Testing Wright's Intermediate Population Size Hypothesis – When Genetic Drift is a Good Thing

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Abstract – In his 1931 monograph, Sewall Wright predicted genetic drift would overwhelm selection in small populations, and selection would dominate in large ones, but he also concluded drift could facilitate selection in populations of intermediate size. The idea that drift and selection would act together in populations of intermediate size has been almost completely ignored even as empirical evidence of rapid evolution associated with population bottlenecks has continued to accumulate. I used forward-time simulations with random mating and discrete generations to test the hypothesis that drift can facilitate selection. I find that selection generates biased distributions of Δq, and this bias is greatest for population sizes between 20 and 200, resulting in drift facilitation. Drift facilitation reduces the accumulation of drift load and segregation load for populations of intermediate size. Small populations accumulated higher levels of drift load and large populations maintained high levels of segregation load. Fixation of beneficial mutations is facilitated in intermediate populations when dominance is low and selection is weak. Accumulation of beneficial mutations over time (fixation flux) was higher across small to intermediate size populations and declined rapidly for large populations. Compared to predictions of fixation time for codominant beneficial mutations from diffusion equations, drift facilitation accelerates fixation in populations of intermediate size, but fixation time is slower in large populations when selection is weak. These results suggest drift facilitation in small and intermediate populations promote purging of genetic load and fixation of beneficial mutations, and may result in relatively rapid adaptation compared to large populations.

Impact Summary – After the recognition of Gregor Mendel's contributions to our understanding of the inheritance of genetically-determined traits around 1900, there was confusion as to whether the type of variation Mendel studied could account for evolution by natural selection, as described by Charles Darwin. This controversy was resolved when three theoreticians (Ronald Fisher, Sewell Wright, and J.B.S. Haldane) published books that integrated Mendelian genetics with evolution. Their contributions (referred to as the Modern Synthesis), focused on evolutionary processes occurring within and among populations of a species, and established a mathematical foundation for our understanding of evolutionary biology. The mathematical models developed by the three architects of the modern synthesis, and those who followed, predicted that the effects of natural selection would be overwhelmed by random genetic changes (referred to as Genetic Drift) in small populations, and that genetic drift would be minimal, while selection would be most effective in large populations. Even though one of Wright's major conclusions was that genetic drift and selection would work together (Drift Facilitation) to promote adaptive evolution in intermediate-sized populations, this idea has been almost completely ignored since it was first introduced in 1931. In this study, I use simulations of evolution in natural populations to evaluate the potential for drift facilitation to promote evolution in intermediate-sized populations. My work largely confirms Wright's predictions; the removal of deleterious mutations and promotion of adaptive evolution are enhanced in population sizes ranging from about 10 to 200. These results indicate that a new paradigm for our understanding of evolution

within populations is needed – one that emphasizes the importance of drift facilitation in small and intermediate size populations, and recognizes that periods of reduced population size are opportunities for enhanced levels of adaptive evolution.

Keywords: Adaptative evolution, conservation genetics, drift facilitation, drift load, inbreeding load, population bottleneck, purging, segregation load, simulations.

"In a population of intermediate size … there is continual random shifting of gene frequencies … which leads to a relatively rapid, continuing, irreversible, and largely fortuitous, but not degenerative series of changes, even under static conditions." Wright 1931, Page 157.

Introduction

The mathematical models for population genetics developed during the Modern Synthesis (Fisher 1930; Wright 1931; Haldane 1932) and beyond (Crow 1987; Ewens 2004; Charlesworth and Charlesworth 2017) have provided a foundation for a general understanding of evolutionary processes accounting for divergence among populations, adaptation, and diversification among lineages. A fundamental aspect of this framework is the dichotomy between the roles of genetic drift and selection; specifically, that drift governs the accumulation of neutral and degenerative variation while only selection can promote the purging of deleterious mutations and the fixation of beneficial mutations (Crow and Kimura 1970; Kimura 1983). The general prediction is genetic drift will dominate the dynamics of allele frequency change in small populations when selection is weak (i.e. when $s < 1/2N$), resulting in the accumulation of genetic load and limited potential for adaptive evolution. In contrast, selection is expected to overwhelm the effects of drift in large populations leading to fixation of beneficial mutations and the purging of genetic load (Charlesworth 2002; Gossmann et al. 2012; Lanfear et al. 2014; Charlesworth and Charlesworth 2017). However, in his 1931 monograph, Wright emphasized the idea that the rate of fixation of beneficial mutations would be much slower in large populations, but there was potential for genetic drift and selection to act together to promote rapid adaptation in populations of "intermediate" size. He proposed a range of population sizes where both drift and selection are effective enough to allow "fortuitous" shifts in allele frequencies to facilitate selection resulting in accelerated accumulation of adaptive genetic variation. This idea (hereafter referred to as "drift facilitation") was seized upon by George Gaylord Simpson (1944), who proposed small population size was a likely explanation for the lack of fossilization during rapid transitions that resulted in the origin of novel forms, including new genera and families. This idea of "quantum evolution" (i.e. periods of rapid evolution when selection is facilitated by genetic drift; Simpson 1944) inspired a number of evolutionary biologists, who subsequently identified a wide range of examples of adaptation associated with reduced population size (Mayr 1954; Lewis and Raven 1958). Verne Grant (1963, 1981) expanded on the idea of quantum evolution to include rapid speciation events in small, isolated populations at the periphery of a widespread species' range (budding or peripatric speciation; Mayr 1954). While interest in the idea of quantum evolution has waned, evidence of rapid evolution associated with population bottlenecks continues to accumulate (e.g., Carvalho et al. 1996; Rosenblum et al. 2007; Tepolt et al. 2009; Marsico et al. 2011; Cruzan 2019; Rego et al. 2019; Cruzan et al. 2021; Mahrt et al. 2021; Yin et al. 2021; van der Zee et al. 2022). Surprisingly, there have been no attempts to assess the potential for drift facilitation of selection in populations of intermediate size using analytical or numerical approaches.

In this study, I use forward-time, individual-based simulations of populations to evaluate the potential for drift facilitation to promote evolution in intermediate-sized populations. I evaluate the effects of selection (*s*), dominance (*h*), population size ($N = N_e$), and the composite variable of population size and selection (*Ns*) on the accumulation of deleterious and beneficial mutations. In all cases, generations are discrete, and populations are assumed to be dioecious with equal sex ratios and random mating. Changes in allele frequencies and fixation of alleles are examined for a set of unlinked, biallelic loci that have independent effects on fitness. For genetic load, I examine the proportion of loci that became fixed for deleterious mutations (drift load), and the proportion of deleterious mutations that remain segregating after a number of generations (segregation load). In separate simulations, I examine the proportion of loci fixing for beneficial mutations, the rate of fixation of individual mutations, and fixation flux (the rate at which beneficial alleles accumulate; Otto and Whitlock 1997). My results indicate that drift facilitation of selection promotes purging of genetic load and the accumulation of beneficial mutations across a range of small and intermediate population sizes.

