INTRODUCTION

Since its introduction by Wright (1931), the concept of effective population size (Ne) has been enormously influential. The main reasons are its conceptual simplicity and broad utility, as it brings under a common denominator species and populations that may differ profoundly in their biological characteristics. According to a standard textbook definition (Hartl & Clark, 2006) ‘the effective population size of an...
actual population is the number of individuals in a theoretically ideal population having the same magnitude of random genetic drift as the actual population. The theoretically ideal population in this definition is the Wright–Fisher population. Effective population size is a key evolutionary parameter that reflects the strength of drift, and thus determines the efficacy of selection and the levels of genetic variation. The interest in the subject has led to the formulation of several Ne definitions that use and emphasise various aspects of drift (Box 1). Because the action of key evolutionary processes and their balance depend on Ne, and because suitable genetic data have become increasingly available, the interest in estimation of Ne increased markedly over the last decades. Estimation and interpretation of Ne are essential in diverse areas of evolutionary and conservation biology, ranging from assessing the evolutionary potential or extinction risk to empowering research on the genomic basis of adaptation.

The approaches for Ne estimation utilise the information contained in genetic data, as outlined below. The relationship between the definitions and estimates of Ne can, however, be complex. To put it simply, it may become unclear what kind of Ne (inbreeding, variance, eigenvalue, something in between) is being estimated and how should the estimated quantities be interpreted within a given biological context (Ryman et al., 2019; Waples, 2010). Another complication is the division of the field into the research on the ‘contemporary’ (or ‘recent’) and ‘long-term’ (or ‘historical’) population size, which has emerged from the diverging methodological approaches and applications of the concept (see the excellent review by Hare et al., 2011). Contemporary Ne, defined as Ne in the previous or over several previous generations, has been widely used in the areas such as animal and plant breeding, conservation and management of wild and captive populations. The
estimation of long-term Ne has been of interest in, for example, phylogeography, historical demography and speciation research. This subdivision into sub-fields that use different kinds of data, estimation methods and even terminology is unfortunate, as it limits the exchange of ideas and raises the entry bar for newcomers to the field. Thus, the success, broad adoption and application of the Ne concept notwithstanding, two major issues have slowed down the progress of the field:

1. Increasingly sophisticated and precise methods are available, but it is often unclear which biologically interpretable quantity they estimate and how their results can be interpreted in the context of the questions that motivated their use.

2. The subdivision into contemporary and long-term Ne has dominated the field, while both our understanding of the biological reality and the newly available methods emphasise the temporal continuum of Ne. Importantly, the growing appreciation of the continuum makes the issues outlined above even more pressing.

The recently published reviews of effective population size cover the general properties and theoretical underpinning of the concept (Charlesworth, 2009; Walsh & Lynch, 2018), methods for its prediction and estimation (Wang et al., 2016), interpretation of various Ne estimates (Ryman et al., 2019), the estimates of Ne in various taxonomic groups (Palstra & Fraser, 2012), the use of genomic data to reconstruct historical demography (Beichman et al., 2018), as well as the effect of various properties of natural populations on the estimation and interpretation of Ne estimates (Hare et al., 2011; Waples, 2010). Although temporal aspects of Ne feature in several of these reviews, no review focusing on the temporal continuum of effective population size has been available to date. Here, we aim to provide a thorough yet accessible overview of temporal aspects of Ne, spanning both contemporary and long-term Ne. We will guide the reader through the diversity of the available approaches, discuss the question of interpretation and illustrate how the recently developed approaches can be combined to reconstruct the entire Ne continuum. We will provide a general overview of the key methods and refer the reader to the existing methodological reviews for more details. We will also integrate, where necessary, spatial aspects of Ne estimation and interpretation, present recent examples of the application of the Ne concept and outline prospects for integrative Ne research. Importantly, we stress throughout that probing the entire temporal Ne continuum can provide invaluable insights into the evolution, biology and conservation of natural populations only when accompanied by a thorough understanding of the Ne concept and biases associated with various approaches to Ne estimation.

2 | DIVISION OF THE FIELD: CONTEMPORARY AND LONG-TERM Ne

A long-standing interest in the effective size of natural, domesticated and experimental populations resulted in extensive theoretical Ne research that together with novel techniques for assessing genome-wide variation facilitated the development of Ne theory as well as inference methods (Hössjer et al., 2014, 2015, 2016; Hui & Burt, 2015; Husemann et al., 2016; Ryman et al., 2019; Wang, 2005; Wang et al., 2016). In the vast literature on Ne methodology and application two main lines of research, focusing either on contemporary or long-term Ne are easily distinguishable (Figure 1). These two subfields use different methodological approaches, are associated with different challenges and, importantly, differ in the timeframe over which they estimate Ne.

2.1 | Contemporary Ne

Contemporary Ne represents effective population size in the previous or over several previous generations. It is informative about the current rate of the loss of variation and adaptive potential. Estimation
The two main approaches to the estimation of contemporary Ne include direct or indirect (genetic) methods (Wang, 2005; Wang et al., 2016; Gilbert & Whitlock, 2015). Direct estimation requires extensive knowledge about population's parameters, including census size, sex ratio, variance in reproductive success, mating system and/or pedigree (Caballero, 1994; Wang, 2005; Wang & Caballero, 1999; Waples & England, 2011). Unfortunately, demographic parameters are particularly difficult to obtain for natural populations and, in consequence, direct Ne estimates are relatively rare.

Indirect methods are easier to apply and require an assessment of genetic variation in a population. Using various types of genetic data, Ne can be estimated from:

1. the excess of heterozygosity relative to Hardy–Weinberg expectations (Pudovkin et al., 1996); an offspring population generated from a limited number of males and females, that differ in allele frequencies due to drift, is expected to exhibit a deficit of homozygotes and an excess of heterozygotes, increasing with the decreasing parental population size;
2. frequencies of half and full siblings in a random sample from a population (Wang, 2009; Waples & Waples, 2011); relatedness between individuals is directly related to the inbreeding effective population size, the smaller Ne the higher probability that two randomly sampled individuals share one or both parents;
3. analysis of a set summary statistics (such as number of alleles, expected heterozygosity, homozygosity, inbreeding coefficient and linkage disequilibrium) using simulations and the approximate Bayesian computation (ABC) framework (Tallmon et al., 2008);
4. changes in allele frequencies over time (Waples, 1989), the smaller the population the more pronounced changes in allele frequencies from generation to generation (for more details see below); or
5. linkage disequilibrium (LD) among genetic markers (Hill, 1981; Waples & Do, 2010), the magnitude of which is related to the size of a population (for more details see below)

While the heterozygosity excess method has rather limited applications due to its poor performance except when Ne is very small, the other methods have been successfully applied to infer contemporary Ne of organisms from various taxonomic groups (Hare et al., 2011; Palstra & Fraser, 2012; Wang et al., 2016). In particular, methods based on LD patterns or allele frequency changes over time (so-called temporal methods, not to be confused with temporal Ne trajectories) have been widely adopted and are under constant development as examples from the special issue of Heredity published in 2016 (https://www.nature.com/collections/tjhfwyyxzy) testify.

Temporal methods, which rely on the comparison of samples taken one or (better) several generations apart, provide an intuitive estimate of drift, where the magnitude of changes in neutral allele frequencies over time is inversely proportional to Ne over that period. Ne can be estimated with temporal methods using moment-based (Do et al., 2014; Jorde & Ryman, 1995, 2007; Nei & Tajima, 1981), likelihood (Hui & Burt, 2015; Wang, 2001; Wang & Whitlock, 2003) or Bayesian approaches (Berthier et al., 2002, Beaumont, 2003). The biggest challenge for the use of temporal methods is the requirement of sampling several generations apart. This is particularly important when species are characterised by overlapping generations (sampling at least three to five generations apart is recommended, Waples & Yokota, 2007). This limits the utility of temporal methods to species with a rather short generation time (but also makes it useful in experimental evolution; Jónás et al., 2016).
In contrast to the temporal methods, LD-based methods rely on a sample taken at a single time point. The LD methods are based on the observation that in a finite population random genetic drift creates associations between alleles from unlinked loci as well as increases LD between physically linked ones (Hill, 1981). This information can be used to estimate Ne. Initially, LD-based methods were used for a limited number of physically unlinked loci for which quantification of the strength of drift and Ne is rather straightforward (Waples et al., 2016). The performance of the LD methods can be improved by incorporating thousands of loci. Some of them will, by necessity, be physically linked, which elevates LD and biases Ne estimates. Waples et al. (2016) provided equations that use the number of chromosomes or the total length of linkage map to correct for this bias.

