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Models of the spread of non-autonomous selfish transposable elements when transposition and fitness are coupled

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Summary

I investigate models of the spread of transposable elements, such as the *Drosophila melanogaster* P elements, that can exist in autonomous and non-autonomous forms. Elements which have their major impact on host fitness in the process of transposition can, under certain conditions, come to a stable balance between transposition and selection. This stable balance for autonomous elements can be disrupted by the invasion of further elements, which do not produce a transposase enzyme, and may produce a repressor of transposition. I examine this secondary invasion process, and show that a stable equilibrium copy number for intact elements is neither a necessary nor a sufficient condition for non-autonomous elements to invade. Nevertheless, invasion occurs under a broad range of models and conditions. This requires neither that the non-autonomous elements produce a *trans*-acting repressor of transposition, nor that they titrate transposase. The elimination of autonomous elements follows the increase in non-autonomous elements unless the latter encode powerful repressors of transposition. Approximate solutions for the equilibrium copy number of autonomous elements and rate of invasion of non-autonomous elements can be found under some models for transposition and selection. The predictions of the model are compared with recent empirical studies of the *D. melanogaster* P system.

1. Introduction

Many families of transposable genetic elements are found in two forms: as intact, or autonomous elements, which include all sequences required for transposition, and as deleted forms, in which sequences required in *trans* have been lost, and only sequences required in *cis* remain. These deleted forms are still capable of transposition if they are found in the same cell as active transposable elements encoding a *trans*-acting transposase protein. Such pairs of elements include numerous transposable element families from *Zea mays*, such as *Activator* (autonomous) and *Dissociation* (non-autonomous) and autonomous and defective *Suppressor-mutator* elements (for reviews see Federoff, 1989; Gierl *et al.*, 1989). Perhaps the best studied example is the *Drosophila melanogaster* P element family (Engels, 1989). This element has spread rapidly through *D. melanogaster* populations in this century. This has occurred as a result of a transposition mechanism which, while conservative at the molecular level, is made effectively replicative by subsequent gap repair, in which the double-strand break generated by excision is repaired using a donor P element from the homologue or sister chromatid (Gloor *et al.*, 1991; Nassif *et al.*, 1994). In this family, it appears that the intact form is being replaced in many parts of the world by deleted forms (Anxolabéhère *et al.*, 1985, 1987, 1988). Some of these deleted forms apparently act as repressors of transposition (Kidwell, 1985; Black *et al.*, 1987; Raymond *et al.*, 1991; Heath & Simmons, 1991). One in particular, called KP, is very common in Eurasian populations and may repress transposition (Black *et al.*, 1987; Jackson *et al.*, 1988). It rapidly increases its copy number in some laboratory populations in the presence of intact P elements (Jackson *et al.*, 1988).

There is also a maternally inherited system of regulation called P-cytotype, such that transposition occurs at high frequency only in the germ cells of animals lacking P-cytotype (described as being of M-cytotype). This is in addition to the zygotically acting repression that can be provided by repressor elements. The intact P element can, by alternative splicing pathways, produce an 87 kDa transposase protein, and a 66 kDa protein now shown directly to be a repressor of transposition (Misra & Rio, 1990). This

protein, produced from some modified P elements, is strongly implicated in P-cytotype (Nitasaka *et al.*, 1987; Robertson & Engels, 1989), but the precise mechanism for the maternal inheritance remains obscure (Rio, 1990). A pair of P elements on the distal end of the X chromosome have been identified in some European populations of *D. melanogaster* which are able, by themselves, to produce a maternally inherited repression of P movements (Ronsseray *et al.*, 1991).

Unrepressed transposition is associated with hybrid dysgenesis, a syndrome of traits including low fertility, particularly at elevated temperatures. This occurs in the F_1 if males from a P strain (bearing intact P elements) are crossed to females which lack P elements (M strains). (M′ strains have also been observed, and act genetically as M strains, despite possessing some P elements.) The restriction of the harmful effects of transposition to the germline results from transposase expression being germline-specific, produced through the cell-type-specific splicing of the P transcript (Laski *et al.*, 1986). When high levels of transposition are induced somatically a lethal phenotype can result (Engels *et al.*, 1987). Hybrid dysgenesis implies that the selection coefficients associated with transposition may be very much higher for P elements than for other transposable element families.

In an effort to understand this spread of deleted forms, I (Brookfield, 1991) investigated, using computer simulation, the interaction between transposition and selection which occurs when a population of parasitic transposable elements contains both intact and deleted elements (some of which may encode proteins which are repressors of transposition). Crucial to the situation was the nature of the fitness reduction imposed by the transposable element on the host. For many elements, in which the harmful effects of transposable elements arise through their interspersed pattern making them targets for ectopic recombination, deleted elements, transposing less quickly, cannot spread (Charlesworth & Langley, 1986, 1989). When, however, it is transposition itself that harms the host, deleted elements may spread. My models included one specifically designed to approximately duplicate the situation of the P family of transposable elements (model B). One result was general to all the simulations that I performed, which differed greatly in their parameters and initial conditions. This was that, given that a stable copy number of intact elements can be generated as a result of the balance between transposition and selection, the population can be invaded by deleted elements which can spread to replace the intact ones. As a result of the elimination of the *trans*-acting proteins required for transposition, the elements now become stable, and host fitness is restored to 100%. Deleted elements were defined as being of two types: inert elements, which could be mobilized by the transposase generated by intact elements, but which encoded no proteins of their own, and repressor elements, which were also transposable and which generated a protein which acted as a repressor of transposition. Both element types spread, but repressor elements do so more quickly.

Here I investigate model B in more detail. Specifically, I ask three questions:

(i) Elements with a *trans*-acting repressor function spread more rapidly than inert elements. How does increasing the power of such repressors affect their spread?
(ii) Inert elements still titrate transposase, thereby reducing the transposition rate of any intact element which shares their cell, although their presence still increases the total amount of transposition. Does transposase titration explain the spread of inert elements?
(iii) Is the invasion of deleted elements conditional upon the presence of a stable equilibrium between transposition and selection for the intact forms, or can deleted forms replace intact copies even when these would otherwise spread without limit and drive the population extinct?

