

PyPop User Guide

User Guide for Python for Population Genomics

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Richard M. Single, and Owen D. Solberg

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Preface

Introduction

PyPop (*Python for Population Genomics*) is an environment developed at UC Berkeley for doing large-scale population genetic analyses including:

- conformity to Hardy-Weinberg expectations
- tests for balancing or directional selection
- estimates of haplotype frequencies and measures and tests of significance for linkage disequilibrium (LD).

PyPop is an object-oriented framework implemented in the programming language **Python**. Python is a flexible scripting language which allows rapid prototyping of code and has powerful features for interfacing with other languages, such as C (in which we have already implemented many routines and which is particularly suited to computationally intensive tasks).

The output of the analyses are stored in the XML format (XML is the eXtensible Markup Language devised by the World Wide Web Consortium, and is a platform-independent, open standard for storing data). These output files can then be transformed using standard tools into many other data formats suitable for machine input (such as PHYLIP or input for spreadsheet programs such as Excel or statistical packages, such as R), plain text, or HTML for human-readable format. Storing the output in XML allows the final viewable output format to be redesigned at will, without requiring the (often time-consuming) re-running of the analyses themselves.

PyPop was originally developed for the analysis of data for the 13th **International Histocompatibility Workshop and Conference** held in Seattle, Washington in 2002 ([Meyer:etal:2007], [Single:etal:2007a], [Single:etal:2007a]). For more details on the design and technical details of PyPop, please consult [Lancaster:etal:2003], [Lancaster:etal:2007a] and [Lancaster:etal:2007b].

How to use this guide

This guide to PyPop contains three parts:

- Chapter 1 describes how to download and install a standalone binary version of the application. Programmers and other interested parties can download source and can build the application themselves.
- Chapter 2 describes how to run PyPop.
- Chapter 3 details the population genetic methods and statistics that PyPop computes.

Except where noted in the source, PyPop is distributed under the terms of the **GNU General Public License** (see Section A.1). The list of authors and contributors follows in the section called “**Authors of software components**”.

Recent changes to PyPop

PyPop NEWS --- history of user-visible changes to PyPop. -*- outline -*-
Copyright (C) 2003, 2004, 2005, 2006, 2007 Regents of the University of California

* Release Notes for PyPop 0.7.0

** New features

*** 'makeNewPopFile' option has been changed. This option allows user to generate intermediate output of filtered files. Now option should be of the format: 'type:order' where 'type' is one of 'separate-loci' or 'all-loci' so that the user can specify whether a separate file should be generated for each locus ('separate-loci') or a single file with all loci ('all-loci'). 'order' should be the order in the filtering chain where the matrix is generated, there is no default, for example, for generating files after the first filter operation use '1'.

*** New command-line option '--generate-tsv', will generate the '.dat' tab-separated values (TSV) files on the the generated -out.xml files (aka "popmeta") directly from pypop without needing to run additional script. Now output from pypop can be directly read into spreadsheet.

*** New feature: add individual genotype tests to Hardy-Weinberg module (gthwe), now computes statistics based on individual genotypes in the HWP table. The [HardyWeinbergGuoThompson] or [HardyWeinbergGuoThompsonMonteCarlo] options must be enabled in the configuration ".ini" file in order for these tests to be carried out.

*** Major improvements to custom and random binning filters (Owen Solberg).

*** New feature: generate homozygosity values using the Ewens-Watterson test for all pairwise loci, or all sites within a gene for sequence data ([homozygosityEWSlatkinExactPairwise] in .ini file). Note: this really only works for sequence data where the phase for sites within an allele are known.

*** Haplotype and LD estimation module 'emhaplofreq' improvements

**** improved memory usage and speed for emhaplofreq module.

**** maximum sample size for emhaplofreq module increased from 1023 to 5000 individuals.

**** maximum length of allele names increased to 20

** Bug fixes

*** Support Python 2.4 on GCC 4.0 platforms.

*** Add missing initialisation for non-sequence data when processing haplotypes. Thanks to Jill Hollenbach for the report.

*** Fix memory leak in xslt translation.

*** Various fixes relating to parsing XML output.

*** Fixed an incorrect parameter name.

*** Handle some missing sections in .ini better. Thanks to Owen Solberg for report.

*** Various build and installation fixes (SWIG, compilation flags)

*** Make name of source package be lowercase "pypop".

*** Change data directory: /usr/share/pypop/ to /usr/share/PyPop/

*** Print out warning when maximum length of allele exceeded, rather than crashing. Thanks to Steve Mack for report.

** Other issues

*** Sequence filter

**** In the Sequence filter, add special case for Anthony Nolan HLA data: mark null alleles ending in "N" (e.g. HLA-B*5127N) as "missing data" (****).

**** Also in Sequence, keep track of unsequenced sites separately (via unsequencedSites variable) from "untyped" (aka "missing data"). Treat unsequencedSite as a unique allele to make sure that those sites don't get treated as having a consensus sequence if only one of the sequences in the the set of matches is typed.

**** If no matching sequence is found in the MSF files, then return a

- sequence of * symbols (ie, will be treated as truly missing data, not untyped alleles.
- **** Add another special case for HLA data: test for 7 digits in allele names (e.g. if 2402101 is not found insert a zero after the first 4 digits to form 24020101, and check for that). This is to cope with yet-another HLA nomenclature change.
 - *** Change semantics of batchsize, make "0" (default) process files separately if only R dat files is enabled. If batchsize not set explicitly (and therefore 0) set batchsize to '1' if PHYLIP mode is enabled.
- * Release Notes for PyPop 0.6.0
- ** New features
- *** Allow for odd allele counts when processing an allele count data (i.e "semi"-typing). When PyPop is dealing with data that is originally genotyped, the current default is preserved i.e. we dis-allow individuals that are typed at only allele, and set allowSemiTyped to false.
 - *** New command-line option '-f' (long version '--filelist') which accepts a file containing a list of files (one per line) to process (note that this is mutually exclusive with supplying INPUTFILES, and will abort with an error message if you supply both simultaneously).
 - *** In batch version, handle multiple INPUTFILES supplied as command-line arguments and support Unix shell-globbing syntax (e.g. 'pypop.py -c config.ini *.pop'). (NOTE: This is supported *only* in batch version, not in the interactive version, which expects one and only one file supplied by user.
 - *** Allele count files can now be filtered through the filter apparatus (particularly the Sequence and AnthonyNolan) in the same way as genotype files transparently. [This has been enabled via a code refactor that treats allele count files as pseudo-genotype files for the purpose of filtering]. This change also resulted in the removal of the obsolete lookup-table-based homozygosity test.
 - *** Add '--disable-ihwg' option to popmeta script to disable hardcoded generation of the IHWG header output, and use the output as defined in the header in the original .pop input text file. This is disabled by default to preserve backwards compatibility.
 - *** Add '--batchsize' ('-b' short version) option for popmeta. Does the processing in "batches". If set and greater than one, list of XML files is split into batchsize group. For example, if there are 20 XML files and option is via using ("-b 2" or "--batchsize=2") then the files will be processed in two batches, each consisting of 10 files. If the number does not divide evenly, the last list will contain all the "left-over" files. This option is particularly useful with large XML files that may not fit in memory all at once. Note this option is mutually exclusive with the '--enable-PHYLIP' option because the PHYLIP output needs to calculate allele frequencies across all populations before generating files.
 - *** New .ini file option: [HardyWeinbergGuoThompsonMonteCarlo]: add a plain Monte-Carlo (randomization, without the Markov chain test) test for the HardyWeinberg "exact test". Add code for Guo & Thompson test to distribution (now under GNU GPL).
- ** Bug fixes
- *** HardyWeinbergGuoThompson overall p-value test was numerically unstable because it attempted to check for equality in greater than or equal to constructs (" \leq ") which is not reliable in C. Replaced this with a GNU Scientific Library (GSL) function gsl_fcmp() which compares floats to within an EPSILON (defaults to $1e-6$).

