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Research article

Temperature dependent developmental time for the larva stage of Aedes aegypti

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Abstract: We first verify that the time from the emergence of larva to the emergence of pupa (i.e., the duration of the larva stage) for Aedes aegypti is approximately gamma distributed, provided that the pupation process is successful. This is illustrated by fitting a multi-stage model to temperature-controlled pupation rate data of Aedes aegypti. We then determine the temperature dependent gamma distribution parameters, and found that both the shape and rate parameters and the survival probability are unimodal functions of temperature. We then use a Gaussian unimodal function to describe the dependence of these parameters on temperature, and fit the model to the pupation rate data. We found that the optimal pupation temperature is about 28°C, with a mean time from the emergence of larva to the emergence of pupa about 3.8 days, and standard deviation of 0.5 days. For very high and very low temperatures, the death rate is 1.

Keywords: Gaussian function; developmental time; maximum likelihood estimation; gamma distribution

1. Introduction

The life cycle of mosquitoes has four major stages, namely egg, larva, pupa and adult (see Figure 1). To predict the population density of mosquitoes, we need to estimate the developmental time of each stage. The developmental time is determined by many factors, such as food availability, moisture, temperature etc. In this paper, we aim to find a mathematical relationship between developmental time distribution and temperature, while keeping the other conditions constant. Understanding how the developmental time of mosquitoes depends on temperature is crucial for predicting the seasonal population variation and the effect of climate change on mosquito population. For example, Gong et al. [1] developed a discrete time multi-stage model for population density. Many of the model parameters, such as the survival probabilities of the adults and larvae, are temperature dependent. Interestingly, the model is linear, and can fit the observed mosquito density data well [2]. This implies that the seasonal oscillations of mosquito density may be fully explained by seasonal weather conditions.

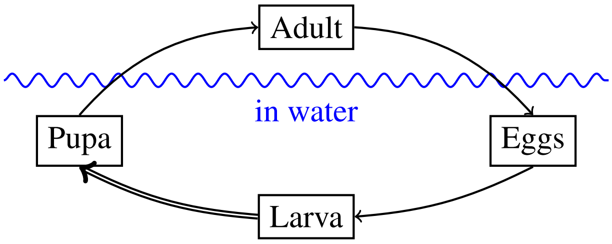

Figure 1. The life cycle of mosquito can be divided into four major stages, with three stages in water (eggs, larva and pupa) and the adult stage above water. In this paper, we aim to estimate the distribution of the time from the emergence of larva to the emergence of pupa (i.e., the duration of the larva stage, as indicated by the double line).

A commonly used model for temperature dependent developmental rate is proposed by Sharpe and DeMichele [3], which is a four-parameter model with a shape of a slightly skewed single humped curve. This model is derived from the enzyme reaction rates, and has been used in many mosquito population models for mosquito developmental rate [1, 2, 4, 5]. Jian et al. [6] established the model of between developmental rate and temperature based on logistic model. Bayoh and Lindsay [7] used the non-linear expression to describe the relationship between overall developmental rate and temperature. Healy et al. [8] proposed another empirical model for temperature dependent mosquito developmental rate using a standard regression equation between developmental rate and temperature.

These models assume that the developmental rate is constant under a constant temperature. A constant rate corresponds to an exponentially distributed developmental time, which unrealistically implies that the development occurs on the first day with the largest probability. A more realistic characterization of how fast the developmental proceeds is the distribution of developmental time, which is most likely unimodal as suggested by laboratory experiments [9]. In fact, Aznar et al. [10] used a multi-stage mathematical model to show that, when food is not limiting, each stage is identically exponentially distributed, and thus the total developmental time for a stage is best estimated by a gamma distribution.

