SimPrily Documentation

Release 1.0.1

Ariella Gladstein

Mar 12, 2020

Contents:

CHAPTER 1

Introduction

SimPrily runs genome simulations with user defined parameters or parameters randomly generated by priors and computes genomic statistics on the simulation output.

1. Run genome simulation with model defined by prior distributions of parameters and demographic model structure.
2. Take into account SNP array ascertainment bias by creating pseudo array based on priors of number of samples of discovery populations and allele frequency cut-off.
3. Calculate genomic summary statistics on simulated genomes and pseudo arrays.

This is ideal for use with Approximate Bayesian Computation on whole genome or SNP array data.

Uses c++ programs macs and GERMLINE. For more information on these programs, see: https://github.com/gchen98/macs https://github.com/sgusev/GERMLINE

CHAPTER 2

Use Cases

Is SimPrily right for your research?

	Use case	Can SimPrily be used?	Notes
Type of simulation	Coalescent simulation	yes	
	Forward simulation	no	
Model	Selection	no	
	Demographic model	yes	See MaCS/ms documentation
	Recombination map	yes	Not necessary, but sims will be more accurate
	Constant mutation rate	yes	
	Constant model parameters	yes	
	Uniform priors of parameters	yes	
	Non-uniform priors	no	
	Known SNP ascertainment	yes	
	Unknown SNP ascertainment	yes	See Quinto-Cortes et al. (2018)
Size of simulation	Chromosome-size loci	yes	
	Whole genome	no	Must simulate each chromosome separately
	1000's of samples	no	Try msprime
Type of simulated data	Sequence (variant) data	yes	
	Exome data	yes	
	SNP array data	yes	
	Microsatellite/str data	no	
Returned data	AFS Summary statistics	yes	
	IBD Summary statistics	yes	Only with SNP array option
	Raw simulated output	no	
	PLINK ped/map output	yes	Only with SNP array option
Programing experience	None	yes	Use the Discovery Environment app
	Beginner command line	yes	Can use the Open Science Grid
	Python	yes	Not necessary, but can add own functions and make pull requests

If you still are not sure if SimPrily is right for your research check out other simulators at https://popmodels.cancercontrol.cancer.gov/gsr

CHAPTER 3

Install and Environment Set up

A SimPrily Docker or Singularity container with the necessary code and environment can be easily pulled.

```
docker pull agladstein/simprily
```

or

```
singularity pull docker://agladstein/simprily
```

For more information see the developers documentation.

CHAPTER 4

Usage

4.1 Required Input

-p PARAM	The location of the parameter file
-m MODEL	The location of the model file
-i ID	The unique identifier of the job
-o OUT	The location of the output directory

or

--param PARAM	The location of the parameter file
--model MODEL	The location of the model file
--id ID	The unique identifier of the job
--out OUT	The location of the output directory

4.2 Optional Input

-h	Shows a help message and exists
-v	Increase output verbosity. This includes 3 levels, `-v`, `-vv`, and `-vvv`
--profile	Print a log file containing the time in seconds and memory use in Mb for main functions
-g MAP	The location of the genetic map file
-a ARRAY	The location of the array template file, in bed format. The third column is used as the physical positions of the SNP for the pseudo array.

or

--help	Shows a help message and exists

-v	Increase output verbosity. This includes 3 levels, `-v`, `-vv`, and `-vvv`
--profile	Print a log file containing the time in seconds and memory use in Mb for main functions
--map MAP	The location of the genetic map file
--array ARRAY	The location of the array template file, in bed format. The third column is used as the physical positions of the SNP for the pseudo array.

4.3 Command line argument to run

`simprily.py` takes 4 required arguments and 2 optional arguments, and help, verbose, and profile options.

```
python simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

For quick help:

```
python simprily.py --help
```

4.3.1 How to run with a Container

Docker

```
docker run -t -i --mount type=bind,src="$(pwd)",dst=/app agladstein/simprily python /
↪app/simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

Singularity

```
singularity exec simprily.simg python /app/simprily.py [-h] -p PARAM -m MODEL -i ID -
↪o OUT [-g MAP] [-a ARRAY] [-v] [--profile]
```

4.3.2 Examples

One simulation (with pseudo array and genetic map):

```
python simprily.py -p examples/eg1/param_file_eg1_asc.txt -m examples/eg1/model_file_
↪eg1_asc.csv -g genetic_map_b37/genetic_map_GRCh37_chr1.txt.macshs -a array_template/
↪ill_650_test.bed -i 1 -o output_dir -v
```

One simulation (genetic map, no pseudo array):

```
python simprily.py -p examples/eg1/param_file_eg1.txt -m examples/eg1/model_file_eg1.
↪csv -g genetic_map_b37/genetic_map_GRCh37_chr1.txt.macshs -i 1 -o output_dir -v
```

4.4 Additional information on input arguments

4.4.1 ID

This is a unique identifier for the job. It is used in the names of the output files. For example, the output file with parameter values and summary statistics is named `results_{IDid}.txt`.

4.4.2 output_dir

This is where all the output goes. Within the output_dir the directory `results` will always be created. The `results` directory contains the results file `results_{jobid}.txt` with the parameter values and summary statistics. Additionally, the directories `germline_out` and `sim_data` are also created, but will be empty if the `germline` or `pedmap` arguments in the model file are not included.

Be careful when running large numbers of jobs (>2000). It is bad practice to run large numbers of jobs and direct all the output to the same directory, because listing the contents of the directory becomes very slow. Instead, we recommend creating directory "buckets". See section Recommendations for other HTC workflows.

4.4.3 param_file.txt

Examples of param_file.txt can be found in examples. The param_file.txt must define the parameters of the demographic model and the minimum derived allele frequency to be used to create the pseudo array, if a pseudo array is to be created.

All time parameters must end in `_t`.

All parameter values should be given in pre-coalescent scaled units. That is, Ne should be given in units of chromosomes, and time should be given in units of generations. The code will scale to the appropriate coalescent units for the simulation.

The definition can be hard-coded parameter values, such as:

```
A = 1000
B = 1000
T1_t = 100
```

The definition can be a prior, such as:

```
A = (1e3.0:1e4.0)
B = (1e3.0:1e4.0)
T1_t = (10:500)
```

Log base 10 can be used for the parameter definitions by using `1eX` or `1Ex`. This is recommended when using a prior with a very large range (See ABCtoolbox manual).

If pseudo arrays are to be created, the derived allele frequency must be defined. For example,

```
A = (1e3.0:1e4.0)
B = (1e3.0:1e4.0)
T1_t = (10:500)
daf = (0.01:0.1)
```

currently only a range of values is supported for daf. Therefore if you want to hard code a value, use the same value as the min and max of the prior.

4.4.4 model_file.csv

Examples of model_file.csv can be found in examples.

