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The importance of density dependence in juvenile mosquito development and survival: A model-based investigation

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ABSTRACT

Mosquitoes are vectors of numerous pathogens that cause infectious diseases, and they pose a significant global health burden as a result. As such, more reliable field-relevant models to study mosquito population dynamics and life history traits such as development time and survival of mosquito larva would be of great value. In *Aedes* mosquitoes, progression through early life stages is known to be density-dependent. Despite its importance, density dependence is largely ignored or oversimplified in many existing simulation models, leading to less accurate predictions of development and survival during the early life stages. Furthermore, density dependence is frequently assumed to impact only larval survival and not development time in models, despite empirical evidence for density-dependent development. Here, we develop a discrete-time model of mosquito larval population dynamics which accounts for density impacts on both survival and development time. We demonstrate the validity of our model using publicly available semi-field data of larval density and pupation time across a six-month experiment. Using our model, we found that incorporating density dependence during larval development is important to the accurate prediction of mosquito pupation. This is especially true when considering density-dependent development time for mosquito larva as opposed to density-dependent larval survival. We determined that the incorporation of simple functional forms to describe density dependence in simulation models gives improved prediction results over models that ignore density dependence entirely. Such simple functional forms can easily be incorporated into existing models, and thus help improve field-relevant models of mosquito population dynamics, particularly in *Aedes* and other container-inhabiting mosquitoes that are known to experience density dependence during larval development.

1. Introduction

Mosquitoes pose a significant global health burden; they are responsible for millions of cases of mosquito-borne diseases such as malaria and dengue each year (WHO, 2018; Bhatt et al., 2013). A vast amount of time, money, and effort is spent on methods to control mosquitoes. In 2016, the U.S. Center for Disease Control budgeted $222 million to fight Zika, and the WHO estimates that $3.1 billion was spent on combating malaria in 2017 (Tavernise, 2016; WHO, 2018). Global efforts to reduce diseases spread by mosquitoes primarily involve insecticides, but mosquitoes are now becoming resistant to many common insecticides (Ranson and Lissenden, 2016). There is a need for new and innovative ways to decrease the size and geographic distribution of mosquito populations. To that end, efforts to better understand mosquito population dynamics have increased with hopes of finding ways to exploit those dynamics through control measures.

Mosquitoes go through several life stages before emerging as adults. The duration of each life stage is dependent on species, but the order of progression is similar for most species. First an adult mosquito will lay a batch of eggs, which, depending on environmental factors and species, can include up to as many as 200 eggs (Hancock et al., 2016a). After hatching in water, juvenile mosquitoes go through four larval stages (instars), followed by a pupal stage. After the pupal stage, the mosquitoes emerge from the water as adults. In the adult stage, the female mosquitoes require bloodmeals in order for their eggs to develop (Klowden and Briegel, 1994). The source of bloodmeals depend on the mosquito species, but some mosquitoes preferentially bite humans, which facilitates mosquito-borne disease spread (Harrington et al., 2001; Ponlawat and Harrington, 2005).

In some mosquito populations, progression through developmental stages is regulated by density dependence, a process of nonlinear feedback that may affect survival, development, fecundity, and other life history characteristics. For example, there is significant evidence that

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for mosquitoes in the genus *Aedes* there is density dependence in survival and development time (Briegel and Timmermann, 2001; Couret et al., 2014; Hancock et al., 2016a). *Aedes* are container-inhabiting mosquitoes, meaning they lay eggs in small containers, which can be natural or man-made. The amount of resources available in the small containers is limited, so survival and development times change with respect to density as a result of competition. Laboratory studies have shown a significant increase in development time for large increases in density. In one study of *Aedes albopictus*, an increase in larvae of a factor of five led to a doubling of development time (Briegel and Timmermann, 2001). A study of *Aedes aegypti* showed an increase in development time by approximately 50% when increasing the density by a factor of eight (Couret et al., 2014).

Mathematical models have long been used to study mosquito populations (Ross, 1911) and spread of mosquito-borne disease (Macdonald, 1957; Ross, 1911; Reiner et al., 2013). In such models, processes are often simplified so that studies may focus on specific questions. For instance, in many mosquito-borne disease models, only the susceptible and infectious adult mosquitoes are included and all other life stages are ignored. In a review of mathematical modeling of mosquitoes that looked at 388 papers, Reiner et al. (2013) found that only 45 explicitly modeled the aquatic stages. Without the aquatic stages, density dependence is typically not explicitly included. Many more recent models still ignore larval stages and consider constant birth rate with no density dependence, e.g. (Agusto et al., 2017; Dodero-Rojas et al., 2020; Kamiya et al., 2020; Olawoyin and Kribs, 2020; Sanchez et al., 2018; Zhang and Wang, 2020).

In the past decade, it has become more common for modeling studies to include density dependence; however, the form in which it appears and the stages which it affects vary. Density-dependent birth is common, with or without the explicit larval stages, and typically is found in the form of a logistic term, e.g. (Abdelrazec and Gumel, 2017; Cardona-Salgado et al., 2020; Iftikhar et al., 2020; Lega et al., 2017; Liu et al., 2020b,a; Pliego-Pliego et al., 2020; Rafikov et al., 2019; Suarez et al., 2020; Zhang and Lui, 2020). Other models consider a density-dependent death rate which increases with reduced resources (Natiello and Solari, 2020) or with greater density as measured by population size, e.g. (El Moustaid and Johnson, 2019; Haramboure et al., 2020; Marini et al., 2019; Tran et al., 2020; Pasquali et al., 2020; Zhang et al., 2020; Robert et al., 2014). Excluding density dependence in models or making faulty assumptions about how density dependence affects a population could impede a model's ability to describe the system appropriately.

Models that do include density dependence typically introduce it as an effect on survival. Often the process is simplified by only considering non-linear emergence or non-linear death. In particular, in the review by Reiner et al. (2013), most of the models which incorporated density did so in the birth term in the form of logistic growth with carrying capacity. Some others considered a density-dependent death term. In early work, Bellows (1981) shows the importance of density in survival of beetles compared to constant survival. This work examines multiple functions which determine the proportion of beetles surviving from the density. In Legros et al. (2009), the authors examine the model form that Bellows determined as most flexible (Equation 2a in Table 1 of the present work), using experimental survival of larval stages to identify the density-dependent and independent parameters. They find that there are multiple parameter sets that give similar fits, but conclude evidence of the importance of density in survival.

Density dependence may alter other life history traits in addition to survival, such as development time. In comparison to effects on survival, very little mathematical modeling work has considered density in development time. One notable exception is work by Hancock et al. (2016a). Using an extensive semi-field experiment, they analyze how dynamical changes in the density of larvae affect the variation of development times among cohorts of mosquitoes. In particular, they constructed a data fitted statistical model to estimate the number of larvae pupating each week. This modeling study follows work aimed at empirically exploring the relationship between larval density and development time in *Ae. aegypti*, such as the study by Couret et al. (2014) in which the authors found that density is an important factor because it alters the amount of food available to each larva, which in turn increases development time.

Table 1
Functional forms incorporating density dependence.

Label	Function
1a	$(1+D)^{-a}$
1b	$\exp(-aD)$
1c	$(1+aD)^{-1}$
2a	$\exp(-aD^{b})$
2b	$(1+(aD)^{b})^{-1}$
2c	$(1+aD)^{-b}$
2d	$(1+\exp(bD-a)-\exp(-a))^{-1}$

Seven functional forms used to incorporate density dependence into development time or survival of larval populations. D is the total number of larvae included in the density component of the calculation. Based on the length of history considered, the total number of larvae was averaged over a variable number of days from 1 to 36.

In the present work, we aim to develop a simple treatment of density dependence in the larval population that is sufficient to capture the dynamics of mosquito pupation. We examine the impact of density dependence on both larval development time and survival. Specifically, we consider how development of *Aedes aegypti* in a semi-field cage experimental population is impacted by the density of the population. This data was generated from an extensive and laborious experiment, and is not indicative of data that is available for many studies. Thus, we construct a simple mathematical model to estimate the number of larvae that pupate based, in part, on the density of larvae in the population. We use this model to determine the best way to incorporate density dependence into models in a simple way.