In this paper, we first verify the result of [10] that a gamma distribution is a good approximation for the duration of the larva stage (i.e., the time from the emergence of larva to the emergence of pupa) for mosquitoes (Aedes aegypti), and by fitting a multi-stage ordinary differential equation model to the data published in Mohammed and Chadee [9]. Aedes aegypti is the vector for many mosquito-borne diseases, such as Zika [11], dengue [12], and chikungunya [13], etc.

To understand how temperature affects the pupation process, we describe the parameters of the gamma distribution as unimodal functions of temperature. The parameters are determined by fitting the model to the same datasets in Mohammed and Chadee [9].

2. Data

In this paper, we use the dataset of pupation developmental rate from laboratory experiments, specifically, the study on how pupation of Aedes aegypti dependents on temperature published by

Mohammed and Chadee [9]. They set up temperature regulated water baths at 24–25°C, 26–27°C, 29–30°C, 32–33°C and 34–35°C. At each temperature 6–8 one-liter beakers containing 800 milliliter of water were acclimatized for 24 hours, then 100 newly hatched Aedes aegypti larvae were placed in each beaker and fed daily with 0.1 gram of ground fish food. The percentages of pupation for larvae reared at different temperatures are summarized in Table 1, which is recalculated from Table 1 in Mohammed and Chadee [9] (the original data contains the cumulative percentages).

Table 1. Percentages of pupation for larvae reared at different temperatures for the constant temperature. The unit is percentage. Data published in Mohammed and Chadee [9]

Day	25°C	27°C	30°C	33°C	35°C
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0.5	39.6	78.4	14.1	18.8
5	29.3	45.2	13.8	49.4	16
6	47	13.8	3.4	15.9	26
7	10.9	0.5	1.6	8	13.4
8	6.4			4.4	5.6

3. A multi-stage model for the larva stage

To verify that the gamma distribution is a good approximation to the distribution of the time from the emergence of larva to the emergence of pupa, as proposed by [10]. We use an approach that is motivated by [10] but much simpler, and assume that the developmental process can be divided into many substages, while the duration in each substage may be approximated by an exponential distribution. This gives a multistage oridnary differential equation model. A larva of Aedes aegypti undergoes four molting stages before becoming a pupa, and thus the development may be divided into 4 stages [14]. We established an ordinary differential equation four-stage model to describe the four molting process. Since the data in Table 1 are fractions while the total number is unspecified, our model considers the fraction of larvae in each stage. Let S_i (i=1, 2, 3, 4) be the fraction of larvae in the ith molting stage, condition on successful pupation.

$$\begin{aligned}
S_1' &= -\mu_1 S_1, \\
S_2' &= \mu_1 S_1 - \mu_2 S_2, \\
S_3' &= \mu_2 S_2 - \mu_3 S_3, \\
S_4' &= \mu_3 S_3 - \mu_4 S_4, \\
p' &= (1-d)\mu_4 S_4,
\end{aligned} \tag{3.1}$$

where p is the cumulative fraction of larvae pupated by time t; d is the rate of death before pupation; μ_i is the developmental rate of larvae in the ith stage. Note that this model can also be considered as the master equation of a Markov process governing the probability that a larva is in each molting stage.

This model assumes that the duration in each stage is exponentially distribution. To be more realistic, we approximate the duration in each stage by a gamma distribution. To do so, we divide each stage into k sub-stages, with a constant developmental rate for each substage. Thus, the developmental time for each stage is a sum of identical exponential distributions, i.e., a gamma distribution with a shape parameter k. The model can be written as:

$$\begin{aligned}
S'_{11} &= -k\mu_1 S_{11}, \\
S'_{1,i} &= k\mu_1 S_{1,i-1} - k\mu_1 S_{1,i}, \quad i = 2, 3, \ldots, k \\
S'_{21} &= k\mu_1 S_{1,k} - k\mu_2 S_{21}, \\
S'_{2,i} &= k\mu_2 S_{2,i-1} - k\mu_2 S_{2,i}, \quad i = 2, 3, \ldots, k \\
S'_{31} &= k\mu_2 S_{2,k} - k\mu_3 S_{31}, \\
S'_{3,i} &= k\mu_3 S_{3,i-1} - k\mu_3 S_{3,i}, \quad i = 2, 3, \ldots, k \\
S'_{41} &= k\mu_3 S_{3,k} - k\mu_4 S_{41}, \\
S'_{4,i} &= k\mu_4 S_{4,k-1} - k\mu_4 S_{4,i}, \quad i = 2, 3, \ldots, k \\
p' &= (1-d)k\mu_4 S_{4,k}.
\end{aligned} \tag{3.2}$$

The initial conditions are $S_{11}(0) = 1, S_{ji}(0) = 0$ for all $(j, i) \neq (1, 1)$ and $p(0) = 0$.

3.1. Parameter estimation

We assume that the number of pupa emerged on t day follows a multinomial distribution with the probability $p(t) - p(t-1)$. However, the data in [9] and Table 1 are not pupa counts, but percentages. For each temperature, the total number n of larvae used for each temperature in the experiment was either 600, 700, or 800 (6 to 8 beakers with 100 larvae per beaker), but the exact value was unspecified. We assume that the three values of n were equally likely to be used for each temperature in Table 1. So we can convert the percentages $P(t)$ in the table to pupa counts by rounding $nP(t)$ to the nearest integer, i.e.,

$$C(t) = \text{Round}(nP(t)).$$

So,

$$\{C(t)\}_{t=1}^{8} \sim \text{Multinomial}(\{p(t) - p(t-1)\}_{t=1}^{8}, n)\,.$$

We used the Maximum Likelihood Estimation (MLE) method to fit Model (3.2) to the mosquito pupation data listed in each column of Table 1, and estimated model parameters under each temperature. The log likelihood function is

$$\ell(\theta) = \frac{1}{3}\sum_{m=6}^{8}\sum_{t=1}^{8} C(t) \ln\left(p(t) - p(t-1)\right) + \left(100m - \sum_{t=1}^{8} C(t)\right) \ln\left(1 - p(8)\right), \tag{3.3}$$

where $1 - p(8)$ is the probability that a pupa had not emerged by day 8, and

$$\theta = (\mu_1, \ldots, \mu_4, d).$$

3.2. Results

We take $k = 2, 3, 4, 5$ in model (3.2). The point estimates of the parameters for each temperature and k value are shown in Table 2. The results show that the developmental rates $\mu_1, \ldots, \mu_4$ are approximately the same at each temperature (except for 35°C with a large k), in addition the log likelihood increases with larger k. The estimated developmental rates indicate that developmental time at each molting stage should be identically gamma distributed. In addition, the total developmental time, which is the sum of these identical gamma distributions, is also a gamma distribution. This is independent of the value of k that we have used.

Our results show that the model fits the data better with a larger number of substages k. Instead of increasing k to find an optimal value, we take an alternative approach: our results agree with [10] that the developmental time can be well approximated by a gamma distribution with a shape parameter $4k$. In the next section, we approximate the distribution of time from the emergence of larva to the emergence of pupa as a gamma distribution, and directly estimate the shape and rate parameters.

Table 2. For $k = 2, 3, 4, 5$ the point estimates of developmental rates and the death rate of (3.2) obtained and log likelihood function value at each temperature

