simuPOP User's Guide

Release 0.7.6 (Rev: 758)

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December 2004

Last modified
18th January 2007

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Acknowledgements:

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Dr. François Balloux
Dr. William Amos
SWIG user community
Python user community
Keck Center for Computational and Structural Biology

Abstract

simuPOP is a forward-time population genetics simulation environment. Unlike coalescent-based programs, simuPOP evolves populations forward in time, subject to arbitrary number of genetic and environmental forces such as mutation, recombination, migration and population/subpopulation size changes. Statistics of populations can be calculated and visualized dynamically which makes simuPOP an ideal tool to demonstrate population genetics models; generate datasets under various evolutionary settings, and more importantly, study complex evolutionary processes and evaluate gene mapping methods.

simuPOP can be used at two levels. The core of simuPOP is a scripting language (Python) that provides a large number of building blocks (populations, mating schemes, various genetic forces in the form of functions, operators, simulators and gene mapping methods) to construct a simulation. This provides a R/S-Plus or Matlab-like environment where users can interactively create, manipulate and evolve populations; monitor and visualize population statistics and apply gene mapping methods. The full power of simuPOP and Python (even R) can be utilized to simulate arbitrarily complex evolutionary scenarios.

simuPOP also comes with an increasing number of pre-defined simulation scenarios. If one of them happens to fit your need, all you need to do is running the script file with appropriate parameters. No knowledge of Python or simuPOP is required. To make simuPOP readily usable for time-limited users, users of simuPOP are strongly encouraged to submit their simulations to this collection.

This user's guide covers the basic usage of simuPOP, including installation, basic usage, brief introduction to built-in scripts, and how to write simuPOP scripts. Detailed information about simuPOP components, functions and operators is available in the *simuPOP Reference Manual.* All resources, including a pdf version of this guide and a mailing list can be found at the simuPOP homepage `http://simupop.sourceforge.net`.

How to cite simuPOP:

Bo Peng and Marek Kimmal (2005) simuPOP: a forward-time population genetics simulation environment. *bioinformatics*, **21**(18): 3686-3687

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Introduction

1.1   What is simuPOP?

`simuPOP` is a forward-time population genetics simulation environment. Unlike coalescent-based simulation programs, simuPOP evolves population(s) forward in time, subject to arbitrary number of genetic and environmental forces (mutation, recombination, migration, population size change etc.). simuPOP allows users to control every aspects of the evolutionary process and observe the details at each generation. For example, users can start with a population of identical individuals, manually introduce a mutant and observe the spread of this mutant in the population from generation to generation. Population substructure, recombination, migration, selection etc can be added to the simulation as needed.

simuPOP consists of a number of Python objects and functions, including populations that store and provide access to individual genotypes; mating schemes that determine how populations evolve to the next generation; operators that manipulate populations and calculate population statistics; simulators that coordinate the evolution process and functions that perform tasks ranging from saving/loading populations to doing gene mapping. It is user's responsibility to write a Python script to glue these pieces together and form a simulation. Since these modules are mostly independent to each other, it is easy to add additional operators to an existing simulation. There is no limit on the number of operators, and thus no limit on the complexity of a simulation.

simuPOP does not aim at any specific result or outcome. It is more like a workshop, where users use various components and tools to assemble a simulation and study its properties, or manipulated populations without evolving them. Just like any such programming environments such as R/Splus and Matlab, users will have to learn how to use the environment (various Python IDE) and how to program in this language (Python and the simuPOP module). A graphic user interface of simuPOP is planned but its usefulness is in doubt (just like the R/GUI) and will not be available any time soon.

On the other hand, simuPOP also has an increasing number of built-in scripts. These script are written in simuPOP/Python language and can be used without knowing their underlying mechanism. It is strongly recommended that users of simuPOP submit their own scripts to his collection and so other users can learn and adapt their own simulations from these scripts.

As a summary, simuPOP is suitable for the following applications:

- Teaching tool for population genetic courses. Compared to other existing programs, the biggest advantage of simuPOP is its flexibility. There is no limit on the complexity of the simulation and students can change the script and try new things (such as viewing another statistics or adding another genetic force) at will.

- Observe the dynamics of population evolution. This is where the power of simuPOP lies and is where coalescent-based simulations frown. Coalescent, by its nature, focus only on samples, and ignore genealogy information that are irrelevant to the final sample. It is therefore impractical to trace the population properties of ancestral populations. Forward-based simulation does not have this problem, at a cost of performance.

- Generating samples that can be analyzed by other programs. This area is dominated by coalescent-based meth-

ods, but the facts that coalescent-based methods can not simulate complex (non-additive) selection or penetrance models and supports, at least till now, only one disease susceptibility locus, make it unsuitable to simulate the evolution of complex human diseases. A simuPOP script `simuComplexDisease.py` provides a powerful alternative.

1.2 Features

Currently, simuPOP provides the following features:

- Population with one-level subpopulation structure. (family structure can be attached as individual information) Sex chromosomes can be modeled.

- Arbitrary information, such as age, fitness, parents, can be attached to each individual.

- There is no limit on ploidy, number of chromosomes, number of loci and population size. For single-CPU versions of simuPOP, the size of population is limited by available RAM. The MPI version of simuPOP can spread populations to a cluster of machines and allows simulations of huge populations.

- Allele can be short (<255 allelic states), long (2^{16} allelic states) or binary (0 or 1). Binary alleles are stored as bits so a large number of SNP markers can be simulated.

- A population can hold arbitrary number of ancestral generations (default to none) for easy pedigree analyses.

- Population/subpopulation sizes can be changed during mating. Subpopulations can be created/changed as a result of migration.

- Several replicates of populations can be evolved simultaneously.

- Mating schemes include random mating, binomial selection etc. Number of offspring per mating can be constant, or follow a random distribution.

- Populations can be saved and loaded in text, binary, XML, Fstat, GC formats. Methods to deal with other formats are provided.

- Simulation can be paused, saved and resumed easily.

- Easy developing/debugging using Python interactive shell, or run in batch as python scripts.

- A wide variety of operators are provided. They can act on the populations at selected generations, at different stages of a life-cycle, on different replicate or replicate group.

- Built-in operators for arbitrary migration model.

- Operators for k-allele, stepwise and generalized stepwise mutation models. Hybrid operators can be used for more complicated mutation models.

- Support uniform or non-uniform (differ-by-loci) recombinations. Male/female individuals can have different recombination rates/intensities.

- Support many single-locus selection model and multiplicative/additive multi-loci selection models. Hybrid operator is provided for arbitrary selection model.

- Built-in support for allele, genotype, heterozygote, haplotype number/frequency calculation. As well as some more complicated statistics like F_{st}. Other statistics can be calculated from these basic statistics.

- Has support for plotting through RPy (use R through Python). Other methods are supported.

- Operators to calculate quantitative trait, penetrance and draw samples from current population.

- Built-in ascertainment methods including case/control, affected sibpair, random sample.

- Maybe most importantly: *a complete and detailed reference manual!*

1.3   Availability

Binary libraries of `simuPOP` are provided for linux, windows, solaris and mac systems. Source code and development documentations are also available for easy porting to other platforms. Both source code and binaries can be distributed free-of-charge under GPL license. All resources, including a pdf version of this manual and a mailing list can be found at the simuPOP homepage.

1.4   Special notes for windows users

Due to the limits of the windows operating systems, several features are unavailable for a windows system.

- **compression of native simuPOP file formats**. Because large populations tend to take lots of disk spaces, simuPOP compresses text, binary or XML output in gzip format by default, despite the slower saving time. Because gzip format is not well supported under windows, this feature is disabled under windows. The `compress=True` option of `savePopulation` is ignored.

- **unique random seed for each simuPOP session**. Under *nix systems, simuPOP reads `/dev/urandom` to set random seed and can gurantee different seeds for concurrent simuPOP sessions. Under windows, system time is used to seed the random number generator so two simuPOP sessions may get the same seeds and produce the same results.

- **MPI modules.** Although windows port of Message Passing Interface implementations are available, I only have access to Linux multi-processor systems and Linux-based clusters. Therefore, windows MPI modules are not yet supported.

I welcome suggestions on how to make these features available for windows.

1.5   Naming Conventions

`simuPOP` follows the following naming conventions.

- Classes (objects), member functions and parameter names start with small character and use capital character for the first character of each word afterward. For example

  ```
  population, population::subPopSize(), individual::setInfo()
  ```

- Standalone functions start with capital character. This is how you can differ an operator from its function version. For example, `initByFreq(vars)` is an operator and `InitByFreq(pop, vars)` is its function version (equivalent to `initByFreq(vars).apply(pop)`).

- Constants start with Capital characters. For example

  ```
  MigrByProportion, StatNumOfFemale
  ```

- The following words in function names are abbreviated:

  ```
  pos (position),  info (information), migr (migration), subPop (subpopulation),
  (rep) replicate, gen (generation), grp (group(s)), ops (operators),
  expr (expression), stmts (statements)
  ```

1.6   How to read this manual

There are a lot of functions/operators in simuPOP and there is no reason you should memorize all of them. (I admit that I can not.) If you are a first time simuPOP user, my suggestion is that you read through this manual quickly only to get the big picture of how simuPOP works and what simuPOP can do. Then, if you decide to write some simulations, you should

- Read some examples under `scripts` directory. From easy to difficult, you can read `simuLDDecay.py`, `simuCDCV.py` and `simuComplexDisease.py`. Scripts from the `examples` directory can also be studied.

- Copy one of the scripts as a template and modify it. For whatever function/operator you need, read the relevant sections in detail.

Installing simuPOP

2.1   Installing simuPOP

Compiled libraries for Linux (RHEL4 and Mandriva) and windows XP. Solaris and MacOSX binaries are currently not provided due to machine availability. In most cases, you will only need to download simuPOP and follow the usual installation process of your platform. For example, if you use a windows system and have Python 2.3.3 installed, you should download `simupop-x.x.x-py23-win32.exe`. Double click the `.exe` file to install.

Things can get complicated when you have an earlier/later versions of OS, compiler or Python and have to compile simuPOP from source. The `installation` section of simuPOP homepage has detailed instructions. A single command `python setup.py install` will usually suffice.

Python has a large number of modules. For simple tasks like dataset generation, simuPOP modules alone are enough. However, it is highly recommended that you install

- R and a python module rpy: although other piloting modules/methods can be used, simuPOP mainly uses R for this purpose. The advantage of this method is that R is not only an excellent plotting tool, but also a widely used statistical analysis package. It also has some genetic packages that can be used to analyze simuPOP generated datasets.

- wxPython: By default, simuPOP uses Tkinter to get parameters (the parameter dialog). It will use wxPython automatically if wxPython is available. This will enable a bunch of other GUI improvements including a nicer version of `ListVars()` function.

2.2   Starting simuPOP

After installation, you will have the following files and directories (use windows as an example)

- Many `simuXXX.py` files under `c:\python23\Lib\site-packages`. These are simuPOP modules.