The signals of drift and inbreeding are strongest in small populations. For this reason, both temporal and LD-based methods were mainly used to estimate Ne in small populations (<1,000). Several simulation studies suggested that contemporary Ne estimation methods can be used to estimate Ne of larger populations when genome-wide data are used (Hui & Burt, 2015; Wang et al., 2016). However, empirical studies showed that estimation of Ne in large populations using LD-based methods remains challenging, often resulting in infinite credible intervals (DeFaveri & Merilä, 2015; Marandel et al., 2019; Nadachowska-Brzyska et al., 2021). In addition to the ongoing research on contemporary Ne includes inferring Ne in populations with different modes of reproduction, populations under selection (reviewed in Wang et al., 2016) or for complex metapopulation structures (Hössjer et al., 2014, 2015, 2016; Ryman et al., 2019).

Strictly speaking, contemporary Ne should refer to the previous generation (generation prior to sampling). However, obtaining a Ne estimate for a single specific time point may be problematic and depends on the approach and data used (Ryman et al., 2019; Waples, 2005). In particular, temporal and LD-based methods may provide information about Ne from different generations/periods (Waples, 2005, Figure 1).

Overall, temporal methods estimate harmonic mean Ne over the time the samples were collected and LD-based methods reflect Ne of the parental generation or several generations back in time. To what time exactly the estimates apply depends on species life history (discrete or overlapping generations), sampling strategy (whether juveniles or adults were sampled) and whether the population experienced recent demographic changes (Waples, 2005). Additionally, analysis of individuals belonging to a single cohort only (born in the same year) may provide information on the effective number of breeders over a reproductive cycle (Nb) instead of the Ne (Ruzzante et al., 2016). In such case, Ne can be estimated based on Nb when additional information on generation time and/or other life-history traits is available (e.g. age of maturation, adult life span, variance in reproductive success; Waples et al., 2013, 2014). Active research on contemporary Ne includes also inference of Ne in populations with different modes of reproduction, populations under selection (reviewed in Wang et al., 2016) or for complex metapopulation structures (Hössjer et al., 2014, 2015, 2016; Ryman et al., 2019).

### 2.2 Long-term Ne

Long-term Ne can be defined as the harmonic mean of per-generation Ns over an extended period (hundreds of generations or more) of the evolutionary history of the species in question (Figure 1). In contrast to contemporary Ne, estimation of long-term Ne can only be based on genetic data. It is an essential part of research on phylogeography, speciation and historical demography, where the inferences are based on the principle that demographic events (e.g. population bottlenecks, expansions and subdivision) leave distinct signatures in the genome-wide patterns of variation. It is thus possible, for any population (or species), to construct various demographic models that describe a sequence of historical events and include information about their magnitude, for example, strength of a bottleneck or intensity of gene flow. In a classic estimation pipeline, the competing models are compared, the most likely (or ‘best’) model(s) is(are) selected and model parameters, such as Ne, are estimated. Such inferences provide insights into species evolutionary history, as well as allow us to assess the extinction risk. For example, demographic modelling of two closely related species with incomplete reproductive isolation informs on the process of speciation by providing estimates of Ne of ancestral and descendant populations, time of divergence and the amount of gene flow between diverging populations. Demographic modelling of small endangered populations facilitates the assessment of the status of threatened species by, for example, providing information on the probability of inbreeding depression conditional on long-term Ne (Robinson et al., 2019). Knowledge of historical demography is also essential for inferring selection. Since natural selection and some demographic events leave similar signatures in genetic variation, it is crucial to test whether variation patterns of potentially selected loci could have been produced by demographic history under neutrality (Yi et al., 2010).

Model-based methods/approaches to infer long-term Ne can be classified according to the data used (site frequency spectrum (SFS), identity by descent (IBD), haplotypes, LD), analytical framework applied (Bayesian, likelihood) or the underlying biological model. These aspects of demographic inference have been described in several recent reviews (Beichman et al., 2018; Salmana et al., 2017; Schraiber & Akey, 2015) that illustrated also the evolution of the field from simple models of a single or two populations (IM model, Hey & Nielsen, 2004; Wakeley & Hey, 1997) to more complex (but still simplified compared to the actual demographic histories) demographic models including many populations of various Ne and incorporating events such as expansions, bottlenecks or gene flow between populations (Beaumont, 2010; Hey, 2010). Advances in both theory and data acquisition (Beaumont & Rannala, 2004; Griffiths, 1991; Griffiths & Marjoram, 1996; Griffiths & Tavaré, 1998; Kelleher et al., 2019; Marchi et al., 2021; Polanski & Kimmel, 2003) allowed researchers to infer long-term Ne of descendant as well as ancestral populations of hundreds of species from various taxonomic groups (Nadachowska-Brzyska et al., 2013; Zielinski et al., 2016).

However, it is important to note that despite the growing complexity of inferred models, they are always a simplified version of
BOX 2  Demographic model versus long-term Ne

To understand the difference and the relationship between a demographic model and long-term Ne, let us take a simple example of an isolated population for which we can draw a simplistic demographic scenario (Figure Box 2). In this example, the population originated from a larger ancestral population and its Ne fluctuated over time (yellow line). The proposed demographic model (grey boxes in Figure Box 2) is a good approximation of the true demography (yellow line) if we average Ne trajectories of the descendant and ancestral population. Assuming the proposed model, the historical demographic inference would involve estimation of Ne for the ancestral population and Ne for a descendant population in a form of long-term Ne. However, the true demographic history is more complex, in particular, there has been a substantial recent decline which could not be inferred in a simplistic demographic model.

Figure Box 2 True Ne changes over time (yellow line) in relation to the simplistic demographic model (grey boxes)

3  |  TEMPORAL CONTINUUM OF Ne

Information on temporal Ne changes is a crucial aspect of the demographic history often missing in demographic inferences described above. For example, temporal Ne trajectories can provide insights on species response to past climate oscillations (Miller et al., 2012; Nadachowska-Brzyska et al., 2016). A longstanding interest in temporal aspects of Ne dynamics resulted in a wide range of methods developed to infer Ne changes. The history of these developments goes back to the classic skyline plots. This method infers genealogy from DNA sequence data and uses it to estimate piecewise constant population size over time using the principles of coalescent theory (Ho & Shapiro, 2011; Pybus et al., 2000). The first skyline plot methods used information from single genetic markers and have been further extended to include information from multiple loci (Heled & Drummond, 2008). The explosion of methods reconstructing temporal Ne trajectories came with the advances in sequencing that have made genome-wide information widely available (Beichman et al., 2018; Li & Durbin, 2011; Spence et al., 2018).

Temporal changes in Ne can be incorporated into explicit demographic models that describe population splits, mergers, size changes and migration rates (as described in the previous section on long-term Ne). Unfortunately, under a model-based approach, both the number and complexity of models that can be compared are limited, because the number of parameters to be estimated from the data increases quickly with the increasing complexity of the models. As a consequence, changes in Ne population size can be only roughly reconstructed. A major advance towards the reconstruction of the temporal Ne continuum was the development of nonparametric models that are more flexible and allow the exploration of a much larger model space (Li & Durbin, 2011; Liu & Fu, 2020; Schiffels & Durbin, 2014; Terhorst et al., 2017).

