Genet. Res., Camb. (2007), **89**, *pp.* 7–18. © 2007 Cambridge University Press
doi:10.1017/S0016672307008658 Printed in the United Kingdom

Small-world networks decrease the speed of Muller's ratchet

JAIME COMBADÃO[1], PAULO R. A. CAMPOS[2], FRANCISCO DIONISIO[1,3] AND ISABEL GORDO[1]*
[1] *Instituto Gulbenkian de Ciência, 2781-901 Oeiras, Portugal*
[2] *Departamento de Física e Matemática, Universidade Federal Rural de Pernambuco, 52171-900, Dois Irmãos, Recife-PE, Brazil*
[3] *Departamento de Biologia Vegetal, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Ed.C2, 1749-016, Lisbon, Portugal*

(*Received 6 June 2006 and in revised form 29 November 2006 and 30 January 2007*)

Summary

Muller's ratchet is an evolutionary process that has been implicated in the extinction of asexual species, the evolution of non-recombining genomes, such as the mitochondria, the degeneration of the Y chromosome, and the evolution of sex and recombination. Here we study the speed of Muller's ratchet in a spatially structured population which is subdivided into many small populations (demes) connected by migration, and distributed on a graph. We studied different types of networks: regular networks (similar to the *stepping-stone* model), *small-world* networks and completely random graphs. We show that at the onset of the *small-world* network – which is characterized by high local connectivity among the demes but low average path length – the speed of the ratchet starts to decrease dramatically. This result is independent of the number of demes considered, but is more pronounced the larger the network and the stronger the deleterious effect of mutations. Furthermore, although the ratchet slows down with increasing migration between demes, the observed decrease in speed is smaller in the *stepping-stone* model than in *small-world* networks. As migration rate increases, the structured populations approach, but never reach, the result in the corresponding panmictic population with the same number of individuals. Since *small-world* networks have been shown to describe well the real contact networks among people, we discuss our results in the light of the evolution of microbes and disease epidemics.

1. Introduction

The accumulation of deleterious mutations in the absence of recombination due to genetic drift is known as Muller's ratchet (Felsenstein, 1974). This process was first proposed by Muller (1964) as a major mechanism distinguishing the evolutionary fate of asexual populations from that of sexual populations. Muller's ratchet has since been one of the theories invoked to explain the evolution of sex (Barton & Charlesworth, 1998). It has also been suggested to play a major role in the evolution of sex chromosomes (Charlesworth, 1978; Gordo & Charlesworth, 2001) and mitochondrial genomes (Loewe, 2006; Lynch, 1996), and the extinction of small asexual populations (Lynch *et al.*, 1993). Briefly the process works as follows: because the vast majority of newly arising mutations are deleterious, natural populations are continuously subjected to the mutation pressure to new deleterious alleles and their elimination by natural selection. This creates a standing level of diversity for fitness in populations, which is known as mutation–selection balance. But in small populations, the role of genetic drift can become significant, in addition to mutation and selection. In such cases the class of individuals that is free from deleterious mutations may be lost, especially if it is small. This is likely to occur when either the population size is small and/or the mutational input is high and/or the effects of mutations are small (Gessler, 1995; Gordo & Charlesworth, 2000*b*; Loewe, 2006). If the population lacks recombination, that class can only be recovered through the rare event of a back-mutation. The irreversible loss of the best class constitutes a click of the ratchet (Haigh, 1978). Successive clicks result in

* Corresponding author. e-mail: igordo@igc.gulbenkian.pt

the continuous decline in mean fitness of the population and can even lead to its extinction. The decline in fitness as a consequence of the ratchet as well as its signature at the molecular level (Gordo *et al*., 2002) have been subject to several tests against empirical data (Bachtrog & Charlesworth, 2002; Chao, 1990; Filatov *et al*., 2000; Liu *et al*., 2004; Rice, 1994).

The accumulation of slightly deleterious mutations is also important in conservation biology. It has been shown to be important in diminishing the long-term viability of natural populations with small effective population sizes (see for example Lande (1995) for a review). Muller's ratchet has also been thought to play a role in the evolution of asexual RNA viruses (Moya *et al*., 2004), which have high mutation rates.

Most population genetic models for studying the accumulation of deleterious mutations through the ratchet have assumed that populations are homogeneous and that every individual competes with every other individual in the whole population (Butcher, 1995; Charlesworth & Charlesworth, 1997; Fontanari *et al*., 2003; Gordo & Charlesworth, 2000*b*; Kondrashov, 1994; Rouzine *et al*., 2003; Stephan *et al*., 1993). However the vast majority of species are to some extent structured into populations where individuals compete with other individuals locally. In particular, microbial populations are naturally structured and this has gained increasing recognition in the context of epidemiology (see for example Keeling & Eames, 2005).

It is therefore important to understand how population structure influences evolutionary mechanisms such as Muller's ratchet. Recently a few studies have addressed the problem of accumulation of deleterious mutations in subdivided populations (Bergstrom *et al*., 1999; Gabriel & Burger, 2000; Gordo & Campos, 2006; Higgins & Lynch, 2001; Salathe *et al*., 2006). For example Higgins & Lynch (2001) have shown that the risk of extinction due to the accumulation of mildly deleterious alleles can be increased in species that have a metapopulation structure. More recently, Salathe *et al*. (2006) studied the maintenance of sexual reproduction by elimination of deleterious mutations in a spatially structured population and proposed that spatial structure can help maintaining sexual reproduction. It is also known that the rate of fixation of beneficial mutations is lower in a spatially structured population when the mutation rate to beneficial alleles is high (Gordo & Campos, 2006).

Here we study how population structure influences the speed of Muller's ratchet in asexual organisms. The speed of the ratchet is the inverse of the mean time between its successive clicks, and it is proportional to the decline in mean population fitness.

The influence of population structure on the dynamics of mutations and the role of migration in patterns of neutral variability has been established for some models of population structure (Maruyama, 1970, 1974; Nagylaki, 1980, 1982; Slatkin, 1981; Wright, 1931). The first model of population subdivision, the *island* model, was introduced by Sewall Wright (1931) and has been used since then as a reference. In Wright's *island* model, the species are subdivided into several subpopulations, called demes, within which there is random mating. Migrants are exchanged between the demes and it is assumed that they come, with equal probability, from any other deme. The model is very simple and, to some extent, allows one to equate the influence of structure in evolutionary change. For example, Maruyama (1970) has shown that, under certain types of population structure (such as the *island* model), the probability of fixation of adaptive mutations is the same as in an undivided population. Nevertheless, the result that the fixation rate of adaptive mutations is independent of population structure is not valid for all types of structures. For instance, in a somewhat more realistic model, where extinction and recolonization are allowed to occur, that result is no longer valid (see Barton, 1993; Roze & Rousset, 2003; Whitlock, 2003). Another characteristic of real biological species is that there is some isolation by distance. Even though in the *island* model each deme is isolated, all islands are equally distant from each other. Kimura (1953) considered a very simple model of spatial isolation, in which demes are arrayed in a chain and migrants are exchanged only between demes that are situated close by in the population. This is known as the *stepping-stone* model of population subdivision.

