Dynamics of a linked Medea-Underdominance Population Transformation System

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Many proposed genetic pest management approaches rely on the introduction of genetic modifications, such as disease resistance in a vector species, using an evolutionary based population-transformation system. Predominantly, only systems with a single selective element have been envisioned. Here we describe the predicted properties of a combined system genetically linking a Medea construct with underdominance. While Medea elements can, in theory, transform populations with the release of small numbers of individuals, they are poorly suited to being spatially contained or removed from the wild. Conversely, underdominant systems typically require the release of very large numbers of individuals to result in a stable population transformation but are more likely to be spatially contained and can be, if desired, completely removed from the wild. We show that a combination of currently available techniques results in a system with desirable theoretical properties, which in broad circumstances surpass those of the single systems considered individually. These enhanced properties include more ideal population transformation thresholds with potential reversibility, mutational stability, and enhanced spatial stability. Finally, we also show that in small finite populations Medea elements can invade from very low frequencies with elevated probabilities, even with corresponding fitness costs. This has implications for understanding the evolution of natural Medea elements as well as consequences for the use of synthetic Medea in population-transformations.

Keywords: applied evolution, disease elimination, dynamical systems, gene drive, genetic pest management

I. INTRODUCTION

There are cases where the use of genetic methods to modify pest populations can be argued to be preferable to alternatives such as insecticides and classical biological control (release of non-native predators or parasites), for example, tropical conservation settings. Current approaches to developing genetic mechanisms that usefully transform a species, predominantly envisage the development of transgenic constructs that render insect vectors refractory to acting as disease vectors. There has been rapid success in the malaria and dengue fever models (e.g. Ito et al. 2002; Franz et al. 2006; Jasinskiene et al. 2007; Corby-Harris et al. 2010). However, for these refractory constructs to spread effectively into experimental or ultimately wild populations, it is widely recognized that they will need to be linked to elements that, through evolutionary effects over several generations, have the capacity to transform wild populations (reviewed in Sinkins and Gould 2006; see also Hay et al. 2010). There are also broad potential applications of this type of technology beyond insects (e.g. Gould 2008).

The earliest such proposed population-transformation system exploited the predicted underdominant fitness configurations of chromosomal translocations (Curtis 1968). In a single population rarer alleles tend to be heterozygous, with underdominance, where heterozygotes are less fit than homozygotes. Hence a threshold allele frequency arises that is an unstable equilibrium (Fisher 1922; Wright 1931; Li 1955). Once this threshold is surpassed, for instance with releases of insects with rearranged chromosomes, an allele with underdominant effects is predicted to proceed to fixation within the population and to be stable over the following generations (Fig. 1 A). This process is inherently reversible. If the removal of genetically modified organisms is desired, releases of wildtype individuals that bring the population allele frequency below this threshold is predicted to result in the complete removal of underdominant alleles from the wild. For small migration rates this system also exhibits spatial stability (Karlin and McGregor 1972; Piálek and Barton, 1997; Altrock et al., 2010). This implies that initial wild releases can be made on a restricted local scale where permissions and informed consent for the study (which by nature are geographically restricted) are more possible to attain and more appropriate (cf. Angulo and Gilna 2008). Laboratory generated organisms were generally too unfit to result in useful underdominant constructs. It has proved exceedingly difficult to engineer viable, fit translocated stocks (e.g. Lorimer et al. 1972; Robinson 1977; Boussy 1988). Thus, the low fitness of individuals homozygous for lab engineered chromosomes appeared to be the main disadvantage of utilizing engineered underdominance to stably and reversibly transform wild populations.

In a different kind of genetic system, alleles at multiple loci in Tribolium flour beetle species have been discovered where there is a specific distortion in expected Mendelian transmission (Beeman et al. 1992). These maternal-effect selfish alleles are known as Medea elements and have also been reported in the mouse (Peters and Barker 1993; We-

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ichenhan et al. 1996). In Medea systems, by producing both a poison and a rescue, organisms that contain Medea elements can be viable. However, if the poison is deposited by the mother into oocytes and the resulting zygote does not contain an endogenous rescue; heterozygous (carrier) mothers can effectively kill off their homozygous wildtype offspring. Thus, Medea elements can increase in frequency in a population, even if they are not beneficial to the organism in the sense of Darwinian adaptation (Beeman et al. 1992; Wade and Beeman 1994). A synthetic Medea system has also recently been engineered in Drosophila melanogaster that exhibits the properties found in natural Medea systems and has been proposed as a transformation system to genetically modify wild populations (Chen et al. 2007). There is also interest in screening for inducible maternal-effect lethal phenotypes in order to develop Medea systems in additional species (Hay et al. 2010).

Medea elements have very different predicted dynamics from underdominant systems and can potentially invade a population from very low frequencies (Wade and Beeman 1994). This predicts that, with low rates of migration, Medea elements can spread from population to population, possibly species wide. This also implies that it may be very difficult or impossible to reverse Medea transformed population(s) to the wildtype state and remove all genetically modified alleles from the wild. If there is a fitness cost to the organism carrying Medea elements, an unstable threshold equilibrium at a low frequency may arise (Fig. 1 B). This point must be surpassed in order for the Medea effect to overcome the fitness loss and for the allele to rise in frequency in the population, in a manner similar to underdominance. However, this unstable equilibrium can be much lower in frequency than that expected from underdominance between engineered and wildtype chromosomes (i.e. $\ll 50\%$ versus $\gg 50\%$). A fitness cost also predicts a second high-frequency stable equilibrium that the frequency of Medea elements is predicted to approach but is not expected to surpass (Fig. 1 B). Thus, unlike underdominance, Medea is not necessarily predicted to completely fix in a population (Wade and Beeman 1994). However, if the Medea effect is 100% efficient (complete lethality) with a fitness cost a population can still result in all Medea carriers, some of which are heterozygous (e.g. Chen et al. 2007). If a linked effector construct (e.g. disease resistance) is dominant then this may have the desired effect. However, if an effector is recessive, a disease may not be completely eradicated from a population (Boëte and Koella 2002, 2003). Also, if a Medea allele does not achieve complete fixation, matings between heterozygotes still experience a loss of offspring, which provides selective pressure for resistance to Medea to evolve and can disrupt the system (Smith 1998).

We have briefly introduced two very different genetic systems, underdominance and Medea. These are not always mutually exclusive. Underdominance is a result of the organismal fitness associated with the genotypes of an allele. Medea effect results from a selfish genetic process during gametogenesis and formation of the zygote that can be thought of as separate from the underlying organismal genotype fitnesses (in the adaptive sense). Here, we present some of the predicted dynamics of a combined Medea-underdominant system in a population genetic framework (Fig. 1 C). The effects of combining different types of artifical selective systems have been considered before (Huang et al. 2007), but not this particular combination. We discuss the advantages of this combined system over the individual systems and briefly discuss the feasibility of engineering such a system.

