Muller’s ratchet and the degeneration of Y chromosomes: a simulation study

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ABSTRACT

A typical pattern in sex chromosome evolution is that Y chromosomes are small and have lost many of their genes. One mechanism that might explain the degeneration of Y chromosomes is Muller’s ratchet, the perpetual stochastic loss of linkage groups carrying the fewest number of deleterious mutations. This process has been investigated theoretically mainly for asexual, haploid populations. Here, I construct a model of a sexual population where deleterious mutations arise on both X and Y chromosomes. Simulation results of this model demonstrate that mutations on the X chromosome can considerably slow down the ratchet. On the other hand, a lower mutation rate in females than in males, background selection and the emergence of dosage compensation are expected to accelerate the process.
INTRODUCTION

Many animal and plant species have sex determination systems that involve distinct X and Y chromosomes (Bull 1983; Solari 1993). It is generally believed that these sex chromosomes evolved from common autosomal ancestors. However, Y chromosomes often have lost many of their genes, are highly heterochromatic and exhibit a high density of transposable elements (reviewed in Graves 2006). In humans, for example, the Y chromosome spans about 60 Mb and contains only a few dozen protein coding genes in its non-recombining region (Skaletsky et al. 2003). Moreover, the Y is rich in repetitive DNA without apparent function, and a large proportion is heterochromatic. By contrast, the human X chromosome measures about 155 Mb and contains more than one thousand genes (Ross et al. 2005).

Several mechanisms have been proposed for why Y chromosomes erode, but their relative importance is not fully understood and may vary between species (reviewed in Charlesworth & Charlesworth 2000; Bachtrog 2006). It is clear, however, that the ultimate cause of erosion is the lack of recombination between X and Y chromosomes over most of their length. For example, this lack of recombination can lead to ‘hitchhiking effects’ of deleterious mutations (Maynard Smith & Haigh 1974): if a beneficial mutation arises on a Y chromosome and spreads to fixation, it will drag along all mildly deleterious mutations at other loci on the Y chromosome (Rice 1987). Another mechanism that leads to accumulation of mildly deleterious alleles is a reduction in effective population size due to ‘background selection’ against linked, strongly deleterious alleles that arise continually by mutation (B. Charlesworth et al. 1993).
Deleterious mutations may also accumulate through a process termed ‘Muller’s ratchet’ (Muller 1964; Felsenstein 1974). Consider a population where deleterious mutations arise at many loci. In an infinitely large population, the distribution of the number of mutations that individuals carry will converge to an equilibrium determined by the balance of mutation and selection. If all loci contribute equally to fitness and there is no epistasis, the equilibrium number of mutations follows a Poisson distribution with mean $U/s$, where $U$ is the genomic mutation rate and $s$ the selection coefficient (Kimura & Maruyama 1966). In a finite population, however, genetic drift will produce fluctuations around this equilibrium, particularly if the effective population size is small. Eventually, the class of chromosomes that carry the smallest number of mutations may become extinct. In the absence of recombination and back mutations, this loss of least loaded chromosomes marks an irreversible ‘click’ of the ratchet. The new least loaded class may then become lost in the same way and the ratchet may continue to operate on the Y chromosome, leading to its gradual deterioration.

Several theoretical studies have attempted to characterise Muller’s ratchet quantitatively, in particular the speed of the process (e.g., Haigh 1978; Gabriel et al. 1993; Stephan et al. 1993; Gessler 1995; Charlesworth & Charlesworth 1997; Gordo & Charlesworth 2000a; Gordo & Charlesworth 2000b; Gordo & Charlesworth 2001). However, none of the models has been tailored directly to the situation of sex chromosome evolution. Rather, asexual populations with haploid individuals were usually assumed, with the exception of D. Charlesworth et al. (1993) and Charlesworth & Charlesworth (1997), who also studied asexual diploid populations and sexual diploid populations with non-recombining autosomes.

