

1 **ANALYSIS AND REJECTION SAMPLING OF WRIGHT-FISHER**
2 **DIFFUSION BRIDGES**

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ABSTRACT. We investigate the properties of a Wright-Fisher diffusion process started from frequency x at time 0 and conditioned to be at frequency y at time T . Such a process is called a bridge. Bridges arise naturally in the analysis of selection acting on standing variation and in the inference of selection from allele frequency time series. We establish a number of results about the distribution of neutral Wright-Fisher bridges and develop a novel rejection sampling scheme for bridges under selection that we use to study their behavior.

4 1. INTRODUCTION

5 The Wright-Fisher Markov chain is of central importance in population genetics
6 and has contributed greatly to the understanding of the patterns of genetic variation
7 seen in natural populations. Much recent work has focused on developing sampling
8 theory for neutral sites linked to sites under selection [Smith and Haigh, 1974, Ka-
9 plan et al., 1989, Nielsen et al., 2005, Etheridge et al., 2006]. Typically, the site
10 under selection is assumed to have dynamics governed by the diffusion process limit
11 of the Wright-Fisher chain, in which case the genealogy of linked neutral sites can
12 be constructed using the framework of Hudson and Kaplan [1988]. However, due to
13 the complicated nature of this model, analytical theory is necessarily approximate
14 and the main focus is on simulation methods. In particular, a number of simu-
15 lation programs, including mbs [Teshima and Innan, 2009] and msms [Ewing and
16 Hermisson, 2010] have recently appeared to help facilitate the simulation of neutral
17 genealogies linked to sites undergoing a Wright-Fisher diffusion with selection.

18 Simulations of Wright-Fisher paths under selection can be easily carried out
19 using standard techniques for simulating diffusions. Frequently, however, it is nec-
20 essary to simulate a Wright-Fisher path conditioned on some particular outcome.
21 For example, to simulate the path of an allele under selection that is currently at
22 frequency x , a time-reversal argument shows that it is possible to simulate a path
23 starting at x conditioned to hit 0 eventually [Maruyama, 1974]. However, more
24 complicated scenarios, including the action of natural selection on standing genetic
25 variation, require more elaborate simulation methods [Peter et al., 2012].

26 The stochastic process describing an allele that starts at frequency x at time 0
27 and is conditioned to end at frequency y at time T is called a bridge between x

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28 and y in time T or a bridge between x and y over the time interval $[0, T]$. Wright-
 29 Fisher diffusion bridges appear naturally in the study of selection acting on standing
 30 variation because it is necessary to know the path taken by an allele at current
 31 frequency y that fell under the influence of natural selection at a time T generations
 32 in the past when it was segregating neutrally at frequency x . Wright-Fisher diffusion
 33 bridges are also of interest for their application to inference of selection from allele
 34 frequency time series [Bollback et al., 2008, Malaspinas et al., 2012, Mathieson
 35 and McVean, 2013, Feder et al., 2013]. In particular, analysis of bridges can help
 36 determine the extent to which more signal is gained by adding further intermediate
 37 time points.

38 In addition to their applied interest, there are interesting theoretical questions
 39 surrounding Wright-Fisher diffusion bridges. For alleles conditioned to eventually
 40 fix, Maruyama [1974] showed that the distribution of the trajectory does not de-
 41 pend on the sign of the selection coefficient; that is, both positively and negatively
 42 selected alleles with the same absolute value of the selection coefficient exhibit the
 43 same dynamics conditioned on eventual fixation. It is natural to inquire whether
 44 the analogous result holds for a bridge between any two interior points. Moreover,
 45 the degree to which a Wright-Fisher bridge with selection will differ from a Wright-
 46 Fisher bridge under neutrality is not known (in connection with this question, we
 47 recall the well-known fact that the distribution of a bridge for a Brownian motion
 48 with drift does not depend on the drift parameter, and so it is conceivable that
 49 the presence of selection has little or no effect on the behavior of Wright-Fisher
 50 bridges). Lastly, the characteristics of the sample paths of the frequency of alleles
 51 destined to be lost in a fixed amount of time are not only interesting theoretically
 52 but may also have applications to geographically structured populations [Slatkin
 53 and Excoffier, 2012].

54 Here we investigate various features of Wright-Fisher diffusion bridges. The
 55 paper is structured as follows. First, we establish analytical results for neutral
 56 Wright-Fisher bridges. Then, we derive a novel rejection sampler for Wright-Fisher
 57 bridges with selection and use it to study the properties of such processes. For
 58 example, we estimate the distribution of the maximum of a bridge from 0 to 0
 59 under selection and investigate how this distribution depends on the strength of
 60 selection.

61

2. BACKGROUND

62 A Wright-Fisher diffusion with genic selection is a diffusion process $\{X_t, t \geq 0\}$
 63 with state space $[0, 1]$ and infinitesimal generator

$$(2.1) \quad \mathcal{L} = \gamma x(1-x) \frac{\partial}{\partial x} + \frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2}.$$

64 When $\gamma = 0$, the diffusion is said to be neutral; otherwise, the drift term captures
 65 the strength and direction of natural selection.

66 The corresponding Wright-Fisher diffusion bridge, $\{X_t^{x,z,[0,T]}, 0 \leq t \leq T\}$ is
 67 the stochastic process that results from conditioning the Wright-Fisher diffusion to
 68 start with value x at time 0 and end with value z at time T . Denote by $f(x, y; t)$ the
 69 transition density of the diffusion corresponding to (2.1). By the Markov property
 70 of the Wright-Fisher diffusion, the bridge is a time-inhomogeneous diffusion and
 71 the transition density for the bridge going from state u at time s to state v at time

72 t is

$$(2.2) \quad f_{x,z,[0,T]}(u, v; s, t) = \frac{f(u, v; t-s)f(v, z; T-t)}{f(u, z; T-s)}.$$

73 The time-inhomogeneous infinitesimal generator of the bridge acting on a test func-
74 tion g at time s is

$$(2.3) \quad \begin{aligned} \mathcal{L}_{x,z,[0,T];s}g(u) &= \lim_{t \downarrow s} \frac{\mathbb{E}[g(X_t) | X_0 = x, X_s = u, X_T = z] - g(u)}{t-s} \\ &= u(1-u) \left(\gamma + \frac{\partial}{\partial u} \log f(u, z; T-s) \right) \frac{\partial g}{\partial u}(u) \\ &\quad + \frac{1}{2} u(1-u) \frac{\partial^2 g}{\partial u^2}(u). \end{aligned}$$

75 An obvious method for simulating a Wright-Fisher bridge would be to simulate
76 the stochastic differential equation (SDE) corresponding to this infinitesimal gen-
77 erator. There are two obstacles to this approach. Firstly, analytic expressions for
78 the transition density f are only known for the neutral case, and even there they
79 are in the form of infinite series. Secondly, note that the first order coefficient in
80 the infinitesimal generator becomes increasing singular as $s \uparrow T$; consequently, an
81 attempt to simulate the bridge by simulating the SDE would be quite unstable
82 because the drift term in the SDE would explode at times close to the terminal
83 time T . It is because this naive approach is infeasible that we need to consider the
84 more sophisticated simulation methods explored in this paper.

85 In addition to conditioning the process to obtain a particular value at a particular
86 time, it is possible to condition a process's long term behavior. The transition den-
87 sities of the conditioned process, $f_h(x, y; t)$ are related to the transition densities
88 of the unconditioned process by the usual Doob h -transform formula,

$$f_h(x, y; t) := h(x)^{-1} f(x, y; t) h(y).$$

89 The h -transformed process has infinitesimal generator

$$(2.4) \quad \mathcal{L}^h := x(1-x) \left(\gamma + \frac{h'(x)}{h(x)} \right) \frac{\partial}{\partial x} + \frac{x(1-x)}{2} \frac{\partial^2}{\partial x^2}.$$

90 Note that the finite dimensional marginal distribution at times $0 \leq t_1 \leq \dots \leq t_n \leq$
91 T of the Wright-Fisher diffusion bridge starting at x at time 0 and ending at y at
92 time T has density

$$\frac{f(x, v_1; t_1) f(v_1, v_2; t_2 - t_1) \cdots f(v_n, y; T - t_n)}{f(x, y; T)}$$

93 whereas the analogous density for the corresponding bridge of the h -transformed
94 process is

$$\begin{aligned} &\frac{h(x)^{-1} f(x, v_1; t_1) h(v_1) h(v_1)^{-1} f(v_1, v_2; t_2 - t_1) h(v_2) \cdots h(v_n)^{-1} f(v_n, y; T - t_n) h(y)}{h(x)^{-1} f(x, y; T) h(y)} \\ &= \frac{f(x, v_1; t_1) f(v_1, v_2; t_2 - t_1) \cdots f(v_n, y; T - t_n)}{f(x, y; T)}. \end{aligned}$$

95 Thus, the the bridges for the two processes have the same distribution.

96 Typical h -transforms include the conditioning a process to eventually hit a par-
97 ticular value, and for the sake of future reference we recall from standard diffusion

theory [Rogers and Williams, 2000] that the probability that the Wright-Fisher diffusion started from x eventually hits y is

$$(2.5) \quad p_{xy} = \begin{cases} \frac{S(x)-S(0)}{S(y)-S(0)}, & \text{if } y > x, \\ \frac{S(1)-S(y)}{S(1)-S(x)}, & \text{if } y < x, \end{cases}$$

where S is the scale function given by

$$S(x) = \begin{cases} \frac{1-e^{-2\gamma x}}{1-e^{-2\gamma}}, & \text{if } \gamma \neq 0, \\ x, & \text{if } \gamma = 0. \end{cases}$$

Thus,

$$(2.6) \quad p_{xy} = \begin{cases} \frac{1-e^{-2\gamma x}}{1-e^{-2\gamma y}}, & \text{if } y > x, \\ \frac{e^{-2\gamma y}-e^{-2\gamma}}{e^{-2\gamma x}-e^{-2\gamma}}, & \text{if } y < x, \end{cases}$$

when $\gamma \neq 0$ and

$$(2.7) \quad p_{xy} = \begin{cases} \frac{x}{y}, & \text{if } y > x, \\ \frac{1-y}{1-x}, & \text{if } y < x. \end{cases}$$

103

3. ANALYTIC THEORY FOR NEUTRAL BRIDGES

3.1. Transition densities for the neutral Wright-Fisher diffusion. When there is no natural selection (i.e., $\gamma = 0$), the transition densities of the Wright-Fisher diffusion can be expressed

$$(3.1) \quad f(x, y; t) = \sum_{l=2}^{\infty} q_l(t) \sum_{k=1}^{l-1} \binom{l}{k} x^k (1-x)^{l-k} \mathcal{B}(y; k, l-k),$$

where the $q_l(t)$ are the transition functions of a death process starting at infinity with death rate $\frac{1}{2}n(n-1)$ when n individuals are left alive and $\mathcal{B}(\cdot; \alpha, \beta)$ is the density of the Beta distribution with parameters α and β [Ethier and Griffiths, 1993]. That is, $q_l(t)$ is the probability that a Kingman coalescent tree with infinitely many leaves at time 0 has l lineages present t units of time in the past. In the Appendix we present a related pair of eigenfunction expansions of the transition density.

