Introducing transgenes into insect populations using combined gene-drive strategies: Modeling and analysis

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Abstract

Engineered underdominance (EU), meiotic drive (MD) and \textit{Wolbachia} have been proposed as mechanisms for driving anti-pathogen transgenes into natural populations of insect vectors of human diseases. EU can drive transgenes to high and stable frequencies but requires the release of sizeable numbers of engineered insects. MD and \textit{Wolbachia} either cannot maintain high frequencies of transgenes or lack appropriate expression in critical tissues, but both can drive the transgenes to spread from very low initial frequencies. Here we use mathematical models to assess the utility of combining EU with MD or with \textit{Wolbachia}. Under some conditions, the combination of EU and MD results in a more efficient transgene-drive strategy than either mechanism alone. This combined strategy could drive the transgenes to stable fixation and would require fewer released insects than EU alone, especially when only males are released. However, a combination of EU and \textit{Wolbachia} does not work better than EU alone because it requires the release of even more engineered insects.

Keywords: Insect vectors; Anti-pathogen transgene; Gene-drive; Combined strategy; Release threshold; Theoretical assessment

1. Introduction

Replacement of a wild mosquito strain with a genetically modified strain that does not transmit pathogens is a potential strategy for combating mosquito-borne human diseases such as dengue, malaria and yellow fever (Scott et al., 2002; James, 2005). The success of this strategy requires both an anti-pathogen transgene and a genetic mechanism that can drive the transgene to spread in the natural population. A number of drive mechanisms have been proposed but most of them have specific characteristics that make them less than ideal (Sinkins and Gould, 2006; Gould et al., 2006).

For example, engineered underdominance (EU) is a transgene-drive mechanism that involves releasing indivi-
response allele on the Aedes equivalent of an X chromosome (Craig et al., 1960; Hickey and Craig, 1966a,b). This results in an excess of males in the population and selects for insensitive response alleles and any genes linked to these alleles. One way of using this MD system to introduce transgenes into natural A. aegypti populations is the release of males with a Y-linked MD gene and an X-linked insensitive response allele to which an anti-pathogen gene is linked (Mori et al., 2004). An earlier modeling study (Huang et al., 2007) demonstrated that under suitable conditions, the frequency of the transgene in the natural population could increase to a very high level that can lead to fixation in a finite population due to stochastic events. However, the frequency of the transgene can decrease due to immigration of natural genotypes with a sensitive response allele or mutation of the transgenic insensitive response allele (Huang et al., 2007).

Wolbachia, a maternally inherited intracellular bacterium that is common in many insects (O’Neill et al., 1992; Werren et al., 1995; Werren, 1997; Kittayapong et al., 2000), may also have potential for driving transgenes into populations. Cytoplasmic incompatibility (CI), in which a cross between an infected male and an uninfected female is completely or partially sterile, is the most common effect of Wolbachia on infected insect species (Yen and Barr, 1974; O’Neill and Karr, 1990; Turelli and Hoffmann, 1991, 1995). The CI mechanism provides a reproductive advantage for infected females and hence allows the maternally transmitted bacteria to spread without any additional external forces. Wolbachia does not occur naturally in A. aegypti, but was recently transferred to this species and shown to have potential for spread (Xi et al., 2005). Unfortunately, Wolbachia has not been engineered to express transgenes and Wolbachia bacteria occur at low density in insect tissues that harbor the disease-causing pathogen, so it is not clear that expression levels will be high enough in the critical tissues.

In this paper we explore the potential of strategies in which EU is combined with (1) MD or (2) Wolbachia. Based on models of each mechanism alone, both MD and Wolbachia are expected to enable increase in frequency of the anti-pathogen genes from very low frequencies while EU is expected to keep the gene frequency high and expression levels appropriate. If a combined strategy could maintain the best properties of each drive mechanism, the final product would be a gene drive system that would only require the release of a small fraction of transgenic insects but would drive the transgenes to a stable high frequency with appropriate expression. In contrast, the distinct drive systems could interfere with each other and yield a non-functional drive system.

In this paper we use two criteria to determine if a combined strategy is better than the single strategies: the release threshold (i.e. the minimum proportion of released transgenic individuals required for the transgenes to spread) and the expectation that the transgenes will be fixed or maintained at very high frequency.