We begin by reviewing the results of Hancock et al. (2016a) and describe how we utilize their data for our study. Then, we outline our underlying discrete model of pupation including density dependence and larval age. Next, we present results for fitting several variations of the model to the data from Hancock et al. (2016a). Finally, we discuss these results and their implications for future studies.

2. Material and methods

2.1. Study area

We build upon work by Hancock et al. (2016a), in which the authors conducted an extensive semi-field experiment. Using their experimental data, they model number of pupae and timing of pupation based on larval density. Details of their full methodology can be found in Hancock et al. (2016a). In short, the authors monitor the number of larvae and pupae over a six-month period. Three times per week, they feed the female mosquitoes and allow them to lay eggs into a single container in the semi-field cage. The eggs are collected and incubated for hatching. Upon hatching all larvae are placed together into the same larval container in the semi-field cage. Three times a week, the total larvae are counted, while newly emerged pupae are counted daily. Using the number pupating each day as their output variable, they fit the distribution of larval development time for cohorts grouped by week. They use a Markov Chain Monte Carlo Metropolis–Hasting algorithm, and estimate 40 total parameters: the mean and standard deviation of a shifted gamma distribution for each of 20 weeks. In addition, they estimate the larval survival rate for each day by extrapolating daily

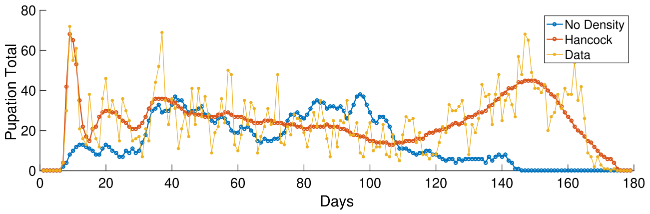


Fig. 1. Pupation data and model output. Pupation data from Hancock et al. (2016a) (gold), output of modeling in Hancock et al. (2016a) (red), and output of variation A (blue), which does not include dependence on larval density and uses a single gamma distribution of larval-age dependent maturation used for all cohorts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

survival based on the three observations of total larval population each week. They compare the total number predicted to pupate on a given day compared to the actual number recorded (Fig. 1, gold and red lines in the present work). An additional major component of their results is how density dependence in the larvae population affects *Wolbachia* invasion, which is beyond the scope of this paper (Hancock et al., 2016a).

We use raw data reported in the Hancock et al. (2016a) study in two ways. First, each new cohort in our model is determined from the number of new larvae input into the container on a particular day. Second, we estimate parameters by comparing the reported number of mosquitoes pupating on each day that pupation was reported to our model output (Fig. S1).

Our model is formulated to test different density functions using the data from Hancock et al. (2016a), so we do not consider the egg stage because the experimental data removes the eggs, hatches them elsewhere, and returns the larvae. In their paper, a different gamma distribution is fit specifically to the data from each week. The change in the resulting gamma distribution for each week is how they determine the effects of density. We instead consider a single functional form for all weeks with density as an input. Thus, what is experienced by the larvae changes based on density but individuals encountering the same density are impacted identically. We consider various functional forms for the density input and how to incorporate them (described in detail in the next section). In order to compare these models, we calculate the error between the number of predicted pupae appearing each day and the number of new pupae observed. We consider our computation of their error as a best case scenario; as we use a model with many fewer parameters utilizing a single function for pupation, we do not expect to be able to fit the data as precisely. We will use our computed error of the data in Hancock et al. (2016a) throughout this paper to compare all model selections. Note that in the present study, we consider in our calculations of error only nineteen of the twenty fitted gamma distributions in the work of Hancock et al. (2016a). We omit the first gamma distribution fitted in their work as it is completely separated from the rest and appears differently in the data set.

2.2. Model formulation

We develop a discrete-time model of mosquito development from the first larval stage through pupation. We explicitly account for groups of larvae appearing on the same day by including age-structured compartments for larvae. In the model, we track each *cohort* separately; we use the term cohort to refer to a group of larvae hatching on the same day. We denote each cohort with a superscript, and denote model time with a subscript (e.g., $L_j^{(i)}$ is the number of larvae remaining in the ith cohort on day j, Fig. 2). For example, $L_7^{(3)}$ represents the number of larvae in the third cohort alive on day 7. Using the data provided we have 54 cohorts, which we label from 1 to 54 in order of time of birth. Each day, some larvae are lost to mortality. The timing of pupation is dictated by a function of larval age and larval density. Once larvae have pupated, we reduce the number of larvae accordingly. We compare the number pupated each day in our discrete model with experimental data on pupation. In Fig. 2, we show a schematic of the model structure for three representative cohorts.

We consider several variations to our model. We begin with a simple form without density dependence, but where larval age is the only factor determining development time to the pupal stage. Survival is accounted for in this variation through the probability of daily survival, s, which varies between 0 and 1. We denote this variation A (for age). Then we investigate adding density dependence into the model without removing age as a factor in development time, denoted variation AD (for age and density). We consider seven possible functions to incorporate density into our discrete model (Table 1). As the goal is to find a simple functional form to include in simulation models, we then consider removing the impacts of age on development time, denoted variation D (for density). As it is more common to assume density dependence alters survival and not development time we consider variations AD and D with density impacting either development time or daily survival. We consider impacts on development time and survival separately to better understand the individual impacts of density on development and survival without either being influenced by the other.

2.3. Larval development time without density

As a baseline (Variation A), we fit the pupation output from our model without including larval density. We assume that in the absence of density-dependent factors, the probability of pupating on a given day follows a fixed distribution. We considered several distributions including gamma, negative binomial, normal, Poisson, and exponential. As the choice of distribution had little impact on our results (Fig. S2), we chose to focus on the gamma distribution for consistency of comparison to previous work. We restrict larvae such that they cannot pupate until the fifth day, which we represent by $g(t-t^{(i)}-4)$, where the value of $t^{(i)}$ is the day cohort i hatches, and fit the mean and variance of the gamma distribution. We fit a single gamma distribution for all weeks, which assumes a single underlying distribution of pupation time in the absence of density. In addition, we set constraints on the mean and variance in order for the distribution to be biologically relevant. Specifically, we constrain the variance of the gamma distribution to be above 0.5 and the mean of the gamma distribution to be between 1 and 35 days, such that after the shift the mean pupation time is between 5 and 39 days.

2.4. Larval development time with density

To incorporate the impact of density dependence, we let the function $f(D_t)$ be the fraction of larvae that pupate at time $t+1$, where D_t is the total larval density at time t (Table 1). We incorporate this function in both variations AD and D with effects on either development time or survival.

To include development time with variation AD, we multiply $f(D_t)$ by the gamma distribution, which extends development time. For example, $L_t^{(i)}$ is the number of larvae from cohort i alive on day t and $P_t^{(i)}$ is the number of pupae that pupate from larval cohort i on day t. The model for cohort i can be written is as follows:

$$L_{t+1}^{(i)} = sL_t^{(i)}\left(1 - f(D_t)\, g(t - t^{(i)} - 4)\right),$$

$$P_{t+1}^{(i)} = sL_t^{(i)}\, f(D_t)\, g(t - t^{(i)} - 4),$$

where $g(t-t^{(i)}-4)$ is the cumulative gamma distribution at time $t-t^{(i)}-4$. We restrict pupation prior to day 5 such that, if $t - t^{(i)} < 5$, then $g(t - t^{(i)} - 4) = 0$. This is due to the assumption that all larvae need a minimum time prior to pupation, which we take to be 5 days (Hancock et al., 2016a).

