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A model of the evolution of the unusual sex chromosome system of *Microtus oregoni*

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In the creeping vole, *Microtus oregoni*, females are X0 and males are XY. In the female germ line, mitotic nondisjunction ensures that the products of meiosis all carry the X chromosome. Similarly, mitotic nondisjunction in the male germ line leads to the production of 0 and Y sperm. We propose that the present situation in *M. oregoni* has evolved by invasion of a normal XX/XY system by a mutant X chromosome, X′, with a complete transmission advantage in X′X females, and a complete transmission disadvantage in X′Y males. X′ is at best initially nearly neutral, but can gain a transmission advantage if it reaches a high enough frequency. This is due to the production of X0 females in matings between XX females and X′Y males; low fertility and embryo loss of such females reduce the fitness of the X chromosome in females, relative to that of X′. Under some conditions, however, the enhanced reproductive value of males, caused by the production of inviable Y0 embryos in X0 × X′Y matings, can outweigh any advantage to X′. Inbreeding also reduces any advantage to X′.

Keywords: inbreeding, segregation distortion, sex chromosomes, voles.

Introduction

Sex chromosome evolution has long attracted the attention of both cytogeneticists and evolutionary biologists (White, 1973; Bull, 1983). A major challenge has been the elucidation of the forces responsible for the evolution of dimorphic X and Y (or Z and W) chromosomes, which are present in a wide range of taxa. While it cannot be claimed that this problem has been completely solved, a number of processes compatible with population genetics theory have been described, which seem likely to be involved in the evolution of such systems (Bull, 1983; Charlesworth, 1996; Rice, 1996; Charlesworth & Charlesworth, 2000). In addition, possible paths by which an XX/XY system can evolve into an XX/X0 system, in which there is no Y chromosome left, have been suggested by Charlesworth (1996). There is also a body of theory relevant to the evolution of systems of neo-X and neo-Y chromosomes, formed by translocations or fusions between true sex chromosomes and autosomes (Charlesworth & Charlesworth, 1980; Bull, 1983; Charlesworth, 1985; Charlesworth & Wall, 1999). Certain cases of sex reversal in arvicolid rodents, such that some females in the population are XY instead of XX, can be interpreted in terms of an associated transmission advantage (Bengtsson, 1977; Bull & Bulmer, 1981; Bull, 1983; Fredga *et al*., 1993).

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There are, however, several other sex chromosome systems which currently lack any evolutionary explanation. One of these is represented by the New Zealand species of frog, *Liopelma hochstetteri*, in which females are apparently W0 in constitution and males are 00 (Green, 1988). Another is that of the mole voles of the genus *Ellobius*, where several species have XX males and XX females (Fredga, 1983, 1994; Vogel *et al*., 1998). In *E. lutescens*, and in the Ammami spinous rat *Tokudaia osumensis*, both sexes appear to be X0 (Fredga, 1994). Finally, in the creeping vole, *Microtus oregoni*, females are X0 and males are XY. In the female germ line, mitotic nondisjunction occurs, such that XX and 00 oogonia are produced. Only the former survive, so the products of meiosis are X egg cells. Similarly, in the male germ line mitotic nondisjunction causes the production of XXY and 0Y cells, of which only 0Y differentiate into spermatogonia, leading to 0 and Y sperm (Ohno *et al*., 1963, 1966; Fredga, 1994). The *M. oregoni* system is the subject of this paper.

A model of *M. oregoni*

Cytogenetic assumptions

One scenario to explain the *M. oregoni* system is through a mutation to a new type of X, X′ say, in a conventional XX/XY system, which causes the nondisjunction events described above. It seems reasonable to

assume that such a mutation would have caused males to behave *ab initio* essentially as at present, such that 0 and Y sperm of X′Y males are produced in equal frequencies. X′ thus suffers a complete transmission disadvantage in males, which must be offset by a corresponding advantage in females if it is to spread in any but a very small population. There is no obvious difference between the X chromosome of *M. oregoni* and those of related species, other than a terminal deletion (Modi, 1987), so that there is no clue to the nature of the event that created the X′ chromosome.

