SLiM: Simulating Evolution with Selection and Linkage

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ABSTRACT SLiM is an efficient forward population genetic simulation designed for studying the effects of linkage and selection on a chromosome-wide scale. The program can incorporate complex scenarios of demography and population substructure, various models for selection and dominance of new mutations, arbitrary gene structure, and user-defined recombination maps.

RECENT studies suggest that linkage effects such as genetic draft and background selection can profoundly alter the patterns of genetic variation in many species (Sella *et al.* 2009; Lohmueller *et al.* 2011; Weissman and Barton 2012; Messer and Petrov 2013). Understanding the potential impact of these linkage effects on population genetic methods requires efficient forward simulations that can model the evolution of whole chromosomes with realistic gene structure.

Forward simulations have a long-standing tradition in population genetics and many programs have been developed (Carvajal-Rodriguez 2010; Hoban *et al.* 2011). For any such program, there is typically a trade-off between efficiency and flexibility. Simulations based on combined forward-backward approaches, such as MSMS (Ewing and Hermisson 2010), can be very fast but remain limited to scenarios with only a single selected locus. Current programs that can model scenarios with multiple linked selected polymorphisms, such as FREGENE (Chadeau-Hyam *et al.* 2008), GENOMEPOP (Carvajal-Rodriguez 2008), simuPOP (Peng and Kimmel, 2005), forwsim (Padhukasahasram *et al.* 2008), or SFS_CODE (Hernandez 2008), either lack the ability to model realistic gene structure or are not efficient enough to allow for simulations on the scale of a whole chromosome in reasonably large populations.

Here I present SLiM, a population genetic simulation targeted at bridging the gap between efficiency and flexibility for the simulation of linkage and selection on a chromosome-wide scale. The program can incorporate complex scenarios of demography and population substructure, various models for selection and dominance, realistic gene structure, and user-defined recombination maps. Special emphasis was further placed on the ability to model and track individual selective sweeps—both complete and partial. While retaining all capabilities of a forward simulation, SLiM utilizes sophisticated algorithms and optimized data structures that enable simulations in reasonably large populations. All these features are implemented in an easy-to-use C++ command line program. The source code is freely available under the GNU General Public License and can be downloaded from http://www.stanford.edu/~messer/software.

SLiM simulates the evolution of diploid genomes in a population of hermaphrodites under an extended Wright–Fisher model with selection (Figure 1A). In each generation, a new set of offspring is created, descending from the individuals in the previous generation. The probability of becoming a parent is proportional to an individual's fitness, which is determined by the selection and dominance effects of the mutations present in its diploid genome. Gametes are generated by recombining parental chromosomes (both crossing over and gene conversion can be modeled) and adding new mutations.

Mutations can be of different user-defined mutation types, specified by their dominance coefficients and distributions of fitness effects (DFE); examples could be synonymous, adaptive, and lethal mutations. The possibility to specify arbitrary dominance effects allows for the simulation of a variety of evolutionary scenarios, including balancing selection and recessive deleterious mutations. Genomic regions can be of different user-defined genomic element types, specified by the particular mutation types that can occur in such elements and their relative proportions; examples could be exons and introns.

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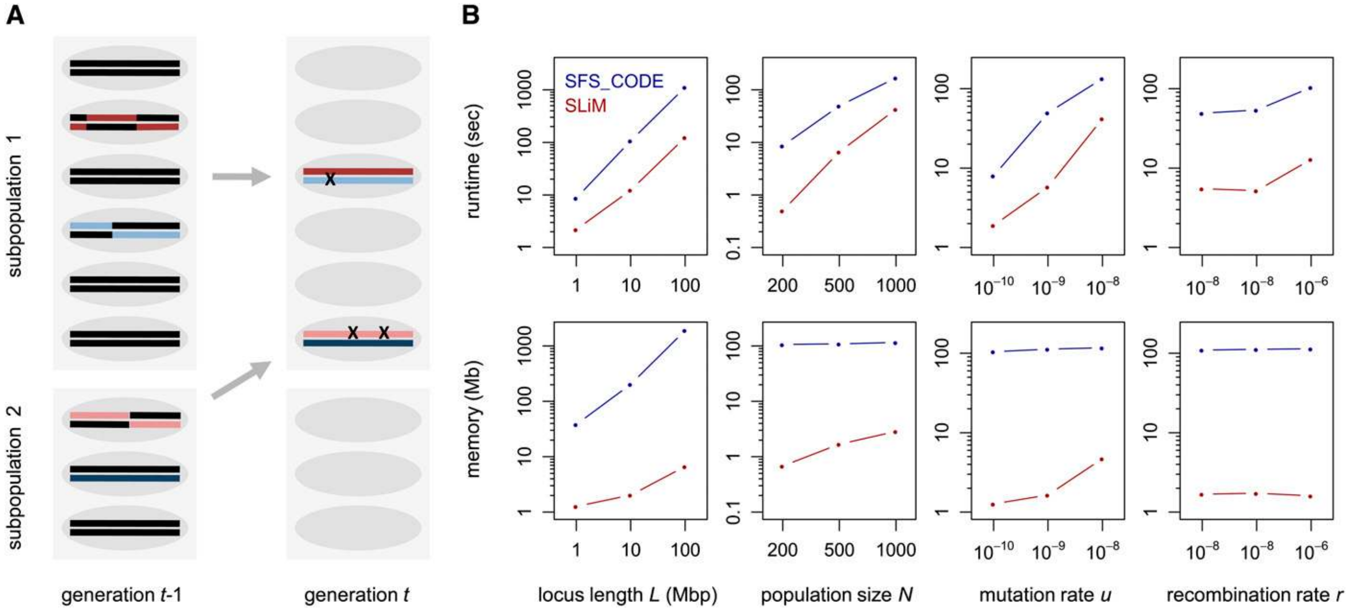

Figure 1 (A) Illustration of SLiM's core algorithm for a scenario with two subpopulations. In each generation, a new set of offspring is created from the individuals in the previous generation. Parents are drawn with probabilities proportional to their fitness. Gametes are generated by recombining parental chromosomes and adding new mutations. Migration is modeled by choosing parents from the source subpopulation. (B) Comparison of runtimes and peak resident set size memory requirements between SLiM and SFS_CODE for different evolutionary scenarios. In each column, one of the four parameters L, N, u, and r was varied, while the others were kept constant at their respective base values (L = 5 Mbp, N = 500, $u = 10^{-9}$, and $r = 10^{-8}$). Simulations were run for 10N generations. Data points show the observed runtimes and memory requirements averaged over 10 simulation runs.

Each mutation has a specified position along the chromosome but remains abstract in the sense that the simulation does not specify the particular nucleotide states of ancestral and derived alleles. Note, however, that the user has the freedom to associate abstract mutation types with specific classes of events. There are no back mutations in the simulations. Fixed mutations are removed from the population and recorded as substitutions.

SLiM is capable of modeling complex scenarios of demography and population substructure. The simulation can include arbitrary numbers of subpopulations that can be added at user-defined times, initialized either with new individuals or with individuals drawn from another subpopulation to model a population split or colonization event. Subpopulation sizes, migration rates, and selfing rates can be changed over time.

To establish genetic diversity, simulations first have to go through a burn-in. Alternatively, simulations can be initialized with a set of predefined genomes provided by the user or with the output of a previous simulation run. The user can further specify predetermined mutations to be introduced at certain time points. Such mutations can be used, for example, to investigate individual selective sweeps or to track the frequency trajectories of particular mutations in the population. Predetermined adaptive mutations can also be limited to partial selective sweeps, where positive selection ceases once the mutation has reached a particular population frequency.

SLiM provides a variety of output options, including (i) the complete state of the population at specified time points, in terms of all mutations and genomes present in the population; (ii) random samples of specific sizes drawn from a subpopulation at given time points; (iii) lists of all mutations that have become fixed, together with the times when each mutation became fixed; and (iv) frequency trajectories of particular mutations over time.

I ran SLiM under various test scenarios to check whether its output agrees with theoretical predictions. Specifically, I analyzed levels of neutral heterozygosity under different scenarios of demography, population substructure, and selfing, the fixation probabilities of new mutations of different selective effects, and the reduction in neutral diversity around adaptive substitutions. Simulation results conformed with the respective theoretical predictions in all tests (Supporting Information, File S1, section 6).

SLiM utilizes sophisticated algorithms and optimized data structures to achieve its high computational efficiency (File S1, section 7.1). The simulation is based on a hierarchical data architecture that minimizes the amount of information stored redundantly. At many stages of the program, large quantities of random numbers have to be drawn from general probability distributions. To do this efficiently, SLiM uses lookup tables that are precomputed only once per generation and then allow one to draw random numbers in $O(1)$ time. Most algorithms are implemented using fast routines provided in the GNU scientific library (Galassi *et al.* 2009).

To evaluate SLiM's performance I compared its runtime and memory requirements with those of SFS_CODE, a popular forward simulation of similar scope (Hernandez 2008). For these tests, a chromosome of length L was simulated with uniform mutation rate u and recombination rate r in a population of size N over the course of $10N$ generations, assuming an exponential DFE with $2N\bar{s} = -5$ (File S1, section 7.3). The base scenario used values $L = 5$ Mbp, $N = 500$, $u = 10^{-9}$, and $r = 10^{-8}$ per site per generation. I then varied these four parameters independently to analyze how each individually affects the performance of either program. Simulations were conducted on a standard iMac desktop with a 2.8-Ghz Intel core 2 Duo CPU and 4 GB of memory. Figure 1B shows that in all analyzed scenarios SLiM outcompetes SFS_CODE by a substantial margin, typically running 5–10 times faster and requiring 20–100 times less memory. The large discrepancy in memory consumption between the two programs reflects the fact that SFS_CODE simulates the sequence of the whole chromosome, whereas SLiM simulates only the actual mutations.

Its computational performance enables SLiM to simulate entire eukaryotic chromosomes in reasonably large populations. For instance, simulating the functional regions in a typical human chromosome of length $L = 100$ Mbp over 10^5 generations in a population of size $N = 10^4$ with $u = 10^{-8}$ and $r = 10^{-9}$ per site per generation, assuming a functional density of 5% and $2N\bar{s} = -10$, takes ~4 days on a single core.

SLiM has already been successfully applied in several projects that required efficient forward simulations on large genomic scales. For example, Kousathanas and Keightley (2013) used the program to examine how linked selection can affect their method for inferring the DFE from polymorphism data in fruit flies and mice. In Messer and Petrov (2013), SLiM was used to investigate the effects of linked selection on the MK test, and it was shown that such effects can severely bias the test. These studies highlight the need for efficient forward simulations that can model chromosomes with realistic gene structure.

Most of the current machinery of population genetics is still deeply rooted in the mindset of neutral theory, which assumes that adaptation is rare and that linkage effects from recurrent selective sweeps can thus be neglected. However, this assumption may be violated in many species. It is hence essential to verify with forward simulations under realistic scenarios of selection and linkage whether population genetics methods, and our estimates of key evolutionary parameters obtained from them, are robust to linkage effects. SLiM is specifically designed for this purpose and I believe that it will become an important tool for future population genetic studies.

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Literature Cited

Carvajal-Rodriguez, A., 2008 GENOMEPOP: a program to simulate genomes in populations. BMC Bioinformatics 9: 223.

