

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

3 JOSHUA G. SCHRAIBER, ROBERT C. GRIFFITHS, AND STEVEN N. EVANS

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

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

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

100 where  $S$  is the scale function given by

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

101 Thus,

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

102 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

104 3.1. Transition densities for the neutral Wright-Fisher diffusion. When  
105 there is no natural selection (i.e.,  $\gamma = 0$ ), the transition densities of the Wright-  
106 Fisher diffusion can be expressed

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

107 where the  $q_l(t)$  are the transition functions of a death process starting at infinity  
108 with death rate  $\frac{1}{2}n(n-1)$  when  $n$  individuals are left alive and  $\mathcal{B}(\cdot; \alpha, \beta)$  is the  
109 density of the Beta distribution with parameters  $\alpha$  and  $\beta$  [Ethier and Griffiths,  
110 1993]. That is,  $q_l(t)$  is the probability that a Kingman coalescent tree with infinitely  
111 many leaves at time 0 has  $l$  lineages present  $t$  units of time in the past. In the  
112 Appendix we present a related pair of eigenfunction expansions of the transition  
113 density.

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

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

118 Because

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

119 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  $\infty$ , 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 it's 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  $\omega$ , 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  $\pi$ , 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  $\pi$ .

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  $\gamma$ , and so the rejection rate can become very high for large values of  $\gamma$ . 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,  $\omega^\epsilon$  converges as  $\epsilon \downarrow 0$  to a path  $\omega^*$ . Heuristically, we can think of  $\omega^*$   
 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  $\theta$ . We used the particular value  $\theta = 50$  for the examples  
 385 in this paper, but other value of  $\theta$  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  $\omega$  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  $I_\nu$  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



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

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

426 where the constant of proportionality only depends on the endpoints. A few things  
 427 are immediately evident from (4.13). First of all, the likelihood ratio does not  
 428 depend on the sign of the selection coefficient, only the magnitude. This is analogous  
 429 to the result Maruyama [1974] that, conditioned on eventual fixation, the sign of the  
 430 selection coefficient is irrelevant to the distribution of the Wright-Fisher diffusion  
 431 path. Also apparent is that bridges with strong natural selection will be more likely  
 432 to be found near the boundary than bridges under neutrality. Finally, because  
 433  $0 \leq \sin^2(x) \leq 1$ , we see that, very loosely, a bridge will look approximately neutral  
 434 if

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

435

## 5. DISCUSSION

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

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

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

461 However, these differences between selection and neutrality are mostly apparent  
 462 in cases of extreme selection coefficients or very long times. This has important  
 463 implications for maximum likelihood inference of selection coefficients from allele  
 464 frequency time series. Because the realizations are likely to be quite similar for  
 465 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.

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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,

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

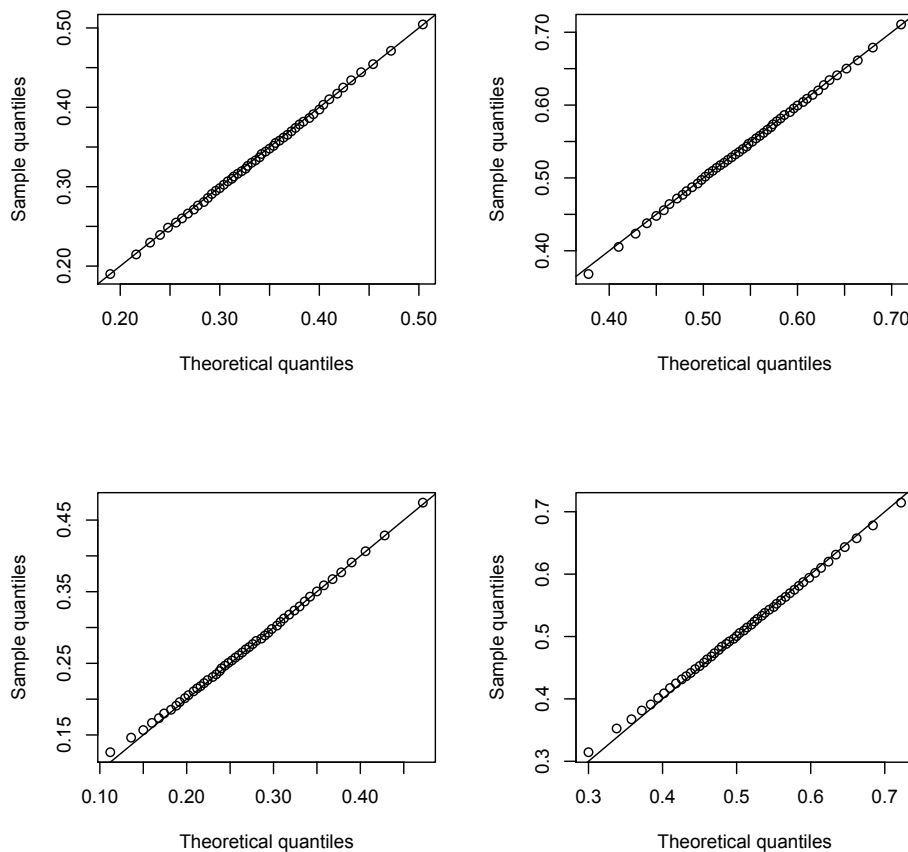


FIGURE 7.1. Q-Q plot showing the accuracy of the rejection sampling scheme. Theoretical quantiles were calculated using the method of Song and Steinrücken [2012] and sample quantiles are determined from 1000 bridges simulated using the method described in the text. The bridge goes from  $x = 0.2$  to  $z = 0.7$  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  $\gamma = 50$ .