Here, I construct an individual-based stochastic model that explicitly incorporates a sex chromosome system, with mutations occurring on both X and Y chromosomes. The
focus is on lethal, partially recessive mutations, but other types of mutations are also investigated. Using computer simulations, I will address the following questions. (1) What is the impact of a finite number of loci on the speed of Muller’s ratchet? Previous models have assumed that the target size for mutations remains constant. In my model, assuming that mutations are always non-functional, the target size becomes smaller as the ratchet proceeds, slowing the process. (2) How do mutations on the X chromosome influence the speed of the ratchet, and how important are different mutation rates in males and females in this respect? Since individuals homozygous for a mutation are assumed to be not viable, mutations arising on the X chromosome cause strong selection against mutations on the Y chromosome; this reduces the speed of the ratchet considerably. (3) What is the effect of background selection on the speed of Muller’s ratchet? It has been demonstrated previously that background selection can accelerate the ratchet in asexual haploid populations (Gordo and Charlesworth 2001), and I confirm this effect for the case of sexual diploid populations. (4) How does the evolution of dosage compensation affect the ratchet? Dosage compensation is the upregulation of gene expression on the single X in males as an evolutionary response to the degeneration of the Y chromosome (reviewed in Marin et al. 2000). If this upregulation encompasses the entire X chromosome, dosage compensation can substantially accelerate the speed of Muller’s ratchet.
THE MODEL

I assume a population of size $N$. Males are characterized by X and Y chromosomes, whilst females carry two X chromosomes. On each of the two sex chromosomes, I consider $k$ homologous loci with two possible alleles: the functional wildtype allele, and a deleterious, non-functional mutant allele. The focus of this study is on recessive lethal mutations, but other types of mutations will also be studied. The life-cycle of individuals in the population consists of the following three steps:

1. **Selection.** All loci contribute equally to fitness, and in a multiplicative way (i.e., there is no epistasis). A locus that is homozygous for a deleterious mutation contributes a factor $(1-s)$ to overall fitness, whilst heterozygous loci contribute a factor $(1-hs)$. $s (0 \leq s \leq 1)$ is referred to as selection coefficient and $h (0 \leq h \leq 1)$ as the dominance level. For the next generation, $N$ pairs of males and females are chosen randomly for reproduction, with a probability that is proportional to their fitness.

2. **Reproduction.** $N/2$ of these pairs are chosen to produce sons, and $N/2$ produce daughters. Fathers always pass on their sex chromosome without recombination (Y to sons and X to daughters). In mothers, free recombination is assumed to take place between the loci, i.e., the X chromosome passed on by a female is a random mixture of alleles from each of her two X chromosomes. Although this assumption is not realistic when there are many loci, it does not seem to affect the results (see below).

3. **Mutation.** Each wildtype allele can mutate to a non-functional allele, but no back mutations occur. Mutation rates, denoted by $\mu$, are the same across all loci and do not depend on the type of chromosome. However, mutation rates may be different in males and females, denoted by $\mu_m$ and $\mu_f$, respectively.
An increase in the minimum number of mutations on the Y chromosomes in the population is referred to as a ‘click’ of the ratchet. In order to compare the speed of the ratchet for different parameters, I either followed the advance of the ratchet over a period of time in which several clicks of the ratchet occurred, or I measured only the time until the first click of the ratchet (i.e., until all individuals in the population had at least one mutation on their Y chromosomes). In the former case, populations were initialised with mutation-free individuals. In the latter case, populations were initialised with an equilibrium distribution of mutations obtained as follows.

For the simulations where mutations occurred on both Y and X chromosomes, I constructed a simple deterministic single-locus model (see Appendix). In this model, the dynamics of the frequencies of the functional and non-functional allele on both X and Y chromosomes are determined under selection and mutational pressure. Equilibrium frequencies obtained numerically from this model were then used as parameters of a binomial distribution describing the size of subpopulations with different numbers of mutations. In each of these subpopulations and for both X and Y chromosomes, the respective number of deleterious mutations was then distributed randomly across individuals and loci. To further equilibrate the system, I performed simulation pre-runs of 500 generations. In the simulations where mutations occurred only on the Y chromosomes, the initial distribution is obtained in a more simple way. Here, the equilibrium distribution in a population of infinite size is expected to follow a Poisson distribution with mean $u/s$ (Kimura & Maruyama 1966), where $u = k\mu$ is the per genome mutation rate. As this approximation was close to the equilibrium distributions obtained in simulations and because times until ratchet clicks were often $<<500$ generations, I performed pre-runs of only 100 generations in this case.
RESULTS