Real populations will, most likely, follow neither a simple *stepping-stone* model nor an *island* model. Most natural populations, and in particular those of microbes that cause infectious diseases, will have a structure in between the *stepping-stone* and the *island* (Keeling & Eames, 2005). Here we analyse a slightly different model of spatial structure from the one first proposed by Wright. We assume a structured population subdivided into small demes, which exchange migrants. In addition, we also consider that the network of demes that comprises the whole population is a network of interactions that can exhibit a *small-world* character. In the model considered in this work each node of the network corresponds to a deme. Following the procedure introduced by Watts & Strogatz (1998), from a one-dimensional ordered lattice, which is similar to the *stepping-stone* model, we build up the *small-world* network structure by rewiring each link between the nodes with probability *p*. *Small-world* networks interpolate between a regular network and random graphs.

Regular networks and random graphs have been considered as models to describe the topology of most systems for a long time. Regular networks have been used as a paradigm for ordered topologies with both a

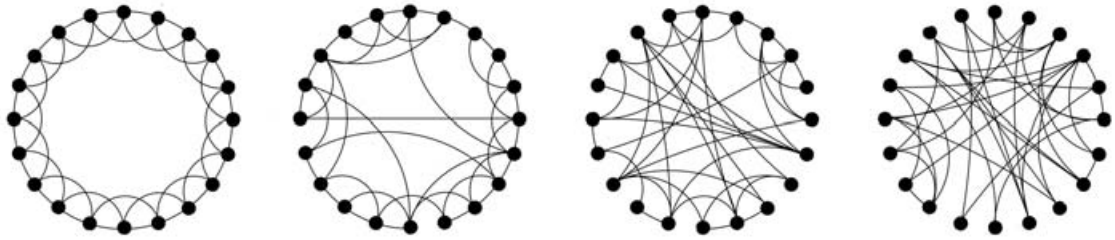

Fig. 1. Diagram showing the topological structure of the population. Each deme (node) has a fixed number of individuals (N_d) and is connected to other demes (represented by lines connecting nodes). Migrants are exchanged between linked demes and the mean number of migrants leaving each deme equals the mean number of migrants entering it. In the leftmost part a regular network is shown ($p=0$), which is similar to the classical *stepping-stone* model of population structure. Then from left to right the rewiring probability increases ($p=0{\cdot}25$, $p=0{\cdot}5$ and, in the rightmost part, $p=1$).

large clustering degree and a large characteristic path length. The clustering degree is defined as the probability that two nodes are connected, given that they share a nearest neighbour. The characteristic path length is defined as the average minimal distance between all pairs of vertices in the network. Unlike regular networks, completely random graph networks present a low clustering coefficient together with a small characteristic path length. Recent studies of the structural properties of networks obtained from distinct systems, which range from biological to social systems, show that regular lattices and completely random graphs do not capture their topological properties (for a review see Albert & Barabasi, 2002). The properties of the networks of these natural systems are between those of an ordered lattice and a completely random graph.

Some models have been proposed to better describe these systems. *Small-world* networks are amongst the most successful (Albert & Barabasi, 2002; Watts & Strogatz, 1998). These networks display a small average path length, like completely random graphs, together with a large clustering coefficient, like regular lattices.

Recent investigations have found these *small-world* properties in many different natural networks such as mammalian cerebral cortical networks, protein–protein interaction networks and metabolic networks (Albert & Barabasi, 2002). The study of *small-world* networks is also of great relevance in studying the effects of the interplay between the underlying disordered network and the dynamics of several systems such as physical systems (Barrat & Weigt, 2000), spread of infectious diseases and epidemics (Kuperman & Abramson, 2001) and social interactions (Klemm *et al*., 2003). In ecology, *small-world* networks are known to describe food webs and some natural structural populations, such as the ones composed of plants and their pollinators (see Lazaro *et al*., 2005; Lundgren & Olesen, 2005; Olesen *et al*., 2006, and references therein).

In the current work, we investigate how population structure, modelled according to regular, *small-world* and totally random topologies, affects the speed of Muller's ratchet in an asexual population. In the context of a network, we study the influence of the rewiring probability, which changes the relative connectivity and average path length between demes, on the speed of the ratchet on the whole population. We also study how random extinction of a deme can influence the accumulation of deleterious mutations in the whole population.

2. Materials and methods

We consider the evolution of spatially structured populations of asexual haploid organisms. We assume non-overlapping generations and the following life cycle: migration, reproduction, mutation and selection. The population is subdivided into D demes, each composed of N_d individuals. Thus, the population has $N_t=DN_d$ individuals. In order to model population structure we follow the model proposed by Watts & Strogatz (1998). We begin from an ordered one-dimensional lattice with D nodes, where each of the nodes is connected to its immediate four neighbours ($k=4$) (Fig. 1), as in the initial Watts & Strogatz (1998) algorithm. In our model, each node corresponds to a single deme. We then rewire each edge of the network, with probability p, excluding self connections and duplicates. The aforementioned procedure will connect nodes that were unconnected and disconnect others, putting in contact nodes that were initially distant from each other. Thus demes can be connected to a varying number of other demes. In this way we produce new neighbourhoods and new local structures. We do not allow for any deme to be completely isolated from the network or networks with more than one component. This is done by choosing a deme and checking whether all the other demes in the network are reachable. If this is not the case another network is constructed.

There are two important limiting cases in these types of networks: regular networks and completely random networks. The case $p=0$ corresponds to regular networks, in which the average distance

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

between pairs of nodes increases linearly with system size (i.e. the number of nodes in the network). Regular networks have also a high clustering coefficient. The case $p=1$ corresponds to random graphs, in which the average path length increases with the logarithm of the system size and the clustering coefficient is very low. Increasing the probability of long-distance connections, p, introduces long-range links in the network. This leads to a decrease in the average path length, which becomes of the order of that for a random network, while the clustering degree remains almost unchanged. These networks which interpolate between an ordered lattice and a random network are named *small-world* networks.

We have studied all the range of values of the rewiring probability from $p=0$ to $p=1$. Each edge of the network connects two demes that exchange migrants with probability m per individual. We have assumed bidirectional migration, where the average number of emigrants and immigrants per link is the same. In order to simulate migration the number of migrants in each deme is taken by sampling from a Poisson distribution with mean $N_d m K_i$, where K_i is the connectivity of the deme. The individuals that migrate are sampled at random, without replacement, from the original deme and added to the recipient demes. After all migration events have occurred the size of each deme can be different from N_d. Then mutation and selection occur in each deme and after these processes all demes have their sizes restored to N_d. During the mutation–selection process each individual is chosen randomly, with replacement, to give rise to new offspring. The offspring of a given individual can acquire a given amount of new deleterious mutations, which is taken from a Poisson distribution of mean U. To make the model simple, every mutation is assumed to cause the same decrease in fitness, s, and a multiplicative fitness assumption is made, i.e. the fitness of an offspring with i deleterious mutations is $(1-s)^i$. Offspring survive and become part of the next generation with probability proportional to their fitness.

