Journal of Theoretical Biology 365 (2015) 311–324

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

A model for the development of *Aedes* (*Stegomyia*) *aegypti* as a function of the available food

Victoria Romeo Aznar [a], María Sol De Majo [b], Sylvia Fischer [b], Diego Francisco [a], Mario A. Natiello [c], Hernán G. Solari [a,*]

[a] Departamento de Física, FCEN-UBA and IFIBA-CONICET, Argentina
[b] Departamento de Ecología, Genética y Evolución and Instituto IEGEBA (UBA-CONICET), FCEN-UBA, Argentina
[c] Centre for Mathematical Sciences, Lund University, Sweden

HIGHLIGHTS

- Food in environment determines body size & time-statistics of adult emergence.
- Delay in pupation and dispersion of the cohort are captured by a single model.
- Larvae development sometimes waits to produce energy reserves before continuing.

ARTICLE INFO

Article history:
Received 26 December 2013
Received in revised form
3 October 2014
Accepted 14 October 2014
Available online 24 October 2014

Keywords:
Larvae maturation
Time
Statistics
Body-size
Aedes aegypti

ABSTRACT

We discuss the preimaginal development of the mosquito *Aedes aegypti* from the point of view of the statistics of developmental times and the final body-size of the pupae and adults. We begin the discussion studying existing models in relation to published data for the mosquito. The data suggest a developmental process that is described by exponentially distributed random times. The existing data show as well that the idea of cohorts emerging synchronously is verified only in optimal situations created at the laboratory but it is not verified in field experiments. We propose a model in which immature individuals progress in successive stages, all of them with exponentially distributed times, according to two different rates (one food-dependent and the other food-independent). This phenomenological model, coupled with a general model for growing, can explain the existing observations and new results produced in this work. The emerging picture is that the development of the larvae proceeds through a sequence of steps. Some of the steps depend on the available food. While food is in abundance, all steps can be thought as having equal duration, but when food is scarce, those steps that depend on food take considerably longer times. For insufficient levels of food, increase in larval mortality sets in. As a consequence of the smaller rates, the average pupation time increases and the cohort disperses in time. Dispersion, as measured by standard deviation, becomes a quadratic function of the average time indicating that cohort dispersion responds to the same causes than delays in pupation and adult emergence. During the whole developmental process the larva grows monotonically, initially at an exponential rate but later at decreasing rates, approaching a final body-size. Growth is stopped by maturation when it is already slow. As a consequence of this process, there is a slight bias favoring small individuals: Small individuals are born before larger individuals, although the tendency is very weak.

1. Introduction

Aedes (*Stegomyia*) *aegypti* (*Ae. ae.*) is a mosquito of epidemiological relevance, responsible for the transmission of several diseases such as yellow fever and dengue (Dégallier et al., 1988). Current attempts to produce methods for controlling the populations of *Ae. ae.* require the use of theoretical understanding, sometimes referred to as *models*, that extrapolate the present knowledge of the life-cycle of the mosquito to the new conditions

* Corresponding author.
E-mail addresses: vromeoaznar@gmail.com (V. Romeo Aznar), msdemajo@ege.fcen.uba.ar (M.S. De Majo), sylvia@ege.fcen.uba.ar (S. Fischer), ddhhff@gmail.com (D. Francisco), Mario.Natiello@math.lth.se (M.A. Natiello), solari@df.uba.ar (H.G. Solari).

http://dx.doi.org/10.1016/j.jtbi.2014.10.016
0022-5193/

that the control method would create. See for example (Focks et al., 1993; Huang et al., 2007; Magori et al., 2009; Legros et al., 2009; Walker et al., 2011; Ellis et al., 2011). The correct theoretical evaluation of the response of the mosquito to control methods depends on the ability of the models to simulate the adaptation of the species to different (and changing) environmental conditions.