Deceleration of the ratchet over time

Let us first assume that mutations occur only on the Y chromosome. This corresponds to an asexual population of size $N/2$, as has been studied before. The novel question that can be studied with my model is how a finite number of loci and possible alleles influences the speed of the ratchet. Specifically, I assume in my model that each mutation event leads to a non-functional allele, such that further mutations have no additional detrimental effect and are thus equivalent. Therefore, as the ratchet advances and mutations are fixed at an increasing number of loci, the target size for new mutations decreases. Since the speed of Muller’s ratchet depends crucially on the genomic mutation rate, the speed of the ratchet is expected to decline over time (Gerrard & Filatov 2005).

Simulation results confirming this reasoning are shown in Fig. 1. As the ratchet proceeds over time, the within-population distribution of the number of deleterious mutations on the Y chromosome shifts upwards, but does so in a decelerating pace (Fig. 1a). Fig. 1b shows how Muller’s ratchet itself also advances with decreasing speed. This plot also indicates that the average number of loci at which the deleterious mutation is fixed follows closely the clicks of the ratchet, as has been reported previously (D. Charlesworth et al. 1993; Charlesworth & Charlesworth 1997).

Several formulae approximating the speed of Muller’s ratchet have been derived (e.g., Gabriel et al. 1993; Charlesworth & Charlesworth 1997; Gordo & Charlesworth 2000a; Gordo & Charlesworth 2000b). To assess whether the approximation proposed by Gordo & Charlesworth (2000a,b) can satisfactorily describe the entire process of a ratchet with a finite number of loci, I make the following simple amendment. Let $T(u)$
be the estimated time until the first click of the ratchet, as given in Gordo & Charlesworth (2000a,b). Here, $u$ is the per genome mutation rate. $T(u)$ consists of three addends, estimating (1) the average time that the population spends in a state where the frequency of the least loaded class of Y chromosomes is below its equilibrium value, (2) the time spend above its equilibrium value, and (3) the time it takes from a click of the ratchet until the new least loaded class reaches a certain size.

In the beginning of the process, we have $u = k\mu$, such that the first click of the ratchet can be estimated by $T(k\mu)$. Assuming that fixation of a deleterious allele will quickly follow each loss of the least loaded class of Y chromosomes, the number of loci at which mutations may occur decreases linearly with each click of the ratchet. Thus, we get $T((k-i+1)\mu)$ as an approximation for the time it takes for the $i$th click of the ratchet. Figure 1c compares average times of clicks of the ratchet obtained by simulations with this approximation. For two of the parameter combinations tested, the speed of the ratchet is approximated reasonably well by the formula of Gordo & Charlesworth (2000a,b). However, for a third parameter combination (grey triangles in Fig. 1c), the approximation does not fit the simulation results, and in fact increases with each click of the ratchet (not shown). This failure of the formula to approximate the simulation results is likely to be explained by the assumption that the equilibrium number $n_0$ of least-loaded individuals is substantially larger than one, whereas it is less than one (0.23) for this parameter combination.

The decelerating rate of the ratchet is a general phenomenon that is also observed when mutations arise on both the X and the Y chromosomes (see, for example, Fig. 3). However, no analytical approximation for the time between clicks of the ratchet has
been derived for this case, so that quantification similar to that given above is not yet possible.

**The effect of mutations on the X chromosome: lethal recessive mutations**

Now assume that mutations occur on both Y and X chromosomes. This will result in occasional homozygote individuals and therefore, depending on the dominance level of the mutations, there may be stronger selection against non-functional alleles on the Y chromosome. Thus, increased times between clicks of the ratchet can be expected.

Let us first assume that mutations are lethal when homozygous (i.e., \( s = 1 \)) and partially recessive. The simulation results for this case shown in Table 1 indicate that the ratchet can indeed be slowed down considerably if mutations arise on the X chromosome at the same rate as on the Y chromosome. Specifically, the time until the first click of the ratchet is increased by at least one and up to more than three orders of magnitude for the parameter combinations tested.

