Genet. Res., Camb. (2005), **85**, *pp.* 171–181. *With* 1 *figure.*
doi:10.1017/S0016672305007585 Printed in the United Kingdom

Review

Models of the population genetics of transposable elements

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Summary

Although transposable elements (TEs) have been found in all organisms in which they have been looked for, the ways in which they invade genomes and populations are still a matter of debate. By extending the classical models of population genetics, several approaches have been developed to account for the dynamics of TEs, especially in *Drosophila melanogaster*. While the formalism of these models is based on simplifications, they enable us to understand better how TEs invade genomes, as a result of multiple evolutionary forces including duplication, deletion, self-regulation, natural selection and genetic drift. The aim of this paper is to review the assumptions and the predictions of these different models by highlighting the importance of the specific characteristics of both the TEs and the hosts, and the host/TE relationships. Then, perspectives in this domain will be discussed.

1. Introduction

The existence of mobile genetic elements was posited in *Zea mays* in the 1940s by Barbara McClintock (for a detailed chronology, see McClintock, 1984). During the last two decades, hundreds of transposable element (TE) families have been identified from almost all living organisms, including bacteria, fungi, protozoa, green plants and animals (Craig *et al*., 2002). TE copy number can be high enough to represent a significant part of the nuclear DNA, as in *Drosophila melanogaster* (15%: Adams *et al*., 2000), *Homo sapiens* (40%: Lander *et al*., 2001) or *Zea mays* (70–85%: Craig *et al*., 2002).

The complex relationships between TEs and genomes suggest several hundred million years of co-evolution. Transposition events, leading to TE insertions into coding, intronic, promotor or intergenic sequences, may increase the mutation rate and modify gene expression or regulation patterns. In specific situations, such as stress, activation of TEs may contribute to genetic and phenotypic variability (Arnault & Dufournel, 1994; Capy *et al*., 2000). Although there are well-known examples of TE insertions fixed in genomes that have become structural genes by a molecular domestication process (Miller *et al*., 1999; Kidwell & Lisch, 2001; Maside *et al*., 2002; Jordan *et al*., 2003; Schlenke & Begun, 2004), most TE movements are deleterious for the host (Mackay, 1989; Pasyukova *et al*., 2004). The reason for the presence of TEs in genomes is thus certainly not only due to their ability to cause rare adaptive mutations, but rather to their capacity to invade genomes by transposition (Brookfield, 2003).

Further analysis needs *ad hoc* population genetics models. During the last 20 years, several models of TE dynamics have been proposed (Charlesworth *et al*., 1994*a*), from universal models to highly specific ones. The acquisition of new population and molecular data has led to a modification of the initial models and has suggested new fields of investigation. In this review, a short synthesis of these two decades of TE evolution modelling is presented. The major types of models are discussed, focusing on their specific assumptions, the consistency of their respective predictions and their relevance to biological situations.

2. Population genetics of TEs

Transposition is the mechanism by which TEs move in a genome. The copy number change can be positive (increase in TE copy number by duplication), negative

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(loss of TE copies by transposition-related excision) or null (TE movements by excisions followed by insertions). TEs can also be lost by transposition-independent genomic events, such as deletion due to recombination between the long terminal repeats or between elements in direct orientation on the same chromatid. If the probability of duplication is the same as that of deletion, the element can, however, spread through a population by chance. The dynamics of such sequences, sometimes called 'ignorant DNA' (Dover & Doolittle, 1980), is characterized by an increase in the variance of the genomic copy number (Ohta, 1981; Ohta & Kimura, 1981). Thus, even if they are selectively neutral, TEs will eventually be lost by drift. In these conditions, the only way to maintain a TE in a population is by the regular introduction of new copies by mutation, migration, recurrent horizontal transfers (Ohta, 1983) or more duplication than excision. Indeed, since individuals carrying numerous deleterious elements will be eliminated through natural selection, another mechanism, such as replicative transposition, has to counterbalance the decrease in the mean TE copy number (Hickey, 1982). This last process makes the 'parasitic' or 'semi-parasitic' hypothesis mathematically possible.