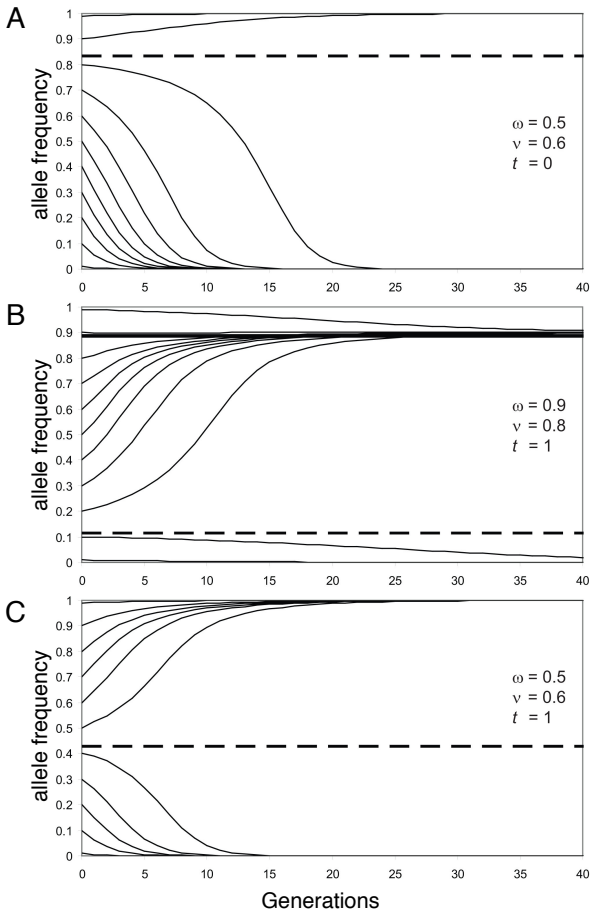

FIG. 1. **Dynamics of Medea and underdominance in a single population.** Example trajectories of allele frequencies over several generations from a range of starting frequencies are plotted, thin solid lines. Allele frequencies, p, are on the y-axis and generations on the x-axis. Discrete, non-overlapping, Wright-Fisher generations were assumed. The underlying genotype frequencies were actually used to calculate trajectories, starting at Hardy-Weinberg equilibrium in the initial generation, and are summarized by reducing them to a corresponding allele frequency. Homozygote fitness is indicated by ν and heterozygote fitness by ω, relative to a wildtype homozygote fitness of 1. The degree of Medea lethality is given by t. An unstable equilibrium is indicated by a dashed line. A stable equilibrium is indicated by a thick line. A) Underdominance with a high transformation threshold. B) Medea with a semi-dominant fitness cost. C) A combination of underdominance and Medea.

II. METHODS AND RESULTS

A. Ideal Minimum Release Sizes

In order to reach a target frequency in a population of $\hat{p}$, releases would have to be made of a minimum size of $R = \hat{p}/(1-\hat{p})$ relative to the wild population size. To cross this boundary and then recross it (i.e. to reverse the population transformation after an engineered allele has reached fixation) requires two releases with a minimum combined size of $R = \hat{p}/(1-\hat{p})+(1-\hat{p})/\hat{p} = 1/(1-\hat{p})+1/\hat{p}-2$. This function approaches positive infinity at $\hat{p} = 0$ and $\hat{p} = 1$ and has a minimum at $\hat{p} = \frac{1}{2}$, with $R = 2$ (Fig. 2). Thus, an unstable threshold of $\hat{p} = \frac{1}{2}$ is ideal from the perspective of potential population transformation *and* reversibility. It is still much lower than releases sizes used in successful applications of the sterile insect technique (e.g. Asman et al. 1981; Krafsur 1998).

In an actual applications, genotypes will be released instead of alleles. Thus it may be possible to enter the basin of attraction for transformation and reversal at different points in the full genotype space to take advantage of specific dynamics in these two-dimensions.However, the essential consideration remains the same; elements that can invade from arbitrarily low frequencies are all but impossible to reverse and remove from the wild, elements with very high threshold values are difficult to impossible to succesfully establish. Threshold equilibria near the center of the state space are optimal with regard to local spatial stability and reversibility.

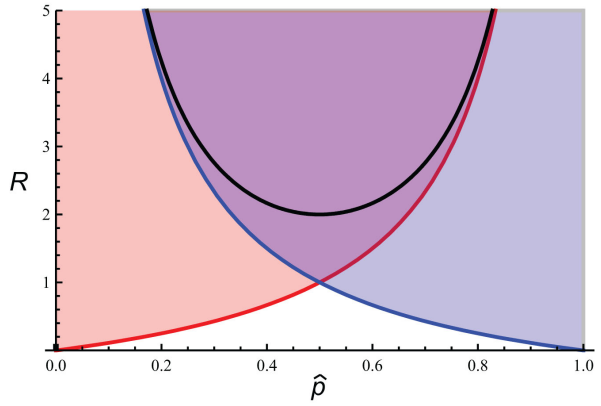

FIG. 2. **Directional and reversible transformation thresholds.** The release size relative to the wild population is given by R. The corresponding threshold allele frequency, an unstable equilibrium, is $\hat{p}$. Simplistically, in order to genetically transform a population, R must be above the red line (in the region of light red or purple). The reverse minimum transformation back to a wildtype state is indicated by the blue line. The combined total release size required for reversibility is above the black line. If releases can be made in the red area but not in the purple area, i.e. very low $\hat{p}$, the system is not reversible. Individual releases that can be made in the purple area (or combined sums above the black line) are reversible.

B. Genotype fitnesses and expected dynamics

When selection is only dependent on the organisms genotype, expected genotype frequencies can be generated under the random mating assumption (Hardy-Weinberg independent pairing of alleles). These frequencies are then adjusted each generation according to their corresponding fitnesses. However, in cases where the action of selection extends over, or is conditional on, more than one generation, this assumption can not be used, and the contribution to the next generation from each genotype class must be accounted for individually. With Medea the action of selection on wildtype homozygotes depends not only on their current state but is also coupled to the maternal genotype. For example, the number of wildtype homozygotes (and thus the allele frequency) expected in the next generation after selection is very different in a population composed entirely of heterozygotes (where all wildtype homozygotes in the next generation are exposed to the Medea effect) versus one near Hardy-Weinberg equilibrium (where only a fraction of wildtype homozygotes are exposed). In both cases the allele frequencies may be identical. Thus, the expected proportions of zygotes produced under random mating are expected to be equal, but not the fitness effects. Here we have a Medea allele, M, and a wildtype allele, $+$; which generate three genotypes, MM, $M+$, and $++$. We set the fitness of the wildtype homozygote, $++$, to 1; use ω to indicate the heterozygote, $M+$, fitness relative to wildtype; and ν to indicate the MM fitness. The parameter t measures the degree of lethality of homozygous wildtype offspring from Medea carrying mothers. This can range from zero, no lethality and no Medea effect, to 1, complete lethality of homozygous wildtype offspring from heterozygote mothers. From Table. I we can calculate the expected frequencies of all three genotypes in the next generation as,

$$\begin{aligned}
\bar{G}x' &= \nu\left(x^2 + xy + \frac{y^2}{4}\right) \\
\bar{G}y' &= \omega\left(xy + yz + 2xz + \frac{y^2}{2}\right) \\
\bar{G}z' &= 1\left(z^2 + \frac{yz}{2} + (1-t)\frac{yz}{2} + (1-t)\frac{y^2}{4}\right)
\end{aligned} \tag{1}$$

where x, y, and z are the frequencies of MM, $M+$, and $++$ respectively in the current generation and x', y', and z' are the expected frequencies in the next generation (note that in Wade and Beeman (1994) differences in fitness were only ascribed to differences in maternal fecundity rather than zygotic genotypes as is done here). The total contribution from all genotypes in the population (i. e., the average fitness) is given by $\bar{G}$. It is the sum of the right hand sides of the set of Eqs. (1) (Hofbauer et al. 1982). Some example dynamics of the expected change in frequency of genotypes in a population are given in Fig. 3.