Temperature	k	μ_1	μ_2	μ_3	μ_4	d	ℓ
25	2	0.71	0.71	0.71	0.71	0	-276.43
	3	0.71	0.7	0.71	0.72	0	-191.43
	4	0.71	0.71	0.71	0.71	0	-144.71
	5	0.72	0.72	0.72	0.72	0.03	-114.34
27	2	0.93	0.93	0.93	0.93	0	-287.55
	3	0.94	0.94	0.94	0.94	0.01	-194.52
	4	0.94	0.94	0.94	0.94	0.01	-136.01
	5	0.95	0.94	0.94	0.94	0.01	-97.16
30	2	1.06	1.06	1.06	1.06	0.02	-461.35
	3	1.07	1.07	1.07	1.07	0.03	-358.69
	4	1.07	1.07	1.07	1.07	0.03	-293.9
	5	1.07	1.07	1.07	1.06	0.03	-250.16
33	2	0.78	0.78	0.78	0.78	0.01	-188.9
	3	0.81	0.81	0.81	0.81	0.06	-130.62
	4	0.82	0.82	0.82	0.82	0.07	-97.15
	5	0.82	0.82	0.83	0.82	0.08	-78.73
35	2	0.71	0.71	0.71	0.71	0.09	-83.99
	3	0.75	0.75	0.75	0.75	0.15	-59.53
	4	0.86	0.77	0.83	0.64	0.18	-52.52
	5	1.14	1.13	1.14	0.38	0.17	-51.39

4. Gamma distributed time from larva to pupa

We assume that, conditioned on successful pupation, the time of pupation process follows a gamma distribution. The probability that a larva becomes a pupa at time t is thus

$$p(t; \theta) = \text{Gamma}(t, s, r)(1 - d) = \frac{r^s}{\Gamma(s)} t^{s-1} e^{-rt} (1 - d)\,, \tag{4.1}$$

where d is the death rate, s is the shape parameter, r is the rate parameter, and

$$\theta = (s, r, d).$$

Note that, for the corresponding gamma distribution in (3.2), the shape parameter $s = 4k$, and the rate $r = \mu$ provided that $\mu = \mu_1 = \mu_2 = \mu_3 = \mu_4$.

We use the MLE method with the same log likelihood function (3.3) to fit model (4.1) to each column of Table 1, and estimate the shape parameter s, the rate parameter r, and the death rate d. The point estimates of the parameter values are shown in Table 3. The dependence of these parameters on the temperature is as shown in Figure 2. The comparison of the original pupation data in Table 1 and the predicted pupation probability using model (4.1) are shown in Figure 3.

Table 3. The point estimates of the parameters of (4.1) at different temperatures in the pupation stage

Temperature	s	r	d
25°C	47.3	8.7	0.058
27°C	45.5	10.7	0.015
30°C	51.5	13.6	0.028
33°C	26.9	5.6	0.081
35°C	16.4	3.1	0.180

5. Temperature dependent duration of the larva stage

The key question that we plan to answer in this paper is the temperature dependence of the developmental time. We have shown that the time from the emergence of larva to the emergence of pupa follows a gamma distribution under each temperature. We thus will need to determine the temperature dependence of the parameters of the gamma distribution, namely the shape parameter s and the rate parameter r.

Figure 2 shows that the parameters s, r and the survival probability $1 - d$ all show a unimodal relationship with the temperature. Sharpe and DeMichele [3] gives an biological explanation to this unimodal relationship, and produce a model that captures the relationship between developmental rate (the reciprocal of developmental time) and temperature that agrees well with data. However, their model gives a constant rate when all parameters are fixed, i.e., an exponentially distributed waiting time. The Sharpe-DeMichele model may be used to describe a single substage of the molting process, but is not realistic for the total developmental time from the emergence of larva to the emergence