Because in natural populations there is a chance that some of the demes can go extinct, we also studied the effect of extinction in our network model. This was implemented as follows. Extinction was modelled by assuming that at each generation each deme can go extinct with probability e. The extinction procedure takes place before migration events. If a deme goes extinct then it can be recolonized in the next generation by new individuals that migrate from demes that are connected to the deme in question. All the simulations start with individuals that are free of deleterious mutations. Measurements are then performed after the population has evolved for an initial equilibration period of $5/s$ generations (Johnson, 1999). Every generation, after this initial period, we count

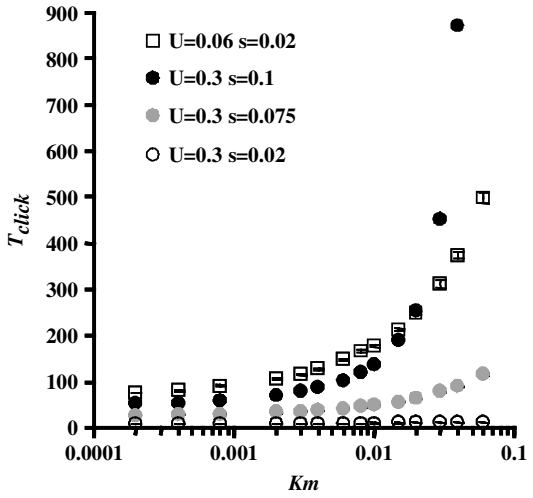

Fig. 2. The mean time between clicks of Muller's ratchet, T_{click}, in a regular network. On the x-axis we plot the value of Km, where $K=4$ in this network. The mutation rate and fitness effect of each deleterious mutation are given on the figure. The population is composed of 60 demes, each with 100 individuals and error bars correspond to 2 SE, in all parts of the figure.

the number of individuals that have the lowest number of deleterious mutations, for each deme and for the whole population. If this least-loaded class is lost in the whole population, a click of the ratchet is recorded. If more than one class is lost in the same generation, the corresponding number of clicks is counted. Therefore the number of clicks corresponds to the number of least-loaded classes lost. For each set of parameters 100 simulations were run and in each simulation run at least 30 clicks occurred.

3. Results

(i) *Muller's ratchet in the* stepping-stone *model*

The rate of Muller's ratchet is defined as the inverse of the mean time between its clicks. We have studied this time in a population that is composed of many demes arranged in a network.

We start by studying the ratchet in a regular network which is similar to the classical *stepping-stone* model of population structure (Kimura, 1953), but slightly modified. In our regular network, each deme connects to 4 neighbours instead of 2 (one-dimensional *stepping-stone* model). Under this model we wish to access the effect of migration in the speed of the ratchet. In Fig. 2 we show how migration increases the mean time between clicks of the ratchet (T_{click}) in a regular lattice with 60 demes each with 100 individuals. When there is no migration, demes are independent and, as expected, the rate of the ratchet is simply the same as in an isolated population of 100 individuals. For example for the case of $U=0{\cdot}3$ and $s=0{\cdot}1$ $T_{click}(m=0)=49$. This result remains

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

essentially unchanged for very low values of the migration rate. But when the migration rate achieves an intermediate value, T_{click} starts to increase rapidly with m. The value of the migration rate at which this happens is approximately given by the condition $n_{0d}Km \sim 1/T_{click}(m=0)$, where K is the number of neighbour demes and n_{0d} is the mean number of individuals in the least loaded class in a deme. The observed value of n_{0d} is very close to $N_d \exp(-U/s)$ for parameter sets where $N_d \exp(-U/s) > 1$ (as it is in the case of $U=0{\cdot}3$ and $s=0{\cdot}1$) (Gessler, 1995; Gordo & Charlesworth, 2000*b*; Gordo & Charlesworth, 2001; Loewe, 2006; Stephan & Kim, 2002). The condition $n_{0d}Km \sim 1/T_{click}(m=0)$ reflects the fact that, when the rate at which 'good migrants' are exchanged between demes equals the rate at which they are lost within demes, then increasing migration slows down the ratchet. This means that, for the case $U=0{\cdot}3$ and $s=0{\cdot}1$ in Fig. 2, when $Km>0{\cdot}001$, the speed of the ratchet starts to get closer to the one expected in a undivided population with $N_t=N_dD=6000$ individuals. For such a panmictic population and with these parameters of mutation and selection, the ratchet does not click (we have run 20 simulations for a panmictic population and did not observe any click of the ratchet during 100 000 generations). For our structured population, when $Km=0{\cdot}4$, $U=0{\cdot}3$ and $s=0{\cdot}1$, we also did not observe any click of the ratchet, in 20 simulations each with 100 000 generations. With a slightly smaller value of the selection coefficient ($s=0{\cdot}075$) we observe that the value of m above which the ratchet starts to slow down significantly (relative to the case $m=0$) increases. For this value of s the mean time between clicks of the ratchet in an undivided population is 12 944 ($\pm$834). Although increasing migration does slow the ratchet down, its speed is always higher in the structured population, for all values of m tested. For example with $Km=0{\cdot}5$, $U=0{\cdot}3$ and $s=0{\cdot}075$ the ratchet is around 12 times faster in the structured population than in the undivided population. When the value of the selection coefficient decreases to $s=0{\cdot}02$, with $U=0{\cdot}3$, then the speed of the ratchet is almost invariant over all the range of migration considered. For this set of parameter values the time between clicks of the ratchet in the undivided population is 16·2 (+0·4), whereas in a structured population with $Km=0{\cdot}01$ it is 10·0 (+0·9) and with $Km=0{\cdot}5$ it is 14·3 (+0·7).

(ii) *Muller's ratchet in* small-world *networks*

We now study the ratchet in more complex and realistic networks and try to access the effects of the rewiring probability and network size on its rate. In Fig. 3 we show the results of the mean time between clicks of Muller's ratchet as a function of the rewiring probability. We have studied different network sizes:

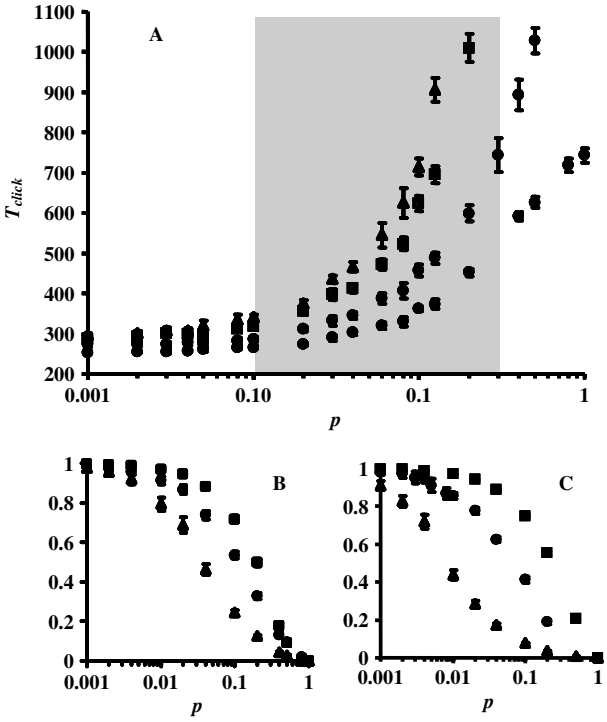

Fig. 3. (*A*) The mean time between clicks of Muller's ratchet, T_{click}, and the rewiring probability, p. The population is composed of D demes each with 100 individuals. The mutation rate and fitness effect of each deleterious mutation is $U=0{\cdot}3$ and $s=0{\cdot}1$, respectively. The migration rate is $m=0{\cdot}005$ for all data points. Open circles correspond to T_{click} for $D=60$, filled circles for $D=100$, squares for $D=200$ and triangles for $D=300$. The grey shading refers to the approximate *small-world* region for the networks considered. (*B*), (*C*) The normalized average path length (open triangles), the normalized average clustering coefficient (open squares) and the normalized speed of the ratchet (open circles) – see text for details – are shown for comparison with the properties of the network. On the left side $D=60$ and on the right $D=300$. In all points error bars correspond to 2 SE.

