

GENETICS

Supporting Information

<http://www.genetics.org/cgi/content/full/genetics.110.124479/DC1>

***Semele*: A Killer-Male, Rescue-Female System for Suppression and Replacement of Insect Disease Vector Populations**

John M. Marshall, Geoffrey W. Pittman, Anna B. Buchman and Bruce A. Hay

Copyright © 2011 by the Genetics Society of America
DOI: 10.1534/genetics.110.124479

FILE S1

I. Local stability analysis:

To calculate the local stability of an equilibrium point, we calculate the eigenvalues of the Jacobian matrix. The equilibrium is locally stable if all eigenvalues have modulus less than one. If one or more of the eigenvalues have modulus greater than one, the equilibrium is unstable. If the eigenvalue with the largest modulus has a modulus equal to one, then the linear stability analysis is inconclusive. In the case of an inconclusive analysis, we use numerical simulation to determine stability; however a nonlinear analysis can be used for more rigorous determination (Elaydi 1995).

No fitness costs: For a *Semele* element without fitness costs, the proportions of the k th generation that are individuals of genotypes tt , Tt and TT may then be denoted by u_k , v_k and w_k . The system of difference equations for this system is:

$$u_{k+1} = (u_k^2 + 0.25v_k^2 + u_k v_k (1 - 0.5e_T)) / W_{k+1} \quad (14)$$

$$v_{k+1} = (0.5v_k^2 + v_k w_k + u_k v_k (1 - 0.5e_T) + u_k w_k (2 - e_T)) / W_{k+1} \quad (15)$$

$$w_{k+1} = (w_k^2 + 0.25v_k^2 + v_k w_k) / W_{k+1} \quad (16)$$

where W_{k+1} , the normalizing term, is given by:

$$W_{k+1} = u_k^2 + u_k (v_k + w_k)(2 - e_T) + v_k^2 + 2v_k w_k + w_k^2 \quad (S1)$$

This system has three biologically-feasible equilibrium points:

$$(u_*, w_*) = (0,1), (1,0), \left(0.5, 0.5(3 - e_T - \sqrt{e_T^2 - 6e_T + 8}) \right) \quad (17)$$

The first of these points represents allele fixation, the second represents absence or loss of the *Semele* allele, and the third represents coexistence of wild, heterozygous and homozygous individuals in the population. We can calculate the stabilities of these points by calculating the eigenvalues of the Jacobian matrix:

$$\left(\begin{array}{cc} \frac{\partial u_{k+1}}{\partial u_k} & \frac{\partial u_{k+1}}{\partial w_k} \\ \frac{\partial w_{k+1}}{\partial u_k} & \frac{\partial w_{k+1}}{\partial w_k} \end{array} \right)_{(u_k, w_k) = (u_*, w_*)} \quad (\text{S2})$$

The equilibrium $(u_*, w_*) = (0, 1)$ has eigenvalues equal to 0 and 1, suggesting an inconclusive analysis; however numerical simulation indicates that fixation is stable over full range of $e_T \in (0, 1]$. The equilibrium $(u_*, w_*) = (1, 0)$ has eigenvalues equal to 0 and $1 - 0.5e_T$. Both of these eigenvalues are less than one for $e_T \in (0, 1]$, suggesting that element loss is also a stable equilibrium. The third equilibrium point has eigenvalues equal to:

$$1 + e_T + z - \frac{4(2 - e_T)}{z} + \frac{\sqrt{(4 - e_T)^5 (4 - e_T (17 - 6z - 2e_T (6 - e_T - z)))}}{(4 - e_T)^3} \quad (\text{S3})$$

and:

$$1 + e_T + z - \frac{4(2 - e_T)}{z} - \frac{\sqrt{(4 - e_T)^5 (4 - e_T (17 - 6z - 2e_T (6 - e_T - z)))}}{(4 - e_T)^3} \quad (\text{S4})$$

where $z = \sqrt{e_T^2 - 6e_T + 8}$. The first of these eigenvalues is greater than 1 for $e_T \in (0, 1]$, suggesting that the third equilibrium point is locally unstable. The stability analysis therefore shows that both fixation and loss of the element are represented by stable equilibrium points separated by an unstable intermediate equilibrium.

