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Clone mixtures and a pacemaker: new facets of Red-Queen theory and ecology

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Host–parasite antagonistic interaction has been proposed as a potential agent to promote genetic polymorphism and to favour sex against asex, despite its twofold cost in reproduction. However, the host–parasite gene-for-gene dynamics often produce unstable cycles that tend to destroy genetic diversity. Here, we examine such diversity destroying coevolutionary dynamics of host and parasite, which is coupled through local or global migration, or both, between demes in a metapopulation structure. We show that, with global migration in the island model, peculiar out-of-phase islands spontaneously arise in the cluster of islands converging to a global synchrony. Such asynchrony induced by the 'pacemaker islands' serves to restore genetic variation. With increasing fraction of local migration, spots of asynchrony are converted into loci or foci of spiral and target patterns, whose rotating arms then cover the majority of demes. A multi-locus analogue of the model reproduces the same tendency toward asynchrony, and the condition arises for an advantage of asexual clones over their sexual counterpart when enough genetic diversity is maintained through metapopulation storage—migration serves as a cheap alternative to sex.

Keywords: gene-for-gene; host–parasite coevolution; Red Queen; metapopulation; asynchrony; evolution of sex

1. INTRODUCTION

Suppose a species in an archipelago is synchronously repeating a series of changes in gene and genotype frequencies. One may think either that cyclical climatic factors underlie the variation—sunspot, 'El Niño' or similar effects (Grenfell *et al*. 1998)—or else that some predator or parasite cycle may be in progress, with an inter-island migration rate high enough to ensure synchrony (Adler 1993). But suppose that a single island in the group is found in cyclical change with the *same period* as the rest (or nearly) but it changes with a *lesser amplitude and is permanently out of phase with all of the others*. Suppose further that nothing in the environment, either physical or biotic and excepting its different oscillation, distinguishes the odd island—it is not, for example, peripheral, it emits and receives exactly as much migration as all the others, and so on. What mechanism can account for such an odd behaviour?

In figure 1*a* we illustrate that such a paradoxical stable out-of-phase island may spontaneously arise in so-called 'island' models of population structure (Crow & Kimura 1970) that manifest oscillations of host and parasite genotypes. Two facts, one new (with its analysis to be published later) and one old, are noteworthy. First, such a spontaneous 'pacemaker deme', as we entitle the anomalous island in these situations, is more, not less, likely to arise when the cluster of like islands is more numerous. Second, when the odd island fails to arise (which most often occurs for small groups of islands), then globally synchronized expansive ('heteroclinic') fluctuations in gene and genotype frequencies of host and parasites occur and ultimately destroy variation through gene fixations. When a pacemaker island does arise, however, both that island and the main set quickly settle into two *different*, mutually stabilizing limit cycles.

We show in this paper how such peculiar asynchrony of gene and genotype frequency fluctuation develops in a globally and locally coupled metapopulation under standard dynamics of host–parasite coevolution, the gene-for-gene (in § 2) and the multi-locus matching allele dynamics (in § 3). In § 2, a spontaneous emergence of a small fraction of peculiar phase outlier deme (the pacemaker) in globally coupled gene-for-gene metapopulation dynamics is detailed, together with its effect on the maintenance of genetic diversity in the whole population and the relationship with foci and loci of spirals and target patterns that arise in locally coupled metapopulation. In § 3, the multi-locus matching genotype dynamics between host and parasite (HAMAX model) is analysed in metapopulation structure. The factors that favour sex over asex mixture under the host–parasite interaction in a metapopulation are clarified. The characteristic relationship between the abundance (and its temporal fluctuation patterns) of asex clones and the genetic distance observed in this system are detailed. The implications of these findings to classical geographical parthenogenesis is discussed. In § 4, our findings are compared with the spatial and temporal fluctuation patterns of the snail clones in New Zealand lakes. Furthermore, statistical analyses are conducted for the quantitative relationship between the genetic distances and the abundance of clones using the time series data of boreal zooplankton *Daphnia pulex* and of the intestinal flora of *Escherichia coli*. The statistical analysis is aimed to test the predictions of the Red Queen hypothesis for the evolution of sex, with the deleterious mutation hypothesis as an alternative.

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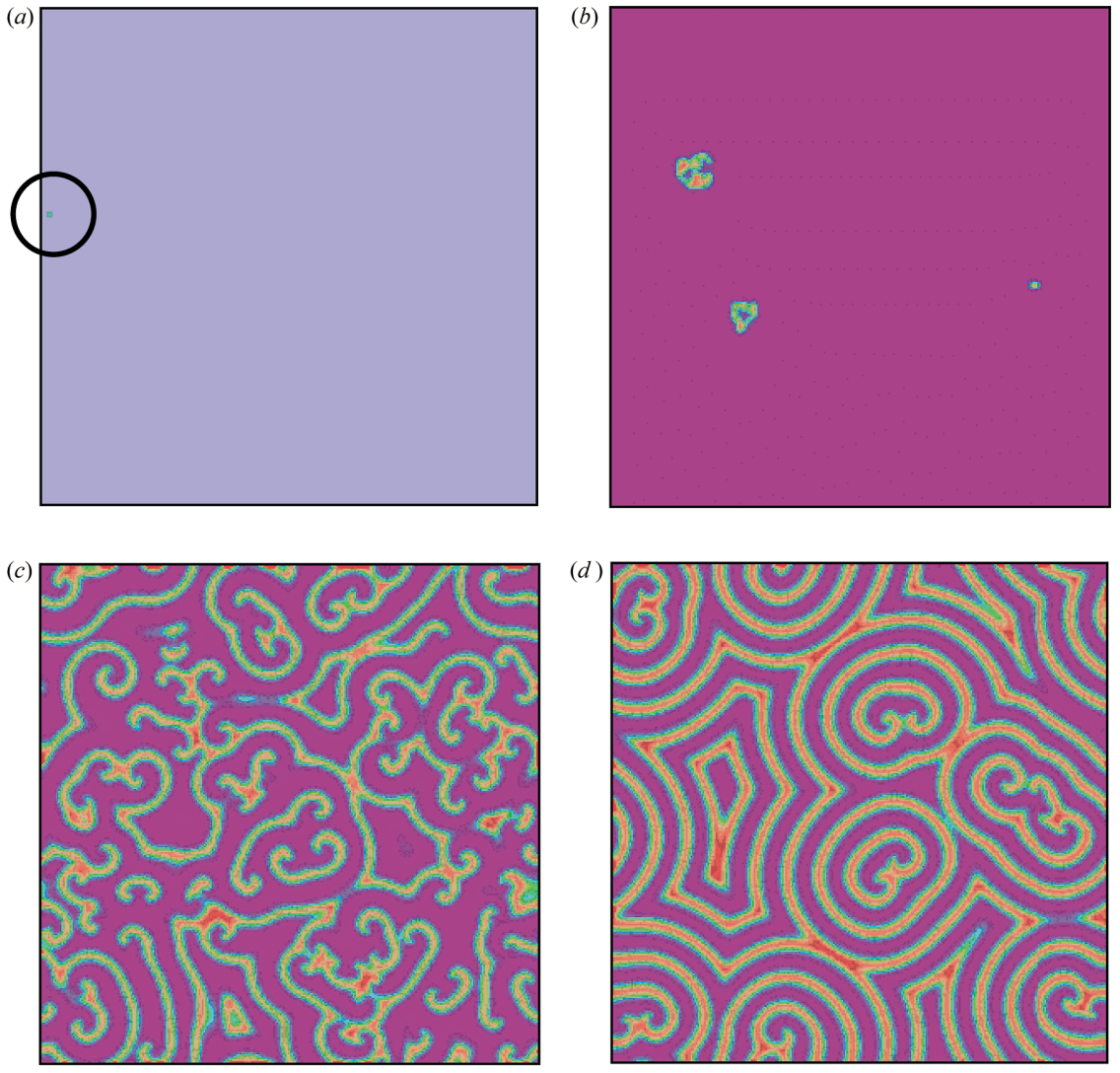

