCIES=true
SEED=1000
```


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help
File Edit Options Buffers Tools Help

```
#file names
FILENAME_INPUT=../populationData_a.dat
FILENAME_HAPLOTYPES=run/haplotypes.dat
FILENAME_GENOTYPES=run/genotypes.dat
FILENAME_HAPLOTYPEFREQUENCIES=run/estimatedHaplotypeFrequencies.dat
FILENAME_EPSILON_LOGL=run/epsilon.dat
#reports
LOCI_AND_RESOLUTIONS=A:g,B:g,DRB1:4d
MINIMAL_FREQUENCY_GENOTYPES=1e-5
DO_AMBIGUITYFILTER=false
EXPAND_LINES_AMBIGUITYFILTER=false
#EM-algorithm
INITIALIZATION_HAPLOTYPEFREQUENCIES=perturbation
EPSILON=1e-6
CUT_HAPLOTYPEFREQUENCIES=1e-6
RENORMALIZE_HAPLOTYPEFREQUENCIES=true
SEED=0
```

-uu-:---F1 parametersMA   All L18   (Fundamental)----------------------

Do not forget to create the folder “run” by typing “mkdir run”.

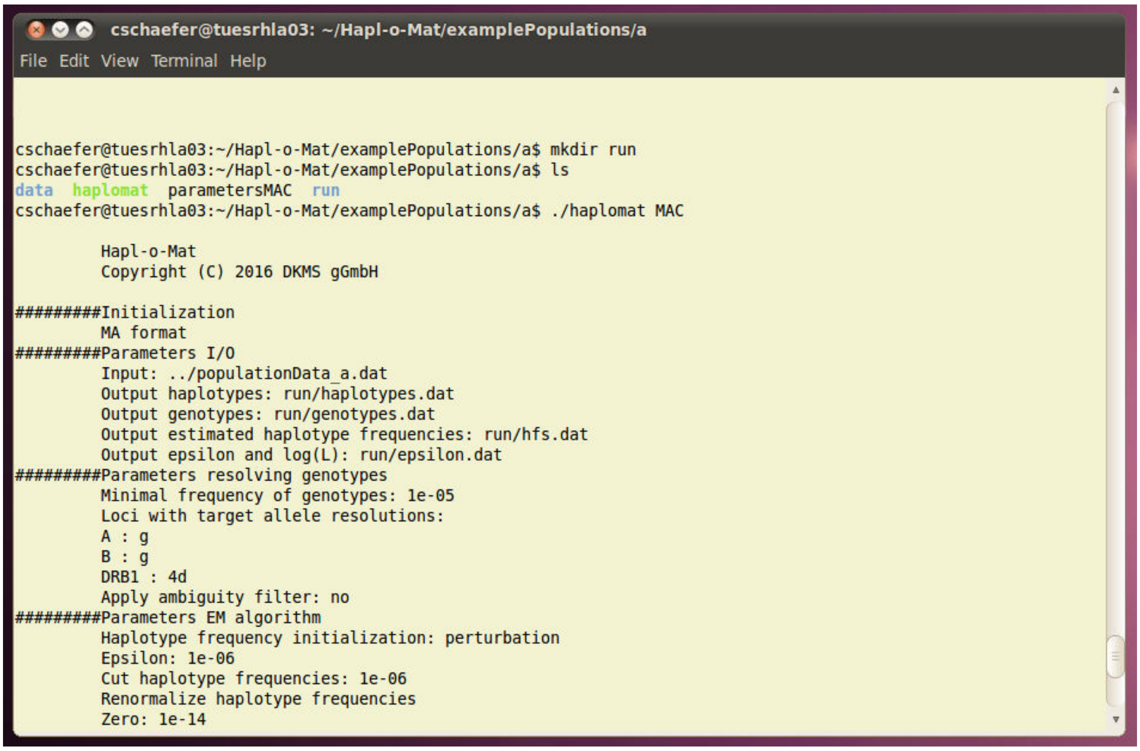
Run Hapl-o-Mat

Compute haplotype frequencies from the genotype input data by running Hapl-o-Mat. If you are not already there, go to folder “a” and run Hapl-o-Mat via

```
./haplomat MAC
```

It produces some output on the screen including your chosen parameters, statistics on the resolved genotype data and the expectation-maximization algorithm, and the run time. You can easily write this output to an extra file by starting Hapl-o-Mat with