60, 100, 200 and 300 demes. From Fig. 3 we see that, for a given network size, the mean time between clicks of the ratchet is constant for low values of p but increases considerably above a given value of p. For example, for $D=60$ the T_{click} values for $p<0{\cdot}01$ are not significantly different from the one obtained when $p=0$. When $p=0{\cdot}02$ a significant difference starts to be observed.

To relate the speed of the ratchet with the topological properties of these networks we show, in the bottom panel of Fig. 3, two of the most important properties of these networks for two different network sizes ($D=60$, Fig. 3*B*; $D=300$, Fig. 3*C*). The average path length (L) measures the number of links in the shortest path between two nodes, averaged over all pairs of nodes, and the average clustering coefficient (C) measures the extent to which neighbours of a particular node are connected between themselves (more specifically if a node has K_i neighbours then at

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

most $K_i(K_i-1)/2$ links can exist between them, if C_i is the fraction of these allowable links that actually exist then the average clustering coefficient C is the average of C_i over all i) (Watts & Strogatz, 1998). In the bottom panel of Fig. 3 we show these properties normalized by their values at $p=0$ and $p=1$, as well as a normalized speed of the ratchet. The logarithmic scale resolves the rapid drop of L with p. For example, by normalized average path length we mean:

$$L_n = \frac{L(p)-L(p=1)}{L(p=0)-L(p=1)},$$

which will be between 0 and 1. In the region of low p values, the average path length, L, is high, which implies that the mean distance between demes is high. The connectivity between demes (a local property of the network) is also high in this region. But above a given value of p, there is a drop in the value of L and immediately after such a drop the speed of the ratchet decreases very rapidly. The region where L drops while C stays high corresponds to the region where the *small-world* effect starts, as defined in Watts & Strogatz (1998). The region corresponding to the *small-world* effect is defined by the conditions low L (as in random networks) and high C (as in regular networks). In this region, the time between clicks of the ratchet starts to increase rapidly. From studies of the topology of these types of networks it is known that the onset of the *small-world* behaviour takes place when $p \sim 1/D$ (Albert & Barabasi, 2002). We observe that for a given value of the network size, for values of p below $1/D$, the ratchet speed has a value not significantly different from that in a regular network, which is expected since in this case the number of long-range interactions is negligible. On the other hand, when p is larger than $1/D$, the ratchet steadily slows down with increasing p. As we have seen above, increasing migration causes the ratchet to slow down and the same applies for the rewiring probability. In a regular lattice ($p=0$), because the degree of isolation of each deme is very high (here, by isolation we mean that the interactions take place only between nearby demes), both globally (large L) and locally (large C), one expects the ratchet to click very rapidly. This is due to the fact that if a deme loses its best class it is very difficult to regain it from another deme, because the strength of migration is locally limited. As p reaches a value close to $1/D$, the value of L decreases and so the degree of isolation of a deme decreases. If now it has lost its best class it has a higher chance of regaining it from another deme. So the value of p where T_{click} is expected to start increasing is the one corresponding to a decrease in L. After the sharp decrease in L, as p continues to increase, C starts decreasing, so the level of isolation of a deme continues to decrease and T_{click} continues to increase.

Fig. 3 also shows the results with different numbers of demes. As expected the absolute value of the ratchet speed depends on the size of the whole population. All else being equal, the speed is lower the larger the value of N_dD. However, the effect of increasing network size is different according to the value of p. The slowdown of the speed of the ratchet with increasing D is much smaller for values of p below $1/D$ than for values of p above $1/D$. For example, with $p=0{\cdot}002$ the speed of the ratchet drops from 0·0039 to 0·0033 when the network size increases from $D=60$ to $D=300$. With $p=0{\cdot}1$ the drop is from 0·0028 to 0·0013. Therefore the deceleration of the ratchet for $p=0{\cdot}002$ is about 15% but for $p=0{\cdot}1$ it is about 53%.

There are two important limits with which to compare the results of Fig. 3: the value of T_{click} in a single isolated deme and the value of T_{click} in an undivided population with the same total number of individuals. These limits can be compared with analytical approximations available in the literature for the speed of the ratchet without population structure (Gessler, 1995; Gordo & Charlesworth, 2000*a*, *b*; Stephan & Kim, 2002). For an isolated deme with 100 individuals and with the values of U and s considered in Fig. 3, it is 49. In an unstructured population the ratchet does not click (over 100 000 generations in 20 simulations) for these values of U and s or for any of the values of $N_t=N_dD$ considered in Fig. 3. Clearly when $p=0$, T_{click} is higher than 49 generations. This is because the value of migration in Fig. 3 is higher than $m=0{\cdot}00025$, which is the critical value of m below which we do not expect to observe significant differences in the speed of the ratchet from that in a isolated deme (see above and Fig. 2). Increasing p (above $1/D$) slows down the ratchet in all cases, but even with $p=1$ we do not achieve the panmictic result. For example, with $D=60$ and $p=1$ the mean time between clicks of the ratchet is 743 ± 18 generations, a result very different from the panmictic case.

In Fig. 4 (*A*, *B*) we have considered a fixed number of demes and show that for different values of U and s the mean time between clicks of the ratchet always increases in the *small-world* region, with increasing p. Clearly the increase depends on the particular values of U and s. For a given value of U that increase is larger when selection is stronger. Furthermore in the parameter range where $N_d\exp(-U/s)>1$ (see for example Fig. 4*B*; $s=0{\cdot}01$ and 0·0075), that increase is more easily seen and stronger (for $p>1/60$). For parameter sets that lead to $N_d\exp(-U/s)\ll 1$ this increase, although present, is much less pronounced. For example, in Fig. 4*A* we can see that for $U=0{\cdot}3$, $s=0{\cdot}1$ ($N_d\exp(-U/s)>1$), we have T_{click} $(p=0)=251(\pm 2)$ and T_{click} $(p=1)=743$ (± 18). This corresponds to a 3-fold increase from the regular network to the random network. With $s=0{\cdot}04$ ($N_d\exp(-U/s)\ll 1$),