Figure 1. Asynchrony of cycles of a resistant allele frequency in a metapopulation model of classic host–parasite gene-for-gene-like interaction. Two host genotypes, susceptible (S) and resistant (R) and two parasite genotypes, avirulent (A) and virulent (V), are segregating respectively with frequencies $1 - x$ and x in host and $1 - p$ and p in parasite in each of 100×100 demes. In each deme, the host and parasite allele frequencies change according to the dynamics of equations 2.1–2.3. After the change by selection, the host and parasite migrate with migration rates m_H and m_P, where the fraction v of migrants comes from one of z (= 4) nearest neighbour demes (local migration) and the fraction $1 - v$ from one of n (= 100×100) demes in the whole population (global migration).

Panels show the different ways by which, depending on the fraction of local migration, the asynchrony developed in metapopulation prevents monomorphism and leads to stable limit cycles in each deme. (*a*) A single deme out of 10 000 demes refuses to join the global synchronized cycles of the rest. The migration is totally global ($v = 0$). (*b*) Snapshot when a small fraction (20%) of local migration is introduced ($v = 0.2$). A few spots of differently beating demes originate and release circular waves into 'the sea of synchrony' surrounding them. (*c*) Spots develop as the foci of spirals when local migration becomes dominating ($v = 0.85$). (*d*) For further increased local migration ($v = 1$), spirals give way mostly to target patterns with double spirals in their centre.

Parameters: $\beta_H = \beta_P = 5$, $c_H = c_P = 2$, $m_H = m_P = 0.2$. Boundaries of the metapopulation are periodic. All snapshots are taken about 250 generations after the simulations started from randomly chosen initial frequencies in each deme. All sources of asynchrony (pacemaker demes and foci of spirals, targets—not shown—and double spirals) are stationary, once formed.

2. GENE-FOR-GENE DYNAMICS IN A METAPOPULATION

To see how the asynchrony is developed in the host–parasite frequency cycles in a metapopulation, we first consider the host–parasite allele frequency dynamics of classic gene-for-gene interaction. Two host genotypes, susceptible (S) and resistant (R) and two parasite genotypes, avirulent (A) and virulent (V), are segregating with frequencies $1 - x$ and x in host and $1 - p$ and p in parasite in each deme. The fitness of each genotype is:

$$\begin{aligned}
&\text{susceptible host: } w_S = \exp(-\beta_H),\\
&\text{resistant host: } w_R = \exp(-c_H - \beta_H p),\\
&\text{avirulent parasite: } w_A = \exp(\beta_P(1 - x)),\\
&\text{virulent parasite: } w_V = \exp(-c_P + \beta_P),
\end{aligned} \tag{2.1}$$

where β_H and β_P are the loss in a host and the gain in a parasite of their fitness due to a successful infection, respectively. An underlying assumption is that a resistant host is infected only by virulent parasites and an avirulent parasite can infect only susceptible hosts. The costs of resistance and virulence are denoted by c_H and c_P. The

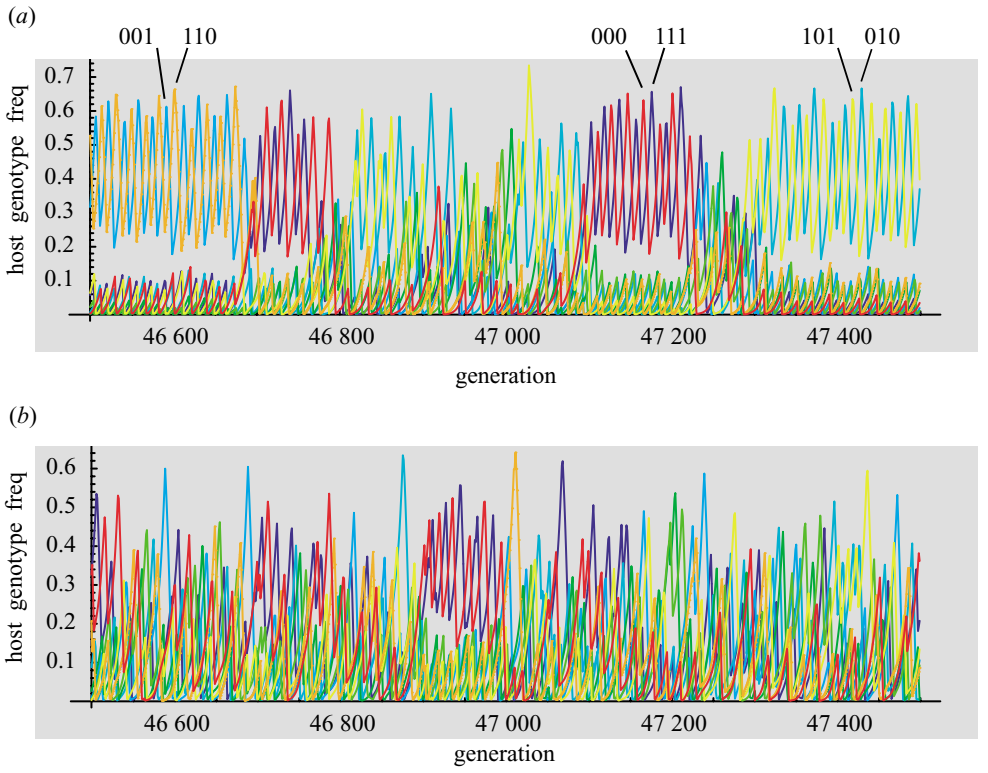

Figure 2. Multi-locus haploid genotype frequencies in a single population under soft truncation selection based on host–parasite matching of genotypes. L of resistance loci of hosts correspond with virulence loci of parasite, each with two alleles 0 and 1. (*a*) A trajectory of host genotype ($L = 3$, $\theta_H = 0.1$, $\theta_P = 0.9$, $r = 0.2$, $\mu_H = 10^{-4}$, $\mu_P = 0.01$) shown here can be divided into the periods in which one of the pairs of most distant genotypes are common ('prominent') and alternate their frequencies. (*b*) When recombination rate is further increased ($r = 0.5$, the other parameters remaining unchanged), host genotype frequencies fluctuate in more chaotic fashion, though a tendency of most distant pairs to be prominent remains. In both panels, the trajectory for genotype 110 is marked with dots to indicate the amount of change between generations.