Methods

Forward-time, individual-based simulations were conducted using the SimuPOP module (Peng and Kimmel 2005) in Python and the COEUS High-Performance Computing Cluster at Portland State University. A set of *N* individuals, each homozygous for a single locus, were generated using the sim.Population simulator and mutations introduced ($a \rightarrow a'$) that were affected by varying levels of selection (*s*) and dominance (*h*). Transmission of alleles between generations was governed by the sim. MendelianGenoTransmitter. Selection was imposed at the time of mating by defining the fitness of each diploid genotype using MapSelector in SimuPOP. Depending on the goals of the simulation, mutations were either introduced once in the first generation, or at a per-generation rate determined by μ. Each population size of *N* individuals was replicated *k* times. For each replication, the proportion of individuals with fixed mutations (q_{fixed}), and the average allele frequency across individuals ($\bar{q}$) were extracted after *g* generations. Two sets of simulations were run; the first set examined levels of drift and segregation load, and the second set focused on beneficial mutations by evaluating the proportion of loci fixed for mutations, the rate of fixation of individual mutations, and the fixation flux over *g* generations.

Genetic Load – The frequency of fixed deleterious mutations (drift load) across loci and of the proportion of loci segregating for deleterious mutations after *g* generations (segregation load) was assessed for population sizes ranging from $N = 2$ to 5000. For each of $k = 1000$ replications for each population size, *s* was randomly generated from a Poisson distribution (range: 0.0 – 0.25; $\bar{s} = 0.07$), and *h* was generated from a uniform distribution between 0.0 and 0.2 (assuming that deleterious mutations are generally recessive with $\bar{h} = 0.10$; Willis 1999; García-Dorado and Caballero 2000; Agrawal and Whitlock 2011; Ruzicka et al. 2021). Fitness of the *aa, aa',* and *a'a'* genotypes were set to 1.0, *1-hs*, and *1-s*, respectively. The initial allele frequency of *a'* was set at $q = 0$ and mutations were allowed to accumulate for $g = 1000$ generations with $\mu = 1x10^{-3}$ This assumes that each locus consists of thousands of base pairs (i.e. if the per bp/generation mutation rate is on the order of $1x10^{-9}$), but the same qualitative results are obtained for lower mutation rates over longer timeframes.

The proportion of loci fixed for deleterious mutations (q_{fixed}) and selection (*s*) for each mutation were used to estimate the fitness effects of fixed deleterious mutations (drift load) for each replication of

each population size as the reduction in fitness due to the selection coefficient weighted by the proportion of loci fixed for the mutation;

$$w_{fixed} = 1 - sq_{fixed}$$

Segregation load was assessed as the inbreeding effects on fitness for segregating mutations (inbreeding depression; Charlesworth and Willis 2009; Willi et al. 2013) for 1000 replicates for each population size after 1000 generations. Inbreeding depression was estimated based on the mean fitness of hypothetical progeny that would be the result of self-fertilization compared to progeny from random outcrossing. Fitness after selfing was estimated as,

$$\bar{w}_s = 2\bar{p}\bar{q}(1 - (0.25 + 0.5hs + 0.25s)^F);$$

where $\bar{p}$ and $\bar{q}$ are the mean frequencies of the normal (*a*) and mutant (*a'*) alleles across segregating loci (individuals), and *F* is the number of segregating sites at the end of 1000 generations. I calculated the expected fitness of progeny from random outcrossing within each population as,

$$\bar{w}_o = 1 - (\bar{p}^2 + hs2\bar{p}\bar{q} + s\bar{q}^2)^F$$

Segregation load was then estimated for each *N* as inbreeding depression for selfed progeny compared to outcrossed progeny (Charlesworth and Willis 2009) as,

$$\delta_{s/o} = 1 - \frac{\bar{w}_s}{\bar{w}_o}$$

These estimates of drift load and segregation load assume independent fitness effects across unlinked loci.

Beneficial Mutations – I examined the processes of accumulation of beneficial mutations in populations using simulations to evaluate the probability of fixation of beneficial mutations, the rate of fixation of individual alleles, and the fixation flux for a range of population sizes (*N*), selection (*s*), dominance (*h*), and the combination of population size and selection (*Ns*). For beneficial mutations (*a* → *a'*), the fitness of the *aa, aa',* and *a'a'* genotypes were set to *1-s*, *1-hs*, and *1.0*, respectively.

The first simulations compared the fixation of beneficial alleles across a range of initial allele frequencies from *q = 0.01* to *0.50* when *Ns = 2* for population sizes of *N = 100* (*s = 0.02*) and *N = 1000* (*s = 0.002*). Initial frequency of the *a'* allele was set at *q = 1/2N* (*μ = 0*) and the proportion of loci fixing for the mutant allele was compared to the diffusion prediction for the probability of fixation (Φ_q) derived by Kimura (1957; 1962). Alleles were codominant in simulations (*h = 0.5*) to match the assumptions of the diffusion approximation;

$$\Phi_q = \frac{1-\exp(-2Nsq)}{1-\exp(-2Ns)}$$

A second simulations examined the probability of fixation over population sizes ranging from $N = 2$ to 4000 with s randomly drawn from a Poisson distribution ($s = 0.0$ to 0.25) and h drawn from a uniform distribution ($h = 0.0$ to 0.2) as described above. Initial frequency of the *a'* allele was set at $q = 1/2N$ ($\mu = 0$) and the proportion of loci fixing for the mutant allele was recorded after 1000 generations. The results indicated the greatest degree of drift facilitation occurs when $N \approx 100$ (see below). Consequently, I considered the probability of fixation over a broader range of dominance ($h = 0.0$ to 1.0) and initial allele frequencies ($q = 0.0$ to 0.5) for a population size of $N = 100$ with $k = 10$ replicates for each combination of q and h.

I examined the rate of fixation for beneficial alleles starting at an initial frequency of $q = 1/2N$ ($\mu = 0$) across a range of population sizes from $N = 2$ to 1000 for $s = 0.02$ to 0.20 and with $h = 0.5$. The observed numbers of generations required for fixation ($\bar{t}_{gens}$ across $k = 10$ replicates per population size) from these simulations were compared to the predicted rate of fixation ($\bar{t}$) from the diffusion approximation (Ewens 1979; Otto and Whitlock 2013);

$$\bar{t} \approx \int_{1/2N}^{0.999} \frac{(e^{4Nsx} - 1)(e^{4Ns(1-x)} - 1)}{sx(1-x)(e^{4Ns} - 1)} dx$$

This integral is undefined when the upper limit is 1.0, and the approach to fixation is asymptotic, so an arbitrary upper limit of 0.999 was chosen for comparison to fixation frequencies from the simulations.

While this approach describes fixation rates for individual alleles, it does not account for the contribution of the number of mutations entering populations each generation based on population size for the accumulation of beneficial mutations over time (fixation flux; Otto and Whitlock 1997). In particular, we might expect that more mutations would occur in larger populations and consequently flux should increase with population size. I examined fixation flux for population sizes ranging from $N = 4$ to 3000 with $\mu = 1x10^{-4}$, $Ns = 2$ ($s = 2/N$), and $h = 0.5$ with 1000 loci and 10 replicates per population size for time periods of $g = 1000, 2000,$ and 4000 generations. Fixation flux under selection was compared to fixation with only genetic drift ($s = 0$) over 1000 generations across the same range of population sizes. I estimated the mean and standard deviation of Δq across generations for beneficial mutations that ultimately fixed in populations across a range of populations sizes ($N = 4$ to 3000) and selection coefficients ($s = 0.01$ to 0.20 for $N = 100$ and 1000.

Results

Genetic Load – Fixation frequencies for populations subject to mutation were highest for small populations (< 100), and was effectively zero for population sizes larger than N = 3000 (Fig. 1A). Mutations fixing in populations > 100 had negligible fitness effects so that drift load was near zero for populations sizes greater than $N = 100$ (Fig. 1B). Larger proportions of loci continued to segregate for deleterious mutations after 1000 generations in populations of less than N = 10 and more than N = 75, while segregation load was lower in intermediate-sized populations ($10 > N < 75$; Fig. 2).