More precise numerical models (Brookfield, 1982) fail to generate stable equilibrium in copy number when a set of simple parameters is considered (constant duplication rate and selection coefficient). As TEs seem to maintain themselves in genomes, this last result shows that studies of TE dynamics require more detailed population genetics models. The aim is to define the conditions of TE maintenance, i.e. stable copy number equilibrium. Indeed, without any mechanism except transposition, TE copy number is expected to grow exponentially, which cannot be realistic. Charlesworth & Charlesworth (1983) have proposed models of TE dynamics based on two non-exclusive assumptions. In the first model, termed 'neutral', the TE copy number is supposed to be limited by a decrease in the transposition rate in the course of the invasion. In the second one, termed 'selection model', the TE colonization is restrained by selection against the deleterious effects of element insertions.

(i) *Neutral model*

Dynamics of self-regulated elements. The first case analysed by Charlesworth & Charlesworth (1983), the self-regulation of copy number, assumes neutrality of TE insertions. The first version of this model is derived for a population of infinite size. The equation obtained is based on the idea that the strength of self-regulation varies slightly with the copy number, u_n representing the rate of replicative transposition per copy and per generation, for an individual with n copies. The higher the TE copy number, the more the rate of transposition is reduced (i.e. u_n decreases with n). In this case, the average copy number varies each generation approximately as follows:

$$\Delta\bar{n} \approx \bar{n}(u_{\bar{n}} - v) \tag{1}$$

where v is the rate of deletion (considered to be constant). The elements are able to invade the genome provided $u_{\bar{n}} > v$ when $\bar{n}$ is small. The non-trivial equilibrium point, $\bar{n}^*$, is obtained when $u_{\bar{n}^*} = v$, and is locally stable because the rate of transposition decreases with n. Moreover, it can be shown that, under both assumptions (neutral and selection), when the number of available insertion sites T is large relative to $\bar{n}^*$, the distribution of copies over all sites becomes uniform and tends to a Poisson distribution with mean $\bar{n}^*$.

In a finite population, this self-regulation model can be analysed through the equation known as the forward Kolmogorov equation or 'diffusion equation' (Crow & Kimura, 1970). As for a diallelic locus with reversible mutation (Wright, 1931) the equilibrium distribution of the frequencies of elements at individual sites is a beta distribution (Fig. 1). Langley *et al.* (1983) reached an equivalent conclusion for infinite T.

Emergence of regulation. The source of this regulation can come from the host (e.g. if transposition depends on a host factor: Badge & Brookfield, 1997) or from the element itself. This latter possibility requires the emergence of mutant copies with regulatory ability, either locally (transposition immunity) or over the whole genome (transposition repression). Transposition immunity is known for some TEs in bacteria (bacteriophage Mu or Tn7) but has not been identified in eukaryotes (Chandler & Mahillon, 2002), while transposition repression is a more widespread phenomenon (e.g. *KP* element and *A1* element which repress the *P* element: Jackson *et al.*, 1988; Marin *et al.*, 2000).

In an asexual species, if TE accumulation is deleterious, individuals having a mutant regulatory copy of a TE clearly have an advantage, and their offspring will invade the whole population (Doolittle *et al.*, 1984). When the host reproduces sexually, meiosis breaks the association between regulatory mutants and low TE copy numbers in the genomes, leading to a more complex situation. Charlesworth & Langley (1986) studied the dynamics of a rare mutant TE in a population of a sexual species which had previously reached a balance between transposition and selection (see next subsection). This model shows that, for an organism with free recombination, evolution of self-regulation seems unlikely, especially under the transposition repression hypothesis, unless a fraction of transpositions result in dominant lethal mutations. However, the rates of lethal mutations required seem to be too high to be realistic in a deleterious TE

https://doi.org/10.1017/S0016672305007585 Published online by Cambridge University Press

	α	β
neutral model	$\frac{4N\bar{n}u_{\bar{n}}}{T-\bar{n}}$	$4Nv$
selection model	$\frac{4N\hat{n}u}{T-\hat{n}}$	$4N(v+\left\|\frac{\partial \ln w_{\hat{n}}}{\partial \hat{n}}\right\|)$
+ migration	$+\frac{4Nm\bar{n}}{T}$	$+\frac{4Nm(T-\bar{n})}{T}$