The demographic model, SNP ascertainment model, and additional options are defined in the model_file.csv. The demographic model defines events in populations' history, including population divergence, instantanious effective population size changes, exponential growth, gene flow and admixture. We use a coalescent simulation, so models must be defined backwards in time, starting from the present, with each event going back in the past. The SNP ascertainment model defines how to create a pseudo SNP array using a template SNP array, a set of discovery populations and a minor allele frequency cutoff. The SNP ascertainment model should be used when comparing to real SNP array data.

All instances of any argument must start with a dash followed by the corresponding argument parameters, and value(s). Each new argument must be a new line. All variables and values must be separated by commas (white space will be ignored, so it is okay to include spaces). The model arguments can appear in any order.

All parameters must be called with a name corresponding to its definition in the param file. This is how parameter values are assigned to the simulation model. For example,

```
-macs,./bin/macs,
-length,5000000,
-s,1231414,
-t,2.5e-8,
-r,1e-8,
-h,1e5,
# define a sample size of 50 haploid individuals for populations 1 and 2
-I, 2, 50, 50
# define the effective population size at present for population 1
-n, 1, A
# define the effective population size at present for population 2
-n, 2, B
# define a divergence event (join backwards in time) between populations 1 and 2
-ej, T1, 1, 2
```

Setup simulation arguments

One of the following two flags must be included:

`-macs` use the original simulator MaCS. This option will stream the MaCS simulation output directly to be read into a python bitarray.

`-macs_file` read in static output from MaCS. This should only be used for rigorous testing.

Following the `-macs` and `-macs_file` flags there should be a path to either the executable or static file in relation to the working directory. For example:

If you are using a virtual environment the path to macs should be

```
-macs, ./bin/macs
```

If you are using Docker or Singularity the path to macs should be

```
-macs, /app/macs
```

or if you want to use a static file,

```
-macs_file, tests/test_data/sites1000000.txt
```

-length The number base pairs you want to simulate. Must be included.

-s random seed. Must be an integer. If no input is given, no seed will be used, and everything will be random. If a seed is provided, reproducible parameters will be picked from the priors. Using a seed will also cause reproducible simulations with macs.

Demographic simulation arguments

All argument flags are based on macs arguments (see macs and ms manual for more detail).

`-t`: mutation rate per site per 4N generations

`-d`: enable debugging messages. No entry will default to allowing debugging messages. This will not work when using macsswig

`-h`: history. Refers to the number of previous base pairs to retain

`-r [r]`: recombination rate per site per 4N generations

`-c [f lambda]`: f = ratio of gene conversion rate to crossover rate. track len(lambda) is mean length of tract in base pairs. *This has not been tested.*

`-T`: Print each local tree in Newick format to standard out. *This has not been tested.*

`-G [alpha]`: Assign growth rate alpha across populations where alpha=-log(Np/Nr).

`-I [n n_n]`: Assign all elements of the migration matrix for n populations. Values in matrix set to mig_rate/(n-1). The length of n_n should be equal to n

`-m [i,j m]`: i, j is associated with a location in the migration matrix m is assigned to the value at (i, j)

`-ma [m_nn]`: Assign values to all elements of migration matrix for n populations

`-n [i size]`: Population i set to size

`-g [i alpha]`: assigns alpha value as explained in -G to population i

`-eG [t alpha]`: t is a time value. alpha behaves the same as in -G

`-eg [t i alpha]`: t is a time value. alpha behaves the same as in -G. i is a population that alpha is assigned to at time t.

`-eM [t m]`: t is a time value. Assign migration rate m to all elements in migration matrix at time t

`-em [t i,j m_ij]`: t is a time value. i and j make up point in a population matrix. assigns migration rate m_ij to the population at i, j at time t

`-ema [t n m_nn]`: t is a time value. Assign migration rates within the migration matrix for n populations at time t.

`-eN [t size]`: t is a time value. Assigns size to all populations at time t

`-en [t i size_i]`: t is a time value. assigns size_i to population i at time t

`-es [t i p]`: t is a time value. splits population i by p at time t

`-ej [t i j]` t is a time value. joins population i with population j at time t

SNP array ascertainment arguments

If the user would like to create a pseudo array from the simulation, the array template must be included in the command line argument with the flag `-a`, and four additional arguments must be included in the model_file:

`-discovery`, followed by the populations (defined by their numbers from `-n`) that should be used to discover the SNP (e.g. the HapMap populations). These are the populations that will be used to create the pseudo array. When calculating summary statistics, summary statistics based on whole genome simulation and pseudo array will be calculated for these populations.

`-sample`, followed by the populations (defined by their numbers from `-n`) that are the samples of interest for demographic interest.

`-daf`, followed by the parameter name for daf.

`-random_discovery`, followed by `True` or `False`. True will add a random number of individuals to the discovery populations to use as the "panel" to create the pseudo array. When this option is False, the total number of simulated discovery populations is equal to the number "genotyped" and in the "panel".

For example:

```
-macs,./bin/macs,
-length,5000000,
-s,1231414,
-t,2.5e-8,
-r,1e-8,
-h,1e5,
-I, 2, 50, 50
-n, 1, A
-n, 2, B
-ej, T1, 1, 2
-discovery, 1
-sample, 2
-daf, daf
-random_discovery, True
```

An example of an array template is:

```
chr22       0       15929526
chr22       0       15991515
chr22       0       16288162
chr22       0       16926611
chr22       0       16990146
chr22       0       17498992
chr22       0       17540297
chr22       0       17728199
chr22       0       17760714
chr22       0       18180154
chr22       0       18217275
chr22       0       18220413
```

Ordering of time-specific events

When using priors, if some demographic events must happen in a certain order, the order can be specified by adding the order number to the argument. For example say there are two demographic events, a population split and instantaneous growth, but the instantaneous growth must happen before the population split, we can indicate that in the model file:

```
-en_1, Tgrowth, 1, A2
-ej_2, Tsplit, 2, 1
```

Additionally, the same format can be used to indicate that multiple events should happen at the same time. If there are multiple events that should happen at the same time, the word `inst` should be used instead of a time parameter after

the first definition of the time. *(this will actually cause the times to be just different enough that macs is happy.)* For example, say we wanted growth to occur at the same time as the population split:

```
-en_1, Tgrowth, 1, A2
-ej_1, inst, 2, 1
```

In this case, the population split will technically be simulated slightly after the growth.

germline

The option `-germline` can be included in the model_file to use GERMLINE to find shared IBD segments between all simulated individuals from pseudo array. Does not use the genetic map to run GERMLINE. Runs GERMLINE as:

```
bash ./bin/phasing_pipeline/gline.sh ./bin/germline-1-5-1/germline  ped_name map_name␣
↪out_name "-bits 10 -min_m min_m"
```

where `min_m` = 300bp (this is so GERMLINE should also produce output on very small SNP data for testing purposes).

If GERMLINE does not run, try rebuilding it on the machine you are trying to run on:

```
cd ./bin/germline-1-5-1
make clean
make
```

pedmap

The option `-pedmap` can be included in the model_file to print a ped and map file of the pseudo array data.