As we have previously observed (Romeo et al., 2013), much of the literature extrapolates understandings produced under optimal environments to the natural environment. Such an approach was put forward in the earlier times of physiological research on the mosquito (Christophers, 1960) and was later found inappropriate (Dye, 1982; Subra and Mouchet, 1984; Arrivillaga and Barrera, 2004; Barrera et al., 2006). In what follows, we will critically consider the existing theories of developmental time in relation to the data and we shall propose an improved description that is consistent with existing data and with new data produced for this work. In particular, we will show that the time-dispersion of the immature cohorts increases going from optimal feeding to food-deficit conditions. Dispersal in time represents an important adaptive response not yet incorporated to the theories, nor discussed in experimental terms, yet clearly shown by (old and new) available data. We will discuss these observations introducing a simple theory of development potentially usable for other insects.

The focus of this work is the preimaginal part of the life-cycle and, in particular, the appropriate statistical description of preimaginal times and adult body-size. Mosquitoes are born out of eggs in an aquatic environment, where they develop as larvae, undergoing three moults until pupation and later emerging as adults. During this preimaginal life, the size of the adult is determined. Considering that in general (Honěk, 1993) and in particular for *Ae. ae.* (Heuvel, 1963), adult female body-size correlates linearly with fecundity, we come to understand that two key elements in the description of development and fitness are the time spent in the preimaginal stages and the individual weight of adults (which is determined during the preimaginal development).

The development of *Ae. ae.* depends on the environmental conditions. Temperature (Bar-Zeev, 1958; Heuvel, 1963; Rueda et al., 1990) and food abundance (Subra and Mouchet, 1984; Arrivillaga and Barrera, 2004; Padmanabha et al., 2011) are two factors that have been identified so far. In this work we will focus on the effects of food and will keep temperature constant.

In terms of models, two main classes of models have been proposed. The first class is associated with the concept of cohort (defined by hatching-time and environment), assigning one time for all members of the cohort such as in Focks et al. (1993), or presenting some narrow fluctuations in terms of temperature-corrected time, the (so called) physiological time (Stinner et al., 1975; Rueda et al., 1990). These models originate in Gilpin and McClelland (1979) who introduced a developmental model where pupation is reached when two conditions are met: a minimal developmental time and a minimal weight. The model is known by the name of "window model" (WM). The relation between average weight and average pupation (or adult emergence) time has been put to test (Carpenter, 1984; Gimnig et al., 2002). Whether the same relation exists at the individual level or not, has not been investigated according to our knowledge. It is also important to notice that if experimental results are to be matched, the minimal weight must depend on the available food as it is clear from the data reported in Jirakanjanakit et al. (2008); Maciá (2009). A multiple WM for *Ae. ae.* has been implemented (Magori et al., 2009). The model describes longer developmental times and smaller final weight as a function of decreasing amounts of food and incorporates some stochasticity.

In his work, Gilpin indicates that a second class of models, compartmental models, would have been more desirable but the search for such a model failed. However, a deterministic compartmental model was proposed as a general insect development model in Manetsch (1976). In this case, no biological data were offered in support of it.

The model in Manetsch (1976) can be thought as a developmental sequence where the steps are completed in sequential order. Each step (corresponding to moving from one compartment to the next in the sequence) takes a time t_j with $j=1,\ldots,E$, where E is the number of steps needed to complete the development. Hence, the time to complete development is $Td=\sum_{j=1}^{E} t_j$. If all the times t_j are identical independently distributed random variables with exponential distribution (mean τ), the time Td is associated with a Gamma distribution $\Gamma(E,rt)=1/(E-1)!\int_0^{rt} e^{-s}s^{E-1}\,ds$ with mean $E\tau$ and variance $E\tau^2$ (E is called the *shape parameter* and r the *rate*, while $\tau=1/r$ is the *scale factor*; for more details see Section 3). Manetsch's equations are recovered in the large population limit by standard methods (Ethier and Kurtz, 1986).