Furthermore, using a simplified model for the relationship between copy number and transposition (model C (P2) of Brookfield, 1991), I produce approximate analytical solutions for the equilibrium number of intact elements and for the rate of increase of deleted elements introduced at low frequency. These are compared with the exact solutions. I investigate the effect of relaxing the assumption of a Poisson distribution of elements across individuals. I further show that a stable equilibrium of intact copies is not a sufficient condition for the invasion of deleted elements, and, in an approximate treatment, show why the intact elements are eliminated.

2. Simulations: overview of model B (Brookfield, 1991)

An infinite population of hosts can contain transposable elements of three types: intact elements, encoding a transposase; repressor elements, which encode a repressor protein; and inert elements, which encode no proteins. The numbers of transposable elements of the three types in a given individual are represented by X, Y and Z respectively. The proportion of the population with values of X, Y and Z elements of the three types is given by the product of three Poisson terms derived from distributions with means of $\bar{X}$, $\bar{Y}$ and $\bar{Z}$ respectively. Thus the proportion of individuals with exactly X, Y and Z elements is

$$\frac{e^{-\bar{X}-\bar{Y}-\bar{Z}}.\bar{X}^X.\bar{Y}^Y.\bar{Z}^Z}{X!.Y!.Z!} \quad (1)$$

The Poisson distribution will arise if there is linkage equilibrium and site frequencies are all very low. I

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discuss the possibility of linkage disequilibria between sites below.

The concentrations of transposase and repressor polypeptides are assumed to vary linearly with the numbers of transposable elements encoding them. For simplicity, I treat the constant of proportionality as 1. The cellular concentrations of the two protein types are represented by x and y molecules per cell. I hypothesize that the rate of transposition is determined by a second-order chemical reaction in which single transposase proteins bind to single DNA targets. Thus, for a given number of intact elements, and hence a given level of transposase in the cell, the inert elements will decrease the rate of transposition of intact elements by a titration of the transposase. The repressing elements will, in addition to this effect, lower the rate of transposition of intact elements through their protein products binding to intact element DNAs and thereby making them unavailable to bind transposase. I hypothesize that the rate of binding of each of the two species of protein to all of the three forms of DNA is the same. This means that we can usefully use A $(=X+Y+Z)$ and B $(=x+y)$ to represent the total concentrations of P elements and P proteins in the cell. I hypothesize that the rate-limiting step determining the rate of transposition in a cell is the binding of a P protein to a P element. This rate of binding will depend on the concentrations of unbound DNAs and unbound proteins. If we use b to represent the proportion of protein molecules that are bound to DNA, then the concentrations of unbound proteins and unbound DNA will be $B(1-b)$ and $(A-Bb)$ respectively. The rate of binding in term of molecules of protein bound per second per cell will thus be

$$kB(1-b)(A-Bb)$$

where k is a constant of proportionality of dimension molecules^{-1} seconds^{-1}. I supposed that the proteins and DNAs remain bound together for h seconds, during which time transposition occurs if the protein is a transposase but nothing occurs if the protein is a repressor. The rate of transposition is thus equal to the rate of unbinding, multiplied by the probability that the bound protein is a transposase. The total rate of unbinding is Bb/h, and the rate of transposition is xb/h. The rate of unbinding will, at equilibrium, be equal to the rate of binding. This allows the solution of a quadratic equation to yield b:

$$b=\frac{1+kh(A+B)-\sqrt{[(1-kh(A+B))^2-4k^2h^2AB]}}{2hkB}$$

(equation (1) of Brookfield, 1991).

Neither the precise form of this equation, nor any numerical values for transposition produced using it, will be quantitatively accurate. It is merely designed as an example of an interaction between elements which allows a rate of transposition of an element that is dependent on transposase concentration, coupled with repressive effects of some elements and only transposase titration by others. I use xb/h to represent not the number of transposition events per second, but the total amount of transposition that occurs in a germ cell over the period when transposition is occurring.

I assume here that there is no phenomenon of cytotype, partly because the model for cytotype in Brookfield (1991) is inconsistent with some subsequent data (Gloor *et al.*, 1993, Ronsseray *et al.*, 1991). I also assume that there is no mutation to non-autonomous elements, but rather introduce these into the population at very low frequency at the start of the simulation. Thus, when a total of xb/h transposition events occur, they will generate new intact repressor and inert elements in proportions $X/(X+Y+Z)$, $Y/(X+Y+Z)$ and $Z/(X+Y+Z)$ respectively. These values for new elements are added to X, Y and Z respectively, to give the expected numbers of elements of the three types in two random gametes from this individual.

The model specifies that the fitness of an individual decreases with increasing transposition rate, and specifically that the fitness of an individual with a level xb/h of total transposition is

$$\exp(-s(xb/h)^2)$$

where s is a dimensionless selection constant. The squaring of total transposition in the formula for fitness is somewhat arbitrary and has, as its main advantage, the fact that this will stabilize copy number. The fitness drop from transposition arises from the loss of germ cells, which probably depends in a non-linear way on total transposition, since high transposition may cross a threshold at which double-strand breaks are generated more rapidly than the cell can repair them, and the chromosomes fragment. The relationship between fitness and the proportion of germ cells surviving may also be non-linear, particularly in males.

This model can be used to examine three questions.