Let $\{T_j\}_{j=1}^{\infty}$ be a sequence of independent exponential random variables with rates $\{j(j-1)/2\}_{j=1}^{\infty}$. We think of T_j as the length of time in a Kingman coalescent tree when j lineages are present. Thus, $\sum_{j=l}^{\infty} T_j$ is the time to $l-1$ lineages being present. Write $h_l(t)$ for the density of this sum. The Laplace transform of h_l is

$$(3.2) \quad \begin{aligned} \phi_l(\lambda) &= \int_0^{\infty} e^{-\lambda t} h_l(t) dt \\ &= \prod_{j=l}^{\infty} \left(1 + \frac{2\lambda}{j(j-1)} \right)^{-1}. \end{aligned}$$

Because

$$h_l(t) = \frac{1}{2}l(l-1)q_l(t), \quad t > 0,$$

we see that

$$(3.3) \quad \int_0^{\infty} e^{-\lambda t} q_l(t) dt = \frac{2}{l(l-1)} \phi_l(\lambda), \quad l > 0.$$

120 Thus, the Laplace transform of $f(x, y; \cdot)$ is

$$(3.4) \quad f^*(x, y; \lambda) = \sum_{l=2}^{\infty} \frac{2}{l(l-1)} \phi_l(\lambda) \sum_{k=1}^{l-1} \binom{l}{k} x^k (1-x)^{l-k} \mathcal{B}(y; k, l-k).$$

121 To construct bridges with 0 as their initial or final points, we need to consider
 122 the behavior of the transition density $f(x, y; t)$ as $x \downarrow 0$. Discarding terms that are
 123 $O(x^2)$, (3.4) is asymptotic to

$$(3.5) \quad 2x \sum_{l=2}^{\infty} (1-y)^{l-2} \phi_l(\lambda).$$

124 Note that

$$(3.6) \quad \sum_{l=2}^{\infty} y(1-y)^{l-2} \phi_l(\lambda)$$

125 is the Laplace transform of the density of

$$(3.7) \quad \sum_{l=N}^{\infty} T_l,$$

126 where $N-2$ is distributed as the number of failures before the first success in a
 127 sequence of i.i.d. Bernoulli trials with success probability y .

128 **3.2. Bridge from 0 to 0 over $[0, T]$.** For $x, y \notin \{0, 1\}$, it follows from (2.2) that
 129 the density of X_t given that $X_0 = x$ and $X_T = z$ is

$$(3.8) \quad \begin{aligned} f_{x,z,[0,T]}(y; t) &= \frac{f(x, y; t) f(y, z; T-t)}{f(x, z; T)} \\ &= \frac{f(x, y; t) f(z, y; T-t) y(1-y)}{f(x, z; T) z(1-z)} \\ &= \frac{x^{-1} f(x, y; t) z^{-1} f(z, y, T-t) y(1-y)}{x^{-1} f(x, z; T) (1-z)}. \end{aligned}$$

130 In the second line of (3.8) we used reversibility (before hitting 0 or 1) with respect
 131 to the speed measure $z^{-1}(1-z)^{-1}$. From (3.4) we know the asymptotic form of
 132 (3.8). The limit of

$$x^{-1} f(x, z; T)$$

133 as $x \downarrow 0$ is

$$(3.9) \quad 2 \sum_{l=2}^{\infty} (1-z)^{l-2} h_l(T).$$

134 If $z \downarrow 0$ as well, then the limit is

$$(3.10) \quad 2 \sum_{l=2}^{\infty} h_l(t).$$

135 Therefore,

$$(3.11) \quad \begin{aligned} f_{0,0,[0,T]}(y; t) &= \frac{2y(1-y) \sum_{k=2}^{\infty} (1-y)^{k-2} h_k(t) \times \sum_{l=2}^{\infty} (1-y)^{l-2} h_l(T-t)}{\sum_{m=2}^{\infty} h_m(T)}. \end{aligned}$$

136 The density h_l is given by

$$(3.12) \quad h_l(t) = \frac{1}{2} l(l-1) \sum_{j=l}^{\infty} e^{-\frac{j(j-1)}{2}t} (-1)^{j-l} \frac{(2j-1)l_{(j-1)}}{l!(j-l)!},$$

137 where $a_{(b)} := a(a+1)\cdots(a+b-1)$. In addition, an eigenfunction expansion of the
138 transition density in the Appendix shows that

$$(3.13) \quad 2 \sum_{l=2}^{\infty} h_l(t) = \sum_{n=2}^{\infty} e^{-\frac{1}{2}n(n-1)t} (2n-1)n(n-1).$$

139 It is clear from the above that the random variable $X_t^{0,0,[0,T]}$ has the same distri-
140 bution as $X_{T-t}^{0,0,[0,T]}$ for $0 \leq t \leq T$, and an elaboration of this argument using (2.2)
141 to compute the finite dimensional distributions of the process $X^{0,0,[0,T]}$ shows the
142 following invariance under time-reversal

$$\{X_t^{0,0,[0,T]}, 0 \leq t \leq T\} \stackrel{\mathcal{D}}{=} \{X_{T-t}^{0,0,[0,T]}, 0 \leq t \leq T\},$$

143 where $\stackrel{\mathcal{D}}{=}$ denotes equality in distribution.

144 As $T \rightarrow \infty$, the density of $X_t^{0,0,[0,T]}$ for a fixed $t > 0$ converges to

$$(3.14) \quad 2y(1-y)e^t \sum_{k=2}^{\infty} (1-y)^{k-2} h_k(t).$$

145 By a similar calculation, we find that, centering around $T/2$, the limiting density
146 of $X_{T/2+t}$ for $-T/2 < t < T/2$ fixed is just $6y(1-y)$, independent of t .

147 Moreover, from (2.2) we see that the transition densities of $X_t^{0,0,[0,T]}$ satisfy

$$(3.15) \quad \begin{aligned} f_{0,0,[0,T]}(u, v; s, t) &= \lim_{z \downarrow 0} \frac{f(u, v; t-s)f(v, z; T-t)}{f(u, z; T-s)} \\ &= \lim_{z \downarrow 0} \frac{f(u, v; t-s)f(v, z; T-t)z(1-z)}{f(u, z; T-s)z(1-z)} \\ &= \lim_{z \downarrow 0} \frac{f(u, v; t-s)f(z, v; T-t)v(1-v)}{f(z, u; T-s)u(1-u)} \\ &= f(u, v; t-s) \frac{\sum_{l=2}^{\infty} (1-v)^{l-2} h_l(T-t)v(1-v)}{\sum_{l=2}^{\infty} (1-v)^{l-2} h_l(T-s)u(1-u)}. \end{aligned}$$

148 For fixed $0 < s < t$, this transition density converges to

$$(3.16) \quad \lim_{T \rightarrow \infty} f_{0,0,[0,T]}(u, v; s, t) = e^{t-s} u^{-1} (1-u)^{-1} f(u, v; t-s) v(1-v),$$

149 the transition density of the neutral Wright-Fisher diffusion conditioned on non-
150 absorption, a process with infinitesimal generator

$$(3.17) \quad (1-2y) \frac{\partial}{\partial y} + \frac{1}{2} y(1-y) \frac{\partial^2}{\partial y^2}.$$

151 For fixed $-\infty < s < t < \infty$, the transition density $f_{0,0,[0,T]}(u, v; T/2+s, T/2+t)$
152 converges as $T \rightarrow \infty$ to the same limit, and so the finite-dimensional distributions
153 of the process $\{X_{T/2+t}^{0,0,[0,T]}, -T/2 < t < T/2\}$ converge to those of the stationary
154 Markov process indexed by the whole real line that is obtained by taking the neutral
155 Wright-Fisher diffusion conditioned on non-absorption in equilibrium.

156 **3.3. Bridge from x to 0 over $[0, T]$.** The density of X_t given that $X_0 = x$ and
 157 $X_T = 0$ is

$$(3.18) \quad f_{x,0,[0,T]}(y; t) = f(x, y; t) \frac{\sum_{l=2}^{\infty} y(1-y)^{l-1} h_l(T-t)}{\sum_{l=2}^{\infty} x(1-x)^{l-1} h_l(T)}.$$

158 The derivation of (3.18) is similar to that of (3.11). Note from (2.3) that $X^{x,0,[0,T]}$
 159 is a time inhomogeneous diffusion with time inhomogeneous infinitesimal generator

$$(3.19) \quad \begin{aligned} \mathcal{L}_t = & \frac{1}{2}y(1-y) \frac{\partial^2}{\partial y^2} \\ & + (1-y) \left[1 - \frac{y \sum_{k=2}^{\infty} (k-1)(1-y)^{k-2} h_k(T-t)}{\sum_{k=2}^{\infty} (1-y)^{k-1} h_k(T-t)} \right] \frac{\partial}{\partial y}. \end{aligned}$$

160 The transition densities of $X^{x,0,[0,T]}$ are the same as those of $X^{0,0,[0,T]}$, and so they
 161 converge as $T \rightarrow \infty$ to those of the neutral Wright-Fisher diffusion conditioned on
 162 non-absorption. As one would expect, the first order coefficient in (3.19) converges
 163 as $T \rightarrow \infty$ to $(1-2y)$, the first order coefficient in the infinitesimal generator of
 164 the neutral Wright-Fisher diffusion conditioned on non-absorption.