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

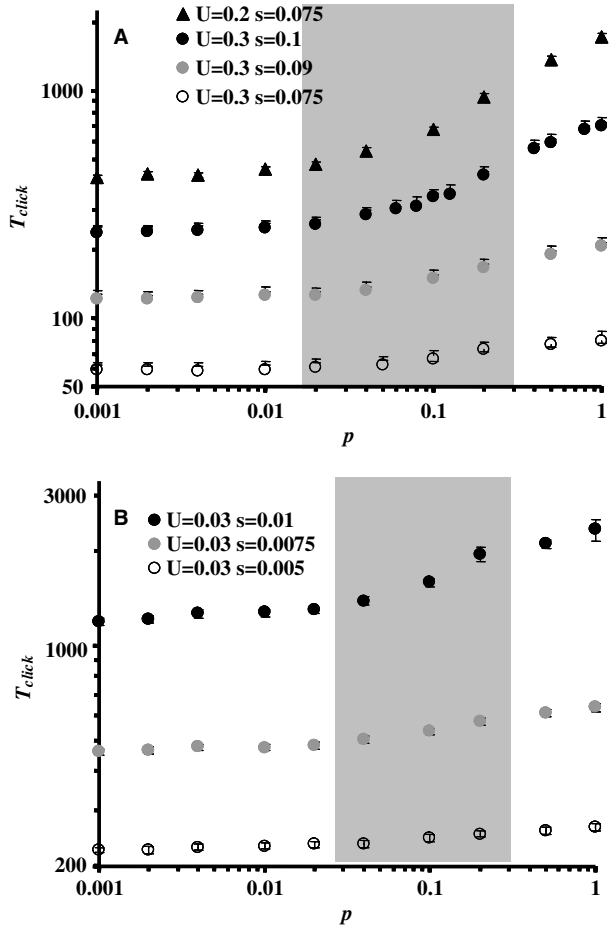

Fig. 4. Effect of mutation and selection parameters and p on the speed of the ratchet. (*A*) $D=60$, $N_d=100$; other parameters are as indicated in the figure. As p reaches $1/60$ the time between clicks of the ratchet increases for all parameter combinations, except for very low values of s ($<0{\cdot}01$). (*B*) $U=0{\cdot}03$, $D=40$, $N_d=300$, As in (*A*), when p reaches $1/D$ ($0{\cdot}025$) the time between clicks of the ratchet increases in all the parameter combinations shown, except for very low values of s ($<0{\cdot}0033$). Error bars correspond to 2 SE. The grey shading refers to the *small-world* region for the networks considered.

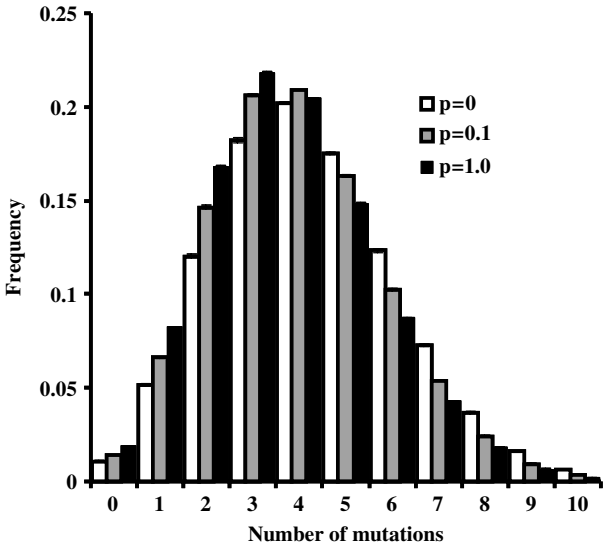

Fig. 5. The distribution of deleterious mutations in the network and the rewiring probability, p. On the figure we plot the frequencies of individuals in the least-loaded class and the subsequent classes. The population is composed of $D=60$ demes each with 100 individuals. The mutation rate and fitness effect of each deleterious mutation are $U=0{\cdot}3$ and $s=0{\cdot}1$, respectively. Migration rate is $m=0{\cdot}005$. Black bars correspond to $p=1$, grey bars to $p=0{\cdot}1$ and open bars to $p=0$. The mean number of deleterious mutations observed was 4·3 for $p=0$, 3·95 for $p=0{\cdot}1$ and 3·7 for $p=1$. Each distribution of deleterious mutations is calculated as the mean of 100 independent simulations, where the distribution was measured at multiple time points.

T_{click} $(p=0)=19$ (± 1) and T_{click} $(p=1)=23$ (± 3), leading to a minute increase. For these parameters, in the undivided population $T_{click}=47$ (± 6), so the speed of the ratchet is higher than in the panmictic case, even in the random network.

(iii) *Size of the least-loaded class in* small-world *networks*

One of the key parameters that determines the rate of the ratchet in an unstructured population is the size of the class with the lowest number of mutations, also known as the least-loaded class (Gordo & Charlesworth, 2000*b*; Haigh, 1978). In Fig. 5 we show how the distribution of classes of deleterious mutations, in the whole population, changes with the type of network. We have run 100 replicate simulations for three different values of p (for the case $D=60$) and measured the average size of the class with the least number of mutations as well as the following classes. In a population without any spatial structure and without accumulation of deleterious mutations this distribution is Poisson with mean U/s (Haigh, 1978). In our network model the mean number of deleterious mutations is higher than U/s. In fact, as shown in Fig. 5, the mean number of mutations in the whole population decreases as the rewiring probability increases. In particular, the size of the least-loaded class increases as p increases. This is consistent with the observed decrease in the rate of the ratchet with increasing values of p. The distributions for $p=0{\cdot}1$ and $p=1$ are significantly different from the distribution for $p=0$ ($P<0{\cdot}001$ by a χ^2 test).

(iv) *Effect of migration in* small-world *networks*

Another important parameter in this process is the level of migration in the population. The expectation for a given topology of the network is that if migration rates between demes are low the ratchet will click much more rapidly than if migration is high. In Fig. 6 we have studied the effect of migration on the ratchet speed. In our networks we observe that when

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

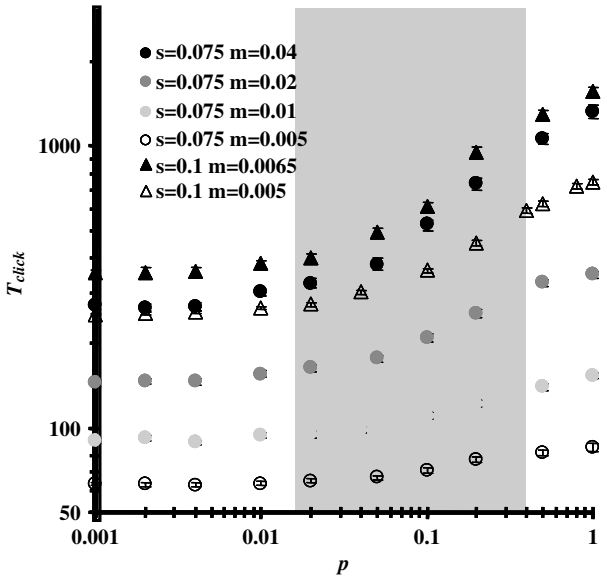

Fig. 6. The mean time between clicks of Muller's ratchet, T_{click}, and the probability of migration, m. The population is composed of 60 demes with $N_d=100$ and $U=0{\cdot}3$. Other parameters are as shown in the figure. Error bars correspond to 2 SE. The grey shading refers to the *small-world* region for the networks considered.

