
Expanding the `stdpopsim` species catalog, and lessons learned for realistic genome simulations

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Abstract

Simulation is a key tool in population genetics for both methods development and empirical research, but producing simulations that recapitulate even the main features of genomic datasets remains a major obstacle. Today, more realistic simulations are possible thanks to large increases in the quantity of available data and the sophistication of inference and simulation software. However, implementing these simulations ~~can~~ require still requires substantial time and specialized knowledge. These challenges are especially pronounced for simulating less well-studied species, since it is not always clear what level of realism is sufficient to confidently answer a given question, or what information is required to produce simulations of that desired realism. `stdpopsim` is a community-developed framework that seeks to lower this barrier by making it easy to simulate complex population genetic models using up-to-date information. The initial version of `stdpopsim` ~~, the species catalog contained information for six species, most of which are focused on establishing this framework using six~~ well-characterized model ~~organisms~~ species. Here, we report on updates made in the new release of `stdpopsim` (version 0.2) ~~. In particular, we describe the~~ , which include substantial additions to simulation capabilities and a significant expansion of the species catalog. Features added to improve the realism of the simulated genomes include non-crossover recombination and provision of species-specific genomic annotations. Expansion of the species catalog involved community-driven ~~efforts to expand the catalog~~ efforts to increase coverage more broadly across the tree of life ~~, which now contains to~~ 21 species, with 25 demographic models and 37 genetic maps. Our experience ~~through the community engagement involved in~~ throughout this process was that people are indeed keen to put in the time and effort to include their study species, but that simple, clear guidance is vital. Our intention with this paper is in part to provide another learning modality to meet that need, by reporting on the main lessons learned through this process for best practices in population genomic simulation. We describe the input data required for generating a realistic simulation, suggest good practices for obtaining the relevant information, and discuss common pitfalls and major considerations. ~~We also introduce several major advances to the realism of 's simulation ability, including non-crossover recombination and provision of species-specific genomic annotations. Together, these~~ These advances to `stdpopsim` ~~will strengthen efforts to use and develop simulation-based population genomic inference methods, with particular advances for~~ aim to further promote the use of realistic whole-genome population genetic simulations, especially in non-model organisms, making them available, transparent, and accessible to everyone.

Introduction

Dramatic reductions in sequencing costs are enabling the generation of unprecedented amounts of genomic data for a huge variety of species (Ellegren, 2014). Ongoing efforts to systematically sequence life on Earth by initiatives such as the Earth Biogenome (Lewin et al., 2022) and its affiliated project networks (for example, Vertebrate Genomes (Rhie et al., 2021), 10,000 Plants (Cheng et al., 2018) and others (Darwin Tree of Life Project Consortium, 2022)) are providing the backbone for enormous increases in the amount of population-level genomic data available for model and non-model species. These data are being used to answer questions across scales from deep evolutionary time to ongoing ecological dynamics. Methods that use these data, for example to infer demographic history and natural selection, are also flourishing (Beichman et al., 2018). While past methods development focused on humans and a few key model systems such as

Drosophila, more recent efforts are generalizing these methods to include important population dynamics not initially accounted for, such as inbreeding or selfing (Blischak et al., 2020), skewed offspring distributions (Montano, 2016), and intense artificial selection (MacLeod et al., 2013, 2014).

Simulations can be useful at all stages of this work – for planning studies, analyzing data, testing inference methods, and validating findings from empirical and theoretical research. For instance, simulations provide training data for inference methods based on machine learning (Schridder and Kern, 2018) and Approximate Bayesian Computation (Csilléry et al., 2010). They can also serve as baselines for further analyses: for example, simulations incorporating demographic history serve as null models when detecting selection (Hsieh et al., 2016) or seed downstream breeding program simulations (Gaynor et al., 2020). More recently, population genomic simulations have begun to be used to help guide conservation decisions for threatened species (Teixeira and Huber, 2021; Kyriazis et al., 2022).

Increasing amounts of data and sophistication of inference methods have enabled researchers to ask ever more specific and precise questions. Consequently, simulations must incorporate more and more detailed elements of a species’ biology. Important elements include genomic features such as mutation and recombination rates that strongly affect genetic variation and haplotype structure (Nachman, 2002). These have particularly strong ramifications when linked selection is important in the patterns of genomic diversity being studied (Cutter and Payseur, 2013). Furthermore, the demographic history of a species, encompassing population sizes and distributions, divergences, and gene flow, can dramatically affect patterns of genomic variation (Teshima et al., 2006). Thus species-specific estimates of these and other ecological and evolutionary parameters (e.g., those governing the process of natural selection) are fundamentally important when developing simulations. This presents challenges, especially to new researchers, as it takes a great deal of specialized knowledge not only to code the simulations themselves but also to find and choose appropriate estimates of the parameters underlying the simulation model.

`Stdpopsim` is a community resource recently developed to provide easy access to detailed population genomic simulations (Adrion et al., 2020). It lowers the technical barriers to performing these simulations and reduces the possibility of erroneous implementation of simulations for species with published demographic models. The initial release of `stdpopsim` was restricted to only six well-characterized model species, such as *Drosophila melanogaster* and *Homo sapiens*, but feedback we received from the community identified a widespread desire to simulate a wider range of non-model species, and ideally to incorporate these into the `stdpopsim` catalog for future use. This feedback, and subsequent efforts to expand the catalog, also uncovered the need for a better understanding of when it is practical to create a realistic simulation of a species of interest, and indeed what “realistic” means in this context.

