Definition and Properties of Disequilibria Within Nuclear-Mitochondrial-Chloroplast and Other Nuclear-Dicytoplasmic Systems

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ABSTRACT

We define and determine the interrelationships among five sets of disequilibrium parameters that measure two- and three-locus nonrandom associations in nuclear-dicytoplasmic systems. These assume a diploid nuclear locus and two haploid cytoplasmic loci, with special reference to nuclear-mitochondrial-chloroplast systems. Three sets of two-locus disequilibria measure the association between haplotypes at the two cytoplasmic loci (D_{MC}) and associations between each cytoplasmic locus and nuclear alleles or genotypes (D_M, D_{1M}, D_{2M}, D_{3M}; D_C, D_{1C}, D_{2C}, D_{3C}). In addition, we present two classes of higher-order disequilibria that measure nonrandom allelic or genotypic associations involving all three loci. The first class quantifies associations between the nuclear locus and the two cytoplasmic loci taken jointly ($D_{A/MC}$, $D_{AA/MC}$, $D_{Aa/MC}$, $D_{aa/MC}$, etc.), whereas the second measures only those associations remaining after all two-locus associations have been taken into account ($D_{A/M/C}$, $D_{AA/M/C}$, $D_{Aa/M/C}$, $D_{aa/M/C}$). Based on combinations of these five sets of measures, we suggest a variety of parameterizations of three-locus, nuclear-dicytoplasmic systems. The dynamics of these disequilibria are then investigated under models of random and mixed mating, either with both cytoplasmic genomes inherited through the same parent or through opposite parents. Except for associations between the cytoplasmic haplotypes, which are constant when the two cytoplasmic genomes are inherited through the same parent, all disequilibria ultimately decay to zero. These randomizations do not necessarily occur monotonically, however, and in some cases are preceded by an initial increase in magnitude or sign change. For both inheritance patterns, the asymptotic decay rates are steadily retarded by increasing levels of self-fertilization. This behavior contrasts with that in the extreme case of complete selfing, for which only the heterozygote disequilibria always decay to zero. For all models considered, the dynamics of the two-locus cytonuclear subsystems are solely a function of the mating system, whereas the dynamical behavior and sign patterns of the cytoplasmic and three-locus disequilibria also depend strongly on the mode of cytoplasmic inheritance.

ALTHOUGH important interactions between nuclear and cytoplasmic genes have been recognized for a large variety of organisms (SLOTT, SHADE and LANSMAN 1983; MERRIL and HARRINGTON 1985; BENNE 1988; MACRAE and ANDERSON 1988), no other group has a greater potential for nuclear-cytoplasmic interactions than plants. This is because plant cells contain two major cytoplasmic genomes, mitochondrial (mtDNA) and chloroplast (cpDNA), both of which code for gene products involved in metabolic processes, such as respiration and photosynthesis, that are under joint cytonuclear control (BEALE and KNOWLES 1978; BORST, TABAK and GRIVELL 1983; WHITFELD and BOTTOMLEY 1983). As pointed out by BEAVIS, POLLACK and FREY (1987), it is therefore not surprising that cytonuclear interactions have been found to influence a number of quantitative traits in plants (IWANAGA *et al.* 1978; RAO and FLEMING 1978; ROBERTSON and FREY 1984; BEAVIS and FREY 1987).

Cytonuclear interactions are also important in the reproductive biology of many plant species. For instance, many of the cases of male sterility encountered in over 140 cultivated species have been attributed to interactions between one or more nuclear genes and a mitochondrial locus (CONDE *et al.* 1982; HANSON and CONDE 1985; DEWEY, LEVINGS and TIMOTHY 1986; HÅKANSSON *et al.* 1988). The related phenomenon of gynodioecy, which has been reported to occur in 543 species from 178 families (DEMYANOVA 1985), is often thought to result from similar interactions (*e.g.*, SUN 1987; ROUWENDAL, VAN DAMME and WESSELS 1987). The close relationship among all three genomes is further highlighted by evidence of DNA transfer between the nucleus and both organelles (KEMBLE *et al.* 1983; TIMMIS and SCOTT 1983), as well as DNA transfer from the chloroplast to the mitochondrion (STERN and LONSDALE 1982; STERN and PALMER 1984).

All of these important cytonuclear interactions in plants have the potential to generate statistical associations among the loci involved. Moreover, the pres-

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ence of three major genomes allows for a wide variety of nonrandom cytonuclear associations, which together can provide a qualitatively new kind of information about the evolutionary history of plant populations. For example, pairwise associations can arise between nuclear alleles or genotypes and haplotypes (cytotypes) at either of the cytoplasmic genomes (ASMUSSEN, ARNOLD and AVISE 1987, 1989; ARNOLD, ASMUSSEN and AVISE 1988). Pairwise associations between mitochondrial and chloroplast cytotypes are also possible. More significantly, higher-order nonrandom associations could develop among all three genomes. The possibility of both pairwise disequilibria involving all three loci (*e.g.*, between nuclear genotypes or alleles and joint cytotypes) and full three-way disequilibria highlights the potential wealth of information contained within nuclear-dicytoplasmic systems.

The dynamical behavior of such three-locus associations is apt to be strongly dependent on the mode of inheritance of the cytoplasmic loci. Although several plant species show biparental plastid inheritance (KIRK and TILNEY-BASSETT 1978; METZLAFF, BÖRNER and HAGEMANN 1981; MEDGYESY, PÁY and MÁRTON 1986), the majority of species exhibit maternal inheritance of both chloroplasts and mitochondria (BIRKY 1978; GILLHAM 1978; KIRK and TILNEY-BASSETT 1978; SEARS 1980; DEWEY, LEVINGS and TIMOTHY 1986; PALMER 1987; NEALE and SEDEROFF 1988). In conifers, however, a growing body of evidence suggests that chloroplasts and mitochondria can have contrasting uniparental modes of inheritance; in some species, mitochondria appear to exhibit maternal inheritance, whereas chloroplasts appear to be inherited paternally (OHBA *et al.* 1971; NEALE, WHEELER and ALLARD 1986; SZMIDT, ALDÉN and HÄLLGREN 1987; WAGNER *et al.* 1987; NEALE and SEDEROFF 1988). For most plant species, then, all cytoplasmic loci behave as if completely linked (BEAVIS, POLLACK and FREY 1987), which would presumably simplify the potential three-locus cytonuclear disequilibria. The dynamics of three-locus associations in certain conifer populations, on the other hand, are potentially very complex, but may also be uniquely informative about the genetic structure and evolutionary history of those populations. In order to take better advantage of the joint nuclear-mtDNA-cpDNA frequency data currently being gathered (D. B. WAGNER and D. R. GOVINDARAJU, personal communication), it is necessary to develop a theoretical framework to quantify disequilibria in such systems and to determine what force or forces could account for observed values.

Although there have been numerous mathematical analyses of cytonuclear interactions in plants, none have examined three-locus, nuclear-dicytoplasmic systems. Most theoretical treatments have focused on the evolution and maintenance of gynodioecy (WATSON and CASPARI 1960; CASPARI, WATSON and SMITH 1966; COSTANTINO 1971; CHARLESWORTH and GANDERS 1979; CHARLESWORTH 1981; DELANNAY, GOUYON and VALDEYRON 1981; ROSS and GREGORIUS 1985). Other studies have addressed the effects of cytonuclear interactions on quantitative traits (BEAVIS, POLLACK and FREY 1987) and the conditions for the maintenance of cytoplasmic polymorphisms under joint cytonuclear selection (CLARK 1984; GREGORIUS and ROSS 1984). Most relevant to the present discussion has been the extension of the theory of gametic disequilibrium to nonrandom pairwise associations between nuclear and cytoplasmic loci (CLARK 1984; ASMUSSEN, ARNOLD and AVISE 1987, 1989; ARNOLD, ASMUSSEN and AVISE 1988). ASMUSSEN, ARNOLD and AVISE (1987), in fact, have introduced and analyzed a novel set of two-locus, cytonuclear disequilibrium statistics that estimate both allelic and genotypic associations between nuclear and individual cytoplasmic loci.

In this paper, we extend the basic cytonuclear framework of ASMUSSEN, ARNOLD and AVISE (1987) by defining disequilibrium measures that quantify nonrandom associations within three-locus, nuclear-dicytoplasmic systems. In addition, we provide a foundation for the interpretation of observed disequilibria by describing their expected behavior under two standard mating models, random mating and mixed mating. For each model, we consider both patterns of uniparental cytoplasmic inheritance described above. The first, which is applicable to most plant species, assumes that the two cytoplasmic genomes are transmitted by the same parent. The second pattern, which is specifically applicable to certain coniferous species, assumes that the two are inherited through opposite parents. Although the discussion is couched in terms of associations among nuclear, mitochondrial, and chloroplast loci in plants, the basic results also apply to associations in other nuclear-dicytoplasmic systems within both plants and animals, such as those that include the nucleus, a single organelle, and an intracellular microorganism. The same framework is also relevant to associations in the heterogametic sex among autosomal, sex-linked, and cytoplasmic genes.

DEFINITION OF VARIABLES

Frequencies: We are concerned with the dynamics and patterns of two- and three-locus cytonuclear associations in a population of diploid plants. The three loci under consideration are an autosomal nuclear locus with two alleles, A and a, a haploid mitochondrial locus with two types, M and m, and a haploid chloroplast locus with two types, C and c. The 12 possible three-locus genotype frequencies are shown in Table 1. In this table, summation of each column gives the marginal nuclear genotype frequencies, u, v and w,

TABLE 1

Three-locus genotype frequencies

Joint cytotype	Nuclear genotype			
	AA	*Aa*	*aa*	Total
M/C	u_{11}	v_{11}	w_{11}	x_{11}
M/c	u_{12}	v_{12}	w_{12}	x_{12}
m/C	u_{21}	v_{21}	w_{21}	x_{21}
m/c	u_{22}	v_{22}	w_{22}	x_{22}
Total	u	v	w	1.0

whereas summation across rows gives the four *joint cytotype* frequencies, x_{11}, x_{12}, x_{21}, x_{22}. From these the nuclear allele frequencies are calculated as

$$p = \text{freq. } (A) = u + \tfrac{1}{2}v \qquad q = \text{freq. } (a) = w + \tfrac{1}{2}v, \quad (1)$$

and the mitochondrial and chloroplast haplotype frequencies are computed as

$$\begin{aligned} x_M &= \text{freq. } (M) = x_{11} + x_{12} \\ y_M &= \text{freq. } (m) = x_{21} + x_{22} \\ x_C &= \text{freq. } (C) = x_{11} + x_{21} \\ y_C &= \text{freq. } (c) = x_{12} + x_{22}, \end{aligned} \quad (2)$$

where "freq." denotes "frequency of." Note that the first index of all subscripted variables in Table 1 refers to the mitochondrial type and the second index refers to the chloroplast type, with an index of 1 indicating M (or C), and an index of 2 indicating m (or c).

Joint frequency variables describing each of the two cytonuclear subsystems can also be derived from the variables in Table 1. These include the six nuclear-mitochondrial frequencies and the six nuclear-chloroplast frequencies (Table 2), which correspond to the u_i, v_i, and w_i variables of ASMUSSEN, ARNOLD and AVISE (1987). The frequencies of the associated two-locus allelic combinations (e_1, e_2, e_3, e_4, in ASMUSSEN, ARNOLD and AVISE 1987) are rewritten here using the notation in Table 3. Note that the row and column sums in Tables 2 and 3 provide alternative decompositions of the single-locus frequencies.