2. Methods and results

2.1. The basic population genetic models of EU, MD and Wolbachia

EU involves the release of individuals carrying two co-dependent engineered constructs a and b. A diploid individual with the two constructs inserted into two non-homologous autosomes is denoted as aabb. The corresponding wild type is denoted as AABB. When the engineered individuals aabb are released into a wild population and crossed with wild type individuals, there may be as many as nine genotypes in the second generation: AABB, AABB, AaBb, AaBb, AAaB, aaBB, Aabb, AaBb and aabb. Among these genotypes only five are viable: AABB, AaBb, Aabb, aaBb and aabb. Each EU construct (type a or type b) is assumed to result in an equal fitness cost c. Individuals with k copies of the EU constructs are assumed to have fitnesses (1 − c)^k, so the fitness is calculated multiplicatively. When mating is random and the population considered has non-overlapping generations the frequencies of all gamete types and genotypes can be simply tracked from generation to generation based on the panel in Fig. 1. The details of the basic model are found in Davis et al. (2001) and Magori and Gould (2006).

EU requires the release of a minimum proportion of engineered insects relative to the size of the total population in order for the EU constructs to increase in frequency even if there is no fitness cost associated with the EU constructs. We will denote this minimum proportion as p_m and refer to it as the release threshold throughout the paper.

MD involves the release of males carrying a Y-linked MD gene and an X-linked insensitive response allele to which a transgene is tightly linked (Huang et al., 2007). The Y chromosome with the drive gene is denoted as Y^D. The
normal Y chromosome is denoted as $Y^d$. The X chromosomes with the transgene-linked insensitive response allele and a sensitive response allele are denoted as $X^H$ and $X^s$, respectively. When the drive males ($X^H Y^D$) are released into a sensitive natural population, there may be as many as four male genotypes $X^H Y^D$, $X^d Y^d$, $X^H Y^D$, $X^s Y^d$ and three female genotypes $X^H X^H$, $X^s X^s$ and $X^H X^s$ after the second generation. The relative fitness of the four male genotypes are $(1-h_C)(1-C_i)(1-C_D)$, $(1-h_C)(1-C_i)$, $(1-C_D)$ and 1, respectively, while the relative fitness of the three female genotypes are $(1-C_i)(1-C_i)^2$, $(1-h_C)(1-C_i)$ and 1, respectively. Note that the fitness cost of a female with two homologous X-linked insensitive alleles is assumed to be $C_i$, whereas the fitness cost of a male with only one X-linked insensitive allele is $h_C$ (so $h$ is the degree of dominance). The meaning of the parameters $h$, $C_i$, $C_d$ and $C_D$ can be found in Table 1. The male genotype $X^H Y^D$ with a combination of the drive gene and a sensitive response allele produces more $Y$ gametes than $X$ gametes. The degree of sex distortion caused by the MD is described by the parameter $d_{an}$ ($0 < d_{an} < 0.5$) with the fraction of male and female offspring being $0.5 + d_{an}$ and $0.5 - d_{an}$, respectively. When mating is random and the population has non-overlapping generations, the frequencies of all gamete types and genotypes can be tracked from generation to generation (see model details in Huang et al., 2007).

The dynamics of the frequency of CI-causing Wolbachia in insect populations can be described by models that use a series of simplified assumptions. First, the bacterium is assumed to only be maternally transmitted with a probability $0 < \sigma_w < 1$. Second, the CI is assumed to occur only when an infected male mates with an uninfected female (see Fig. 2). The relative hatch rate for this mating is $0 \leq H_w < 1$. Third, infected females are assumed to have a fecundity $0 < f_w \leq 1$ relative to those uninfected. With these assumptions, the relative frequency of infected individuals can be tracked by a discrete-generation model (Caspi and Watson, 1959; Fine, 1978; Turelli and Hoffmann, 1999; Wade and Stevens, 1994).

