5 Clonal Evolution

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5.1 Introduction

Asexual reproduction is probably the most widespread means of biological propagation (De Meeûs et al., 2007b, 2009b) and is probably the oldest one, though recombination might be almost as old (Cavalier-Smith, 2002). But this of course depends on what is meant and what is understood (not always the same thing) by clonality and recombination.

Asexual reproduction has been the subject of numerous studies and reviews from diverse biological disciplines (Bell, 1982; Jackson et al., 1985; Hughes, 1989; Asker and Jerling, 1992; Savidan, 2000; Otto and Lenormand, 2002). The issue appears to be perceived differently for specialists working on Bacteria, Archaea, Eukaryota, unicellular, or pluricellular animals or plants. In this review, we will therefore first deal with specific definitions, as this subject area is littered with vocabulary that sometimes has ambiguous meanings. We will then try to go back in time to the origin of asexual reproduction and recombination and attempt to describe the diversity of ways in which prokaryotes and eukaryotes reproduce asexually and recombine. Following this, we will describe the various ways that asexual reproduction is incorporated in eukaryotic life cycles. After a brief attempt to quantify the importance of asexuality in living organisms, the genetic consequences of asexuality are reviewed, followed by a section on the evolution and the paradox of sex. What evolutionary advantages are brought by clonality? What disadvantages result from clonality? What is the so-called twofold cost of sex? The last section will deal with clonal microevolution. It will consist of two parts: the first one treating neutral gene variability in clonal populations (population genetics structure), and the second addressing selective issues like the evolution of resistance or virulence in clonal populations. Finally, we will conclude with economic and medical issues linked to asexual organisms.

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5.2 Definitions

Asexual reproduction is a process of genetic propagation of genomes, following which the genomes that descend from this process are strictly identical to the parental genome, in terms of quantity and quality, with the exception of uncorrected errors during the duplication process (i.e., mutations) (De Meeûs et al., 2007b). Besides cell division (e.g., mitosis in unicellular eukaryotes), many other processes correspond to clonal propagation as agametic (animals) or vegetative (plants) reproduction, ameiotic thelytokous parthenogenesis, endomitotic automictic parthenogenesis with pair formation of sister chromatids occurring before meiosis, automictic parthenogenesis with fusion of two polar bodies, deuterokous parthenogenesis, gynogenesis, apomixy, or agamospermy (reviewed in De Meeûs et al., 2007b).

Sexual reproduction is not initially a propagation mode even if it is now 100% correlated with the multiplication of many organisms (e.g., mammals). It is a recombinational repair tool (Cavalier-Smith, 2002; Ramesh et al., 2005; Glansdorff et al., 2009a), hence the use of sexual recombination (SR) in the rest of this paper as a synonymous for meiotic sex. Recombination in the wide sense is present in the three domains of life (Archaea, Bacteria, and Eukaryota), although through very different means (Cavalier-Smith, 2002), while SR is a eukaryotic hallmark (Cavalier-Smith, 2002; Solari, 2002; Glansdorff et al., 2009a). Recombination can take three forms in Bacteria and Archaea: conjugation, transformation, and transduction (Luo and Wasserfallen, 2001; Cavalier-Smith, 2002; Poole, 2009). Conjugation concerns plasmid exchange through a specialized structure called pilus. It is unidirectional in Bacteria (donor and recipient) and apparently bidirectional in Archaea (Luo and Wasserfallen, 2001). Transformation is the absorption of soluble naked DNA present in the microenvironment by a recipient cell and its further inclusion (recombination), if compatible, in the chromosome. Transduction is a horizontal gene transfer (HGT) mediated by viruses. Calling transduction, transformation and conjugation sex is unsound and true sex, with meiosis and syngamy, is only found in eukaryotes and never in prokaryotes (Cavalier-Smith, 2002).

