

Navigating the temporal continuum of effective population size

Krystyna Nadachowska-Brzyska¹  | Mateusz Konczal²  | Wiesław Babik¹ 

¹Jagiellonian University in Kraków, Faculty of Biology, Institute of Environmental Sciences, Kraków, Poland

²Adam Mickiewicz University, Faculty of Biology, Poznań, Poland

Correspondence

Krystyna Nadachowska-Brzyska
Email: krystyna.nadachowska@uj.edu.pl

Funding information

Narodowe Centrum Nauki, Grant/Award Number: 2018/30/E/NZ8/00105 and 2018/31/D/NZ8/00091

Handling Editor: Pablo Duchon

Abstract

1. Effective population size, N_e , is a key evolutionary parameter that determines the levels of genetic variation and efficacy of selection. Estimation and interpretation of N_e 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.
2. The diverse applications of the N_e concept resulted in largely independent methodological developments using different N_e definitions and focusing on the estimation of either contemporary or long-term N_e . Recently, several novel approaches appeared that allow the estimation of temporal N_e trends at various parts of the temporal N_e continuum.
3. Here, we provide an overview of the temporal aspects of N_e , asking whether the existing methods and available data provide N_e estimates for the entire temporal continuum. We outline the apparent division into contemporary and long-term N_e existing in the literature, review N_e estimation methods across the temporal continuum and navigate the reader through it pointing to the important biological and methodological limitations inherent to the estimation procedures. Finally, we provide examples of recent research and future perspectives.
4. We conclude that the entire temporal N_e continuum can now be inferred using several complementary approaches, bringing together contemporary and long-term perspectives. Further rapid progress in the field is expected from the 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 N_e theory behind the methods, their assumptions and inherent limitations.

KEYWORDS

contemporary N_e , effective population size, long-term N_e , temporal continuum

1 | INTRODUCTION

Since its introduction by Wright (1931), the concept of effective population size (N_e) 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

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Methods in Ecology and Evolution* published by John Wiley & Sons Ltd on behalf of British Ecological Society.

Glossary

Approximate Bayesian computations (ABCs)—an approach to model testing and parameter estimation that relies on using summary statistics and a large number of computer simulations to estimate the posterior probability of a model and posterior distributions of model parameters without the need for calculation of the likelihood function.

Balancing selection—any form of natural selection that maintains variation within populations.

Bottleneck—an abrupt reduction of population size.

Coalescent theory—theory that provides a mathematical model linking the properties of the genealogy (which traces the ancestry of a sample of gene copies backwards in time to their most recent common ancestor), with the demographic parameters, such as effective population size, population size changes or migration between populations; it allows the estimation of demographic parameters from a sample of DNA sequences.

Diffusion approximation—an approximation of allele frequency changes under evolutionary forces of drift, selection and migration obtained by applying mathematical techniques developed to study the process of diffusion; diffusion approximation assumes that these forces are weak.

Drift—random changes in allele frequencies over generations caused by the sampling of a finite number of gametes to form the new generation.

Harmonic mean—the reciprocal of the mean of reciprocals; is smaller than the arithmetic mean and more affected by small values.

Identity by descent (IBD)—two DNA segments are IBD if they are descended from a single ancestral DNA segment.

Identity by state (IBS)—two DNA segments are identical by state if their sequence is identical. IBS may be a consequence of common ancestry (IBD) or parallel mutations.

Inbreeding—(1) a mating between individuals that are more closely related than individuals picked from a population at random, (2) increase in the probability that two gene copies in a population will be identical by descent.

Inbreeding depression—reduction of offspring fitness as a consequence of mating among relatives; its main cause is the unmasking of phenotypic effects of recessive deleterious mutations in homozygotes.

Linkage disequilibrium—nonrandom association between alleles at different loci; may be a consequence of: (i) physical linkage, (ii) mixing of genetically differentiated populations, (iii) genetic drift and (iv) selection acting on more than one locus.

Phasing and phased data—data are phased when we know which variants from different loci are located on the same parental chromosome (or, form a haplotype); phasing is a process that produces phased data.

Run of homozygosity (RoH)—an uninterrupted segment of homozygous genotypes, caused by the transmission of two identical haplotypes by both parents.

Site frequency spectrum—the distribution of allele frequencies in a sample, usually presented as the histogram, showing the absolute or relative number of sites that have particular counts of the derived (unfolded SFS) or major (folded SFS) allele.

Wright–Fisher population—an idealised population with non-overlapping generations, in which the next generation is formed by binomial or multinomial (in case of more than two alleles) sampling of gene copies from a pool of gametes to which all individuals contribute equally. In such a population the number of offspring produced by an individual is given by a Poisson distribution.

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 N_e definitions that use and emphasise various aspects of drift (Box 1). Because the action of key evolutionary processes and their balance depend on N_e , and because suitable genetic data have become increasingly available, the interest in estimation of N_e increased markedly over the last decades. Estimation and interpretation of N_e 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 N_e estimation utilise the information contained in genetic data, as outlined below. The relationship between the definitions and estimates of N_e can, however, be complex. To put it simply, it may become unclear what kind of N_e (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 N_e , defined as N_e 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

BOX 1 Definitions of effective population size.

Initially (Wright, 1931, 1938), effective population size was defined based on the increase in inbreeding coefficient (probability of identity by descent) or based on the variance in allele frequency between generations with these two approaches considered equivalent. Then Crow (1954) noticed that under some situations, in particular when population size changes rapidly, the two approaches may produce different results, which led to the distinction between **inbreeding** and **variance Ne**. Ewens (1979) introduced **eigenvalue Ne**, which reflects the loss of heterozygosity over time and is based on the leading non-unit eigenvalue of the allele frequency transition matrix. Ewens (1982) showed that eigenvalue Ne differs from both inbreeding and variance Ne, and is defined for many theoretical models for which variance Ne does not exist. **Coalescent Ne**, which is similar to inbreeding Ne, was defined as a factor by which time needs to be rescaled to obtain a standard coalescent process in a constant size Wright–Fisher population (Nordborg & Krone, 2002; Sjödin et al., 2005). If such rescaling cannot be found, then coalescent Ne does not exist, indicating that a given model cannot be approximated by the Wright–Fisher model. A large number of other definitions, depending on how changes in the genetic composition of populations are quantified, have been discussed in Ryman et al. (2019). This multitude emphasises the elusive simplicity of the concept of Ne. As Ewens (2004) put it: 'the concept of the effective population size is widely misused in the literature, especially in areas outside of, but associated with, evolutionary genetics'.