Parameters and notation used in these basic models are listed in Table 1. We use the same notation for these parameters in our models for the combined strategies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>$p_m$</td>
<td>All</td>
<td>The release threshold</td>
</tr>
<tr>
<td>$c$</td>
<td>EU</td>
<td>The fitness cost per EU construct ($a$ or $b$)</td>
</tr>
<tr>
<td>$C_D$</td>
<td>MD</td>
<td>The fitness cost of the Y-linked drive gene ($Y^D$)</td>
</tr>
<tr>
<td>$C_i$</td>
<td>MD</td>
<td>The fitness cost of the X-linked insensitive response allele ($X^i$)</td>
</tr>
<tr>
<td>$C_s$</td>
<td>MD</td>
<td>The fitness cost of a transgene</td>
</tr>
<tr>
<td>$h$</td>
<td>MD</td>
<td>The degree of dominance</td>
</tr>
<tr>
<td>$d_{an}$</td>
<td>MD</td>
<td>The degree of sex distortion for a combination of the drive gene and a sensitive response allele</td>
</tr>
<tr>
<td>$p_m$</td>
<td>MD</td>
<td>The initial frequency of the X-linked natural insensitive allele in the wild population ($X^m$)</td>
</tr>
<tr>
<td>$H_w$</td>
<td>Wolbachia</td>
<td>The relative hatch rate when Wolbachia-caused CI occurs</td>
</tr>
<tr>
<td>$\sigma_w$</td>
<td>Wolbachia</td>
<td>The maternal transmission probability of Wolbachia</td>
</tr>
<tr>
<td>$f_w$</td>
<td>Wolbachia</td>
<td>The relative fecundity of females infected with Wolbachia</td>
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**Fig. 2.** The table describing the maternal inheritance and cytoplasmic incompatibility associated with the Wolbachia bacteria. M and F represent male and female parent respectively.

**2.2. The combined strategy of EU and MD**

We consider the release of engineered drive males ($X^H Y^D A^D Y^b U^b$) that carry the EU construct $a$ on the sex chromosomes (X and Y) and the EU construct $b$ on autosomes (U). The construct $a$ on X and Y is tightly linked to the insensitive responder allele and the drive gene (so they are denoted as $ia$ and $Da$), respectively. In addition to males, we also release engineered females ($X^s X^s A^U U^b$) homozygous for an X-linked response allele that is insensitive to the effect of the drive gene. These females carry construct $a$ on the sex chromosomes and $b$ on their autosomes. The natural population is assumed to consist of non-drive males ($X^s H Y^D U^b U^b$) and females ($X^s A Y^D U^b U^b$) that carry an X-linked sensitive response allele.

There are in total 12 male genotypes and 9 female genotypes after the $F_2$ generation. The viability and the ratio of mature gametes from a genotype are determined by the EU and the MD mechanism, respectively. For instance, the male genotype $X^s H Y^D A^D U^b U^b$ is viable because both EU constructs are present and it produces a
fraction $0.5 - d_{\text{in}}$ of X-bearing gametes $X^a U^b$ and a fraction $0.5 + d_{\text{in}}$ of Y-bearing gametes $Y^{Da} U^b$ due to the meiotic drive mechanism ($0 \leq d_{\text{in}} \leq 0.5$).

The fitness of an individual carrying more than one type of detrimental gene is calculated multiplicatively. For instance, the relative fitness ($W$) of the drive male $X^{ai} Y^{D}{b} U^b U^b$ is

$$W^{(2)}_{\text{D}} = (1 - hC_i)(1 - C_D)(1 - c)^i.$$

Here the superscript $(2)$ in $W^{(2)}_{\text{D}}$ indicates that there are 2 copies of the EU construct $b$ on autosomes. Note that $i$ and $D$ represent the X-linked insensitive allele and the Y-linked drive gene to which the EU construct $a$ is tightly linked. This genotype thus contains four copies of EU constructs. Since we assume that both $a$ and $b$ result in the same fitness cost ($c$), there is a factor $(1 - c)^i$ in the fitness function defined above. The relative fitnesses of the other male and female genotypes can be calculated similarly (see a complete list in the Supplementary materials).

Incorporating these assumptions we can track the frequencies of genotypes and gametes from generation to generation. The recursion equations are given in the Supplementary materials; we study their dynamics by computer simulation.

Compared with EU alone the combination of EU with MD substantially reduces the release threshold if the fitness costs of the drive gene and the insensitive allele are low and the drive-caused sex distortion is strong. Fig. 3a shows that a strong MD (e.g. $d_{\text{in}} = 0.4$ or equivalently 90% males) reduces the release threshold $p_m$ from 0.27 to 0.18 when $C_D = C_i = c = 0$. When $C_D = C_i = 0.05$ the difference in $p_m$ between the two models is about 0.06 (Fig. 3b). When $C_D = C_i = 0.1$ the difference between the two models is very small even if the MD is very strong (about 0.02) (Fig. 3c).