Finally, in the three-locus context, it is useful to specify the frequencies of the eight possible three-locus allelic combinations, as in Table 4. These variables, whose indices follow the convention in Table 1, in turn provide additional formulas for the frequencies of all two-locus allelic combinations. Summing across rows of Table 4 shows, for instance, that each of the four joint cytotype frequencies can be written as $x_{ij} = p_{ij} + q_{ij}$, for $i, j = 1, 2$. Similarly, the eight nuclear-cytoplasmic, allelic combinations in Table 3 can be written as $p_{iM} = p_{i1} + p_{i2}$, $q_{iM} = q_{i1} + q_{i2}$, $p_{iC} = p_{1i} + p_{2i}$, and $q_{iC} = q_{1i} + q_{2i}$, for $i = 1, 2$.

Two-locus disequilibria: Three sets of pairwise associations are possible among the three loci. Two of these involve nuclear-cytoplasmic associations, which are specified here in terms of the *genotypic* and *allelic disequilibria* introduced by ASMUSSEN, ARNOLD and AVISE (1987). In the present notation, the nonrandom associations between the three nuclear genotypes and each cytoplasmic locus are measured by

$$\begin{aligned} D_{1M} &= u_{1M} - ux_M & D_{1C} &= u_{1C} - ux_C \\ D_{2M} &= v_{1M} - vx_M & D_{2C} &= v_{1C} - vx_C \\ D_{3M} &= w_{1M} - wx_M & D_{3C} &= w_{1C} - wx_C, \end{aligned} \quad (3)$$

where, for instance, D_{1M} = freq. (AA/M) − freq. (AA) freq. (M) and D_{1C} = freq. (AA/C) − freq. (AA) freq. (C). The corresponding allelic disequilibria, D_M = freq. (A/M) − freq. (A) freq. (M) and D_C = freq. (A/C) − freq. (A) freq. (C), are

$$D_M = p_{1M} - px_M \qquad D_C = p_{1C} - px_C. \quad (4)$$

The two-locus constraints within each cytonuclear subsystem require that

$$\begin{aligned} -ux_M \le D_{1M} \le uy_M \qquad & -ux_C \le D_{1C} \le uy_C \\ -vx_M \le D_{2M} \le vy_M \qquad & -vx_C \le D_{2C} \le vy_C \\ -wx_M \le D_{3M} \le wy_M \qquad & -wx_C \le D_{3C} \le wy_C \\ -px_M,\ -qy_M \le D_M \le py_M,\ qx_M & \\ -px_C,\ -qy_C \le D_C \le py_C,\ qx_C. & \end{aligned} \quad (5)$$

Although it is useful to consider all these eight measures of cytonuclear disequilibria, there are only two independent disequilibrium parameters for each nuclear-cytoplasmic pair, since the measures within each set are interrelated by

$$\begin{aligned} D_{1M} + D_{2M} + D_{3M} = 0 \qquad & D_{1C} + D_{2C} + D_{3C} = 0 \\ D_M = D_{1M} + \tfrac{1}{2}D_{2M} \qquad & D_C = D_{1C} + \tfrac{1}{2}D_{2C}. \end{aligned} \quad (6)$$

The third set of possible two-locus disequilibria quantifies nonrandom associations between the two cytoplasmic loci. This *cytoplasmic disequilibrium*, D_{MC}, is defined as the departure of the joint cytoplasmic frequencies from expectations under random association,

$$\begin{aligned} D_{MC} &= \text{freq. } (M/C) - \text{freq. } (M) \text{ freq. } (C) \\ &= x_{11} - x_M x_C, \end{aligned} \quad (7)$$

and is subject to the standard two-locus constraints

$$-x_M x_C,\ -y_M y_C \le D_{MC} \le x_M y_C,\ y_M x_C. \quad (8)$$

The two-locus allelic disequilibria in turn allow useful alternative expressions for the frequencies of the two-locus, cytonuclear allelic combinations (Table 3):

$$\begin{aligned} p_{1M} &= px_M + D_M & p_{1C} &= px_C + D_C \\ p_{2M} &= py_M - D_M & p_{2C} &= py_C - D_C \\ q_{1M} &= qx_M - D_M & q_{1C} &= qx_C - D_C \\ q_{2M} &= qy_M + D_M & q_{2C} &= qy_C + D_C, \end{aligned} \quad (9)$$

TABLE 2

Nuclear-mitochondrial and nuclear-chloroplast genotype frequencies

Cytotype	Nuclear genotype *AA*	*Aa*	*aa*	Total
M	$u_{1M} = u_{11} + u_{12}$	$v_{1M} = v_{11} + v_{12}$	$w_{1M} = w_{11} + w_{12}$	x_M
m	$u_{2M} = u_{21} + u_{22}$	$v_{2M} = v_{21} + v_{22}$	$w_{2M} = w_{21} + w_{22}$	y_M
Total	u	v	w	1.0
C	$u_{1C} = u_{11} + u_{21}$	$v_{1C} = v_{11} + v_{21}$	$w_{1C} = w_{11} + w_{21}$	x_C
c	$u_{2C} = u_{12} + u_{22}$	$v_{2C} = v_{12} + v_{22}$	$w_{2C} = w_{12} + w_{22}$	y_C
Total	u	v	w	1.0

TABLE 3

Frequencies of nuclear-mitochondrial and nuclear-chloroplast allelic combinations

Cytotype	Nuclear allele *A*	*a*	Total
M	$p_{1M} = u_{1M} + \frac{1}{2}v_{1M}$	$q_{1M} = w_{1M} + \frac{1}{2}v_{1M}$	x_M
m	$p_{2M} = u_{2M} + \frac{1}{2}v_{2M}$	$q_{2M} = w_{2M} + \frac{1}{2}v_{2M}$	y_M
Total	p	q	1.0
C	$p_{1C} = u_{1C} + \frac{1}{2}v_{1C}$	$q_{1C} = w_{1C} + \frac{1}{2}v_{1C}$	x_C
c	$p_{2C} = u_{2C} + \frac{1}{2}v_{2C}$	$q_{2C} = w_{2C} + \frac{1}{2}v_{2C}$	y_C
Total	p	q	1.0

and the four joint cytotype frequencies:

$$x_{11} = x_M x_C + D_{MC} \qquad x_{12} = x_M y_C - D_{MC}$$
$$x_{21} = y_M x_C - D_{MC} \qquad x_{22} = y_M y_C + D_{MC}. \tag{10}$$

Three-locus disequilibria: In addition to the pairwise associations defined in the previous section, there can be higher order associations involving all three loci. We focus here on two forms, which represent either pairwise three-locus associations or full three-way associations. The first type measures nonrandom associations between the four joint cytotypes and the nuclear genotypes and alleles. For instance, in direct analogy to the original cytonuclear disequilibria in (3)–(4) defined by ASMUSSEN, ARNOLD and AVISE (1987), the *joint genotypic disequilibrium* involving *AA* and *M/C* is defined as $D_{AA/MC}$ = freq. $(AA/M/C)$ − freq. (AA) freq. $(M/C) = u_{11} - ux_{11}$. The treatment of the mitochondrial and chloroplast types as a joint cytotype is emphasized by removing the "/" between the *M* and *C* in the subscript of $D_{AA/MC}$.

In total, 12 joint genotypic disequilibria can be defined, as shown in Table 5. Note that in order to obtain the marginal totals of Table 5, the disequilibria in any row or column must sum to zero. Within this group of 12 disequilibria there are thus only six independent measures. Moreover, choosing any two disequilibria involving a given joint cytotype from Table 5, we can write the remaining ten disequilibria as simple linear combinations of those two and the original two-locus genotypic disequilibria in (3).

For simplicity, subsequent discussion will focus on

TABLE 4

Frequencies of three-locus allelic combinations

Joint cytotype	Nuclear allele *A*	*a*	Total
M/C	$p_{11} = u_{11} + \frac{1}{2}v_{11}$	$q_{11} = w_{11} + \frac{1}{2}v_{11}$	x_{11}
M/c	$p_{12} = u_{12} + \frac{1}{2}v_{12}$	$q_{12} = w_{12} + \frac{1}{2}v_{12}$	x_{12}
m/C	$p_{21} = u_{21} + \frac{1}{2}v_{21}$	$q_{21} = w_{21} + \frac{1}{2}v_{21}$	x_{21}
m/c	$p_{22} = u_{22} + \frac{1}{2}v_{22}$	$q_{22} = w_{22} + \frac{1}{2}v_{22}$	x_{22}
Total	p	q	1.0

TABLE 5

Joint genotypic disequilibria

Joint cytotype	Nuclear genotype *AA*	*Aa*	*aa*	Total
M/C	$ux_{11} + D_{AA/MC}$	$vx_{11} + D_{Aa/MC}$	$wx_{11} + D_{aa/MC}$	x_{11}
M/c	$ux_{12} + D_{AA/Mc}$	$vx_{12} + D_{Aa/Mc}$	$wx_{12} + D_{aa/Mc}$	x_{12}
m/C	$ux_{21} + D_{AA/mC}$	$vx_{21} + D_{Aa/mC}$	$wx_{21} + D_{aa/mC}$	x_{21}
m/c	$ux_{22} + D_{AA/mc}$	$vx_{22} + D_{Aa/mc}$	$wx_{22} + D_{aa/mc}$	x_{22}
Total	u	v	w	1.0

the parameterization in Table 6, based on $D_{AA/MC}$ and $D_{Aa/MC}$. The decomposition of $D_{AA/Mc}$, for instance, is obtained by writing

$$\begin{aligned} D_{AA/Mc} &= \text{freq. } (AA/M/c) - \text{freq. } (AA) \text{ freq. } (M/c) \\ &= \text{freq. } (AA/M) - \text{freq. } (AA/M/C) \\ &\quad - \text{freq. } (AA)\,[\text{freq. } (M) - \text{freq. } (M/C)] \\ &= \text{freq. } (AA/M) - \text{freq. } (AA) \text{ freq. } (M) \\ &\quad - [\text{freq. } (AA/M/C) - \text{freq. } (AA) \text{ freq. } (M/C)] \\ &= D_{1M} - D_{AA/MC}. \end{aligned}$$

Substitution of the disequilibrium relations from Table 6 and (10) into Table 5 provides a complete parameterization of the 12 genotype, three-locus system in terms of the marginal single-locus frequencies, the two-locus disequilibria, and the two joint genotypic disequilibria, $D_{AA/MC}$ and $D_{Aa/MC}$. Since the 12 genotype frequencies must all be nonnegative, the new disequilibrium measures are bounded within the

TABLE 6

Interrelationships among the joint and two-locus genotypic disequilibria

$D_{AA/MC} = u_{11} - ux_{11}$	$D_{Aa/MC} = v_{11} - vx_{11}$	$D_{aa/MC} = -D_{AA/MC} - D_{Aa/MC}$
$D_{AA/Mc} = -D_{AA/MC} + D_{1M}$	$D_{Aa/Mc} = -D_{Aa/MC} + D_{2M}$	$D_{aa/Mc} = D_{AA/MC} + D_{Aa/MC} + D_{3M}$
$D_{AA/mC} = -D_{AA/MC} + D_{1C}$	$D_{Aa/mC} = -D_{Aa/MC} + D_{2C}$	$D_{aa/mC} = D_{AA/MC} + D_{Aa/MC} + D_{3C}$
$D_{AA/mc} = D_{AA/MC} - D_{1M} - D_{1C}$	$D_{Aa/mc} = D_{Aa/MC} - D_{2M} - D_{2C}$	$D_{aa/mc} = -D_{AA/MC} - D_{Aa/MC} - D_{3M} - D_{3C}$