Equal fitness costs: For a *Semele* element with equal fitness costs in males and females, the system of difference equations is:

$$u_{k+1} = (u_k^2 + 0.25v_k^2 + u_k v_k (1 - 0.5e_T)) / W_{k+1} \quad (22)$$

$$v_{k+1} = (0.5v_k^2 + v_k w_k + u_k v_k (1 - 0.5e_T) + u_k w_k (2 - e_T))(1 - hs) / W_{k+1} \quad (23)$$

$$w_{k+1} = (w_k^2 + 0.25v_k^2 + v_k w_k)(1 - s) / W_{k+1} \quad (24)$$

where W_{k+1} , the normalizing term, is given by:

$$\begin{aligned}
W_{k+1} &= u_k^2 + 0.25v_k^2 + u_k v_k (1 - 0.5e_T) + (w_k^2 + 0.25v_k^2 + v_k w_k)(1 - s) \\
&+ ((u_k v_k + 2u_k w_k)(1 - 0.5e_T) + 0.5v_k^2 + v_k w_k)(1 - hs)
\end{aligned} \tag{S5}$$

This system has four biologically-feasible equilibrium points; however only two of them are analytically tractable; namely:

$$(u_*, w_*) = (0,1), (1,0) \tag{S6}$$

The first of these points represents allele fixation, and the second represents absence or loss. We can calculate the stabilities of these points by calculating the eigenvalues of the Jacobian matrix (Equation S2).

The equilibrium $(u_*, w_*) = (0,1)$ has eigenvalues equal to 0 and

$$1 + \frac{s(1-h)}{1-s} \tag{S7}$$

The second eigenvalue is greater than one for $s \in (0,1)$ and $h \in [0,1)$, and is equal to one for two cases – the absence of fitness costs ($s = 0$), and the case of a completely dominant fitness cost ($s > 0$, $h = 1$). Numerical simulation suggests that fixation is a stable equilibrium in both these cases. The stability analysis therefore shows that fixation is unstable for a fitness cost that is recessive or shows any degree of heterozygosity, but is stable for a completely dominant fitness cost.

The equilibrium $(u_*, w_*) = (1,0)$ has eigenvalues equal to 0 and $(1 - 0.5e_T)(1 - hs)$. Both of these eigenvalues are less than one for $e_T \in (0,1]$, $h \in [0,1]$ and $s \in [0,1)$, suggesting that allele loss is stable for all scenarios.

Recessive antidote: For a *Semele* element with a recessive antidote, the system of difference equations is:

$$u_{k+1} = (u_k^2 + 0.5u_k v_k + (0.25v_k^2 + 0.5u_k v_k)(1 - e_T)) / W_{k+1} \tag{31}$$

$$\begin{aligned}
v_{k+1} &= (u_k w_k + 0.5u_k v_k + 0.5v_k w_k \\
&+ (0.5v_k^2 + 0.5v_k w_k + 0.5u_k v_k + u_k w_k)(1 - e_T))(1 - hs) / W_{k+1}
\end{aligned} \tag{32}$$

$$w_{k+1} = (w_k^2 + 0.5v_k w_k + (0.5v_k w_k + 0.25v_k^2)(1 - e_T))(1 - s) / W_{k+1} \tag{33}$$

where W_{k+1} , the normalizing term, is given by:

$$\begin{aligned}
W_{k+1} &= u_k^2 + 0.5u_k v_k + (0.25v_k^2 + 0.5u_k v_k)(1 - e_T) \\
&+ (u_k w_k + 0.5u_k v_k + 0.5v_k w_k \\
&+ (0.5v_k^2 + 0.5v_k w_k + 0.5u_k v_k + u_k w_k)(1 - e_T))(1 - hs) \\
&+ (w_k^2 + 0.5v_k w_k + (0.5v_k w_k + 0.25v_k^2)(1 - e_T))(1 - s)
\end{aligned} \tag{S8}$$

This system has three biologically-feasible equilibrium points; however, for the general case, only two are analytically tractable:

$$(u_*, w_*) = (0,1), (1,0) \tag{S9}$$

The first of these points represents allele fixation, and the second represents absence or loss. We can calculate the stabilities of these points by calculating the eigenvalues of the Jacobian matrix (Equation S2).