CHAPTER 5

High Throughput Computing

5.1 Open Science Grid

1. Create an OSG Connect account. https://osgconnect.net/signup
2. Join the project SimPrily
3. Create an ssh key pair

Log onto Open Science Grid Connect

```
ssh user-name@login01.osgconnect.net
```

Clone the entire repository. *We only need the pegasus_workflow directory*

```
git clone https://github.com/agladstein/SimPrily.git
```

5.1.1 Test with interactive Singularity container

Start the Singularity container and run a small test.

```
[agladstein@login02 ~]$ singularity shell --home $PWD:/srv --pwd /srv /cvmfs/
↪singularity.opensciencegrid.org/agladstein/simprily\:latest
Singularity: Invoking an interactive shell within container...

$ bash
agladstein@login02:~$ export PATH=/usr/local/bin:/usr/bin:/bin
agladstein@login02:~$ python /app/simprily.py examples/eg2/Param_file_eg2.txt␣
↪examples/eg2/model_file_eg2.csv 2 out_dir
```

5.1.2 Submit a Pegasus workflow

All components of the Pegasus workflow are located in the directory `pegasus_workflow`.

Start the workfow by running `submit` on the command line from the `pegasus_workflow` directory. There are 3 required arguments and 2 optional arguments

```
./submit -p PARAM -m MODEL -j NUM [-g MAP] [-a ARRAY]
```

Required

-p PARAM	The location of the parameter file
-m MODEL	The location of the model file
-j NUM	The number of jobs to run. The `ID` will go from 1 to `NUM`.

Optional

-g MAP	The location of the genetic map file
-a ARRAY	The location of the array template file, in bed form

We recommend that all testing be done before submiting workflows to OSG. Therefore we do not include the verbose options. Pegasus provides run information, so we do not include the profile option with the OSG workflow.

Example workflow submissions

e.g. (No pseudo array and no recombination map)

```
./submit -p ../examples/eg2/param_file_eg2.txt -m ../examples/eg2/model_file_eg2.csv -
↪j 10
```

e.g. (include pseudo array, but no recombination map)

```
./submit -p ../examples/eg2/param_file_eg2_asc.txt -m ../examples/eg2/model_file_eg2_
↪asc.csv -j 10 -a ../array_template/ill_650_test.bed
```

e.g. (recombination map, but no pseudo array)

```
./submit -p ../examples/eg2/param_file_eg2.txt -m ../examples/eg2/model_file_eg2.csv -
↪j 10 -g ../genetic_map_b37/genetic_map_GRCh37_chr1.txt.macshs
```

e.g. (include pseudo array, and recombination map)

```
./submit -p ../examples/eg2/param_file_eg2_asc.txt -m ../examples/eg2/model_file_eg2_
↪asc.csv -j 10 -a ../array_template/ill_650_test.bed -g ../genetic_map_b37/genetic_
↪map_GRCh37_chr1.txt.macshs
```

5.1.3 Monitoring and Debugging

To find the run times of the executable:

```
pegasus-statistics -s all
```

Then, look at `Transformation statistics`.

5.1.4 How the Pegasus workflow works

`submit` -> `tools/dax-generator` -> `wrappers/run-sim.sh`

`submit` will run `tools/dax-generator`, which constructs the workflow. The `dax-generator` is the main Pegasus file. The `dax-generator` creates the HTCondor dag file. It also tells Pegasus where the local files are and transfers files (from submit host to compute node) so they are available for the job. It also defines how to handle output files.

`wrappers/run-sim.sh` is the wrapper that runs in the container. It modifies the environment, and runs SimPrily.

5.2 Recommendations for other HTC workflows

Coming soon!

In the meantime see this example of running SimPrily on an HPC cluster with PBS https://github.com/agladstein/ECOL-346-HPC-demo

CHAPTER 6

Calculating summary statistics on real data

6.1 Data format

Real data must be in PLINK .tped file with 0's and 1's. Sites in rows, individuals in columns (first 4 columns chr, rsnumber, site_begin, site_end). The populations must be in the same order as specified in the model file for the simulations.

Put the individuals in the correct order https://www.cog-genomics.org/plink2/data#indiv_sort

```
plink --bfile bfile --indiv-sort f sample_order.txt --make-bed --out bfile_ordered
```

To get in the .tped format from .bed .bim .fam with 0's and 1's refer to https://www.cog-genomics.org/plink2/formats#tped

```
plink --bfile bfile --recode transpose 01 --output-missing-genotype N --out tfile01
```

6.2 Usage

`real_data_ss.py` takes 5 arguments:

1. `model_file`
2. `param_file`
3. `output_dir`
4. `genome_file`
5. `array_file`

e.g.

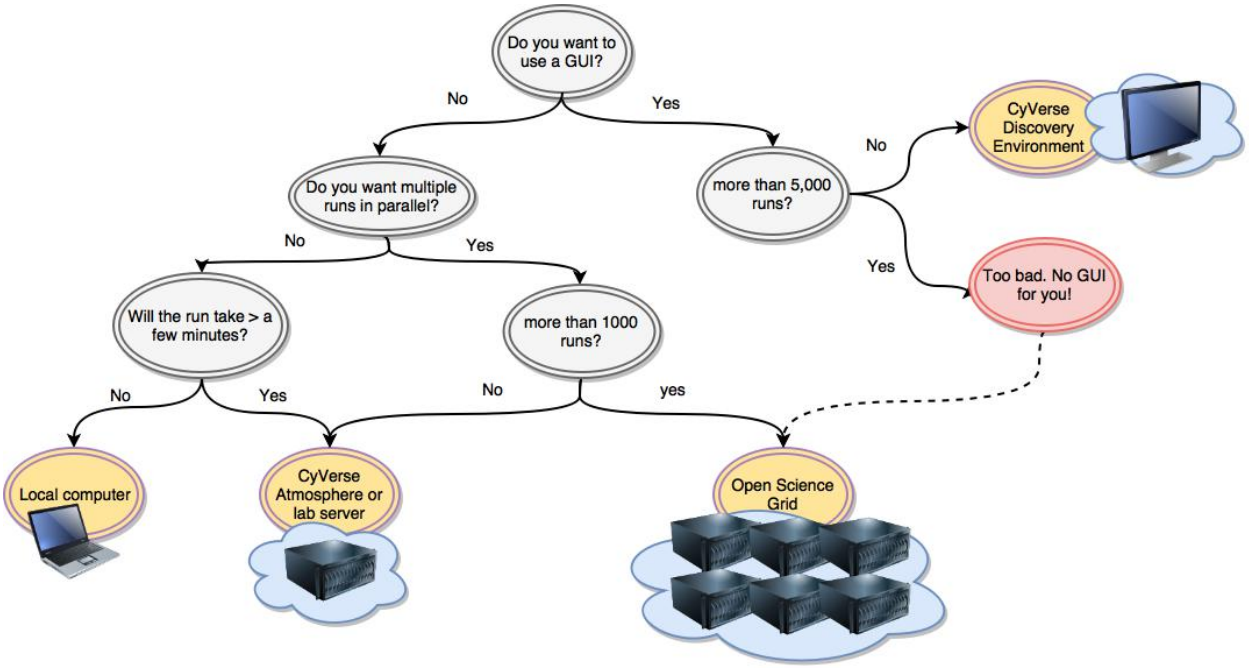
```
python real_data_ss.py examples/eg1/model_file_eg1.csv examples/eg1/param_file_eg1.
↪txt out_dir ~/data/HapMap_example/test_10_YRI_CEU_CHB.tped ~/data/HapMap_example/
↪test_10_YRI_CEU_CHB_KHV_hg18_ill_650.tped
```