This paper reports on the updates made in the current release of `stdpopsim` (version 0.2), and is also intended as a resource for any researcher who wishes to develop whole-genome simulations for their own species of interest. We start by describing the main idea behind the standardized simulation framework of `stdpopsim`, and then outline the main updates made to the `stdpopsim` catalog and simulation framework in the past two years. We then devote a major section of the paper to provide guidelines for generating population genomic simulations, either for the purpose of using them in one specific study, or with the intent of adding these simulations to `stdpopsim`. Among other things, we discuss when a whole-genome simulation is more useful than simulations based on either individual loci or generic (non-species specific) loci. We specify the required input data, mention common pitfalls in choosing appropriate parameters, and suggested courses of action for species that are missing estimates of some necessary inputs. We conclude with examples from a couple of species recently added to `stdpopsim`, which demonstrate some of the main considerations involved in the process of designing realistic whole-genome simulations. While the guidelines provided in this paper are intended for any researcher interested in implementing a population genomic simulation using any software, we do highlight the ways in which the framework set up by `stdpopsim` eases the burden involved in this process.

The utility of `stdpopsim` for genome-wide simulations

We begin by providing a brief overview of the importance of genome-wide simulations and the main rationale behind `stdpopsim`; see Adrion et al. (2020) for more on the topic. The main objective of population genomic simulations is to recreate patterns of sequence variation along the genome under known conditions that

model a given species (or population) of interest. `stdpopsim` is built on top of the `msprime` (Kelleher et al., 2016; Nelson et al., 2020; Baumdicker et al., 2021) and `SLiM` (Haller and Messer, 2019) simulation engines, ~~that~~ which are capable of producing fairly realistic patterns of sequence variation if provided with accurate descriptions of the genome architecture and evolutionary history of the simulated species. The required parameters include the number of chromosomes and their lengths, mutation and recombination rates, the demographic history of the simulated population, and, potentially, the landscape of natural selection along the genome. A key challenge when setting up a population genomic simulation is to obtain estimates of all of these quantities from the literature and then correctly implement them in an appropriate simulation engine. Detailed estimates of all of these quantities are increasingly available due to the growing availability of population genomic data coupled with methodological advances. Incorporating this data into a population genomic simulation often involves integrating this data between different literature sources, which can require specialized knowledge of population genetics theory. Thus, the process of coding a realistic simulation can be quite time consuming and often error-prone.

The main objective of `stdpopsim` is to streamline this process, and to make it more robust and more reproducible. Contributors collect parameter values for their species of interest from the literature, and then specify these parameters in a template file for the new model. This model then goes through a vital peer-review process, which involves recreating the model based on the provided documentation, and executing automated scripts to compare the two models. If discrepancies are found in this process, they are resolved by discussion between the contributor and reviewer, and if necessary with input of additional members of the community. This quality control process quite often finds subtle bugs (e.g., as in Ragsdale et al., 2020) or highlights parts of the model that are ambiguously defined by the literature sources. ~~Importantly, this~~ This increases the reliability of the resulting simulations in any downstream analysis.

Another ~~central~~ important goal of `stdpopsim` is to promote whole-genome simulations, as opposed to the common practice of simulating many short segments (see, e.g., Harris and Nielsen, 2016). Simulation of long sequences, on the order of 10^7 bases, has until recently been computationally prohibitive, but this has changed with the development of modern simulation engines, such as `msprime` and `SLiM`. Generating chromosome-scale simulations has several ~~important~~ key benefits. First, the organization of genes on chromosomes is a key feature of a species' genome that is ~~clearly ignored in~~ ignored in many traditional population genomic simulations (see Schrider (2020) for a notable exception). Second, modeling physical linkage allows simulations to capture important correlations between genetic variants along the same chromosomes. These correlations reduce variance relative to independent simulations of equivalent genetic material. This has a particularly striking effect in long stretches of low recombination rates, as observed for instance on the long arm of human chromosome 22 (Dawson et al., 2002). In bacteria, a similar effect occurs due to genome-wide linkage that is broken only by recombination of short segments ~~Didelot and Maiden (2010)~~ (Didelot and Maiden, 2010). When conducting simulations with natural selection, linkage has an even stronger effect. Selection acting on a small number of sites can indirectly influence levels and patterns of genetic variation at linked neutral sites, which has been shown to have a widespread effect on patterns of genome variation in myriad species (e.g., McVicker et al., 2009; Charlesworth, 2012). In addition, the lengths of chromosome-scale shared haplotypes within and between populations provides valuable information on their demographic history. Demography inference methods that use such information, such as MSMC (Schiffels and Wang, 2020), or IBDNe (Browning and Browning, 2015), perform best on long genomic segments with realistic recombination rates. Chromosome-scale simulations are clearly required to test (or, train) such methods, or to conduct power analyses for design of empirical studies that use them.

Additions to stdpopsim

~~Since its initial publication in Adrion et al. (2020), we have increased the number of species in the catalog nearly fourfold, added multiple demographic models and genetic maps, and improved the simulation framework of in several ways.~~

When first published, the `stdpopsim` catalog included six species: *Homo sapiens*, *Pongo abelii*, *Canis familiaris*, *Drosophila melanogaster*, *Arabidopsis thaliana*, and *Escherichia coli* (Figure 1). One way the catalog has expanded is through introduction of additional demographic models for *Homo sapiens*, *Pongo abelii*, *Drosophila melanogaster*, and *Arabidopsis thaliana*, enabling a wider variety of simulations for these

mostly model thoroughly studied species. However, ~~these species represent the initial collection of six species~~ represents a small slice of the tree of life. This is a concern not only because there is a large community of researchers studying other organisms, but also because methods developed for application to model species (such as humans) may not perform well when applied to other species with very different biology. Adding species to the `stdpopsim` catalog will allow developers to easily test their methods across a wider variety of organisms.