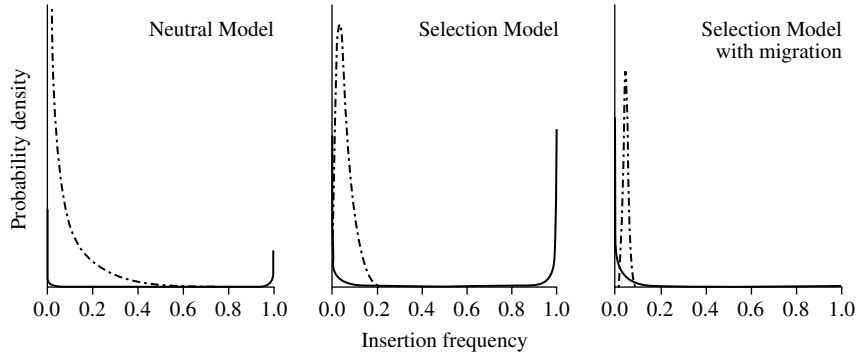

Fig. 1. In a finite population, stationary distribution of insertions generally follows a beta, or a beta-like distribution, defined by two parameters, α and β. The form of distribution depends on the value of α: if $\alpha<1$, then the curve admits a vertical asymptote at 0 (most sites occupied by low-frequency elements), or if $\alpha\geqslant 1$, the associated graph admits a mode (many sites with a frequency close to this mode). α and β parameters can be computed for the self-regulation model and the selection model as described in the upper part of the figure. The average copy number in finite population is denoted by $\hat{n}$. Moreover, an additional term can be added in order to take account for migration (Charlesworth & Charlesworth, 1983). In practice, the estimates from natural populations suggest $\beta>2$ (Charlesworth & Lapid, 1989; Charlesworth *et al.*, 1992*a*; Biémont *et al.*, 1994) although their variances are substantial (Quesneville *et al.*, 1994). The lower part of the figure shows the shape of the distribution with an equilibrium copy number in an infinite population of $\bar{n}^*=50$. For the neutral model, we used the transposition function $u_n=u_0/(1+kn)$ with $u_0=0{\cdot}01$ in equation (1), and for the selection model, the fitness function in equation (2) was $w_n=1-sn$ (Charlesworth & Charlesworth, 1983), with s fixed to obtain an equilibrium of 50 copies in an infinite population. Other parameter values were: $u=0{\cdot}001$, $v=0{\cdot}0001$, and $m=0{\cdot}01$ if migration is allowed. Dotted lines, population size $N=10\,000$; continuous lines, population size $N=50$.

insertion model, because damage due to TE insertions is probably at least partially recessive (Mackay, 1989). Nevertheless, self-regulation could evolve if a proportion of the transposition events directly induce sterility (Brookfield, 1991), as is found in the *P-M* hybrid dysgenesis system in *Drosophila* (Kidwell, 1985).

Whatever the class of the element, average transposition rates are usually estimated to be around 10^{-4} or 10^{-3} whereas excision rates are at least one order of magnitude smaller (Charlesworth *et al.*, 1992*a*; Nuzhdin & Mackay, 1995; Suh *et al.*, 1995; Vieira & Biémont, 1997; Maside *et al.*, 2000). Genomic deletions which are not transposition-related may also eliminate TE copies in a way which is formally equivalent to excision. Their frequency and size can be very different among species (Petrov *et al.*, 1996; Petrov, 2002). The neutral model is therefore unlikely to be the sole factor, because in this model $u=v$ at equilibrium.