(continues on next page)

(continued from previous page)

CHAPTER 7

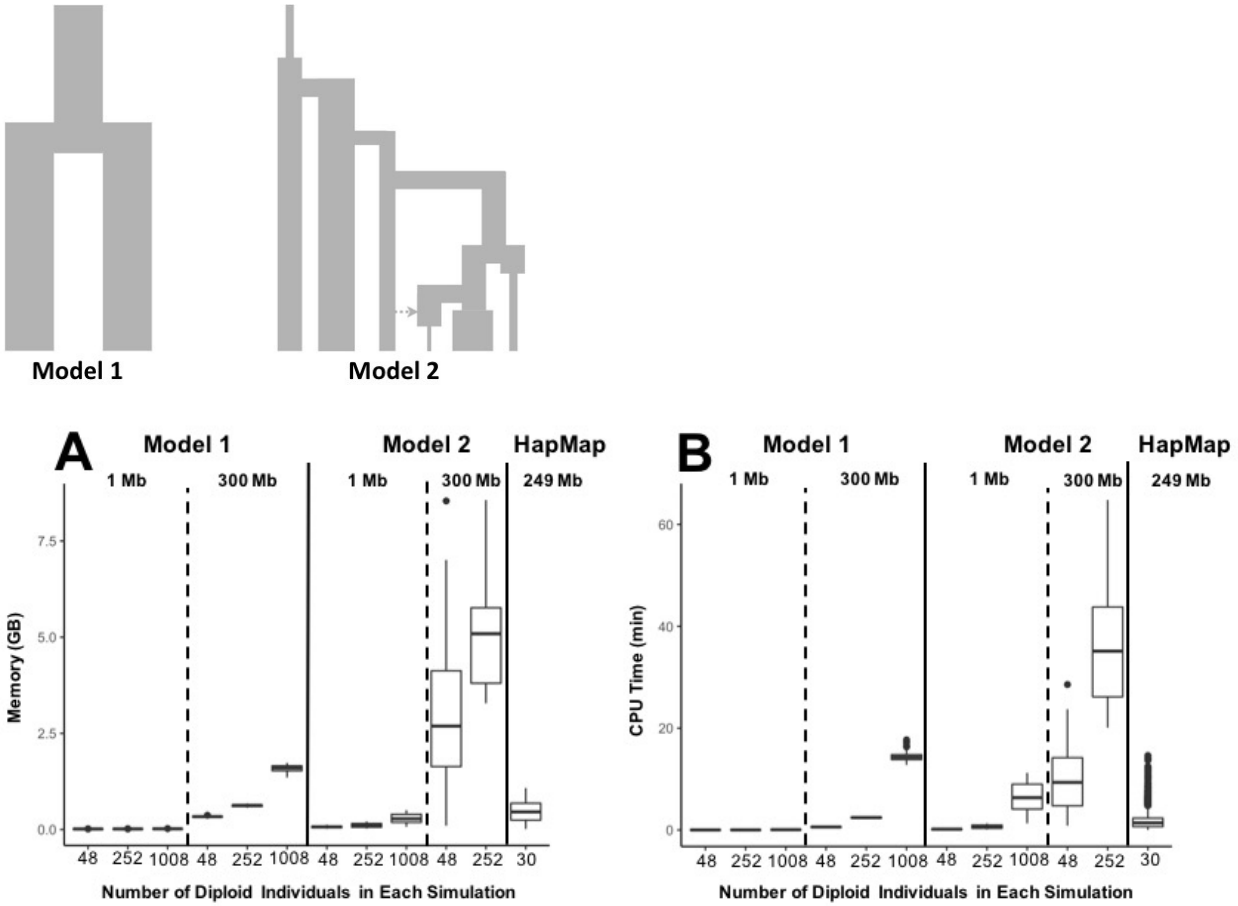
Where to run SimPrily



CHAPTER 8

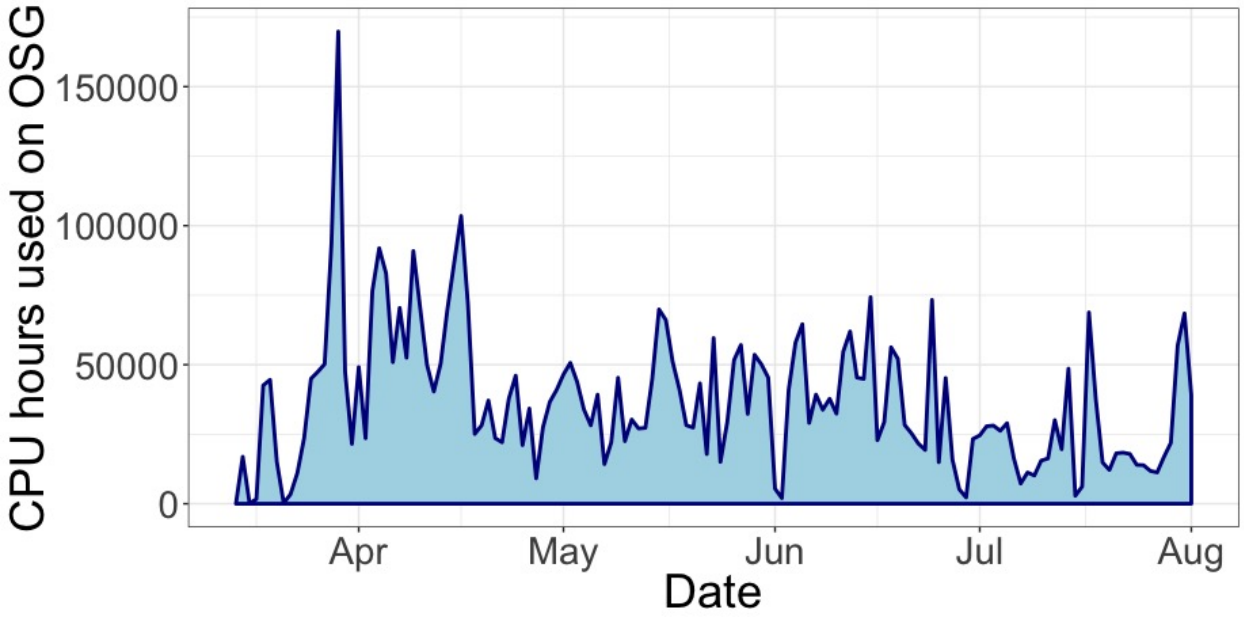
Benchmarking

How much time and memory does SimPrily need?