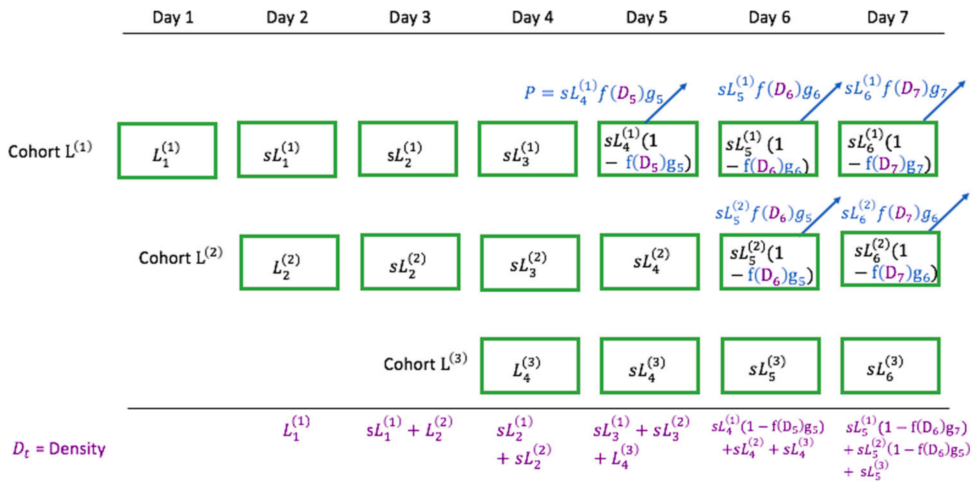


Fig. 2. Schematic diagram of discrete time model. To demonstrate, we represent three cohorts $L^{(1)}$, $L^{(2)}$, and $L^{(3)}$ from day 0 to day 6. The superscript indicates the cohort and the subscript indicates the time. The value for the total larval density, D_t, assuming a single day of larval density is included in history, is given at the bottom. The expression in each box represents the mosquitoes that remain as larvae. The blue arrows indicate pupation with the formula for the number pupating indicated to the left of the arrow.

When considering density-dependent survival (rather than development time) for variation AD, we incorporate density dependence into the probability of survival. This amounts to a subtle mathematical change, where $f(D_t)$ replaces s from the previous model as shown by :

$$L_{t+1}^{(i)} = f(D_t)\ L_t^{(i)}\left(1 - g(t - t^{(i)} - 4)\right),$$

$$P_{t+1}^{(i)} = f(D_t)\ L_t^{(i)}\ g(t - t^{(i)} - 4).$$

For variation D, we remove the gamma distribution, so that the larval age does not impact development time. Instead, we replace the gamma distribution with the density function and include the survival constant s as given by:

$$L_{t+1}^{(i)} = sL_t^{(i)}\left(1 - f(D_t)\right),$$

$$P_{t+1}^{(i)} = sL_t^{(i)}\ f(D_t).$$

However, in the case of variation D with density-dependent survival, our function for fraction of larvae that pupate becomes a constant (ρ):

$$L_{t+1}^{(i)} = f(D_t)\ L_t^{(i)}\left(1 - \rho\right),$$

$$P_{t+1}^{(i)} = f(D_t)\ L_t^{(i)}\rho.$$

2.5. Functional forms for density dependence

For the incorporation of density, $f(D_t)$, we consider seven different functional forms, listed in Table 1. All of these forms are adapted from Bellows (1981) to ensure that $f(0) = 1$. This equates to the assumption that in the absence of larvae there would be no effect of density. Bellows (1981) uses these forms to show the importance of density in survival of beetles compared to constant survival. The author examines multiple functions which determine the proportion of beetles surviving daily based on the density. We use adjusted forms of the functions to modify development time and survival of larvae in mosquitoes. As population size approaches infinity, all of these forms approach zero.

2.6. History of density dependence

To begin, we consider the larval density, D_t, only on the day immediately prior to pupation. In this case, D_t is the total number of larvae on day $t-1$. In Fig. 2, D_t, assuming the simplest form, for a given day is listed at the bottom for each day. We also considered history of density across various time periods, from 2 to 36 days. For example, a history of three days means that we averaged the number of larvae present on days $t-3$, $t-2$ and $t-1$. If we consider the illustrative example in Fig. 2 on day 6, both cohort $L^{(1)}$ and $L^{(2)}$ are able to pupate, as they have survived the minimum five day period prior to pupation. If we consider a history of three days, then we sum up all larvae on days 3, 4, and 5, and then divide by three, i.e. to compute $D_{3,4,5}$:

$$D_3 = L_2^{(1)}s + L_2^{(2)}s,$$

$$D_4 = L_3^{(1)}s + L_3^{(2)}s + L_4^{(3)},$$

$$D_5 = L_4^{(1)}s\left(1 - f\left(D_{2,3,4}\right)g_1\right) + L_4^{(2)}s + L_4^{(3)}s,$$

$$D_{3,4,5} = \frac{D_3 + D_4 + D_5}{3}.$$

Notice that on day 5 new larvae enter the population through the term $L_4^{(3)}$ rather than survival of larvae from previous days as in other terms. This is the only appearance of new larvae in this example shown in Fig. 2. In our simulations, new larvae enter the population according to the data.

In addition to a simple average, described above, we also considered weighting the density differently, e.g. giving more weight to most recent history. However, we did not see significant differences (Fig. S3). Thus, in this work, when we refer to density history, we use a simple arithmetic average.

2.7. Parameter estimation

The number of parameters varies with the complexity of the model variation. We run three different variations (Table 3) in order to compare the importance of larval age and larval density. Variation A is without any consideration of density. Larvae pupate solely based on larval age, i.e the time since hatching. We fit three parameters in this variation: the survival constant and the mean and standard deviation of the gamma distribution. In Variation AD, we include both effects of larval age and larval density. In this variation we fit three to five parameters: the survival constant (in the case when density affects development time), the mean and variance of the gamma distribution, and one (or two) parameters related to the density functions. In Variation D, we only include density as there is no dependence on larval age. In other words, we do not assume there is an underlying distribution of time until pupation. In this variation we fit two or three parameters: a constant on survival or development time; and one or two parameters related to the density functions. Recall that we consider two versions of Variation AD and D: one with the density function

Table 2
Restrictions on parameters.

Parameter	Bounds for LHS	Constraint
Gamma mean	5–26	1–35
Gamma standard deviation	0.5–30	>0.5
Parameters for density	0.001–10 or 1000	$>10^{-8}$ (1st parameter only) for functions 1a and 2b
Survival constant	0.7–1	0–1

The ‘Bounds for LHS’ (Latin Hypercube Sampling) gives the range of initial values of parameters for fitting, and ‘Constraint’ gives any constraints placed on parameters in the fitting algorithm.

Table 3
Overview of variations including parameters fitted.

Parameters	Units	DT			S	
		A	AD	D	AD	D
Mean of gamma distribution	unitless	x	x		x	
Standard deviation of gamma distribution	unitless	x	x		x	
Survival constant	day^{-1}	x	x	x		
Development time constant	day^{-1}					x
Density parameter a	unitless		x	x	x	x
Density parameter b (two-parameter functions)	unitless		x	x	x	x

Abbreviations: DT, development time; S, survival; A, variation depending on larval age; AD, variation depending on larval age and density; D, variation depending only on larval density.

effecting development time and the other effecting survival. If the density function does not impact survival, the probability of survival is constant.

For each functional form and variation, we fit the daily pupation count from our model with the recorded daily pupation counts from the data. We use the fminsearch function in Matlab to minimize the root mean-squared error from fifty different initial values under a set of constraints. Our initial values come from Latin Hypercube sampling (LHS) of each parameter range. Our LHS divides each parameter range into 50 segments, and only a single value is chosen per segment. We choose bounds for the initial values which are narrower than our optimization constraints. For instance, we choose the initial values of the standard deviation of the gamma distribution between 0.5 and 30, but during the optimization algorithm, the constraint given to fminsearch is such that it may choose any value greater than 0.5 for the standard deviation of the gamma distribution. See Table 2 for the full list of bounds and constraints. We record the final error and optimized parameters after fminsearch terminated. The algorithm terminated either if it had converged to a local minimum or if it had reached the maximum iterations allowed. In Fig. S4, we show box plots of all 50 values recorded; the bar indicates the minimum error found among all 50 runs, where Fig. 3 only includes the bar indicating the minimum error of all 50 runs. For the remainder of this work, we report only the minimum error.

In order to compare the different density functions, we use the Aikake Information Criteria (AIC) given by

$$\mathrm{AIC} = n \log\left(\frac{\sum \epsilon_i^2}{n}\right) + 2K,$$

where K is the number of parameters in the model; n is the sample size of the data; and ϵ_i is the error of the model on the ith day (Burnham and Anderson, 2004). The AIC evaluates goodness of fit but penalizes for using more parameters, which is important as we consider both one- and two-parameter density functions. The number of parameters, K, differs by variation, as discussed above. The sample size, n, is more complicated. The data set of pupation data from Hancock et al. (2016a) includes 172 days of pupation data; however, as pupation is a biological process dependent on time and environment, these 172 time points are not truly independent of each other. Thus, we consider n to be the effective sample size, which we take to be $n = 172/d$, where d is the number of days included in the density history. We consider a history length of one day initially and then also consider 2 to 36 days of history. In other words, if there are d days effecting the outcome, then we would expect that two data points d days apart would be independent, which leads to $172/d$ independent samples. Finally, the $\frac{\sum \epsilon_i^2}{n}$ is also an estimated value for all models, so we include one extra parameter in all AIC calculations (Burnham and Anderson, 2004).

