
PyPop User Guide

Release 0.0

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Jul 27, 2023

PyPop User Guide

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Document release: 0.0.post2318+g74fe534

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PyPop (Python for Population Genomics) is an environment 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).

It is an object-oriented framework implemented in [Python](http://www.pypop.org/) (<http://www.pypop.org/>), a language with 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 XML. 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.

An outline of PyPop can be found in our 2007 *Tissue Antigens* and 2003 *PSB* papers.

How to cite PyPop

When citing PyPop, please cite the (2007) paper from *Tissue Antigens*:

- A. K. Lancaster, R. M. Single, O. D. Solberg, M. P. Nelson and G. Thomson (2007) “PyPop update - a software pipeline for large-scale multilocus population genomics” *Tissue Antigens* 69 (s1), 192-197. [[journal page](http://dx.doi.org/10.1111/j.1399-0039.2006.00769.x) (<http://dx.doi.org/10.1111/j.1399-0039.2006.00769.x>), [preprint PDF \(112 kB\)](http://pypop.org/tissue-antigens-lancaster-2007.pdf) (<http://pypop.org/tissue-antigens-lancaster-2007.pdf>)].

In addition, you can also cite our 2003 Pacific Symposium on Biocomputing paper:

- Alex Lancaster, Mark P. Nelson, Richard M. Single, Diogo Meyer, and Glenys Thomson (2003) “PyPop: a software framework for population genomics: analyzing large-scale multi-locus genotype data”, in *Pacific Symposium on Biocomputing* vol. 8:514-525 (edited by R B Altman. et al., World Scientific, Singapore, 2003) [[PubMed Central](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891851/) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891851/>), [PDF \(344 kB\)](http://pypop.org/psb-pypop.pdf) (<http://pypop.org/psb-pypop.pdf>)].

PyPop was originally developed for the analysis of data for the 13th [International Histocompatibility Workshop and Conference](http://www.ihwg.org/) (<http://www.ihwg.org/>) 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](#)].

Acknowledgements

This work has benefited from the support of NIH grant AI49213 (13th IHW) and NIH/NIAID Contract number HHSN266200400076C N01-AI-40076. Thanks to Steven J. Mack, Kristie A. Mather, Steve G.E. Marsh, Mark Grote and Leslie Louie for helpful comments and testing.

How to use this guide

This guide to PyPop contains four main parts:

- [Installing PyPop](#) describes how to install PyPop, including pre-release binaries.
- [Getting started with PyPop](#) describes how to run PyPop.
- [Interpreting PyPop output](#) details the population genetic methods and statistics that PyPop computes.
- [Contributing to PyPop](#) details how to contribute to ongoing PyPop code and documentation.

INSTALLING PYPOP

Attention: The package name for installation purposes is `pypop-genomics` - to avoid conflicting with an unrelated package with the name `pypop` already on [PyPI](https://pypi.org) (<https://pypi.org>). This is a working name and may change and is not yet the final package name until the package is released to PyPI.

1.1 Quickstart Guide

Installing pypop-genomics

If you already have Python and `pip` *installed*, install a test pre-releases using the following:

```
pip install pypop-genomics --extra-index-url https://test.pypi.org/simple/
```

Warning: These pre-release versions are being made available for initial testing, they are not intended to be used for production applications or analysis, and are not yet included in the main `pypi.org` index

Once `pypop-genomics` is installed, depending on your platform, you may also need to *adjust* your `PATH` environment variable.

Upgrading pypop-genomics

```
pip install -U pypop-genomics --extra-index-url https://test.pypi.org/simple/
```

Uninstalling pypop-genomics

```
pip uninstall pypop-genomics
```

For more, including handling common installation issues, see the *detailed installation instructions* .

Once you have installed `pypop-genomics`, you can move on to try some *example runs*.

1.2 Examples

These are examples of how to check that the program is installed and some minimal use cases.

1.2.1 Checking version and installation

```
pypop --version
```

This simply reports the version number and other information about PyPop, and indirectly checks that the program is installed. If all is well, you should see something like:

```
pypop 1.0.0a23
Copyright (C) 2003-2006 Regents of the University of California.
Copyright (C) 2007-2023 PyPop team.
This is free software. There is NO warranty; not even for
MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE.
```

You can also run `pypop --help` to see a full list and explanation of all the options available.

1.2.2 Run a minimal dataset:

Download test `.ini` and `.pop` files: [minimal.ini](https://github.com/alexlancaster/pypop/blob/main/tests/data/minimal.ini) (<https://github.com/alexlancaster/pypop/blob/main/tests/data/minimal.ini>) and [USAFEL-UchiTelle-small.pop](https://github.com/alexlancaster/pypop/blob/main/tests/data/USAFEL-UchiTelle-small.pop) (<https://github.com/alexlancaster/pypop/blob/main/tests/data/USAFEL-UchiTelle-small.pop>). You can then run them

```
pypop -c minimal.ini USAFEL-UchiTelle-small.pop
```

If you have already cloned the git repository and it is your working directory, you can simply run

```
pypop -c tests/data/minimal.ini tests/data/USAFEL-UchiTelle-small.pop
```

This will generate the following two files, an XML output file and a plain text version:

```
USAFEL-UchiTelle-small-out.xml
USAFEL-UchiTelle-small-out.txt
```

1.3 Detailed installation instructions

There are three main steps:

1. install Python and `pip`
2. install package from Test PyPI
3. adjusting your `PATH` variable after installation

1.3.1 Install Python 3 and pip

A full description of installing Python and pip on your system is beyond the scope of this guide, we recommend starting here:

<https://wiki.python.org/moin/BeginnersGuide/Download>

Here are some additional platform-specific notes that may be helpful:

- Most Linux distributions come with Python 3 preinstalled. On most modern systems, pip and python will default to Python 3.
- MacOS 10.9 (Jaguar) up until 12.3 (Catalina), used to ship with Python 2 pre-installed, but it now has to be manually installed. See the [MacOS quick-start guide](https://docs.python.org/3/using/mac.html) (<https://docs.python.org/3/using/mac.html>) in the official documentation for how to install Python 3. (Note that if Python is installed on Mac via the MacOS developer tools, it may include the version 3 suffix on commands, e.g. python3 and pip3, so modify the below, accordingly).
- For Windows, see also the [Windows quick-start guide](https://docs.python.org/3/using/windows.html) (<https://docs.python.org/3/using/windows.html>) in the official documentation. Running python in the Windows command terminal in Windows 11 and later will launch the installer for the Microsoft-maintained Windows package of Python 3.

1.3.2 Install package from PyPI

Once you have both python and pip installed, you can use pip to install pre-compiled binary “wheels” of pypop-genomics pre-releases, test packages for PyPop available directly on the [Test PyPI](https://test.pypi.org/) (<https://test.pypi.org/>).