Beneficial Mutations – There was a close fit between the diffusion approximation for the probability of fixation across initial allele frequencies (Φ_q) and the proportion of loci fixed for beneficial mutations with population sizes of 100 and 1000 with $Ns = 2$ and codominance ($h = 0.5$; Fig. 3). When beneficial

alleles were recessive, the frequency of fixation was low for $N < 30$ and $N > 1000$, and was greatest when population size was between 100 and 200 (Fig. 4). Fixation frequencies were generally greater than the diffusion approximation for $N = 100$ and $Ns = 2$ when $h < 0.5$ across a range of initial allele frequencies, but was lower for dominant mutations when starting at a low initial allele frequency (Fig. 5).

The rate of fixation of individual alleles ($\bar{t}_{\text{gens}}$) was similar to the diffusion approximation ($\bar{t}$) when selection was stronger ($s = 0.1$ and 0.2), but substantially faster for population sizes $N > 10$, but was slower when $N > 100$ when $s = 0.04$, and for $N > 200$ when $s = 0.02$ (Fig. 6). Accumulation of beneficial mutations increased over longer time periods (fixation flux was greater after 4000 generations compared to 2000, and 1000 generations; Fig. 7A). Fixation flux and the loss of beneficial mutations was higher when $N < 100$, but generally declined with increasing population size ($h = 0.5$; Figs. 7A, B). The number of mutations that remained segregating was not strongly affected by the length of the time period, and was consistently low when $N < 100$, and increased rapidly when $N > 100$ (Fig. 7C). Fixation flux was much higher for $Ns = 4$ compared to very weak ($Ns = 0.2$) or no selection (Appendix Fig. S1). The higher rates of fixation flux correspond closely with higher means and standard deviations of Δq across population sizes of $N < 100$ (Figs. S2, S3). Mean Δq increased with the strength of selection, but the standard deviation remained fairly constant across a range from $s = 0.01$ to 0.20 (Figs. S4, S5). When selection was held constant ($s = 0.02$), fixation flux increased rapidly and loss of beneficial mutations decreased rapidly for populations sizes less than $N = 1000$, and then plateaued across larger populations (Appendix Fig. S6).

Discussion

Forward-time simulations of natural populations indicate that segregation load is lower, and rates of fixation and fixation flux of beneficial mutations are higher for small- to intermediate-sized populations ($N < \sim 100$) compared to larger populations. Drift load was relatively high for small populations, but was negligible for populations larger than $N = 100$. Results of simulations for beneficial mutations were consistent with diffusion approximations of the probability of fixation when $h = 0.5$ (Kimura 1957; Kimura 1962), but fixation probabilities for recessive mutations were higher than predicted in intermediate-sized populations ($N = 100$). Observed rates of fixation matched the diffusion approximation ($\bar{t}$) fairly well when selection was strong ($s \geq 0.10$ and $h = 0.5$), but rates of fixation were substantially faster when $s < 0.10$ for population sizes between $N = 10$ and 100, and slower for population sizes of $N > 100$. The accumulation of beneficial mutations (fixation flux) was higher across small populations, and declined rapidly when population size was greater than $N = 100$ with constant Ns across population sizes. Fixation flux was greater under selection than for neutral alleles, which indicates that genetic drift facilitates selection to promote fixation of beneficial alleles even in very small populations. These results suggest the roles of drift and selection across population sizes is more complex than predictions from analytical models, and periods of reduced population size may represent opportunities for enhanced levels of purging, and for rapid acquisition of adaptive genetic variation.

The results presented here generally support Wright's (1931) predictions about the potential for interactions between drift and selection to promote rapid fixation of beneficial alleles, but the population sizes where drift facilitation of selection is effective are smaller than he predicted. Wright specifically defined intermediate populations as ranging between $Ns = 2.5$ and 20 (page 148). Simpson (1944) also assumed that the dynamics described by Wright would apply to very large population sizes

262 (i.e. up to $N = 25,000$) compared to the range of population sizes where drift facilitation was found to be
263 effecting in the simulations presented. In contrast to the predictions of Wright and Simpson, higher
264 rates and probabilities of fixation of beneficial mutations were observed in simulations for $Ns = 2$ and
265 less. Moreover, drift facilitation was effective only for populations sizes less than $N = 100$, regardless of
266 value of Ns. This is an important result because Ns has been used to represent the compensatory effects
267 between genetic drift and selection in analytical models including diffusion equation analyses of
268 population genetic processes (Kimura 1957; Kimura 1962; Ewens 2004). Given the results presented
269 above, more careful evaluation of the separate effects of selection and population size may be
270 warranted.
271
272 While population genetic models have mostly ignored the potential for selection in small populations,
273 empirical evidence for the effectiveness of selection during population bottlenecks continues to
274 accumulate. For example, there are cases of rapid adaptation to novel conditions during establishment
275 when population sizes were small including in artificial introductions of Trinidadian guppies (Carvalho et
276 al. 1996; van der Zee et al. 2022), Eastern fence lizards on novel substrates in New Mexico (Rosenblum
277 et al. 2007), European green crabs on the west coast of North America (Tepolt et al. 2009), the cactus-
278 feeding moth, *Cactoblastis cactorum*, in Florida (Marsico et al. 2011), steelhead trout in Lake Michigan
279 (Willoughby et al. 2018), the invasive grass, *Brachypodium sylvaticum*, in Oregon (Cruzan 2019; Marchini
280 et al. 2019), during evolutionary rescue in the seed beetle *Callosobruchus maculatus* (Rego et al. 2019),
281 and after migration into Lake Champlain by the Atlantic sea lamprey (Yin et al. 2021). In one case, there
282 was rapid evolution of antibiotic resistance in *Pseudomonas aeruginosa* even when population
283 bottlenecks were severe and selection was weak (Mahrt et al. 2021). Rapid acquisition of adaptive
284 genetic variants also seems to have occurred in a case of recent budding speciation (peripatric
285 speciation; Mayr 1954) in a range-restricted species of buttercup (Cruzan et al. 2021). In all of these
286 cases, adaptation to novel conditions appears to have occurred quickly during periods of reduced
287 population size and suggests drift facilitation of selection may be a widespread phenomenon.
288
289 One of the more surprising results of simulations was the observation of higher rates of fixation flux of
290 beneficial mutations when $N < 1000$, suggesting drift facilitation can enhance rates of adaptation in
291 small to intermediate size populations. This result is in stark contrast to diffusion analyses, which
292 predicts flux estimated as $4NsU$ (where U is the genome-wide mutation rate) will remain constant across
293 population sizes if Ns is held constant, and will increase with population size if s is held constant (Otto
294 and Whitlock 1997; Ewens 2004). Contrary to expectations from diffusion estimates, fixation flux was
295 high across smaller populations, but declined in larger populations ($N > 100$) while the strength of
296 selection relative to population size remained constant ($Ns = 2$). With constant selection ($s = 0.02$), flux
297 increased rapidly across smaller population sizes, but then appeared to be limited by demographic
298 constraints (i.e. the time required for allele replacement in a large population; Otto and Whitlock 1997)
299 when population size was greater than $N \approx 500$.
300
301 Consistent with expectations from diffusion analyses, fixation flux was higher when selection was
302 stronger (i.e. when $Ns = 4$), closely matched neutral flux when selection was very weak (i.e., when $Ns =$
303 0.2; and $s < 1/2N$), and fixation of deleterious mutation contributing to drift load increased for
304 population sizes less than $N = 1500$. In contrast, drift facilitation increased fixation flux in small
305 populations even under the assumptions of diffusion equation estimates of fixation probability (i.e. with