2.8. Model implementation

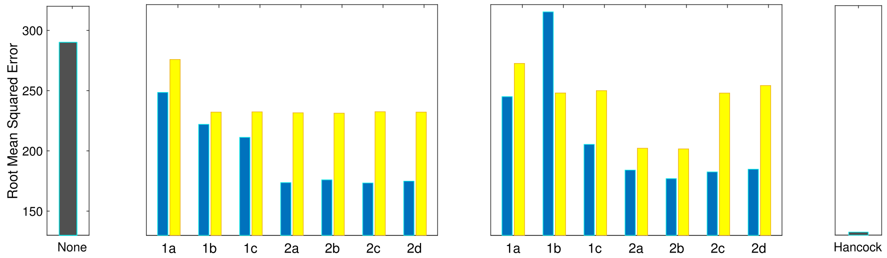
All results were implemented in Matlab version 2016b. The Latin hypercube sampling was implemented using the Matlab command lhs with the upper and lower bound shifted to the values described in Table 2. For each variation of the model we looped through the 50 initial values created with the Latin hypercube sampling and ran the fminsearch to minimize the root mean-squared error. The full code is available on GitHub: https://github.com/melody289/Simple_Functional_density.

3. Results

We fit our model to the semi-field cage data by considering the three variations of the model: (A) larval age-structured model without density dependence, (AD) larval age-structured model with density dependence, and (D) non-age-structured model with density dependence. We consider the impact of larval density on two components of the model: development time and larval survival.

3.1. Minimum root mean squared error for comparison

For a baseline comparison, we calculated the root mean squared error for variation A, which excludes the impact of larval density. In this case, all larvae only pupate based on larval age, incorporated as a gamma distribution from time since hatching. The best fit model without density has a root mean squared error of 290 (Fig. 1). To compare to previous work, we calculate a root mean squared error of approximately 132 from the fits reported in Hancock et al. (2016a). These two values are used as comparisons against the variations in which larval density in development time and survival are included. Given the higher complexity of the model in Hancock et al. (2016a), we expect the error from their fit to be lower than from the models in our simpler and more broadly implementable framework.



(a) Var A (b) Var AD (c) Var D (d)

Fig. 3. Minimum root mean square error under variations. Root mean square error (rMSE) values when larval density impacts *development time* (blue) or *survival* (yellow). (a) Variation A, which excludes larval-density dependence; (b) Variation AD, which includes larval age and density; (c) Variation D, which excludes larval-age dependence; and (d) The rMSE value from the fit done in Hancock et al. (2016a). When larval-age dependent, pupation occurs from a gamma distribution based on time since hatching. When larval-density dependent, a function of density is included in development time (blue) or to replace the survival constant (yellow). Each of the seven density functions is a function of the total larvae in the previous time step. For (a)–(c) the results are the minimum from 50 sample model runs for each condition. See Fig. S4 for a box plot of all 50 runs. See Fig. S5 for each best fit line and a comparison to the pupation data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Both larval age and larval density are important for modeling realistic pupation times

We found that the model that included both larval age structure and density dependence impacting development time (variation AD) provided the best model fit to the data. Importantly, the model without any density dependence was generally the worst fit to the data (Fig. 3). In particular, this model predicted no pupation after day 145, despite observed pupation until day 174 (Fig. 1). Additionally, the model including both larval age structure and density-dependent development time (variation AD) captured the temporal trends in pupation observed in the data much better than the model with density alone (variation D), which only captures average behavior of the trends in pupation observed in the data (Fig. S5). Furthermore, the model with density-dependent survival and no age structure (variation D) provided a better fit to the data than the model with age structure alone (variation A) or age structure and density-dependent survival (variation AD) (Fig. 3).

We consider a simple incorporation of larval density dependence on development time via changes to the daily probability of pupation. Furthermore, we assume that larval density dependence is only dependent on density of larvae from the previous day. In this context, we consider each of the seven functional forms (found in Table 1) for the incorporation of larval density. The minimum root mean square error is lower for nearly all formulations incorporating larval density dependence on development time, both with and without the underlying gamma distribution based on larval age (Fig. 3, blue bars). The exception is function 1b when density dependence alone is considered (variation D). All two parameter functions result in similar minimum root mean square error values, although 2b slightly outperforms the others. There is significantly more variation in the root mean square error for the functions with a single parameter describing density dependence than those with two parameters (Fig. 3). Amongst the one parameter functions describing density dependence, function 1c is the best, and, in some cases, has an error comparable to those of the two parameter functions.

There is less variation between functional forms when larval density impacts the survival term. The best overall for describing survival is function 2b with variation D (Fig. 3c). Survival as a function of density has a lower root mean squared error in all cases than in the model without density (Fig. 3a and yellow bars in Fig. 3b,c). Density in survival does not follow the temporal trend well. In variation AD, the peaks and low points of pupation have no correlation to the actual data, or they are flat without much variation (Fig. S5). In variation D, our model results are more similar to the data in that the noise is greater than in other cases. However, it does not show high enough peaks and pupation ceases much earlier than in the data (Fig. S6).

3.3. Larval density is important for realistic variation in timing to pupation

Unlike with experimental data, our mathematical model allows us to study properties of individual cohorts such as the distribution of pupation times. Without the inclusion of larval density (variation A), every cohort pupates similarly with no variation (Figs. 4, S6). In contrast, with the inclusion of larval density (variations AD and D), the amount of variation on time to pupation extends as the larval density in the experiment increases (Fig. 4, middle panels). Without effects of larval age and only including effects of larval density (variation D), the time to pupation becomes more varied by the amount of larvae (Fig. 4, bottom panel). This is particularly evident when larval density impacts development time. Furthermore, when no larval density is included (variation A), the larvae finish pupating well before the actual end of pupation seen in the data, indicating the importance of larval density (Figs. 1, S6).

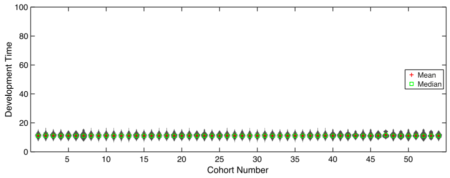
3.4. Density-dependent development time leads to a better model fit to data than density-dependent survival

In every case (except function 1b in variation D) including density-dependent development time has a lower minimum root mean squared error than density-dependent survival (Fig. 3). Only in variation D does density-dependent survival have root mean squared error comparable to density-dependent development time for two parameter functions. This is not true with one parameter functions. Comparing the temporal trends, density-dependent development time is much closer to the overall trend of the data than density-dependent survival (Fig. S5). This suggests that including density effects on development time is more accurate than including it on survival of larvae.

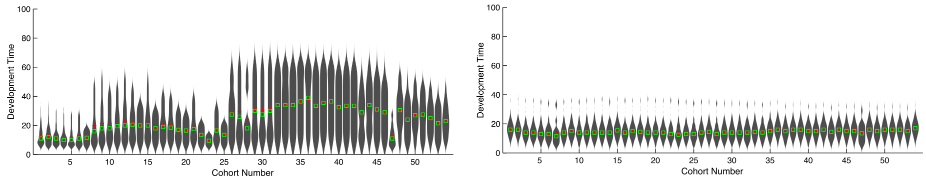
3.5. Larval density from the previous day best predicts pupation

Next, we expand on variations that include larval density (variations AD and D) and consider history beyond a single day: from 2 to 36 days. Recall, in these cases the input to the density function is the average total larval density of all days considered. Note that if a cohort has been alive for fewer days than the length of history, then for that cohort we only average the days on which the cohort was alive. The density functions with two parameters have similar error, in each of the variations (Fig. 5). Overall, the two parameter functions have lower error when both larval density and larval age are included in development time (variation AD), compared with larval density alone in development time (variation D). The lowest error observed is around 168 for all two parameter density functions, which occurs when we include 20 days of larval density history in the average for function

Variation A



Variation AD



Variation D

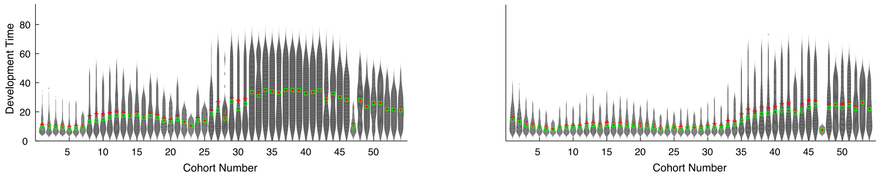


Fig. 4. Distribution of development time by variation. Violin plots of development time by cohort under variation A (top), variation AD (middle) and variation D (bottom). For variations AD and D, on the left is density-dependent development time and on the right is density-dependent survival. The green marker shows the median development time for each cohort and the red marker shows the mean development time. There are 54 different cohorts, each released on a different day. Whereas most cohorts have over 200 new larvae on a given day, cohort 47 is the smallest with 44 and cohort 15 is the largest with 1286.