Warning: These pre-release versions are being made available for initial testing, they are not intended to be used for production applications or analysis, and are not yet included in the main pypi.org index

```
pip install pypop-genomics --extra-index-url https://test.pypi.org/simple/
```

Note: If, for whatever reason, you cannot use these binaries (e.g. the pre-compiled binaries are not available for your platform), you may need to follow the [developer installation instructions](http://pypop.org/docs/guide-chapter-contributing.html#installation-for-developers) (<http://pypop.org/docs/guide-chapter-contributing.html#installation-for-developers>) in the contributors guide.

Upgrade an existing PyPop installation

To update an existing installation to a newer version, use the same command as above, but add the --upgrade (short version: -U) flag, i.e.

```
pip install -U pypop-genomics --extra-index-url https://test.pypi.org/simple/
```

Issues with installation permission

By default, pip will attempt to install the pypop-genomics package wherever the current Python installation is installed. This location may be a user-specific virtual environment (like conda, see below), or a system-wide installation. On many Unix-based systems, Python will generally already be pre-installed in a “system-wide” location (e.g. under /usr/lib) which is read-only for regular users. (This can also be true for system-installed versions of Python on Windows and MacOS.)

When pip install cannot install in a read-only system-wide location, pip will gracefully “fall-back” to installing just for you in your home directory (typically ~/.local/lib/python<VER> where <VER> is the version number of your current Python). In general, this is what is wanted, so the above instructions are normally sufficient.

However, you can also explicitly set installation to be in the user directory, by adding the --user command-line option to the pip install command, i.e.:


```
pip install pypop-genomics --user --extra-index-url https://test.pypi.org/simple/
```

This may be necessary in certain cases where `pip install` doesn't install into the expected user directory.

Installing within a conda environment

In the special case that you installing from within an activated user-specific conda virtual environment that provides Python, then you should **not** add the `--user` because it will install it in `~/.local/lib/` rather than under the user-specific conda virtual environment in `~/.conda/envs/`.

1.3.3 Install package from GitHub Releases (advanced)

We also sometimes make binary packages also available from the GitHub release page:

<https://github.com/alexlancaster/pypop/releases>

To install these is similar to installing via PyPI above, except that you need to explicitly provide a URL to the release page.

1. First, visit the release page, and choose the release version you wish to install (usually the most recent), and note the release tag (e.g. `v1.0.0-a23`).

Release version numbers

Note that version of the release is slightly different to the `git` tag. This is because the `git` tag follows [Semantic Versioning](https://semver.org/) (<https://semver.org/>), which Python internally normalizes and abbreviates. So the release with the `git` tag `v1.0.0-a23` is actually version `1.0.0a23` of the `pypop-genomics` package, and the version that `pip` “sees”.

2. Next, use `pip` to install the package by running a command of the form (this will select and install the correct wheel for your Python version and operating system automatically):

```
pip install pypop-genomics -f https://github.com/alexlancaster/pypop/releases/expanded_
assets/<TAG_NAME>
```

where `<TAG_NAME>` is replaced with a specific tag, e.g. for the example given above, you would run:

```
pip install pypop-genomics -f https://github.com/alexlancaster/pypop/releases/expanded_
assets/v1.0.0-a23
```

You can also manually download the specific wheel from the github release webpage and install directly, e.g.:

```
pip install pypop-genomics-1.0.0a23-cp311-cp311-manylinux_2_17_x86_64.manylinux2014_x86_
64.whl
```

1.3.4 Post-install PATH adjustments

You may need to adjust the PATH settings (especially on Windows) for the pypop scripts to be visible when run from your console application, without having to supply the full path to the pypop executable file.

Warning: Pay close attention to the “WARNINGS” that are shown during the pip installation, they will often note which directories need to be added to the PATH.

- On Linux and MacOS, systems this is normally fairly simple and only requires edit of the shell .profile, or similar and addition of the \$HOME/.local/bin to the PATH variable, followed by a restart of the terminal.
- For Windows, however, as noted in most online [instructions](https://www.computerhope.com/issues/ch000549.htm) (<https://www.computerhope.com/issues/ch000549.htm>), this may need additional help from your system administrator if your user doesn't have the right permissions, and also require a system reboot.

1.3.5 Uninstalling PyPop

To uninstall the current version of pypop-genomics:

```
pip uninstall pypop-genomics
```

1.4 Support and development

Please submit any bug reports, feature requests or questions, via our GitHub issue tracker (see our [bug reporting guidelines](http://pypop.org/docs/guide-chapter-contributing.html#reporting-and-requesting) (<http://pypop.org/docs/guide-chapter-contributing.html#reporting-and-requesting>) for more details on how to file a good bug report):

<https://github.com/alexlancaster/pypop/issues>

Please do not report bugs via private email to developers.

The development of the code for PyPop is via our GitHub project:

<https://github.com/alexlancaster/pypop>

GETTING STARTED WITH PYPOP

2.1 Introduction

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

As mentioned in the installation chapter, a minimal working example of a [configuration file \(.ini\)](https://github.com/alexlanaster/pypop/blob/main/tests/data/USAFEL-UchiTelle-small.pop) (<https://github.com/alexlanaster/pypop/blob/main/tests/data/USAFEL-UchiTelle-small.pop>), and a [population file \(.pop\)](https://github.com/alexlanaster/pypop/blob/main/tests/data/minimal.ini) (<https://github.com/alexlanaster/pypop/blob/main/tests/data/minimal.ini>), can be found by clicking the respective links.

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 simplest 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.

Note: The following assumes you have already *installed PyPop*, done any *post-install adjustments* needed for your platform, and verified that you can run the main commands (see the *Examples* section).

2.1.1 Interactive mode

To run PyPop in interactive mode, with a minimal “GUI”, on Windows or MacOS, you can directly click on the `pypop-interactive` file in the directory where the scripts were installed (see [post-install adjustments](#)).

You can also type `pypop-interactive` after starting a console application on all platforms (on MacOS and GNU/Linux, this is normally the **Terminal** program, on Windows, it’s **Command prompt**).

In most cases, this will launch a console with the following:

```
PyPop: Python for Population Genomics (1.0.0a15)
Copyright (C) 2003-2006 Regents of the University of California
Copyright (C) 2007-2023 PyPop team.
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.
```

(continues on next page)

(continued from previous page)

Select both an '.ini' configuration file and a '.pop' file via the system file dialog.

Following this:

1. the system file dialog will appear prompting you to select an *.ini configuration file*.
2. a second system file dialog will prompt you for a *.pop data file*.
3. after both files are selected the console will display the processing of the file:

```
PyPop is processing sample.pop ...
PyPop run complete!
XML output(s) can be found in: ['sample-out.xml']
Plain text output(s) can be found in: ['sample-out.txt']
Press Enter to continue...
```

4. when the run is completed, the last line will prompt you to press Enter to leave the console window (highlighted above).