165 **3.4. First passage time distribution.** To determine the density of the maximum
 166 in a Wright-Fisher diffusion bridge, we will require the first passage time densities
 167 of the Wright-Fisher diffusion. Let $g(\cdot; x, y)$ be the first passage time density from x
 168 to y . Note that because the Wright-Fisher diffusion starting at x may be absorbed
 169 before hitting y , the density $g(\cdot; x, y)$ is improper; that is,

$$\int_0^{\infty} g(t; x, y) dt < 1.$$

170 Taking the Laplace transform of the identity

$$f(x, y; t) = \int_0^t g(\tau; x, y) f(y, y; t - \tau) d\tau,$$

171 we see that the Laplace transform of $g(\cdot; x, y)$ is

$$(3.20) \quad g^*(\lambda; x, y) = \frac{f^*(x, y; \lambda)}{f^*(y, y; \lambda)}.$$

172 Although the Laplace transform (3.20) is easy to evaluate, it appears to be difficult
 173 to invert it explicitly because of the denominator.

174 To gain more insight into first passage times, we consider moments of the first
 175 passage time from x to y conditioned on hitting y . By (2.7), the first passage time
 176 distribution, conditioned on hitting y , has Laplace transform

$$g^*(\lambda; x, y) \frac{y}{x}.$$

177 Combined with (3.20), the limit of this Laplace transform as $x \downarrow 0$ is

$$(3.21) \quad \lim_{x \downarrow 0} \frac{f^*(x, y; \lambda) y}{f^*(y, y; \lambda) x} = \frac{2 \sum_{l=2}^{\infty} y(1-y)^{l-2} \phi_l(\lambda)}{f^*(y, y; \lambda)}.$$

178 It follows that

$$(3.22) \quad g_{\#}(t; y) := \lim_{x \downarrow 0} g(t; x, y) \frac{y}{x}$$

179 exists and gives the density of the limit as $x \downarrow 0$ of the first passage time from x to
 180 y conditional on y being hit. For later use, we record the definition

$$(3.23) \quad g_{\circ}(t; y) := y^{-1} g_{\#}(t; y) = \lim_{x \downarrow 0} x^{-1} g(t; x, y).$$

181 We can now use (3.21) to calculate the mean first passage time from 0 to y
 182 conditioned on hitting y . The transition density satisfies the backward equation

$$\frac{\partial}{\partial t} f(x, y; t) = \frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2} f(x, y; t).$$

183 Take $y > x$, multiply by t , integrate from 0 to ∞ , and use integration-by-parts to
 184 get

$$(3.24) \quad tf(x, y; t) \Big|_0^{\infty} - \int_0^{\infty} f(x, y; t) dt = \frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2} \int_0^{\infty} tf(x, y; t) dt.$$

185 Set

$$\mu(x, y) := \int_0^{\infty} tf(x, y; t) dt.$$

186 Use the fact that $\int_0^{\infty} f(x, y; t) dt = 2x/y$ to rewrite (3.24) as

$$\frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2} \mu(x, y) = -2x/y.$$

187 This ordinary differential equation has the general solution

$$(3.25) \quad \mu(x, y) = -\frac{4}{y}(1-x) \log(1-x) + C(y)x + D(y).$$

188 Differentiating (3.5) and sending $\lambda \downarrow 0$, we find that asymptotically as $x \downarrow 0$,

$$\begin{aligned} \mu(x, y) &\sim 2x \sum_{l=2}^{\infty} (1-y)^{l-2} \sum_{k=l}^{\infty} \frac{2}{k(k-1)} \\ &= -\frac{4x}{1-y} \log y. \end{aligned}$$

189 Thus,

$$\frac{4x}{y} + C(y)x + D(y) \equiv -\frac{4x}{1-y} \log y$$

190 for small x , and hence

$$(3.26) \quad \mu(x, y) = \frac{4}{y} [-(1-x) \log(1-x) - x] - 4 \frac{x}{1-y} \log y.$$

191 To find the mean first passage time from 0 to y conditional on y being hit (or,
 192 more correctly, the mean of the limit as $x \downarrow 0$ of the first passage time from x
 193 to y conditional on y being hit), differentiate (3.21), set $\lambda = 0$, and recall that
 194 $f^*(y, y, 0) = 2$ to get

$$(3.27) \quad \frac{2 \sum_{l=2}^{\infty} y(1-y)^{l-2} \sum_{k=l}^{\infty} \frac{2}{k(k-1)}}{2} - \frac{2\mu(y, y)}{4} = 2 + 2 \frac{1-y}{y} \log(1-y).$$

195 Note that this mean increases monotonically from 0 to 2 as y goes from 0 to 1.

196 **3.5. Joint density of a maximum and time to hitting in a bridge.** For the
 197 class of diffusions with inaccessible boundaries, Csáki et al. [1987] studied the joint
 198 density of a maximum and its hitting time. This theory is not directly applicable
 199 to the Wright-Fisher diffusion because of the absorbing boundaries. However, we
 200 may condition the Wright-Fisher process to not be absorbed, thereby making the
 201 boundaries inaccessible. By an argument similar to that made in Section 2 for
 202 h -transforms, the bridges of this process are the same as the bridges of the uncon-
 203 ditioned process. The transition density, $\tilde{f}(x, y; t)$ and infinitesimal generator, $\tilde{\mathcal{L}}$ of
 204 the conditioned process are given in (3.16) and (3.17), respectively. We will also
 205 need the first passage time density for the conditioned process,

$$\tilde{g}(t; x, y) = e^t x^{-1} (1-x)^{-1} g(t; x, y) y (1-y),$$

206 along with its scale density,

$$S(x) = x^{-2} (1-x)^{-2}$$

207 and speed density

$$m(x) = x(1-x).$$

208 Applying the formula in Theorem A of Csáki et al. [1987], we find that the joint
 209 density of the maximum and time of hitting for an arbitrary bridge from x to z in
 210 time T is

$$\frac{g(t; x, y) g(T-s; z, y) z^{-1} (1-z)^{-1}}{f(x, z; T)}.$$

211 Taking limits as $x, z \downarrow 0$, we see that joint density for a bridge from 0 to 0 is

$$2 \frac{g_\circ(t; y) g_\circ(T-t; y)}{\sum_{m=2}^{\infty} h_m(T)}.$$

212 **3.6. Maximum in a bridge.** Let $M^{x,z,[0,T]}$ be the maximum of the bridge
 213 $\{X_t^{x,z,[0,T]}, 0 \leq t \leq T\}$, where $0 \leq x, z \leq 1$.

214 The occurrence of the event $\{M^{x,z,[0,T]} \geq y\}$ is equivalent to the Wright-Fisher
 215 diffusion making a first passage from x to y at some time $t \in [0, T]$ and then going
 216 on to hit z at time T . Recalling that $g(\cdot; x, y)$ is the density of the first passage
 217 from x to y , for $0 < x, z < 1$ we have

$$(3.28) \quad \mathbb{P}\{M^{x,z,[0,T]} \geq y\} = \frac{\int_0^T g(t; x, y) f(y, z; T-t) dt}{f(x, z; T)}.$$

218 We wish to obtain an expression for $\mathbb{P}\{M^{0,0,[0,T]} \geq y\}$. Multiply the numerator
 219 and denominator of the right-hand side of (3.28) by x^{-1} , re-write the numerator
 220 using the relationship

$$f(y, x; T-t) = \frac{x^{-1} (1-x)^{-1}}{y^{-1} (1-y)^{-1}} f(x, y; T-t)$$

221 that follows from the reversibility of the neutral Wright-Fisher process with respect
 222 to the speed measure $y^{-1} (1-y)^{-1} dy$, and $x, y \downarrow 0$ to get

$$\begin{aligned} & \mathbb{P}\{M^{0,0,[0,T]} \geq y\} \\ &= \frac{y(1-y) \int_0^T g_\circ(t; y) \sum_{i=1}^{\infty} (2i+1) i(i+1) P_{i-1}(1-2y) e^{-\frac{1}{2}i(i+1)(T-t)} dt}{\sum_{i=1}^{\infty} (2i+1) i(i+1) e^{-\frac{1}{2}i(i+1)T}}, \end{aligned}$$

223 where g_\circ was defined in (3.23) and the sequence of polynomials $(P_n)_{n=0}^\infty$ are defined
224 in the Appendix.

225 The Laplace transform of $t \mapsto g_\#(t; y) = yg_\circ(t; y)$ is given by (3.21). Although
226 the numerator and denominator of (3.21) can be computed accurately using the
227 orthogonal function expansion, however there is not a simple way to invert the
228 Laplace transform of the first passage time.