In females, the X′ chromosome must have been present initially in X′X individuals (even if the first X′ female was X′0, matings with XY males would produce X′X daughters). The behaviour of this currently unobserved genotype must therefore be specified. The natural assumption is that X′X females produce a 1:1 ratio of X′ to X eggs. But the lack of transmission advantage to X′ in females under this assumption means that X′ is always at a selective disadvantage (this has been confirmed by computer modelling; results not shown). An extreme alternative is to assume that X′X females produce only X′ gametes, i.e. there is effectively segregation distortion in favour of X′. This produces a transmission advantage that exactly balances the lack of transmission of X′ through males. We will assume this to be the case in what follows. Matings of XX females with X′Y males produce X0 females (Table 1); as shown below, the properties of X0 females play a critical role in the evolution of the system.

This assumption concerning the behaviour of X′X females raises two questions: (a) How could it happen at the level of cellular mechanisms? (b) What are the population dynamics of such an X′ chromosome? Our prime concern is with (b); we can only offer the following conjectures concerning (a). Assume that the kinetochore of the X′ chromosome is altered in some way that causes it to misalign with the spindle microtubules at a critical mitotic division during germline formation, so that the kinetochores of each X′ chromatid are attached to microtubules from the same spindle pole. Both X′ chromatids will then move to the same pole at anaphase (Nicklas, 1997). If this alteration of the X′ kinetochores also causes them to outcompete the kinetochores of the homologous X chromosome for some component involved in binding to the spindle microtubules, the X chromosome will fail to attach to the spindle and will be lost at cell division. A lack of similarity between the X and Y chromosome kinetochores would prevent this type of competition, and allow the pattern of segregation of X′ and Y seen in X′Y males.

Table 1 Genetics of all possible matings (*l*, lethal)

Mating type	Female progeny	Male progeny
1 XX × XY	XX	XY
2 X0 × XY	k XX:(1 − k) X0	k XY:(1 − k) Y0 (l)
3 X′X × XY	X′X	X′Y
4 X′0 × XY	X′X	X′Y
5 XX × X′Y	X0	XY
6 X0 × X′Y	k X0:(1 − k) 00 (l)	k XY:(1 − k) Y0 (l)
7 X′X × X′Y	X′0	X′Y
8 X′0 × X′Y	X′0	X′Y

A difficulty with these proposals is that the postulated misalignments of kinetochores in germline mitosis, and the lack of a pairing partner for the Y in male meiosis, would activate the cell cycle checkpoint that delays onset of anaphase in response to lack of tension on kinetochores (Nicklas, 1997; Taylor, 1999; Waters *et al*., 1999). However, as noted by Rieder *et al*. (1994) and Li & Nicklas (1995), there is evidence that the checkpoint delays, but does not completely prevent, division if there are kinetochores that are not under tension. The successful completion of meiosis in X0 sex chromosome systems (Nicklas, 1997), and the systems of regular mitotic chromosome elimination via failure of chromosome attachment to the spindle in groups such as Cecidomyids (Nicklas, 1960), also show that the checkpoint is not an insuperable obstacle to the postulated behaviour of chromosomes in X′X and X′Y individuals of *M. oregoni*.

Population genetic assumptions

Question (b) has been tackled by means of simple algebra, and numerical calculations of the trajectories of populations with different starting frequencies of X′. The model allows for various levels of inbreeding, such that the proportion of matings between full-siblings is α, the remainder being between unrelated individuals (Charlesworth & Wall, 1999). In addition, we allow for reproductive compensation, i.e. a lack of reduction of litter size in proportion to the fraction of inviable embryos, in matings where lethal 00 or Y0 embryos are produced. Following Charlesworth (1994), the extent of reproductive compensation can be conveniently measured by a coefficient C, such that the litter size of matings with frequency l of lethal embryos is multiplied by $(1 - l)^{-C}$. If $C = 1$, the litter size is completely unaffected by embryonic mortality; if $C = 0$, litter size is proportional to the number of nonlethal embryos.

In addition, X0 house mice are known to exhibit unequal segregation of gametes. They produce a large excess of XX over X0 females in their progeny, more than can be explained by selective elimination of embryos alone (Cattanach, 1962). Direct observations

of oocytes taken from X0 females has shown that X bearing eggs outnumber nullo-X eggs by almost 2:1 (Kaufman, 1972). There is thus a preferential loss of nullo-X oocytes during oogenesis. Although no direct evidence is available, it is possible that a similar phenomenon may have occurred among the X0 females postulated to have been present during the evolution of the *M. oregoni* system. This segregation distortion can be represented by setting the frequency of X among the eggs of X0 females to $k \geq 0.5$.

