fte: A Coalescent Simulator

Mark Reppell

University of Michigan

January 6, 2012

This document is meant to outline how to use the fte program for coalescent simulation. This program allows the user to generate sample haplotypes from populations which have undergone a range of demographic histories including instantaneous growth or contraction events, population subdivision with migration, and continuous growth slower, equal to, or faster than an exponential rate. Samples are generated using the standard coalescent approach where the time to coalescent, recombination, and migration events are independent exponential variables, with mutation events placed on the tree after a sample's ancestry has been simulated [2]. For continuous growth models the ideas of Donnelly and Tavaré [1] have been employed to shift times from a neutral model to those for a population with deterministically varying past size. The program was written in C++ and runs from the command line.

Downloading and Compiling fte

Fte is currently only available directly from its author. Please email `mreppell@umich.edu` to receive a copy of the code. The TCLAP and Boost libraries are also required to run the FTE program, these libraries and reference materials are available at:

http://www.boost.org/

http://tclap.sourceforge.net/

Once you have downloaded and installed TCLAP and Boost, FTE can be compiled using the following command:
g++ -o fte fte_vX.cpp -I /path_to_library/tclap-x.x.x/include/
Where the exes in the line above should be filled in with the latest version numbers of each program.

Command Overview

The following sections list and describe the parameters recognized by fte. Program parameters can be entered in any order on the command line. For each parameter listed the number of dashes shown before the corresponding parameter flag represents the exact number of dashes required at the command line. For example -N requires a single dash while --time requires two dashes. Some parameters can be entered multiple times on the command line in order to vary their value over time. Parameters that can be entered multiple times are indicated as such in the text, and are an exception to the rule that parameters can be entered in any order on the command line. Parameters that can be entered multiple times need to be entered in chronological order backwards in time from the present.

Basic Commands

-n The total number of haplotype samples to model. This is a required value.

-x The number of independent simulation repetitions to perform. This value defaults to one.

-N The *present day* effective size (diploid) of the population samples are being drawn from. Time for the simulations will be scaled in coalescent units of 2N generations, where N is the value entered with this flag. This is a required value and is also referred to as the initial population size in this document.

--time Boolean, prints the final running time for current series of simulations.

-m Mutation rate, this value should be entered as the per base mutation rate times the number of bases being simulated per sample haplotype. The program will calculate the value of θ as 4Nm where N is the initial population size you specified with the -N command. This is a required value.

-r Recombination rate, the fte program handles recombinations as a uniform process across the haplotypes simulated. The recombination rate parameter should be entered as the per base recombination rate times the number of bases being simulated per haplotype sample. The program will calculate ρ as 4Nr where N is the initial population size specified with the -N command. This value defaults to zero.

-L Boolean, prints time to most recent common ancestor and total tree length for each simulation. Values are given in coalescent units of 2N generations.

-h Boolean, this displays all command line parameters recognized by the program, with a brief description of each.

--seed Random number generator seed, this value allows for repetition of the same experiment by entering the same parameters along with the same seed value. If nothing is entered a random number based on the current time will be used. The seed value used for a given series of simulations can be seen on the second line of program output.

Population Growth

Both instantaneous and continuous population size changes can be modeled using fte.

Continuous Growth

To model a population which has expanded at a faster than exponential rate, we begin with a differential equation relating the rate of change in population size to current population size [3]

$$\frac{dN}{dt} = -\alpha N^c$$

Here N is population size, t is time, α and c are constants, with $\alpha < 0$ due to the coalescent modeling time backwards from the present. When we use the current population size N_0 as an initial condition, this equation has a general solution

$$N(t) = \begin{cases} [\frac{N_0^{c-1}}{1+N_0^{c-1}(c-1)\alpha t}]^{\frac{1}{c-1}}, & \text{for } c \neq 1 \\ N_0 e^{-\alpha t}, & \text{for } c = 1 \end{cases} \quad (1)$$

For c > 1 equation (1) models a population expanding at a faster than exponential rate. N(t) can be transformed as $\Lambda(t) = \int_0^t \frac{N_0}{N(s)} ds$ to "shift" coalescent times from the standard model into coalescent times for a population with varying size [1].

Commands

-g Type of continuous growth, recognized values of this parameter are 1 or 2. If set to 1 the program models exponential growth, if set to 2 the program will model faster or slower than exponential growth. If no value is entered population size is modeled as constant backwards in time.

-t Time of growth, the value entered is the amount of time backwards from the present, in coalescent units of 2N, during which the population being sampled from underwent continuous growth. A coalescent unit is equivalent to 2N generations, where for our model N is the current diploid population size entered using the -N flag.

-a Growth constant α, this value controls the rate of growth in continuous growth models.

-c Faster/slower than exponential growth exponent. If the -g parameter is entered as 2 the -c value represents the exponent c in equation 2, controlling how much faster or slower than the exponential growth is occurring. An entry of 1 is invalid, to model exponential growth set the -g flag to 1 and refrain from entering a -c value.

