simuPOP User's Guide

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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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ONE

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 genetics 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 arbitrary subpopulation structure. Sex chromosome is 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.
- 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!*
- selfing is introduced as a way to produce offspring from a parent
- pyMating can work with different, including a hybrid, parent choosers and different offspring generator including selfing.
- recombinator and gene conversion.
- allow different ways to specify offspring sex.

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 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), ops (operators),
  expr (expression), stmts (statements)
  ```

1.5 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.

CHAPTER

TWO

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 2.1) 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.

Listing 2.1: Import simuPOP module

```
>>> from simuPOP import *
simuPOP : Copyright (c) 2004-2008 Bo Peng
Version snapshot (Revision 9999, Sep  5 2008) for Python 2.4.3
[GCC 4.1.2 20070626 (Red Hat 4.1.2-14)]
Random Number Generator is set to mt19937 with random seed 0x7d5728e0884377a4
This is the standard short allele version with 256 maximum allelic states.
For more information, please visit http://simupop.sourceforge.net,
or email simupop-list@lists.sourceforge.net (subscription required).
>>>
```

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 2.2.

Listing 2.2: 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 is 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. Also, as of version 0.7.9, the MPI modules are not yet fully implemented (and most likely unusable for your simulations). You will have to compile simuPOP by yourself to make use of them.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.

Listing 2.3: 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 comma-separated 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`.

CHAPTER

THREE

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

Listing 3.1: 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)
...     ],
...     gen=100
... )
  0   0.196182    0.197365    0.193262
 25   0.014390    0.008462    0.030377
 50   0.001276    0.009310    0.008917
 75   0.003279    0.008931    0.009785
True
>>> r.dev_print(file='log/LDdecay.eps')
```

```
{'X11': 2}
>>>
```

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.
- `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, but aribitrary temprary subpopulation structure can be defined. Such temporary subpopulations are called *virtual subpopulations*, where individuals can be grouped by sex, affection status, genotype, or values of 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
- control virtual subpopulation structure.

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 3.1, 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.
- Choose parent(s) to generate offspring to populate the next generation. The number of offspring per mating event can be a fixed number (default to 1), or a random number following one of geometric, Poisson or binomial distribution. Customized (hybrid) parent choosers can be used. Offspring sex can be assigned randomly, with specified or default (0.5) probability, or arranged to have certain number of males/females per mating event.
- 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. Non-random mating can be achieved using `pyMating` and `heteroMating`, which is explained in detailed in *simuPOP reference manual*.

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, begin, step, end` and `at`. The first two indicate that the operator only applies to one replicate, 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.

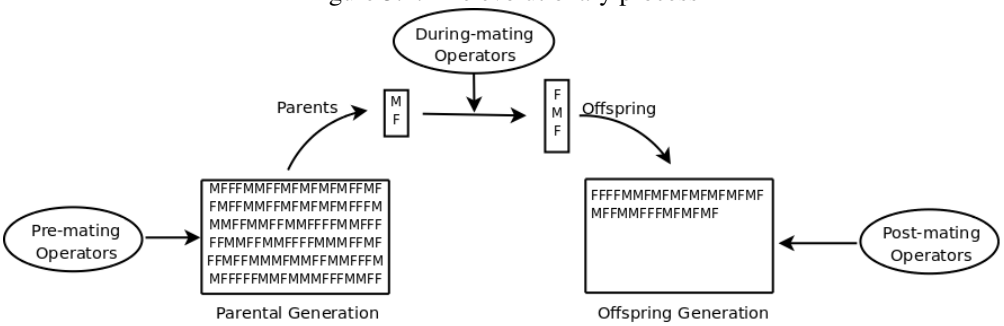
A simuPOP life cycle (each generation) can be divided into pre-mating, during-mating and post-mating and an operator can be applied to one or more of them. For example, a `stat` operator usually applies post-mating, but if you prefer, you can change its `stage` parameter to `preMating` and apply it pre-mating.

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, begin, end, step, at, stage` properties and act accordingly.

