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Seirin Lee, S. ; Baker, R.E.; Gaffney, E.A.; White, S.M. 2013. **Modelling Aedes aegypti mosquito control via transgenic and sterile insect techniques: endemics and emerging outbreaks**. *Journal of Theoretical Biology*, 331. 78-90. 10.1016/j.jtbi.2013.04.014

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Modelling *Aedes aegypti* mosquito control via transgenic and sterile insect techniques: endemics and emerging outbreaks

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Abstract

The invasion of pest insects often changes or destroys a native ecosystem, and can result in food shortages and disease endemics. Issues such as the environmental effects of chemical control methods, the economic burden of maintaining control strategies and the risk of pest resistance still remain, and mosquito-borne diseases such as malaria and dengue fever prevail in many countries, infecting over 100 million worldwide in 2010. One environmentally friendly method for mosquito control is the Sterile Insect Technique (SIT). This species-specific method of insect control relies on the mass rearing, sterilization and release of large numbers of sterile insects. An alternative transgenic method is the Release of Insects carrying a Dominant Lethal (RIDL). Our objective is to consider contrasting control strategies for two invasive scenarios via SIT and RIDL: an endemic case and an emerging outbreak. We investigate how the release rate and size of release region influence both the potential for control success and the resources needed to achieve it, under a range of conditions and control strategies, and we discuss advantageous strategies with respect to reducing the release resources and strategy costs (in terms of control mosquito numbers) required to achieve complete eradication of wild-type mosquitoes.

Keywords: Biological control, *Aedes aegypti*, RIDL, SIT, transgenic insects.

1. Introduction

The history of pest control is as old as human agriculture or disease. The invasion of pest insects often changes or destroys a native ecosystem, and can result in food shortages and disease endemics. As a result, the development of biological control methods has received widespread attention and, in some cases, they have been successful (Benedict and Robinson 2003; Dyck et al. 2005; Vreysen et al. 2007). However, issues such as the environmental effects of chemical control methods, the economic burden of maintaining control strategies and the risk of pest resistance still remain, and mosquito-borne diseases such as Malaria and Dengue fever prevail in many countries

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in East Asia, South America and Africa, infecting over 100 million and killing at least half a million in 2010 (WHO 2012a,b,c). Furthermore, repeated invasions are observed in regions where the vector mosquitoes have been eradicated completely in the past. For example, *Aedes aegypti* and *Aedes albopictus* are observed in Northern European countries as well as Asia (Hulden and Hulden 2008; Paupy et al. 2012). Global warming and the human transportation system also promote such situations (Enserink 2010). As such, continued research into the development of better pest control methods remains vital (Dyck et al. 2005; Pimentel 2011).

One environmentally friendly alternative for mosquito control is the sterile insect technique, SIT (Knipling 1955). This species-specific method of insect control relies on the mass rearing, sterilization and release of large numbers of sterile insects, preferably males (Dyck, Hendrichs, and Robinson 2005), which, it is hoped, mate with wild-type insects, thereby reducing their reproductive output and, potentially, the pest population abundance (see Black et al. (2011) and Wilke et al. (2012) for recent reviews). Mixed-sex sterile releases are avoided where practical as they are generally less efficient and, for species such as mosquitoes, it is only the females that bite. This means that their release could potentially aid disease spread in the short-term (see Alphey et al. (2010) for a recent review).

Other transgenic technologies have recently been developed to improve SIT control (Benedict and Robinson 2003; Wimmer 2003; Alphey et al. 2010); these include genetic sexing (Robinson et al. 1999), genetic marking (Peloquin et al. 2000) and genetic female-specific lethality (Seawright et al. 1978). One such transgenic strategy is RIDL, i.e. "Release of Insects carrying a Dominant Lethal" (Thomas et al. 2000; Phuc et al. 2007). Here the released transgenic males are homozygous for a dominant lethal gene that is expressed in both male and female (bisex) progeny that result from mating with wild-type insects. Female-specific RIDL strategies have also been developed (Fu et al. 2010), but here we focus on bisex RIDL control strategies. Hereafter, we use the terms SIT and sterile to refer to early-acting lethality of the progeny of released insects, for example classical SIT using radiation-induced sterility, and the terms RIDL and transgenic to refer to late-acting lethality in both sexes.

We note also that the developmental stage at which the dominant lethal gene is expressed, for instance the embryonic or the larval stages, can have a substantial effect on the control strategy. In particular, late acting genes, which induce death after the density-dependent larval stage, have a significant advantage over SIT strategies because of an additional reduction in pest abundance that arises as a result of larval competition (Atkinson et al. 2007; Phuc et al. 2007; White et al. 2010).

The details of mosquito dispersal behaviour are not completely understood (Reiter et al. 1995; Harrington et al. 2005), though there have been mathematical modelling studies highlighting that *Ae. aegypti* invasion rates have a critical influence on the success of the control strategy (Lewis and Driessche 1993; Takahashi et al. 2004; Yakob et al. 2008; Magori et al. 2009; Seirin-Lee et al. 2013). Nonetheless, studies that explore the effects of *Ae. aegypti* invasive dynamics upon the efficacy of SIT and RIDL control strategies in eliminating mosquitoes are limited to those by Yakob et al. (2008) and Yakob and Bonsall (2009), which consider the interplay of stage structuring and dispersion on a lattice with a small control region that is embedded within an established pest population. These investigations a reveal complex dynamics and focus on the differences between SIT and RIDL control strategies for a very limited variation in spatial parameters, other than dispersal rates. However, firstly, it is not clear whether a strategy aimed at eliminating an

established pest is appropriate for eradicating an emergent, invading, outbreak. In addition, the influence of systematically varying the size of the region in which control insects are released is an aspect of spatially heterogeneous models that is essentially unexplored and merits detailed study, given the concern that spatial dynamics such as mosquito invasion is becoming a critical issue on global scale (Benedict et al. 2007; Jansen and Beebe 2010). Furthermore, such detailed investigations are facilitated in the continuum modelling approach considered here, which allows the ready prediction of scaling laws, as illustrated below for the influence of dispersal rates. More generally the continuum approach is typically an appropriate and efficient framework, and thus often advantageous, when the lengthscale and timescale under consideration are large compared to those describing the population's individuals.

Our objective is thus to consider control strategies for two control scenarios via SIT and RIDL: an endemic case and an emerging outbreak for a mosquito vector. In the former case, a mosquito vector is endemic. In contrast, in the latter case invading mosquitoes establish and cause a local outbreak in a previously mosquito-free region; see Fig 1. An important question is how such differences in the initial scenario induce different response to variations in control strategies with SIT and RIDL. In particular, we are concerned with how these responses are influenced by spatial parameters such as dispersal rates and especially the lengthscales of the regions in which control insects are released. Thus for the two contrasting scenarios, we investigate how varying the release rate in conjunction with the size of release region influence both the potential for control success and the resources needed to achieve it, in terms of control mosquito numbers, under a range of conditions. We thus discuss the relationships between the size of the control zone, the mosquito dispersal rate and advantageous strategies with respect to reducing control insect numbers and thus improving the strategy costs required to achieve eradication of mosquitoes. Finally, we briefly note that in the emerging outbreak case, we explore release efforts and strategy-costs with a control strategy that can *eradicate* the wild-type females. This is in distinct contrast to *halting* the spread of an outbreak using a barrier zone method of our previous study (Seirin-Lee et al. 2013).

2. Materials and Methods

2.1. Mathematical models

We build upon the temporal model of mosquito population dynamics developed by Dye (1984), which was validated on data for the larval and adult ecology of *Ae. aegypti* in Wat Samphaya, Bangkok, Thailand, published in Sheppard et al. (1969) and Southwood et al. (1972), and from unpublished reports of the World Health Organization's Aedes Research Unit (ARU) in Bangkok [*ibid*].

The densities of wild-type female mosquitoes and sterile/transgenic male mosquitoes at time t are respectively denoted by $N(t)$, $S(t)$. Following Dye (1984) we firstly assume that mosquito proliferation proceeds via a stage-structured process approximated by a delayed density-dependent mortality acting on a pre-adult developmental stage, reflecting larval competition. In addition, equal numbers of male and female wild-type mosquitoes are assumed, and it is taken that wild-type females mate in proportion to their relative abundance (Knipling 1955; Phuc et al. 2007), at a rate given by $N(t)/(N(t) + cS(t))$ where $0 < c \leq 1$ represents the reduced mating competitive ability of sterile male or transgenic male mosquitoes. We also impose the same per capita death rate, denoted μ below, for the female wild-type and male sterile/transgenic mosquitoes. In addition,

the control framework is modelled by the release of sterile or transgenic male mosquitoes at a constant rate, denoted $\kappa = \theta N^*$, where N^* is the control-free equilibrium density of wild-type mosquitoes and θ is defined as the release rate ratio.

By balancing mosquito numbers, these assumptions yield the following equations:

$$\begin{aligned} \frac{\mathrm{d}N(t)}{\mathrm{d}t} &= rN(t-T)\left(\frac{N(t-T)}{N(t-T)+cS(t-T)}\right)\Phi(t) - \mu N(t), \\ \frac{\mathrm{d}S(t)}{\mathrm{d}t} &= \kappa - \mu S(t). \end{aligned} \tag{1}$$

Here $\Phi(t)$ captures density-dependent competition in the larval stage, the delay time, T, represents the mosquito developmental time in the stage-structuring and, finally, the egg production rate per adult female is denoted by r and is multiplied by a corrective factor to account for futile matings with steriles and imperfect survival while reaching the adult stage.

The late-acting lethal induced by RIDL is anticipated to participate in larval competition and thus Φ is unaffected by the perturbations induced by such control strategies and hence is independent of transgenic mosquitoes. Following the classical insect population dynamics of Gurney et al. (1980), we therefore have

$$\Phi(t) = \exp\big[-\alpha E^{\beta} N^{\beta}(t-T)\big], \tag{2}$$

with RIDL control. Here β is a parameter representing the strength of density-dependent competition that facilitates fitting with field data, as detailed by Dye (1984). Note that α, E occur only in the parameter grouping αE^{β} and thus one cannot separate the interpretation of these two parameters. They are distinct here to maintain notational similarity with Dye's (1984) model formulation, where $1/\alpha$ is interpreted as the size at which the wild-type female mosquito population reproduces at maximum rate and E is the egg production rate of adult mosquitoes. Nonetheless, below we treat αE^{β} as a single parameter grouping.

For SIT, the matings with control mosquitoes do not give rise to any offspring, and thus larval competition is reduced in proportion to the number of futile matings. Hence, for SIT, we have (Phuc et al. 2007; White et al. 2010; Seirin-Lee et al. 2013)

$$\Phi(t) = \exp\left[-\alpha E^{\beta}\left(N(t-T)\left(\frac{N(t-T)}{N(t-T)+cS(t-T)}\right)\right)^{\beta}\right], \tag{3}$$

thus accounting for how the SIT interventions interfere with larval competition. The general extent to which such models concur with alternative representations of stage structure in mosquito dynamics, for instance the models based on the framework of Focks et al. (1993a,b) such as Erickson et al. (2010), is an open question that we do not address here.