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

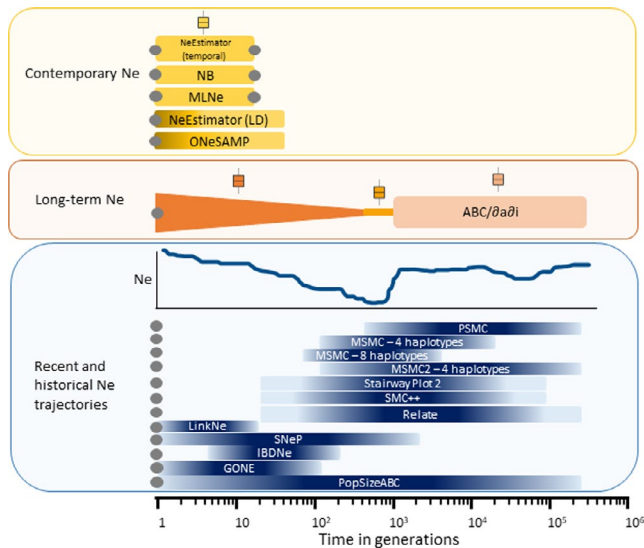


FIGURE 1 Examples of the key methods to infer N_e with the timeframe for which the N_e estimate is obtained. The insets correspond to contemporary (yellow), long-term (orange) and recent and historical N_e trajectories (blue). In each inset, particular methods/approaches are represented by horizontal bars spanning the time for which they provide information. The long-term N_e inset is divided into three parts, representing simple demographic changes over time possible to model with this approach. Boxplots in contemporary and long-term N_e insets (above the horizontal bars) represent point N_e estimates produced by these methods. This is in contrast to the blue N_e trajectory in the blue inset that represents N_e changes over time. Particular methods that infer recent or historical N_e trajectories provide information about a specific part of the N_e trajectory. Time is in generations on a logarithmic scale. Grey circles represent sampling time(s) for which genetic data were obtained. Note that the spans of the timeframes are approximate since they depend on the data used and the true demographic history; this applies particularly for SFS-based methods and recent times

of contemporary N_e is particularly important for endangered, managed or harvested populations (Hare et al., 2011; Marandel et al., 2019; Waples & Do, 2010). Endangered populations are often characterised by small census size (N_c) as well as small N_e . In such cases the signal of drift is strong and its quantification relatively easy. In contrast, many harvested populations, such as, for example, marine fish, may have enormous N_c but their N_e is much smaller resulting in very low N_e/N_c ratios (Hauser & Carvalho, 2008; Palstra & Ruzzante, 2008, but see Waples et al., 2018). Assessment of N_e in small, threatened populations as well as in extensively harvested populations is essential for successful conservation and sustainable management.

The two main approaches to the estimation of contemporary N_e 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 N_e 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, N_e 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 N_e 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 N_e is very small, the other methods have been successfully applied to infer contemporary N_e 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 N_e trajectory) 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/tjhfwwxyzy>) 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 N_e over that period. N_e 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 N_e . Initially, LD-based methods were used for a limited number of physically unlinked loci for which quantification of the strength of drift and N_e 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 N_e 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 N_e in small populations ($<1,000$). Several simulation studies suggested that contemporary N_e estimation methods can be used to estimate N_e of larger populations when genome-wide data are used (Hui & Burt, 2015; Wang et al., 2016). However, empirical studies showed that estimation of N_e 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 N_e includes inferring N_e 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 N_e should refer to the previous generation (generation prior to sampling). However, obtaining a N_e 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 N_e from different generations/periods (Waples, 2005, Figure 1). Overall, temporal methods estimate harmonic mean N_e over the time the samples were collected and LD-based methods reflect N_e 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 (N_b) instead of the N_e (Ruzzante et al., 2016). In such case, N_e can be estimated based on N_b 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 N_e includes also inference of N_e 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 N_e

Long-term N_e can be defined as the harmonic mean of per-generation N_e s over an extended period (hundreds of generations or more) of the evolutionary history of the species in question (Figure 1). In contrast to contemporary N_e , estimation of long-term N_e 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 N_e , 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 N_e 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 N_e (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 N_e 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; Salmona 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 N_e 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 N_e of descendant as well as ancestral populations of hundreds of species from various taxonomic groups (Nadachowska-Brzyska et al., 2013; Ziełński 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 N_e

To understand the difference and the relationship between a demographic model and long-term N_e , 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 N_e 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 N_e trajectories of the descendent and ancestral population. Assuming the proposed model, the historical demographic inference would involve estimation of N_e for the ancestral population and N_e for a descendant population in a form of long-term N_e . 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.

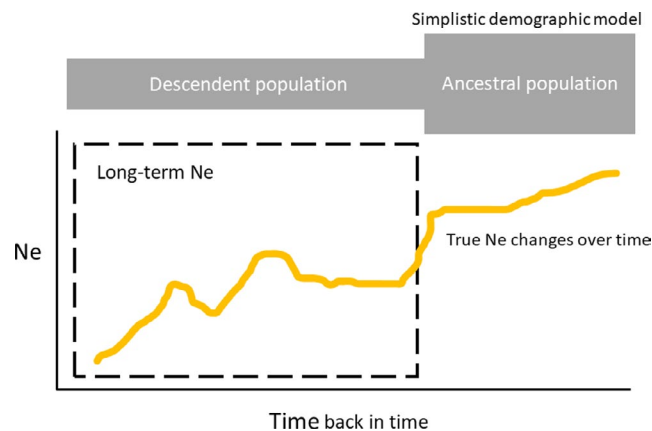


Figure Box 2 True N_e changes over time (yellow line) in relation to the simplistic demographic model (grey boxes)

reality and are limited by the number of parameters that can be estimated from the data. In consequence, estimated N_e s are a result of complex demographic events not necessarily explicitly captured by the model, and both ancestral N_e and long-term N_e estimates may differ from true N_e (Box 2).

3 | TEMPORAL CONTINUUM OF N_e

Information on temporal N_e changes is a crucial aspect of the demographic history often missing in demographic inferences described above. For example, temporal N_e 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 N_e dynamics resulted in a wide range of methods developed to infer N_e 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 N_e 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 N_e 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 N_e). 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 N_e population size can be only roughly reconstructed. A major advance towards the reconstruction of the temporal N_e 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 N_e over time differ in the time-frame 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 N_e 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 N_e 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 time-point samples, genetic map for LD-based method	http://www.molecularfisherieslaboratory.com.au/neesimulator-software/	Do et al. (2014)
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 statistics	https://github.com/kingufl/ONeSAMP	Tallmon et al. (2008)
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)
∂a∂i	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	https://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/jpopgen/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)

TABLE 1 (Continued)

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/popsi-zeabc	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/snepnetren-ds/	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				
Co-inferring demography and selection				
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 N_e 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 N_e 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 N_e 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 N_e .

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 N_e 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 N_e 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 N_e estimates for the time interval between 300–400 generations before present (gbp) and hundreds of thousands of gbp (kbp). 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 gbp (Figure 1). The exact timeframe of inference may differ among species, but very recent N_e dynamics cannot be inferred using these methods.