- *** Allow HardyWeinbergGuoThompson test to be run if at least two alleles present (test was originally failing with a 'too-few-alleles' message if there were not at least 3 alleles). Thanks to Kristie Mather for the report.
 - *** Checks to see if a locus is monomorphic, if it is, it generates an allele summary report, but skips the rest of the single locus analyses which do not make sense for monomorphic locus. Thanks to Steve Mack and Owen Solberg for the bug report(s).
 - *** Now builds against recent versions of SWIG (no longer stuck at version 1.3.9), should be compatible with versions of SWIG > 1.3.10. (Tested against SWIG 1.3.21).
 - *** Homozygosity module: Prevent math errors by in Slatkin's exact test by forcing the homozygosity to be positive (only a problem for rare cases, when the result is so close to zero that the floating point algorithms cause a negative result.)
- * Release Notes for PyPop 0.5.2 (public beta) 2004-03-09
- ** Bug fixes
 - *** Add missing RandomBinning.py file to source distribution
Thanks to Hazael Maldonado Torres for the bug report.
 - *** Fixed line endings for .bat scripts for Win32 so they work under Windows 98 thanks to Wendy Hartogensis for the bug report.
- * Release Notes for PyPop 0.5.1 (public beta) 2004-02-26
- ** Changes
 - *** New parameter 'numInitCond', number of initial conditions by the haplotype estimation and LD algorithm used before performing permutations. Defaults to 50.
 - *** Remove some LOG messages/diagnostics that were erroneously implying an error to the user (if nothing is wrong, don't say anything). Add some more useful messages for what is being done in haplo/LD estimation step.
 - *** Add popmeta.py to the distribution: this is undocumented and unsupported as yet, it is at alpha stage only, use at your own risk!
- ** Bug fixes
- *** Remember to output plaintext version of LD for specified loci.
- * Release Notes for PyPop 0.5 (public beta) 2003-12-31
- ** Changes
 - *** All Linux wrapper scripts no longer have .sh file suffixes for consistency with DOS (all DOS bat files can be executed without specifying the .bat extension).
- ** Bug fixes
- *** Add wrapper scripts for interactive and batch mode for both DOS and Linux so that correct shared libraries are called.
 - *** Pause and wait for user to press a key at end of DOS .bat file so that output can be viewed before window close.
 - *** Set PYTHONHOME in wrapper scripts to prevent messages about missing <prefix> being displayed.
- * Release Notes for PyPop 0.4.3beta
- ** Bug fixes
 - *** Fixed bug in processing of 'popname' field.
Thanks to Richard Single for the report.

Authors of software components

PYPOP

Alex Lancaster alexl@users.sourceforge.net Co-designer of Python framework: author of main engine, text file parser, Python extension module framework using SWIG, XML output and XSLT post-processing framework (to generate plain text and HTML output).

Mark P. Nelson Co-designer of Python framework: implemented and maintained Python modules, particularly the module for Hardy-Weinberg analysis. Updated and maintained XSLT code.

Richard M. Single Richard.Single@uvm.edu Author of haplotype frequency and linkage disequilibrium analysis module "emhaplofreq", author of R programs to do further statistical analysis and generate graphs and figures in PostScript.

Diogo Meyer diogo@ib.usp.br Contributed further statistical analysis code for the R programs.

Owen Solberg solberg@berkeley.edu Implemented filter modules, including conversion to allele name information to sequence data.

Yingsu Tsai Implemented prototype of the allele names to sequence conversion filter module.

Glenys Thomson glenys@berkeley.edu Principal investigator and project lead.

THIRD-PARTY MODULES

gthwe The Hardy-Weinberg "exact test" implementation is a modified version of Guo & Thompson's [Guo:Thompson:1992] code. Dr. Sun-Wei Guo has kindly allowed us to release the code under the [GNU General Public License](#). Original code available at <http://www.stat.washington.edu/~thompson/Genepi/Hardy.shtml>.

slatkin-exact/monte-carlo.c Montgomery Slatkin's implementation of a Monte Carlo approximation of the Ewens-Watterson exact test of neutrality ([Slatkin:1994], [Slatkin:1996]). Original code can be found at: http://ib.berkeley.edu/labs/slatkin/monty/Ewens_exact.program.

pval The code in the 'pval' directory (with the exception of 'pval.c' the SWIG wrapper, 'pval_wrap.i' and the Makefile) is part of the R project's 'nmath' numerical library <http://www.r-project.org/> and is also licensed under the GNU General Public License (GPL). Minor modifications have been made to allow the module to build correctly.

Acknowledgements

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Chapter 1

Installing PyPop

Last updated: 2008/08/17

1.1 Installing standalone binary

Standalone binary versions are provided for PyPop that make minimal assumptions about external software installed on your system, and for the majority of users, will be the simplest way to install PyPop. We have only tested them on a subset of the possible operating systems and have noted them in the relevant section below.

1.1.1 Installing on GNU/Linux

System requirements Your GNU/Linux system should contain at least 2.6 version of `glibc` (the GNU C library).

Systems tested Fedora 8 (may work on other distributions but untested at present, earlier versions were tested on Red Hat 9 Fedora Core 2, 3, 7, Slackware 9.1 but may now have out of date versions of `glibc`)

1. Download the latest stable release and save it somewhere in your home directory:
 - <http://www.pypop.org/PyPopLinux-0.7.0.tar.gz>
2. From the command-line terminal untar and uncompress the package (typically using the GNU `tar` program):

```
$ tar xzf PyPopLinux-0.7.0.tar.gz
```

At this point PyPop should be successfully installed. To test your installation, run the program and use the sample test files with the following steps:

1. Change directory into the extracted directory

```
$ cd PyPopLinux-0.7.0
```

2. Now you can run the interactive version of the program, by typing `./pypop`, at the command line.

A short message describing PyPop will be displayed, followed by prompts to supply the name of the configuration file and then the population file. Select the file, `sample.ini` and `sample.pop`, respectively (noted in the sample screen output below, in **bold**).

```
PyPop: Python for Population Genomics (0.4.3)
Copyright (C) 2003 Regents of the University of California
This is free software. There is NO warranty; not even for
MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.
```

```
You may redistribute copies of PyPop under the terms of the
GNU General Public License. For more information about these
matters, see the file named COPYING.
```

```
To accept the default in brackets for each filename, simply press
return for each prompt.
```

```
Please enter config filename [config.ini]: sample.ini
Please enter population filename [no default]: sample.pop
PyPop is processing sample.pop
```

```
(Note:some messages with the prefix "LOG:" may appear here.They are
informational only and do not indicate improper operationof the program)
```

```
PyPop run complete!
XML output can be found in: sample-out.xml
Plain text output can be found in: sample-out.txt
```

PyPop will remember the names of the configuration and population files you used last, and will provide those as defaults in subsequent runs.

1.1.2 Installing on Windows

System requirements At least Windows 98

Systems tested Windows 2000, Windows XP (may work on other platforms but untested at present)

1. Before starting an install on Windows, you must first make sure you have a copy of a zip file extractor such as PowerArchiver or WinZip.
2. Download the latest stable Windows release of PyPop and save it in one of your directories or on the Desktop:
 - <http://www.pypop.org/PyPopWin32-0.7.0.zip>
3. Once you have downloaded the file, you should double-click it. If you have correctly installed one of the zip compression utilities, it should open using that zip program. Extract the contents of the zip file to your desktop, or wherever you normally save your programs and data. Consult the documentation for your archiving utility for details on how to do this (it should be reasonably self-explanatory).

To test your installation:

1. Once you have the PyPopWin32-0.7.0 directory extracted, open the directory and double-click on the pypop.bat file.
2. A DOS shell should then open running the program inside it.

A short message describing PyPop will be displayed, followed by prompts to supply the name of the configuration file and then the population file. Select the file, `sample.ini` and `sample.pop`, respectively (noted in the sample screen output below, in **bold**).

```
PyPop: Python for Population Genomics (0.4.3)
Copyright (C) 2003 Regents of the University of California
This is free software. There is NO warranty; not even for
MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.
```

```
You may redistribute copies of PyPop under the terms of the
GNU General Public License. For more information about these
matters, see the file named COPYING.
```

```
To accept the default in brackets for each filename, simply press
return for each prompt.
```

```
Please enter config filename [config.ini]: sample.ini
```

```
Please enter population filename [no default]: sample.pop
PyPop is processing sample.pop

(Note:some messages with the prefix "LOG:" may appear here.They are
      informational only and do not indicate improper operationof the program)

PyPop run complete!
XML output can be found in: sample-out.xml
Plain text output can be found in: sample-out.txt
```

1.2 Installing from source

The source code for PyPop can be obtained here:

- <http://www.pyPOP.org/pyPOP-0.7.0.tar.gz>
- In addition, because the Windows binary distributes a copy of the `cygwin1.dll`, we are required under the terms of the GNU GPL to provide a copy of the Cygwin source which we compiled the binary from: <http://www.pyPOP.org/cygwin-1.5.24-2.tar.bz2>.