We proceed to generalise the temporal model (1)–(3) to consider spatial dynamics in a one-dimensional homogeneous domain (See Fig. 1 for a schematic). The larvae are not motile and hence there is no dispersive kernel linking the stages of mosquito maturation, though the adults are taken to diffuse at constant rate. Hence, for $t > 0$ we have

$$\begin{aligned} \frac{\partial N(x,t)}{\partial t} &= D\frac{\partial^2 N(x,t)}{\partial x^2} + rN(x,t-T)\left(\frac{N(x,t-T)}{N(x,t-T)+cS(x,t-T)}\right)\Phi(x,t) - \mu N(x,t), \\ \frac{\partial S(x,t)}{\partial t} &= D\frac{\partial^2 S(x,t)}{\partial x^2} + \kappa(x) - \mu S(x,t), \end{aligned} \tag{4}$$

where $x \in \Omega$, the spatial domain, with D denoting the diffusion rate of both wild-type females and sterile/transgenic males. The competition term, $\Phi(x,t)$, is given by (2) or (3) by simply exchanging $S(t)$ and $N(t)$ for $S(x,t)$ and $N(x,t)$ respectively. We also assume the boundary of region Ω does not permit mosquito transport and thus we have zero flux boundary conditions,

$$\frac{\partial N}{\partial x} = \frac{\partial S}{\partial x} = 0, \qquad x \in \partial\Omega.$$

To model control strategies we consider the continuous release of sterile/transgenic males within the delivery region at a constant rate per unit length, θN^*, which defines θ given N^* denotes the control free equilibrium pest insect density. This is described in detail via the release function

$$\kappa(x) = \theta N^* \chi(x), \qquad \chi(x) = \begin{cases} 1 & x \in A \\ 0 & x \in \Omega \backslash A \end{cases}, \tag{5}$$

where A is the region of Ω in which sterile/transgenic males are released at rate θN^*. In Fig. 1, A becomes the interval $[\bar{x},\ \bar{x} + \gamma_s]$. We use this general functional form to explore two different scenarios and their respective control strategies.

2.2. Scenarios and control strategies

We consider two scenarios. The first is an *endemic* case in which female mosquitoes are widespread over an isolated region Ω, so that the width of the wild-type female habitat, γ_N, is equal to $|\Omega|$. The control is applied by releasing sterile/transgenic males locally within the region (Fig. 1(a)). The second scenario is an *emerging outbreak* case, in which female mosquitoes are invading a new environment. In this case, Ω is large enough so that $\gamma_N \ll |\Omega|$ (Fig. 1(b)). For both cases, control success will mean a complete eradication of wild-type female mosquitoes rather than just an invasion arrest or a decrease in pest population density.

2.2.1. Endemic outbreaks and the local release strategy

This scenario is described in Fig. 1(a) in detail and we call it the *local release strategy*. We assume that the female wild-type mosquito population has already approached carrying capacity in an isolated homogeneous region. The simplest control strategy for complete eradication in this scenario is the release of a sufficiently large number of sterile/transgenic males over the whole region, $\gamma_S = \gamma_N$, where γ_S is the width of the release region. The success of this control method can be explored in a straightforward manner via the temporal model, (1), because success depends only on the release rate of sterile/transgenic males per unit time. We obtain a minimal release ratio for complete eradication, as in Phuc et al. (2007) and Seirin-Lee et al. (2013). However, it is not clear how the minimal release ratios change when release is over only a portion of the region, $\gamma_S < \gamma_N$, nor how critically this ratio depends on the mosquito dispersal rate. Hence, we explore a measure of the resource cost required for the successful eradication of female mosquitoes, namely the product of the release region size and the release ratio, which below we refer to as the release effort, $[EF]_{loc}$. This measure therefore is the total number of released sterile/transgenic males per unit time, and is given mathematically by

$$[EF]_{loc} = \gamma_S \theta N^*. \tag{6}$$

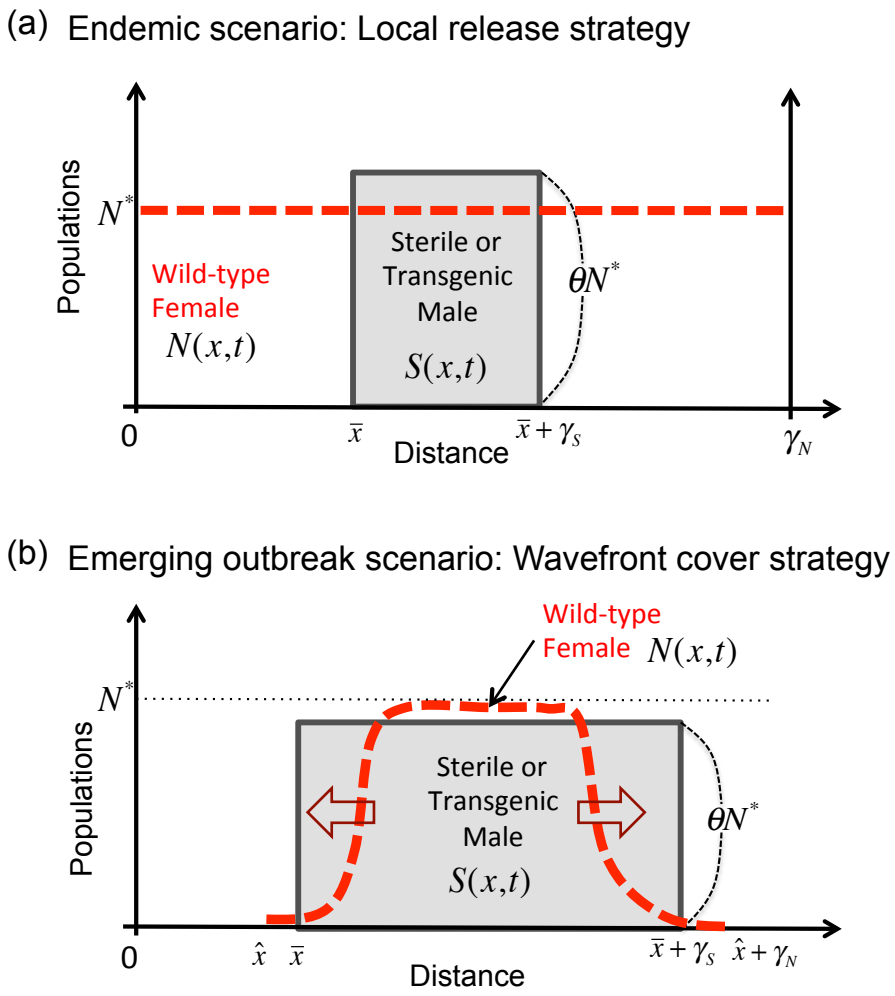

Figure 1: Control strategy scenarios. (a) Endemic case. Wild-type female mosquitoes are distributed uniformly on an isolated region and the sterile/transgenic male mosquitoes are released locally. (b) Emerging outbreak case. The wild-type female mosquitoes form a wave, invading pest-free territory in both directions, whose spatial variation can be determined from the solutions of the model in the absence of control. The spatial extent of this wave, denoted γ_N, requires a detection (or tolerance) threshold density, which is denoted by $\bar{\epsilon}$. Thus γ_N is the size of the region for which, at initial time, the mosquito density is above threshold, $N > \bar{\epsilon}$. In the model, the total spatial region considered is of size $|\Omega|$, with the assumption $|\Omega| \gg \gamma_N$. In attemptive control, the release region of the sterile/transgenic mosquitoes is denoted represented by the interval $[\bar{x},\ \bar{x}+\gamma_S]$.

As mentioned in the Introduction, the indefinite release of sterile/transgenic mosquitoes imposes a heavy economic burden, and hence we estimate the time to complete eradication, in particular because many of the insects involved are likely to be influenced either seasonally or by climate change (Purse et al. 2005; White et al. 2010). The time required for complete control will also be a very important issue in determining improved strategies. Thus we also define the strategy-cost as the product (release effort $\times$ time to eradication). Mathematically, this is given by

$$[SC]_{loc} = [EF]_{loc} \times T_{ex}, \tag{7}$$

where T_{ex} is the extinction time of the wild-type female mosquito population, which requires definition in terms of a tolerance (or detection threshold), characterised by ε below. In particular, T_{ex} is the smallest time such that whenever $t > T_{ex}$ we have,

$$\frac{1}{|\Omega|}\int_{\Omega}\frac{N(x,t)}{N^*}\,\mathrm{d}x < \varepsilon \ll 1. \tag{8}$$

Typically in our simulations we take $\varepsilon = 10^{-2}$. The strategy-cost is therefore the total number of sterile/transgenic males released up until effective eradication of the wild-type female mosquito population.

2.2.2. Emerging outbreaks and the wavefront cover strategy

In the modern era of developed human transport systems, the transmission of disease over several thousands of kilometres by vector insects is common (Shigesada and Kawasaki 1997; Enserink 2010). We expect, with a uniform environment, mosquitoes will disperse in a wave-like manner away from their initial site of invasion, with the population approaching its carrying capacity behind the wave. We suppose that sterile/transgenic males are released over a single region of length γ_S, as depicted in Fig. 1(b), which covers the invasive wavefront.

As a measure of cost resource, we define the release effort by

$$[EF]_{cov} = \frac{\gamma_S \theta N^*}{\gamma_N}, \tag{9}$$

where γ_N denotes the above-threshold region which wild-type female mosquitoes have invaded when control is initiated. Noting the invasive profile is unimodal, as depicted in Fig. 1(b), we have γ_N satisfies the constraint $N(\hat{x},0)/N^* = N(\hat{x}+\gamma_N,0)/N^* = \bar{\epsilon}$ where $\bar{\epsilon}$ is the threshold and thus an extremely small density (which the results are insensitive to).

However, note that γ_N is defined differently for parameter sets A and B in the numerical simulation, as these induce invasive waves with different spatial profiles. Thus the release effort function (9) has been defined per unit length and the release effort for an emerging outbreak (9) constitutes the average number of sterile/transgenic males released per unit time and per unit length of the initial above-threshold outbreak domain. With the extinction time given by (8) the strategy-cost is

$$[SC]_{cov} = [EF]_{cov} \times T_{ex} \times \gamma_N \ = \gamma_S \theta N^* \times T_{ex}, \tag{10}$$

which is the total number of sterile/transgenic males released during the control period.

2.3. Parameter values

As with many other studies (e.g. Phuc et al. (2007); Yakob et al. (2008); White et al. (2010)) we use Dye's (1984) estimates for the life-history parameter values for *Ae. aegypti*, which incorporate a range of values for the intrinsic birth rate, r, and the density-dependent coefficient, β. As presented in Table 1, we focus on two sets of parameters which represent the extremes of r and β (White et al. 2010; Seirin-Lee et al. 2013), with the grouping αE^{β} chosen so that the equilibrium density, N^*, is the same for each parameter set and of the order of one million mosquitoes per kilometre for the spatial models. The first parameter set, denoted A, has a lower intrinsic birth rate, r, in combination with weaker density-dependent competition, β, and gives rise to a stable equilibrium which is approached monotonically in the absence of control strategies. In contrast, parameter set B has substantially larger birth rate, r, and higher density-dependent competition, β, which induces overcompensating density-dependent competition, giving rise to oscillatory dynamics in an uncontrolled population for the spatially homogeneous model. This dynamics arises as a peak in the adult population results in an increase in reproduction, leading to competition and a subsequent drop in the following generation. Population recovery then follows as a result of a drop in competition.

These two parameter sets also result in very different predictions concerning the control of *Ae. aegypti* mosquitoes (see, for example, Phuc et al. (2007)). While SIT and RIDL control strategies give rise to similar results in decreasing the population wild-type female mosquitoes in the case of parameter set A, for parameter set B, a moderate release rate of sterile mosquitoes may undesirably increase the wild-type mosquito population due to a reduction in competition offsetting the reduced birth rate.

It should be noted that we take the density-dependence parameters from Dye (1984), following many previous studies. However, Legros et al. (2009) has called these values into question by using an alternative technique, and finding different values. The qualitative results that follow do not change for these alternative values and we detail this further in the Discussion and both parameter sets are considered given the uncertainty in their estimates. Also, in the absence of explicit empirical estimates for the diffusion rates of sterile or transgenic *Ae. aegypti* mosquitoes (Reiter et al. 1995; Harrington et al. 2005), we assume that the sterile/transgenic mosquitoes have the same diffusion rate as wild-type mosquitoes, and this is varied across a broad range, from hundreds of square meters per day to several square kilometres per day.