Figure 3.1: The evolutionary process



CHAPTER

FOUR

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 [2007], 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 $P(A \to a) \gg P(a \to A)$ 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, are shown in 4.1

Listing 4.1: 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 are needed 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 4.2. Note that because we use loci with more than 255 allele states, the long allele module is used.

Listing 4.2: 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(incScenario):
    simu = simulator(
# create a simulator
        population(subPop=incScenario(0), loci=[1,1],
            infoFields=['fitness']),
# inital population
        randomMating(newSubPopSizeFunc=incScenario)
# 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 with 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 4.3:

Listing 4.3: Run the simulator

```
def simulate(incScenario):
    simu = simulator(
# create a simulator
        population(subPop=incScenario(0), loci=[1,1],
            infoFields=['fitness']),
# inital population
        randomMating(newSubPopSizeFunc=incScenario)
# random mating
    )
    simu.evolve(                            # start evolution
        preOps=[                            # operators that will be applied before evol
            # 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 (listing 4.4) 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.

Listing 4.4: 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(incScenario):
    simu = simulator(
# create a simulator
        population(subPop=incScenario(0), loci=[1,1],
            infoFields=['fitness']),
# inital population
        randomMating(newSubPopSizeFunc=incScenario)
# random mating
    )
    simu.evolve(                            # start evolution
        preOps=[                            # operators that will be applied before evol
            # 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 population 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 using 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 4.5 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.

Listing 4.5: 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 (.ep
    },
]

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)
```

CHAPTER

FIVE

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), gene conversion (new in v 0.8.5), 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 5.1 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.

Listing 5.1: 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
```

Example 5.1 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 5.2 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 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.

Listing 5.2: A frequency dependent selection operator

```
#!/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 5.3), 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.

Listing 5.3: 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
```

Information fields can also be manipulated during evolution, using one of the Python operators, or operators `infoEval` and `infoExec` (new in version 0.8.4). Please refer to simuPOP reference manual for details.

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 5.4, 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.

Listing 5.4: 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
... )
Parameter end is obsolete in simulator::evolve(), please use gen instead.
[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 5.4, 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.

Listing 5.5: 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
... )
Parameter end is obsolete in simulator::evolve(), please use gen instead.
[1000]
[1000]
[1000]
[159, 341, 500]
[116, 411, 473]
[90, 445, 465]
[78, 472, 450]
[75, 487, 438]
[71, 493, 436]
[70, 499, 431]
[64, 520, 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 5.6, 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.

Listing 5.6: 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
... )
Parameter end is obsolete in simulator::evolve(), please use gen instead.
From [1000]     to: [1000]
From [1000]     to: [1000]
From [1000]     to: [1000]
From [231, 769] to: [400, 500]
From [332, 568] to: [400, 500]
From [81, 511, 308]     to: [300, 400, 600]
From [191, 483, 626]    to: [300, 400, 600]
From [177, 484, 639]    to: [300, 400, 600]
From [187, 496, 617]    to: [300, 400, 600]
From [182, 469, 649]    to: [300, 400, 600]
From [169, 483, 648]    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 5.7 demonstrate an exponentially increase population with free migration between subpopulations.

Listing 5.7: 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
... )
Parameter end is obsolete in simulator::evolve(), please use gen instead.
From [1000]     to: [2000]
From [2000]     to: [4000]
From [4000]     to: [8000]
From [1941, 6059]       to: [3882, 12118]
From [3105, 12895]      to: [6210, 25790]
From [1215, 24174, 6611]        to: [2430, 48348, 13222]
From [2308, 45232, 16460]       to: [4616, 90464, 32920]
From [5200, 85865, 36935]       to: [10400, 171730, 73870]
From [11612, 163981, 80407]     to: [23224, 327962, 160814]
From [25263, 315858, 170879]    to: [50526, 631716, 341758]
From [54388, 612448, 357164]    to: [108776, 1224896, 714328]
True
>>>
```

5.4 Non-random mating

Random-mating implies random choices of parents. Non-random mating is much more difficult to implement because there are numerous way to introduce non-randomness. One of the ways to achive non-random mating in simuPOP is to use a hybrid operator `pyMating`.