In the present work, we will first re-examine the developmental times reported by Southwood et al. (1972) for a field-experiment performed in Thailand (Section 2). We will show that the observed dispersions in pupation and emergence times are substantially larger than those observed by Rueda et al. (1990) in laboratory experiments and, in particular, that the coefficients of variation (standard deviation divided by mean) in both experiments are substantially different, meaning that synchronous emergence of cohort members depends on environmental conditions. We also discuss in this Section how the multiple WM can be put to test. In Section 3 we will fully reformulate Manetsch's model, including its biological content, in stochastic terms along with a description of weight-gain and then, of adult weight. A minimal model for the dependency of developmental rates with food is proposed. In Section 4 we describe experiments performed with *Ae. ae.* developing at the same temperature but different feeding conditions. In Section 5 we show that the experimental data are compatible with the proposed model. The data in conjunction with the model suggest that only a few developmental steps present a strong dependency with the available food, in situations when food-scarcity is not life-threatening. This insight allows us to explain the observed delay in pupation under food-restriction conditions and the dispersion in time of the cohorts as two aspects of the same phenomena, thus bridging from observations performed in the laboratory (Rueda et al., 1990) to observations performed in the field (Southwood et al., 1972). In the discussion section (Section 6), we show that the predictions of the multiple WM are not verified. We discuss as well the problems experienced developing the present model. Further, in Appendix A.2 the proposed theoretical probability distribution is developed from basic principles, Appendix B is devoted to the computation of confidence intervals via the bootstrap technique, while Appendix C displays a table of symbols.

Epistemological note: This manuscript presents and tests a set of ideas that can be freely used to understand elements of the developmental process of *Ae. ae.* For this reason, we recall the distinction between *theory* – meaning an idea or set of ideas that is intended to explain facts or events – and *description* – meaning statements that tell how something looks, sounds, etc. While theories usually produce descriptions as well, descriptions do not produce theories; their content being exhausted in themselves. A proper understanding of the philosophical underpinnings of theories indicates that theories belong to the world of forms (ideas) in Plato, 360 BC (2014) while descriptions of the observed are themselves copies and not forms.

Elaborating beyond (Kuhn, 1962) there are a few basic properties related to theories. Consistency is a mandatory property for scientific theories, which are further characterized by their scope, simplicity, and fruitfulness. In addition, accuracy is an ingredient

related to the particular description in use emanating from the theory rather than to the theory proper. Appraisal of theories -which is our main goal- is therefore a complex task that entails to produce statements (predictions) that can be directly confronted with observations: if the theory fails to give a fair (idealized) prediction of the observations it can be disposed of. Theories are to be appraised by how they shed light to the observations rather than by their ability to reproduce minor detail relevant to accuracy. An excess of focus on accuracy often conflicts with the basic properties (Salmon, 1990). The role of statistical tests in the appraisal of theories enters only on the accuracy side of the predictions and it is an auxiliary one, complementary to qualitative assessments such as those produced with graphs: cf. the discussion around Fig. 7, where a theory is dismissed without resorting to statistical tests. As another example, compare Fig. 4 with the statistical estimation of Appendix B regarding how much the thesis put forward of a quadratic relation between mean and variance can be trusted.

2. Previously proposed models

Window model: The intuition behind the WM of Gilpin and McClelland (1979) is simple. There are two requirements to be met for the emergence of an adult completing the developmental process: a physiological development and minimal body-size. Both requirements are considered independent. The duration of the preimaginal life results then from

$$\max\{T_{ph}, T_B\} \tag{1}$$

where T_{ph} is the physiological time required and T_B is the time required to reach the target body-mass. If one or the other in $\{T_{ph}, T_B\}$ can be the largest one, the expectation is that $T_{ph} > T_B$ under optimal feeding conditions, while in sub-optimal feeding conditions $T_B > T_{ph}$. We notice that the formulation of criterion (1) has to be complemented with a law for the evolution in time of body-mass.

Pictorially, the model defines a *pupation window,* shaped as a letter "L" in a weight vs time-to-pupation diagram. For optimal feeding conditions, weight gain has a larger slope and the weight curve hits the window on the vertical side. Under suboptimal conditions and slower weight gain, the pupation window is hit on the horizontal side. The hitting point determines pupation.