We thus made a concerted effort to recruit members of the population and evolutionary genetics community to add their species of interest to the `stdpopsim` catalog. This effort involved a series of workshops to introduce potential contributors to `stdpopsim`, followed by a “Growing the Zoo” hackathon organized alongside the 2021 ProbGen conference. The seven workshops allowed us to reach a broad community of more than 150 researchers, many of whom expressed interest in adding non-model species to `stdpopsim`. The hackathon was then structured based on feedback from these participants. One month before the hackathon, we organized a final workshop to prepare interested participants for the hackathon, by introducing them to the process of developing a new species model and adding it to the `stdpopsim` code base. Roughly 20 scientists participated in the hackathon, which resulted in the addition of 15 species to the `stdpopsim` catalog (Figure 1). The catalog now includes a teleost fish (*Gasterosteus aculeatus*), a bird (*Anas platyrhynchos*), a reptile (*Anolis carolinensis*), a livestock species (*Bos taurus*), six insects including two vectors of human disease (*Aedes aegypti* and *Anopheles gambiae*), a nematode (*Caenorhabditis elegans*), two flowering plants including a crop (*Helianthus annuus*), an algae (*Chlamydomonas reinhardtii*), two bacteria, four primates and a common mammalian associate of primates (*Canis familiaris*). Not all of these have genetic maps or demographic models (see Figure 1), but this lays the framework for future contributions.

Expanding the species catalog required adding several functionalities to the simulation framework of `stdpopsim`. Some features were added by upgrading the neutral simulation engine, `msprime`, from version 0.7.4 to version 1.0. (Baumdicker et al., 2021). Among other things, this upgrade includes a discrete site model of mutation, which enables simulating sites with multiple mutations and possibly more than two alleles. Another key functionality added to the simulation framework of `stdpopsim` was modeling of non-crossover recombination. In bacteria and archaea, recombination occurs primarily through the transfer of DNA segments from one organism to another (Thomas and Nielsen, 2005; Didelot and Maiden, 2010; Gophna and Altman-Price, 2022). As a result, such species cannot be realistically simulated with a recombination model that considers only crossovers, as did the initial version of `stdpopsim`. To address this, we made use of features of the `msprime` and `SLiM` simulation engines for modeling non-crossover recombination. Modeling recombination in a bacterial or (archaeal) species in `stdpopsim` is done by setting a flag in the species model to indicate that recombination should be modeled without crossovers, and specifying an average recombination tract length. For example, the model for *Escherichia coli* has been updated in the `stdpopsim` catalog to use non-crossover recombination at an average rate of 8.9×10^{-11} (per base per generation), with an average tract length of 542 bases (Wielgoss et al., 2011; Didelot et al., 2012).

Recombination without crossover is also prevalent in sexually reproducing species, where it is termed *gene conversion*. Gene conversion affects shorter segments than crossover recombination and creates distinct patterns of genetic diversity along the genome (Korunes and Noor, 2017). Indeed, gene conversion rates in some species are estimated to occur at similar or even higher rates than crossover recombination (Gay et al., 2007; Comeron et al., 2012; Wijnker et al., 2013). To accommodate this in `stdpopsim` simulations, one needs to specify the fraction of recombinations that occur due to gene conversion (i.e., without crossover), and the average tract length. For example, the model for *Drosophila melanogaster* has been updated in the `stdpopsim` catalog to have a fraction of gene conversions of 0.83 (in all chromosomes with recombination) and an average tract length of 518 bases (Comeron et al., 2012). We note, however, that since non-crossover recombination incurs a high computation load in simulation, it is turned off by default in `stdpopsim`, and must be explicitly invoked by the simulation model.

Another important extension of `stdpopsim` allows augmenting a genome assembly by genome annotations, such as coding regions, promoters, conserved elements, etc. These annotations can be used to simulate selection at a subset of sites (e.g., the annotated coding regions) using parametric distribution(s) of fitness effects. Standardized, easily accessible simulations that include the reality of pervasive linked selection in a species-specific manner has long been identified as a goal for evolutionary genetics (e.g., McVicker et al., 2009; Comeron, 2014). Thus, we expect this extension of `stdpopsim` to be transformative in the way simulations are carried out in population genetics. These significant new capabilities of the `stdpopsim` library will be