Panmixia defines a population where zygotes (eggs) are produced by the random syngamy (union) of available sexual cells. It can thus only occur in eukaryotes, if any. Then, talking about panmictic bacteria is inappropriate as well. The genetic consequence of panmixia is the establishment of the famous Hardy−Weinberg (HW) genotypic proportions of the form p^2, $2pq$ and q^2 (for two alleles of frequencies p and q). These proportions are only expected to be approximately met in populations of highly mobile monoecious individuals with panmictic sex. Consequently, talking of panmixia for a microbe is also fairly unsound.

Linkage disequilibrium (LD) reflects the statistical association between different alleles at different loci in the genome. LD can be generated by virtually all evolutionary forces. Besides the obvious physical linkage, selection, population structure (small subpopulation sizes and migration), mutation, and reproductive system (except panmixia) all have a positive impact on LD. Estimation and testing of

positive LD is a hard task and only very strong signals are expected to be detected, the variance of which is expected to be substantial (De Meeûs and Balloux, 2004; De Meeûs et al., 2009a). Furthermore, very strong interactions between sampling design, reproductive system, and population structure can considerably bias LD perception (Prugnolle and De Meeûs, 2010). Consequently, assessing reproductive systems through LD measures is at best risky, and measuring it through the proportion of significant LD tests found is definitely flawed.

5.3 The Origin of Life, the Origin of Propagation and Recombination

Whether a RNA phase came before the DNA world will not be discussed here. There is nevertheless a large consensus on the fact that all extant life is the descent of a single ancestor (Glansdorff et al., 2009b). The last universal common ancestor (LUCA), also known as the cenancestor (Cavalier-Smith, 2002), originated some 3−3.5 billion years ago (Vaneechoutte and Fani, 2009). The emergence of LUCA probably followed a phase of extensive HGT between the different arising entities (Glansdorff et al., 2009a,b). The order of branching of Bacteria, Eukaryota, and Archaea domains is controversial, one interesting hypothesis being that eukaryotes emerged as the result of a symbiotic fusion of some bacterial and archaeal lineages (Gargaud et al., 2009). Confusion finds its origin in the potential important disturbing HGT believed to occasionally or often occur between prokaryotic organisms (Gribaldo and Brochier, 2009). Evolution of meiosis is viewed by certain as a defense mechanism that evolved against HGT to promote the best coordination between coevolved functions. When chromosomes pair during meiosis, a number of mechanisms such as repair, conversion, and recombination are triggered, allowing the elimination of deleterious differences, which is viewed as a protection against HGT (Glansdorff et al., 2009a). Nevertheless, meiosis probably arose from mitosis, which is also specific to eukaryotes (Cavalier-Smith, 2002). According to this author, SR appeared about 850 million years ago as a cell cycle repair mechanism to correct accidental polyploidy. Many of the enzymes involved in meiosis have related enzymes in prokaryotic toolkits for controlling replication fidelity (rescue of broken or stalled replication forks, recombination or mismatch corrections) (Cavalier-Smith, 2002; Solari, 2002).

Consequently, clonality evolved first (whether prokaryotes appeared first or not), but recombination probably arose soon after or at the same time to control for intensive HGT and/or polyploidy, and this was then followed by SR in eukaryotes. It is noteworthy that SR emergence is not presented as a response to a changing environment (red queen hypothesis) or to prevent Muller's ratchet of deleterious allele accumulation (e.g., Otto and Lenormand, 2002; De Meeûs et al., 2007b for review) but as a mechanism for restoring genomic harmony after replication mistakes or any DNA damage. The fact SR did not evolve in prokaryotes probably comes from the constraints resulting from their particular peptidoglycan envelope

said to act as a "chastity belt" (Cavalier-Smith, 2002). It is nevertheless a proof that SR is by no means a necessity to adapt to variable environments or fight against Muller's ratchet.

Microbes represent the major part of genetic diversity on earth, most of which is still represented by uncultivated organisms (Gribaldo and Brochier, 2009). Clonality is thus as old as life. It does not evolve in competition with recombination or SR but coevolves with it in most situations.