(ii) *Selection model*

As many mutations are induced by TEs in *Drosophila*, Charlesworth & Charlesworth (1983) proposed a model of selection against the deleterious effects of TE insertions. The average fitness of the population was approximated by $w_{\bar{n}}$, the fitness of an individual with an average number of copies. When the number of available insertion sites T is large compared with the mean copy number per genome, the change in the average copy number between generations thus becomes:

$$\Delta\bar{n}\approx\bar{n}(\partial \ln w_{\bar{n}}/\partial\bar{n})+\bar{n}(u-v). \quad (2)$$

Copy number grows and a stable equilibrium point exists provided $u>|(\partial \ln w_n/\partial n)_{n=0}|+v$. Moreover, the local stability of this point is guaranteed if the fitness function satisfies $-1/\bar{n}^*<\partial^2 \ln w_{\bar{n}^*}/\partial\bar{n}^{*2}<0$. In a finite population, when the effective size is large enough for efficient selection, the insertion frequencies are beta distributed, as for the neutral model (Fig. 1). However, here, as natural selection becomes less efficient in a small isolated population, the expected equilibrium copy number is higher than $\bar{n}^*$, the value for the infinite population model.

(a) *Nature of selective forces*

A deleterious impact of TE insertions, predicted by theory and repeatedly observed in experiments

https://doi.org/10.1017/S0016672305007585 Published online by Cambridge University Press

(Biémont *et al*., 1997*a*; Charlesworth *et al*., 1997; Mackay, 1989), appears to be generally valid. Initially, the models implicitly supposed that fitness was coupled with such deleterious effects of TE insertions, as in Charlesworth & Charlesworth (1983). However, some experimental evidence suggests that this deleterious insertion model is probably not the only selective effect involved in TE dynamics (see below). Persistence of TEs in natural populations thus needs to be explained by modifying the deleterious insertion model, or by assuming other modes of selection, such as ectopic recombination or deleterious transposition.

Deleterious insertion model. Charlesworth (1991) refined his previous model by relaxing the assumption of homogeneity of selection coefficients. If the genome contains neutral, slightly selected and strongly selected TE sites, the sufficient conditions to maintain TEs are restrictive and generally involve the accumulation of copies in the neutral sites. Only the parameter values close to the limit of the extinction condition for TEs predict a realistic number of copies in the neutral sites, with at least several tens of times fewer copies in the strongly selected sites. However, the neutral sites might correspond to heterochromatic regions, mainly composed of non-coding repeated DNA sequences. If TEs inserted in neutral sites cannot transpose, a realistic equilibrium of the copy number for each type of site is possible if the selected sites are only subject to very slight selection. Tsitrone *et al*. (1999) reached very similar conclusions by assuming recessivity for TE insertions for some sites. Moreover, they showed that, in this situation, the slowness of the process is such that a non-equilibrium state could be maintained over a relatively long period of time. Factors such as random genetic drift can therefore maintain the system far from equilibrium.

Ectopic recombination model. Accumulation of TE copies in a genome leads to a multiplication of homologous sequences along the chromosomes. Recombination between elements inserted into different sites can cause various chromosomal rearrangements, such as inversions, deletions or translocations (Langley *et al*., 1988; Capy *et al*., 1997). Because unequal exchange can induce the formation of aneuploid gametes, this process leads to a reduction in the fertility of the host. The ectopic recombination model seems to be an attractive explanation for the restriction of the TE expansion, partly because its effects on fitness probably increases with the square of copy number, so that the equilibrium conditions suggested by equation (2) can be satisfied for a wider range of parameters, increasing its likelihood.

Modelling of selection against ectopic recombination induced by TEs has been carried out assuming the existence of a non-trivial equilibrium (Langley *et al*., 1988). When the rate of ectopic exchanges in each region is assumed to be proportional to the regular meiotic exchange, and neglecting the rate of excision, it is expected that the number of TE copies inserted in a given region is inversely proportional to its rate of regular exchange for recombination occurring randomly between all copies, or to its square root if recombination only occurs between nearby copies. In other words, TEs can accumulate in the low-recombination parts of the chromosomes.