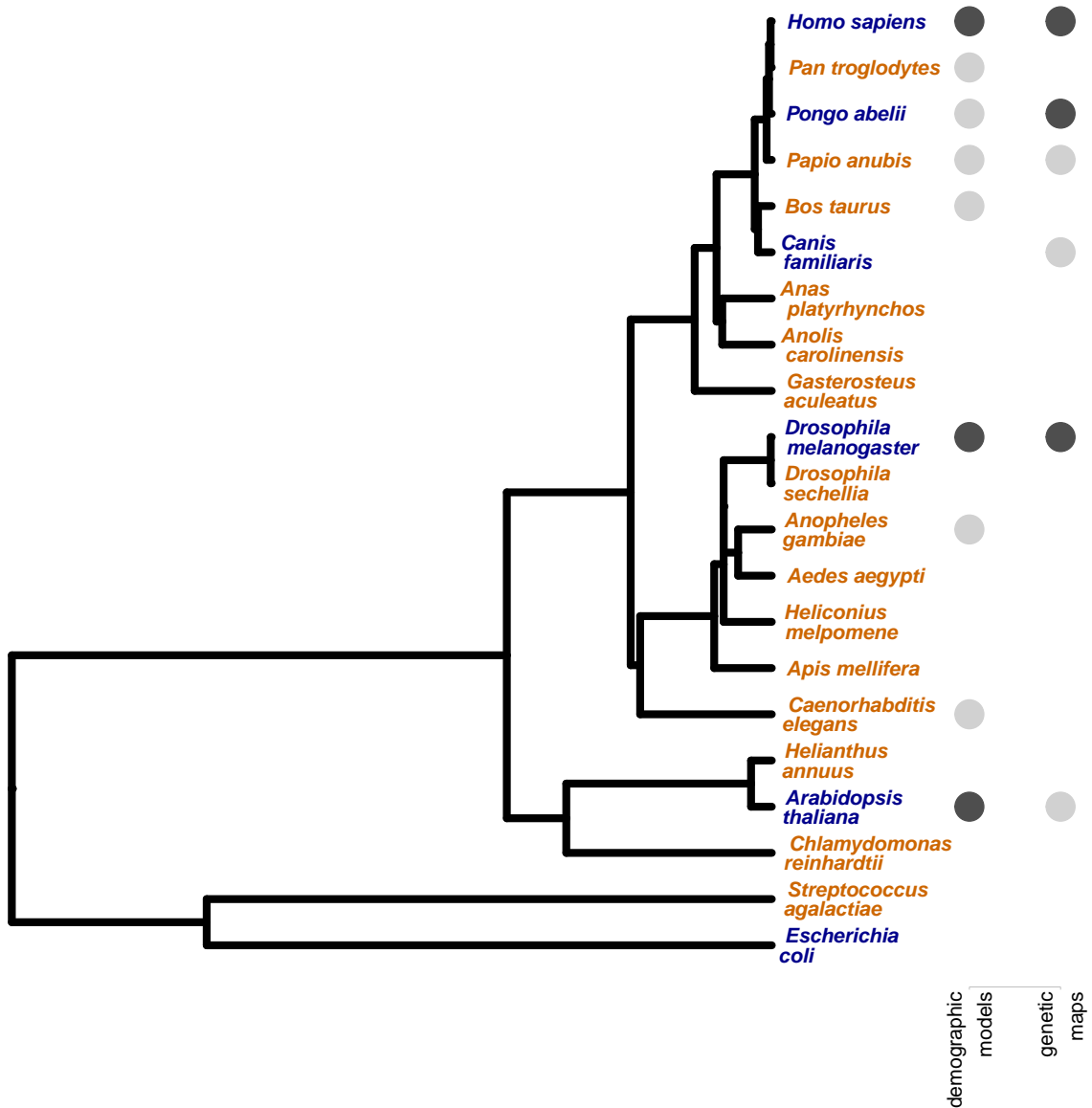


Figure 1: Phylogenetic tree of species available in the `stdpopsim` catalog, including the six species we published in the original release (Adrion et al., 2020, in blue), and 15 species that have since been added (in orange). Solid circles indicate species that have one (light grey) or more (dark grey) demographic models and genetic maps. [Branch length were derived from the divergence times provided by TimeTree5 \(Kumar et al., 2022\).](#)

detailed in a forthcoming publication, and are not the focus of this paper.

Guidelines for implementing a population genomic simulation

The concentrated effort to add species to the `stdpopsim` catalog has led to a series of important insights about this process, which we summarize [in the following section here](#) as a set of guidelines for implementing realistic simulations [of for](#) any species. Our intention is to provide general guidance that applies to any population genomic simulation software, but we also mention specific requirements that apply to simulations done in the framework of `stdpopsim`.

Basic setup for chromosome-level simulations

Implementing a realistic population genomic simulation for a species of interest requires a fairly detailed description of the organism’s demography and mechanisms of genetic inheritance. While simulation software requires unforgivingly precise values, in practice, we may only have rough guesses for most of the parameters describing these processes. In this section, we list these parameters and provide guidelines for how to set them based on current knowledge.

1. **A chromosome-level genome assembly**, which consists of a list of chromosomes or scaffolds and their lengths. Having a good quality assembly with complete chromosomes, or at least very long scaffolds, is necessary if chromosome-level population genomic simulations are to reflect the genomic architecture of the species. Currently, the number of species with complete chromosome-level assemblies is small, but we expect this number to dramatically increase in the near future due to genome initiatives such as the Earth Biogenome (Lewin et al., 2022) and its affiliated project networks (e.g., Vertebrate Genomes (Rhie et al., 2021), 10,000 Plants (Cheng et al., 2018)). Furthermore, the development of new long-read sequencing technologies (Amarasinghe et al., 2020, 2021) and concomitant advances in assembly pipelines (Chakraborty et al., 2016) are likely to boost these initiatives. When expanding the `stdpopsim` catalog, we decided to focus on species with near-complete chromosome-level genome assemblies (i.e., close to one contig per chromosome). This restriction was set mainly because species with less complete genome builds typically do not have good estimates of recombination rate or genetic maps, making chromosome-level simulation much less useful. Therefore, the utility of adding such species to the catalog does not justify the maintenance and storage burden incurred by the large number of contigs in these partial assemblies (see also discussion below).
2. **An average mutation rate** for each chromosome (per generation per bp). This rate estimate can be based on sequence data from pedigrees, mutation accumulation studies, or comparative genomic analysis calibrated by fossil data (i.e., phylogenetic estimates). At present, `stdpopsim` simulates mutations at a constant rate under the Jukes-Cantor model of nucleotide mutations (Jukes and Cantor, 1969). However, we anticipate future development will provide support for more complex, heterogeneous mutational processes, as these are easily specified in both the `SLiM` and `msprime` simulation engines. Such progress will further improve the realism of simulated genomes, since mutation rates and processes are known to vary along the genome and through time (Benzer, 1961; Ellegren et al., 2003; Supek and Lehner, 2019).
3. **Recombination rates** (per generation per bp). Ideally, a population genomic simulation should make use of a chromosome-level **recombination map**, since the recombination rate is known to vary widely across chromosomes (Nachman, 2002), and this can strongly affect the patterns of linkage disequilibrium and shared haplotype lengths. When this information is not available, we suggest specifying an average recombination rate for each chromosome. At minimum, an average genome-wide recombination rate needs to be specified, which is typically available for well assembled genomes. Recall that for bacteria and archaea, which primarily experience non-crossover recombination, the average tract length should also be specified (see details in previous section). If one wishes to model gene conversion together with crossover recombination, then they should specify the fraction of recombinations done by gene conversion as well as the average tract length (per chromosome).