5.4 Clonal Modes

Prokaryotes have various ways to recombine and only one way to divide (Cavalier-Smith, 2002). On the contrary, eukaryotes, and in particular pluricellular ones, have barely a single way for recombination (if we exclude possible gene transfer through viruses or with endosymbionts) and many different ways to propagate clonally. Reviewing all these modes would be tedious and unnecessary as most was already presented in a recent review (De Meeûs et al., 2007b). It is interesting, though, to focus briefly on a particular family of clonal modes that diverted SR to, so to speak, reintegrate back clonal reproduction. The different forms of parthenogenesis that produce daughters identical to their mother (see earlier) correspond to that. It is obvious that these cases attracted the most attention of the evolutionary biologists working on the evolution of sex, in particular the famous asexual scandal of bdelloid rotifers (Judson and Normark, 1996; Mark Welch and Meselson, 2000). In fact, fixed clonality has rarely been demonstrated, but the coexistence of both systems is much more the rule as in aphids, other rotifers (except purely sexual acanthocephalans), cycliophorans, and many others (De Meeûs et al., 2007b). The fact that it must have been a real challenge to divert meiosis apparatus and that this nevertheless evolved many times in complex eukaryotes appears as a spectacular illustration of how costly SR must be, hence the impressive amount of works dedicated to this issue (see later).

In recent reviews, De Meeûs et al. (2007b, 2009b) found it convenient to classify organisms according to the kind of cycle they are involved in with regard to clonal propagation. We will stick to this classification in the following. This classification separates four kinds of cycles: (1) the purely sexual cycle (Sex) corresponds to organisms that can only reproduce through SR; (2) complex life cycles with an instantaneous clonal phase with only one (I) clonal generation per cycle; (3) complex life cycles with several generations of asexuality (S) where the clonal phase involves more than one clonal generation; and (4) life cycles where sexual reproduction is more or less frequent (or even absent) with an acyclic pattern (A). In cases (2) and (3), and for all surviving individuals, SR must intervene at one point in the cycle to form zygotes. In case (4) the life cycle is not defined by a regular pattern of sexual or asexual reproduction. Case (1) is typical of vertebrates, especially mammals and birds but also cestodes, lice, or nematodes. Cycle (2) applies to all species with polyembryony and many budding species. For example, this cycle is typical of trematodes (flukes). Case (3) is typical of aphids,

monogonont rotifers, cladocerans, many fungi, and most Sporozoa (parasitic unicellular organisms, including the malaria agents *Plasmodium* spp.). Finally, case (4) is common in plants and unicellular organisms. In particular, it is found for strictly clonal organisms, or at least those organisms for which sex is unknown, such as bdelloid rotifers, imperfect fungi (e.g., *Candida albicans*), Parabasalia (*Trichomonas vaginalis*), Metamonadina (*Giardia lamblia*), parasitic amoebas, and kinetoplastid parasites (*Leishmania*, *Trypanosoma*).

5.5 Quantifying the Importance of Asexuality in the Biosphere

There are two ways to comprehend this issue. In terms of described (known) species, purely sexual species are the most represented (De Meeûs et al., 2009b). Nevertheless, there is an obvious bias in accounting biological diversity through described species (De Meeûs and Renaud, 2002; De Meeûs et al., 2003). As quoted earlier, microbes (cycles S or A) represent the major part of genetic diversity on earth, most of which is still represented by uncultivated organisms (Gribaldo and Brochier, 2009). It can thus be safely postulated that organisms with a clonal phase represent the major part of biodiversity. If this was accounted for in terms of energy devoted to clonality and SR on earth per second, SR would probably look like an epiphenomenon. This should be trivial as the real way to propagate for life is through cell (hence asexual) division while SR is in fact meant to DNA repair and/or control DNA replication fidelity.

The numeric importance of clonal parasitic eukaryotes was already reviewed by De Meeûs et al. (2009b). Whole described species again give a biased advantage to purely sexual species. Nevertheless, a glance at the most documented human parasitic fauna completely reverses the tendency, thus suggesting that: (1) parasites represent the most important part of eukaryotic biodiversity, and (2) that clonal species (i.e., using this mode at one stage of their life cycle) are the majority among them. If Archaea and Bacteria are included, known species number is useless. There are indeed more known bird species than the sum of known Archaea and Bacteria, which is nonsense. Prokaryotes are so numerous everywhere that estimating how much of their diversity specialized in parasitism looks impossible. We can, however, suspect this number to be tremendous regarding all bacterial diseases that can affect mankind (around 43 after a quick and dirty look in the web). For eukaryotic parasites, it was recently estimated that more than a billion people are affected by such diseases (De Meeûs et al., 2009b), some of which are the most severe ones (e.g., malaria). Clonality in infectious disease cannot thus be treated lightly.