TABLE 7

Parameterization of the three-locus allele frequencies in terms of the joint disequilibrium, $D_{A/MC}$

Joint cytotype	Nuclear allele A	Nuclear allele a	Total
M/C	$px_Mx_C + pD_{MC} + D_{A/MC}$	$qx_Mx_C + qD_{MC} - D_{A/MC}$	x_{11}
M/c	$px_My_C - pD_{MC} - D_{A/MC} + D_M$	$qx_My_C - qD_{MC} + D_{A/MC} - D_M$	x_{12}
m/C	$py_Mx_C - pD_{MC} - D_{A/MC} + D_C$	$qy_Mx_C - qD_{MC} + D_{A/MC} - D_C$	x_{21}
m/c	$py_My_C + pD_{MC} + D_{A/MC} - D_M - D_C$	$qy_My_C + qD_{MC} - D_{A/MC} + D_M + D_C$	x_{22}
Total	p	q	1.0

intervals

$$
\begin{aligned}
&-ux_Mx_C - uD_{MC},\ -uy_My_C - uD_{MC} + D_{1M} + D_{1C} \\
&\le D_{AA/MC} \le ux_My_C - uD_{MC} + D_{1M},\ uy_Mx_c \\
&- uD_{MC} + D_{1C} \\
&-vx_Mx_C - vD_{MC},\ -vy_My_C - vD_{MC} + D_{2M} + D_{2C} \\
&\le D_{Aa/MC} \le vx_My_C - vD_{MC} + D_{2M},\ vy_Mx_C \\
&- vD_{MC} + D_{2C} \\
&-wx_Mx_C - wD_{MC},\ -wy_My_C - wD_{MC} + D_{3M} + D_{3C} \\
&\le D_{aa/MC} \le wx_My_C - wD_{MC} + D_{3M},\ wy_Mx_C \\
&- wD_{MC} + D_{3C},
\end{aligned}
\tag{11}
$$

where $D_{aa/MC} = -D_{AA/MC} - D_{Aa/MC}$.

In conjunction with the joint genotypic disequilibria, it is also of interest to consider joint allelic associations. For instance, the *joint allelic disequilibrium*,

$$
\begin{aligned}
D_{A/MC} &= \text{freq.}\,(A/M/C) - \text{freq.}\,(A)\,\text{freq.}\,(M/C) \\
&= p_{11} - px_{11},
\end{aligned}
\tag{12}
$$

measures the pairwise association between the nuclear allele, A, and the joint cytotype, M/C. The remaining three joint allelic disequilibria involving the A nuclear allele are closely related to $D_{A/MC}$:

$$
\begin{aligned}
D_{A/Mc} &= p_{12} - px_{12} = -D_{A/MC} + D_M \\
D_{A/mC} &= p_{21} - px_{21} = -D_{A/MC} + D_C \\
D_{A/mc} &= p_{22} - px_{22} = D_{A/MC} - D_M - D_C,
\end{aligned}
\tag{13}
$$

where $D_{A/MC} + D_{A/Mc} + D_{A/mC} + D_{A/mc} = 0$. Definitions (12)–(13) determine three independent measures, which, in fact, fully describe the pairwise associations between the two nuclear alleles and the four joint cytotypes, since the corresponding disequilibria involving the nuclear allele, a, are simply the negatives of those involving A (*e.g.*, $D_{a/MC} = q_{11} - qx_{11} = -D_{A/MC}$, etc.). Moreover, the rightmost sides of (13) show that all joint allelic disequilibria can be expressed in terms of a single joint allelic association, say $D_{A/MC}$, and the two-locus allelic associations, D_M and D_C, between the nuclear locus and each cytoplasmic locus. The resulting parameterization of the eight three-locus allele frequencies in Table 7 implies that the basic measure, $D_{A/MC}$, is subject to the following constraints:

$$
\min D_{A/MC} \le D_{A/MC} \le \max D_{A/MC},
\tag{14}
$$

where

$$
\begin{aligned}
\min D_{A/MC} = \max\{&-px_Mx_C - pD_{MC}, \\
&- py_My_C - pD_{MC} + D_M + D_C, \\
&- qx_My_C + qD_{MC} + D_M, \\
&- qy_Mx_C + qD_{MC} + D_C\} \\
\max D_{A/MC} = \min\{&px_My_C - pD_{MC} + D_M, \\
&py_Mx_C - pD_{MC} + D_C, \\
&qx_Mx_C + qD_{MC}, \\
&qy_My_C + qD_{MC} + D_M + D_C\}.
\end{aligned}
$$

The three-locus, joint allelic and genotypic disequilibria have analogous interrelationships to those found in (6) among the original two-locus, cytonuclear disequilibria. In particular,

$$
\begin{aligned}
&D_{AA/MC} + D_{Aa/MC} + D_{aa/MC} = 0 \quad \text{and} \\
&\qquad D_{A/MC} = D_{AA/MC} + \tfrac{1}{2}D_{Aa/MC}.
\end{aligned}
\tag{15}
$$

The same set of interrelationships holds for each of the three remaining sets of disequilibria involving the M/c, m/C, and m/c joint cytotypes.

Four consequences of these interrelationships are especially important. First, the four joint genotypic and allelic disequilibria involving any one joint cytotype represent two independent measures, since the values of all four can be gotten from the values of any two of them. Any two, then, will complete the parameterization of the three-locus system, in conjunction with the single-locus frequencies and the two-locus disequilibria. Second, if two joint disequilibria involving a given joint cytotype are zero, then all four are zero. Third, it is possible for a joint cytotype to be randomly associated with the nuclear alleles and yet be nonrandomly associated with all three nuclear genotypes. Last, the only possible patterns for the four associations involving a given joint cytotype are that all four are zero, one is zero and three are nonzero, or all four are nonzero.

A final set of observations follows from the fact, previously mentioned in conjunction with Table 5 and (12)–(13), that the four joint disequilibria involving any one nuclear allele or genotype must sum to zero (*i.e.*, $D_{N/MC} + D_{N/Mc} + D_{N/mC} + D_{N/mc} = 0$ for $N = AA$, Aa, aa, or A). This implies that any given nuclear type (allele or genotype) can be 1) randomly associated with all four joint cytotypes; 2) randomly associated with two joint cytotypes and nonrandomly associated with the other two; 3) randomly associated with only one joint cytotype; or 4) nonrandomly associated with all four joint cytotypes.

Taken together, these two sets of interrelationships allow for a wide variety of possible (zero and nonzero) patterns of associations among the 16 disequilibria that can arise between the four joint cytotypes and the nuclear genotypes and alleles (*i.e.*, the 12 involving the three nuclear genotypes plus the four involving the nuclear alleles). Because of this richness of detail, the observed pattern may provide a useful test of alternative hypotheses concerning a population's structure and its evolutionary history.

Although the nuclear-dicytoplasmic system can be completely characterized using the variables defined above, it is also important to consider true three-way associations. Such disequilibria measure nonrandom associations among the three loci after taking account of all two-locus associations. To this end, one can define the *three-way allelic disequilibrium*

$$D_{A/M/C} = p_{11} - px_Mx_C - pD_{MC} - x_MD_C - x_CD_M, \quad (16)$$

which is analogous to the three-way gametic disequilibrium among three nuclear loci (BENNETT 1954). In contrast to the multiple joint allelic measures in (12)–(13), there is only one such three-way measure, since the seven remaining three-way allelic disequilibria are either equal to, or are the negative of $D_{A/M/C}$.

A set of *three-way genotypic disequilibria* can be formulated in a similar fashion. The three-way genotypic disequilibria involving the M/C cytotype, for instance, are defined as

$$\begin{aligned} D_{AA/M/C} &= u_{11} - ux_Mx_C - uD_{MC} \\ &\quad - x_MD_{1C} - x_CD_{1M} \\ D_{Aa/M/C} &= v_{11} - vx_Mx_C - vD_{MC} \\ &\quad - x_MD_{2C} - x_CD_{2M} \\ D_{aa/M/C} &= w_{11} - wx_Mx_C - wD_{MC} \\ &\quad - x_MD_{3C} - x_CD_{3M}, \end{aligned} \quad (17)$$

and satisfy $D_{AA/M/C} + D_{Aa/M/C} + D_{aa/M/C} = 0$ (see APPENDIX A for a formal derivation). In contrast to the joint associations, these completely describe all 12 possible three-way genotypic disequilibria, since for any nuclear genotype $N = AA$, Aa, aa, it can be shown that $D_{N/M/c} = D_{N/m/C} = -D_{N/m/c} = -D_{N/M/C}$. Paralleling the three-way allelic association, there is effectively only one three-way disequilibrium measure for each nuclear genotype, and thus only two independent three-way genotypic disequilibria.

Despite this major difference, the two sets of three-locus associations share several important features. In particular, the four three-way associations have analogous interrelationships to those shown in (15) for the corresponding joint disequilibria. The analogous consequences of those relationships apply as well. The range of three-way association patterns (zero *vs.* nonzero) is much less than for the joint measures, however, because the three-way pattern is completely described by that for the measures involving M/C.

The two types of three-locus disequilibria are actually closely connected through the relations

$$\begin{aligned} D_{A/M/C} &= D_{A/MC} - x_MD_C - x_CD_M \\ D_{AA/M/C} &= D_{AA/MC} - x_MD_{1C} - x_CD_{1M} \\ D_{Aa/M/C} &= D_{Aa/MC} - x_MD_{2C} - x_CD_{2M} \\ D_{aa/M/C} &= D_{aa/MC} - x_MD_{3C} - x_CD_{3M}. \end{aligned} \quad (18)$$

The corresponding three-locus measures (joint and three-way) are thus equivalent if the original two-locus cytonuclear disequilibria are all zero. The interrelations in (18) can also be combined with the joint disequilibrium constraints in (11) and (14) to yield the general bounds on the four three-way associations.

Three-locus constraints on pairwise disequilibria: An additional, technical observation is that, as in the case of three nuclear loci (THOMSON and BAUR 1984), there are additional constraints on two-locus disequilibria in a nuclear-dicytoplasmic system. In particular, the two-locus allelic disequilibria, D_M, D_C, and D_{MC}, must satisfy

$$\begin{aligned} D_M + D_C + D_{MC} &\geq -(px_Mx_C + qy_My_C) \\ D_M + D_C - D_{MC} &\leq \quad py_My_C + qx_Mx_C \\ D_M - D_C + D_{MC} &\leq \quad py_Mx_C + qx_My_C \\ D_M - D_C - D_{MC} &\geq -(px_My_C + qy_Mx_C), \end{aligned} \quad (19)$$

in addition to the 12 standard two-locus constraints in (5) and (8). The four new three-locus constraints in (19) are a direct consequence of the bounds on the three-locus allelic associations. The complete 16 constraints on the two-locus disequilibria follow immediately, for example, from the 16 inequalities imposed by the bounds in (14) on $D_{A/MC}$; each of the four expressions determining $\min D_{A/MC}$ must be less than or equal to each of the four expressions determining $\max D_{A/MC}$. The same two-locus restrictions are dictated by the constraints on $D_{A/M/C}$. Although the bounds on the three-locus genotypic disequilibria impose no new restrictions on the two-locus, genotypic associations in (3), the latter are nonetheless also subject to additional three-locus constraints due to (19) and the close relationship in (6) between allelic and genotypic disequilibria.