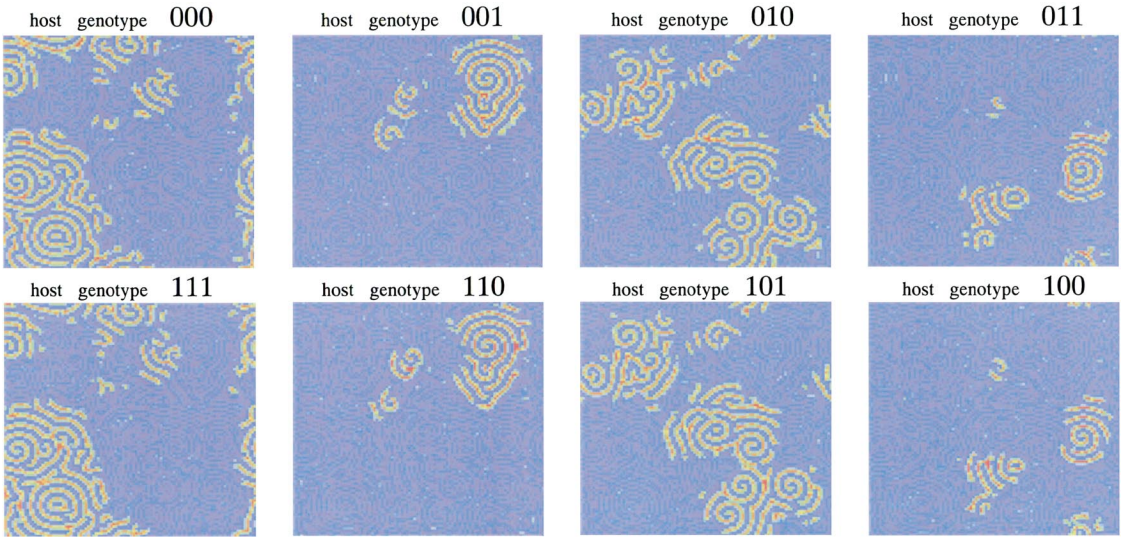

Figure 3. Host genotype frequency distributions in a two-dimensional stepping stone metapopulation in which host–parasite matching genotype dynamics occur as described in the legend of figure 2. The number of resistance loci in the host and of virulence loci in the parasite is three, giving eight genotypes in each species. After a random start, the whole space quickly divides into four regions in each of which a pair of most distant genotypes (e.g. 001 and 110) is 'prominent'. These regions form mutually exclusive centred patterns (in this case spirals) that compete at their margins. Under conditions like that shown, long-term quasi-permanent limit cycles in all demes are attained after a slow adjustment in the total pattern; development may, however, be extremely slow: for example the closer-spaced waves of spirals may, once they form, slowly 'eat back' the slower wave patterns from some types of target centre (for the rationale see Boerlijst *et al.* 1993). Parameters: $L = 3$, $r = 0.5$, $m_H = m_P = 0.25$, $\theta_H = \theta_P = 0.5$, $\mu_H = 0$, $\mu_P = 10^{-5}$.

In addition to the wave patterns shown we have also observed a wide variety of parameter states generating more irregular and non-repetitive dynamical patterns as well as other types of centre.

frequencies of the resistant host and the virulent parasite after selection are:

$$x^* = F(x,p) = w_R x/(w_R x + w_S(1-x)),$$
$$p^* = G(x,p) = w_V p/(w_V p + w_A(1-p)). \quad (2.2)$$

The gene frequencies in the metapopulation are then coupled by migration:

$$x_i' = (1-m_H)F(x_i,p_i) + v\frac{m_H}{z}\sum_{|i-j|=1}F(x_j,p_j) + (1-v)\frac{m_H}{n}\sum_j F(x_j,p_j),$$
$$p_i' = (1-m_P)G(x_i,p_i) + v\frac{m_P}{z}\sum_{|i-j|=1}G(x_j,p_j) + (1-v)\frac{m_P}{n}\sum_j G(x_j,p_j), \quad (2.3)$$

where x_i and p_i are the gene frequencies in the i-th deme, m_H and m_P are the migration probabilities of host and parasite, where the fraction v of migrants come from one of z (= 4) nearest neighbour demes (local migration) and the fraction $1-v$ from one of n (= 100×100) demes in the whole population (global migration). The case $v = 0$ corresponds to the Wrightian 'island' model where all demes are 'equally distant' from each other; $v = 1$ to the 'stepping stone' model where migration occurs only between the nearest neighbours; and $0 < v < 1$ to the mixture of the migration modes. Without metapopulation structure and migration, the genetic dynamic described by equation (2.2) is invariably unstable and the frequencies of the resistant host and the virulent parasite fluctuate with increasing amplitudes, spending increasing periods of time near monomorphic vertices of genotype space. Increasing extremity in these cycles makes eventual allele extinctions inevitable for finite populations.

(a) *Asynchrony under global and local migrations*

Metapopulation structure, however, drastically changes the situation. Asynchrony in gene frequency fluctuation develops in either globally or locally coupled metapopulations and serves to maintain genetic diversity that is inevitably depleted in a single population dynamics. The asynchronous fluctuation pattern observed with globally coupled metapopulation is particularly interesting (figure 1*a*), in which a single deme out of 10 000 demes refuses to join the globally synchronized cycles of the rest. This unique deme rules the period of the whole system and leads to 'stable' polymorphism, even in the case of totally global migration, as here ($v = 0$). Mathematical analysis in a subsequent paper will show that this form of asynchrony with a tiny fraction of out-of-phase demes is much more likely in coupled gene-for-gene systems than an asynchrony with different phases assigned to more equal numbers of demes, and is also more likely to arise as metapopulation size is increased.

When a small fraction (20%) of local migration is introduced, a few spots of differently beating demes originate and release circular waves into 'the sea of synchrony' surrounding them (figure 1*b*). The waves dissipate into the sea but still affect it enough to prevent occupation of a monomorphic vertex of gene frequencies to which the whole system otherwise converges. Spots develop as the foci of spirals when local migration becomes dominating ($v = 0.85$) and ever-outward-moving arms now mostly cover the whole lattice, although regions of global fluctuation still remain (figure 1*c*). For further increased local migration ($v = 1$), spirals give way (in this case) mostly to double spirals in which one spiral pairs with (or helps to create) another opposite centre close by (figure 1*d*). A wave generated at an oscillating centre or a focus of rotation travels undiminished until it meets another and then vanishes. In the genotype space, the total frequencies of genotypes stay nearly constant and central.