5.6 Genetic Consequences of Asexuality

This issue was reviewed many times (e.g., in Suomalainen et al., 1976; Jackson et al., 1985; Tibayrenc et al., 1990, 1991; Maynard-Smith et al., 1993; Carvalho,

1994; Tibayrenc, 1995, 1998, 1999; Judson and Normark, 1996; Milgroom, 1996; Taylor et al., 1999; Savidan, 2000; Tibayrenc and Ayala, 2002; Halkett et al., 2005; De Meeûs et al., 2006, 2007a,b, 2009b), so we will be brief and stick to the essential. In haploid organisms, clonality tends to create and maintain statistical associations between the different loci of the genome irrespective of their location. In purely asexuals this should end with the presence of numerous repetitions of a certain clone, and hence of the same multilocus genotype (MLG). Depending on population structure, MLG diversity will vary from low (e.g., a single MLG) to high variability (several MLGs). As linkage is total, MLGs can be considered as the different alleles of a single locus. If no SR is involved it is expected that the different MLGs that can be maintained can potentially be highly divergent. This may represent a problem because at a given level of divergence it is probable that adaptive differences will arise. Moreover, especially in small subpopulations that are not expected to maintain much equivalent different MLGs, the stable maintenance of highly diverged MLGs of the same "species" might lead to interpret it as an ecological divergence. When some SR is involved, the combination between drift, reproduction, and sampling renders difficult the interpretation of the patterns of genetic variability in haploids. This is also true for diploids even if, when the amount of SR is large enough, populations display patterns of genetic variability close to that observed for a sexual population.

In diploids, haplotypic consequences are similar, but here in the absence of SR, the two alleles of a lineage will continuously diverge since the last SR event. Consequently, as illustrated in Figure 5.1, divergence between the two alleles of the same individual will be higher than mean divergence between lineages. This is the Meselson effect (Judson and Normark, 1996; Mark Welch and Meselson, 2000). Another way to see it is that in lineages that have stayed clonal for a sufficient amount of time, all loci will be heterozygous for all individuals. Genomic fixed heterozygosity can thus represent an unambiguous signature of full clonality.

5.7 Evolution and the Paradox of Sex

The paradox of sex essentially concerns parthenogenetic multicellular organisms and, as explained earlier, microbes are not concerned. This has been the subject of an impressive amount of literature and, except for plant parasitic arthropods (insects, mites) and nematodes, very few animal parasites are parthenogenetic (some nematodes, gyrodactilid monogens, rare cestodes, and trematodes) (De Meeûs et al., 2007b). It would be useless to do something more than a short reminder here. Parthenogenetic females produce twice as many offspring as sexually reproducing females that need to produce half "useless" males, which themselves cannot produce eggs. This has been called the twofold cost of sex (Hurst and Peck, 1996). Consequently, parthenogenetic females should quickly invade the whole planet. There are several reasons why this is not so, most of which are not exclusive and probably account together for the maintenance of sex in such situations.