IMPORTANT When entering t, c, and a on the command line it is important to remember that during faster than exponential growth, unlike exponential growth, a population shrinking from 2N to N over a given time

does not have the same growth constant α as a population shrinking from 4N to 2N over the same time interval, so make sure to enter effective population size in *chromosomes* and *not* individuals.

Instantaneous Population Size Changes

The fte program allows population sizes to change instantaneously in the past.

Commands

These commands can be entered multiple times for multiple instantaneous size changes. The sizes entered with -b will correspond in order to the times entered with --t_instant.

-b Effective population size after contraction/expansion event, as a proportion of initial population size (N_0).

--t_instant Time of contraction/expansion event in coalescent units of 2N. If multiple instantaneous size change events are modeled their times should be entered in chronological order backwards from the present. In the current version of the program if continuous growth is being modeled instantaneous events can only occur further in the past than the conclusion of continuous growth.

Population Subdivision

The fte program has the ability to simulate a two subpopulation island model of population subdivision. Mutation and recombination rates are assumed to be the same in the two populations. With the exception of the command -n, which remains the *total* number of haplotypes to sample, the values entered for any of the parameter labels in previous sections of this document are taken to be values for population one, with parameters for population 2 entered using the commands in this section.

0.1 Commands

-s Boolean, indicates current series of simulations involve population subdivision.

--migration Migration rate between populations, entered as the fraction of chromosomes leaving each population each generation. If no --migration2 value is entered the value given to --migration is taken to be the rate at which chromosomes move in both directions between populations 1 and 2. If a --migration2 value is entered, --migration controls the rate of chromosomes moving from population 1 to population 2. For migration rate changes over time this parameter can be entered multiple times along with --migration_time values. The first --migration value will be taken as the starting migration rate and each additional --migration value should have a corresponding --migration_time entry. This value defaults to zero.

--migration2 Migration rate for individuals migrating from population 2 to population 1, entered as the fraction of chromosomes leaving each population each generation. If no value is entered for this parameter but a value is given to --migration that value is taken to the equal migration rate between populations. For migration rate changes over time this parameter can be entered multiple times along with --migration_time2 values. The first --migration2 value will be taken as the starting migration rate and each additional --migration2 value should have a corresponding --migration_time2 entry.

--migration_time Time at which migration rate changes, entered in coalescent units of 2N generations. Requires entry of multiple --migration values, with a total of one more --migration value than --migration_time values. If multiple --migration_time values are entered they should be in chronological order backwards from the present.

--migration_time2 Time at which migration rate from population 2 to population 1 changes, entered in coalescent units of 2N generations. Requires entry of multiple --migration2 values, with a total of one more --migration2 value than --migration_time2 values. If multiple --migration_time2 are entered they should be in chronological order backwards from the present.

--merge_time Time until the divided subpopulations merge into a single population, in coalescent units of 2N generations. If no value is entered the two subpopulations never merge.

--merge_size The size of combined population at the time the two subpopulations merge, as a proportion of the initial population 1 size (N_0). If a value for --merge_time is entered but this parameter is not set the default sets the effective population size at the time they merge as the sum of the effective sizes of the two subpopopulations.

--p2prop Current effective size of population 2 as a proportion of initial population 1 size (N_0).

--p2n Number of simulated samples originating in population 2. fte subtracts --p2n from the -n value to calculate the number of samples originating in population 1.

--g2 Type of continuous growth in population 2. A value of 1 indicates population 2 grew at an exponential rate, a value of 2 indicates population 2 grew at a faster or slower than exponential rate. If nothing is entered population 2 is modeled with as having a constant size backwards in time.

--t2 Time of growth in population 2, the amount of time backwards from the present, in coalescent units of 2N, during which population 2 underwent continuous growth.

--a2 Growth constant α for population 2, this value controls the rate of growth in continuous growth models for population 2.

--c2 Faster/slower than exponential growth exponent. If the --g2 parameter is entered as 2 the --c2 value represents the exponent c in equation 2, controlling how much faster or slower than the exponential growth is occurring. An entry of 1 is invalid, to model exponential growth set the --g2 flag to 1 and refrain from entering a --c2 value.

--b2 Population 2 size after instantaneous expansion/contraction event, as proportion of population 1 initial size (N_0). This parameter can be entered multiple times for multiple instantaneous size changes in population 2.