Mutation rates can be higher in males than in females (denoted here by \( \mu_M \) and \( \mu_F \)). In mammals, for example, estimates range from two- to five-fold differences (e.g., Anagnostopoulos et al. 1999; Makova & Li 2002; Lawson & Hewitt 2002). Recently, an approximately twofold higher mutation rate in males than in females has also been reported in *Drosophila miranda* (Bachtrog 2008). These differences are generally thought to stem from the larger number of germ cell divisions in males vs. females. By contrast, to date no difference in mutation rates has been detected *Drosophila melanogaster* (Bauer & Aquadro 1997). Since the Y chromosome is always passed on through males, its effective mutation rate will equal that of males, \( \mu_M \). On the other hand, the X chromosome is passed on two thirds of the time by females and one third of the time by males, yielding an effective mutation rate of \( (2\mu_F + \mu_M)/3 \). Thus, if
mutation rates are higher in males than in females, the effective mutation rate on the X chromosome will be lower than that on the Y chromosome.

Comparing simulation results for the first click of the ratchet for constant $\mu_m$ but varying $\mu_f$ suggests that the ratchet becomes faster with decreasing $\mu_f$, sometimes substantially so (Table 1). This is because as $\mu_f$ decreases, fewer mutations will arise on the X chromosomes, which leads to relaxed selection against mutations on the Y chromosome. Although this was not simulated, the same effect is expected if the average mutation rate rather than $\mu_m$ is kept constant in comparing different mutation biases.

Figure 2 presents some of the simulation results on the time until the first click of the ratchet in relation to the genomic mutation rate $u$ (given by $k\mu_u$) and the strength of selection in relation to population size, $Nhs$. As expected, both decreasing $u$ and increasing $N$s tend to slow down the ratchet. Note, however, that $N$s does not correspond exactly to the corresponding value in haploid asexual models, because (1) $N$ is the total population size and not the number of Y chromosomes and (2) selection against homozygotes is not included in the term $Nhs$.

**The effect of mutations on the X chromosome: non-lethal mutations**

To investigate the ratchet with mutations other than recessive lethals, simulations were conducted with a wide range of dominance levels $h$ and selection coefficients $s$ (Figure 3). With constant fitness reduction $hs$ at heterozygous loci, the fitness reduction $s$ at loci homozygous for the deleterious mutation can be decisive for the speed of the ratchet (Figure 3a), as is the dominance level $h$ when $s$ is kept constant (Figure 3b). As is expected intuitively, stronger selection against both homozygotes and – to lesser extent
– individuals homozygous for deleterious mutations leads to lower rates of the ratchet.

These results are in accord with previous reports of the effect of the dominance level on the speed of the ratchet in sexual, diploid populations with non-recombining autosomes (Charlesworth & Charlesworth 1997).

Interestingly, with dominant mutations, the ratchet is faster when mutations occur on both X and Y chromosomes than when mutations occur on the Y chromosome only (Figure 3d). This is because the presence of deleterious mutations on the X chromosome relaxes selection against deleterious mutations on the Y chromosome, as the latter do not further reduce the fitness of males that already have mutations at the homologous loci on the X chromosome. Thus, it seems that the haploid model of Muller’s ratchet has no clear-cut analogous counterpart within the diploid sex chromosome model: for a given selection coefficient $hs$ against mutations in the heterozygous state or in the haploid model, dominance of the mutations increases the speed of the ratchet in the sex chromosome compared to the haploid model, whereas partial recessivness reduces the speed of the ratchet.

**Background selection**

Strongly deleterious mutations that are recurrently produced and eliminated by selection will reduce the effective size of non-recombining populations (B. Charlesworth et al. 1993). This effect, termed background selection, arises because other, weakly selected mutations (neutral, beneficial or slightly deleterious) can only spread in the population if they arise on a chromosome free of strongly deleterious mutations. Background selection has been proposed as a mechanism that by itself can lead to Y chromosome deterioration (Charlesworth 1996). Here, I study the extent to which this effect accelerates Muller’s ratchet.
To this end, a number $n$ of ‘background selection’ (BS) loci on the X and Y chromosome was incorporated into the model, in addition to the $k$ focal loci at which Muller’s ratchet is studied. Mutations at the BS loci are assumed to be lethal when homozygous and selected against in heterozygous individuals with dominance level $h_{BS}$. Mutation rates are assumed to be the same for all loci. Simulations were initialised with equilibrium distributions of mutations at BS loci, analogous to initialisation of mutations at the focal loci.