Deleterious transposition model. In the particular case of an element existing in autonomous and mutant form, such as the *P* element in *D. melanogaster*, Brookfield (1991, 1996) proposed that selection against transposons (i.e. the DNA-based elements) would not act against insertions but against the transposition process, which can directly reduce fitness. The decrease in fitness generated by element transposition results mainly from the failure to repair double-strand breaks. Mutant copies, which do not produce the necessary enzymes for transposition, can eventually invade populations and eliminate the complete copies. Using a specific variant of this model for a metapopulation, Quesneville & Anxolabéhère (1998) have shown that migration favours an increase in the number of mutant copies. In contrast, defective mutants of retrotransposons (i.e. the RNA-based elements) would quickly be eliminated because selection acts in the same way on complete and mutant copy insertions. This conclusion regarding the difference between transposons and retrotransposons in the dynamics of mutants has also been reached for a neutral model, where one-way mutation from active to mutant copies was assumed (Kaplan *et al*., 1985). Contrary to other cases, this model predicts TE extinction after less than 100 generations for a population of 100 individuals to more than 100 000 generations for a population of 10 000 individuals.

(b) *Confrontation of models with data*

There is still no consensus on the way in which selection acts on TEs. For example, as the X chromosome is hemizygous in *D. melanogaster*, it is expected that selection tends to reduce its proportion of insertions with respect to the autosomes. The different models of selection thus predict different proportions of euchromatic insertions on the X chromosome compared with the autosomes at equilibrium, but the results of these tests are very difficult to interpret and it has been shown that the abundance of TE copies on the X chromosome relative to the autosomes is very heterogeneous between TE families (Biémont, 1992; Charlesworth *et al*., 1992*b*; Biémont *et al*., 1994; Carr *et al*., 2002). For instance, a recent mobilization of elements can skew the tests in favour of the neutral model, because if any selection acts against TEs, time is necessary to detect some visible effects. Different TE

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transposition rates in the female or male germlines can also influence the proportion of TE copies on the X chromosome in comparison with the autosomes, leading thus to an incorrect rejection of some models. Several other results must also be considered. According to equation (2), and following the deleterious insertion model, the selection coefficient associated with the deleterious effect of one insertion must be of the same order of magnitude as the transposition rate for a realistic, non-null copy number equilibrium to be reached (Charlesworth, 1991, 1996). Several studies report selection coefficients close to or above 1%, against either genomic mutations in general (probably mainly due to TE-derived mutations: Keightley, 1994; Charlesworth *et al*., 2004), *P* element insertions (Eanes *et al*., 1988) or *copia* insertions (Houle & Nuzhdin, 2004). Even though these estimates have large errors, the likelihood of the deleterious insertion model seems nevertheless very low.

During experiments, several authors have observed TE accumulation in the regions where recombination rate is reduced or null, such as the proximal and distal regions of the major chromosome arms in *Drosophila* (Langley *et al*., 1988; Charlesworth *et al*., 1992*b*, 1994*b*). However, these regions are known to be heterochromatic regions, in which nearly all models predict increased TE abundance (Biémont *et al*., 1997*b*; Charlesworth *et al*., 1997). Nevertheless, some analyses of the *D. melanogaster* genome show that TEs seem to accumulate not only in heterochromatic regions but also in euchromatic regions with low recombination rate (Bartolomé *et al*., 2002), where some copies are fixed (Bachtrog, 2003; Bartolomé & Maside, 2004). This suggests that the less a TE copy is affected by recombination, the less it will be under selective constraints, which could imply that ectopic recombination is an important selective factor in TE dynamics. However, a negative correlation between element density and the recombination rate is not always observed in *Drosophila* (Hoogland & Biémont, 1996; Rizzon *et al*., 2002). In other organisms, such as *Arabidopsis thaliana* (Wright *et al*., 2003) or *Caenorhabditis elegans* (Rizzon *et al*., 2003), TE insertions do not accumulate in low-recombination regions, maybe because of the high selfing rate of these species. The accumulation of TEs in low-recombination regions could also reflect a reduction of the selection efficiency on linked insertion sites, the Hill–Robertson effect (Hill & Robertson, 1966). Therefore, even if conditions where the intensity of ectopic exchange is relaxed seem to be associated with higher element abundances and frequencies, elements do not necessarily go to fixation in these regions, suggesting either that other factors may be limiting their spread, or that ectopic exchange is still occurring at a sufficient rate to be effective.