Carvajal-Rodriguez, A., 2010 Simulation of genes and genomes forward in time. Curr. Genomics 11: 58–61.

Chadeau-Hyam, M., C. J. Hoggart, P. F. O'Reilly, J. C. Whittaker, M. De Iorio *et al.*, 2008 Fregene: simulation of realistic sequence-level data in populations and ascertained samples. BMC Bioinformatics 9: 364.

Ewing, G., and J. Hermisson, 2010 MSMS: a coalescent simulation program including recombination, demographic structure and selection at a single locus. Bioinformatics 26: 2064–2065.

Galassi, M., J. Davies, J. Theiler, B. Gough, G. Jungman *et al.*, 2009 *GNU Scientific Library: Reference Manual*, Ed. 3. Network Theory, Bristol, UK.

Hernandez, R. D., 2008 A flexible forward simulator for populations subject to selection and demography. Bioinformatics 24: 2786–2787.

Hoban, S., G. Bertorelle, and O. E. Gaggiotti, 2011 Computer simulations: tools for population and evolutionary genetics. Nat. Rev. Genet. 13: 110–122.

Kousathanas, A., and P. D. Keightley, 2013 A comparison of models to infer the distribution of fitness effects of new mutations. Genetics 193: 1197–1208.

Lohmueller, K. E., A. Albrechtsen, Y. Li, S. Y. Kim, T. Korneliussen *et al.*, 2011 Natural selection affects multiple aspects of genetic variation at putatively neutral sites across the human genome. PLoS Genet. 7: e1002326.

Messer, P. W., and D. A. Petrov, 2013 Frequent adaptation and the McDonald-Kreitman test. Proc. Natl. Acad. Sci. USA 110: 8615–8620.

Padhukasahasram, B., P. Marjoram, J. D. Wall, C. D. Bustamante, and M. Nordborg, 2008 Exploring population genetic models with recombination using efficient forward-time simulations. Genetics 178: 2417–2427.

Peng, B., and M. Kimmel, 2005 simuPOP: a forward-time population genetics simulation environment. Bioinformatics 21: 3686–3687.

Sella, G., D. A. Petrov, M. Przeworski, and P. Andolfatto, 2009 Pervasive natural selection in the Drosophila genome? PLoS Genet. 5: e1000495.

Weissman, D. B., and N. H. Barton, 2012 Limits to the rate of adaptive substitution in sexual populations. PLoS Genet. 8: e1002740.

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SLiM: Simulating Evolution with Selection and Linkage

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File S1: Supporting Information

Contents

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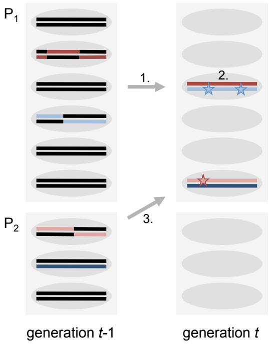
Overview

SLiM (Selection on Linked Mutations) is a forward population genetic simulation for studying linkage effects such as hitchhiking under recurrent selective sweeps, background selection, and Hill-Robertson interference. The program can incorporate complex scenarios of demography and population substructure, various models for selection and dominance of new mutations, realistic gene and chromosome structure, and user-defined recombination maps. Special emphasis was further placed on the ability to model and track individual selective sweeps – both complete and partial. While retaining all capabilities of a forward simulation, SLiM utilizes sophisticated algorithms and optimized data structures that enable simulations on the scale of entire eukaryotic chromosomes in reasonably large populations. All these features are implemented in an easy-to-use C++ command line program.

In a forward simulation, every individual in the population is followed explicitly. While this is computationally more intensive than coalescent approaches, it remains a prerequisite for modeling scenarios with multiple linked polymorphisms of different selective effects. Forward simulations have a long-standing tradition in population genetics and many programs have been developed, see [1–3]. For any such program, there is typically a trade-off between efficiency, flexibility, and ease of use. For example, simulations such as msms [4] use a combined forward-backward approach, making them very efficient, yet at the cost that they remain limited to scenarios with only a single selected locus. Other simulations, such as SFS_CODE [5], FREGENE [6], forwsim [7], and GENOMEPOP [8] provide high flexibility, but these programs are typically less efficient. Yet other programs such as simuPOP [9] require the user to specify evolutionary scenarios by writing their own scripts in Python. These approaches can provide high flexibility but are complicated to use. SLiM is targeted at bridging the gap between efficiency, flexibility, and ease of use for studying the effects of linked selection.

1 Simulation features

SLiM simulates the evolution of diploid genomes in a population of hermaphrodites. The simulation is based on an extended Wright-Fisher model with selection [10], resembling one of the standard frameworks in population genetics theory [11]. The Wright-Fisher model assumes discrete generations, where the two parents of each child are drawn from the population in the previous generation with probabilities proportional to their fitnesses. Fitness is a function of the mutations present in an individual. Gametes are generated by recombining parental chromosomes and adding new mutations. Once all offspring are created, they become the parents for the next generation (Figure 1). The **fitness model** implemented in SLiM assigns fitness $w_i = 1 + 2h_i s_i$ to individuals heterozygous for the particular mutation i with selection coefficient s_i and dominance coefficient h_i. Homozygotes for the mutation have fitness $w_i = 1 + 2s$. A dominance coefficient $h = 0.5$, for instance, specifies a codominant mutation, $h = 0.1$ a partially recessive mutation, and $h = 1.2$ an overdominant mutation. The fitness of an individual is assumed to be multiplicative over all sites: $w = \prod_i w_i$.



- Calculate the fitnesses of all parents according to the mutations present in their genomes.
- In each subpopulation:
  1. For every child, draw two individuals from the parent generation. The probability for an individual to be drawn is proportional to its fitness.
  2. Generate gametes by recombining parental chromosomes and add new mutations according to the specified mutational parameters.
  3. For the fraction of children that are supposed to be made up by migrants from other subpopulations, draw the parents from the respective subpopulations.
- Make children the new parents for the next generation.

Figure 1. Illustration of SLiM's core algorithm for simulating evolution in each generation. The diagram on the left depicts a scenario with two subpopulations, P$_1$ with six individuals and P$_2$ with three individuals.

Mutations can be of different abstract **mutation types** to be defined by the user. Examples could be synonymous mutations, adaptive mutations, and lethal mutations. A mutation type is specified by the distribution of fitness effects (DFE) and the dominance coefficient. Genomic regions can be assigned to different user-defined **genomic element types**. Examples could be exon, intron, and UTR. A specific genomic element type is defined by the different mutation types and their relative proportions that can occur in these elements. The **chromosome organization** is finally defined by the locations of specific genomic elements along the chromosome.

Each mutation has a specified position along the chromosome. SLiM allows more than one mutation to be present in one individual at the same site and there are no back-mutations. Mutations remain abstract entities in the sense that the simulation does not specify the actual nature of a mutation, such as the particular nucleotide states of ancestral and derived alleles or whether the mutation is a single nucleotide mutation, an insertion or deletion, an inversion, etc. Note, however, that the user always has the freedom to associate abstract mutation types with specific classes of events.

As an illustration of the concept of mutation types and genomic element types, consider the following example: Suppose one intends to model the evolution of exons under recurrent selective sweeps and background selection. In this case, one could define three different mutation types: ‘synonymous’, ‘deleterious’, and ‘adaptive’. The synonymous mutations would all be assigned a fixed selection coefficient $s = 0$. The selection coefficient of the deleterious mutations could be drawn from a gamma distribution with mean $\overline{s} = -0.05$, shape parameter $\alpha = 0.2$, and dominance coefficient $h = 0.2$. The adaptive mutations would be modeled with fixed selection and dominance coefficients, say $s = 0.001$ and $h = 0.5$. The single genomic element type in this example would be ‘exon’, defined by the presence of all three mutation types with relative proportions 0.25 for synonymous mutations, 0.74 for deleterious mutations, and 0.01 for adaptive mutations. The chromosome organization would finally be specified by the locations of exons along the chromosome.

The **recombination model** implemented in SLiM can incorporate both crossing-over and gene-conversion. Recombination events during meiosis are drawn from a user-specified recombination map. The ratio between gene conversion and crossing over can be specified by the user, as can be the average length of gene conversion tracts.

SLiM can model complex scenarios of **demography** and **population substructure**. The simulation allows for arbitrary numbers of subpopulations to be added at user-defined times, either initialized with new individuals, or from the individuals drawn from another subpopulation to model a population split or colonization event. The size of each subpopulation can be changed at any time to model demographic events such as population bottlenecks or expansions. The rates of **migration** between any two subpopulations can be specified or changed by the user at any time. The simulation also allows to model **selfing** by specifying selfing rates that can vary over time and between subpopulations.

The simulation keeps track of all mutations that become fixed in the population over the course of a run. Once fixed, such mutations are removed and recorded as **substitutions**, as they can no longer cause fitness differences between individuals. However, in scenarios with more than one subpopulation, only the mutations that have become fixed in all subpopulations are removed.

A simulation run starts with empty genomes. In order to establish genetic diversity, simulations first have to undergo a burn-in period. Alternatively, SLiM can be initialized from a set of pre-defined genomes provided by the user. This can also be the output from a previous simulation run.

The user can specify **predetermined mutations** to be introduced at specific time points in a simulation run. Such mutations can be used, for example, to investigate individual selective sweeps or to track the frequency trajectories of specific mutations in the population. Predetermined adaptive mutations can further be assigned to undergo only **partial selective sweeps**, where positive selection ceases once the mutation has reached a predefined population frequency.

SLiM provides several options for the **output** of its simulation results: (i) Output of the complete state of the population at specified time points – in terms of all mutations and genomes present in the population. (ii) Random samples of specific size drawn from a particular subpopulation at given time points. (iii) List of all mutations that have become fixed until a specific time point, together with the times when each mutation became fixed. (iv) The frequency trajectories of individual mutations over time.

2 Installation

SLiM is a command line program written in the C++ programming language. The source code 'slim.cpp' can be downloaded from http://www.stanford.edu/∼messer/software. To compile the program, it is recommended to use the GNU gcc compiler, which should be installed on most Unix-type operating systems. On Mac OS X, the gcc compiler is not installed by default but is freely available in the xcode suite of development tools. To install the gcc compiler on Mac OS X, first download and then install the xcode package from http://connect.apple.com. SLiM also requires the GNU scientific library (GSL) [12], which provides essential routines for the algorithms implemented in the simulation. GSL should already be installed on many systems, but may need to be installed manually on some systems. To check whether GSL is already installed on your system, type in your command-line terminal (Windows users should download and install Cygwin from http://www.cygwin.com or another such application):

```
$ gsl-config
```

This command should return a usage description and a list of options if GSL is properly installed. A quick tutorial for installing GSL on Linux, Mac OS X, or Windows is provided at http://www.brianomeara.info/tutorials/brownie/gsl. To compile SLiM, change into the directory where the source code is located and type:

```
$ g++ -O3 ./slim.cpp -lgsl -lgslcblas -o slim
```

On Mac OS X, the option `-O3`, which specifies the optimization level applied by the compiler, should be replaced with `-fast`. The options `-lgsl` and `-lgslcblas` link the program with the GSL library.