- `c:\python23\share\simuPOP\doc`: documentations in pdf format.

- `c:\python23\share\simuPOP\test`: all unit test cases. You can run run_tests.py to test if your simuPOP installation is correct.

- `c:\python23\share\simuPOP\scripts`: This directory has all the built-in scripts.

You should be able to load simuPOP library by running command `import simuPOP` (example 1) from python interactive shell. From the initial output, you can see the version (and revision number) of simuPOP, type of module, random number generator, etc.

In case that you do not have administrative privilege, you may not be able to install simuPOP to the system python directory. In this case, you can install simuPOP locally and load simuPOP as shown in example 2.

Example 1 Import simuPOP module

```
>>> from simuPOP import *
simuPOP : Copyright (c) 2004-2006 Bo Peng
Version 0.7.3 (Revision 470, Oct 10 2006) for Python 2.3.4
[GCC 3.4.6 20060404 (Red Hat 3.4.6-3)]
Random Number Generator is set to mt19937 with random seed 0x1eb7c646939a8b00
This is the short allele version with 256 maximum allelic states.
You are running in standard mode with strict boundary check etc.
For more information, please visit http://simupop.sourceforge.net,
or email simupop-list@lists.sourceforge.net (subscription required).
>>>
```

Example 2 Import locally installed simuPOP module

```
>>> import sys
>>> sys.path.append('/path/to/simuPOP')
>>> from simuPOP import *
>>>
```

2.3   simuPOP Modules

simuPOP is composed of twelve libraries: standard short, long and binary alleles (3), each of them have standard and optimized ($\times 2$), and single-CPU and Message Passing Interface (MPI) versions ($\times 2$). The short libraries use 1 byte to store each allele which limits the possible allele states to 256. This is enough most of the times but not so if you need to simulate models like the infinite allele model. In those cases, you should use the long allele version of the modules, which use 2 bytes for each allele and can have 2^{16} possible allele states. On the other hand, if you would like to simulate a large number of binary (SNP) markers, binary libraries can save you a lot of RAM. Depending on applications, binary alleles can be faster or slower than regular modules.

Standard libraries have detailed debug and run-time validation mechanism to make sure the simulations run correctly. Whenever something unusual is detected, simuPOP would terminate with detailed error messages. The cost of such run-time checking varies from simulation to simulation but can be high under some extreme circumstances. Because of this, optimized versions for all libraries are provided. They bypass all parameter checking and run-time validations and will simply crash if things go wrong. It is recommended that you use standard libraries whenever possible and only use the optimized version when performance if needed and you are confidence that your simulation is running as expected.

The MPI modules are not provided in the binary distributions since many MPI implementations are available for different platforms. You will have to compile simuPOP by yourself to make use of them. (As of version 0.7.5, MPI modules are not ready). Due to the overhead of inter-CPU communication, the MPI versions are not necessarily much faster than single-CPU modules. However, since the MPI version of the modules spread the populations across nodes, they can handle much larger populations then single-CPU modules, and can save you some time when you have multiple CPU/Core workstations.

Example 3 set options through simuOpt

```
>>> import simuOpt
>>> simuOpt.setOptions(optimized=False, alleleType='long', quiet=True)
>>> from simuPOP import *
>>>
```

You can control the choice of modules in the following ways:

- Set environment variable SIMUALLELETYPE to be 'short', 'long' or 'binary', SIMUOPTIMIZED to use the optimized modules, and SIMUMPI to use MPI modules. The default module is the standard short module.

- Before you load simuPOP, set options using `simuOpt.setOptions(optimized, mpi, alleleType, quiet, debug)`. `alleleType` can be `short`, `long` or `binary`. `mpi` can be `True` or `False`. `quiet` means suppress initial output, and `debug` should be a list of debug options specified by `listDebugCode()`.

- If you are running a simuPOP script that conforms to simuPOP convention, you should be able to use optimized library using command line option `--optimized`, and the MPI version using `--mpi`.

SimuPOP components

The core of simuPOP is a scripting language based on the Python programming language. Like any other python module, you can start a python session, import simuPOP module, create and evolve populations interactively. Or, you can create a python script and run it as a batch file.

In this chapter, I will start from an simple example and them explain several import simuPOP components. Detailed info about each components is given in the *simuPOP reference manual*.

3.1   A simple example

Example 4 is a log file of an interactive Python session. User input text after the > > > prompt and Python will interpret and run your command interactively.

This example demonstrates the dynamics of linkage disequilibrium when recombination is in effect.

- The `import` line import simuPOP module (output suppressed). `simuRPy` defines a pure-python operator `varPlotter` that plot given variable using R.

- `simulator` creates a simulator from a population created by the `population` function. The population is diploid (`ploidy=2`), has 1000 individuals (`size=1000`) each has two loci on the first chromosome (`loci=[2]`). The simulator has three copies of this population (`rep=3`) and will evolve through random mating (`randomMating()`).

- `simu.evolve` evolves these populations 100 generations subject to some operators.

- `preOps=[initByValue]`: operators in parameter `preOps` (accept a list of operators) will be applied to the populations at the beginning of evolution. `initByValue` is an `initializer` that set the same genotype to all individuals. In this case, everyone will have genotype `12/21` (`1 2` on the first chromosome and `2 1` on the second copy of the chromosome) so linkage disequilibrium is 0.25 (maximum possible value).

- operators in `ops` parameter will be applied to all populations at each generation. (Not exactly, operators can be inactive at certain generations.)

- `recombinator` is a *during-mating operator* that recombine parental chromosomes with probability 0.1 during mating.

- `stat` is a *post-mating* operator. Parameter `LD=[0,1]` tells the operator to calculate the linkage disequilibrium between locus 0 and 1 (note the 0 index of loci). When this operator is applied to a population, it will calculate the LD for the population and store the result in the population's local variable namespace. For this case, variables `LD`, `LD_prime` and `R2` will be set.

- `varPlotter` is a pure python operator that plot variable `LD[0][1]` for each replicate of the populations. Title, labels on the x, y axis, and a wealth of other options can be set. This operator evaluate the expression in each population's local namespace to get the LD value of each population.

Example 4 A simple example

```
>>> from simuPOP import *
>>> from simuRPy import *
>>> simu = simulator(
...       population(size=1000, ploidy=2, loci=[2]),
...       randomMating(),
...       rep = 3)
>>> simu.evolve(
...       preOps = [initByValue([1,2,2,1])],
...       ops = [
...           recombinator(rate=0.1),
...           stat(LD=[0,1]),
...           varPlotter('LD[0][1]', numRep=3,
...                       ylim=[0,.25], xlab='generation',
...                       ylab='D', title='LD Decay'),
...           pyEval(r"'%3d   ' % gen", rep=0, step=25),
...           pyEval(r"'%f    ' % LD[0][1]", step=25),
...           pyEval(r"'\n'", rep=REP_LAST, step=25)
...       ],
...       end=100
... )
   0   0.202693    0.199472    0.197768
  25   0.010660    0.012400    0.008596
  50   0.011854    0.009987    0.001932
  75   0.011672    0.013654    0.001059
 100   0.006409    0.003923    0.000734
True
>>> r.dev_print(file='log/LDdecay.eps')
{'X11': 2}
>>>
```

- `pyEval` accepts any python expression, evaluate it in each replicates' local namespace and return the result. In this example, `pyEval` get the value of `gen` (generation number), `LD[0][1]` and print them. Note the we use `rep` parameter to let operators apply to first (`rep=0`), last (`rep=REP_LAST`) or all (no `rep`) replicates and result in a table. We also use step=25 to apply these operators at 25 generations interval.

- `end=100`: evolve 100 generations (To be exact: 0 - 100, 101 generations).

- `r.dev_print`: is a direct call to the rpy module. This line saves the figure to a file `ld/LDdecay.eps`. Note that `'.'` in R function names need to be replaced by `'_'`. (Refer to rpy manual).

The output is a table of LD values of each replicate at 0, 25, 50, 57 and 100 generations, as well as a figure at generation 100.

Most simuPOP scripts have similar steps. You can add more operators to the `ops` list to build more complicated simulations. Obvious choices are `mutator`, `migrator`, or some proper visualizer to plot the dynamics of variables.

3.2   Genotype structure

Genotypic structure refers to the number of copies of basic number of chromosomes, number of chromosomes, existence of sex chromosome, number of loci on each chromosome, locus location on chromosome and allele names. It presents the common genetic configuration for all the individuals in a population.

Individuals in the same population share the same genotypic structure. Consequently, *genotypic information can be retrieved from individual, population and simulator* (consists of populations with the same genotypic structure) *level*.

3.3   Population

`population` objects are essential to simuPOP. They are composed of subpopulations each with certain number of individuals, all have the same genotypic structure. A population can store arbitrary number of ancestral populations to facilitate pedigree analysis.

simuPOP uses one-level population structure. That is to say, there is no sub-subpopulation or families in subpopulations. Any complicated structure, however, can be achieve by the use of individual information fields. Mating is within subpopulations only. Exchange of genetic information across subpopulations can only be done through migration. Population and subpopulation sizes can be changed, as a result of mating or migration.

A very important feature of this population object is that you can store many generations of the population in a single population object. You can choose to store all or a limited number of generations during evolution. In the latter case, the oldest generation will be removed if a new generation is pushed in and the number of stored generations has exceeded the specified level.

simuPOP provides a large number of population related functions, they are used to

- access genotype structure

- access individuals and their genotypes

- manipulate subpopulations

- access ancestral generations

- manipulate genotype

- sample (subset) from the population

- access population variables

- save/load populations in various formats

You usually do not need to use these functions explicitly unless you need to write pure python functions/operators that involves complicated manipulation of populations, or when you need to manipulate populations directly for gene mapping, import/export purposes.

3.4   Individuals

Individuals can not be created without population. You can create a population and access its individuals through the `individual()`, `individuals()` functions. The returned `individual` object has its own member functions, with which you can

- access genotype structure

- retrieve/set genotype

- retrieve/set sex, affected status and some other auxiliary information (information fields)

3.5   Population Variables

Populations are associated with python variables. These variables are usually set by various operators. For example, `stat` operator calculates many population statistics and store results in population namespace. However, you can also make use of this mechanism to pass parameters, store variables etc.

The interface functions are `population::vars()` and `population::dvars()` function. They are identical except that `vars()` returns a python dictionary and `dvars()` returns a wrapper class so that you can access this dictionary as attributes. For example, `pop.vars()['alleleFreq'][0]` is the same as `pop.dvars().alleleFreq[0]`. To have a look at all associated variables of a population, you can print `pop.vars()`, or better pass `pop.vars()` to a function `ListVars()`. A nice GUI will be used if wxPython is installed.

It is important to know that this dictionary forms a local namespace in which expressions can be evaluated. As we can see from example 4, the same expression "`'%f ' % LD[0][1]`" can be evaluated in each population's local namespace and yield different results.