Recent studies in radiation dose optimisation has led to marked improvements in SIT in general, with some studies showing little competitive reduction from radiation (Mastrangelo et al. 2012; Oliva et al. 2012; Sow et al. 2012). Similarly, the mating competitiveness of genetically sterile RIDL male mosquitoes has been shown to comparable to that of their wild-type counterparts in semi-field conditions (Lee et al. 2013). Therefore we assume that, for both control strategies, the mating competition coefficient (c) is close to unity, reflecting a small fitness cost. An extensive investigation into this parameter can be found in White et al. (2010).

Note that, although we present numerical results with representative diffusion rates and the parameter sets in Table 1, simple parameter rescaling using nondimensionalisation leads to the same results for a three-dimensional family of parameter choices so that our results are not restricted to the parameters listed in Table 1. For instance the effect of variations in the parameter

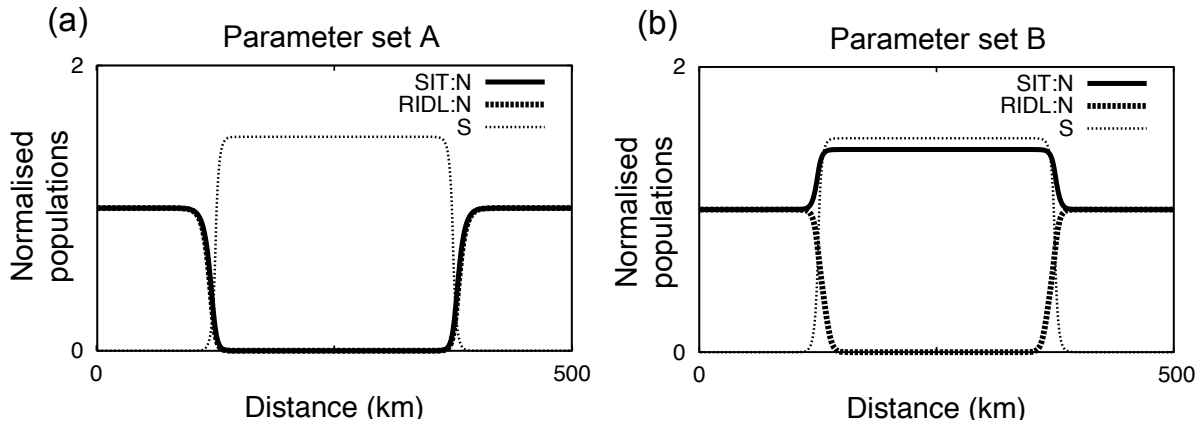

Figure 2: The effect of the local release strategy for an insufficient release of sterile/transgenic males. The wild-type female habitat size is $\gamma_N = 500$ km and the release region size is $\gamma_S = 250$ km. The release rate ratio, θ, is 1.5. The plots show the normalised female wild-type population and sterile/transgenic male population relative to the wild-type female equilibrium, N^*.

grouping αE^β can be inferred from the fact the model equations are invariant under the mapping

$$\alpha E^\beta \to (\alpha E^\beta)_1 = \frac{1}{\zeta^\beta}\alpha E^\beta, \quad N \to N_1 = \zeta N, \quad N^* \to N_1^* = \zeta N^*, \quad S \to S_1 = \zeta S.$$

Finally, a detailed numerical scheme for the model given by equations (4)–(5) is described in Appendix A.

3. Results

3.1. Endemic outbreaks and the local release strategy

We consider the local release strategy, asking two main questions: (i) To what extent does the dispersal rate affect the potential for eradicating female mosquitoes? (ii) If the local release strategy is effective, what is the minimal release region and how does it relate to the release rate ratio and dispersal rate? Our simulation results show that for some release regions and rates the local release strategy is not always successful in eradicating female wild-type mosquitoes (see Fig. 2). In particular, with parameter set B, application of a local release strategy using SITs in fact induces an increase in the total female population if the release rate is not large enough, as observed in spatially homogeneous modelling (Phuc et al. 2007). Below, we explore the relationship between duration for complete eradication, the release rate and the release region size, plus their influence in reducing resources, as measured via control mosquito numbers.

3.1.1. Minimal release region size for complete eradication

We denote the minimal release region size by γ_S^{min} and define it as the release region size at which we are able to achieve complete eradication for a given release rate ratio, θ. In order to find the minimal release region size required for complete eradication of female wild-type mosquitoes we plot, in Fig. 3(a), the threshold values of (γ_S, θ) at which female mosquitoes become extinct

Table 1: The values of (r, β) associated with parameter sets A and B have been chosen from the parameter ranges estimated by Dye (1984), as also used in other modelling investigations (Phuc et al. 2007; White et al. 2010). The parameter grouping αE^{β} for parameter set B has been fixed to ensure the same control-free equilibrium of approximately six million mosquitoes per kilometre.

Parameter /Variable	**Definition**	**Value**
N	Density/number of female wild-type mosquitoes	
S	Density/number of male sterile or transgenic mosquitoes	
Ω	Whole spatial region	500 km
γ_N	Width of wild-type females habitat†	(0, 500 km]
γ_S	Width of sterile/transgenic male release region	(0, 500 km]
D	Diffusion coefficient for mosquitoes	[0.01, 25] (km^2/day)
T	Mosquito development time	18.84 days
c	Coefficient of reduced mating competitive ability of sterile/ transgenic male mosquitoes	0.95
μ	Death rate of wild-type adult females	0.12 days^{-1}
κ	Release rate of control strategy males	θN^* days^{-1} ††
θ	Release rate ratio of control strategy males	(0, 20](days^{-1})
	Parameter set A	
r	Birth rate of adults corrected for egg to adult survival	0.367 days^{-1}
β	Density-dependent coefficient	0.302
αE^{β}	Density-dependent coefficient	0.01 ††
N^*	Control-free female mosquito equilibrium $([(1/\alpha)\ln(r/\mu)]^{1/\beta}/E)$	6.064×10^6 ††
	Parameter set B	
r	Birth rate of adults corrected for egg to adult survival	1.31 days^{-1}
β	Density-dependent coefficient	1.0
αE^{β}	Density-dependent coefficient	3.94×10^{-7} ††
N^*	Control-free female mosquito equilibrium	6.064×10^6 ††

† $\gamma_N = |\Omega|$ in the endemic scenario (Fig. 1(a)); γ_N is taken to satisfy

$$N(\hat{x}, 0)/N^* = N(\hat{x} + \gamma_N, 0)/N^* = \bar{\epsilon} \text{ such that } \bar{\epsilon} < O(1/N^*), \tag{11}$$

in the emerging outbreak scenario (Fig. 1(b)).

†† For the spatial model, this value is given with appropriate length units, i.e. per (km)$^{\beta}$ for αE^{β} and per km for N^*.

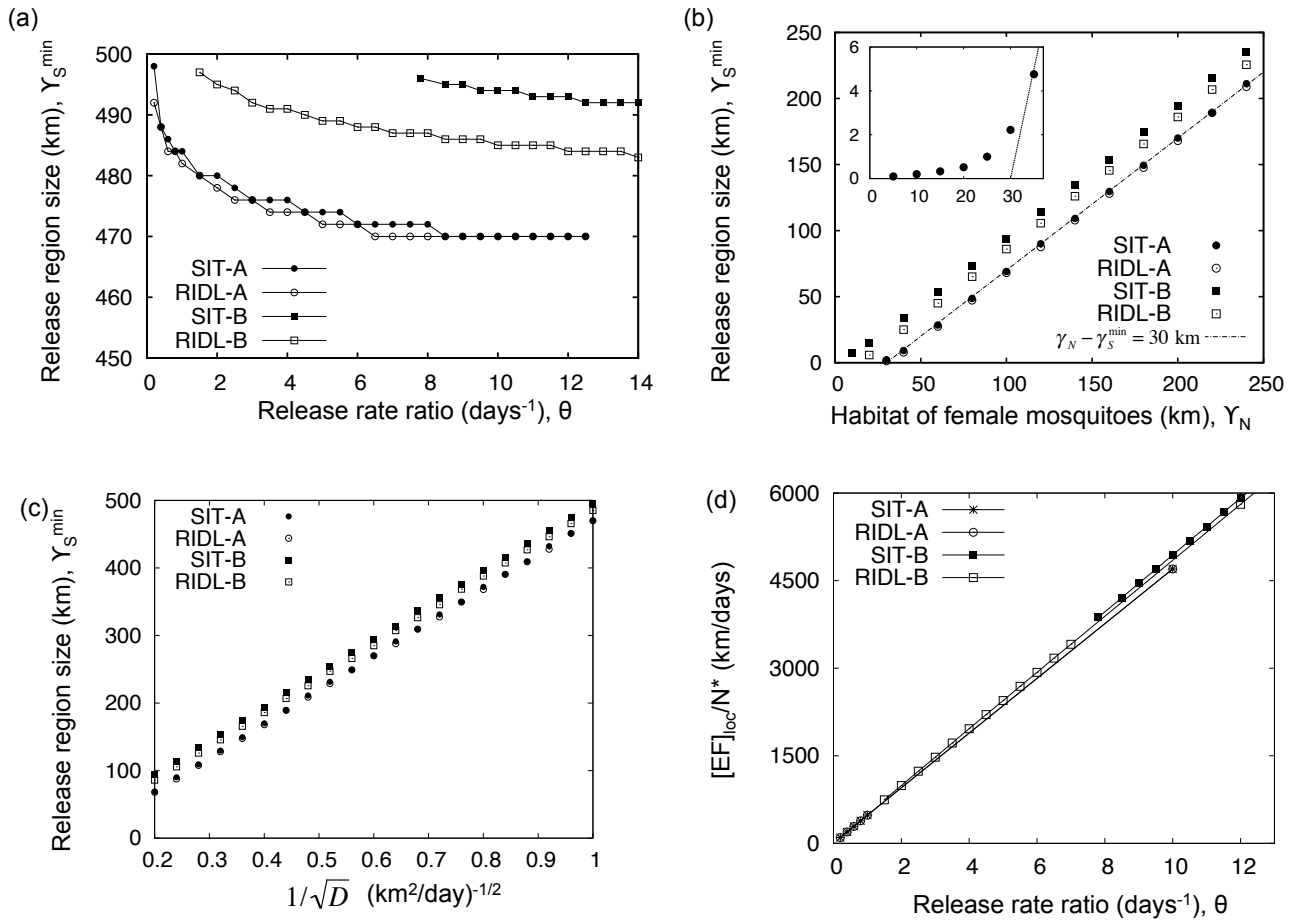

Figure 3: Minimal release region size and release effort for complete eradication using the local release strategy in the endemic scenario. For (b) and (c), the control release rate ratio, $\theta = 10$, is fixed. Diffusion rates are 1 km^2/day except for (c). SIT-A and RIDL-A imply parameter set A, and SIT-B and RIDL-B imply parameter set B. (a) The threshold curves for successful local release control strategies. The region above each curve is associated with control success, whilst below each curve corresponds to control failure, with levels of normalised release effort given by $[EF]_{loc}/N^* = \theta \times \gamma_S$. (b) The relation between the female habitat size, γ_N, and the minimal release region size γ_S^{min}. For parameter set A, $\gamma_N - \gamma_s^{min} \approx 30$ km in both SIT and RIDL for γ_N sufficiently large, with the small $\gamma_N < 35$ km behaviour illustrated for the SIT strategy in the inset and is analogous for RIDL. (c) The dependence of γ_S^{min} on diffusion rates for $\gamma_N = 500$ km. (d) The release effort as a function of release rate ratio, (6), while restricted to the curve $\gamma_s = \gamma_s^{min}$. The values for SIT-A and RIDL-A are very similar so that the points overlap. The release effort values in all cases increase monotonically.