4. **A demographic model** describing ancestral population sizes, split times and migration rates. Selection of a reasonable demographic model is often crucial, since misspecification of the model can generate unrealistic patterns of genetic variation that will affect downstream analyses (e.g., Navascués and Emerson, 2009). A given species might have more than one demographic model, fit from different data or by different methods. Thus, when selecting a demographic model, one should examine the data sources and methods used to obtain it to ensure that they are relevant to their study. At a minimum, simulation requires a single estimate of **effective population size**. This estimate, which may correspond to some sort of historical average effective population size, should reproduce in simulation the average observed genetic diversity in that species. Note, however, that this average effective population size will not capture features of genetic variation that are caused by recent changes in population size and the presence of population structure (MacLeod et al., 2013; Eldon et al., 2015). For example, a recent population expansion will produce an excess of low frequency alleles that no simulation of a constant-sized population will reproduce (Tennessen et al., 2012).
5. **An average generation time** for the species. This parameter is an important part of the species' natural history. This value does not directly affect the simulation, since `stdpopsim` uses either the Wright-Fisher model (in `SLiM`) or the Moran model (in `msprime`), both of which operate in time units of generations. Thus, the average generation time is only currently used to convert time units to years, which is useful when comparing among different demographic models.

These five categories of parameters are sufficient for generating simulations under neutral evolution. Such simulations are useful for a number of purposes, but they cannot be used to model the influence of natural selection on patterns of genetic variation. As mentioned above, it is a widely appreciated fact that linked selection modulates patterns of variation within genomes. Therefore, its incorporation into simulations is crucial for many purposes. To achieve this, the simulator needs to know which regions along the genome are subject to selection, and the nature and strength of this selection. The current version of `stdpopsim` enables simulation with selection (using the `SLiM` engine) by specifying genome annotations and distributions of fitness effects, as specified below. We note that the ability to simulate chromosomes with realistic models of selection is still under development and will be finalized in the next release of `stdpopsim`.

6. **Genome annotations**, specifying regions subject to selection (e.g., as GFF3/GTF file). For instance, annotations can contain information on the location of coding regions, the position of specific genes, or conserved non-coding regions. Regions not covered by the annotation file are assumed to be neutrally evolving.
7. **Distributions of fitness effects** (DFEs) for each annotation. Each annotation is associated with a DFE describing the probability distribution of selection coefficients (deleterious, neutral, and beneficial) for mutations occurring in the region covered by the annotation. DFEs can be inferred from population genomic data (reviewed in Eyre-Walker and Keightley, 2007), and are available for several species (e.g., Ma et al., 2013; Huber et al., 2018).

Extracting parameters from the literature

Simulations cannot of course precisely match reality, but in setting up simulations it is desirable to choose parameters that best reflect our current understanding. In practice a researcher may choose each parameter to match a fairly precise estimate or a wild guess, which may be obtained from a peer-reviewed publication or from word of mouth. However, values in `stdpopsim` are always chosen to match published estimates, so that the underlying data and methods are documented and can be validated. Because the process of converting information reported in the literature to parameters used by a simulation engine is quite error-prone, some kind of independent validation of the simulation code is crucial. We highly recommend following a quality control procedure similar to the one used in `stdpopsim`, in which each species or model added to the catalog is independently recreated or thoroughly reviewed by a separate researcher.

Obtaining reliable and citeable estimates for all model parameters is not a trivial task. Oftentimes, values for different parameters must be gleaned from multiple publications and combined. For example, it is not uncommon to find an estimate of a mutation rate in one paper, a recombination map in a separate paper, and

a suitable demographic model in a third paper. Integrating information from different publications requires some care, because some of these parameter estimates are entangled in non-trivial ways. For instance, consider simulating a demographic model estimated in a specific paper that assumes a certain mutation rate. Naively using the demographic model, as published, with a new estimate of mutation rate will lead to levels of genetic diversity that do not fit the genomic data. This is addressed in `stdpopsim` by allowing a demographic model to be simulated using a mutation rate that differs from the default rate specified for the species. See, for example, the model implemented for *Bos taurus*, which is described in the next section. This important feature does not necessarily fix all potential inconsistencies caused by assumptions made by the demographic inference method (such as assumptions on recombination rates). It is therefore recommended, when possible, to take the demographic model, mutation rates, and recombination rates from the same study, and to proceed carefully when mixing sources. An additional tricky source for inconsistency is coordinate drift between subsequent versions of genome assemblies. In `stdpopsim`, we follow the approach from the UCSC Genome Browser and use `liftover` to convert the coordinates of genetic maps and genome annotations that we curate to the coordinates of the genome assembly we use for that species.

Filling out the missing pieces

For many species it is difficult to obtain estimates of all necessary model parameters. Table 1 provide suggestions for ways to deal with missing values of various central model parameters. The table also mentions the main discrepancies between the simulated data and real genomic data, which can be caused by mis-specification of each parameter.

Several researchers who participated in the “Growing the Zoo” hackathon wished to add species whose genome assemblies are composed of many relatively small contigs, unanchored to chromosome-level scaffolds. Although we had not previously put restrictions on which species might be added, we decided that we would only add species with chromosome-level assemblies. The main justification for this restriction is that species with less complete genome builds typically do not have good estimates of recombination rate, genetic maps, and demographic models, making chromosome-level simulation much less useful in such species. Another issue is the storage burden and long load times involved in dealing with hundreds of contigs. Finally, each species requires validation of its code before it is added to the `stdpopsim` catalog, as well as long-term maintenance to keep it up-to-date ~~after changes with changes made~~ to the `stdpopsim` framework. So, the benefit of including species with very partial genome builds in `stdpopsim` would be outweighed by the substantial extra burden on `stdpopsim` maintainers as well as downstream users of these models.