229 If we write the Laplace transform of $g_\#(t; y)$

$$(3.29) \quad g_\#^*(\lambda; y) = \frac{\lim_{x \downarrow 0} \frac{1}{2} f^*(x, y; \lambda) / (x/y)}{\frac{1}{2} f^*(y, y; \lambda)},$$

230 we see that the numerator and denominator are both Laplace transforms of prob-
231 ability distributions because Green function of the neutral Wright-Fisher diffusion
232 is given by

$$f^*(x, y; 0) = \int_0^\infty f(x, y; t) dt = 2 \frac{x}{y}.$$

233 Equation (3.29) can be rewritten as

$$g_\#^*(\lambda; y) \frac{1}{2} f^*(y, y; \lambda) = \lim_{x \downarrow 0} \frac{1}{2} f^*(x, y; \lambda) \frac{y}{x},$$

234 which implies the convolution equation

$$(3.30) \quad g_\#(\cdot; y) * \left(\frac{1}{2} f(y, y; \cdot) \right) = \lim_{x \downarrow 0} \frac{1}{2} f(x, y; \cdot) \frac{y}{x}.$$

235 The easiest way to solve this equation numerically is by discretization. Take
236 $\epsilon > 0$ and positive integer K . Let $P^{\epsilon, K}$ and $Q^{\epsilon, K}$ be the discrete probability
237 distributions on the set $\{0, \epsilon, 2\epsilon, \dots\}$ given by

$$a_k^{\epsilon, K} := P^{\epsilon, K}(\{k\epsilon\}) := \begin{cases} \int_0^{\epsilon/2} \lim_{x \downarrow 0} \frac{1}{2} f(x, y; t) \frac{y}{x} dt, & k = 0, \\ \int_{(k-1/2)\epsilon}^{(k+1/2)\epsilon} \lim_{x \downarrow 0} \frac{1}{2} f(x, y; t) \frac{y}{x} dt, & 1 \leq k \leq K-1, \\ \int_{(K-1/2)\epsilon}^\infty \lim_{x \downarrow 0} \frac{1}{2} f(x, y; t) \frac{y}{x} dt, & k = K, \\ 0, & k > K, \end{cases}$$

238 and

$$b_k^{\epsilon, K} := Q^{\epsilon, K}(\{k\epsilon\}) := \begin{cases} \int_0^{\epsilon/2} \frac{1}{2} f(y, y; t) dt, & k = 0, \\ \int_{(k-1/2)\epsilon}^{(k+1/2)\epsilon} \frac{1}{2} f(y, y; t) dt, & 1 \leq k \leq K-1, \\ \int_{(K-1/2)\epsilon}^\infty \frac{1}{2} f(y, y; t) dt, & k = K, \\ 0, & k > K. \end{cases}$$

239 Note that the quantities $a_k^{\epsilon, K}$ and $b_k^{\epsilon, K}$ can be computed accurately using orthogonal
240 function expansions.

241 Equation (3.30) implies that if $R^{\epsilon, K}$ is the probability distribution on the set
242 $\{0, \epsilon, 2\epsilon, \dots\}$ given by

$$R^{\epsilon, K}(\{k\epsilon\}) := \begin{cases} \int_0^{\epsilon/2} g_\#(t; y) dt, & k = 0, \\ \int_{(k-1/2)\epsilon}^{(k+1/2)\epsilon} g_\#(t; y) dt, & 1 \leq k \leq K-1, \\ \int_{(K-1/2)\epsilon}^\infty g_\#(t; y) dt, & k = K, \\ 0, & k > K, \end{cases}$$

243 then $P^{\epsilon, K}$ should be approximately the convolution $Q^{\epsilon, K} * R^{\epsilon, K}$. That is,
 244 $P^{\epsilon, K}(\{k\epsilon\})$ should be approximately c_k for $0 \leq k \leq K$, where c_0, \dots, c_K is the
 245 solution of the system of equations

$$a_k = \sum_{j=0}^k c_j b_{k-j}, \quad 0 \leq k \leq K.$$

246 Therefore, $c_0 = a_0/b_0$ and we obtain c_1, \dots, c_K recursively by

$$(3.31) \quad c_k = (a_k - \sum_{j=0}^{k-1} c_j b_{k-j})/b_0.$$

247 Thus,

$$(3.32) \quad \mathbb{P}\{M^{0,0,[0,T]} \geq y\} = \frac{(1-y) \sum_{i=1}^{\infty} (2i+1)i(i+1)P_{i-1}(w)g_{\#}^*(\frac{1}{2}i(i+1); T, y)}{\sum_{i=1}^{\infty} (2i+1)i(i+1)e^{-\frac{1}{2}i(i+1)T}},$$

248 where

$$g_{\#}^*(\lambda; T, y) = \int_0^T e^{-\lambda(T-t)} g_{\#}(t; y) dt \approx \sum_{k=0}^K \mathbb{1}\{(k+1/2)\epsilon \leq T\} \exp\{\lambda(T - (k+1/2)\epsilon)\} c(k).$$

249 **3.7. Numerical calculations.** The infinite series in (3.32) was approximated using
 250 the first 3000 terms. The step size in the discrete first passage time approximation
 251 was taken to be $\epsilon = 0.001$ and the number of points was taken to be $K = 5000$.
 252

253 Distribution function of the maximum in a bridge M .

T	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
0.5	0.0	0.02	0.17	0.43	0.66	0.83	0.92	0.96	0.99	0.99
1.0			0.0	0.02	0.09	0.21	0.36	0.52	0.66	0.77
1.5				0.0	0.01	0.03	0.08	0.17	0.28	0.40
2.0						0.0	0.02	0.04	0.09	0.17
T	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.0
0.5	1.0									
1.0	0.85	0.91	0.95	0.97	0.99	0.99	1.0			
1.5	0.52	0.63	0.73	0.82	0.88	0.93	0.96	0.99	1.0	
2.0	0.26	0.37	0.48	0.59	0.70	0.97	0.87	0.93	0.97	1.0

254

T	0.01	0.02	0.03	0.04	0.05	0.06
0.1	0.00	0.01	0.14	0.37	0.59	0.76
T	0.07	0.08	0.09	0.10	0.11	0.12
0.1	0.86	0.93	0.96	0.98	0.99	1.0

255

256 The distribution function behaves as expected. If T is 0.1 the maximum is very
 257 small, with the distribution function shown in a separate table with a small scale.
 258 M is less than 0.06 with probability 0.76 and less than 0.12 with probability 1.0. If

259 $T=0.5$ the maximum is still small, but larger than when $T = 0.1$, with a probability
 260 of 0.17 of being greater than 0.3 and a probability of 1.0 of being less than 0.55. If
 261 $T = 1.0, 1.5, 2.0$ the maximum is increasingly larger with respective probabilities of
 262 exceeding 0.5 of 0.23, 0.60, 0.83 and when $T = 2$ the probability of exceeding 0.75
 263 is 0.30. Recall that the mean to coalescence of a population to a single ancestor is
 264 2 time units.

265 4. REJECTION SAMPLING WRIGHT-FISHER BRIDGE PATHS

266 **4.1. General framework.** When selection is incorporated into the Wright-Fisher
 267 model, there is no known series formula for the transition density akin to (3.1) (but
 268 see Kimura [1955] and Kimura [1957b] for attempts using perturbation theory, as
 269 well as Song and Steinrücken [2012] and Steinrücken et al. [2012] for methods of
 270 approximating an eigenfunction expansion computationally). Therefore, analytical
 271 results for distributions associated with the corresponding bridge like those we
 272 obtained in the neutral case are not available. Instead, we develop a rejection
 273 sampling method that can sample paths of Wright-Fisher diffusion bridges with
 274 genic selection efficiently for the purpose of investigating their properties.

275 Before we explain how rejection sampling can be used to sample paths of a
 276 Wright-Fisher bridge, we first describe the analogous, but simpler, method for
 277 sampling paths of diffusion bridges that have distributions which are absolutely
 278 continuous with respect to that of a Brownian bridge. Fix $x, z \in \mathbb{R}$ and $T > 0$.
 279 Let \mathbb{W} be the distribution of Brownian bridge from x to z over the time interval
 280 $[0, T]$, and let \mathbb{P} be the distribution of the path of a bridge from x to z over the
 281 time interval $[0, T]$ for a diffusion with infinitesimal generator

$$(4.1) \quad \mathcal{G} = a(x) \frac{\partial}{\partial x} + \frac{1}{2} \frac{\partial^2}{\partial x^2}.$$

282 It follows from Girsanov's theorem (see, for example, Rogers and Williams [2000])
 283 that the probability measure \mathbb{P} is absolutely continuous with respect to \mathbb{W} with
 284 Radon-Nikodym derivative (that is, density)

$$(4.2) \quad \frac{d\mathbb{P}}{d\mathbb{W}}(\omega) = \exp \left\{ \int_0^T a(\omega_t) d\omega_t - \frac{1}{2} \int_0^T a^2(\omega_t) dt \right\}$$

285 for the path ω , where the first integral in (4.2) is an Itô integral – see Beskos
 286 and Roberts [2005] for the details of the disintegration argument that concludes
 287 this fact about Radon-Nikodym derivatives with respect to the Brownian bridge
 288 distribution from the usual statement of Girsanov's theorem, which is about Radon-
 289 Nikodym derivatives with respect to the distribution of Brownian motion. Because
 290 a Brownian bridge can be constructed using a simple transformation of a Brownian
 291 motion (namely, if B is a standard Brownian motion, then the process $\{x + (B_t -$
 292 $\frac{t}{T}B_T) + \frac{t}{T}(z - x), 0 \leq t \leq T\}$ has the distribution \mathbb{W}), it is computationally feasible
 293 to obtain fine-grained samples of the Brownian bridge. Once we have a sequence
 294 of Brownian bridge paths, (4.2) can be used to compute a likelihood ratio, and a
 295 standard rejection sampling scheme can then be utilized to obtain realizations of
 296 diffusion bridge paths; see Beskos and Roberts [2005] for examples of extensions to
 297 this approach.

298 This method is not immediately applicable to the Wright-Fisher bridge because
 299 its infinitesimal generator is not of the form (4.1). However, it was shown on pp

300 119-120 of Wright [1931] that if X is the Wright-Fisher process with infinitesimal
 301 generator (2.1), then the transformation

$$(4.3) \quad Y_t := \arccos(1 - 2X_t)$$

302 suggested in Fisher [1922] produces a diffusion process Y on the state space $[0, \pi]$
 303 with infinitesimal generator

$$\mathcal{L}_Y = \frac{1}{2}(\gamma \sin(y) - \cot(y)) \frac{\partial}{\partial y} + \frac{1}{2} \frac{\partial^2}{\partial y^2}.$$

304 Because Y has absorbing boundaries at 0 and π , sampling paths of bridges for
 305 Y by sampling Brownian bridges can involve extremely high rejection rates. More
 306 specifically,

$$\frac{1}{2}(\gamma \sin(y) - \cot(y)) \approx -\frac{1}{2y}, \quad \text{as } y \downarrow 0,$$

307 and so the likelihood ratio (4.2) becomes extremely small for paths that spend a
 308 significant amount of time near 0. A similar phenomenon occurs near π .