(i) *What is the effect of increasing the power of repressing elements?*

In previous simulations, the repressing effect of a repressor element was weak, in that the protein produced merely bound to P elements in the same way as transposase, but without producing transposition. It thereby reduced transposition by making DNA substrates less available for transposase binding. More powerful repressors can be envisaged, which interfere directly with transposase. One simple way to model this, as with the negative complementation model of Brookfield (1991), is to imagine the polypeptides forming dimers, but with only the transposase homodimer being active. This suggests an obvious extension to more powerful repressors, in which the

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numbers of polypeptides involved is larger. Thus, if x and y are the cellular concentrations of transposase and repressor polypeptides, the concentration of active transposase protein is given by $x^n/(x+y)^{n-1}$, where increases in n increase repression. The model supposes that transposase and repressor polypeptides combine randomly, and thus the proportion of multimer molecules with i transposase polypeptides out of a possible n is given by a binomial distribution. The proportion with only transposase polypeptides is thus $x^n/(x+y)^n$. The total concentration of the multimers is $(x+y)/n$. The product of these gives the concentration of active transposase. This predicts, however, as in the earlier model, that the amount of protein should be divided by 2 in the dimeric case, and correspondingly divided by n in other cases. I do not adopt this policy here, since I do not imagine that the $n > 2$ cases correspond specifically to the formation of multimeric proteins, and I wish the behaviour of the intact elements in the absence of repression to be independent of n. The details of this model, in which the effect of repressor polypeptides is through their capacity to form inactive multimers, and thereby sequester transposase polypeptides, are inconsistent with some recent data showing that repression acts at the level of transcription (Kaufman & Rio 1991; Lemaitre & Coen 1991). However, the net effect of strong repressors, which is to reduce the concentration of active transposase in the cell, is duplicated in this model. Thus any consistent effects of strong repression seen here will also hold for models of a transcriptionally based repression system.

The simulations were performed using $h = k = 1$ (where these are the constants describing the second-order reaction between P proteins and DNA), s (the constant quantifying the strength of selection) = 0·2, $\bar{X}$ (the initial mean number of intact elements) = 0·01, $\bar{Z} = 0$, and $\bar{Y}$ (the initial mean of number of repressors) = 0·00001. The value of n was varied from 1 to 4.

(ii) *Is the replacement of intact elements by inert elements the result of transposase titration?*

Transposase titration arises through the binding of transposase to inert elements, lowering the availability of transposase for the intact elements. Thus inert elements lower the transposition rate for the intact elements. To investigate the role that transposase titration plays in the replacement of intact elements by inert ones, one can vary the product hk in the simulations. The value k represents a quantity analogous to the constant of binding of protein to DNA, and h represents the time that the two molecules are bound. Thus a high hk product will result in most of the protein being bound to DNA, and thus a high level of transposase titration, whereas a low hk implies a high cellular concentration of unbound protein, and very little transposase titration. I repeated the simulations with $s = 0{\cdot}2$, $\bar{X} = 0{\cdot}01$, $\bar{Z}$ (the initial mean number of inert elements) = 0·00001, and the product hk set at 10 and 0·1. Differences in hk potentially have strong effects on the transposition rate, and thus on the position of equilibrium between transposition and selection. I therefore adjusted h and k until the equilibrium copy number of intact elements was the same in both cases. The resulting values for h and k were, respectively, 1·1967 and 8·3465 and 0·5340 and 0·1873.

(iii) *Is a stable equilibrium for intact elements necessary for the spread of insert elements?*

It is possible to consider cases in which intact elements increase without limit. One such case is where $w_X = \exp(-st_X)$, where t_X is total transposition in and w_X the fitness of an individual with X copies of the intact element. I introduce into a population of intact elements, which will normally increase without limit, various initial numbers of inert elements. I assume that $\bar{X}$ is initially 0·01, $s = 0{\cdot}5$, and $h = k = 1{\cdot}0$. The initial value of $\bar{Z}$, the mean number of inert elements, was varied across simulations.

Simulations were performed through programs written in BBC BASIC, initially, and later C+. The frequencies of all genotypes (differing in copy numbers of the three element types) in the population are calculated on the basis of eqn (1). Then transposition is allowed, and the resulting expected numbers of elements of each type in the gametes of each genotype are calculated. The contribution of this genotype to the gamete pool is the product of its initial frequency and its fitness (which itself depends on transposition). The sum across all genotypes of this product is the mean population fitness. The mean numbers of elements per genome of the three types in the next generation are the sums across all possible genotypes of the products of the expected number of that element type per gamete produced by the genotype, the genotype frequency, and the genotype fitness, all divided by the mean population fitness. From the mean element numbers, eqn (1) is again used to calculate the genotypic frequencies in the next generation.

3. Results of simulations

(i) *The effect of stronger repression*

Figs. 1 and 2 show the results of the simulations with weak and powerful repressors, with n set at 1 and 4 respectively. Increasing the power of repressors increases the rate at which they spread. When the mean number of repressors, $\bar{Y}$, exceeds the mean number of intact elements, transposition rate is low in most individuals in the population. Since it is selection

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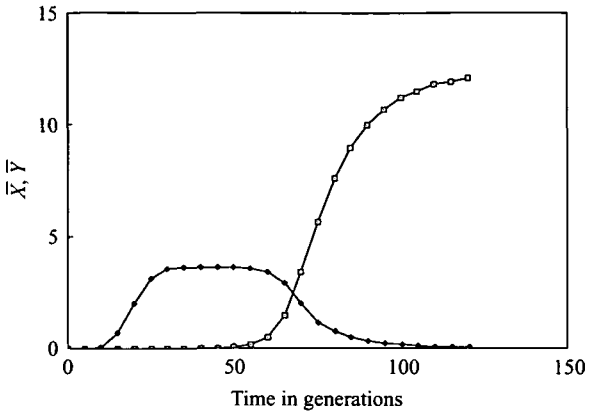

Fig. 1. Spread of weak repressors. Intact elements rise from an initial abundance ($\bar{X}$), of 0·01 copies per individual, to stabilize at $\bar{X} = 3{\cdot}64$. Repressors, initially at 10^{-5} copies per individual, rapidly invade and replace them. $h = k = 1$, $s = 0{\cdot}2$. Intact elements, —◆—; repressor elements, —⊡—.