3 Running SLiM

SLiM is a command line program. The parameters for a simulation run have to be provided to the program in the form of a standardized parameter file (we chose to use a parameter file instead of command line arguments for reasons of comprehensibility when complex evolutionary scenarios with many parameters are simulated). To run the simulation with the parameter file *<filename>*, type:

```
$ ./slim <filename>
```

The parameter file is a standard text file. Each line preceded by '#' in this file indicates that in the following section, until either the next occurrence of a line preceded with '#' or the end of the file, a specific parameter will be defined. The following parameters can be specified:

```
#MUTATION TYPES
#MUTATION RATE
#GENOMIC ELEMENT TYPES
#CHROMOSOME ORGANIZATION
#RECOMBINATION RATE
#GENERATIONS
#DEMOGRAPHY AND STRUCTURE
#OUTPUT (optional)
#GENE CONVERSION (optional)
#PREDETERMINED MUTATIONS (optional)
#INITIALIZATION (otional)
#SEED (optional)
```

Comments can be added throughout the parameter file by preceding a comment with '/', in which case all subsequent text in the line will be ignored by the program. Empty lines will be ignored. Make sure that the last line of the parameter file ends with a newline character as it will be ignored otherwise.

4 Simulation parameters

4.1 Mutation types and mutation rate

Mutation types are specified by the DFE from which the selection coefficients of mutations of this type are drawn and their dominance coefficient. The syntax for defining mutation types is:

```
#MUTATION TYPES
<mutation-type-id> <h> <DFE-type> [DFE parameters]
...
```

The `<mutation-type-id>` is used to identify the mutations of this type and can be any number preceded by the letter 'm', for example `m4`. This id will be used to specify the mutation types that are present in a particular genomic element type. The value of `<h>` specifies the dominance coefficient assigned to mutations of this type, for example `0.5` for codominant mutations or `0.1` for partially recessive mutations.

`<DFE-type>` specifies the DFE from which the selection coefficients of mutations of this type are drawn, followed by the specific parameters needed to define the particular DFE. Possible DFE types are:

1. fixed selection coefficient:	`f <s>`
2. exponential distribution:	`e <mean-s>`
3. gamma distribution:	`g <mean-s> <shape-alpha>`

Under the exponential DFE, selection coefficients are drawn from a probability density $P(s\,|\,\overline{s}) = \overline{s}^{-1}\exp(-s/\overline{s})$. An exponential DFE is often used to model advantageous mutations [13]. Under the gamma DFE, selection coefficients are drawn from a gamma distribution with probability density $P(s\,|\,\alpha,\beta) = [\Gamma(\alpha)\beta^{\alpha}]^{-1}\exp(-s/\beta)$. The shape parameter α specifies the kurtosis of the distribution. The mean of the distribution is given by $\overline{s} = \alpha\beta$. A gamma DFE is often used to model deleterious mutations at functional sites [13]. Note that selection coefficients are always defined in terms of their absolute values and not multiplied by an effective population size.

The simulation assumes a uniform mutation rate `<u>` per nucleotide per generation along the chromosome that is set by the parameter:

```
#MUTATION RATE
<u>
```

The mutation rate can be specified in either decimal or scientific e-notation (for example `2.5e-8`).

4.2 Genomic element types

A genomic element type is specified by a list of mutation types and their relative proportions in the elements of this type. An example of a genomic element type would be 'exon', defined by the presence of 'synonymous' and 'nonsynonymous' mutations and their respective proportions. The syntax for defining genomic element types is:

```
#GENOMIC ELEMENT TYPES
<element-type-id> <mut-type> <x> [<mut-type> <x> ...]
...
```

The `<element-type-id>` can be any number preceded by the letter 'g', for example `g2`. This id will be used for specifying the chromosome organization in terms of the locations where genomic elements of a specific type are located along the chromosome.

Each following pair of numbers specifies a particular mutation type `<mut-type>` and its relative proportion `<x>` among the mutations in this genomic element type. The proportions do not actually have to add up to one and are interpreted relative to each other (mutations always occur at the per-site rate specified in `#MUTATION RATE`). For example, the genomic element type `g1` defined by

```
#GENOMIC ELEMENT TYPES
g1 m4 0.5 m3 1.0
```

comprises mutations of types m4 and m3, with the mutations of type m3 occurring twice as often as those of type m4.

4.3 Chromosome organization

The organization of the chromosome is specified by the locations of genomic elements along the chromosome. The syntax for defining the chromosomal organization is:

```
#CHROMOSOME ORGANIZATION
<element-type> <start> <end>
...
```

Each line represent a genomic element, specified by its *<element-type>* and followed by its *<start>* and *<end>* position on the chromosome in base pairs. The specified genomic regions do not have to cover the entire chromosome, but mutations will only occur in the regions that have been specified. Thus, one can easily model the evolution of only a subset of regions on a chromosome. Genomic elements do not need to be specified in the same order as they are located along the chromosome. However, overlap between genomic regions is not permitted.

4.4 Recombination

SLiM allows the user to specify arbitrary recombination rates that are also allowed vary along the chromosome. Recombination rates are specified by the syntax:

```
#RECOMBINATION RATE
<interval-end> <r>
...
```

The first row specifies the recombination rate from the start of the chromosome up to the position specified by *<interval-end>*. In subsequent rows, the recombination rates for consecutive intervals can be specified. The recombination rate *<r>* for a particular interval is defined in terms of recombination events per nucleotide per generation and can be specified in either decimal or scientific e-notation. Note that the commonly used unit of 1 cM/Mb corresponds to a per nucleotide recombination rate of 1e-8. Intervals have to be defined in ascending order and the end of the last interval should extend up to the end of last genomic element defined in the chromosome organization, as recombination rate will automatically be set to zero to the right of the last specified interval. Recombination rates can be specified in either decimal or scientific e-notation (for example 1.5e-7).

4.4.1 Crossing over and gene conversion

By default, every recombination event results in a crossing over of the two parental chromosomes during meiosis (Figure 1). Optionally, a fraction of recombination events can be specified to result in gene conversion. Gene conversion is modeled by excising a genomic conversion stretch of a particular length to the right of the recombination breakpoint. The length of the conversion stretch is drawn from a geometric distribution. The syntax for modeling gene conversion is:

```
#GENE CONVERSION
<fraction> <stretch-length>
```

The parameter *<fraction>* specifies the probability that a recombination event results in gene conversion rather than crossing over. In the remainder of events, recombination still leads to crossing-over. *<stretch-length>* specifies the mean of the geometric distribution from which the lengths of the conversion stretches are drawn.

4.5 Demography and population structure

The number of generations `<t>` for which the simulation is to be run is set by the parameter:

```
#GENERATIONS
<t>
```

Time is specified in actual generations and not rescaled by any sort of effective population size. In contrast to many coalescent simulations, time is also specified in the forward direction; that is, a simulation run starts in generation one and ends after generation `<t>`.

By default, at the start of a simulation run all genomes in the population are empty since no mutations have yet occurred. Therefore, simulations have to undergo a burn-in period in order to establish the required levels of genetic diversity. For neutral mutations, as a rule of thumb, evolution typically needs to be simulated for $10N_e$ generations in order to obtain stationary levels of neutral polymorphism, where N_e is the variance effective population size over the initial time period in the specific evolutionary scenario. Stationary levels of polymorphism for deleterious and advantageous mutations can be approached considerably faster.

Demography and population structure is modeled by specifying events such as the introduction of a new subpopulation or the change of a subpopulation's size at specific time points. The general syntax for specifying such events is:

```
#DEMOGRAPHY AND STRUCTURE
<time> <event-type> [event parameters]
...
```

The first parameter, `<time>`, specifies the particular generation in which `<event-type>` will be executed, followed by a list of parameters for the particular event. Events do not have to be specified in the same order as they occur; they will be sorted automatically by the program. Events are always executed at the beginning of a generation. For example, changing the size of a subpopulation from N_1 to N_2 in generation t implies that N_2 children will be generated in generation t. Events can be of three different types, which will be discussed in order below:

adding new subpopulation:	`<time> P <pop> <N> [<source-pop>]`
changing population size:	`<time> N <pop> <N>`
changing migration rate:	`<time> M <target-pop> <source-pop> <m>`
changing selfing rate:	`<time> S <pop> <σ>`

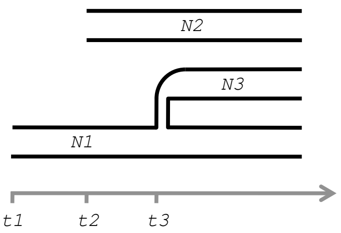
4.5.1 Adding new subpopulations and modeling population splits

An event of type '`P`' adds a new subpopulation of size `<N>` with identifier `<pop>` in generation `<time>`. The syntax for introducing a new subpopulation is:

```
<time> P <pop> <N> [<source-pop>]
```

The identifier `<pop>` of the new subpopulation can be any number preceded by the letter 'p', for example `p3`. The identifier values for different subpopulations do not need to be in any particular order. By default, the new subpopulation consists of individuals with empty genomes; that is, no mutations are yet present. Alternatively, the new subpopulation can be initialized with individuals drawn from an already existing subpopulation `<source-pop>`, allowing to model population splits and colonization events. In this case, the probability of being chosen as a migrant is proportional to an individual's fitnesses in the source population. Note that migrants are not actually removed from the source population, they will rather be used as parents when generating the children in the new subpopulation (Figure 1).

Importantly, all simulations should start with an event of the form '`1 P <pop> <N>`', unless an initialization file is provided (see section 4.9). This introduces an initial population of size `<N>` in the first generation. Figure 2 shows an illustration for the usage of the '`P`' event type to add new subpopulations and to model a population split:



```
#DEMOGRAPHY AND STRUCTURE
<t1> P p1 <N1>
<t2> P p2 <N2>
<t3> P p3 <N3> p1
```

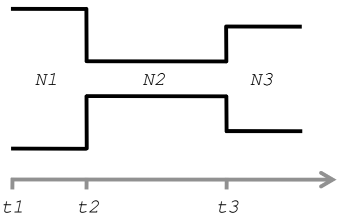
Figure 2. Illustration of the '`P`' event type. Subpopulation `p1` of size `<N1>` is created in generation `<t1>` and subpopulation `p2` of size `<N2>` in generation `<t2>`. In generation `<t3>`, subpopulation `p3` splits off from `p1`.

4.5.2 Changing population sizes and deleting subpopulations

An event of type '`N`' sets the size of subpopulation `<pop>` to `<N>` in generation `<time>`. The syntax for setting population size is:

```
<time> N <pop> <N>
```

If the size of a particular subpopulation is set to zero, this subpopulation is deleted and all migration rates from or to this subpopulation are also reset to zero. Population size changes are always executed at the beginning of a generation. In the Wright-Fisher model, population size changes are treated as 'instantaneous' events by adjusting the number of children that are generated in subsequent generations. If a continuously changing population size is to be modeled, the population sizes have to be specified explicitly for each generation.



```
#DEMOGRAPHY AND STRUCTURE
<t1> P p1 <N1>
<t2> N p1 <N2>
<t3> N p1 <N3>
```

Figure 3. Illustration of the '`N`' event type. Subpopulation `p1` of size `<N1>` is created in generation `<t1>`. In generation `<t2>`, its population size is reduced to `<N2>` but recovers in generation `<t3>` to size `<N3>`.