3.2 | Inference of recent N_e 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 N_e of a population (discussed in the previous section; Wang et al., 2016; Waples, 2006; Waples & Do, 2008) and N_e 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 N_e at different times in the recent past. Distribution of IBD, which can be inferred from population genomic data, carries information about recent N_e dynamics (Hayes et al., 2003; MacLeod et al., 2009, 2013). Numerous long IBD tracks shared by individuals indicate recent common ancestry, suggesting small N_e , and analogously, a large number of short IBD tracks implies larger N_e (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 N_e changes over time (MacLeod et al., 2009, 2013).

There is an extensive variation among methods in the temporal resolution of recent N_e trajectories (Figure 1). Some methods can only infer N_e changes for the last 15–20 gbp (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 gbp (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 N_e changes between a few and 100–200 gbp (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 N_e CONTINUUM

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

4.1 | Data-related limitations

Different methods estimating N_e 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 N_e) 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 N_e 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 N_e 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 N_e 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) N_e in a panmictic population, and showed that this measure necessarily confounds N_e changes with the effects of population structure. In an attempt to co-estimate N_e 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.

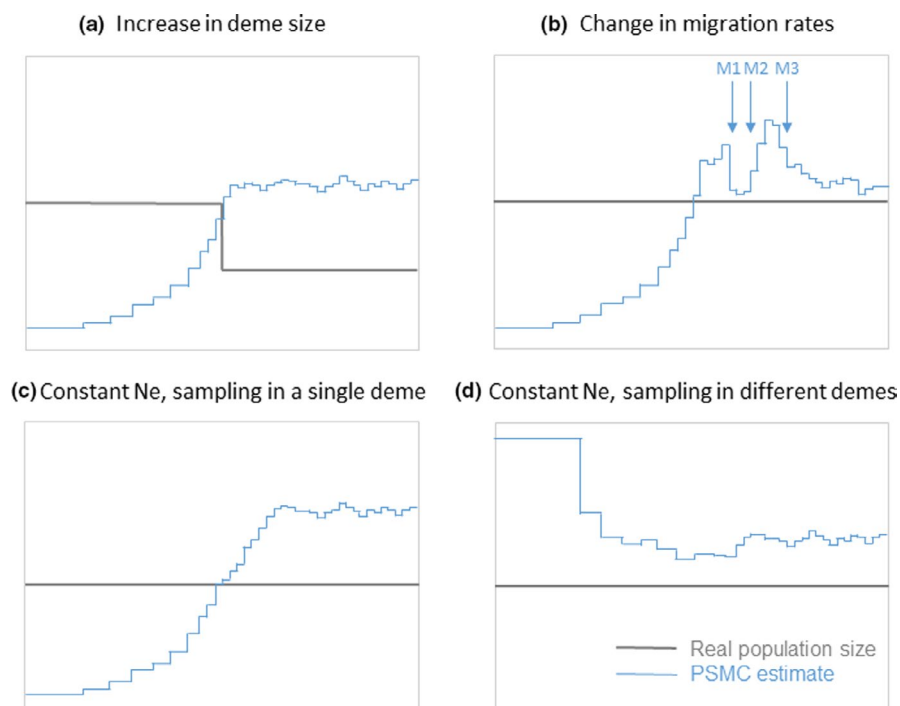


Figure Box 3 The behaviour of PSMC-like methods under population subdivision (adapted from Mazet et al., 2016). (a) The actual increase in the size of a subdivided population is reconstructed by PSMC-like methods as a demographic decline when subdivision is ignored, (b) Changes in migration rates (M1–M3) in a constant size subdivided populations are reconstructed by PSMC-like methods as demographic fluctuation, (c and d) in a constant size subdivided population PSMC-like methods would infer demographic decline (c) or expansion (d) depending on the sampling scheme

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 Figure). 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 (Sjödín 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) Nes 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 N_e 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 N_e 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) N_e 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 N_e 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 N_e may lead to false inferences and interpretation.

5 | EXAMPLES OF RECENT RESEARCH AND FUTURE PERSPECTIVES

To jointly infer contemporary and long-term N_e 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 N_e 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 N_e (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 N_e 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 N_e 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 N_e 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; Ruzzante et al., 2019; Waples & Feutry, 2021). The same data can be used to assess N_e , establishing a direct link between N_c and N_e estimates, which led, for example, to the discovery that the N_e/N_c ratio in southern bluefin tuna is orders of magnitude larger than previously thought (Waples et al., 2018). N_e/N_c 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 N_e . Only the reconstruction of the entire temporal N_e continuum provides the required information about N_e oscillations and the relationship between N_e and N_c . Such knowledge helps to predict the population's future.

Joint analyses of contemporary and long-term N_e 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 N_e . Examples of such work include the analysis of Crested ibis genomes (Feng et al., 2019), where historical changes in N_e 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 N_e . 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 directly, 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 N_e trajectories. In particular, in this species genes associated with reproductive biology evolve under constant selective 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 species (Alexander & Dutoit, 2020).

While the relative role of selection and demography in shaping 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 N_e trajectory (Charlesworth, 2009; Ellegren & Galtier, 2016; Ewing & Jensen, 2016; Pouyet et al., 2018). To account for effects of linked selection that reduce N_e around functional regions (much less common balancing selection that can increase N_e is usually ignored), demography can be inferred using two N_e 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 timescales 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 distribution of selection coefficients of new mutations, as well as improve the reconstruction of N_e 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 N_e , as can be seen in analyses of a fruit fly population (Johri et al., 2020). However, if we only aim at approximately correcting N_e trajectory for the confounding 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 (Schridder & 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 N_e 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 compared with wild sorghum, and different scenarios were simulated to understand this difference, where simulations were parameterised with N_e estimates, inferred with SMC++.

These examples demonstrate the flexibility of machine learning which opens up a whole slew of opportunities for population genomic inference in ways that have never before been possible (Schridder & 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 N_e is often applied, even if N_e trajectory is inferred. Certainly, this will change with advances in the field. Machine learning can also be used to automatically estimate parameters in population genetic models, including changes in N_e (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 understanding various biological phenomena in a broader context. For example, trajectories of recent and historical N_e 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 determination 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 picture can be drawn if we could look at the long-term effective population sizes, which can be achieved, for example, by analysing SFS of introgressed fragments, assuming that SFS of introgressed segments reflects SFS of ancestral populations (e.g. Gravel et al., 2013). Different ancestries might harbour different amounts of deleterious variation determined by historical N_e 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 architecture of complex diseases (Szpiech et al., 2019), indicating that rare deleterious recessive mutations accumulating in large populations might excessively contribute to inbreeding depression. A similar explanation based on computer simulations has been proposed for elevated inbreeding depression in the Isle Royal wolf population observed after the arrival of a migrant from a mainland population

(Kyriazis et al., 2021; Robinson et al., 2019). 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 N_e 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 N_e continuum, bridging the gap between contemporary and long-term N_e . 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 N_e 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 N_e 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 N_e 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>

Wiesław Babik  <https://orcid.org/0000-0002-1698-6615>

REFERENCES

- Adrión, 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., Rodríguez, W., Noués, 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., Puzović, 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