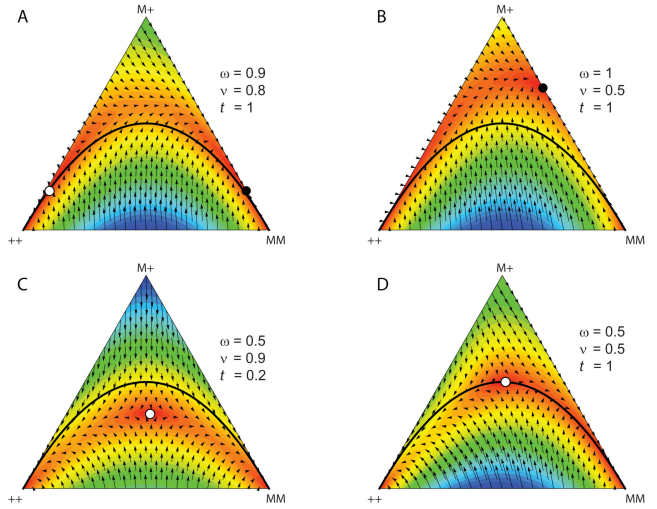

FIG. 3. **Example evolutionary dynamics in infinite populations.** Here the full two-dimensional simplexes are shown for dynamics in changes in genotype frequencies. The corner of each triangle represents 100% frequency of each genotype, which are at intermediate frequencies as distance from the corner increases, and are at a frequency of zero on the opposite edge. The black line indicates Hardy-Weinberg equilibrium for reference. Arrows indicate direction of change and arrow length and background color indicate rate of change (from blue, fast, to red, slow). Stable internal or edge equilibria are indicated with a black circle and unstable or saddle equilibria are indicated with a white circle. A) This represents the conditions given in Fig. 1 B, with a lower unstable equilibria and a stable point on the $M+$ to MM edge where wildtype homozygotes have disappeared from the population. In this case the equilibria are near Hardy-Weinberg. B) This illustrates a case where the sable equilibrium lies far from Hardy-Weinberg. C) An example with a high homozygote fitness and low degree of lethality that has an unstable equilibrium at approximately an allele frequency of $p = 1/2$ in the population ($t = 2-2\nu$, see Appendix). D) An example where the unstable equilibrium is at $p = 1/2$ for a high degree of lethality and low homozygote fitness, see Eq. 11.

C. Dynamics at the corners of the system

When an allele is at the extreme limit of being fixed or lost it is expected to be present as either one copy in a heterozygote or as all copies but one, also in a heterozygote. Thus the change in frequency of the heterozygote near $z = 1$ and $x = 1$ gives the conditions for an allele to invade and/or go on to fixation. The slope of y' at $z = 1$ is

$$\frac{\partial y'}{\partial y}|_{z=1} = \frac{\omega}{1} \tag{2}$$

Thus, the heterozygote fitness must be greater than the wildtype homozygote for the Medea allele to invade. Note that this condition is independent of the maternal lethal parameter t. In smaller finite populations the starting frequency will be at greater initial frequencies and, in this sense, a $t > 0$ will promote invasions. The corresponding dynamic at $x = 1$ is similar,

$$\frac{\partial y'}{\partial y}|_{x=1} = \frac{\omega}{\nu} \tag{3}$$

The Medea homozygote fitness has to be greater than the heterozygote to go to fixation (in an infinite population), and this condition is independent of t and consistent with underdominance. Using alternative models, Wade and Beemans (1994) and Marshalls (2009) results are also consistent with this condition for invasion and fixation.

TABLE I. The expected next generation contribution of individual genotypes in an underdominant Medea system under hard selection.

Parents		Offspring		
♂	♀	MM	$M+$	$++$
$++$	$++$			1
$++$	$M+$		$\omega/2$	$(1-t)/2$
$++$	MM		ω	
$M+$	$++$		$\omega/2$	$1/2$
$M+$	$M+$	$\nu/4$	$\omega/2$	$(1-t)/4$
$M+$	MM	$\nu/2$	$\omega/2$	
MM	$++$		ω	
MM	$M+$	$\nu/2$	$\omega/2$	
MM	MM	ν		

D. Average genotype fitnesses

Another way to view the recursion equations is as a frequency multiplied by its fitness then normalized, for example $x' = xf_x/\bar{G}$, where f_x is the average fitness of the MM genotype, according to discrete time replicator dynamics (e.g., section 2.8.1 of Cressman 2003). This allows us to solve for the average fitness of each genotype (known as marginal fitness in population genetics),

$$\begin{aligned}
\frac{\bar{G}x'}{x} &= f_x = \nu\left(x + y + \frac{y^2}{4x}\right) \\
\frac{\bar{G}y'}{y} &= f_y = \omega\left(x + z + \frac{2xz}{y} + \frac{y}{2}\right) \\
\frac{\bar{G}z'}{z} &= f_z = z + \frac{y}{2} + (1-t)\frac{y}{2} + (1-t)\frac{y^2}{4z}
\end{aligned} \tag{4}$$

Using this set of equations we can solve for the fixed points in the two-dimensional simplex as illustrated in Fig. 3. Considering the average fitness of the genotypes in a pairwise fashion, two genotypes are neither increasing or decreasing relative to each other if their average fitnesses are equal, e.g., $f_x = f_y$. If all three of these zero fitness differences intersect in the interior of the simplex an equilibrium (fixed) point exists. Additionally, if one of these curves intersects an edge corresponding to the genotypes being considered (e.g., $f_x = f_y$ on the $z = 0$ edge), a fixed point exists on that edge.

E. Edge dynamics, analytical solutions for $t = 1$

For $t = 0$ the system is governed only by genotypic fitnesses which have well understood properties and reduces to a simpler one dimensional simplex in terms of allele frequency rather than genotypes (e.g., Altrock et al. 2010). Setting $t = 1$ also allows some analytical results to be derived. Along the edges of the simplex, we look separately at $f_x = f_y$, $f_x = f_z$ and $f_y = f_z$ and set the third genotype frequency to zero to solve for equilibria. We find that only , i.e., only the MMM+ edge can posses a fixed point on the boundary. Setting $t = 1$ and solving for x in this case gives a solution of

$$x = \frac{\nu}{2\omega - \nu}. \tag{5}$$

This is a stable solution for all $\omega > \nu$, for $\omega < \nu$, there is no solution within the edge (compare to Eq. 3 above). Since there are no edge fixed points for $t = 0$ (the classic case along the Hardy-Weinberg simplex) this suggests that for $t < 1$ the fixed points will move away from the edge to the interior. This also makes intuitive sense because some wildtype homozygotes should survive if Medea lethality is not 100% and thus $z > 0$. This higher frequency interior equilibrium is expected to remain stable according to the reasoning of small parameters (Karlin and McGregor 1972) and this is confirmed numerically.

F. Internal dynamics, analytical solutions for $t = 1$

Solving $f_x = f_z$ and $f_y = f_z$ for x and y, and realizing that $z = 1 - x - y$, gives the following coordinates of an internal equilibrium, if it exists within the two-dimensional simplex,

$$\begin{aligned} \hat{x} &= \frac{(\omega - 1)^2}{1 + \nu - \omega} \\ \hat{y} &= \frac{2\omega(1 - \omega)}{1 + \nu - \omega} \\ \hat{z} &= \frac{\omega^2 - \omega + \nu}{1 + \nu - \omega} \end{aligned} \tag{6}$$

Subtracting the frequency from both sides of Eqs. 1 gives the change in genotype frequency per unit time,

$$\begin{aligned} x' - x &= \frac{x f_x}{\bar{G}} - x \\ \bar{G}\Delta x &= x f_x - x\bar{G}. \end{aligned} \tag{7}$$

This can be rescaled by $\bar{G}$ without affecting the dynamical properties of the system. All fixed points remain at the same positions in the state space and flows are rescaled but remain in the same direction. Thus, we can write down the dynamics for all three genotypes in a simplified non-rational form as,

$$\begin{aligned} \Delta x &= x(f_x - \bar{G}) \\ \Delta y &= y(f_y - \bar{G}) \\ \Delta z &= z(f_z - \bar{G}) \end{aligned} \tag{8}$$

Using Eqs. 8, the eigenvalues of the Jacobian at the equilibrium point given in Eqs. 5 are

$$\lambda_{\pm} = \frac{-\nu\omega \pm \sqrt{\nu\left(\nu(2 - \omega)^2 - 4\omega(1 - \omega)^2\right)}}{2(1 + \nu - \omega)}. \tag{9}$$

If $\lambda\pm < 0$ then the equilibrium is stable, if both eigenvalues are positive it is unstable and if the values have opposite signs it is a saddle point.