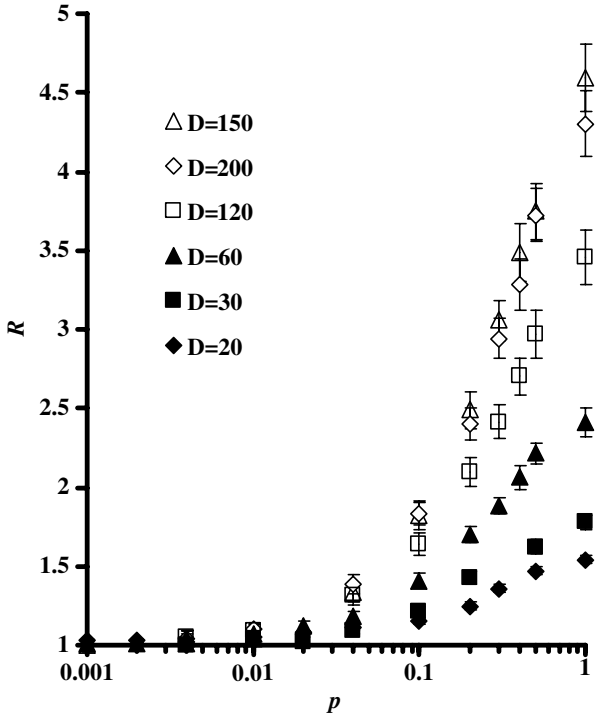

Fig. 7. The ratio $R=T_{click(p)}/T_{click(0)}$ as a function of the rewiring probability, p. Filled diamonds correspond to $m=0{\cdot}0043$, $N_d=150$ and $D=20$; filled squares to $m=0{\cdot}0065$, $N_d=100$ and $D=30$; filled triangles to $m=0{\cdot}013$, $N_d=50$ and $D=60$; open squares to $m=0{\cdot}026$, $N_d=25$ and $D=120$; open triangles to $m=0{\cdot}0325$, $N_d=20$ and $D=150$; and open diamonds to $m=0{\cdot}043$, $N_d=15$ and $D=200$. In all cases, the number of migrants per link is 0·65 and the total population size is 3000. The mutation rate and the fitness effect of each deleterious mutation are $U=0{\cdot}3$ and $s=0{\cdot}1$, respectively. Error bars correspond to 2 SE.

p is small the effect of increasing migration is only slight, but in the region of p corresponding to the onset of the *small-world* effect, the effect of increasing migration is much more pronounced. In Fig. 6 that region starts when $p=0{\cdot}02$. This qualitative result is observed for different values of U and s. When $s=0{\cdot}1$, the ratchet does not click in a panmictic population but with $s=0{\cdot}075$ the observed mean time between clicks of the ratchet in the panmictic case is 12 944 ($\pm$822). For this value of s, in a random network ($p=1$) with a large migration rate ($m=0{\cdot}15$) $T_{click}=$ 6080 ($\pm$605), still smaller than the panmictic result.

In Fig. 6 an increase in the migration rate corresponded to an increase in the overall number of migrants in the whole population. Fig. 7 displays the results of simulations where we have kept both the number of migrants per link ($N_dm=0{\cdot}65$) and the total size of the population ($N_t=N_dD=3000$) constant and have studied different numbers of demes. This means that as we increase the number of demes, the size of each deme will decrease and the rate of migration (m) will increase. In the figure, we plot the ratio between the time between clicks for networks with $p>0$ and the time between clicks in a regular network ($p=0$) as a function of the rewiring probability p. We plot this ratio because the absolute values of T_{click} are different for different system sizes, and because we want to emphasize the comparison with the result of a regular network. From Fig. 7, we clearly notice that as the population becomes structured into a larger number of smaller subpopulations, i.e. as we augment D, the time between clicks (compared with that in a regular network) also increases. However, this effect is only pronounced for intermediate and large values of p. Furthermore we observe that the maximum increase observed is for $p=1$ and intermediate values of D. For example with the parameter values of Fig. 7, the maximum effect is achieved for $D=150$. For larger systems, N_d becomes very small and the effect of drift within demes becomes increasingly pronounced, making the effect of the topology less important.

(v) *Muller's ratchet with extinction on* small-world *networks*

Up to now we have studied cases where the population is subdivided into many stable demes of equal size. A more realistic structure of natural populations, in particular populations of microbes, is that local populations can be pruned to occasional extinction and recolonization (Maruyama & Kimura, 1980). These extinction and recolonization events can lead to substantial reductions in the levels of neutral diversity

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

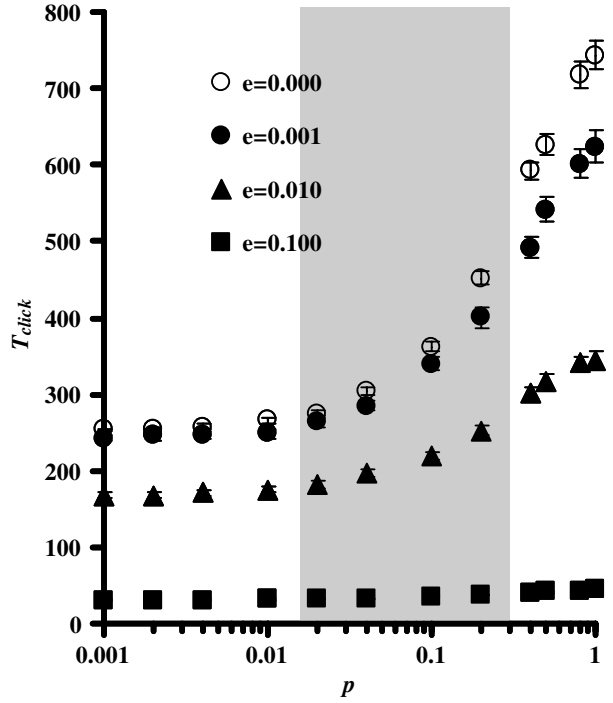

Fig. 8. The effect of random extinction on the mean time between clicks of Muller's ratchet. e is the probability of extinction per deme, per generation. $e=0$ for open symbols, $e=0{\cdot}001$ for filled circles, $e=0{\cdot}01$ for filled triangles and $e=0{\cdot}1$ for filled squares. The population is composed of 6000 individuals, where the number of demes is $D=60$. The mutation rate, the fitness effect of each deleterious mutation and the migration rate are $U=0{\cdot}3$, $s=0{\cdot}1$ and $m=0{\cdot}005$, respectively. Error bars correspond to 2 SE. The grey shading refers to the *small-world* region for the networks considered.

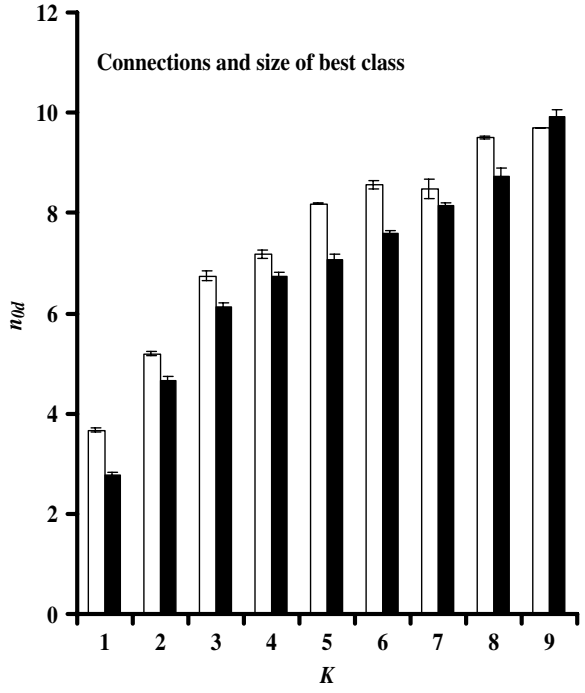

Fig. 9. The effect of the number of connections, k, on the mean size of the best class, n_{0d}. Open bars represent the mean size of the best class in a network with $p=1$ without extinction and the black bars with $e=0{\cdot}01$. The mutation rate, the fitness effect of each deleterious mutation and the migration rate are $U=0{\cdot}3$, $s=0{\cdot}1$ and $m=0{\cdot}005$, respectively. The population is composed of 6000 individuals, where the number of demes is $D=60$. Results are given as averages from 100 independent simulations. Errors bars correspond to 2 SE.