How many CPU hrs can we expect from the Open Science Grid in a day?

To see what's running on the Open Science Grid to go https://gracc.opensciencegrid.org/dashboard/db/gracc-home?orgId=1



CHAPTER 9

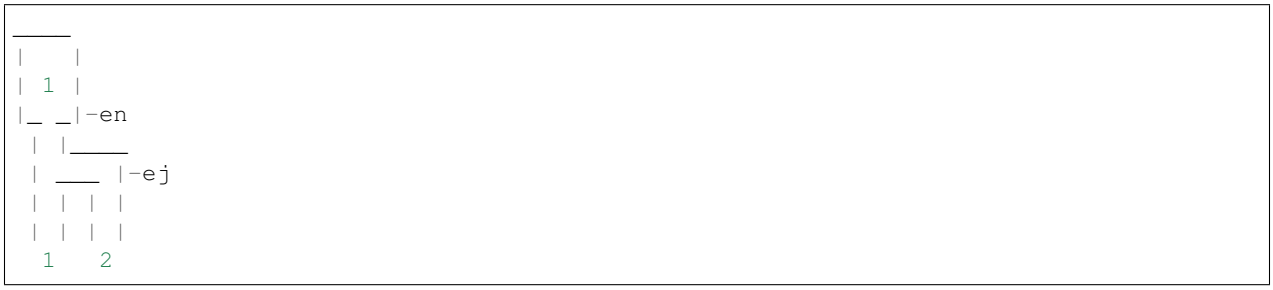
Tutorial with Docker

1. What do you want to simulate? How many simulations?
2. Create your model.csv and param.txt input files.
3. Perform a small test simulation.
4. Perform high-throughput simulations.

9.1 1. Define your simulation

What do you want to simulate? How many simulations? Suppose we want to simulate a full chromosome with a locus size of 200Mb, with a two population split model, with one population size change, where there first population has a sample size of 10 diploid individuals and the second population has a sample size of 70 diploid individuals. And we want to use priors on all of parameters. Suppose we want a total of 50,000 simulations.

Draw your model. Do this on paper first.



9.2 2. Create input files

Create the model_file_tutorial.csv and param_file_tutorial.txt files.

model_file_tutorial.csv

```
# Use the simulator MaCS
-macs,./bin/macs,
# Simulate a locus size of 10kb. Start with 10kb, then increase to 200Mb
-length,10000,
# Use a mutation rate of 2.5e-8
-t,2.5e-8,
# Use a recombination rate of 1e-8
-r,1e-8,
# Tell MaCS to retain 1e5 previous base pairs
-h,1e5,
# Two populations, first with sample size 10 diploid individuals and 2nd with sample␣
↪size 70 diploid individuals
-I,2,20,140,
# Effective population size of population 1 defined as A
-n,1,A,
# Effective population size of population 2 defined as B
-n,2,B,
# Divergence event from 1 to 2
-ej,AB_t,2,1,
# Population size change in population 1 to size AN
-en,AN_t,1,AN
```

param_file_tutorial.txt

```
A = (1e3:1e4.0)
B = (1e3:1e4.0)
AB_t = (1000:4000)
AN_t = (0:4000)
AN = (1e4:1e5.0)
```

9.3 3. Perform test simulation

Docker requires sudo privileges. If you do not have sudo, use Singularity.

Check that Docker is installed:

```
sudo docker run hello-world
```

Quick and easy install script provided by Docker:

```
curl -sSL https://get.docker.com/ | sh
```

See Developer documentation for more information on Docker.

9.3.1 a. Pull Docker image

Pull the latest SimPrily Docker image:

```
sudo docker pull agladstein/simprily
```

Once you have successfully pulled the image you will see something like this:

```
Using default tag: latest
latest: Pulling from agladstein/simprily
f49cf87b52c1: Pull complete
7b491c575b06: Pull complete
b313b08bab3b: Pull complete
51d6678c3f0e: Pull complete
09f35bd58db2: Pull complete
f7e0c30e74c6: Pull complete
c308c099d654: Pull complete
339478b61728: Pull complete
d16221c2883e: Pull complete
df211aed0ee8: Pull complete
94afb574a896: Pull complete
b253919783b5: Pull complete
45cb233ca3a5: Pull complete
Digest: sha256:1de7a99a23264caa22143db2a63794fa34541ccaf9155b9fb50488b5949a9d7d
Status: Downloaded newer image for agladstein/simprily:latest
```

Next, double check the images you've pulled:

```
sudo docker image ls
```

You should see something like this:

```
REPOSITORY                    TAG                 IMAGE ID            CREATED
↪       SIZE
agladstein/simprily           latest              1d3fbe956b00        5 hours ago
↪       938MB
```

9.3.2 b. Run SimPrily

Run one small example with the Docker container

```
sudo docker run -t -i --mount type=bind,source="$(pwd)",target=/app/tutorial␣
↪agladstein/simprily python /app/simprily.py -p /app/tutorial/param_file_tutorial.
↪txt -m /app/tutorial/model_file_tutorial.csv -i tutorial_1 -o /app/tutorial/output_
↪dir -v
```

You should see something like this:

```
debug-1: Debug on: Level 1
JOB tutorial_1
Current Seed: 19924
debug-1: name   total   panel   genotyped
debug-1: A      20      0       20
debug-1: B      140     0       140
debug-1: total samples: 160
debug-1: Perform simulation and get sequences
debug-1: Number of sites in simulation: 3071
debug-1: Calculating summary statistics

#########################
### PROGRAM COMPLETED ###
#########################
```

Then, you should see a new directory created "$(pwd)"/output_dir. In that directory, you should see the directories

```
sim_data
germline_out
results
```

and the directory results should have the file results_tutorial_1.txt, which should look something like this:

```
A       B       AN      AB_t    AN_t    SegS_A_CGI      Sing_A_CGI      Dupl_A_CGI
↪  TajD_A_CGI      SegS_B_CGI      Sing_B_CGI      Dupl_B_CGI      TajD_B_CGI
↪FST_AB_CGI
6803.19290799   5631.76173775   907706.772716   2253.4362688    1707.92117592   2490
↪  500     193     0.648468498628  2210  37        2       2.26242085379   0.
↪146122749866
```

9.4 4. Perform HTC simulations

9.4.1 a. Estimate the required resources

Compare to provided benchmarking First we should compare our model to the benchmark. Our model is "simple", like Model 1, we have 160 diploid samples, and want to simulate 200Mb. So according to the benchmarking, we can expect our model to use approximately 1GB of memory and take about 5 min to run.

1Gb is a reasonable amount of memory for most CPUs.