We assume that there are no genotypic effects on viability, other than the lethality of 00 and Y0 embryos, and no effects on male fertility. But it is likely that some genotypic effects on female fertility must be allowed for. It has long been known that X0 house mice are viable and fertile. However, their reproductive lifespan is approximately half that of XX females (Cattanach, 1962; Morris, 1968). Mean litter size is greatly reduced, to 55% of that for XX females, and the mean total number of offspring produced by an X0 female mouse is 34% of that produced by XX mice (Lyon & Hawker, 1973). These effects are most likely caused by a combination of three factors: reduced secretion of gonadotrophic hormones, lower numbers of primordial germ cells, and pre- and post-implantation loss of embryos (Dyban & Baranov, 1987). The reproductive biology of arvicolid rodents is obviously rather different from that of mice (Tamarin, 1985; Stenseth & Ims, 1993), and so it is uncertain whether this fertility reduction applies to them. Limited data on the wood lemming *Myopus schisticolor* indicate that X0 females can be fertile (Fredga *et al.*, 1993), but no quantitative measure of their relative fertility seems to be available. For completeness, we thus allow the fertility of X0 *M. oregoni* to differ from that of XX, representing their relative fertility (in terms of their mean lifetime production of embryos, before selective loss of Y0 progeny) by f_2. Since X′X and X′0 females do not produce X0 germ cells, it is unlikely that they will differ from XX females, but our general model assigns them relative fertilities of f_3 and f_4, respectively.

Because of the non-Mendelian ratios produced in this system, the usual assumption of Hardy–Weinberg genotype frequencies cannot be made, even with random mating. The system is thus represented in terms of the frequencies of different types of matings, e.g. XX × XY, X′X × XY, etc. (Table 1). These form components of a vector, z, such that the ith component of z, z_i, corresponds to the ith mating type in Table 1. The frequencies of segregants shown in Table 1 enable a set of recursion relations to be obtained that describes the transition from one generation to the next, which are given in the Appendix.

Results

Analytic results

Before describing the detailed results of numerical investigations of these recursions, some useful conclusions derived from the study of special cases will be presented. First, we consider the conditions for the initial increase of X′ when introduced into a randomly mating XX/XY population at a low frequency. If second-order terms in the frequency of X′ are neglected, only two types of mating involving genotypes with X′ need be considered: X′X × XY and XX × X′Y. From Table 1, it is easy to see that, to this order of approximation, the sum of the frequencies of these matings is constant, since the transmission advantage of X′ in females is cancelled by its disadvantage in males (assuming that $f_3 = 1$). Hence, X′ changes in frequency when rare at a rate that is at most second-order in its frequency, unless X′X females have altered fertility. Inbreeding does not significantly modify this conclusion, since its effect is to allow X′X or X′0 females to mate with X′Y males. Since these matings result in a 1:1 ratio of X′0 to X′Y progeny, there is no fitness advantage over XX × XY matings, at least to first-order terms in the frequency of X′, if the fertility of X′0 females is the same as that of XX females.

Thus, the geometric rate of change in frequency of X′ will be expected to be zero, if X′ is sufficiently rare and it does not affect fitness directly. But if X′ reaches a sufficiently high frequency, its effects on mating types other than those just considered will start to influence its dynamics. The fact that its presence in males causes the formation of X0 females promotes the spread of X′. The low fertility of X0 females and/or the loss of embryos among the litters they produce reduces their contribution to the next generation, favouring X′ over X. An opposite effect arises from the fact that the presence of X0 females enhances the reproductive value of male vs. female progeny. This is because X0 × XY matings have a deficiency of male progeny, due to the lethality of Y0 embryos, unless there is complete segregation distortion. Since X′ is not transmitted through males, the greater reproductive value of males reduces its net fitness relative to X. This negative effect is strongest with a high level of reproductive compensation and when k is close to 0.5, since this maximizes the reduction in the proportion of males in the whole population. Thus, unless the fertility of X0 females is low enough to overcome this negative effect, X′ can be at a selective disadvantage at intermediate frequencies, if C is sufficiently high and k is sufficiently low.