- demographic histories. *G3 Genes|genomes|genetics*, 7(11), 3605–3620. <https://doi.org/10.1534/G3.117.300259>
- Berthier, P., Beaumont, M. A., Cornuet, J. M., & Luikart, G. (2002). Likelihood-based estimation of the effective population size using temporal changes in allele frequencies: A genealogical approach. *Genetics*, 160(2), 741–751. <https://doi.org/10.1093/GENETICS/160.2.741>
- Boitard, S., Rodríguez, W., Jay, F., Mona, S., & Austerlitz, F. (2016). Inferring population size history from large samples of genome-wide molecular data - An approximate bayesian computation approach. *PLoS Genetics*, 12(3), e1005877. <https://doi.org/10.1371/JOURNAL.PGEN.1005877>
- Bravington, M. V., Grewe, P. M., & Davies, C. R. (2016). Absolute abundance of southern bluefin tuna estimated by close-kin mark-recapture. *Nature Communications*, 7(1), 13162. <https://doi.org/10.1038/ncomms13162>
- Browning, S. R., & Browning, B. L. (2010). High-resolution detection of identity by descent in unrelated individuals. *American Journal of Human Genetics*, 86(4), 526–539. <https://doi.org/10.1016/J.AJHG.2010.02.021>
- Browning, S. R., & Browning, B. L. (2015). Accurate non-parametric estimation of recent effective population size from segments of identity by descent. *American Journal of Human Genetics*, 97(3), 404–418. <https://doi.org/10.1016/J.AJHG.2015.07.012>
- Browning, S. R., Browning, B. L., Daviglus, M. L., Durazo-Arvizu, R. A., Schneiderman, N., Kaplan, R. C., & Laurie, C. C. (2018). Ancestry-specific recent effective population size in the Americas. *PLoS Genetics*, 14(5), e1007385. <https://doi.org/10.1371/JOURNAL.PGEN.1007385>
- Bubb, K. L., Bovee, D., Buckley, D., Haugen, E., Kibukawa, M., Paddock, M., Palmieri, A., Subramanian, S., Zhou, Y., Kaul, R., Green, P., & Olson, M. V. (2006). Scan of human genome reveals no new loci under ancient balancing selection. *Genetics*, 173(4), 2165–2177. <https://doi.org/10.1534/genetics.106.055715>
- Caballero, A. (1994). Developments in the prediction of effective population size. *Heredity*, 73(6), 657–679. <https://doi.org/10.1038/HDY.1994.174>
- Charlesworth, B. (2009). Fundamental concepts in genetics: Effective population size and patterns of molecular evolution and variation. *Nature Reviews. Genetics*, 10(3), 195–205. <https://doi.org/10.1038/nrg2526>
- Charlesworth, B. (2015). Causes of natural variation in fitness: Evidence from studies of *Drosophila* populations. *Proceedings of the National Academy of Sciences of the United States of America*, 112(6), 1662–1669. <https://doi.org/10.1073/pnas.1502053112>
- Charlesworth, B., & Charlesworth, D. (2010). *Elements of evolutionary genetics*. Roberts and Company.
- Chikhi, L., Rodríguez, W., Grusea, S., Santos, P., Boitard, S., & Mazet, O. (2018). The IICR (inverse instantaneous coalescence rate) as a summary of genomic diversity: Insights into demographic inference and model choice. *Heredity*, 120(1), 13–24. <https://doi.org/10.1038/S41437-017-0005-6>
- Crow, J. F. (1954). Breeding structure of populations. II. Effective population number. In *Statistics and Mathematics in Biology* (pp. 543–556). Iowa State College Press.
- De Coster, W., Weissensteiner, M. H., & Sedlazeck, F. J. (2021). Towards population-scale long-read sequencing. *Nature Reviews Genetics*, 22(9), 572–587. <https://doi.org/10.1038/S41576-021-00367-3>
- de Jong, M. J., Li, Z., Qin, Y., Quéméré, E., Baker, K., Wang, W., & Hoelzel, A. R. (2020). Demography and adaptation promoting evolutionary transitions in a mammalian genus that diversified during the Pleistocene. *Molecular Ecology*, 29(15), 2777–2792. <https://doi.org/10.1111/MEC.15450>
- de Manuel, M., Barnett, R., Sandoval-Velasco, M., Yamaguchi, N., Garrett Vieira, F., Zepeda Mendoza, M. L., Liu, S., Martin, M. D., Sinding, M.-H., Mak, S. S. T., Carøe, C., Liu, S., Guo, C., Zheng, J., Zazula, G., Baryshnikov, G., Eizirik, E., Koepfli, K.-P., Johnson, W. E., ... Gilbert, M. T. P. (2020). The evolutionary history of extinct and living lions. *Proceedings of the National Academy of Sciences of the United States of America*, 117(20), 10927–10934. <https://doi.org/10.1073/PNAS.1919423117>
- DeFaveri, J., & Merilä, J. (2015). Temporal stability of genetic variability and differentiation in the three-spined stickleback (*Gasterosteus aculeatus*). *PLoS One*, 10(4), e0123891. <https://doi.org/10.1371/JOURNAL.PONE.0123891>
- Do, C., Waples, R. S., Peel, D., Macbeth, G. M., Tillett, B. J., & Ovenden, J. R. (2014). NeEstimator v2: Re-implementation of software for the estimation of contemporary effective population size (Ne) from genetic data. *Molecular Ecology Resources*, 14(1), 209–214. <https://doi.org/10.1111/1755-0998.12157>
- Ellegren, H., & Galtier, N. (2016). Determinants of genetic diversity. *Nature Reviews Genetics*, 17(7), 422–433. <https://doi.org/10.1038/NRG.2016.58>
- Elyashiv, E., Sattath, S., Hu, T. T., Strutsosky, A., McVicker, G., Andolfatto, P., Coop, G., & Sella, G. (2016). A genomic map of the effects of linked selection in *Drosophila*. *PLoS Genetics*, 12(8), e1006130. <https://doi.org/10.1371/JOURNAL.PGEN.1006130>
- Ewens, W. J. (1979). *Mathematical population genetics*. Springer Verlag.
- Ewens, W. J. (1982). On the concept of the effective population size. *Theoretical Population Biology*, 21(3), 373–378. [https://doi.org/10.1016/0040-5809\(82\)90024-7](https://doi.org/10.1016/0040-5809(82)90024-7)
- Ewens, W. J. (2004). *Mathematical population genetics. Theoretical introduction*. Springer.
- Ewing, G., & Hermisson, J. (2010). MSMS: A coalescent simulation program including recombination, demographic structure and selection at a single locus. *Bioinformatics*, 26(16), 2064–2065. <https://doi.org/10.1093/bioinformatics/btq322>
- Ewing, G. B., & Jensen, J. D. (2016). The consequences of not accounting for background selection in demographic inference. *Molecular Ecology*, 25(1), 135–141. <https://doi.org/10.1111/MEC.13390>
- Excoffier, L., Dupanloup, I., Huerta-Sánchez, E., Sousa, V. C., & Foll, M. (2013). Robust demographic inference from genomic and SNP data. *PLoS Genetics*, 9(10), e1003905. <https://doi.org/10.1371/JOURNAL.PGEN.1003905>
- Fenderson, L. E., Kovach, A. I., & Llamas, B. (2020). Spatiotemporal landscape genetics: Investigating ecology and evolution through space and time. *Molecular Ecology*, 29(2), 218–246. <https://doi.org/10.1111/MEC.15315>
- Feng, S., Fang, Q. I., Barnett, R., Li, C., Han, S., Kuhlwlilm, M., Zhou, L., Pan, H., Deng, Y., Chen, G., Gamauf, A., Woog, F., Prys-Jones, R., Marques-Bonet, T., Gilbert, M. T. P., & Zhang, G. (2019). The genomic footprints of the fall and recovery of the crested ibis. *Current Biology*, 29(2), 340–349.e7. <https://doi.org/10.1016/J.CUB.2018.12.008>
- Fijarczyk, A., & Babik, W. (2015). Detecting balancing selection in genomes: Limits and prospects. *Molecular Ecology*, 24(14), 3529–3545. <https://doi.org/10.1111/mec.13226>
- Flagel, L., Brandvain, Y., & Schrider, D. R. (2019). The unreasonable effectiveness of convolutional neural networks in population genetic inference. *Molecular Biology and Evolution*, 36(2), 220–238. <https://doi.org/10.1093/MOLBEV/MSY224>
- Fraïsse, C., Popovic, I., Mazoyer, C., Spataro, B., Delmotte, S., Romiguier, J., Loire, É., Simon, A., Galtier, N., Duret, L., Bierne, N., Vekemans, X., & Roux, C. (2021). DILS: Demographic inferences with linked selection by using ABC. *Molecular Ecology Resources*. <https://doi.org/10.1111/1755-0998.13323>
- Fuentes-Pardo, A. P., & Ruzzante, D. E. (2017). Whole-genome sequencing approaches for conservation biology: Advantages, limitations and practical recommendations. *Molecular Ecology*, 26(20), 5369–5406. <https://doi.org/10.1111/MEC.14264>