In the combined strategy the MD causes positive selection for the Y-linked drive gene and the X-linked insensitive response allele. Since the EU constructs are linked to these genes, the relative frequencies of the viable genotypes that contain the EU constructs in the combined strategy are larger than that in the EU strategy alone in the $F_2$ generation for the same release proportion. Therefore, when the fitness costs $C_D$ and $C_i$ are low, the transgenic constructs can spread from a relatively low initial frequency with the aid of the MD, as compared to EU alone.

Note that in Fig. 3c when $d_{\text{in}} = 0.2$ the combined strategy results in an even higher threshold than EU alone. The reason for this is that the drive gene and the insensitive response allele cause additional fitness costs to the transgenic individuals bearing the EU constructs and outweigh the positive effects of the MD. For the same

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**Fig. 3.** Diagrams showing the changes of the release threshold ($p_m$) as the fitness cost per EU construct varies. In panels (a)-(c) the fitness costs of the Y-linked drive gene and the X-linked insensitive response allele (i.e. $C_D$ and $C_i$) are 0, 0.05 and 0.1, respectively. In each panel the results for EU alone (the dashed lines) are contrasted with the results of the combined strategy for two specific degrees of sex distortion caused by the meiotic drive: $d_{\text{in}} = 0.2$ and 0.4. The degree of dominance, $h$, was 0.5.
reason, when $C_D$ and $C_i$ are very high (larger than 0.2 for instance) the combined strategy is expected to result in higher thresholds than EU alone even if the MD is very strong (not shown in the figure).

MD alone can drive transgenes very quickly to very high frequencies, but such high frequencies are not stable and hence can decrease eventually (Fig. 4a). The reason for this is that once the X-linked insensitive response allele to which the transgene is linked reaches a very high frequency close to fixation, there is almost no positive selection for the Y-linked drive gene. If the drive gene has any fitness cost, it will be replaced by a non-drive allele. Once the frequency of the drive gene is very low, any cost associated with the insensitive response allele will cause its frequency to decrease. When the frequency of the insensitive allele decreases to a level where the high proportion of sensitive alleles causes selection for the drive gene to begin again, a new round of selection for the insensitive allele begins. When MD is combined with EU, however, the stabilizing mechanism of EU helps to maintain the frequencies of transgenes at their high levels once they have been reached (Fig. 4b).

There are also obvious differences in the ultimate level of the transgene frequency and/or the time to reach that level between EU alone and the combined strategy. For EU alone, when the initial release proportion exceeds the threshold value the frequency of the transgene goes to fixation if there is no fitness cost to the EU constructs, or to a high stable equilibrium frequency when there is a fitness cost (Fig. 4c). When combined with MD, the frequencies of transgenes increase much faster even if there is a fitness cost to the EU constructs (Fig. 4d).

In the preceding analysis we considered the releases of males and females. We now consider the release of just males ($X^{it}Y^{Dm}U^{Bm}U^{Bm}$). In this case the combination of EU and MD also leads to a lower $p_m$ than EU alone if $C_D$ and $C_i$ are small and $d_{sn}$ is large (Fig. 5). The difference in $p_m$ between EU and the combined strategy can be as much as 0.16. However, the release of just males requires a higher $p_m$ than the release of both males and females.

Up to now, the natural population has been assumed to be uniformly sensitive. However, a natural population is likely to have more than one X-linked response allele and these alleles may vary in sensitivity to the Y-linked drive gene. In a previous study (Huang et al., 2007), we showed that an initially low frequency of a naturally occurring X-linked drive-insensitive response allele (denoted by $p_{mi}$), 0.01 for instance, blocked the spread of the anti-pathogen transgene (see Fig. 6a). We now examine if the combined strategy of MD and EU can overcome this