```
./haplomat MAC > Log.dat
```

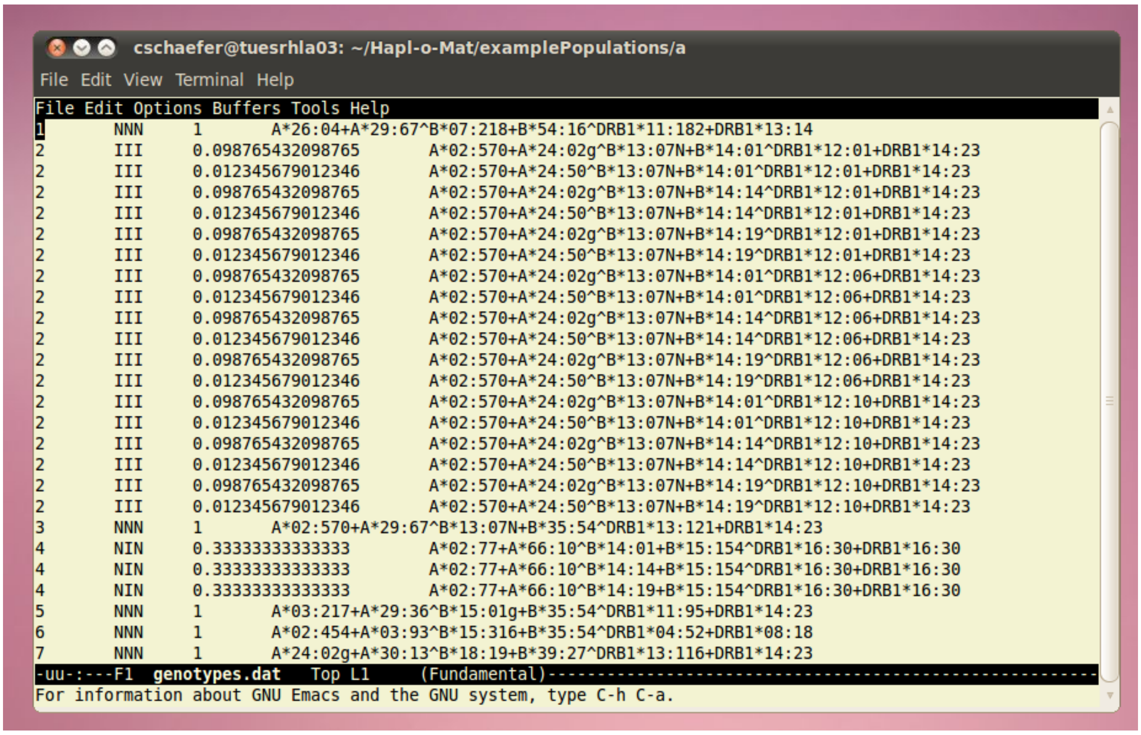


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help

```
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ mkdir run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ ls
data  haplomat  parametersMAC  run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/a$ ./haplomat MAC

         Hapl-o-Mat
         Copyright (C) 2016 DKMS gGmbH

#########Initialization
         MA format
#########Parameters I/O
         Input: ../populationData_a.dat
         Output haplotypes: run/haplotypes.dat
         Output genotypes: run/genotypes.dat
         Output estimated haplotype frequencies: run/hfs.dat
         Output epsilon and log(L): run/epsilon.dat
#########Parameters resolving genotypes
         Minimal frequency of genotypes: 1e-05
         Loci with target allele resolutions:
         A : g
         B : g
         DRB1 : 4d
         Apply ambiguity filter: no
#########Parameters EM algorithm
         Haplotype frequency initialization: perturbation
         Epsilon: 1e-06
         Cut haplotype frequencies: 1e-06
         Renormalize haplotype frequencies
         Zero: 1e-14
```

Results

Now let's examine the results produced by Hapl-o-Mat. We first look into the file with the resolved genotypes, “run/genotypes.dat”.

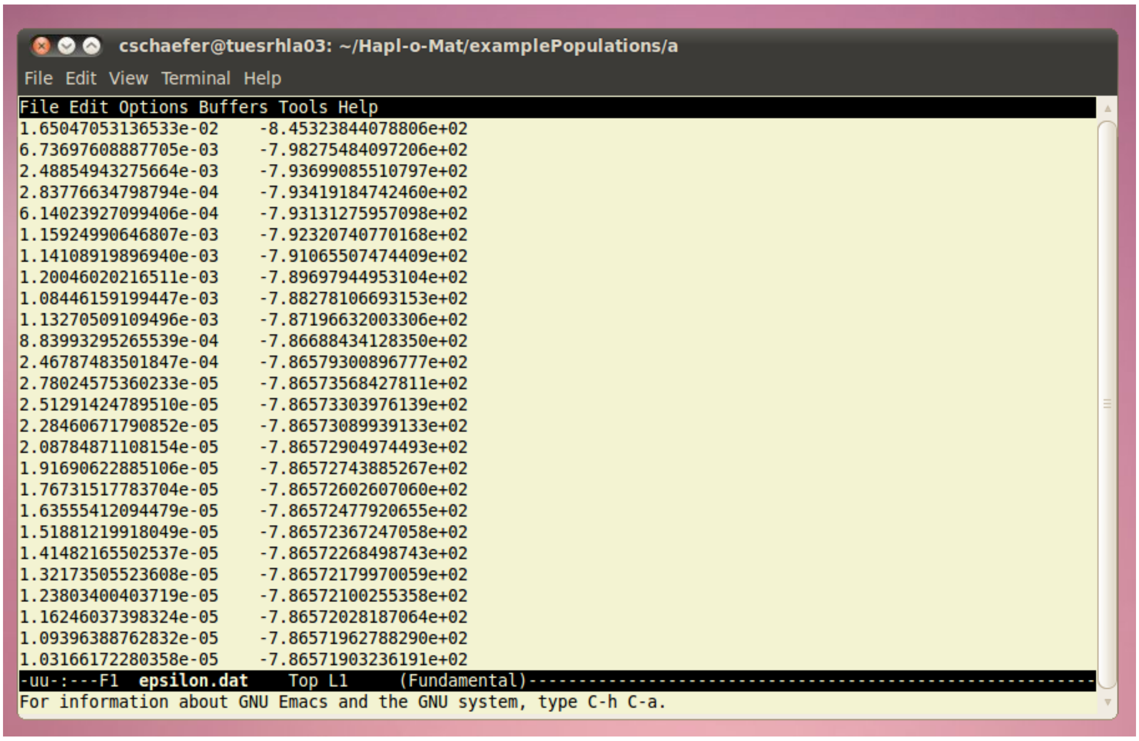


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help
File Edit Options Buffers Tools Help