A second stage consists in accounting for the different values of the physiological time obtained at different temperatures by setting

$$T_{ph} = \int_0^t r(Te(s))\, ds \tag{2}$$

which weights the time to pupation with a temperature dependent rate, $r\,(Te)$, usually modeled following Sharpe and DeMichele (1977), see (Rueda et al., 1990; Focks et al., 1993; Magori et al., 2009). The expression (2) is named *coefficient of development* in other works.

Under optimal feeding conditions (Rueda et al., 1990) showed that the members of cohorts of *Ae. ae.* emerge within a narrow time-window of a few hours with a dispersion in time that can be reproduced by a cumulative distribution function for the time of emergence, $P(x < t)$, of the form

$$P(x<t) = \begin{cases} 0 & T_{ph} < 0.89 \\ (1-z)^{2.0126z^2} & 0.89 \le T_{ph} \le 1.17 \\ 1 & T_{ph} > 1.17 \end{cases} \tag{3}$$

where $z = (1.17 - T_{ph})/(1.17 - 0.89)$. The condition $P(x<t) = 1/2$ for $T_{ph} = 1$ has been imposed to the distribution. We indicate at this point the value of $r(26.1\ ^\circ\mathrm{C}) = 7.68$ days obtained using Eq. (1) in Rueda et al. (1990), taken from Sharpe and DeMichele (1977). This value will be relevant in relation to the experiments reported in the present work. The WM needs one more equation, one that produces body-size as a function of two variables at least, food and time. This element of the model is usually taken from von Bertalanffy (1960) (we present the model in Section 3).

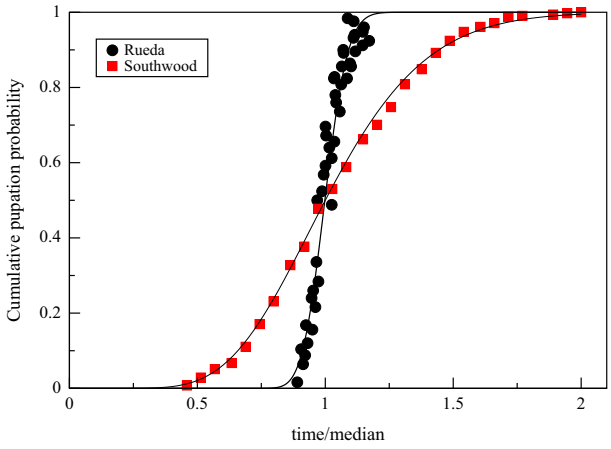

Fig. 1. Southwood et al. (1972) and Rueda et al. (1990) results for the cumulative pupation probability as a function of (time/median). Full lines correspond to data fitting via a Gamma distribution with *shape parameter* $E = 216$ (circles) and $E = 11$ (squares), see below.

Under optimal feeding conditions all members of a cohort emerge within a few hours and as such can be though as synchronously emerging when the time-resolution is one day, as it is frequently the case when modeling.

In contrast, in field experiments in Thailand performed by Southwood et al. (1972), the dispersion of the cohort involves a good number of days, implying that a deterministic use of the WM will suppress this biological element. We show Southwood et al. (1972) results for water jars along with Rueda et al. (1990) results in Fig. 1.

From Southwood's results we can conclude that under sub-optimal feeding conditions two new facts are observed: (i) Lower adult weight and (ii) larger dispersion of cohorts. These observations moved researchers to produce a stochastic WM, named by the authors "multiple window model" (Magori et al., 2009). In the multiple WM the physiological time is a stochastic variable distributed according to Eq. (3). The lower frame of the window (that gives the adult weight when the development is achieved before the body-size condition is met) is modeled by

$$B^{qt} = (0.1 - B^{qt}_{min}) * (T_{ph} - 0.95)/(8 - 0.95) + B^{qt}_{min}, \quad 0.95 \le T_{ph} \le 8 \tag{4}$$

(in *mg*) where the index *qt* stands for "quartile". Thus, a rough cumulative function can be produced by considering that $(qt * 0.25)$ of cohort members have emerged when the body-size has reached the window-frame B^{qt}, $qt = 1, \cdots, 4$. Values for B^{qt}_{min} have been proposed by (Additional material of Magori et al., 2009).