- 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., Zakharia, F., Moreno-Estrada, A., Byrnes, J. K., Muzzio, M., Rodriguez-Flores, J. L., Kenny, E. E., Gignoux, C. R., Maples, B. K., Guiblet, 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., Rodríguez, 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., Damschen, E. I., 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., Ruegg, K., & Palstra, F. (2011). Understanding and estimating effective population size for practical application in marine species management. *Conservation Biology*, 25(3), 438–449. <https://doi.org/10.1111/J.1523-1739.2010.01637.X>
- Harris, K., & Nielsen, R. (2013). Inferring demographic history from a spectrum of shared haplotype lengths. *PLoS Genetics*, 9(6), e1003521. <https://doi.org/10.1371/JOURNAL.PGEN.1003521>
- Hartl, D. L., & Clark, A. G. (2006). *Principles of population genetics* (4th ed.). Sinauer associates.
- Hauser, L., & Carvalho, G. R. (2008). Paradigm shifts in marine fisheries genetics: Ugly hypotheses slain by beautiful facts. *Fish and Fisheries*, 9(4), 333–362. <https://doi.org/10.1111/J.1467-2979.2008.00299.X>
- Hayes, B. J., Visscher, P. M., McPartlan, H. C., & Goddard, M. E. (2003). Novel multilocus measure of linkage disequilibrium to estimate past effective population size. *Genome Research*, 13(4), 635–643. <https://doi.org/10.1101/GR.387103>
- Heled, J., & Drummond, A. J. (2008). Bayesian inference of population size history from multiple loci. *BMC Evolutionary Biology*, 8(1), 289. <https://doi.org/10.1186/1471-2148-8-289>
- Hewitt, G. (2000). The genetic legacy of the quaternary ice ages. *Nature*, 405(6789), 907–913. <https://doi.org/10.1038/35016000>
- Hey, J. (2010). Isolation with migration models for more than two populations. *Molecular Biology and Evolution*, 27(4), 905–920. <https://doi.org/10.1093/MOLBEV/MSP296>
- Hey, J., & Nielsen, R. (2004). Multilocus methods for estimating population sizes, migration rates and divergence time, with applications to the divergence of *Drosophila pseudoobscura* and *D. persimilis*. *Genetics*, 167(2), 747–760. <https://doi.org/10.1534/GENETICS.103.024182>
- Hill, W. G. (1981). Estimation of effective population size from data on linkage disequilibrium. *Genetical Research*, 38(3), 209–216. <https://doi.org/10.1017/S0016672300020553>
- Ho, S. Y. W., & Shapiro, B. (2011). Skyline-plot methods for estimating demographic history from nucleotide sequences. *Molecular Ecology Resources*, 11(3), 423–434. <https://doi.org/10.1111/J.1755-0998.2011.02988.X>
- Hohenlohe, P. A., Funk, W. C., & Rajora, O. P. (2021). Population genomics for wildlife conservation and management. *Molecular Ecology*, 30(1), 62–82. <https://doi.org/10.1111/MEC.15720>
- Hollenbeck, C. M., 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>
- Hössjer, O., Olsson, F., Laikre, L., & Ryman, N. (2015). Metapopulation inbreeding dynamics, effective size and subpopulation differentiation—A general analytical approach for diploid organisms. *Theoretical Population Biology*, 102, 40–59. <https://doi.org/10.1016/J.TPB.2015.03.006>
- 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., Riall, 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>
- Jónás, Á., Taus, T., Kosiol, C., Schlötterer, C., & Futschik, A. (2016). Estimating the effective population size from temporal allele frequency changes in experimental evolution. *Genetics*, 204(2), 723–735. <https://doi.org/10.1534/GENETICS.116.191197>
- Jorde, P. E., & Ryman, N. (1995). Temporal allele frequency change and estimation of effective size in populations with overlapping generations. *Genetics*, 139(2), 1077–1090. <https://doi.org/10.1093/GENETICS/139.2.1077>
- Jorde, P. E., & Ryman, N. (2007). Unbiased estimator for genetic drift and effective population size. *Genetics*, 177(2), 927–935. <https://doi.org/10.1534/GENETICS.107.075481>
- Kelleher, J., Wong, Y., Wohns, A. W., Fadil, C., Albers, P. K., & McVean, G. (2019). Inferring whole-genome histories in large population datasets. *Nature Genetics*, 51(9), 1330–1338. <https://doi.org/10.1038/S41588-019-0483-Y>
- 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. (2015). Exploring population size changes using 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>
- Lowe, 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. *Nature Plants*, 7(1), 17–24. <https://doi.org/10.1038/S41477-020-00834-5>
- 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/MST125>
- MacLeod, I. M., Meuwissen, T. H. E., Hayes, B. J., & Goddard, M. E. (2009). A novel predictor of multilocus haplotype homozygosity: Comparison with existing predictors. *Genetics Research*, 91(6), 413–426. <https://doi.org/10.1017/S0016672309990358>
- Malaspina, A.-S., Westaway, M. C., Muller, C., Sousa, V. C., Lao, O., Alves, I., Bergström, A., Athanasiadis, G., Cheng, J. Y., Crawford, J. E., Heupink, T. H., Macholdt, E., Peischl, S., Rasmussen, S., Schiffels, S., Subramanian, S., Wright, J. L., Albrechtsen, A., Barbieri, C., ... Willerslev, E. (2016). A genomic history of Aboriginal Australia. *Nature*, 538(7624), 207–214. <https://doi.org/10.1038/NATURE18299>
- Marandel, F., Lorange, P., Berthel, O., Trenkel, V. M., Waples, R. S., & Lamy, J. B. (2019). Estimating effective population size of large marine populations, is it feasible? *Fish and Fisheries*, 20(1), 189–198. <https://doi.org/10.1111/FAF.12338>
- Marchi, N., Schlichta, F., & Excoffier, L. (2021). Demographic inference. *Current Biology*, 31(6), R276–R279. <https://doi.org/10.1016/J.CUB.2021.01.053>
- Marjoram, P., & Wall, J. D. (2006). Fast 'coalescent' simulation. *BMC Genetics*, 7. <https://doi.org/10.1186/1471-2156-7-16>
- Mazet, O., Rodríguez, W., Grusea, S., Boitard, S., & Chikhi, L. (2016). On the importance of being structured: Instantaneous coalescence rates and human evolution-lessons for ancestral population size inference? *Heredity*, 116(4), 362–371. <https://doi.org/10.1038/HDY.2015.104>
- McVean, G. A. T., & Cardin, N. J. (2005). Approximating the coalescent with recombination. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1459), 1387–1393. <https://doi.org/10.1098/RSTB.2005.1673>
- Meier, J. I., Salazar, P. A., Kučka, M., Davies, R. W., Dréau, A., Aldás, I., Box Power, O., Nadeau, N. J., Bridle, J. R., Rolian, C., Barton, N. H., 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/jcsb.1000168>
- Miller, W., Schuster, S. C., Welch, A. J., Ratan, A., Bedoya-Reina, O. C., Zhao, F., Kim, H. L., Burhans, R. C., Drautz, 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., Dutoit, 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 malécot* (pp. 194–232). Oxford University Press.
- Ongaro, L., Scliar, M. O., Flores, R., Raveane, A., Marnetto, D., Sarno, S., Gnecci-Ruscione, G. A., Alarcón-Riquelme, M. E., Patin, E., Wangkumhang, P., Hellenthal, G., Gonzalez-Santos, M., King, R. J., Kouvatsi, A., Balanovsky, O., Balanovska, E., Atramentova, 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., Lencz, T., Darvasi, 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

