DOI: 10.1534/genetics.107.084012

The Temporal Dynamics of Processes Underlying Y Chromosome Degeneration

Doris Bachtrog[1]

Division of Biological Sciences, University of California, San Diego, California 92093

Manuscript received October 31, 2007
Accepted for publication May 12, 2008

ABSTRACT

Y chromosomes originate from ordinary autosomes and degenerate by accumulating deleterious mutations. This accumulation results from a lack of recombination on the Y and is driven by interference among deleterious mutations (Muller's ratchet and background selection) and the fixation of beneficial alleles (genetic hitchhiking). Here I show that the relative importance of these processes is expected to vary over the course of Y chromosome evolution due to changes in the number of active genes. The dominant mode of degeneration on a newly formed gene-rich Y chromosome is expected to be Muller's ratchet and/or background selection due to the large numbers of deleterious mutations arising in active genes. However, the relative importance of these modes of degeneration declines rapidly as active genes are lost. In contrast, the rate of degeneration due to hitchhiking is predicted to be highest on Y chromosomes containing an intermediate number of active genes. The temporal dynamics of these processes imply that a gradual restriction of recombination, as inferred in mammals, will increase the importance of genetic hitchhiking relative to Muller's ratchet and background selection.

Y chromosomes are unusual relative to the rest of the genome, since they carry few functional genes and accumulate repetitive DNA (Skaletsky *et al.* 2003; Carvalho and Clark 2005). Sex chromosomes arose independently in several different taxa from ordinary autosomes, and the Y chromosome degenerates over evolutionary time due to its lack of genetic recombination (Charlesworth 1996; Rice 1996). Thus, Y chromosomes have been important case studies for understanding the evolutionary significance of sex and recombination (Charlesworth 1996; Rice 1996; Barton and Charlesworth 1998). Several evolutionary models have been proposed to account for the loss of functional genes on a nonrecombining Y chromosome (Charlesworth 1996; Rice 1996), but their dynamics and relative importance over the course of Y chromosome evolution have not yet been studied.

Here, I investigate the temporal dynamics of three different models of Y chromosome degeneration (Charlesworth and Charlesworth 2000): Muller's ratchet, which involves the stochastic loss of the class of Y chromosomes carrying the fewest number of deleterious mutations from a finite population (Charlesworth 1978; Gordo and Charlesworth 2000); background selection, which refers to the reduction in the effective population size (N_e) of Y chromosomes due to the elimination of strongly deleterious mutations, resulting in an accelerated fixation of weakly deleterious mutations (Charlesworth 1996); and genetic hitchhiking, in which beneficial mutations drag along to fixation any deleterious mutations they are initially associated with (Rice 1987; Bachtrog and Gordo 2004).

Models of Y chromosome degeneration depend critically on several properties of advantageous and deleterious mutations, such as their rates of occurrence or their effects on fitness (Charlesworth 1978; Rice 1987; Stephan *et al.* 1993; Charlesworth 1996; Gordo and Charlesworth 2000; Bachtrog and Gordo 2004). These considerations are particularly important when evaluating the relative importance of these models because the number of active genes, and thus potential targets for deleterious and beneficial mutations, decreases over the course of Y chromosome evolution; a newly formed Y chromosome might contain several thousand genes (Bachtrog 2005), while few active genes remain on ancient degenerated Y's (Skaletsky *et al.* 2003; Carvalho and Clark 2005). The change in gene number over the course of Y chromosome evolution implies that chromosomewide mutation rates to beneficial (U_a) and deleterious (U_d) alleles change accordingly. Given g active genes on a proto-Y chromosome and rates per gene for advantageous (u_a) and deleterious (u_d) mutations, chromosomewide mutation rates will be $U_a = g \times u_a$ and $U_d = g \times u_d$. The inactivation of Y-linked genes over time (*i.e.*, a decline in g) will result in a gradual decline in both U_a and U_d. Corresponding changes in rates of degeneration caused by Muller's ratchet, background selection, or genetic hitchhiking, and their relative importance, are complex. Here I study the relative contributions and

[1]*Address for correspondence:* Division of Biological Sciences, University of California, 9500 Gilman Dr., MC 0116, La Jolla, CA 92093.
E-mail: dbachtrog@ucsd.edu

dynamics of simple models of Muller's ratchet, background selection, and genetic hitchhiking over evolutionary time to the decay of a nonrecombining Y chromosome. In particular, I explore a genetic hitchhiking model with fixed selection coefficients for both beneficial and deleterious mutations, a simple model of Muller's ratchet with constant selection coefficients against deleterious mutations, and a background selection model with two categories of deleterious mutations (large- and small-effect mutations, each of uniform size). These considerations are helpful in detailing the temporal dynamics of these models and their sensitivity to various underlying population parameters. In addition, I also present some simulation results on the rate of degeneration under Muller's ratchet with a distribution of selection coefficients, and I explore the joint action of Muller's ratchet and genetic hitchhiking, to gain intuitions on more complex scenarios of Y degeneration over time.

MATERIALS AND METHODS

Theoretical approximations: All population parameters for deleterious and beneficial mutation models of Y chromosome degeneration are given in Table 1. Assuming a population of Y chromosomes of size N_e, with g active genes, mutations of effects s_d, $s_{d,weak}$, and s_a occur at rates u_d, $u_{d,weak}$, and u_a per gene per generation. Multiplicative fitness effects are assumed among mutations (see Table 1 for fitness functions).

Under Muller's ratchet, the rate of degeneration, K_{MR}, depends on the speed at which the class of Y chromosomes with the least number of deleterious mutations (the n_0 class) is lost from the population by genetic drift. At equilibrium, the size of this class is $n_0 = N_e \exp(-(u_d g/s_d))$, and the rate of the ratchet depends on n_0 in a complex manner (Gessler 1995; Gordo and Charlesworth 2000). I modify Equations 3a and 3b from Gordo and Charlesworth (2000) to calculate the speed of the ratchet K_{MR} as $K_{MR} = 1/\left(\int_0^{f_0}(2N_e/xG(x))\left\{\int_0^x G(x')dx'\right\}dx + \int_{f_0}^1(2N_e/xG(x))\left\{\int_0^{f_0} G(x')dx'\right\}dx\right)$, where $G(x) = \exp[(2N_e 0.6 s_d/f_0)x(x/2 - f_0)]$ and $f_0 = \exp(-(u_d g/s_d))$ if $n_0 s_d > 1$ and using the shifted Poisson distribution as proposed by Gessler (1995) if $n_0 s_d < 1$, while assuming that each fixation of a deleterious mutation reduces the number of active genes g by one.

Background selection was first described as the effect of recurrent deleterious mutations on levels of linked neutral variability (Charlesworth *et al.* 1993) but has since been extended to consider the effect of strongly deleterious mutations on linked weakly deleterious mutations (Charlesworth 1994). The rate of accumulation of weakly deleterious mutations under background selection, K_{BS}, depends on the relative reduction in the effective population size of Y chromosomes caused by strongly deleterious mutations [$f_0 = \exp(-(u_d g/s_d))$] and on mutation parameters for weakly selected, effectively neutral mutations. Note that very weakly deleterious mutations are also expected to accumulate by genetic drift on the X chromosomes or on autosomes; the rate of accumulation, however, can be substantially increased on a nonrecombining Y chromosome, due to its markedly smaller effective population size caused by selection against strongly deleterious mutations (*i.e.*, background selection). K_{BS} can be calculated following Charlesworth (1996) as $K_{BS} = 2f_0 N_e s_{d,weak} u_{d,weak} g/(\exp(2f_0 N_e s_{d,weak}) - 1)$. I track the reduction in the number of active genes on the Y by decreasing g, if the number of weakly deleterious mutations within a gene is larger than a set value of *n_acc* (*i.e.*, *n_acc* is the number of weakly deleterious mutations necessary to inactive a gene). The number of inactivated genes is calculated by assuming that the weakly deleterious mutations are Poisson distributed among genes and calculating the number of genes in the classes *n_acc* or larger.

Under genetic hitchhiking, the rate of degeneration, K_{GH}, depends on the rate of adaptation and the probability that a beneficial mutation drags along a deleterious allele to fixation (Johnson and Barton 2002; Bachtrog and Gordo 2004). K_{GH} can be calculated following Bachtrog and Gordo (2004) as $K_{GH} = N_e u_a g \sum_{k=1}^{k_{max}} k f_k 2(s_a - k s_d)$, where f_k is the frequency of individuals with k deleterious mutations, given by a Poisson distribution with mean $u_d g/s_d$, and $k_{max} = \max\{k : (1 + s_a)(1 - s_d)^k > 1\}$, assuming that only beneficial mutations whose net effect is bigger than the combined deleterious effects on that chromosome can contribute to adaptation. As for the Muller's ratchet model, the fixation of a deleterious mutation is assumed to reduce g by 1.