309 To overcome the difficulty near 0, we develop a rejection sampling scheme where
 310 the proposals are realizations of a process other than the Brownian bridge.

311 As a first step, consider the Wright-Fisher diffusion conditioned to be eventually
 312 absorbed at 1. By the argument given in Section 2, this process has the same
 313 bridges as the unconditional process. It follows from (2.6) and (2.7) with $y = 1$
 314 that the probability the process starting from x is absorbed at 1 is

$$h(x) := \begin{cases} \frac{1-e^{-2\gamma x}}{1-e^{-2\gamma}}, & \gamma \neq 0, \\ x, & \gamma = 0. \end{cases}$$

315 The transition densities of the conditioned process, $f_h(x, y; t)$, are related to the
 316 unconditional transition densities by the usual Doob h -transform formula

$$f_h(x, y; t) := h(x)^{-1} f(x, y; t) h(y).$$

317 The corresponding infinitesimal generator is

$$(4.4) \quad \mathcal{L}^h := \begin{cases} \gamma x(1-x) \cot(\gamma x) \frac{\partial}{\partial x} + \frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2}, & \gamma \neq 0, \\ (1-x) \frac{\partial}{\partial x} + \frac{1}{2} x(1-x) \frac{\partial^2}{\partial x^2}, & \gamma = 0. \end{cases}$$

318 Applying the transformation (4.3) to the process with infinitesimal generator
 319 (4.4) results in a process with infinitesimal generator

$$(4.5) \quad \mathcal{L}_Y^h := \begin{cases} \frac{1}{2} (\gamma \sin(y) \coth(\gamma \sin^2(y/2)) - \cot(y)) \frac{\partial}{\partial y} + \frac{1}{2} \frac{\partial^2}{\partial y^2}, & \gamma \neq 0, \\ \frac{1}{2} (\sin(y) \csc^2(y/2) - \cot(y)) \frac{\partial}{\partial y} + \frac{1}{2} \frac{\partial^2}{\partial y^2}, & \gamma = 0. \end{cases}$$

320 Note that

$$(4.6) \quad \frac{1}{2} (\gamma \sin(y) \coth(\gamma \sin^2(y/2)) - \cot(y)) \approx \frac{3}{2y} \quad \text{as } y \downarrow 0$$

321 and

$$(4.7) \quad \frac{1}{2} (\sin(y) \csc^2(y/2) - \cot(y)) \approx \frac{3}{2y} \quad \text{as } y \downarrow 0.$$

322 Moreover, if \mathbb{Q} is the distribution of a bridge from x to z over the time interval
 323 $[0, T]$ for some diffusion with infinitesimal generator

$$\mathcal{G} = b(x) \frac{\partial}{\partial x} + \frac{1}{2} \frac{\partial^2}{\partial x^2}$$

324 and \mathbb{P} is the distribution of a bridge from x to z over the time interval $[0, T]$ for the
 325 diffusion with infinitesimal generator (4.1), then

$$\begin{aligned} \frac{d\mathbb{P}}{d\mathbb{Q}}(\omega) &= \frac{d\mathbb{P}}{d\mathbb{W}}(\omega) \frac{d\mathbb{W}}{d\mathbb{Q}}(\omega) \\ &= \frac{d\mathbb{P}}{d\mathbb{W}}(\omega) \Big/ \frac{d\mathbb{Q}}{d\mathbb{W}}(\omega) \\ &= \exp \left\{ \int_0^T a(\omega_t) - b(\omega_t) d\omega_t - \frac{1}{2} \int_0^T a^2(\omega_t) - b^2(\omega_t) dt \right\}. \end{aligned}$$

326 This suggests that a better rejection sampling scheme for bridges of the process Y
 327 with end points close to zero will result when the proposals come from a diffusion
 328 with an infinitesimal generator having a first order coefficient with a singularity at
 329 zero matching the one appearing in both (4.6) and (4.7).

330 For such a modified scheme to be feasible, it is necessary to work with a pro-
 331 posal diffusion for which it is easy to simulate the associated bridges. We now
 332 introduce such a process. The 4-dimensional Bessel process is the radial part of a
 333 4-dimensional Brownian motion. That is, if $\{B_t = (B_t^{(i)})_{i=1}^4, t \geq 0\}$ is a vector of
 334 4 independent one-dimensional Brownian motions, then

$$\beta_t := |B_t| = \sqrt{(B_t^{(1)})^2 + (B_t^{(2)})^2 + (B_t^{(3)})^2 + (B_t^{(4)})^2}, \quad t \geq 0,$$

335 is a 4-dimensional Bessel process (see Revuz and Yor [1999, Section XI.1] for a
 336 thorough discussion of Bessel processes). The 4-dimensional Bessel process is a
 337 diffusion with infinitesimal generator

$$\mathcal{B} := \frac{3}{2} \frac{1}{x} \frac{\partial}{\partial x} + \frac{1}{2} \frac{\partial^2}{\partial x^2}.$$

338 Letting \mathbb{P} (resp. \mathbb{B}) be the distribution of the bridge for the process with infinites-
 339 imal generator (4.5), and hence the distribution of the transformed Wright-Fisher
 340 diffusion Y , (resp. the 4-dimensional Bessel bridge) from x to z over the time
 341 interval $[0, T]$, we have

$$\begin{aligned} \frac{d\mathbb{P}}{d\mathbb{B}}(\omega) &= \frac{d\mathbb{P}}{d\mathbb{W}}(\omega) \frac{d\mathbb{W}}{d\mathbb{B}}(\omega) \\ &= \exp \left\{ \int_0^T \frac{1}{2} \left(\gamma \sin(\omega_t) \coth(\alpha \sin^2(\omega_t/2)) - \cot(\omega_t) - \frac{3}{\omega_t} \right) d\omega_t \right. \\ (4.8) \quad &\left. - \frac{1}{2} \int_0^T \frac{1}{4} \left((\gamma \sin(\omega_t) \coth(\alpha \sin^2(\omega_t/2)) - \cot(\omega_t))^2 - \frac{9}{\omega_t^2} \right) dt \right\}. \end{aligned}$$

342 We next explain how to simulate a 4-dimensional Bessel bridge. We can construct
 343 the bridge from $u \in \mathbb{R}^4$ to $v \in \mathbb{R}^4$ over the time interval $[0, T]$ for the 4-dimensional
 344 Brownian motion as

$$C_t := \left(1 - \frac{t}{T}\right) u + \frac{t}{T} v + \left(B_t - \frac{t}{T} B_T\right),$$

345 where $B_0 = 0$. The distribution of $u + B_T$ conditional on $|u + B_T| = z$ has density
 346 proportional to $w \mapsto \exp(w \cdot u/T)$ with respect to the normalized surface measure
 347 on the sphere centered at the origin with radius y , where $w \cdot u$ is the usual scalar

348 product of the two vectors $w, u \in \mathbb{R}^4$. Hence, a 4-dimensional Bessel bridge from x
 349 to z over the time interval $[0, T]$ is given by

$$\gamma_t := \left| \left(1 - \frac{t}{T} \right) u + \frac{t}{T} V + \left(B_t - \frac{t}{T} B_T \right) \right|,$$

350 where $B_0 = 0$, $u \in \mathbb{R}^4$ is any vector with $|u| = x$, and V is random vector taking
 351 values on the sphere centered at the origin with radius z that is independent of B
 352 and has a density with respect to the normalized surface measure that is propor-
 353 tional to $w \mapsto \exp(w \cdot u/T)$. Note that the random vector V/z , which takes values
 354 on the unit sphere centered at the origin, has a Fisher – von Mises distribution
 355 with mean vector u/x and concentration parameter xz/T (see, for example, Mardia
 356 et al. [1979, Ch. 15]).

357 Increasing the strength of natural selection causes the Wright-Fisher bridge to
 358 move faster for intermediate frequencies, but the method proposed above uses the
 359 same 4-dimensional Bessel bridge regardless of the value of the selection parameter
 360 γ , and so the rejection rate can become very high for large values of γ . To deal
 361 with this phenomenon, we introduce the following further refinement to the proposal
 362 process.

363 With \mathbb{P} the distribution of the transformed Wright-Fisher bridge from x to z
 364 over the time interval $[0, T]$ as above, let $\omega^\epsilon : [0, T] \rightarrow [0, \pi]$, $\epsilon > 0$, be the path
 365 with $\omega_0^\epsilon = x$ and $\omega_T^\epsilon = z$ that maximizes

$$\omega \mapsto \mathbb{P} \left\{ \omega' : \sup_{0 \leq t \leq T} |\omega'_t - \omega_t| \leq \epsilon \right\}.$$

366 Then, ω^ϵ converges as $\epsilon \downarrow 0$ to a path ω^* . Heuristically, we can think of ω^*
 367 as the path that has “maximum probability” or is “modal” for \mathbb{P} . This path is
 368 sometimes called an Onsager-Machlup function and it can be found by solving a
 369 certain variational problem – see, for example, Ikeda and Watanabe [1989]. For
 370 the transformed Wright-Fisher bridge, an analysis of the variational problem shows
 371 that the maximum probability path satisfies the second order ordinary differential
 372 equation

$$(4.9) \quad \ddot{\omega}^* = \frac{\gamma^2}{8} \sin \omega^* - \frac{3}{4} \cot \omega^* \csc^2 \omega^*$$

373 with boundary conditions $\omega_0^* = x$ and $\omega_T^* = z$.