- persistence? *Molecular Ecology*, 17(15), 3428–3447. <https://doi.org/10.1111/J.1365-294X.2008.03842.X>
- Patton, A. H., Margres, M. J., Stahlke, A. R., Hendricks, S., Lewallen, K., Hamede, R. K., Ruiz-Aravena, M., Ryder, O., McCallum, H. I., Jones, M. E., Hohenlohe, P. A., & Storer, A. (2019). Contemporary demographic reconstruction methods are robust to genome assembly quality: A Case Study in Tasmanian Devils. *Molecular Biology and Evolution*, 36(12), 2906–2921. <https://doi.org/10.1093/MOLBEV/MSZ191>
- Peart, C. R., Tusso, S., Pophaly, S. D., Botero-Castro, F., Wu, C.-C., Auriolles-Gamboa, D., Baird, A. B., Bickham, J. W., Forcada, J., Galimberti, F., Gemmell, N. J., Hoffman, J. I., Kovacs, K. M., Kunasranta, M., Lydersen, C., Nyman, T., de Oliveira, L. R., Orr, A. J., Sanvito, S., ... Wolf, J. B. W. (2020). Determinants of genetic variation across eco-evolutionary scales in pinnipeds. *Nature Ecology and Evolution*, 4(8), 1095–1104. <https://doi.org/10.1038/S41559-020-1215-5>
- Polanski, A., & Kimmel, M. (2003). New explicit expressions for relative frequencies of single-nucleotide polymorphisms with application to statistical inference on population growth. *Genetics*, 165(1), 427–436. <https://doi.org/10.1093/GENETICS/165.1.427>
- Pouyet, F., Aeschbacher, S., Thiéry, A., & Excoffier, L. (2018). Background selection and biased gene conversion affect more than 95% of the human genome and bias demographic inferences. *Elife*, 7. <https://doi.org/10.7554/ELIFE.36317>
- Pudovkin, A. I., Zaykin, D. V., & Hedgecock, D. (1996). On the potential for estimating the effective number of breeders from heterozygote-excess in progeny. *Genetics*, 144(1), 383–387. <https://doi.org/10.1093/GENETICS/144.1.383>
- Pybus, O. G., Rambaut, A., & Harvey, P. H. (2000). An integrated framework for the inference of viral population history from reconstructed genealogies. *Genetics*, 155(3), 1429–1437. <https://doi.org/10.1093/GENETICS/155.3.1429>
- Ralls, K., Sunnucks, P., Lacy, R. C., & Frankham, R. (2020). Genetic rescue: A critique of the evidence supports maximizing genetic diversity rather than minimizing the introduction of putatively harmful genetic variation. *Biological Conservation*, 251. <https://doi.org/10.1016/J.BIOCON.2020.108784>
- Robinson, J. D., Coffman, A. J., Hickerson, M. J., & Gutenkunst, R. N. (2014). Sampling strategies for frequency spectrum-based population genomic inference. *BMC Evolutionary Biology*, 14(1). <https://doi.org/10.1186/S12862-014-0254-4>
- Robinson, J. A., Räikkönen, J., Vucetich, L. M., Vucetich, J. A., Peterson, R. O., Lohmueller, K. E., & Wayne, R. K. (2019). Genomic signatures of extensive inbreeding in Isle Royale wolves, a population on the threshold of extinction. *Science Advances*, 5(5). <https://doi.org/10.1126/SCIADV.AAU0757>
- Rodríguez, W., Mazet, O., Grusea, S., Arredondo, A., Corujo, J. M., Boitard, S., & Chikhi, L. (2018). The IICR and the non-stationary structured coalescent: Towards demographic inference with arbitrary changes in population structure. *Heredity*, 121(6), 663–678. <https://doi.org/10.1038/S41437-018-0148-0>
- Rougemont, Q., Moore, J.-S., Leroy, T., Normandeau, E., Rondeau, E. B., Withler, R. E., Van Doornik, D. M., Crane, P. A., Naish, K. A., Garza, J. C., Beacham, T. D., Koop, B. F., & Bernatchez, L. (2020). Demographic history shaped geographical patterns of deleterious mutation load in a broadly distributed Pacific Salmon. *PLoS Genetics*, 16(8). <https://doi.org/10.1371/JOURNAL.PGEN.1008348>
- Rougeux, C., Bernatchez, L., & Gagnaire, P. A. (2017). Modeling the multiple facets of speciation-with-gene-flow toward inferring the divergence history of lake whitefish species pairs (*Coregonus clupeaformis*). *Genome Biology and Evolution*, 9(8), 2057–2074. <https://doi.org/10.1093/GBE/EBV150>
- Ruzzante, D. E., McCracken, G. R., Førlund, B., MacMillan, J., Notte, D., Buhariwalla, C., Mills Flemming, J., & Skaug, H. (2019). Validation of close-kin mark-recapture (CKMR) methods for estimating population abundance. *Methods in Ecology and Evolution*, 10(9), 1445–1453. <https://doi.org/10.1111/2041-210X.13243>