Simulation methods: A haploid, nonrecombining population of N_e individuals was simulated, assuming the following life cycle: mutations, reproduction, and selection. In each generation, individuals were sampled randomly with replacement from the previous generation. Gametes were subject to mutations according to a Poisson distribution of mean U ($U = g \times u_a$ for beneficial mutations, $U = g \times u_d$ for deleterious mutations, and $U = g \times u_{d,weak}$ for weakly deleterious mutations). Multiplicative fitness effects are assumed among mutations (see Table 1 for fitness functions), and individuals are assigned probabilities of survival according to their fitness. A new generation of N_e individuals is constructed by comparing the probability of survival of each individual with a pseudorandom number drawn from a uniform distribution in the interval [0, maximum fitness]. Each generation, the numbers of beneficial, deleterious, and weakly deleterious mutations in every individual were counted, to determine the number of fixed mutations of each class. If a deleterious mutation of effect s_d fixes in the population, the number of active genes g was reduced by one. For mutations of effect $s_{d,weak}$, I assume that *n_acc* deleterious mutations are necessary to inactivate a gene. Each generation, the expected number of genes containing *n_acc* or more weakly deleterious mutations was drawn from a Poisson distribution and used to calculate the number of active genes g remaining on the Y. To calculate the rate of degeneration (*i.e.*, the number of genes inactivated per generation), the average of at least three independent simulations was taken. C code to carry out these simulations is available on request.

RESULTS

Temporal dynamics under Muller's ratchet: Under Muller's ratchet, the expected time to loss of the class of Y chromosomes with the least number of deleterious mutations (the inverse of the rate of degeneration) depends on the following parameters (Stephan *et al.* 1993; Gessler 1995; Gordo and Charlesworth 2000; see Table 1): the effective number of Y chromosomes (N_e), the deleterious mutation rate per gene (u_d), the effect of each deleterious mutation on fitness (s_d), and the number of active genes (g). Each loss of the class of Y chromosomes with the minimum number of

TABLE 1

Parameters and fitness functions for different models of Y chromosome degeneration

	Parameters[a]	Fitness function[b]
Muller's ratchet	N_e, g, u_d, s_d	$w = (1 - s_d)^k$
Background selection	N_e, g, u_d, s_d, $u_{d,weak}$, $s_{d,weak}$	$w = (1 - s_d)^k \times (1 - s_{d,weak})^n$
Genetic hitchhiking	N_e, g, u_d, s_d, u_a, s_a	$w = (1 - s_d)^k \times (1 + s_a)^m$

[a] N_e is the number of Y chromosomes in the population, g is the number of active genes on the Y, u_d is the mutation rate to deleterious mutations per gene with an effect on fitness of s_d, $u_{d,weak}$ is the mutation rate to weakly deleterious, nearly neutral mutations per gene with an effect on fitness of $s_{d,weak}$, and u_a is the mutation rate to beneficial mutations per gene with an effect on fitness of s_a.

[b] w is the fitness of an individual, k is the number of deleterious mutations of an individual with effect s_d, n is the number of deleterious mutations of an individual with effect $s_{d,weak}$, and m is the number of beneficial mutations of an individual with effect s_a.

deleterious mutations (a *click* of Muller's ratchet) is associated with the fixation of a deleterious mutation in the entire population (Charlesworth and Charlesworth 1997). Here I assume that such a fixation reduces the number of active genes by one (an assumption that influences the rate of degeneration, but only weakly affects the total number of genes ultimately lost, see below).

Figure 1A shows the theoretical expectation and results from forward simulations for the rate of degeneration and the fraction of active genes remaining over the course of 50 million generations of Y chromosome evolution, starting with a Y containing 2000 active genes (the value expected for a typical Drosophila autosomal element). On a nascent, gene-rich Y chromosome, degeneration by Muller's ratchet is maximized, due to the large number of functional genes (*i.e.*, large U_d). Once deleterious mutations that inactivate genes start to accumulate on the Y, however, the speed of Muller's ratchet declines rapidly. Thus, while degeneration by Muller's ratchet probably is an important process on young, gene-rich Y chromosomes, its contribution diminishes over time. For the parameters considered, Muller's ratchet becomes exceedingly slow on older Y chromosomes containing few genes and is unlikely to account for the almost complete loss of active genes observed on ancient Y chromosomes (Skaletsky *et al.* 2003; Carvalho and Clark 2005).

Temporal dynamics under background selection: Degeneration of a proto-Y chromosome by background selection depends on an interaction between two types of deleterious mutations (Charlesworth 1994, 1996; see Table 1): mutations with large effects on fitness (s_d) that cause the *background selection effect* (which is a reduction, f_0, in the effective population size, N_e, of Y chromosomes) and mutations with weak fitness effects [$s_{d,weak} < 1/(N_e \times f_0)$] that accumulate by random genetic drift as a result of the reduced population size, causing degeneration. The fact that the (strongly deleterious) mutations *causing* the accumulation of weakly deleterious mutations fail to accumulate themselves distinguishes the background selection model from Muller's ratchet. Strongly and weakly deleterious mutations are assumed to occur at a rate u_d and $u_{d,weak}$ per gene, respectively. The reduction in N_e (*i.e.*, f_0) depends on u_d, s_d, and g, with a higher mutation rate U_d resulting in a larger reduction (Charlesworth 1994). The weakly deleterious mutations accumulating under background selection are probably too weak to individually knock out gene function; instead I assume that a gene becomes nonfunctional if it accumulates 10 such mutations. As with Muller's ratchet, this assumption influences the rate of degeneration, but only weakly affects the total number of genes degenerated (see below).

Figure 1B shows simulation results and the theoretical expectation of the rate of mutation accumulation of weakly deleterious mutations under background selection (Charlesworth 1994, 1996). Similar to Muller's ratchet, degeneration under the background selection model is fastest on a young, gene-rich Y chromosome. As mutations accumulate and inactivate genes, degeneration by background selection slows down, not only because $U_{d,weak}$ ($= u_{d,weak} \times g$) decreases, but also because f_0 increases (since U_d decreases). In particular, as the scaled intensity of selection increases (*i.e.*, $N_e \times f_0 \times s_{d,weak} \gg 1$), purifying selection will eventually become efficient enough to prevent the further fixation of slightly deleterious mutations on the Y. Thus, the rate of mutation accumulation by this process is also predicted to abruptly decline over time (Figure 1B).

The theoretical predictions of the rate of degeneration under background selection substantially underestimate the simulation results. An assumption in the model is that weakly deleterious mutations are independent (Charlesworth 1996), which holds reasonably well as long as the weakly deleterious mutations are very close to neutral (*i.e.*, $N_e \times f_0 \times s_{d,weak} < 1$). However, if the intensity of selection on these mutations is appreciable (due to an increase in f_0), this assumption breaks down and deleterious mutations continue to accumulate in a Muller's ratchet-like manner (Figure 1B). Thus, once enough genes are inactivated on the Y chromosome, the background selection model essentially transforms into a Muller's ratchet-like model, with the strongly deleterious mutations causing a reduction in the effective population size, and weakly deleterious mutations accumulating by Muller's ratchet (Gordo and Charlesworth 2001). The rate of degeneration observed in the simulations is well predicted by considering the joint effects of background selection and Muller's ratchet in a population of size $N_e \times f_0$ (Figure 1B; see Gordo and Charlesworth 2001). Thus, the