in populations (Maruyama & Kimura, 1980; Pannell & Charlesworth, 1999). We have introduced in our random-network model these events in order to assess how important extinction is for the speed of the ratchet. In our model each deme can go extinct, with probability e, and be recolonized by individuals from neighbouring demes to which the deme in question is connected. Similar models of extinction and recolonization have been considered by Slatkin (1977) and Whitlock & McCauley (1990). It is known that the effective size of a population is decreased when extinction and recolonization occur (Maruyama & Kimura, 1980; Pannell & Charlesworth, 1999; Whitlock & Barton, 1997). If this reduction also holds in our model we should observe an increase in the speed of the ratchet with increasing levels of e. Fig. 8 shows that this is in fact the case. In the figure we show several values of the probability of extinction, e, in networks with different rewiring probabilities. For every value of p we observe that the mean time between clicks of ratchet decreases with increasing e. However, we can see that the effect of extinction is not the same for all network structures. Extinction has a much more pronounced effect when p is high than when it is low, and the boundary is given by the *small-world* region. To better understand the differentiated effect of extinction with p, we have studied how the size of the best class in a given deme relates to the number of connections that a deme makes (K). Fig. 9 shows that better-connected demes have larger best classes. This implies that extinction of a highly connected deme has a stronger impact on the speed of the ratchet than extinction of a deme that has few connections. This fact leads to the pattern observed in Fig. 8, with high values of p showing a stronger effect on the extinction/recolonization events.

4. Discussion

We have introduced a model of population structure to study the patterns of mutation accumulation in asexual organisms. The model tries to capture some characteristics of the spatial structure observed in real biological populations. We have focused our study on the effects of the spatial structure on the speed of mutation accumulation due to the evolutionary process known as Muller's ratchet. This process has been implicated in several evolutionary features. In particular it has been suggested that Muller's ratchet can

https://doi.org/10.1017/S0016672307008658 Published online by Cambridge University Press

be an important mechanism in the evolution of microorganisms, specially those with a high mutation rate (Chao, 1990; Moran, 1996), in the evolution of recombination (Barton & Charlesworth, 1998) and of the Y chromosome (Charlesworth, 1978; Gordo & Charlesworth, 2001).

We have seen that the speed of the ratchet is highly dependent on the type of structure of the population. In particular, in regular networks, such as those considered in the *stepping-stone* model of population subdivision, the ratchet clicks much faster than in *small-world* networks. Furthermore the importance of migration rates in slowing down the ratchet is much more pronounced in *small-world* networks than in regular ones. In addition the effect of extinction and recolonization events in local populations will have an impact in *small-world* networks, whereas it has much less influence in regular networks. We have also seen that the ratchet clicks faster in *small-world* networks than in a corresponding unstructured population.

There is evidence that some microbial populations, such as *Escherichia coli*, are structured (Whittam *et al*., 1983). It is natural to think that microbial population structure is associated with the structure of contacts of their hosts. For example, in humans it has been suggested that such contacts have a *small-world* property (Liljeros *et al*., 2001; Milgram, 1967). With the results obtained in this study we can observe that such host contact networks tend to minimize the rate of fitness decline of their asexual parasites. Although we have considered low values of the parasite effective population size within a host (N_d), possibly lower than those in real populations, the speed of the ratchet is far more sensitive to the values of mutation rate and selection coefficient than on N_d. Furthermore the relevant value of N_e of the parasite within a host strongly depends on the number of parasites that initiate infection (Gordo & Dionisio, 2005), which is normally small. We have also considered, for simplicity, a model with constant effects of mutations, whereas a model assuming a distribution of effects is closer to the real situation. Although the distribution of deleterious fitness effects of mutations is at present poorly established, we expect that the qualitative results presented here will apply in a more complex and realistic model for the effects of mutations.

Although we have only addressed the rate of accumulation of deleterious mutations, in natural populations both adaptive and deleterious mutations occur. If we ignore deleterious mutations, Maruyama's result (1970) shows that the probability of fixation of adaptive mutations is independent of structure if there is conservative migration. It is also known that deleterious mutations have an impact on rates of adaptation in asexual organisms (Bachtrog & Gordo, 2004; Charlesworth *et al*., 1993; Orr, 2002); roughly, the rate of adaptation is reduced by the fraction of individuals that are free of deleterious mutations. As we have shown here, the size of the class of individuals free of deleterious mutations increases with the rewiring probability p. Given this, we would expect that the rate of fixation of adaptive mutations in asexuals, where both adaptive and deleterious mutations occur, should increase in *small-world* networks.

We thank António Coutinho, Michael Whitlock and two anonymous referees for helpful suggestions. J.C. and I.G. are supported by fellowships SFRH/BD/5235/2001 and SFRH/BPD/8104/2002. This work was financed by Fund. para a Ciência e Tecnologia and FEDER through grants POCTI/BSE/46856/2002 and POCI/BIA-BDE/55758/2004. P.C. is supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

Albert, R. & Barabasi, A. L. (2002). Statistical mechanics of complex networks. *Reviews of Modern Physics* **74**, 47–97.

Bachtrog, D. & Charlesworth, B. (2002). Reduced adaptation of a non-recombining neo-Y chromosome. *Nature* **416**, 323–326.

Bachtrog, D. & Gordo, I. (2004). Adaptive evolution of asexual populations under Muller's ratchet. *Evolution* **58**, 1403–1413.

Barrat, A. & Weigt, M. (2000). On the properties of small-world network models. *European Physical Journal B* **13**, 547–560.

Barton, N. H. (1993). The probability of fixation of a favoured allele in a subdivided population. *Genetical Research* **62**, 149–157.

Barton, N. & Charlesworth, B. (1998). Why sex and recombination? *Science* **281**, 1986–1990.

Bergstrom, C. T., McElhany, P. & Real, L. A. (1999). Transmission bottlenecks as determinants of virulence in rapidly evolving pathogens. *Proceedings of the National Academy of Sciences of the USA* **96**, 5095–5100.

Butcher, D. (1995). Muller's ratchet, epistasis and mutation effects. *Genetics* **141**, 431–437.

Chao, L. (1990). Fitness of RNA virus decreased by Muller's ratchet. *Nature* **348**, 454–455.

Charlesworth, B. (1978). Model for evolution of Y-chromosomes and dosage compensation. *Proceedings of the National Academy of Sciences of the USA* **75**, 5618–5622.

Charlesworth, B. & Charlesworth, D. (1997). Rapid fixation of deleterious alleles can be caused by Muller's ratchet. *Genetical Research* **70**, 63–73.

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

Felsenstein, J. (1974). Evolutionary advantage of recombination. *Genetics* **78**, 737–756.

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

Fontanari, J. F., Colato, A. & Howard, R. S. (2003). Mutation accumulation in growing asexual lineages. *Physical Review Letters* **91**, 218101.

Gabriel, W. & Burger, R. (2000). Fixation of clonal lineages under Muller's ratchet. *Evolution* **54**, 1116–1125.