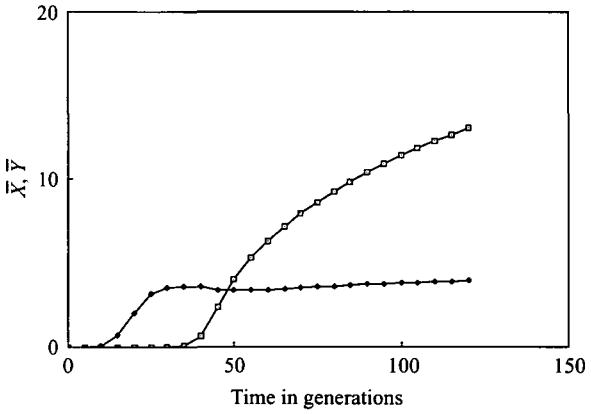

Fig. 2. Spread of strong repressors: $n = 4$. The rise in repressor elements is now quicker than in Fig. 1, but the intact elements, after an initial drop, start to increase in numbers very slowly. Intact elements, —◆—; repressor elements, —⊡—.

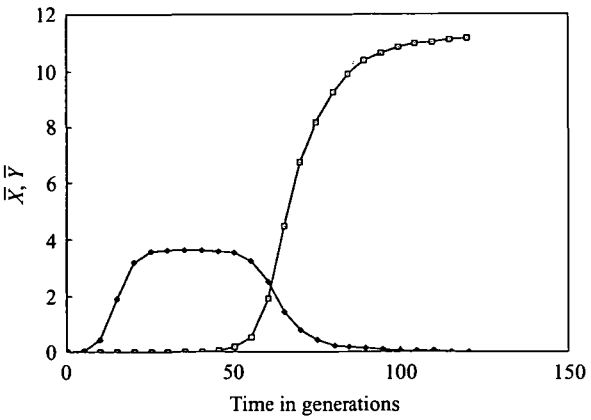

Fig. 3. Spread of inert elements when there is a high degree of transposase titration. Initially, $\bar{X} = 0{\cdot}01$ and $\bar{Z} = 10^{-5}$. $s = 0{\cdot}2$, $k = 8{\cdot}3465$, $h = 1{\cdot}1967$. The inerts replace the intact elements. Intact elements, —◆—; repressor elements, —⊡—.

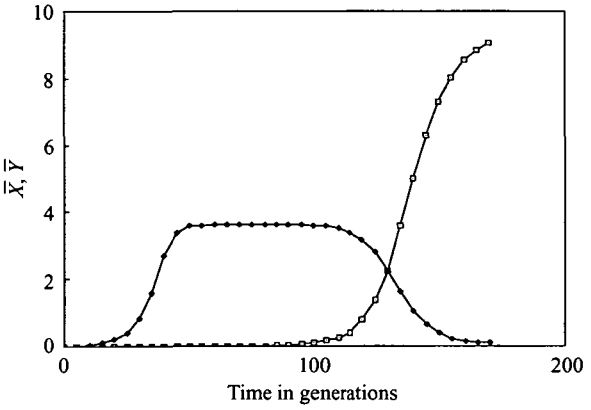

Fig. 4. Spread of inerts with a very low degree of transposase titration. The conditions are as in Fig. 3 except that $k = 0{\cdot}1873$ and $h = 0{\cdot}5340$. The process is slowed but is otherwise very similar. Intact elements, —◆—; repressor elements, —⊡—.

that spreads the repressors, the resulting increase in mean fitness lowers the rate at which the repressors spread. Furthermore, since, with very powerful repressors, the population has high fitness when $\bar{Y}$ greatly exceeds $\bar{X}$, the selective pressure reducing $\bar{X}$ is low. Thus for $n = 2$, the rate of loss of intact elements is much slower than for $n = 1$. When n is 3 or 4, intact elements start to increase again in number once $\bar{Y}$ becomes high. This is because intact elements are now always found in situations in which total transposition is very low, which means that selection has little effect, and the lower rate of transposition allows a very slow increase in the numbers of intacts. The repressors are still increasing considerably more quickly. For $n = 3$ and $n = 4$, this steady slow increase in both element types appears to persist indefinitely. At this point the increase in copy number in these simulations may have been artificially restricted by the maximum size of the arrays.

(ii) *The effect of transposase titration*

Figs. 3 and 4 show the results when inert elements invade a population of intact elements with differing values (10 and 0·1 respectively) of the product hk. When $\bar{X}$ is low, transposition is more frequent when hk is high, and both the spread of intact copies and their subsequent replacement by inerts occur more quickly when $hk = 10$ than when $hk = 0{\cdot}1$. Otherwise, however, there is very little difference between the figures, despite the large change in the degree of transposase titration expected. It seems that the spread of inert copies is not the result of transposase titration.

(iii) *The invasion of a non-equilibrium population*

Fig. 5 shows the increase in inert elements in a population of intact elements which would otherwise increase without limit. When these are introduced at a twentieth of the initial number of the intacts, $\bar{X}$

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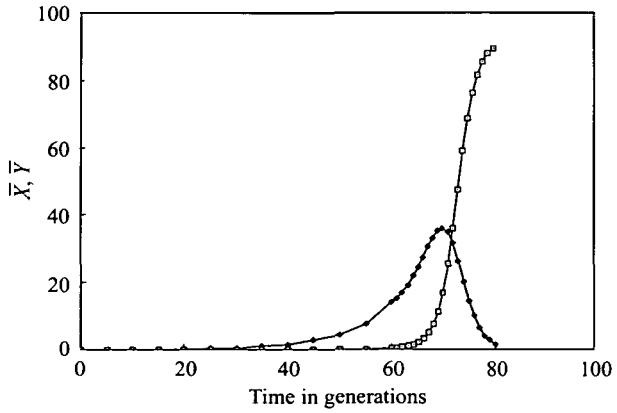