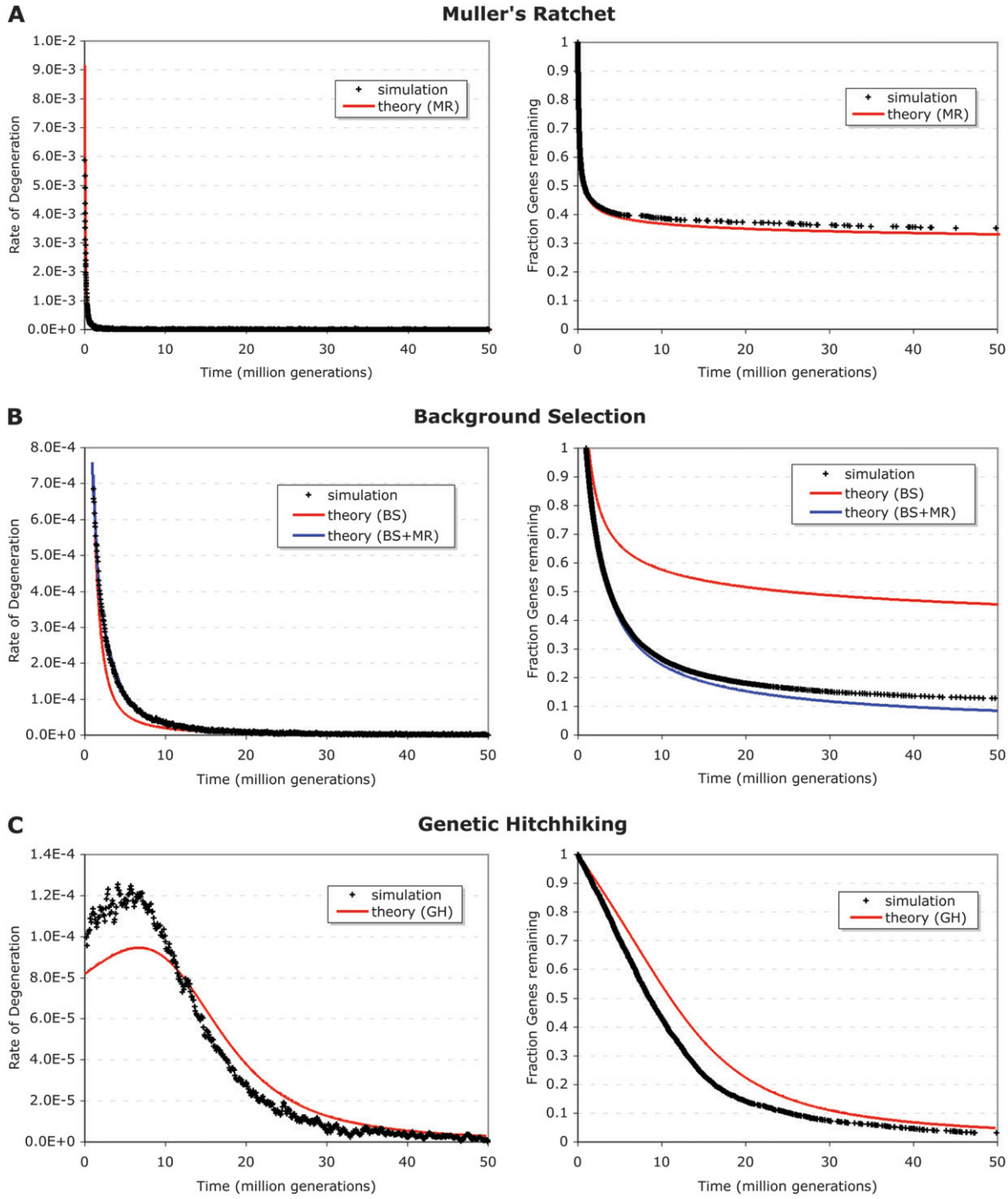

Figure 1.—The rate of Y chromosome degeneration (*i.e.*, the number of genes inactivated by deleterious mutations per generation) and the fraction of functional genes remaining over time, under different models of Y chromosome degeneration. Theoretical expectations are based on equations described in materials and methods, while the observed points (+) are from computer simulations. A Y chromosome initially carries $g = 2000$ active genes in a population of $N_e = 10{,}000$ chromosomes. The total mutation rate per gene u is assumed to be 5×10^{-5}, which corresponds to an initial chromosomewide mutation rate of 0.1. Selection coefficients were varied, according to the model studied. (A) Muller's ratchet: Deleterious mutations of effect $s_d = 1.5\%$ are modeled. (B) Background selection: 90% of the mutations are assumed to be strongly deleterious ($s_d = 3\%$) and cause a reduction in the effective population size ($f_0 = 0.05$) but do not accumulate on the Y chromosome. The remaining 10% of mutations are weakly deleterious ($s_{d,weak} = 0.15\%$) and cause degeneration. Ten such weakly deleterious mutations are assumed to be required to inactivate a gene (see Figure 2). The blue theory line models mutation accumulation by the joint action of background selection and Muller's ratchet in a population of size $N_e \times f_0$. (C) Genetic hitchhiking: Deleterious mutations of effect $s_d = 3.5\%$ are modeled. Beneficial mutations of effect $s_a = 6\%$ are assumed to occur at a fraction 10^{-5} of the total mutation rate.

rate of mutation accumulation under this model also decreases sharply over time and it is less important on old Y chromosomes.

Temporal dynamics under genetic hitchhiking: The genetic hitchhiking model of Y chromosome degeneration requires an interaction between beneficial and deleterious mutations, with the former having greater effects on fitness on average than the latter (*i.e.*, $s_a > s_d$; see Rice 1987; Johnson and Barton 2002; Bachtrog and Gordo 2004). Beneficial and deleterious mutations occur at rates u_a and u_d per gene on a chromosome with g active genes, in a population of size N_e (Table 1). Under the hitchhiking model, the rate of degeneration depends on the number of beneficial mutations arising each generation ($N_e \times u_a \times g$) and on the probability that a beneficial mutation will go to fixation and drag along linked deleterious mutations (which depends on s_a, s_d, u_d, and g; see Rice 1987; Johnson and Barton 2002; Bachtrog and Gordo 2004). As for the Muller's ratchet model, I assume that the fixation of at least one deleterious mutation inactivates a gene. The relationship between degeneration by genetic hitchhiking and the number of active genes on the Y is complex due to opposing interactions between positively and negatively selected mutations (Orr 2000; Bachtrog and Gordo 2004; see Figure 1C). The chromosomal beneficial mutation rate U_a is largest on a gene-rich, young Y chromosome. Thus, the rate of adaptation (and hitchhiking) is predicted to be high. On young Y chromosomes, however, U_d is also maximized. This implies that many deleterious mutations segregate in the population, and Y chromosomes typically carry multiple deleterious alleles (Orr 2000; Bachtrog and Gordo 2004). Thus, most beneficial alleles might not confer a net fitness advantage in the population since they occur on Y chromosomes containing several deleterious mutations. In this case, the rate of adaptation (and genetic hitchhiking) is reduced on a young Y chromosome. As genes begin to degenerate, both U_a and U_d decrease; fewer beneficial mutations arise, but a higher fraction will occur on chromosomes where they have a net fitness benefit (Orr 2000). Therefore, the rate of adaptation and the corresponding fixation of deleterious mutations may increase temporarily (Figure 1C). On older Y chromosomes, adaptation and hitchhiking of deleterious mutations slow down. Since the rate of adaptation depends linearly on U_a, even degenerate Y's continue to adapt and the process slows down less abruptly than that in deleterious mutation models (Figure 1C). Thus, while degeneration by genetic hitchhiking may proceed slowly on gene-rich, young Y chromosomes (due to interference with deleterious mutations), hitchhiking is most important on Y chromosomes of intermediate age and may be the only mode of selection that is able to account for the almost complete loss of gene function observed on many old Y chromosomes (Skaletsky *et al.* 2003; Carvalho and Clark 2005).

Dependence on model parameters: In what follows, I use theoretical approximations described in materials and methods to quantify the dependence of the different processes of Y chromosome degeneration on their underlying parameters. To investigate the influence of a particular parameter, I use the same parameter values as in Figure 1, but vary the one parameter of interest.

Number of mutations required to inactivate a gene (n_acc): In Muller's ratchet and the genetic hitchhiking simulations, I assume that a single deleterious mutation inactivates a gene. If multiple mutations are required to render a gene nonfunctional, the rate of degeneration decreases under each process of Y chromosome degeneration (Figure 2). In particular, if many mutations are required to inactivate a gene, deleterious mutations accumulate on the Y chromosome over the first few million generations at many genes (*i.e.*, the mean number of deleterious mutations per gene steadily increases), but few genes are rendered nonfunctional initially. Genes start to become inactivated later and the rate of degeneration is slower for larger values of *n_acc* (Figure 2). However, over long evolutionary time periods, the fraction of genes remaining on the Y chromosome is similar for different values of *n_acc* (Figure 2). Thus, while the number of mutations required to inactivate a gene will influence the rate of degeneration, it will have little effect on the fraction of active genes remaining on the Y.

Effective population size (N_e): The rate of degeneration resulting from Muller's ratchet and background selection declines with increasing population size, while the rate of degeneration caused by genetic hitchhiking increases with increasing population size (Figure 3). Thus, degeneration by genetic hitchhiking is more important in larger populations, relative to Muller's ratchet and background selection.

Number of active genes initially present on the Y chromosome (g): The rate of degeneration resulting from Muller's ratchet and background selection is predicted to be a monotonically decreasing function of the number of genes originally present on the Y chromosome (Figure 4). In contrast, the rate of degeneration caused by genetic hitchhiking is maximized for an intermediate number of active genes (g_{max}). If a Y chromosome contains more genes, the rate of degeneration due to genetic hitchhiking increases initially until g_{max} and then decreases thereafter. If the Y initially contains fewer than g_{max} genes, the rate of degeneration due to hitchhiking monotonically decreases with the number of active genes. While Muller's ratchet and background selection will essentially not operate on very gene-poor Y chromosomes, degeneration due to genetic hitchhiking can continue on Y's containing only few genes. This implies that if recombination between the nascent sex chromosomes is restricted gradually, involving a subset of genes at a time on a Y chromosome (as has been