Note that when population sizes are changed, selection coefficients are not rescaled, as sometimes done in other forward simulations. Thus, an increase in population size can lead to stronger effective selection and vice versa. Figure 3 shows an illustration for the usage of the '`N`' event type to simulate a simple bottleneck scenario.

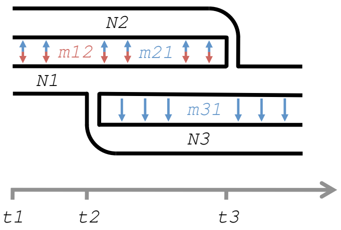
4.5.3 Migration and admixture

An event of type '`M`' sets the migration rate from the source population `<source-pop>` to the target population `<target-pop>` to the value `<m>` in generation `<time>`. The syntax for this event type is:

```
<time> M <target-pop> <source-pop> <m>
```

The value of `<m>` specifies the fraction of individuals of the target population that will be made up of migrants from the source population in each generation. The probability of being drawn as a migrant is proportional to the individual's fitness in the source population.

Note that in the Wright-Fisher model, migrating individuals are not actually removed from the source population, they will rather be used as parents when generating the children in the target population (Figure 1). Migration has therefore no effect on actual population sizes. However, when setting migration rates, it needs to be assured that for any subpopulation the sum of the overall fractions of migrants from other subpopulations, $M_i = \sum_j m_{ij}$, never exceeds one. Events of type 'M' can also be used to model population admixture, as shown in Figure 4.



```
#DEMOGRAPHY AND STRUCTURE
<t1> P p1 <N1>
<t1> P p2 <N2>
<t1> M p1 p2 <m12>
<t1> M p2 p1 <m21>
<t2> P p3 <N3> p1
<t2> M p3 p1 <m31>
<t3> M p1 p2 0.5
<t3+1> N p2 0
```

Figure 4. Illustration of the 'M' event type. In generation <t1> two subpopulations p1 and p2 are created. The migration rate is set to <m21> from p1 to p2 and <m12> in the other direction. In generation <t2>, subpopulation p3 splits off from p1 and migration from p1 to p3 is set to rate <m31>. In generation <t3>, subpopulation p2 admixes with subpopulation p1, implemented by setting the fraction of p1 made up by migrants from p2 to 0.5 for that particular generation, and then eliminating p2 by setting its size to 0 in the following generation.

4.5.4 Self-fertilization

SLiM assumes random mating by default. However, some species, such as certain plants, can also reproduce through selfing. This can be simulated in SLiM by specifying the probability that a child results from self-fertilization rather than from random mating. To do this, one has to specify an event of type 'S', which sets the selfing rate in population <pop> to the value <σ> in generation <time>. The syntax for this event type is:

```
<time> S <pop> <σ>.
```

A value <σ>=1 specifies a subpopulation that reproduces exclusively through selfing, whereas <σ>=0.5 specifies a scenario where both selfing and outcrossing occur equally likely. The default selfing rate, if not otherwise specified, is <σ>=0. Note that this implementation allows the user to change the selfing rate over time and also to have different selfing rates in different subpopulations.

4.5.5 Remarks on complex demographic scenarios

While SLiM is designed to allow for arbitrarily complex scenarios of demography and population substructure, one needs to be aware that the directives required for specifying such scenarios can quickly become difficult to follow. This raises the potential for inconsistent directives, for instance, changing the size of a subpopulation that is not actually present. In most of the situations where inconsistent directives are encountered, SLiM will exit with an error message reporting the particular type of problem. However, it is important to keep in mind that some of these problems might only show up during the simulation. The list of directives is not checked for consistency prior to the simulation. Thus, computation time might be lost if the problem is encountered only after the program has already been running for some time. To prevent this from happening, it is strongly recommended that prior to running long simulations, initial test runs are conducted to check the list of directives for consistency. The mutation rates, recombination rates, and population sizes in these test runs can be set to small values so that the simulation finishes quickly.

4.6 Output

Specifying the output of simulation results is handled in a similar fashion to the specification of demographic events described in the previous section. For each requested output, the user has to specify the <time> at which the output should be returned, the particular <output-type>, and the required parameters for this type of output in the #OUTPUT section of the parameter file. The syntax is:

```
#OUTPUT
<time> <output-type> [output parameters]
...
```

The following types of output can be requested from the simulation and each type will be discussed in detail with the help of examples in a subsequent section:

Output state of entire population:	`<time> A [<filename>]`
Output random sample from subpopulation:	`<time> R <pop> <size>`
Output list of all fixed mutations:	`<time> F`
Track mutations of particular type:	`<time> T <mut-type>`

Before any such user-specified output is provided, the simulation first prints the input parameters of the particular run, including the value of the seed used for the random number generator (see section 4.10). For instance, the initial output for the simple neutral scenario from section 5.1 will look as follows:

```
#INPUT PARAMETER FILE
./input_example_1.txt
#MUTATION TYPES
m1 0.5 f 0.0
#MUTATION RATE
1e-8
#GENOMIC ELEMENT TYPES
g1 m1 1.0
#CHROMOSOME ORGANIZATION
g1 1 100000
#RECOMBINATION RATE
100000 1e-8
#GENERATIONS
10000
#DEMOGRAPHY AND STRUCTURE
1 P p1 500
#OUTPUT
10000 R p1 10
10000 F
#SEED
1346284673
```

Note that from this initial output it is possible to reproduce the particular simulation run exactly, since all simulation runs with the same simulation parameters starting with the same seed will yield exactly the same simulation output (see section 4.10).

User-requested output will be printed whenever the simulation run has reached the specific time point for which the output is requested. Each such output starts with a line ‘`#OUT: <time> <output-type> [output parameters]`’, followed by the particular output in the subsequent lines.

4.6.1 Output entire population

The output type ‘`A`’ returns the complete state of the population at the end of generation `<time>`. Optionally the output will not be printed on the screen but instead written into the file `<filename>`. The syntax is:

```
<time> A [<filename>]
```

The information about the state of the population is presented in the form of three list, specifying all subpopulations, all mutations, and all genomes present in the population in the particular generation. The following is an example for the output obtained using the 'A' option after generation 20 in a simulation run with two small subpopulations, consisting of two individuals each. On the right, short explanations for the particular output lines are given:

```
#OUT: 20 A                                Header:
Populations:                              List of all populations:
p1 2                                      <pop> <N>
p2 2                                      ...
Mutations:                                List of all mutations:
1 m2 7149 -0.00364166 0.2 3               <id> <type> <x> <s> <h> <n>
2 m2 6181 -0.00715424 0.2 4               ...
3 m2 8179 -0.009072 0.2 2                 ...
4 m1 5636 0 0.5 1                         ...
Genomes:                                  List of all genomes:
p1:1 1                                    <pop:genome> <id> ...
p1:2 1                                    ...
p1:3                                      ...
p1:4 1                                    ...
p2:1 4 2 3                                ...
p2:2 2                                    ...
p2:3 2 3                                  ...
p2:4 2                                    ...
```

The section Populations lists all subpopulations. Each subpopulation is denoted by its population identifier <*pop*> and size <*N*> in terms of numbers of diploid individuals.

The following section, Mutations, lists all mutations that are polymorphic in the population. Each mutation is assigned a unique <*id*> in ascending order that is used to identify this particular mutation in the genomes that carry it. Note that mutation ids are not necessarily kept constant between generations; the same mutation will likely be assigned a different id in another generation. Each mutation is further described, in order, by its mutation type <*type*>, position <*x*> on the chromosome, selection coefficient <*s*>, dominance coefficient <*h*>, and the overall number <*n*> of genomes carrying this mutation. Note that the output of the mutation prevalences for each mutation provides an easy way to calculate polymorphism frequency distributions.

The last list, Genomes, specifies all genomes in the population. Each line is a genome. The starting string <*pop*:*genome*> specifies the subpopulation identifier <*pop*>, followed by a number used to enumerate the genomes of this subpopulation in ascending order. Genomes can easily be mapped onto individuals as individual i has the two genomes $2i-1$ and $2i$. The subsequent numbers list the <*id*> values of the different mutations present in the particular genome. For example, the line '<p2:1> 4 2 3' specifies genome 1 in subpopulation p2 and this genome carries the mutations 4, 2, and 3.

4.6.2 Output random sample from a subpopulation

The output type 'R' returns a sample of <*size*> genomes drawn randomly from subpopulation <*pop*> at the end of generation <*time*>. The syntax is:

```
<time> R <pop> <size>
```

All genomes present in the population have equal probability of being drawn and the same genome can be drawn several times. The following is an example for the output obtained with the 'R' option when requesting a random sample of 4 genomes from subpopulation p1 in generation 10 of a simulation run:

```
#OUT: 10 R p1 4                          Header:
Mutations:                               List of all mutations:
1 m1 2383 0 0.5 3                        <id> <type> <x> <s> <h> <n>
2 m1 9828 0 0.5 3                        ...
3 m1 211 0 0.5 1                         ...
4 m2 7576 -0.0186089 0.2 1               ...
Genomes:                                 List of all genomes:
p1:3 1 2                                 <pop:genome> <id> ...
p1:4 3 4                                 ...
p1:2 1 2                                 ...
p1:1 1 2                                 ...
```

Note that the output style is very similar to the output under the option 'A', with the primary difference that only the mutations and genomes present in the sample are shown. Here, the values of *<n>* denote prevalences of the mutations in the sample, not in the whole population.

4.6.3 Output list of all fixed mutations

The program records all mutations that have become fixed over the course of a simulation run and removes these mutations from the populations. This is reasonable because fixed mutations can no longer generate fitness differences between individuals and back mutations do not occur. The output type 'F' returns the list of all mutations that have become fixed until the end of generation *<time>*. The syntax is:

```
<time> F
```

The following is an example for output obtained with the 'F' option in a simulation after 1000 generations:

```
#OUT: 1000 F                             Header:
Mutations:                               List of all fixed mutations:
1 m1 6281 0 0.5 23                       <id> <type> <x> <s> <h> <t>
2 m1 4693 0 0.5 552                      ...
3 m1 1261 0 0.5 675                      ...
4 m2 2531 -0.002165 0.2 683              ...
5 m1 9458 0 0.5 719                      ...
```

The last number in each mutation row, *<t>*, denotes the generation in which the particular mutation has become fixed. Note that in scenarios with several supopulations, a mutation has to be fixed in all subpopulations to be recorded and removed. This can slow down scenarios with population substructure and low migration rates if subpopulations accumulate many private mutations.

4.6.4 Track mutations of particular types

SLiM allows to track the frequency trajectories of particular mutations in the population using the output type 'T'. For this purpose, one needs to specify the particular mutation type *<mut-type>* of the mutations that are to be tracked and the generation *<time>* at which the tracking is supposed to start. The syntax for the 'T' output type is:

```
<time> T <mut-type>
```

In every generation after *<time>*, the population will then be screened for all mutations of type *<mut-type>* and every such mutation will be reported with an output line of the form:

```
#OUT: <generation> <mut-type> <x> <s> <h> <n>
```

The value of <n> specifies the prevalence of the particular mutation in the population in <generation>. Note that if several mutations of the specified <mut-type> are present in the population, a separate output line is provided for each of those mutations. Thus, if a single mutation is to be tracked, this mutation should be given a unique <mut-type>. This can easily be attained for predetermined mutations, as described in section 4.7. In scenarios with several subpopulations <n> specifies the abundance of the mutation in the overall population, not just a particular subpopulation.