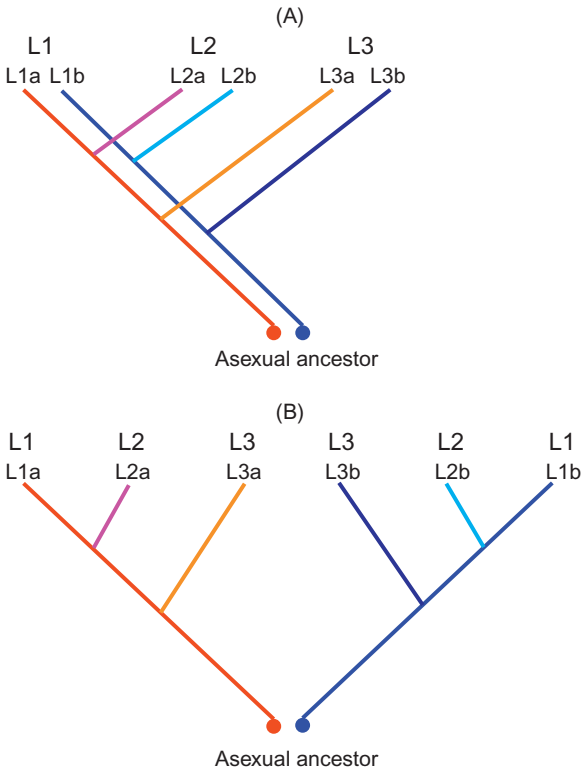

Figure 5.1 Illustration of the Meselson effect. In (A) the evolutionary relationships among three asexual diploid lineages are represented (L1−3). The genetic divergence is also represented with varying colors providing the two alleles present in each taxon (alleles a and b). If we develop the tree corresponding to all DNA sequences (all alleles) as in (B), it is easily seen that the maximum divergence is obtained between the two alleles of the same lineage. This is what is expected in ancient clones and can be used as a criterion for detecting a long absence of sex in a group of taxa (Meselson method). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this book.)

First of all, as mentioned earlier, the hijacking of SR for producing clonal descents is probably extremely difficult, and the diversity of tricks that evolved to achieve it, sometimes through extremely (at least in appearance) odd means, can be the sign of how difficult it is to reach that point. For instance, automictic parthenogenesis with fusion of two polar bodies illustrates this last point (see Figure 3b in De Meeûs et al., 2007b). The rarity of emergence of parthenogenesis, apparently restricted in few lineages (but this can be misleading because of biases in the intensity of work devoted to certain groups), can thus largely be explained by such constraints. For instance, it seems impossible to evolve in mammals or in birds.

Secondly, the problem only arises for populations that exclusively reproduce either sexually or parthenogenetically and for which these two morphs compete for the same resources. This might be rare. Some aphids might correspond to this, as for instance *Rhopalosiphum padi* (Delmotte et al., 2002), though it is not well established how similar the ecological niche of these two morphs is.

According to the red queen hypothesis (Judson and Normark, 1996), pure parthenogenetic females cannot efficiently fight against the continuously evolving aggressors (parasites and predators) or victims (preys or hosts) as compared to sexual females that produce many different combinations of offspring at each generation. This hypothesis alone has two important drawbacks. First, in pure sexuals, the

best combination is lost in the next generation. Second, most populations are not that polymorphic and often are small and thus inbred. The possible combinations created by SR might not be that diverse or new.

Muller's ratchet (Kondrashov, 1993) imposes to parthenogenetic lineages an accumulation of deleterious mutations that could lead to an eventual collapse of such lineages as compared to sexual lineages where deleterious mutations are more efficiently removed. This model alone also has two drawbacks. First it requires several generations to work efficiently, and might even be almost silent in diploids. Second, as above, small sexually reproducing populations might also be affected by Muller's ratchet.

Finally, as mentioned earlier and elsewhere (Schaefer et al., 2006), SR may also be viewed as a resetting process that evolved to restore the best combinations, a purpose for which it indeed evolved for in the first eukaryotes. Such a view also has the advantage to explain why SR often concerns genetically related partners, hence the evolution of reproductive isolation often observed in pluricellular eukaryotes (De Meeûs et al., 2003).

5.8 Clonal Microevolution

This aspect can be tackled differently depending on what kind of genetic information we are dealing with: neutral variation, and its use as a signature of demographic events, and variation under selection.