Gessler, D. D. (1995). The constraints of finite size in asexual populations and the rate of the ratchet. *Genetical Research* **66**, 241–253.
Gordo, I. & Campos, P. R. A. (2006). Adaptive evolution in a spatially structured asexual population. *Genetica* **127**, 217–229.
Gordo, I. & Charlesworth, B. (2000*a*). The degeneration of asexual haploid populations and the speed of Muller's ratchet. *Genetics* **154**, 1379–1387.
Gordo, I. & Charlesworth, B. (2000*b*). On the speed of Muller's ratchet. *Genetics* **156**, 2137–2140.
Gordo, I. & Charlesworth, B. (2001). The speed of Muller's ratchet with background selection, and the degeneration of Y chromosomes. *Genetical Research* **78**, 149–161.
Gordo, I. & Dionisio, F. (2005). Nonequilibrium model for estimating parameters of deleterious mutations. *Physical Review E* **71**, 031907.
Gordo, I., Navarro, A. & Charlesworth, B. (2002). Muller's ratchet and the pattern of variation at a neutral locus. *Genetics* **161**, 835–848.
Haigh, J. (1978). Accumulation of deleterious genes in a population: Muller's ratchet. *Theoretical Population Biology* **14**, 251–267.
Higgins, K. & Lynch, M. (2001). Metapopulation extinction caused by mutation accumulation. *Proceedings of the National Academy of Sciences of the USA* **98**, 2928–2933.
Johnson, T. (1999). The approach to mutation–selection balance in an infinite asexual population, and the evolution of mutation rates. *Proceedings of the Royal Society of London, Series B* **266**, 2389–2397.
Keeling, M. J. & Eames, K. T. D. (2005). Networks and epidemic models. *Journal of the Royal Society Interface* **2**, 295–307.
Kimura, M. (1953). The ''stepping-stone'' model of population. *Annual Report of the National Institute of Genetics* **3**, 62–63.
Klemm, K., Eguiluz, V. M., Toral, R. & San Miguel, M. (2003). Nonequilibrium transitions in complex networks: A model of social interaction. *Physical Review E* **67**, 026120.
Kondrashov, A. S. (1994). Muller's ratchet under epistatic selection. *Genetics* **136**, 1469–1473.
Kuperman, M. & Abramson, G. (2001). Small world effect in an epidemiological model. *Physical Review Letters* **86**, 2909–2912.
Lande, R. (1995). Mutation and conservation. *Conservation Biology* **9**, 782–791.
Lazaro, A., Mark, S. & Olesen, J. M. (2005). Bird-made fruit orchards in northern Europe: nestedness and network properties. *Oikos* **110**, 321–329.
Liljeros, F., Edling, C. R., Amaral, L. A. N., Stanley, H. E. & Aberg, Y. (2001). The web of human sexual contacts. *Nature* **411**, 907–908.
Liu, Z. Y., Moore, P. H., Ma, H., Ackerman, C. M., Ragiba, M., Yu, Q. Y., Pearl, H. M., Kim, M. S., Charlton, J. W., Stiles, J. I., Zee, F. T., Paterson, A. H. & Ming, R. (2004). A primitive Y chromosome in papaya marks incipient sex chromosome evolution. *Nature* **427**, 348–352.
Loewe, L. (2006). Quantifying the genomic decay paradox due to Muller's ratchet in human mitochondrial DNA. *Genetical Research* **87**, 133–159.
Lundgren, R. & Olesen, J. M. (2005). The dense and highly connected world of Greenland's plants and their pollinators. *Arctic Antarctic and Alpine Research* **37**, 514–520.
Lynch, M. (1996). Mutation accumulation in transfer RNAs: molecular evidence for Muller's ratchet in mitochondrial genomes. *Molecular Biology and Evolution* **13**, 209–220.
Lynch, M., Burger, R., Butcher, D. & Gabriel, W. (1993). The mutational meltdown in asexual populations. *Journal of Heredity* **84**, 339–344.
Maruyama, T. (1970). On fixation probability of mutant genes in a subdivided population. *Genetical Research* **15**, 221–225.
Maruyama, T. (1974). Simple proof that certain quantities are independent of geographical structure of population. *Theoretical Population Biology* **5**, 148–154.
Maruyama, T. & Kimura, M. (1980). Genetic-variability and effective population-size when local extinction and recolonization of sub-populations are frequent. *Proceedings of the National Academy of Sciences of the USA* **77**, 6710–6714.
Milgram, S. (1967). Small-world problem. *Psychology Today* **1**, 61–67.
Moran, N. A. (1996). Accelerated evolution and Muller's ratchet in endosymbiotic bacteria. *Proceedings of the National Academy of Sciences of the USA* **93**, 2873–2878.
Moya, A., Holmes, E. C. & Gonzalez-Candelas, F. (2004). The population genetics and evolutionary epidemiology of RNA viruses. *Nature Reviews Microbiology* **2**, 279–288.
Muller, H. J. (1964). The relation of recombination to mutational advance. *Mutation Research* **1**, 2–9.
Nagylaki, T. (1980). The strong-migration limit in geographically structured populations. *Journal of Mathematical Biology* **9**, 101–114.
Nagylaki, T. (1982). Geographical invariance in population-genetics. *Journal of Theoretical Biology* **99**, 159–172.
Olesen, J. M., Bascompte, J., Dupont, Y. L. & Jordano, P. (2006). The smallest of all worlds: pollination networks. *Journal of Theoretical Biology* **240**, 270–276.
Orr, H. A. (2002). The population genetics of adaptation: the adaptation of DNA sequences. *Evolution* **56**, 1317–1330.
Pannell, J. R. & Charlesworth, B. (1999). Neutral genetic diversity in a metapopulation with recurrent local extinction and recolonization. *Evolution* **53**, 664–676.
Rice, W. R. (1994). Degeneration of a nonrecombining chromosome. *Science* **263**, 230–232.
Rouzine, I. M., Wakeley, J. & Coffin, J. M. (2003). The solitary wave of asexual evolution. *Proceedings of the National Academy of Sciences of the USA* **100**, 587–592.
Roze, D. & Rousset, F. (2003). Selection and drift in subdivided populations: a straightforward method for deriving diffusion approximations and applications involving dominance, selfing and local extinctions. *Genetics* **165**, 2153–2166.
Salathe, M., Salathe, R., Schmid-Hempel, P. & Bonhoeffer, S. (2006). Mutation accumulation in space and the maintenance of sexual reproduction. *Ecology Letters* **9**, 941–946.
Slatkin, M. (1977). Gene flow and genetic drift in a species subject to frequent local extinctions. *Theoretical Population Biology* **12**, 253–262.
Slatkin, M. (1981). Fixation probabilities and fixation times in a subdivided population. *Evolution* **35**, 477–488.
Stephan, W. & Kim, Y. (2002). Recent applications of diffusion theory to population genetics. In *Modern Developments in Theoretical Population Genetics* (ed. M. S. M. Veuille), pp. 72–93. Oxford: Oxford University Press.

Stephan, W., Chao, L. & Smale, J. G. (1993). The advance of Muller's ratchet in a haploid asexual population: approximate solutions based on diffusion-theory. *Genetical Research* **61**, 225–231.
Watts, D. J. & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature* **393**, 440–442.
Whitlock, M. C. (2003). Fixation probability and time in subdivided populations. *Genetics* **164**, 767–779.
Whitlock, M. C. & Barton, N. H. (1997). The effective size of a subdivided population. *Genetics* **146**, 427–441.
Whitlock, M. C. & McCauley, D. E. (1990). Some population genetic consequences of colony formation and extinction: genetic correlations within founding groups. *Evolution* **44**, 1717–1724.
Whittam, T. S., Ochman, H. & Selander, R. K. (1983). Multilocus genetic structure in natural populations of *Escherichia coli*. *Proceedings of the National Academy of Sciences of the USA* **80**, 1751–1755.
Wright, S. (1931). Evolution in Mendelian populations. *Genetics* **16**, 97–159.