Three-locus parameterizations: A wide variety of parameterizations are possible for the 12-genotype, three-locus cytonuclear system, each involving 11 independent variables. Based on the M/C cytotype, for instance, several sets incorporating both two- and three-locus disequilibria can be formed using three allele frequencies (p, x_M, x_C), one nuclear genotype frequency (u, v, or w), two of the four nuclear-mitochondrial disequilibria (D_M, D_{1M}, D_{2M}, D_{3M}), two of the four nuclear-chloroplast disequilibria (D_C, D_{1C}, D_{2C}, D_{3C}), the cytoplasmic disequilibrium (D_{MC}), and two independent three-locus disequilibria. *Many possible pairs of three-locus associations can be used,* including 1) two of the four joint disequilibria ($D_{A/MC}$, $D_{AA/MC}$, $D_{Aa/MC}$, $D_{aa/MC}$); 2) two of the four three-way disequilibria ($D_{A/M/C}$, $D_{AA/M/C}$, $D_{Aa/M/C}$, $D_{aa/M/C}$); 3) one joint and one three-way disequilibrium, with one being allelic and the other genotypic (*e.g.*, $D_{A/MC}$ and $D_{Aa/M/C}$ *or* $D_{Aa/MC}$ and $D_{A/M/C}$); or 4) one joint genotypic and one three-way genotypic disequilibrium involving different nuclear genotypes (*e.g.*, $D_{AA/MC}$ and $D_{Aa/M/C}$).

These parameterizations of the 12 three-locus genotype frequencies can be obtained as follows. First, as noted above, a full parameterization using the two joint genotypic disequilibria, $D_{AA/MC}$ and $D_{Aa/MC}$, follows directly from (1), (10), and Tables 5 and 6. This can then be easily converted to a parameterization using another pair of joint M/C disequilibria via the relations in (15), or to a parameterization involving one or two three-way disequilibria via the relations in (18). Analogous parameterizations can be made based on one of the other three cytoplasmic combinations.

Many other three-locus parameterizations are possible, of course, such as ones based on six independent joint disequilibria and five independent variables that specify the marginal nuclear and cytoplasmic frequencies. From the relations in Table 5, (1), and (10), one such set is given by p, x_M, x_C, u, D_{MC}, $D_{AA/MC}$, $D_{Aa/MC}$, $D_{AA/Mc}$, $D_{Aa/Mc}$, $D_{AA/mC}$ and $D_{Aa/mC}$. It should be born in mind that whatever 11-variable set is used as the basic parameterization of the system, the values of all the other variables can be calculated from the definitions and relations above. Which of the many variable sets is most useful will depend on the specific system under consideration. Presumably, the joint three-locus disequilibria should be particularly relevant to systems in which both cytoplasmic loci are inherited through the same parent, whereas the full three-way associations may be of greater utility when cytotypes are inherited through opposite parents.

DYNAMICS OF CYTONUCLEAR DISEQUILIBRIA

In this section, we investigate the dynamical behavior of three-locus, nuclear-dicytoplasmic systems under models of random and mixed mating. The effects of two forms of uniparental, cytoplasmic transmission are discussed for each mating system. The first assumes mitochondria and chloroplasts are jointly inherited through the same parent, whereas the second assumes the two genomes are inherited through opposite parents. The assumptions common to all models are (i) discrete, nonoverlapping generations; (ii) normal Mendelian inheritance of the nuclear locus; (iii) equal cytonuclear frequencies in the two sexes; (iv) no selective differences among the cytonuclear genotypes; and (v) large population size with no outside recruitment, so that the effects of drift and migration can be ignored.

Random mating with joint inheritance of mitochondria and chloroplasts through the same parent: As in the three subsequent models, the underlying recursions can be obtained from a table of all possible matings, together with their frequencies and offspring distributions. In this case, only 36 distinct matings need be considered, those between the 12 three-locus genotypes of the parent transmitting the cytoplasmic genes and the three nuclear genotypes of the other parent. For example, with joint maternal inheritance, the mating $AA/M/C$ ♀ × Aa ♂ has frequency $u_{11}v$ and produces $\frac{1}{2}AA/M/C$ and $\frac{1}{2}Aa/M/C$ progeny. Applying this procedure to all possible matings shows that the values of the 12 genotype frequencies are, after one generation:

$$\begin{aligned} u'_{ij} &= p_{ij}p \\ v'_{ij} &= p_{ij}q + q_{ij}p \\ w'_{ij} &= q_{ij}q, \quad \text{for} \quad i, j = 1, 2. \end{aligned} \tag{20}$$

Note that the new genotype frequencies are simply the product of the three-locus allele frequencies (Table 4) for the parent transmitting the cytoplasmic genes and the appropriate nuclear allele frequency of the other parent. Combining these transformations with the relations in Tables 1 and 4 and equations (1), (2) and (7) shows that *the three gene frequencies* (p, x_M, x_C), *the four joint cytotype frequencies* (x_{11}, x_{12}, x_{21}, x_{22}), *and the cytoplasmic disequilibrium* (D_{MC}) *are all constant through time.* The nuclear genotypes, of course, im-

mediately stabilize at their Hardy-Weinberg frequencies. Moreover, in conjunction with the recursions in (20), the definitions in (3)–(4) and Tables 2 and 3 show that the original, two-locus cytonuclear disequilibria have the usual random-mating dynamics derived by ASMUSSEN, ARNOLD and AVISE (1987). Those for the nuclear-mitochondrial associations are

$$\begin{aligned} D_M^{(t)} &= \tfrac{1}{2}D_M^{(t-1)} &&= D_M^{(0)}(\tfrac{1}{2})^t \\ D_{1M}^{(t)} &= pD_M^{(t-1)} &&= pD_M^{(t-1)}(\tfrac{1}{2})^{t-1} \\ D_{2M}^{(t)} &= (q-p)D_M^{(t-1)} &&= (q-p)D_M^{(0)}(\tfrac{1}{2})^{t-1} \\ D_{3M}^{(t)} &= qD_M^{(t-1)} &&= -qD_M^{(0)}(\tfrac{1}{2})^{t-1} \end{aligned} \qquad (21)$$

where t indicates time in generations. The corresponding dynamics for the nuclear-chloroplast associations are identical to (21), except that M is replaced by C in the subscripts of the disequilibrium measures.

Turning to the three-locus associations, the definitions in (12) and Table 6, plus the formulas in Tables 4 and 7, show in conjunction with the recursions in (20) that the dynamics of the joint disequilibria involving M/C are

$$\begin{aligned} D_{A/MC}^{(t)} &= \tfrac{1}{2}D_{A/MC}^{(t-1)} &&= D_{A/MC}^{(0)}(\tfrac{1}{2})^t \\ D_{AA/MC}^{(t)} &= pD_{A/MC}^{(t-1)} &&= pD_{A/MC}^{(0)}(\tfrac{1}{2})^{t-1} \\ D_{Aa/MC}^{(t)} &= (q-p)D_{A/MC}^{(t-1)} &&= (q-p)D_{A/MC}^{(0)}(\tfrac{1}{2})^{t-1} \\ D_{aa/MC}^{(t)} &= -qD_{A/MC}^{(t-1)} &&= -qD_{A/MC}^{(0)}(\tfrac{1}{2})^{t-1}. \end{aligned} \qquad (22)$$

The trajectories for the disequilibria involving the other three joint cytotypes are identical to (22), with all occurrences of MC replaced by Mc, mC or mc. Direct substitution of the solutions in (21)–(22) into (18) next shows that the dynamics for the three-way disequilibria ($D_{A/M/C}$, $D_{AA/M/C}$, $D_{Aa/M/C}$ and $D_{aa/M/C}$) are also equivalent to those in (22), with the two-locus cytotypes rewritten as M/C, M/c, m/C and m/c.

A comparison of (21) and (22) reveals that *in a randomly mating population where the chloroplast and mitochondrial genomes are inherited through the same parent, the three-locus cytonuclear disequilibria have the same relative sign patterns and qualitative behavior as do the corresponding two-locus cytonuclear disequilibria.* In particular, from the first generation on, all two- and three-locus AA (aa) disequilibria have the same (opposite) sign as the corresponding allelic association, whereas the Aa disequilibria have either the same or opposite sign as the corresponding allelic association, depending on whether the nuclear allele frequency, p, is below or above 0.5. In the special case of $p = 0.5$, all Aa disequilibria stabilize at zero in the first generation. Furthermore, depending on whether the initial allelic association is zero or nonzero, either all four disequilibria in a set are fixed at zero from the first generation or all (except possibly the Aa disequilibrium) are nonzero and decaying at a constant geometric rate of ½ per generation.

The disequilibrium solutions also allow a complete description of the dynamical behavior of the nuclear-dicytoplasmic system. In particular, explicit time-dependent trajectories for the frequencies of all 12 three-locus genotypes (see APPENDIX B) depend solely on the values of seven key variables, only three of which change through time: the three constant gene frequencies (p, x_M, x_C), the constant cytoplasmic disequilibrium (D_{MC}), the two-locus cytonuclear allelic disequilibria ($D_M^{(t)}$, $D_C^{(t)}$), and the joint allelic disequilibrium ($D_{A/MC}^{(t)}$). All 12 genotypes monotonically approach equilibrium values that are products of their respective nuclear Hardy-Weinberg and joint cytotype frequencies. A three-locus genotype reaches equilibrium in a single generation if its two-locus cytotype is initially randomly associated with the nuclear alleles. Otherwise, the deviations from equilibrium are halved each generation. The one exception occurs if $p = 0.5$, when the four heterozygous genotypes reach equilibrium in a single generation, regardless of the initial allelic associations.

Random mating with mitochondria and chloroplasts inherited through opposite parents: There are again 36 possible matings, which in this case involve the six nuclear-mitochondrial genotypes of one parent and the six nuclear-chloroplast genotypes of the other parent. The mating AA/M ♀ × Aa/c ♂, for example, has frequency $u_{1M}v_{2C}$ and produces ½$AA/M/c$ and ½$Aa/M/c$ progeny (assuming mitochondria are maternally inherited and chloroplasts are paternally inherited). After one generation, the 12 three-locus genotype frequencies are products of the two-locus cytonuclear allelic combinations in Table 3:

$$\begin{aligned} u'_{ij} &= p_{iM}p_{jC} \\ v'_{ij} &= p_{iM}q_{jC} + q_{iM}p_{jC} \\ w'_{ij} &= q_{iM}q_{jC}, \quad \text{for} \quad i, j = 1, 2. \end{aligned} \qquad (23)$$

The same recursions hold regardless of which cytoplasmic genome is maternally inherited. The transformations for the nuclear-mitochondrial and nuclear-chloroplast subsystems are the same as when the two cytoplasmic genomes are jointly inherited through the same parent. Consequently, the gene frequencies do not change from their original values, the nuclear genotypes immediately reach Hardy-Weinberg equilibrium, and the two-locus cytonuclear disequilibria have the usual random-mating trajectories shown in (21).