3.6 Mating Scheme

Mating schemes specify how to generate offspring from the current population. It must be provided when a simulator is created. Mating can perform the following tasks:

- change population/subpopulation sizes. This is where demographic models are handled in simuPOP. There are a few methods to control population sizes. The most flexible one is through a user-provided function that returns population (subpopulation) sizes at each generation.

- Randomly choose parent(s) to generate offspring to populate the next generation. The number of offspring per mating event can be controlled. This can be a fixed number (default to 1), or a random number following one of geometric, Poisson or binomial distribution. More complicated schemes are allowed.

- During-mating operators are applied to all offspring. The most commonly used during mating operator is a recombinator that can recombine parental chromosomes and form offspring genotype.

- Apply selection if applicable. If individual fitness are given (usually returned by a selector operator), a mating scheme will choose an individual to mate, according to its relative fitness.

A few mating schemes are available, among which `randomMating()` is the most important.

3.7 Operators

Operators are objects that act on populations. They (there are exceptions) can be applied to populations directly, but most of the time they are managed and applied by a simulator. There are three kinds of operators:

- *built-in:* written in C++, fastest. They do not interact with Python shell except that some of them set variables that are accessible from Python.

- *hybrid*: written in C++ but calls python function when execution. Less efficient. For example, a hybrid mutator `pyMutator` will determine if an allele will be mutated and call a user–defined Python function to mutate it.

- *pure python*: written in python. Same speed as python. For example, a `varPlotter` can plot python variables that are set by other operators.

You do not have to know the type of an operator to use them. The interface of them are all the same. Namely, they all accept a standard set of parameters, and are used in the same fashion. Such parameters include `rep, grp, begin, step, end` and `at`. The first two indicate that the operator only applies to one or a group of replicates, and the rest

control which generation(s) the operator will be applied to. There are also parameters that redirect operator output to files. For details please refer to the reference manual.

A simuPOP life cycle (each generation) can be divided into pre-mating, during-mating and post-mating and an operator can be applied to one or more of them. For example, a `stat` operator usually applies post-mating, but if you prefer, you can change its `stage` parameter to `preMating` and apply it pre-mating.

3.8   Simulator

Simulators combine three important components of simuPOP: population, mating scheme and operators together. A simulator is usually created with an instance of population, a replicate number and a mating scheme. It makes 'rep' replicates of this population and control the evolution process of these populations.

The most important function of a simulator is `evolve()`. It accepts arrays of operators as its parameters, among which, 'preOps' and 'postOps' will be applied to the populations at the beginning and end of evolution, respectively, whereas 'ops' will be applied at every generation. Of course, a simulator will probe and respect each operator's `rep, grp, begin, end, step, at, stage` properties and act accordingly.

Writing simuPOP scripts

In this chapter, I will show you, step by step, how to write a simuPOP script. The example is a simplified version of `scripts/simuCDCV.py` which uses a python operator to calculate and save many more statistics, and use rpy to display the dynamics of disease allele frequency.

4.1 Simulation scenario

Reich and Lander [2001] proposed a population genetics framework to model the evolution of allelic spectra (the number and population frequency of alleles at a locus). The model is based on the fact that human population grew quickly from around 10,000 to 6 billion in 18,000 -150,000 years. His analysis showed that at the founder population, both common and rare diseases have simple spectra. After the sudden expansion of population size, the allelic spectra of simple diseases become complex; while those of complex diseases remained simple.

I use simuPOP to simulate this evolution process and observe the allelic spectra of both types of diseases. The results are published in Peng and Kimmel [2006], which has much more detailed discussion about the simulations, and the parameters used.

4.1.1 Demographic model

The initial population size is set to 10,000, as suggested in the paper. The simulation will evolve 500 generations with constant population size to reach mutation-selection equilibrium. Then, the population size will increase by around 20,000 every 10 generations and reach 1,000,000 at generation 1000. The population growth takes around 12,500 years if we assume 25 years per generation.

4.1.2 Mutation model

The maximum number of alleles at each locus is set to be 2000, a number that is hopefully big enough to mimic the infinite allele model. Allele 0 is the wild type (A) and all others are disease alleles (a). The $k-$allele mutation model is used. That is to say, an allele can mutate to any other allele with equal probability. An immediate implication of this model is that $P(A \rightarrow a) \gg P(a \rightarrow A)$ since there are many more a than A. The mutation rate is set to $\mu = 3.2 \times 10^{-5}$ per locus per generation.

4.1.3 Selection on a common and a rare disease

Two diseases are simulated: a common disease with initial allele frequency of $f_0 = 0.2$; and a rare disease with initial allele frequency of $f_0 = 0.001$. The diseases are unlinked in the sense that their corresponding loci reside on separated

chromosomes. The allelic spectra of both diseases are set to be $[.9, .02, .02, .02, .02, .02]$. I.e., one allele accounts for 90% of the disease cases.

Both diseases are recessive in that their fitness values are $[1, 1, 1 - s]$ for genotype AA, Aa and aa respectively. $s_c = 0.1$, $s_r = 0.9$ are used in the simulation which imply weak selection on the common disease and strong selection on the rare disease. If an individual has both diseases, his fitness value follows a multiplicative model, i.e., $(1 - s_c) \times (1 - s_r) = 0.09$.

These parameters, translated to python, is shown in 5

Example 5 Set parameters

```
initSize =  10000              # initial population size
finalSize = 1000000            # final population size
burnin = 500                   # evolve with constant population size
endGen = 1000                  # last generation
mu = 3.2e-5                    # mutation rate
C_f0 = 0.2                     # initial allelic frequency of *c*ommon disease
R_f0 = 0.001                   # initial allelic frequency of *r*are disease
max_allele = 255               # allele range 1-255 (1 for wildtype)
C_s = 0.0001                   # selection on common disease
R_s = 0.9                      # selection on rare disease
psName = 'lin_exp'             # filename of saved figures

# allele spectrum
C_f = [1-C_f0] + [x*C_f0 for x in [0.9, 0.02, 0.02, 0.02, 0.02, 0.02]]
R_f = [1-R_f0] + [x*R_f0 for x in [0.9, 0.02, 0.02, 0.02, 0.02, 0.02]]
```

4.2   Create a simulator

Several parameters need to be used to create a population:

- `ploidy`: 2, default

- `size`: initial population size, known

- `subPop`: no subpopulation (or one single population). size can be ignored if `subPop` is given.

- `loci`: number of chromosomes and number of loci on each chromosome: we use two unlinked loci. use `loci=[1,1]`. This array gives the number of loci on each chromosome.

- loci name and position: no need to specify

- `infoFields`: This parameter is tricky since you need to specify what auxiliary information to attach to each individual. During the simulation, `fitness` is needed because all selectors generate this information and mating schemes will make use of it. If you forget to provide this parameter, never mind, the simulation will fail and tell you that a information field `fitness` is needed. Similar information fields include `father_idx` and `mother_idx` when you want to track each individual's parents using `taggers`.

You can then create a population with:

```
population(size=1000, loci=[1,1], infoFields=['fitness'])
```

To create simulator, we need to decide on a mating scheme. `randomMating` should of course be used, but we need to tell `randomMating` how population size should be changed. By default, all mating schemes keep the population size of ancestral population, but we need an instant population expansion model.

The easiest way to achieve this is defining a function that accept generation number and the population size of previous generation, and return the size of this generation. The input and output population sizes need to be arrays, indicating sizes of all subpopulations. In our case, something like [1000] should be used. The instant population growth model is actually quite easy to write:

```
def ins_exp(gen, oldSize=[]):
    if gen < burnin:
        return [initSize]
    else:
        return [finalSize]
```

With a little adjustment of how population size is given to `population()`, and use demographic function as a parameter to allow other demographic models to be used, we end up with example 6. Note that because we use loci with more than 255 allele states, the long allele module is used.

Example 6 Create a simulator

```
from simuOpt import setOptions
setOptions(alleleType='long')
from simuPOP import *

# instantaneous population growth
def ins_exp(gen, oldSize=[]):
    if gen < burnin:
        return [initSize]
    else:
        return [finalSize]

def simulate(incSenario):
    simu = simulator(                                    # create a simulator
        population(subPop=incSenario(0), loci=[1,1],
            infoFields=['fitness']),                     # inital population
        randomMating(newSubPopSizeFunc=incSenario)       # random mating
    )

simulate(ins_exp)
```

4.3   Initialization

We start the simulation with initial allele spectra at the two loci. This can be achieved by operator `initByFreq`, which allows you to initialize individuals with alleles proportional to given allele frequencies. Using a large number of parameters, this operator can initialize any subset of loci, for any subset(s) of individuals, even given ploidy. We need only to specify locus to initialize, and use it like

```
# initialize locus 0 (for common disease)
initByFreq(atLoci=[0], alleleFreq=C_f),
# initialize locus 1 (for rare disease)
initByFreq(atLoci=[1], alleleFreq=R_f),
```

4.4   Mutation and selection

You will need to read the relative sections of the reference manual to pick suitable mutator and selectors. What we need in this case are

---

- k-allele mutator will given number of allele states (k). This is exactly

```
kamMutator(rate=mu, maxAllele=max_allele)
```

- single locus selector that treat 0 as wildtype, and any other allele as mutant. The selector to use is

```
maSelector(locus=0, fitness=[1,1,1-C_s], wildtype=[0])
```

and

```
maSelector(locus=1, fitness=[1,1,1-R_s], wildtype=[0])
```

- Because an individual has only one fitness value, fitness values obtained from two selectors need to be combined (another choice is that you can use a selector that handle multiple loci.). Therefore, we use a multi-locus selector as follows:

```
mlSelector([
    maSelector(locus=0, fitness=[1,1,1-C_s], wildtype=[0]),
    maSelector(locus=1, fitness=[1,1,1-R_s], wildtype=[0])
    ], mode=SEL_Multiplicative)
```

With these operators, the simulator can be started. It first initialize a population with given allelic spectra, and then evolve it, subject to mutation and selection, specific to each locus. The program is listed in example 7:

Example 7 Run the simulator

```
def simulate(incSenario):
    simu = simulator(                                        # create a simulator
        population(subPop=incSenario(0), loci=[1,1],
            infoFields=['fitness']),                         # inital population
        randomMating(newSubPopSizeFunc=incSenario)          # random mating
    )
    simu.evolve(                            # start evolution
        preOps=[                            # operators that will be applied before evolution
            # initialize locus 0 (for common disease)
            initByFreq(atLoci=[0], alleleFreq=C_f),
            # initialize locus 1 (for rare disease)
            initByFreq(atLoci=[1], alleleFreq=R_f),
        ],
        ops=[                                # operators that will be applied at each gen
            # mutate: k-alleles mutation model
            kamMutator(rate=mu, maxAllele=max_allele),
            # selection on common and rare disease,
            mlSelector([                    # multiple loci - multiplicative model
                maSelector(locus=0, fitness=[1,1,1-C_s], wildtype=[0]),
                maSelector(locus=1, fitness=[1,1,1-R_s], wildtype=[0])
            ], mode=SEL_Multiplicative),
        ],
        end=endGen
    )

simulate(ins_exp)
```

4.5 Output statistics

We first want to output total disease allele frequency of each locus. This is easy since `stat()` operator can calculate allele frequency for us. What we need to do is use `stat()` operator to calculate allele frequency and set variable `alleleFreq` (and `alleleNum`) in each population's local namespace,

```
stat(alleleFreq=[0,1]),
```

and then use a `pyEval` (python expression) operator to print out the values:

```
pyEval(r' "%.3f\t%.3f\n" % (1-alleleFreq[0][0], 1-alleleFreq[1][0])')
```

The `pyEval` operator can accept any valid python expression so the above expression calculate $f_0 = \sum_{i=1}^{\infty} f_i$ at each locus (0 and 1) and print it in the format of `'%.3f\t%.3f\n'`.