That being said, simulation is still ~~possible and~~ potentially useful for species with partial genome builds. One way to deal with this situation is to ~~include only treat~~ the longer contigs or scaffolds ~~, treating them in these builds~~ as separate chromosomes in the simulation. ~~Some of these contigs will~~ This approach allows us to model genetic linkage within each contig, but linkage between different contigs that map to the same chromosome ~~, so simulating them separately will not capture the genetic linkage between them. However,~~

Table 1: **Guidelines for dealing with missing parameters.** For each parameter, we provide a suggested course of action, and mention the main discrepancies between the simulated data and real genomic data, which can be caused by mis-specification of that parameter.

Missing parameter	Suggested action	Possible discrepancies
Mutation rate	Borrow from closest relative with a citeable mutation rate	Number of polymorphic sites
Recombination rate	Borrow from closest relative with a citeable recombination rate	Patterns of linkage disequilibrium
Gene conversion rate and tract length	Set rate to 0 or borrow from closest relative with a citeable rate	Lengths of shared haplotypes across individuals
Demographic model	Set the effective population size (N_e) to a value that reflects the average observed genetic diversity in the simulated population	Features of genetic diversity that are captured by the site frequency spectrum, such as the prevalence of low-frequency alleles

~~this will not be captured by the simulation. This~~ provides a reasonable approximation for many purposes, at least for genomic regions far from the contig edges. Short contigs can either be omitted from simulation, or lumped together into one (or several) longer pseudo-chromosome(s). ~~Creating pseudo-chromosomes allows the simulation to fit~~ When lumping short contigs together, one should weigh the benefits of fitting the amount of data of real genomes, ~~but it artificially increases the~~ and capturing the linkage structure within each contig, against the adverse effects of inducing false or inaccurate correlation between variants from different contigs. In some extreme cases, a species genome build may solely be comprised of very short sequence contigs. One viable option in such a case is to simulate an anonymous chromosome from which patterns of genetic variation can be extracted (if important, in chunks of size similar to the contigs). Despite not providing an accurate model for linkage along chromosomes, this artificial construct does have some benefits, such as reproducing the main statistical properties of background selection. Finally, we note that for some ~~situations purposes~~ it may be sufficient to ~~rely on simulation of simulate~~ a large number of unlinked sites (Gutenkunst et al., 2009; Excoffier et al., 2013), which can be generated without any sort of genome assembly. However, this approach would not have the many benefits of whole-chromosome simulations, which we ~~discussed in detail earlier~~ promote in stdpopsim.

Examples of added species

In this section, we provide examples of two species recently added to the stdpopsim catalog, *Anopheles gambiae* and *Bos taurus*, to demonstrate ~~some of~~ the key considerations of the process.

Anopheles gambiae (mosquito)

Anopheles gambiae, the African malaria mosquito, is a non-model organism whose population history has direct implications for human health. Several large-scale studies in recent years have provided information

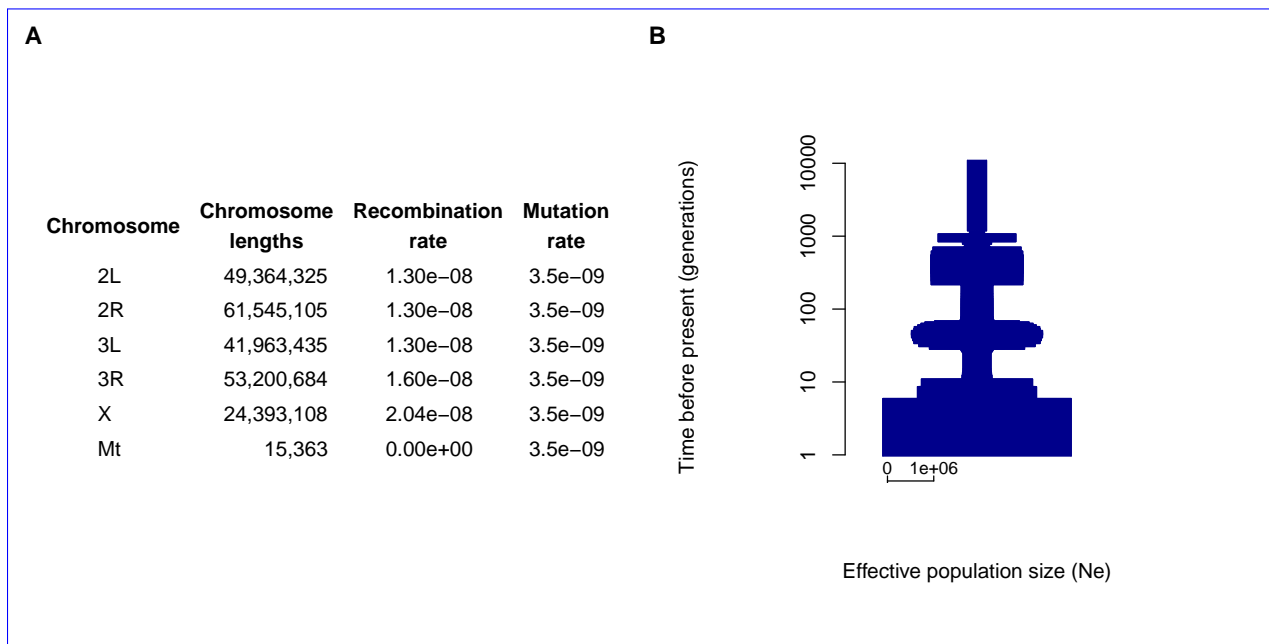


Figure 2: The species parameters and demographic model used for *Anopheles gambiae* in the stdpopsim catalog. (A) The parameters associated with the genome build and species, including chromosome lengths, average recombination rates (per base per generation), and average mutation rates (per base per generation). (B) A graphical depiction of the demographic model, which consists of a single population whose size changes throughout the past 11,260 generations in 67 time intervals. ~~The width at each point depicts the effective population size (Ne), with the horizontal bar at the bottom indicating the scale for Ne=10⁶.~~

about the population history of this species on which population genomic simulations can be based (e.g., Miles et al., 2017; Clarkson et al., 2020). The genome assembly structure used in the species model is based on the AgamP4 **genome assembly** (Sharakhova et al., 2007), which was downloaded from Ensembl (Howe et al., 2020) via `stdpopsim`'s utilities that interact with Ensembl. These utilities make it easy to accurately retrieve basic genome information and construct the appropriate Python data structures.