The equilibrium $(u_*, w_*) = (0,1)$ has eigenvalues equal to 0 and

$$\frac{(2 - e_T)(1 - hs)}{2(1 - s)} \tag{S10}$$

Both of these eigenvalues are less than one for $e_T \in (0,1)$, $h \in [0,1]$ and $s \in [0,1)$, suggesting that fixation is stable for all scenarios. The equilibrium $(u_*, w_*) = (1,0)$ has eigenvalues equal to 0 and $(1 - 0.5e_T)(1 - hs)$.

Both of these eigenvalues are less than one for $e_T \in (0,1)$, $h \in [0,1]$ and $s \in [0,1)$, suggesting that element loss is also stable for all scenarios.

If we assume 100% toxin efficiency, then all three of the biologically-feasible equilibrium points are analytically tractable:

$$(u_*, w_*) = (0,1), (1,0), (0,0) \tag{34}$$

We have already shown that allele fixation and loss are stable equilibria for all scenarios. The eigenvalues of the Jacobian matrix for the third equilibrium point are indeterminate; however numerical simulation confirms that the intermediate equilibrium point is unstable for the full range of fitness costs ($h \in [0,1]$ and $s \in [0,1)$).

II. Assortative mating:

Several models have been proposed to describe the effects of assortative mating due to one allele on the distribution of another (Jennings 1917; Wright 1920). We consider two variations of a two-locus model to describe

the effect of assortative mating on the spread of a *Semele* allele. In both models, we account for the fact that male mosquitoes must compete in order to find a female mating partner. We consider an unlinked allele, “*A*”, to be responsible for the degree of unattractiveness of transgenic males to females. Such an allele could be considered the product of laboratory inbreeding. We then use a series of 81 dihybrid crosses to keep track of the proportions of each generation that are males and females of genotypes *TTAA*, *TTAa*, *TTaa*, *TtAA*, *TtAa*, *Ttaa*, *ttaa*, *tTAA*, *tTAa* and *ttaa*.

For simplicity, we assume equal fitness costs due to the *T* allele and 100% toxin efficiency. All crosses between males having the *T* allele and females lacking the *T* allele are unviable. In model A, we assume that wild females are less attracted to transgenic males, while transgenic females are less discerning. Crosses between *AA* males and *aa* females have a reduced weighting of $1 - a$, where a is the strength of assortative mating. We assume that the *A* allele is additive in its effect, and hence crosses between *AA* males and *Aa* females have a reduced weighting of $1 - 0.5a$, as do crosses between *Aa* males and *aa* females (Figure S1).

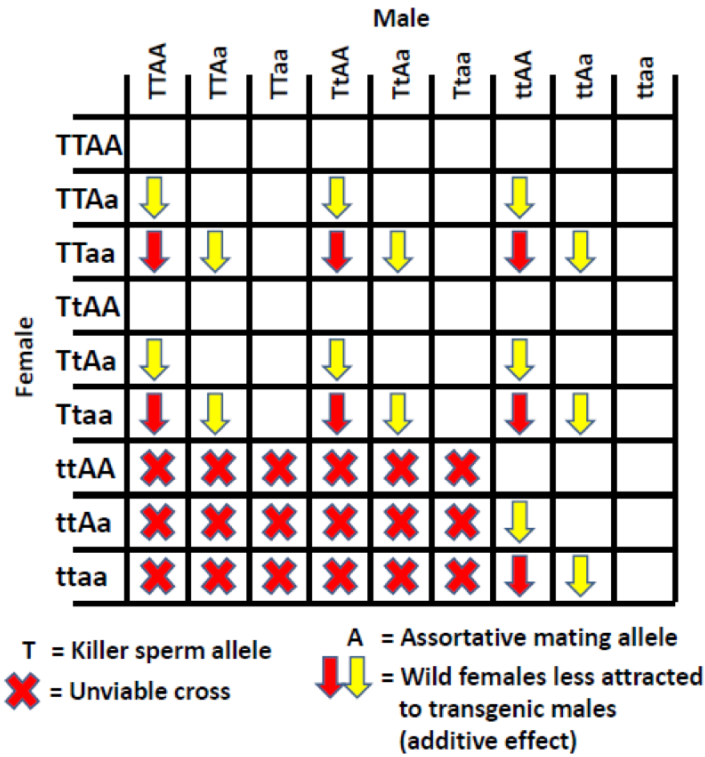


FIGURE S1.—Schematic diagram used to model the spread of a *Semele* allele, *T*, and an unlinked assortative mating allele, *A*, assumed to be the product of laboratory inbreeding. Each box represents a dihybrid cross used to keep track of the proportions of each genotype in discrete generations. All crosses between males having the *T* allele and females lacking the *T* allele are unviable. In this model (model A), *aa* females are less attracted to *AA* males, and so these crosses have a reduced weighting. The *A* allele is assumed to be additive in its effect and so crosses between *aa* females and *Aa* males and between *Aa* females and *AA* males also have reduced weight.