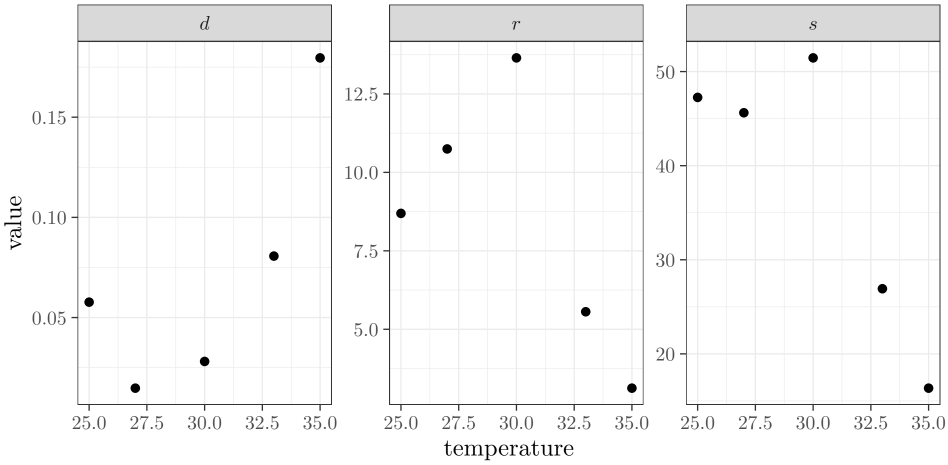

Figure 2. The temperature dependence of the point estimates of the parameters for (4.1) for the time distribution from the emergence of larva to the emergence of pupa.

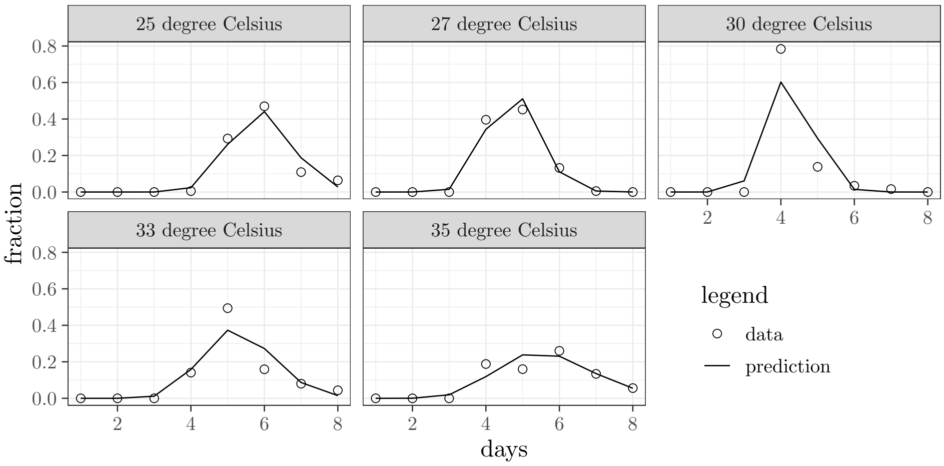

Figure 3. The comparison of the pupation data in Table 1 and the predicted pupation probability of (4.1) using the point estimates in Table 3.

of pupa. Yet this requires to estimate four additional parameters of the Sharpe and DeMichele in addition to the shape parameter of the gamma distribution. Given the limited data, this approach risks overfitting. Instead, we take a simpler empirical approach and assume that

$$\begin{aligned} s &= a_s - b_s e^{-(T-\mu_s)^2/c_s} . \\ r &= a_r - b_r e^{-(T-\mu_r)^2/c_r} . \\ d &= a_d - b_d e^{-(T-\mu_d)^2/c_d} , \end{aligned} \tag{5.1}$$

with $a_s, a_r, a_d \geq 0$, and $c_s, c_r, c_d > 0$. Note that b_s, b_r, b_d may be either positive or negative. The model parameters are thus

$$\theta = (a_s, b_s, c_s, \mu_s, a_r, b_r, c_r, \mu_r, a_d, b_d, c_d, \mu_d) .$$

Our temperature dependent model thus combines (4.1) with (5.1).