Fig. 5. The rise of inert elements initially at 0·0005 copies per individual when $w_X = \exp(-st_X)$, such that intact elements increase without limit. Here $\bar{X}$ is initially 0·01, $s = 0{\cdot}5$ and $h = k = 1{\cdot}0$. The inert elements catch and replace the intact copies, raising fitness to 100%. Intact elements, —◆—; repressor elements, —⊡—.

reaches a maximum at 35·9, but then the intacts are replaced. In this model, the inert elements, whatever their initial abundance, always ultimately catch and finally eliminate the intacts. How high the value of $\bar{X}$ rises prior to this depends on the initial abundances of the two types of element. However, since the replacement of intacts with inerts sometimes occurs only after fitness has grown vanishingly small, this process may have no biological relevance. For example, in Fig. 5 the mean fitness, $\bar{w}$, drops to a minimum of $1{\cdot}6 \times 10^{-6}$. It subsequently rises to 100% through the elimination of the intact sequences, and thus the ending of all transposition.

Other models allow intact elements to increase without limit but do not allow the invasion of inert elements. An example is when fitness, w_X, is $0{\cdot}2 + 0{\cdot}8\exp(-st_X^2)$. Now, for high $\bar{X}$ values, inert elements spread proportionately more slowly than intact ones and will not catch them.

4. Analysis

(i) *An analysis of the equilibrium number of intact elements and the capacity of inert elements to invade*

While the results given above and in Brookfield (1991) are qualitatively similar in many simulations under different conditions, it is unsatisfactory to draw conclusions merely from inferences from simulations. It is better to seek an analytical understanding of why the addition of inert elements (even if they do not titrate transposase) to a population of intact elements at a stable transposition–selection equilibrium can result in invasion and elimination of the intact elements.

Consider a population with only intact elements, with a mean number $\bar{X}$ per individual. A general model, but one in which mutation between the element types is excluded, follows.

Let the total amount of duplicative transposition of an individual with X intact elements be t_X.

Let the fitness of an individual with X elements be w_X.

Let the proportion of the population with X elements be p_X.

From the definition of a mean, $\sum_{X=0}^{\infty} Xp_X = \bar{X}$

and the mean population fitness is defined as $\bar{w} = \sum_{X=0}^{\infty} p_X w_X$

Let the expected number of elements contributed to the next generation by an intact element in an individual with X copies be c_X. Thus

$$c_X = (1 + t_X/X)\, w_X/\bar{w} \tag{2}$$

This is the expected total number in two gametes from such an individual. This follows from the assumption that the expected number of daughter elements, following transposition, from a given element is t_X/X, and the representation in the next generation of gametes from an individual with X copies is determined by $w_X/\bar{w}$.

The mean number of copies in the next generation is:

$$\bar{X}' = \sum_{X=0}^{\infty} Xp_X c_X \tag{3}$$

Thus the change in $\bar{X}$, $\Delta\bar{X}$, is $\bar{X}' - \bar{X}$. At equilibrium, $\Delta\bar{X} = 0$, and if $\mathrm{d}\Delta\bar{X}/\mathrm{d}\bar{X}$ is negative, this equilibrium is stable.

If we define the mean contribution of an element to the next generation, c, as

$$\sum_{X=0}^{\infty} Xp_X c_X/\bar{X}$$

then when $X' = X$, $c = 1{\cdot}00$.

Suppose that there is such a population at stable equilibrium, and we introduce into it inert elements at a very low abundance, so low that $\bar{w}$ is not affected. Will the inert elements invade? I define t'_X as the total transposition rate in an individual with X elements, one of which is inert, and w'_X as the fitness of such an individual. (Since the abundance of the inert elements is very low, I assume that an inert element will always be found in an individual in which it is the only inert element.) I further assume, as in all the models discussed, that the difference between an inert and an intact element is entirely *trans*-acting. Thus the expected transposition rate of an intact element and of an inert element in the same genome will always be the same. For an individual inert element, the probability that it finds itself in a genome with $X-1$ intact elements will be the same as the corresponding

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probability for an intact element, or $Xp_X/\bar{X}$. The expected number of daughter elements that such an element will leave in the next generation, c_{iX}, will be $(1+t'_X/X)w'_X/\bar{w}$. (Here i represents inert.) The expected contribution, c_i, of daughter elements in the next generation left by an inert element, is given by

$$c_i = \sum_{X=0}^{\infty} Xp_X c_{iX}/\bar{X} \tag{4}$$

If this is greater than 1 when the population of intacts is at equilibrium, then the inert elements can invade. Thus, by the calculation of c_i when $\Delta\bar{X}=0$, the conditions for invasion can be rapidly established.

(ii) *An approximate solution to a special case*

The above analysis will generally be true, but its interpretation depends upon a particular model, such as model B, for t_X, w_X, t'_X, w'_X and p_X. A simpler model, which I here investigate more analytically, is model C (P2) of Brookfield (1991). I make the adjustment that the mutation process is here removed. In this model

$$t_X = TX^2, t'_X = TX(X-1), \quad w_X = \exp(-s(t_X)^2),$$
$$w'_X = \exp(-s(t'_X)^2) \quad \text{and} \quad p_X = e^{-X}X^X/X!$$

T and s are constants of transposition and selection. This model allows invasion of an equilibrium intact population by inert elements under a wide range of conditions, except when T and s are very high and the resulting equilibrium $\bar{X}$ is much less than 1.