50,000 simulations X 5 min / 60 per simulation = 4,167 hrs for all simulations.

Profile the Simulation After performing the test simulation and before starting high-throughput simulations, the memory use and run time of this model should be assessed.

- Edit model_file_tutorial.csv so it has the desired length of 200Mb. Change it to:

```
-length,200000000,
```

- Run the simulation and time it with time:

```
time sudo docker run -t -i --mount type=bind,source="$(pwd)",target=/app/tutorial
↪agladstein/simprily python /app/simprily.py -p /app/tutorial/param_file_tutorial.
↪txt -m /app/tutorial/model_file_tutorial.csv -i tutorial_1 -o /app/tutorial/output_
↪dir -v
```

We expect the simulation to take about 5 minutes, but the time depends on the parameters randomly chosen from the priors, so it could take less or more time.

- While that is running check top to see how much memory is being used.

```
top
```

You should see something like this:

```
top - 18:29:42 up  1:59,  3 users,  load average: 1.00, 0.63, 0.28
Tasks: 142 total,   2 running, 140 sleeping,   0 stopped,   0 zombie
%Cpu(s): 98.7 us,  1.3 sy,  0.0 ni,  0.0 id,  0.0 wa,  0.0 hi,  0.0 si,  0.0 st
KiB Mem :  8175420 total,  5298016 free,   237632 used,  2639772 buff/cache
```

(continues on next page)

(continued from previous page)

```
KiB Swap:        0 total,        0 free,        0 used.  7599724 avail Mem

  PID USER      PR  NI    VIRT    RES    SHR S %CPU %MEM     TIME+ COMMAND
20053 root      20   0   26492  16596   2988 R 97.3  0.2   4:35.89 macs
20022 root      20   0  172476  34128  11044 S  2.3  0.4   0:07.51 python
11488 root      20   0  442116  27524  13588 S  0.3  0.3   0:12.62 docker-containe
    1 root      20   0   37952   6128   4104 S  0.0  0.1   0:08.21 systemd
    2 root      20   0       0      0      0 S  0.0  0.0   0:00.00 kthreadd
```

In this case we see that Python is using about 170Mb of virtual memory.

9.4.2 b. Decide where to run your simulations

Depending on how fast we want all the runs to finish, we pick the number of cores we want to run on. In this case, since we expect it to only take about 4,000 hrs we could run this on the Open Science Grid or a smaller HPC, server, or cloud.

9.4.3 c. Run in parallel on large server

If we have a server with at least 100 cores, we could run the simulations in about 2 days with `parallel`:

```
seq 1 50000 | parallel -j 100 sudo docker run -t -i --mount type=bind,source="$(pwd)",
↪target=/app/tutorial agladstein/simprily python /app/simprily.py -p /app/tutorial/
↪param_file_tutorial.txt -m /app/tutorial/model_file_tutorial.csv -i tutorial_{} -o /
↪app/tutorial/output_dir
```

9.4.4 d. Run as workflow on Open Science Grid

Or we can use the Pegasus workflow on the Open Science Grid.

- Log onto Open Science Grid Connect

```
ssh user-name@login01.osgconnect.net
```

- Clone the entire repository. *We only need the pegasus_workflow directory*

```
git clone https://github.com/agladstein/SimPrily.git
```

- Go into the `pegasus_workflow` directory:

```
cd SimPrily/pegasus_workfow
```

- Copy or create the model_file_tutorial.csv and param_file_tutorial.txt from above.
- Submit a small test workflow:

```
./submit -p param_file_tutorial.txt -m model_file_tutorial.csv -j 10
```

We should see something like:

```
2018.06.25 11:02:08.849 CDT:   ----------------------------------------------------------
↪----------------
2018.06.25 11:02:08.855 CDT:   File for submitting this DAG to HTCondor           :␣
↪simprily-0.dag.condor.sub
2018.06.25 11:02:08.860 CDT:   Log of DAGMan debugging messages                 :␣
↪simprily-0.dag.dagman.out
2018.06.25 11:02:08.865 CDT:   Log of HTCondor library output                   :␣
↪simprily-0.dag.lib.out
2018.06.25 11:02:08.870 CDT:   Log of HTCondor library error messages           :␣
↪simprily-0.dag.lib.err
2018.06.25 11:02:08.876 CDT:   Log of the life of condor_dagman itself          :␣
↪simprily-0.dag.dagman.log
2018.06.25 11:02:08.881 CDT:
2018.06.25 11:02:08.886 CDT:   -no_submit given, not submitting DAG to HTCondor.  You␣
↪can do this with:
2018.06.25 11:02:08.897 CDT:   ----------------------------------------------------------
↪----------------
2018.06.25 11:02:11.948 CDT:   Your database is compatible with Pegasus version: 4.8.0
2018.06.25 11:02:12.078 CDT:   Submitting to condor simprily-0.dag.condor.sub
2018.06.25 11:02:12.174 CDT:   Submitting job(s).
2018.06.25 11:02:12.180 CDT:   1 job(s) submitted to cluster 19334.
2018.06.25 11:02:12.185 CDT:
2018.06.25 11:02:12.190 CDT:   Your workflow has been started and is running in the␣
↪base directory:
2018.06.25 11:02:12.196 CDT:
2018.06.25 11:02:12.201 CDT:     /local-scratch/agladstein/workflows/simprily_
↪1529942525/workflow/simprily_1529942525
2018.06.25 11:02:12.206 CDT:
2018.06.25 11:02:12.212 CDT:   *** To monitor the workflow you can run ***
2018.06.25 11:02:12.217 CDT:
2018.06.25 11:02:12.222 CDT:     pegasus-status -l /local-scratch/agladstein/
↪workflows/simprily_1529942525/workflow/simprily_1529942525
2018.06.25 11:02:12.227 CDT:
2018.06.25 11:02:12.233 CDT:   *** To remove your workflow run ***
2018.06.25 11:02:12.238 CDT:
2018.06.25 11:02:12.243 CDT:     pegasus-remove /local-scratch/agladstein/workflows/
↪simprily_1529942525/workflow/simprily_1529942525
2018.06.25 11:02:12.248 CDT:
2018.06.25 11:02:12.760 CDT:   Time taken to execute is 5.657 seconds
```

We can monitor the workflow by using the command given in the printed statement. In this case:

```
pegasus-status -l /local-scratch/agladstein/workflows/simprily_1529942525/workflow/
↪simprily_1529942525
```

Which outputs:

```
STAT  IN_STATE  JOB
Run      02:11  simprily-0 ( /local-scratch/agladstein/workflows/simprily_1529942525/
↪workflow/simprily_1529942525 )
Run      00:58   run-sim.sh_ID0000009
Summary: 2 Condor jobs total (R:2)

UNRDY READY   PRE  IN_Q  POST  DONE  FAIL %DONE STATE   DAGNAME
    4     0     0     1     0    12     0  70.6 Running *simprily-0.dag
Summary: 1 DAG total (Running:1)
```

This means that the `simprily` workflow is running (in the directory shown), and currently one simulation is running

(the 9th simulation). We see that 12 processes have completed and the entire workflow is 70.6% done.