Estimates of average **recombination rates** for each of the chromosomes (excluding the mitochondrial genome) were taken from a recombination map inferred by Pombi et al. (2006) which itself included information from Zheng et al. (1996) (Figure 2A). As direct estimates of **mutation rate** (e.g., via mutation accumulation) do not currently exist for *Anopheles gambiae*, we used the genome-wide average mutation rate of $\mu = 3.5 \times 10^{-9}$ mutations per generation per site, estimated for *D. melanogaster* by Keightley et al. (2009) and used for analysis of *A. gambiae* data in Miles et al. (2017). To obtain an estimate for the default **effective population size** (N_e), we used the formula $\theta = 4\mu N_e$, with the above mutation rate ($\mu = 3.5 \times 10^{-9}$), and a mean nucleotide diversity of $\theta \approx 0.015$, as reported by Miles et al. (2017) for the Gabon population. This resulted in an estimate of $N_e = 1.07 \times 10^6$, which we rounded down to one million. These steps were documented in the code for the `stdpopsim` species model, to facilitate validation and future updates. We acknowledge that some of these steps involve somewhat arbitrary choices, such as the choice of the Gabon population and rounding down of the final value. However, this should not be seen as a considerable source of misspecification, since this value of N_e is meant to provide only a rough approximation to historic population sizes, which is to be overwritten by a more detailed demographic model.

Miles et al. (2017) inferred **demographic models** from *Anopheles* samples from nine different populations (locations) using the stairway plot method (Liu and Fu, 2015). We chose to include in `stdpopsim` the model inferred from the Gabon sample, which consists of a single population whose size ~~changes throughout the past 11,260 generations in 67 time intervals (Figure 2B)~~ ~~During this time period, the population size was inferred to have~~ fluctuated from below 80,000 (an ancient bottleneck roughly 10,000 generations ago) to the present-day estimate of over 4 million individuals (Figure 2B). To convert the timescale from generations to years, we used an average generation time of 1/11 years, as in Miles et al. (2017).

All of these parameters were set in the appropriate source files in the `stdpopsim` catalog, accompanied by the relevant citation information, and the model underwent the standard quality control process. The model may be refined in the future by adding more demographic models, updating or refining the recombination map, or updating the mutation rate estimates based on ones directly estimated for this species. Note that even if the mutation rate is ever updated, the demographic model mentioned above should still be associated with the current mutation rate ($\mu = 3.5 \times 10^{-9}$), since this was the rate used in its inference.

Bos taurus (cattle)

Bos taurus (cattle) was added to the `stdpopsim` catalog during the 2020 hackathon because of its agricultural importance. Agricultural species experience strong selection due to domestication and selective breeding, leading to a reduction in effective population size. These processes, as well as admixture and introgression, produce patterns of genetic variation that can be very different from typical model species (Larson and Burger, 2013). These processes have occurred over a relatively short period of time, since the advent of agriculture roughly 10,000 years ago, and they have increasingly intensified over the years to improve food production (Gaut et al., 2018; MacLeod et al., 2013). High quality genome assemblies are now available for several breeds of cattle (e.g., Rosen et al., 2020; Heaton et al., 2021; Talenti et al., 2022) and the use of genomic data has become ubiquitous in selective breeding (Meuwissen et al., 2001; MacLeod et al., 2014; Obsteter et al., 2021; Cesarani et al., 2022). Modern cattle have extremely low and declining genetic diversity, with estimates of effective population size around 90 in the early 1980s (MacLeod et al., 2013; VanRaden, 2020; Mekanjuola et al., 2020). On the other hand, the ancestral effective population size is estimated to be roughly $N_e = 62,000$ (MacLeod et al., 2013). This change in effective population size presents a challenge for demographic inference, selection scans, genome-wide association, and genomic prediction (MacLeod et al., 2013, 2014; Hartfield et al., 2022). For these reasons, it was useful to develop a detailed simulation model for cattle to be added to the `stdpopsim` catalog.

We used the most recent **genome assembly**, ARS-UCD1.2 (Rosen et al., 2020), a constant **mutation rate** $\mu = 1.2 \times 10^{-8}$ for all chromosomes (Harland et al., 2017), and a constant **recombination rate** $r = 9.26 \times 10^{-9}$ for all chromosomes other than the mitochondrial genome (Ma et al., 2015). With respect

to the **effective population size**, it is clear that simulating with either the ancestral or current effective population size will not generate realistic genome structure and diversity (MacLeod et al., 2013; Rosen et al., 2020). Since `stdpopsim` does not allow for a missing value of N_e , we chose to set the species default N_e to the ancestral estimate of 6.2×10^4 . However, we strongly caution that simulating the cattle genome with any fixed value for N_e will generate unrealistic patterns of genetic variation, and recommend using a reasonably detailed demographic model. We implemented the **demographic model** of the Holstein breed, which was inferred by MacLeod et al. (2013) from runs of homozygosity in the whole-genome sequence of two iconic bulls. This demographic model specifies the reduction from the ancestral effective population size ($N_e = 62,000$) beginning around 33,000 generations ago, consisting of a series of 13 instantaneous population size changes, ultimately reaching the current effective population size ($N_e = 90$) in the 1980s (taken from Supplementary Table S1 in MacLeod et al., 2013). To convert the timescale from generations to years, we used an average **generation time** of 5 years (MacLeod et al., 2013). Note that this demographic model does not capture the intense selective breeding since the 1980s that has even further reduced the effective population size of cattle (MacLeod et al., 2013; VanRaden, 2020; Mekanjuola et al., 2020). These effects can be modeled with downstream breeding simulations (e.g., Gaynor et al., 2020).