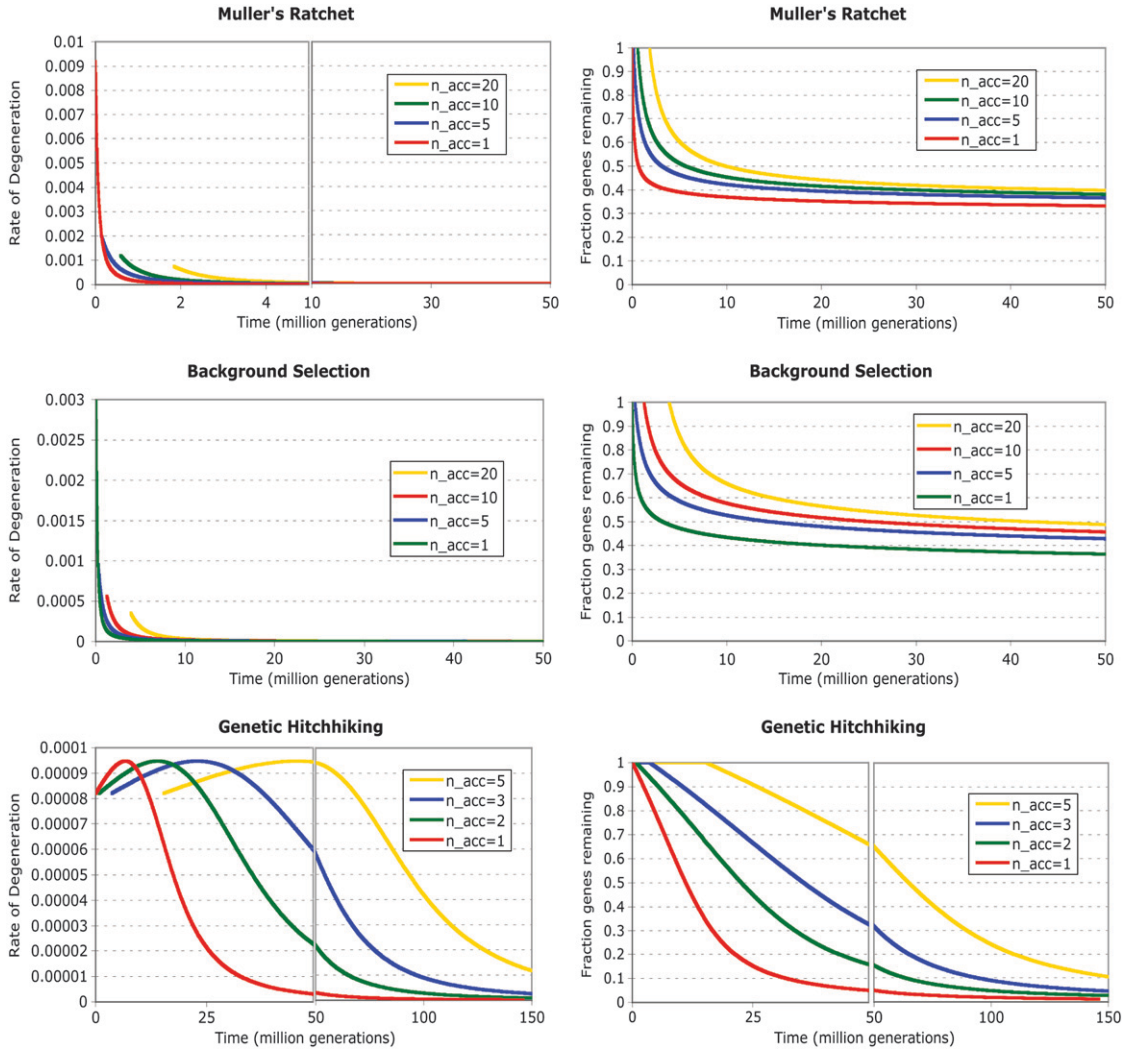

FIGURE 2.—The effect of the number of mutations required to inactivate a gene (*n_acc*) on processes underlying Y chromosome degeneration. Red lines represent parameter values assumed in Figure 1. For each model, the rate of degeneration decreases with increasing *n_acc*. However, over long evolutionary time periods, the number of genes inactivated on the Y is similar for different values of *n_acc*. Note that the fitness effects of accumulating mutations vary among models, following parameters used in Figure 1.

posited for Y chromosomes in several taxa), the relative contribution of genetic hitchhiking to Y degeneration increases (see DISCUSSION below). For similar reasons, genetic hitchhiking is also predicted to be the dominant process on old, gene-poor Y chromosomes, relative to Muller's ratchet or background selection.

Deleterious selection coefficients (s_d and $s_{d,weak}$): For all three models of Y chromosome degeneration, the rate of degeneration increases with decreasing selection coefficients (Figure 5). Under the background selection model, decreasing s_d decreases f_0 and thus reduces the effective population size of Y chromosomes (increasing the effect of genetic drift). Decreasing $s_{d,weak}$ increases the probability of fixation of the weakly deleterious mutation. Note, however, that with decreasing s_d or $s_{d,weak}$, the effect of these mutations on fitness decreases as well. Thus, multiple mutations might become necessary to inactivate genes if fitness effects are smaller (see above for the effect of *n_acc*). Note that genetic hitchhiking is the only model that can drag very strongly deleterious mutations ($s_d > 3.5\%$ for the parameters considered here) to fixation. On old Y chromosomes, remaining genes often lack X-linked homologs (because they are either recruited from elsewhere or have long since diverged in function). Thus, negative selection models are predicted to be less important on older Y's, since mutations that occur in genes that lack X-linked homologs are probably more strongly deleterious (since mutations are hemizygous and thus always visible to selection).

Beneficial selection coefficients (s_a) and the fraction of newly arising mutations that are beneficial (f): The rate of degeneration by genetic hitchhiking increases with increasing the selection coefficients for beneficial mutations (Figure 6A) or with increasing the fraction of newly arising mutations that are beneficial (Figure 6B).

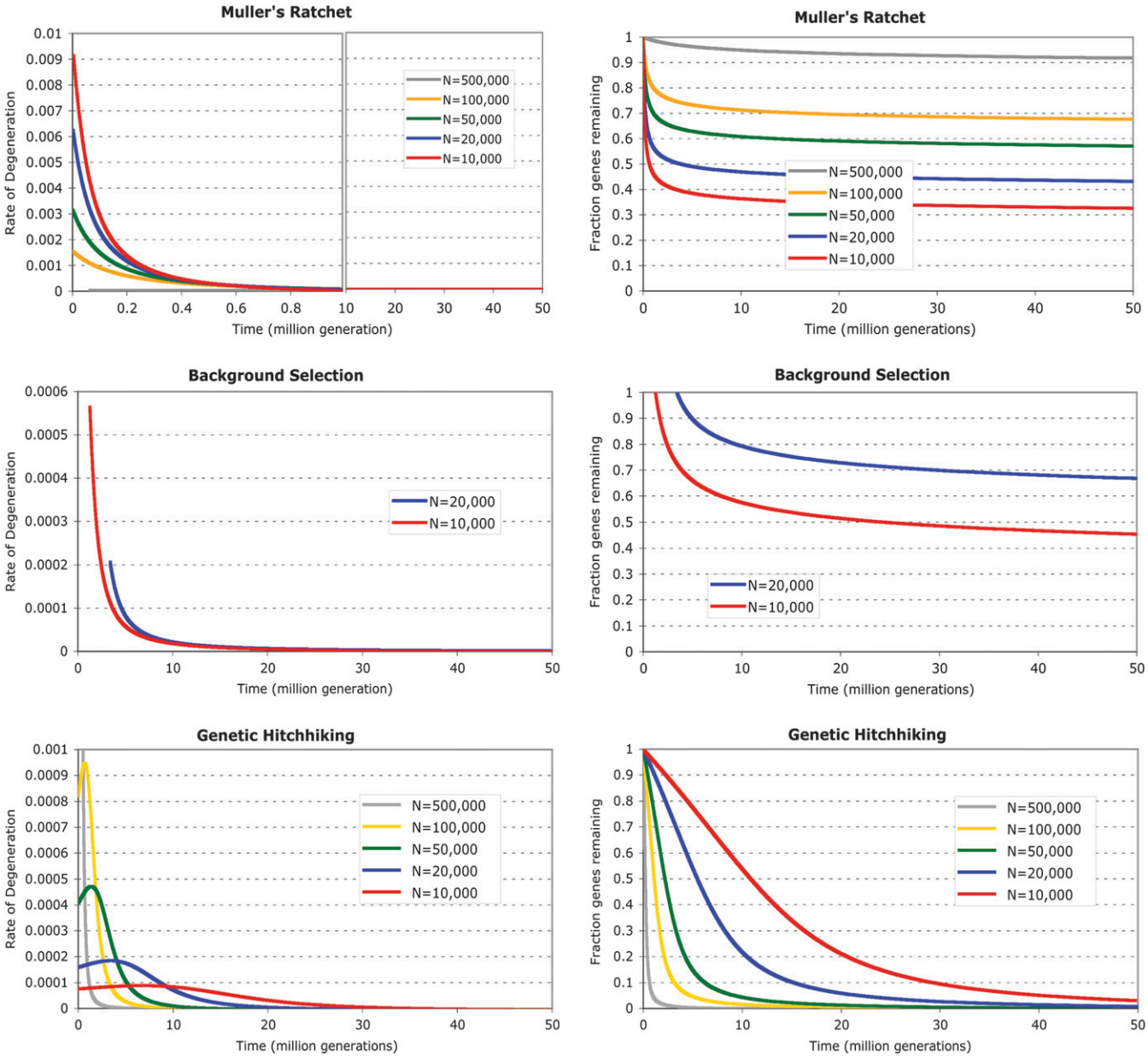

Figure 3.—The effect of population size (N_e) on processes of Y chromosome degeneration. Red lines represent parameter values assumed in Figure 1. For the mutational parameters used, essentially no weakly deleterious mutations accumulate under the background selection model in a population of ≥50,000 Y chromosomes. Similarly, Muller's ratchet essentially stops in a population of size ≥1,000,000.

Thus, genetic hitchhiking is more important if beneficial mutations are strong and frequent (*i.e.*, higher rates of adaptation).