(b) *The pacemaker island*

Most of the time (in some cases, all of the time), the phase of the odd island is advanced relative to the rest, hence our chosen term 'pacemaker'. That a minority set of pacemaker islands 'pulling' the rest, however large, is essential in maintaining such stabilizing asynchronous limit cycles. In doing so, it balances the continual tendency of the rest towards overshoot and expansion. If the whole system was divided into similarly sized phase groups, as opposed to the extremely asymmetric division shown in figure 1, the advanced islands send too many migrants to allow the followers to catch up, resulting in a diversity destroying global synchrony. In its spontaneous appearance during the random start of our systems, the pacemaker is different from the imagined or actual externally imposed, forcing oscillators or 'pace makers' sometimes discussed in dynamical and physiological contexts (Murray 1989). On the other hand, the effect seems to be indeed closely related to the still mysterious spontaneous 'pacemaker' concept of pulsing tissue systems, such as the vertebrate heart and the pheromonally unified aggregations of cellular slime moulds. Generally, the spontaneous pacemaker with its associated wave features arising under local migration (described below) appear generic and are certainly not restricted to the classic 'gene-for-gene' model used for figure 1. For example, a more simplistic gene-for-gene model (Hamilton 1980) can reproduce all of the above results, though showing a lesser variety of types of oscillator that can appear under local migration. Below, we also show that multi-locus models with quite different schemes of host–parasite fitness interdependence (approaching truncation selection) produce similar features.

Especially under the panmictic conditions of migration so far described (the 'island model'; Crow & Kimura 1970), our pacemaker deme is usually unique: all other islands, including the phase-amplitude outliers that might have seemed equal initial candidates to become pacemakers, eventually converge to the majority rhythm—that is, all converge but one. In the past, the classic gene-for-gene model underlying figure 1, in the case shown using a single-locus interaction of host with parasite (Crute *et al.* 1997) and with costs of virulence and resistance also assumed, has been treated as a system unlikely to cycle permanently because, if the costs are low, states of fixation are reached directly and if they are high enough to induce cycling, the system is unstable and permanently escalates, as already described, ending in allele fixation (Hofbauer & Sigmund 1984; Parker 1994; but see also Frank 1996*b*). For a natural metapopulation, however, our demonstration of control by a spontaneous pacemaker or other

self-differentiating set(s) shows this conclusion to be questionable.

(c) *Spirals and target patterns under local migration*

When, under conditions otherwise identical, migration is predominantly local instead of global, there is even less threat to continued variety in the metapopulation. Our models show how structured systems of cyclical wave-like variation readily occur (figure 1*b*,*c*; and see figure 3) and, reinforcing previous results (Judson 1995), imply strong asynchrony on the metapopulation scale. In our illustrated case, waves spreading from spontaneous centres (in which sites seem picked from the phase outliers in the random starts that would be the candidate or actual pacemakers under the Wrightian 'island' migration pattern) generate 'spiral' and/or 'target' patterns similar to those already known (either by models or real demonstration) in chemical, biological and populational systems that constitute 'excitable spatial media' (Winfree 1980; Murray 1989; Comins *et al.* 1992; Boerlijst *et al.* 1993; White *et al.* 1996; Rohani *et al.* 1997). Our diagrams only illustrate the more common patterns that we have observed, notably 'targets', spirals and what may be called 'detached curl-ended waves'. In many regions of parameter space, especially under moderate or/and multi-locus selection, all these well-formed patterns (among a variety of others) dissolve into flickering, patchy, irregular designs of varying grain, amplitude and period. As far as any of the above dynamic patterns exist in nature, or, correspondingly, there exist other still more complex and irregular alternatives such as may be imposed by real land forms and ecology, they may help to explain not only some puzzling actual cases of out-of-phase population dynamics (Thomas 1991) but also, as in our next topic, help explain various long-known spatial and temporal phenomena in the ecology of sex and of clone mixtures.

3. SEX VERSUS CLONAL MIXTURES IN A METAPOPULATION

It has been recognized for some years that spontaneously asynchronous variation in metapopulations potentially stores variation both within species, as genetic variation (Judson 1995), and at the community level, as species diversity (Zeigler 1977; Hanski 1989; Ruxton 1994). The evidence is already substantial for some wild situations (Hanski 1989; Thomas 1991; Schmid 1994). As stated, the importance of multi-locus varietal asynchrony in this picture has also been recognized (Hamilton 1982; Ladle *et al.* 1993; Judson 1995). However, the possibility that clone mixtures in a metapopulation might achieve storage of 'anti-parasite' adaptations *better* than can sex itself has been addressed so far only in peripheral comments. In our present models, by contrast, we have been forced to recognize broad parameter swathes where *mixtures of asexuals* effect the storage. By the fact of particular widely divergent pairs being in prominent frequencies at any one time, such mixtures greatly lower infestation (and thereby damage) from the coevolving parasites.

We first summarize the characteristics of multi-locus matching-genotype dynamics in a single locus (Hamilton *et al.* 1990). Figure 2 shows cycles of host genotypic frequencies in a single deme host–parasite multi-locus matching-genotype dynamics (HAMAX) model in which soft truncation selection based on the matching score of host loci and corresponding parasite loci is underway (Hamilton *et al.* 1990)—see Appendix A. Striking features of these trajectories are: (i) that in a short time span, the most distant pair of host genotypes ('prominent pairs') is common; (ii) that they alternate in taking the highest abundance; and (iii) that in a longer time span, the prominent pair is switched to another prominent pair when the parasite genotypes catch up with the currently common host genotypes. Figure 3 demonstrates a snapshot of spatio-temporal waves of host genotype frequencies when the above single deme model is extended into a metapopulation structure where demes are connected by local migration between nearest neighbours (see the legend to figure 3 for detail).

(a) *Trajectories in hypercube*

The pairs that we call 'prominent' in this context have: (i) genotypes as opposite as are available; and (ii) frequencies at a given time above those of all others. As we illustrate for a single population in figure 2, prominent pairs of genotypes alternate in taking highest frequency. As both morphs are common, they provide a continuously difficult problem to the parasite population, which at best can match only one-half of the hosts, even in an ideal situation that the parasite trails just behind the host by switching its own maximally distant pairs.

When the number of loci involved in host–parasite interaction is small, as illustrated in figure 2, such systems successfully exclude sex when this has its characteristic halved efficiency due to unproductive maleness. In the cases in figure 2, the situation is sexual with no asexual competitors present; if they are brought in, they very quickly replace sex and a permanent symmetrical alternation of just two asexual opposites follows (the period is about 9 and the amplitude about 0.5 in the case chosen). In this unrealistic infinite population model all possible asexual genotypes are present, albeit some only at extremely low frequencies.

The threat to sex of mimetic and more efficient prominent pair-cycles persists if, from the state in figure 2, we simply raise the number L of loci even though (with $L = 8$, for example) successful invasion by an opposite pair becomes very slow. However, as the selection on host is increased (from host culling fraction $\theta_H = 0.1$ in figure 2 to about $\theta_H = 0.16$—see Appendix A for the definitions of θ_H and θ_P), the stability of a prominent pair cycle is lost and thereafter opposite pairs have only brief tenures, even in pure asexual populations. Now recombination plays a part in assisting transitions from one pair vibration to another. At an even stronger selection on host, $\theta_H = 0.2$, we find as few loci as $L = 5$ gives full security to sex once it is established; asex may make occasional incursions but is always repelled as parasites adapt to each new common genotype. In metapopulations with local migration and with consequent spreading waves of local synchrony, as in figure 1, escalation is prevented by local migration and particular pairs persist (with alternation) without difficulty, and asex, without wasteful segregation, normally wins.