306 $h = 0.5$ and Ns constant across N), and the influence of drift facilitation for the probability of fixation for
307 beneficial mutations was even greater when dominance was low ($h < 0.5$) and selection was weak ($s <$
308 0.1).
309
310 The observation of higher flux in small populations is consistent with some previous analyses that
311 predicted genetic drift and selection could interact to increase rates of divergence among populations
312 (Cohan 1984; Lynch 1986), and with selection experiments in maize and simulations where enhanced
313 rates of fixation of small effect mutations were observed when subjected to high genetic drift (Desbiez-
314 Piat et al. 2021). While diffusion analyses have led to numerous insights for evolution in populations,
315 alternative approaches may provide analysis of a broader range of parameters including population size
316 in combination with different levels of selection and dominance.
317
318 Previous studies that have found evidence of drift facilitation did not identify its causes (Cohan 1984;
319 Lynch 1986), but the evaluation of Δq across population sizes sheds some light on the mechanisms
320 responsible for enhancement of fixation rates in small populations. The mean and standard deviation of
321 Δq increased in smaller populations suggesting they are at least partly responsible for the observed
322 effects on allele frequency change and fixation. For mutations at intermediate frequencies, it appears
323 that "fortuitous" fluctuations due to drift are promoted by selection and generate a "ratcheting effect"
324 that biases and accelerates changes in allele frequencies. This idea is supported by the observation that
325 the mean of Δq is positively associated with selection. The effects of drift facilitation are different when
326 allele frequencies are close to $q = 0$ (for deleterious mutations) or fixation (i.e. $q = 1$ for beneficial
327 mutations). When allele frequencies are close to fixation, higher levels of drift in smaller populations
328 increase the probability for random fluctuations to result in absorption, while minimal drift in larger
329 populations results in persistent segregation. Consequently, larger populations appear to accumulate
330 higher levels of inbreeding load and standing variation for beneficial mutations while having lower drift
331 load and rates of fixation flux compared to smaller populations (i.e. for $N < 100$).
332
333 The observation that large populations maintain higher levels of segregation load and standing variation
334 for beneficial mutations suggests that episodes of reduced population size may be disproportionally
335 important for rapid evolution in novel or changing environments. Because of higher frequencies of
336 segregating mutations, large populations entering bottlenecks would have enhanced potential for
337 purging of segregation load and for the fixation of beneficial mutations. Moreover, reductions in
338 population size due to bottlenecks and founder events are likely to be associated with increased
339 environmental stress, and consequently we expect selection to often increase during population
340 bottlenecks (Fowler and Whitlock 2002; Matute 2013). Higher frequencies of segregating mutations
341 along with drift facilitation may be responsible for elevated levels of purging following population
342 bottlenecks (Bouzat 2010), and may help explain the substantial number of cases of rapid adaption
343 during episodes of reduced population size (e.g., Carvalho et al. 1996; Rosenblum et al. 2007; Tepolt et
344 al. 2009; Marsico et al. 2011; Cruzan 2019; Rego et al. 2019; Cruzan et al. 2021; Mahrt et al. 2021; Yin et
345 al. 2021; van der Zee et al. 2022). On the other hand, we expect population bottlenecks and founder
346 events to result in elevated accumulation of drift load (Lynch et al. 1995; Willi et al. 2013), but the
347 simulations presented here indicate the potential for purging segregation load and the fixation of
348 deleterious mutations depends on the severity of the reduction in population size. It is notable that the
349 standard guideline of a minimal effective population size of $N = 50$ (i.e. the 50/500 rule; Jamieson and

Allendorf 2012) is too small to prevent the accumulation of drift load, but is in the right range for drift facilitation of beneficial mutations. Further analyses may help resolve more specific effects of changes in population size for adaptation to novel conditions and for the purging of deleterious mutations.

Conclusions

The results of individual-based, forward-time simulations are consistent with a wide range of observations from natural populations, but contrast with many of the predictions from models based on diffusion equations (Ewens 2004). In general, it appears that Wright's (1931) intuitive predictions about the potential for genetic drift to facilitate selection were correct, but the population sizes where drift facilitation is most effective are smaller than he suggested. Furthermore, while Wright saw the potential for weak deleterious mutations to fix in small populations, he did not anticipate that drift facilitation could lead to more effective purging of segregation load. One of the most striking results from these simulations, and one that stands in stark contrast to widely-accepted assumptions about the effects of population size for adaptive evolution (Charlesworth 2002; Bouzat 2010; Gossmann et al. 2012; Lanfear et al. 2014), is that fixation flux of beneficial mutations is substantially higher in small populations ($N < 100$) compared to larger populations under the assumption that Ns remains constant. The assumption selection is stronger in small populations may generally hold true especially under conditions where population declines are precipitated by increased levels of environmental stress. Moreover, the probability of fixation and rate of fixation of beneficial mutations were higher when $h < 0.5$ and selection was weak, so the prediction of rapid evolution due to drift facilitation is not dependent on the assumption of increased selection in small populations.

The potential for rapid evolution in small populations may be further enhanced as large populations experience reductions in population size. While it is generally assumed population bottlenecks will result in decreased fitness due to the accumulation of genetic load, and that there will be limited potential for adaptive evolution, this is not always true (Bouzat 2010). The simulation results presented here indicate drift facilitation of selection in small to intermediate size populations leads to effective removal of segregating deleterious mutations, and increases the rate and probability of fixation for beneficial mutations. While there has been some speculation and evidence for enhanced evolution in small populations (Simpson 1944; Grant 1981; Cohan 1984; Lynch 1986), no previous study has provided a detailed characterization of the potential for drift facilitation to promote rapid evolution.

Results from these simulations emphasize the importance of the adaptive evolution potential in small populations. Furthermore, more attention should be paid to the consequences of deleterious mutations as they depend heavily on population size; a clear distinction needs to be made between the fixation of deleterious mutations contributing to drift load in small populations, and the persistent of deleterious mutations in large populations resulting in inbreeding depression due to segregation load. The results of these simulations highlight genetic drift as a generative, beneficial process that promotes evolution in small populations. Alternatively, the lack of drift in large populations effectively stalls purging of segregation load and the fixation of beneficial mutations. While further analyses of drift facilitation are needed, the results presented here give more weight to Wright's (1931, 1932) suggestion that adaptive evolution is more likely to occur in small populations (Wade and Goodnight 1998), then to Fisher's (1930) argument that large populations are more important for fixation of beneficial mutations (Coyne et al. 1997). Further work on evolution in small populations from modeling and empirical perspectives

will clarify the potential for drift facilitation to promote evolution, and ultimately determine whether the current paradigm for our understanding of population genetic processes of evolution needs to be refined.

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Author Contributions

MBC is solely responsible for the development of the SimuPOP simulations in Python, data analyses, and writing of the manuscript.