2c. However, including other lengths of history produce similar error. Density-dependent survival does best in the case of variation D for functions 2a and 2b, without the age-structure. This is consistent with (Bellows, 1981), as they looked at these functions applied to survival, and found that generally the data for survival fit better with functions 2a and 2b. As with simpler history, the density-independent case (variation A) is always worse than the two parameter density functions regardless of the history considered. The exception is function 1b with density-dependent development time, which performs similarly to variation A under most histories (Fig. 5).

3.6. The history of larval density is likely important, despite an absence of signal in our data

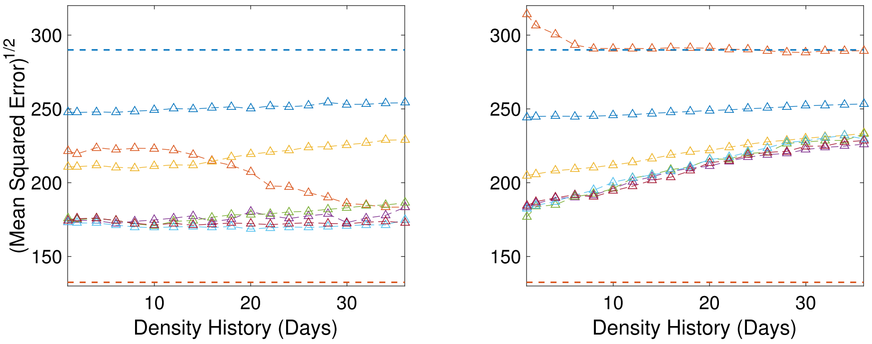
While fitting the experimental data, we find that larval density from only the previous day (no history) predicts pupation time best. However, there are several potential reasons why there could be importance of a history of larval density that is masked including (i) the implicit incorporation of history dependence due to the continuity of the experiment and (ii) noise in the experimental data. To test the latter, we created simulated data from a chosen underlying larval density function and added noise to varying degrees. We then attempted to recover the density history used. We find that at lower levels of noise, we can recover the accurate number of days of larval density used, but at greater amounts of noise we can no longer determine this value (Figs. 6, S7). It is possible that the noise in the experimental data is above this threshold.

3.7. Two parameter density functions outperform one parameter density functions

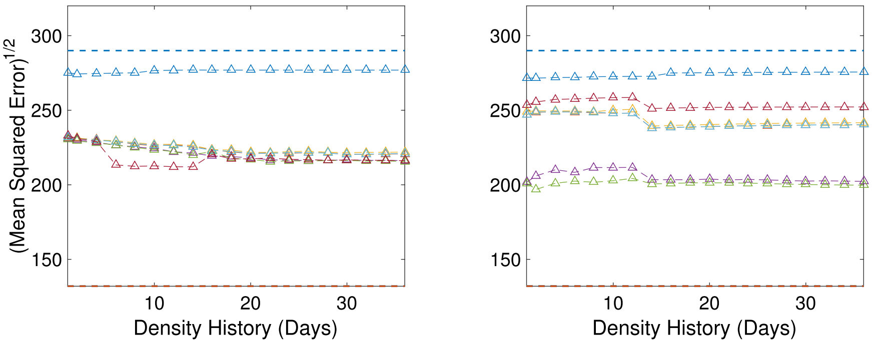
In general, we aim to choose a more parsimonious model but have models that differ in the number of parameters. We focus on the best one parameter and two parameter density functions, functions $1c$ and $2b$, respectively, and compare AIC with varying lengths of history. The AIC gives a penalty for the extra parameters, so we can compare between the one and two parameter density functions. The sample size, however, is not independent as we vary the length of density history, so we cannot compare AIC values with different history lengths. Despite this, we can compare between functions when considering the same history length, as all functions have the same sample size in that case. In order to visually compare AIC, we consider a relative AIC, where we divide all AIC by the largest value for a given density history. With this penalty, the best one parameter function, function $1c$, is relatively better than the best two parameter function, function $2b$, for both variations AD and D when more than six days of history are included (Fig. 7). Prior to six days of density history, the two parameter function $2b$ is better than $1c$. If we then look at function $1c$ and $2b$ with a penalty for the number of parameters by using the AIC, we see that given any length of history, density-dependent development time captures the number of larvae that pupate better than density-dependent survival. When longer history is considered, then density-dependent survival with variation D using function $1c$ is second best, but putting the exact same density function on development time is still better (Fig. 7). Generally, larval density alone on development time (variation D) has the smallest error when extra parameters are penalized (Fig. 7).

4. Discussion

In this paper, we developed a modeling approach to investigate the importance of multiple facets of density-dependent development and survival on the pupation of *Ae. aegypti* mosquitoes. We showed that overall, the inclusion of density-dependent effects improved the model's fit to the data; however, choices of functional form, the life process directly impacted, and inclusion of larval density history all played a role in the quality of the model fit. While the importance of density in the life cycle of *Ae. aegypti* has long been known, inclusion of density dependence in modeling studies often lies at the extremes of complexity — very simple (Dye, 1984; Bellows, 1981) or very complex (Magori et al., 2009; Focks et al., 1993; Hancock et al.,



(a) Variation AD - development time (b) Variation D - development time



(c) Variation AD - survival (d) Variation D - survival

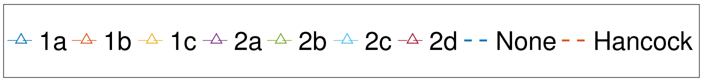
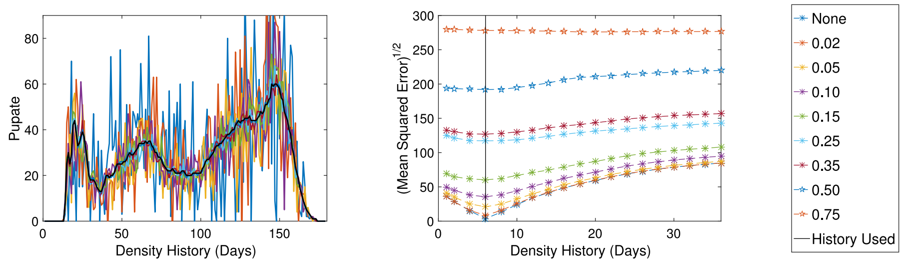


Fig. 5. Comparing fits as the history of density is varied. The root mean squared error (rMSE) of each of seven functions (found in Table 1) as the number of previous days of history included when averaging the total density of larvae changes. For each amount of history, we report the minimum rMSE for 50 sample runs for each function. In (a)–(b), development time is density-dependent, while in (c)–(d) survival is density-dependent. In (a) and (c), variation AD is modeled while in (b) and (d) variation D is modeled.



(a) Simulated data as noise varies (b) Minimum error for simulated data

Fig. 6. Simulated data with varying levels of noise. We used function 2b to generate simulated data with a history of six days and varied the levels of noise from none to a variance of 0.75 of the pupated amount. (a) The data including noise added and (b) the minimum error for each noise are shown. The Gaussian noise added has a variance relative to the amount pupated on a given day. Notice that with a large amount of noise, access to history is not necessarily better, even though the simulated data assumed a history of six days in the model.