Importantly, methods inferring Ne over time differ in the timeframe in which they operate. Depending on a particular approach and data used, one can access different portions of demographic history that together can cover the entire temporal continuum. Below we shortly present the key methods that infer Ne trajectories from genome-wide data, focusing on the temporal scales these methods provide information for. We also discuss the interpretation of the results and show how we can infer the temporal Ne continuum by combining different approaches (Table 1).
### Table 1: Examples of tools used to infer Ne across time continuum

| Name                        | Short description of functionalities                                                                 | Data required                                      | Link                                                                 | Reference                        |
|-----------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|----------------------------------|
| **Contemporary Ne**         |                                                                                                      |                                                    |                                                                      |                                  |
| NeEstimator V2              | Implements a wide range of temporal and LD-based methods to infer Ne                                 | Microsatellites or SNP data, temporal or single    | http://www.molecularfisherieslaboratory.com/neestimator-software/     | Do et al. (2014)                 |
|                             |                                                                                        time-point samples, genetic map for LD-based method                        |                                                    |                                                                      |                                  |
| MLNe                        | Moment-based and maximum likelihood approach to estimate Ne and migration                           | Temporal samples                                   | https://www.zsl.org/science/software/mlne                           | Wang and Whitlock (2003)         |
| ONeSAMP                     | ABC approach                                                                                         | Microsatellites data summarised by different      | https://github.com/kingufi/ONeSAMP                                   | Tallmon et al. (2008)           |
|                             |                                                                                        statistics                                           |                                                    |                                                                      |                                  |
| NB(R package)               | Likelihood-based temporal method                                                                     | Microsatellites or SNP data, temporal samples      | http://cran.r-project.org/web/packages/NB/                           | Hui and Burt (2015)             |
| **Long-term Ne**            |                                                                                                      |                                                    |                                                                      |                                  |
| ABCToolbox                  | A toolbox facilitating ABC analysis using different algorithms and simulation software chosen by the user | User defined                                       | http://cmpg.unibe.ch/software/ABCtoolbox/                           | Wegmann et al. (2010)           |
| daði                        | Infers demographic history based on diffusion approximation modelling of the allele frequency spectrum | Folded/unfolded SFS from tens to hundreds of samples | https://bitbucket.org/gutenkunstlab/dadi/src/master/                  | Gutenkunst et al. (2009)        |
| fastsimcoal                 | One of the simulation programs to simulate data under user-defined demographic scenario               | Folded/unfolded SFS from tens to hundreds of samples | http://cmpg.unibe.ch/software/fastsimcoal2/                           | Excoffier et al. (2013)         |
| **Historical Ne trajectories** |                                                                                                      |                                                    |                                                                      |                                  |
| PSMC                        | Estimates rate of coalescence across time and translates it to piecewise constant temporal Ne trajectory | Single diploid genome sequenced to a high coverage | https://github.com/lh3/psmc                                          | Li and Durbin (2011)            |
| MSMC                        | Extension of PSMC                                                                                     | Up to eight phased genomes sequenced to high coverage | http://www.github.com/stschiff/msmc                                 | Schiffels and Durbin (2014)     |
| MSMC2                       | Extension of the method used in MSMC, software under development                                      | Phased or unphased genomes sequenced to high coverage | http://www.github.com/stschiff/msmc2                               | Schiffels and Wang (2020)       |
| SMC++                       | Combines SFS-based approach with the sequentially Markovian coalescent                                | Tens to thousands of unphased genomes              | https://github.com/popgenmethods/smcpp                              | Terhorst et al. (2017)          |
| Relate                      | Estimates genome-wide genealogies in the form of trees that adapt to changes in local ancestry caused by recombination | Thousands of phased genomes                        | https://myersgroup.github.io/relate/index.html                       | Speidel et al. (2019)           |
| Stairway Plot               | Infers Ne from SFS without predefined demographic models                                              | Unfolded SFS from hundreds of samples              | https://sites.google.com/site/jpogen/stairway-plot                  | Liu and Fu (2015)              |
| Stairway Plot2              | Improved version of Stairway Plot                                                                     | Folded/unfolded SFS from hundreds of samples       | https://github.com/xiaoming-liu/stairway-plot-v2                     | Liu and Fu (2020)              |

(Continues)
| Name       | Short description of functionalities                                                                 | Data required                                       | Link                                                                 | Reference                  |
|------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|-----------------------------|
| PopSizeABC | Infers demographic parameters from multiple summary statistics, which are compared with results of coalescent simulations. Model-constrained method. | Tens to hundreds of unphased genomes                | https://forge-dga.jouy.inra.fr/projects/popsizeabc                    | Boitard et al. (2016)      |
| **Recent Ne trajectories** |                                                                                                      |                                                    |                                                                      |                             |
| LinkNe     | LD-based method to estimate Ne                                                                      | Genome-wide SNP data, recombination map            | https://github.com/chollenbeck/LinkNe                               | Hollenbeck et al. (2016)    |
| SNeP       | LD-based method to estimate Ne                                                                      | Genome-wide SNP data, recombination map            | https://sourceforge.net/projects/snpnetrends/                        | Barbato et al. (2015)      |
| IBDNe      | Calculates ancestry-specific Ne using inferred segments of IBD                                       | List of IBD segments from at least a few hundred samples | https://faculty.washington.edu/browning/ibdne.html                   | Browning et al. (2018)      |
| GONE       | LD-based method to estimate Ne taking into account the cumulative contributions of all of the previous generations to the observed LD | User defined                                       | https://github.com/esrud/GONE                                         | Santiago et al. (2020)      |
| **Other recent advances** |                                                                                                      |                                                    |                                                                      |                             |
| MMC-ABC    | Extension of ABC for multiple-merger coalescent                                                      | User defined                                       | https://github.com/sackmana/MMC-ABC                                  | Sackman et al. (2019)       |
| DILS       | Extension of ABC allowing co-infer Ne changes, linked selection and gene flow between populations     | User defined                                       | https://github.com/popgenomics/DILS_web                               | Fraisse et al. (2021)       |
| **Machine learning approaches** |                                                                                                      |                                                    |                                                                      |                             |
| evoNet     | Implements deep learning algorithms for population genetic inference                               |                                                    | https://sourceforge.net/projects/evonet/                              | Sheehan and Song (2016)     |
| DNADNA     | Provides utility functions for neural networks in population genetics with repo specific to the code of Sanchez et al., 2020 | User defined                                       | https://gitlab.com/mlgenetics/dnadna                                 | Sanchez et al. (2020)       |
| pg-gan     | Estimates parameters in population genetic models that automatically adapts to data from a population | Tens to hundreds of phased genomes                 | https://github.com/mathiesonlab/pg-gan                                | Wang et al. (2021)          |
3.1 Inference of historical Ne trajectories

Pairwise sequentially Markovian coalescent (PSMC), was introduced by Li and Durbin in 2011 and is one of the most widely used methods to infer historical Ne changes over time. It is based on the coalescent hidden Markov model (coalescent-HMM) theory with roots in the influential work of Wiuf and Hein (1999; further developed by McVean and Cardin (2005) and Marjoram and Wall (2006)). The huge popularity of PSMC can partially be attributed to the fact that the method infers Ne changes over time using only a single diploid genome sequence. Shortly, PSMC identifies segments that most likely did not experience recombination prior to coalescence, so all the positions within the segment share the same time to the most recent common ancestor (TMRCA). PSMC uses the information on the distribution of TMRCA to estimate the rate of coalescence over time and translate it to the effective population size trajectory. Unfortunately, PSMC resolution is limited and the method does not provide information on recent Ne.

An impressive number of new methods trying to improve resolution over recent timescales have been developed since the publication of the original PSMC study (Sellinger et al., 2021; Spence et al., 2018). In general, these methods improve the resolution by analysing genetic information from more individuals, from a few (Malaspina et al., 2016; Schiffels & Durbin, 2014) to thousands (Speidel et al., 2019). Many of these methods are, like PSMC, based on sequentially Markovian coalescent (SMC) theory (Barroso et al., 2019; Harris & Nielsen, 2013; Malaspina et al., 2016; Schiffels & Durbin, 2014), others use site frequency spectrum (SFS) information (Liu & Fu, 2015, 2020) or a combination of both, SMC and SFS (Terhorst et al., 2017). For example, the MSMC method uses coalescent-HMM to approximate the coalescent process under recombination and infer Ne changes over time (Schiffels & Durbin, 2014). The MSMC operates on a few diploid genomes sequenced to high coverage and phased, and shifts the time window by a few hundred generations towards the present (Figure 1). In contrast, SMC++ does not require phased data and uses hundreds of samples to span the vast majority of Ne continuum by combining information contained in SFS and LD, which is possible because the method effectively combines the Poisson random field and coalescent-HMM approaches (Figure 1).