Data Accessibility

All Python scripts and data generated will be deposited in Data Dryad …

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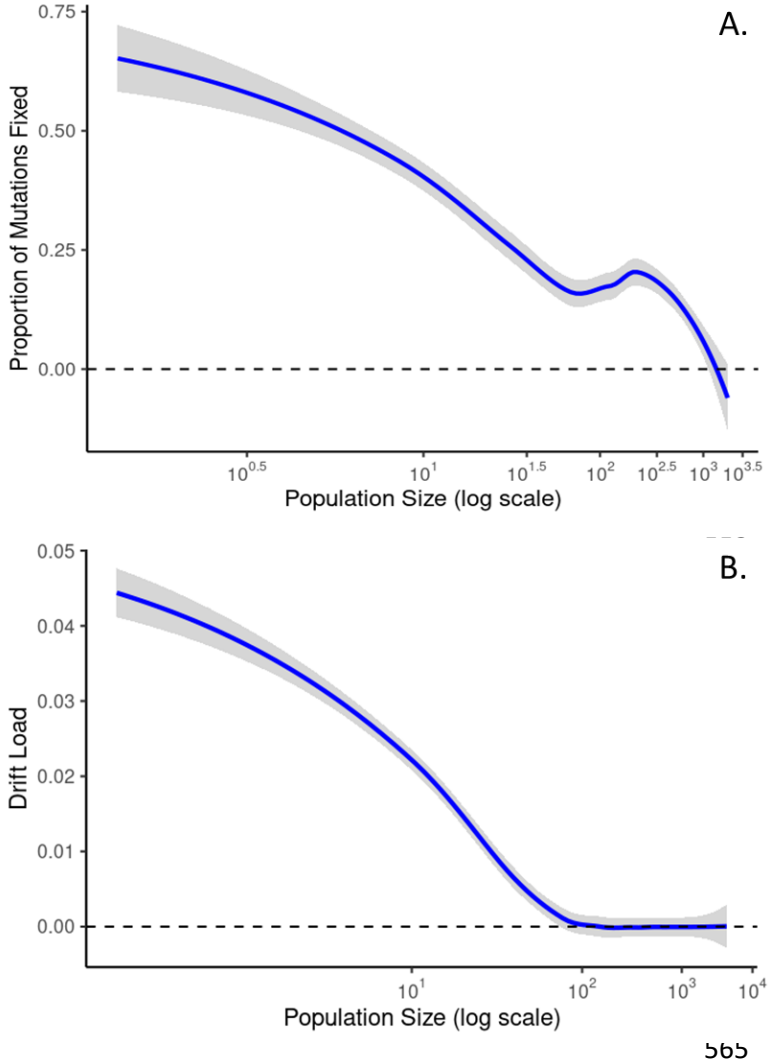

566
567 Fig. 1. The proportion of deleterious mutations fixing (A) and the levels of drift load (B) across
568 population sizes of $N = 2$ to 4000 after 1000 generations ($\mu = 1x10^{-3}$). Selection on mutations ranged
569 from 0.0 to 0.25 and were drawn randomly from a Poisson distribution, and dominance ranged from 0.0
570 to 0.2 and were drawn randomly from a uniform distribution. The blue lines represent the loess-
571 smoothed means from 1000 replications for each *N*, and gray shading indicate 95% confidence intervals.
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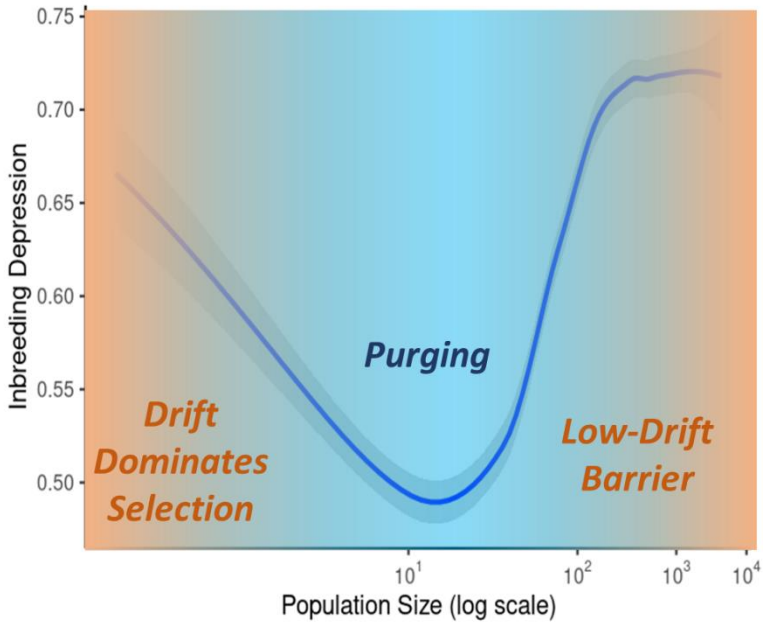

Fig. 2. Levels of inbreeding load due to loci segregating for deleterious mutations across population sizes of $N = 2$ to 4000 after 1000 generations ($\mu = 1x10^{-3}$). Selection on mutations ranged from 0.0 to 0.25 and were drawn randomly from a Poisson distribution, and dominance ranged from 0.0 to 0.2 and were drawn randomly from a uniform distribution. The blue lines represent the loess-smoothed means from 1000 replications for each *N*, and gray shading indicate 95% confidence intervals.

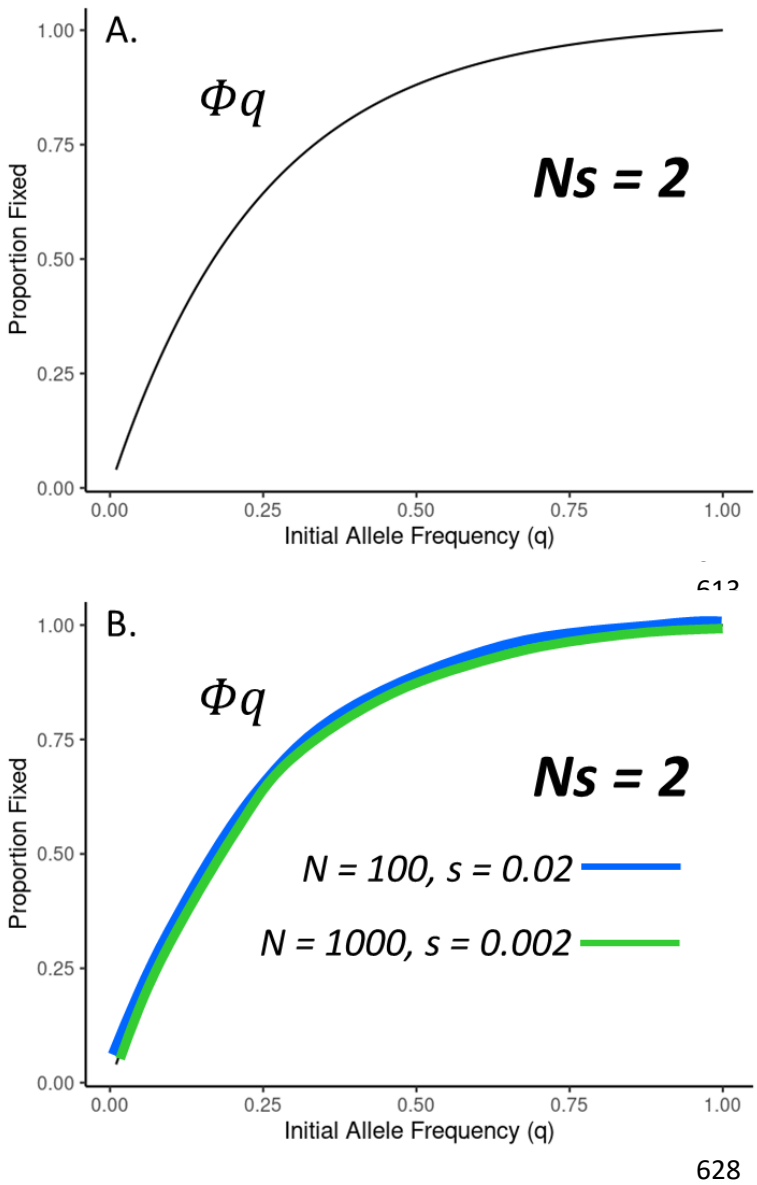

Fig. 3. The diffusion approximation for the probability of fixation (Φ_q) in response to initial allele frequency with *Ns = 2* (A), and the proportion of fixed alleles across 100 loci after 1000 generations for population sizes of *N = 100* and 1000 with *Ns = 2* (B; the relationship for Φ_q is obscured). Lines represent the loess-smoothed relationship of means for 20 replications per population size.