4.7 Introducing predetermined mutations

SLiM provides the option to introduce predetermined mutations into the population at user-defined time points and positions on the chromosome. This option can be used, for example, to investigate selective sweeps or track the trajectories of specific mutations in the population. There is no limit on the possible number of predetermined mutations. The syntax for introducing predetermined mutations is:

```
#PREDETERMINED MUTATIONS
<time> <mut-type> <x> <s> <h> <pop> <nAA> <nAa> [P <f>]
...
```

This directive introduces a mutation of type <mut-type> at genomic position <x> with selection coefficient <s> and dominance coefficient <h> at the end of generation <time>. The mutation will be added in homozygous form to <nAA> random individuals and in heterozygous form to another <nAa> random individuals in the subpopulation <pop>. The optional parameter P <f> can be used to model partial selective sweeps and will be discussed in section 4.8.

Technically, SLiM introduces such mutations to both genomes of the first 1,...,<nAA> individuals in the subpopulation and then to only the first genome of the subsequent <nAA>+1,...,<nAA>+<nAa> individuals in the subpopulation. This is effectively equivalent to introducing the mutation into random individuals. However, should more than one mutation be introduced in the same generation, they will end up in the same individuals. If full control is needed over which mutations are introduced into which genomes, it is recommended to start the simulation with a user-defined initialization file, where all mutations and genomes can be specified explicitly. This possibility is described in section 4.9.

Note that for predetermined mutation the mutation type does not play the same role it does for regular mutations, where it determines the DFE from which their selection coefficients are drawn and their dominance coefficient. Nevertheless, for predetermined mutations the mutation type can still play a crucial role for identifying a particular mutation in the simulation output and for tracking such mutations. For this purpose, one can assign a unique mutation type to a predetermined mutation that has not been used already in the #MUTATION TYPES section of the input parameter file. This way the predetermined mutation can be tracked individually. Note that <mut-type> can be any number preceded by the letter 'm', for example m17.

4.8 Simulating complete and partial selective sweeps

One application for predetermined mutations is the possibility to model individual selective sweeps. Furthermore, SLiM allows to simulate partial selective sweep by specifying the 'P' option for a predetermined mutation:

```
#PREDETERMINED MUTATIONS
<time> <mut-type> <x> <s> <h> <pop> <nAA> <nAa> P <f>
...
```

In this case, the selection coefficient of the mutation will be set to zero once the mutation has reached population frequency <f>. Note that in scenarios with several subpopulations <f> refers to the overall frequency of the mutation in all subpopulations.

When modeling selective sweeps using predetermined mutations, one always has to keep in mind that even a strongly advantageous mutation can still become lost from the population due to random genetic drift. A mutation with selection coefficient s and dominance coefficient h, when present initially in only one copy, has probability $\approx 4hs$ of reaching its establishment frequency $(4hsN)^{-1}$ in the population, where selection outweighs drift and the mutation is thus unlikely to still get lost.

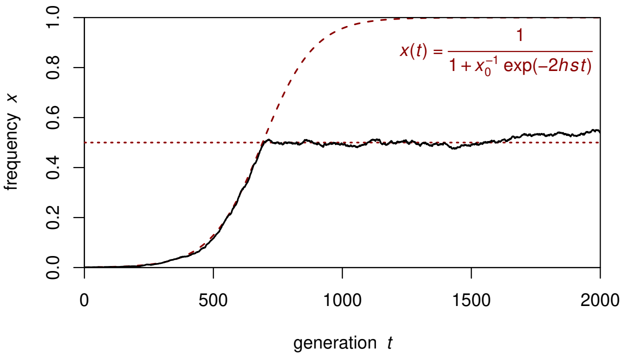


Figure 5. Illustration of the trajectory of a partial selective sweeps ($s = 0.01$ and $h = 0.5$) in a population of 5×10^4 individuals with a destined frequency of 0.5. The mutation was introduced into 100 heterozygous individuals in the first generation. No other mutations were present. The dashed red line shows the theoretically expected trajectory during the selected phase.

SLiM does not condition on the establishment of predetermined mutations. Thus, if a selective sweep is to be simulated, one has to verify from the simulation output that the mutation has not actually been lost. Since the establishment probability of a advantageous mutation is proportional to the product of its initial frequency, its selection coefficient, and its dominance coefficient, increasing any of these parameters can increase establishment probability.

However, for many analyses the selection and dominance coefficients will be fixed, possibly at values where loss of the mutation is still very common. And increasing the initial population frequency of an advantageous mutation via the `<nAA>` and `<nAa>` parameters can raise the problem that the mutation might then be present on many different genomic backgrounds, which can be unrealistic when modeling adaptation from *de novo* mutation.

One possible approach to this problem is to link the mutation to a second 'booster mutation' undergoing a partial selective sweep, which raises the first mutation to its establishment frequency but thereafter becomes selectively neutral. For example, consider the following scenario:

```
#PREDETERMINED MUTATIONS
100 m1 5000 0.01 0.5 p1 0 1
100 m2 5000 0.25 1.0 p1 0 1 P 0.01
```

Here two advantageous mutations are introduced at position `5000` in one copy. Since the two mutations are also introduced in the same generation `100`, both will actually end up in the same genome (remember that several mutations can be present at the same site in one genome in SLiM). However, the first mutation has an establishment probability of only $4h_1s_1 = 0.02$, whereas the second mutation, which undergoes a partial sweep, has an establishment probability of $4h_2s_2 = 0.5$. Hence, in 50% of the runs the second mutation will drag the first mutation to population frequency of 1%, its establishment frequency in a population of size $N = 500$.

Figure 5 demonstrates the ability of SLiM to simulate and track a partial selective sweep with a destined population frequency of 0.5. The frequency trajectory of the mutation during its selected phase agrees with the theoretically expected trajectory for the given selection and dominance coefficients. Once the mutation has reached its destined population frequency, it drifts neutrally

4.9 Initializing the population from a file

By default, at the start of a simulation run all genomes in the population are empty since no mutations have yet occurred. Alternatively, SLiM can be initialized with the populations, mutations, and genomes specified in an initialization file. The format of this initialization file is the same format used for the output of the complete state of the population described in section 4.6.1, that is, a list of all subpopulations and their sizes, all mutations and their parameters, and all genomes present in the population. Any such output file can serve as an initialization file for another simulation run. Note, however, that only the sections `Populations`, `Mutations`, and `Genomes` are required, while the evolutionary parameters specified in the header will be ignored. Of course, one can also use a custom initialization file, as long as it contains valid data in the sections `Populations`, `Mutations`, and `Genomes`. Every genome can then be defined by the user explicitly. The syntax for initializing a simulation run from the data provided in the file `<filename>` is:

```
#INITIALIZATION
<filename>
```

In this case, all populations, mutations, and genomes specified in this file will automatically be carried over into the new simulation run at the start of generation one. The populations do not need to be added again in the section `#DEMOGRAPHY AND STRUCTURE` of the parameter file (doing so would actually cause an error as the particular populations already exist). However, all other evolutionary parameters, such as mutation types, chromosome organization, recombination rate, migration rates, etc., still have to be specified in the parameter file if evolution is to proceed under these parameters. These parameters are intentionally not provided in the initialization file so that the simulation run can be started with different parameters. One should be particularly careful when specifying the parameter file to avoid inconsistencies with the data provided in the initialization file.

Starting a simulation run from an initialization file provides a straightforward way to split up a simulation into different stages. This can can be very useful, for example, when analyzing the reproducibility of evolution under specific scenarios, such as in the example described in section 5.4.

4.10 Random number generator seed

SLiM uses a maximally equidistributed combined Tausworthe random number generator [14]. By default, the seed is a combination of the starting time of the program and its process id. This procedure assures that every time the program is called, a different seed will be used, even if several instances of the program are started simultaneously. Alternatively, a user-defined value for the seed can be specified via:

```
#SEED
<seed>
```

The `<seed>` can be any 4-byte integer number $(-2^{31} \ldots 2^{31})$. Since all simulation runs starting with the same seed will yield exactly the same output, this option can be very useful when simulation runs have to be reproduced.

5 Examples

5.1 Simple neutral scenario

This example simulates a 100 kbp long genomic region evolving under a uniform mutation rate of $u = 10^{-7}$ per site per generation and a uniform recombination rate of $r = 1$ cM/Mbp. All mutations are neutral. The population of size $N = 500$ is simulated over 10^4 generations. Samples of 10 random chromosomes are drawn every $4N$ generations. At the end of the simulation, all fixed mutations are reported.

```
#MUTATION TYPES
m1 0.5 f 0.0 / neutral
#MUTATION RATE
1e-7
#GENOMIC ELEMENT TYPES
g1 m1 1.0 / only one type comprising the neutral mutations
#CHROMOSOME ORGANIZATION
g1 1 100000 / uniform chromosome of length 100 kbp
#RECOMBINATION RATE
100000 1e-8
#GENERATIONS
10000
#DEMOGRAPHY AND STRUCTURE
1 P p1 500 / one population of 500 individuals
#OUTPUT
2000 R p1 10 / output sample of 10 genomes
4000 R p1 10
...
10000 F / output fixed mutations
```

5.2 Hitchhiking of deleterious mutations under recurrent selective sweeps

In this example we want to analyze the complex dynamics resulting from the interactions between deleterious and beneficial mutations under recurrent selective sweeps. In particular, we are interested in the polymorphism frequency distributions and fixation probabilities of functional mutations.

For this purpose, we simulate the evolution of a chromosome of length 10 Mbp in a panmictic population of constant size $N = 10^3$. Functional mutations should occur on each chromosome at a uniform rate of $u = 2.5 \times 10^{-9}$ per site per generation. The selection coefficients of these functional mutations are drawn from an exponential distribution with mean $\overline{s} = -0.01$, and they are assumed to be partly recessive with a dominance coefficient $h = 0.2$. However, 1 out of 2000 mutations is assumed to be adaptive with a selection coefficient $s = 0.01$ and dominance coefficient $h = 0.5$. Recombination occurs uniformly along the chromosome at rate $r = 1$ cM/Mbp.

We simulate the evolution of this chromosome for 10^5 generations. Every 10^4 generations, a random sample of 50 genomes is drawn from the population. At the end of the simulation run we want to obtain a list of all the mutations that have become fixed. This parameter file for this scenario is:

```
#MUTATION TYPES
m1 0.2 e -0.01 / deleterious (exponential DFE, h=0.2)
m2 0.5 f 0.01 / advantageous (fixed s=0.01, h=0.5)
#MUTATION RATE
2.5e-9
#GENOMIC ELEMENT TYPES
g1 m1 0.9995 m2 0.0005 / 1 in 2000 mutations is adaptive
#CHROMOSOME ORGANIZATION
g1 1 10000000 / uniform chromosome of length 10 Mbp
#RECOMBINATION RATE
10000000 1e-8 / uniform recombination rate (1 cM/Mbp)
#GENERATIONS
100000
#DEMOGRAPHY AND STRUCTURE
1 P p1 1000 / single population of 1000 individuals
#OUTPUT
10000 R p1 50 / output sample of 50 genomes
20000 R p1 50
...
100000 F / output fixed mutations
```

5.3 Background selection with gene structure and varying recombination rate

In this third example we want to investigate how background selection affects the patterns of neutral and functional polymorphism under varying recombination rate along a gene. The gene of interest is supposed to resemble an ‘average’ human gene (Figure 6). Mutations in exons are assumed to be neutral (25%) or deleterious (75%), with the selection coefficients of the deleterious mutations drawn from a gamma distribution with mean $\overline{s} = -0.05$ and shape parameter $\alpha = 0.2$. The deleterious mutations are assumed to be recessive with dominance coefficient $h = 0.1$. In UTRs, half of the mutations are assumed to be neutral, the remainder deleterious with the same selection parameters as used for exons.