We assume that all released mosquitoes are inbred and are therefore homozygous for the A allele. Considering a release of $TTAA$ males and females at generation 0, the initial condition for the system is given by:

$$P_{TTAA,0} = w_0 \tag{S11}$$

$$P_{taa,0} = 1 - w_0 \tag{S12}$$

Using this initial condition and the model described above, the dynamics of the T and A alleles can be calculated.

Assortative mating, modeled in this way, has only very minor effects on the spread of the *Semele* allele. Figure S2A depicts the time-series dynamics of a *Semele* allele having a 10% fitness cost for strengths of assortative mating between 10% and 90%. In all cases, for a 45% transgenic release, the *Semele* allele spreads to a transgenic frequency of ~99% within 40 generations. Increasing assortative mating strength from 10% to 90% retards its spread by approximately five generations. In all cases, for a 42% transgenic release, the *Semele* allele is lost from the population. This suggests that the release threshold varies by less than 3% over the full range of assortative mating strengths.

An interesting side-note for this system is that the A allele also displays threshold behavior. For a 50% transgenic release, both the T and A alleles spread (Figure S2B); however for a 45% release, only the T allele spreads (Figure S2C). Figure S2D depicts release thresholds and equilibrium frequencies for a *Semele* allele associated with a range of fitness costs and assortative mating strengths. Assortative mating has no effect on the equilibrium frequency, increases the release threshold for the *Semele* allele by up to 2.3% and retards spread by less than six generations. These results suggest that a *Semele* allele will spread into a population even in the presence of strong assortative mating tendencies if only wild females are less attracted to transgenic males.