NOTE



Note that this only required for Windows and is *not* required for compilation even under Windows if you install within the Cygwin environment (because it already contains a copy `cygwin1.dll`) and is only provided for legal reasons.

1.2.1 System requirements

- **Python 2.4** or later.
- **Numerical Python (Numeric) 24.0** or later (note that this is the old "Numeric" not the newer Numpy, on Fedora the package is known as `python-numeric`)
- **Simple Wrapper Interface Generator (SWIG)**: uses "development" version (should now be compatible with all recent SWIG versions: last tested against SWIG 1.3.31).
- **libxml2/libxslt** including **libxml2-python**, a Python interface to the GNOME XML/XSLT parser (This is a fast C library-based parser. Most recent GNU/Linux distributions will install `libxml2/libxslt` as part of the base distribution, but you may need to install `libxml2-python` and `libxslt-python` separately).
(Untested recently: **4Suite** a pure Python XML/XSLT parsing engine.)
- The GNU Scientific Library (**GSL**) On Fedora you will want to install the `gsl-devel` package.

1.2.2 Installation

Before starting, you must ensure you have installed all the system requirements listed above. In particular, make sure Python is installed correctly.

Unzip and untar the above tar ball. Build and install PyPop by changing into the `PyPop-0.7.0` directory, and type:

```
python setup.py build
python setup.py install
```

If you need to do additional configuration (e.g. changing the base directory) please type **python setup.py**, or see the documentation for Distutils.

1.2.3 Test suite

None as yet.

1.2.4 Contributions, bug reports

Please send all bug reports and contributions to alexl@users.sourceforge.net

1.2.5 Distribution structure

```
AUTHORS --      A list of people who have contributed.
emhaplofreq/ -- LD and haplotype estimation extension module
pval/ --        Modified code from R project for p-value calculation
slatkin-exact/ Slatkin's code for Ewens-Watterson exact test
gthwe/         Modified Guo and Thompson Hardy-Weinberg code
SWIG/ --       Helper code for SWIG for generating C-Python wrappers
xslt/ --       XSLT for generating text and other output from XML
COPYING --     License information for this package
MANIFEST.in -- Tells distutils what files to distribute
NEWS --        Release notes and news
README --      Information and TODO list.
INSTALL --     This file
setup.py --    Installation file.
```

Chapter 2

Getting started with PyPop

Last updated: 2008/11/19

2.1 Introduction

You may use PyPop to analyze many different kinds of data, including allele-level genotype data (as in Example 2.1), allele-level frequency data (as in Example 2.6), microsatellite data, SNP data, and nucleotide and amino acid sequence data.

There are two ways to run PyPop:

- *interactive* mode (where the program will prompt you to directly type the input it needs); and
- *batch* mode (where you supply all the command line options the program needs).

For the most straightforward application of PyPop, where you wish to analyze a single population, the interactive mode is the simplest to use. We will describe this mode first then describe batch mode.

2.1.1 Interactive mode

To run PyPop, click the `pypop.bat` file (Windows) or type `./pypop` at the command prompt (GNU/Linux). You should see something like the following output (this is also described in detail in the instructions in the installation guide):

```
PyPop: Python for Population Genomics (0.4.3)
Copyright (C) 2003 Regents of the University of California
This is free software.  There is NO warranty; not even for
MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.
```

```
You may redistribute copies of PyPop under the terms of the
GNU General Public License.  For more information about these
matters, see the file named COPYING.
```

```
To accept the default in brackets for each filename, simply press
return for each prompt.
```

```
Please enter config filename [config.ini]: sample.ini
Please enter population filename [no default]: sample.pop
PyPop is processing sample.pop
```

(Note: some messages with the prefix "LOG:" may appear here. They are informational only and do not indicate improper operation of the program)

```
PyPop run complete!
XML output can be found in: sample-out.xml
Plain text output can be found in: sample-out.txt
```

You should substitute the names of your own configuration (e.g., `config.ini`) and population file (e.g., `Guatemalan.pop`) for `sample.ini` and `sample.pop`. The formats for these files are described in Section 2.2 and Section 2.3, below.

2.1.2 Batch mode

To run PyPop in batch mode, you can start PyPop from the command line (in Windows: open a DOS shell, GNU/Linux: open a terminal window), change to the directory where you unpacked PyPop and type

```
pypop-batch Guatemalan.pop
```

NOTE



If your system administrator has installed PyPop the name of the script may be renamed to something different.

Batch mode assumes two things: that you have a file called `config.ini` in your current folder and that you also have your population file also in the current folder. You can specify a particular configuration file for PyPop to use, by supplying the `-c` option as follows:

```
pypop-batch -c newconfig.ini Guatemalan.pop
```

You may also redirect the output to a different directory (which must already exist) by using the `-o` option:

```
pypop-batch -c newconfig.ini -o altdir Guatemalan.pop
```

For a full list of options supported by PyPop, type **pypop-batch --help**. You should receive a screen resembling the following:

```
Usage: pypop [OPTION] INPUTFILE
```

```
Process and run population genetics statistics on an INPUTFILE.
```

```
Expects to find a configuration file called 'config.ini' in the
current directory or in /usr/share/PyPop/config.ini.
```

```
-l, --use-libxslt      filter XML via XSLT using libxslt (default)
-s, --use-4suite       filter XML via XSLT using 4Suite
-x, --xsl=FILE         use XSLT translation file FILE
-h, --help             show this message
-c, --config=FILE      select alternative config file
-d, --debug            enable debugging output (overrides config file setting)
-i, --interactive      run in interactive mode, prompting user for file names
-g, --gui              run GUI (currently disabled)
-o, --outputdir=DIR   put output in directory DIR
-V, --version          print version of PyPop
```

```
INPUTFILE  input text file
```

WARNING



Documentation for these options is underway, but not currently available.

2.1.3 What happens when you run PyPop?

The most common types of analysis will involve the editing of your `config.ini` file to suit your data (see Section 2.3) followed by the selection of either the interactive or batch mode described above. If your input configuration file is `configfilename` and your population file name is `popfilename.txt` the initial output will be generated quickly, but your the PyPop execution will not be finished until the text output file named `popfilename-out.txt` has been created. A successful run will produce two output files: `popfilename-out.xml`, `popfilename-out.txt`. A third output file will be created if you are using the Anthony Nolan HLA filter option for HLA data to check your input for valid/known HLA alleles: `popfilename-filter.xml`).

The `popfilename-out.xml` file is the primary output created by PyPop and the human-readable `popfilename-out.txt` file is a summary of the complete XML output. It is generated from the XML output via XSLT (eXtensible Stylesheet Language for Transformations) using the default XSLT stylesheet `text.xsl`, which is located in the `xslt` directory. The XML output can be further transformed using customized XSLT stylesheets into other formats for input to statistical software (e.g., R/Splus, SAS) or other population genetic software (e.g., PHYLIP). The **popmeta** script (`popmeta.bat` on Windows, `popmeta` on GNU/Linux) calls on other XSLT stylesheets to aggregate results from a number of output XML files from individual populations into a set of tab-separated (TSV) files containing summary statistics. These TSV files can be directly imported into a spreadsheet or statistical software. This script will be further documented in the next release.

A typical PyPop run might take anywhere from a few of minutes to a few hours, depending on how large your data set is and who else is using the system at the same time. Note that performing the `al-1PairwiseLDWithPermu` test may take several **days** if you have highly polymorphic loci in your data set.

2.2 The data file

2.2.1 Sample files

Data can be input either as genotypes, or in an allele count format, depending on the format of your data.

As you will see in the following examples, population files begin with header information. In the simplest case, the first line contains the column headers for the genotype, allele count, or, sequence information from the population. If the file contains a population data-block, then the first line consists of headers identifying the data on the second line, and the third line contains the column headers for the genotype or allele count information.

Note that for genotype data, each locus corresponds to two columns in the population file. The locus name must be repeated, with a suffix such as `_1`, `_2` (the default) or `_a`, `_b` and must match the format defined in the `config.ini` (see `validSampleFields`). Although PyPop needs this distinction to be made, phase is NOT assumed, and if known it is ignored.