Figure 3 shows the results of simulations that compare the time until the first click of the ratchet (at the focal loci) for varying numbers of BS loci. As expected, the times until the first click become shorter with increasing number of BS loci. With the parameter combinations that I tested, the effect can be substantial, accelerating the ratchet by a factor of up to ten when there are twice as many BS loci as focal loci. Results of a similar order of magnitude have been reported in a previous theoretical study of the effect of background selection on the rate of Muller’s ratchet in an asexual haploid population (Gordo & Charlesworth 2001).

**Dosage compensation**

How will the evolution of dosage compensation affect the degeneration of the Y chromosome? If expression of a particular X-linked allele is upregulated only once the homologous non-functional mutant on the Y has become fixed, no effect on the speed of Muller’s ratchet is expected. On the other hand, upregulation of X-linked alleles may not proceed in a gene-by-gene fashion, but by upregulation of chromosome fragments containing many loci. In this case, a modifier allele that induces twofold upregulation of X-linked genes will be selected for if the fitness advantage due to compensatory upregulation of alleles without a functional copy on the Y chromosome is not
outweighed by deleterious overexpression of alleles that do have a functional Y-linked homologue. If the upregulating allele spreads in the population, selection against non-functional alleles on the Y chromosome is expected to become weaker.

To study this effect, I assume an additional, X-linked locus with a mutant allele that upregulates the X-linked alleles in males. For simplicity, I assume that the entire X chromosome is affected, that upregulation is exactly twofold and that it is strictly male-specific. Overexpression of a gene occurs when a functional X-linked copy is upregulated and when the homologous Y-linked copy is also functional; fitness is then assumed to be reduced by a factor \((1-c)\). Thus, males carrying the upregulating allele that have \(m\) non-functional alleles on the Y and \(j\) non-functional alleles on the X at different loci have a fitness of \((1-s)^j(1-c)^{k-j-m}\). Finally, I assume that the upregulating allele arises by mutation with rate \(\nu\) and that back mutations to the wildtype allele occur at the same rate.

Several series of simulations demonstrate that Muller’s ratchet is indeed accelerated through the spread of the upregulating allele (Figure 5). With decreasing \(c\) (i.e., decreasing fitness cost of overexpression of alleles), invasion of the upregulating allele becomes more rapid and, correspondingly, the acceleration of the ratchet commences earlier. However, the overall effect of varying \(c\) on the speed of the ratchet is rather the reverse: higher values of \(c\) lead to delayed, but more substantially increased speed of the ratchet, resulting in earlier degeneration of the entire Y. This is because once the upregulating allele has become fixed, selection against non-functional alleles on the Y chromosome will be reduced. The larger \(c\) becomes, the weaker selection against Y-linked mutant becomes, and in fact – depending on the mutational load on the X
chromosome – selection may even favour non-functional alleles on the Y if $c$ is sufficiently large.

**The impact of recombination**

In the previous sections, I have assumed free recombination between all loci in females. This assumption is particularly strong when many loci are considered, in which case recombination rates between adjacent loci may be substantially lower than 1/2. To investigate how relevant the recombination rate between X chromosomes is for the speed of Muller’s ratchet, I conducted simulations of all versions of the model (different types of mutations, background selection, dosage compensation) in which only a single crossover event at a randomly chosen position takes place in females. In none of these simulations was a substantial difference in the speed of the ratchet between the two recombination scenarios observed (see Figure 6 for some of the results). Given that a single crossing-over event is likely to represent the lower limit of recombination rates, these results suggest that employing realistic recombination rates rather than free recombination will not have a significant influence on the speed of the ratchet.
DISCUSSION

Most previous models have considered mildly deleterious mutations in haploid asexual populations (e.g., Haigh 1978; Gabriel et al. 1993; Gordo & Charlesworth 2000b, but see also Charlesworth & Charlesworth 1997). In the context of Y chromosome evolution, this is equivalent to the somewhat artificial situation where no mutations occur on the X chromosome. The results reported here suggest that if mutations occur at homologous loci on both X and Y chromosomes, haploid models of Muller’s ratchet are inappropriate in predicting the speed of the ratchet. In particular, the presence of mutations on the X chromosomes can both increase (with recessive mutations) and decrease (with dominant mutations) the speed of the ratchet compared to the haploid scenario. In the case of partially recessive lethal mutations, the reduction in the speed of the ratchet through mutations on the X chromosome can be substantial, ranging up to more than three orders of magnitude.