We observe that when coupled with the body-size model (see Eq. (5) below) at constant temperature, T_{ph} is proportional to time. Also, in an environment at constant temperature and offering a constant amount of food (such as the experimental design in Section 4), $B(t)$ is a monotonically increasing function of time. Hence, the multiple WM predicts that in optimal conditions adult emergence will occur with little dispersion in time (rather synchronously) and comparatively larger dispersion in pupation weights, while under suboptimal feeding conditions we will obtain lower pupation weights, less dispersion in weight and larger dispersion in time.

The epistemological status of the WM is uncertain to us: is it a conceptualization of the biological process (a theory) or is it only a description of the times and weights of emerging adults? In particular, if considered as a theory, is it correct that physiological development is not delayed by insufficient amount of food? Is it correct that under optimal feeding conditions the optimal weight is reached before the physiological time? In this later respect, Padmanabha et al. (2012) indicates, based on experiments under optimal feeding conditions, that commitment to pupation is achieved *before* reaching the pupation body-weight. Such observation by itself severely undermines the WM as a theory and forces us to consider it as a descriptive model.

Compartmental model: Manetsch (1976) model has received considerably less attention than the WM. While it is a model where stochasticity can be naturally incorporated, its biological foundations are obscure. The compartments in Manetsch (1976) do not correspond to observable stages of development (as for example instars). Rather, there are six compartments for every instar-stage (there is no rationale offered for the number six). These compartments are instruments for introducing time-varying delays, this is, a mean to simulate populations where the time required for maturation from one level of growth (instar) to the next is directly related to the ambient temperature (for example). The biological input of the transitions rates comes through a notion of "accumulated degree days" which is a rudimentary version of physiological time. More often than not, exponentially distributed times, which are within the basic assumptions of the compartmental model, are introduced as a matter of modeling convenience and quite often as a consequence of having predetermined that the model should result in ordinary differential equations.

Therefore, we should first ask whether there are observations of times pertaining to the developmental process that are distributed as sums of exponential times or not; and second, are the rates of all those processes equal among stages? A positive answer to both questions would indicate that stochastic versions of Manetsch's model are suitable candidates as models of the preimaginal developmental process.

We examine the data reported by Southwood et al. (1972) for water jars in search for answers to our questions. The data were fitted to Gamma distributions via a Marquardt-Levenberg algorithm incorporated in the GNU-licensed software *gnuplot*. The hatching-time shown in Fig. 2 adjusts to the *shape parameter* $E=1$ and it is recognized as exponentially distributed (Focks et al., 1993; Magori et al., 2009). We further observe that the cumulative distributions of time of pupation and time for adult emergence can both be adjusted using Gamma distributions with *shape parameters* $E=9$ and $E=11$ respectively (for details about Gamma distributions, see next Section, Eq. (8)). The *shape parameter* in the Gamma distribution corresponds to the inverse of the square of the coefficient of variation, which for adults here takes then the value $1/\sqrt{11}\approx 0.302$. The results found by Rueda et al. (1990) can also be adjusted to a Gamma distribution – with *shape parameter* $E=216$ – but they present substantially less individual variation (coefficient of variation ≈ 0.068, see Fig. 1).

It is worth indicating that Southwood et al. considered that the larvae in the natural environment showed signs of food scarcity while, in contrast, Rueda et al. (1990) were persuaded that food was in excess in their experiment. Contrary to early speculations (Christophers, 1960) food appears not to be in excess in natural environments (Dye, 1982; Arrivillaga and Barrera, 2004; Barrera et al., 2006) except when altered by particular human actions (Subra and Mouchet, 1984).