Fig. 4. Comparisons of MD and EU with their combination, respectively, for the stability and the ultimate level of the frequency of the transgenic construct ($X^{it}$). Note that for the combined strategy $X^{it}$ is equivalent to $X^{iB}$. For MD alone, the frequency of the transgene decreases later at some point after increasing to a very high level initially (panel (a)). When MD is combined with EU, the transgene goes to fixation (panel (b)). For EU alone, the transgene does not go to fixation when it results in fitness costs (panel (c)). When EU is combined with MD, the transgene goes to fixation quickly (panel (d)). In panel (a) and (b), $d_{sn} = 0.4, C_D = C_i = 0.1, h = 0.5$. In panel (d), $d_{sn} = 0.4, C_D = C_i = 0.0$. 

block. As we can see in Fig. 6c, the anti-pathogen transgene does go to fixation in the model with the combined strategy. The reason for this is simple: when the transgene frequency increases to a level that is above the release threshold determined by the EU mechanism and the fitness costs of detrimental genes, the EU mechanism drives the transgenes to stable high frequencies or fixation regardless of the frequency of the insensitive response allele. Note that the release threshold value for the combined strategy ($p_m$) is 0.23 for the given parameter values, which is about 0.05 lower than that for EU alone.

For a larger $p_m$, 0.1 for instance, similar results are observed (Fig. 6b and d). However, a larger $p_m$ increases the release threshold required for the transgenic constructs to increase in frequency in the population. When $d_{sn} = 0.4$, $C_D = C_i = 0.05$ and $c = 0$, the release threshold for the combined strategy increases from 0.21 to 0.29 as $p_m$ increases from 0 to 1 (Fig. 7). When $p_m = 0.66$, the combined strategy requires the same release threshold value as the EU strategy alone; the combined strategy thus has no advantage over the EU alone in terms of the release threshold level.

2.3. The combined strategy of EU and Wolbachia

In this section we examine a combination of EU and Wolbachia. We consider the release of insects that are infected with Wolbachia and carry the two EU constructs (a and b) in non-homologous autosomes. We will denote the genotypes and gamete types in the same ways as in the basic EU model except for attaching a letter w to indicate the presence of Wolbachia. For instance, the released
homozygous genotype with *Wolbachia* is denoted as \( aabbw \) and the gamete type produced by this genotype is denoted as \( abw \). In this case we will have 10 viable genotypes and eight gametic types.

The eight parental gametes can be classified into two categories: those produced by parents who are infected with *Wolbachia* (\( ABw, Abw, aBw \) and \( abw \)) and those produced by parents who are not infected (\( AB, Ab, aB \) and \( ab \)). Based on Figs. 1 and 2 it is straightforward to derive a 8 by 8 Punnett square. Using this square and incorporating the assumptions about the basic EU and *Wolbachia* models, we can track the frequencies of both genotypes and gametic types from generation to generation (see the detailed model in the Supplementary materials).

When we release equal numbers of engineered males and females infected with *Wolbachia*, we find that the combined strategy requires release of more engineered insects than EU alone (Fig. 8). For a fixed maternal transmission probability (i.e. \( \sigma_m \)), the release threshold (i.e. \( p_m \)) increases as the CI-related relative hatch rate \( H_w \) decreases. For a fixed \( H_w \), the release threshold increases as the maternal transmission probability decreases, but the magnitude of this increase is not significant unless the CI effect is strong. These results suggest that the higher release threshold is caused by CI. To examine how CI results in a higher release threshold, we contrast the dynamics of the frequencies of the wild-type and transgenic individuals between EU alone and the combined strategy, for the same initial frequency of the transgenic individuals (Fig. 9). In this figure we assume perfect maternal transmission, no fecundity loss and a complete CI, so that the effect of *Wolbachia* is solely reflected by CI. In Fig. 9a and b we take the initial frequency of transgenic individuals to be \( p_0 = 0.27 \), which is the release threshold for EU when there are no fitness costs. In the first generation, the frequency of transgenic individuals increases to about 0.47 with EU alone (Fig. 9a), whereas it increases to only about 0.35 with the combined strategy (Fig. 9b). When \( p_0 = 0.325 \) (which is the release threshold for the combined strategy), the transgene goes to fixation for both the EU alone and the combined strategy, but it takes longer for the latter strategy due to the lower frequency of the transgenic individuals in the first generation (Fig. 9c and d). The differences suggest that CI results in a loss of engineered constructs from the \( F_0 \) generation to the \( F_1 \) generation and hence results in an increase in the release threshold for the combined strategy.