Distribution of selection coefficients: In all analyses above, I have modeled discrete selection coefficients, instead of a distribution. No theoretical approximation has been obtained for the speed of any of these models considered for a distribution of selection coefficients. To investigate the effect of a distribution of selection coefficients, I performed forward simulations, modeling two classes of deleterious mutations ($s_{d,strong} = 1.5\%$ and $s_{d,weak} = 0.5\%$) that both can accumulate on a Y chromosome by Muller's ratchet. Assume a mutation rate of $u_d = 5 \times 10^{-5}$/gene and 2000 active genes initially (*i.e.*, a chromosomewide mutation rate $U_d = 0.1$). Mutations of effect $s_{d,strong}$ occur at rate $f_{strong} \times u_d$ and mutations of effect $s_{d,weak}$ occur at rate $f_{weak} \times u_d$. I model both classes of deleterious mutations simultaneously ($f_{strong} = 0.5$ and $f_{weak} = 0.5$) and compare these to simulations with strong or weak mutations modeled in isolation (*i.e.*, $f_{strong} = 1$ or $f_{weak} = 1$). Simulations modeling only the weak mutations render a larger fraction of genes nonfunctional than modeling only the strong ones (Figure 7A). The amount of

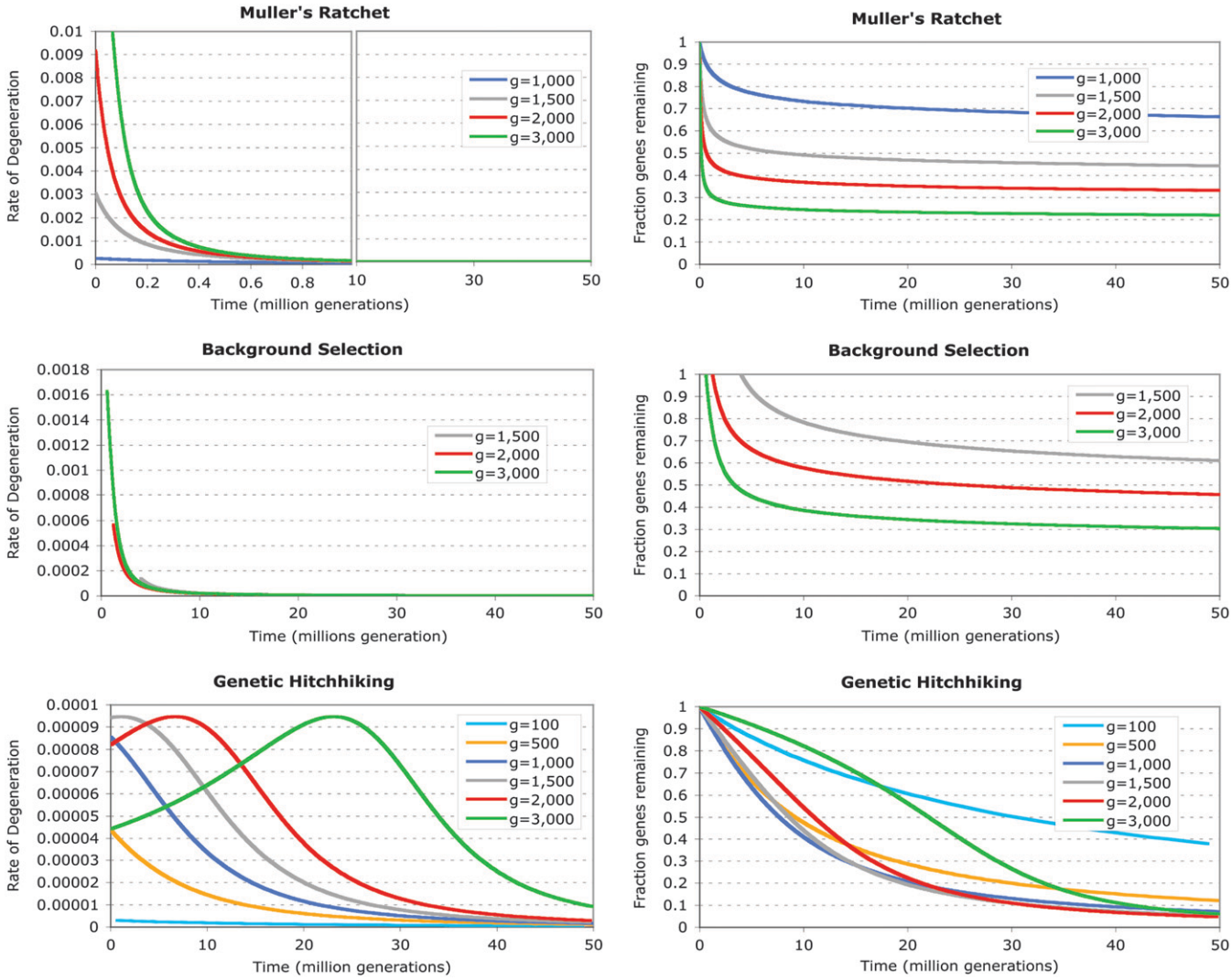

Figure 4.—The effect of the number of active genes (g) present on a newly formed Y chromosome on processes of Y chromosome degeneration. Red lines represent parameter values assumed in Figure 1. For the parameters used, Muller's ratchet essentially does not operate on a Y chromosome containing <500 active genes. Similarly, essentially no weakly deleterious mutations accumulate under the background selection model if the Y chromosome contains ≤1000 active genes. Genetic hitchhiking operates even on very gene-poor Y chromosomes.

degeneration caused by two types of deleterious mutations simultaneously lies in between the amount of degeneration caused by considering each class separately (Figure 7A). Figure 7B shows the rate of degeneration caused by the strongly and weakly deleterious mutations if occurring simultaneously (in red), using the parameters above. The simulation results shown in black depict simulations of the two types of deleterious mutations separately, but assuming only half the mutation rate for each class of mutations (*i.e.*, $u_d = 2.5 \times 10^{-5}$/gene). Thus, for a given total mutation rate, the amount of degeneration resulting from a distribution of selection coefficients will always be less than that using a single value of s_d that maximizes degeneration.

Muller's ratchet and genetic hitchhiking in concert: Clearly, processes underlying Y chromosome degeneration do not act in isolation. Deleterious mutations can accumulate on a Y chromosome due to the simultaneous action of Muller's ratchet and genetic hitchhiking, if deleterious mutations are weak enough to accumulate by Muller's ratchet, and $s_a > s_d$. The rate of degeneration due to the combined action of these processes can be estimated by summing up the rates of degeneration caused by Muller's ratchet and by genetic hitchhiking (Bachtrog and Gordo 2004). Figure 8 shows the rate of degeneration and the fraction of genes remaining over time, on a Y chromosome where deleterious mutations can accumulate both by Muller's ratchet and by genetic hitchhiking. Similar to considering these forces in isolation, Muller's ratchet is most important in the early stages of Y chromosome degeneration (*i.e.*, Muller's ratchet essentially stops operating after 1 million

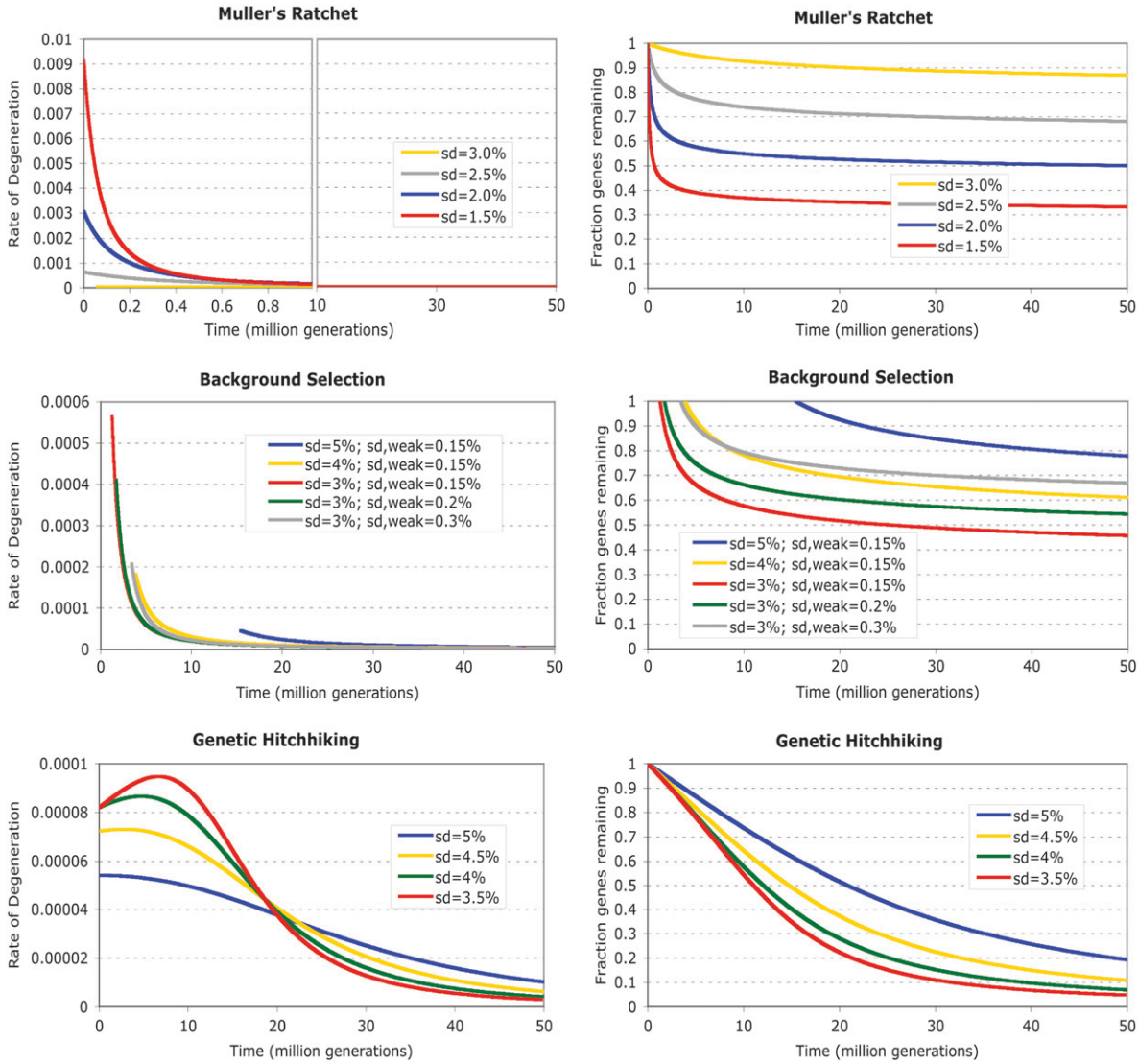

FIGURE 5.—The effect of the deleterious selection coefficients (s_d or $s_{d,weak}$) on processes of Y chromosome degeneration. Red lines represent parameter values assumed in Figure 1. Muller's ratchet will essentially not operate if $s_d \geq 3.5\%$. The genetic hitchhiking model requires $s_d < s_a$; for $s_d < 3\%$ degeneration would occur by both genetic hitchhiking and Muller's ratchet (see Figure 8 for this effect).

generations for the parameters considered), while degeneration by genetic hitchhiking can continue over longer periods of evolution (Figure 8). For the specific parameters used, Muller's ratchet and genetic hitchhiking are individually responsible for the inactivation of a similar number of genes. Thus, if Muller's ratchet and genetic hitchhiking simultaneously operate to cause Y degeneration, Muller's ratchet is more important in the early stages of Y degeneration, while genetic hitchhiking dominates later on.