Of interest is the case where the unstable equilibrium frequency is equal to one half,

$$x + y/2 = 1/2, \tag{10}$$

because this is an ideal transformation threshold according to the reasoning given in the previous section. Substituting the equilibrium values in Eqs. 5 into Eq. 10 gives

$$\nu + \omega = 1 \tag{11}$$

at $t = 1$ (Fig. 3 D). Again, coupled with the reasoning for the stable point on the edge above, for $t < 1$, there may exist two internal equilibria, the lower allele frequency one is unstable and the higher frequency one is stable, this is verified numerically (e.g., Fig. 3) and supported by the Hardy-Weinberg approximation given in the Appendix. However, if $1 > \nu > \omega$ (underdominance) and (Eq. 11) only the unstable internal equilibrium at $p = 1/2$ exists.

G. Dynamics in finite populations with overlapping generations

The Moran process is a tractable birth-death process used to model well-mixed finite populations (e.g. Karlin and Taylor 1975; see Traulsen and Hauert 2009 for a general introduction). Here, in each time step, a single individual is chosen at random to be removed from the population and another individual is chosen for reproduction according to fitness.

One quality of particular interest in Medea systems are the properties of invasion when rare due to the female killing effect. If genotype fitnesses are equal, M alleles are predicted to invade infinitely slowly in infinitely large populations (Eq. (2) and Wade and Beeman 1994). In small finite populations, a single M allele has a greater starting frequency and the wildtype individuals killed by Medea also make up a greater proportion of a smaller population. In larger finite populations, selection is more able to overcome drift when rare, but the allele has a smaller starting frequency. It is not intuitively clear how these trade-offs affect fixation probabilities. The two-dimensional simplex of genotype frequencies prevents us from using standard analytical tools of the Moran model.

To address this, we simulated the trajectories of loss or fixation of initially a single Medea allele present in a heterozygous individual. In each time step a "mother" and "father" are chosen from the population with a probability proportional to their number and relative fitnesses. Conditional on the parental genotypes, an offspring is generated

TABLE II. The expected next generation contribution of individual genotypes in an underdominant Medea system with soft selection.

Parents		Offspring		
♂	♀	MM	$M+$	$++$
$++$	$++$			1
$++$	$M+$		$\omega(1+t)/2$	$(1-t)/2$
$++$	MM		ω	
$M+$	$++$		$\omega/2$	$1/2$
$M+$	$M+$	$\nu(1+t/3)/4$	$\omega(1+t/3)/2$	$(1-t)/4$
$M+$	MM	$\nu/2$	$\omega/2$	
MM	$++$		ω	
MM	$M+$	$\nu/2$	$\omega/2$	
MM	MM	ν		

according to the genotype cross (Table. I) and the degree of Medea lethality (if the offspring dies due to Medea the parents are repicked and another child is generated). Then the resulting offspring replaces a single individual in the population at random. If population sizes are small then, even with a modest fitness cost relative to wildtype of $10-20\%$, a single Medea allele can invade a new population with a probability elevated over that of neutrality. However, heterozygote fitness reductions of 30% or greater help prevent Medea invasion in new populations. The scenario just described represents a "hard selection" regime.

However, if there is resource limiting sibling competition, where a larger number of initial zygotes result, according to fitness, in a smaller number of individuals that survive to reproduction, (and/or remating compensation effects) there can be a "soft selection" scenario (cf. Wade 1985). This case assumes that a given pairing will ultimately produce an offspring (i.e., wildtype homozygotes lost due to Medea are replaced by alternative genotypes, Table. II). This was also modeled as before except that when offspring lethality was encountered offspring were repicked within the pairing instead of picking new parents (i.e., these two scenarios represent the extreme limits of hard and soft selection). This soft selection scenario corresponds to the following recursions,

$$\begin{aligned}\bar{G}x' &= \nu\left(x^2+xy+\frac{y^2}{4}+t\left(\frac{1}{3}\frac{y^2}{4}\right)\right)\\ \bar{G}y' &= \omega\left(xy+yz+2xz+\frac{y^2}{2}+t\left(\frac{yz}{2}+\frac{2}{3}\frac{y^2}{4}\right)\right)\\ \bar{G}z' &= 1\left(z^2+\frac{yz}{2}+(1-t)\frac{yz}{2}+(1-t)\frac{y^2}{4}\right).\end{aligned} \quad (12)$$

In this second regime, one result that becomes clear is that Medea alleles can invade and fix in a population with a probability that is dramatically elevated over that of neutrality (a similar result is also found in Wade and Beeman 1994). If there is no fitness cost, this probability is approximately a constant $\Phi \approx 1/3$ over a wide range of population sizes (Fig. 4 B). A large heterozygous fitness reduction of $40\%-50\%$ relative to wildtype is required to bring the fixation probability down to approximate neutrality ($\Phi = 1/2N$). Even in an infinite population, a dominant fitness cost as high as 30% can still yield an invasion/fixation trajectory (Fig. 5 A). A closer look at some individual examples reveals a highly asymmetric trajectory. Even when genotype fitnesses are all equal to one, the initial rise in frequency is quite fast, then there is a long time spent waiting at high frequencies before ultimate fixation (Fig. 5 B). This potentially increases the opportunity for alleles resistant to Medea to arise which can destabilize the system and return to a wildtype state (Smith 1998).

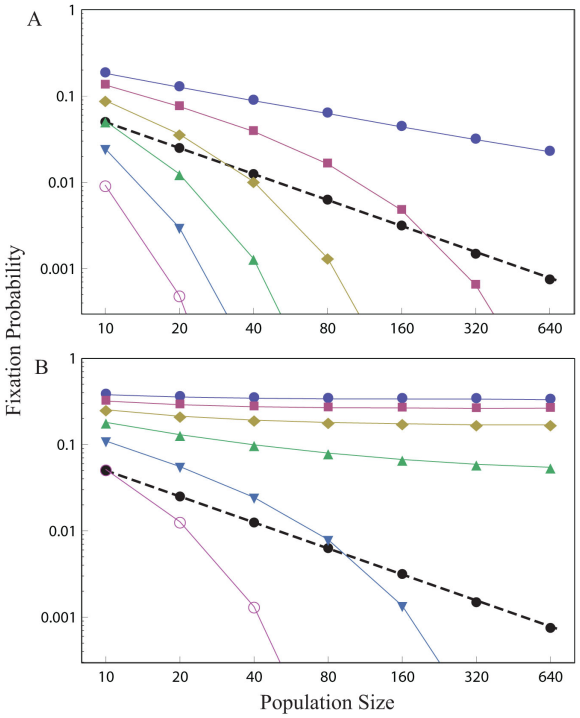

FIG. 4. **The probability of invasion of a Medea allele.** Fixation probability versus diploid population size for a Medea allele starting as a single heterozygote in the population. The probability of fixation under neutrality is given by the black dashed line with circles for reference. A heterozygote fitness equal to homozygotes, $\omega = 1$, is given by the top dark blue line with circles, $\omega = 0.9$ red squares, $\omega = 0.8$ yellow diamonds, $\omega = 0.7$ light blue triangles, $\omega = 0.6$ blue upside down triangles, $\omega = 0.5$ red open circles. A) Fixation probabilities under the standard hard selection model. B) Fixation probabilities under soft selection with, for example, sibling competition.

H. Population structure dynamics

Next we consider a two-deme model of population structure, where two discrete populations of large size are couple by a symmetrical fraction of migrants between the popula-

tions each generation. Genotype frequencies in each population are adjusted each generation for exchanging migrants, at a fraction m, and retaining non-migrants, at fraction $1-m$. In population i the expected genotype frequency for genotype k after migration (g') is

$$g'_{k,i} = (1-m)g_{k,i} + mg_{k,j}, \tag{13}$$

where here $g_{k,i}$ is the frequency of the k^{th} allele in population i and $g_{k,j}$ is the k^{th} allele frequency in population j. These adjusted genotype frequencies can then be substituted into Eqs. 1 and the equivalent recursion for the second population, $g'_{k,j}$, can be found by interchanging i and j in Eq. 13.