If the system file GUI dialog does not appear (e.g. if you are running on a terminal without a display), it will fall-back to text-mode entry for the files, where you need to type the full (either relative or absolute) paths to the files. The output should resemble:

```
PyPop: Python for Population Genomics (1.0.0a15)
Copyright (C) 2003-2006 Regents of the University of California
Copyright (C) 2007-2023 PyPop team.
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 ...
PyPop run complete!
XML output(s) can be found in: ['sample-out.xml']
Plain text output(s) can be found in: ['sample-out.txt']
Press Enter to continue...
```

Note: Some messages with the prefix “LOG:” may appear during the console operation. They are informational only and do not indicate improper operation of the program.

In both cases 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* (highlighted above). The formats for these files are described in the sections on the *data file* and *configuration file*, below.

2.1.2 Batch mode

To run PyPop in the more common “batch mode”, you can run PyPop from the console (as noted above, on Windows: open **Command prompt**, aka a “DOS shell”; on MacOS or GNU/Linux: open the **Terminal** application). Change to a directory where your `.pop` file is located, and type the command:

```
pypop 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 in the current folder, otherwise you will need to supply the full path to the file. You can specify a particular configuration file for PyPop to use, by supplying the `-c` option as follows:

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

Please see [pypop usage](#) for the full list of command-line options.

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 [The configuration file](#)) 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. The XML output can be further transformed into plain text TSV files, either directly via `pypop` if invoked on multiple input files (using the `--enable-tsv` option, see [pypop usage](#)), or via the `popmeta` tool that aggregates results from different `pypop` runs (see [Using popmeta to aggregate results](#)).

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 `allPairwiseLDWithPermu` test may take several **days** if you have highly polymorphic loci in your data set.

2.2 Using popmeta to aggregate results

The `popmeta` script (`popmeta.bat` on Windows, `popmeta` on GNU/Linux) can aggregate results from a number of output XML files from individual populations into a set of tab-separated (TSV) files containing summary statistics via customized XSLT (eXtensible Stylesheet Language for Transformations) stylesheets. These TSV files can be directly imported into a spreadsheet or statistical software (e.g., **R**, **SAS**). In addition, there is some preliminary support for export into other formats, such as the population genetic software (e.g., **PHYLIP**).

Here is an example of a `popmeta` run, following on from the XML outputs generated in similar fashion in the previous `pypop` runs:

```
popmeta -o altdir Guatemalan-out.xml NorthAmerican-out.xml
```

This will generate a number of `.dat` files, including `1-locus-allele.dat`.

Note: It's highly recommended to use the `-o` option to save the output in a separate subdirectory, as the output `.dat` files have fixed names, and will overwrite any files in the local directory with the same name). See [popmeta usage](#) for the full list of options.

Note that a similar effect can be achieved directly from a `pypop` run (assuming that the configuration file can be used for both `.pop` population files), by invoking `pypop` with the `--enable-tsv` option:

```
pypop -c newconfig.ini -o altdir Guatemalan.pop NorthAmerican.pop --enable-tsv
```

2.3 Command-line interfaces

Described below is the usage for both programs, including a full list of the current command-line options and arguments. Note that you can also view this full list of options from the program itself by supplying the `--help` option, i.e. `pypop --help`, or `popmeta --help`, respectively.

2.3.1 pypop usage

```
usage: pypop [-h] [-o OUTPUTDIR] [-V] [-c CONFIG] [-m] [-d] [-x XSLFILE] [-t]
            [--enable-ihwg] [--enable-phylip] [-i] [-f FILELIST]
            [POPFILe ...]
```

Options for pypop

-o, --outputdir	put output in directory OUTPUTDIR
-V, --version	show program's version number and exit
-c, --config	select config file
	Default: "config.ini"
-m, --testmode	run PyPop in test mode for unit testing
-d, --debug	enable debugging output (overrides config file setting)
-x, --xsl	override the default XSLT translation with XSLFILE

TSV output options

Note that `--enable-` flags only valid if `--enable-tsv/-t` selected

-t, --enable-tsv	generate TSV output files (aka run 'popmeta')
--enable-ihwg	enable 13th IWHG workshop populationdata default headers
--enable-phylip	enable generation of PHYLIP <code>.phy</code> files

Mutually exclusive input options

-i, --interactive	run in interactive mode, prompting user for file names
-f, --filelist	file containing list of files (one per line) to process (mutually exclusive with supplying POPFILEs)
POPFILE	input population (.pop) file(s) Default: []

2.3.2 popmeta usage

```
usage: popmeta [-h] [-o OUTPUTDIR] [-V] [--disable-tsv] [--output-meta]
               [-x XSLDIR] [--enable-ihwg] [--enable-phylip | -b FACTOR]
               XMLFILE [XMLFILE ...]
```

Positional Arguments

XMLFILE	XML (.xml) file(s) generated by pypop runs Default: []
----------------	---

Options for popmeta

-o, --outputdir	put output in directory OUTPUTDIR
-V, --version	show program's version number and exit
--disable-tsv	disable generation of .dat TSV files
--output-meta	dump the meta output file to stdout, ignore xslt file
-x, --xsldir	use specified directory to find meta XSLT
--enable-ihwg	enable 13th IWHG workshop populationdata default headers

Mutually exclusive popmeta options

--enable-phylip	enable generation of PHYLIP .phy files
-b, --batchsize	process in batches of size total/FACTOR rather than all at once, by default do separately (batchsize=0) Default: 0

2.4 The data file

2.4.1 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.

[Listing 2.7](#) shows the relevant lines for the configuration to read in the data shown in [Listing 2.1](#) through to [Listing 2.6](#).

Listing 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.

Listing 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`).

Listing 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
```

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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 [Listing 2.2](#), but which includes population level information.

Listing 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).

Listing 2.5: Sequence genotype data with header information

labcode	file				
BLOGGS	C_New				
popName	ID	TGFB1cdn10(1)	TGFB1cdn10(2)	TGFBhapl(1)	TGFBhapl(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 TGFBhapl locus is actually haplotype data, but PyPop simply treats each combination as a separate “allele” for subsequent analysis.

Listing 2.6: Allele count data

populat	method	ethnic	country	latit	longit
UchiTelle	PCR-SSO	Klingon	QZ	052.81N	100.25E
dqa1	count				
0101	31				
0102	37				
0103	17				
0201	21				
0301	32				
0401	9				

(continues on next page)

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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 **LibreOffice**, export the file as tab-delimited text, in order to use it as PyPop data file.

2.4.2 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.

Warning:

- 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)¹

2.5 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**.