For very high or very low temperatures, we would expect that the pupation process does not occur, i.e., the death rate $d = 1$. Thus, we compare this model to an alternative model that assumes $a_d = 0$, and choose the model with the lower Akaike Information Criterion with small sample size correction (AICc). We fit both models to the data combining all columns of Table 1, using the same log likelihood function (3.3), summing over all temperatures. For the full model (4.1) and (5.1) that estimates $a_d = 0$, the AICc value is 758.56, while for the model (4.1) and (5.1) with $a_d = 1$, the AICc value is 755.46. Thus, the optimal model is the one that assumes

$$a_d = 1.$$

For the optimal model, we estimate the 95% confidence intervals of the model parameters using the likelihood profile method [15]. The point estimates and the confidence intervals of the parameters are listed in Table 4. Figure 4 compares the model predicted parameter values with those shown in Figure 2. The comparison of the pupation data in Table 1 and the predicted pupation probability of the best-fit model is shown in Figure 5.

Table 4. The point estimates and 95% confidence intervals of the parameters for the temperature dependent the distribution of the time from the emergence of larva to the emergence of pupa (4.1) and (5.1), with $a_d = 1$.

Parameter	Mean	95% confidence interval
a_s	9.4	(4.1, 11.9)
b_s	-45	(-56, -37.3)
c_s	26.6	(17.3, 45.2)
μ_s	28.1	(27.5, 28.5)
a_r	2.4	(1.5, 3.3)
b_r	-11.8	(-13.4, -10.3)
c_r	15.2	(11.9, 19.4)
μ_r	28.6	(28.3, 28.8)
b_d	0.988	(0.985, 0.990)
c_d	257.6	(210.4, 330.1)
μ_d	28.3	(27.8, 28.6)

6. Conclusion

Starting with a multi-stage pupation model to explain the pupation rate dataset published in [9] of Aedes aegypti, we found that, given that the pupation is successful, the distribution of the time from the emergence of larva to the emergence of pupa under various constant temperature conditions can all be well approximated by a gamma distribution. We then use this pupation rate dataset to estimate the parameters of the gamma distribution and the probability of pupation under the constant temperature conditions. To understand how the parameters of the gamma distribution and the pupation probability depend on the temperature, we consider that each of the parameters is a unimodal function

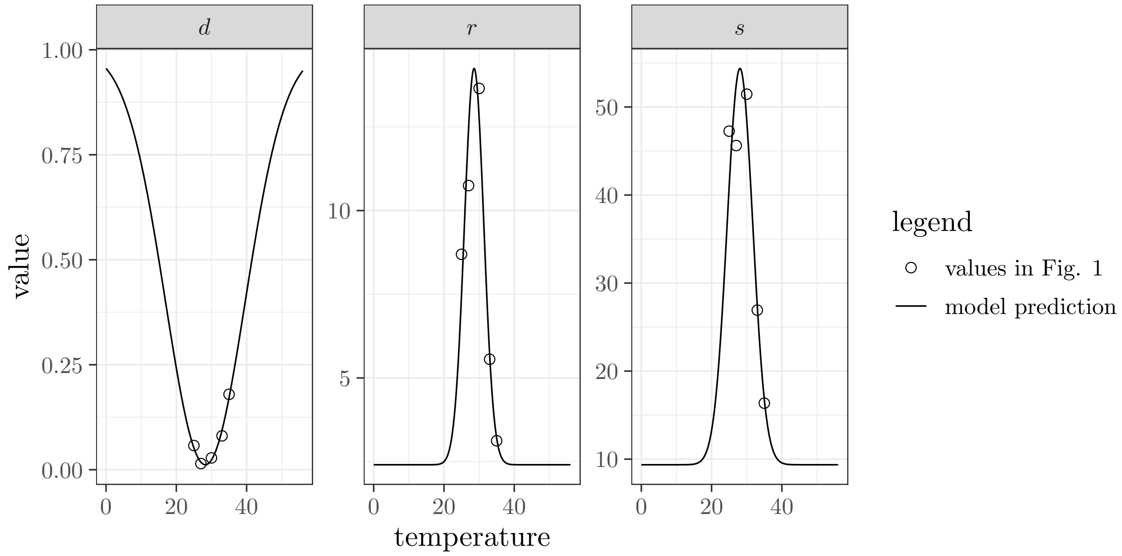

Figure 4. The comparison of model predicted temperature dependent parameters s (the shape parameter), r (the rate parameter) and d (the death rate) and the corresponding values in Figure 2 for the distribution of the time from the emergence of larva to the emergence of pupa.