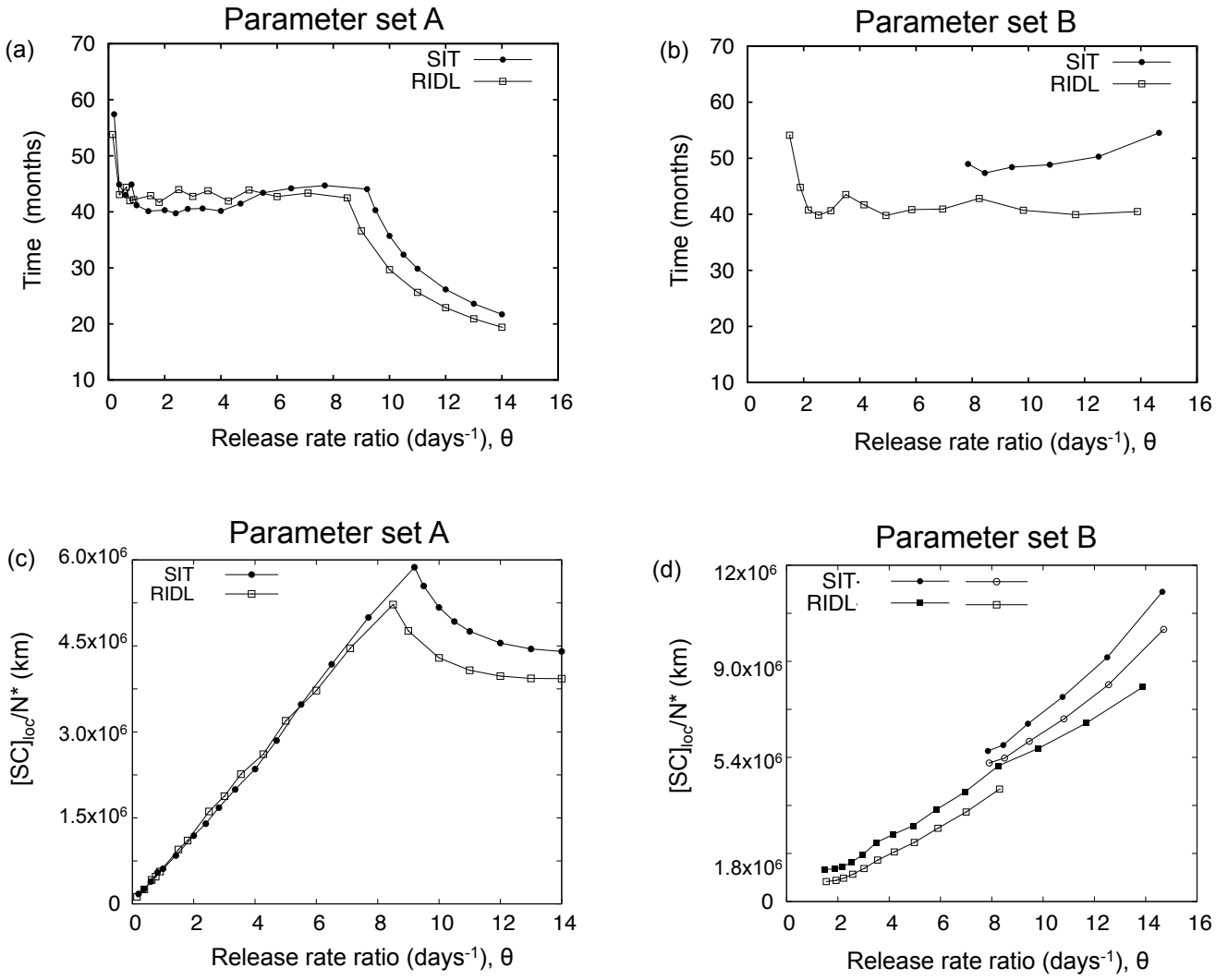

Figure 4: Extinction time and strategy-cost using the local release strategy in the endemic scenario. Diffusion rates are 1 km^2/day. $\gamma_s = \gamma_s^{min}$ here, given by Fig. 3(a). (a)–(b) Extinction time as measured by the equation (8) for data restricted to the curve $\gamma_s = \gamma_S^{min}$, Fig. 3(a). (c)–(d) The normalised strategy-cost $[SC]_{loc}/N^*$, where $[SC]_{loc}$ is given by equation (7), is plotted as a function of the release rate ratio. The white points (○, □) in (d) show how the strategy cost, $[SC]_{loc}$, sensitively changes with the size of the release rate ratio. The black points (●, ■) in (d) are calculated by the threshold values of (γ_S^{min}, θ) for complete eradication and each eradication time given in (b). The white points are calculated for these parameter values except that the release rate ratio is increased by a very small amount, 0.05.

throughout the entire habitat. Note that we have assumed in our calculations that complete eradication is achieved when the constraint (8) is satisfied.

Regardless of the control strategy and parameter choice, when the release rate ratio is small, the size of release region required for successful eradication of female mosquitoes depends sensitively on the release rate ratio. However, for large release rate ratios the minimum size of release region becomes insensitive to changes in the release rate, as shown in Fig. 3(a), although the size of release rate ratio at which this insensitivity arises, and the size of release region there, are dependent on the control strategy and parameters chosen.

We explore the dependence of the minimal release region size upon γ_N for a fixed release rate ratio in Fig. 3(b). The results highlight that the minimal release region size increases with female habitat size but, surprisingly, $\gamma_N - \gamma_S^{min}$ ($\stackrel{\text{def}}{=} \delta_{opt}$) is constant (approximately 30 km for parameter set A) when γ_N is sufficiently large; however, $\gamma_N - \gamma_S^{min}$ decreases and tends to zero as γ_N is reduced to zero. This enables us to suggest an intuitive result, that the local release strategy is more effective for a small habitat than a large one. For example, when the female habitat is very large, we need to release sterile/transgenic males over a very wide region to achieve eradication. In contrast, when the habitat is very close in size to δ_{opt} or less than it, release in a very small region compared to γ_N will be sufficient to eradicate the female population over the whole habitat. Furthermore, we note that this result is not highly sensitive to the choice of parameter set or control strategy.

The sensitivity of δ_{opt} to the diffusion rate is shown in Fig. 3(c) where we see the, again, intuitive result that γ_S^{min} decreases as the diffusion rate increases. Further, as detailed in Appendix B, a scaling relation exists for the variation of the minimal release region size with the diffusion rate:

$$\gamma_S^{min}(D) = \frac{\mathcal{C}}{\sqrt{D}} - \delta_{opt}, \tag{12}$$

where $\mathcal{C}$ is a constant given by $\mathcal{C} = \sqrt{D_0}\gamma_N^0$ with D_0, γ_N^0 denoting a fixed diffusion rate and habitat size of wild-type females, respectively. Since the choice of optimal release region is highly sensitive to the value of the diffusion rate, one would require careful experimental measurement of mosquito diffusion rates in order to be able to minimise the release effort. Nonetheless, the local release strategy is potentially applicable to small endemic regions, regardless of the parameter values and control method used.

3.1.2. Release effort and strategy-cost

In Fig. 3(d), we plot the release effort for each strategy and parameter set on restriction to the threshold curve, Fig. 3(a). Note that the minimal release effort is given at the minimal release rate ratio and the release effort increases monotonically as the release rate ratio increases, regardless of the choice of SIT and RIDL, or parameter set.

Further, the extinction time of the wild-type female mosquitoes at points (θ, γ_S^{min}) taken from Fig. 3(a) is fairly constant except for small release rate ratios or sufficiently large release rate ratios, as shown in Fig. 4(a), (b). The reason that the extinction time is almost constant for intermediate release rate ratios is that it is governed by the invasion timescale of the control mosquito for the domain, given γ_s^{min} is approximately constant. Once the minimal release region size, γ_S^{min}, becomes insensitive to increases in the release rate ratio (for example, around $\theta = 8.0$ in Fig. 4(a)), the extinction time decreases as the release rate ratio increases. This is because

the extinction time for wild-type females on $\Omega \backslash \gamma_S^{min}$ decreases as the number of sterile/transgenic males migrating into $\Omega \backslash \gamma_S^{min}$ increases, which is promoted when the sterile/transgenic males are released as quickly as possible. In contrast, with very small numbers of released males, a long time is required for the sterile males to reach each boundary of the female habitat, so that the eradication time of the females increases.

For smaller release rates, we obtain a monotonically increasing strategy-cost, $[SC]_{loc}$, as a function of the release rate ratio, as illustrated in Fig. 4(c). This is because the value of the release effort at small release rates is small enough to counteract the influence of any increase in extinction time in the strategy-cost, equation (7), so that the strategy-cost monotonically increases as a function of the release rate ratio, as shown in Fig. 4(c), (d). However, the strategy cost, $[SC]_{loc}$, slightly decreases around $\theta = 8.0$ because the extinction time decreases with a large release rate ratio, as shown in Fig. 4(a).

Although the strategy cost, $[SC]_{loc}$, decreases with reductions in the release rate ratio, θ, the eradication time is, in fact, sensitive to the fact we are working with the minimum release range, γ_S^{min} of Fig. 3(a). The white points ($\circ$, $\square$) in Fig. 4(d) illustrate this: the strategy cost, $[SC]_{loc}$, of the white points has been calculated with the extinction time for the same release range but a very slightly elevated release rate ratio compared to the black points ($\bullet$, $\blacksquare$). Obviously, the strategy-costs for the white points are smaller than the respective black points, a result of the decrease in T_{ex}. We thus can reduce strategy-costs by selecting higher release rate ratios than the threshold value, at which elimination just occurs.

3.1.3. Sensitivity of the surviving population of wild-type females to the diffusion rate and release rate ratio

In the endemic scenario, γ_N is always greater than γ_S so that if one does not choose the release region size greater than γ_S^{min}, complete eradication of wild-type female mosquitoes will not be achieved. However, one can still achieve local eradication, as shown in Fig. 2. In what follows, we explore how mosquito dispersal rates and release rates affect the decrease in the wild-type female population. The numerical results are shown in Fig. 5 where the average number of surviving wild-type female mosquitoes is plotted as a function of both the mosquito dispersal rate and release rate ratio. The former has a negligible effect when the release rate is small. In contrast, for a large enough release rate and parameter set A, we see that an increase in the dispersal rate causes a decrease in the new population equilibrium. This is because the dispersion of sterile/transgenic mosquitoes to outlying regions increases, though such an effect is negligible for diffusion rates on the order of hundreds m^2/day. For parameter set B, an insufficient number of sterile males using SITs can lead to an increase in the female population as diffusion rates are increased (see Fig. 5(c)). This is consistent with the results of the discrete model formulated by Yakob et al. (2008). In Fig. 5(d), we find that the RIDL method has a clear switch around $\theta = 1.0$ but the average fraction of surviving wild-type females is not sensitive to the release rate ratio for a given diffusion rate.

3.2. Emerging outbreaks and the wavefront cover strategy

One finds four kinds of representative dynamics, determined by the release rate ratio, θ. Fig. 6 illustrates results for SIT controls, whilst RIDL controls exhibit similar dynamics, except for the absence of an increase in the wild-type female population observed in Fig. 6(b), (c).