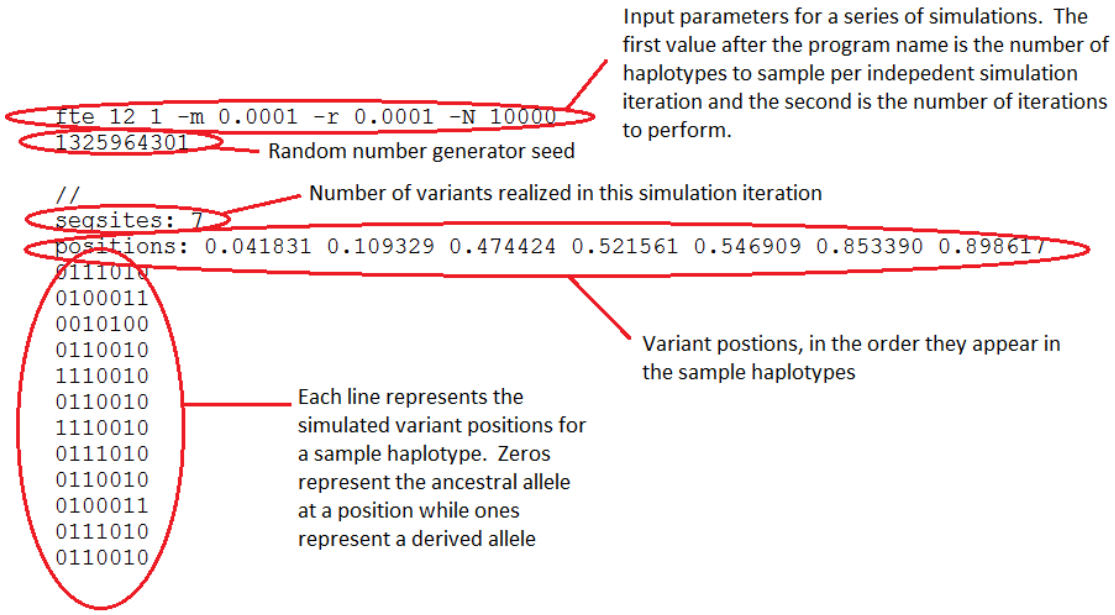
--t_instant2 Time of contraction/expansion event in population 2 in coalescent units of 2N. If multiple instantaneous size change events are modeled in population 2 their times should be entered in chronological

order backwards from the present. To model an instantaneous event after two subdivided populations have merged use the -b and --t_instant values.

Output

Figure 1 demonstrates the format of fte output. Output can be captured from standard out. The segregating site positions, which are randomly and independently chosen, have values between 0 and 1, the arbitrary range covered by the simulated haplotypes. These values are important only in how they relate to each other, for example recombination events are more likely to occur between variants at positions 0.05 and 0.95 than between variants which occur at positions 0.05 and 0.06.

Figure 1: fte simulator output



Example 1

Simulating two independent samples of 5000 haplotypes, each haplotype approximately 50kb in length, from a current day diploid population with a size of N = 5,000,000 that has grown at a faster than exponential rate from an ancestral population of size N = 9,000 over the last 500 generations

- 500 generations is $\frac{500}{10{,}000{,}000} = 5 \times 10^{-5}$ in 2N coalescent units.
- If we use a faster than exponential exponent c of 1.25 we can solve for the growth constant:

  $$18000 = \left(\frac{10000000^{(1.25-1)}}{1+\alpha(10000000^{(1.25-1)})(5\times10^{-5})}\right)^{\frac{1}{1.25-1}} \Rightarrow \alpha = 5484.1$$

- Assume a per base mutation and recombination rate of 10^{-8}, then the m and r values become $50000 \times 10^{-8} = 0.0005$

This gives us the command line input:

```
./fte -N 5000000 -n 5000 -x 2 -m .0005 -r .0005 -g 2 -c 1.25 -t 5e-5 -a 5484.1
```

Example 2

Simulating 1,000 repititions of 2,000 sample haplotypes from two divided subpopulations with 1,000 haplotypes coming from each subpopulation, and each haplotype approximately 25kb in length. Assume the underlying populations have effective sizes N = 5,000,000 and N = 1,000,000 currently but were both 10,000 individuals in size 200 generations in the past. Assume there is no migration between the populations currently but before 100 generations ago the chance of a chromosome moving between populations was 0.0001 per generation.

- Assume a per base mutation and recombination rate of 10^{-8}, then the m and r values become $25000 \times 10^{-8} = 0.00025$
- In coalescent units of 2N, 100 generations = $\frac{100}{10000000} = 10^{-5}$ and 200 generations = 2×10^{-5}

- The second population is $\frac{1}{5}$ the size of the first to begin and both populations have size $\frac{10000}{5000000} = 0.002$ times the initial population 1 size 200 generations in the past

This gives us the command line input:
./fte -N 5000000 -n 2000 -x 1000 -m .00025 -r.00025 -s --p2prop .2 --p2n 1000 --migration 0 --migration .0001 --migration_time 1e-5 -b .002 --t_instant 2e-5 --b2 .002 --t_instant2 2e-5

References

[1] P. Donnelly and S. Tavaré. Coalescents and genealogical structure under neutrality. *Annu. Rev. Genet.*, 29:401–21, 1995.

[2] J.F.C. Kingman. The coalescent. *Stoch. Process Appl.*, 13:235–48, 1982.

[3] J. Tolle. Can growth be faster than exponential, and just how slow is the logarithm? *The Mathematical Gazette*, 87:522–525, 2003.