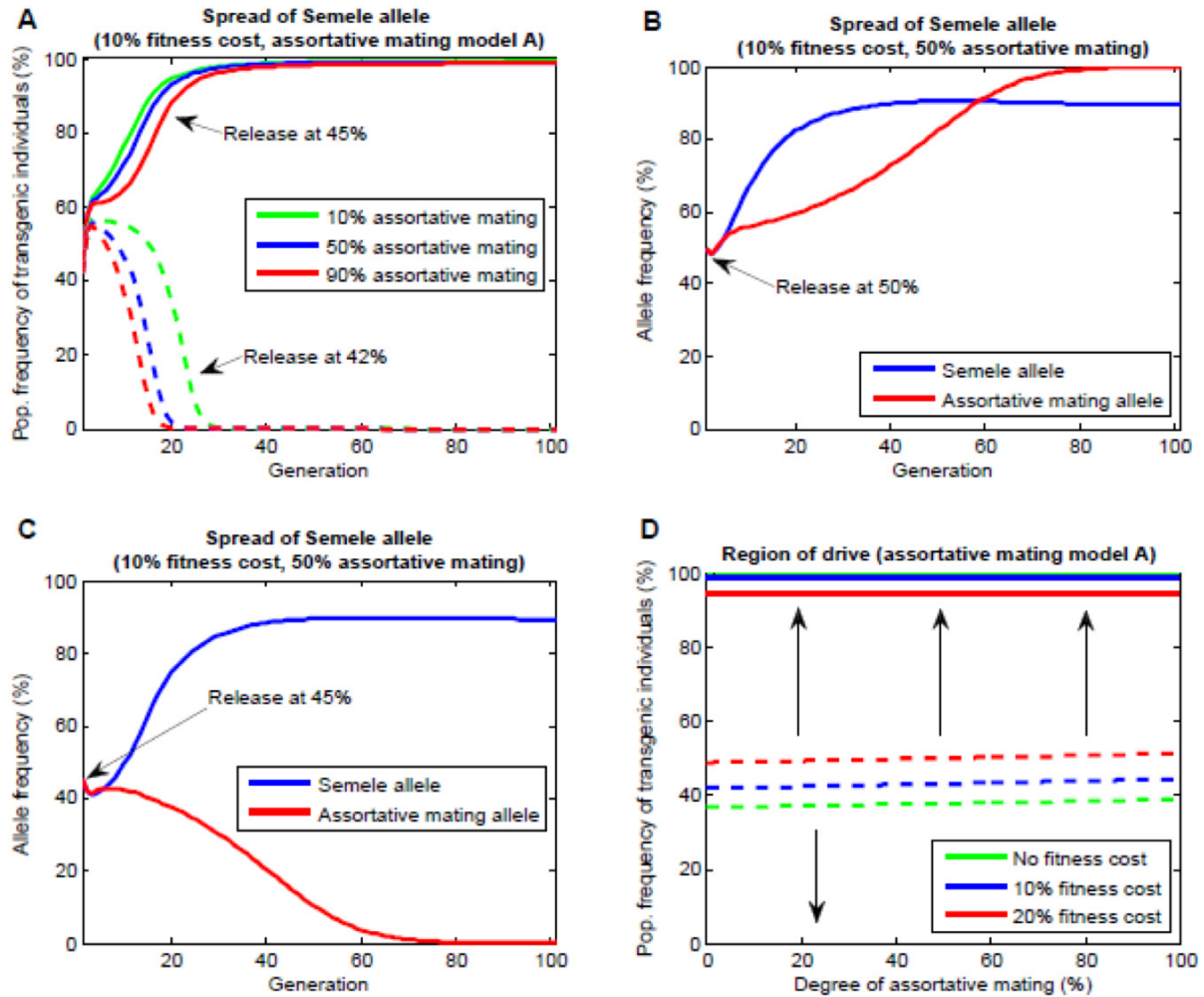


FIGURE S2.—Effects of an assortative mating allele, A , having the property that wild females are less attracted to AA males (model A). A: Time-series dynamics of an element with a 10% fitness cost and a variety of assortative mating strengths. Assortative mating increases the T allele release threshold by less than 3%. B-C: Time-series dynamics of both T and A alleles for an element having a 10% fitness cost and 50% assortative mating strength. The A allele also has a release threshold which is slightly greater than the T allele threshold. D: T allele release thresholds for several fitness costs as a function of assortative mating strength.

In model B, we assume that both transgenic and wild females are less attracted to transgenic males. In this model, all crosses involving AA males have a reduced weighting of $1 - a$. We also assume that the A allele is additive in its effect, and hence all crosses involving Aa males have a reduced weighting of $1 - 0.5a$ (Figure S3). The Matlab code for both models is available from the authors upon request.

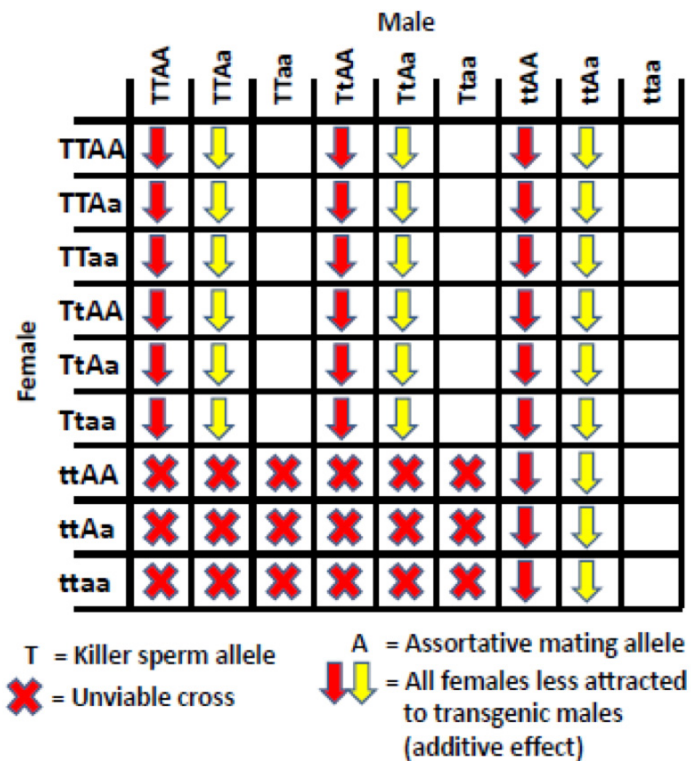


FIGURE S3.—In model B, all females are less attracted to *AA* males, and hence all crosses involving *AA* males have a reduced weighting. The *A* allele is assumed to be additive in its effect, and so crosses involving *Aa* males also have reduced weight.