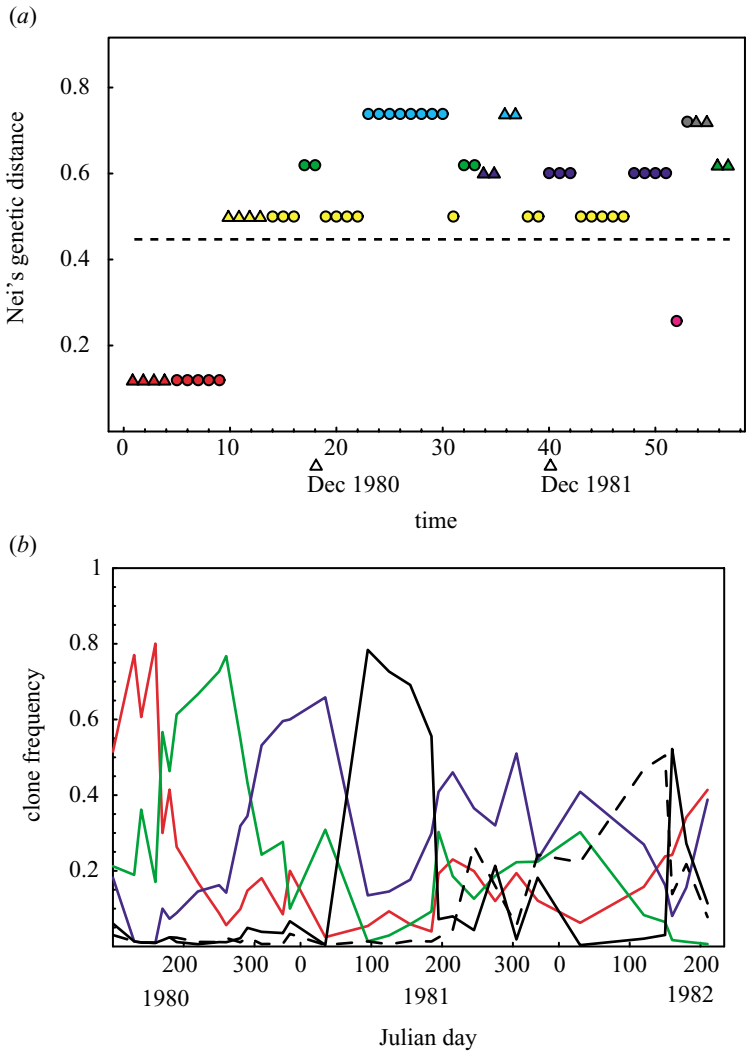

Figure 4. Clone and clone pair abundances of *Daphnia pulex* in an Illinois lake (Weider 1985), and genetic distances, over time. Each time unit represents half a month. (*a*) Colours identify different clones amongst the six overall most common clones. Most abundant pairs: red triangles (1, 2), red circles (2,1); yellow triangles (2, 3), yellow circles (3, 2); green triangles (1, 3), green circles (3, 1); light blue triangles (3, 4), light blue circles (4, 3); dark blue triangles (3, 5), dark blue circles (5, 3); purple triangles (1, 5), purple circles (5, 1); grey triangles (1, 4), grey circles (4, 1). (*b*) Nei's distance in most common clone pairs against time. Colours now identify different common clone pairs. Symbols show which clone is the most frequent within a pair (*i*, *j*): triangle for 'direct' order (*i* more abundant than *j*) and square for 'reverse' order (*j* more abundant than *i*). Red line, clone 1; green line, clone 2; blue line, clone 3; black line, clone 4; dashed line, clone 5. Dashed line indicates the average genetic distance between clones.

A similar but variant outcome is sometimes seen in three-locus asexual metapopulations but this again emphasizes the importance of 'distant' mixtures. Some parameter conditions give rise not to pairs but to prominent 'tetrahedral' quadruples (e.g. 000→011→110→101→000), i.e. sets of four genotypes vibrating in frequencies above those of others and with each member differing in two of its loci from all others in its set. For example, the case of figure 2 put into a stepping-stone lattice metapopulation, with the local migration rates set at 0.25, gives this result. The tetrahedral oscillation that appears is interrupted from time to time by the rise of an opposite pair (one member being contributed from the non-dominant tetrahedral set) but shortly it is always the same tetrahedral set as before that resumes abundance, thus revealing a strong and exclusive dominance to the alternative tetrahedron in spite of high irregularity at all times in the vibration that reigns.

(b) *Factors favouring sex in metapopulation*

In metapopulations, any tendency *away* from finely striped (figure 1*c*,*d*) or speckled (not shown) dynamics towards broader patterns that show local or global synchrony (figure 1*a*,*b*) is relatively favourable to sex. Recombination rather than local migration then becomes the principal producer of the genotypes able to escape current parasite waves. In summary, while it is true that spatially asynchronous dynamic states are favourable to the preservation of variability (Judson 1995), they turn out to be more favourable to its preservation as asexual strain mixtures than as sexual variation by Mendelian segregation and recombination. This is not to say that sex cannot be superior in the metapopulation conditions that have only local migration; this is untrue in the model and also abundantly contradicted in nature. Rather, the point to be made is that any conditions that facilitate steady alternation of opposites, and that make transitions from one

prominent pair (or fleeting rise of opposites) to another pair uncommon (figure 2*b* compared with 2*a*), must be seen as relatively favourable to asex. Our prediction, therefore, is that old parthenogenetic populations in nature will always, apart from brief interludes, consist of distant mixtures.

Our models assume asexual haploid parasites tracking hosts by mutation only. This may be unrealistic in nature, both as regards haploidy and 'mutation only'. It is especially unrealistic for larger parasites that are slower breeding and inevitably more 'visible' to a host's defence system. Restricted ploidy and limitation to facultative change are, however, common for small parasites, especially for viruses and bacteria (Tibayrenc *et al.* 1991). The advantage of a change in axis of oscillation of unlike types for the host population in such cases, where there are two or more loci involved in resistance, is then obvious. In our models, we in fact find that sex is rapidly better maintained against competing asex as:

(i) the number of resistance/virulence loci in the model is increased;
(ii) conditions creating the 'broad patchy' chaotic regimes (or generally more synchrony as induced by global migration) supervene;
(iii) demes are large and thus little subject to drift (Hamilton *et al.* 1990).

In those multi-locus cases, where orderly spirals or target patterns arise in lattices, we find that different regions of the spreading waves often involve different pairs of 'opposites'. In figure 3, we show this effect as occurring, in this case, in a HAMAX-like (Hamilton *et al.* 1990) host–parasite fitness system. This looks at all matches at three loci and severely disadvantages a fixed fraction of the most-matched tail. When such selection (near to a truncation) occurs under sexuality and free recombination, with only two alleles per locus, the mating of opposite genotypes produces potentially all possible genotypes; however, in 'spreading wave' conditions, and subject to the current position of the parasite genotype swarm, such sexual variants are commonly outcompeted by the more efficient low matching being achieved in the pairs of maximally 'opposite' clones.