Alternatively we may consider the release of just engineered females infected with *Wolbachia*. Unfortunately, this results in an even higher release threshold than the release of both males and females (simulation results are not shown). The reason is that the release of just females results in an even higher loss of engineered constructs from the \( F_0 \) generation to the \( F_1 \) generation than the release of both sexes.

### 3. Discussion

Most of the gene-drive mechanisms that have been proposed for increasing the frequency of refractory transgenes in mosquito populations have characteristics that make them less than ideal (Sinkins and Gould, 2006). If two gene-drive mechanisms with unique positive qualities could be combined in a complementary manner, it is possible that combinations would give rise to better gene-drive strategies that merit development.

We specifically chose to analyze the combination of EU with either MD or *Wolbachia* because EU was able to achieve high and stable transgene frequencies while MD and *Wolbachia* could drive the transgene to spread from
low initial frequency (Davis et al., 2001; Magori and Gould, 2006; Cha et al., 2006; Huang et al., 2007; Turelli and Hoffmann, 1999). We initially expected that the combination could give rise to transgene-drive strategies that share these two important properties. In contrast to our intuitive expectations the modeling results demonstrated that the combination of EU with \textit{Wolbachia} is antagonistic and results in even higher release thresholds than EU alone. This combination thus is not worth further consideration even though it requires less work than the combination of EU with MD.

Under some conditions, the combination of EU with MD results in a strategy that requires release of substantially fewer insects than EU alone, and is expected to be more reliable than the MD strategy alone. The advantage of the combination over EU alone would only be economically significant if the fitness costs of insertions were low and the financial costs of factory production of insects were high.

The additional research and development costs for a combined gene-drive system might not seem to be justified by the advantage to be gained at the implementation stage. However, because \textit{A. aegypti} has a naturally occurring MD system (Cha et al., 2006), the development costs would be much lower if there was a means to link an EU construct to the existing MD. This is not currently feasible because transgene insertion in \textit{A. aegypti} is typically mediated by a non-autonomous piggybac transposon and insertion sites of these transposons are nearly random. However, recent advances in transgenic techniques with both \textit{Drosophila} and \textit{A. aegypti} (Beumer et al., 2006; Nimmo et al., 2006; Venken et al., 2006) enable insertion of constructs into pre-engineered docking sites in the genome. As more of these docking sites are established in the \textit{A. aegypti} genome one or more may be tightly linked to natural MD genes. If such a docking site is developed or if a site-specific technique of transgene insertion is available in the future, one of the two EU constructs could be inserted within a few centimorgans of the MD genes to accomplish tight linkage between the EU constructs and the natural MD. As long as this linkage can be maintained for more than five generations (see Fig. 6), the natural MD is expected to complement the EU mechanism in driving the transgene to spread from a relatively low initial frequency.

However, the current transgenic techniques cannot guarantee a strong linkage between the transgenes and their associated driving genes forever, so recombination between the EU constructs and MD genes may occur and...
the combined transgene-drive system may eventually break down. In the ideal situation, where the fitness costs of the transgenic constructs are small and the MD is very strong, the transgenes might be driven to a stable fixation within a short period of time, so we do not have to worry about this recombination once this has happened. Therefore, in order to achieve a long-term disease suppression, it is essential to develop transgenic constructs that result in low cost to individuals' fitness.

There are other gene drive mechanisms such as autonomous transposons that have been suggested for use in disease vectoring mosquitoes. Transposons, like MD, are useful in initially increasing transgene frequencies, but might not be able to yield long-term high frequencies and stable expression due to possible mutations and deletions caused by transposon replication. It would be ideal if a single genetic model could be developed for examining the properties of two-way combinations of all potential gene-drive mechanisms. Unfortunately, this is not possible. We had to develop distinct models for the EU and MD and for the EU and Wolbachia combinations. Modeling the dynamics of transposons require a very different type of model (Rason and Gould, 2005; Struchiner et al., 2005; Le Rouzic and Capy, 2006), so evaluation of combinations of transposons with other gene drive mechanisms will require specific models that account for the specific functions of the combinations.

Models such as the ones presented here are useful in clearly demonstrating strategies that are not worth empirical development based on their population genetic properties. When such models suggest that a specific strategy has theoretical merit, they offer a starting point for discussions that must include an economic assessment of the cost/benefits in the research and implementation phases of the development of a gene-drive strategy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at 10.1016/j.ibmb.2007.06.002.

References