A `pyMating` mating scheme accepts a *parents chooser* and an *offspring generator*. The parents chooser is responsible for choosing one or two parents from the parental generation, and the offspring generator is responsible for generating a number of offspring from the chosen parents. There are a number of default parents choosers and offspring generators and a `pyMating` can be built with them. For example

```
pyMating(randomParentsChooser(), mendelianOffspringGenerator())
```

works exactly as a `randomMating` scheme, and

```
pyMating(randomParentChooser(), selfingOffspringGenerator(numOffspring=2))
```

works as `selfMating(numOffspring=2)`. Note that parent chooser and offspring generator should be compatible , meaning that if a parent chooser chooses one parent each time, the offspring generator should be able to produce offspring from a single parent.

The power of `pyMating` lies in its `pyParentChooser()`, which accepts a user-defined Python generator function, instead of a normal python function. Generally speaking, when a generator function is called, it returns a *generator* object that provides an iterator interface. Each time when the `next()` member function of this object is called, this function resumes where it was stopped last time, executes and returns what the next *yield* statement returns. For example, example 5.8 defines a function that calculate $f(k) = \sum_{i=1}^{k} \frac{1}{i}$ for $k = 1, ..., 10$. It does not calculate each $f(k)$ repeatedly but returns $f(1)$, $f(2)$, ... in a sequence interface.

Listing 5.8: A sample generator function

```
>>> def func():
...     i = 1
...     all = 0
...     while i < 10:
...         all += 1./i
...         i += 1
...         yield all
...
>>> a = func()
>>> a.next()
1.0
>>> a.next()
1.5
>>> for i in a:
...     print '%.3f' % i,
...
1.833 2.083 2.283 2.450 2.593 2.718 2.829
>>>
```

A *parents chooser* takes two parameters, a population and a subpopulation index. It can return different generator objects for different subpopulations.

Listing 5.9: A generator function that mimicks random mating

```
>>> def randomChooser(pop, sp):
...     males = [x for x in range(pop.subPopSize(sp)) \
...         if pop.individual(x, sp).sex() == Male]
...     females = [x for x in range(pop.subPopSize(sp)) \
...         if pop.individual(x, sp).sex() == Female]
...     nm = len(males)
...     nf = len(females)
...     while True:
...         yield males[rng().randInt(nm)], females[rng().randInt(nf)]
...
>>> pop = population(size=[100, 20], loci=[1])
>>> # this will initialize sex randomly
```

```
>>> InitByFreq(pop, [0.2, 0.8])
>>> rc1 = randomChooser(pop, 0)
>>> for i in range(5):
...     print rc1.next(),
...
(57, 14) (98, 22) (78, 12) (59, 96) (57, 28)
>>> rc2 = randomChooser(pop, 1)
>>> for i in range(5):
...     print rc2.next(),
...
(2, 6) (2, 0) (4, 0) (3, 18) (17, 8)
>>>
```

A user defined parents chooser can be very complicated, involving user defined information such as geometric locations. An example is given in `cookbook/Mating_pyMating_cpp.py`. In example 5.9, the parents chooser `randomChooser` collects indexes of males and females and simply return a pair of random male and female repeatedly. This is exactly what `randomMating` does if selection is not considered. It becomes obvious now that whereas a python function can return random male/famale pair, the generator interface is much more efficient because the identification of two sex groups is done only once. Example 5.10 demonstrates how to use this user-defined parent chooser.