DISCUSSION

The dynamics of Y degeneration over time: Y chromosomes originate from ordinary autosomes and degenerate by accumulating deleterious mutations. Here, I show that positive and negative selection models have strikingly different temporal dynamics over the course of Y degeneration. Muller's ratchet and background selection are more likely to contribute to degeneration in the very early stages on gene-rich Y chromosomes, but their contribution diminishes rapidly over time. Genetic hitchhiking, on the other hand, can continue to contribute to degeneration over longer periods of time and is probably most important for Y chromosomes of intermediate age (FILATOV *et al.* 2000; BACHTROG 2004) and very old Y chromosomes (ZUROVCOVA and EANES 1999; GERRARD and FILATOV 2005). While degeneration can proceed very rapidly on newly formed Y chromosomes, the rate of degeneration by all three of these modes of selection eventually diminishes and becomes exceedingly slow on old

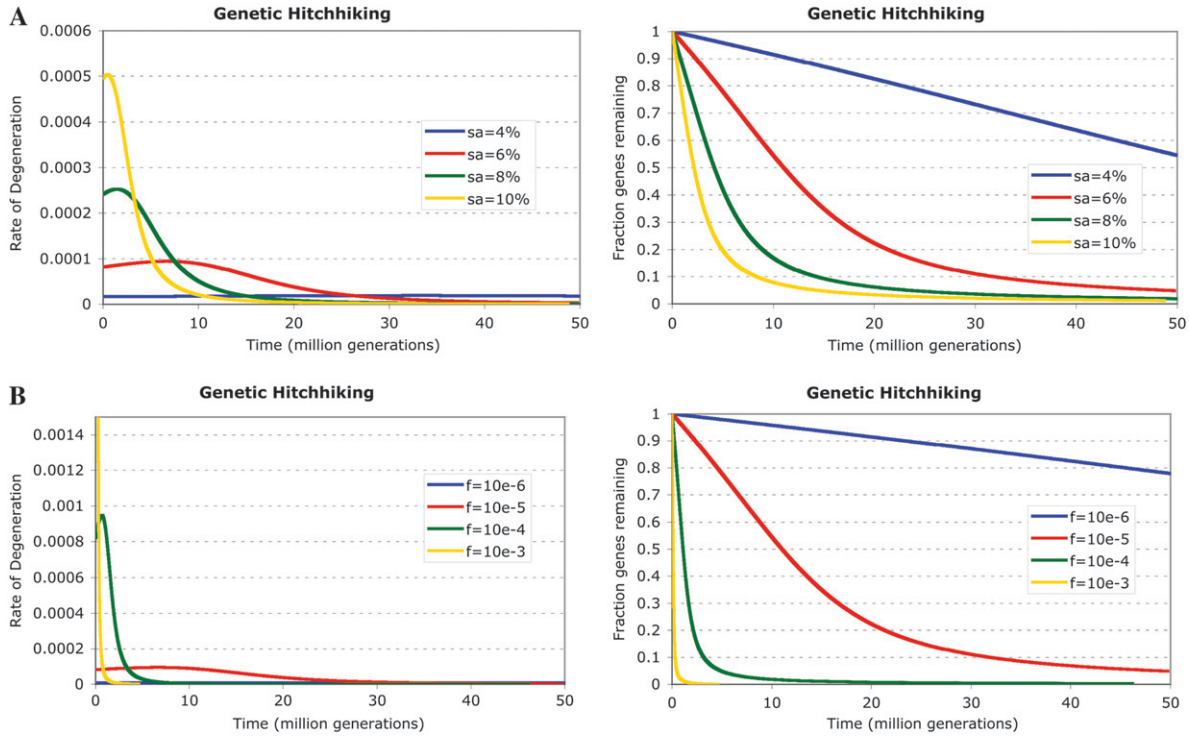

FIGURE 6.—The effect of (A) the beneficial selection coefficient (s_a) and (B) the fraction of newly arising mutations that are beneficial (f) on the rate of Y chromosome degeneration by genetic hitchhiking. Red lines represent parameter values assumed in Figure 1. In this example, $s_d = 3.5\%$ (as in Figure 1C). Genetic hitchhiking will not operate unless $s_a > s_d$.

gene-poor Y's. Note, however, that only a very simple scenario of Y evolution is explored and I ignore evolutionary responses on the X chromosome, such as the acquisition of dosage compensation. Little is known about the evolution of dosage compensation, but compensation could involve several genes at once (the block model of dosage compensation). If dosage compensation indeed evolves in a blockwise manner, the rate of Y degeneration would decrease much less rapidly, and Y degeneration at dosage-compensated genes could actually become adaptive. It will be of interest to study more complex models of Y evolution that take into account the evolutionary dynamics of X chromosomes.

Modeling assumptions: Here, only simple models of Y degeneration are examined. For example, the genetic hitchhiking model studied assumes that strongly beneficial mutations drag along to fixation deleterious alleles that knock out the function of a gene. Inactivation of genes is assumed to be irreversible. Since the frequency of back mutations to a given allele is usually considerably lower than the forward mutation rate to null alleles, this model should apply if deleterious mutations completely inactivate a gene. However, more complex (and realistic) models of genetic hitchhiking are possible, where beneficial mutations restore a previous malfunctional gene. In this case, degeneration would proceed slower than under the model considered here. In addition, if genes accumulate slightly deleterious mutations, the beneficial mutation rate at a given gene might actually increase the farther it is from its optimum fitness. Under this scenario, genetic hitchhiking should become all the more important for older Y chromosomes that have accumulated slightly deleterious mutations at many genes.

Another simplification of the models considered is assuming a simplistic distribution of mutational effects (either a constant selection coefficient or a two-class model of selective effects). Mutations in natural populations cover a wide distribution of fitness effects, both for beneficial and for deleterious alleles (ORR 2003; YAMPOLSKY *et al.* 2005; EYRE-WALKER *et al.* 2006). However, little is known about the empirical distribution of selective effects of newly arising mutations. In addition, no theoretical approximations have been obtained to study the rate of any of the Y degeneration models considered for a distribution of selective effects. In the Muller's ratchet model analyzed, a constant selection coefficient for deleterious mutations is assumed. As the number of functional genes remaining on the Y chromosome declines over time, the number of Y chromosomes in the best class increases until eventually the ratchet stops. A distribution of selection coefficients, however, could result in sufficiently many mutations with very small selection coefficients causing the number of individuals in the best class to be small over longer time periods. In this case, Muller's ratchet may continue to operate even on gene-poor Y chromosomes. To gain intuitions on the dynamics of Muller's