Models of the type that produced figure 3 are also capable of showing pacemakers if the migration is made global. However, the outlier demes in this case are much more changeable and often also remain more numerous. Situations with a single pacemaker (or two in course of a transition) are apt to be interrupted by periods showing several pacemakers, or even by interludes of seeming random asynchrony. Permanent single pacemakers still appear, however, for interactions based on three loci, for example, albeit only through use of different and smoother fitness functions than that of figure 3. Truncation selection as actually used in figure 3 seems adverse to pacemaker phenomena. In general, the complex dynamic polymorphisms of the several to multi-locus cases (sometimes referred to as 'tangled wool' polymorphisms due to their appearance in the gene frequency phase space; Hamilton *et al.* 1990; Hamilton 1993) seem to limit dynamic extremity by their more general asynchrony and they do not need a rhythmic input from a pacemaker to prevent escalation. So far, we have found no situation that can be described as a permanent single pacemaker for four loci, although temporary flickerings of distinct out-of-phase, multiple-though-minority sets lasting through the periods of dynamic near synchrony, are commonly seen.

(c) *Metapopulation storage and geographical parthenogenesis*

Omission of few-locus trials in sex models in the past may explain the relatively limited conditions for success of asex that have been highlighted in other studies on metapopulation models in the past, including previous studies of the HAMAX type (Ladle *et al.* 1993; Judson 1995). As indicated in Hamilton *et al.* (1990), high culling fractions in hosts tend to cause simultaneous loss of all bearers of an allele and thus they initiate an accelerating disaster in the competition with asex. Obviously, as variability is lost at one locus after another there comes to be less and less that recombination can achieve. At the other extreme, culling fractions that are too low give insufficient selection to overcome the efficiency of parthenogenesis. Failure of sex therefore occurs at both high and low culling rates and this happens even though sexuals are always maintaining a greater mean match distance from parasites than are asexuals. Besides the strong effect of number of polymorphic defence loci and of culling rates, other conditions detected as favourable to sex in the present study, mostly confirming previous work (Hamilton *et al.* 1990) (and additional to § 3b(i)–(iii) already mentioned above), include: (iv) low host migration; (v) high parasite migration; (vi) large deme size; and (vii) low host mutation. In our study, synchrony was favourable to sex and local dynamical differentiation is favourable to asex. Synchronization induced in HAMAX-type multi-locus truncation models by low rates of global migration may be accompanied by differentiation of one or more pacemaker demes; but even when 'pacemakers' are absent, escalating cycles seem not to occur when the number of match loci is greater than three. Thus, in these states migration plays a role closely similar to a high reversible mutation rate and makes loss of alleles very unlikely. Pacemakers are, in this sense, not needed. Retrospectively, we rationalize our unexpected finding: that increase in the number of demes and the formation of a local-migration metapopulation is often more favourable to clone mixtures than it is to sex, on the grounds that the metapopulation is providing an alternative mode for the storage and release of species anti-parasite technology compared with that provided by recombination (Hamilton 1982).

The notion hinted by others (Ladle *et al.* 1993; Judson & Normark 1996*a*,*b*; Judson 1997) and supported generally in the models above, that a metapopulation structure may be specially conducive to clone mixtures as an alternative to sexuality and provide a way of reducing parasitism, can be strengthened by three kinds of data taken from biological literature. But first we make points about the actual distribution of parthenogenesis.

It has long been known that parthenogenesis is more frequent on the margins than in the centre of a species range. This 'geographical parthenogenesis' (GP) has been variously explained (Vandel 1932; Bell 1982; Bierzychudek 1985). As follows simply from physical adaptation, all versions tend to accept, however, that species ranges can often be treated as three roughly concentric zones

(Brussard 1984): (a) the largest continuous populations are in the centre of the species range; (c) at the opposite extreme, where the species has physical difficulty in surviving at all, populations tend to be temporary (see especially Peck *et al.* 1998); and in between and less extreme, (b) there is a broad third zone where the species exists as a metapopulation—numerous long-lived local concentrations in suitable habitats and those exchanging migrants with each other. In accordance with the parasite Red-Queen (PRQ) theory of sexuality, the central species range typically has the highest rate of sexuality and it also has the highest prevalence and diversity of parasites. The multi-species diversity of parasitism falls off especially in marginal populations. Much needs to be done to explain the many conspicuous exceptions to this triple correlation (sex–GP–parasitism); reindeer (Bye & Halvorsen 1983; Halvorsen 1986) and large-flowered self-incompatible Arctic–Alpine plants, for example, seem to flout the rule. Are these species in some way *more* parasitized at their margins? PRQ predicts this, but only in a few cases is there some evidence (Bye & Halvorsen 1983; Halvorsen 1986). Overall, however, the trend in sexuality and in parasitism accords with the theory. In the present study we are suggesting a new intermediate form of anti-parasite diversity that participates as a part of the spectrum of GP and also at the same time reveals a new facet of PRQ. We now outline some preliminary data in support of our hypothesis.

4. APPLICATIONS

(a) *Multi-line effect*

The first evidence is a concept that entered agricultural science in the 1950s and has persisted: multi-lines. This concept invokes the advantage of mixtures of varieties in crop stands in conferring partial protection against pests and diseases. The varieties are not asexual but, through the ways they are bred, they are often effectively uniform. That genotype mixtures could impede the spread *and also adaptation* of parasites was conjectured and proven early on (Suneson 1960), but in practice unfortunately the benefits of mixtures were (and remain) generally less attractive to farmers than control by spraying.

(b) *Geographical parthenogenesis in snails*

Second, clone diversity in local populations does often involve, just as our model predicts, the coexistence of deeply divergent clones (Parker 1979; Vrijenhoek 1979; Angus 1980; Jeffries & Gottlieb 1983; Ellstrand & Roose 1987; Hebert 1987; Schmid 1994; Dybdahl & Lively 1995; Jokela *et al.* 1997; Vrijenhoek & Pfeiler 1997). The exceptions are seemingly confined to cases of recent invasions. Such divergent coexistence is quite different from the expectation if GP is described in an extension of a 'deleterious mutation hypothesis' (DMH) about of the function of sexuality; according to the DMH, the differences within a deme should be slight and only due to recent mutation. However, of course, a more powerful test will be whether the coexistence of clones is static or dynamic (see § 4c). The DMH suggests no reason for highly diverse clones to be together, still less why they should be dynamic. Apart from the references already given, that clone associations are generally indeed distant seems particularly well illustrated in Ostracoda and Cladocera of lakes of boreal and formerly glaciated terrain (Hebert & McWalter 1983; Hebert 1987; Weider & Hebert 1987; Beaton & Hebert 1988). For some cases, as we shall see, there is evidence that specializing and resistable predators can play a part in the observed dynamics (Hebert & Crease 1983; Wilson & Hebert 1992, 1993) and various variation-protective aspects of the metapopulation structure have already been noted (Lynch *et al.* 1989). In the temperate zone, *Daphnia* species naturally suffer a wide array of damaging parasites (Ebert 1994; Ebert *et al.* 1998; Little & Ebert 1999). *Daphnia magna* have been shown to have the highest susceptibility to parasite varieties in their own pond and to show asymptotic fall for more distant ones, although some hints of random and maladaptive rises in virulence in cases of exposure to very distant parasites have also been noted (Ebert 1994). These facts, taken together with the modern theory of virulence (Ebert & Herre 1996; Frank 1996*a*), generally accord well with the trend in our models. In some cases, even more detailed correspondence can be found.