```
1       NNN     1       A*26:04+A*29:67^B*07:218+B*54:16^DRB1*11:182+DRB1*13:14
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:01^DRB1*12:01+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:01^DRB1*12:01+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:14^DRB1*12:01+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:14^DRB1*12:01+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:19^DRB1*12:01+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:19^DRB1*12:01+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:01^DRB1*12:06+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:01^DRB1*12:06+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:14^DRB1*12:06+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:14^DRB1*12:06+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:19^DRB1*12:06+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:19^DRB1*12:06+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:01^DRB1*12:10+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:01^DRB1*12:10+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:14^DRB1*12:10+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:14^DRB1*12:10+DRB1*14:23
2       III     0.098765432098765       A*02:570+A*24:02g^B*13:07N+B*14:19^DRB1*12:10+DRB1*14:23
2       III     0.012345679012346       A*02:570+A*24:50^B*13:07N+B*14:19^DRB1*12:10+DRB1*14:23
3       NNN     1       A*02:570+A*29:67^B*13:07N+B*35:54^DRB1*13:121+DRB1*14:23
4       NIN     0.33333333333333        A*02:77+A*66:10^B*14:01+B*15:154^DRB1*16:30+DRB1*16:30
4       NIN     0.33333333333333        A*02:77+A*66:10^B*14:14+B*15:154^DRB1*16:30+DRB1*16:30
4       NIN     0.33333333333333        A*02:77+A*66:10^B*14:19+B*15:154^DRB1*16:30+DRB1*16:30
5       NNN     1       A*03:217+A*29:36^B*15:01g+B*35:54^DRB1*11:95+DRB1*14:23
6       NNN     1       A*02:454+A*03:93^B*15:316+B*35:54^DRB1*04:52+DRB1*08:18
7       NNN     1       A*24:02g+A*30:13^B*18:19+B*39:27^DRB1*13:116+DRB1*14:23
-uu-:---F1  genotypes.dat   Top L1     (Fundamental)----------------------------------------------------
For information about GNU Emacs and the GNU system, type C-h C-a.
```

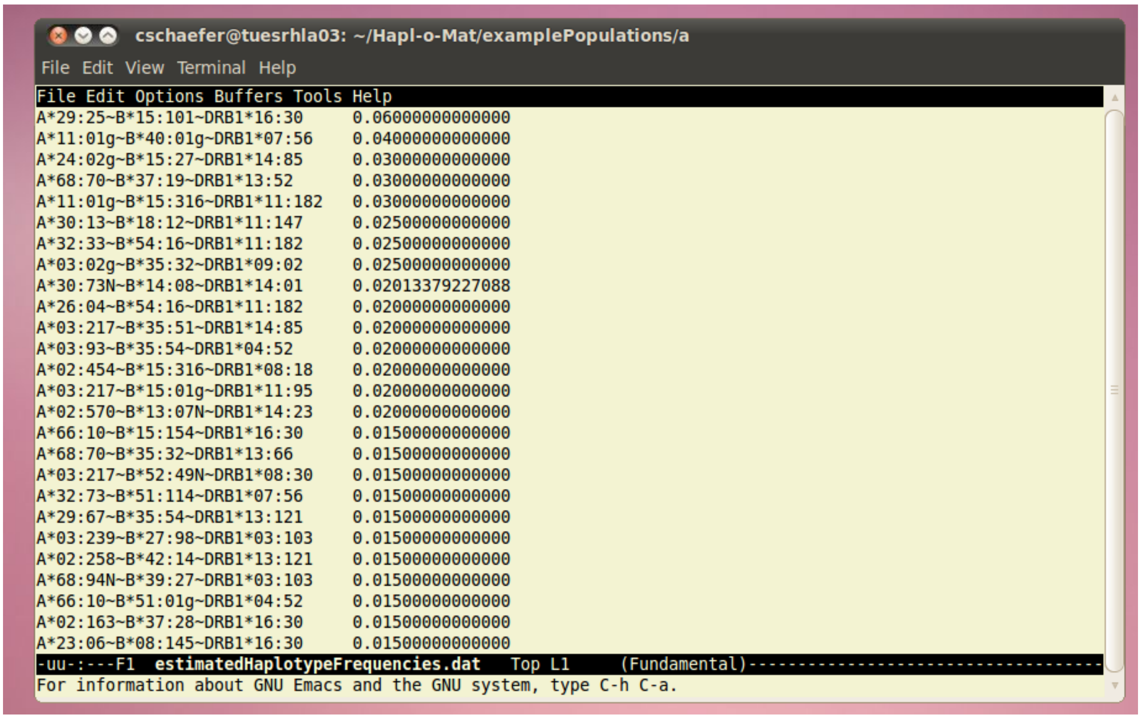
The first column corresponds to the individual's identification number. The second column indicates how ambiguities per single-locus genotypes have been resolved. If no ambiguity occurred or no additional genotypes are formed, the type is N. If an ambiguity occurred and was resolved via building all possible allele combinations, the type is I. Activating the ambiguity filter gives additional types: A, if one matching line in the ambiguity file was found, and M if multiple matching lines were found. The third column gives the frequency of the genotype and the fourth column the genotype itself. The genotype is saved in the GLS format. If an individual's genotype splits into a set of genotypes, each genotype is written to one line starting with the same identification number. The corresponding frequencies become non-integer and sum to one.

The evolution of the stopping criterion and log-likelihood while iterating expectation and maximization steps is written to “run/epsilon.dat”. The first column is the stopping criterion and the second one the not normalized log-likelihood.


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help
File Edit Options Buffers Tools Help