Overall, the methods reliant on the information from a single or a few genomes provide Ne estimates for the time interval between 300–400 generations before present (gpb) and hundreds of thousands of gpb (kgpb). Some methods that base their inferences on SFS and hundreds or thousands of genomes may provide information on more recent times, starting from approximately 40 gpb (Figure 1). The exact timeframe of inference may differ among species, but very recent Ne dynamics cannot be inferred using these methods.

3.2 Inference of recent Ne trajectories

Very recent demography can be inferred from patterns of LD along the genome. The structure of LD can be expressed as correlations between alleles at different loci as well as the distribution of tracts of identity by descent (IBD) or identity by state (IBS), such as runs of homozygosity. Correlations between alleles can be used to assess contemporary Ne of a population (discussed in the previous section; Wang et al., 2016; Waples, 2006; Waples & Do, 2008) and Ne changes over the recent past (Barbato et al., 2015; Hollenbeck et al., 2016; Mezzavilla & Ghirotto, 2015; Santiago et al., 2020). The methods differ in algorithmic details and sensitivity to complex demography (Santiago et al., 2020) but the general logic behind is that LD between single nucleotide polymorphisms (SNPs) at different genetic distances provides information on Ne at different times in the recent past. Distribution of IBD, which can be inferred from population genomic data, carries information about recent Ne dynamics (Hayes et al., 2003; MacLeod et al., 2009, 2013). Numerous long IBD tracks shared by individuals indicate recent common ancestry, suggesting small Ne, and analogously, a large number of short IBD tracks implies larger Ne (Browning & Browning, 2015; Hayes et al., 2003; Palamara et al., 2012). Similarly, the size distribution of genomic segments that are identical by state (IBS), and, importantly, can be directly observed, provides information on Ne changes over time (MacLeod et al., 2009, 2013).

There is an extensive variation among methods in the temporal resolution of recent Ne trajectories (Figure 1). Some methods can only infer Ne changes for the last 15–20 gpb (e.g. LinkNe, Hollenbeck et al., 2016) others cover a few hundred (e.g. IBDNe, GONE; Browning & Browning, 2015; Santiago et al., 2020) or even thousands of gpb (e.g. SNeP, PopSizeABC; Barbato et al., 2015; Boitard et al., 2016). Overall, methods reliant on LD/IBD patterns provide the most reliable information on Ne changes between a few and 100–200 gpb (e.g. IBDNe, Browning & Browning, 2015; GONE, Santiago et al., 2020). Methods that span longer periods often require additional information on SFS and involve complex simulations (e.g. PopSizeABC; Boitard et al., 2016).

4 Biological and methodological limitations for inferring the temporal Ne continuum

In theory, using different approaches presented above, one can infer Ne changes spanning the entire temporal continuum starting from the previous generation to hundreds of thousands of gpb. However, each method has its requirements about data and its assumptions that, if violated, may produce unreliable results. Moreover, even if Ne trajectory can be reconstructed for extended periods, the reliability of estimation can differ across time.

4.1 Data-related limitations

Different methods estimating Ne changes over time are prone to different biases inherently associated with the type of data used. For example, the influence of missing data and coverage on PSMC
**BOX 3** The effect of geographic subdivision on temporal Ne reconstruction

The theory of effective population size under stable subdivision, that is, in migration-drift equilibrium, is relatively well understood (reviewed in Charlesworth & Charlesworth, 2010). However, important analytical results and approximations regarding the expected time to coalescence (proportional to Ne) are mostly available for the sample size of two (Charlesworth & Charlesworth, 2010). These results show that under numerous scenarios of subdivision sequences sampled from a single deme accurately estimate the sum of the long-term population sizes of various demes. Such samples, however, distort SFS and mislead the reconstruction of the temporal Ne trajectory (Städler et al., 2009). An interesting and important result emerges for metapopulation models consisting of many demes that undergo extinction–recolonisation dynamics (Wakeley, 1999; Wakeley & Aliacar, 2001). When the number of demes is large, the details of the migration process between them become less relevant. The genealogical process can be usefully divided into two phases characterised by distinct dynamics. The dynamics of the scattering phase is governed by fast processes of coalescence occurring within demes, while the dynamics of the collecting phase is determined by slower processes as ancestral lineages migrate among demes that usually do not contain other ancestral lineages. If each gene copy is sampled from a different deme, there is no scattering phase in the ancestry of the sample and the genealogical process in the collecting phase converges to standard coalescent with appropriately rescaled time (Wakeley, 1999).

To give a concrete example of the effect of the geographic subdivision on the reconstruction of the temporal Ne trajectory, Wakeley (1999) demonstrated that structured populations may show spurious bottleneck signals even if they are actually growing. Mazet et al. (2016) presented scenarios in which PSMC-like methods under subdivision robustly recovered signal of Ne changes through time even under constant population size (Figure Box 3). Interestingly, both signals of demographic expansion and contraction can be inferred for the same demographically stable subdivided population depending on how the genomes we base our inferences on are sampled (Mazet et al., 2016, Figure Box 3c,d). Such results become easy to understand when we consider the effect of subdivision on the instantaneous rate of coalescence, the inverse of which is equated with effective population size under panmixia. For instance, consider a stable subdivision of a population into several demes connected by a limited gene flow. As we follow the ancestral lineages of gene copies sampled in a single deme, the rate of coalescence would initially be high, determined by the local deme size. Then, as more and more ancestral lineages leave the deme, the rate of coalescence decreases as it becomes determined by the number of demes and migration rates between them. Thus, we will recover an increased coalescence rate in the recent past, exactly as expected under a bottleneck scenario.

In a series of papers, Chikhi and colleagues (Arredondo et al., 2021; Chikhi et al., 2018; Grusea et al., 2019; Mazet et al., 2016; Rodríguez et al., 2018) formalised the problem, defined the inverse instantaneous coalescence rate (IICR), which equals (coalescent) Ne in a panmictic population, and showed that this measure necessarily confounds Ne changes with the effects of population structure. In an attempt to co-estimate Ne and subdivision they proposed a method that fits IICR curves to a piecewise n population model estimating the number of islands, and rates and changes in connectivity (Arredondo et al., 2021). This work brings the promise of incorporating subdivision and its changes into the realm of PSMC-like methods but also points out that we may be reaching limits of demographic inference here.
analysis was investigated by Nadachowska-Brzyska et al. (2016) who found that high quality data (coverage >18x) are essential for proper inference. It has also been shown that high numbers of spurious SNPs (>10%) and unmasked repetitive sequences bias inference in several SMC methods (Sellinger et al., 2021). Many methods appear robust to the assembly quality (fragmentation) but their precision and accuracy differ across timescales (Patton et al., 2019)—often Ne for the most recent as well as ancient times is more difficult to infer. In addition, methods based on SFS or IBD require large sample sizes (Browning & Browning, 2010; Robinson et al., 2014; Liu & Fu, 2015; Terhorst & Song, 2015). Paradoxically, methods relying on smaller sample sizes often require phased data that, if the phase is computationally inferred, require large datasets anyway (Terhorst et al., 2017). Phased-data based methods are sensitive to phasing errors that can result in the overestimation of recent Ne (Terhorst et al., 2017).

4.2 Influence of selection

Selection may influence patterns of variation in data used for Ne estimation. First, any form of pervasive selection violates the assumptions of the methods discussed above. Second, selection at linked sites decreases heterozygosity and distorts SFS, causing, together with variation in recombination rate, significant heterogeneity of diversity across the genome (Elyashiv et al., 2016). As a consequence, selection can lead to overestimation of the severity and rate of Ne changes over time. For example, in classic PSMC, a false signal of a recent bottleneck will be produced by the genomic regions under strong background selection and a false signal of ancient demographic expansion will be due to regions evolving under balancing selection. It is, however, believed that balancing selection plays a minor role in the long-term maintenance of genetic variation (Asthana et al., 2005; Bubb et al., 2006; but see Charlesworth, 2015), while transient balancing selection is very difficult to detect because it only mildly affects the local patterns of variation (Fijarczyk & Babik, 2015). On the other hand, when SFS is analysed, false recent population growth is inferred if background selection is ignored (Johri et al., 2021). Thus, regardless of the applied method, different forms of selection can seriously bias estimation of Ne trajectories, especially in gene-dense genomes and in the case of low recombination rate. Controlling for these effects is, therefore, a critical, but also challenging, aspect of the analyses. Recent advances promise, however, progress in this field (see below).