For some years, C. Lively and co-workers have studied parthenogenesis and parasites in a metapopulation of lake snails in New Zealand that show both geographical (Lively 1987; Dybdahl & Lively 1995) and what may be called 'extremity', or more exactly 'depth', parthenogenesis (Jokela & Lively 1995*a*; Fox *et al.* 1996; Jokela *et al.* 1997, 1999). Intermediate populations, studied on both the local ecological and geographical scales, show many resemblances to the assumptions of present models and to HAMAX studies (Hamilton *et al.* 1990; Judson 1995), including lake-to-lake transferral by water birds of both snails and parasites (but more of the latter; see Dybdahl & Lively 1996) and in the snails being iteroparous (while also, speeding all microevolution, they have 2–3 generations per year). Intensive study of the mixed population of Lake Alexandrina (South Island, New Zealand) over 5 years has revealed that sexual snails occur in the shallow water habitat (Jokela & Lively 1995*a*; Fox *et al.* 1996) and in that zone are much parasitized by trematodes (Jokela & Lively 1995*a*,*b*). In the next zone by depth the proportion of clones is higher, showing a few common clones (Fox *et al.* 1996) and 40 or so rare ones. In this zone, parasitism is still substantial (Jokela & Lively 1995*a*,*b*). A third, deeper zone has a few sexuals, many clones and lower risk of infection (Jokela & Lively 1995*b*; Fox *et al.* 1996). This is equivalent to what happens in zone (C) in the GP scenario above. In the all-clonal population of Lake Peorua (South Island, New Zealand), common clones appear to take turns at being extremely common and then reduced under the lagged rises of genetically coadapted parasite varieties (Dybdahl & Lively 1998; Lively & Dybdahl 2000). Although time has not allowed more than a few clone replacements to be observed and no repeat abundance of any ultra-common clone has yet to be seen, the overall patterns, including high sexuality in the more parasitized shallows, resembling the evidence for other systems (Schmid 1994), are suggestive of the model situations we describe.

(c) *Clone distance and temporal variation*

(i) *Boreal zooplankton*

Third, there is evidence regarding alternation and 'distance' of clones. In the above New Zealand lake study,

there is as yet nothing to support the idea of particular distant clones repeatedly exchanging positions when common; but, returning to published studies on the boreal cyclic zooplankton, we have found signs of this. It needs to be remembered here that the two clearest predictions of our model are that, first, in the intermediate zone of GP, common co-clones in a locality should not be each other's closest clones and, secondly, no frequencies should be static. (Exceptions to the former prediction, however, have to be expected in cases of recent unique introductions—Hauser *et al.* 1992; Little *et al.* 1997—such populations having had time only a few mutations of any kind.) Consequently we have sought other data on clonal organisms that would combine sufficient separate habitats sampled and loci assessed to give varied genetic distances and show the abundance variation of this over real space and time.

We have selected two studies on *Daphnia pulex* in North America (Weider 1985; Weider & Hebert 1987). In one, 20 loci were assessed in the melanic *D. pulex* in Canadian high arctic ponds, serving to distinguish 13 non-rare clones. For each sampling site in turn, we differentiate the two most common clones, i.e. the most common pair, from all other clone pairs in the sampling site (these other clone pairs include pairings involving the top two). Again, for each sampling site we calculated Nei's genetic distance between clone pairs based on the 20 loci. Pooling such distances we compared the distance values of the 'most common pairs' group with the distance values of the 'not most common pairs' group using a Wilcoxon rank sum test. We calculated signed rank sums w for these two groups and, because the distances are not independent from each other, we 'bootstrapped' 400 w values by repeatedly randomly reassigning pairs' pertainance to each group ('most common' versus 'not most common') and evaluating w for every new group allocation. By comparison of the original w with the distribution so formed, we obtained $p = 0.02$ (one-tailed test) for the chance occurrence of a set of Nei's distances between two clones that was as large as we found. We conclude that the two most common *Daphnia pulex* clones, in the sampling sites surveyed, are significantly more genetically distant from each other than would be clones picked at random. For purely parthenogenetic organisms, it seems hard to suggest any explanation for this that does not involve frequency-dependent selection by at least one antagonistic coadapting enemy species. Of course, the loci and alleles involved in the survey are probably not directly involved in parasite defence but, given the known wide dispersal of resistance alleles in genomes generally (O'Brien & Evermann 1988; Kunkel 1996; Holub 1997), it is likely that they are statistically associated with other genes that are involved, having become so due to founder effects and similar.

In a second approach, we looked at the time series of frequencies of the five most common clones in a particular pond in Illinois over a period of almost 2.5 years, as sampled by L. J. Weider. On this time-scale, as seen in figure 4*a*, the changes in relative frequency are clearly too great to be random drift. This is further highlighted in figure 4*b*, where we show the Nei's distances for the two most common clones at half-month intervals (Weider 1985) together with the unweighted mean of distances within all six non-rare pairs (Weider identifies six clones but does not provide temporal data for the rarest). During 24 out of 29 months of data available, the Nei's distance for the most common pair exceeds the mean. Further correspondence with the pattern in our figure 2*b* lies in the numerous immediate or delayed reversals within the temporary top pairs: it is noteworthy that by the end of the study period every one of the five most common clones had taken at least a brief turn at being most abundant clone.

The literature of pond plankton studies has references to 'checkerboard distributions', a term implying a distribution of frequencies among ponds that are both highly variable and spatially over-dispersed, while at the same time seeming to show no connection of the clones or alleles to physical factors. Comparing the very numerous 'spotty' patterns observed in our simulations (highly clumped peaks emerging and disappearing chaotically, which we have not illustrated) also, noting the fact that in the ponds we are not seeing the primary resistance genes but other genes linked to them, we see possible interpretation of these 'checkerboards', again, as parallels to the fine-grain restless asynchrony of our models. In one area, a species said to display the 'checkerboard' type of distribution for two clones, Wilson and Hebert found that the differences were due at least partly to a differential clone-specific susceptibility to a predatory pond copepod, itself patchily distributed (Wilson & Hebert 1992, 1993).