Example 2.7 shows the relevant lines for the configuration to read in the data shown in Example 2.1 through to Example 2.6.

Example 2.1 Multi-locus allele-level genotype data

```

a_1  a_2  c_1  c_2  b_1  b_2
****  ****  0102  02025  1301  18012
0101  0201  0307  0605  1401  39021
0210  03012  0712  0102  1520  1301
0101  0218  0804  1202  35091  4005
2501  0201  1507  0307  51013  1401
0210  3204  1801  0102  78021  1301
03012  3204  1507  0605  51013  39021

```

This is an example of the simplest kind of data file.

Example 2.2 Multi-locus allele-level HLA genotype data with sample information

populat	id	a_1	a_2	c_1	c_2	b_1	b_2
UchiTelle	UT900-23	****	****	0102	02025	1301	18012
UchiTelle	UT900-24	0101	0201	0307	0605	1401	39021
UchiTelle	UT900-25	0210	03012	0712	0102	1520	1301
UchiTelle	UT900-26	0101	0218	0804	1202	35091	4005
UchiTelle	UT910-01	2501	0201	1507	0307	51013	1401
UchiTelle	UT910-02	0210	3204	1801	0102	78021	1301
UchiTelle	UT910-03	03012	3204	1507	0605	51013	39021

This example shows a data file which has non-allele data in some columns, here we have population (populat) and sample identifiers (id).

Example 2.3 Multi-locus allele-level HLA genotype data with sample and header information

labcode	method	ethnic	contin	collect	latit	longit	
USAFEL	12th Workshop	SSOP	Telle	NW Asia	Targen Village	41 deg 12 min N 94 deg ← 7 min E	
populat	id	a_1	a_2	c_1	c_2	b_1	b_2
UchiTelle	UT900-23	****	****	0102	02025	1301	18012
UchiTelle	UT900-24	0101	0201	0307	0605	1401	39021
UchiTelle	UT900-25	0210	03012	0712	0102	1520	1301
UchiTelle	UT900-26	0101	0218	0804	1202	35091	4005
UchiTelle	UT910-01	2501	0201	1507	0307	51013	1401
UchiTelle	UT910-02	0210	3204	1801	0102	78021	1301
UchiTelle	UT910-03	03012	3204	1507	0605	51013	39021

This is an example of a data file which is identical to Example 2.2, but which includes population level information.

Example 2.4 Multi-locus allele-level HLA genotype and microsatellite genotype data with header information

labcode	ethnic	complex					
USAFEL	****	0					
populat	id	drb1_1	drb1_2	dqb1_1	dqb1_2	d6s2222_1	d6s2222_2
UchiTelle	HJK_2	01	0301	0201	0501	249	249
UchiTelle	HJK_1	0301	0301	0201	0201	249	249
UchiTelle	HJK_3	01	0301	0201	0501	249	249
UchiTelle	HJK_4	01	0301	0201	0501	249	249
UchiTelle	MYU_2	02	0401	0302	0602	247	249
UchiTelle	MYU_1	0301	0301	0201	0201	247	249
UchiTelle	MYU_3	0301	0401	0201	0302	249	249
UchiTelle	MYU_4	0301	0401	0201	0302	247	249

This example mixes different kinds of data: HLA allele data (from DRB1 and DQB1 loci) with microsatellite data (locus D6S2222).

Example 2.5 Sequence genotype data with header information

```

labcode file
BLOGGS C_New
popName ID TGFB1cdn10 (1) TGFB1cdn10 (2) TGFBhap1 (1) TGFBhap1 (2)
Urboro XQ-1 C T CG TG
Urboro XQ-2 C C CG CG
Urboro XQ-5 C T CG TG
Urboro XQ-21 C T CG TG
Urboro XQ-7 C T CG TG
Urboro XQ-20 C T CG TG
Urboro XQ-6 T T TG TG
Urboro XQ-8 C T CG TG
Urboro XQ-9 T T TG TG
Urboro XQ-10 C T CG TG

```

This example includes nucleotide sequence data: the TGFB1CDN10 locus consists of one nucleotide, the TGFBhap1 locus is actually haplotype data, but PyPop simply treats each combination as a separate "allele" for subsequent analysis.

Example 2.6 Allele count data

```

populat method ethnic country latit longit
UchiTelle PCR-SSO Klingon QZ 052.81N 100.25E
dgal count
0101 31
0102 37
0103 17
0201 21
0301 32
0401 9
0501 35

```

PyPop can also process allele count data. However, you cannot mix allele count data and genotype data together in the one file.

NOTE

Currently each `.pop` file can only contain allele count data for *one locus*. In order to process multiple loci for one population you must create a separate `.pop` for each locus.

These population files are plain text files, such as you might save out of the Notepad application on Windows (or Emacs). The columns are all tab-delimited, so you can include spaces in your labels. If you have your data in a spreadsheet application, such as Excel or OpenOffice.org, export the file as tab-delimited text, in order to use it as PyPop data file.

2.2.2 Missing data

Untyped or missing data may be represented in a variety of ways. The default value for untyped or missing data is a series of four asterisks (****) as specified by the `config.ini`. You may not "represent" untyped data by leaving a column blank, nor may you represent a homozygote by leaving the second column blank. All cells for which you have data must include data, and all cells for which you do not have data must also be filled in, using a missing data value.

For individuals who were not typed at all loci, the data in loci for which they are typed will be used on all single-locus analyses for that individual and locus, so that you see the value of the number of individuals (n) vary from locus to locus in the output. These individuals' data will also be used for multi-locus analyses. Only the loci that contain no missing data will be included in any multi-locus analysis.

If an individual is only partially typed at a locus, it will be treated as if it were completely untyped, and data for that individual for that locus will be dropped from ALL analyses.

CURRENT LIMITATIONS OF PYPOP



- Do not leave trailing blank lines at the end of your data file, as this currently causes PyPop to terminate with an error message that takes experience to diagnose.
- For haplotype estimation and linkage disequilibrium calculations (i.e., the `emhaplofreq` part of the program) you are currently restricted to a maximum of seven loci per haplotype request. For haplotype estimation there is a limit of 5000 for the number of individuals (n)^a

^a These hardcoded numbers can be changed if you obtain the source code yourself and change the appropriate `#define emhaplofreq.h` and recompile the program.

2.3 The configuration file

The sets of population genetic analyses that are run on your population data file and the manner in which the data file is interpreted by PyPop is controlled by a configuration file, the default name for which is `config.ini`. This is another plain text file consisting of *comments* (which are lines that start with a semi-colon), *sections* (which are lines with labels in square brackets), and *options* (which are lines specifying settings relevant to that section in the `option=value` format).

NOTE



If any option runs over one line (such as `validSampleFields`) then the second and subsequent lines must be indented by exactly **one space**.

2.3.1 A minimal configuration file

Here we present a minimal `.ini` file corresponding to Example 2.1 A section by section review of this file follows. (Note comment lines have been omitted in the above example for clarity). A description of more advanced options is contained in Section 2.3.2.

Example 2.7 Minimal `config.ini` file

```

[General] ❶
debug=0

[ParseGenotypeFile] ❷
untypedAllele=****
alleleDesignator=*
validSampleFields=*a_1
*a_2
*c_1
*c_2
*b_1
*b_2

[HardyWeinberg] ❸
lumpBelow=5

[HardyWeinbergGuoThompson] ❹
dememorizationSteps=2000
samplingNum=1000
samplingSize=1000

[HomozygosityEWSlatkinExact] ❺
numReplicates=10000

[Emhaplofreq] ❻
allPairwiseLD=1
allPairwiseLDWithPermu=0
;;numPermuInitCond=5

```

Configuration file sections**❶** [General]

This section contains variables that control the overall behavior of PyPop.

- **debug=0** This setting is for debugging. Setting it to 1 will set off a large amount of output of no interest to the general user. It should not be used unless you are running into trouble and need to communicate with the PyPop developers about the problems.

❷ Specifying data formats

There are two possible formats: [ParseGenotypeFile] and [ParseAlleleCountFile]

[ParseGenotypeFile] If your data is genotype data, you will want a section labeled: [ParseGenotypeFile].