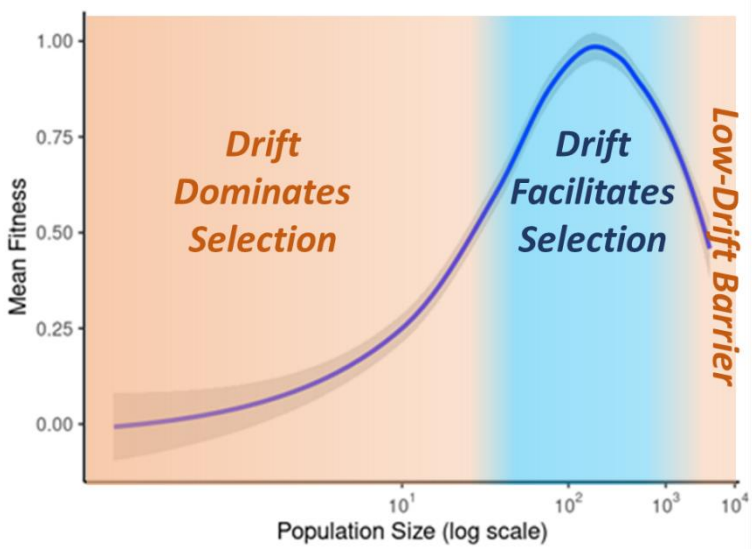

Fig. 4. Mean fitness effects of beneficial mutations across population sizes of *N = 2* to 4000 after 1000 generations with initial *q = 1/2N* (*μ = 0*). Selection on mutations ranged from 0.0 to 0.25 and were drawn randomly from a Poisson distribution, and dominance ranged from 0.0 to 0.2 and were drawn randomly from a uniform distribution. The blue lines represent the loess-smoothed means from 1000 replications for each *N*, and gray shading indicate 95% confidence intervals.

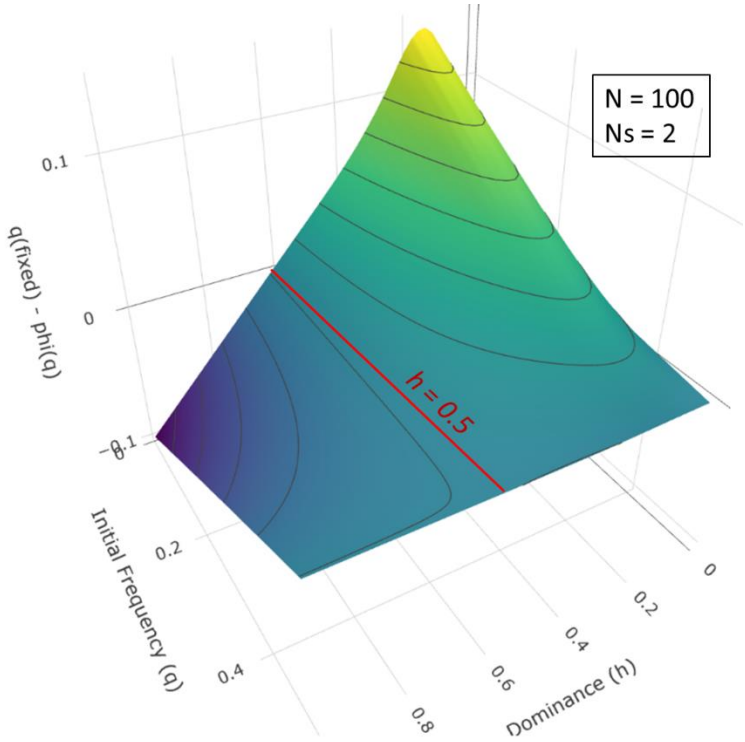

Fig. 5. Deviations between the diffusion approximation for the probability of fixation (Φ_q), and observed frequencies of fixation across initial allele frequencies (*q = 0.01* to *0.5*) and dominance (*h = 0.0* to *1.0*) for a population size of 100 and *s = 0.02* (*Ns = 2*) after 1000 generations with initial *q = 1/2N* (*μ = 0*).

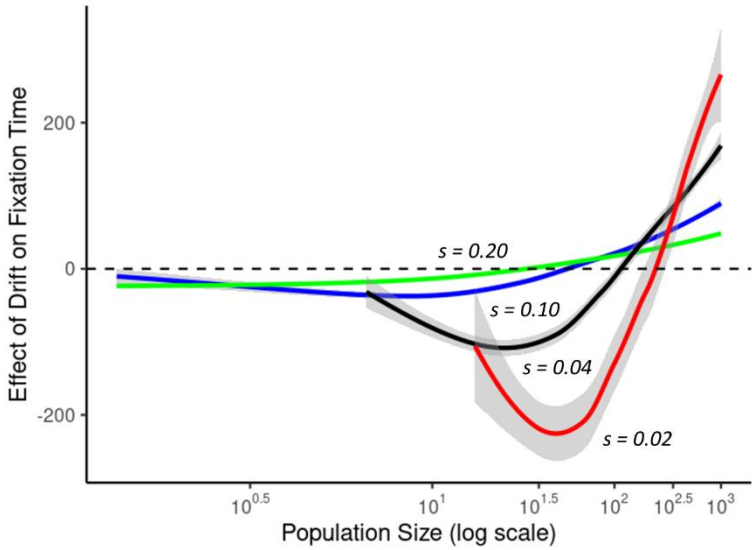

Fig. 6. Effects of population size on rates of fixation of beneficial alleles from simulations (*h = 0.5*) compared to the diffusion approximation averaged across 10 replicates per population size ($\bar{t} - \bar{t}_{gens}$) for *s = 0.02* (red), *0.04* (black), *0.10* (blue), and *0.20* (green). The lines represent the loess-smoothed means across 100 replications for each *N*, and gray shading indicates 95% confidence intervals.