5.8.1 Neutral Loci Variability in Clonal Populations (Population Genetics Structure)

Neutral variation and its distribution in time and space can be used to make useful inferences on the population biology of the targeted organisms. Under certain hypotheses, several inferences can be made as regard to population size, dispersal, and reproductive mode. Most tools were developed for sexual species but recent works have made available equivalent tools for clonal populations (see De Meeûs et al., 2006, 2007a, 2009b for reviews). In that case special care must be given to how to deal with MLGs. For A cycles complete datasets must be kept. For I cycles, it was shown that besides analyzing complete datasets, population subdivision is better assessed if only a single representative of each MLG is kept (Prugnolle et al., 2005; Caillaud et al., 2006). For S cycles, it all depends where in the cycle individuals are sampled. A strategy similar to the one used for I cycles is to be used if individuals are sampled early after the last SR event. If individuals are sampled after a substantial amount of clonal generations, then a strategy similar to the one used for A cycles is preferred.

For A cycles, if clonal reproduction is so prevalent that no perceptible signature of any SR can be noticed, then tools specific to that situation should be used for ecological inferences. This of course must take into account some basic knowledge of the population. When the population can be assumed to be strongly subdivided

in numerous demes, it was shown that the number of migrants can be estimated through the formula (De Meeûs and Balloux, 2005; Nébavi et al., 2006):

$$N(m+u) = -\frac{1+F_{IS}}{4F_{IS}} \tag{5.1}$$

where N is the clonal subpopulation size, m the proportion of migrants that each subpopulation contain, u the mutation rate, and F_{IS} the Wright's fixation index (Wright, 1965; De Meeûs et al., 2007a) measuring inbreeding within individuals relative to inbreeding between individuals. In that case, estimating independently N and m, even if we assume u negligible as compared to m, is not easy and will require further studies. When the population can be assumed to comprise only two subpopulations, then more precise estimates can be made (Koffi et al., 2009):

$$N = -\frac{1+F_{IS}}{8uF_{IS}} \tag{5.2}$$

and

$$m = \frac{1}{2}\left[1 - \sqrt{\frac{F_{ST}}{F_{ST} - 4uF_{IS}}}\right] \tag{5.3}$$

where F_{ST} is Wright's fixation index measuring the between individuals inbreeding within subpopulations relative to inbreeding between subsamples. It also requires knowledge of u. Finally, when subpopulations are assumed completely isolated, their clonal size can be estimated as (Simo et al., 2010):

$$N = -\frac{1+F_{IS}}{4uF_{IS}} \tag{5.4}$$

Now if some SR influences the distribution of genetic diversity, then it is usually wiser to use classical population genetics tools (De Meeûs et al., 2007a) except for cases of extremely rare SR events where the behavior of most parameters is odd and thus inferences can only be very general (De Meeûs et al., 2006). Similar advice can be given for I and S cycles if individuals studied are sampled just after SR.

5.8.2 Selection and Adaptation in Clonal Populations

The vast majority of mutations are neutral or deleterious (Loewe and Hill, 2010). Extensive study of such mutations has explained the genetic diversity in many populations and has been useful for inferring population parameters and histories from data as explained earlier. Yet beneficial mutations, despite their rarity, are what cause long-term adaptation and can also dramatically alter the genetic diversity at linked sites (see Nielsen, 2005 for a review). Unfortunately, our understanding of their dynamics remains poor, especially in asexual populations.

Adaptation by natural selection occurs through the spread and substitution of mutations that improve the performance of an organism and its reproductive success in a particular environment. For example, this happens in a pathogen when an allele increases in frequency in the population because it confers a certain degree of resistance against a particular drug. Most early works on the dynamics of adaptation in asexual populations considered that beneficial mutations only occurred very rarely (Atwood et al., 1951a,b). Under such circumstances, the rates of adaptation of asexual populations is the same (all else being equal) as that of sexual populations and depends only on the time separating the appearance of two beneficial mutations. This conventional model, known as the "periodic selection" model, remained a very influential theory until the 1990s despite the classic works of Muller (1932) that clearly showed that the dynamic of adaptation in sexual and asexual populations could be very different when beneficial mutations were common.