4.3 Temporal and spatial aspects of Ne are intimately linked

As we probe the temporal continuum of Ne deeper and deeper in time, Ne inferences are increasingly based on the rate of coalescence of ancestral lineages, which is either estimated from sequence divergence or inferred from the properties of the SFS. Several processes affect the rate of coalescence and may thus generate signals that can erroneously be taken as evidence of Ne changes, especially when the assumption of panmixia is violated. Structured populations may show bottleneck signals even if they are growing (Wakeley, 1999) and populations of constant size may appear as declining or expanding, depending on a sampling scheme (Mazet et al., 2016; Box 3). These observations are particularly important since real species are usually subdivided and subdivision often changes over time, following natural or anthropogenic environmental processes that affect the distribution of habitats and connectivity between them (Haddad et al., 2015; Hewitt, 2000; Lowe & Walker, 2014). Hence, any serious attempt at reconstructing historical demography needs to take into account the spatiotemporal continuum. This is, unfortunately, not an easy task (Box 3).

Theoretical results show that, while Ne under subdivision can usually be defined in terms of the expected coalescence times (Sjödin et al., 2005; Wakeley & Sargsyan, 2009), interpretation of this quantity is difficult in strictly demographic terms. This is because Ne depends not only on the sum of subpopulation sizes but also on migration rates between them (Box 3). If one is interested in reconstructing demography as the change in the population sizes through time, the very concept of effective population size becomes elusive under subdivision and it becomes difficult to disentangle the local (subpopulation) Ne and global Ne. Depending on the number of subpopulations and the migration patterns between them, we may or may not accurately estimate the sum of the long-term population sizes of various subpopulations or accurately reconstruct (or not) the temporal Ne trajectory (Städler et al., 2009; Box 3).

The reconstruction of demographic history under conditions of non-equilibrium subdivision has commonly involved formulation and comparison of a limited number of models depicting the history of population splits, mergers, admixture events and changes in the effective size of particular populations (similarly to the long-term Ne inference described above, Section 2.2). However, even under a rather simple scenario of a small number of subpopulations, the number of parameters and computational complexity of the model...
increases quickly. This necessitates using simple models, which in itself constitutes a strong assumption about the demographic history.

The advent of PSMC-like methods that are temporal per se has led to the renewed interest and increased recognition of the profound effects subdivision and its changes have on the estimation of the temporal Ne continuum. This interest has been partly motivated by the debate on the history of our species in Africa before the colonisation of Eurasia (Scerri et al., 2018, 2019). The importance of the topic is, however, far-reaching, equally and perhaps even more relevant to other species that experienced drastic alterations in population sizes, geographic ranges and connectivity. To put it simply: when we look at the reconstructed temporal Ne continuum the estimates at its different points mean different things, the more so if the geographic structuring itself also changes over time. This simple observation causes considerable interpretational difficulties. Paradoxically, we can estimate, with increasing precision and resolution, the IICR (Mazet et al., 2016) which equals (coalescent) Ne in a panmictic population, but its meaning becomes increasingly elusive under subdivision (Box 3), especially if subdivision itself has changed over time as we have all the reasons to suspect is the rule (Fenderson et al., 2020). Indeed, Beichman et al. (2017) showed that data simulated under demographic scenarios inferred by PSMC-like methods assuming a single panmictic population did not produce SFS similar to those observed in the natural populations.

Take home message from this section is that when trying to estimate the temporal Ne continuum we must take into account population structure, otherwise, results will not be interpretable. The methods to do so are in their infancy and the limits to their development remain unclear. For the time being the researchers should at the very least be fully aware that uncritical interpretation of the temporal trajectories of the rate of coalescence as Ne may lead to false inferences and interpretation.

5 | EXAMPLES OF RECENT RESEARCH AND FUTURE PERSPECTIVES

To jointly infer contemporary and long-term Ne and to bridge the gap between these two, hundreds of genomes from a contemporary population are required, ideally accompanied by genome sequences of historical samples. PSMC-like and SFS-based methods can then be complemented with temporal and LD-based methods, potentially allowing reconstruction of the entire Ne continuum. Historical samples, including museum specimens, permafrost and archaeological samples of various species are becoming a common target of sequencing projects, facilitating such analyses (Mitchell & Rawlence, 2021; Orlando et al., 2021). Similarly, the use of haplotype information is a promising strategy to improve the estimation of numerous population genetic parameters, including Ne (Leitwein et al., 2020; Meier et al., 2021). We expect that many haplotype datasets will soon become available, as long-read sequencing technologies mature, which allows direct haplotype phasing and thus overcoming computational phasing errors (De Coster et al., 2021).

As a consequence, we should soon be able to take a look into the entire Ne continuum in numerous species. How can our understanding of biology benefit from that?

Perhaps the most basal aspect of wildlife biology that can be addressed with population genomics tools is population size estimation. In the context of conservation, census population size, its oscillations and relation to Ne are of particular interest. Even though the census population sizes generally correlate with effective population sizes, there is a substantial variation between species and a discrepancy between the several orders of magnitude variation in census population sizes and the much narrower range of Ne estimated from genetic variation (Ellegren & Galtier, 2016). An interesting recent development is the introduction of the close-kin mark-recapture (CKMR) approach that estimates census size using the frequency of parent-offspring pairs identified with genomic methods (Bravington et al., 2016; Rizzante et al., 2019; Waples & Feutry, 2021). The same data can be used to assess Ne, establishing a direct link between Nc and Ne estimates, which led, for example, to the discovery that the Ne/Nc ratio in southern bluefin tuna is orders of magnitude larger than previously thought (Waples et al., 2018). Ne/Nc ratio is conditioned on population structure, demographic fluctuations and recent population size changes, as it was discussed above and recently empirically demonstrated for pinnipeds (Peart et al., 2020). Specifically, species of conservation concern typically have census population sizes and current effective population sizes smaller than would be expected from their long-term Ne. Only the reconstruction of the entire temporal Ne continuum provides the required information about Ne oscillations and the relationship between Ne and Nc. Such knowledge helps to predict the population’s future.

Joint analyses of contemporary and long-term Ne can also be used to identify recent changes in genetic variation and their effect on the extinction risk. This can be achieved by sequencing historical samples and comparing contemporary and historical patterns of genetic variation associated with changes in Ne. Examples of such work include the analysis of Crested ibis genomes (Feng et al., 2019), where historical changes in Ne have been reconstructed with PSMC, while more recent demography has been modelled with the ABC approach. Results demonstrated that a recent bottleneck has largely removed ancient polymorphisms and caused elevation of inbreeding coefficient and homozygous deleterious mutation load in contemporary populations. Museum specimens have also been used to investigate the genomic consequences of recent population decline in gorillas, demonstrating reduction of polymorphism, increased inbreeding and genetic load (van der Valk et al., 2019). Historical and contemporary samples were also used to infer the demography of extinct and living lions (de Manuel et al., 2020). All these examples demonstrate that historical snapshots of genetic variation contribute substantially to the understanding of recent changes in Ne. Recent developments that allow the direct inclusion of ancient samples in demographic inferences and linking these samples to past demographic events or historical and climate records promise to uncover the full potential of historical DNA (Loog, 2021). Such analyses should become feasible for many species, as whole-genome
data from contemporary and historical populations are becoming 
routinely generated (Fuentes-Pardo & Ruzzante, 2017; Hohenlohe 
et al., 2021; Orlando et al., 2021).

Recent climate/historical events can also drive, indirectly or di-
rectly, changes in selective pressures. For example, Feng et al. (2019) 
demonstrated that drift outweighs ancestral balancing selection 
in modern populations of the Crested ibis. Conversely, de Jong 
et al. (2020) found evidence for a consistent mode of selection 
across historical periods in several populations of roe deers that 
differ in their Ne trajectories. In particular, in this species genes 
associated with reproductive biology evolve under constant selec-
tive pressure despite reduced effective population size through the 
Pleistocene. These studies show how considering the demographic 
history and natural selection at various timescales can inform about 
the forces shaping genetic diversity and differentiation within spe-
cies (Alexander & Dutoit, 2020).