Many difficulties encountered in the validation of models could come from stochastic noise induced by genetic drift. Population size reductions, decreasing the power of purifying selection, may lead to a proliferation of sequences such as TEs (Lynch & Conery, 2003). Brookfield & Badge (1997) showed that, in very small populations, TEs can keep a much higher mean copy number than expected in an infinite population or, alternatively, may disappear. However, the population sizes involved in such situations are several orders of magnitude below estimated sizes in *Drosophila* (Biémont *et al*., 1994). This would indicate that drift is ineffective when faced with the strength of the forces implied by the distributions of TE insertion frequencies (Charlesworth, 1988).

3. Specific models

(i) *Hybrid dysgenesis and complex regulation systems*

The general models presented above do not take into account the specific features of the TEs or the host species. However, in some cases, as in hybrid dysgenesis (Kidwell, 1985; Engels *et al*., 1990), genetic and molecular studies have highlighted some significant interactions between TEs and the host genome. These interactions are so specific that detailed models have been developed. Hybrid dysgenesis is a syndrome within a species that is dependent on the direction of mating. The offspring of a dysgenic cross exhibit various phenotypic features, including low fertility and male recombination. The syndrome has been described following analysis of several independent crosses in *Drosophila* (Brégliano & Kidwell, 1983), and in each case the genetic factor involved is a TE. The mobilization of these TEs is greatly enhanced in germinal cells of the offspring of a cross between a male carrying elements and a female devoid of the active element. Further studies of the *P-M* system showed the complex pathways involved in transposition regulation, including maternally inherited repressor cytotype and defective *P* elements (Castro & Caratero, 2004). Several models confirm that the dramatic increase in transposition rate that is associated with *P-M* hybrid dysgenesis makes the invasion of a local population possible in a few generations (Uyenoyama, 1985; Brookfield, 1991). Following migration of flies, diffusion of *P* elements in all the species then occurs rapidly (Quesneville & Anxolabéhère, 1998). At the same time, selection against *P* transposition promotes a decrease in the transposition rate by the accumulation of repressor elements. Dependent on the number of active *P* copies present in the population before stabilization, different equilibria will be reached (Brookfield, 1991; Quesneville & Anxolabéhère, 1997). Data from natural

populations agree well with these models. However, they cannot really be validated because their complexity requires several parameters which are difficult to estimate (such as mutation rates). The values of these parameters are therefore generally chosen arbitrarily in order to fit the data (Quesneville & Anxolabéhère, 1998).

(ii) *Breeding system and self-fertilization*

Even though the majority of data come from *Drosophila*, the general models described above apply to all sexual diploid organisms with panmictic populations. However, if panmixia seems to be a good approximation for most animals, this is not the case for autogamous plants. In these organisms, the level of outcrossing is low and there is a deficit in heterozygotes compared with panmictic populations. Genetic and phenotypic variances between individuals increase with self-fertilization, and natural selection is more efficient (Burt & Trivers, 1998). The models of Wright & Schoen (1999) and Morgan (2001) present convergent results. TE dynamics in selfing populations appear to be extremely sensitive to the mode of selection. Under a deleterious insertion model, as the level of self-fertilization increases, the mean TE copy number decreases, and the probability of losing TEs during the first steps of an invasion increases. The ectopic exchange model produces the opposite effects. Indeed, ectopic recombination may be more frequent in heterozygotes compared with homozygotes, because homozygous elements are normally paired during meiosis, preventing them from being subject to ectopic recombination (Charlesworth & Charlesworth, 1995). Thus, the fitness of homozygotes is superior to that of heterozygotes, and, the higher the self-fertilization rate, the higher is the average TE copy number. Comparison of TE copy numbers between species with different mating systems appears to be the best way to identify the selective pressures on TEs.

Comparison of the TE insertions pattern between the autogamous species *Arabidopsis thaliana* and the allogamous closely related species *A. lyrata* seems to agree with the predictions of the ectopic recombination model, since the number of insertion sites is slightly higher in *A. thaliana* despite an approximately 4 times smaller genome (Wright *et al*., 2001, 2002). Nevertheless, this difference implies a very large difference in ectopic recombination frequency between homozygous and heterozygous elements (Morgan, 2001). In selfing species, TE abundance is generally negatively correlated with gene density, but not with recombination rate (as, for instance, in *A. thaliana*: Wright *et al*., 2003; and in *Caenorhabditis elegans*: Rizzon *et al*., 2003). This would imply that a high rate of self-fertilization reduces the role of ectopic exchange in preventing the spread of TEs. However, there is still no clear evidence for a correlation between TE copy number and self-fertilization rate (Morgan, 2001).