One particularity of the dynamic of adaptation of asexual populations when beneficial mutations are common is that beneficial mutations that have arisen independently in different individuals cannot recombine and therefore have to compete for fixation. This effect is called "clonal interference" (Gerrish and Lenski, 1998; Desai and Fisher, 2007; Desai et al., 2007). To date, two main models of clonal interference have been proposed: the one-by-one mutation model (Gerrish and Lenski, 1998) and the multiple mutations model (Desai and Fisher, 2007; Desai et al., 2007). These two models differ in how and where new beneficial mutations appear. We will not enter into the details of these models here and we advise readers to refer to recent reviews for more details. We simply want to stress that, under the two models, beneficial mutations enter into competition and some beneficial mutations are therefore "wasted" during the process of adaptation (Gerrish and Lenski, 1998; Gerrish, 2001; Rozen et al., 2002; Wilke, 2004). This leads to a slowdown in the rate of adaptation in purely asexual populations as compared to sexual populations. Note that a similar effect was described for sexual populations in the case of physically linked genes, which is known as the Hill−Robertson effect (Hill and Robertson, 1966).

Clearly, a complete picture of adaptation in asexual populations should also include the impact of deleterious mutations. They indeed play an important role in adaptation because their presence influences the fate of beneficial mutations, and consequently affects the strength of clonal interference (Felsenstein, 1974; Charlesworth, 1994; Bachtrog and Gordo, 2004). It is indeed well established that deleterious mutations can cause a severe reduction in the adaptation rate, as a consequence of reducing the effective population size. The simplest situation corresponds to the case in which only beneficial mutations that occur in individuals that are mutation-free contribute to the adaptive process.

Here, we have mainly focused on complete clonal organisms (life cycle A with 100% clonality). As shown here, clonal reproduction occurs under several forms and in several life cycles. Models analyzing the dynamic of adaptation under such life cycles have not been done yet, but we think that as soon as a bit of recombination occurs the dynamic of adaptation will be similar to the one described by models dealing with the problem of interference (or Hill−Robertson effect) in sexual

organisms. However, since pure sexuals tend to lose the most beneficial combinations built in previous generations, clonal populations with rare sex probably display much more efficient adaptive dynamics. A rare sexual event can build an "optimal" combination that will be easily and faithfully propagated by clonal reproduction. This might help understanding the formidable adaptive speed of microbes and, in particular, pathogenic microbes.

5.9 Conclusions

Clonal reproduction is as old as life itself and is widespread in the living world. SR appeared in Eukaryota, after this group evolved mitosis, not as a propagation tool alternative to clonal reproduction but as a repairing tool to preserve the most harmonious combinations of the numerous genes necessary to build a eukaryotic cell and because of the mitosis apparatus that evolved only in this lineage, a necessary prerequisite for meiosis. Sex is totally linked to propagation only in two pluricellular lineages (Metazoa and Metabionta). Only in those complex lineages SR can be in competition with clonal reproduction under certain precise circumstances. Clonality is the most important propagation mode used by pathogenic agents and its genetic consequences must be understood precisely, though SR or recombination is also very important to take into account for those diseases that practice it. When SR is so rare that no signature can be found in the genetic architecture of populations, some specific patterns arise as presence of multilocus repeated genotypes and, for diploids, fixed heterozygosity. These patterns can be exploited for demographic inferences using specific tools. If SR has even a small influence, then classical tools of population genetics can be used to infer subpopulation sizes and dispersal. It is thus possible to infer population sizes and dispersal for clonal parasites with the study of variable molecular markers, which is good news as the populations of such organisms are difficult to study directly. Such information can reveal very important to understand the epidemiology of diseases.

Though purely sexual populations are at a theoretical advantage as compared to purely asexual lineages as regards the dynamics of adaptation, things become less clear if the most general case is taken into account. Clones with more or less rare sex (or recombination) may indeed represent an extremely efficient (and hence widespread) way to adapt to the environment. This helps explain the speed at which pathogenic agents respond to defense mechanisms, including pharmacologically mediated ones, of their victims.

Abbreviation list:

HGT Horizontal gene transfer
HW Hardy−Weinberg
LD Linkage disequilibrium
LUCA Last universal common ancestor
MLG Multilocus genotype
SR Sexual recombination

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