(ii) *Intestinal flora*

Intestinal flora of *Escherichia coli* populations in human guts seems to provide further qualitative support. The *E. coli* population in a human gut consists of a mixture of asexual clones, which would be subject to antagonistic selection pressure due to bacteriophages or host immune system. Biotic interaction between *E. coli* and phages/immune system would simulate the coevolution of host and parasite changing in comparable time-scales. This view of human gut as a hostile biotic environment against *E. coli* seems reasonable if we take into consideration the potential danger of this bacteria when the immune response is for some reason weakened. It is therefore probable that some sort of control from the immune system is taking place all the time. Making an analogy with *Daphnia* populations, each human host would play the role of a 'pond', *E. coli* as a 'host' and a certain molecular species of antibodies secreted by the immune system as a 'parasite'.

Such a system would meet all of the conceptual requirements of our model, hence our prediction that a genetic distance between the most common pair of clones would be higher than that expected between randomly chosen pairs and that the temporal substitution of the most frequent pair by another prominent pair would take place. That is exactly what we found in a study conducted on the genetic diversity in the *E. coli* population of a human host (Caugant *et al.* 1981).

From the data of Caugant *et al.* (1981), 13 loci were assessed serving to distinguish 53 non-rare clones in 22 samples collected over a four-month period of time. Following the same kind of analysis applied to *Daphnia* data in the previous section, we calculated Nei's distance for all possible pairs of clones. Ignoring the sampling times, the probability of getting, at random, a genetic dis-

tance equal to or bigger than the one corresponding to the prominent pair (0.572) is equal to 0.024. Clustering the frequencies according to the month in which the sample was taken, we used a Wilcoxon rank sum test together with a bootstrap method to compare the distance values of the 'most common pairs' group with the distance values of the 'not most common pairs' group, as described in the previous section. The only methodological difference in this case is that instead of using a geographical criterion for clustering, we are using a temporal criterion. The result obtained ($w = 3.22327$; $p < 0.001$; one-tailed test; bootstrap of 400 replications) indicates that the two most common clones are significantly more distant than expected if picked at random over the period of time considered. This analysis is viable because in each of the four months' clusters the prominent pairs were different; in fact, only two of the 53 clones were present in more than one month's cluster. This change of prominent pairs every month was described by one of the authors as a 'revolution every four weeks accompanied by a bit of looseness and discomfort'. The change is consistent with the idea that the most abundant types of clones in a period of time are matched by the immune system and reduced to frequency levels that are difficult to detect in the next sampling period. This result, coming from evolutionary microbiology, provides additional evidence for the presence in natural systems of some of the features described in our model.

Independently of these hints of parallels to real distributions, host–parasite interactions, admittedly treated in our models in realistic genetic detail rather than demographically (Korol *et al.* 1996; Kirzhner *et al.* 1998), reveal many simple and unexpected dynamic patterns. The patterns are unexpected in the cases we have displayed in aspects both of their antisymmetry (as in the genetic oppositeness of oscillating clone pairs) and their asymmetry (as of the pacemaker—one emergent different deme 'controlling' an unlimited number of others). Recognized in theory, such 'Red-Queen' patterns can be searched for carefully in nature and, insofar as have been found, give credence to the theory.

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APPENDIX A: MULTI-LOCUS MATCHING GENOTYPE DYNAMICS AND EVOLUTION OF SEX

We here introduce the multi-locus haploid genotype frequency dynamics in a single population under soft truncation selection based on host–parasite matching of genotypes. L of resistance loci of hosts correspond with virulence loci of parasite, each with two alleles 0 and 1. The mean distance of host genotypes (expressed as binary sequences for their allelic states) $\mathrm{s} = s_1 s_2 \cdots s_L (s_i \in \{0,1\})$ from parasites and that of parasite genotypes $\mathrm{t} = t_1 t_2 \cdots t_L (t_i \in \{0,1\})$ from hosts, respectively, are

$$\bar{d}_H(\mathrm{s}) = \sum_{\mathrm{t}} d(\mathrm{s},\mathrm{t}) p(\mathrm{t}),$$

$$\bar{d}_P(\mathrm{t}) = \sum_{\mathrm{s}} d(\mathrm{s},\mathrm{t}) x(\mathrm{s}), \qquad \text{(A 1)}$$

where $x(\mathrm{s})$ and $p(\mathrm{t})$ are the frequencies of host genotype s and parasite genotype t and $d(\mathrm{s},\mathrm{t})$ is the Hamming distance of s and t, i.e. the number of different allelic states in corresponding loci of host genotype s and parasite genotype t. Population sizes are infinite. Truncation selection based on the mean Hamming distance (A 1) of genotypes is assumed for both host and parasite, in which a constant fraction θ_H of hosts having the smallest mean distance from parasites and a constant fraction θ_P of parasites having the largest mean distance from hosts are killed in each year. Vacancies opened by mortality are filled by reproduction of survivors. Both species are therefore iteroparous. Parasites are asexual, transmitting exact copies of their genotypes. Sexual hosts randomly mate and recombine their genotypes before providing the progeny. If both sexual and asexual hosts are present, the fecundity of a sexual host is halved compared with asexuals (the twofold advantage of asexuals due to no investment in males or male functions). The recombination rates between adjacent loci are the same, denoted by r $(0 \leq r \leq 0.5)$. Mutation rate per locus is μ_H in host and μ_P in parasite. The model is simplified from the described model HAMAX (Hamilton *et al.* 1990) in two ways. (i) The populations are infinite and thus the model deterministic, so that any implicit effect of finite population size that may favour sex is absent. (ii) An individual always starts reproduction after the first time unit and there is no menopause.

By having usually a distant pair of genotypes more common than others, the host population provides a situation that, when the two prominent genotypes are in mid-frequency range, cannot be matched to a level > 0.5 by the parasite. If sexual, a prominent opposite pair also generates diverse recombinants at all times and thus provides opportunity to switch to other prominent opposite pairs of genotypes as parasite genotypes optimize their frequencies for the current pair. However, in the particular cases shown (figure 2*a*,*b*), selection is too weak and the genotype space too restricted for clones arriving by mutation to be resisted. Indeed, at the selection strength used ($\theta_H = 0.1$), sex seemingly fails to compete even for $L = 8$ although its defeat becomes very slow at this locus level. With stronger selection ($\theta_H = 0.2$), however, only two more loci than in figure 2 ($L = 5$) are enough to protect sex. If there is very low or zero recombination, the host population loses most of its genotypic diversity and becomes trapped into a single unchanging mode of fluctuation of opposites (case not shown), the particular pair (in our symmetrical model) arising according to the starting conditions. Asexuals can achieve the last mentioned advantage but have no chance of switching to other pair prominences and thus of exploiting the extensive mismatching during prominence changeovers. If the host stays in one fixed mode of fluctuation, the match score of the host is drastically decreased since the parasite, by its shorter generation time plus higher mutation rate, can completely catch up and track the currently commonest genotypes in the host cycle. This indicates that sexual hosts outcompete asexual counterparts in spite of twofold efficiency advantage of the latter when the number of loci is increased: the sexual host jumps by recombination to completely different opposite prominent pairs of genotypes in the high dimensional hypercube of genotypes.

The parasite must find each new prominences step by step by mutations (see also Hamilton *et al.* 1990).

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