(iii) *High-frequency TEs in mammals*

Mammalian TEs are mostly retrotransposons, and particularly non-autonomous (mutated or truncated) elements, such as SINEs (Weiner, 2002). The way in which elements are mobilized varies mainly between two situations: all elements are able to transpose (random template model), or only one element in the genome is active (master copy model), with all intermediates (Clough *et al*., 1996). Contrary to the organisms cited above, the number of active TE families is generally small, but the number of copies per family is very high (e.g. Lander *et al*., 2001; Vassetzky *et al*., 2003). The population structure of mammals is also different, with generally small population sizes, especially in hominoids (Yang, 2002). In addition, the insertion frequency in each site is high compared with *D. melanogaster*, and fixation is common. Such an accumulation is consistent with a mixture of neutral and selected sites (Charlesworth, 1991), suggesting a much greater proportion of neutral sites. Moreover, this accumulation of TEs is consistent with the fact that deletions appear to be far less frequent in a mammalian genome than in *Drosophila* (Charlesworth, 1991; Petrov & Hartl, 1998). Insertions are generally so persistent that they can be used as markers for population genetics (Brookfield, 1986; Ohta, 1986; Tachida & Iizuka, 1993; Tachida, 1996) or phylogenetic studies (e.g. Mamedov *et al*., 2005).

(iv) *Clonal organisms: when elements become advantageous*

The models described above are based on the biology of eukaryotes, and selfish DNA sequences can invade only if there is some sexual or quasi-sexual exchange among individuals (Hickey, 1982). Moreover, when population sizes are large, selection against useless DNA is strongly efficient (Lynch & Conery, 2003); under such conditions, cell lineages carrying deleterious TE insertions will quickly disappear. Prokaryotes are frequently in both situations (i.e. low recombination and large populations), and the presence of TEs in their genomes might appear to be unlikely. However, almost all organisms host TEs, even clonal ones which have a low number of elements (Arkhipova & Meselson, 2000, 2004; Craig *et al*., 2002).

One way to explain TE persistence in clonal organisms is to assume TE copies are frequently exchanged horizontally (e.g. by parasexual transmission in bacteria). This could explain the co-occurrence of several families of insertion sequences coming

from other species observed for *Escherichia coli* (Sawyer *et al*., 1987; Hartl & Sawyer, 1988). Another simple hypothesis may rely on a potentially positive impact of TE insertion on cell fitness. If an active element that is inserted in a precise site in the genome leads to an improvement in the multiplication ability of the cell, then the corresponding clone will spread through the whole population. All the elements of the genome will thus spread by hitch-hiking, even if some of them have a neutral or slightly deleterious effect. A stochastic model confirms that beneficial mutations can realistically show up regularly during thousands of generations in bacteria (Martiel & Blot, 2002). However, if the proportion of adaptive mutations decreases each time a mutant goes to fixation, this model shows that the increase in fitness is bounded. Edwards & Brookfield (2003) have shown that a very long-term persistence of a TE in clonal organisms is possible when populations evolve in two alternative environments: TEs can inactivate useless genes by insertion in one environment and reactivate these genes by excision in the other environment. The range of parameters, notably the environment-cycle period, which leads to the maintenance of the elements is wide enough to let one think that many prokaryote species could be in such a situation.