613 DEPARTMENT OF INTEGRATIVE BIOLOGY, UNIVERSITY OF CALIFORNIA, 3060 VALLEY LIFE SCI-  
 614 ENCES BLDG #3140, BERKELEY, CA 94720-3140, U.S.A.  
 615 *E-mail address:* `jgschraiber@berkeley.edu`

616 DEPARTMENT OF STATISTICS, 1 SOUTH PARKS ROAD, OXFORD OX1 3TG, U.K.  
 617 *E-mail address:* `griff@stats.ox.ac.uk`

618 DEPARTMENT OF STATISTICS, UNIVERSITY OF CALIFORNIA, 367 EVANS HALL #3860, BERKELEY,  
 619 CA 94720-3860, U.S.A.  
 620 *E-mail address:* `evans@stat.berkeley.edu`

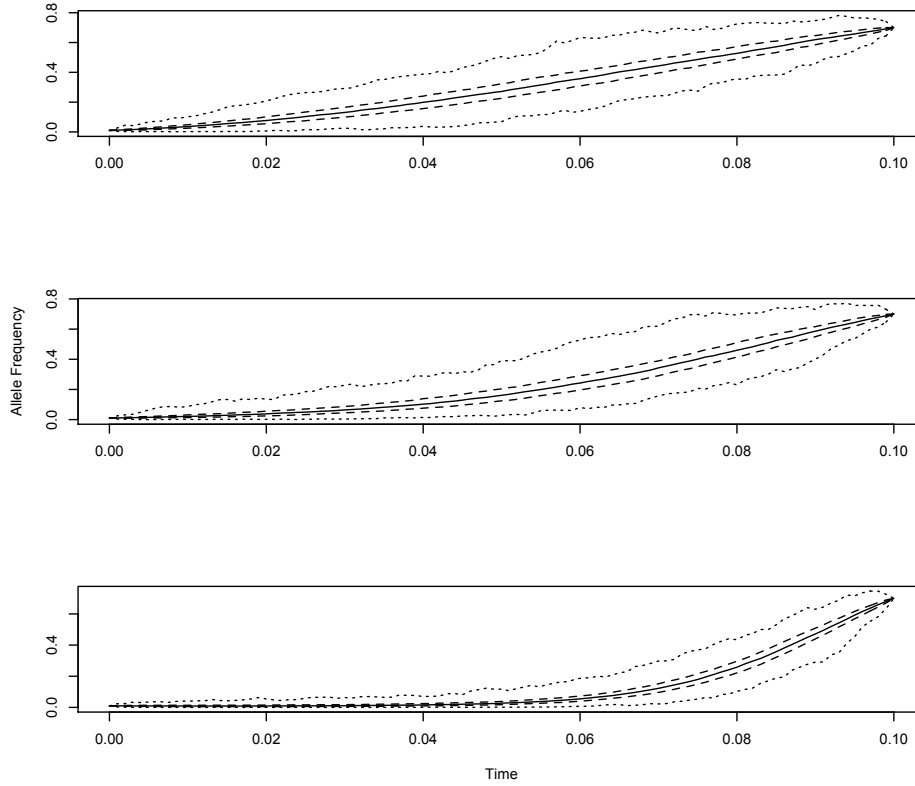


FIGURE 7.2. Plot showing the properties of bridge paths as the strength of selection increases. Each bridge is from  $x = 0.01$  to  $z = 0.8$  over the time interval  $[0, T] = [0, 0.1]$ . The successive selection coefficients are  $\gamma = 0$ ,  $\gamma = 50$  and  $\gamma = 100$ . For each selection 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.



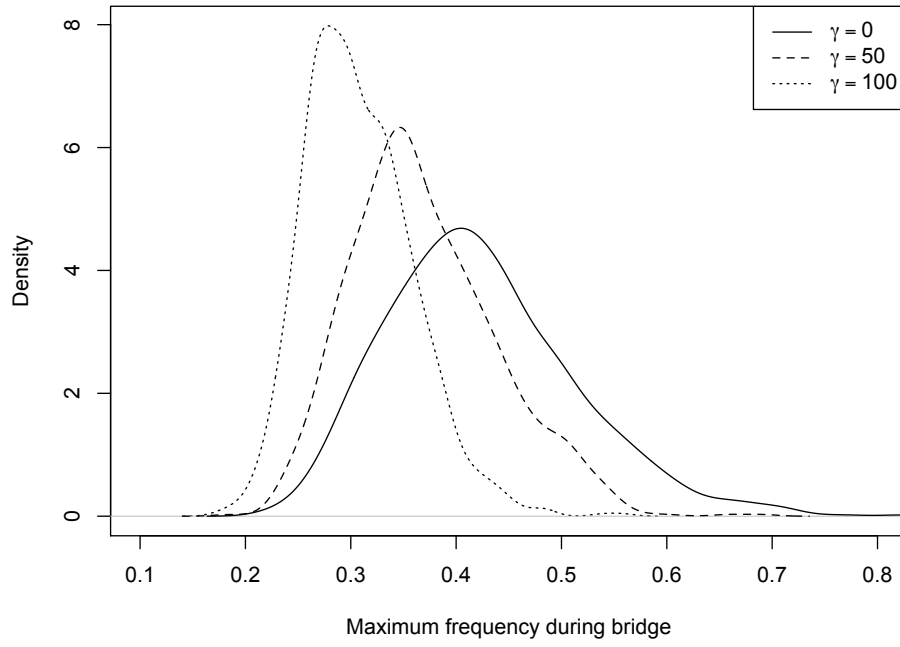


FIGURE 7.3. Densities of the maximum in a 0 to 0 bridge over the time interval  $[0, T] = [0, 0.1]$  for the selection strengths  $\gamma = 0$ ,  $\gamma = 50$  and  $\gamma = 100$ .