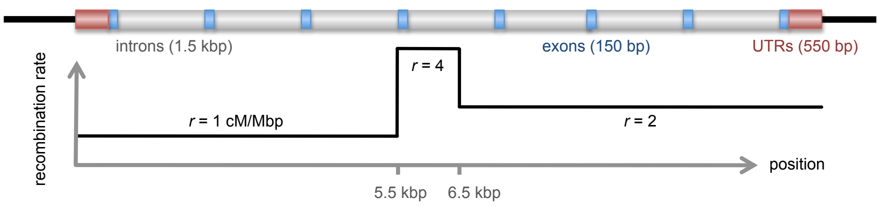


Figure 6. The ‘average’ human gene: 8 exons of length 150 bp each, interspersed by introns of length 1.5 kbp, and flanked by UTRs of length 550 bp. The lower graph specifies the recombination rate along the gene.

The mutations in introns are always neutral. We assume a mutation rate of $u = 10^{-8}$ and a recombination profile as specified in Figure 6. The population of size $N = 10^4$ is simulated over 10^6 generations. To calculate polymorphism statistics, samples of 100 random genomes are drawn every $2N$ generations. The parameter file for this scenario is:

```
#MUTATION TYPES
m1 0.1 g -0.05 0.2 / deleterious (gamma DFE, h=0.1)
m2 0.5 f 0.0 / neutral
#MUTATION RATE
1e-8
#GENOMIC ELEMENT TYPES
g1 m1 0.75 m2 0.25 / exon (75% del, 25% neutral)
g2 m1 0.50 m2 0.50 / UTR (50% del, 50% neutral)
g3 m2 1.0 / intron (100% neutral)
#CHROMOSOME ORGANIZATION
g2 1 550 / UTR
g1 551 700 / first exon
g3 701 2200 / first intron
...
#RECOMBINATION RATE
5500 1e-9 / left region
6500 2e-8 / middle region
12800 5e-9 / right region
#GENERATIONS
1000000
#DEMOGRAPHY AND STRUCTURE
1 P p1 10000 / single population of 10000 individuals
#OUTPUT
20000 R p1 100 / output sample of 100 genomes
...
```

5.4 Adaptive introgression after a population split

In this fourth example we want to investigate the haplotype signatures in a model with adaptive introgression (Figure 7). At some point after population split an adaptive mutation arises in one subpopulation and sweeps to high frequency. Due to ongoing migration from this subpopulation into the other subpopulation, the adaptive mutation eventually migrates into the other subpopulation and sweeps there too. Population samples are taken from both subpopulations during different phases of the sweep. Mutation rate is $u = 10^{-9}$ and recombination rate is $r = 5$ cM/Mbp. The adaptive mutation has selection coefficient $s = 0.01$ and dominance coefficient $h = 0.8$. It is initially introduced into 10 heterozygous individuals from the source population.

We are interested in the patterns of neutral polymorphisms in a 100 kbp region around the sweep locus. Furthermore, we want to estimate the variance of the time it takes until the adaptive mutation becomes prevalent in the new subpopulation and thus want to be able to repeat the simulation many times. It then makes sense to split the simulation into two

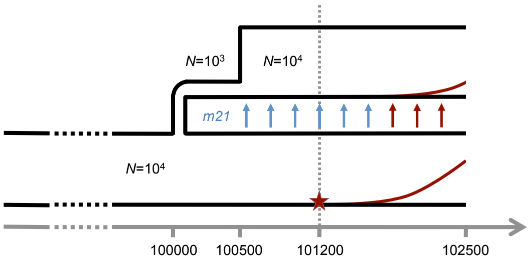


Figure 7. Evolutionary scenario with a population split and subsequent introgression of an adaptive mutation from the source population into the new subpopulation. The new subpopulation goes through an initial population bottleneck. The dashed line specifies the time at which the adaptive mutation is introduced, marking the end of the first simulation stage and the beginning of the second stage.

stages: In the first stage, which ends right before the adaptive mutation is introduced, neutral diversity is established and the complete state of the population is then saved into a file. In the second stage, the simulation is initialized from this file. The adaptive mutation is then introduced and samples of 100 genomes are drawn from both subpopulations every 100 subsequent generations. For analyzing the variance in the sweep times the second stage can be run many times, using the same initialization file. Since the second stage lasts for only 1300 generations, compared to the $\sim 10^5$ generations of the first stage, this will be vastly more efficient than starting the entire simulation anew each time.

```
/ First stage parameter file
#MUTATION TYPES
m1 0.5 f 0.0 / neutral
#MUTATION RATE
1e-9
#GENOMIC ELEMENT TYPES
g1 m1 1.0
#CHROMOSOME ORGANIZATION
g1 1 100000 / uniform chromosome structure (100 kbp)
#RECOMBINATION RATE
100000 5e-8 / uniform recombination rate (5 cM/Mbp)
#GENERATIONS
101200
#DEMOGRAPHY AND STRUCTURE
1 P p1 1e4 / population of 10000 individuals
100000 P p2 1e3 p1 / split off subpopulation p2 from p1
100000 M p2 p1 0.001 / set migration rate p1 to p2
100500 N p2 1e4 / expand subpopulation p2
#OUTPUT
101200 A outfile / save population in outfile
```

```
/ Second stage parameter file
#MUTATION TYPES
m1 0.5 f 0.0 / neutral
#MUTATION RATE
1e-9
#GENOMIC ELEMENT TYPES
g1 m1 1.0
#CHROMOSOME ORGANIZATION
m1 1 100000 / uniform chromosome structure (100 kbp)
#RECOMBINATION RATE
100000 5e-8 / uniform recombination rate (5 cM/Mbp)
#GENERATIONS
1300
#DEMOGRAPHY AND STRUCTURE
1 M p2 p1 0.001 / set migration rate p1 to p2
#OUTPUT
100 R p1 100 / output sample of 100 genomes from p1
100 R p2 100 / output sample of 100 genomes from p2
200 R p1 100
...
#INITIALIZATION
outfile / initialize using output from first stage
#PREDETERMINED MUTATIONS
1 m2 50000 0.01 0.8 p1 0 10 / introduce adaptive mutation
```

6 Program validation

We ran SLiM under various test scenarios to check whether its output conforms to theoretical predictions. First, we measured levels of neutral heterozygosity under different scenarios of demography, population structure, and selfing. These tests allow us to validate the interplay between mutation, migration, and random genetic drift in the simulation. Second, we measured the fixation probabilities of new mutations of different selection coefficients, which allows us to validate the interplay between random genetic drift and selection in the simulation. Finally, we measured the reductions in the levels of neutral diversity around adaptive substitutions during a selective sweep, which allows us to validate the interaction of positive selection with recombination.

6.1 Levels of neutral heterozygosity

Consider a diploid population in which the expected coalescence time between two haploid genomes is $E(\tau_2)$ generations. If u is the neutral mutation rate per site and generation, then $2E(\tau_2)u$ neutral mutations should have occurred, on average, between any two haploid genomes per site. Assuming $E(\tau_2)u \ll 1$, the average level of neutral heterozygosity (π) in a diploid genome will thus be

$$\pi = 2E(\tau_2)u. \tag{1}$$

Expected average coalescence times have been calculated for various evolutionary scenarios: For example, in a diploid Wright-Fisher population of constant size N one obtains the classic result [15]

$$E(\tau_2) = 2N. \tag{2}$$

If population size is allowed to vary, the value of N in Equation (2) needs to be replaced by the harmonic mean estimated over the time-scale of pairwise coalescence. For instance, consider a simple two-regime scenario in which population size switches periodically between N_1 and N_2. The regime of size N_1 always last for t_1 generations, the regime of size N_2 always last for t_2 generations. The population size changes instantaneously between regimes and we assume that $\max(t_1, t_2) \ll \min(N_1, N_2)$. For this scenario, one obtains [16]

$$E(\tau_2) = \frac{2(t_1 + t_2)}{t_1/N_1 + t_2/N_2}. \tag{3}$$

Expected coalescence times have also been derived for certain cases of population substructure. For example, consider a population consisting of two demes of different sizes N_1 and N_2, and let m_{12} and m_{21} be the migration probabilities specifying the fractions of deme 1 and deme 2 that are replaced by migrants from deme 2 and deme 1, respectively, every generation. We assume that migration is symmetric ($m_{12} = m_{21}$) and strong ($N_i m_{ij} \gg 1$). In this case, the expected coalescence time is approximately [15]

$$E(\tau_2) = \frac{8N_1N_2}{N_1 + N_2}. \tag{4}$$

For the case that both demes have equal sizes ($N_1 = N_2 = N/2$) but migration rates between the two demes are asymmetric ($m_{12} \neq m_{21}$), the expected coalescence time is given by [15]

$$E(\tau_2) = N\left(1 + \frac{2m_{12}m_{21}}{m_{12}^2 + m_{21}^2}\right). \tag{5}$$

Another scenario for which expected coalescence times have be calculated analytically is partial selfing. Consider a diploid Wright-Fisher population of constant size N modified such that an individual results with probability σ from a single parent through self-fertilization, whereas it originates from two distinct parents with probability $1 - \sigma$. The expected opalescence time in such a population is [15]

$$E(\tau_2) = N\left(2 - \sigma\right). \tag{6}$$

Equation (1) links expected levels of neutral heterozygosity, which are straightforward to measure in a simulation run, with expected average coalescence times $E(\tau_2)$, for which theoretical predictions exist under the scenarios discussed above. Hence, we can compare the observed levels of neutral diversity in simulation runs under such scenarios with the analytical predictions to validate whether both agree.

scenario		parameters	π_{exp} $(\times 10^4)$	π_{obs} $(\times 10^4)$
(a) constant size	i.	$N = 100$	1.00	0.98 ± 0.05
	ii.	$N = 200$	2.00	2.00 ± 0.11
(b) recurrent bottlenecks	i.	$N_1 = 5N_2 = 500$, $t_1 = t_2 = 50$	1.67	1.69 ± 0.06
	ii.	$N_1 = 20N_2 = 1000$, $t_1 = 4t_2 = 80$	2.08	2.01 ± 0.12
(c) two demes + migration	i.	$N_1 = 4N_2 = 200$, $m_{12} = m_{21} = 0.1$	1.60	1.55 ± 0.06
	ii.	$N_1 = N_2 = 100$, $m_{12} = 10m_{21} = 0.2$	1.20	1.19 ± 0.06
(d) partial selfing	i.	$N = 200$, $\sigma = 0.5$	1.50	1.44 ± 0.10
	ii.	$N = 200$, $\sigma = 1.0$	1.00	0.87 ± 0.14

Table 1. Comparison of the observed levels of neutral heterozygosity per site (π_{obs}) with theoretical expectations (π_{exp}) under various simulation scenarios. In each run, a chromosome of length $L = 10$ Mbp was simulated. The neutral mutation rate was $u = 2.5 \times 10^{-7}$, the recombination rate was $r = 10^{-7}$, and both were uniform along the chromosome. The observed levels of neutral heterozygosity were estimated from all polymorphisms that were present in the population at the end of a simulation run according to $\pi = L^{-1} \sum_i 2p_i(1-p_i)$, where p_i is the population frequency of polymorphism i. Simulations were run until stationary levels of neutral diversity had been established (typically $10N$ generations). Values of π_{obs} show the means estimated over 10 simulation runs, errors specify standard deviations. (a) standard panmictic population of constant size N. In this case, π_{exp} is simply $4N\mu$. (b) panmictic population that undergoes recurrent bottlenecks according to the scenario described by Equation (3). (c) population that consists of two demes of sizes N_1 and N_2 with migration rates m_{12} and m_{21} between them. In scenario (i), migration rates are symmetric and π_{exp} is thus predicted by Equation (4). In scenario (ii), migration is asymmetric while $N_1 = N_2$, and π_{exp} is thus predicted by Equation (5). (d) population of constant size N with partial selfing occurring at rate σ. Here π_{exp} is obtained from Equation (6).