2016a). Herein, we examined density dependence through a model of intermediate complexity to help bridge the gap between the extremes.

When comparing density-dependent survival against density-dependent development, we found that the model with density-dependent development better described the data. This is an important result that adds to the growing body of literature emphasizing the importance of density-dependent *Ae. aegypti* development (Hancock et al., 2016a; Couret et al., 2014). Until recently, the focus on density dependence in *Ae. aegypti* has been primarily on survival (Bellows, 1981; Dye, 1984; Legros et al., 2009; Walsh et al., 2011, 2013). While understanding density-dependent survival of mosquito populations is important, the failure to properly characterize density-dependent effects on mosquito development could have severe consequences on efforts to eliminate or reduce mosquito populations. Modeling studies assessing the feasibility of population reduction strategies indicate that density-dependent regulation of survival could impede success of strategies in which lethality occurs in early larval stages (Phuc et al., 2007; Atkinson et al., 2007), and that the functional form of density-dependent feedback could influence the success of control approaches (Robert et al., 2012). Other modeling studies have shown

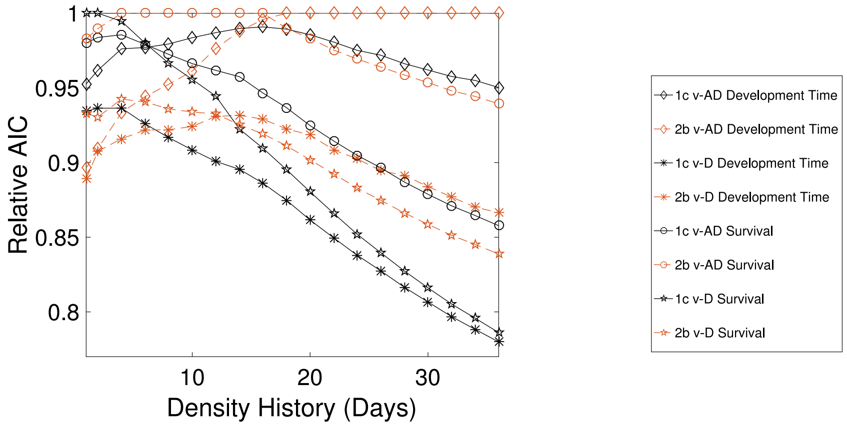


Fig. 7. Comparison of density-dependent development time and survival with history. The best one-parameter (1c) and two-parameter (2b) density functions by variation AD and D with density-dependent development time compared to density-dependent survival. We find a relative AIC from the root mean squared error (rMSE) reported previously, then divide each delay day by the largest rMSE of the variations chosen. As there is a difference in number of days used changing the amount of data needed, these are only to compare functions with a specific day choice, but not between days.

that the success of population replacement or reduction–replacement combination strategies may depend upon the form and strength of density-dependent regulation (Robert et al., 2014; Okamoto et al., 2014; Huang et al., 2011; Hancock et al., 2016b). These studies have focused on the impact of density-dependent larval mortality on control strategies. Studies aimed at understanding the role that density-dependent development could play in population control have been less numerous, and many of those studies utilize complex models that consider numerous biotic and abiotic factors that contribute to larval development and other life stages (Magori et al., 2009; Okamoto et al., 2013; Focks et al., 1993). Our work emphasizes that density-dependent development should be considered alongside density-dependent survival in studies aimed at understanding the impacts of mosquito control measures.

Overall, we showed that the density-dependent functions with two parameters provided a better fit than those with only one parameter, even when penalizing the two parameter functions for the additional parameter. This result is in agreement with previous studies aimed at assessing simple models of density dependence. In particular, the work of Bellows (1981), from which the density-dependent functional forms were taken, showed that the two-parameter models were generally better at describing the data analyzed in that work. Our results here and those of studies prior to the present one indicate that the complex nature of the population response to density is difficult to describe in a parsimonious way; however, the two parameter functions in density-dependent development time were able to reproduce the general trends observed in the data of Hancock et al. (2016a) (Fig. S5). Furthermore, the simplicity of the two parameter functions considered in our model should allow for a fairly straightforward application of our model to other data sets, whereas the complex nature of the model in Hancock et al. (2016a) requires data at a resolution that may be finer than many studies can produce.

While we found that variation A, in which no density is included, provided a worse fit than the other variations we considered, each of the remaining two variations had its own advantages. Future work with this model should choose the variation that is most appropriate for the study being conducted. Variation AD does better at describing the shape of the distribution of pupation timing, but using density alone (variation D) may be sufficient if timing of pupation is not as important. In this case, the total pupation across the experiment is similar although the temporal trends of pupation are not captured. Overall, variation D acts more like an average while variation AD captures more temporal trends. An estimate of the total pupation across an interval may be sufficient for some studies, while more nuanced temporal trends may be required in other cases.

In our analysis of the impact of density history on larval development and survival, we found that, in general, inclusion of density counts across multiple previous days did not improve the fit of the model to the data when compared to only including the density of the previous day. Furthermore, we found this result to hold even when we weighted density differently (i.e., allowing for density of the most recent days to be more important than that of earlier days). This was surprising because previous studies suggest that impacts of density should be cumulative (Walsh et al., 2012, 2013). That is, a larva's response to density should be a function of the density of the population over its lifetime, not just on the day before it pupates. As our investigation suggests, it may be that the variability in the data prevented proper analysis of the cumulative effects of density. While our results did not produce the expected outcome, we feel that this topic is still important to consider in future empirical, statistical, and modeling studies. If density-dependent responses are assumed to be dependent only on the previous day's population, modeling studies aimed at investigating population control strategies will misrepresent the impacts of control measures if density responses are indeed cumulative. This is particularly true of control measures that involve releasing additional mosquitoes into the population such as genetic strategies or strategies involving the release of *Wolbachia*-infected mosquitoes.

We have focused on the role of density dependence in intra-specific competition, primarily within a single species. We have touched on potential impact in a population with the introduction of a similar genetic make up, such as *Wolbachia*-infected mosquitoes. We hypothesize that density dependence could have a more nuanced role in inter-specific competition between similar species that are known to occasionally inhabit the same area, such as *Ae. albopictus* and *Ae. aegypti*. In such a case, other competition factors, such as food availability, would also need to be included (Murrell and Juliano, 2014).

While the work presented here underscores the importance of considering density-dependent emergence in *Ae. aegypti* populations, we emphasize that our results have some limitations. Namely, this analysis was performed on a single data set from one study in which the quality of the data was exceptional beyond what is produced from many similar studies. One goal of this work was to produce a model that provides a simplistic description of density-dependent emergence in mosquito populations so that the model can be easily adapted to different data. Unfortunately, we found a lack of similar available data sets on which to test our model's robustness. It will be important to validate this model across data sets to improve its functionality.

Our work is intended to investigate the impacts of different types of density dependence in juvenile stages. As one goal of this study is to compare among these types, we aimed to reduce the influence of additional factors. Thus, our work does not consider the role of abiotic influences such as temperature and humidity on population regulation nor does it consider density dependence in every life stage supported by empirical work. For example, temperature and its fluctuations are known to impact multiple mosquito life history traits such as mortality rates and development time (Carrington et al., 2013; Couret et al., 2014; Marini et al., 2016). Variation in population density can sometimes be due to either environmental variability or density dependence, and disentangling relative contributions of each can be difficult. Thus, considering individual and combined effects of both is important (Saitoh and Cohen, 2018). In Hancock et al. (2016a), the authors note that they observe a relationship between water temperature and larval development in the data. Importantly, they find the correlation with temperature much weaker than that with larval density. Thus, we focus on larval density as a primary factor and do not consider other dependencies here. They also find that fecundity is influenced by density dependence; however, our work is focused on feedback specific to juvenile stages, which resulted in an extensive study on its own. Future work should consider the impact of density dependence in the juvenile stages on adult fecundity as well the influence of temperature, humidity, and other environmental variables on these processes. Future extensions of our model could also lead to the development of spatial models aimed at investigating interactions between density dependence and spatial heterogeneity and continuous time analogs to the work here. Both of these avenues, while important, are beyond the scope of the present study.