- **alleleDesignator** This option is used to tell PyPop what is allele data and what isn't. You must use this symbol in **validSampleFields** option. The default is *. In general, you won't need to change it. **[Default: *]**
- **untypedAllele** This option is used to tell PyPop what symbol you have used in your data files to represent untyped or unknown data fields. These fields MAY NOT BE LEFT BLANK. You must use something consistent that cannot be confused with real data here. **[Default: ****]**
- **validSampleFields**

This option should contain the names of the loci immediately preceding your genotype data (if it has three header lines, this information will be on the third line, otherwise it will be the first line of the file). **[There is no default, this option must always be present]**

The format is as follows, for each sample field (which may either be an identifying field for the sample such as `populat`, or contain allele data) create a new line where:

- The first line (`validSampleFields=`) consists of the name of your sample field (if it contains allele data, the name of the field should be preceded by the character designated in the `alleleDesignator` option above).
- All subsequent lines after the first *must* be preceded by *one space* (again if it contains allele data, the name of the field should be preceded by the character designated in the `alleleDesignator` option above).

Here is an example:

```
validSampleFields=*a_1
*a_2
*c_1
*c_2
*b_1
*b_2    Note initial space at start of line.
```

Here is example that includes identifying (non-allele data) information such as sample id (`id`) and population name (`populat`):

```
validSampleFields=populat
id
*a_1
*a_2
*c_1
*c_2
*b_1
*b_2
```

[ParseAlleleCountFile] If your data is not genotype data, but rather, data of the allele-name count format, then you will want to use the `[ParseAlleleCountFile]` section INSTEAD of the `[-ParseGenotypeFile]` section. The `alleleDesignator` and `untypedAllele` options work identically to that described for `[ParseGenotypeFile]`.

- **validSampleFields** This option should contain either a single locus name or a colon-separated list of all loci that will be in the data files you intend to analyze using a specific `.ini` file. The colon-separated list allows you to avoid changing the `.ini` file when running over a collection of data files containing different loci. e.g.,

```
validSampleFields=A:B:C:DQA1:DQB1:DRB1:DPB1:DPA1
count
```

Note that each `.pop` file must contain only one locus (see [?note] in Example 2.6). Listing multiple loci simply permits the same `.ini` file to be reused for each data file.

3 [HardyWeinberg]

Hardy-Weinberg analysis is enabled by the presence of this section.

- **lumpBelow** This option value represents a cut-off value. Alleles with an expected value equal to or less than `lumpBelow` will be lumped together into a single category for the purpose of calculating the degrees of freedom and overall p-value for the chi-squared Hardy-Weinberg test.

4 [HardyWeinbergGuoThompson]

When this section is present, an implementation of the Hardy-Weinberg exact test is run using the original [Guo:Thompson:1992] code, using a Monte-Carlo Markov chain (MCMC). In addition, two measures (Chen and Diff) of the goodness of fit of individual genotypes are reported under this option [Chen:etal:1999] By default this section is not enabled. This is a different implementation to the Arlequin version listed in Section 2.3.2, below.

- **dememorizationSteps** Number of steps of to 'burn-in' the Markov chain before statistics are collected. [Default: 2000]
- **samplingNum** Number of Markov chain samples [Default: 1000].

- **samplingSize** Markov chain sample size[Default: 1000].

Note that the **total** number of steps in the Monte-Carlo Markov chain is the product of `samplingNum` and `samplingSize`, so the default values described above would contain 1,000,000 (= 1000 x 1000) steps in the MCMC chain.

The default values for options described above have proved to be optimal for us and if the options are not provided these defaults will be used. If you change the values and have problems, please let us **know**.

5 [HomozygosityEWsSlatkinExact]

The presence of this section enables Slatkin's [Slatkin:1994] implementation of the Ewens-Watterson exact test of neutrality.

- **numReplicates** The default values have proved to be optimal for us. There is no reason to change them unless you are particularly curious. If you change the default values and have problems, please let us know.

6 [Emhaplofreq]

The presence of this section enables haplotype estimation and calculation of linkage disequilibrium (LD) measures.

- **lociToEstHaplo** In this option you can list the multi-locus haplotypes for which you wish the program to estimate and to calculate the LD. It should be a comma-separated list of colon-joined loci. e.g.,

```
lociToEstHaplo=a:b:drb1,a:b:c,drb1:dqa1:dpb1,drb1:dqb1:dpb1
```

- **allPairwiseLD** Set this to 1 (one) if you want the program to calculate all pairwise LD for your data, otherwise set this to 0 (zero).
- **allPairwiseLDWithPermu** Set this to a positive integer greater than 1 if you need to determine the significance of the pairwise LD measures in the previous section. The number you use is the number of permutations that will be run to ascertain the significance (this should be at least 1000 or greater). (Note this is done via permutation testing performed after the pairwise LD test for all pairs of loci. Note also that this test can take *DAYS* if your data is highly polymorphic.)
- **numPermuInitCond** Set this to change the number of initial conditions used per permutation. [Default: 5]. (Note: this parameter is only used if `allPairwiseLDWithPermu` is set and `nonzero`).

2.3.2 Advanced options

The following section describes additional options to previously described sections. Most of the time these options can be omitted and PyPop will choose defaults, however these advanced options do offer greater control over the application. In particular, customization will be required for data that has sample identifiers as in Example 2.2 or header data block as in Example 2.3 and both `validSampleFields` (described above) and `validPopFields` (described below) will need to be modified.

It also describes two extra sections related to using PyPop in conjunction with Arlequin: [Arlequin] and [HardyWeinbergGuoThompsonArlequin].

[General] advanced options

- **txtOutFilename** and **xmlOutFilename** If you wish to specify a particular name for the output file, which you want to remain identical over several runs, you can set these two items to particular values. The default is to have the program select the output filename, which can be controlled by the next variable. [Default: not used]
- **outFilePrefixType** This option can either be omitted entirely (in which case the default will be `filename`) or be set in several ways. The default is set as `filename`, which will result in three output files named `original-filename-minus-suffix-out.xml`, `original-filename-minus-suffix.txt`, and `original-filename-minus-suffix-filter.xml`. [Default: **filename**]

If you set the value to `date` instead of `filename`, you'll get the date incorporated in the filename as follows: `original-filename-minus-suffix-YYYY-nn-dd-HH-MM-SS-out.{xml,txt}`. e.g., `USAFEL-UchiTelle-2003-09-21-01-29-35-out.xml` (where Y, n, d, H, M, S refer to year, month, day, hour, minute and second, respectively).

- **xslFilename** This option specifies where to find the XSLT file to use for transforming PyPop's xml output into human-readable form. Most users will not normally need to set this option, and the default is the system-installed `text.xsl` file.

[ParseGenotypeFile] advanced options

- **fieldPairDesignator** This option allows you to override the coding for the headers for each pair of alleles at each locus; it must match the entry in the config file under `validSampleFields` and the entries in your population data file. If you want to use something other than `_1` and `_2`, change this option, for instance, to use letters and parentheses, change it as follows: `fieldPairDesignator=(a):(b)` [Default: `_1:_2`]
- **popNameDesignator** There is a special designator to mark the population name field, which is usually the first field in the data block. [Default: `+`]

If you are analyzing data that contains a population name for each sample, then the first entry in your `validSampleFields` section should have a prefixed `+`, as below:

```
validSampleFields=+populat
*a_1
*a_2
...
```

- **validPopFields** If you are analyzing data with an initial two line population header block information as in Example 2.3, then you will need to set this option. In this case, it should contain the field names in the first line of the header information of your file. [Default: **required when a population data-block is present in data file**], e.g.:

```
validPopFields=labcode
method
ethnic
country
latit
longit
```

[Emhaplofreq] advanced options

- **permutationPrintFlag** Determines whether the likelihood ratio for each permutation will be logged to the XML output file, this is disabled by default. [Default: `0 (OFF)`].

WARNING



If this is enabled it can *drastically* increase the size of the output XML file on the order of the product of the number of possible pairwise comparisons and permutations. Machines with lower RAM and disk space may have difficulty coping with this.

[Arlequin] extra section

This section sets characteristics of the Arlequin application if it has been installed (it must be installed separately from PyPop as we cannot distribute it). The options in this section are only used when a test requiring Arlequin, such as it's implementation of Guo and Thompson's [Guo:Thompson:1992] Hardy-Weinberg exact test is invoked (see below).