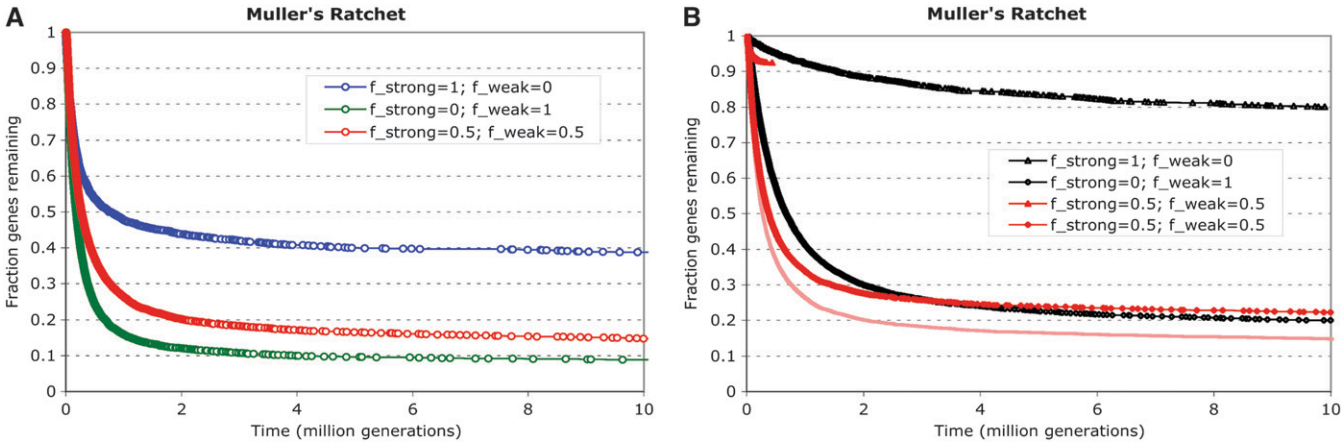

FIGURE 7.—Muller's ratchet with two classes of deleterious mutations. A population of $N_e = 10{,}000$ individuals is modeled, with a Y chromosome originally containing 2000 genes. I assume that one mutation of effect $s_{d,strong} = 1.5\%$ or three mutations with $s_{d,weak} = 0.5\%$ are required to inactivate a gene. (A) A two-class *vs.* one-class model of fitness effects for a given mutation rate. All simulations assume a mutation rate of $u_d = 5 \times 10^{-5}$/gene (*i.e.*, a chromosomewide mutation rate $U_d = 0.1$). Results shown in red are for simulations where both types of mutations are modeled simultaneously, occurring at frequency of $f_{strong} = 0.5$ and $f_{weak} = 0.5$. Results shown in green are for simulations where all mutations are modeled to be of effect $s_{d,weak}$ and results in blue model all mutations of effect $s_{d,strong}$. (B) A more detailed examination of the joint effects of weak and strong deleterious mutations. Simulations in red assume a mutation rate of $u_d = 5 \times 10^{-5}$/gene, modeling weak and strong mutations simultaneously. Shown in red are the fractions of genes inactivated by strong mutations (triangles), weak mutations (diamonds), and their combined effects (the lighter red line, corresponding to red open circles in A). Black lines show the number of genes inactivated by weak or strong mutations occurring at the same rates but in isolation ($u_d = 2.5 \times 10^{-5}$/gene). Both weakly and strongly deleterious mutations cause more degeneration in isolation than in the presence of a second class of deleterious mutations.

ratchet with a distribution of selection coefficients, I performed forward simulations modeling two classes of deleterious mutations (see Figure 7). I show that for a given mutation rate, degeneration resulting from a two-class model of selective effects will always be less than using a single value of deleterious effects that maximize degeneration. Also, for deleterious mutations of very small effects, the assumption of irreversibility of mutations (and thus the presence of Muller's ratchet) will also break down, and back mutations would need to be incorporated into the model. Similar considerations of ignoring a distribution of deleterious fitness effects apply to the background selection model. That is, the slowdown in the rate of degeneration may be overestimated by assuming discrete classes of deleterious mutations. Thus, it will be of great interest for future research to examine the evolutionary dynamics of Muller's ratchet and background selection, assuming a distribution of selective effects. In particular, a distribution of selective effects of negative mutations will allow

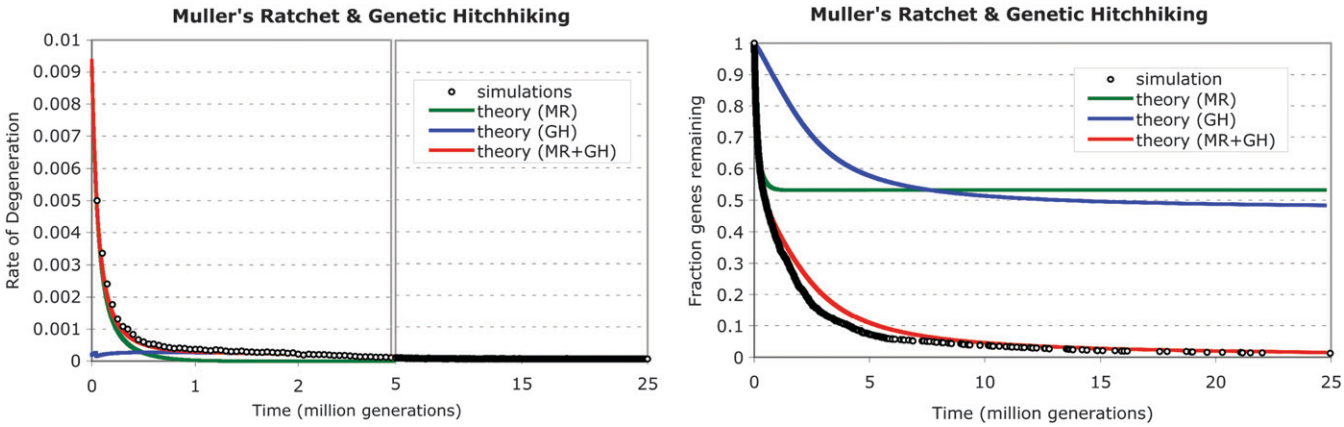

FIGURE 8.—The dynamics of Y chromosome degeneration under the simultaneous operation of Muller's ratchet and genetic hitchhiking. Solid lines are theoretical predictions based on BACHTROG and GORDO (2004), while the observed points are from computer simulations. I model $N_e = 10{,}000$ Y chromosomes that initially carry $g = 2000$ active genes. The total mutation rate per gene u is assumed to be 5×10^{-5} (*i.e.*, corresponding to a chromosomewide mutation rate of 0.1). Selection coefficients against deleterious mutations were set to $s_d = 1.5\%$, and beneficial mutations of effect $s_a = 6\%$ are assumed to occur at a fraction 10^{-5} of the total mutation rate.

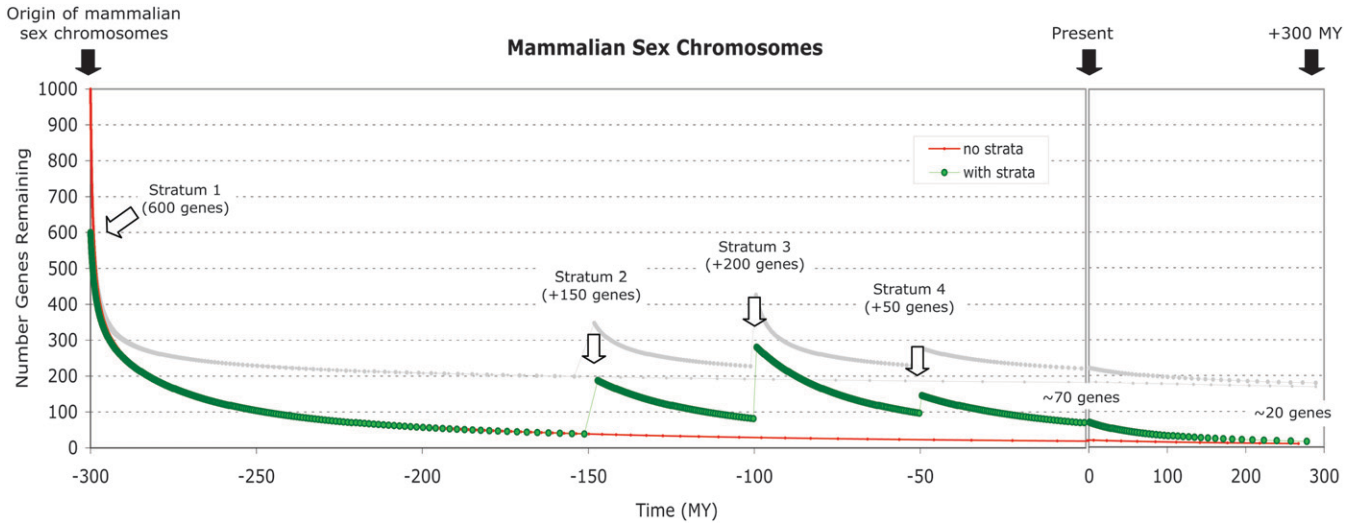

Figure 9.—Temporal dynamics of mammalian Y chromosome evolution. Different parts of the mammalian sex chromosomes (strata 1–4) were incorporated into the nonrecombining region at different times (Lahn and Page 1999; Skaletsky *et al.* 2003). A distribution of selection coefficients for deleterious mutations has recently been estimated (Yampolsky *et al.* 2005; Eyre-Walker *et al.* 2006), and three types of mutations are modeled here: beneficial mutations ($s_a = 1\%$) (Voight *et al.* 2006) occurring at a fraction $f = 10^{-5}$ of the total mutation rate, strongly deleterious mutations that cause a reduction in the effective population size of Y chromosomes but do not accumulate ($s_{d,BS} = 1\%$; $f = 0.25$), and deleterious mutations of intermediate effect that accumulate under Muller's ratchet ($s_{d,MR} = 0.1\%$; $f = 0.15$). The remaining mutations are either effectively neutral ($f = 0.2$) or strongly deleterious and cause only a negligible reduction in N_e ($f = 0.4$) (Yampolsky *et al.* 2005; Eyre-Walker *et al.* 2006). The total mutation rate is assumed to be 3.6×10^{-5}/gene and generation (Eyre-Walker and Keightley 1999). I assume a population size for mammals of 5×10^5 males and a generation time of 1 year. Under these parameters, deleterious mutations of effect $s_{d,MR}$ can accumulate either by Muller's ratchet or by hitchhiking with beneficial mutations, and I modify the approximation proposed by Bachtrog and Gordo (2004) to calculate the rate of degeneration (see Figure 8). Each fixation of a deleterious mutation is assumed to inactivate a gene. The red line indicates genes remaining on the hypothetical Y chromosome, assuming that all 1000 genes stopped recombining at once (*i.e.*, ignoring the evolutionary strata on the mammalian Y), while the green line accounts for the different ages of strata observed on the mammalian Y. The gray line shows Y degeneration ignoring beneficial mutations. The black arrows indicate the origin of the mammalian sex chromosomes ~300 MYA, the present time, and the projected future after an additional 300 MY. Under the joint Muller's ratchet plus hitchhiking model, the Y chromosome of mammals is predicted to have ~70 genes remaining at the present, which is close to the observed 78 protein-coding genes on the human Y (Skaletsky *et al.* 2003). Under the same model, the Y is predicted to still harbor ~20 genes 300 MY in the future (ignoring future recruitment of new genes by additional fusions or transpositions).

the joint evaluation of Muller's ratchet and background selection, instead of treating them as separate processes.