```
1.65047053136533e-02    -8.45323844078806e+02
6.73697608887705e-03    -7.98275484097206e+02
2.48854943275664e-03    -7.93699085510797e+02
2.83776634798794e-04    -7.93419184742460e+02
6.14023927099406e-04    -7.93131275957098e+02
1.15924990646807e-03    -7.92320740770168e+02
1.14108919896940e-03    -7.91065507474409e+02
1.20046020216511e-03    -7.89697944953104e+02
1.08446159199447e-03    -7.88278106693153e+02
1.13270509109496e-03    -7.87196632003306e+02
8.83993295265539e-04    -7.86688434128350e+02
2.46787483501847e-04    -7.86579300896777e+02
2.78024575360233e-05    -7.86573568427811e+02
2.51291424789510e-05    -7.86573303976139e+02
2.28460671790852e-05    -7.86573089939133e+02
2.08784871108154e-05    -7.86572904974493e+02
1.91690622885106e-05    -7.86572743885267e+02
1.76731517783704e-05    -7.86572602607060e+02
1.63555412094479e-05    -7.86572477920655e+02
1.51881219918049e-05    -7.86572367247058e+02
1.41482165502537e-05    -7.86572268498743e+02
1.32173505523608e-05    -7.86572179970059e+02
1.23803400403719e-05    -7.86572100255358e+02
1.16246037398324e-05    -7.86572028187064e+02
1.09396388762832e-05    -7.86571962788290e+02
1.03166172280358e-05    -7.86571903236191e+02
-uu-:---F1  epsilon.dat    Top L1     (Fundamental)------------------------------------------------------
For information about GNU Emacs and the GNU system, type C-h C-a.
```

The inferred haplotypes including estimated frequencies are listed in “run/hfs.dat”. Haplotypes are saved in the GLS format. This is the file you were aiming at. It is sorted by descending frequency and already normalized if you activated the corresponding option (we did in this tutorial).

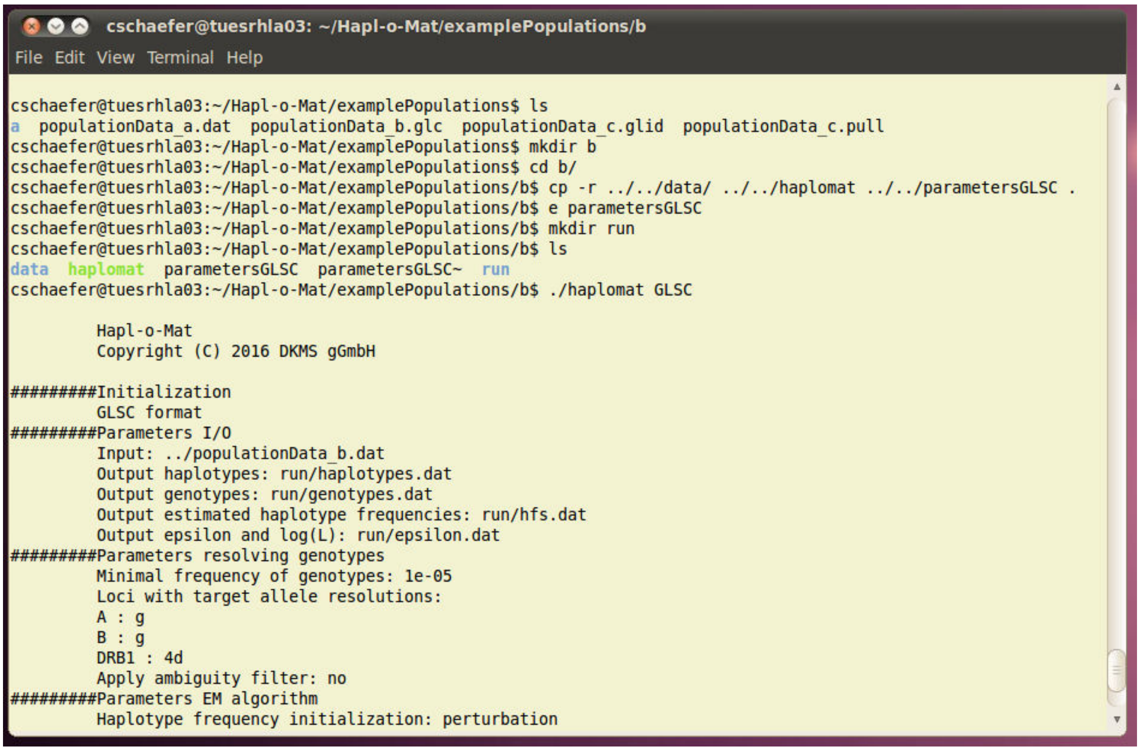

cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/a
File Edit View Terminal Help