It is straightforward to analyse the dynamics of the system when X is introduced at a low frequency into a

randomly mating X′X/X′Y population. The only relevant mating types involving X are X0 × X′Y, X′X × XY, and X′0 × XY (matings between XX and X′Y generate X0 females, so that X in females is always associated with 0 after one generation). We obtain the following recursion relations:

$$z_4' = z_7 f_3 / f_4 \tag{1a}$$

$$z_6' = z_6 f_2 k^{1-C} / f_4 \tag{1b}$$

$$z_7' = z_4. \tag{1c}$$

It easily seen that this system has eigenvalues of $f_2 k^{1-C}/f_4$, $\sqrt{f_3/f_4}$ and $-\sqrt{f_3/f_4}$. If $f_3 = f_4$, a population fixed for X′ will be stable to the introduction of X if and only if

$$f_2 k^{1-C} / f_4 < 1. \tag{2}$$

This implies that fixation of X′ is always stable under random mating if X0 females have lower fertility than X′0 females. Low values of k and C provide the strongest selective advantage to X′ over X. If compensation is complete, a fertility disadvantage to X0 females is a necessary condition for an advantage to X′. If there is inbreeding, we expect this advantage to be diminished, since XX × XY matings now play a role, and are neutral relative to X′0 × X′Y.

Numerical results

The above conclusions were confirmed by numerical results derived from iterations of the general set of recursion relations. The upper panel of Table 2 shows the case of a population with no compensation and with $k = 0.5$, with varying levels of inbreeding and initial frequencies of X′. As expected, even under this relatively favourable case for the spread of X′, its initial geometric rate of spread is negligible if it is very rare. But if X′ is present at a sufficiently high frequency, it can spread rapidly if the level of inbreeding is low, even if there is no fertility disadvantage to X0 females. The lower panel shows the corresponding situation for X introduced into an X′ population; even for as much as 50% sib-mating, invasion by X is strongly resisted by selection.

Table 3 shows the effect of varying the fertility of X0 females, the degree of segregation distortion among their progeny, and the level of reproductive compensation on the rate of spread of X′ when introduced at a low frequency into a population fixed for X. Table 4 is a similar study of the effects of these parameters on the ability of X to invade an X′ population. The results confirm the conclusions reached above; it will be seen that there are parameter sets in which the spread of X′ from a low frequency is resisted, despite the stability of an X′ population against invasion by X. This indicates the existence of an unstable equilibrium with an intermediate frequency of X′.

Table 2 Effects of initial mutation frequency and inbreeding

A. Results of introducing X′ into an X population. Values indicate numbers of generations until X′ frequency exceeds 0.99

Initial X′ frequency	$\alpha = 0$	$\alpha = 0.2$	$\alpha = 0.8$	$\alpha = 0.9$
5×10^{-5}	Neutral	Neutral	Neutral	Neutral
5×10^{-4}	503000	989000	Neutral	Neutral
0.005	5140	10000	641000	Neutral
0.0025	247	470	28500	227000
0.05	83	153	8470	66700
0.25	16	29	1180	8540

B. Results of introducing a normal X into an X′ population. Values indicate numbers of generations until X chromosome frequency is one-tenth the initial level

Initial X frequency	$\alpha = 0$	$\alpha = 0.2$	$\alpha = 0.8$	$\alpha = 0.9$
1×10^{-4}	6	13	584	4177
0.001	6	13	583	4168
0.01	6	13	585	4188
0.1	7	14	615	4428
0.5	9	18	906	6865

$C = 0$, $k = 0.5$, $f_2 = f_3 = f_4 = 1$.
See text for further explanation.

Discussion

We have assumed that the present situation in *M. oregoni* has evolved through invasion of a normal XX/XY system by a mutant X chromosome, X′, with a complete transmission advantage in X′X females, and a complete transmission disadvantage in X′Y males. Our results show that X′ is at best initially nearly neutral, but can gain a transmission advantage if it reaches a high enough frequency, under suitable conditions. This is due to the production of X0 females in matings between XX females and X′Y males; the low fertility and embryo loss for such females reduce the fitness of the X chromosome in females, relative to that of X′. But the enhanced reproductive value of males, caused by the production of inviable Y0 embryos in X0 × X′Y matings, can outweigh any advantage to X′, if compensation is high enough and there is a low level of segregation distortion.