The hypothesis of a distribution of times as sum of independent random times exponentially distributed cannot be ruled out by the

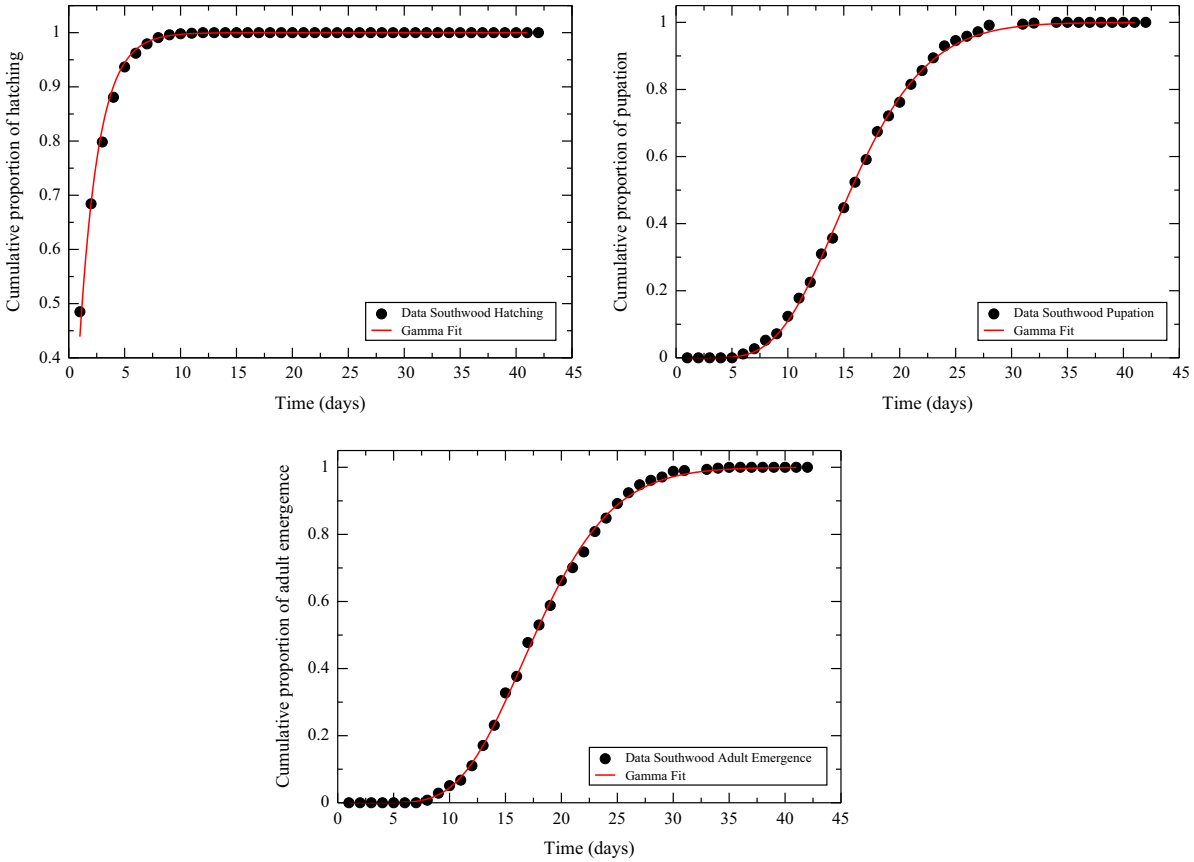

Fig. 2. Cumulative distributions fitted for the hatching, pupation and adult emergence as a function of time in *Ae. ae.* field data.

available data. Therefore, there is a possibility of modeling the distribution of times in the form of integro-differential equations using a fixed and predetermined Gamma distribution such as it is normally done in epidemiology (Keeling and Grenfell, 1997; Wolkowicz et al., 1997; Mittler et al., 1998; Conlan and Rohani, 2010) and has been proposed for more general biological circumstances (Bocharov and Rihan, 2000). However, such possibility should be disregarded since the distribution is not fixed but rather, it depends on the continuously changing environmental conditions, so that for different feeding conditions, different (apparent or effective) *shape parameters* are needed. The problem requires more flexible modeling. Gamma-distributed times can also be modeled using a sequence of compartments, a method sometimes presented as "the Gamma trick" (Lloyd, 2001; Chowell et al., 2007, 2013). The method actually allows us to model any member of the family of sums of exponentially distributed times, including those with rates that change over time. The need of incorporating the changes in the environment produced during the developmental process makes advisable to use the flexible modeling based in compartments and not the integro-differential formulations.