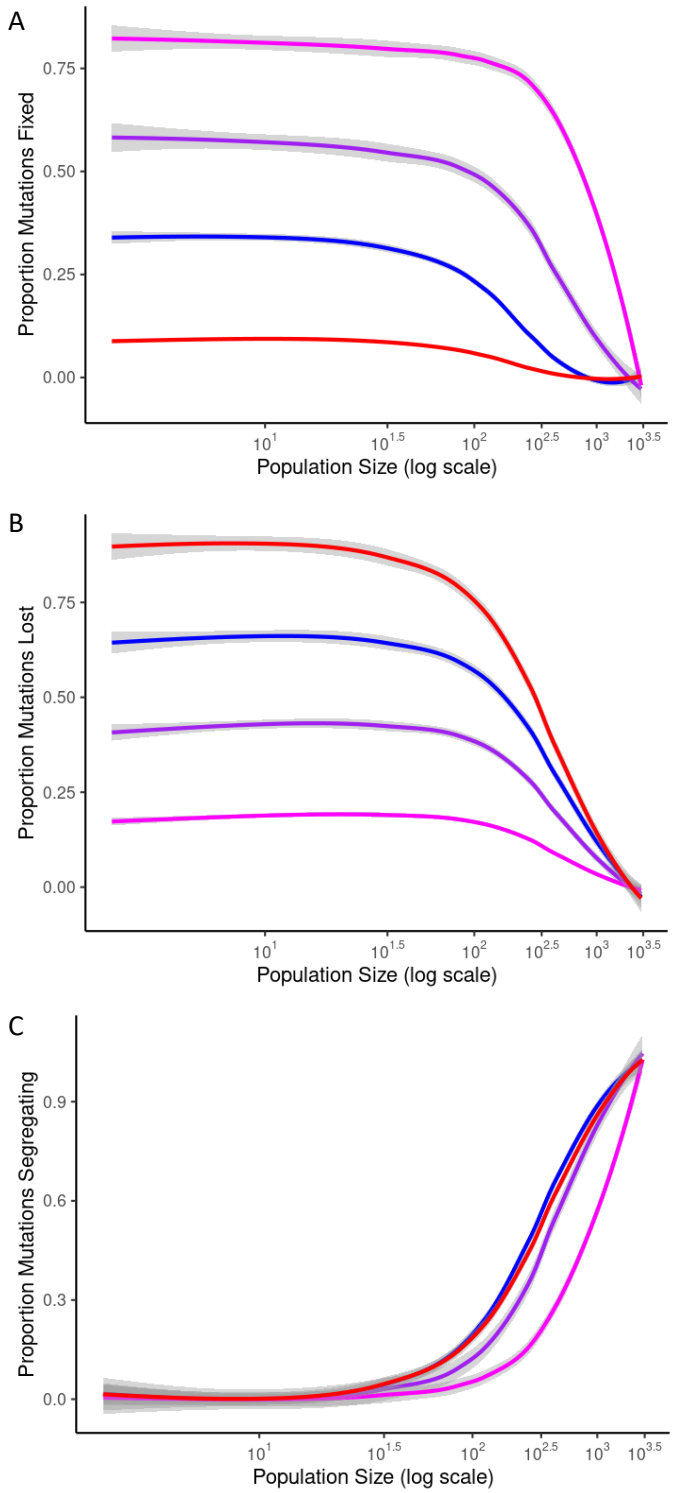

Fig. 7. Accumulation of beneficial mutations (A; fixation flux), mutations lost (B), and the proportion continuing to segregate (C) after 1000 (blue), 2000, (purple), and 4000 (magenta) generations with *Ns = 2*, and over 1000 generations with *s = 0* (red). The lines represent the loess-smoothed means across 100 replications for each *N*, and gray shading indicates 95% confidence intervals.

Appendix 2. Supplemental Figures.

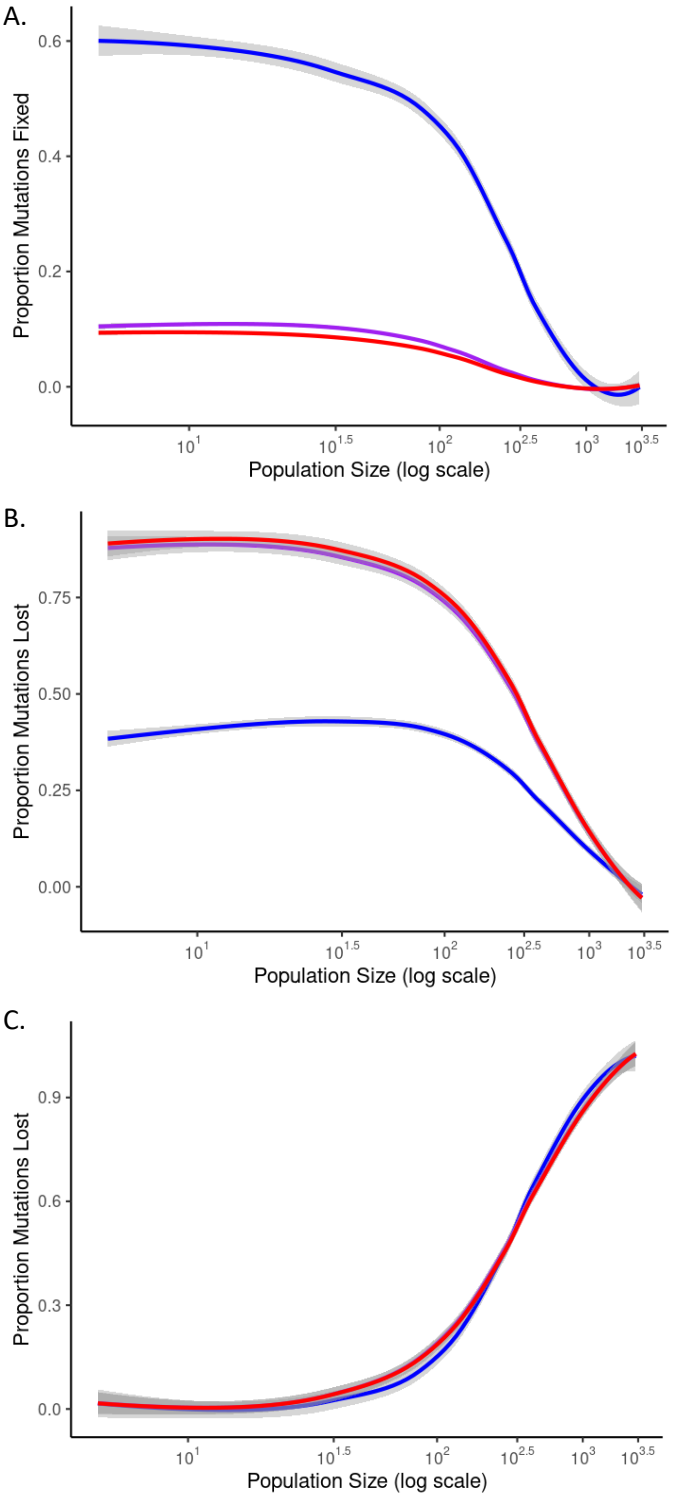

Fig. S1. Accumulation of beneficial mutations (A; fixation flux), mutations lost (B), and the proportion continuing to segregate (C) after 1000 generations with *Ns = 4* (blue), *Ns = 0.02* (purple), and *Ns = 0* (red). The lines represent the loess-smoothed means across 100 replications for each *N*, and gray shading indicates 95% confidence intervals.

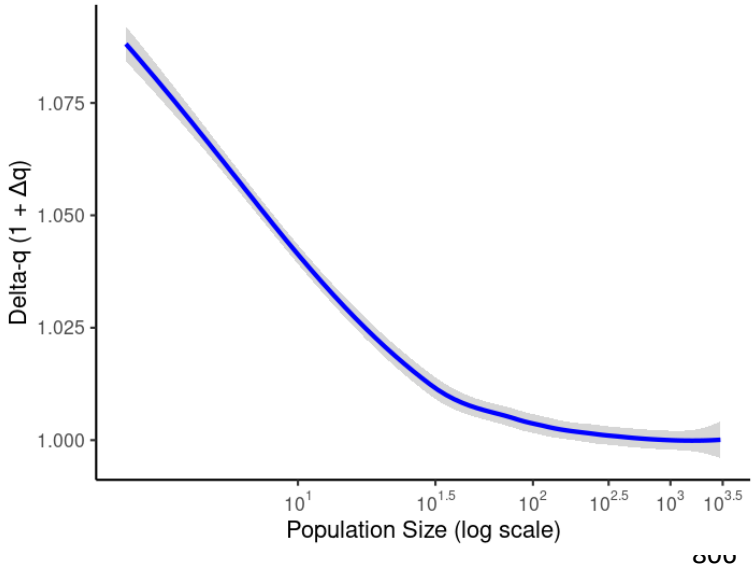

Fig. S2. Mean *Δq* for beneficial mutations going to fixation from an initial frequency of *1/2N* with *s = 2/N* (*Ns = 2*) across population sizes from *N = 4* to *3000*. The line represents the loess-smoothed means across 100 replications for each *N*, and gray shading indicates the 95% confidence interval.