There is no operator to calculate effective number of alleles [Reich and Lander, 2001] so we need to do that by ourselves, using allele frequencies. The formula to calculate effective number of alleles is

$$n_e = \left(\sum_i \left(\frac{f_i}{f_0} \right)^2 \right)^{-1}$$

where f_i is the allele frequency of disease allele i, and f_0 is defined as above. To calculate n_e at the first locus, we can use a `pyEval` operator (a direct translation of the formula):

```
pyEval('1./sum([(x/(1-alleleFreq[0][0]))**2 for x in alleleFreq[0][1:]])')
```

However, this expression looks complicated and can not handle the case when $f_0 = 0$. A more complicated, and robust method is using the `stmts` parameter of `pyEval`, which will be evaluated before parameter `expr`,

```
pyEval(stmts="'ne = [0,0]
for i in range(2):
    freq = alleleFreq[i][1:]
    f0 = 1 - alleleFreq[i][0]
    if f0 == 0:
        ne[i] = 0
    else:
        ne[i] = 1./sum([(x/f0)**2 for x in freq])
"', expr=r"'%.4f\t%.4f\n" % (ne[0], ne[1])')
```

As you can see, the `pyEval` can be really complicated and calculate any statistics. However, if you plan to calculate more statistics, a pure python operator may be easier to write. The simplest form of a python operator is just a python function that accept a population as the first parameter (and an optional parameter),

```
def ne(pop):
    ' calculate effective number of alleles '
    Stat(pop, alleleFreq=[0,1])
    f0 = [0, 0]
    ne = [0, 0]
    for i in range(2):
        freq = pop.dvars().alleleFreq[i][1:]
        f0[i] = 1 - pop.dvars().alleleFreq[i][0]
```

```
        if f0[i] == 0:
            ne[i] = 0
        else:
            ne[i] = 1. / sum([(x/f0[i])**2 for x in freq])
    print '%d\t%.3f\t%.3f\t%.3f\t%.3f\n' % (pop.gen(), f0[0], f0[1], ne[0], ne[1])
    return True
```

Then, you can use this function in a python operator

```
    pyOperator(func=ne, step=5)
```

The biggest difference between `pyEval` and `pyOperator` is that `pyOperator` is no longer evaluated in the population's local namespace. You will have to get the vars explicitly using the `pop.dvars()` function. (This also implies that you can do whatever you want to the population.). In this example, the function form of the `stat` operator is used to explicitly calculate allele frequency. The results are also explicitly printed using the `print` command. The explicities lead to longer, but clearer program. This becomes obvious when you need to calculate and print many statistics.

The following program uses the `pyOperator` solution. In this program, user can input two demographic models as command line parameter. Two other operators are used

- A `ticToc` operator that prints out elapsed time at every 100 generations

- A `pause` operator that pause the simulation whenever you press a key. You can actually enter a python command shell to examine the results.

Example 8 The whole program

```
    #!/usr/bin/env python

    '''
    simulation for Reich(2001):
        On the allelic spectrum of human disease

    '''

    import simuOpt
    simuOpt.setOptions(alleleType='long', optimized=False)
    from simuPOP import *

    import sys

    initSize =  10000              # initial population size
    finalSize = 1000000           # final population size
    burnin = 500                  # evolve with constant population size
    endGen = 1000                 # last generation
    mu = 3.2e-5                   # mutation rate
    C_f0 = 0.2                    # initial allelic frequency of *c*ommon disease
    R_f0 = 0.001                  # initial allelic frequency of *r*are disease
    max_allele = 255             # allele range 1-255 (1 for wildtype)
    C_s = 0.0001                 # selection on common disease
    R_s = 0.9                    # selection on rare disease

    C_f = [1-C_f0] + [x*C_f0 for x in [0.9, 0.02, 0.02, 0.02, 0.02, 0.02]]
    R_f = [1-R_f0] + [x*R_f0 for x in [0.9, 0.02, 0.02, 0.02, 0.02, 0.02]]
```

```
        # instantaneous population growth
        def ins_exp(gen, oldSize=[]):
            if gen < burnin:
                return [initSize]
            else:
                return [finalSize]

        # linear growth after burn-in
        def lin_exp(gen, oldSize=[]):
            if gen < burnin:
                return [initSize]
            elif gen % 10 != 0:
                return oldSize
            else:
                incSize = (finalSize-initSize)/(endGen-burnin)
                return [oldSize[0]+10*incSize]


    def ne(pop):
        ' calculate effective number of alleles '
        Stat(pop, alleleFreq=[0,1])
        f0 = [0, 0]
        ne = [0, 0]
        for i in range(2):
            freq = pop.dvars().alleleFreq[i][1:]
            f0[i] = 1 - pop.dvars().alleleFreq[i][0]
            if f0[i] == 0:
                ne[i] = 0
            else:
                ne[i] = 1. / sum([(x/f0[i])**2 for x in freq])
        print '%d\t%.3f\t%.3f\t%.3f\t%.3f' % (pop.gen(), f0[0], f0[1], ne[0], ne[1])
        return True



    def simulate(incSenario):
        simu = simulator(                                       # create a simulator
            population(subPop=incSenario(0), loci=[1,1],
                infoFields=['fitness']),                        # inital population
            randomMating(newSubPopSizeFunc=incSenario)          # random mating
        )
        simu.evolve(                              # start evolution
            preOps=[                              # operators that will be applied before evolution
                # initialize locus 0 (for common disease)
                initByFreq(atLoci=[0], alleleFreq=C_f),
                # initialize locus 1 (for rare disease)
                initByFreq(atLoci=[1], alleleFreq=R_f),
            ],
            ops=[                                 # operators that will be applied at each gen
                # mutate: k-alleles mutation model
                kamMutator(rate=mu, maxAllele=max_allele),
                # selection on common and rare disease,
                mlSelector([                      # multiple loci - multiplicative model
                    maSelector(locus=0, fitness=[1,1,1-C_s], wildtype=[0]),
                    maSelector(locus=1, fitness=[1,1,1-R_s], wildtype=[0])
                ], mode=SEL_Multiplicative),
                # report generation and popsize and total disease allele frequency.
                pyOperator(func=ne, step=5),
                # monitor time
                ticToc(step=100),
```

```
              # pause at any user key input (for presentation purpose)
              pause(stopOnKeyStroke=1)
          ],
          end=endGen
      )

if __name__ == '__main__':
    if len(sys.argv) != 2:
        print 'Please specify demographic model to use.'
        print 'Choose from lin_exp and ins_exp'
        sys.exit(0)
    if sys.argv[1] == 'lin_exp':
        simulate(lin_exp)
    elif sys.argv[1] == 'ins_exp':
        simulate(ins_exp)
    else:
        print 'Wrong demographic model'
        sys.exit(1)
```

4.6   Option handling

Everything seems to be perfect until you need to run more simulations with different parameters like initial pop-
ulation size. Editing the script again and again is out of the question. Since this script is a python script, it is
tempting to use python modules like `getopt` to parse options from command line. A better choice would be us-
ing the `simuOpt` module. Using this module properly, your simuPOP should be able to get options from short or
long command line option, from a configuration file, from a tkInter of wxPython dialog, or from user input. Taking
`c:\python\share\simuPOP\scripts\simuLDDecay.py` as an example, you can run this script as follows:

- use command 'simuLDDecay.py' or double click the program

- click the help button on the dialog, or run

    > simuLDDecay.py -h

  to view help information.

- enter parameters in a parameter dialog, or use short or long command arguments

    > simuLDDecay.py -s 500 -e 10 --recRate 0.1 --numRep 5 --noDialog

- use the optimized module by

    > simuLDDecay.py --optimized

- save the parameters to a config file

    > simuLDDecay.py --quiet -s 500 -e 10 --saveConfig decay.cfg

  this will result in a config file `decay.cfg` with these parameters.

- and of course use –c or --config,

    > simuLDDecay.py --config decay.cfg

to load parameters from the config file.

The last function is very useful since you frequently need to run many slightly different simulations, saving a configuration file along with your results will make your life much easier.

To achieve all the above, you need to write your scripts in the following order:

1. First line:

```
#!/usr/bin/env python
```

2. Write the introduction of the whole script in a module-wise doc string.

```
"'
This script will ....
"'
```

These comments can be accessed as module __doc__ and will be displayed as help message.

3. Define an option data structure.

```
options = [
... a dictionary of all user input parameters ...
]
```

These parameters will be handled by simuPOP automatically. Users will be able to set them through command line, configuration file, Tkinter- or wxPython-based GUI. The detailed description of this structure is given in simuPOP reference manual.

4. Main simulation functions

5. In the executable part of the script (under __name__ == '__main__'), you should call simuOpt.getParam to let simuOpt handle all parameter input for you and obtain a list of parameters. You usually need to handle some special cases (-h, --saveConfig etc), and they are all standard.

You will notice that simuOpt does all the housekeeping things for you, including parameter reading, conversion, validation, print usage, save configuration file. Since most of the parts are pretty standard, you can actually copy any of the scripts under the scripts directory as a template for your new script. The following example 9 shows the beginning and the execution part of the complete reich.py script, which can be found under the doc directory. For a complete reference of the Options structure, please refer to the reference manual.