4. Conclusion

(i) *What do we know after two decades of modelling?*

As shown in this paper, many models of TE dynamics have been put forward since the selfish DNA hypothesis arose (Doolitle & Sapienza, 1980; Orgel & Crick, 1980). Moreover, a considerable amount of data has been accumulated concerning the molecular characteristics of TEs and their distribution in natural populations and laboratory strains. The main conclusion of almost all the models is that the selfish DNA hypothesis has a robust theoretical base. Even when it is deleterious for its host, a DNA sequence with the capacity to self-replicate is able to invade a genome. In the absence of other factors, self-replication leads to an exponential increase in the element copy number. Two evolutionary forces have been proposed to explain the containment of TE copy number in populations: regulation and selection. Several self-regulation examples are known in various organisms, but regulation alone does not seem able to explain observed insertion patterns, and selection certainly plays an important part in TE dynamics. However, there is still no consensus about the way selection acts against TE accumulation, and the biological evidence is sometimes conflicting (Biémont *et al*., 1997*a*; Charlesworth *et al*., 1997). Once again, these different selective mechanisms certainly coexist, and their respective importance may vary according to the organism and the TE being considered.

(ii) *… and what do we not know?*

Despite a significant amount of both experimental and theoretical work, the evolution and dynamics of TEs still raises many questions. Most theoretical studies provide predictions for populations in which TEs have reached an asymptotic equilibrium state (Charlesworth & Charlesworth, 1983). Consequently, population studies suppose that TEs hosted by natural populations are at equilibrium, even if their true state is clearly unknown. If the equilibrium is not reached, estimates of selection coefficient or beta distribution parameters may be more or less biased. Several new mobilizations (or remobilizations) have been reported that are respectively caused by horizontal transfers (Daniels *et al*., 1990; Simmons, 1992; Silva *et al*., 2004; Sánchez-Gracia *et al*., 2005), responses to stress (Arnault & Dufournel, 1994; Capy *et al*., 2000), mutations of restrictive alleles of the host (Nuzhdin, 1999) or crosses between geographically distant strains (Kidwell & Lisch, 2001). Numerous observations indicate that populations are not at equilibrium (e.g. the recent invasion of *P*, *I* and *hobo* elements in *D. melanogaster*), and mobilization or demographic events may regularly move populations out of equilibrium (Tsitrone *et al*., 1999) and towards new equilibria. Hence, a small number of populations might be at equilibrium while the rest of the species is still in an unstable state. The dynamics during such a transitional stage may be noticeably different from that of the equilibrium state, i.e. with abrupt changes in transposition rates or TE losses in the initial steps of the invasion (Le Rouzic & Capy, 2005). Moreover, in a structured population, the balance between transposition and migration rates can play a major role in the dynamics of TEs (Deceliere *et al*., 2005). Thus experimental data on TE distribution must be used with great care for the validation of models.

TE theoretical dynamics are well known for ideal situations, but more complex and realistic hypotheses lead to analytical difficulties. Precautions are necessary before generalizing the results obtained with a model organism to other organisms, even closely related ones (Kidwell & Evgen'ev, 1999; Vieira *et al*., 1999; Biémont *et al*., 2003). As highlighted above, mammalian TEs are very different from those of *Drosophila*. In fact, most studies of mammalian elements suggest that some families are still expanding in the genomes, which means that equilibrium has not been reached. Selection and deletion, supposed to balance the transposition pressure, appear to be radically different in vertebrates and insects.

The complexity of the TE–host system is partly due to the multiple interactions between TEs and the rest

https://doi.org/10.1017/S0016672305007585 Published online by Cambridge University Press

of the genome. If the whole genome can be considered as an ecosystem, each of its components (i.e. each gene or each sequence) will interact with all other components, in mutualistic, commensal or parasitic ways (Leonardo & Nuzhdin, 2002; Brookfield, 2005). The corresponding modelling background already exists in ecology (Bascompte & Rodriguez-Trelles, 1998; Mauricio, 2005), and its adaptation to this new problem presents an exciting challenge for the understanding of the evolution of junk DNA.

We thank Christian Biémont and Pierre Capy for their careful reading of the manuscript and their comments. We also acknowledge Brian Charlesworth, who provided very insightful suggestions and corrections on an earlier draft of this paper, and anonymous referees, who suggested some substantial improvements. The English text was reviewed by Monika Ghosh. This work was partly supported by the GDR 2157 'Évolution des éléments transposables: du génome aux populations' and by the bioinformatics programme of the French Ministry of Research.

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