The email that was used to create the OSG Connect account will receive an email when the workflow is complete.

In this case the results will be written to `/local-scratch/agladstein/workflows/simprily_1529942525/outputs/`

```
[agladstein@login01 pegasus_workfow]$ ls /local-scratch/agladstein/workflows/simprily_
↪1529942525/outputs/
final_results.txt
```

`final_results.txt` contains the parameter values used to run the simulations and summary statistics calculated from the simulations for all of the simulations from the workflow. For example:

```
[agladstein@login01 pegasus_workfow]$ head /local-scratch/agladstein/workflows/
↪simprily_1529942525/outputs/final_results.txt
A   B       AN      AB_t    AN_t    SegS_A_CGI      Sing_A_CGI      Dupl_A_CGI      ␣
↪TajD_A_CGI      SegS_B_CGI      Sing_B_CGI      Dupl_B_CGI      TajD_B_CGI      FST_
↪AB_CGI
5344.42290079       8823.11026958   23042.8392599   1621.37069753   3576.63582673   ␣
↪66      14      5       0.612131940133  76      11      2       2.36972132977   0.
↪08462380112
8626.21444024       4432.98604274   18027.9154874   3139.75475448   2737.45325718   ␣
↪69      24      9       -0.313129414676 41      22      2.80590304723   0.          ␣
↪163579588626
1204.0872668        2992.49797803   61262.9413354   2599.93721571   438.20762215    ␣
↪243     13      33      1.72441317331   201     00      3.24176945597   0.          ␣
↪124526585551
3696.12346086       5279.87024578   28842.820112    2699.2693586    3226.68324657   ␣
↪74      25      1       0.381684017383  95      63      1.33636580198   0.          ␣
↪129678414366
5456.92727156       4876.88978622   45379.0305936   1742.81453106   620.930047461   ␣
↪182     38      21      0.498313835616  196     25      6       0.762716222206  0.
↪324577494188
4506.50442054       7227.8502438    92238.4468821   2039.10543287   2451.45021427   ␣
↪208     31      2       1.43332513774   361     37      44      0.37981118879   0.
↪294256698297
6305.87444634       8167.64822508   96815.9966437   3923.83195464   2226.21980366   ␣
↪287     76      17      0.619786936616  284     72      2.60377068841   0.          ␣
↪140691639063
1559.12937959       4924.54508638   56393.1667057   2534.56840169   2250.6811166    ␣
↪55      2       1       3.13808514057   154     212     1.43704802413   0.          ␣
↪107439420978
3781.32638852       4356.79072056   33283.5573331   1325.91016803   531.570175129   ␣
↪95      18      18      0.21637274122   96      410     1.03611653739   0.          ␣
↪0946289249489
```

- Once the previous test workflow completes, we can scale up incrementally.

Next run 100 jobs, then run 1000 jobs. If everything there are no errors, we can run the full workflow of 50,000 jobs:

```
./submit -p param_file_tutorial.txt -m model_file_tutorial.csv -j 50000
```

Since we estimated it should take about 4000 CPU hrs to run, we can expect the OSG to finish this full workflow in a day or less, depending on the OSG's current load.

CHAPTER 10

For Developers

10.1 Install and Environment Set up

- Python 2.7.6, 2.7.11, or 2.7.13 is required to run the code, with the requirements installed from requirements.txt. *Environments for Python 3 will soon be available.*
- We highly recommend running SimPrily with the provided Docker, Singularity, or virtual environment.

10.1.1 Container

Docker

A Docker Image built with Python 2.7.13, the requirements, and the SimPrily code can be found on Docker Hub https://hub.docker.com/r/agladstein/simprily/

cd to the directory you want to work in and then pull the Docker image. To pull the Docker container:

```
docker pull agladstein/simprily
```

How to run SimPrily with the Docker container

```
docker run -t -i --mount type=bind,src="$(pwd)",dst=/app agladstein/simprily python /
↪app/simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

Singularity

The Docker image can be pulled as a Singularity container.

To pull the Singularity container:

```
singularity pull docker://agladstein/simprily
```

How to run SimPrily with the Singularity container

```
singularity exec simprily.simg python /app/simprily.py [-h] -p PARAM -m MODEL -i ID -
↪o OUT [-g MAP] [-a ARRAY] [-v] [--profile]
```

10.1.2 Open Science Grid Connect

A prebuilt Singularity Image from the Docker Image is used for the Open Science Grid workflow. The Singularity Image on OSG Connect is available from `/cvmfs/singularity.opensciencegrid.org/agladstein/simprily\:latest`.

10.1.3 Virtual environment

Linux OS

cd to the directory you want to work in and then download the repository,

```
git clone https://github.com/agladstein/SimPrily.git
```

Install the virtual environment and install the requirements.

```
./setup/setup_env_2.7.sh
```

If you get an error during `pip-sync` try rebooting the system.

How to run SimPrily with a virtual environment: `simprily.py` takes 4 required arguments and 2 optional arguments, and help, verbose, and profile options.

```
python simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

For quick help:

```
python simprily.py --help
```

Virtual Machine for non-Linux

If you are running on a non-Linux OS, we recommend using the virtual machine, Vagrant (can be used on Mac or PC). In order to run Vagrant, you will also need VirtualBox.

Download Vagrant from https://www.vagrantup.com/downloads.html

Download VirtualBox from https://www.virtualbox.org/

cd to the directory you want to work in and then download the repository,

```
git clone https://github.com/agladstein/SimPrily.git
```

Start Vagrant, ssh into Vagrant, cd to SimPrily directory.

```
vagrant up
vagrant ssh
cd /vagrant
```

Install the virtual environment and install the requirements.

```
./setup/setup_env_vbox_2.7.sh
```

How to run SimPrily with a virtual environment in Vagrant: `simprily.py` takes 4 required arguments and 2 optional arguments, and help, verbose, and profile options.

```
python simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

For quick help:

```
python simprily.py --help
```

10.1.4 Local installation

We do not recommend this method

cd to the directory you want to work in and then download the repository,

```
git clone https://github.com/agladstein/SimPrily.git
```

If the above options do not work, the correct version of Python can also be installed locally:

```
cd mkdir python_prebuild
wget https://www.python.org/ftp/python/2.7.6/Python-2.7.6.tgz
mkdir python
tar -zxvf Python-2.7.6.tgz
cd Python-2.7.6
./configure --prefix=$(pwd)/../python
make
make install
cd ..
export PATH=$(pwd)/python/bin:$PATH
wget https://bootstrap.pypa.io/get-pip.py
python get-pip.py
pip install -r requirements.txt
python simprily.py --help
```

How to run SimPrily locally `simprily.py` takes 4 required arguments and 2 optional arguments, and help, verbose, and profile options.

