



Commentary

Haigh (1978) and Muller's ratchet

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In the absence of recombination, offspring inherit all the deleterious mutations their parents possess. Since these offspring also occasionally acquire new deleterious mutations, populations will tend to accumulate deleterious mutations over time. This effect is known as Muller's ratchet (Muller, 1964), because each loss of the currently most-fit class of individuals represents an irreversible "click" of a ratchet towards lower fitness. The speed of Muller's ratchet depends on population genetic details, but it should in principle apply both haploid and diploid populations. This seems at first to pose a paradox: how can any genetic information be maintained in the face of this inexorable decay? There are several possible answers, including the potential for recombination to create children with less deleterious load than either parent, or the balancing effect of beneficial reversions or compensatory mutations. Yet despite these "solutions", Muller's ratchet will remain a burden to any population, and in the long term we might expect populations to exist at an equilibrium between the effects of a ratchet and the countervailing forces of recombination and beneficial mutations.

In his 1978 paper, Haigh introduced a theoretical framework which has laid the groundwork for decades of subsequent work analyzing the effects of Muller's ratchet (Haigh, 1978). Haigh set out to investigate the rate at which deleterious mutations accumulate in a standard Wright–Fisher model of a nonrecombining locus. His work made use of several key ideas. First, he recognized that the balance between new deleterious mutations and selection against these mutations would lead to a distribution of fitness within the population, and focused on analyzing this fitness distribution. After computing its deterministic shape, he considered how genetic drift leads to temporal fluctuations in the fitness distribution by thinking about the stochastic dynamics of the most-fit class, and about how this stochasticity then propagates to the rest of the distribution. He recognized the key distinction, set by the expected deterministic size of the mutation-free class, between a "slow-ratchet" regime where "clicks" are relatively rare (and the fitness distribution remains

approximately in its deterministic shape), and a "fast-ratchet" regime where "clicks" are common (and the fitness distribution is narrower than the deterministic prediction). This eventually led him to estimates for the rate of the ratchet, and then to investigate the potential impact of beneficial back-mutations.

The basic approach that Haigh introduced has influenced many further investigations of the ratchet and related topics in the study of natural selection. One line of work used this framework to refine estimates of the rate of the ratchet and the shape of the fitness distribution (Gordo and Charlesworth, 2000; Stephan and Kim, 2002; Etheridge et al., 2009) and to investigate the distinctions between fast and slow ratchet regimes (Gessler, 1995). My own research has been heavily influenced by thinking about these effects, which are also at the heart of "traveling-wave" frameworks that my lab and others used to study the opposite phenomenon: the rate at which beneficial mutations accumulate in rapidly adapting populations (Desai and Fisher, 2007; Hallatschek, 2011; Fisher, 2013). More recently, these traveling-wave models have been extended to analyze more general situations involving beneficial mutations, deleterious mutations, and recombination (Neher and Shraiman, 2011; Goyal et al., 2012; Good and Desai, 2014; Weissman and Hallatschek, 2014). These interactions can result in adaptation, Muller's ratchet, or a complex balance between them.

In recent years, technological advances which have made it possible to directly observe the fitness distribution (and effects of the ratchet) in laboratory evolution experiments have driven continued interest in many of the questions originally considered by Haigh. One critical question is in understanding the structure of temporal fluctuations in fitness distributions — how does genetic drift "propagate" across this distribution over time, and what effects does this propagation have on genetic diversity or rates of adaptation or the ratchet? Some recent work has addressed this issue (Neher and Shraiman, 2012; Fisher, 2013; Hallatschek and Geyrhofer, 2016), but more analysis is needed to understand how these fluctuations affect the repeatability and predictability of evolution. Further work will also have to grapple with effects of epistasis. If for example the fitness effects of beneficial or deleterious mutations tend to change as a population

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adapts or declines in fitness, this could shift the balance between adaptation and the ratchet over evolutionary time. After all, if the ratchet leads to inexorable decline in fitness, we might ask how a population would become well-adapted enough for the ratchet to ever operate in the first place. The answer may be that as populations move in the fitness landscape (and as they change in size), the balance between the ratchet and the forces that counteract it continually shift, leading to a continued dynamic battle that determines how well-adapted a population can be.

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