The dynamics of the three-locus and joint cytoplasmic variables are strongly dependent on the cytoplasmic inheritance pattern. For instance, paralleling the nuclear gene frequencies, the joint cytotype frequencies are

fixed after one round of mating as the products of their constant single-locus frequencies:

$$\begin{aligned} x_{11}^{(t)} &= x_M x_C \\ x_{12}^{(t)} &= x_M y_C \\ x_{21}^{(t)} &= y_M x_C \\ x_{22}^{(t)} &= y_M y_C, \quad \text{for} \quad t \geq 1. \end{aligned} \tag{24}$$

From this and (7), it is apparent that the cytoplasmic disequilibrium immediately stabilizes at zero:

$$D_{MC}^{(t)} = x_{11}^{(t)} - x_M x_C = 0. \tag{25}$$

Thus, *with opposite modes of inheritance, mitochondrial and chloroplast haplotypes become randomly associated in a single generation,* and remain so in all subsequent generations, regardless of the initial genotypic distribution. This is in strong contrast to the behavior when the two cytoplasmic genomes are inherited through the same parent, in which any initial nonrandom cytoplasmic association is fully retained. Both cases contrast with the geometric decay of ½ per generation for disequilibria between alleles at two unlinked nuclear loci, or between alleles at a nuclear locus and a cytoplasmic locus.

The recursions for the joint genotypic disequilibria are now readily obtained by using the equations in (23)–(24) in conjunction with the definitions in Table 6 and the two-locus allelic relations in (9). For example, the transformations for the genotypic disequilibria involving the M/C joint cytotype are

$$\begin{aligned} D_{AA/MC}^{(t)} &= p(x_C D_M^{(t-1)} + x_M D_C^{(t-1)}) \\ &\quad + D_M^{(t-1)} D_C^{(t-1)} \\ D_{Aa/MC}^{(t)} &= (q - p)(x_C D_M^{(t-1)} + x_M D_C^{(t-1)}) \\ &\quad - 2D_M^{(t-1)} D_C^{(t-1)} \\ D_{aa/MC}^{(t)} &= -q(x_C D_M^{(t-1)} + x_M D_C^{(t-1)}) \\ &\quad + D_M^{(t-1)} D_C^{(t-1)}. \end{aligned} \tag{26}$$

Given the formulas in (21) for $D_M^{(t)}$ and $D_C^{(t)}$, these have the explicit solutions

$$\begin{aligned} D_{AA/MC}^{(t)} &= p(x_C D_M^{(0)} + x_M D_C^{(0)})(\tfrac{1}{2})^{t-1} \\ &\quad + D_M^{(0)} D_C^{(0)} (\tfrac{1}{4})^{t-1} \\ D_{Aa/MC}^{(t)} &= (q - p)(x_C D_M^{(0)} + x_M D_C^{(0)})(\tfrac{1}{2})^{t-1} \\ &\quad - 2D_M^{(0)} D_C^{(0)} 1/4)^{t-1} \\ D_{aa/MC}^{(t)} &= -q(x_C D_M^{(0)} + x_M D_C^{(0)})(\tfrac{1}{2})^{t-1} \\ &\quad + D_M^{(0)} D_C^{(0)} (\tfrac{1}{4})^{t-1}. \end{aligned} \tag{27}$$

Substituting the solutions for $D_{AA/MC}^{(t)}$ and $D_{Aa/MC}^{(t)}$ into the second relation in (15) in turn yields the dynamics of the corresponding joint allelic disequilibrium:

$$\begin{aligned} D_{A/MC}^{(t)} &= \tfrac{1}{2}(x_C D_M^{(t-1)} + x_M D_C^{(t-1)}) \\ &= (x_C D_M^{(0)} + x_M D_C^{(0)})(\tfrac{1}{2})^t. \end{aligned} \tag{28}$$

The dynamics of the remaining joint disequilibria are similar to those in (27)–(28) and are presented in APPENDIX C.

An important general observation is that *the behavior of each joint disequilibrium is here a function solely of the constant gene frequencies and the two-locus cytonuclear allelic disequilibria,* $D_M^{(t)}$ and $D_C^{(t)}$. In the simplest case, where the nuclear alleles are initially randomly associated with haplotypes in both cytoplasmic genomes (*i.e.*, $D_M^{(0)} = D_C^{(0)} = 0$), all joint disequilibria stabilize at zero after one generation. If nuclear alleles are instead randomly associated with one cytoplasmic genome and nonrandomly associated with the other (*i.e.*, $D_M^{(0)} = 0 \neq D_C^{(0)}$ or vice versa), all joint disequilibria ordinarily exhibit the typical (two-locus) geometric decay of ½ per generation, which is also the standard dynamic for all cytonuclear disequilibria when both cytoplasmic genomes are inherited through the same parent.

In the general case where $D_M^{(0)}$ and $D_C^{(0)}$ are both nonzero, the dynamics are more complex. Under special initial conditions, the joint allelic association (for a given two-locus cytotype) immediately stabilizes at zero, while the corresponding genotypic associations decay at an accelerated geometric rate of ¼ per generation (*e.g.*, the joint M/C disequilibria when $x_C D_M^{(0)} + x_M D_C^{(0)} = 0$). Ordinarily, however, the joint allelic disequilibria again decay by ½ per generation when $D_M^{(0)} D_C^{(0)} \neq 0$, while the joint genotypic associations only approach this behavior asymptotically, with their full trajectories either (i) monotonically decaying to zero; (ii) initially increasing in magnitude before decaying to zero; or (iii) initially decreasing in magnitude, changing sign, and then increasing in magnitude before decaying to zero. An extensive analytic investigation shows that not only can each of the 12 genotypic measures display any of these dynamics, but the three genotypic associations for a given joint cytotype can each have a qualitatively different trajectory. In fact, each set of joint genotypic disequilibria has many possible combined patterns of behavior under opposite cytoplasmic inheritance, with the trajectory combinations subject only to the constraints that (i) at least one (homozygote) disequilibrium monotonically decays to zero; (ii) at most one genotypic disequilibrium increases; and (iii) the heterozygote disquilibrium does not increase if a homozygote disequilibrium changes sign.

In contrast, the dynamics and sign patterns of the true three-way disequilibria are all straightforward, although nonetheless different from those with joint

cytoplasmic inheritance. The equations in (21) and (26)–(28) can be substituted directly into (18) to show that

$$D^{(t)}_{A/M/C} \equiv 0, \quad \text{for} \quad t \geq 1, \tag{29}$$

and that

$$\begin{aligned} D^{(t)}_{AA/M/C} &= D^{(t)}_{aa/M/C} = D^{(t-1)}_{M} D^{(t-1)}_{C} \\ &= D^{(0)}_{M} D^{(0)}_{C} (1/4)^{t-1} \\ D^{(t)}_{Aa/M/C} &= -2D^{(t-1)}_{M} D^{(t-1)}_{C} = -2D^{(0)}_{M} D^{(0)}_{C} (1/4)^{t-1}. \end{aligned} \tag{30}$$

Like the cytoplasmic disequilibrium (D_{MC}), the three-way allelic disequilibrium ($D_{A/M/C}$) immediately stabilizes at zero regardless of its initial value. The same is true of the three-way genotypic disequilibria, if either $D^{(0)}_{M}$ or $D^{(0)}_{C}$ is zero. In cases where $D^{(0)}_{M}$ and $D^{(0)}_{C}$ are both nonzero, all three-way genotypic associations decay monotonically to zero by 1/4 per generation, which is faster than the usual rate of 1/2 per generation with joint inheritance. A further distinctive feature of the present model is that $D^{(t)}_{AA/M/C}$ and $D^{(t)}_{aa/M/C}$ are equal to one another and have the sign of $D^{(0)}_{M} D^{(0)}_{C}$ for $t \geq 1$, whereas $D^{(t)}_{Aa/M/C}$ has the opposite sign and twice the magnitude of the two homozygous measures.

The recursions in (21) and (23) plus the relations in (9) show that the trajectories of the 12 genotype frequencies (see APPENDIX B) here depend only on the values of the constant gene frequencies (p, x_M, x_C) and the two-locus allelic disequilibria ($D^{(t)}_{M}$, $D^{(t)}_{C}$). The genotype frequencies each approach the three-way product of the nuclear genotype's Hardy-Weinberg frequency and the individual cytoplasmic frequencies. These values are reached in a single generation if the nuclear alleles are initially randomly associated with the haplotypes at each cytoplasmic locus. In general, in addition to approaching different equilibria than those obtained under joint cytoplasmic inheritance, the trajectories under opposite cytoplasmic inheritance are not necessarily monotonic.

Mixed mating with joint inheritance of mitochondria and chloroplasts through the same parent: We next return to the case of joint transmission of mitochondria and chloroplasts through a single parent, but under the standard model of mixed mating (CLEGG 1980). The distinguishing assumptions of this model are that (i) offspring of each individual are the result of either self-pollination, with probability s, or of random outcrossing, with probability $1 - s$, where $0 < s < 1$; and (ii) the distribution of pollen allele frequencies is identical across all maternal individuals.

The recursions for the three-locus genotype frequencies have the general form

$$\begin{aligned} u'_{ij} &= s(u_{ij} + 1/4 v_{ij}) + (1 - s) p_{ij} p \\ v'_{ij} &= 1/2 s v_{ij} + (1 - s)(p_{ij} q + q_{ij} p) \\ w'_{ij} &= s(w_{ij} + 1/4 v_{ij}) + (1 - s) q_{ij} q, \end{aligned} \tag{31}$$

for $i, j = 1, 2$. Note that when no selfing occurs (*i.e.*, $s = 0$), these equations reduce to those in (20), the dynamics under random mating and joint cytoplasmic inheritance. As in that model, the three gene frequencies, the four joint cytotype frequencies, and the cytoplasmic disequilibrium are here constant through time. The nuclear genotype frequencies have the usual mixed-mating dynamics:

$$\begin{aligned} u^{(t)} &= s(u^{(t-1)} + 1/4 v^{(t-1)}) + (1 - s) p^2 = p - 1/2 v^{(t)} \\ v^{(t)} &= 1/2 s v^{(t-1)} + 2(1 - s) pq = \hat{v} + (v^{(0)} - \hat{v}) \left(\frac{s}{2}\right)^t \\ w^{(t)} &= s(w^{(t-1)} + 1/4 v^{(t-1)}) + (1 - s) q^2 = q - 1/2 v^{(t)} \end{aligned} \tag{32}$$

where

$$\hat{v} = \frac{4(1 - s) pq}{(2 - s)}.$$

In conjunction with the definitions in (3)–(4) and Tables 2–4, the equations in (31)–(32) can be used to show that the recursions for the nuclear-mitochondrial disequilibria have the mixed-mating dynamics derived in ASMUSSEN, ARNOLD and AVISE (1987):

$$\begin{aligned} D'_{M} &= 1/2(1 + s) D_{M} \\ D'_{1M} &= [s + (1 - s) p] D_{M} - 1/4 s D_{2M} \\ D'_{2M} &= (1 - s)(q - p) D_{M} + 1/2 s D_{2M} \\ D'_{3M} &= -[s + (1 - s) q] D_{M} - 1/4 s D_{2M}. \end{aligned} \tag{33}$$

Their explicit solutions are rewritten here as

$$\begin{aligned} D^{(t)}_{M} &= D^{(0)}_{M} \left(\frac{1 + s}{2}\right)^t \\ D^{(t)}_{1M} &= [s + 2(1 - s) p] D^{(0)}_{M} \left(\frac{1 + s}{2}\right)^t \\ &\quad - 1/2 [D^{(0)}_{2M} - 2(1 - s)(q - p) D^{(0)}_{M}] \left(\frac{s}{2}\right)^t \\ D^{(t)}_{2M} &= 2(1 - s)(q - p) D^{(0)}_{M} \left(\frac{1 + s}{2}\right)^t \\ &\quad + [D^{(0)}_{2M} - 2(1 - s)(q - p) D^{(0)}_{M}] \left(\frac{s}{2}\right)^t \\ D^{(t)}_{3M} &= -[s + 2(1 - s) q] D^{(0)}_{M} \left(\frac{1 + s}{2}\right)^t \\ &\quad - 1/2 [D^{(0)}_{2M} - 2(1 - s)(q - p) D^{(0)}_{M}] \left(\frac{s}{2}\right)^t. \end{aligned} \tag{34}$$

The corresponding formulas for the nuclear-chloroplast disequilibria are equivalent to those in (33) and (34) with all occurrences of M replaced by C.