- **arlequinExec** This option specifies where to find the Arlequin executable on your system. The default assumes it is on your system path. [Default: `arlecore.exe`]

[HardyWeinbergGuoThompsonArlequin] extra section

When this section is present, Arlequin's implementation of the Hardy-Weinberg exact test is run, using a Monte-Carlo Markov Chain implementation. By default this section is not enabled.

- **markovChainStepsHW** Length of steps in the Markov chain [Default: 2500000].
- **markovChainDememorisationStepsHW** Number of steps of to 'burn-in' the Markov chain before statistics are collected. [Default: 5000]

The default values for options described above have proved to be optimal for us and if the options are not provided these defaults will be used. If you change the values and have problems, please let us know.

[Filters] extra section

When this section is present, it allows you to specify successive filters to the data.

- **filtersToApply** Here you specify which filters you want applied to the data and the order in which you want them applied. Separate each filter name with a colon (:). Currently there are four predefined filter: `AnthonyNolan`, `Sequence`, `DigitBinning`, and `CustomBinning`. If you specify one or more of these filters, you will get the default behavior of the filter. If you wish to modify the default behavior, you should add a section with the same name as the specified filter(s). See next section for more on this. Please note that, while you are allowed to specify any ordering for the filters, some orderings may not make sense. For example, the ordering `Sequence:AnthonyNolan` would not make sense (because as far as PyPop is concerned, your alleles are now amino acid residues.) However, the reverse ordering, `AnthonyNolan:Sequence`, would be logical and perhaps even advisable.

[AnthonyNolan] filter section

This section is *only* useful for HLA data. Like all filter sections, it will only be used if present in the `filtersToApply` line specified above. If so enabled, your data will be filtered through the Anthony Nolan database of known HLA allele names before processing. The data files this filter relies on are *not* currently distributed with PyPop but can be obtained via the [IMGT ftp site](#). Invocation of this filter will produce a `popfile-filter.xml` file output showing what was resolved and what could not be resolved.

- **alleleFileFormat** This options specifies which of the formats the Anthony Nolan allele data will be used. The option can be set to either `txt` (for the plain free text format) or `msf` (for the [Multiple Sequence Format](#)) [Default: `msf`]
- **directory** Specifies the path to the root of the sequence files. For `txt`: [Default: `prefix/share/PyPop/anthonymolan/HIG-seq-pep-text/`]. For `msf` files [Default: `prefix/share/PyPop/anthonymolan/msf/`].
- **preserve-ambiguous** The default behavior of the `AnthonyNolan` filter is to ignore allele ambiguity ("slash") notation. This notation, common in the literature, looks like: `010101/0102/010301`. The default behavior will simply truncate this to `0101`. If you want to preserve the notation, set the option to 1. This will result in a filtered allele "name" of `0101/0102/0103` in the above hypothetical example. [Default: 0].
- **preserve-unknown** The default behavior of the `AnthonyNolan` filter is to replace unknown alleles with the `untypedAllele` designator. If you want the filter to keep allele names it does not recognize, set the option to 1. [Default: 0].
- **preserve-lowres** This option is similar to `preserve-unknown`, but only applies to lowres alleles. If set to 1, PyPop will keep allele names that are shorter than the default allele name length, usually 4 digits long. But if the `preserve-unknown` flag is set, this one has no effect, because all unknown alleles are preserved. [Default: 0].

[Sequence] filter section

This section allows configuration of the sequence filter. Like all filter sections, it will only be used if present in the `filtersToApply` line specified above. If so enabled, your allele names will be translated into sequences, and all ensuing analyses will consider each position in the sequence to be a distinct locus. This filter makes use of the same `msf` format alignment files as used above in the AnthonyNolan filter. It does not work with the `txt` format alignment files.

- **sequenceFileSuffix** Determines the files that will be examined in order to read in a sequence for each allele. (ie, if the file for locus A is `A_prot.msf`, the value would be `_prot` whereas if you wanted to use the nucleotide sequence files, you might use `_nuc`.) [Default: `_prot`].
- **directory** Specifies the path to the root of the sequence files, in the same manner as in the AnthonyNolan section, above.

[DigitBinning] filter section

This section allows configuration of the DigitBinning filter. Like all filter sections, it will be used if present in the `filtersToApply` line specified above. If so enabled, your allele names will be truncated after the `nth` digit.

- **binningDigits** An integer that specifies how many digits to keep after the truncation. [Default: 4].

[CustomBinning] filter section

This section allows configuration of the CustomBinning filter. Like all filter sections, it will only be used if present in the `filtersToApply` line specified above.

You can provide a set of custom rules for replacing allele names. Allele names should be separated by `/` marks. This filter matches any allele names that are exactly the same as the ones you list here, and will also find "close matches" (but only if there are no exact matches.). Here is an example:

```
A=01/02/03
 04/05/0306
 !06/1201/1301
 !07/0805
```

In the example above, `A*03` alleles will match to `01/02/03`, except for `A*0306`, which will match to `04/05/0306`. If you place a `!` mark in front of the first allele name, that first name will be used as the "new name" for the binned group (for example, `A*0805` will be called `07` in the custom-binned data.) Note that the space at the beginning of the lines (following the first line of each locus) is important. The above rules are just dummy examples, provided to illustrate how the filter works. PyPop is distributed with a biologically relevant set of `CustomBinning` rules that have been compiled from several sources¹

¹ [Mack:etal:2007]; [Cano:etal:2007]; The Anthony Nolan list of deleted allele names (<http://www.anthonynolan.com/HIG/lists/delnames.html>); and the Ambiguous Allele Combinations, release 2.18.0 (<http://www.ebi.ac.uk/imgt/hla/ambig.html>).

Chapter 3

Interpreting PyPop output

Last updated: 2008/08/17

As mentioned in Section 2.1.3, The XML file is the primary output created by PyPop and contains the complete set of results. The text output, generated from the XML file via XSLT, contains a human-readable summary of the XML results. Below we discuss the output contained in this text file.

3.1 Population summary

A `Population Summary` is generated for each dataset analyzed. This summary provides basic demographic information and summarizes information about the sample size.

Sample output:

Example 3.1 Population summary sample output

```
Population Summary
=====
Population Name: UchiTelle
      Lab code: USAFEL
      Typing method: 12th Workshop SSOP
      Ethnicity: Telle
      Continent: NW Asia
Collection site: Targen Village
      Latitude: 41 deg 12 min N
      Longitude: 94 deg 7 min E

Population Totals
-----
Sample Size (n): 47
Allele Count (2n): 94
Total Loci in file: 9
Total Loci with data: 8
```

3.2 Single locus analyses

3.2.1 Basic allele count information

Information relevant to individual loci is reported. Sample size and allele counts will differ among loci if not all individuals were typed at each locus. Untyped individuals are those for which one or two alleles were not reported. The alleles are listed in descending frequency (and count) in the left hand column, and are sorted numerically in the right column. The number of distinct alleles k is reported.

Example 3.2 Basic locus information sample output

I. Single Locus Analyses

1. Locus: A

1.1. Allele Counts [A]

```

Untyped individuals: 2
Sample Size (n): 45
Allele Count (2n): 90
Distinct alleles (k): 10

```

Counts ordered by frequency			Counts ordered by name		
Name	Frequency	(Count)	Name	Frequency	(Count)
0201	0.211111	19	0101	0.133333	12
0301	0.155556	14	0201	0.211111	19
0101	0.133333	12	0210	0.100000	9
2501	0.122222	11	0218	0.100000	9
0210	0.100000	9	0301	0.155556	14
0218	0.100000	9	2501	0.122222	11
3204	0.088889	8	3204	0.088889	8
6901	0.044444	4	6814	0.033333	3
6814	0.033333	3	6901	0.044444	4
7403	0.011111	1	7403	0.011111	1
Total	1.000000	90	Total	1.000000	90

In the cases where there is no information for a locus, a message is displayed indicating lack of data. Sample output:

4. Locus: DRA

```
No data for this locus!
```

3.2.2 Chi-square test for deviation from Hardy-Weinberg proportions (HWP).

For each locus, the observed genotype counts are compared to those expected under Hardy Weinberg proportions (HWP). A triangular matrix reports observed and expected genotype counts. If the matrix is more than 80 characters, the output is split into different sections. Each cell contains the observed and expected number for a given genotype in the format `observed/expected`.