Example 9 Option handling

```
options = [
    {'arg': 'h',
     'longarg': 'help',
     'default': False,
     'description': 'Print this usage message.',
     'allowedTypes': [types.NoneType, type(True)],
     'jump': -1                      # if -h is specified, ignore any other parameters.
    },
    {'longarg': 'initSize=',
     'default': 10000,
     'label': 'Initial population size',
     'allowedTypes': [types.IntType, types.LongType],
     'description': '''Initial population size. This size will be maintained
```

```
                    till the end of burnin stage''',
         'validate': simuOpt.valueGT(0)
        },
        {'longarg': 'finalSize=',
         'default': 1000000,
         'label': 'Final population size',
         'allowedTypes': [types.IntType, types.LongType],
         'description': 'Ending population size (after expansion.',
         'validate': simuOpt.valueGT(0)
        },
        {'longarg': 'burnin=',
         'default': 500,
         'label': 'Length of burn-in stage',
         'allowedTypes': [types.IntType],
         'description': 'Number of generations of the burn in stage.',
         'validate': simuOpt.valueGT(0)
        },
        {'longarg': 'endGen=',
         'default': 1000,
         'label': 'Last generation',
         'allowedTypes': [types.IntType],
         'description': 'Ending generation, should be greater than burnin.',
         'validate': simuOpt.valueGT(0)
        },
        {'longarg': 'growth=',
         'default': 'instant',
         'label': 'Population growth model',
         'description': '''How population is grown from initSize to finalSize.
                    Choose between instant, linear and exponential''',
         'chooseOneOf': ['linear', 'instant'],
        },
        {'longarg': 'name=',
         'default': 'cdcv',
         'allowedTypes': [types.StringType],
         'label': 'Name of the simulation',
         'description': 'Base name for configuration (.cfg) log file (.log) and figures (.eps)'
        },
    ]


def getOptions(details=__doc__):
    # get all parameters, __doc__ is used for help info
    allParam = simuOpt.getParam(options,
        'This program simulates the evolution of a common and a rare direse\n' +
        'and observe the evolution of allelic spectra\n', details)
    #
    # when user click cancel ...
    if len(allParam) == 0:
        sys.exit(1)
    # -h or --help
    if allParam[0]:
        print simuOpt.usage(options, __doc__)
        sys.exit(0)
    # automatically save configurations
    name = allParam[-1]
    if not os.path.isdir(name):
        os.makedirs(name)
    simuOpt.saveConfig(options, os.path.join(name, name+'.cfg'), allParam)
    # return the rest of the parameters
    return allParam[1:-1]
```

```
#
# IGNORED
#

if __name__ == '__main__':
    # get parameters
    (initSize, finalSize, burnin, endGen, growth) = getOptions()
    #
    from simuPOP import *
    #
    if initSize > finalSize:
        print 'Initial size should be greater than final size'
        sys.exit(1)
    if burnin > endGen:
        print 'Burnin gen should be less than ending gen'
        sys.exit(1)
    if growth == 'linear':
        simulate(lin_exp)
    else:
        simulate(ins_exp)
```

Selected topics

simuPOP is large, consisting of more than 80 operators and various functions that covers all important aspects of genetic studies. These includes mutation (*k*-allele, stepwise, generalized stepwise), migration (arbitrary, can create new subpopulation), recombination (uniform or nonuniform), quantitative trait, selection, penetrance (single or multi-locus, hybrid), ascertainment (case-control, affected sibpairs, random), statistics calculation (allele, genotype, haplotype, heterozygote number and frequency; expected heterozygosity; bi-allelic and multi-allelic D, D' and r^2 linkage disequilibrium measures; F_{st}, F_{it} and F_{is}); pedigree tracing, visualization (using R or other Python modules), load/save in text, XML, Fstat or Linkage format. In this chapter, I will discuss some practical usages of simuPOP.

5.1   Hybrid and pure-Python operator

Despite the large number of built-in operators, it is obviously not possible to implement every genetics models available. For example, although simuPOP provides several penetrance models, a user may want to try a customized one. In this case, one can use a simuPOP feature called *hybrid operator*. Such operators accept a Python function and will call this function with appropriate parameter(s) when needed. For example, example 10 defines a three-locus heterogeneity penetrance model [Risch, 1990] that yields positive penetrance only when at least two disease susceptibility alleles are available. The underlying mechanism of this operator is that for each individual, simuPOP will collect genotype at specified loci (`loci`) and send them to function `myPenetrance` and evaluate. The return values are used as the penetrance value of the individual, which is then interpreted as the probability of being affected.

Example 10 uses the function form of operator `pyPenetrance` and `stat` and you should use the operator form in a simulator. In these functions, operators are created with the same set of parameters as their operator form, applied to the population, and are destroyed afterward. For example,

```
PyPenetrance(pop, parameters)
```

is the same as

```
pyPenetrance(parameters).apply(pop)
```

Of course, parameters `begin, end, step` etc become meaningless in the function form. Note that if you need to apply the same operator to dozens of populations, creating one operator and applying it to all populations is more efficient than using the function form, since dozens of operators will be created and destroyed for each population in the latter usage.

If hybrid operators are still not flexible enough, you can write operators in Python. Such operators will have full access to the evolving population, and can therefore perform arbitrary operations on it. A pure-python operator has been used in the previous chapter where complex statistics are calculated and printed.

Example 11 uses a python operator to define a frequency-dependent selection operator which has different selection pressures depending on current disease allele frequency. In this example, a population is initialized with disease

Example 10 An example of hybrid operators

```
#!/usr/bin/env python
'''
Demonstrate the use of hybrid operator
'''

from simuOpt import setOptions
setOptions(alleleType='binary', quiet=True)
from simuPOP import *

def myPenetrance(geno):
    'return penetrance given genotype at spcified disease loci'
    if geno.count(1) < 3:
        return 0.
    else:
        return 1-(1-(geno[0]+geno[1])*0.25)* \
                 (1-(geno[2]+geno[3])*0.25)* \
                 (1-(geno[4]+geno[5])*0.25)

pop = population(1000, loci=[3, 4])
InitByFreq(pop, [0.3, 0.7])
PyPenetrance(pop, loci=[2, 3, 6], func=myPenetrance)
Stat(pop, numOfAffected=True)
print pop.dvars().numOfAffected
```

allele frequency 0.3 (allele 1). Then, at each generation, a python function `freqDependSelector` is called. This function

- unpact parameters (`DSL, min, max`)

- calculate allele frequency at the disease locus

- if disease allele frequency is less than `min`, apply a multi-allele selector and give disease allele strong advantage selection;

- if disease allele frequency is greater than `max`, apply a multi-allele selector and give disease allele strong purifying selection;

The result of this operator, unseen to users, is individual `fitness` values set by one of (maybe none of) the multi-allele selector, which will be used by `randomMating()` to select individuals accordingly to population the next generation.

One tricky point of this python operator is that although selectors are `PreMating`, namely fitness will be calculated before mating, `pyOperator` is `PostMating`. To calculate `fitness` before mating, a `stage=PreMating` parameter should be used. Otherwise, the fitness will be calculated for the offspring generation, not the current generation, as shown below:

```
preMating | mating -> offspring generation | postMating, fitness calculated
preMating | mating -> ...
```

Then, because the simulator clears selection flag at the beginning of each generation, the fitness will not be used. Tricky enough, right? The good news is that

- If you are using non-optimization libraries, simulation will fail if selection flag is on at the beginning of a generation. This prevents the use of post-mating selectors.

- If you are not sure in which order the operators are applied, use the `dryrun=True` in the evolve function. `evolve()` function will do nothing but printing out when and in which order operators will be applied.

Pure-python operators are extremely flexible and even more complicated form can be used. For example, `varPlotter` in `simuRPy.py` is a class with an instance of different plotters, and a python operator is used to call one of them. Such advanced usage of pure Python operator is beyond the scope of this guide.

Example 11 A frequency dependent selection operator

```python
#!/usr/bin/env python
'''
Demonstrate the use of pure python operator
'''

from simuPOP import *

def freqDependSelector(pop, param):
    ''' This selector will try to control disease allele
        frequency by applying advantage/purifying selection
          to DSL according to allele frequency at each DSL. '''
    # parameters are stored with population
    (DSL, min, max) = param
    # Calculate allele frequency
    Stat(pop, alleleFreq=[DSL])
    # apply harsh advantage/purifying selection to bring
    # allele frequency back to [min, max]
    if 1-pop.dvars().alleleFreq[DSL][0] < min:
        MaSelect(pop, locus=DSL, fitness=[1, 1.5, 2])
    elif 1-pop.dvars().alleleFreq[DSL][0] > max:
        MaSelect(pop, locus=DSL, fitness=[1, 0.8, 0.6])
    return True

pop = population(1000, loci=[3, 4], infoFields=['fitness'])
simu = simulator(pop, randomMating())
simu.evolve(
    preOps = [ initByFreq(alleleFreq=[0.7, 0.3]) ],
    ops = [
        pyOperator(func=freqDependSelector, param=[2, 0.2, 0.4],
            stage=PreMating),
        pyEval(r'''"%.4f\n" % (1-alleleFreq[2][0])''', step=20),
    ],
    end = 1000)
```

5.2   Information fields

Information fields are, in short, double values attached to each individual. Since different applications require different information fields, simuPOP takes a minimal approach in that no information field will be used (to save RAM) by default. When you apply an operator that needs a particular field, and your population does not have it, an error message will be given so that you can add appropriate fields to the `infoFields` parameter of `population()`, or use `setInfoFields()`, `addInfoField()`, `addInfoFields()` member functions to add them. Commonly used information fields are

- `fitness`: used by all selectors, and by mating schemes

- `father_idx`, `mother_idx`: used by taggers to track parental information

- `spouse, pedindex, oldindex:` used by ascertainment operators to obtain pedigree information.

Besides these standard information fields, you can define any fields for your use. The most frequently used functions are `individual::setInfo(value, field)`, `individual::info(field)`, `population::setIndInfo(values, field)` and `population::indInfo(field)`. Here field can be the name of the field, or an id returned by `population::infoIdx(field)`. Accessing information fields using indices is faster than using names.

In the following example (Example 12), a proportional hazard model is used to determine the age of onset of an individual with given genotype. Briefly,

- The base hazard is $h_0(t) = \beta_0 t$, the corresponding survival function is $S(s) = \exp\left(-\int_0^s h(t)\,dt\right)$. The age of onset is determined randomly by the survival function. ($F(x) = 1 - S(x)$ is used in the example.) The relevant functions are `hazard, cumHazard, cdf, ageOfOnset`. In the last function, β is the fold change of the hazard function so $h(t, \beta) = \beta\beta_0 t$.

- Date of birth is calculated as 2005 - age, where age is $U(0, 75)$.

- The proportional hazard model is
$$h(t, X) = h_0(t)\exp(\beta X)$$
where X is the number of disease alleles at the given disease susceptibility loci. The age of onset is determined by individual $h(t, X)$.

- Affection status is determined by date of birth + age of onset < 2005.

The program is pretty self-explainary so I do not comment on the code here. The resulting population has information fields `DateOfBirth, betaX` and `ageOfOnset`. Note that this example does not any operator or simulator, and demonstrate simuPOP's ability to manipulation populations.