374 With a solution to (4.9) in hand, it is possible to construct a better proposal
 375 distribution by linking together bridges that are “close” to the maximum probability
 376 path. First, choose a number of discretization points N and take times $0 < t_1 <$
 377 $\dots < t_N < T$. Then, sample independent random variables U_1, U_2, \dots, U_N with
 378 densities g_1, g_2, \dots, g_N to be specified later. Put $t_0 = 0$, $t_{N+1} = T$, $U_0 = x$ and
 379 $U_{N+1} = z$. Build conditionally independent 4-dimensional Bessel bridges from U_i
 380 to U_{i+1} over the time intervals $[t_i, t_{i+1}]$. The distribution of U_i should be chosen
 381 so that U_i is close to the maximum probability path at time t_i ; we choose re-scaled
 382 Beta distributions with mode at the solution of (4.9) at time t_i . More specifically,
 383 we set $U_i = \pi X_i$, where X_i has the Beta distribution with parameters

$$\left(\frac{1 + \frac{x_{t_i}^*}{\pi}(\theta - 2)}{1 - \frac{x_{t_i}^*}{\pi}}, \theta \right).$$

384 for some free parameter θ . We used the particular value $\theta = 50$ for the examples
 385 in this paper, but other value of θ could be used in a given situation in an attempt
 386 to optimize the frequency of rejection.

387 By stringing these bridges together, we get a path going from x to z over the
 388 time interval $[0, T]$. However, the distribution of this path is certainly not that of
 389 the 4-dimensional Bessel bridge because of the manner in which we have chosen the
 390 endpoints of the component bridges. Therefore, we can't simply use the Radon-
 391 Nikodym derivative (4.8) as it stands to construct a rejection sampling procedure.
 392 Rather, if we let \mathbb{Q} be the distribution of the path built by stringing the bridges
 393 together, then we must accept a path ω with probability proportional to

$$(4.10) \quad \frac{d\mathbb{P}}{d\mathbb{B}}(\omega) \frac{d\mathbb{B}}{d\mathbb{Q}}(\omega).$$

394 Note that

$$(4.11) \quad \frac{d\mathbb{B}}{d\mathbb{Q}}(\omega) = \frac{\prod_{i=0}^N \rho(\omega_{t_i}, \omega_{t_{i+1}}; t_{i+1} - t_i)}{\rho(x, z; T) \prod_{i=1}^N g_i(\omega_{t_i})},$$

395 where

$$(4.12) \quad \rho(x, z; t) := I_1\left(\frac{xy}{t}\right) \frac{y^2}{xt} e^{-\frac{x^2+z^2}{2t}}$$

396 is the transition density of the 4-dimensional Bessel process with I_ν the modified
 397 Bessel function of the first kind.

398 To demonstrate the effectiveness of the rejection sampling scheme, Figure 7.1
 399 shows Q-Q plots of the one-dimensional marginal at time t of a Wright-Fisher
 400 bridge with genic selection as estimated using the rejection sampler compared to
 401 an approximation that uses the method of Song and Steinrücken [2012] to compute
 402 the cumulative distribution function of the marginal. For both rows, the bridge
 403 goes from $x = .2$ to $z = 0.7$ over the time interval $[0, T] = [0, 0.1]$. The left
 404 panels correspond to $t = 0.03$ and the right panels correspond to $t = 0.07$. The
 405 top row corresponds to $\gamma = 10$ and the bottom row to $\gamma = 50$, demonstrating
 406 the effectiveness of the rejection sampling scheme over a wide range of selection
 407 coefficients.

408 Figure 7.2 demonstrates the behavior of a Wright-Fisher diffusion bridge as the
 409 selection coefficient increases. A bridge from $x = 0.01$ to $z = 0.8$ over the time
 410 interval $[0, T] = [0, 0.1]$ is shown for $\gamma = 0$, $\gamma = 50$ and $\gamma = 100$. As the selection
 411 coefficient increases, the proportion of time the bridge spends near the boundary
 412 also increases, because the Wright-Fisher diffusion moves faster when it is away from
 413 the boundaries. In addition, the paths that the bridge takes become more tightly
 414 centered around the most probable path as the selection coefficient increases.

415 Being able to sample Wright-Fisher bridge paths makes it very easy to numer-
 416 ically approximate the distribution and expectation of various functionals of the
 417 path. As an example, Figure 7.3 shows the density of the maximum in a bridge
 418 from $x = 0$ to $z = 0$ over the time interval $[0, T] = [0, 0.1]$ for $\gamma = 0$, $\gamma = 50$ and
 419 $\gamma = 100$. Note that the maximum in the bridge decreases as the strength of selection
 420 increases, and also becomes more tightly concentrated around its expectation.

421 To gain a more quantitative understanding of the extent to which a bridge for
 422 an allele experiencing natural selection looks different from the bridge for a neutral
 423 allele, it is possible to compute the Radon-Nikodym derivative (i.e. the likelihood

ratio) of the distribution under selection against the distribution under neutrality. Using an argument similar to that which led to (4.8), the likelihood ratio is

$$(4.13) \quad \frac{d\mathbb{P}_\gamma}{d\mathbb{P}_0}(\omega) \propto \exp \left\{ -\frac{1}{8} \int_0^T \gamma^2 \sin^2(\omega_t) dt \right\},$$

where the constant of proportionality only depends on the endpoints. A few things are immediately evident from (4.13). First of all, the likelihood ratio does not depend on the sign of the selection coefficient, only the magnitude. This is analogous to the result Maruyama [1974] that, conditioned on eventual fixation, the sign of the selection coefficient is irrelevant to the distribution of the Wright-Fisher diffusion path. Also apparent is that bridges with strong natural selection will be more likely to be found near the boundary than bridges under neutrality. Finally, because $0 \leq \sin^2(x) \leq 1$, we see that, very loosely, a bridge will look approximately neutral if

$$(4.14) \quad \frac{1}{8} \gamma^2 T \approx 0.$$

5. DISCUSSION

We have examined the behavior of Wright-Fisher diffusion bridges under both neutral models and models with genic selection. Although various conditioned Wright-Fisher diffusions have been studied in the past, Wright-Fisher diffusions conditioned to obtain a specific value at a predetermined time have not been studied extensively. We have elucidated some of the properties of Wright-Fisher bridges using a combination of analytical theory and simulations.

In contrast to Brownian motion with drift, for which the distribution of a bridge does not depend on the magnitude of the drift coefficient, the distribution of a Wright-Fisher bridge does depend on the magnitude of the selection coefficient. As one might expect, bridges under strong selection are more constrained than neutral bridges. This can clearly be seen in Figure 7.2, in which the bridge with $\gamma = 0$ has a broad range, but when $\gamma = 100$ the paths of the bridge are highly likely to be confined near the boundary at 0 until quite late in the bridge. A similar conclusion can be drawn from Figure 7.3 which shows the density of the maximum in a bridge from 0 to 0 over the time interval $[0, T] = [0, 0.1]$. The expected maximum of a neutral bridge is much higher than one with strong selection, and there is significantly more variance about that maximum under neutrality.

Much of the behavior of Wright-Fisher bridges under selection can be understood in terms of the likelihood ratio (4.13). Because $\sin(x)$ takes its smallest values for $x \approx 0$ and $x \approx \pi$, very strong selection will confine a bridge of the transformed process Y to near these boundaries. Intuitively, this is because the Wright-Fisher diffusion has the largest magnitude of drift and diffusion coefficients at $x = 0.5$, and thus the diffusion moves “faster” when it is away from the boundaries 0 and 1. In order for a diffusion with a large selection coefficient to reach an interior point after a large amount of time, it must spend most of that time near the boundary.

However, these differences between selection and neutrality are mostly apparent in cases of extreme selection coefficients or very long times. This has important implications for maximum likelihood inference of selection coefficients from allele frequency time series. Because the realizations are likely to be quite similar for a selected allele and a neutral allele when the selection coefficient is moderate,

466 most of the information about the selection coefficient comes from the end-points.
467 Therefore, in many cases increasing the time-density of samples may not provide
468 much additional information about the selection coefficient. Because many allelic
469 time-series are obtained via costly ancient DNA techniques, this is an important
470 consideration for the many researchers who are interested in the history of selection
471 acting on a particular allele.

472 In addition to results directly concerning bridges, we have made several technical
473 advances in the analysis of the Wright-Fisher diffusion. We have developed the
474 theory of first passage times of a neutral Wright-Fisher diffusion starting from low
475 frequency and we were able to provide a closed-form for the density of the maximum
476 in a neutral bridge that goes from 0 to 0.

477 While our rejection sampling scheme is similar to that of Beskos and Roberts
478 [2005] in some regards, there are several differences. Primarily, we do not provide
479 exact samples, in the sense that Beskos and Roberts [2005] does. Because we store a
480 discrete representation of our proposal bridges in computer memory, the calculation
481 of (4.8) is necessarily an approximation, and hence the samples are only approxi-
482 mate. However, Figure 7.1 shows that they are extremely accurate. Also, because
483 we are concerned with a specific model, we used 4-dimensional Bessel bridges, in-
484 stead of Brownian bridges, in our proposal mechanism. This choice is superior for
485 the Wright-Fisher diffusion because both the Bessel bridge and the Wright-Fisher
486 bridge have boundaries at 0 with asymptotically equivalent singularities in the drift
487 coefficient, while the Brownian bridge can assume negative values and hence result
488 an unacceptably high rejection rate when it is used as a proposal distribution. Ide-
489 ally, we would sample from a proposal distribution that describes a diffusion that
490 was also bounded above and had a suitable singularity in its drift coefficient at the
491 upper boundary; however, we have not yet discovered an appropriate diffusion for
492 which it is easy to sample the corresponding bridges. Finally, we make use of the
493 “most likely” bridge path as a means of guiding samples of bridges that are likely
494 to be extremely different from those generated by the 4-dimensional Bessel bridge
495 proposal distribution. This modification is akin to shifting the mean of a proposal
496 distribution when doing rejection sampling of a 1-dimensional random variable, and
497 it greatly increases the efficiency of sampling.