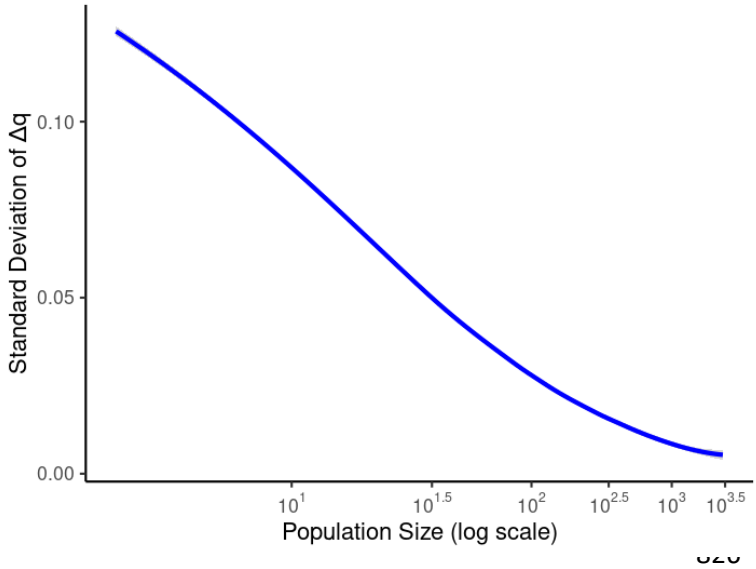

Fig. S3. Standard deviation of *Δq* for beneficial mutations going to fixation from an initial frequency of *1/2N* with *s = 2/N* (*Ns = 2*) across population sizes from *N = 4* to *3000*. The line represents the loess-smoothed means across 100 replications for each *N*, and gray shading indicates the 95% confidence interval.

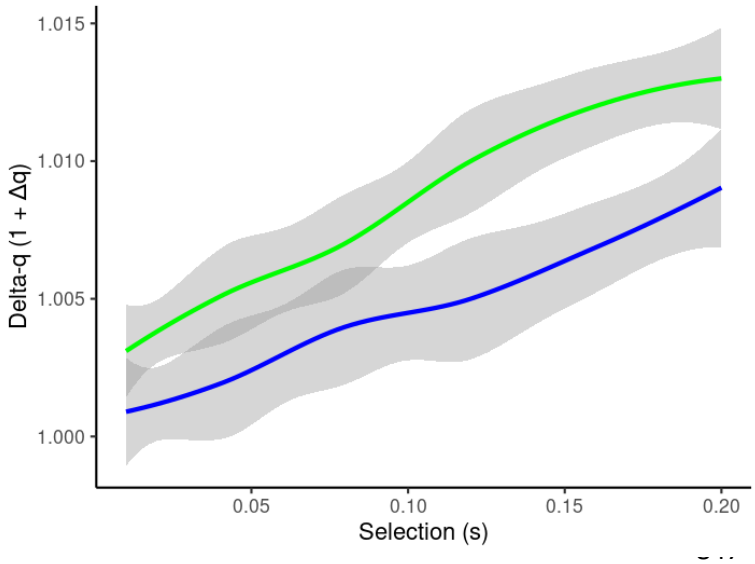

Fig. S4. Mean *Δq* for beneficial mutations going to fixation from an initial frequency of *1/2N* across selection coefficients from *s = 0.01* to 0.20 for *N = 100* (green line) and *N = 1000* (blue line). The line represents the loess-smoothed means across 100 replications for each *N*, and gray shading indicates the 95% confidence interval.

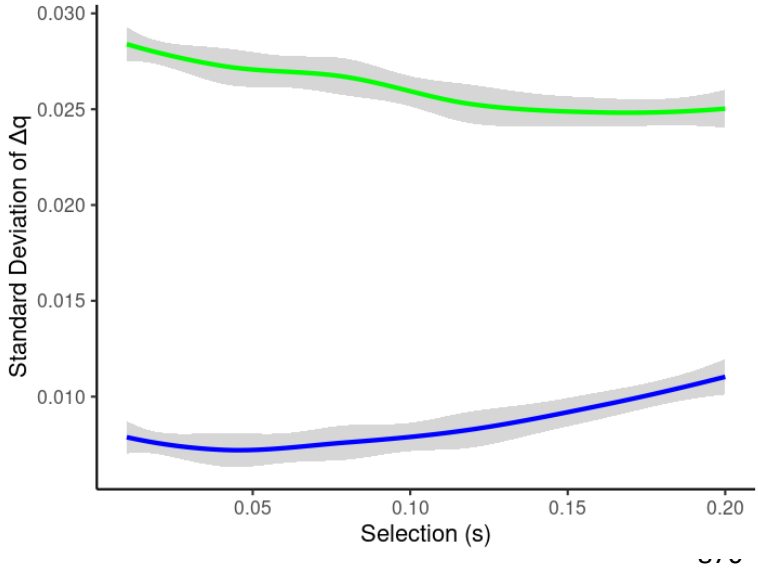

Fig. S5. Standard deviation of *Δq* for beneficial mutations going to fixation from an initial frequency of *1/2N* across selection coefficients from *s = 0.01* to 0.20 for *N = 100* (green line) and *N = 1000* (blue line). The line represents the loess-smoothed means across 100 replications for each *N*, and gray shading indicates the 95% confidence interval.

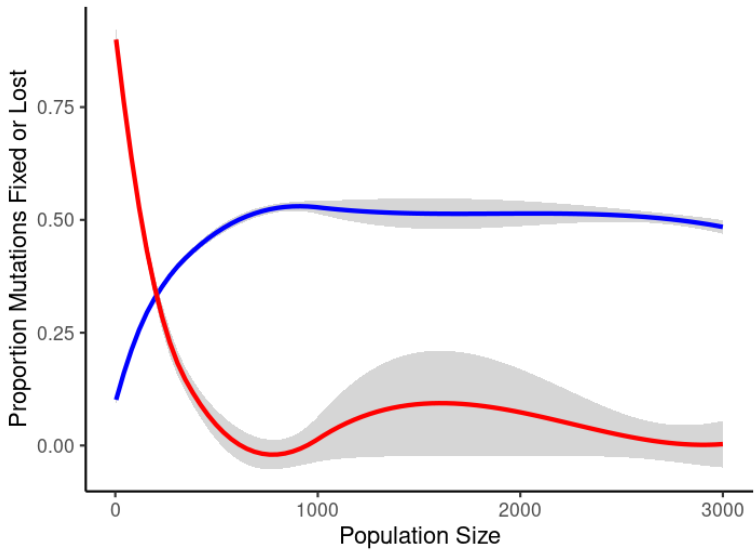

Fig. S6. Accumulation of beneficial mutations (fixation flux; blue) and mutations lost (red) across population sizes after 1000 generations with *s = 0.02*. The lines represent the loess-smoothed means across 100 replications for each *N*, and gray shading indicates 95% confidence intervals.