As in the case of random mating with joint cytoplasmic inheritance, the dynamics of the three-locus disequilibria are all exact parallels of those for the corresponding two-locus cytonuclear associations. In

particular, the recursions and solutions for the joint M/C cytotype are equivalent to (33)–(34) with D_M replaced by $D_{A/MC}$, D_{1M} by $D_{AA/MC}$, D_{2M} by $D_{Aa/MC}$, and D_{3M} by $D_{aa/MC}$ (see APPENDIX D). The dynamics of the other three-locus disequilibria have the same form, with all occurrences of MC replaced by Mc, mC, or mc, or alternatively by M/C, M/c, m/C or m/c.

Several other generalizations are evident from the full system of equations. For example, *under mixed mating with joint cytoplasmic inheritance, all the frequency and disequilibrium recursions are the weighted averages of those under random mating and pure selfing.* This simple relation, however, does not extend to the actual trajectories. In addition, although all cytonuclear disequilibria eventually go to zero under either full or partial random outcrossing, there are two distinctive features to the mixed-mating dynamics. First, *within each set of joint or three-way disequilibria involving a given two-locus cytotype, the allelic disequilibrium may be zero in a mixed-mating population at the same time that the three genotypic disequilibria are nonzero.* Second, with partial self-fertilization, the allelic and genotypic associations comprise two distinct classes of disequilibrium dynamics. All allelic disequilibria monotonically decay to zero at the constant geometric rate of $(1 + s)/2$ per generation. The genotypic disequilibria also ultimately decay to zero at this same rate, but an analytic investigation shows that they may initially increase or change sign, exhibiting the same range of behavior found for the joint genotypic disequilibria in (27) under random mating with opposite cytoplasmic inheritance.

The complete trajectories for the frequencies of the 12 three-locus genotypes can be obtained by substituting the nuclear genotypic trajectories from (32), along with the genotypic disequilibrium solutions, into the relations in Tables 5 and 6. These require a full 11 independent variables, of which only four, the three gene frequencies and the cytoplasmic disequilibrium, are constant through time. Paralleling the completely random mating case, the genotype frequencies all approach the products of the nuclear genotypic equilibria under mixed mating (32) and the constant joint cytotype frequencies, but with partial self-fertilization their trajectories are not necessarily monotonic.

Mixed mating with mitochondria and chloroplasts inherited through opposite parents: The general forms of the genotypic transformations are

$$\begin{aligned} u'_{ij} &= s(u_{ij} + \tfrac{1}{4}v_{ij}) + (1 - s)p_{iM}p_{jC} \\ v'_{ij} &= \tfrac{1}{2}sv_{ij} + (1 - s)(p_{iM}q_{jC} + q_{iM}p_{jC}) \\ w'_{ij} &= s(w_{ij} + \tfrac{1}{4}v_{ij}) + (1 - s)q_{iM}q_{jC}. \end{aligned} \tag{35}$$

These can be used to show that the gene frequencies (p, x_M, x_C) are constant, and the nuclear genotypes and two-locus cytonuclear disequilibria have the usual mixed-mating dynamics in (32)–(34).

The trajectory for the cytoplasmic disequilibrium is in this case

$$D_{MC}^{(t)} = sD_{MC}^{(t-1)} = D_{MC}^{(0)}(s)^t. \tag{36}$$

Direct substitution of $D_{MC}^{(t)}$ from (36) into the relations in (10) in turn yields the dynamics of the two-locus cytoplasmic frequencies

$$\begin{aligned} x_{11}^{(t)} &= x_M x_C + sD_{MC}^{(t-1)} = x_M x_C + D_{MC}^{(0)}(s)^t \\ x_{12}^{(t)} &= x_M y_C - sD_{MC}^{(t-1)} = x_M y_C - D_{MC}^{(0)}(s)^t \\ x_{21}^{(t)} &= y_M x_C - sD_{MC}^{(t-1)} = y_M x_C - D_{MC}^{(0)}(s)^t \\ x_{22}^{(t)} &= y_M y_C + sD_{MC}^{(t-1)} = y_M y_C + D_{MC}^{(0)}(s)^t. \end{aligned} \tag{37}$$

The formulas in (36)–(37) show that *unless the selfing rate is high, nonrandom associations between the cytoplasmic genomes rapidly disappear,* and as a result, the joint cytoplasmic frequencies quickly approach the products of their individual cytoplasmic frequencies. As mentioned above, this randomization is established within a single generation under complete outcrossing (*i.e.*, $s = 0$). Moreover, this behavior contrasts strongly with that under joint inheritance, for which any initial cytoplasmic association is fully retained under both mating systems.

Turning to the three-locus associations, the recursions in (35) and (37) together with the definition in (12) show, for example, that the transformation for the allelic disequilibrium involving the M/C joint cytotype is

$$D_{A/MC}^{(t)} = sD_{A/MC}^{(t-1)} + \left(\frac{1 - s}{2}\right)(x_C D_M^{(t-1)} + x_M D_C^{(t-1)}), \tag{38}$$

and the resulting solution is

$$D_{A/MC}^{(t)} = (x_C D_M^{(0)} + x_M D_C^{(0)})\left(\frac{1 + s}{2}\right)^t + D_{A/M/C}^{(0)}(s)^t. \tag{39}$$

The dynamics of the other three joint allelic associations have similar forms (APPENDIX C), and can be obtained by substituting those for $D_M^{(t)}$, $D_C^{(t)}$, and $D_{A/MC}^{(t)}$ in (33)–(34) and (38)–(39) into the relations in (13). Note that thus far, as with joint cytoplasmic inheritance, the recurrence relations for the frequency and disequilibrium variables are weighted averages of those under pure selfing and random mating.

The recursions for the joint genotypic disequilibria, on the other hand, here include a third, higher order interaction term, corresponding to the covariance between nuclear genotypic and joint cytoplasmic frequencies across the randomly mating and self-fertilizing segments of the population. For example, equations (32), (35), and (37), in conjunction with the formulas in (9)–(10) and Table 6, show that the recursions for the

M/C genotypic disequilibria are

$$\begin{aligned}
D'_{AA/MC} &= s(D_{A/MC} - \tfrac{1}{4}D_{Aa/MC}) \\
&\quad + (1 - s)[p(x_C D_M + x_M D_C) + D_M D_C] \\
&\quad + s(1 - s)(pq - \tfrac{1}{4}v)D_{MC} \\
D'_{Aa/MC} &= \tfrac{1}{2}sD_{Aa/MC} \\
&\quad + (1 - s)[(q - p)(x_C D_M + x_M D_C) - 2D_M D_C] \\
&\quad - 2s(1 - s)(pq - \tfrac{1}{4}v)D_{MC} \\
D'_{aa/MC} &= -s(D_{A/MC} + \tfrac{1}{4}D_{Aa/MC}) \\
&\quad - (1 - s)[q(x_C D_M + x_M D_C) - D_M D_C] \\
&\quad + s(1 - s)(pq - \tfrac{1}{4}v)D_{MC}.
\end{aligned} \tag{40}$$

Although explicit solutions can be derived for the 12 joint genotypic disequilibria (see APPENDIX C), they are complex, with each being a linear combination of five geometric terms. With the geometric factors written in decreasing magnitude, the solutions for each nuclear genotype $N = AA, Aa, aa$ and joint cytotype $J = MC, Mc, mC, mc$ have the common form

$$D^{(t)}_{N/J} = d_1\left(\frac{1 + s}{2}\right)^t + d_2\left(\frac{1 + s}{2}\right)^{2t} + d_3(s)^t + d_4\left(\frac{s}{2}\right)^t + d_5\left(\frac{s^2}{2}\right)^t,$$

where in each case the constant coefficients $d_1, \cdots, d_5$ are distinctive functions of the initial conditions and the selfing rate (s).

The three-way disequilibria have somewhat simpler recursions than the joint disequilibria. This is especially true for the allelic disequilibrium, whose recursion is obtained by substituting the transformations for $D^{(t)}_M$, $D^{(t)}_C$, and $D^{(t)}_{A/MC}$ from (33) and (38) into the relations in (18):

$$D^{(t)}_{A/M/C} = sD^{(t-1)}_{A/M/C} = D^{(0)}_{A/M/C}(s)^t. \tag{41}$$

A comparison of (41) and (36) reveals that, as under random mating and opposite cytoplasmic inheritance, *the three-way allelic association and the cytoplasmic association have the same qualitative behavior.* In this case, both decay to zero by s per generation, whereas both instantly reach zero in randomly mating populations. Moreover, as for all variables except the three-locus genotypic disequilibria, the recursion for $D^{(t)}_{A/M/C}$ is the weighted average of those under random mating and pure selfing.

The recursions for the three-way genotypic disequilibria are analogous to those in (40) for the corresponding joint genotypic disequilibria, except that each lacks the term involving the cytoplasmic frequencies. For instance, substitution of the recursions from (33) and (40) into the last three relations in (18) shows that the transformations for the three-way genotypic disequilibria involving M/C are

$$\begin{aligned}
D'_{AA/M/C} &= s(D_{A/M/C} - \tfrac{1}{4}D_{Aa/M/C}) \\
&\quad + (1 - s)D_M D_C + s(1 - s)(pq - \tfrac{1}{4}v)D_{MC} \\
D'_{Aa/M/C} &= \tfrac{1}{2}sD_{Aa/M/C} - 2(1 - s)D_M D_C \\
&\quad - 2s(1 - s)(pq - \tfrac{1}{4}v)D_{MC} \\
D'_{aa/M/C} &= -s(D_{A/M/C} + \tfrac{1}{4}D_{Aa/M/C}) \\
&\quad + (1 - s)D_M D_C + s(1 - s)(pq - \tfrac{1}{4}v)D_{MC}.
\end{aligned} \tag{42}$$

Paralleling the joint genotypic disequilibria, the explicit solutions for the three-way genotypic associations are complex (see APPENDIX C), with each in this case being the linear combination of four geometric terms (again listed in order of decreasing magnitude): $[(1 + s)/2]^{2t}$, $(s)^t$, $(s/2)^t$, $(s^2/2)^t$.

It is clear from the solutions that all three-locus disequilibria eventually decay to zero. Of these, however, only $D^{(t)}_{A/M/C}$ always does so monotonically. The remaining three-locus disequilibria potentially have more complex behavior. A detailed analytical investigation of their explicit solutions reveals that the joint allelic disequilibria either immediately stabilize at zero or have one of the three qualitative trajectories found for all genotypic disequilibria under mixed mating with joint cytoplasmic inheritance, and for the joint genotypic disequilibria under random mating with opposite cytoplasmic inheritance. Based on numerical examples, these patterns also appear to be the most common ones exhibited here by the joint and three-way genotypic disequilibria.