- Ruzzante, D. E., McCracken, G. R., Parmelee, S., Hill, K., Corrigan, A., MacMillan, J., & Walde, S. J. (2016). Effective number of breeders, effective population size and their relationship with census size in an iteroparous species, *Salvelinus fontinalis*. *Proceedings of the Royal Society B: Biological Sciences*, 283(1823). <https://doi.org/10.1098/RSPB.2015.2601>
- Ryman, N., Laikre, L., & Hössjer, O. (2019). Do estimates of contemporary effective population size tell us what we want to know? *Molecular Ecology*, 28(8), 1904–1918. <https://doi.org/10.1111/MEC.15027>
- Sackman, A. M., Harris, R. B., & Jensen, J. D. (2019). Inferring demography and selection in organisms characterized by skewed offspring distributions. *Genetics*, 211(3), 1019–1028. <https://doi.org/10.1534/GENETICS.118.301684>
- Salmona, J., Heller, R., Quéméré, E., & Chikhi, L. (2017). Climate change and human colonization triggered habitat loss and fragmentation in Madagascar. *Molecular Ecology*, 26(19), 5203–5222. <https://doi.org/10.1111/MEC.14173>
- Sanchez, T., Cury, J., Charpiat, G., & Jay, F. (2020). Deep learning for population size history inference: Design, comparison and combination with approximate Bayesian computation. *Molecular Ecology Resources*. <https://doi.org/10.1111/1755-0998.13224>
- Santiago, E., Novo, I., Pardiñas, A. F., Saura, M., Wang, J., & Caballero, A. (2020). Recent demographic history inferred by high-resolution analysis of linkage disequilibrium. *Molecular Biology and Evolution*, 37(12), 3642–3653. <https://doi.org/10.1093/MOLBEV/MSAA169>
- Scerri, E. M. L., Chikhi, L., & Thomas, M. G. (2019). Beyond multiregional and simple out-of-Africa models of human evolution. *Nature Ecology and Evolution*, 3(10), 1370–1372. <https://doi.org/10.1038/S41559-019-0992-1>
- Scerri, E. M. L., Thomas, M. G., Manica, A., Gunz, P., Stock, J. T., Stringer, C., Grove, M., Groucutt, H. S., Timmermann, A., Rightmire, G. P., d'Errico, F., Tryon, C. A., Drake, N. A., Brooks, A. S., Dennell, R. W., Durbin, R., Henn, B. M., Lee-Thorp, J., deMenocal, P., ... Chikhi, L. (2018). Did our species evolve in subdivided populations across Africa, and why does it matter? *Trends in Ecology & Evolution*, 33(8), 582–594. <https://doi.org/10.1016/J.TREE.2018.05.005>
- Schiffels, S., & Durbin, R. (2014). Inferring human population size and separation history from multiple genome sequences. *Nature Genetics*, 46(8), 919–925. <https://doi.org/10.1038/NG.3015>
- Schiffels, S., & Wang, K. (2020). MSMC and MSMC2: The multiple sequentially Markovian coalescent. *Methods in Molecular Biology*, 2090, 147–166. https://doi.org/10.1007/978-1-0716-0199-0_7
- Schraiber, J. G., & Akey, J. M. (2015). Methods and models for unravelling human evolutionary history. *Nature Reviews Genetics*, 16(12), 727–740. <https://doi.org/10.1038/NRG4005>
- Schrider, D. R., & Kern, A. D. (2018). Supervised machine learning for population genetics: A new paradigm. *Trends in Genetics*, 34(4), 301–312. <https://doi.org/10.1016/J.TIG.2017.12.005>
- Sellinger, T. P. P., Abu-Awad, D., & Tellier, A. (2021). Limits and convergence properties of the sequentially Markovian coalescent. *Molecular Ecology Resources*. <https://doi.org/10.1111/1755-0998.13416>
- Sheehan, S., & Song, Y. S. (2016). Deep learning for population genetic inference. *PLoS Computational Biology*, 12(3). <https://doi.org/10.1371/JOURNAL.PCBI.1004845>
- Sjödén, P., Kaj, I., Krone, S., Lascoux, M., & Nordborg, M. (2005). On the meaning and existence of an effective population size. *Genetics*, 169(2), 1061–1070. <https://doi.org/10.1534/GENETICS.104.026799>
- Speidel, L., Forest, M., Shi, S., & Myers, S. R. (2019). A method for genome-wide genealogy estimation for thousands of samples. *Nature Genetics*, 51(9), 1321–1329. <https://doi.org/10.1038/S41558-019-0484-X>