Previous theoretical studies have cast doubt on the importance of Muller’s ratchet as a general mechanism to explain the erosion of Y chromosomes. This is because with selection coefficients in heterozygotes of about 1-2%, as have been demonstrated to be common in mutation-accumulation experiments in Drosophila (Powell 1997; Charlesworth et al. 2004), rather small population sizes are needed in order to make Muller’s ratchet work within reasonable time frames. This has led to the contention (e.g., Charlesworth 1996) that if Muller’s ratchet is important at all, it will be most relevant for species like mammals with effective population sizes in the order of $10^4$ to $10^5$ (e.g., Nachman 1998). Other studies in Drosophila, however, yielded much lower estimates ($10^{-4}$ to $10^{-3}$) of heterozygous selection coefficients (Langley et al. 1981;
Loewe et al. 2006), for which the conditions for Muller’s ratchet to work will be less restrictive.

The simulation results presented here for the case of partially recessive lethal mutations confirm the notion that Muller’s ratchet is unlikely to be important for Y chromosome degeneration in Drosophila. Throughout, small selection coefficients against heterozygotes \((h_s \leq 1\%)\), small population sizes \((N \leq 10,000)\) and high mutation rates \((\geq 5 \times 10^{-5} \text{ per locus})\) had to be employed in order to make the process computationally tractable; population sizes that appear realistic for \(Drosophila\) \((N=10^6)\) would lead to astronomical times between clicks of the ratchet (see also Charlesworth 1996).

Empirical evidence against a prominent role of Muller’s ratchet in \(Drosophila\) comes from the neo-Y chromosome of \(Drosophila miranda\), which arose only about one million years ago by fusion of an autosome to the ancestral Y chromosome (Bachtrog 2003). Patterns of molecular variation on this neo-Y indicate that positive selection models (i.e., hitchhiking effects) rather than negative selection models (Muller’s ratchet or background selection) are responsible for the Y degeneration observed in \(D. miranda\) (Bachtrog 2004).

In addition to the requirement of small populations, the simulation results reported here suggest that the mutational bias observed in mammals (Anagnostopoulos et al. 1999; Makova & Li 2002; Lawson & Hewitt 2002) might be another reason for why Muller’s ratchet might have been particularly important to mammalian Y chromosomes. When mutation rates are lower in females than in males, fewer mutations accumulate on the X chromosomes, which in turn leads to reduced selection against deleterious alleles on the Y chromosome. Mutational bias has also been reported in \(Drosophila miranda\) (Bachtrog 2008), but not in other \(D. melanogaster\) (Bauer & Aquadro 1997). Finally, as
has been suggested earlier (Gerrard & Filatov 2005), my results indicate that Muller’s ratchet is most important during early stages of Y deterioration because the process becomes very slow once only few genes are retained on the Y chromosome.

Differential expression of X-linked genes in the two sexes is generally believed to be an adaptive compensation for the loss of Y-linked genes in males, such that total expression in males and females is equalised (Charlesworth 1996; Marin et al. 2000). For example, in *Drosophila melanogaster* this is achieved by twofold upregulation of the single X in males (reviewed in Baker *et al.* 1994). Whilst dosage compensation is an evolutionary result of Y degeneration, its evolution may also influence the degeneration of Y chromosomes if it evolves on a block-by-block basis (Charlesworth 1996; Orr & Kim 1998). In my model, assuming a global upregulation of the entire X chromosomes in males, dosage compensation was found to substantially accelerate the speed of Muller’s ratchet. This is because once upregulation of the single X in males has evolved, selection against non-functional alleles on the Y chromosome will become weaker and may even become positive if overexpression of genes (three instead of two units) is deleterious. Dosage compensation that evolves more localised on a gene-by-gene scale may also accelerate Muller’s ratchet if more than one deleterious allele per locus is considered. In this case, fixation of a deleterious mutation on the Y may lead to upregulation of the X-linked homologous allele, which in turn through overexpression may facilitate fixation of an even more deleterious allele at that locus.