In this study, we focused our analysis on *Ae. aegypti* mosquitoes, which are important vectors of pathogens and are known to experience density-dependent population regulation in the juvenile stages. With some species-specific modifications, our analysis can be extended to other mosquito species, particularly other container-inhabiting mosquito species that experience density-dependent regulation in the juvenile stages such as *Aedes albopictus*, *Culex pipiens*, *Culex quinquefasciatus*, and *Culex tarsalis*, all of which have been implicated in pathogen transmission (Vezzani, 2007; Goddard et al., 2002; Gratz, 2004). A number of other *Aedes* and *Culex* species are also container-inhabiting and likely to be regulated by density dependence in the juvenile stages (Vezzani, 2007). Efforts to model density dependence in these mosquito populations have been similar to those for *Ae. aegypti* in which models are simplified and density dependence, when included, is most often in mortality terms in juvenile mosquitoes (Erickson et al., 2010; Tran et al., 2013; Bowman et al., 2005; Ahumada et al., 2004; Ewing et al., 2016). Our results will likely contribute to improvements in modeling density dependence in multiple container-inhabiting mosquitoes in addition to *Ae. aegypti*, although differences in parameterization of the life history traits must be considered when applying these results to other species.

4.1. Conclusion

Our model and the present work follow a decades long history aimed at investigating the importance of density dependence in *Ae. aegypti* populations via both empirical and modeling studies. Our model lies near the center of a spectrum of complexity. At one extreme, many of the complex models consider explicit day-to-day changes in survival and emergence and require high resolution data to validate. At the other extreme are models that are more simplistic and generally aimed at studying density dependence primarily from a qualitative perspective. With its intermediate level of complexity, our model will be a useful tool both for studying density dependence with data at high or low resolutions and for investigating interesting theoretical questions. The present work has underscored that density dependence in *Ae. aegypti* populations is a complex process that impacts both survival and development of larvae. That density-dependent emergence was more important to consider in our study than density-dependent survival is an important, significant result that needs to be investigated further given its potential impacts on mosquito population and infectious disease control strategies.

CRediT authorship contribution statement

Melody Walker: Conceptualization, Methodology, Software, Validation, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Michael A. Robert:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Visualization, Supervision. **Lauren M. Childs:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.ecolmodel.2020.109357.

References

Abdelrazec, A., Gumel, A.B., 2017. Mathematical assessment of the role of temperature and rainfall on mosquito population dynamics. J. Math. Biol. 74 (6), 1351–1395.

Agusto, F.B., Bewick, S., Fagan, W., 2017. Mathematical model of Zika virus with vertical transmission. Infect. Dis. Model. 2 (2), 244–267.

Ahumada, J.A., Laoointe, D., Samuel, M.D., 2004. Modeling the population dynamics of *Culex quinquefasciatus* (Diptera: *Culicidae*), along an elevational gradient in Hawaii. J. Med. Entomol. 41 (6), 1157–1170.

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. Proc. Natl. Acad. Sci. 104 (22), 9540–9545.

Bellows, T., 1981. The descriptive properties of some models for density dependence. J. Anim. Ecol. 139–156.

Bhatt, S., Gething, P.W., Brady, O.J., Messina, J.P., Farlow, A.W., et al., 2013. The global distribution and burden of dengue. Nature 496, 504–507.

Bowman, C., Gumel, A., Van den Driessche, P., Wu, J., Zhu, H., 2005. A mathematical model for assessing control strategies against West Nile virus. Bull. Math. Biol. 67 (5), 1107–1133.

Briegel, H., Timmermann, S.E., 2001. *Aedes albopictus* (Diptera: *Culicidae*): physiological aspects of development and reproduction. J. Med. Entomol. 38 (4), 566–571.

Burnham, K.P., Anderson, D.R., 2004. Multimodel inference: understanding AIC and BIC in model selection. Sociol. Methods Res. 33 (2), 261–304.

Cardona-Salgado, D., Campo-Duarte, D.E., Sepulveda-Salcedo, L.S., Vasilieva, O., 2020. *Wolbachia*-based biocontrol for dengue reduction using dynamic optimization approach. Appl. Math. Model. 82, 125–149.

Carrington, L.B., Armijos, M.V., Lambrechts, L., Barker, C.M., Scott, T.W., 2013. Effects of fluctuating daily temperatures at critical thermal extremes on *Aedes aegypti* life-history traits. PLoS One 8 (3).

Couret, J., Dotson, E., Benedict, M.Q., 2014. Temperature, larval diet, and density effects on development rate and survival of *Aedes aegypti* (Diptera: *Culicidae*). PLoS One 9 (2), e87468.

Dodero-Rojas, E., Ferreira, L.G., Leite, V.B., Onuchic, J.N., Contessoto, V.G., 2020. Modeling Chikungunya control strategies and Mayaro potential outbreak in the city of Rio de Janeiro. PLoS One 15 (1), e0222900.

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

El Moustaid, F., Johnson, L.R., 2019. Modeling temperature effects on population density of the dengue mosquito *Aedes aegypti*. Insects 10 (11), 393.

Erickson, R.A., Presley, S.M., Allen, L.J., Long, K.R., Cox, S.B., 2010. A stage-structured, *Aedes albopictus* population model. Ecol. Model. 221 (9), 1273–1282.

Ewing, D.A., Cobbold, C.A., Purse, B., Nunn, M., White, S.M., 2016. Modelling the effect of temperature on the seasonal population dynamics of temperate mosquitoes. J. Theoret. Biol. 400, 65–79.

Focks, D.A., Haile, D., Daniels, E., Mount, G.A., 1993. Dynamic life table model for *Aedes aegypti* (Diptera: Culicidae): analysis of the literature and model development. J. Med. Entomol. 30 (6), 1003–1017.

Goddard, L.B., Roth, A.E., Reisen, W.K., Scott, T.W., 2002. Vector competence of California mosquitoes for West Nile virus. Emerg. Infect. Diseases 8 (12), 1385.

Gratz, N., 2004. Critical review of the vector status of *Aedes albopictus*. Med. Vet. Entomol. 18 (3), 215–227.

Hancock, P.A., White, V.L., Callahan, A.G., Godfray, C.H., Hoffmann, A.A., Ritchie, S.A., 2016a. Density-dependent population dynamics in *Aedes aegypti* slow the spread of wMel *Wolbachia*. J. Appl. Ecol. 53 (3), 785–793.

Hancock, P.A., White, V.L., Ritchie, S.A., Hoffmann, A.A., Godfray, H.C.J., 2016b. Predicting *Wolbachia* invasion dynamics in *Aedes aegypti* populations using models of density-dependent demographic traits. BMC Biol. 14 (1), 96.

Haramboure, M., Labbé, P., Baldet, T., Damiens, D., Gouagna, L.C., Bouyer, J., Tran, A., 2020. Modelling the control of *Aedes albopictus* mosquitoes based on sterile males release techniques in a tropical environment. Ecol. Model. 424, 109002.

Harrington, L.C., Edman, J.D., Scott, T.W., 2001. Why do female *Aedes aegypti* (Diptera: *Culicidae*) feed preferentially and frequently on human blood? J. Med. Entomol. 38 (3), 411–422.

Huang, Y., Lloyd, A.L., Legros, M., Gould, F., 2011. Gene-drive into insect populations with age and spatial structure: A theoretical assessment. Evol. Appl. 4 (3), 415–428.

Iftikhar, M., Iftikhar, S., Sohail, A., Javed, S., 2020. AI-modelling of molecular identification and feminization of *Wolbachia* infected *Aedes aegypti*. Prog. Biophys. Mol. Biol. 150, 104–111.

Kamiya, T., Greischar, M.A., Wadhawan, K., Gilbert, B., Paaijmans, K., Mideo, N., 2020. Temperature-dependent variation in the extrinsic incubation period elevates the risk of vector-borne disease emergence. Epidemics 30, 100382.

Klowden, M.J., Briegel, H., 1994. Mosquito gonotrophic cycle and multiple feeding potential: contrasts between *Anopheles* and *Aedes* (Diptera: *Culicidae*). J. Med. Entomol. 31 (4), 618–622.

Lega, J., Brown, H.E., Barrera, R., 2017. *Aedes aegypti* (Diptera: Culicidae) abundance model improved with relative humidity and precipitation-driven egg hatching. J. Med. Entomol. 54 (5), 1375–1384.