Simulations were performed of the two-population system to find the critical migration rate allowing stable differences in allele frequencies between the two populations. To do this the allele frequencies were started at opposite values ($p_1 = 0, p_2 = 1$) with an initial migration rate of zero. The migration rate was slowly incremented in units of 10^{-4}. For each value of migration, the allele frequency recursions were iterated until the difference in allele frequencies between generations was less than 10^{-12} (i.e. effective equilibrium was reached). This process was stopped once the absolute difference in allele frequencies between the two populations fell below 1% and the corresponding migration rate was recorded as the critical migration rate boundary where stability is lost (i.e., at lower migration rates the combined systems will not spread far from a successfully transformed zone, and will be resistant to loss by immigration). Results plotted for a range of fitness and Medea values show that the combined system can have enhanced stability against migration, tolerating higher migration rates while maintaining geographic stability (Fig. 6). However, at $\omega = 0$, there are no heterozygotes reproducing and thus Medea has no effect and the dynamics are equivalent to that expected with only underdominance (Fig. 6).

III. DISCUSSION

The major disadvantage of classical underdominance is its high transformation thresholds. The major disadvantages of Medea systems are their low transformation thresholds and, possibly, a lack of complete fixation within a population if there is a fitness cost. A reduction in homozygote fitness seems to be unavoidable with classically engineered translocations (see also Boussy 1988). Note that radiation induced translocations are rare single events that are then made homozygous, and translocations typically suppress recombination over a neighboring chromosomal region (Dobzhansky 1931, Wallace 1956).

In a Medea system, even with a fitness cost, if migration rates are sufficiently high, once a single population is above a transformation threshold, the accumulation of the M allele in neighboring populations by migration can be sufficient to also raise the neighboring allele frequency above this threshold and the system is expected to spread. Furthermore, in some cases, results from infinite population models can be misleading when intuitively applied to finite populations. As illustrated above, Medea alleles that are otherwise equivalent to wildtypes in terms of fitness, have an elevated probability of invasion in finite populations with overlapping generations and can even overcome the effects of mild underdominance (Fig. 4). A related caution in using fertility reducing translocations to help limit the spread of Medea is that soft selection can also act to relax the fitness cost of the translocation in addition to promoting the invasiveness and spread of Medea. Thus, the degree of sibling competition and/or remating compensation should be studied for target species to better understand if this may be a relevant factor; e.g. if a singly mated female mosquito predominantly laid all the eggs present in a small pool with density dependant larval mortality (cf. Madder et al. 1983; Dye 1984; Teng and Apperson 2000; see also the discussion of this in Hay et al. 2010). Related examples from Tribolium and mouse can be found in (Beeman and Friesen 1999; Lorenzen et al. 2008, Winking et al. 1991) Perhaps, if Medea alleles were more common across species (as suggested by Beeman and Friesen 1999), they, in conjunction with soft selection, could contribute to explanations of how chromosomal rearrangements accumulate between species despite underdominance (suggested for meiotic drive, Sandler and Novitski 1957; Bengtsson and Bodmer 1976). Thus, local fine-scaled population stratification (in addition to density regulated soft selection within families, Wade and Beeman 1994) may promote the invasion of rare Medea migrants and is an important consideration in the applicability of analytic results.

By linking Medea and underdominance the combined system can result in ideal properties in terms of population transformation ability and reversibility. Medea gives potentially underdominant alleles an "upward boost" at intermediate frequencies, where Medea acts most efficiently, and underdominance can give Medea alleles an "outward push" at lower and higher allele frequencies, where underdominance acts more efficiently (Fig. 1). These complementary properties not only potentially include a transformation threshold closer to $p = 1/2$ (at $\nu + \omega = 1$ for $t = 1$, Eq. 11, or at $t = 2 - 2\nu$, from Eq. A6 using the Hardy Weinberg approximation) for reversibility (Fig. 2), but also the property that the genetic construct can completely fix within a single population and can also be completely removed (if $\nu > \omega < 1$, Fig. 1). Furthermore, a combined system can have enhanced stability against migration along the edges of a transformed zone, even beyond that of underdominance alone, both in terms of preventing unwanted spread of genetic modifications and in maintaining a local transformation against wildtype immigrants (Fig. 6).

The tools already exist to attempt to engineer a system with these combined properties in Drosophila. A Medea poison-rescue element (Chen et al. 2007) could be inserted near a translocation breakpoint that has underdominant properties (a reduction in heterozygote fertility). New approaches have been developed to target insertions to specific points in the genome (such as the $\varphi C31 - attP$ integration system; Bischof et al. 2007) and translocations can

also be designed with breakpoints at specific sites (for example, by using the FRT-FLP system, Beumer et al. 1998; or by double strand breaks and homologous recombination, Egli et al. 2004), so it should be possible to accomplish this insertion close to a breakpoint. If an effector construct designed to provide disease refractoriness has a substantial fitness cost, then even a "fit" translocation that may otherwise be equivalent to wildtype fitness. This system will have a predicted threshold frequency near $p = 1/2$ and may benefit from being combined with a Medea element to give an upward boost to the fitness reducing effector. Since translocations essentially reduce fertility by $1/2$, but not to zero, genetic variation in the wild can introgress into the genetically modified population. This could allow local adaptation to persist in the majority of the genome alongside a targeted genetic transformation. It should also be possible to engineer a system that is resistant to recombination breaking up the linkage both between Medea and the translocation as well as the effector gene (Dobzhansky 1931, Coyne et al. 1993; Sherizen et al. 2005). (Alternative efforts to design a system resistant to disruption by recombination result in a greater fitness cost, Chen et al. 2007.)

There are methods to engineer underdominance with much lower threshold frequencies than the single locus system considered here (two-locus poison-rescue underdominance, Davis et al. 2001); however, this also results in lowered stability against spread by migration. Geographic stability may have particular value both in initial testing of genetically modified vectors and in species conservation applications (e.g. the Galápagos, Bataille et al. 2009, and Hawaiian, Warner 1968, archipelagoes).

In a combined system, if the Medea effect was inactivated by mutation, the presence of a translocation enables reversibility, and possibly stability, to be maintained. However, it can be seen that disruption of the Medea effect in a combined system would shift the system closer to loss of the transgene (compare Fig. 1 C to Fig. 1 A), providing a degree of fail-safe to restore the system to a wildtype state. Also, if a third allele resistant to the female killing Medea effect arose in the population, the presence of underdominance may inhibit a resistance allele from becoming established in the population (Altrock et al. 2010).

We agree that it is not a trivial engineering challenge to combine the two systems in a way that meets optimal fitness combinations. However, we also feel that the combined system described here should not be simply viewed as a baroque second-generation elaboration on existing technologies. A system with these predicted advantages; enhanced spatial stability, reversibility, and robustness to mutation and recombination would be ideal not only for reducing the likelihood of artificial Medea constructs becoming irreversibly established in the wild in model organisms, but additionally for first generation testing of population-transformation systems.

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Appendix A: Hardy-Weinberg Approximations

Here we briefly present some general analytic solutions assuming one-dimensional dynamics along Hardy-Weinberg equilibrium within the two-dimensional simplex of genotype frequencies. As described in the main text, this is inadequate to fully describe the system; however, there are some useful approximations that can be made , particularly when t is small and/or ν is large (in these cases the stable points can approach the Hardy-Weinberg axis).

Assuming Hardy-Weinberg equilibrium allows the dynamics to be written in terms of allele frequency. Let the frequency of the Medea allele (M) be written as p with a corresponding fitness f_M and the frequency of the wildtype allele ($+$) is $(1-p)$ with a fitness f_+. The Medea allele is unaffected by (i.e. rescues) maternal induced lethality, thus the average fitness of an M allele is only the relative genotype fitness weighted by the probability of appearing in heterozygote or homozygote form,

$$f_M = p\nu + (1-p)\omega. \tag{A1}$$

The mean population fitness is the sum of the Medea allele's average fitness and the average fitness of the wildtype allele, f_+, weighted by their corresponding frequencies,

$$\bar{w} = pf_M + (1-p)f_+. \tag{A2}$$

The average fitness of the wildtype allele can be written as,

$$f_+ = p\omega + (1-p)(1-pt). \tag{A3}$$

The wildtype allele is heterozygous at frequency p, with a relative fitness of ω. Alternatively, the wildtype allele is paired with another wildtype allele at a frequency of $1-p$, and its average fitness is reduced from 1 by an amount proportional to the frequency of the Medea allele in the popualtion and the degree of lethality due to Medea, pt. Medea lethality only reduces the expected proportion of wildtype homozygotes by t from Medea carrying mothers. In this case we know that one allele in the mother has to be wildtype, given that the offspring is wildtype homozygous, and the chance that this wildtype allele is paired with a Medea allele in the mother is p. The remaining wildtype homozygotes that do not have heterozygous mothers have a relative genotype fitness of 1.