- Spence, J. P., Steinrücken, M., Terhorst, J., & Song, Y. S. (2018). Inference of population history using coalescent HMMs: Review and outlook. *Current Opinion in Genetics and Development*, 53, 70–76. <https://doi.org/10.1016/j.cde.2018.07.002>
- Städler, T., Haubold, B., Merino, C., Stephan, W., & Pfaffelhuber, P. (2009). The impact of sampling schemes on the site frequency spectrum in nonequilibrium subdivided populations. *Genetics*, 182(1), 205–216. <https://doi.org/10.1534/GENETICS.108.094904>
- Szpiech, Z. A., Mak, A. C. Y., White, M. J., Hu, D., Eng, C., Burchard, E. G., & Hernandez, R. D. (2019). Ancestry-dependent enrichment of deleterious homozygotes in runs of homozygosity. *The American Journal of Human Genetics*, 105(4), 747–762. <https://doi.org/10.1016/j.ajhg.2019.08.011>
- Tallmon, D. A., Koyuk, A., Luikart, G., & Beaumont, M. A. (2008). ONeSAMP: A program to estimate effective population size using approximate Bayesian computation. *Molecular Ecology Resources*, 8(2), 299–301. <https://doi.org/10.1111/j.1471-8286.2007.01997.x>
- Teixeira, J. C., & Huber, C. D. (2021). The inflated significance of neutral genetic diversity in conservation genetics. *Proceedings of the National Academy of Sciences of the United States of America*, 118(10), e2015096118. <https://doi.org/10.1073/pnas.2015096118>
- Terhorst, J., Kamm, J. A., & Song, Y. S. (2017). Robust and scalable inference of population history from hundreds of unphased whole genomes. *Nature Genetics*, 49(2), 303–309. <https://doi.org/10.1038/NG.3748>
- Terhorst, J., & Song, Y. S. (2015). Fundamental limits on the accuracy of demographic inference based on the sample frequency spectrum. *Proceedings of the National Academy of Sciences of the United States of America*, 112(25), 7677–7682. <https://doi.org/10.1073/PNAS.1503717112>
- van der Valk, T., Díez-del-Molino, D., Marques-Bonet, T., Guschanski, K., & Dalén, L. (2019). Historical genomes reveal the genomic consequences of recent population decline in Eastern Gorillas. *Current Biology*, 29(1), 165–170.e6. <https://doi.org/10.1016/j.cub.2018.11.055>
- Wakeley, J. (1999). Nonequilibrium migration in human history. *Genetics*, 153(4), 1863–1871. <https://doi.org/10.1093/GENETICS/153.4.1863>
- Wakeley, J., & Aliacar, N. (2001). Gene genealogies in a metapopulation. *Genetics*, 159(2), 893–905. <https://doi.org/10.1093/GENETICS/159.2.893>
- Wakeley, J., & Hey, J. (1997). Estimating ancestral population parameters. *Genetics*, 145(3), 847–855. <https://doi.org/10.1093/GENETICS/145.3.847>
- Wakeley, J., & Sargsyan, O. (2009). Extensions of the coalescent effective population size. *Genetics*, 181(1), 341–345. <https://doi.org/10.1534/GENETICS.108.092460>
- Walsh, B., & Lynch, M. (2018). *Evolution and selection of quantitative traits* (1st ed.). Oxford University Press.
- Wang, J. (2001). A pseudo-likelihood method for estimating effective population size from temporally spaced samples. *Genetical Research*, 78(3), 243–257. <https://doi.org/10.1017/S0016672301005286>
- Wang, J. (2005). Estimation of effective population sizes from data on genetic markers. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1459), 1395–1409. <https://doi.org/10.1098/RSTB.2005.1682>
- Wang, J. (2009). A new method for estimating effective population sizes from a single sample of multilocus genotypes. *Molecular Ecology*, 18(10), 2148–2164. <https://doi.org/10.1111/J.1365-294X.2009.04175.X>
- Wang, J., & Caballero, A. (1999). Developments in predicting the effective size of subdivided populations. *Heredity*, 82(2), 212–226. <https://doi.org/10.1038/SJ.HDY.6884670>
- Wang, J., Santiago, E., & Caballero, A. (2016). Prediction and estimation of effective population size. *Heredity*, 117(4), 193–206. <https://doi.org/10.1038/HDY.2016.43>
- Wang, J., & Whitlock, M. C. (2003). Estimating effective population size and migration rates from genetic samples over space and time. *Genetics*, 163(1), 429–446. <https://doi.org/10.1093/GENETICS/163.1.429>
- Wang, Z., Wang, J., Kourakos, M., Hoang, N., Lee, H. H., Mathieson, I., & Mathieson, S. (2021). Automatic inference of demographic parameters using generative adversarial networks. *Molecular Ecology Resources*. <https://doi.org/10.1111/1755-0998.13386>
- Waples, R. S. (1989). A generalized approach for estimating effective population size from temporal changes in allele frequency. *Genetics*, 121(2), 379–391. <https://doi.org/10.1093/genetics/121.2.379>
- Waples, R. S. (2005). Genetic estimates of contemporary effective population size: To what time periods do the estimates apply? *Molecular Ecology*, 14(11), 3335–3352. <https://doi.org/10.1111/J.1365-294X.2005.02673.X>
- Waples, R. S. (2006). A bias correction for estimates of effective population size based on linkage disequilibrium at unlinked gene loci. *Conservation Genetics*, 7(2), 167–184. <https://doi.org/10.1007/S10592-005-9100-Y>
- Waples, R. S. (2010). Spatial-temporal stratifications in natural populations and how they affect understanding and estimation of effective population size. *Molecular Ecology Resources*, 10(5), 785–796. <https://doi.org/10.1111/J.1755-0998.2010.02876.X>
- Waples, R. S., Antao, T., & Luikart, G. (2014). Effects of overlapping generations on linkage disequilibrium estimates of effective population size. *Genetics*, 197(2), 769–780. <https://doi.org/10.1534/GENETICS.114.164822>
- Waples, R. S., & Do, C. (2008). LDNE: A program for estimating effective population size from data on linkage disequilibrium. *Molecular Ecology Resources*, 8(4), 753–756. <https://doi.org/10.1111/J.1755-0998.2007.02061.X>
- Waples, R. S., & Do, C. (2010). Linkage disequilibrium estimates of contemporary Ne using highly variable genetic markers: A largely untapped resource for applied conservation and evolution. *Evolutionary Applications*, 3(3), 244–262. <https://doi.org/10.1111/J.1752-4571.2009.00104.X>
- Waples, R. S., & England, P. R. (2011). Estimating contemporary effective population size on the basis of linkage disequilibrium in the face of migration. *Genetics*, 189(2), 633–644. <https://doi.org/10.1534/GENETICS.111.132233>
- Waples, R. S., & Feutry, P. (2021). Close-kin methods to estimate census size and effective population size. *bioRxiv*. 2021.01.19.427337. <https://doi.org/10.1101/2021.01.19.427337>
- Waples, R. S., Grewe, P. M., Bravington, M. W., Hillary, R., & Feutry, P. (2018). Robust estimates of a high Ne/N ratio in a top marine predator, southern bluefin tuna. *Science Advances*, 4(7), eaar7759. <https://doi.org/10.1126/sciadv.aar7759>
- Waples, R. K., Larson, W. A., & Waples, R. S. (2016). Estimating contemporary effective population size in non-model species using linkage disequilibrium across thousands of loci. *Heredity*, 117(4), 233–240. <https://doi.org/10.1038/HDY.2016.60>
- Waples, R. S., Luikart, G., Faulkner, J. R., & Tallmon, D. A. (2013). Simple life-history traits explain key effective population size ratios across diverse taxa. *Proceedings of the Royal Society B: Biological Sciences*, 280(1768). <https://doi.org/10.1098/RSPB.2013.1339>
- Waples, R. S., & Waples, R. K. (2011). Inbreeding effective population size and parentage analysis without parents. *Molecular Ecology Resources*, 11(Suppl. 1), 162–171. <https://doi.org/10.1111/J.1755-0998.2010.02942.X>
- Waples, R. S., & Yokota, M. (2007). Temporal estimates of effective population size in species with overlapping generations. *Genetics*, 175(1), 219–233. <https://doi.org/10.1534/GENETICS.106.065300>
- Wegmann, D., Leuenberger, C., Neuenschwander, S., & Excoffier, L. (2010). ABCtoolbox: A versatile toolkit for approximate Bayesian computations. *BMC Bioinformatics*, 11. <https://doi.org/10.1186/1471-2105-11-116>

- 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>