Legros, M., Lloyd, A.L., Huang, Y., Gould, F., 2009. Density-dependent intraspecific competition in the larval stage of *Aedes aegypti* (Diptera: *Culicidae*): revisiting the current paradigm. J. Med. Entomol. 46 (3), 409–419.

Liu, Z., Tian, C., Ruan, S., 2020a. On a network model of two competitors with applications to the invasion and competition of *Aedes Albopictus* and *Aedes Aegypti* mosquitoes in the United States. SIAM J. Appl. Math. 80 (2), 929–950.

Liu, X., Wang, Y., Zhao, X.-Q., 2020b. Dynamics of a climate-based periodic Chikungunya model with incubation period. Appl. Math. Model. 80, 151–168.

Macdonald, G., 1957. The epidemiology and control of malaria. Oxford Univ. Pr..

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 Negl. Trop. Dis. 3 (9).

Marini, G., Arnoldi, D., Baldacchino, F., Capelli, G., Guzzetta, G., Merler, S., Montarsi, F., Rizzoli, A., Rosà, R., 2019. First report of the influence of temperature on the bionomics and population dynamics of *Aedes koreicus*, a new invasive alien species in Europe. Parasites Vectors 12 (1), 524.

Marini, G., Poletti, P., Giacobini, M., Pugliese, A., Merler, S., Rosà, R., 2016. The role of climatic and density dependent factors in shaping mosquito population dynamics: the case of *Culex pipiens* in northwestern Italy. PLoS One 11 (4), e0154018.

Murrell, E.G., Juliano, S.A., 2014. Detritus type alters the outcome of interspecific competition between *Aedes aegypti* and *Aedes albopictus* (*Diptera: Culicidae*). J. Med. Entomol. 45 (3), 375–383.

Natiello, M.A., Solari, H.G., 2020. Modelling population dynamics based on experimental trials with genetically modified (RIDL) mosquitoes. Ecol. Model. 424, 108986.

Okamoto, K.W., Robert, M.A., Gould, F., Lloyd, A.L., 2014. Feasible introgression of an anti-pathogen transgene into an urban mosquito population without using gene-drive. PLoS Negl. Trop. Dis. 8 (7), e2827.

Okamoto, K.W., Robert, M.A., Lloyd, A.L., Gould, F., 2013. A reduce and replace strategy for suppressing vector-borne diseases: insights from a stochastic, spatial model. PLoS One 8 (12), e81860.

Olawoyin, O., Kribs, C., 2020. Coinfection, altered vector infectivity, and antibody-dependent enhancement: The Dengue–Zika interplay. Bull. Math. Biol. 82 (1), 1–20.

Pasquali, S., Mariani, L., Calvitti, M., Moretti, R., Ponti, L., Chiari, M., Sperandio, G., Gilioli, G., 2020. Development and calibration of a model for the potential establishment and impact of *Aedes albopictus* in Europe. Acta Trop. 202, 105228.

Phuc, H.K., Andreasen, M.H., Burton, R.S., Vass, C., Epton, M.J., Pape, G., Fu, G., Condon, K.C., Scaife, S., Donnelly, C.A., et al., 2007. Late-acting dominant lethal genetic systems and mosquito control. BMC Biol. 5 (1), 11.

Pliego-Pliego, E., Vasilieva, O., Velázquez-Castro, J., Collar, A.F., 2020. Control strategies for a population dynamics model of *Aedes aegypti* with seasonal variability and their effects on dengue incidence. Appl. Math. Model. 81, 296–319.

Ponlawat, A., Harrington, L.C., 2005. Blood feeding patterns of *Aedes aegypti* and *Aedes albopictus* in Thailand. J. Med. Entomol. 42 (5), 844–849.

Rafikov, M., Meza, M.E.M., Ferruzzo Correa, D.P., Wyse, A.P., 2019. Controlling *Aedes aegypti* populations by limited *Wolbachia*-based strategies in a seasonal environment. Math. Methods Appl. Sci. 42 (17), 5736–5745.

Ranson, H., Lissenden, N., 2016. Insecticide resistance in African *Anopheles* mosquitoes: a worsening situation that needs urgent action to maintain malaria control. Trends Parasitol. 32 (3), 187–196.

Reiner, Jr., R.C., Perkins, T.A., Barker, C.M., Niu, T., Chaves, L.F., Ellis, A.M., George, D.B., Le Menach, A., Pulliam, J.R., Bisanzio, D., et al., 2013. A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010. J. R. Soc. Interface 10 (81), 20120921.

Robert, M.A., Legros, M., Facchinelli, L., Valerio, L., Ramsey, J.M., Scott, T.W., Gould, F., Lloyd, A.L., 2012. Mathematical models as aids for design and development of experiments: the case of transgenic mosquitoes. J. Med. Entomol. 49 (6), 1177–1188.

Robert, M.A., Okamoto, K.W., Gould, F., Lloyd, A.L., 2014. Antipathogen genes and the replacement of disease-vectoring mosquito populations: a model-based evaluation. Evol. Appl. 7 (10), 1238–1251.

Ross, R., 1911. The Prevention of Malaria. John Murray, London.

Saitoh, T., Cohen, J.E., 2018. Environmental variability and density dependence in the temporal Taylor's law. Ecol. Model. 387, 134–143.

Sanchez, F., Barboza, L.A., Burton, D., Cintrón-Arias, A., 2018. Comparative analysis of dengue versus Chikungunya outbreaks in Costa Rica. Ricerche Mat. 67 (1), 163–174.

Suarez, G.P., Udiani, O., Allan, B.F., Price, C., Ryan, S.J., Lofgren, E., Coman, A., Stone, C.M., Gallos, L.K., Fefferman, N.H., 2020. A generic arboviral model framework for exploring trade-offs between vector control and environmental concerns. J. Theoret. Biol. 110161.

Tavernise, S., 2016. U.S. Funding for fighting zika virus is nearly spent, C.D.C. says. URL https://www.nytimes.com/2016/08/31/health/us-funding-for-fighting-zika-virus-is-nearly-spent-cdc-says.html.

Tran, A., l'Ambert, G., Lacour, G., Benoît, R., Demarchi, M., Cros, M., Cailly, P., Aubry-Kientz, M., Balenghien, T., Ezanno, P., 2013. A rainfall-and temperature-driven abundance model for *Aedes albopictus* populations. Int. J. Environ. Res. Public Health 10 (5), 1698–1719.

Tran, A., Mangeas, M., Demarchi, M., Roux, E., Degenne, P., Haramboure, M., Le Goff, G., Damiens, D., Gouagna, L.-C., Herbreteau, V., et al., 2020. Complementarity of empirical and process-based approaches to modelling mosquito population dynamics with *Aedes albopictus* as an example — Application to the development of an operational mapping tool of vector populations. PLoS One 15 (1), e0227407.

Vezzani, D., 2007. Artificial container-breeding mosquitoes and cemeteries: a perfect match. Trop. Med. Int. Health 12 (2), 299–313.

Walsh, R.K., Aguilar, C.L., Facchinelli, L., Valerio, L., Ramsey, J.M., Scott, T.W., Lloyd, A.L., Gould, F., 2013. Regulation of *Aedes aegypti* population dynamics in field systems: quantifying direct and delayed density dependence. Am. J. Trop. Med. Hyg. 89 (1), 68–77.

Walsh, R.K., Bradley, C., Apperson, C.S., Gould, F., 2012. An experimental field study of delayed density dependence in natural populations of *Aedes albopictus*. PLoS One 7 (4).

Walsh, R., Facchinelli, L., Ramsey, J., Bond, J., Gould, F., 2011. Assessing the impact of density dependence in field populations of *Aedes aegypti*. J. Vector Ecol. 36 (2), 300–307.

WHO, 2018. Malaria: Fact sheet. URL https://www.who.int/news-room/fact-sheets/detail/malaria.

Zhang, X., Liu, Q., Zhu, H., 2020. Modeling and dynamics of *Wolbachia*-infected male releases and mating competition on mosquito control. J. Math. Biol.

Zhang, H., Lui, R., 2020. Releasing *Wolbachia*-infected *Aedes aegypti* to prevent the spread of dengue virus: a mathematical study. Infect. Dis. Model.

Zhang, L., Wang, S.-M., 2020. A time-periodic and reaction–diffusion Dengue fever model with extrinsic incubation period and crowding effects. Nonlinear Anal. RWA 51, 102988.