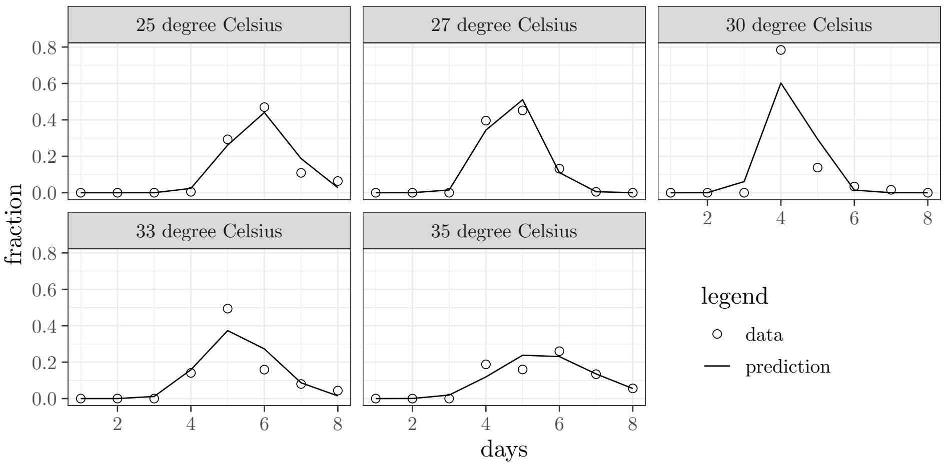

Figure 5. The comparison of the pupation data in Table 1 and the predicted pupation probability of model (4.1) with (5.1) and $a_d = 1$ using the point estimates in Table 4. This result shows that our temperature dependent model (4.1) with (5.1) gives almost identical predictions to the pupation probability as in Figure 3.

of temperature (represented by a Gaussian curve). We then fit the models to the pupation rate dataset. Our results show that the optimal temperature for pupation is approximately 28°C, where the death rate is the lowest at 1.1%, the mean time from the emergence of larva to the emergence of pupa (s/r) is shortest at about 3.8 days, and has the least variation (with a standard deviation of about 0.5 days). The optimal temperature for the shape parameter s and the rate parameter r of the gamma distribution of the time from the emergence of larva to the emergence of pupa and the death rate are not identical, even though they are very close. This may be due to limited data samples. Our results also predict that, for very high or very low temperatures, the death rate $d = 1$. However, as the data only covers 5 temperatures from 25 to 35 degrees Celsius, the predicted parameter values may not be very precise for very low or very high temperatures. This may be improved by more data at higher and lower temperatures.

The dataset contains no data in lower temperatures, and so our results on temperature dependence may not be reliable for temperatures well below 25°C. In addition, more data points may be helpful to justify assumption of a gamma distributed developmental time.

Our results may be incorporated into mosquito population models, to consider the influence of the temperature on the pupation rate. This is important in evaluating the seasonal risk of mosquito-borne diseases.

One model considers that the temperature remains approximately the same from the emergence of larvae to the end of pupation. However, the temperature may vary significantly during this period, which is not considered here. It is possible to extend our model beyond this limitation. To do so, we may assume that the time distributions for the four stages of the pupation process are gamma distributions with identical dependence on the temperature, i.e., their shape parameters are $s(T)/4$ and rate parameters are $r(T)$ (as justified by our fitting results to Model (3.2)). This allows the temperature to change between stages.

It is very likely that this method may be applied to other insect species, and also other developmental stages. Though further investigation and validation may be needed to verify this conjecture.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest in this paper.

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