Assortative mating has a significantly greater effect on *Semele* spread when transgenic females are also less attracted to transgenic males; however the *Semele* allele is still very capable of spreading into the population. Figure S4A depicts the time-series dynamics of a *Semele* allele having a 10% fitness cost for a range of assortative mating strengths. In all cases, for a 76% transgenic release, the *Semele* allele spreads to a transgenic frequency of ~99% within 50 generations. However, increasing the assortative mating strength from 10% to 90% increases the release threshold by more than 30% and retards the spread of the *Semele* allele by more than 30 generations.

Figure S2D depicts release thresholds and equilibrium frequencies for a *Semele* allele associated with a range of fitness costs and assortative mating strengths. As for model A, assortative mating has no effect on the equilibrium frequency reached by the *Semele* allele; however, unlike for model A, assortative mating increases the release threshold by up to 47% regardless of fitness costs. These results suggest that strong assortative mating tendencies may require increased introduction frequencies if all females are less attracted to transgenic males; however, provided that the new release threshold is exceeded, the *Semele* allele will spread to the same equilibrium frequency in the population.

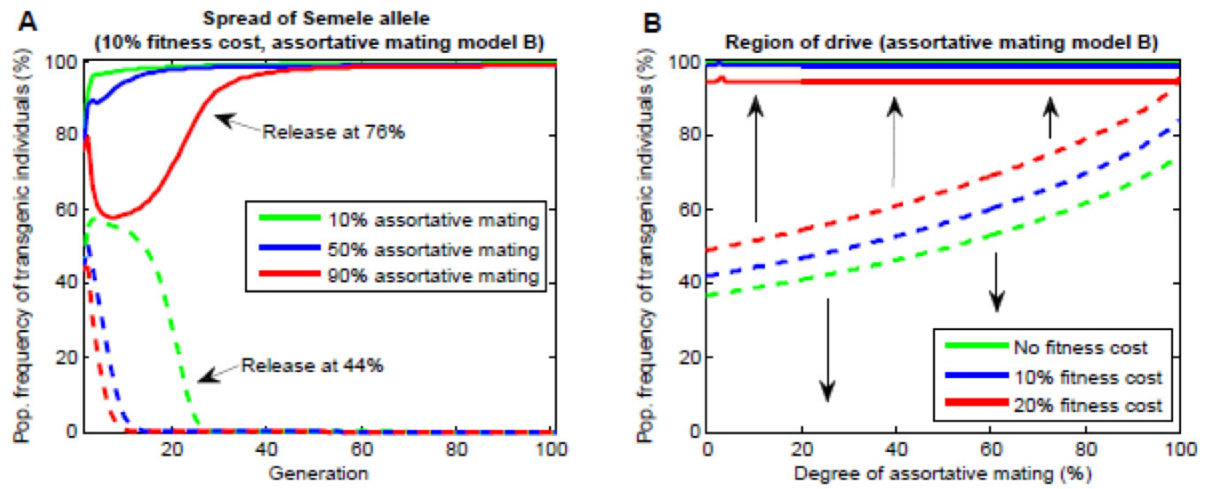


FIGURE S4.—Effects of an assortative mating allele, A , having the property that all females are less attracted to AA males (model B). A: Time-series dynamics of an element with a 10% fitness cost and a variety of assortative mating strengths. D: T allele release thresholds and equilibria for several fitness costs as a function of assortative mating strength. Assortative mating increases the T allele release threshold by up to 47%.

III. References:

Elaydi, S. N., 1995 An Introduction to Difference Equations. Springer, New York.

Jennings, H. S., 1917 The numerical results of diverse systems of breeding with respect to two pairs of characters, linked or independent, with special relation to the effect of linkage. *Genetics* **2**: 97-154.

Wright, S., 1920 Systems of mating. III. Assortative mating based on somatic resemblance. *Genetics* **6**: 144-161.