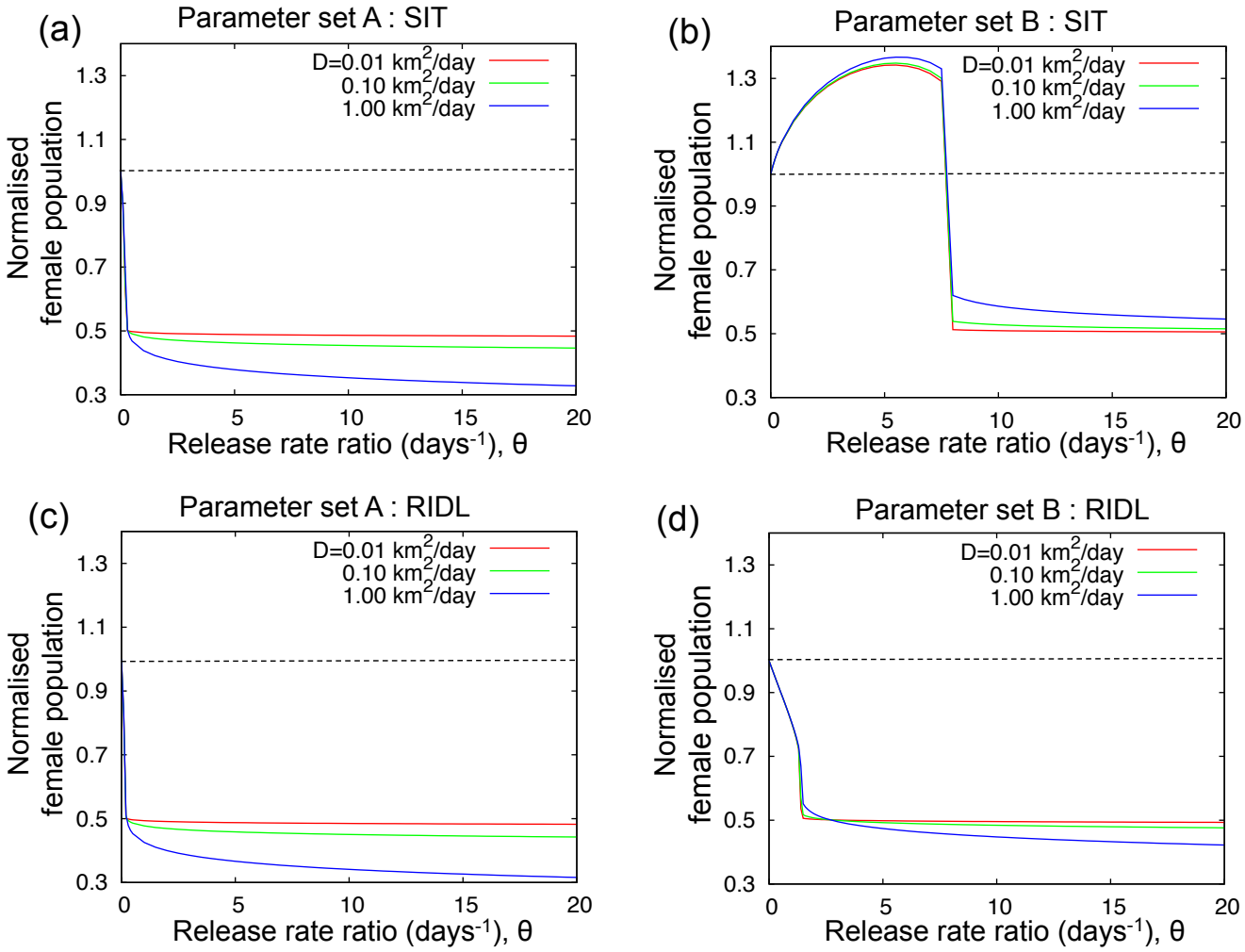

Figure 5: Average fraction of surviving wild-type females for different diffusion rates and release rate ratio with $\gamma_N = 500$ km and $\gamma_S = 250$ km, whereby eradication is not feasible. The plots give the normalised equilibrium female wild-type population in terms of θ, the control release rate ratio. The dotted line indicates 1.0 which is the normalised equilibrium population of female mosquitoes before control.

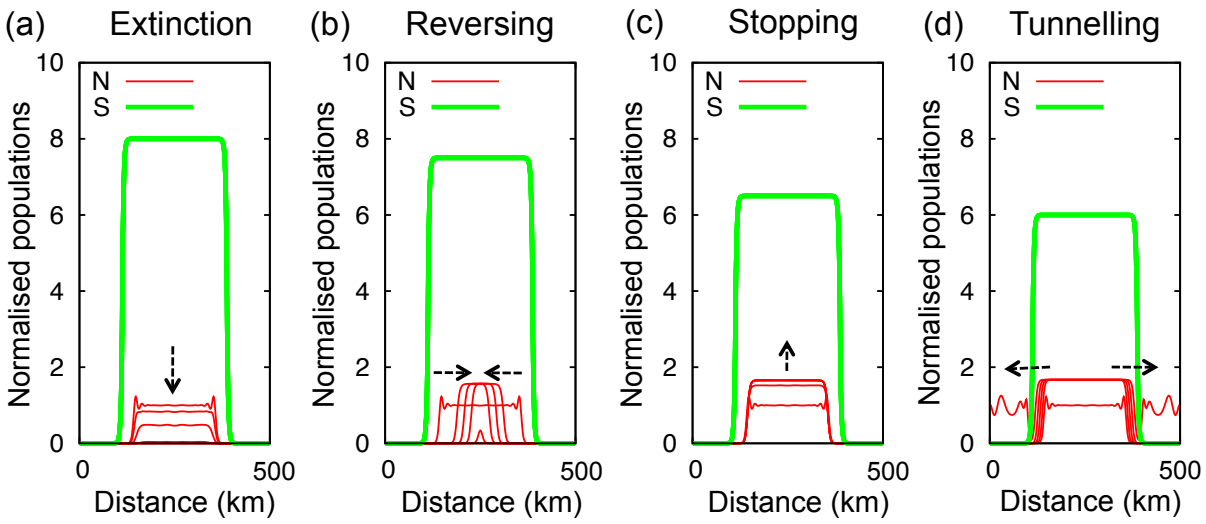

Figure 6: Control success/fail scenarios for the emerging outbreak scenario. (a)–(d) plot representative cases for the SIT method with parameter set B. Similar dynamics are observed for the other parameter set or RIDL except that local increases in female density are not observed in cases (b), (c). $D = 1$ km^2/day. The initial value of γ_N in the numerical simulations is 325.5 km and is obtained from equation (11). The release region size, γ_S, is 275 km and the release rate ratio, θ, is varied. (a) $\theta = 8.0$: the female population decreases monotonically over the habitat. (b) $\theta = 7.5$: the wave of females reverses direction and the wild-type female population becomes extinct. (c) $\theta = 6.5$: the female population increases over the habitat so that the control fails locally but succeeds in blocking dispersion of the female mosquitoes. (d) $\theta = 6.0$: not only does the wild-type female population increase but also the wave escapes the control region and control fails completely.

In Fig. 6(a) a sufficiently large release rate ratio drives the wave of wild-type female mosquitoes extinct before it can extensively disperse outside of the sterile male release region, and successful control is established. In (b), with a decrease in the release rate ratio, the invading wave of female mosquitoes reverses its direction of travel (i.e. the infested region contracts) and eventually the population becomes, again, extinct, though the wild-type female population size increases on reversal using SIT with parameter set B. In (c), in contrast, the wave of female mosquitoes ceases contraction and, in the SIT case, the female population increases. Eradication is not achieved. Finally, in (d), with a further decrease in the release rate ratio we see that the female population wave is able to invade through the boundaries of the control region and eventually occupy the entire habitat. In cases (a) and (b), control is successful but in the cases (c) and (d), control fails. In what follows, we explore optimal strategies for control success.

3.2.1. Minimal release region size needed for complete eradication

Fig. 7 shows that the values of $(\theta, \gamma_S^{min}/\gamma_N)$ are not sensitive to the choice of SIT or RIDL methods. For both parameter sets A and B, the variation in γ_S^{min}/γ_N is very small for $\theta \in [0, 10]$. This implies that the minimal release region size, γ_S^{min}, varies only within several kilometres on a dimensional scale. Hence, the sensitivity of the minimal release region size to the release rate ratio is much less than in the case of the local release strategy. Such insensitivity is observed regardless of diffusion rates (results not shown). Since γ_S^{min} converges to a constant value as the release rate

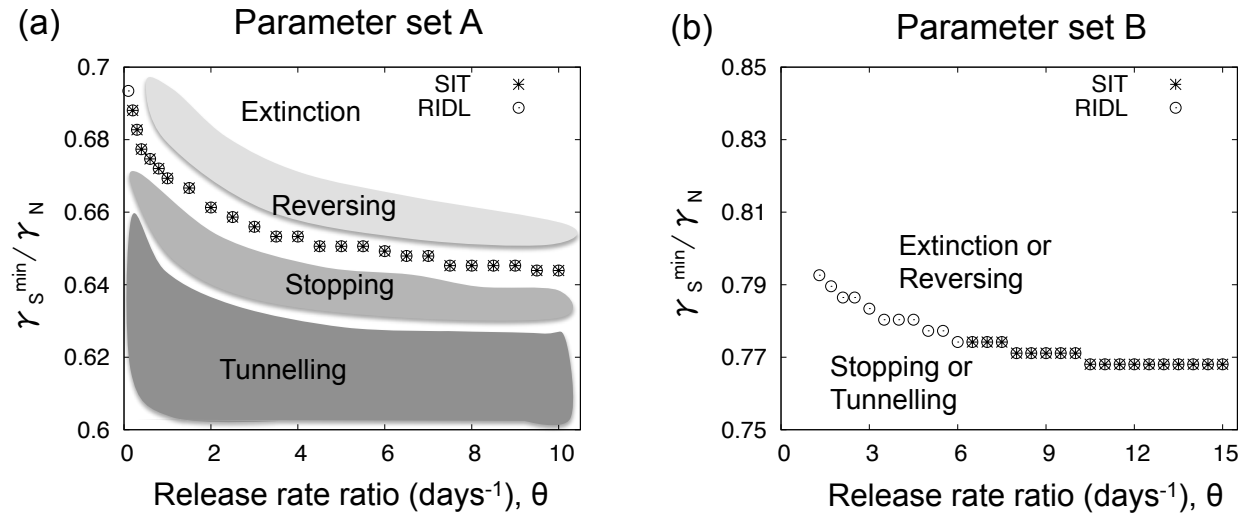

Figure 7: Wavefront cover strategy in the emerging outbreak scenario. Release rate ratio and relative release region size for complete eradication of the wild-type female mosquitoes. The threshold curve indicates successful control strategies. Above the curve control is successful and below the curve control fails. In (a), the parameter regions for the four representative dynamics of Fig. 6 are sketched. Similar parameter regions are also obtained in the case of parameter set B (details not shown). $D = 1$ km^2/day, $\gamma_N = 373.5$ km in (a) and $\gamma_N = 325.5$ km in (b). For numerical simulations, we calculate γ_N using equation (11). As we take very small values for $\bar{\epsilon}$ in (11), the value of γ_N used in our result is usually larger than γ_S^{min} so that γ_S^{min}/γ_N is less than 1.

ratio increases, once γ_S is less than the threshold of γ_S^{min}, the sterile/transgenic males always fail to impede the female wild-type wave, even for large release rate ratios. However, if $\gamma_S > \gamma_S^{min}$, the release rate ratio critically influences the dynamics of the wild-type females, as shown in Fig. 6 and the parameter region sketches of Fig. 7, and it determines the extent of control success.