Charlesworth & Charlesworth (1983, equation 19b) showed that the increase in mean copy number resulting from selection, $\Delta\bar{X}$, is given by (using my symbolism, and assuming Poisson variation in copy number)

$$\Delta\bar{X} = \frac{\bar{X}\partial \ln(\bar{w}_{\bar{X}})}{\partial\bar{X}}$$

Here $\bar{w}_{\bar{X}}$ is the mean population fitness conditional on the mean copy number $\bar{X}$. Mean fitness is hard to calculate and it can be estimated by $w_{\bar{X}}$, the fitness of an individual with $\bar{X}$ copies. The increase in copy number resulting from transposition in their model is a linear function of $\bar{X}$, and is $\bar{X}(u-v)$, where u is the per copy transportation rate and v the per copy deletion rate. In my model there is no deletion, and transposition is a quadratic function of copy number, so I estimate $\sum_{X=0}^{\infty} p_X TX^2$ by $T\bar{X}^2$ in a similar way to the above.

If selection and transposition are both included,

$$\Delta\bar{X} = \frac{\bar{X}\partial \ln(\exp(-sT^2\bar{X}^4)}{\partial\bar{X}} + T\bar{X}^2$$
$$= -4sT^2\bar{X}^4 + T\bar{X}^2$$

Thus, when $\Delta\bar{X}=0$, and $T \neq 0$,

$$\bar{X} = 1/(2\sqrt{sT}) \tag{5}$$

Now consider the expected change in copy number in individuals with one inert element and $\bar{X}-1$ intact elements, $\Delta\bar{X}_i$. This again is the sum of two terms corresponding to the effects of selection and transposition, respectively:

$$\Delta\bar{X}_i = \frac{\bar{X}\partial \ln(-sT^2\bar{X}^2(\bar{X}-1)^2)}{\partial\bar{X}} + T\bar{X}(\bar{X}-1) \tag{6}$$
$$= T\bar{X}(\bar{X}-1) - sT^2\bar{X}^2(4\bar{X}^2-6\bar{X}+2)$$

When $\bar{X} = 1/(2\sqrt{sT})$,

$$\Delta\bar{X}_i = \bar{X}T(\bar{X}-1)/2$$

Since the difference between intact and inert copies is entirely *trans*-acting, the proportional increase of all elements in individuals that possess inert elements will be the same as the proportional increase in inert elements, and thus this proportional increase, which I shall call ΔZ, is given by

$$\Delta Z = \Delta\bar{X}_i/\bar{X} = T(\bar{X}-1)/2 \tag{7}$$

(this will be approximately equal to c_i-1). Thus, in this approximation, the inerts will increase for all $\bar{X} > 1$.

The accuracy of these approximations can be tested. For various T and s values, I calculate $\bar{X}$ accurately by iterating eqn (3) until $\Delta\bar{X}=0$, and then, using eqn (4), calculate ΔZ conditional on $\bar{X}$. I estimate corresponding values using eqns (5) and (7). The results can be seen in the first four columns of Table 1. The approximations seem to work fairly well for these parameter values.

(iii) *What happens when a Poisson distribution of copy number is not assumed?*

The model assumes that the distribution of element numbers across individuals is Poisson, as expected when site frequencies are low and there is linkage equilibrium. However, John Maynard Smith (personal communication) has pointed out to me that the high rates of transposition in some individuals may generate strong positive linkage disequilibrium between elements, and thus increase the variance in element number and with it the efficacy of selection. There are models for the variation in p_X, the proportions of the population with different numbers of elements, which do not produce the behaviour seen here. An asexual model, for example, in which individuals lacking transposable elements always produce offspring which also lack them, always results in the elimination of a parasitic transposable element, however high the transposition rate. This occurs because the subset of the population with no elements will have a higher fitness than those individuals with elements, and will selectively replace them (Hickey, 1982). However, John Maynard Smith (personal communication) has shown by simulation that the replacement of intact

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Table 1. *Exact and approximate values for the equilibrium number of intact elements, $\bar{X}$, and the proportional increase in inert elements, ΔZ, when intacts are at equilibrium, in model C (P2)*

Conditions		Poisson variation				Non-Poisson variation		
s	T	$\bar{X}$ eqn (3)	ΔZ eqn (4)	$\bar{X}$ eqn (5)	ΔZ eqn (7)	$\bar{X}$	Variance in X	ΔZ eqn (4)
0·1	0·01	16·15	0·067	15·81	0·074	24·83	13·34	0·198
0·1	0·02	11·55	0·089	11·18	0·102	17·11	10·49	0·228
0·1	0·05	7·45	0·126	7·07	0·152	10·03	7·60	0·237
0·1	0·10	5·36	0·158	5·00	0·200	5·69	5·66	0·167
0·1	0·15	4·42	0·176	4·08	0·231	3·59	4·45	0·103
0·1	0·20	3·85	0·188	3·54	0·254	2·54	3·58	0·065
0·1	0·25	3·47	0·196	3·16	0·270	1·91	2·98	0·037
0·05	0·01	24·43	0·095	22·36	0·107	31·98	21·69	0·187
0·05	0·02	17·84	0·128	15·81	0·148	22·44	17·17	0·220
0·05	0·05	11·91	0·182	10·00	0·225	13·68	12·67	0·243
0·05	0·10	8·85	0·233	7·07	0·304	8·60	9·81	0·208
0·05	0·15	7·46	0·264	5·77	0·358	5·92	8·07	0·153
0·05	0·20	6·61	0·287	5·00	0·400	4·38	6·79	0·112
0·05	0·25	6·02	0·304	4·47	0·434	3·34	5·80	0·081

The table shows the equilibrium mean and variance in the number of intact elements under a non-Poisson model for copy number, along with the corresponding ΔZ.

elements by inerts still occurs in some sexual models with more accurate copy number distributions.