The equilibria in this approximate treatment are found when the two average allele fitnesses are equal, which is

given by

$$f_M - f_+ = -tp^2 + (1 + t + \nu - 2\omega)p - 1 + \omega = 0. \quad \text{(A4)}$$

Solving for p gives the two possible internal equilibria along the Hardy-Weinberg axis (e.g. Fig. 1 B),

$$\hat{p}_\pm = \frac{1 + t + \nu - 2\omega \pm \sqrt{(1 + t + \nu - 2\omega)^2 + 4t(\omega - 1)}}{2t} \quad \text{(A5)}$$

Eq. A4 is a quadratic polynomial of the general form $ax^2 + bx + c$. The coefficient of the squared term, a, is $-t$ and t can either be zero or positive. Hence, whenever $t > 0$ the parabola determined by this function will always open downward. Thus, if both roots exist inside the simplex, the lower root (closer to $p = 0$) will always be unstable and the greater root will always be stable for any combination of ν, ω, and $t > 0$.

As described before, a "threshold" unstable equilibrium of $\hat{p}_- = 1/2$ can be thought of as an ideal situation from the standpoint of systems that are stable and reversible in terms of release numbers required to repeatedly cross this threshold. Setting $\hat{p}_- = 1/2$ and solving Eq. 18 for ν results in

$$\nu = 1 - t/2. \quad \text{(A6)}$$

In other words, with this approximation, in order to maintain an unstable equilibrium at $\hat{p}_- = 1/2$, a lower homozygote fitness can be compensated for by a higher degree of Medea lethality (Fig. 3 C and D).

REFERENCES

Altrock, P. M., A. Traulsen, R. G. Reeves, and F. A. Reed 2010 Using underdominance to bi-stably transform local populations. J. Theor. Biol. 267: 62-75.

Angulo, E. and B. Gilna, 2008 International law should govern release of GM mosquitoes. Nature 454: 158.

Asman, S. M., P. T. McDonald, and T. Prout, 1981 Field studies of genetic control systems for mosquitoes. Annu. Rev. Entomol. 26: 289-318.

Barton, N. H., 1979 The dynamics of hybrid zones. Heredity 43: 341-359.

Barton, N. H. and S. Rouhani, 1991 The probability of fixation of a new karyotype in a continuous population. Evolution 45: 499-517.

Bataille, A., A. A. Cunningham, V. Cedeo, M. Cruz, G. Eastwood, et al., 2009 Evidence for regular ongoing introductions of mosquito disease vectors into the Galápagos Islands. Proc. Biol. Sci. 276: 3769-3775.

Beeman, R. W., and K. S. Friesen, 1999 Properties and natural occurrence of maternal-effect selfish genes ("Medea" factors) in the red flour beetle, Tribolium castaneum. Heredity 82: 529-534.

Beeman, R. W., K. S. Friesen and R. E. Denell, 1992 Maternal-effect selfish genes in flour beetles. Science 256: 89-92.

Bengtsson, B. O. and W. F. Bodmer, 1976 On the increase of chromosome mutations under random mating. Theoretical Population Biology 9: 260-281.

Beumer, K. J., S. Pimpinelli, and K. G. Golic, 1998 Induced Chromosomal Exchange Directs the Segregation of Recombinant Chromatids in Mitosis of Drosophila. Genetics 150: 173-188.

Bischof, J., R. K. Maeda, M. Hediger, F. Karch, and K. Basler. 2007 An optimized transgenesis system for Drsophila using germ-line-specific ?C31 integrases. Proc. Natl. Acad. Sci. U.S.A. 104:3312-3317.

Boëte, C. and J. C. Koella, 2002 A theoretical approach to predicting the success of genetic manipulation of malaria mosquitoes in malaria control. Malaria Journal 1: 3

Boëte, C. and J. C. Koella, 2003 Evolutionary ideas about genetically manipulated mosquitoes and malaria control. Trends in Parasitology 19: 32-38.

Boussy, I. A., 1988 A Drosophila model of improving the fitness of translocations for genetic control. Theoretical and Applied Genetics 76: 627-639.

Chen, C. H., H. Huang, C. M. Ward, J. T. Su, L. V. Schaeffer, et al., 2007 A synthetic maternal-effect selfish genetic element drives population replacement in Drosophila. Science 316: 597-600.

Clark, T., 2002 Mosquitoes minus malaria. Nature 419: 429-430.

Corby-Harris, V., A. Drexler, L. W. de Jong, Y. Antonova, N. Pakpour, et al. 2010 Activation of Akt Signaling Reduces the Prevalence and Intensity of Malaria Parasite Infection and Lifespan in Anopheles stephensi Mosquitoes. PLoS Pathog. 6: e1001003.

Coyne, J. A., W. Meyers, A. P. Crittenden, and P. Sniegowski, 1993 The Fertility Effects of Pericentric Inversions in Drosophila melanogaster. Genetics 134: 487-496.

Cressman, R., 2003 Evolutionary dynamics and extensive form games. Massachusetts Institute of Technology Press. Cambridge, Massachusetts.

Curtis, C. F., 1968 Possible use of translocations to fix desirable genes in insect pest populations. Nature 218: 368-369.

Davis, S., N. Bax, and P. Grewe, 2001 Engineered underdominance allows efficient and economical introgression of traits into pest populations. J. Theor. Biol. 7: 83-98.

Dobzhansky, T., 1931 The decrease of crossing-over observed in translocations, and its probable explanation. Am. Nat. 65: 214-232.

Dye, C., 1984 Models for the population dynamics of the yellow fever mosquito Aedes aegypti. J. Anim. Ecol. 53: 247-268.

Egli, D., E. Hafen, and W. Schaffner, 2004 An Efficient Method to Generate Chromosomal Rearrangements by Targeted DNA Double-Strand Breaks in Drosophila melanogaster. Genome Res. 14: 1382-1393.

Fisher, R. A., 1922 On the dominance ratio. Proc. Roy. Soc. Edinburgh 42: 321-341.

Fitz-Earle, M., D. G. Holm and D. T. Suzuki, 1973 Genetic control of insect population. I. Cage studies of chromosome replacement by compound autosomes in Drosophila melanogaster. Genetics 74: 461-475.

Foster, G. G., M. J. Whitten, T. Prout and R. Gill, 1972 Chromosome rearrangements for the control of insect pests. Science 176: 875-880.

Foster, G. G., R. H. Maddern, R. A. Helman, and E. M. Reed, 1985 Field trial of a compound chromosome strain for genetic control of the sheep blowfly Lucilia cuprina. Theoretical and Applied Genetics 70: 13-21.

Franz, A. W. E., I. Sanchez-Vargas, Z. N. Adelman, C. D. Blair, B. J. Beaty, et al., 2006 Engineering RNA interference-based resistance to dengue virus type-2 in genetically-modified Aedes aegypti. Proc. Natl. Acad. Sci. U.S.A. 103: 4198-4203.

Gould, F. 2008 Broadening the application of evolutionarily based genetic pest management. Evolution 62: 500-510.

Haldane, J. B. S., 1942 Selection against heterozygosis in man. Ann. Eugen. 11: 333-340.