In contrast to the results for the local release strategy, shown in Fig. 3(a), the threshold requirement of complete eradication for either the SIT or RIDL strategy induces relatively small changes in the minimal release region size even for parameter set B (Fig. 7(b)). In particular, the female wild-type population in the local release strategy for the endemic scenario remains at high levels and the density-dependency impacts strongly at the edges of the released sterile/transgenic male zone inducing different minimal release region sizes not only between SIT and RIDL but also between parameter sets. However, for wavefront covering strategies both edges of the female wild-type wave have low population density so that the effect of the density-dependence is slight, explaining the similarity of the behaviour of the SIT and RIDL strategies here.

3.2.2. Time to extinction and release rate ratio

In Fig. 8, we show the dependence of extinction time upon release rate ratio, given a sufficiently large and fixed release region size, γ_S. Since the extinction time is not measured precisely in the deterministic model, we define the extinction time for the female mosquitoes to be the minimal time satisfying equation (8). As expected, and also observed in a spatially homogeneous study by Atkinson et al. (2007), this eradication time increases drastically as the release rate ratio reduces towards the threshold. Indeed, for a release rate ratio on the order of the threshold value, and an eradication time of several years is predicted (Fig. 8(a),(c)). In contrast, release rate

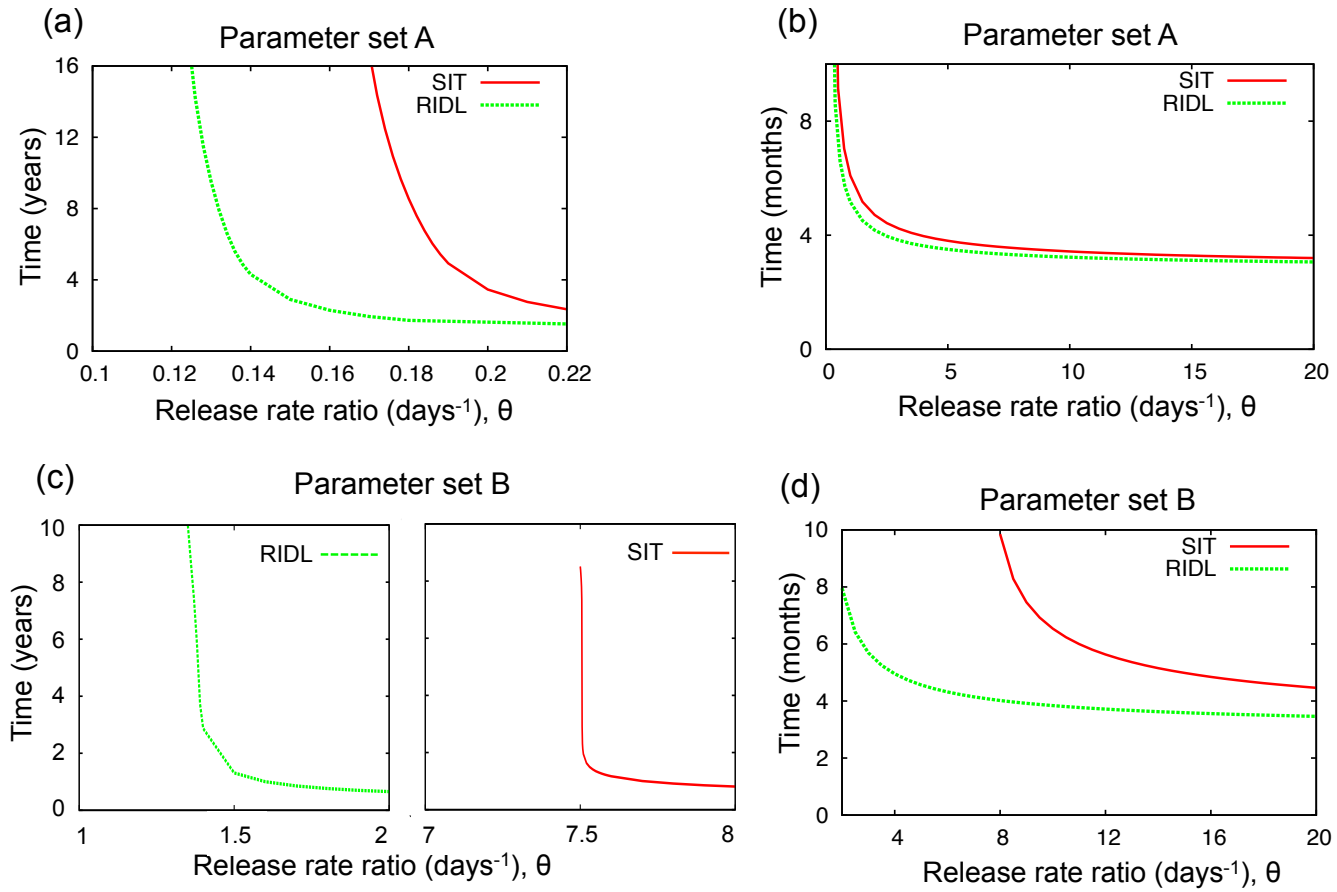

Figure 8: The dependence of extinction time on release rate ratio using the wavefront cover strategy in the emerging outbreak scenario given a fixed release region, γ_s, above γ_s^{min} for all θ. The diffusion constant is $D = 1$ km^2/day. When the release rate ratio is small, the extinction time shows extreme sensitivity to the choice of control method. (a)–(b): Parameter set A. (c)–(d): Parameter set B.

ratios significantly higher than threshold can reduce the time to extinction to the order of months (Fig. 8(b),(d)). Such predictions of the temporal dynamics can be made regardless of the choice of parameters or SIT/RIDL strategies. Nevertheless, the threshold release rate ratio for the RIDL technique is less than for SIT and RIDL always offers faster eradication, especially near threshold.

3.2.3. Release effort and strategy-cost

Before discussing results, we note that $[EF]_{cov}$ and $[SC]_{cov}$ given by equations (9) and (10), respectively, depend on the initial size of the female mosquito wave, γ_N, which is determined slightly differently depending on parameter sets A and B because the initial size of the wild-type female wave is given by simulation data for an invasive wave, using equation (4) with $S(x,t) \equiv 0$. This differs between parameter sets A and B. Thus, strictly, we cannot use these two strategy measures directly for comparing the influence of the choice of parameter set. However, these two measurements are effective for exploring the effectiveness of SIT or RIDL using the same parameter set.

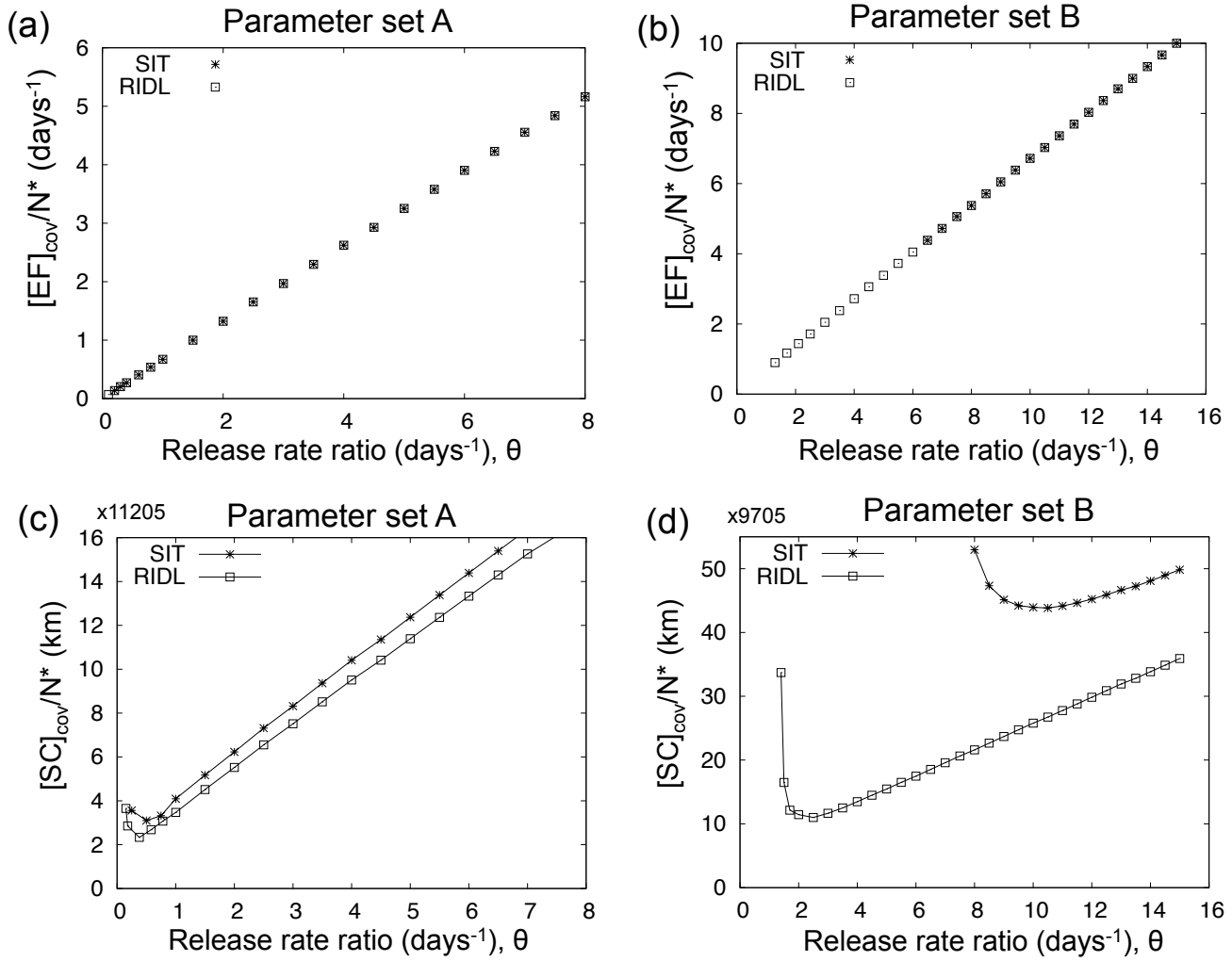

Figure 9: Release effort and strategy-cost values. The diffusion rate is $D = 1$ km^2/day and the release region is the same as Fig 8, and thus fixed above γ_s^{min} for all θ. (a)–(b) are the release effort values as a function of release rate ratio, and (c)–(d) are the strategy cost values, as given by (10), for varying release rate ratio, θ

In Fig. 9 we present the results of a more detailed exploration of the release effort and strategy-cost for a fixed domain size γ_s, in excess of γ_s^{min} for all release rates considered. The minimal effort values are subsequently given by the minimal release rate ratio regardless of the choice of SIT/RIDL strategies or parameter sets. Furthermore, as expected from Fig. 7, the release efforts using SIT and RIDL are identical. Nonetheless, we see non-trivial results for the strategy-cost, $[SC]_{cov}$, as shown in Fig. 9(c)–(d). Note the eradication time decreases very rapidly once the release rate ratio is increased above the minimal release rate ratio required for complete eradication for the fixed value of γ_s used; furthermore, it becomes a constant as the release rate ratio increases, as shown in Fig. 8. Therefore, the minimal value of strategy-cost exists not at the minimal release rate ratio but at a slightly larger value than the minimum, and it increases monotonically as the release rate ratio is further increased.

In general, the extinction time will decrease if we take a small initial size, γ_N. This means that

$[SC]_{cov}$ is dependent on γ_N and will decrease for smaller initial values of γ_N. Obviously, an earlier initiation of a control strategy will be economically beneficial in the emerging outbreak scenario.