While the relative role of selection and demography in shap-
ing genetic variation is still a matter of intense discussion (Jensen 
et al., 2019; Kern & Hahn, 2018), these two forces certainly interact, 
producing complex patterns of genetic diversity across the genome 
and influencing inferences of Ne trajectory (Charlesworth, 2009; 
Ellegren & Galtier, 2016; Ewing & Jensen, 2016; Pouyet et al., 2018). 
To account for effects of linked selection that reduce Ne around 
functional regions (much less common balancing selection that can 
increase Ne is usually ignored), demography can be inferred using 
two Ne classes, one for neutral and the other for functional genomic 
regions (Rougemont et al., 2020; Rougeux et al., 2017). Alternatively, 
joint inference of demography and selection across different times-
ccales can be performed using ABCtoolbox (Wegmann et al., 2010) 
combined with msms simulator (Ewing & Hermisson, 2010) or using 
other ABC-based approaches (e.g. Fraïsse et al., 2021; Sackman 
et al., 2019). Such analyses can provide information about the distri-
bution of selection coefficients of new mutations, as well as improve 
the reconstruction of Ne trajectories (e.g. Johri et al., 2020). The 
analyses are, however, computationally intensive, and thus at this 
moment can only be applied to simple models, while still requiring 
some expectations regarding ancient and current Ne, as can be seen 
in analyses of a fruit fly population (Johri et al., 2020). However, if 
we only aim at approximately correcting Ne trajectory for the 
con founding effects of negative selection, demographic history can be 
inferred with reasonable accuracy, by averaging selection effects 
across all possible shapes of the distribution of fitness effects (Johri 
et al., 2021).

Selection (both directional and balancing) and demography can 
also be co-inferred using the rapidly developing machine learning 
approaches. For example, a deep neural network was developed to 
jointly infer simple demographic changes and detect hard and 
soft selective sweeps (Sheehan & Song, 2016). Machine learning has 
also the potential to detect complex patterns left by selection 
using training sets, usually produced by simulations conditioned on 
known/inferred demographic history (Schrider & Kern, 2018). Deep 
learning methods can also extract other information from sequence 
alignments, often outperforming expert-derived statistical methods 
(Flagel et al., 2019). For example, Adrion et al. (2020) demonstrated 
a method to infer recombination rates, where data for training can 
be generated on a Ne trajectory inferred with PSMC-like methods. 
Another example includes work by Lozano et al. (2021) who applied 
machine learning to estimate deleterious gene index in sorghum and 
maize. They found decreased deleterious burden in landraces com-
pared with wild sorghum, and different scenarios were simulated to 
understand this difference, where simulations were parameterised 
with Ne estimates, inferred with SMC++.

These examples demonstrate the flexibility of machine learn-
ing which opens up a whole slew of opportunities for population 
genomic inference in ways that have never before been possible 
(Schrider & Kern, 2018). An inherent part of these investigations is 
generating training sets, based on known demographic parameters. 
Currently, because of the complexity of the analyses, the simplifying 
assumption of constant Ne is often applied, even if Ne trajectory 
is inferred. Certainly, this will change with advances in the field. 
Machine learning can also be used to automatically estimate param-
eters in population genetic models, including changes in Ne (Sanchez 
et al., 2020; Wang et al., 2021). In such a case, even without expert 
knowledge about summary statistics, accuracy similar to that of ABC 
can be achieved. Furthermore, combining machine learning and ABC 
can improve performance while combining the advantages of both 
frameworks (Sanchez et al., 2020).

Joint inferences across the time continuum can help us in un-
derstanding various biological phenomena in a broader context. For 
example, trajectories of recent and historical Ne can be used to infer 
the amount of deleterious variation and risk of inbreeding depression 
associated with particular ancestries in contemporary populations. 
In particular, IBD-based methods, which can infer approximately 100 
generations of demographic history and can be applied to ancestry-
specific segments, can reveal effective population sizes of different 
ancestral populations that contributed to an admixed population 
(Browning et al., 2018; Ongaro et al., 2019). This approach requires 
relatively large sample sizes (>100 individuals) and accurate deter-
mination of local ancestry (Browning & Browning, 2015; Browning 
et al., 2018), but with technological advances, such analyses can also 
be applied to non-model organisms. An even more interesting pic-
ture can be drawn if we could look at the long-term effective pop-
ulation sizes, which can be achieved, for example, by analysing SFS 
of introgressed fragments, assuming that SFS of introgressed seg-
ments reflects SFS of ancestral populations (e.g. Gravel et al., 2013). 
Different ancestries might harbour different amounts of deleterious 
variation determined by historical Ne trajectories, disproportionately 
affecting inbreeding depression in bottlenecked populations. 
Such analyses of admixed human populations suggested that African 
 haplotypes might play a particularly important role in the genetic ar-
chitecture of complex diseases (Szpiech et al., 2019), indicating that 
rare deleterious recessive mutations accumulating in large popula-
tions might excessively contribute to inbreeding depression. A sim-
lar explanation based on computer simulations has been proposed for 
elevated inbreeding depression in the Isle Royal wolf population 
oberved after the arrival of a migrant from a mainland population.
(Kyriazis et al., 2021; Robinson et al., 2020), on the other hand, these analyses have been criticised for applying unrealistic assumptions and parameter distributions (Ralls et al., 2020), but yet another recent analysis demonstrated no simple general relationship between neutral genetic diversity (aka long-term effective population size) and the risk of species extinction (Teixeira & Huber, 2021). To address such controversies, we need a better understanding of how demographic history and functional genetic diversity shape deleterious variation segregating in populations. That would be possible only when we reconstruct Ne trajectories over the entire temporal continuum. They can later serve as a groundwork for generating meaningful predictions based on theoretical expectations and computer simulations.

6 | OUTLOOK

With the new analytical methods, the increasing amount and quality of genomic data we can now access the entire temporal Ne continuum, bridging the gap between contemporary and long-term Ne. Still, most of the available methods provide reliable information only for parts of the continuum and it is difficult to imagine a single method that would perform well across the entire continuum. Indeed, the few existing solutions that promise the reconstruction of the entire continuum are not fully satisfactory, as they rely heavily on time-consuming simulations. The complex interaction among data quantity, quality and sometimes restrictive assumptions of the methods cause interpretational difficulties. Therefore, using several complementary approaches to infer the temporal Ne continuum should be adopted as the gold standard in the field, and there is an urgent need for the development of software packages that make multiple methods available for the user. In particular, exploratory analysis with model-flexible methods may be followed up by more complex analyses of a restricted set of models that refine the estimates and incorporate additional factors, such as spatial complexity. Judging from the growing appreciation of the temporal Ne continuum and its increasing usage in diverse areas of evolutionary biology, we expect rapid progress in the coming years. The two exciting developments are likely to be game changers: wide adoption of machine learning and transition to haplotype-resolved population genomic data. The expected progress notwithstanding, interpretational difficulties are likely to remain, emphasising the need for a thorough understanding of the Ne theory behind the methods, their assumptions and inherent limitations.

ACKNOWLEDGEMENTS

We thank members of the Genomics and Experimental Evolution Group at Jagiellonian University and Evolutionary Biology Group at Adam Mickiewicz University for their help in improving this manuscript. We thank two anonymous reviewers and Daniel Ruzzante for helpful comments that improved our manuscript. This work was funded by Polish National Science Center 2018/30/E/NZ8/00105 grant to K.N.-B. and 2018/31/D/NZ8/00091 grant to M.K.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS

K.N.-B., M.K. and W.B. conceived the idea of the review and wrote the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/2041-210X.13740.

DATA AVAILABILITY STATEMENT

Manuscript contains no data.