Harewood, L, F. Schtz, S. Boyle, P. Perry, M. Delorenzi, et al., 2010 The effect of translocation-induced nuclear re-organization on gene expression. Genome Res. 20: 554-564.

Hay, B. A., C.-H. Chen, C. M. Ward, H. Huang, J. T. Su, and M. Guo, 2010 Engineering the genomes of wild insect popualtions: Challenges, and opportunities provided by synthetic Medea selfish genetic elements. J. Insect Physiol. 56: 1402-1413.

Hofbauer, J., P. Schuster, and K. Sigmund, 1982 Game Dynamics in Mendelian Populations. Biol. Cybern. 43: 51-57.

Huang, Y., K. Magori, A. L. Lloyd and F. Gould, 2007 Introducing transgenes into insect populations using combined gene-drive strategies: Modeling and analysis. Insect Biochem. Molec. 37: 1054-1063.

Huang, Y., A. L. Lloyd, M. Legros, and F. Gould, 2008 Gene-drive in age-structured insect populations. Evolutionary Applications 2: 143-159.

Huang, Y., A. L. Lloyd, M. Legros, and F. Gould, 2010 Gene-drive into insect populations with age and spatial structure: a theoretical assessment. Evolutionary Applications (Early View, published online in advance of print).

Ito, J., A. Ghosh, L. A. Moreira, E. A. Wimmer, and M. Jacobs-Lorena, 2002 Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite. Nature 417: 452-455.

Jasinskiene, N., J. Coleman, A. Ashikyan, M. Salampessy, O. Marinotti, et al., 2007 Genetic control of malaria parasite transmission: threshold levels for infection in an avian model system. Am. J. Trop. Med. Hyg. 76: 1072-1078.

Karlin, S., and J. McGregor, 1972 Application of method of small parameters to multi-niche population genetic models. Theor. Pop. Biol. 3: 186-209.

Karlin, S. and H. M. A. Taylor, 1975 A First Course in Stochastic Processes, 2nd Edition. Academic, London.

Krafsur, E. S., 1998 Sterile insect technique for suppressing and eradicating insect populations: 55 years and counting. J. Ag. Entomol. 15: 303-317.

Lande, R., 1985 The fixation of chromosomal rearrangements in a subdivided population with local extinction and colonization. Heredity 54: 323-332.

Laponte, D. and J. Burgett, 2005 Mosquitoes in Hawaii. Position paper of the Hawaiian Conservation Alliance

Li, C. C. 1955 The Stability of an Equilibrium and the Average Fitness of a Popualtion. Am. Nat. 89: 281-295.

Lorenzen, M. D., A. Gnirke, J. Margolis, J. Garnes, M. Campbell, et al., 2008 The maternal-effect, selfish genetic element Medea is associated with a composite Tc1 transposon. Proc. Natl. Acad. Sci. USA 105: 10085-10089.

Lorimer, N., E. Hallinan, and K. S. Rai, 1972 Translocation homozygotes in the yellow fever mosquito, Aedes aegypti. J. Hered. 63: 158-166.

Madder, D., G. Surgeoner, and B. Helson, 1983 Number of generations, egg production and developmental time of Culex pipens and Culex restuans (Diptera: Culicidae) in southern Ontario. J. Med. Entomol. 20: 275-287.

Magori, K., M. Legros, M. E. Puente, D. A. Focks, T. W. Scott, et al., 2009 Skeeter Buster: A Stochastic, Spatially Explicit Modeling Tool for Studying Aedes aegypti Population Replacement and Population Suppression Strategies. PLoS Neglected Tropical Diseases 3: e508.

Marshall, J. C., J. Pinto, J. D. Charlwood, G. Gentile, F. Santolamazza, et al., 2008 Exploring the origin and degree of genetic isolation of Anopheles gambiae from the islands of So Tom and Prncipe, potential sites for testing transgenic-based vector control. Evolutionary Applications 1: 631-634.

Marshall, J. M., 2009 The effect of gene drive on containment of transgenic mosquitoes. J. Theor. Biol. 258: 250-265.

McGovern, D. P. B., M. R. Jones, K. D. Taylor, K. Marciante, X. Yan, et al. 2010 Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. Hum. Mol. Genet. 19: 3468-3476.

Newburg, D. S., G. M. Ruiz-Palacios, and A. L. Morrow 2005 Human Milk Glycans Protect Infants Against Enteric Pathogens. Annu. Rev. Nutr. 25: 37-58.

Peters, L. L., and J. E. Barker, 1993 Novel inheritance of the murine severe combined anemia and thrombocytopenia (scat) phenotype. Cell 74: 135-142.

Piálek, J. and N. H. Barton, 1997 The spread of an advantageous allele across a barrier: The effects of random drift and selection against heterozygotes. Genetics 145: 493-504.

Pinto, J., M. J. Donnelly, C. A. Sousa, J. malta-Vacas, V. Gill, et al., 2003 An island within an island: genetic differentiation of Anopheles gambiae in So Tom, West Africa, and its relevance to malaria vector control. Heredity 92: 407-414.

Robinson, A. S., 1977 Translocations and a Balanced Polymorphism in a Drosophila Population. Genetica 47: 231-236.

Robinson, A. S. and C. F. Curtis, 1973 Controlled Crosses and Cage Experiments with a Translocation in Drosophila. Genetica 44: 591-601.

Ruvoën-Clouet, N., E. Mas, S. Marionneau, P. Guillon, D. Lombardo, and J. Le Pendu 2006 Bile-salt-stimulated lipase and mucins from milk of 'secretor' mothers inhibit the binding of Norwalk virus capsids to their carbohydrate ligands. Biochem. J. 393: 627-634.

Sandler, L. and E. Novitski, 1957 Meiotic drive as an evolutionary force. Am. Nat. 41: 105-110.

Seager, R. D., F. J. Ayala, and R. W. Marks, 1982 Chromosome Interactions in Drosophila melanogaster. II. Total Fitness. Genetics 102: 485-502.

Sherizen, D., J. K. Jang, R. Bhagat, N. Kato and K. S. McKim, 2005 Meiotic Recombination in Drosophila Females Depends on Chromosome Continuity Between Genetically Defined Boundaries. Genetics 169: 767-781.

Sinkins, S. P., and F. Gould, 2006 Gene drive systems for insect disease vectors. Nat. Rev. Gen. 7: 427-435.

Smith, N. G., 1998 The dynamics of maternal-effect selfish genetic elements. J. Theor. Biol. 191: 173-180.

Soboleva, T. K., P. R. Shorten, A. B. Pleasants, and A. L. Rae, 2003 Qualitative theory of the spread of a new gene into a resident population. Ecol. Model 163: 33-44.

Teng, H. and C. Apperson, 2000 Development and survival of immature Aedes albopictus (Diptera: Culicidae) in the laboratory: effects of density, food and competition on response to temperature. J. Med. Entomol. 37: 40-52.

Traulsen, A. and C. Hauert, 2009 Stochastic evolutionary game dynamics. In Reviews of Nonlinear Dynamics and Complexity, Vol. II, Ed. H. G. Schuster, Wiley-VCH.

Wade, M. J., 1985 Hard selection, soft selection, kin selection, and group selection. Am. Nat. 125: 61-73.

Wade, M. J., and R. W. Beeman, 1994 The Population Dynamics of Maternal-Effect Selfish Genes. Genetics 138: 1309-1314.

Wallace, B., 1956 Studies on irradiated populations of D. melanogaster. J. Genetics 54: 280-293.

Warner, R. E., 1968 The role of introduced diseases in the extinction of the endemic Hawaiian avifauna. Condor 70: 101-120.

Weichenhan, D., W. Traut, B. Kunze, and H. Winking, 1996 Distortion of Mendelian recovery ratio for a mouse HSR is caused by maternal and zygotic effects. Genet. Res. 68: 125-129.

Wiener, A. S., 1942 The Rh factor and racial origins. Science 96: 407-408.