Example 12 Proportional hazard model and use of information fields

---

```
#!/usr/bin/env python
'''
Demonstrate the use of information fields.
'''
from simuOpt import setOptions
setOptions(alleleType='binary')
from simuPOP import *
from random import *
from math import exp

def hazard(t, beta):
    return beta*t

def cumHazard(t, beta):
    ''' cumulative hazard function'''
    return sum([hazard(x, beta) for x in range(0, t+1)])

def cdf(t, beta):
    ''' F(x) = 1-exp(-H(x)) '''
    return 1-exp(-cumHazard(t, beta))

def ageOfOnset(u, beta, beta0):
    ''' u is Unif(0,1), beta is fold change '''
```

```
        aa = 75
        for age in range(75):
            if cdf(age, beta*beta0) > u:
                aa = age
                break
        return aa

    def simuDateOfBirth(pop):
        dobIdx = pop.infoIdx('DateOfBirth')
        for ind in pop.individuals():
            age = randint(0, 75)
            ind.setInfo(2005-age, dobIdx)

    def simuBetaX(pop, DSL, beta):
        bxIdx = pop.infoIdx('betaX')
        for ind in pop.individuals():
            X = sum([ind.allele(i, 0) + ind.allele(i, 1) for i in DSL])
            ind.setInfo(beta*X, bxIdx)

    def simuAgeOfOnset(pop, beta0):
        bxIdx = pop.infoIdx('betaX')
        aaIdx = pop.infoIdx('ageOfOnset')
        for (idx, ind) in enumerate(pop.individuals()):
            bx = ind.info(bxIdx)
            ind.setInfo(ageOfOnset(uniform(0,1), exp(bx), beta0), aaIdx)

    def setAffection(pop):
        'set affected if age of onset + date of birth < 2005'
        aaIdx = pop.infoIdx('ageOfOnset')
        dobIdx = pop.infoIdx('DateOfBirth')
        for ind in pop.individuals():
            if ind.info(aaIdx) + ind.info(dobIdx) < 2005:
                ind.setAffected(True)
            else:
                ind.setAffected(False)

pop = population(1000, loci=[5, 9])
InitByFreq(pop, [.9, .1])
# suppose we load population from somewhere else, need to add information fields
pop.setInfoFields(['DateOfBirth', 'betaX', 'ageOfOnset'])
simuDateOfBirth(pop)
simuBetaX(pop, [4, 7], 1)
simuAgeOfOnset(pop, 0.0001)
setAffection(pop)
Stat(pop, numOfAffected=True)
print pop.dvars().numOfAffected
```

5.3   Population structure and migration

You first need to understand that mating schemes populate subpopulations from their corresponding ancestral subpopulations one by one, so it can not change number of subpopulations. Split and merge of subpopulations are done by operators `splitSubPop` and `mergeSubPops` respectively. In example 13, these two operators are used to split and merge subpopulations, but keep total population size untouched. Note that after subpopulation merge, subpopulation 2 still exists, but with size 0. This is used to keep subpopulation id of other subpopulations unchanged.

Example 13 Population split and merge

```
>>> from simuPOP import *
>>> pop = population(1000, loci=[1])
>>> simu = simulator(pop, binomialSelection())
>>> simu.evolve(
...      ops=[
...           splitSubPop(0, proportions=[0.2, 0.8], at = [3]),
...           splitSubPop(1, proportions=[0.4, 0.6], at = [5]),
...           mergeSubPops([0,2], at = [7]),
...           stat(popSize=True),
...           pyEval(r'"%s\n" % subPopSize'),
...      ],
...      end = 10
... )
[1000]
[1000]
[1000]
[200, 800]
[200, 800]
[200, 320, 480]
[200, 320, 480]
[680, 320, 0]
[680, 320, 0]
[680, 320, 0]
[680, 320, 0]
True
>>>
```

Migration can change subpopulation size, but not total population size. In example 13, two migrators are used. The first migrator moves individuals from subpopulation 0 to subpopulation 1. The second migrator moves individuals around, with given proportions. For example, the migration rate

$$\begin{pmatrix} 0. & 0.2 & 0.4 \\ 0. & 0. & 0.1 \\ 0.1 & 0.1 & 0. \end{pmatrix}$$

means moving 20% of individuals from subpop 0 to 1, 40% of individuals from subpop 0 to 1, and keep 40% (automatically determined). Subpopulation sizes change accordingly.

Example 14 Population split and migration

```
        >>> from simuPOP import *
        >>> pop = population(1000, loci=[1])
        >>> simu = simulator(pop, binomialSelection())
        >>> simu.evolve(
        ...     ops=[
        ...         splitSubPop(0, proportions=[0.2, 0.3, 0.5], at = [3]),
        ...         migrator(rate = [0.2], fromSubPop=[0], toSubPop=[1],
        ...             begin = 3, end = 4),
        ...         migrator(rate = [
        ...             [0, 0.2, 0.4],
        ...             [0, 0,   0.1],
        ...             [0.1, 0.1, 0]],
        ...             begin = 4),
        ...         stat(popSize=True),
        ...         pyEval(r'"%s\n" % subPopSize'),
        ...     ],
        ...     end = 10
        ... )
        [1000]
        [1000]
        [1000]
        [162, 338, 500]
        [102, 421, 477]
        [88, 429, 483]
        [80, 458, 462]
        [81, 454, 465]
        [75, 487, 438]
        [76, 503, 421]
        [80, 504, 416]
        True
        >>>
```

But what if you need to control total population size? In this case, a demographic function is needed to specify the size of each subpopulation, at each generation. In example 15, function popSize returns exact subpopulation size at each generation, and the population will behave accordingly. It might surprise you that migration can no longer control the size of subpopulation sizes. What exactly happened is that, for example

- subpopulation size = [200, 400, 400], at the beginning of a generation

- apply migrator, subpopulation size changed to [100, 470, 430]

- pre mating operator stat is applied and report subpopulation sizes

- during mating, with given subpopulation sizes 200, 400, 400 of the offspring generation, the mating scheme generate 200 offspring from 100 parents in subpopulation 0, 400 offspring from 470 parents in subpopulation 1, and 400 offspring from 430 parents in subpopulation 2.

- post mating operator stat is applied and get the new subpopulation size.

This example also demonstrates the use of stage parameter. As a matter of fact, you can use only one stat operator by using stage=PrePostMating. If you are confused by the order of operators, use the dryrun=True parameter of evolve to check.

Example 15 Population split with changing population size

```
>>> from simuPOP import *
>>> pop = population(1000, loci=[1])
>>> def popSize(gen, oldSize=[]):
...     if gen < 3:
...         return [1000]
...     elif gen < 5:
...         return [400, 500]
...     else:
...         return [300, 400, 600]
...
>>> simu = simulator(pop, binomialSelection(newSubPopSizeFunc=popSize))
>>> simu.evolve(
...     ops=[
...         splitSubPop(0, proportions=[0.3, 0.7], at = [3]),
...         migrator(rate = [0.2], fromSubPop=[0], toSubPop=[1],
...             begin = 3, end = 4),
...         splitSubPop(0, proportions=[0.3, 0.7], at = [5]),
...         migrator(rate = [
...             [0, 0.2, 0.4],
...             [0, 0,   0.1],
...             [0.1, 0.1, 0]],
...             begin = 5),
...         stat(popSize=True, stage=PreMating),
...         pyEval(r'"From %s\t" % subPopSize', stage=PreMating),
...         stat(popSize=True),
...         pyEval(r'"to: %s\n" % subPopSize'),
...     ],
...     end = 10
... )
From [1000] to: [1000]
From [1000] to: [1000]
From [1000] to: [1000]
From [243, 757] to: [400, 500]
From [316, 584] to: [400, 500]
From [81, 505, 314] to: [300, 400, 600]
From [182, 485, 633] to: [300, 400, 600]
From [164, 477, 659] to: [300, 400, 600]
From [172, 493, 635] to: [300, 400, 600]
From [176, 485, 639] to: [300, 400, 600]
From [200, 464, 636] to: [300, 400, 600]
True
>>>
```

You might say, OK, this looks nice, but how can I grow a population with migration acting freely? This is also easy, all you need to do is using the oldSize parameter of a demographic function in a clever way. The underlying story is that

- before mating, a mating scheme calculates current subpopulation sizes

- it calls the given demographic function with current generation number and current subpopulation sizes

- it uses the return value as the new subpopulation sizes.

Example 16 demonstrate an exponentially increase population with free migration between subpopulations.

Example 16 Population split with changing population size

```
>>> from simuPOP import *
>>> pop = population(1000, loci=[1])
>>> def popSize(gen, oldSize=[]):
...     return [x*2 for x in oldSize]
...
>>> simu = simulator(pop, binomialSelection(newSubPopSizeFunc=popSize))
>>> simu.evolve(
...     ops=[
...         splitSubPop(0, proportions=[0.3, 0.7], at = [3]),
...         migrator(rate = [0.2], fromSubPop=[0], toSubPop=[1],
...             begin = 3, end = 4),
...         splitSubPop(0, proportions=[0.3, 0.7], at = [5]),
...         migrator(rate = [
...             [0, 0.2, 0.4],
...             [0, 0,   0.1],
...             [0.1, 0.1, 0]],
...             begin = 5),
...         stat(popSize=True, stage=PrePostMating),
...         pyEval(r'"From %s\t" % subPopSize', stage=PreMating),
...         pyEval(r'"to: %s\n" % subPopSize'),
...     ],
...     end = 10
... )
From [1000] to: [2000]
From [2000] to: [4000]
From [4000] to: [8000]
From [1955, 6045] to: [3910, 12090]
From [3163, 12837] to: [6326, 25674]
From [1188, 23937, 6875] to: [2376, 47874, 13750]
From [2305, 44829, 16866] to: [4610, 89658, 33732]
From [5225, 84972, 37803] to: [10450, 169944, 75606]
From [11816, 162553, 81631] to: [23632, 325106, 163262]
From [25660, 313688, 172652] to: [51320, 627376, 345304]
From [55089, 609441, 359470] to: [110178, 1218882, 718940]
True
>>>
```

5.4 Sex chromosomes

Supports for sex chromosomes are done in simuPOP in the following ways:

- If sexChrom=True is specified in population(), the last chromosome is assumed to be the sex chromosome. For female, it is XX, for male, it is XY, in that order.

- During mating, sex of offspring is determined by sex chromosome. (It is otherwise determined randomly with probability 0.5).

- Recombination can not happen between X and Y chromosomes. That is to say, offspring can get recombined X from his/her mother, but untouched X or Y from father.

As of version 0.7.5, no other operator recognize sex chromosome. Most notably, stat counts allele frequencies etc regardless sex chromosome and can not count allele frequency for X or Y separately.

5.5 Pedigree tracking

simuPOP provides the following functions to manipulate pedigrees

- If you set ancestral depth of a population to a positive number (default 0), ancestral depth number of ancestral generations will be saved to the population, which makes a total of ancestral depth + 1 generations.

- You can use `population::useAncestralPop(idx)` to use current (0), parental (1), grand-parental (2) generations etc. Just remember to call `population::useAncestralPop(0)` to set current generation back.

- You can set `ancestralDepth` dynamically using operator `setAncestralDepth.` Usually, this operator is called, for example, as `setAncestralDepth(at=[-2])`, to allow last several generations to be saved at the end of evolution.

- No parental information is saved by default we usually do not know the parents of an offspring. This can be changed by using the `father_idx` and `mother_idx` information fields, and an appropriate tagger such as `parentTagger()`, which is a during mating operator that will record the parents' indices in the parental generation to offspring's information fields.