I have performed simulations in which the distribution of frequencies p_X of genomes with copy numbers X is not Poisson. Specifically, I represent the population by the frequencies q_i of haploid genomes with i intact elements. Diploids are formed by bringing together such haploids in random pairs. Such a diploid has a total number of elements which determines both its fitness and the expected number of new elements created by transposition and introduced into the gametes. The diploid produces gametes bearing numbers of copies which are continuously distributed between the values of the two haploid genomes that make up the diploid. Thus, if there are i and j copies in the two haploid genomes, and $i \geqslant j$, the proportion of gametes that have $j+x$ elements (x ranges from 0 to $i-j$) is $1/(i+1-j)$. Into these gametes are inserted a further number of new elements generated by transposition, with this number being Poisson distributed with a mean equal to half the total transposition in this diploid individual. This is, of course, only one of many models for the distribution of copy number that can be imagined. When t_X, t'_X, w_X and w'_X are as shown for model C (P2) above, this model can be iterated on the computer for various values of s and T until an equilibrium $\bar{X}$ is obtained. Such values are shown in the fifth column of Table 1. The variance in copy number at equilibrium is also shown, as is ΔZ for this equilibrium (calculated using eqn (4)). When s and T are small, and the equilibrium $\bar{X}$ therefore large, the variance is less than the mean (and thus also less than the variance in the Poisson model). The reduced variance lowers the effect of selection, and thus allows the equilibrium $\bar{X}$ to be higher. When s and T are larger, the equilibrium variance is higher than for the Poisson model, and the equilibrium $\bar{X}$ is less. When the variance is higher than Poisson the inert elements invade less quickly, and when the variance is lower than Poisson the inert elements invade more quickly.

(iv) *Why do inert elements invade?*

An intuitive way of viewing the situation is to note that, in the region of $\bar{X}$, a condition for the stability of the equilibrium is that the slope of c against $\bar{X}$ is negative. For most models it will also be true that the slope of c_X against X is negative near $\bar{X}$. If so, increases in X increase the rate of transposition and, by doing so, reduce c_X. The replacement of an intact element with an inert element will reduce the total transposition, and thus, usually, $c_{1X} > c_X$, at least near $\bar{X}$. However, it will not necessarily be true that

$$\sum_{X=0}^{\infty} X p_X c_{1X} > \sum_{X=0}^{\infty} X p_X c_X$$

when intact elements are at equilibrium.

A specific example illustrates this. Imagine that in an individual with X intact elements and Z inert ones, the total rate of transposition, t, is

$$T(X+Z)(1-e^{-mX})$$

where T is a transposition constant and m is a constant and is greater than one. Thus when X is large, total transposition will be virtually unaffected by the substitution of an inert for an intact element.

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Table 2. *For* $t_X = T(X+Z)(1-e^{-mX})$ *and* $w_X = \exp(-st_X^2)$, *values for* $\bar{X}$ *and* ΔZ *when* $\bar{X}$ *is at equilibrium;* $m = 1{\cdot}5$

Conditions			
s	T	$\bar{X}$ eqn (3)	ΔZ eqn (4)
0·2	0·2	6·51	−0·0005
0·2	0·6	2·03	−0·0277
0·6	0·2	3·34	−0·0053
0·6	0·6	0·84	−0·0797

When X is small, total transposition will be greatly reduced by such a substitution, but, when X is small, transposition produces little selective harm, and a reduction in transposition may decrease c_X. Table 2 shows simulation results for equilibrium $\bar{X}$ and ΔZ (derived from eqns (3) and (4) respectively) with this model when $m = 1{\cdot}5$, $w_X = \exp(-st^2)$, variation in X is Poisson, and a range of T and s values are used. The negative values for ΔZ show that the inert elements cannot invade when rare.

(v) *Why are the intact elements replaced?*

Simulations reveal that the invasion of inert elements is accompanied by the elimination of intact elements. Using the tractable model C (P2) above, some insight can be gained into the mechanism for the replacement. Suppose that an individual has, in addition to X intact elements, a further Z inert elements. Total transposition in such an individual, t, is $TX(X+Z)$ and fitness is $\exp(-st^2)$. Using an argument similar to that leading to eqn (6) above, the change in $\bar{X}$, i.e. $\Delta\bar{X}$, is approximately given by

$$\Delta\bar{X} \approx \frac{\bar{X}\partial \ln(\exp(-sT^2\bar{X}^2(\bar{X}+Z)^2))}{\partial\bar{X}} + T\bar{X}^2$$

Solving,

$$\Delta\bar{X} = T\bar{X}^2(1-2sT(2\bar{X}^2+3\bar{X}Z+Z^2))$$

Thus, if $\Delta\bar{X} = 0$, and $\bar{X}$, $T \neq 0$

$$\bar{X} = \frac{3sTZ \pm \sqrt{[4sT+(sTZ)^2]}}{-4sT} \qquad (8)$$

Similarly, the change in $\bar{Z}$, i.e. $\Delta\bar{Z}$, can be found approximately as a function of $\bar{Z}$ and X, assuming X to be constant. (Note that there is a subtle change in the meaning of $\Delta\bar{Z}$ here relative to ΔZ above, since there ΔZ represented the proportional change in $\bar{Z}$ when $\bar{Z}$ was vanishingly small, while here $\Delta\bar{Z}$ represents the absolute change in $\bar{Z}$ when $\bar{Z}$ may be large.) As with eqn (6) above,

$$\Delta\bar{Z} \approx \frac{\bar{Z}\partial \ln(\exp(sT^2X^2(X+\bar{Z})^2))}{\partial\bar{Z}} + TX\bar{Z}$$

Table 3. *Values of* $\bar{X}$, *from eqns (8) and (9), that make* $\Delta\bar{X}$ *and* $\Delta\bar{Z}$ *equal to zero for various values of* sT *and* Z

Conditions			
sT	Z	$\bar{X}$ for $\Delta\bar{X} = 0$	$\bar{X}$ for $\Delta\bar{Z} = 0$
0·025	0·0	3·16	4·47
0·025	0·5	2·79	4·23
0·025	1·0	2·42	4·00
0·025	1·5	2·06	3·78
0·025	2·0	1·70	3·58
0·025	2·5	1·35	3·39
0·025	3·0	1·00	3·22
0·025	4·0	0·32	2·90
0·025	5·0	No positive solution	2·62
0·0005	0·0	22·36	31·62
0·0005	1·0	21·61	31·13
0·0005	2·0	20·87	30·64
0·0005	5·0	18·65	29·22
0·0005	10·0	15·00	27·02
0·0005	15·0	11·42	25·00
0·0005	20·0	7·91	23·17
0·0005	25·0	4·47	21·51
0·0005	30·0	1·09	20·00
0·0005	35·0	No positive solution	18·64