When setting up the parameters of the demographic model, we noticed that the inference by MacLeod et al. (2013) assumed a genome-wide fixed recombination rate of $r = 10^{-8}$, and a fixed mutation rate $\mu = 9.4 \times 10^{-9}$ (considering also sequence errors). The more recently updated mutation rate assumed in the species model (~~1.2×10^{-8} from Harland et al., 2017, as used above~~) (1.2×10^{-8} from Harland et al., 2017) is thus 28% higher than the rate used for inference. As a result, if one were to simulate the demographic model with the species' default mutation rate, they would produce synthetic genomes with considerably higher sequence diversity than actually observed in real genomic data. To address this, we specified a mutation rate of $\mu = 9.4 \times 10^{-9}$ in the demographic model, which then overrides the species' mutation rate when this demographic model is applied in simulation. The issue of fitting the rates used in simulation with those assumed during inference was discussed during the independent review of this demographic model, and it raised an important question about recombination rates. Since MacLeod et al. (2013) use runs of homozygosity to infer the demographic model, their results depends on the assumed recombination rate. The recombination rate assumed in inference ($r = 10^{-8}$) is 8% higher than the one used in the species model ($r = 9.26 \times 10^{-9}$). In its current version, `stdpopsim` does not allow specification of a separate recombination rate for each demographic model, so we had no simple way to adjust for this. Future versions of `stdpopsim` will enable such flexibility. Thus, we note that ~~simulated genomes~~ genomes simulated under the demographic model as currently implemented in `stdpopsim` might have slightly higher linkage disequilibrium than observed in real cattle genomes. However, we anticipate that this would affect patterns less than selection due to domestication and selective breeding, which are ~~not modeled hereas of yet~~ not modeled at all in the simulations of `stdpopsim`.

Conclusion

As our ability to sequence genomes continues to advance, the need for population genomic simulation of new model and non-model ~~organism genomes~~ organisms is becoming acute. So too is the concomitant need for an expandable framework for implementing such simulations ~~for species of interest and the resources for understanding when and~~ and guidance for how to do so. ~~Simulating species of interest, both model and non-model,~~ Generating realistic whole-genome simulations presents significant challenges in coding and the choice of parameter values on which to base the simulation. `Stdpopsim` is a resource that is uniquely poised to address these challenges as it provides easy access to ~~simulations incorporating species-specific information, easy inclusion of~~ state-of-the-art simulation engines and practices and an easy procedure for including new species genomes, ~~and~~. Moreover, the choices of new species to include are driven by the needs of the population genomics community. In this manuscript we describe the expansion of `stdpopsim` in two ways: the ~~expansion of its underlying framework to~~ addition of new features to the simulation framework that incorporate new evolutionary processes, such as non-crossover recombination, which ~~broadens~~ broaden the diversity of species that can be realistically modeled; and the considerable expansion of the catalog itself to include more species and demographic models.

We also ~~present basic considerations~~ compiled a series of guidelines for implementing population genomic

simulations, ~~agnostic to simulation software, which are~~ based on insights from the community-driven process of expanding the stdpopsim catalog. We ~~describe the steps of determining if a species-specific population genomic simulation is appropriate for the species and question, what data is necessary and why, list the basic requirements for generating a useful chromosome-level simulation for a given species, and explain the rationale behind these requirements. We discuss~~ special considerations for ~~finding and using that data, how to proceed when collecting relevant information from the literature, and what to do if~~ some of that ~~data information~~ is not available, ~~and why~~. ~~Because this process is quite error-prone,~~ we encourage everyone implementing simulations to have their parameter choices and implementation reviewed by at least one other researcher. These steps can be followed ~~independently if you are implementing a simulation independently for your own use,~~ or, as we encourage, ~~through the when you add your simulation code to stdpopsim framework for quality control and to make the species model,~~ to ensure its robustness and make it available for future standardized research. Currently, large-scale efforts such as the Earth Biogenome and its affiliated project networks are generating tens of thousands of genome assemblies. Each of these assemblies ~~, with some prior knowledge of mutation and recombination rates,~~ will become a candidate for inclusion into the stdpopsim catalog following the steps we have outlined above, ~~assuming it satisfies our baseline requirements~~. As annotations of those genome assemblies improve over time this information too can easily be added to the stdpopsim catalog.

~~Moreover, one of the goals of One of the important objectives of the PopSim consortium~~ is to leverage stdpopsim ~~itself as a springboard for as means to promote~~ education and inclusion of new communities into computational biology and software development. We are keen to use outreach, ~~for instance in the form of such as the~~ workshops and hackathons described here, as a way to ~~democratize development of population genomic simulation as well as~~ grow the stdpopsim catalog and library ~~generally. By enabling researchers of and democratize the development of population genomic simulations in general. We predict that the increased use of whole-genome simulations in~~ non-model species ~~with simulation platforms that will lead to an improvement in inference methods, which~~ traditionally have been quite narrowly focused ~~with respect to organism on well-studied model organisms. Thus,~~ we hope ~~to that further expansion of stdpopsim will~~ improve the ease and reproducibility of research across a ~~large larger~~ number of systems, while simultaneously expanding the community of software developers ~~at work in the among~~ population and evolutionary ~~genetics world. Our experience with such outreach over the past two years is that people are indeed keen to put in the time and effort to include their study species, but that simple, clear guidance is vital. Our intention with this paper is in part to provide another learning modality to meet that need.~~ ~~geneticists.~~

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