- `randomMating()` only produce one offspring per mating event. This makes full siblings very unlikely. You usually need to change this at the last several generations.

You can see that generating multi-generation populations are quite different from the usual evolutionary process where random mating is used, and one offspring is generated for each mating event. In practice (see `scripts/simuComplexDisease.py`), if we need to prepare a population for pedigree sampling, we do something like this

```
simu.evolve(
    preOps=[...],
    ops = operators,
    end = 1000 - 2
)
# need to do this to all replicate if you have more
simu.population(0).setAncestralDepth(2)
simu.population(0).addInforFields(['father_idx', 'mother_idx'])
operators.append(parentsTagger())
simu.setMatingScheme(randomMating(numOffspring=2))
simu.evolve(ops=operators, end=1000)
```

That is to say, we separate the simulation into two parts. The first part is geared toward performance and maximum effective population size (use true random mating), and the second part is tweaked for the fianl multi-generation population.

Now, at the end of the simulation, you get a population with multiple generations, with parental information. But it is still not easy to obtain pedigrees. As a matter of fact, since pedigrees can have intersections, it is not even easy to define a pedigree. simuPOP provides two pedigree ascertainment operators

- `AffectedSibpairSample`: sample affected sibpairs, along with their parents from a population. Affection status should have been set by other means such as a penetrance operator.

- `LargePedigreeSample`: sample grand parents, their children, and the spouse and children of them. Affection status is ignored, although the minimal number of affected individuals in each family can be specified.

If you need to sample more complicated pedigrees, you should first use `sample::findOffspringAndSpouse` to locate each individual's offspring and spouse, then use `useAncestralPop()` to go through the generations and set `pedIndex` for the pedigree you choose, and then use `setSubPopID()`, `newPopByIndID()` to exclude and remove unneeded individuals. `sample::resetParentalIndex()` should also be used to reset the `father_idx` and `mother_idx` fields. Sound complicated? It is complicated! I hope that I can get some better idea and make this process a bit easier, but this is where simuPOP is at right now.

Finally, you can save the sample populations in a pedigree-aware format like Linkage or Merlin/QTDT format. simuPOP can do this easily for you.

5.6   Save and load to other formats

simuPOP data structure is open in that many functions are provided to access every aspect of the population. This makes it easy to save and load populations in other formats. As an example, I will explain `SaveTDT` function in detail here, which is available in `simuUtil.py`.

Although all file formats have different characteristics, `simuPOP` tries to provide a uniform interface to them. Common parameters are

- pop: population to save, can be a file name, or a file object (loaded simuPOP population)

- output and outputExpr: output is the base filename, and outputExpr should be evaluated from pop's local namespace.

- loci: loci to output, default is [], meaning output all loci

- fields: information fields to output.

- combine: a python function, if given, used to combine two alleles at the same locus. For example

    ```
    def comb(geno):
        return geno[0]+geno[1]+1
    ```

  returns 1 for genotype(0, 0), 2 for genotype (0, 1) and so on.

- shift: default to 1. simuPOP uses 0 based allele and many formats use 1 based allele. Setting shift=1 output (1,2) for genotype (0,1).

The `Merlin/QTDT` format uses several files to store genotype and phenotype information. Namely a `.dat` file for phenotype, `.map` file for chromosome structure, and `.ped` for pedigree. The population given must have `pedindex`, `father_idx` and `mother_idx` information fields to indicate family id and parents of each individual. These information fields will be available if the sample is obtained from `affectedSibpairSample` or `largePedigreeSample` operators.

The first part of the function is the usual housekeeping part (see example 17). It loads population if `pop` is a name, evaluate `outputExpr` if needed, and open the files to write. This part is likely to be similar for all such functions.

Example 17 Function SaveQTDT, part one

```
            def SaveQTDT(pop, output='', outputExpr='', loci=[],
                    fields=[], combine=None, shift=1, **kwargs):
            """ save population in Merlin/QTDT format. The population must have
                pedindex, father_idx and mother_idx information fields.

                pop: population to be saved. If pop is a filename, it will be loaded.

                output: base filename.
                outputExpr: expression for base filename, will be evaluated in pop's
                    local namespace.

                loci: loci to output

                fields: information fields to output

                combine: an optional function to combine two alleles of a diploid
                    individual.

                shift: if combine is not given, output two alleles directly, adding
                    this value (default to 1).
            """
            if type(pop) == type(''):
                pop = LoadPopulation(pop)
            if output != '':
                file = output
            elif outputExpr != '':
                file = eval(outputExpr, globals(), pop.vars())
            else:
                raise exceptions.ValueError, "Please specify output or outputExpr"
            # open data file and pedigree file to write.
            try:
                datOut = open(file + ".dat", "w")
                mapOut = open(file + ".map", "w")
                pedOut = open(file + ".ped", "w")
            except exceptions.IOError:
                raise exceptions.IOError, "Can not open file " + file + " to write."
            if loci == []:
                loci = range(0, pop.totNumLoci())
```

Part two of the code (example 18) output data file. There are three kinds of phenotype, affection status, trait and markers. We determine if a user wants to output affection from the `fields` parameter. We remove `affection` from `fields` because `affection` is not a real information field (that can be retrieved by `info()` function). You can learn how to use the `locusName` function from this part.

Part three (example 19) of the function output a map file. We need to know the chromosome number (+1 to use 1 based index), locus name and locus position, all of which can be retrieved from simple `simuPOP` functions. Note that if locus name, position are not given explicitly when a population is created, they all have default values.

The next part (example 20) prepares pedigree output. It determines the code to output for sex and affection status. These are likely to be different from format to format so we define explicitly here. The `writeInd` output the line for one individual, given family id, id, father and mother. For QTDT format, two alleles of a genotype are outputted separately so the `combine` parameter is ignored.

The last part of the code (example 21) look most complicated. It first get the `pedindex` information field of the whole population, and figure out how many pedigrees to output. Then, it go from ancestral generation 2, 1, 0 and look for individuals within each pedigree. A map is used to map absolute index to within pedigree index. Of course, this

Example 18 Function SaveQTDT, part two

```
# write dat file
#
if 'affection' in fields:
    outputAffectation = True
    fields.remove('affection')
    print >> datOut, 'A\taffection'
else:
    outputAffectation = False
for f in fields:
    print >> datOut, 'T\t%s' % f
for marker in loci:
    print >> datOut, 'M\t%s' % pop.locusName(marker)
datOut.close()
```

Example 19 Function SaveQTDT, part three

```
# write map file
print >> mapOut, 'CHROMOSOME MARKER POSITION'
for marker in loci:
    print >> mapOut, '%d\t%s\t%f' % (pop.chromLocusPair(marker)[0] + 1,
        pop.locusName(marker), pop.locusPos(marker))
mapOut.close()
```

part would be easier if you do not need to handle pedigree, for example, when outputting case control samples.

Example 20 Function SaveQTDT, part four

```
# write ped file
def sexCode(ind):
    if ind.sex() == Male:
        return 1
    else:
        return 2
# disease status: in linkage affected is 2, unaffected is 1
def affectedCode(ind):
    if ind.affected():
        return 'a'
    else:
        return 'u'
#
pldy = pop.ploidy()
def writeInd(ind, famID, id, fa, mo):
    print >> pedOut, '%d %d %d %d %d' % (famID, id, fa, mo, sexCode(ind)),
    if outputAffectation:
        print >> pedOut, affectedCode(ind),
    for f in fields:
        print >> pedOut, '%.3f' % ind.info(f),
    for marker in loci:
        for p in range(pldy):
            print >> pedOut, "%d" % (ind.allele(marker, p) + shift),
    print >> pedOut
```

Example 21 Function SaveQTDT, part five

```
# number of pedigrees
# get unique pedgree id numbers
from sets import Set
peds = Set(pop.indInfo('pedindex', False))
# do not count peds -1
peds.discard(-1)
#
newPedIdx = 1
#
for ped in peds:
    id = 1
    # -1 means no parents
    pastmap = {-1:0}
    # go from generation 2, 1, 0 (for example)
    for anc in range(pop.ancestralDepth(), -1, -1):
        newmap = {-1:0}
        pop.useAncestralPop(anc)
        # find all individual in this pedigree
        for i in range(pop.popSize()):
            ind = pop.individual(i)
            if ind.info('pedindex') == ped:
                dad = int(ind.info('father_idx'))
                mom = int(ind.info('mother_idx'))
                if dad == mom and dad != -1:
                    print ("Something wrong with pedigree %d, father and mother " + \
                        "idx are the same: %s") % (ped, dad)
                writeInd(ind, newPedIdx, id, pastmap.setdefault(dad, 0), \
                    pastmap.setdefault(mom, 0))
                newmap[i] = id
                id += 1
        pastmap = newmap
    newPedIdx += 1
pedOut.close()
```

5.7 Gene mapping

Once you output your sample into a format that can be processed by other applications, you can handle them in whatever way you want. If you are interested in processing the data in simuPOP (actually, in python), you can use python to call these programs.

Example 22 Example of gene mapping

```
def VC_merlin(file, merlin='merlin'):
    ''' run variance component method
        file: file.ped, file.dat, file.map and file,mdl are expected.
            file can contain directory name.
    '''
    cmd = 'merlin -d %s.dat -p %s.ped -m %s.map --pair --vc' % (file, file, file)
    resline = re.compile('\s+([\d.+-]+|na)\s+([\d.+-]+|na)%\s+([\d.+-]+|na)\s+([\d.+-]+|na)
    print "Running", cmd
    fout = os.popen(cmd)
    pvalues = []
    for line in fout.readlines():
        try:
            # currently we only record pvalue
            (pos, h2, chisq, lod, pvalue) = resline.match(line).groups()
            try:
                pvalues.append(float(pvalue))
            except:
                # na?
                pvalues.append(-1)
        except AttributeError:
            pass
    fout.close()
    return pvalues
```

An example is given in example 22. In this function, `merlin` [Abecasis et al., 2002] is called to process file produced by the `SaveQTDT` function. The output is fed into a pipe (`popen`) and be filtered by the python `re` (regex) module. Only the p-values are obtained and returned.

5.8 MPI version of simuPOP

The mpi version of simuPOP spread the population across multiple instances of python/simuPOP. These instances (processes) can be executed on the same physical processor, mutliple cores on the same processor, multiple processoars on the same machine, or multiple nodes on a cluster system. The communication between these processes are done using Message Passing Interface (MPI). I will call these processes as nodes from now on.

When simuPOP/MPI is started, the head node does not store any genotype information, only auxillary information such as information fields. The chromosomes are spread over multiple nodes according to a chromosome map. For example, for individuals with 23 chromosomes, the first 10 chromosomes can be on the second node, and the rest on the third node. The map is then [10, 13]. Three nodes will be used for this simulation.

Chromosome map can be given in several ways:

- By default, each chromosome occupies one node. The map is then [1]*number of chromosomes

- By using parameter `chromMap` of population function. This parameter is ignored in non-MPI mode.