Also, the genetic hitchhiking model examined considers only constant effects of beneficial mutations. The evolutionary dynamics of genetic hitchhiking, however, may be less sensitive to the underlying distribution of selective effects of beneficial mutations, as long as there are sufficiently many mutations that have an advantage that is greater than the negative fitness effects of segregating deleterious mutations. If most beneficial mutations have only very weak fitness benefits (such that $s_a < s_d$ for most mutations), genetic hitchhiking will become less important.

Modeling the evolution of the mammalian Y chromosome: The theoretical considerations above have important implications for the evolution of the mammalian Y chromosome. Not all of the ~1000 original genes in the differentiated region of the human Y chromosome stopped recombining simultaneously on the Y (Lahn and Page 1999; Skaletsky *et al.* 2003). Instead, mammalian sex chromosome evolution was probably punctuated by at least four independent events, each suppressing recombination for specific regions at different evolutionary time points (Lahn and Page 1999). Using mutation and selection parameters estimated for humans (Yampolsky *et al.* 2005; Eyre-Walker *et al.* 2006), we can estimate the relative importance of positive and negative selection in mammalian Y chromosome degeneration (see Figure 9). If the mammalian Y chromosome had formed as a single nonrecombining unit 300 MYA, we estimate that ~40% of the degeneration would have resulted from genetic hitchhiking and 60% by Muller's ratchet (using the parameters described in Figure 9). Using the same population and mutation parameters, but accounting for the observed mosaic structure of the mammalian Y chromosome, however, we estimate that genetic hitchhiking would have caused almost 75% of degeneration. Clearly, the absolute contributions of positive and negative selection to Y chromosome degeneration will depend on the exact parameter values of beneficial and deleterious mutations (see Figures 2–8). In general,

however, if recombination between the sex chromosomes is restricted gradually as has been found for other species, including birds (Handley *et al.* 2004) and some plants (Filatov 2005; Nicolas *et al.* 2005), this reduces the general importance of Muller's ratchet and background selection relative to genetic hitchhiking as a cause for Y chromosome degeneration.

Further, while degeneration can proceed very rapidly on newly formed Y chromosomes (or whenever new strata are added to the Y), the rate of degeneration by both positive and negative selection models eventually diminishes and becomes exceedingly slow on ancient gene-poor Y chromosomes. For example, at the rate of degeneration inferred for the mammalian Y, the human Y would still have ~20 genes left in another 300 MY (Figure 9). Of course, the continued accumulation of new genes via additional autosomal fusions or transposition (Graves 2006) will also contribute to maintaining active genes on the Y chromosome. Moreover, if some of these genes are essential for males (*i.e.*, $s_d = 1$), the probability of losing such a gene would be extremely small (Crow and Kimura 1970). These considerations imply that predictions of the future loss of all functional genes on the human Y chromosome within 10 MY (Aitken and Marshall Graves 2002; Graves 2004, 2006) are not supported by theoretical models of Y chromosome degeneration. Instead, evolutionary theory suggests that the Y chromosome of humans is likely to survive for the foreseeable future.

I am grateful to Peter Andolfatto and Isabel Gordo for comments on the manuscript. This research is funded by National Institutes of Health grant GM076007 and an A.P. Sloan Fellowship in Molecular and Computational Biology to D.B.

LITERATURE CITED

Aitken, R., and J. Marshall Graves, 2002 The future of sex. Nature **415:** 963.

Bachtrog, D., 2004 Evidence that positive selection drives Y-chromosome degeneration in *Drosophila miranda*. Nat. Genet. **36:** 518–522.

Bachtrog, D., 2005 Sex chromosome evolution: molecular aspects of Y chromosome degeneration in Drosophila. Genome Res. **15:** 1393–1401.

Bachtrog, D., and I. Gordo, 2004 Adaptive evolution of asexual populations under Muller's ratchet. Evol. Int. J. Org. Evol. **58:** 1403–1413.

Barton, N. H., and B. Charlesworth, 1998 Why sex and recombination? Science **281:** 1986–1990.

Carvalho, A., and A. Clark, 2005 Y chromosome of D. pseudoobscura is not homologous to the ancestral Drosophila Y. Science **307:** 108–110.

Charlesworth, B., 1978 Model for evolution of Y chromosomes and dosage compensation. Proc. Natl. Acad. Sci. USA **75:** 5618–5622.

Charlesworth, B., 1994 The effect of background selection against deleterious mutations on weakly selected, linked variants. Genet. Res. **63:** 213–227.

Charlesworth, B., 1996 The evolution of chromosomal sex determination and dosage compensation. Curr. Biol. **6:** 149–162.

Charlesworth, B., and D. Charlesworth, 1997 Rapid fixation of deleterious alleles can be caused by Muller's ratchet. Genet. Res. **70:** 63–73.

Charlesworth, B., and D. Charlesworth, 2000 The degeneration of Y chromosomes. Philos. Trans. R. Soc. Lond. B Biol. Sci. **355:** 1563–1572.

Charlesworth, B., M. T. Morgan and D. Charlesworth, 1993 The effect of deleterious mutations on neutral molecular variation. Genetics **134:** 1289–1303.

Crow, J. F., and M. Kimura, 1970 *An Introduction to Population Genetics Theory*. Burgess Publishing Company, Minneapolis.

Eyre-Walker, A., and P. D. Keightley, 1999 High genomic deleterious mutation rates in hominids. Nature **397:** 344–347.

Eyre-Walker, A., M. Woolfit and T. Phelps, 2006 The distribution of fitness effects of new deleterious amino acid mutations in humans. Genetics **173:** 891–900.

Filatov, D., 2005 Evolutionary history of *Silene latifolia* sex chromosomes revealed by genetic mapping of four genes. Genetics **170:** 975–979.

Filatov, D. A., F. Moneger, I. Negrutiu and D. Charlesworth, 2000 Low variability in a Y-linked plant gene and its implications for Y-chromosome evolution. Nature **404:** 388–390.

Gerrard, D., and D. Filatov, 2005 Positive and negative selection on mammalian Y chromosomes. Mol. Biol. Evol. **22:** 1423–1432.

Gessler, D., 1995 The constraints of finite size in asexual populations and the rate of the ratchet. Genet. Res. **66:** 241–253.

Gordo, I., and B. Charlesworth, 2000 The degeneration of asexual haploid populations and the speed of Muller's ratchet. Genetics **154:** 1379–1387.

Gordo, I., and B. Charlesworth, 2001 The speed of Muller's ratchet with background selection, and the degeneration of Y chromosomes. Genet. Res. **78:** 149–161.

Graves, J., 2004 The degenerate Y chromosome—Can conversion save it? Reprod. Fertil. Dev. **16:** 527–534.

Graves, J., 2006 Sex chromosome specialization and degeneration in mammals. Cell **124:** 901–914.

Handley, L., H. Ceplitis and H. Ellegren, 2004 Evolutionary strata on the chicken Z chromosome: implications for sex chromosome evolution. Genetics **167:** 367–376.

Johnson, T., and N. H. Barton, 2002 The effect of deleterious alleles on adaptation in asexual populations. Genetics **162:** 395–411.

Lahn, B. T., and D. C. Page, 1999 Four evolutionary strata on the human X chromosome. Science **286:** 964–967.

Nicolas, M., G. Marais, V. Hykelova, B. Janousek, V. Laporte *et al.*, 2005 A gradual process of recombination restriction in the evolutionary history of the sex chromosomes in dioecious plants. PLoS Biol. **3:** e4.

Orr, H. A., 2000 The rate of adaptation in asexuals. Genetics **155:** 961–968.

Orr, H. A., 2003 The distribution of fitness effects among beneficial mutations. Genetics **163:** 1519–1526.

Rice, W. R., 1987 Genetic hitchhiking and the evolution of reduced genetic activity of the Y sex chromosome. Genetics **116:** 161–167.

Rice, W. R., 1996 Evolution of the Y sex chromosome in animals. BioScience **46:** 331–343.

Skaletsky, H., T. Kuroda-Kawaguchi, P. Minx, H. Cordum, L. Hillier *et al.*, 2003 The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. Nature **423:** 825–837.

Stephan, W., L. Chao and J. G. Smale, 1993 The advance of Muller's ratchet in a haploid asexual population: approximate solutions based on diffusion theory. Genet. Res. **61:** 225–231.

Voight, B., S. Kudaravalli, X. Wen and J. Pritchard, 2006 A map of recent positive selection in the human genome. PLoS Biol. **4:** e72.

Yampolsky, L., F. Kondrashov and A. Kondrashov, 2005 Distribution of the strength of selection against amino acid replacements in human proteins. Hum. Mol. Genet. **14:** 3191–3201.

Zurovcova, M., and W. F. Eanes, 1999 Lack of nucleotide polymorphism in the Y-linked sperm flagellar dynein gene Dhc-Yh3 of *Drosophila melanogaster* and *D. simulans*. Genetics **153:** 1709–1715.

Communicating editor: D. M. Rand