We ran SliM under several test scenarios and measured the observed levels of neutral heterozygosity in each run. The scenarios we investigated included standard panmictic populations of constant size, panmictic populations experiencing recurrent bottlenecks, populations consisting of two demes with migration between them, and populations with partial selfing. The comparisons of theoretically predicted levels of neutral heterozygosity per site (π_{exp}) and observed levels (π_{obs}) are shown in Table 1. Observed and predicted values are generally in very good agreement. Differences between π_{exp} and π_{obs} are always within the statistically expected margins of error.

6.2 Fixation probabilities of new mutations

In a diploid Wright-Fisher population of constant size N, new mutations with heterozygous fitness $1+s$ that arise in a single copy and evolve independently of any other mutation eventually fix in the population with probability [17]

$$P(s, N) = \frac{1 - e^{-2s}}{1 - e^{-4Ns}}. \tag{7}$$

For neutral mutations, we obtain $P = 1/(2N)$. Strongly deleterious mutations can still fix but only with an exponentially vanishing probability $P \approx -2s \exp(4Ns)$, whereas strongly beneficial mutations will fix with probability $P \approx 2s$. The fact that not every beneficial mutation ultimately becomes fixed in the population, while deleterious mutations can still fix occasionally, reflects the interplay between selection and random genetic drift in the population. Hence, by comparing the observed fixation probabilities of mutations of different selective effects in simulation runs with the theoretically predicted values from Equation (7) we can validate whether the interplay between drift and selection is modeled correctly by SLiM. Figure 8A confirms that over all investigated selection coefficients there is excellent agreement between the observed fixation probabilities in simulations and the theoretically predicted values from Equation (7).

6.3 Diversity patterns around selective sweeps

As a final validation of SLiM we investigate the interplay between selection and recombination. Unfortunately, these effects are generally not well understood and theoretical predictions are rather limited. Here we analyze one of the few

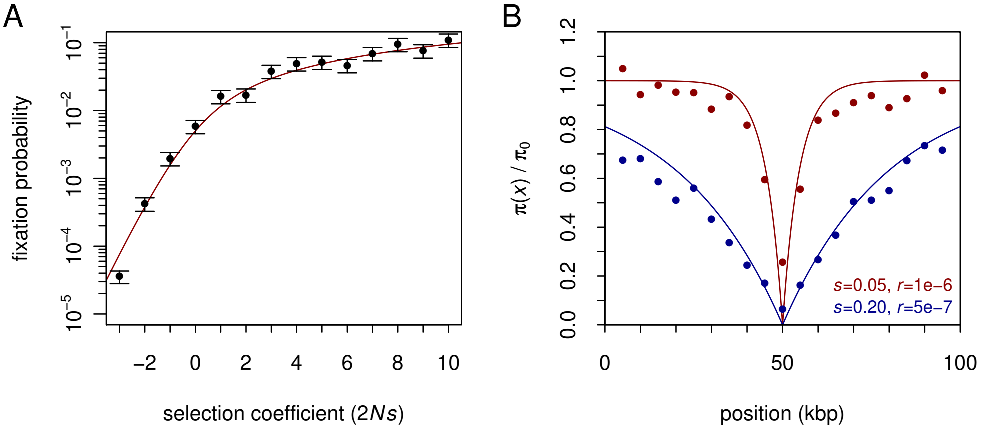


Figure 8. (A) Observed fixation probabilities of new mutations with selection coefficient s in simulation runs compared with the theoretical predictions according to Equation (7). In each run, a single mutation was introduced in the first generation and followed. If the mutation was lost, the run was started anew. The fixation probabilities were then calculated by counting how many runs had to be performed until 20 mutations of the specific selection coefficient had successfully fixed; errors specify standard deviations assuming Poisson counts. Population size was $N = 100$ and only a single mutation was present in each run. (B) Comparison of the observed and predicted reductions in the levels of neutral heterozygosity in a genomic region of length 100 kbp around an adaptive substitution. Each of the two sweep scenarios is specified by its particular selection coefficient s and recombination rate r (uniform along the region). Prior to a sweep, neutral diversity had been established over $10N$ generations in a population of size $N = 1000$ with a uniform neutral mutation rate of $u = 10^{-8}$ per site. An adaptive mutation was then introduced in a single copy at position 50 kbp and followed. If the mutation fixed, neutral heterozygosity $\pi(x)$ was immediately recorded. Data points were calculated over intervals of 5 kbp and averaged over 1000 successful sweeps for each scenario. The base level was calculated as $\pi_0 = 4N\mu$. Lines show the corresponding theoretical predictions according to Equation (8).

scenarios for which such predictions do exist: the reduction in neutral diversity around an adaptive substitution after a single selective sweep. In particular, it has been calculated that in a diploid Wright-Fisher population, immediately after fixation of an adaptive mutation, the level of neutral heterozygosity should be reduced relative to the base level before the sweep by [18]

$$\frac{\pi(x)}{\pi_0} = 1 - (4Ns)^{-2rx/s}. \tag{8}$$

Here x specifies the genomic distance from the adaptive site, r is the recombination rate (assumed to be uniform along the genome), N is the population size (assumed to be constant), and s is the heterozygous selection coefficient of the adaptive mutation. Equation (8) describes the classic sweep signature of a dip in neutral diversity around the adaptive site.

We ran SLiM to simulate large numbers of individual sweeps in the presence of surrounding neutral variation. Figure 8B shows the observed average reduction in the surrounding level of neutral heterozygosity as a function of genomic distance from the adaptive site for two different sweep scenarios. Again, the observed reductions in the simulation are in very good agreement with theoretical predictions.

7 Implementation and performance

SLiM utilizes sophisticated algorithms and optimized data structures. In this section, we describe the specific design concepts and their implementations that allow SLiM to achieve its high performance. We also discuss general dependencies of runtime behavior on simulation parameters inherent to forward simulations. Finally, we compare the runtime and memory requirements of SLiM with that of another popular forward simulation, SFS_CODE [5], which is similar in scope.

7.1 Program implementation

SliM is built on a highly hierarchical data architecture. The basic class in the simulation is a single mutation, specified by its mutation-type identifier (integer), location on the chromosome (integer), selection coefficient (float), and dominance coefficient (float). Each mutation further has a unique id (integer) through which it can be accessed in $O(1)$ time. A single haploid genome is a multi-map that links the positions (keys) of all mutations present on the genome to their mutation ids (values). Multi-maps are an optimal data-structures for this purpose as they allow to efficiently traverse through all n mutations present on a chromosome, to quickly access a mutation given its location in $O(\log n)$ time, and to efficiently add new mutations in $O(\log n)$ time. An individual is a pair of two genomes and a subpopulation is a vector of individuals. The population is finally described by a list of all subpopulations. This hierarchical organization minimizes the amount of information that is stored redundantly, thereby optimizing memory consumption.

Mutations remain abstract entities in SLiM in the sense that the simulation does not specify the actual nature of a mutation, such as the particular nucleotide states of ancestral and derived alleles or whether the mutation is a single nucleotide mutation, an insertion or deletion, an inversion, etc. SLiM does also not store any sequence information of the simulated chromosome. This allows to greatly reduces the amount of data stored by the program compared with other, sequence-based, simulations, such as SFS_CODE [5]. Note, however, that the user still has the freedom to associate abstract mutation types with specific classes of events and to map the simulation output on a given sequence.

At many stages of the program, large quantities of random numbers have to be drawn from general probability distributions. For example, during the Wright-Fisher process, the parents of each child have to be drawn randomly from the individuals in the previous generation with probabilities proportional to their fitnesses, which can be different for each individual. The location of each recombination event is drawn from a user-defined recombination rate map that can vary arbitrarily along the genome. Similarly, the location of each new mutation, its type, and selection coefficient are drawn from distributions specified by the user. Hence, an efficient implementation for the drawing of random numbers from general discrete probability distributions is key for SLiM's computational performance. This is achieved through the use of precomputed lookup tables. For example, once all children have been created at the end of a generation, a lookup table is computed from their fitnesses (which has to be done only once per generation). In the next generation, random parents can then be drawn with probabilities proportional to their fitnesses with the help of this lookup table in $O(1)$ time. All random number generation algorithms in SLiM are implemented this way, using routines provided in the GSL [12].

SLiM records mutations that have become fixed in the population as substitutions. Such mutations can no longer cause fitness differences between individuals and should therefore be removed from the population in order to prevent unnecessary allocation of resources. If not removed, these mutations would accumulate over time and resources consumption would thus steadily increase. To efficiently remove all fixed mutations, every mutation has a counter that is reset to zero at the beginning of each generation and increased by one whenever the mutation is added to a new child genome. At the end of a generation mutations are screened for those that are present in $2N$ copies, which are then removed.

7.2 Algorithmic complexity

In a forward simulation, every individual in the population is modeled explicitly and N new children are created every generation. In each child, $L\pi$ mutations will be present on average, where L is the overall length of sequence regions in which mutations can occur and π is the average heterozygosity per site. All these mutations have to be copied into every new genome. Thus, the simulation of a single generation requires $O(NL\pi)$ time. If the simulation is to be run for T generations, the overall runtime is then expected to scale as $O(\pi LNT)$. Note that when simulating neutral evolution, the expected level of neutral heterozygosity is proportional to $N\mu$ and the simulation typically has to be run over at least N generations (the time-scale of drift). In this case, one expects a cubic dependency on population size.

Fortunately, for many analyses it is not primarily the actual population size that is relevant but rather products of the form Nu (overall rate at which new mutations arise), Ns (effective strength of selection), Nr (effective rate of recombination), and Nm (effective rate of migration). Simulations can thus often be sped up dramatically by modeling a much smaller population and simply rescaling all other parameters accordingly, as is commonly done in the field [5].