In the next section we will develop a stochastic compartmental model that describes both previous and new experiments, being also compatible with previously known facts about pupation such as e.g., Padmanabha et al. (2012) observations.

3. Mathematical model for developmental times and adult weight

In order to describe the maturation process and compute developmental times we use the following assumptions.

1. Each larva has an individual fate independent of the fate of other larvae. They only influence each other indirectly by modifying the environment.
2. As a consequence, if $\psi(z_1,\ldots,z_E)$ is the generating function for the stochastic maturation process of one larva and if N is the number of eggs, then $\Psi(z_1,\ldots,z_E,N)=\psi(z_1,\ldots,z_E)^N$ is the generating function for the whole system.
3. Each larva can be in one of E mutually exclusive maturation stages with probability $p_j(t)$, where $\sum_{j=1}^{E} p_j = 1$.
4. The larva progresses from one stage to the next with a transition rate $W_j(Te,F)$ and may die in the stage j with transition rate $D_j(Te,F,B)$, where Te stands for temperature, F for density of available food and B stands for body-size (weight). Mortality and progress run an exponential race (Durrett, 2001). Hence, the probability of death in stage$j$ is then $P_{dj}=D_j(Te,F,B)/D_j(Te,F,B)+W_j(Te,F)$ (Durrett, 2001).
5. Body-size is gained following the general form proposed in von Bertalanffy (1960). Body-size is lost at a rate proportional to the body-size as a result of catabolic processes and it is gained at a rate aB^{α} where $0<\alpha\le 1$ as a result of anabolic processes. Hence, weight follows a Bernoulli equation of the form

$$\frac{dB}{dt}=aB^{\alpha}-bB. \tag{5}$$

Additionally, we expect $a=a(Te,F)$ and $b=b(Te,F)$ (larvae slow down their metabolism under starvation conditions (Barrera, 1996)). During a time interval $[t_i,t_f]$ where conditions are held constant, the body-size changes as

$$B(t_f)=\left(\frac{a}{b}+\left(B(t_i)^{1-\alpha}-\frac{a}{b}\right)\exp(-(t_f-t_i)(1-\alpha)b)\right)^{1/(1-\alpha)} \tag{6}$$

which is the solution of (5). We have that $B(\infty)=(a/b)^{1/(1-\alpha)}$ is the asymptotic body-size. Body-size loss is described in the proposed form by considering that "the rate of catabolism can be assumed to be directly proportional to body weight" (von Bertalanffy, 1960). This form, or a slightly more general form bB^{β} proposed as well in von Bertalanffy (1960), has been generally adopted so far. The qualitative behaviour of monotonic growth up to a finite asymptotic value shown in Eq. (6) still holds as long as $\alpha<\beta$.

At the individual level, the development of a larva is represented by a sequence of transitions between stages that may end in death or reach the final stage (pupae or adult depending on the development under consideration). The transition from stage j occurs at a time t_j which is an exponentially distributed random number with cumulative probability for the next event

$$P(0\le t_j<\Delta t)=1-\exp\left(-\int_0^{\Delta t}(W_j+D_j)\,ds\right). \tag{7}$$

The probability of this transition being death, given that an event occurred, is P_{dj} as calculated above (see item 4), while the probability of reaching the $j+1$ stage is, correspondingly, $P_{mj}=1-P_{dj}=W_j/(W_j+D_j)$.

3.1. Simple models

A model such as the one described above has a large number of free parameters, which sharply contrasts with the availability of data and the precision of the measurements. If any understanding is going to come from the model, a simpler, more qualitative, proposal is needed.