4. Discussion

When the release region of sterile/transgenic insects is sufficiently large, a temporal model for sterile/transgenic technologies may be enough to understand the potential for controlling pest insect populations. However, in practical situations this requires the release of sterile or transgenic insects over a long lengthscale, and therefore results in a heavy economic burden (Vreysen et al. 2007). Thus we are interested in finding the minimal value of the release region size, the release rate ratio (i.e. the number of sterile/transgenic males released per unit time) and time required for complete eradication. In particular, the minimal release region size is likely to be affected by the dispersal rate of the mosquitoes (Seirin-Lee et al. 2013). Thus a temporal model is insufficient and spatial models must be investigated carefully for a given invasion scenario. In addition, though an immediate difficulty in modelling studies is determining the levels of insect dispersal, with very limited empirical data and, potentially, a very wide range of estimates (Reiter et al. 1995; Harrington et al. 2005), a simple rescaling analysis can be used to account for the influence of dispersion in our modelling study, as illustrated in Appendix B.

In the first scenario where the wild-type female mosquitoes are endemic, our study demonstrates that sterile/transgenic males released locally in the habitat of the wild-type female mosquitoes can eradicate the vector insects completely with a larger size of release region. Nonetheless such a local release strategy easily fails if the diffusion rate of sterile/transgenic males is not high enough to ensure dispersal over the entire habitat. This result is consistent with those of a previous discrete model (Yakob et al. 2008).

Furthermore, our theoretical observations suggest that the local strategy is likely to be more applicable in a small region rather than a wide region because $\delta^{opt} = \gamma_N - \gamma_S^{min}$ is determined independently of γ_N but depends on the diffusion rate. Furthermore, this difference in the size of the minimal release region relative to the region containing the established pest is predicted to be substantially larger than one might expect from the diffusive scale and the timescale of either mosquito reproduction or death. Hence a local release strategy is predicted to be more readily applicable than one might initially anticipate from the scales of mosquito population dynamics. Nonetheless, in the local release strategy, the mosquito diffusion rate is a critical parameter in determining the optimal release region size, though the relation is a simple scaling law that can be readily predicted (see Appendix B). In turn, this means that one must carefully estimate mosquito dispersal rates in order to reduce control costs. Finally, we note that minimal overall strategy costs, in terms of total released mosquito numbers, are not minimised at the threshold of mosquito extinction, as shown in Fig. 4(d). Hence, increases in the release efforts, i.e. the unit time rate of release of control insects, can reduce the overall strategy cost regardless of the influence of spatial heterogeneity.

In the emerging outbreak scenario, our modelling study shows that several possible types of dynamics, depending on the release rate of sterile/transgenic males. However, the population dynamics is relatively insensitive to the release region size once the latter is larger than γ_S^{min} for all release rates. Furthermore, control interventions with a smaller strategy-cost do not always correspond to values of (γ_S, θ) that induce smaller release efforts. This demonstrates that a longer

term picture, also considering eradication times, is required for efficient interventions aimed at eradicating an emerging outbreak.

The detailed requirements for inducing cost effective controls are predicted to differ with these two scenarios of a stable endemic and an emerging outbreak. For the endemic, the mosquito diffusion rate critically influences the minimal release region size for complete eradication. In contrast, control success is not highly sensitive to the diffusion coefficient for an emerging outbreak; instead the release rate ratio is an important and relatively sensitive parameter in determining the dynamics of the wild-type female wave.

Observations of the improved outcomes associated with RIDL strategies are inherited from the temporal model dynamics. In particular, once the suppression of larval competition by SIT interventions induces dynamically significant effects, as with parameter set B, RIDL strategies are substantially more effective in almost all aspects of control. Consequently, the typical conclusions that RIDL interventions are superior to SIT as a result of previous modelling (Atkinson et al. 2007; Phuc et al. 2007; White et al. 2010) do transfer in the context of local release and wavefront cover strategies. Similarly, local increases in pest populations can be associated with a SIT local release strategy or wavefront cover strategy, as observed in other contexts with overcompensating density-dependent competition (as in parameter set B) (Yakob et al. 2008; Yakob and Bonsall 2009). These conclusions hinge on the fact that SITs reduce larval populations, enhancing the survival of insects resulting from wild-type matings and thus offsetting the reductions in proliferation. Thus RIDL strategies are never inferior in either control scenario considered. Nonetheless, once the release rate is chosen sufficiently large, both SIT and RIDL perform similarly for wavefront cover strategies with either parameter set, indicating the governing dynamics of the model is then driven by the wild-type wavefront, where larval competition is minimal. This is in distinct contrast to predictions for control strategies designed to act as barriers to prevent the spread of mosquitoes into a pest-free region from an endemic area; here RIDL is predicted to be significantly superior (Seirin-Lee et al. 2013), highlighting that the control strategies are highly context dependent.

The timescale for a vector insect to become extinct is critical in terms of preventing a pandemic disease in a human society (Atkinson et al. 2007) and its increases are likely to induce serious fluctuations in insect populations by combining with external effects such as seasonality (Purse et al. 2005; Altizer et al. 2006; Yang et al. 2009; White et al. 2010). Large timescales are observed, in a spatially homogeneous modelling study on approaching the extinction threshold, by Atkinson et al. (2007) and we have analogous observations in our spatially heterogeneous setting. Thus, although a low release rate reduces the production costs of sterile/transgenic mosquitoes, it is also likely to be difficult to estimate or confirm control success in a situation where several years are required for eradication. Such long extinction times also drive our observation that the strategic cost illustrated in Fig. 9(d) for the emerging case has a local minimum, further reflecting the need to consider the longer term picture when designing interventions.

Throughout this manuscript, we have used fecundity and density-dependence parameter values based upon Dye (1984), concentrating on the extreme best and worst case scenarios, following previous approaches (Phuc et al. 2007; Yakob et al. 2008; White et al. 2010; Seirin-Lee et al. 2013). These parameters are derived from field data to which a simple regression is used to obtain the values. Legros et al. (2009) questioned this method and used a two-stage fitting method. They concluded that for their method a) when density-independent processes are taken into consideration they account for a large part of the mortality of immature stages and density-

dependence is much weaker than the Dye approach, b) the functional responses of the two approaches are significantly different for the range of densities in the study, and c) whilst both methods give reasonable accounts of the "characteristics of density-dependence", they deviate when low densities are concerned, primarily due to the lack of data. Hence, it is critical that full life-table analyses are conducted in order to ensure that suitable estimates of these, and other (e.g. development periods, dispersal distances, differential density-dependent coefficients throughout the larval stages), life-history parameters be calculated, and at a local scale. For example, it has recently been shown that the dispersal ability of two lines of RIDL *Ae. aegypti* mosquitoes may be reduced compared to their wild-type counterparts in laboratory conditions (Bargielowski et al. 2012). This is likely to have an impact of the effectiveness of barrier zone techniques for population control. However, the difference in diffusion rates of the transgenic and wild-type mosquitoes is likely to add greater model complexity (Billingham and King 2001). Furthermore, since it is likely that many additional biotic and abiotic factors may dynamically influence the life-histories of *Ae. aegypti* populations, both spatially and temporally (e.g. seasonality), further fine-tuning of control strategies will require these factors to be explicitly modelled. Extensions to our modelling approach could be adopted to incorporate these processes, but alternative approaches may also yield informative results, such as simulation models (e.g. Focks et al. (1993a,b)), additionally motivating a comparative study of differing modelling formulations.

In summary, the dispersion of mosquitoes appears in various invasive scenarios and our modelling study suggests successful control strategies for each scenario. Our results show that the requirements for understanding control effectiveness and efficient control strategy vary depending on the invasive and endemic scenario. Furthermore, SIT control is never more effective though the difference between RIDL and SIT strategies can be weak in the emerging outbreak strategy as the dynamics is dictated by the wavefront where competition is weak. Finally, we note the long term picture is important in considering controls, due to the sensitivity of the extinction time for instance.

Finally, although the focus of our models is the mosquito, *Ae. aegypti*, which can spread yellow fever, dengue fever and Chikungunya disease, our modelling approach and results can be applied more broadly to other species. A further generalisation would be the consideration of more realistic measures of economic cost rather than ones based on simply mosquito numbers. In addition, a pulsed releasing schedule for sterile/transgenic mosquitoes may be more pragmatic and thus merits study, generalising the spatially homogeneous study of White et al. (2010). This is in progress, along with comparing whether and when modelling predictions are sensitive to the detailed representation of stage structure, for example contrasting models built on Dye's (1984) delay formulation on the one hand and ordinary differential equation representations of stage structure on the other (Focks et al. 1993a,b; Erickson et al. 2010). Questions concerning higher dimensional geometries are also relevant, including smaller scale, three-dimensional models in high-rise buildings' water tanks. In general the eikonal approximation indicates that the local behaviour of wavefronts possess a curvature correction, which is sufficient to stabilise perturbations of a planar wave as well offering the prospect of complex global spatial dynamics such as spiral and scroll waves (Grindrod 1991); whether such behaviours exist in mosquito models is a further open question.

Acknowledgements

S.S.L. was partially funded by the Japan Society for the Promotion of Science (JSPS Excellent Young Researcher Overseas Visit Program and Grant-in-Aid for JSPS Young Researcher). This publication was based on work supported in part by Award No KUK-C1-013-04, made by King Abdullah University of Science and Technology (KAUST).

Appendix A. Numerical method

The reaction-diffusion systems formulated in this paper were solved numerically via standard techniques, which can readily accommodate the time delay; in particular the kinetics are considered explicitly within a standard, fully implicit, finite difference treatment of the parabolic transport term (Morton and Mayers 1994). In particular, storing the history of the system for the duration of the time delay allows the generation of the kinetic terms within the numerical algorithm. A fully implicit treatment of the diffusive terms then generates a set of linear algebraic equations for the mosquito populations at each new timepoint, which may be solved using a choice of numerical techniques; we use an LU-decomposition. This numerical algorithm has been validated against independent code simulations, used in Seirin-Lee et al. (2010), and we have checked timestep and grid spacing refinements do not influence the results presented.

Appendix B. Minimal release region size and diffusion rates

To explore the effects of diffusion rate in the model we use a scaling argument. Let D_{ndim} be a non-dimensionalised diffusion coefficient and define an arbitrary diffusion rate

$$D = kD_0, \tag{B.1}$$

for a given diffusion rate D_0 and arbitrary positive constant k. Then for a time scale T and a given spatial length γ_N^0, we have

$$D_{ndim} = \frac{DT}{(\gamma_N^0)^2} = \frac{kD_0T}{(\gamma_N^0)^2} = \frac{D_0T}{\left(\frac{\gamma_N^0}{\sqrt{k}}\right)^2}.$$

From the above equation, we set a female habitat size, γ_N, to be an arbitrary value by taking

$$\gamma_N = \gamma_N^0/\sqrt{k}, \tag{B.2}$$

instead of choosing the diffusion rates arbitrarily.

On the one hand, from Fig. 3(b) we know the optimal release region size, δ_{opt}, is independent of the spatial length scale so that it is also independent of the diffusion rate. That is, we have

$$\delta_{opt} = \gamma_N(D) - \gamma_S^{opt}(D). \tag{B.3}$$

Hence, we obtain the relationship between the diffusion rate and the optimal release region size directly from equations (B.1), (B.2) and (B.3), as

$$\gamma_S^{opt}(D) = \gamma_N(D) - \delta_{opt} = \frac{\gamma_N^0}{\sqrt{k}} - \delta_{opt} = \frac{\sqrt{D_0}\gamma_N^0}{\sqrt{D}} - \delta_{opt}.$$

In Fig. 3(c), $D_0 = 1\text{km}^2/\text{day}$, $\gamma_N^0 = 500$ km and $\delta_{opt} = 30$ km have been chosen.