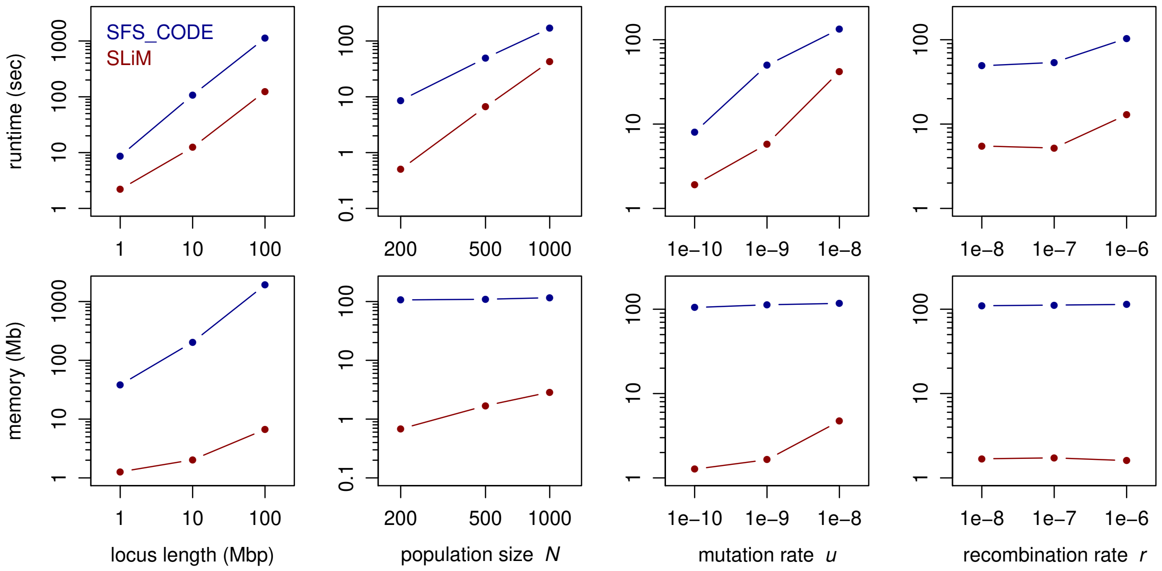


Figure 9. Comparison of runtimes and peak RSS memory requirements between SLiM and SFS_CODE under different evolutionary scenarios. In each column, one of the four parameters L, N, u, and r was varied, while the others were kept constant at their respective base values: $L = 5$ Mbp, $N = 500$, $u = 10^{-9}$ and $r = 1$ cM/Mbp. Simulations were run for $10N$ generations. Data points show the observed runtimes in seconds and peak RSS memory requirements in Megabytes obtained by averaging over 10 simulation runs.

7.3 Runtime and memory usage

We evaluated the performance of SLiM by comparing its runtime and memory requirements with that of SFS_CODE [5], a popular forward simulation of similar scope. For this test, a single chromosome of length L was simulated in a population of size N over the course of $10N$ generations (including burn-in). New mutations were introduced at a uniform rate u per site per generation and the selection coefficients of these mutations were drawn from an exponential distribution with mean $2N\bar{s} = -5$. Recombination occurred at a uniform rate r along the chromosome.

For the base scenario, we chose $L = 5$ Mbp, $N = 500$, $u = 10^{-9}$ and $r = 1$ cM/Mbp. We then varied the four parameters independently to analyze how each individually affects the runtime and memory consumption of the two programs. Since SFS_CODE is limited to simulating loci smaller than 10 Mbp, we simulated a corresponding number of linked loci of length 1 Mbp each. Simulations were conducted on a standard iMac desktop with a 2.8 Ghz Intel core 2 Duo CPU and 4 GB of memory. Figure 9 shows the measured runtimes and peak RSS memory requirements of the two programs.

In all analyzed scenarios, SLiM outcompetes SFS_CODE by a substantial margin, typically running 5 to 10 times faster and requiring 20 to 100 times less memory. The large discrepancy in memory consumption between the two programs likely reflects the fact that SFS_CODE simulates the entire sequence of a chromosome, whereas SLiM only simulates the actual mutations. Thus, even in a population with only low diversity, SFS_CODE will still always create and store an entire chromosome of length L base pairs. This is also consistent with the observation that in the analyzed scenarios the memory consumption of SFS_CODE depends strongly on the length of the simulated region, but only very weakly on population size and mutation rate, whereas in SLiM it depends on all three parameters.

The computational performance of SLiM enables simulations on the scale of entire eukaryotic chromosomes in reasonably large populations. For instance, simulating the evolution of the functional regions in a typical human chromosome of length $L = 100$ Mbp over 10^5 generations in a population of size $N = 10^4$ with $u = 10^{-8}$ per site per generation and $r = 1$ cM/Mbp, assuming a functional density of 5%, takes approximately four days on a single core. Here we again assumed an exponential DFE with $2N\bar{s} = -10$. Note that these values for population size, mutation rate, and recombination rate resemble commonly used population genetic estimates for human evolution.

Input parameter reference sheet

#MUTATION TYPES <mutation-type-id> <h> <DFE-type> [DFE parameters] ... m1 0.2 g -0.05 0.2 m2 0.0 f 0.0 m3 0.5 e 0.01	Each mutation type is specified by its dominance coefficient h and DFE type. The mutation type id can be any number but has to be preceded by the letter 'm', e.g. m3. DFE types can be: 1. fixed: f <s> 2. exponential: e <mean-s> 3. gamma: g <mean-s> <shape-alpha>
#MUTATION RATE <u>	Specifies the mutation rate per base pair per generation in all simulated genomic elements.
#GENOMIC ELEMENT TYPES <element-type-id> <mut-type> <x> [<mut-type> <x> ...] ... g1 m3 0.8 m2 0.01 m1 0.19	Each genomic element type is specified by the mutation types <mut-type> that are present in the element type and their relative proportions <x>. Element type ids always have to start with 'g', e.g. g2.
#CHROMOSOME ORGANIZATION <element-type> <start> <end> ... g2 1000 1999	Specifies the <start> and <end> position and the genomic <element-type> for the simulated genomic elements on the chromosome.
#RECOMBINATION RATE <interval-end> <r> ... 10000 1e-8 20000 4.5e-8	Specifies the recombination rates <r> for consecutive intervals along the chromosome. Rates are defined in expected recombination events per base pair per generation (1 cM/Mbp corresponds to $r = 10^{-8}$).
#GENERATIONS <t>	Specifies the overall number of generations after which the simulation will end.
#DEMOGRAPHY AND STRUCTURE <time> <event-type> [event parameters] ... 1 P p1 1000 1 S p1 0.2 1000 P p2 100 p1 2000 N p1 1e4 2000 M p2 p1 0.01	1. Adding a new population (population ids always have to start with 'p', e.g. p7): <time> P <pop> <N> [<source-pop>] 2. Changing population size: <time> N <pop> <N> 3. Changing migration rate (default 0.0): <time> M <target-pop> <source-pop> <m> (<m>: fraction of target population made up of migrants from source population in each generation) 4. Changing selfing rate (default 0.0): <time> S <pop> <σ> (<σ>: probability of self-fertilization in population <pop>)
#OUTPUT (optional) <time> <output-type> [output parameters] ... 2000 A outfile 1000 R p1 10 2000 F 1 T m3	1. Output state of entire population: <time> A [<file>] 2. Output random sample from subpopulation: <time> R <pop> <size> 3. Output list of all fixed mutations: <time> F 4. Track mutations of particular type: <time> T <mut-type>
#GENE CONVERSION (optional) <fraction> <stretch-length> ... 0.2 25	Specifies the <fraction> of recombination events that result in gene conversion rather than crossing-over (which happens in the remaining fraction of events). The length of the conversion stretch is drawn from a geometric distribution with mean <stretch-length>.
#PREDETERMINED MUTATIONS (optional) <time> <mut-type> <x> <s> <h> <pop> <nAA> <nAa> [P <f>] ... 5000 m7 45000 0.05 0.5 p1 0 1 8000 m9 2e5 0.02 1.0 p1 0 10 P 0.5	Introduces a mutation with selection coefficient <s> and dominance coefficient <h> at position <x> in <nAA> homozygotes and <nAa> heterozygotes in population <pop>. Use a unique <mut-type> id for this mutation if it should be tracked individually and easily identified in the output. The option P <f> specifies a partial sweep, where s is set to zero once the mutation has reached population frequency <f>.
#INITIALIZATION (optional) <file>	Initializes the simulation with the mutations, genomes, and populations specified in <file>.
#SEED (optional) <seed>	Specifies the value of the seed used for the random number generator $(-2^{31} \dots 2^{31})$.

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References

[1] Liu Y, Athanasiadis G, Weale ME (2008) A survey of genetic simulation software for population and epidemiological studies. Hum Genomics 3: 79–86.

[2] Carvajal-Rodriguez A (2010) Simulation of genes and genomes forward in time. Curr Genomics 11: 58–61.

[3] Hoban S, Bertorelle G, Gaggiotti OE (2011) Computer simulations: tools for population and evolutionary genetics. Nat Rev Genet 13: 110–122.

[4] Ewing G, Hermisson J (2010) MSMS: a coalescent simulation program including recombination, demographic structure and selection at a single locus. Bioinformatics 26: 2064–2065.

[5] Hernandez RD (2008) A flexible forward simulator for populations subject to selection and demography. Bioinformatics 24: 2786–2787.

[6] Chadeau-Hyam M, Hoggart CJ, O'Reilly PF, Whittaker JC, De Iorio M, et al. (2008) Fregene: simulation of realistic sequence-level data in populations and ascertained samples. BMC Bioinformatics 9: 364.

[7] Padhukasahasram B, Marjoram P, Wall JD, Bustamante CD, Nordborg M (2008) Exploring population genetic models with recombination using efficient forward-time simulations. Genetics 178: 2417–2427.

[8] Carvajal-Rodriguez A (2008) GENOMEPOP: a program to simulate genomes in populations. BMC Bioinformatics 9: 223.

[9] Peng B, Kimmel M (2005) simuPOP: a forward-time population genetics simulation environment. Bioinformatics 21: 3686–3687.

[10] Fisher R (1930) The genetical theory of natural selection. Oxford: Clarendon Press.

[11] Charlesworth B, Charlesworth D (2010) Elements of Evolutionary Genetics. Greenwoord Village, Colorado, USA: Roberts and Company.

[12] Galassi M, Davies J, Theiler J, Gough B, Jungman G, et al. (2009) GNU scientific library: Reference manual. Bristol, UK: Network Theory, 3rd edition.

[13] Eyre-Walker A, Keightley PD (2007) The distribution of fitness effects of new mutations. Nat Rev Genet 8: 610–618.

[14] L'Ecuyer P (1996) Maximally equidistributed combined tausworthe generators. Math Comput 65: 203-213.

[15] Wakeley J (2008) Coalescent Theory: An Introduction. Greenwood Village, Colorado: Roberts & Company Publishers.

[16] Charlesworth B (2009) Fundamental concepts in genetics: effective population size and patterns of molecular evolution and variation. Nat Rev Genet 10: 195–205.

[17] Kimura M (1983) The Neutral Theory of Molecular Evolution. Cambridge: Cambridge University Press.

[18] Barton NH (2000) Genetic hitchhiking. Philos Trans R Soc Lond, B, Biol Sci 355: 1553–1562.