Listing 5.10: pyMating with a user-defined parent chooser

```
>>> simu = simulator(pop,
...     pyMating(pyParentsChooser(randomChooser),
...         mendelianOffspringGenerator()))
>>> simu.step()
True
>>>
```

Because arbitrary information can be stored with an individual through information fields, `pyMating` can be very complicated. For example, one can choose individuals according their age, and/or geographic information. For populations with well-defined structure, virtual subpopulations can be used. Basically, one needs to specify a virtual subpopulation splitter to a subpopulation. Then, different mating schemes can be applied to different virtual subpopulations. A simple example is given in Example 5.11 where the first subpopulation is divided into two parts. The first 20% of individuals undergo selfing, and the rest of the subpopulation undergoes usual sexed random mating. Note that two mating schemes produce different number of offspring per mating event, and the family sizes are recorded in a shared variable `famSizes` when `DBG_MATING` is turned on.

Listing 5.11: A heterogeneous mating scheme

```
>>> TurnOnDebug(DBG_MATING)
>>> pop = population(100, loci=[2])
>>> pop.setVirtualSplitter(proportionSplitter([0.2, 0.8]))
>>> simu = simulator(pop, heteroMating(
...     [selfMating(numOffspring=5, subPop=0, virtualSubPop=0),
...     randomMating(numOffspring=20, subPop=0, virtualSubPop=1)]))
>>>
>>> simu.step()
True
>>> print simu.dvars(0).famSizes
[5, 5, 5, 5, 20, 20, 20, 20]
>>> TurnOffDebug(DBG_MATING)
Debug code DBG_MATING is turned off. cf. ListDebugCode(), TurnOnDebug().
>>>
```

5.5 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.

5.6 Pedigree tracking

simuPOP provides the following functions to manipulate pedigrees

- If you set `ancestralDepth` of a population to a positive number (default 0), `ancestralDepth` number of ancestral generations will be saved to the population, which makes a total of `ancestralDepth + 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 can run a simulator like this

Listing 5.12: One-stage simulation for pedigree tracking

```
pop = population(...., ancestralDepth=2,
    infoFields=['father_idx', 'mother_idx'])
simu = simulator(pop, randomMating(numOffspring=2))
simu.evolve(
    preOps=[...],
    ops = operators,
    end = 1000
)
```

The problem with this approach is that two generations are saved at all generations, and all mating events produce two offspring. The former is not a big deal but the latter will reduce effective population size of the resulting population. To avoid these problems, a two-stage simulation can be done

Listing 5.13: Two-stage simulation for pedigree tracking

```
pop = population(....)
simu = simulator(pop, randomMating())
simu.evolve(
    preOps=[...],
    ops = operators,
    end = 1000 - 2
)
simu.setAncestralDepth(2)
simu.addInfoFields(['father_idx', 'mother_idx'])
simu.setMatingScheme(randomMating(numOffspring=2))
operators.append(parentsTagger())
simu.evolve(ops=operators, end=2)
```

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 final multi-generation population. Note that `setAncestralDepth` and `addInfoFields` should be done at the simulator level so that every replicates in the simulator have the same new information fields. `simu.population(0).addInfoFields(['father_idx', 'mother_idx'])` will compromise the integrity of the simulator and is disallowed. (Integrity refers to the fact that all populations in a simulator should have the same genotypic structure as the simulator).

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 individuals can belong to multiple pedigrees, it is not even easy to define a pedigree. simuPOP provides a few 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.
- `NuclearFamilySample`: sample two-generation pedigrees.

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.

5.7 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 5.14). 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.

Listing 5.14: 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 5.15) 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.

Listing 5.15: 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()
```

Part three (example 5.16) 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.

Listing 5.16: 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()
```

The next part (example 5.17) 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.

Listing 5.17: 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
```

The last part of the code (example 5.18) 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 part would be easier if you do not need to handle pedigree, for example, when outputting case control samples.

Listing 5.18: 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()
```

5.8 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.

Listing 5.19: 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.+
    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 5.19. 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.

CHAPTER

SIX

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) list: a list file (actually a python file) that specifies variale script and joblist
- -a (--all): use all jobs defined in the list file
- -r (--run): run the jobs, by default, this script will only list the jobs and generate job file.
- -p (--repeat) n: execute command n times.
- -f (--force): 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 6.1 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.

Listing 6.1: 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 [2007].

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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