Paralleling the fully random-mating case with opposite cytoplasmic inheritance, the two- and three-locus disequilibria as a group display three different asymptotic decay rates. *Under both mating systems, the cytoplasmic disequilibrium (D_{MC}) and the three-way allelic disequilibrium ($D_{A/M/C}$) exhibit the fastest decay rate (s per generation).* Similarly, the ultimate decay rate of $[(1 + s)/2]^2$ per generation for the three-way genotypic disequilibria is faster than the asymptotic decay rate of $(1 + s)/2$ per generation exhibited by all remaining two- and three-locus disequilibria. The latter, common rate also characterizes the ultimate approach to equilibrium by the 12 three-locus genotypes. Their final frequencies are in this case three-way products of the nuclear genotypes' equilibrium frequencies under mixed mating (32) and the individual cytoplasmic frequencies. As under mixed mating with joint inheritance, a full 11 variables are needed to describe their trajectories. In this case, all but the three gene frequencies vary through time.

DISCUSSION

We have expanded the original work of ASMUSSEN, ARNOLD and AVISE (1987) by defining and determining the interrelationships among five sets of disequi-

TABLE 8

Generalized disequilibrium dynamics for generations $t \geq 1$, under three mating systems with joint or opposite cytoplasmic inheritance

Mating system	Cytoplasmic inheritance	Disequilibrium				
		Cytoplasmic	Allelic		Genotypic	
Random	Joint	Constant	All forms	$d(1/2)^t$	All forms	$d(1/2)^t$
	Opposite	0	Two-locus	$d(1/2)^t$	Two-locus	$d(1/2)^t$
			Joint	$d(1/2)^t$	Joint	$d_1(1/2)^t + d_2(1/4)^t$
			Three-way	0	Three-way	$d(1/4)^t$
Mixed	Joint	Constant	All forms	$d\left(\frac{1+s}{2}\right)^t$	All forms	$d_1\left(\frac{1+s}{2}\right)^t + d_2\left(\frac{s}{2}\right)^t$
	Opposite	$d(s)^t$	Two-locus	$d\left(\frac{1+s}{2}\right)^t$	Two-locus	$d_1\left(\frac{1+s}{2}\right)^t + d_2\left(\frac{s}{2}\right)^t$
			Joint	$d_1\left(\frac{1+s}{2}\right)^t + d_2(s)^t$	Joint	$d_1\left(\frac{1+s}{2}\right)^t + \cdots + d_5\left(\frac{s^2}{2}\right)^t$
			Three way	$d(s)^t$	Three-way	$d_1\left(\frac{1+s}{2}\right)^{2t} + \cdots + d_4\left(\frac{s^2}{2}\right)^t$
Selfing		Constant	All forms	Constant	AA and aa	$d_1 + d_2(1/2)^t$
					Aa	$d(1/2)^t$

librium parameters that measure nonrandom associations within nuclear-mitochondrial-chloroplast and other nuclear-dicytoplasmic systems. Three sets of pairwise disequilibria measure the association between haplotypes at the two cytoplasmic loci (D_{MC}) and associations between each cytoplasmic locus and nuclear alleles or genotypes (D_M, D_{1M}, D_{2M}, D_{3M}; D_C, D_{1C}, D_{2C}, D_{3C}). These are complemented by two classes of novel higher order disequilibria involving all three loci. The first class quantifies nonrandom associations between nuclear alleles or genotypes and joint two-locus cytotypes ($D_{A/MC}$, $D_{AA/MC}$, $D_{Aa/MC}$, $D_{aa/MC}$, etc.), whereas the second measures the extent of full three-way allelic and genotypic associations ($D_{A/M/C}$, $D_{AA/M/C}$, $D_{Aa/M/C}$, $D_{aa/M/C}$). Any of the three-locus disequilibria can be nonzero even in the absence of pairwise associations, and, like the original two-locus cytonuclear disequilibria (ASMUSSEN, ARNOLD and AVISE 1987), the three-locus genotypic measures all serve to partition the corresponding allelic association. In addition to nuclear-dicytoplasmic systems, this framework also applies to associations in the heterogametic sex among alleles and genotypes at autosomal, sex-linked, and cytoplasmic loci.

In order to form a basis for interpreting data from such three-locus systems, we examined the dynamics under random and mixed mating, with either joint or opposite inheritance of the two cytoplasmic genomes. All models considered are neutral in that the three gene frequencies do not change through time. The joint inheritance models also apply to certain two-locus cytonuclear systems. Specifically, the three-locus frequencies and joint disequilibria within these models also describe the two-locus frequencies and associations between a nuclear locus and a single cytoplasmic (or sex-linked) locus with four alleles.

To facilitate an overview of the results, the general forms of the disequilibrium dynamics are summarized in Table 8 for each of the four models, as well as for pure selfing. The behavior of all disequilibria (as well as all other variables) under pure selfing is obtained by setting $s = 1$ in the formulas for mixed mating populations with joint cytoplasmic inheritance. Note that Table 8 gives only the basic forms of the disequilibrium solutions, which, unless constant, are either fixed multiples or linear combinations of various geometric terms. The value of any particular, generalized coefficient (d, d_1, $\cdots$, d_5) depends on the disequilibrium in question.

The main general observation from Table 8 is that any amount of random outcrossing causes all cytonuclear disequilibria to decay to zero. The cytoplasmic disequilibrium, D_{MC}, is an anomaly, in that it is constant under joint cytoplasmic inheritance for all selfing rates, $0 \leq s \leq 1$. A second generalization is that, in all other circumstances, partial self-fertilization serves to retard the decay of the disequilibria. This process culminates in the extreme case of complete selfing, where the cytoplasmic disequilibria and all cytonuclear allelic disequilibria are constant, and all two- and three-locus disequilibria involving nuclear homozygotes monotonically approach the values (or negatives) of their corresponding allelic disequilibria. Only the heterozygote disequilibria always decay to zero under complete self-fertilization. These associations are lost at the constant geometric rate of ½ per generation, due to the corresponding loss of nuclear heterozygotes. Interestingly, this is equivalent to their usual decay rate in completely randomly mating populations with joint cytoplasmic inheritance and is faster than their asymptotic decay rate of $(1 + s)/2$ under partial self-fertilization.

Several other, more technical observations are evident from Table 8. First, the dynamics of the two-locus cytonuclear subsystems are solely a function of the mating system, whereas the dynamical behavior and sign patterns of the cytoplasmic and three-locus disequilibria also depend strongly on the mode of cytoplasmic inheritance. For example, for every fixed selfing rate, $0 \leq s < 1$, all three-way associations have faster decay rates with opposite inheritance than with joint inheritance. In contrast, although their functional forms vary with the mode of cytoplasmic inheritance, the joint disequilibria have identical asymptotic decay rates in both cases. The various models also differ significantly in the complexity of their complete disequilibrium trajectories. At one extreme are the two random-mating models, for which all cytonuclear disequilibria generally decay monotonically. The one exception occurs under opposite inheritance, where the joint genotypic disequilibria can increase or change sign in the early stages of their trajectories. At the opposite extreme are the two mixed-mating models, for which all genotypic disequilibria can exhibit these more complex patterns of behavior, as can also the joint allelic disequilibria when the two cytoplasmic genomes are inherited through opposite parents.

There are many possible forms and levels of nonrandom associations within nuclear-dicytoplasmic systems, just as within multilocus nuclear systems (*e.g.*, WEIR and WILSON, 1986). We have suggested several parameterizations, each of which includes at least two of our three-locus disequilibria. In order to utilize these two new classes of disequilibrium measures, it is important to fully understand the kind of information they contain as well as the interrelationships between them. The three-way disequilibria, on the one hand, measure only those associations remaining after all pairwise two-locus associations have been taken into account. They consequently have complex definitions (APPENDIX A), but have the logical advantage that there is only one such measure involving each nuclear allele or genotype. Moreover, the values of all four three-way disequilibria can be completely determined by the values of any two.

The joint disequilibria, on the other hand, are simply defined as the difference between the observed frequency of a given three-locus combination and its expected frequency given random association between the nuclear type and the joint cytotype. These are thus natural parameters with a direct basis in the table of observed three-locus frequencies. The joint disequilibria are composite measures, however, that encompass the combined effects of three-way and pairwise cytonuclear associations among the loci [see (18)]. If the nuclear alleles and genotypes are randomly associated with the four joint cytotypes, then all other two- and three-locus cytonuclear associations are also necessarily zero. In further contrast to the three-way disequilibria, there are multiple joint disequilibria for each nuclear type, giving a total of six independent joint measures. (A full three-locus parameterization can be obtained from only two of these if the two-locus cytonuclear disequilibria are also explicitly included.)

The two classes of three-locus measures thus provide qualitatively different kinds of information about the population, and are equivalent only under special conditions such as when the nuclear alleles and genotypes are randomly associated with each individual cytoplasmic locus. Which of the three-locus measures is most informative in any given study will depend in large part on the specific nuclear-dicytoplasmic system under investigation. For instance, both sets of disequilibria may be informative when the cytoplasmic genomes are transmitted through opposite parents (*e.g.*, mtDNA and cpDNA in conifers), although the three-way disequilibria would appear to be the most meaningful biologically. Moreover, the dynamics of the three-way measures in this case are always simpler than those of the joint disequilibria (Table 8), especially for species that, like conifers, are almost completely outcrossing. The choice is less obvious with joint cytoplasmic inheritance, where the two types of three-locus measures have the same qualitative dynamics, which parallel those of the two-locus cytonuclear measures. The joint disequilibria might be preferred here, however, due to the natural tendency in this case to consider the two cytoplasmic genomes jointly.

In general, the contrasting modes of inheritance shown by nuclear and cytoplasmic genes allow cytonuclear disequilibria to provide a qualitatively new kind of information about the structure and evolutionary history of natural populations. This is especially true of nuclear-dicytoplasmic systems where the two cytoplasmic genomes can themselves exhibit different inheritance patterns. The present results are the first step toward a theoretical framework for using and interpreting data from these novel three-locus systems. Subsequent work will address the statistical estimation of nuclear-dicytoplasmic disequilibria and their behavior under other evolutionary forces.

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APPENDIX A

Derivation of three-way genotypic disequilibria: The three-way disequilibrium, $D_{AA/M/C}$, is formally defined as the mathematical expectation, across individuals in the population, of $(X - \mu_X)(Y - \mu_Y)(Z - \mu_Z)$, where the three random variables,

$$X \begin{cases} 1 & \text{if } AA \\ 0 & \text{if } Aa \text{ or } aa \end{cases} \quad Y = \begin{cases} 1 & \text{if } M \\ 0 & \text{if } m \end{cases} \quad Z = \begin{cases} 1 & \text{if } C \\ 0 & \text{if } c, \end{cases}$$

represent the indicator functions of the associated nuclear genotypes and cytotypes and have means

$$\mu_X = E(X) = u \qquad \mu_Y = E(Y) = x_M \qquad \mu_Z = E(Z) = x_C.$$

Expansion of this expectation immediately yields

$$\begin{aligned} D_{AA/M/C} &= E[(X - u)(Y - x_M)(Z - x_C)] \\ &= E(XYZ) - x_C E(XY) - x_M E(XZ) - uE(YZ) \\ &\quad + x_M x_C E(X) + u x_C E(Y) + u x_M E(Z) - u x_M x_C. \end{aligned}$$

Finally, after substituting the expectations for X, Y, and Z above, plus

$$\begin{aligned} E(XY) &= u_{1M} = ux_M + D_{1M} \\ E(XZ) &= u_{1C} = ux_C + D_{1C} \\ E(YZ) &= x_{11} = x_M x_C + D_{MC} \\ E(XYZ) &= u_{11}, \end{aligned}$$

this simplifies to the definition given in (17):

$$D_{AA/M/C} = u_{11} - ux_M x_C - uD_{MC} - x_M D_{1C} - x_C D_{1M}.$$

Using the relations in (10) and Table 6, the three-way association can be rewritten in terms of the joint disequilibrium $D_{AA/MC}$, as in (18):

$$D_{AA/M/C} = D_{AA/MC} - x_M D_{1C} - x_C D_{1M}.$$

The three-way genotypic disequilibria involving the Aa and aa nuclear genotypes are defined analogously, with the random variable X replaced in turn by the indicator function for Aa or aa.