```
python simprily.py [-h] -p PARAM -m MODEL -i ID -o OUT [-g MAP] [-a ARRAY] [-v] [--
↪profile]
```

For quick help:

```
python simprily.py --help
```

10.2 Additional Information on Containers

10.2.1 Docker

Notes on installing Docker, creating a Docker image, and running a Docker container. *The following instructions for Docker require sudo privaliges. Check the Docker documentation for what to do if you do not have sudo.*

Installing Docker

Check that Docker is installed:

```
sudo docker run hello-world
```

Quick and easy install script provided by Docker:

```
curl -sSL https://get.docker.com/ | sh
```

OR

If not on Linux, you can use Vagrant.

```
vagrant up
vagrant ssh
```

Then, continue with Linux steps.

See https://docs.docker.com/engine/installation/linux/docker-ce/ubuntu/#install-docker-ce

For Mac or Windows see Docker documentation.

Dockerize

1. Create Dockerfile
2. Build Docker image
3. Push Docker image to Docker Hub

1. Create Dockerfile In the directory with the necessary code and requirements.txt

Dockerfile

```
# Use an official Python runtime as a parent image
FROM python:2.7

# Set the working directory to /app
WORKDIR /app

# Copy the current directory contents into the container at /app
ADD . /app

# Install any needed packages specified in requirements.txt
RUN pip install -r requirements.txt

# Create directory for OSG
RUN mkdir -p /cvmfs

# Make executable
RUN chmod +x /app/simprily.py

# Make port 80 available to the world outside this container
EXPOSE 80

# Define entry point
#ENTRYPOINT ["python", "/app/simprily.py"]
```

See https://docs.docker.com/engine/reference/builder/

2. Build Docker imiage

```
sudo docker build -t agladstein/simprily .
```

3. Push Docker image to Docker Hub

Must first login to Docker Hub

```
sudo docker login
```

```
sudo docker push agladstein/simprily
```

Run program with Docker container

Pull image:

```
sudo docker pull agladstein/simprily
```

Run program:

```
docker run -t -i --mount type=bind,src=/home/agladstein/docker_test/SimPrily,dst=/app␣
↪agladstein/simprily_autobuild:version1 python /app/simprily.py -p examples/eg1/
↪param_file_eg1.txt -m examples/eg1/model_file_eg1.csv -g genetic_map_b37/genetic_
↪map_GRCh37_chr1.txt.macshs -a array_template/ill_650_test.bed -i 1 -o output_dir -v
```

try running with port ‘‘-p‘‘

or Run Docker container interactively to poke around

```
docker run --rm -it --entrypoint=/bin/bash agladstein/simprily_autobuild:version1
```

Cheat sheet

Some useful commands

```
docker build -t friendlyname .  # Create image using this directory's Dockerfile
docker run -p 4000:80 friendlyname  # Run "friendlyname" mapping port 4000 to 80
docker run -d -p 4000:80 friendlyname         # Same thing, but in detached mode
docker container ls                                # List all running containers
docker container ls -a             # List all containers, even those not running
docker container stop <hash>           # Gracefully stop the specified container
docker container kill <hash>         # Force shutdown of the specified container
docker container rm <hash>        # Remove specified container from this machine
docker container rm $(docker container ls -a -q)         # Remove all containers
docker image ls -a                             # List all images on this machine
docker image rm <image id>            # Remove specified image from this machine
docker image rm $(docker image ls -a -q)   # Remove all images from this machine
docker rmi $(docker images -q)  # Remove all containers from this machine
docker login             # Log in this CLI session using your Docker credentials
docker tag <image> username/repository:tag  # Tag <image> for upload to registry
docker push username/repository:tag            # Upload tagged image to registry
docker run username/repository:tag                   # Run image from a registry
```

Resources

https://docs.docker.com/get-started/ https://github.com/wsargent/docker-cheat-sheet https://docs.docker.com/engine/installation/linux/docker-ce/ubuntu/#install-docker-ce https://docs.docker.com/engine/reference/builder/ https://docs.docker.com/engine/reference/commandline/run/#add-bind-mounts-or-volumes-using-the-mount-flag http://codeblog.dotsandbrackets.com/persistent-data-docker-volumes/

10.2.2 Singularity

These are preliminary notes, not specific to a SimPrily Singularity container.

Installing Singularity

To install Singularity:

```
git clone https://github.com/singularityware/singularity.git
cd singularity
sudo apt-get install libtool
sudo apt-get install autotools-dev
sudo apt-get install automake
./autogen.sh
./configure --prefix=/usr/local
make
sudo make install
```

Create empty image

To create an empty Singularity image:

```
create --size 2048 simprily-little.img
```

Make or pull a container

1. Make container by dumping docker layers into empty image:

```
import simprily-little.img docker://agladstein/simprily-little
```

or

2. Pull container

```
singularity pull docker://centos:latest
```

or

3. Bootstrap

Create Singularity specification file.

For example:

```
Bootstrap: docker
From: ubuntu:latest

%runscript

    echo "I can put here whatever I want to happen when the user runs my container!"
    exec echo "Hello Monsoir Meatball" "$@" #The $@ is where arguments go

%post

   echo "Here we are installing software and other dependencies for the container!"
   apt-get update
   apt-get install -y git
```

Then build image from Singularity file:

```
sudo singularity bootstrap analysis.img Singularity
```

Run container

1. from Singularity Hub

```
singularity run shub://vsoch/hello-world
```

or

2. from local container with input arguement

```
singularity run analysis.img Ariella
```

Shell into a container

```
singularity shell centos7.img
```

Resources

- http://singularity.lbl.gov/quickstart
- http://singularity.lbl.gov/singularity-tutorial
- https://singularity-hub.org/faq

10.3 Testing

The shell script `autoTesting.sh` is included for quick automated testing of included examples.

It is run as:

```
./autoTesting.sh PYTHON [EXAMPLE_INT]
```

Where,

`PYTHON` is the python to use
`EXAMPLE_INT` is the specific example number to test (optional). If it is not specified, it will test all of the examples.

10.4 Creating Documentation

- Install Sphinx:

```
pip install Sphinx
```

- To edit the Read The Docs, edit the Sphinx .rst files in `SimPrily/docs`.
- Build the html from restructured text:

```
~/simprily_env/bin/sphinx-build -b html source build
```

10.4.1 Resources

- http://www.sphinx-doc.org/en/stable/tutorial.html
- https://github.com/ralsina/rst-cheatsheet/blob/master/rst-cheatsheet.rst
- https://thomas-cokelaer.info/tutorials/sphinx/rest_syntax.html#headings
- http://rest-sphinx-memo.readthedocs.io/en/latest/ReST.html

10.5 Other Notes

- If you use import a new Python package make sure you add it to the requirements.txt file then create the requirements.in. This will insure that the package installed in the virtual environment and Docker image.

```
pip-compile --output-file requirements.txt requirements.in
```

CHAPTER 11

Indices and tables

- genindex
- modindex
- search