¹ These hardcoded numbers can be changed if you obtain the source code yourself and change the appropriate `#define emhaplofreq.h` and recompile the program.

2.5.1 A minimal configuration file

Here we present a minimal .ini file corresponding to [Listing 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 *Advanced options*.

Listing 2.7: Minimal config.ini file

```
[General]
debug=0

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

[HardyWeinberg]
lumpBelow=5

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

[HomozygosityEWSlatkinExact]
numReplicates=10000

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

Configuration file sections (highlighted above)

- [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.

- 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 :ref:`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_title](#) in [Listing 2.6](#)). Listing multiple loci simply permits the same .ini file to be reused for each data file.

- [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.

- [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 [Advanced options](#), 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**.

- [HomozygosityEWSlatkinExact]

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.

- [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).

2.5.2 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 [Listing 2.2](#) or header data block as in [Listing 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-out.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 *Multi-locus allele-level HLA genotype data with sample and header information*, 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 (i.e. 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](ftp://ftp.ebi.ac.uk/pub/databases/imgt/mhc/hla/) (<ftp://ftp.ebi.ac.uk/pub/databases/imgt/mhc/hla/>). 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](http://www.ebi.ac.uk/imgt/hla/download.html) (<http://www.ebi.ac.uk/imgt/hla/download.html>)) [**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 will 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 *n*th 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 sources²

² [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>).

INTERPRETING PYPOP OUTPUT

As mentioned in *What happens when you run PyPop?*, 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:

```
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.

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	0.21111	19	0101	0.13333	12
0301	0.15556	14	0201	0.21111	19
0101	0.13333	12	0210	0.10000	9
2501	0.12222	11	0218	0.10000	9
0210	0.10000	9	0301	0.15556	14
0218	0.10000	9	2501	0.12222	11
3204	0.08889	8	3204	0.08889	8
6901	0.04444	4	6814	0.03333	3
6814	0.03333	3	6901	0.04444	4
7403	0.01111	1	7403	0.01111	1
Total	1.00000	90	Total	1.00000	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.

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:

	Observed	Expected	Chi-square	DoF	p-value
Common	N/A	N/A	4.65	1	0.0310*
Lumped genotypes	N/A	N/A	1.17	1	0.2797
Common + lumped	N/A	N/A	5.82	1	0.0158*
All homozygotes	21	13.01	4.91	1	0.0268*
All heterozygotes	26	33.99	1.88	1	0.1706
Common heterozygotes by allele					
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					
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			

- **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.

- **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).

- **Common + lumped.**

The result for goodness of fit to HWP for both the common and the lumped genotypes.

- **All homozygotes.**

The result for goodness of fit to HWP for the pooled set of homozygous genotypes.

- **All heterozygotes.**

The result for goodness of fit to HWP for the pooled set of heterozygous genotypes.

- **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`.

- **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 ($p < 0.05$) 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.

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
```

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

```
-----
Observed heterozygosity: 0.553190
Expected heterozygosity: 0.763900
Std. deviation: 0.000630
```

(continues on next page)

(continued from previous page)

```
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.

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.

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, as shown in the sample output below.

II. Multi-locus Analyses

=====

Haplotype/ linkage disequilibrium (LD) statistics

Pairwise LD estimates

Locus pair	D	D'	Wn	ln(L_1)	ln(L_0)	S	ALD_1_2	ALD_2_1
A:C	0.01465	0.49229	0.39472	-289.09	-326.81	75.44	0.41435	0.37525
A:B	0.01491	0.50895	0.40145	-293.47	-330.84	74.73	0.40726	0.39512
A:DRB1	0.01299	0.42896	0.38416	-282.00	-309.16	54.32	0.32934	0.38370
A:DQA1	0.01219	0.33413	0.36466	-269.57	-286.08	33.02	0.25803	0.34897
A:DQB1	0.01356	0.39266	0.37495	-275.58	-297.62	44.07	0.29931	0.37489
A:DPA1	0.01681	0.32397	0.36666	-219.78	-226.97	14.38	0.19446	0.35360
A:DPB1	0.01362	0.42240	0.40404	-237.85	-262.06	48.42	0.33848	0.41739
C:B	0.04125	0.88739	0.85752	-210.37	-342.68	264.63	0.84781	0.86104
C:DRB1	0.01698	0.48046	0.47513	-280.34	-317.66	74.62	0.32308	0.47691
C:DQA1	0.02072	0.47797	0.49368	-263.23	-293.74	61.01	0.31386	0.50338
C:DQB1	0.01766	0.45793	0.49879	-269.55	-305.28	71.46	0.30479	0.50122
C:DPA1	0.02039	0.41030	0.46438	-224.72	-236.52	23.61	0.21172	0.46433
C:DPB1	0.01898	0.46453	0.37002	-242.45	-268.46	52.01	0.33462	0.45327
B:DRB1	0.01723	0.50254	0.41712	-286.79	-320.50	67.42	0.32654	0.43913
B:DQA1	0.01845	0.44225	0.43582	-271.36	-296.59	50.45	0.28877	0.44993
B:DQB1	0.01958	0.49040	0.43654	-277.30	-308.13	61.65	0.31328	0.45679
B:DPA1	0.01875	0.37441	0.40117	-229.76	-239.16	18.80	0.20689	0.40443
B:DPB1	0.01898	0.46082	0.38001	-247.84	-272.77	49.86	0.32227	0.45680
DRB1:DQA1	0.06138	0.92556	0.92465	-164.06	-271.56	214.99	0.82051	0.93006
DRB1:DQB1	0.06058	1.00000	1.00000	-147.74	-283.10	270.72	0.93302	1.00000

...

For each locus pair, we report three measures of overall linkage disequilibrium. D' [Hedrick:1987] weights the contribution to LD of specific allele pairs by the product of their allele frequencies (D' in the output); W_n [Cramer:1946] is a re-expression of the chi-square statistic for deviations between observed and expected haplotype frequencies (W_n in the output). $W_{A/B}$ and $W_{B/A}$ (ALD_1_2 and ALD_2_1, respectively in the output) are extensions of W_n that account for asymmetry when the

number of alleles differs at two loci [Thomson:Single:2014]. Below we describe the measures, each of which is 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.