ORCID

Krystyna Nadachowska-Brzyska https://orcid.org/0000-0002-8457-310X
Mateusz Konczal https://orcid.org/0000-0002-7691-8075
Wieslaw Babik https://orcid.org/0000-0002-1698-6615

REFERENCES

Adrion, J. R., Galloway, J. G., & Kern, A. D. (2020). Predicting the landscape of recombination using deep learning. Molecular Biology and Evolution, 37(6), 1790–1808. https://doi.org/10.1093/MOLBEV/MSAA038
Alexander, A., & Dutoit, L. (2020). Roe deer on ice: Selection despite limited effective population size through the Pleistocene. Molecular Ecology, 29(15), 2765–2767. https://doi.org/10.1111/MEC.15511
Arredondo, A., Mourato, B., Nguyen, K., Boitard, S., Rodrigue, W., Noûs, C., Mazet, O., & Chikhi, L. (2021). Inferring number of populations and changes in connectivity under the n-island model. Heredity, 126(6), 896–912. https://doi.org/10.1038/s41437-021-00426-9
Asthana, S., Schmidt, S., & Sunyaev, S. (2005). A limited role for balancing selection. Trends in Genetics, 21(1), 30–32. https://doi.org/10.1016/j.tig.2004.11.007
Barbato, M., Orozco-terWengel, P., Tapio, M., & Bruford, M. W. (2015). SNEP: A tool to estimate trends in recent effective population size trajectories using genome-wide SNP data. Frontiers in Genetics, 6(Mar). https://doi.org/10.3389/FGENE.2015.00109
Barroso, G. V., Puzovic, N., & Dutheil, J. Y. (2019). Inference of recombination maps from a single pair of genomes and its application to ancient samples. PLoS Genetics, 15(11). https://doi.org/10.1371/JOURNAL.PGEN.1008449
Beaumont, M. A. (2003). Estimation of population growth or decline in genetically monitored populations. Genetics, 164(3), 1139–1160. https://doi.org/10.1093/GENETICS/164.3.1139
Beaumont, M. A. (2010). Approximate Bayesian computation in evolution and ecology. Annual Review of Ecology, Evolution, and Systematics, 41, 379–406. https://doi.org/10.1146/ANNUREV-ECOLSYS-102209-144621
Beaumont, M. A., & Rannala, B. (2004). The Bayesian revolution in genetics. Nature Reviews Genetics, 5(4), 251–261. https://doi.org/10.1038/NRG1318
Beichman, A. C., Huerta-Sanchez, E., & Lohmueller, K. E. (2018). Using genomic data to infer historic population dynamics of nonmodel organisms. Annual Review of Ecology, Evolution, and Systematics, 49, 433–456. https://doi.org/10.1146/ANNUREV-ECOLSYS-110617-062431
Beichman, A. C., Phung, T. N., & Lohmueller, K. E. (2017). Comparison of single genome and allele frequency data reveals discordant
Gilbert, K. J., & Whitlock, M. C. (2015). Evaluating methods for estimating local effective population size with and without migration. *Evolution*, 69(8), 2154–2166. https://doi.org/10.1111/evo.12713

Gravel, S., Zacchia, F., Moreno-Estrada, A., Byrnes, J. K., Muzzio, M., Rodríguez-Flores, J. L., Kenny, E. E., Cignoux, C. R., Maples, B. K., Guillet, W., Dutil, J., Via, M., Sandoval, K., Bedoya, G., Oleksyk, T. K., Ruiz-Linares, A., Burchard, E. G., Martinez-Cruzado, J. C., & Bustamante, C. D. (2013). Reconstructing native American migrations from whole-genome and whole-exome data. *PLoS Genetics*, 9(12). https://doi.org/10.1371/JOURNAL.PGEN.1004023

Griffiths, R. (1991). The two-locus ancestral graph. In I. V. Basawa & R. L. Taylor (Eds.), *Proceedings of the symposium on applied probability* (pp. 100–117). Institute of Mathematical Statistics.

Griffiths, R., & Marjoram, P. (1996). Ancestral inference from samples of DNA sequences with recombination. *Journal of Computational Biology*, 3(4), 479–502. https://doi.org/10.1089/cmb.1996.3.479

Griffiths, R., & Tavaré, S. (1998). The age of a mutation in a general coalescent tree. *Stochastic Models*, 14(1-2), 273–295. https://doi.org/10.1080/15326349808807471

Grusea, S., Rodriguez, W., Pinchon, D., Chikhi, L., Boitard, S., & Mazet, O. (2019). Coalescence times for three genes provide sufficient information to distinguish population structure from population size changes. *Journal of Mathematical Biology*, 78(1-2), 189–224. https://doi.org/10.1007/S00285-018-1272-4

Gutenkunst, R. N., Hernandez, R. D., Williamson, S. H., & Bustamante, C. D. (2009). Inferring the joint demographic history of multiple populations from multidimensional SNP frequency data. *PLoS Genetics*, 5(10), e1000695. https://doi.org/10.1371/JOURNAL.PGEN.1000695

Haddad, N. M., Brudvig, L. A., Clobert, J., Davies, K. F., Gonzalez, A., Holt, R. D., Lovejoy, T. E., Sexton, J. O., Austin, M. P., Collins, C. D., Cook, W. M., Dasmen, I. E., Ewers, R. M., Foster, B. L., Jenkins, C. N., King, A. J., Laurance, W. F., Levey, D. J., Margules, C. R., ... Townshend, J. R. (2015). Habitat fragmentation and its lasting impact on Earth’s ecosystems. *Science Advances*, 1(2). https://doi.org/10.1126/SCIADV.1500052

Hare, M. P., Nunney, L., Schwartz, M. K., Ruzzante, D. E., Burford, M., Waples, R. S., Portnoy, D. S., & Gold, J. R. (2016). A method for detecting recent changes in contemporary effective population size from linkage disequilibrium at linked and unlinked loci. *Heredity*, 117(4), 207–216. https://doi.org/10.1038/HDY.2016.30

Hössjer, O., Laikre, L., & Ryman, N. (2016). Effective sizes and time to migration–drift equilibrium in geographically subdivided populations. *Theoretical Population Biology*, 112, 139–156. https://doi.org/10.1016/J.TPB.2016.09.001

Hössjer, O., Olsson, F., Laikre, L., & Ryman, N. (2014). A new general analytical approach for modeling patterns of genetic differentiation and effective size of subdivided populations over time. *Mathematical Biosciences*, 258, 113–133. https://doi.org/10.1016/J.MBS.2014.10.001

Hui, T. Y. J., & Burt, A. (2015). Estimating effective population size from temporally spaced samples with a novel, efficient maximum-likelihood algorithm. *Genetics*, 200(1), 285–293. https://doi.org/10.1534/GENETICS.115.174904

Husemann, M., Zachos, F. E., Paxton, R. J., & Habel, J. C. (2016). Effective population size in ecology and evolution. *Heredity*, 117(4), 191–192. https://doi.org/10.1038/HDY.2016.75

Jensen, J. D., Payseur, B. A., Stephan, W., Aquadro, C. F., Lynch, M., Charlesworth, D., & Charlesworth, B. (2019). The importance of the neutral theory in 1968 and 50 years on: A response to Kern and Hahn 2018. *Evolution*, 73(1), 111–114. https://doi.org/10.1111/EVO.13650

Johri, P., Charlesworth, B., & Jensen, J. D. (2020). Toward an evolutionarily appropriate null model: Jointly inferring demography and purifying selection. *Genetics*, 215(1), 173–192. https://doi.org/10.1534/GENETICS.119.303002

Johri, P., Riial, K., Becher, H., Excoffier, L., Charlesworth, B., & Jensen, J. D. (2021). The impact of purifying and background selection on the inference of population history: Problems and prospects. *Molecular Biology and Evolution*, 38(7), 2986–3003. https://doi.org/10.1093/MOLBEV/MSAB050

Kern, A. D., & Hahn, M. W. (2018). The neutral theory in light of natural selection. *Molecular Biology and Evolution*, 35(6), 1366–1371. https://doi.org/10.1093/MOLBEV/MSY092
Kyriazis, C. C., Wayne, R. K., & Lohmueller, K. E. (2021). Strongly deleterious mutations are a primary determinant of extinction risk due to inbreeding depression. *Evolution Letters*, 5(1), 33–47. https://doi.org/10.1002/EVL3.209

Leitwein, M., Duranton, M., Rougemont, Q., Gagnaire, P. A., & Bernatchez, L. (2020). Using haplotype information for conservation genomics. *Trends in Ecology & Evolution*, 35(3), 245–258. https://doi.org/10.1016/j.tree.2019.10.012

Li, H., & Durbin, R. (2011). Inference of human population history from individual whole-genome sequences. *Nature*, 475(7357), 493–496. https://doi.org/10.1038/NATURE10231

Liu, X., & Fu, Y. X. (2020). Stairway Plot 2: Demographic history inference from SNP frequency spectra. *Nature Genetics*, 47(5), 555–559. https://doi.org/10.1038/ng.3254

Liu, X., & Fu, Y. X. (2020). Stairway Plot 2: Demographic history inference with folded SNP frequency spectra. *Genome Biology*, 21(1). https://doi.org/10.1186/s13059-020-02196-9

Loog, L. (2021). Sometimes hidden but always there: The assumptions underlying genetic inference of demographic histories: Demographic inference from genetic DNA. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 376(1816). https://doi.org/10.1098/RSTB.2019.0719RSTB20190719

Low, J. J., & Walker, M. (2014). Reconstructing quaternary environments. Routledge.