In mammals, there is also evidence that gene expression on the single X chromosome in males is upregulated relative to autosomal gene expression (Nguyen & Disteche 2006). However, the situation is more complicated here because in most mammals, one of the two X chromosomes in females is inactivated early in embryogenesis (Lyon 1961; reviewed in Chow *et al.* 2005). The evolution of X chromosome inactivation is usually
explained by a two-step process involving sexual antagonistic selection on X chromosome expression levels (Charlesworth 1996; Engelstädter & Haig 2008; but see also Haig 2006 for an alternative hypothesis). According to this view, expression is initially upregulated in both males and females (leading to deleterious overexpression in females). In a second evolutionary step one X chromosome is then inactivated in females, restoring optimal gene expression.

When upregulation affects not only the X chromosome in males (as assumed in my model), but also to some extent the X chromosomes in females, the upregulating allele may be subject to positive selection in males, but negative selection in females (Engelstädter & Haig 2008). Therefore, spread of the upregulating allele may be impeded or even prevented, and the accelerating effect on Muller’s ratchet is expected to be weaker. On the other hand, if X chromosome inactivation evolves, this will expose all recessive X-linked alleles to selection. As a result, purging of deleterious recessive alleles on the X chromosome will become more efficient, which may accelerate the ratchet on the Y chromosome. These intricate mutual influences of Y chromosome degeneration, the evolution dosage compensation and the evolution of X chromosome inactivation remain to be explored.

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APPENDIX: EQUILIBRIUM ALLELE FREQUENCY ON X AND Y CHROMOSOMES

To generate starting allele frequencies, I used the following deterministic model describing the dynamics of allele frequencies on X and Y chromosomes under mutation and selection at a single locus. I assume a randomly mating population of infinite size. Mutations are assumed to be lethal when homozygous (s=1). Let \( p, q \) and \( r \) denote the frequencies of the mutant allele among X chromosomes in eggs, X chromosomes in sperm and Y chromosomes in sperm, respectively. As in the main model, the lifecycle consists of the steps selection, reproduction (without any change in allele frequencies), and mutation. The recursion equations are then given by

\[
p' = \mu_F + (1 - \mu_F) \frac{(p + q - 2pq)(1 - h)}{2 - 2pq - 2h(p + q - 2pq)}, \tag{A1a}
\]

\[
q' = \mu_M + (1 - \mu_M) \frac{p(1 - r)(1 - h)}{1 - pr - h(p + r - 2pr)}, \tag{A1b}
\]

\[
r' = \mu_M + (1 - \mu_M) \frac{r(1 - p)(1 - h)}{1 - pr - h(p + r - 2pr)}. \tag{A1c}
\]

Since I was not able to derive the equilibrium of this system analytically, the equilibrium distributions were determined numerically. For \( \mu_F = \mu_M \), equilibrium frequencies of the mutant allele are always the same on X and Y chromosomes. For \( \mu_F < \mu_M \), equilibrium frequencies can be substantially higher on the Y than on the X chromosome.
Table 1. Times until the first click of Muller’s ratchet with $s=1$.

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<th>Parameters</th>
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Table 1: For different parameter combinations, average times until the first click of the ratchet and standard deviations (SD) are shown. Throughout, mutations are assumed to be lethal in the homozygous state ($s=1$). Each average time is based on 100 simulations. Mutations occurred on either the Y chromosome only, or on both X and Y chromosomes. In the latter case, three mutation rates in females relative to males have been tested. In one case (indicated by a question mark), no simulation results could be obtained.