Example 3.3 Sample output of Hardy-Weinberg genotype table

6.2. HardyWeinberg [DQA1]

Table of genotypes, format of each cell is: observed/expected.

```

0201 8/5.1
0301 4/4.0 1/0.8
0401 3/6.9 1/2.7 6/2.3
0501 8/9.9 5/3.8 5/6.7 6/4.8
      0201 0301 0401 0501
                                [Cols: 1 to 4]

```

The values in this matrix are used to test hypotheses of deviation from HWP. The output also includes the chi-square statistic, the number of degrees of freedom and associated p-value for a number of classes of genotypes and is summarized in the following table:

Example 3.4 Sample output of HW genotype classes

	Observed	Expected	Chi-square	DoF	p-value	
Common	N/A	N/A	4.65	1	0.0310*	❶
Lumped genotypes	N/A	N/A	1.17	1	0.2797	❷
Common + lumped	N/A	N/A	5.82	1	0.0158*	❸
All homozygotes	21	13.01	4.91	1	0.0268*	❹
All heterozygotes	26	33.99	1.88	1	0.1706	❺
Common heterozygotes by allele						❻
0201	15	20.78	1.61		0.2050	
0301	10	10.47	0.02		0.8850	
0401	9	16.31	3.28		0.0703	
0501	18	20.43	0.29		0.5915	
Common genotypes						❼
0201:0201	8	5.11	1.63		0.2014	
0201:0401	3	6.93	2.23		0.1358	
0201:0501	8	9.89	0.36		0.5472	
0401:0501	5	6.70	0.43		0.5109	
Total	24	28.63				

Explanation of each genotype class

- ❶ **Common** The result for goodness of fit to HWP using only the genotypes with at least `lumpBelow` expected counts (the common genotypes) (in the output shown throughout this example `lumpBelow` is equal to 5).

If the dataset contains no genotypes with expected counts equal or greater than `lumpBelow`, then there are no common genotypes and the following message is reported:

```
No common genotypes; chi-square cannot be calculated
```

The analysis of common genotypes may lead to a situation where there are fewer classes (genotypes) than allele frequencies to estimate. This means that the analysis cannot be performed (degrees of freedom < 1). In such a case the following message is reported, explaining why the analysis could not be performed:

```
Too many parameters for chi-square test.
```

To obviate this as much as possible, only alleles which occur in common genotypes are used in the calculation of degrees of freedom.

- ❷ **Lumped genotypes** The result for goodness of fit to HWP for the pooled set of genotypes that individually have less than `lumpBelow` expected counts.

The pooling procedure is designed to avoid carrying out the chi-square goodness of fit test in cases where there are low expected counts, which could lead to spurious rejection of HWP. However, in certain cases it may not be possible to carry out this pooling approach. The interpretation of results based on lumped genotypes will depend on the particular genotypes that are combined in this class.

If the sum of expected counts in the lumped class does not add up to `lumpBelow`, then the test for the lumped genotypes cannot be calculated and the following message is reported:

```
The total number of expected genotypes is less than 5
```

This may be remedied by combining rare alleles and recalculating overall chi-square value and degrees of freedom. (This would require appropriate manipulation of the data set by hand and is not a feature of PyPop).

- 3 **Common + lumped** The result for goodness of fit to HWP for both the common and the lumped genotypes.
- 4 **All homozygotes** The result for goodness of fit to HWP for the pooled set of homozygous genotypes.
- 5 **All heterozygotes** The result for goodness of fit to HWP for the pooled set of heterozygous genotypes.
- 6 **Common heterozygotes** The common heterozygotes by allele section summarizes the observed and expected number of counts of all heterozygotes carrying a specific allele with expected value \geq lumpBelow.
- 7 **Common genotypes** The common genotypes by genotype section lists observed, expected, chi-square and p-values for all observed genotypes with expected values \geq lumpBelow.

3.2.3 Exact test for deviation from HWP

If enabled in the configuration file, the exact test for deviations from HWP will be output. The exact test uses the method of [Guo:Thompson:1992]. The p-value provided describes how probable the observed set of genotypes is, with respect to a large sample of other genotypic configurations (conditioned on the same allele frequencies and $2n$). p-values lower than 0.05 can be interpreted as evidence that the sample does not fit HWP. In addition, those individual genotypes deviating significantly (p-values < 0.05) from expected HWP as computed with the Chen and "diff" measures are reported.

There are two implementations for this test, the first using the gthwe implementation originally due to Guo & Thompson, but modified by John Chen, the second being Arlequin's [Schneider:etal:2000] implementation.

Example 3.5 Sample output for exact test using gthwe

6.3. Guo and Thompson HardyWeinberg output [DQA1]

```
-----
Total steps in MCMC: 1000000
Dememorization steps: 2000
Number of Markov chain samples: 1000
Markov chain sample size: 1000
Std. error: 0.0009431
p-value (overall): 0.0537
```

Example 3.6 Sample output for exact test using the Arlequin implementation

6.4. Guo and Thompson HardyWeinberg output (Arlequin's implementation) [DQA1]

```
-----
Observed heterozygosity: 0.553190
Expected heterozygosity: 0.763900
Std. deviation: 0.000630
Dememorization steps: 100172
p-value: 0.0518
```

Note that in the Arlequin implementation, the output is slightly different, and the only directly comparable value between the two implementation is the p-value. These p-values may be slightly different, but should agree to within one significant figure.

3.2.4 The Ewens-Watterson homozygosity test of neutrality

For each locus, we implement the Ewens-Watterson homozygosity test of neutrality ([Ewens:1972]; [Watterson:1978]). We use the term *observed homozygosity* to denote the homozygosity statistic (F), computed as the sum of the squared allele frequencies. This value is compared to the *expected homozygosity* which is computed by simulation under neutrality/equilibrium expectations, for the same sample size ($2n$) and number of unique alleles (k). Note that the homozygosity F statistic, $F = \sum_{i=1}^k p_i^2$, is often referred to as the *expected homozygosity* (with *expectation* referring to HWP) to distinguish it from the observed proportion of homozygotes. We avoid referring to the observed F statistic as the "*observed expected homozygosity*" (to simplify and hopefully avoid confusion) since the homozygosity test of neutrality is concerned with comparisons of observed results to expectations under neutrality. Both the *observed* statistic (based on the actual data) and *expected* statistic (based on simulations under neutrality) used in this test are computed as the sum of the squared allele frequencies.

The *normalized deviate of the homozygosity* (F_{nd}) is the difference between the *observed homozygosity* and *expected homozygosity*, divided by the square root of the variance of the expected homozygosity (also obtained by simulations; [Salamon:etal:1999]). Significant negative normalized deviates imply *observed homozygosity* values lower than *expected homozygosity*, in the direction of balancing selection. Significant positive values are in the direction of directional selection.

The p-value in the last row of the output is the probability of obtaining a homozygosity F statistic under neutral evolution that is less than or equal to the observed F statistic. It is computed based on the null distribution of homozygosity F values simulated under neutrality/equilibrium conditions for the same sample size ($2n$) and number of unique alleles (k). For a one-tailed test of the null hypothesis of neutrality against the alternative of balancing selection, p-values less than 0.05 are considered significant at the 0.05 level. For a two-tailed test against the alternative of either balancing or directional selection, p-values less than 0.025 or greater than 0.975 can be considered significant at the 0.05 level.

Example 3.7 Sample output of homozygosity test from Monte-Carlo implementation

The standard implementation of the test uses a Monte-Carlo implementation of the exact test written by Slatkin ([Slatkin:1994]; [Slatkin:1996]). A Markov-chain Monte Carlo method is used to obtain the null distribution of the homozygosity statistic under neutrality. The reported p-values are one-tailed (against the alternative of balancing selection), but can be interpreted for a two-tailed test by considering either extreme of the distribution (< 0.025 or > 0.975) at the 0.05 level.

```
1.6. Slatkin's implementation of EW homozygosity test of neutrality [A]
```

```
-----
Observed F: 0.1326, Expected F: 0.2654, Variance in F: 0.0083
Normalized deviate of F (Fnd): -1.4603, p-value of F: 0.0029**
```

WARNING

The version of this test based on tables of simulated percentiles of the Ewens-Watterson statistics is now disabled by default and its use is deprecated in preference to the Slatkin exact test described above, however some older PyPop runs may include output, so it is documented here for completeness. This version differs from the Monte-Carlo Markov Chain version described above in that the data is simulated under neutrality to obtain the required statistics.