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

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^2_{LD} , normalized to be between zero and one. When there are only two alleles per locus, W_n is equivalent to the correlation coefficient between the two loci, defined as:

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

two alleles case

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

$W_{A/B}$ and $W_{B/A}$

When there are different numbers of alleles at the two loci, the direct correlation property for the r correlation measure is not retained by W_n , its multi-allelic extension. The complementary pair of conditional asymmetric LD (ALD) measures, $W_{A/B}$ and $W_{B/A}$, were developed to extend the W_n measure. $W_{A/B}$ is (inversely) related to the degree of variation of A locus alleles on haplotypes conditioned on B locus alleles. If there is no variation of A locus alleles on haplotypes conditioned on B locus alleles, then $W_{A/B} = 1$ $W_{A/B} = W_{B/A} = W_n$ when there is symmetry in the data and thus for bi-allelic SNPs.

$$W_{A/B} = \left[\frac{\sum_{i=1}^I \sum_{j=1}^J D_{ij}^2 / q_j}{1 - F_A} \right]^{\frac{1}{2}}$$

$$W_{B/A} = \left[\frac{\sum_{i=1}^I \sum_{j=1}^J D_{ij}^2 / p_i}{1 - F_B} \right]^{\frac{1}{2}}$$

In addition to the LD measures described above, for each locus pair, we describe three additional measures related to the log-likelihood that are displayed in the output above:

$\ln(L_1)$

the log-likelihood of obtaining the observed data given the inferred haplotype frequencies ($\ln(L_1)$ in the output)

$\ln(L_0)$

the log-likelihood of the data under the null hypothesis of linkage equilibrium ($\ln(L_0)$ in the output)

S

the statistic (S in the output) 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. If a permutation test is requested (by setting the option `allPairwiseLDWithPermu` to a number greater than zero in the *.ini file*), the empirical distribution of S is generated by shuffling genotypes among individuals, separately for each locus, thus creating linkage equilibrium. The additional column `# permu` that will be generated (not shown in the example output above) will indicate how many permutations were carried out. The p -value (also not shown) will be the fraction of permutations that results in values of S greater or equal to that observed. A $p < 0.05$ 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 [What happens when you run PyPop?](#)).

3.3.2 Haplotype frequency estimation

```
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**).

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
...					

CONTRIBUTING TO PYPOP

Contributions to PyPop are welcome, and they are greatly appreciated! Every little bit helps, and credit will always be given.

4.1 Reporting and requesting

4.1.1 Did you find a bug?

When [reporting a bug](https://github.com/alexlancaster/pypop/issues) (<https://github.com/alexlancaster/pypop/issues>) please use one of the provided issue templates if applicable, otherwise just start a blank issue and describe your situation.

- Ensure the bug was not already reported by searching on GitHub under [Issues](https://github.com/alexlancaster/pypop/issues) (<https://github.com/alexlancaster/pypop/issues>).
- If you're unable to find an open issue addressing the problem, open a new one. Be sure to include a title and clear description, as much relevant information as possible, and a code sample or an executable test case demonstrating the expected behavior that is not occurring.
- If possible, use the relevant bug report templates to create the issue.
- When reporting bugs, especially during installation, please run the following and include the output:

```
echo $CPATH
echo $LIBRARY_PATH
echo $PATH
which python
```

If you are running on MacOS, and you used the MacPorts installation method, please also run and include the output of:

```
port installed
```

4.1.2 Documentation improvements

pypop could always use more documentation, whether as part of the official docs, in docstrings, or even on the web in blog posts, articles, and such. Write us a [documentation issue](https://github.com/alexlancaster/pypop/issues/new) (<https://github.com/alexlancaster/pypop/issues/new>) describing what you would like to see improved in here.

If you are able to contribute directly (e.g., via a pull request), please read our [website contribution guide](#).

4.1.3 Feature requests and feedback

The best way to send feedback is to file an issue using the [feature template](https://github.com/alexlancaster/pypop/issues/new?assignees=&labels=&projects=&template=feature_request.md) (https://github.com/alexlancaster/pypop/issues/new?assignees=&labels=&projects=&template=feature_request.md).

If you are proposing a feature:

- Explain in detail how it would work.
- Keep the scope as narrow as possible, to make it easier to implement.
- Remember that this is a volunteer-driven project, and that code contributions are welcome

4.2 Making a code contribution

To contribute new code that implement a feature, or fix a bug, this section provides a step-by-step guide to getting you set-up. The main steps are:

1. forking the repository (or “repo”)
2. cloning the main repo on to your local machine
3. making a new branch
4. *installing a development version* on your machine
5. updating your branch when “upstream” (the main repository) has changes to include those changes in your local branch
6. updating the changelog in `NEWS.rst`
7. checking unit tests pass
8. making a pull request

4.2.1 Fork this repository

Fork [this repository before contributing](https://github.com/alexlancaster/pypop/network/members) (<https://github.com/alexlancaster/pypop/network/members>). Forks creates a cleaner representation of the [contributions to the project](https://github.com/alexlancaster/pypop/network) (<https://github.com/alexlancaster/pypop/network>).

4.2.2 Clone the main repository

Next, clone the main repository to your local machine:

```
git clone https://github.com/alexlancaster/pypop.git
cd pypop
```

Add your fork as an upstream repository:

```
git remote add myfork git://github.com/YOUR-USERNAME/pypop.git
git fetch myfork
```

4.2.3 Make a new branch

From the main branch create a new branch where to develop the new code.

```
git checkout main
git checkout -b new_branch
```

Note the main branch is from the main repository.

4.2.4 Build locally and make your changes

Now you are ready to make your changes. First, you need to build `pypop` locally on your machine, and ensure it works, see the separate section on *building and installing a development version*.

Once you have done the installation and have verified that it works, you can start to develop the feature, or make the bug fix, and keep regular pushes to your fork with comprehensible commit messages.

```
git status
git add # (the files you want)
git commit # (add a nice commit message)
git push myfork new_branch
```

While you are developing, you can execute `pytest` as needed to run your unit tests. See *run unit tests with pytest*.

4.2.5 Keep your branch in sync with upstream

You should keep your branch in sync with the upstream main branch. For that:

```
git checkout main # return to the main branch
git pull # retrieve the latest source from the main repository
git checkout new_branch # return to your devel branch
git merge --no-ff main # merge the new code to your branch
```

At this point you may need to solve merge conflicts if they exist. If you don't know how to do this, I suggest you start by reading the [official docs](https://docs.github.com/en/pull-requests/collaborating-with-pull-requests/addressing-merge-conflicts/resolving-a-merge-conflict-on-github) (<https://docs.github.com/en/pull-requests/collaborating-with-pull-requests/addressing-merge-conflicts/resolving-a-merge-conflict-on-github>)

You can push to your fork now if you wish:

```
git push myfork new_branch
```

And, continue doing your developments as previously discussed.

4.2.6 Update `NEWS.rst`

Update the changelog file under `NEWS.rst` with an explanatory bullet list of your contribution. Add that list under the “Notes towards the next release” under the appropriate category, e.g. for a new feature you would add something like:

```
Notes towards next release
-----
(unreleased)

New features
```

(continues on next page)

(continued from previous page)

```
AAAAAAAAAAAA
```

```
* here goes my new additions
* explain them shortly and well
```

Also add your name to the authors list at `website/docs/AUTHORS.rst`.

4.2.7 Run unit tests with pytest

Once you have done your initial installation, you should first check that the build worked, by running the test suite, via `pytest`:

```
pytest tests
```

If `pytest` is not already installed, you can install via:

```
pip install pytest
```

If you run into errors during your initial installation, please first carefully repeat and/or check your installation. If you still get errors, file a bug, and include the output of `pytest` run in verbose mode and capturing the output

```
pytest -s -v tests
```

You should also continuously run `pytest` as you are developing your code, to ensure that you don't inadvertently break anything.

Also before creating a Pull Request from your branch, check that all the tests pass correctly, using the above.

These are exactly the same tests that will be performed online via Github Actions continuous integration (CI). This project follows CI good practices (let us know if something can be improved).

4.2.8 Make a Pull Request

Once you are finished, you can create a pull request to the main repository and engage with the developers. If you need some code review or feedback while you're developing the code just make a pull request.

However, before submitting a Pull Request, verify your development branch passes all tests as *described above* . If you are developing new code you should also implement new test cases.

Pull Request checklist

Before requesting a finale merge, you should:

1. Make sure your PR passes all `pytest` tests.
2. Add unit tests if you are developing new features
3. Update documentation when there's new API, functionality etc.
4. Add a note to `NEWS.rst` about the changes.
5. Add yourself to `website/docs/AUTHORS.rst`.

4.3 Installation for developers

Once you have setup your branch as described in *making a code contribution*, above, you are ready for the four main steps of the developer installation:

1. install a build environment
2. build
3. run tests

Note: Note that you if you need to install PyPop from source, but do not intend to contribute code, you can skip creating your own forking and making an additional branch, and clone the main upstream repository directly:

```
git clone https://github.com/alexlancaster/pypop.git
cd pypop
```

For most developers, we recommend using the miniconda approach described below.

4.3.1 Install the build environment

To install the build environment, you should choose either conda or system packages. Once you have chosen and installed the build environment, you should follow the instructions related to the option you chose here in all subsequent steps.

Install build environment via miniconda (recommended)

1. Visit <https://docs.conda.io/en/latest/miniconda.html> to download the miniconda installer for your platform, and follow the instructions to install.

In principle, the rest of the PyPop miniconda installation process should work on any platform that is supported by miniconda, but only Linux and MacOS have been tested in standalone mode, at this time.

2. Once miniconda is installed, create a new conda environment, using the following commands:

```
conda create -n pypop3 gsl swig python=3
```

This will download and create a self-contained build-environment that uses of Python to the system-installed one, along with other requirements. You will need to use this this environment for the build, installation and running of PyPop. The conda environment name, above, pypop3, can be replaced with your own name.

When installing on MacOS, before installing conda, you should first to ensure that the Apple Command Line Developer Tools (XCode) are installed (<https://mac.install.guide/commandlinetools/4.html>), so you have the compiler (clang, the drop-in replacement for gcc), git etc. conda is unable to include the full development environment for clang as a conda package for legal reasons.

3. Activate the environment, and set environments variables needed for compilation:

```
conda activate pypop3
conda env config vars set CPATH=${CONDA_PREFIX}/include:${CPATH}
conda env config vars set LIBRARY_PATH=${CONDA_PREFIX}/lib:${LIBRARY_PATH}
conda env config vars set LD_LIBRARY_PATH=${CONDA_PREFIX}/lib:${LD_LIBRARY_PATH}
```

4. To ensure that the environment variables are saved, reactivate the environment:

```
conda activate pypop3
```

5. Skip ahead to *Build PyPop*.

Install build environment via system packages (advanced)

Unix/Linux:

1. Ensure Python 3 version of pip is installed:

```
python3 -m ensurepip --user --no-default-pip
```

Note the use of the `python3` - you may find this to be necessary on systems which parallel-install both Python 2 and 3, which is typically the case. On newer systems you may find that `python` and `pip` are, by default, the Python 3 version of those tools.

2. Install packages system-wide:

1. Fedora/Centos/RHEL

```
sudo dnf install git swig gsl-devel python3-devel
```

2. Ubuntu

```
sudo apt install git swig libgsl-dev python-setuptools
```

MacOS X

1. Install developer command-line tools: <https://developer.apple.com/downloads/> (includes `git`, `gcc`)
2. Visit <http://macports.org> and follow the instructions there to install the latest version of MacPorts for your version of MacOS X.
3. Set environment variables to use macports version of Python and other packages, packages add the following to `~/ .bash_profile`

```
export PATH=/opt/local/bin:$PATH
export LIBRARY_PATH=/opt/local/lib/:$LIBRARY_PATH
export CPATH=/opt/local/include:$CPATH
```

4. Rerun your bash shell login in order to make these new exports active in your environment. At the command line type:

```
exec bash -login
```

5. Install dependencies via MacPorts and set Python version to use (FIXME: currently untested!)

```
sudo port install swig-python gsl py39-numpy py39-lxml py39-setuptools py39-pip py39-
  pytest
sudo port select --set python python39
sudo port select --set pip pip39
```

6. Check that the MacPorts version of Python is active by typing: `which python`, if it is working correctly you should see `/opt/local/bin/python`.

Windows

(Currently untested in standalone-mode)

4.3.2 Build PyPop

You should choose *either* of the following two approaches. Don't try to mix-and-match the two. The build-and-install approach is only recommended if don't plan to make any modifications to the code locally.

Build-and-install (not recommended for developers)

Once you have setup your environment and cloned the repo, you can use the following one-liner to examine the `setup.py` and pull all the required dependencies from `pypi.org` and build and install the package.

Note that if you use this method and install the package, it will be available to run anywhere on your system, by running `pypop`.

If you use this installation method, changes you make to the code, locally, or via subsequent `git pull` requests will not be available in the installed version until you repeat the `pip install` command.

1. if you installed the conda development environment, use:

```
pip install .[test]
```

(the `[test]` keyword is included to make sure that any package requirements for the test suite are installed as well).

2. if you installed a system-wide environment, the process is slightly different, because we install into the user's `$HOME/.local` rather than the conda environment:

```
pip install --user .[test]
```

3. PyPop is ready-to-use, you should *run unit tests with pytest*.
4. if you later decide you want to switch to using the developer approach, below, follow the *cleaning up build* before starting.

Build-and-run-from-checkout (recommended for developers)

1. First manually install the dependencies via `pip`, note that if you are running on Python `<= 3.8`, you will need to also add `importlib-resources` to the list of packages, below.

1. conda