```
File Edit Options Buffers Tools Help
A*29:25~B*15:101~DRB1*16:30     0.06000000000000
A*11:01g~B*40:01g~DRB1*07:56    0.04000000000000
A*24:02g~B*15:27~DRB1*14:85     0.03000000000000
A*68:70~B*37:19~DRB1*13:52      0.03000000000000
A*11:01g~B*15:316~DRB1*11:182   0.03000000000000
A*30:13~B*18:12~DRB1*11:147     0.02500000000000
A*32:33~B*54:16~DRB1*11:182     0.02500000000000
A*03:02g~B*35:32~DRB1*09:02     0.02500000000000
A*30:73N~B*14:08~DRB1*14:01     0.02013379227088
A*26:04~B*54:16~DRB1*11:182     0.02000000000000
A*03:217~B*35:51~DRB1*14:85     0.02000000000000
A*03:93~B*35:54~DRB1*04:52      0.02000000000000
A*02:454~B*15:316~DRB1*08:18    0.02000000000000
A*03:217~B*15:01g~DRB1*11:95    0.02000000000000
A*02:570~B*13:07N~DRB1*14:23    0.02000000000000
A*66:10~B*15:154~DRB1*16:30     0.01500000000000
A*68:70~B*35:32~DRB1*13:66      0.01500000000000
A*03:217~B*52:49N~DRB1*08:30    0.01500000000000
A*32:73~B*51:114~DRB1*07:56     0.01500000000000
A*29:67~B*35:54~DRB1*13:121     0.01500000000000
A*03:239~B*27:98~DRB1*03:103    0.01500000000000
A*02:258~B*42:14~DRB1*13:121    0.01500000000000
A*68:94N~B*39:27~DRB1*03:103    0.01500000000000
A*66:10~B*51:01g~DRB1*04:52     0.01500000000000
A*02:163~B*37:28~DRB1*16:30     0.01500000000000
A*23:06~B*08:145~DRB1*16:30     0.01500000000000
-uu-:---F1  estimatedHaplotypeFrequencies.dat   Top L1     (Fundamental)--------------------------------------
For information about GNU Emacs and the GNU system, type C-h C-a.
```

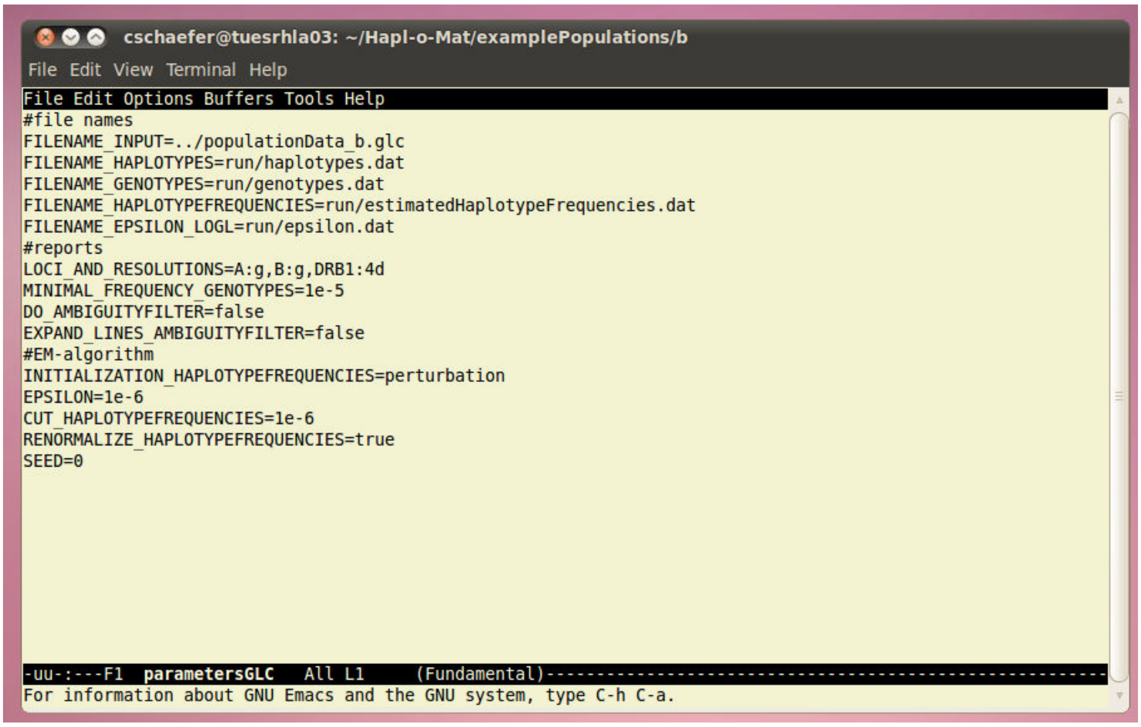
Input Format GLSC

This time ambiguities in the genotypic population data are recorded via genotype list strings. The file with the population data is called “populationData_b.glc”. As all the information is in one file, the input format is GLSC. Running Hapl-o-Mat works exactly as in the first tutorial. You just use the parameter file “parametersGLSC” instead of “parametersMAC” and make the appropriate changes. Run Hapl-o-Mat in folder “b” with

```
./haplomat GLSC
```


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/b
File Edit View Terminal Help

```
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ ls
a  populationData_a.dat  populationData_b.glc  populationData_c.glid  populationData_c.pull
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ mkdir b
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ cd b/
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/b$ cp -r ../../data/ ../../haplomat ../../parametersGLSC .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/b$ e parametersGLSC
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/b$ mkdir run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/b$ ls
data  haplomat  parametersGLSC  parametersGLSC~  run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/b$ ./haplomat GLSC