Example 3.8 Sample output of homozygosity test from simulation look-up tables (disabled by default)

```
1.4. Ewens-Watterson homozygosity test of neutrality [A]
-----
Observed F: 0.1326, Expected F: 0.2651, Normalized deviate ( ←
  Fnd): -1.4506
p-value range: 0.0000 < p <= 0.0100 *
```

3.3 Multi-locus analyses

Haplotype frequencies are estimated using the iterative Expectation-Maximization (EM) algorithm ([Dempster:1977]; [Excoffier:Slatkin:1995]). Multiple starting conditions are used to minimize the possibility of local maxima being reached by the EM iterations. The haplotype frequencies reported are those that correspond to the highest logarithm of the sample likelihood found over the different starting conditions and are labeled as the maximum likelihood estimates (MLE).

The output provides the names of loci for which haplotype frequencies were estimated, the number of individual genotypes in the dataset (*before-filtering*), the number of genotypes that have data for all loci for which haplotype estimation will be performed (*after-filtering*), the number of unique phenotypes (unphased genotypes), the number of unique phased genotypes, the total number of possible haplotypes that are compatible with the genotypic data (many of these will have an estimated frequency of zero), and the log-likelihood of the observed genotypes under the assumption of linkage equilibrium.

3.3.1 All pairwise LD

A series of linkage disequilibrium (LD) measures are provided for each pair of loci.

Example 3.9 Sample output of all pairwise LD

```

II. Multi-locus Analyses
=====

Haplotype/ linkage disequilibrium (LD) statistics
-----

Pairwise LD estimates
-----
Locus pair      D'      Wn      ln(L_1)  ln(L_0)      S # permu p-value
A:C             0.49229  0.39472 -289.09   -326.81     75.44  1000 0.8510
A:B             0.50895  0.40145 -293.47   -330.83     74.73  1000 0.8730
A:DRB1         0.44304  0.37671 -282.00   -309.16     54.32  1000 0.7540
A:DQA1         0.29361  0.34239 -257.94   -269.88     23.88  1000 0.9020
A:DQB1         0.39266  0.37495 -275.58   -297.61     44.07  1000 0.8140
A:DPA1         0.31210  0.37987 -203.89   -206.99      6.21  1000 0.8840
A:DPB1         0.42241  0.40404 -237.84   -262.05     48.42  1000 0.5930
C:B             0.88739  0.85752 -210.36   -342.68    264.63  1000 0.0000***
C:DRB1         0.48046  0.47513 -280.34   -317.65     74.62  1000 0.2140
C:DQA1         0.42257  0.49869 -250.36   -276.72     52.73  1000 0.0370*
C:DQB1         0.45793  0.49879 -269.54   -305.27     71.46  1000 0.0580
C:DPA1         0.37214  0.46870 -208.99   -215.36     12.74  1000 0.7450
C:DPB1         0.46436  0.36984 -242.45   -268.45     52.01  1000 0.6290
B:DRB1         0.50255  0.41712 -286.79   -320.50     67.42  1000 0.4140
B:DQA1         0.41441  0.42844 -259.86   -279.56     39.40  1000 0.3880
B:DQB1         0.49040  0.43654 -277.29   -308.12     61.65  1000 0.2870
B:DPA1         0.29272  0.38831 -213.43   -218.01      9.14  1000 0.8780
B:DPB1         0.46082  0.38001 -247.83   -272.77     49.86  1000 0.7320
DRB1:DQA1      0.91847  0.91468 -164.06   -254.54    180.96  1000 0.0000***
DRB1:DQB1      1.00000  1.00000 -147.73   -283.09    270.72  1000 0.0000***

...

```

We report two measures of overall linkage disequilibrium. D' [Hedrick:1987] weights the contribution to LD of specific allele pairs by the product of their allele frequencies; W_n [Cramer:1946] is a re-expression of the chi-square statistic for deviations between observed and expected haplotype frequencies. Both measures are normalized to lie between zero and one.

D' Overall LD, summing contributions ($D'_{ij} = D_{ij} / D_{\max}$) of all the haplotypes in a multi-allelic two-locus system, can be measured using Hedrick's D' statistic, using the products of allele frequencies at the loci, p_i and q_j , as weights.

$$D' = \sum_{i=1}^I \sum_{j=1}^J p_i q_j |D'_{ij}| \quad (3.1)$$

W_n Also known as Cramer's V Statistic [Cramer:1946], W_n , is a second overall measure of LD between two loci. It is a re-expression of the Chi-square statistic, X_{LD}^2 , normalized to be between zero and one.

$$W_n = \left[\frac{\sum_{i=1}^I \sum_{j=1}^J D_{ij}^2 / p_i q_j}{\min(I-1, J-1)} \right]^{\frac{1}{2}} = \left[\frac{X_{LD}^2 / 2N}{\min(I-1, J-1)} \right]^{\frac{1}{2}} \quad (3.2)$$

When there are only two alleles per locus, W_n is equivalent to the correlation coefficient between the two loci, defined as $r = \sqrt{D_{11} / p_1 p_2 q_1 q_2}$.

For each locus pair the log-likelihood of obtaining the observed data given the inferred haplotype frequencies [$\ln(L_1)$], and the likelihood of the data under the null hypothesis of linkage equilibrium [$\ln(L_0)$] are given. The statistic S is defined as twice the difference between these likelihoods. S

has an asymptotic chi-square distribution, but the null distribution of S is better approximated using a randomization procedure. The empirical distribution of S is generated by shuffling genotypes among individuals, separately for each locus, thus creating linkage equilibrium (`# permu` indicates how many permutations were carried out). The p -value is the fraction of permutations that results in values of S greater or equal to that observed. A p -value < 0.05 is indicative of overall significant LD.

Individual LD coefficients, D_{ij} , are stored in the XML output file, but are not printed in the default text output. They can be accessed in the summary text files created by the `popmeta` script (see Section 2.1.3).

3.3.2 Haplotype frequency estimation

Example 3.10 Sample output of haplotype estimation parameters

```
Haplotype frequency est. for loci: A:B:DRB1
-----
Number of individuals: 47 (before-filtering)
Number of individuals: 45 (after-filtering)
Unique phenotypes: 45
Unique genotypes: 113
Number of haplotypes: 188
Loglikelihood under linkage equilibrium [ln(L_0)]: -472.700542
Loglikelihood obtained via the EM algorithm [ln(L_1)]: -340.676530
Number of iterations before convergence: 67
```

The estimated haplotype frequencies are sorted alphanumerically by haplotype name (left side), or in decreasing frequency (right side). Only haplotypes estimated at a frequency of 0.00001 or larger are reported. The first column gives the allele names in each of the three loci, the second column provides the maximum likelihood estimate for their frequencies, (`frequency`), and the third column gives the corresponding approximate number of haplotypes (`# copies`).

Example 3.11 Sample output of estimated haplotype frequencies

Haplotypes sorted by name			Haplotypes sorted by frequency		
haplotype	frequency	# copies	haplotype	frequency	# copies
0101:1301:0402:	0.02222	2.0	0201:1401:0402:	0.03335	3.0
0101:1301:1101:	0.01111	1.0	3204:1401:0802:	0.03333	3.0
0101:1401:0901:	0.01111	1.0	0301:1401:0407:	0.03333	3.0
0101:1520:0802:	0.01111	1.0	0301:1301:0402:	0.03333	3.0
0101:1801:0407:	0.01111	1.0	0201:1401:1101:	0.03332	3.0
0101:3902:0404:	0.01111	1.0	0301:1520:0802:	0.02222	2.0
0101:3902:1602:	0.01111	1.0	0101:4005:0802:	0.02222	2.0
0101:4005:0802:	0.02222	2.0	0301:3902:0402:	0.02222	2.0
0101:8101:0802:	0.01111	1.0	0201:1301:1602:	0.02222	2.0
0101:8101:1602:	0.01111	1.0	0218:1401:0404:	0.02222	2.0
0201:1301:1602:	0.02222	2.0	0210:5101:1602:	0.02222	2.0
0201:1401:0402:	0.03335	3.0	0218:1401:1602:	0.02222	2.0
0201:1401:0404:	0.01111	1.0	0101:1301:0402:	0.02222	2.0
0201:1401:0407:	0.02222	2.0	2501:4005:0802:	0.02222	2.0
0201:1401:0802:	0.01111	1.0	2501:1301:0802:	0.02222	2.0
...					

Chapter 4

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