498 6. ACKNOWLEDGMENTS

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501 REFERENCES

- 502 Alexandros Beskos and Gareth O. Roberts. Exact simulation of diffusions.
503 *Ann. Appl. Probab.*, 15(4):2422–2444, 2005. ISSN 1050-5164. doi: 10.1214/
504 105051605000000485.
- 505 Jonathan P. Bollback, Thomas L. York, and Rasmus Nielsen. Estimation of 2Nes
506 from temporal allele frequency data. *Genetics*, 179(1):497–502, May 2008. ISSN
507 0016-6731. doi: 10.1534/genetics.107.085019.
- 508 James F. Crow and Motoo Kimura. *An introduction to population genetics theory*.
509 Harper & Row Publishers, New York, 1970.

- 510 Endre Csáki, Antónia Földes, and Paavo Salminen. On the joint distribution of the
511 maximum and its location for a linear diffusion. *Ann. Inst. H. Poincaré Probab.*
512 *Statist.*, 23(2):179–194, 1987. ISSN 0246-0203.
- 513 Alison Etheridge, Peter Pfaffelhuber, and Anton Wakolbinger. An approximate
514 sampling formula under genetic hitchhiking. *Ann. Appl. Probab.*, 16:685–729,
515 2006. doi: 10.1214/105051606000000114.
- 516 S. N. Ethier and R. C. Griffiths. The transition function of a Fleming-Viot process.
517 *Ann. Probab.*, 21(3):1571–1590, 1993. ISSN 0091-1798.
- 518 Gregory Ewing and Joachim Hermisson. MSMS: a coalescent simulation program
519 including recombination, demographic structure and selection at a single locus.
520 *Bioinformatics (Oxford, England)*, 26(16):2064–5, August 2010. ISSN 1367-4811.
521 doi: 10.1093/bioinformatics/btq322.
- 522 Alison Feder, Sergey Kryazhinskiy, and Joshua B. Plotkin. Identifying signatures
523 of selection in genetic time series. *arXiv preprint arXiv:1302.0452*, 2013.
- 524 R.A. Fisher. On the dominance ratio. *Proceedings of the Royal Society of Edinburgh*,
525 42:321–341, 1922.
- 526 Robert C. Griffiths and Dario Spanó. Diffusion processes and coalescent trees. In
527 *Probability and mathematical genetics*, volume 378 of *London Math. Soc. Lecture*
528 *Note Ser.*, pages 358–379. Cambridge Univ. Press, Cambridge, 2010.
- 529 R. R. Hudson and N. L. Kaplan. The coalescent process in models with selection
530 and recombination. *Genetics*, 120(3):831–40, November 1988. ISSN 0016-6731.
- 531 Nobuyuki Ikeda and Shinzo Watanabe. *Stochastic differential equations and diffu-*
532 *sion processes*, volume 24 of *North-Holland Mathematical Library*. North-Holland
533 Publishing Co., Amsterdam, second edition, 1989. ISBN 0-444-87378-3.
- 534 N. L. Kaplan, R. R. Hudson, and C. H. Langley. The “hitchhiking effect” revisited.
535 *Genetics*, 123(4):887–99, December 1989. ISSN 0016-6731.
- 536 Motoo Kimura. Stochastic processes and distribution of gene frequencies under
537 natural selection. In *Cold Spring Harbor Symposia on Quantitative Biology*, vol-
538 ume 20, pages 33–53. Cold Spring Harbor Laboratory Press, 1955.
- 539 Motoo Kimura. Some problems of stochastic processes in genetics. *Ann. Math.*
540 *Statist.*, 28:882–901, 1957a. ISSN 0003-4851.
- 541 Motoo Kimura. Some problems of stochastic processes in genetics. *The Annals of*
542 *Mathematical Statistics*, pages 882–901, 1957b.
- 543 Anna-Sapfo Malaspinas, Orestis Malaspinas, Steven N. Evans, and Montgomery
544 Slatkin. Estimating allele age and selection coefficient from time-serial data.
545 *Genetics*, 192(2):599–607, 2012.
- 546 Kantilal Varichand Mardia, John T. Kent, and John M. Bibby. *Multivariate analy-*
547 *sis*. Academic Press [Harcourt Brace Jovanovich Publishers], London, 1979. ISBN
548 0-12-471250-9. Probability and Mathematical Statistics: A Series of Monographs
549 and Textbooks.
- 550 T. Maruyama. The age of an allele in a finite population. *Genetical Research*, 23
551 (2):137–43, April 1974.
- 552 Iain Mathieson and Gil McVean. Estimating selection coefficients in spatially struc-
553 tured populations from time series data of allele frequencies. *Genetics*, 193(3):
554 973–984, 2013.
- 555 Rasmus Nielsen, Scott Williamson, Yuseob Kim, Melissa J. Hubisz, Andrew G.
556 Clark, and Carlos Bustamante. Genomic scans for selective sweeps using SNP
557 data. *Genome Research*, 15(11):1566–75, November 2005. ISSN 1088-9051. doi:

- 558 10.1101/gr.4252305.
- 559 Benjamin M. Peter, Emilia Huerta-Sanchez, and Rasmus Nielsen. Distinguishing
560 between selective sweeps from standing variation and from a de novo mutation.
561 *PLoS Genetics*, 8(10):e1003011, 2012.
- 562 Daniel Revuz and Marc Yor. *Continuous martingales and Brownian motion*, volume
563 293 of *Grundlehren der Mathematischen Wissenschaften [Fundamental Principles
564 of Mathematical Sciences]*. Springer-Verlag, Berlin, third edition, 1999. ISBN 3-
565 540-64325-7.
- 566 L. C. G. Rogers and David Williams. *Diffusions, Markov processes, and mar-
567 tingales. Vol. 2*. Cambridge Mathematical Library. Cambridge University Press,
568 Cambridge, 2000. ISBN 0-521-77593-0. Itô calculus, Reprint of the second (1994)
569 edition.
- 570 Montgomery Slatkin and Laurent Excoffier. Serial founder effects during range
571 expansion: a spatial analog of genetic drift. *Genetics*, 191(1):171–181, 2012.
- 572 J. M. Smith and J. Haigh. The hitch-hiking effect of a favourable gene. *Genetical
573 Research*, 23(1):23–35, February 1974.
- 574 Yun S. Song and Matthias Steinrücken. A simple method for finding explicit an-
575 alytic transition densities of diffusion processes with general diploid selection.
576 *Genetics*, 190(3):1117–1129, 2012. doi: 10.1534/genetics.111.136929.
- 577 Matthias Steinrücken, Y.X. Wang, and Yun S. Song. An explicit transition density
578 expansion for a multi-allelic wright–fisher diffusion with general diploid selection.
579 *Theoretical Population Biology*, 2012.
- 580 Kosuke M. Teshima and Hideki Innan. mbs: modifying Hudson’s ms soft-
581 ware to generate samples of DNA sequences with a biallelic site under se-
582 lection. *BMC Bioinformatics*, 10:166, January 2009. ISSN 1471-2105. doi:
583 10.1186/1471-2105-10-166.
- 584 S. Wright. Evolution in Mendelian Populations. *Genetics*, 16(2):97–159, March
585 1931. ISSN 0016-6731.

586

7. APPENDIX

587 **7.1. Eigenfunction expansions of the transition density.** Eigenfunction ex-
588 pansion of the Wright-Fisher transition densities in the case of no mutation were
589 first explored in Kimura [1957a]. The form given in Crow and Kimura [1970] is

$$f(x, y; t) = \sum_{i=1}^{\infty} \frac{4(2i+1)x(1-x)}{i(i+1)} C_{i-1}^{(3/2)}(1-2x) C_{i-1}^{(3/2)}(1-2y) e^{-\frac{1}{2}i(i+1)t},$$

590 where $C_{i-1}^{(3/2)}$ is the Gegenbauer polynomial $C_{i-1}^{(\lambda)}$ with $\lambda = 3/2$.

591 An explicit formula for the Gegenbauer polynomial is

$$C_n^{(\lambda)}(x) = \sum_{k=0}^{\lfloor n/2 \rfloor} (-1)^k \frac{\Gamma(n-k+\alpha)}{\Gamma(\alpha)k!(n-2k)!} (2x)^{n-2k}$$

592 The generating function for the sequence $(C_n^\lambda)_{n=0}^\infty$ is

$$\sum_{n=0}^{\infty} C_n^\lambda(x) t^n = (1 - 2xt + t^2)^{-\lambda}.$$

593 Note that

$$C_n^\lambda(1) = \frac{(2\lambda)_{(n)}}{n!},$$

594 and the right-hand side is $(n+1)(n+2)/2$ when $\lambda = 3/2$.

595 The sequence of polynomials $(C_n^{(3/2)})_{n=0}^\infty$ satisfies the three-term recurrence

$$nC_n^{(3/2)}(x) = (2n+1)x C_{n-1}^{(3/2)}(x) - (n+1)C_{n-2}^{(3/2)}(x)$$

596 with initial conditions $C_0^{(3/2)}(x) = 1$ and $C_1^{(3/2)}(x) = 3x$. It is convenient in
597 computations to use the scaled polynomials $P_n(x) = C_n^{(3/2)}(x)/C_n^{(3/2)}(1)$ which are
598 bounded in modulus by unity on the interval $[-1, +1]$. The corresponding three-
599 term recurrence for the sequence $(P_n)_{n=0}^\infty$ is

$$(n+2)P_n(x) = (2n+1)xP_{n-1}(x) - (n-1)P_{n-2}(x)$$

600 with initial conditions $P_0(x) = 1$ and $P_1(x) = x$.