```
pip install numpy lxml psutil pytest
```

2. system-wide

```
pip install --user numpy lxml psutil pytest
```

2. Run the build

```
./setup.py build
```

3. You will be running PyPop, directly out of the `src/PyPop` subdirectory (e.g. `./src/PyPop/pypop.py` and `./src/PyPop/popmeta.py`). Note that you have to include the `.py` extension when you run from an uninstalled checkout, because the script is not installed.

Cleaning up build

If you installed using the approach in *Build-and-install (not recommended for developers)*, above, follow the end-user instructions on *Uninstalling PyPop*. In addition, to clean-up any compiled files and force a recompilation from scratch, run the `clean` command:

```
./setup clean --all
```

4.4 Making a documentation or website contribution

Interested in maintaining the PyPop website and/or documentation, such as the *PyPop User Guide*? Here are ways to help.

4.4.1 Overview

All the documentation (including the website homepage) are maintained in this directory (and subdirectories) as *reStructuredText* (<https://docutils.sourceforge.io/rst.html>) (`.rst`) documents. *reStructuredText* is very similar to GitHub markdown (`.md`) and should be fairly self-explanatory to edit (especially for pure text changes). From the `.rst` “source” files which are maintained here on github, we use *sphinx* (<https://www.sphinx-doc.org/en/master/>) to generate (aka “compile”) the HTML for both the `pypop.org` user guide and and PDF (via LaTeX) output. We have setup a GitHub action, so that as soon as a documentation source file is changed, it will automatically recompile all the documentation, update the `gh-pages` branch (which is synced to the GitHub pages) and update the files on the website.

Here’s an overview of the process:

```
.rst files -> sphinx -> HTML / PDF -> push to gh-pages branch -> publish on pypop.org
```

This means that any changes to the source will automatically update both website home page the documentation.

Once any changes are pushed to a branch (as described below), the GitHub action will automatically rebuild the website, and the results will be synced to a “staging” version of the website at:

- <https://alexlanaster.github.io/beta.pypop.org/>

4.4.2 Structure

Here’s an overview of the source files for the website/documentation located in the `website` subdirectory at the time of writing. Note that some of the documentation and website files, use the `include::` directive to include some “top-level” files, located outside `website` like `README.rst` and `CONTRIBUTING.rst`:

- `index.rst` (this is the source for the homepage at <http://pypop.org/>)
- `conf.py` (Sphinx configuration file - project name and other global settings are stored here)
- `docs` (directory containing the source for the *PyPop User Guide*, which will eventually live at <http://pypop.org/docs>).
 - `index.rst` (source for the top-level of the *PyPop User Guide*)
 - `guide-chapter-install.rst` (pulls in parts of the top-level `README.rst`)
 - `guide-chapter-usage.rst`
 - `guide-chapter-instructions.rst`
 - `guide-chapter-contributing.rst` (pulls in top-level `CONTRIBUTING.rst` that contains the source of the text that you are reading right now)
 - `guide-chapter-changes.rst` (pulls in top-level `NEWS.rst` and `AUTHORS.rst`, which is local to `website`)

- AUTHORS.rst
- licenses.rst (pulls in top-level LICENSE)
- biblio.rst
- html_root (any files or directories committed in this directory will appear at the top-level of the website)
 - psb-pypop.pdf (e.g. this resides at <http://pypop.org/psb-pypop.pdf>)
 - tissue-antigens-lancaster-2007.pdf
 - PyPopLinux-0.7.0.tar.gz (old binaries - will be removed soon)
 - PyPopWin32-0.7.0.zip
 - popdata (directory - Suppl. data for Solberg et. al 2018 - <https://pypop.org/popdata/>)
- reference (directory containing the old DocBook-based documentation, preserved to allow for unconverted files to be converted later, this directory is ignored by the build process)

4.4.3 Modifying documentation

Minor modifications

For small typo fixes, moderate copyedits at the paragraph level (e.g. adding or modifying paragraphs with little or no embedded markup), you can make changes directly on the github website.

1. navigate to the .rst file you want to modify in the GitHub code directory, you'll see a preview of how most of the .rst will be rendered
2. hover over the edit button - you'll see an **"Edit the file in a fork in your project"** (if you are already a project collaborator, you may also have the optional of creating a branch directly in the main repository).
3. click it and it will open up a window where you can make your changes
4. make your edits (it's a good idea to look at the preview tab periodically as you make modifications)
5. once you've finished with the modifications, click **"Commit changes"**
6. put in an a commit message, and click **"Propose changes"**
7. this will automatically create a new branch in your local fork, and you can immediately open up a pull-request by clicking **"Create pull request"**
8. open up a pull-request and submit - new documentation will be automatically built and reviewed. if all is good, it will be merged by the maintainer and made live on the site.

Major modifications

For larger structural changes involving restructuring documentation or other major changes across multiple .rst files, **it is highly recommended** that you should make all changes in your own local fork, by cloning the repository on your computer and then building the documentation locally. Here's an overview of how to do that:

The commands in the "Sphinx build" section of the workflow [.github/workflows/documentation.yaml](https://github.com/alexlancaster/pypop/blob/main/.github/workflows/documentation.yaml) (<https://github.com/alexlancaster/pypop/blob/main/.github/workflows/documentation.yaml>) which are used to run the GitHub Action that builds the documentation when it is deployed, is the best source for the most update-to-date commands to run, and should be consulted if the instructions in this document become out of date.

1. install sphinx and sphinx extensions

```
pip install setuptools_scm sphinx piccolo-theme sphinx_rtd_theme myst_parser rst2pdf_
↳ sphinx_togglebutton sphinx-argparse
```

2. make a fork of pypop if you haven't already (see [previous section](#))
3. *clone the fork and add your fork as an upstream repository* on your local computer, and *make a new branch*. Note that you do not need to build pypop first in order to build the documentation - you can do them separately.
4. make your changes to your `.rst` files and/or `conf.py`
5. build the HTML documentation:

```
sphinx-build website _build
```

6. view the local documentation: you can open up browser and navigate to the `index.html` in the top-level of the newly-created `_build` directory
7. use `git commit` to commit your changes to your local fork.
8. open up a pull-request against the upstream repository

Building the PDF for the *PyPop User Guide* is a bit more involved, as you will need to have various TeX packages installed.

1. install the LaTeX packages (these are packages needed for Ubuntu, they may be different on your distribution):

```
sudo apt-get install -y latexmk texlive-latex-recommended texlive-latex-extra texlive-
↳ fonts-recommended texlive-fonts-extra texlive-luatex texlive-xetex
```

2. build the LaTeX and then compile the PDF:

```
sphinx-build -b latex website _latexbuild
make -C _latexbuild
```

3. the user guide will be generated in `_latexbuild/pypop-guide.pdf`

AUTHORS AND HISTORY

5.1 Authors of software components

Alex Lancaster

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

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

Contributed further statistical analysis code for the R programs.

Owen Solberg

Implemented filter modules, including conversion to allele name information to sequence data.

Yingssu Tsai

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

Glenys Thomson

Principal investigator and project lead.

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](http://www.gnu.org/licenses/gpl.html) (<http://www.gnu.org/licenses/gpl.html>). 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.

5.2 PyPop Release History

5.2.1 Notes towards next release

(unreleased)

New features

- Updated to Python 3
- Implement new assymetric LD (ALD) measure
- New wrapper module Haplostats. This wraps a portion of the `haplo.stats` R package `haplo-stats` for haplotype estimation. [Implementation in alpha-phase].
- `popmeta`: now accepts the `-o/--outputdir` option for saving generated files.
- `pypop`: renamed `--generate-tsv` to `--enable-tsv`

5.2.2 Release Notes for PyPop 0.7.0

(2008-09-09)

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 PHYLP mode is enabled.

5.2.3 Release Notes for PyPop 0.6.0

(2005-04-13)

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 (“`<=`”) 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.)

5.2.4 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.

5.2.5 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.

5.2.6 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.

5.2.7 Release Notes for PyPop 0.4.3beta

Bug fixes

- Fixed bug in processing of `popname` field. Thanks to Richard Single for the report.

LICENSES

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PyPop: Python for Population Genomics

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BIBLIOGRAPHY

- [Cano:etal:2007] Pedro Cano. 2007. "Common and well-documented HLA alleles: report of the ad-hoc committee of the American Society for Histocompatibility and Immunogenetics". 68. 5. 392-417. *Human Immunology*.
- [Chen:etal:1999] JJ Chen, JA Hollenbach, EA Trachtenberg, JJ Just, M Carrington, KS Ronningen, A Begovich, MC King, SK McWeeney, SJ Mack, HA Erlich, and G Thomson. 1999. "Hardy-Weinberg testing for HLA class II (DRB1, DQA1, DQB1 and DPB1) loci in 26 human ethnic groups". 54. 533-542. *Tissue Antigens*.
- [Cramer:1946] H Cramer. *Mathematical Models of Statistics*. 1946. Princeton University Press. Princeton NJ.
- [Dempster:1977] A Dempster, N Laird, and D Rubin. 1977. "Maximum likelihood estimation from incomplete data using the EM algorithm". 39. 1-38. *J Royal Stat Soc*.
- [Ewens:1972] W Ewens. 1972. "The sampling theory of selectively neutral alleles.". *Theor. Pop. Biol.* 3. 87-112.
- [Excoffier:Slatkin:1995] Laurent Excoffier and Montgomery Slatkin. 1995. "Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population". *Molecular Biology and Evolution*. 12. 5. 921-927.
- [Guo:Thompson:1992] S W Guo and E A Thompson. 1992. "Performing the exact test of Hardy-Weinberg proportion for multiple alleles". *Biometrics*. 48. 361-72.
- [Hedrick:1987] P W Hedrick. 1987. "Gametic disequilibrium measures: proceed with caution". 117. 2. 331-41. *Genetics*.
- [Lancaster:etal:2003] Alex Lancaster, Mark P Nelson, Richard M Single, Diogo Meyer, and Glenys Thomson. 2003. "PyPop: a software framework for population genomics: analyzing large-scale multi-locus genotype data". *Pacific Symposium on Biocomputing*. R B Altman. et al.. vol 8. 514-525. .. [PDF (344 kB)].
- [Lancaster:etal:2007a] Alex Lancaster, Mark P Nelson, Richard M Single, Diogo Meyer, and Glenys Thomson. 2007a. *Software framework for Biostatistics Core*. JA Hansen. *Immunobiology of the Human MHC: Proceedings of the 13th International Histocompatibility Workshop and Conference*. IHWG Press. Seattle, Washington. I. 510-517.
- [Lancaster:etal:2007b] Alex Lancaster, Richard M Single, Owen D Solberg, Mark P Nelson, and Glenys Thomson. 2007b. "PyPop update - a software pipeline for large-scale multilocus population genomics.". *Tissue Antigens*. 69 Suppl 1. 192-197. .. [PDF (150 kB)].
- [Mack:etal:2007] Steven J. Mack, Alicia Sanchez-Mazas, Diogo Meyer, Richard M Single, Yingssu Tsai, and Henry Erlich. 2007. *Methods used in the generation and preparation of data for analysis in the 13th International Histocompatibility Workshop*. JA Hansen. *Immunobiology of the Human MHC: Proceedings of the 13th International Histocompatibility Workshop and Conference*. IHWG Press. Seattle, Washington. I. 564-579.
- [Meyer:etal:2007] Diogo Meyer, Richard M Single, Steven J. Mack, Alex Lancaster, Mark P Nelson, M. Fernández-Viñaa, Henry Erlich, and Glenys Thomson. 2007. *Haplotype frequencies and linkage disequilibrium among classical HLA genes*. JA Hansen. *Immunobiology of the Human MHC: Proceedings of the 13th International Histocompatibility Workshop and Conference*. IHWG Press. Seattle, Washington. I. 705-746.
- [Salamon:etal:1999] H Salamon, W Klitz, S Easta, X Gao, HA Erlich, M Fernandez-Vina, and EA Trachtenberg. 1999. "Evolution of HLA class II molecules: Allelic and amino acid site variability across populations". 152. 393-400. *Genetics*.

- [Schneider:etal:2000] S Schneider, D Roessli, and L Excoffier. 2000. “Arlequin: A software for population genetics data analysis. <http://lgb.unige.ch/arlequin/>”. Ver 2.000. Genetics and Biometry Lab, Dept. of Anthropology, University of Geneva.
- [Single:etal:2007a] RM Single, D Meyer, and G Thomson. 2007a. *Statistical methods for analysis of population genetic data*. JA Hansen. *Immunobiology of the Human MHC: Proceedings of the 13th International Histocompatibility Workshop and Conference*. IHWG Press. Seattle, Washington. I. 518-522.
- [Slatkin:1994] M Slatkin. 1994. “An exact test for neutrality based on the Ewens sampling distribution”. *Genetical Research*. 64. 71-74.
- [Slatkin:1996] M Slatkin. 1996. “A correction to the exact test based on the Ewens sampling distribution”. *Genetical Research*. 68. 259-260.
- [Solberg:etal:2008] Owen D. Solberg, Steven J. Mack, Alex K. Lancaster, Richard M. Single, Yingssu Tsai, Alicia Sanchez-Mazas, and Glenys Thomson *Hum Immunol* (2008), doi: 10.1016/j.humimm.2008.05.001
- [Thomson:Single:2014] Glenys Thomson and Richard M. Single. 2014. “Conditional Asymmetric Linkage Disequilibrium (ALD): Extending the Biallelic r^2 Measure” *Genetics*, 198, 321–331.
- [Watterson:1978] G Watterson. 1978. “The homozygosity test of neutrality”. *Genetics*. 88. 405-417.