APPENDIX B

Genotypic trajectories under random mating with joint inheritance of cytotypes:

$$\begin{aligned}
u_{11}^{(t)} &= p^2 x_{11} + pD_{A/MC}^{(0)}(1/2)^{t-1} \\
v_{11}^{(t)} &= 2pqx_{11} + (q - p)D_{A/MC}^{(0)}(1/2)^{t-1} \\
w_{11}^{(t)} &= q^2 x_{11} - qD_{A/MC}^{(0)}(1/2)^{t-1} \\
u_{12}^{(t)} &= p^2 x_{12} + p(D_M^{(0)} - D_{A/MC}^{(0)})(1/2)^{t-1} \\
w_{12}^{(t)} &= q^2 x_{12} - q(D_{A/MC})(1/2)^{t-1} \\
u_{21}^{(t)} &= p^2 x_{21} + p(D_C^{(0)} - D_{A/MC}^{(0)})(1/2)^{t-1} \\
v_{21}^{(t)} &= 2pqx_{21} + (q - p)(D_C^{(0)} - D_{A/MC}^{(0)})(1/2)^{t-1} \\
w_{21}^{(t)} &= q^2 x_{21} - q(D_C^{(0)} - D_{A/MC}^{(0)})(1/2)^{t-1} \\
u_{22}^{(t)} &= p^2 x_{22} + p(D_{A/MC}^{(0)} - D_M^{(0)} - D_C^{(0)})(1/2)^{t-1} \\
v_{22}^{(t)} &= 2pqx_{22} + (q - p)(D_{A/MC}^{(0)} - D_M^{(0)} - D_C^{(0)})(1/2)^{t-1} \\
w_{22}^{(t)} &= q^2 x_{22} - q(D_{A/MC}^{(0)} - D_M^{(0)} - D_C^{(0)})(1/2)^{t-1}
\end{aligned}$$

Genotypic trajectories under random mating with opposite inheritance of cytotypes:

$$\begin{aligned}
u_{11}^{(t)} &= p^2 x_M x_C + p(x_C D_M^{(0)} + x_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
v_{11}^{(t)} &= 2pqx_M x_C + (q - p)(x_C D_M^{(0)} + x_M D_C^{(0)})(1/2)^{t-1} - 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
w_{11}^{(t)} &= q^2 x_M x_C - q(x_C D_M^{(0)} + x_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
u_{12}^{(t)} &= p^2 x_M y_C + p(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
v_{12}^{(t)} &= 2pqx_M y_C + (q - p)(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} + 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
w_{12}^{(t)} &= q^2 x_M y_C - q(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
u_{21}^{(t)} &= p^2 y_M x_C - p(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
v_{21}^{(t)} &= 2pqy_M x_C - (q - p)(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} + 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
w_{21}^{(t)} &= q^2 y_M x_C + q(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
u_{22}^{(t)} &= p^2 y_M y_C - p(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
v_{22}^{(t)} &= 2pqy_M y_C - (q - p)(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} - 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
w_{22}^{(t)} &= q^2 y_M y_C + q(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1}
\end{aligned}$$

APPENDIX C

Three-locus disequilibrium trajectories with opposite cytoplasmic inheritance: *Joint disequilibria under random mating*: The trajectories for the allelic and genotypic disequilibria involving the joint M/C cytotype are given in (27) and (28). The explicit solutions for the remaining joint disequilibria are

$$\begin{aligned}
D_{A/Mc}^{(t)} &= (y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^t \\
D_{AA/Mc}^{(t)} &= p(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{Aa/Mc}^{(t)} &= (q - p)(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} + 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{aa/Mc}^{(t)} &= -q(y_C D_M^{(0)} - x_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{A/mC}^{(t)} &= -(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^t \\
D_{AA/mC}^{(t)} &= -p(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{Aa/mC}^{(t)} &= -(q - p)(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} + 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{aa/mC}^{(t)} &= q(x_C D_M^{(0)} - y_M D_C^{(0)})(1/2)^{t-1} - D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{A/mc}^{(t)} &= -(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^t \\
D_{AA/mc}^{(t)} &= -p(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{Aa/mc}^{(t)} &= -(q - p)(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} - 2D_M^{(0)} D_C^{(0)}(1/4)^{t-1} \\
D_{aa/mc}^{(t)} &= q(y_C D_M^{(0)} + y_M D_C^{(0)})(1/2)^{t-1} + D_M^{(0)} D_C^{(0)}(1/4)^{t-1}
\end{aligned}$$

Joint and three-way disequilibria under mixed mating: With

$$a = 4\left(\frac{1-s}{1+s^2}\right)D_M^{(0)}D_C^{(0)}, \qquad b = \hat{v}D_{MC}^{(0)}, \qquad c = (v^{(0)} - \hat{v})D_{MC}^{(0)},$$

the general solutions for the trajectories of the joint allelic and genotypic disequilibria for $J = MC, Mc, mC, mc$ are

$$D_{A/J}^{(t)} = d_{1,J}\left(\frac{1+s}{2}\right)^t \pm D_{A/M/C}^{(0)}(s)^t$$

$$D_{AA/J}^{(t)} = [s + 2(1-s)p]d_{1,J}\left(\frac{1+s}{2}\right)^t \pm a\left(\frac{1+s}{2}\right)^{2t}$$
$$\pm (\tfrac{1}{2}b + D_{A/M/C}^{(0)})(s)^t \mp \tfrac{1}{2}d_{2,J}\left(\frac{s}{2}\right)^t \pm \tfrac{1}{2}c\left(\frac{s^2}{2}\right)^t$$

$$D_{Aa/J}^{(t)} = 2(1-s)(q-p)d_{1,J}\left(\frac{1+s}{2}\right)^t \mp 2a\left(\frac{1+s}{2}\right)^{2t}$$
$$\mp b(s)^t \pm d_{2,J}\left(\frac{s}{2}\right)^t \mp c\left(\frac{s^2}{2}\right)^t$$

$$D_{aa/J}^{(t)} = -[s + 2(1-s)q]d_{1,J}\left(\frac{1+s}{2}\right)^t \pm a\left(\frac{1+s}{2}\right)^{2t}$$
$$\pm (\tfrac{1}{2}b - D_{A/M/C}^{(0)})(s)^t \mp \tfrac{1}{2}d_{2,J}\left(\frac{s}{2}\right)^t \pm \tfrac{1}{2}c\left(\frac{s^2}{2}\right)^t$$

where the upper sign in $\pm, \mp$ is taken for MC and mc, the lower sign for Mc and mC, and

$$d_{1,MC} = x_C D_M^{(0)} + x_M D_C^{(0)}$$
$$d_{1,Mc} = y_C D_M^{(0)} - x_M D_C^{(0)}$$
$$d_{1,mC} = -x_C D_M^{(0)} + y_M D_C^{(0)}$$
$$d_{1,mc} = -y_C D_M^{(0)} - y_M D_C^{(0)}$$

$$d_{2,MC} = 2a - 2(1-s)(q-p)d_{1,MC} + v^{(0)}D_{MC}^{(0)} + D_{Aa/MC}^{(0)}$$
$$d_{2,Mc} = 2a + 2(1-s)(q-p)d_{1,Mc} + v^{(0)}D_{MC}^{(0)} + D_{Aa/MC}^{(0)} - D_{2M}^{(0)}$$
$$d_{2,mC} = 2a + 2(1-s)(q-p)d_{1,mC} + v^{(0)}D_{MC}^{(0)} + D_{Aa/MC}^{(0)} - D_{2C}^{(0)}$$
$$d_{2,mc} = 2a - 2(1-s)(q-p)d_{1,mc} + v^{(0)}D_{MC}^{(0)} + D_{Aa/MC}^{(0)} - D_{2M}^{(0)} - D_{2C}^{(0)}.$$

The solutions for the three-way genotypic disequilibria are

$$D_{AA/M/C}^{(t)} = a\left(\frac{1+s}{2}\right)^{2t} + (\tfrac{1}{2}b + D_{A/M/C}^{(0)})(s)^t - \tfrac{1}{2}g\left(\frac{s}{2}\right)^t + \tfrac{1}{2}c\left(\frac{s^2}{2}\right)^t$$

$$D_{Aa/M/C}^{(t)} = -2a\left(\frac{1+s}{2}\right)^{2t} - b(s)^t + g\left(\frac{s}{2}\right)^t - c\left(\frac{s^2}{2}\right)^t$$

$$D_{aa/M/C}^{(t)} = a\left(\frac{1+s}{2}\right)^{2t} + (\tfrac{1}{2}b - D_{A/M/C}^{(0)})(s)^t - \tfrac{1}{2}g\left(\frac{s}{2}\right)^t + \tfrac{1}{2}c\left(\frac{s^2}{2}\right)^t,$$

where

$$g = D_{Aa/M/C}^{(0)} + v^{(0)}D_{MC}^{(0)} + 2a.$$

APPENDIX D

Three-locus disequilibrium trajectories under mixed-mating with joint cytoplasmic inheritance: Substituting the recursions from (31)–(33) into definitions (12)–(13) and Tables 5 and 6, for instance, shows that the transformations for the joint M/C genotypic associations are

$$\begin{aligned} D'_{A/MC} &= \tfrac{1}{2}(1+s)D_{A/MC} \\ D'_{AA/MC} &= [s + (1-s)p]D_{A/MC} - \tfrac{1}{4}sD_{Aa/MC} \\ D'_{Aa/MC} &= (1-s)(q-p)D_{A/MC} + \tfrac{1}{2}sD_{Aa/MC} \\ D'_{aa/MC} &= -[s + (1-s)q]D_{A/MC} - \tfrac{1}{4}sD_{Aa/MC}. \end{aligned} \tag{D1}$$

These dynamics are homologous to those in (33) and thus have the explicit solutions

$$D_{A/MC}^{(t)} = D_{A/MC}^{(0)}\left(\frac{1+s}{2}\right)^t$$

$$D_{AA/MC}^{(t)} = [s + 2(1-s)p]D_{A/MC}^{(0)}\left(\frac{1+s}{2}\right)^t$$
$$- \tfrac{1}{2}[D_{Aa/MC}^{(0)} - 2(1-s)(q-p)D_{A/MC}^{(0)}]\left(\frac{s}{2}\right)^t$$

$$D_{Aa/MC}^{(t)} = 2(1-s)(q-p)D_{A/MC}^{(0)}\left(\frac{1+s}{2}\right)^t \tag{D2}$$
$$+ [D_{Aa/MC}^{(0)} - 2(1-s)(q-p)D_{A/MC}^{(0)}]\left(\frac{s}{2}\right)^t$$

$$D_{aa/MC}^{(t)} = -[s + 2(1-s)q]D_{A/MC}^{(0)}\left(\frac{1+s}{2}\right)^t$$
$$- \tfrac{1}{2}[D_{Aa/MC}^{(0)} - 2(1-s)(q-p)D_{A/MC}^{(0)}]\left(\frac{s}{2}\right)^t.$$

Substituting these equations into the relations in (13), (18), and Table 6 in turn shows that the dynamics of the other three-locus disequilibria are analogous to (D1)–(D2), with MC replaced by Mc, mC or mc, or alternatively by M/C, M/c, m/C or m/c.