601 The transition density written with the scaled polynomials is

$$f(x, y; t) = x(1-x) \sum_{i=1}^{\infty} (2i+1)i(i+1)P_{i-1}(r)P_{i-1}(s)e^{-\frac{1}{2}i(i+1)t}.$$

602 The asymptotic form of the transition density as $x \downarrow 0$ is

$$(7.1) \quad f(x, y; t) \approx x \sum_{i=1}^{\infty} (2i+1)i(i+1)P_{i-1}(s)e^{-\frac{1}{2}i(i+1)t}$$

603 Also,

$$\lim_{x, y \downarrow 0} x^{-1} f(x, y; t) = \sum_{i=1}^{\infty} (2i+1)i(i+1)e^{-\frac{1}{2}i(i+1)t}.$$

604 We also use a form of the expansion that is formally equivalent to the one above
605 – see Griffiths and Spanó [2010]. The expansion is

$$(7.2) \quad f(x, y; t) = y^{-1}(1-y)^{-1} \sum_{n=2}^{\infty} e^{-\frac{1}{2}n(n-1)t} Q_n(x, y),$$

606 where

$$(7.3) \quad Q_n(x, y) := (2n-1) \sum_{m=1}^n (-1)^{n-m} \frac{m_{(n-1)}}{m!(n-m)!} \xi_m,$$

607 and

$$(7.4) \quad \xi_m := \sum_{l=1}^{m-1} \binom{m}{l} \frac{(m-1)!}{(l-1)!(m-l-1)!} (xy)^l [(1-x)(1-y)]^{m-l}.$$

608 Note that

$$\xi_m = xm(m-1)y(1-y)^{m-1} + O(x^2)$$

609 as $x \downarrow 0$. Therefore,

$$(7.5) \quad f(x, y; t) \sim x \sum_{n=2}^{\infty} e^{-\frac{1}{2}n(n-1)t} (2n-1) \sum_{m=1}^n (-1)^{n-m} \frac{m_{(n-1)}}{m!(n-m)!} m(m-1)(1-y)^{m-2},$$

610 which is equal to (3.9). To calculate

$$\lim_{x, y \downarrow 0} x^{-1} f(x, y; t) = 2 \sum_{l=2}^{\infty} h_l(t)$$

611 we observe that

$$(7.6) \quad \sum_{m=1}^n (-1)^{n-m} \frac{m_{(n-1)}}{m!(n-m)!} m(m-1) = n(n-1).$$

612 Therefore,

$$(7.7) \quad 2 \sum_{l=2}^{\infty} h_l(t) = \sum_{n=2}^{\infty} e^{-\frac{1}{2}n(n-1)t} (2n-1)n(n-1).$$

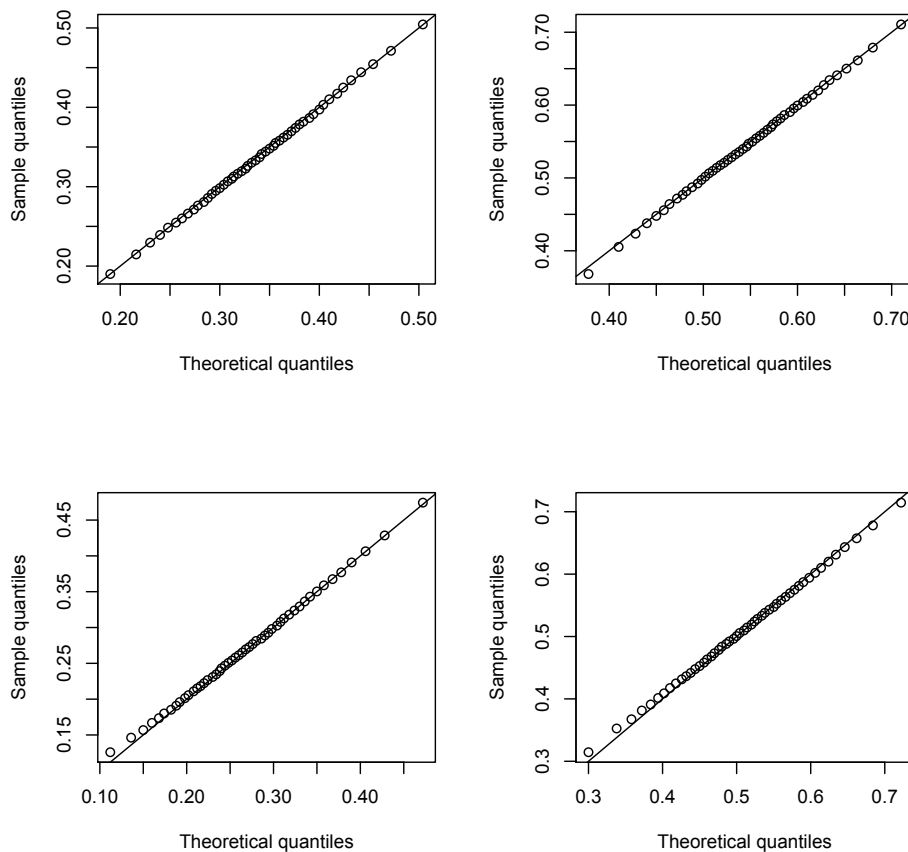


FIGURE 7.1. Q-Q plot showing the accuracy of the rejection sampling scheme. Theoretical quantiles were calculated using the method of Song and Steinrücken [2012] and sample quantiles are determined from 1000 bridges simulated using the method described in the text. The bridge goes from $x = 0.2$ to $z = 0.7$ over the time interval $[0, T] = [0, 0.1]$. The left panels correspond to $t = 0.03$ and the right panels correspond to $t = 0.07$. The top row corresponds to $\gamma = 10$ and the bottom row to $\gamma = 50$.

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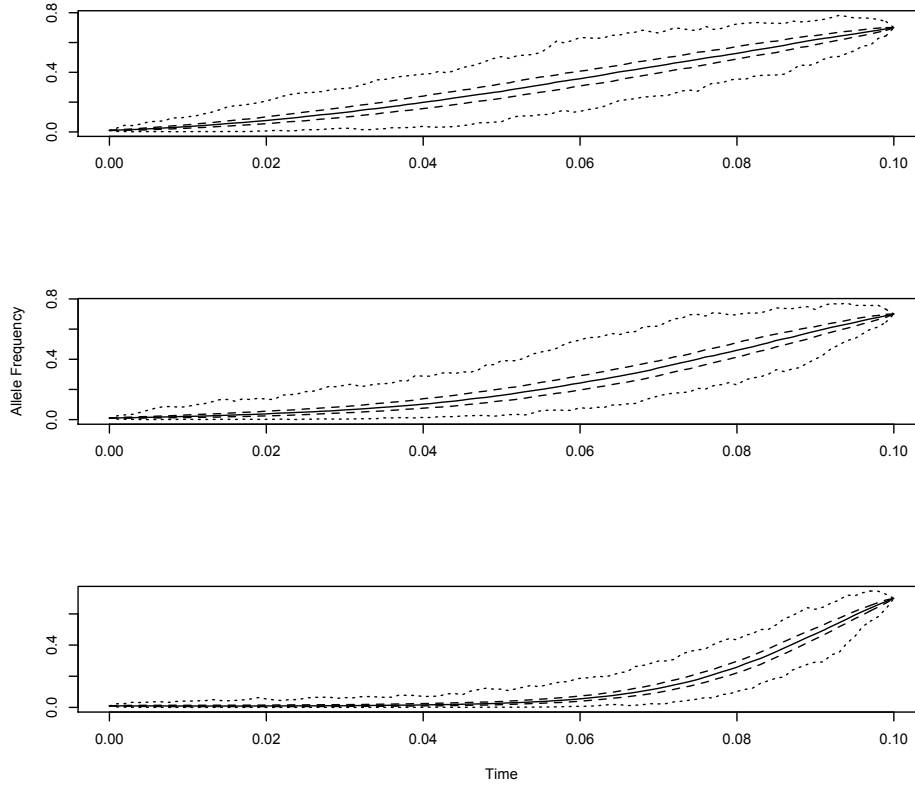


FIGURE 7.2. Plot showing the properties of bridge paths as the strength of selection increases. Each bridge is from $x = 0.01$ to $z = 0.8$ over the time interval $[0, T] = [0, 0.1]$. The successive selection coefficients are $\gamma = 0$, $\gamma = 50$ and $\gamma = 100$. For each selection coefficient, pointwise 0%, 25%, 50%, 75% and 100% quantiles are calculated. Solid line is the 50% quantile, dashed line indicates 25% and 75% quantiles, and the dotted line indicates 0% and 100% quantiles.

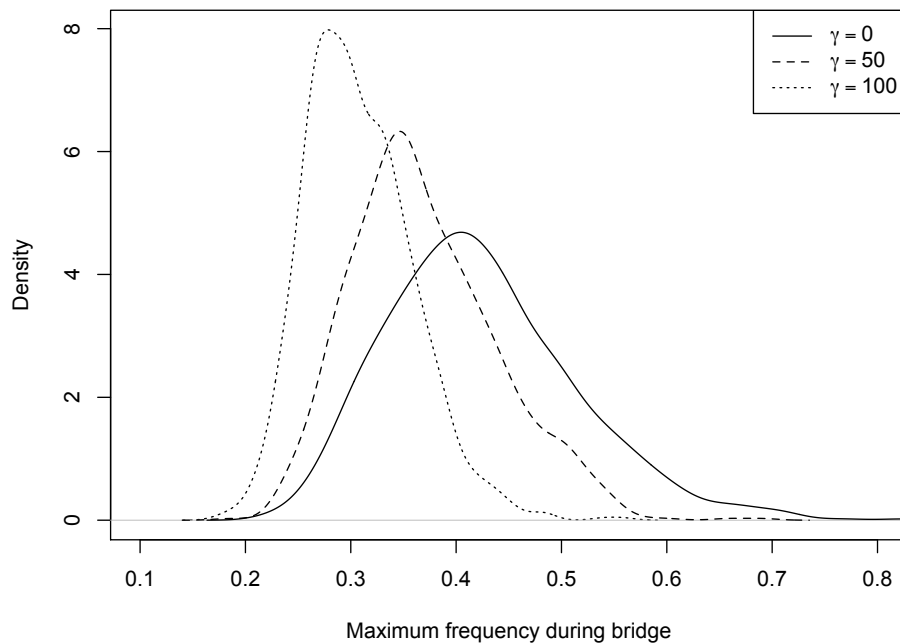


FIGURE 7.3. Densities of the maximum in a 0 to 0 bridge over the time interval $[0, T] = [0, 0.1]$ for the selection strengths $\gamma = 0$, $\gamma = 50$ and $\gamma = 100$.