         Hapl-o-Mat
         Copyright (C) 2016 DKMS gGmbH

#########Initialization
         GLSC format
#########Parameters I/O
         Input: ../populationData_b.dat
         Output haplotypes: run/haplotypes.dat
         Output genotypes: run/genotypes.dat
         Output estimated haplotype frequencies: run/hfs.dat
         Output epsilon and log(L): run/epsilon.dat
#########Parameters resolving genotypes
         Minimal frequency of genotypes: 1e-05
         Loci with target allele resolutions:
         A : g
         B : g
         DRB1 : 4d
         Apply ambiguity filter: no
#########Parameters EM algorithm
         Haplotype frequency initialization: perturbation
```



cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/b
File Edit View Terminal Help
File Edit Options Buffers Tools Help

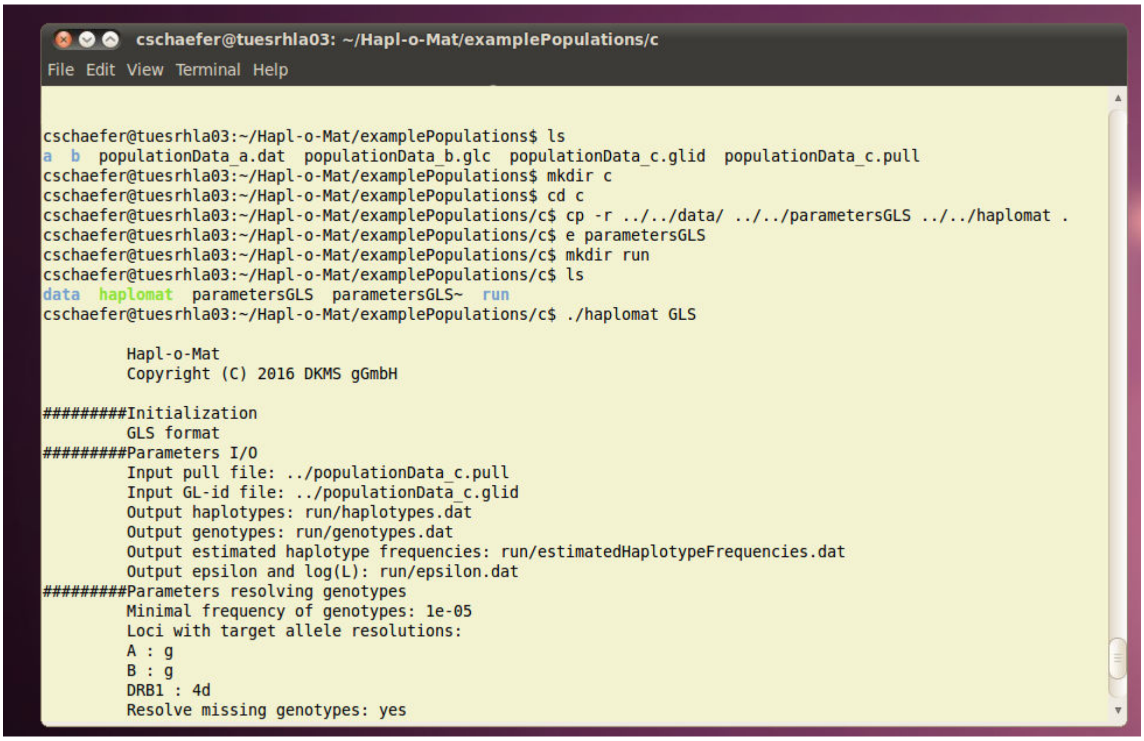
```
#file names
FILENAME_INPUT=../populationData_b.glc
FILENAME_HAPLOTYPES=run/haplotypes.dat
FILENAME_GENOTYPES=run/genotypes.dat
FILENAME_HAPLOTYPEFREQUENCIES=run/estimatedHaplotypeFrequencies.dat
FILENAME_EPSILON_LOGL=run/epsilon.dat
#reports
LOCI_AND_RESOLUTIONS=A:g,B:g,DRB1:4d
MINIMAL_FREQUENCY_GENOTYPES=1e-5
DO_AMBIGUITYFILTER=false
EXPAND_LINES_AMBIGUITYFILTER=false
#EM-algorithm
INITIALIZATION_HAPLOTYPEFREQUENCIES=perturbation
EPSILON=1e-6
CUT_HAPLOTYPEFREQUENCIES=1e-6
RENORMALIZE_HAPLOTYPEFREQUENCIES=true
SEED=0
```

-uu-:---F1 parametersGLC   All L1   (Fundamental)----
For information about GNU Emacs and the GNU system, type C-h C-a.

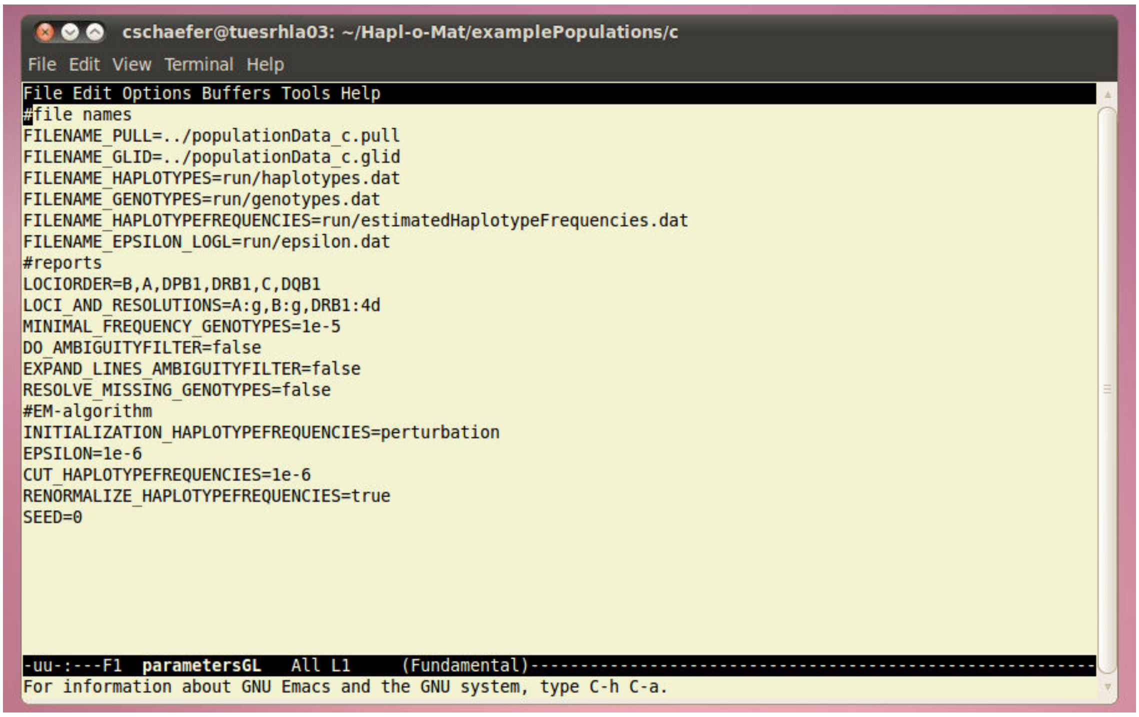
Input Format GLS

Again, ambiguities in the genotypic population data are recorded via genotype list strings. Since the data is saved in two different files, the input format is GLS. Follow the steps from tutorial a), but use the parameter file “parametersGLS” and name the created folder “c”. The file names for the population data are “populationData_c.pull” and “populationData_c.glid”. I guess, you can figure out the matching positions in the parameter file. GLS input format requires the order of loci as input, which can be obtained by looking in the pull- and glid-file. The first individual from “populationData_c.pull” has GLS-ids 1, 2, 3, 4, 5, and 6. We know from “populationData_c.pull” that they correspond to loci B, A, DPB1, DRB1, C, and DQB1, respectively. Because of that we set “LOCIORDER=B,A,DPB1,DRB1,C,DQB1”. Finally, set the additional option RESOLVE_MISSING_GENOTYPE to “false”. Run Hapl-o-Mat in folder “c” with