Lozano, R., Gazave, E., dos Santos, J. P. R., Stetter, M. G., Valluru, R., Bandillo, N., Fernandes, S. B., Brown, P. J., Shakoor, N., Mockler, T. C., Cooper, E. A., Taylor Perkins, M., Buckler, E. S., Ross-Ibarra, J., & Gore, M. A. (2021). Comparative evolutionary genetics of deleterious load in sorghum and maize. *Science*, 369(6500), 1162–1166. https://doi.org/10.1126/SCIENCE.abb3752

Lamy, J. B. (2019). Estimating effective population size of large mammals from patterns of linkage disequilibrium between SNPs. *Molecular Biology and Evolution*, 36(9), 2209–2223. https://doi.org/10.1093/molbev/msz125

MacLeod, I. M., Larkin, D. M., Lewin, H. A., Hayes, B. J., & Goddard, M. E. (2013). Inferring demography from runs of homozygosity in whole-genome sequence, with correction for sequence errors. *Molecular Biology and Evolution*, 30(9), 2209–2223. https://doi.org/10.1093/molbev/msm093

McMillan, W. O., Jiggins, C. D., & Chan, Y. F. (2021). Haplotype tagging reveals parallel formation of hybrid races in two butterfly species. *Proceedings of the National Academy of Sciences of the United States of America*, 118(25), e2015005118. https://doi.org/10.1073/PNAS.2015005118

Mezzavilla, M., & Ghirotto, S. (2015). Neon: An R package to estimate human effective population size and divergence time from patterns of linkage disequilibrium between SNPS. *Journal of Computer Science & Systems Biology*, 8(1). 1. https://doi.org/10.4172/jcssb.1000168

Miller, W., Schuster, S. C., Welch, A. J., Ratan, A., Bedoya-Reina, O. C., Zhao, F., Kim, H. L., Burhans, R. C., Dratz, D. I., Wittekindt, N. E., Tomsho, L. P., Ibarra-Laclette, E., Herrera-Estrella, L., Peacock, E., Farley, S., Sage, G. K., Rode, K., Obbard, M., Montiel, R., ... Lindqvist, C. (2012). Polar and brown bear genomes reveal ancient admixture and demographic footprints of past climate change. *Proceedings of the National Academy of Sciences of the United States of America*, 109(36), e2382–e2390. https://doi.org/10.1073/pnas.1210506109

Mitchell, K. J., & Rawlence, N. J. (2021). Examining natural history through the lens of palaeogenomics. *Trends in Ecology & Evolution*, 36(3), 258–267. https://doi.org/10.1016/J.TREE.2020.10.005

Nadachowska-Brzyska, K., Burri, R., Olason, P. I., Kawakami, T., Smeds, L., & Ellegren, H. (2013). Demographic divergence history of pied flycatcher and collared flycatcher inferred from whole-genome re-sequencing data. *PLoS Genetics*, 9(11), e1003942. https://doi.org/10.1371/JOURNAL.PGEN.1003942

Nadachowska-Brzyska, K., Burri, R., Smeds, L., & Ellegren, H. (2016). PSMC analysis of effective population sizes in molecular ecology and its application to black-and-white *Ficedula flycatchers*. *Molecular Ecology*, 25(5), 1058–1072. https://doi.org/10.1111/MEC.13540

Nadachowska-Brzyska, K., Dortoi, L., Smeds, L., Kardos, M., Gustafsson, L., & Ellegren, H. (2021). Genomic inference of contemporary effective population size in a large island population of collared flycatchers (*Ficedula albicollis*). *Molecular Ecology*. https://doi.org/10.1111/mec.16025

Nei, M., & Tajima, F. (1981). Genetic drift and estimation of effective population size. *Genetics*, 98(3), 625–640. https://doi.org/10.1093/GENETICS/98.3.625

Nordborg, M., & Krone, M. (2002). Separation of time scales and convergence to the coalescent in structured populations. In M. Slatkin & M. Veuille (Eds.), *Modern developments in theoretical population genetics: The legacy of Gustave Malecot* (pp. 194–232). Oxford University Press.

Ongaro, L., Sciar, M. O., Flores, R., Raveane, A., Marnetto, D., Sarno, S., Gnecci-Ruscone, G. A., Alarcón-Riquelme, M. E., Pátin, E., Wangkumhang, P., Hellenthal, G., Gonzalez-Santos, M., King, R. J., Kouvatsi, A., Balanovsky, O., Balanovsky, E., Atramventa, L., Turdikulova, S., Mastana, S., ... Montinaro, F. (2019). The genomic impact of European colonization of the Americas. *Current Biology*, 29(23), 3974–3986.e4. https://doi.org/10.1016/J.CUB.2019.09.076

Orlando, L., Allaby, R., Skoglund, P., Der Sarkissian, C., Stockhammer, P. W., Ávila-Arcos, M. C., Fu, Q., Krause, J., Willerslev, E., Stone, A. C., & Warinner, C. (2021). Ancient DNA analysis. *Nature Reviews Methods Primers*, 1(1), 1–26. https://doi.org/10.1038/s43586-020-00011-0

Palamara, P. F., Lenz, T., Darvsi, A., & Pe’er, I. (2012). Length distributions of identity by descent reveal fine-scale demographic history. *American Journal of Human Genetics*, 91(5), 809–822. https://doi.org/10.1016/J.AJHG.2012.08.030

Palstra, F. P., & Fraser, D. J. (2012). Effective/census population size ratio estimation: A compendium and appraisal. *Ecology and Evolution*, 2(9), 2357–2365. https://doi.org/10.1002/ECE3.329

Palstra, F. P., & Ruzzante, D. E. (2008). Genetic estimates of contemporary effective population size: What can they tell us about the importance of genetic stochasticity for wild population

...
Wiuf, C., & Hein, J. (1999). Recombination as a point process along sequences. *Theoretical Population Biology, 55*(3), 248–259. https://doi.org/10.1006/tpbi.1998.1403

Wright, S. (1931). Evolution in mendelian populations. *Genetics, 16*, 97–159. https://doi.org/10.1093/genetics/16.2.97

Wright, S. (1938). Size of population and breeding structure in relation to evolution. *Science, 87*, 430–431.

Yi, X., Liang, Y. U., Huerta-Sanchez, E., Jin, X., Cuo, Z. X. P., Pool, J. E., Xu, X., Jiang, H., Vinckenbosch, N., Korneliussen, T. S., Zheng, H., Liu, T., He, W., Li, K., Luo, R., Nie, X., Wu, H., Zhao, M., Cao, H., … Wang, J. (2010). Sequencing of 50 human exomes reveals adaptation to high altitude. *Science, 329*(5987), 75–78. https://doi.org/10.1126/science.1190371

Zieliński, P., Nadachowska-Brzyska, K., Dudek, K., & Babik, W. (2016). Divergence history of the Carpathian and smooth newts modelled in space and time. *Molecular Ecology, 25*(16), 3912–3928. https://doi.org/10.1111/MEC.13724

**How to cite this article:** Nadachowska-Brzyska, K., Konczal, M., & Babik, W. (2022). Navigating the temporal continuum of effective population size. *Methods in Ecology and Evolution*, 13, 22–41. https://doi.org/10.1111/2041-210X.13740