- Using `--chromMap='[2,3,4]'` as an parameter to simuPOP scripts, `simuOpt.setOptions(chromMap)`, or set environment variable `SIMUCHROMMAP`. These usage allows flexibility in setting chromosome map independent of a simuPOP script, and are thus recommended.

It is critical for you to remember how many nodes a simuPOP simulation will need, since the usual way to start the simulation is

```
$ mpirun -n 4 python /path/to/a/simuPOP/script --mpi --chromMap='[2,3,4]' --other-opti
```

Other than these, everything should work them same as non-MPI modules.

Introduction to bundled scripts

Several scripts are bundled with simuPOP, under the `/usr/share/simuPOP/scripts` directory under a *nix system and `c:\python25\share\simuPOP\scripts` under windows. These scripts all use `simuOpt` module to organize help messages so you can get detailed information about the scripts and the parameter used by clicking on help button of the parameter dialog, or use commands like 'simuComplexDisease.py -h' to get the help messages.

In this chapter, I will briefly explain what these scripts do, from a more methodology side of view. Be warned, though, that these scripts are less actively maintained than simuPOP core and I mostly rely on user bug report to identify problems in these scripts.

6.1 Examples and teaching scripts

6.1.1 `simuLDDecay.py`

This is the simplest script under the `scripts` directory, showing the decay of linkage disequilibrium under recombination. It is intended to be a template for many more such simulations for teaching a population genetics course.

6.1.2 `demoPyOperator.py`

This script demonstrate the use of a during-mating pure-Python operator. Since such operator will be called very frequently (at each mating event), the performance of such operators tend to be bad. Since most of the task performed by such an operator can be achieved by other means (for example a post-mating operator), it is rarely used.

6.2 Utility scripts

These scripts are not necessarily written in simuPOP. It is written to facilitate the use of simuPOP.

6.2.1 `simuViewPop.py`

`simuViewPop.py` is a `wxPython` application written to view simuPOP populations. You will need to have `wxPython` installed to use it. There are two ways to use this script:

- Import this script and call `viewPop(pop)` to view population `pop`
- Run from command line

```
$ simuViewPop.py /path/to/population.txt
```

This script shows four tabs to show the information of a population

- basic information

- a table view of all genotype

- calculation of statistics, with a tree-view of local name space

- save to other formats

6.2.2 `simuCluster.py`

`simuCluster.py` helps you manage a large number of simulations on a cluster system. You only need to maintain a single job-description file and `simuCluster.py` will help you submit them. The command line options are

```
$ simuCluster.py -l simulation.lst -a  -r -f key=val jobs
```

where

- `-l list:` a list file (actually a python file) that specifies variale `script` and `joblist`

- `-a:` use all jobs defined in the list file

- `-r:` run the jobs, by default, this script will only list the jobs and generate job file.

- `-f:` force the execution even if the generated job scripts have $ character.

- `key=val:` additional subsitution key/value pair that will be used to replace $key in the job scripts. Commonly used, or machine-specific, `key=val` pairs can be defined in a configuration file $HOME/.simuCluster with content like:

  ```
  command = 'bsub -J $name <'
  queue = 'batch'
  job_dir = '/scratch/jobs'
  ```

- `job:` a list of jobs, a simple form of regular expression can be used. Namely, `job1_3` means `job1`, `job2` and `job3`.

The list file can be any python script, that defines variables `script` and `joblist` after execution, where `script` is a simple script with variables $name or ${name}. and `joblist` is a string with lines of comma (can be other charater if you define a variable `separator`) separated fields, that will be used to replace $0 (also $name, the name of a job), $1, $2, ... etc.

Then, what `simuCluster.py` will do is process this list file, replace $name, $var, $1, $2 ... etc with environmental variables, command line paramters, configuration file and joblist and generate job scripts. If `-r` is given, the job will be submitted. Example 23 gives a sample job list file. Command

```
$ python scripts/simuCluster.py -l joblist.lst -a
```

will generate files `job1.pbs`, ... and if `-r` option is given, these files will be submitted using `qsub job1`, unless you specify another `command` variable.

Example 23 A sample job list file

```
# list file for some simulations, should be processed by
# scripts/simuCluster.py

script = r"""
#!/bin/bash
#PBS -S /bin/bash
#PBS -N $name
#PBS -q $queue
#PBS -l walltime=$time:00:00
#PBS -o $job_dir
#PBS -e $job_dir
#
PYTHONPATH=/home/user/PythonModules/lib64/python2.3/site-packages
export PYTHONPATH
cd $job_dir
[ -d $job_dir ] || mkdir -p $job_dir
/bin/rm -rf $job_dir/$name
/bin/mkdir -p $job_dir/$name
python /home/bpeng/simuPOP/scripts/simuComplexDisease.py --noDialog --optimized \
    --simuName=$name --numChrom=5 --DSL='[5, 15, 25, 25, 45]' \
    --splitGen=8000 --numSubPop=1 \
    --fitness=$1 --alleleDistInSubPop=even \
    --recRate="0.0005" --curAlleleFreq='[0.2]*5' --numLoci="10" --DSLLoc="(0.5)" \
    --initSize="10000" --endingSize="200000" --burninGen="5000" --markerType="SNP" \
    --growthModel='exponential' --mixingGen="10000" --endingGen="10000" --savePop=[] \
    --minMutAge=0 --maxMutAge=0 --migrRate="0." --migrModel='stepping stone'\
    --selMultiLocusModel="additive" --mutaRate=$2 --saveFormat='txt'
"""

joblist = ''

idx = 0
for fit in [0.001, 0.0005]:
    for mut in [0.0001, 0.00001]:
        joblist += 'jobs_%d: %s*5: %f\n' % (idx, [1, 1+fit/2., 1+fit], mut)
```

6.2.3 simuUtil.py

simuUtil.py is a standard part of simuPOP and is installed along with simuPOP.py (other utility scripts are installed under scripts directory). These function include

1. extra python operators, the two potentially useful ones are

   - **tab**
   - **endl**

   These two operators output, as their names suggest, '\t' and '\n'.

2. Pre-defined demographic functions:

   - constSize
   - LinearExpansion
   - ExponentialExpansion
   - InstantExpansion

These functions return a demographic function with given event times.

3. Pre-defined migration rate functions

   - `MigrIslandRates`
   - `MigrSteppingStoneRates`

   These functions return a migration matrix of given migration model and parameter.

4. Save and load from other formats

   - `SaveFstat (saveFstat), LoadFstat`
   - `LoadGCData`
   - `SaveLinkage (saveLinkage), LoadLinkage`
   - `SaveQTDT`
   - `SaveCSV`

   These functions save and load simuPOP populations in various formats.

5. Gene mapping functions

   - `TDT_gh, LOD_gh`
   - `ChiSq_test`
   - `LOD_merlin, VC_merlin`
   - `Sibpair_TDT_gh, Sibpair_LOD_gh`
   - `Sibpair_LOD_merlin, QtraitSibs_Reg_Merlin, QtriatSibs_VC_merlin`
   - `LargePeds_Reg_merlin, LargePeds_VC_merlin`

   These functions call GENEHUNTER or MERLIN to map disease genes. Various parameters like penetrance, quantitative trait functions, sample size are needed. These functions are tested only under Linux and are subject to frequent changes.

In general, these utility functions are provided as it is and you may need to read the source code to make it work should errors occur. Unit test will be added later when these functions are more or less stablized/standardized.

6.3 General simulation scripts

6.3.1 `simuCDCV.py`

This script is used to simulate the evolution of allelic spectra (number and allele freqencies of alleles at a locus) for monogenic or polygenic, rare or common diseases. The goal of the simulations is to validate the common disease common variant hypothesis[Lander, 1996]. I used this script to verify two theoretical models proposed by Pritchard [2001] and Reich and Lander [2001]. The results are published in Peng and Kimmel [2006].

6.3.2 `simuRecHotSpots.py`

I wrote this script to simulate the evolution of a chromosome, subject to recombination of uniform recombination rate. Using this script, I would like to see how many recombination hotspots can be observed if there is no physical recombination hotspots, i.e. actual variation of recombination rate on the chromosome. The population is saved in LDhat format to be analyzed by LDhat [Myers et al., 2005].

6.3.3 `simuNeutralSNPs.py`

This script is adapted from `simuRecHotSplots.py`, the main purpose is to observe the evolution of allele frequency under more complicated scenarios than classical population genetics theory can handle.

6.4 Simulations of the evolution of complex human diseases

6.4.1 `simuForward.py`

This script presents my first attempt to simulate the evolution of complex human diseases in a forward-time manner and generate samples for gene mapping purposes. The script goes like this:

- initialize a small (likely 10K) founder population with a few haplotypes

- burn-in this founder population for a few thousands generations to break down linkage disequilibrium

- after this stage, the population starts to expand. It can be split into several subpopulations (simulate human subpopulations), with and/or without migration and be merged back to a single population.

- At the beginning of population expansion, several disease mutants are introduced to the population. Positive or negative selection is applied to individuals with disease mutants. We hope to harvest a final population with certain disease allele frequency.

This process is problematic in that

- The disease allele can get lost

- We can not control the disease allele frequency at the last generation

To solve the first problem, I re-introduce disease mutants if they get lost. I also apply, optionally, strong positive selection pressure during an disease-introduction stage to artificially boost the disease allele frequency, until it reach a designed range of allele frequencies. If the disease allele still get lost after the disease introduction stage, the simulation will be restarted. By manipulating parameters like designed allele frequency and population size, the impact of genetic drift can be moderate and give me a final population with designed disease allele frequency. This simulation scenario roughly follows that of Calafell et al Calafell et al. [2001].

To save simulation time, population at the end of the burnin stage is reused if simulation gets restarted.

6.4.2 `simuComplexDisease.py`

The previous simulation scenario is not satisfactory in that

- The age of mutant is fixed, but they should be somehow random

- Mutants can get lost and the simulation needs to be restarted repeatedly. This problem can be severe if we simulate mutants under purifying selection.

- We still can not control the final disease allele frequency well. The variation of disease allele frequencies in the final generation makes fair comparison between gene mapping methods difficult.

Therefore, I propose a simulation method, which is still under review, that

- simulate, backward in time, the trajectory of disease allele frequencies. The age of mutant is determined by trajectory length, and is random.

- Then, the script simulate forward in time using a controlled random mating scheme that follow the pre-simulated disease allele trajectories. The resulting population will have exact designed allele frequency.

An obvious advantage of this approach is that the simulation does not have to be restarted, and the disease allele frequency at the last generation can be controlled exactly.

6.4.3 `analComplexDisease.py`

I use `simuComplexDiseas.py` to simulate many population under various genetic and demographic models. The resulting populations are analyzed by this script. The analyses involved are

- merlin variance component method [Abecasis et al., 2002, Amos, 1994]

- merlin regression [Sham et al., 2002]

- TDT [Spielman et al., 1993]

- Linkage, and

- Case control association study.

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