```
./haplomat GLS
```


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/c
File Edit View Terminal Help

```
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ ls
a  b  populationData_a.dat  populationData_b.glc  populationData_c.glid  populationData_c.pull
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ mkdir c
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ cd c
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/c$ cp -r ../../data/ ../../parametersGLS ../../haplomat .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/c$ e parametersGLS
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/c$ mkdir run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/c$ ls
data  haplomat  parametersGLS  parametersGLS~  run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/c$ ./haplomat GLS

         Hapl-o-Mat
         Copyright (C) 2016 DKMS gGmbH

#########Initialization
         GLS format
#########Parameters I/O
         Input pull file: ../populationData_c.pull
         Input GL-id file: ../populationData_c.glid
         Output haplotypes: run/haplotypes.dat
         Output genotypes: run/genotypes.dat
         Output estimated haplotype frequencies: run/estimatedHaplotypeFrequencies.dat
         Output epsilon and log(L): run/epsilon.dat
#########Parameters resolving genotypes
         Minimal frequency of genotypes: 1e-05
         Loci with target allele resolutions:
         A : g
         B : g
         DRB1 : 4d
         Resolve missing genotypes: yes
```

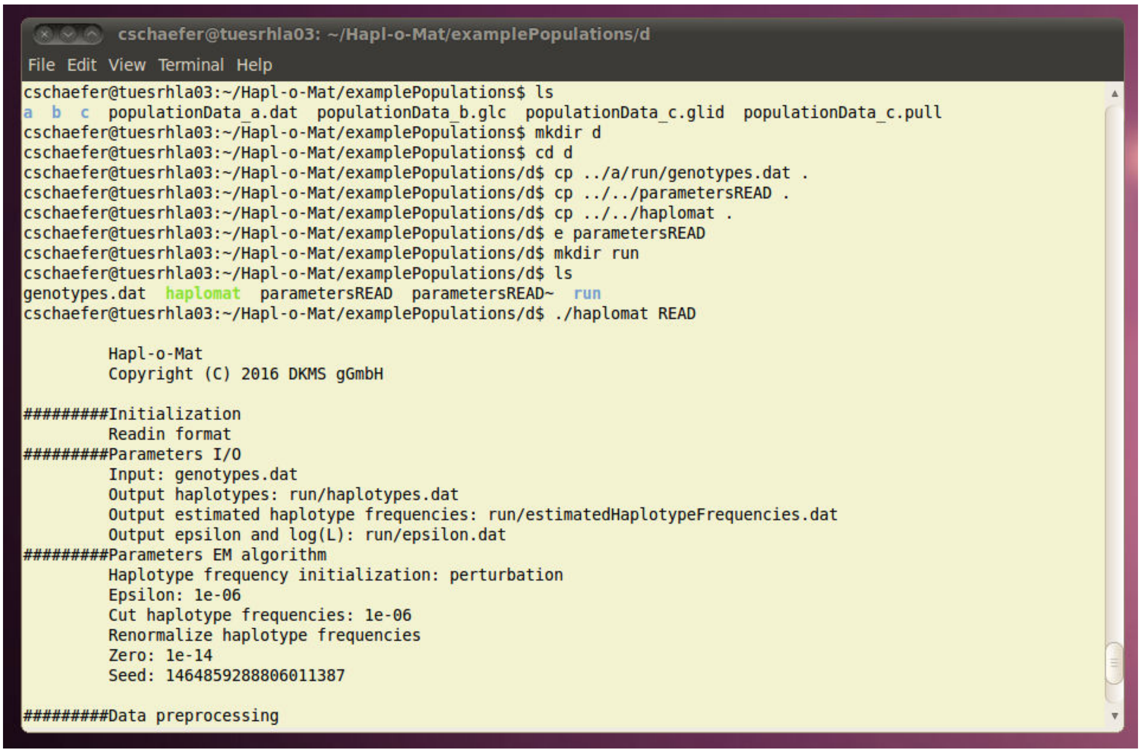

cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/c
File Edit View Terminal Help
File Edit Options Buffers Tools Help

```
#file names
FILENAME_PULL=../populationData_c.pull
FILENAME_GLID=../populationData_c.glid
FILENAME_HAPLOTYPES=run/haplotypes.dat
FILENAME_GENOTYPES=run/genotypes.dat
FILENAME_HAPLOTYPEFREQUENCIES=run/estimatedHaplotypeFrequencies.dat
FILENAME_EPSILON_LOGL=run/epsilon.dat
#reports
LOCIORDER=B,A,DPB1,DRB1,C,DQB1
LOCI_AND_RESOLUTIONS=A:g,B:g,DRB1:4d
MINIMAL_FREQUENCY_GENOTYPES=1e-5
DO_AMBIGUITYFILTER=false
EXPAND_LINES_AMBIGUITYFILTER=false
RESOLVE_MISSING_GENOTYPES=false
#EM-algorithm
INITIALIZATION_HAPLOTYPEFREQUENCIES=perturbation
EPSILON=1e-6
CUT_HAPLOTYPEFREQUENCIES=1e-6
RENORMALIZE_HAPLOTYPEFREQUENCIES=true
SEED=0