Table 3 Effects of reproductive compensation, unequal gamete segregation and reduced fertility of X0 females on X′ fixation

		f_2				
C	k	0.1	0.3	0.7	0.9	1.0
0	0.5	120	137	232	518	5138
	0.6	121	141	257	613	7690
	0.7	122	146	283	713	11900
	0.8	123	151	310	823	20500
	0.9	125	156	338	945	46000
	1.0	126	160	367	1093	Neutral
0.5	0.5	121	142	324	—	—
	0.6	122	146	334	—	—
	0.7	123	150	343	2408	—
	0.8	124	154	352	1518	—
	0.9	125	157	360	1227	—
	1.0	126	160	367	1093	Neutral
0.95	0.5	122	149	659	—	—
	0.6	123	152	504	—	—
	0.7	124	155	440	—	—
	0.8	125	157	405	10150	—
	0.9	125	159	383	1700	—
	1.0	126	160	367	1093	Neutral

Values indicate number of generations until X′ frequency exceeds 0.99 from an initial frequency of 0.01.
— indicates selection against X′.
$f_3 = f_4 = 1$.

Table 4 Effects of reproductive compensation, unequal gamete segregation and reduced fertility of X0 females on introduction of normal X into an X′ population

		f_2				
C	k	0.1	0.3	0.7	0.9	1.0
0	0.5	4	4	5	6	6
	0.6	4	5	6	7	8
	0.7	4	5	7	9	11
	0.8	4	5	8	11	16
	0.9	4	5	9	17	31
	1.0	5	6	11	31	Neutral
0.5	0.5	4	5	7	9	11
	0.6	4	5	7	11	14
	0.7	4	5	8	13	19
	0.8	4	5	9	16	29
	0.9	4	5	10	21	59
	1.0	5	6	11	31	Neutral
0.95	0.5	5	5	10	24	92
	0.6	5	5	11	26	124
	0.7	5	5	11	27	177
	0.8	5	5	11	28	282
	0.9	5	5	11	30	594
	1.0	5	6	11	31	Neutral

X chromosome is introduced at low frequency; initial frequency of mating type 6 = 0.01.
Values indicate number of generations until X chromosome frequency is one tenth the initial level.

Furthermore, inbreeding reduces any advantage to X′; in the extreme case of complete inbreeding, X′ is neutral. If inbreeding is not complete, an X′ population can always resist invasion by X, unless compensation and segregation distortion are complete and there is no fertility disadvantage of X0 females.

We have therefore succeeded in providing a set of population genetic conditions under which the evolution of the *M. oregoni* system is no longer mysterious. Given the evidence from house mice concerning the low fertility of X0 females (Lyon & Hawker, 1973), there seems to be a strong possibility that a mutant X chromosome could start to spread once it reaches a sufficiently high frequency. Division of the species into partially isolated subpopulations of small size would allow genetic drift to produce a locally high frequency of X′, and hence trigger its spread by selection. While there are apparently no data on the population structure of *M. oregoni*, a study of the related European species *M. oeconomus* (Leijs *et al.*, 1999) provides evidence for high levels of genetic differentiation as measured by F_{ST} for enzyme markers between local populations. This is in accordance with the evidence from many other studies of small rodent populations (e.g. Dallas *et al.*, 1995). A direct test on *M. oregoni* is clearly desirable.

Our model also suggests that a high level of close inbreeding, as distinct from population subdivision, is unlikely to be compatible with the spread of X′, although it is quite robust to levels of sib-mating of up to 50%. Examination of the level of inbreeding in *M. oregoni* populations could be carried out relatively easily, by estimating F_{IS}. Estimates of F_{IS} in *M. agrestis* (Frykman, 1988) and *M. oeconomus* (Leijs *et al.*, 1999) do not suggest high levels of inbreeding in these species.

These population genetic conclusions do not, of course, provide any insights into how a change in the X chromosome can produce the suite of characteristics that appear to be necessary for the system to evolve. This is a challenge to cell biologists.