Winking, H., A. Weith, B. Boldyreff, K. Moriwaki, K. Fredga, et al., 1991 Polymorphic HSRs in chromosome 1 of the two semispecies Mus musculus musculus and Mus m. domesticus have a common origin in an ancestral population. Chromosoma 100: 147-151.

Woodworth, B. L., C. T. Atkinson, D. A. LaPointe, P. J. Hart, C. S. Spiegel, et al., 2005 Host population persistence in the face of introduced vector-borne diseases: Hawaii amakihi and avian malaria. Proc. Natl. Acad. Sci. USA 102: 1531-1536.

Wright, S., 1931 Evolution in mendelian populations. Genetics 16: 97-159.

Wright, S., 1941 On the probability of fixation of reciprocal translocations. Am. Nat. 75: 513-522.

Zivkovic, A. M., J. B. German, C. B. Lebrilla and D. A. Mills 2010 Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc. Natl. Acad. Sci. USA (PNAS Early Edition)

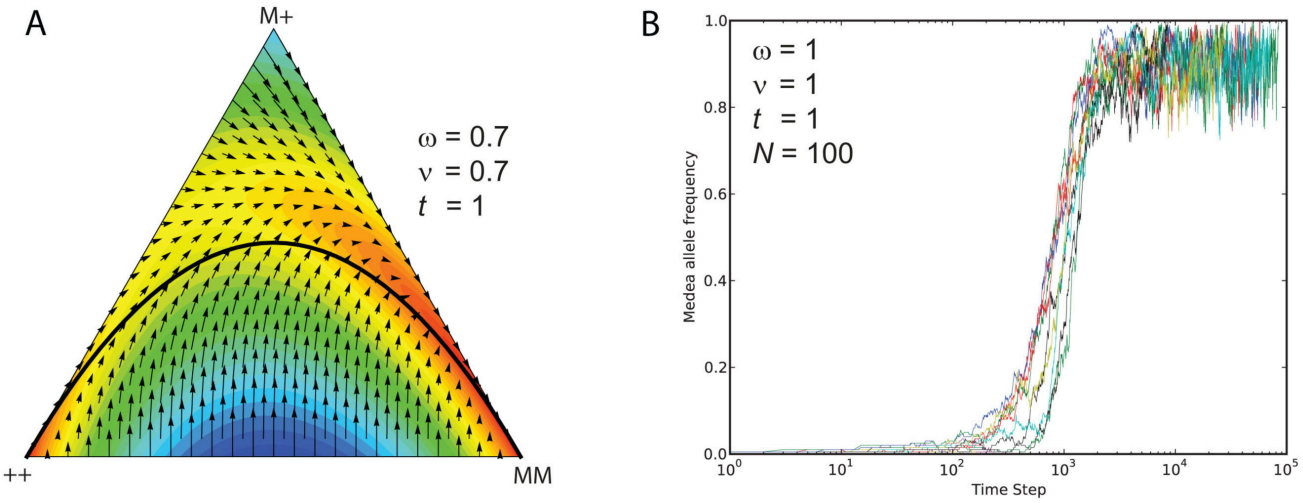

FIG. 5. **Illustrative dynamics for examples of soft selection.** A) A simplex similar to those in Fig. 3 except the soft selection genotype frequency recursions given in Equations 12 are used. B) Example trajectories for 20 replicate simulations. Time steps here refer to a single birth-death replacement under the Moran model. Eleven of the replicate frequencies were lost while rare; nine trajectories achieved fixation but segregated at high frequency for a substantial period of time before fixing (note that time is on a log scale). This may increase the time for alleles resistant to Medea lethality to occur in the population. With underdominance, fixation is rarer but achieved faster.

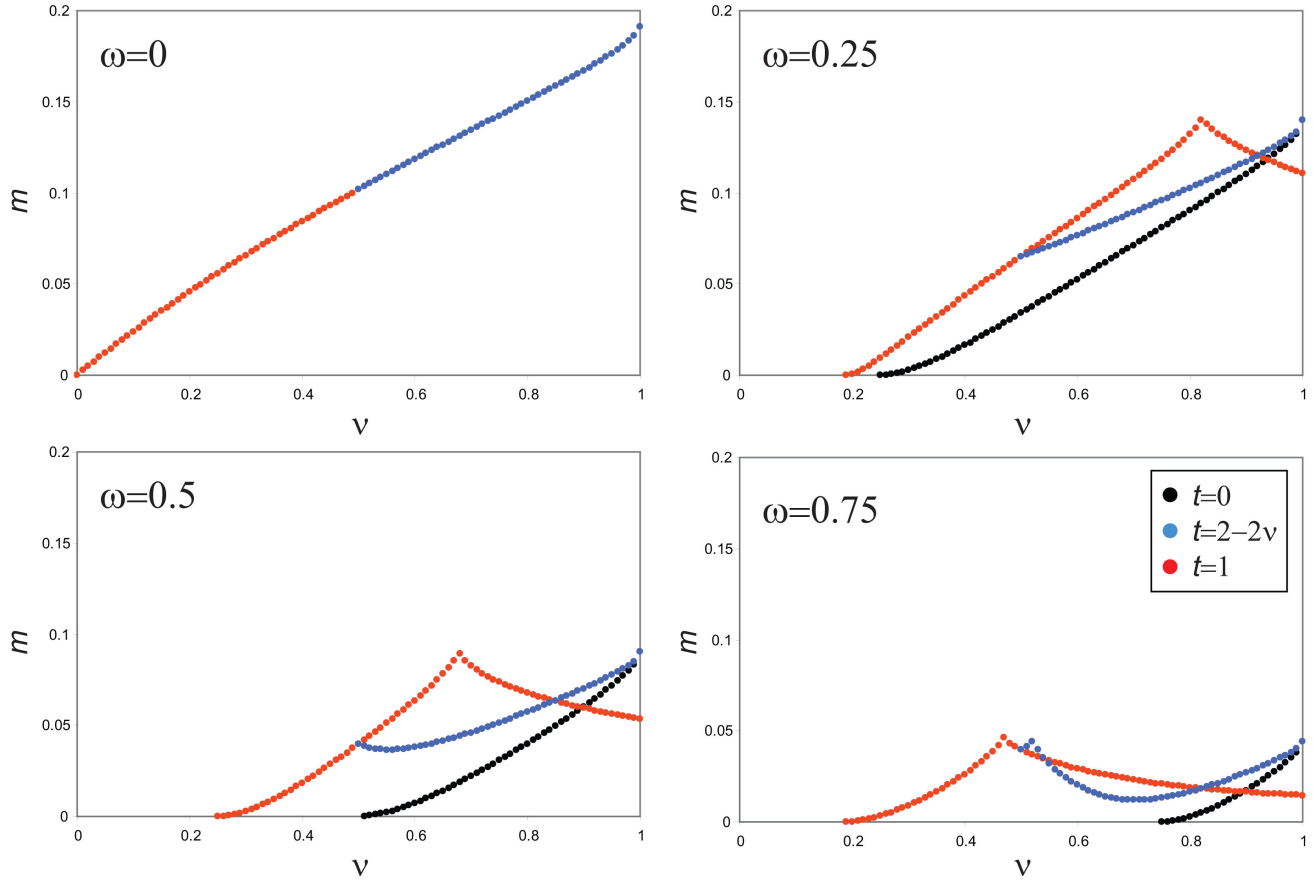

FIG. 6. **Critical migration rates allowing stable local transformations over a range of genotype fitness and Medea parameter configurations.** Migration rates are on the y-axis and homozygous MM fitness on the x-axis for four different heterozygous fitness values. Simulated parameter combination outcomes are indicated with dots. Pure underdominance with no Medea effect ($t = 0$) is plotted in black. Full Medea, 100% lethality ($t = 1$), is plotted in red. Intermediate Medea strengths that maintain an approximate unstable equilibrium at $p = 1/2$ are plotted in blue ($t = 2 - 2\nu$). Note that for $\omega = 0$ the points with Medea exactly correspond to the points without Medea (i.e., Medea has no effect and only underdominance determines the stability).