-uu-:---F1  parametersGL    All L1      (Fundamental)-----------------------------------------------------------
For information about GNU Emacs and the GNU system, type C-h C-a.
```

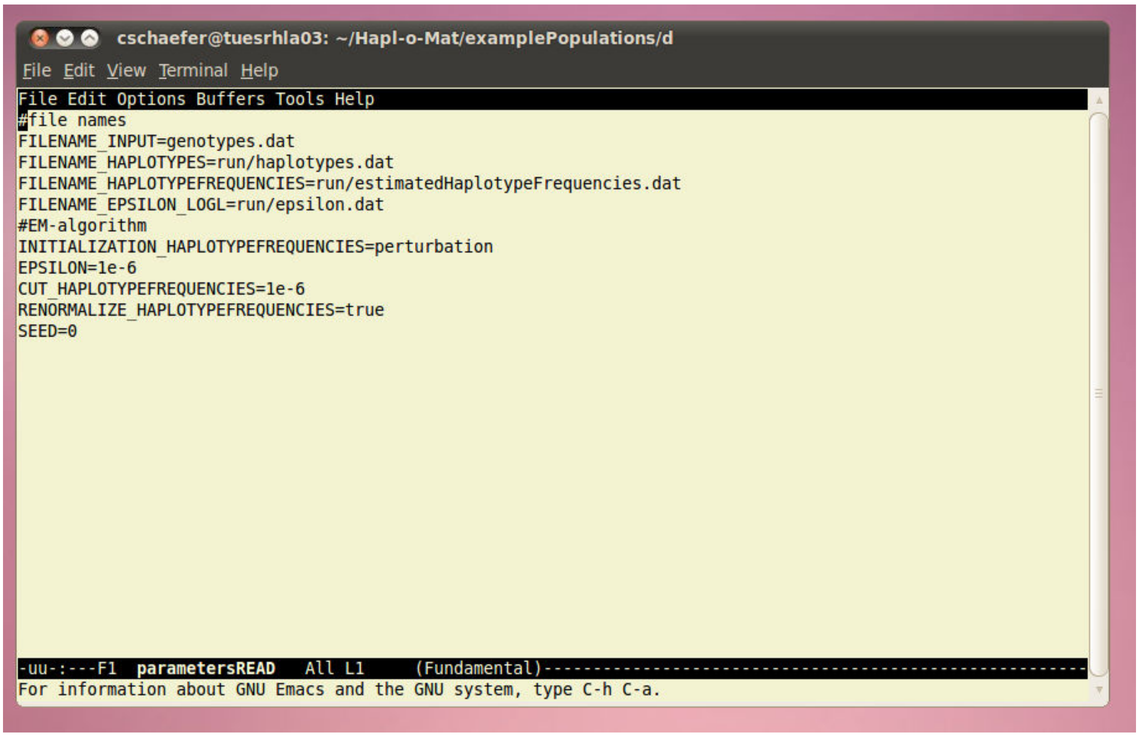
Input Format READ

Finally, we test the input format READ. Create a folder “d” and copy one file with resolved genotypes, say “a/run/genotypes.dat” there. Add “haplomat” and “parametersREAD” to this folder. Using the input format READ, Hapl-o-Mat does not resolve ambiguities or translates alleles, but reads in already resolved genotype data. Because of that the folder “data” is not required and the parameter file “parameterREAD” misses some options. Just adjust the file names and set parameters for the haplotype frequency estimation. Run Hapl-o-Mat in folder “d” via

./haplomat READ


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/d
File Edit View Terminal Help

```
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ ls
a  b  c  populationData_a.dat  populationData_b.glc  populationData_c.glid  populationData_c.pull
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ mkdir d
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations$ cd d
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ cp ../a/run/genotypes.dat .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ cp ../../parametersREAD .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ cp ../../haplomat .
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ e parametersREAD
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ mkdir run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ ls
genotypes.dat  haplomat  parametersREAD  parametersREAD~  run
cschaefer@tuesrhla03:~/Hapl-o-Mat/examplePopulations/d$ ./haplomat READ

         Hapl-o-Mat
         Copyright (C) 2016 DKMS gGmbH

#########Initialization
         Readin format
#########Parameters I/O
         Input: genotypes.dat
         Output haplotypes: run/haplotypes.dat
         Output estimated haplotype frequencies: run/estimatedHaplotypeFrequencies.dat
         Output epsilon and log(L): run/epsilon.dat
#########Parameters EM algorithm
         Haplotype frequency initialization: perturbation
         Epsilon: 1e-06
         Cut haplotype frequencies: 1e-06
         Renormalize haplotype frequencies
         Zero: 1e-14
         Seed: 1464859288806011387

#########Data preprocessing
```


cschaefer@tuesrhla03: ~/Hapl-o-Mat/examplePopulations/d
File Edit View Terminal Help
File Edit Options Buffers Tools Help

```
#file names
FILENAME_INPUT=genotypes.dat
FILENAME_HAPLOTYPES=run/haplotypes.dat
FILENAME_HAPLOTYPEFREQUENCIES=run/estimatedHaplotypeFrequencies.dat
FILENAME_EPSILON_LOGL=run/epsilon.dat
#EM-algorithm
INITIALIZATION_HAPLOTYPEFREQUENCIES=perturbation
EPSILON=1e-6
CUT_HAPLOTYPEFREQUENCIES=1e-6
RENORMALIZE_HAPLOTYPEFREQUENCIES=true
SEED=0
```

```
-uu-:---F1  parametersREAD    All L1     (Fundamental)------------------------------------------------
For information about GNU Emacs and the GNU system, type C-h C-a.
```