Our model may not, of course, be the only possible path by which this system has evolved, but it does have the merit of invoking only a single chromosomal mutation. Other possibilities would seem to require at least two changes in quick succession. For example, a reviewer has suggested the following alternative scenario. A Y chromosome causing meiotic drive arises,

and spreads rapidly through the population, inducing a highly male-biased sex ratio (Hamilton, 1967). A mutation to an X′ chromosome arises, which causes the observed mitotic nondisjunction in X′0 females and in males, but has no effect on X′X females. X′0 progeny produced by matings of X′-carrying males with X′X females will produce a 1:1 sex ratio when mated to X′ males with a driving Y. If the sex ratio is highly male biased, the resulting very high reproductive value of female progeny could nearly overcome the transmission disadvantage to X′ in males and any fertility disadvantage to X′0 females. The problems with this model are: first, there is a requirement for the mutation to X′ to spread before the driving Y has reached such a high frequency that the species goes extinct. Second, the most likely matings when X′ is rare are between XX females and X′Y males, which disfavour X′. A high level of inbreeding is thus needed, so that there is a good chance that an X′X female mates with a driving male with an X′ chromosome, otherwise X′ will be eliminated. This is in contrast to the prediction of the model we are proposing.

It is difficult to devise conclusive tests of our model, since it depends on the properties of X′X females, which can no longer be observed. The extensive chromosomal differences between New World species of *Microtus* (Gaines, 1985; Modi, 1987) probably preclude intercrossing of *M. oregoni* with other species, to create X′X females, despite the evidently very recent radiation of this group (Chaline, 1987; Modi, 1996). A possible approach is through comparative studies of molecular variation on the X chromosome in *M. oregoni* and its relatives. On our model, the X′ chromosome is transmitted entirely without the opportunity to cross over with a homologue, whereas alternative scenarios where X′ undergoes meiosis in company with a normal X would allow crossing-over between the two chromosomes. On our model, the whole X′ chromosome thus behaves as a non-recombining block, and its spread would therefore eliminate variability at marker loci as a result of the hitch-hiking event (Maynard Smith & Haigh, 1974; Charlesworth & Charlesworth, 1998). Given the recent origin of the species group to which *M. oregoni* belongs (Chaline, 1987; Modi, 1996), there should be little opportunity for variation to have been regained by mutation, resulting in a sharp reduction in the level of variability at X chromosomal loci in *M. oregoni*, compared with loci on other chromosomes. In contrast, the model which invokes a driving Y chromosome predicts no generalized reduction in variation on the X chromosome, except as a result of hitch-hiking events or background selection effects (Maynard Smith & Haigh, 1974; Charlesworth & Charlesworth, 1998) that took place after the establishment of the current system, but there should be a sharp reduction in variation on the Y chromosome. A lack of signature of a hitch-hiking effect on the X chromosome, coupled with evidence for one on the Y, would falsify the predictions of our model.

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Appendix: Recursion relations for the general model

Let $p = ([1 + k]/2)^{-C}$ and $q = k^{-C}$ be the effect of compensation on the sizes of litters of types 2 and 6 of Table 1, respectively. Inspection of Table 1 yields the following set of expressions for the (unnormalized) genotype frequencies of XX, X0, X′0, X′X and X′0, respectively, among females (weighted by their fertilities):

$$x_1 = z_1 + pkz_2 \tag{A1a}$$

$$x_2 = f_2(p[1 \quad k]z_2 + z_5 + qkz_6) \tag{A1b}$$

$$x_3 = f_3(z_3 + z_4) \tag{A1c}$$

$$x_4 = f_4(z_7 + z_8). \tag{A1d}$$

Similarly, the frequencies of XY and X′Y among males are given by:

$$y_1 = z_1 + pkz_2 + z_5 + qkz_6 \tag{A2a}$$

$$y_2 = z_3 + z_4 + z_7 + z_8. \tag{A2b}$$

These can be used to generate a vector r of contributions from random matings to the new vector of mating type frequencies, such that $r_i = x_i y_1$ and $r_{i+4} = x_i y_2$ ($i = 1$ to 4).

From Table 1, a similar vector, s, of contributions from sib-matings can be defined. The only non-zero components are:

$$s_1 = z_1 + pkz_2 \tag{A3a}$$

$$s_2 = f_2(p[1 \quad k]z_2 + z_5 + qkz_6) \tag{A3b}$$

$$s_7 = f_3(z_3 + z_4) \tag{A3c}$$

$$s_8 = f_4(z_7 + z_8). \tag{A3d}$$

The new vector of mating type frequencies has components

$$z'_i = \frac{\alpha s_i + (1 \quad \alpha) r_i}{\sum_{j=1}^{8} \{\alpha s_j + (1 \quad \alpha) r_j\}}. \tag{A4}$$