References

Alphey, L., Benedict, M. Q., Bellini, R., Clark, G. G., Dame, D., Service, M., Dobson, S., 2010. Sterile-insect methods for control of mosquito-borne diseases: An analysis. Vector-Borne and Zoonotic Diseases 10, 295–311.

Altizer, S., Dobson, A., Hosseini, P., Hudson, P., Pascual, M., Rohani, P., 2006. Seasonality and the dynamics of infectious diseases. Ecology Letters 9, 467–484.

Atkinson, M. P., Su, Z., Alphey, N., Alphey, L. S., Coleman, P. G., Wein, L. M., 2007. Analyzing the control of mosquito-borne diseases by a dominant lethal genetic system. Proceedings of the National Academy of Sciences 104 (2), 9540–9545.

Bargielowski, I., Kaufmann, C., Alphey, L., Reiter, P., Koella, J., 2012. Flight performance and teneral energy reserves of two genetically-modified and one wild-type strain of the yellow fever mosquito *Aedes aegypti*. Vector-Borne and Zoonotic Diseases 12 (12), 1053–1058.

Benedict, M. Q., Levine, R. S., Hawley, W. A., Lounibos, L. P., 2007. Spread of the tiger: Global risk of invasion by the mosquito *Aedes albopictus*. Vector-born and Zoonotic Diseases 7, 76–85.

Benedict, M. Q., Robinson, A. S., 2003. The first releases of transgenic mosquitoes: an argument for the sterile insect technique. Trends in Parasitology 19, 349–356.

Billingham, J., King, A., 2001. Wave Motion. Cambridge Texts in Applied Mathematics. Cambridge University Press.

Black, W. C., Alphey, L., James, A. A., 2011. Why RIDL is not SIT. Trends in Parasitology 27 (8), 362–370.

Dyck, V. A., Hendrichs, J., Robinson, A. S. (Eds.), 2005. Sterile Insect Technique - Principles and Practice in Area-Wide Integrated Pest Management. Springer, Netherlands.

Dye, C., 1984. Models for population dynamics of the yellow fever mosquito, *Aedes aegypti*. Journal of Animal Ecology 53, 247–268.

Enserink, M., 2010. Yellow fever mosquito shows up in Northern Europe. Science 329, 736.

Erickson, R., Presley, S., Allen, L., Long, K., Cox, S., 2010. A stage-structured, aedes albopictus population model. Ecological Modelling 221, 1273–1282.

Focks, D., Haile, D., Daniel, E., Mount, G., 1993a. Dynamic life table model for aedes aegypti (diptera: Culicidae): Analysis of the literature and model development. Journal of Medical Entomology 30, 1013–1017.

Focks, D., Haile, D., Daniel, E., Mount, G., 1993b. Dynamic life table model for aedes aegypti (diptera: Culicidae): Simulation results and validation. Journal of Medical Entomology 30, 1018–1028.

Fu, G., Lees, R. S., Nimmo, D., Aw, D., Jin, L., Gray, P., Berendonk, T. U., White-Cooper, H., Scaife, S., Phuc, H. K., Marinotti, O., Jasinskiene, N., James, A. A., Alphey, L., 2010. Female-specific flightless phenotype for mosquito control. Proceedings of the National Academy of Sciences 107, 4550–4554.

Grindrod, P., 1991. Patterns and Waves in Reaction-Diffusion: Techniques and Applications. OUP, Oxford.

Gurney, W. S. C., Blythe, S. P., Nisbet, R. M., 1980. Nicholson's blowflies revisited. Nature 287 (4), 17–21.

Harrington, L. C., Scott, T. W., Lerdthusnee, K., Coleman, R. C., Costero, A., Clark, G., Jones, J., Kitthawee, S., Kittayapong, P., Sithiprasasna, R., Edman, J., 2005. Dispersal of the dengue vector *Aedes aegypti* within and between rural communities. The American Journal of Tropical Medicine and Hygiene 72, 209–220.

Hulden, L., Hulden, L., 2008. Dynamics of positional warfare malaria: Finland and Korea compared. Malaria Journal 7 (171), 1–13.

Jansen, C. C., Beebe, N. W., 2010. The dengue vector *Aedes aegypti*: what comes next. Microbes and Infection 12, 272–279.

Knipling, E. F., 1955. Possibilities of insect control or eradication through the use of sexually sterile males. Journal of Economic Entomology 48, 459–462.

Lee, H., Vasan, S., Ahmad, N., Idris, I., Hanum, N., Selvi, S., Alphey, L., Murad, S., 2013. Mating compatibility and competitiveness of transgenic and wild type *Aedes aegypti* (l.) under contained semi-field conditions. Transgenic Research 22, 47–57.

Legros, M., Lloyd, A., Huang, Y., Gould, F., 2009. Density-dependent intraspecific competition in the larval stage of *Aedes aegypti* (Diptera: Culicidae): Revisiting the current paradigm. Journal of Medical Entomology 46, 409–419.

Lewis, M. A., Driessche, P. V. D., 1993. Wave extinction from sterile insect release. Mathematical Biosciences 116, 221–247.

Magori, K., Legros, M., Puente, M. E., Focks, D. A., Scott, T. W., Lloyd, A. L., Gould, F., 2009. Skeeter buster: A stochastic, spatially explicit modeling tool for studying *Aedes aegypti* population replacement and population suppression strategies. PLoS Neglected Tropical Diseases 3 (9), e508.

Mastrangelo, T., Chaudhury, M. F., Skoda, S. R., Welch, J. B., Sagel, A., Walder, J. M. M., 2012. Feasibility of using a caribbean screwworm for sit campaigns in Brazil. Journal of Medical Entomology 49 (6), 1495–1501.

Morton, K. W., Mayers, D. F., 1994. Numerical Solution of Partial Differential Equations. Cambridge University Press.

Oliva, C. F., Jacquet, M., Gilles, J., Lemperiere, G., Maquart, P.-O., Quilici, S., Schooneman, F., Vreysen, M. J. B., Boyer, S., 2012. The sterile insect technique for controlling populations of *Aedes albopictus* (diptera: Culicidae) on reunion island: Mating vigour of sterilized males. PLoS ONE 7 (11), e49414.

Paupy, C., Kassa, F., Caron, M., Nkogh, D., Leroy, E. M., 2012. A chikungunya outbreak associated with the vector *Aedes albopictus* in remote villages of gabon. Vector-Borne and Zoonotic Diseases 12 (2), 167–169.

Peloquin, J. J., Thibault, S. T., Staten, R., Miller, T. A., 2000. Germ-line transformation of pink bollworm (*Lepidoptera: Gelechiidae*) mediated by the *piggyBac* transposable element. Insect Molecular Biology 9, 323–333.

Phuc, H., Andreasen, M., Burton, R., Vass, C., Epton, M., Pape, G., Fu, G., Condon, K., Scaife, S., Donnelly, C., Coleman, P., White-Cooper, H., Alphey, L., 2007. Late-acting dominant lethal genetic systems and mosquito control. BMC Biology 5 (11), 1–11.

Pimentel, D. (Ed.), 2011. Biological Invasions: Economic and Environmental Costs of Alien Plant, Animal, and Microbe Species, 2nd Edition. CRC Press.

Purse, B. V., Mellor, P. S., Rogers, D. J., Samuel, A. R., Mertens, P. P. C., Baylis, M., 2005. Climate change and the recent emergence of bluetongue in Europe. Nature Reviews Microbiology 3, 171–181.

Reiter, P., Amador, M. A., Anderson, R. A., Clark, G. G., 1995. Short report: dispersal of *Aedes aegypti* in an urban area after blood feeding as demonstrated by rubidium-marked eggs. The American Journal of Tropical Medicine and Hygiene 52, 177–179.

Robinson, A. S., Franz, G., Fisher, K., 1999. Genetic sexing strains in the medfly, *Ceratitis capitata*: Development, mass rearing and field application. Trends in Entomology 2, 81–104.

Seawright, J. A., Kaiser, P. E., Dame, D. A., Lofgren, C. S., 1978. Genetic method for the preferential elimination of females of *Anopheles albimanus*. Science 200, 1303–1304.

Seirin-Lee, S., Baker, R. E., Gaffney, E. A., White, S. M., 2013. Optimal barrier zones for stopping the invasion of *Aedes aegypti* mosquitoes via transgenic or sterile insect techniques. Theoretical Ecology, DOI 10.1007/s12080–013–0178–4.

Seirin-Lee, S., Gaffney, E. A., Monk, N. A. M., 2010. The influence of gene expression time delays on Gierer-Meinhardt pattern formation systems. Bulletin of Mathematical Biology 72, 2139–2160.

Sheppard, P., MacDonald, W., Tonn, R., Grab, B., 1969. The dynamics of an adult populationo of *Aedes aegypti* in relation to dengue haemorrhagic fever in Bangkok. Journal of Animal Ecology 38, 661–702.

Shigesada, N., Kawasaki, K., 1997. Biological Invasions: Theory and Practice. Oxford University Press.

649 Southwood, T., Murdie, G., Yasuno, M., Tonn, R., Reader, P., 1972. Studies on the life budget of
650 aedes aegypti in Wat Samphaya, Bangkok, Thailand. Bulletin of the World Health Organisation
651 46, 211–226.

652 Sow, A., Sidibe, I., Bengaly, Z., Bance, A. Z., Sawadogo, G. J., Solano, P., Vreysen, M. J. B.,
653 Lancelot, R., Bouyer, J., 2012. Irradiated male tsetse from a 40-year-old colony are still
654 competitive in a Riparian Forest in Burkina Faso. PLoS ONE 7 (5), e37124.

655 Takahashi, L., Maidana, N. A., Ferreira, W. C. J., Pulino, P., Yang, H. M., 2004. Mathematical
656 models for the *Aedes aegypti* dispersal dynamics: Travelling waves by wing and wind. Bulletin
657 of Mathematical Biology 67, 509–528.

658 Thomas, D. D., Donnelly, C. A., Wood, R. J., Alphey, L. S., 2000. Insect population control using
659 a dominant, repressible, lethal genetic system. Science 287, 2474–2476.

660 Vreysen, M. J. B., Robinson, A. S., Hendrich, J. (Eds.), 2007. Area-Wide Control of Insect Pests.
661 IAEA, Springer, Netherlands.

662 White, S. M., Rohani, P., Sait, S. M., 2010. Modelling pulsed releases for sterile insect techniques:
663 fitness costs of sterile and transgenic males and the effects on mosquito dynamics. Journal of
664 Applied Ecology 47 (6), 1329–1339.

665 WHO, 2012a, http://www.who.int/mediacentre/factsheets/fs117/en/.

666 WHO, 2012b, http://www.who.int/features/factfiles/malaria/en/index.html.

667 WHO, 2012c. Roll Back Malaria, http://www.rbm.who.int/keyfacts.html.

668 Wilke, B., Barretto, A., Marrelli, Toledo, M., 2012. Genetic control of mosquitoes: Population
669 suppression strategies. Revista do Instituto de Medicina Tropical de Sap Paulo 54 (5), 287–292.

670 Wimmer, E. A., 2003. Applications of insect transgenesis. Nature Reviews Genetics 4, 225–232.

671 Yakob, L., Alphey, L., Bonsall, M. B., 2008. *Aedes aegypti* control: the concomitant role of
672 competition, space and transgenic technologies. Journal of Applied Ecology 45, 1258–1265.

673 Yakob, L., Bonsall, M. B., 2009. Importance of space and competition in optimizing genetic control
674 strategies. Journal of Economic Entomology 102 (1), 50–57.

675 Yang, G., Brook, B. W., Bradshaw, C. J. A., 2009. Predicting the timing and magnitude of tropical
676 mosquito population peaks for maximizing control efficiency. PLoS Neglected Tropical Disease
677 3 (2), e385.