Solving,

$$\Delta\bar{Z} = X\bar{Z}T(1-2sTX(X+\bar{Z}))$$

Thus, if $\Delta\bar{Z} = 0$, T, X, $\bar{Z} \neq 0$,

$$X, \text{ here treated as } \bar{X} = \frac{sT\bar{Z} \pm \sqrt{[2sT+(sT\bar{Z})^2]}}{-2sT} \qquad (9)$$

Thus, for any value of $\bar{Z}$ we can find, from eqns (8) and (9) respectively, the positive values of $\bar{X}$ such that $\Delta\bar{X} = 0$ and $\Delta\bar{Z} = 0$. Table 3 gives illustrations for when $sT = 0{\cdot}025$ and $sT = 0{\cdot}0005$. (These represent the extreme values in Table 1.) For all $\bar{Z}$, the value of $\bar{X}$ required for $\Delta\bar{X} = 0$ is less than the value of $\bar{X}$ required for $\Delta\bar{Z} = 0$. Thus, if $\bar{X}$ and $\bar{Z}$ were such that $\Delta\bar{X} = 0$ then $\Delta\bar{Z} > 0$, if $\bar{X}$, $\bar{Z}$, $T > 0$. Thus $\bar{X}$ will be reduced to zero.

5. Discussion

I have sought to explain the result that, if transposition and host fitness are coupled, deleted transposable elements can invade a population in which intact elements are in a transposition–selection equilibrium. While such an invasion usually occurs in the models, the presence of a stable equilibrium between selection determined by transposition and transposition itself is neither a necessary nor a sufficient condition for the invasion of deleted elements. The spread of deleted elements is accompanied by the elimination from the population of intact elements, unless the deleted elements are strong repressors, in which case the intact elements may persist, and, indeed, increase.

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It is possible for this process of replacement of intact elements with deleted ones to occur even in situations in which the intact elements would otherwise drive the population to extinction. For the deleted elements to catch the intact ones while the host population is still extant the inert elements have to be introduced at a sufficiently high initial frequency (which could arise through a high mutation rate to deleted elements). Thus, if a transposition–selection equilibrium can exist, models predict that there will usually be a subsequent spread of deleted elements (provided these can be produced by mutation). If a transposition–selection equilibrium cannot exist, then the spread of deleted elements is a necessary condition for the persistence of the host population. In either situation a population at equilibrium would be expected to lack intact elements.

When transposition rates are low, or population sizes are low, individual site frequencies, assumed to be negligible in the Poisson assumption, may become appreciable, and the copy number variance will drop considerably below the mean. This would reduce the power of natural selection, and with it the rate of elimination of complete elements.

While the modelling here is quite general it is for the P elements that the model is open to the most direct tests. A number of experiments have monitored changes in the distributions of elements, and consequent changes in the patterns of P activity and repression, in laboratory populations (Jackson *et al.*, 1988; Preston & Engels, 1989; Ronsseray *et al.*, 1989). Some populations were started bearing only intact elements, following germ-line transformation of pure M strains, whereas others were founded with small numbers of both intact and deleted elements. Some of the former populations became extinct as a result of P element effects. For the others, the fewer deleted elements there were initially present, the more likely the populations were to evolve P-cytotype. If this did not happen, there was an increase in non-autonomous elements, a process often accompanied by the build-up of chromosomally inherited repression, and the elimination of intact elements. These data agree broadly with the models described here. The models also predict that the stable persistence of intact elements should occur only in Q strains. (Q strains possess some P elements but show few if any P element movements in their F_1 progeny when crossed in either direction to either P or M strains.) Stable persistence of intact elements should be impossible in M′ strains. Some M′ strains with such elements do appear to be stable, but this may be the result of the small population size effect mentioned above.

Some wild populations appear stable in their P element constitutions, notwithstanding their possession of full-length P elements. These seem to be populations possessing either powerful zygotic repressors or P-cytotype. Once some such a system of repression is established, the population dynamics of P elements may come to resemble those of the less rapidly moving, and longer established, retrotransposons. The frequency spectrum of sites of the P element can be very similar (Biémont *et al.*, 1994) to that of retrotransposons in the same population. Also, P elements have been found to be over-represented in minority inversions, suggesting that ectopic recombination, thought to control retrotransposon numbers, and attenuated in regions of reduced recombination, may play a role in regulating P abundance also (Eanes *et al.*, 1992). However, the short time during which the P element has existed in *D. melanogaster* suggests that the frequency spectra of sites in wild populations are unlikely to have reached equilibrium. Furthermore, high-frequency sites, such as that at 1A, seen in 11 of 12 sampled X chromosomes from one population (Biémont *et al.*, 1994), are thought to have reached high frequencies through selection for the repressor capacity of the P elements that they possess (Ronsseray *et al.*, 1991).

Kaplan *et al.*, (1985) have produced a model for a heterogeneous transposable element family, which predicts that such a family will evolve towards a distribution that is strongly biased towards deleted copies, in the absence of any selection at the level of the host. This arises from a one-way mutation process coupled with the ability of intact elements to complement the *trans*-acting functions of deleted elements in the same genome. For P, however, the observations of very great fitness losses arising from the element's activities makes it improbable that an accurate description of element dynamics can be based on a neutral model of this kind.

There are some analogies, although not formal ones, between the dynamics of the interaction between intact and defective transposable elements and the interaction between complete and defective viruses (Bangham & Kirkwood, 1990; Szathmáry, 1992).

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