Figure 1: Deceleration of the Muller’s ratchet over time. The plots show the averaged results of 100 simulations where mutations occurred on the Y chromosome only. Simulations were initiated with the equilibrium distribution of mutations on the Y and then run for 50,000 generations. (a) Distribution of the number of mutations on Y chromosomes (darker colours denotes higher frequencies of individuals carrying the respective number of mutations). Parameters: $N=10,000$ (i.e., $N/2=5000$ Y chromosomes), $k=50$, $\mu=0.0001$, $hs=0.001$. (b) Advance of Muller’s ratchet. The bold line shows the average number of ratchet clicks over time, with ±1 SD indicated by the grey area. The dotted line gives the number of loci where fixation of the mutant allele has occurred. The plot is based on the same results as in (a). (c) Speed of the ratchet. Symbols show average numbers of generations for each click of the ratchet, with parameters $N=10,000$, $\mu=0.0001$ and $k=50$, $s=0.001$ (black squares), $k=100$, $s=0.001$ (grey triangles) or $k=100$, $s=0.002$ (empty circles). The two lines show approximations for the duration between subsequent clicks based on Eq. (1), with parameters as for the respective simulation results. The line for the third, non-fitting approximation is not shown (see text).
Figure 2: Graphical representation of the times until the first click of the ratchet for \( \mu_F = \mu_M / 2 \), based on the results in Table 1. Each circle represents a set of simulations. The position of the circles indicates the parameters used, where \( Ns \) is the population size times the selection coefficient against heterozygotes and \( u = k \mu_M \) is the genomic mutation rate in males. The colour of each circles illustrates the average time \( T \) until the first click of the ratchet as follows, ranging from \( T < 10^{2.75} \) (white circles) to \( T > 10^{3.75} \) (black circles). In-between this range, four shades of grey correspond to logarithmically scaled \( T \) intervals of length 0.25.

Figure 3: The advance of Muller’s ratchet with different types of mutations. (a) Constant selection coefficient of \( h_s = 0.001 \) in heterozygotes, with varying selection coefficient \( s \) in homozygous individuals. (b) Constant selection coefficient \( s = 0.01 \) in homozygotes, varying dominance level \( h \). (c) Semidominant mutations \( (h = 0.5) \) with varying \( s \). (d) Dominant mutations with varying \( s \). Also shown in plot (d), with dotted lines, is the advance of the ratchet when mutations occur only on the Y chromosome. The selection coefficient for each of the dotted lines is the same as that for the respective solid curve above. In each plot, the curves represent averages of 100 simulations that where initiated with mutation-free individuals. Other parameters take the values \( N = 5000, k = 50 \) and \( \mu = 10^{-4} \).

Figure 4: The effect of background selection on the speed of Muller’s ratchet. Shown are times until the first click of the ratchet for varying numbers of BS loci. Each value is based on 1000 (empty squares, grey triangles) or 2000 (black circles) simulations. Other parameters take the values \( \mu_M = 0.00005, N = 5000, h = 0.001, h_{BS} = 0.005 \) (black circles), \( \mu_M = 0.0002, N = 2000, h = 0.005, h_{BS} = 0.05 \) (empty squares) and \( \mu_M = 0.0005, N = 2000, h = 0.01, h_{BS} = 0.05 \) (grey triangles); in all simulations, \( s = 1, k = 50 \) and \( \mu_f = \mu_M / 2 \).
Figure 5: The impact of dosage compensation on Muller’s ratchet. The plots show how
the ratchet proceeds over time, averaged over 100 simulations. The bold lines give the
average ratchet click, and the grey areas denote the ±1 SD deviation. The dotted lines
give the average frequency of the upregulating allele in the population. All simulations
were initiated with mutation-free populations. Parameters take the values $N=2000$,
$k=50$, $s=1$, $h=0.005$, $\mu_f=0.001$, $\mu_M=0.002$, $\nu=0.0001$, and (a) $c=0.005$, (b) $c=0.0025$, (c)
$c=0.001$. Plot (d) provides a comparison to the case without the evolution of dosage
compensation.

Figure 6: Influence of recombination between the X chromosomes in females on the
speed of the ratchet. For three different scenarios, the advance of the ratchet is shown
with free recombination between all loci (solid lines) and with a single crossing-over
event in females (dotted lines). (a): Partially recessive, lethal mutations; $N=2000$, $s=1$,
h=0.005, $\mu_M=0.002$, $\mu_F=0.001$; (b): Dominant mutation; $N=5000$, $s=0.0005$, $h=1$,
$\mu_M=\mu_F=0.0001$; (c) With evolution of dosage compensation; $c=0.005$, other parameters
as in (a). In all three scenarios, $k=50$. Simulations were initiated with mutation-free
individuals.
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5
Figure 6