The simplest proposal is to consider all the transition rates equal, i.e., independent of the stage. It is shown in the Appendix that in the case of equal rates $W_j=r$ and no mortality, the probability of having achieved pupation by the time t is

$$A(t)=\Gamma(E,rt)=\frac{r^E}{(E-1)!}\int_0^t e^{-rx}x^{E-1}\,dx=\frac{1}{(E-1)!}\int_0^{rt}e^{-s}s^{E-1}\,ds$$

while taking larval mortality into account, with corresponding rate $D_j=q$, it becomes

$$A(t)=\frac{r^E}{(E-1)!}\int_0^t e^{-(q+r)x}x^{E-1}\,dx=\left(\frac{r}{q+r}\right)^E\Gamma(E,(q+r)t). \tag{8}$$

Eq. (8) expresses the probability $(r/(q+r))^E$ of surviving E stages times a Gamma-distributed time.

For a *Gamma distribution* as above, the number of stages E is called the *shape parameter*, while the rate (the inverse of the *scale factor*) $q+r$ has units of $1/time$. Hence, the mean developmental time satisfies $T=E/(q+r)$ while the variance of this time is $\sigma^2=E/(q+r)^2$. This model predicts that the relation between the variance of the developmental time, σ^2, and the mean value, T, is of the form $\sigma^2=T^2/E$, a relation that does not depend on the environmental condition. Such a model would require to change the number of developmental stages as a function of environmental conditions, a requirement both difficult to implement in a continuously changing environment and difficult to associate with biology. The number of stages, this is the *shape parameter* of the Gamma-distribution, would be simply an adjustable parameter *a posteriori* (i.e., only known after the shape of the empirical distribution is observed).

We consider then the possibility that the developmental rates, $W_j(Te,F)$, belong to two classes: those that do not depend on the available food and those that are sensitive to the food density. We assign to the first class an environment-independent rate, $r_0=1/\tau_0$ and to the other a rate that depends on the available

food but is the same in all the stages in the class, $r_F = 1/\tau_F$. The developmental stages are now divided into $n > 0$ stages at a rate r_0 and $m \geq 0$ stages at a rate r_F, with $E = n + m$, yielding the relations

$$T = n\tau_0 + m\tau_F$$
$$\sigma^2 = n\tau_0^2 + m\tau_F^2 \quad (9)$$

Solving the variance as a function of the mean for the different food regimes, we get

$$\sigma^2 = n\tau_0^2 + (T - n\tau_0)^2/m \quad (10)$$

Minimum variance is obtained when $\tau_F = \tau_0$.

Hence, this model in principle has the possibility of accounting for the observed features of the statistics of pupation times or emergence times, this is to say that the longer pupation and adult emergence times observed for decreasing levels of food and the corresponding dispersion of the cohorts could be accounted for in an unified way by the model.

The theoretical cumulative probability (say for pupation, p) by the time t is

$$P_{Th}(s < t) = \int_0^t \Gamma'(n_p, (s\, r_0))\Gamma(m_p, (t-s)r_F)\, ds \quad (11)$$

Here, $\Gamma(k, rt) = 1/\Gamma(k) \int_0^{rt} s^{k-1}\exp(-s)\, ds$ and $\Gamma'(k, rt) = (d/dt)\Gamma(k, rt)$.

3.2. Model predictions

We list here quantitative and qualitative results that are implied by the model. In experiments performed at constant temperature and maintaining a constant food density:

1. A quadratic relation such as (10) will be observed between the variance and the mean value of the developmental time, be it pupation time or adult emergence time.
2. The total number of stages, of any particular class, from hatching to pupation is smaller or equal than the total number of steps, of the same class, from hatching to adult emergence. We define class as the set of compartments (stages) having the same developmental rate. Our model has two classes: food-dependent compartments and food-independent compartments.
3. The null hypothesis "the data are distributed according to the probability distributions resulting from the simple model (11) using the estimated parameters" cannot be rejected using standard statistical tests.
4. The body-size, B, follows a growth-law with $\alpha < 1$ contrary to what is conjectured in von Bertalanffy (1960), namely $\alpha = 1$ for insects.
5. Body-size differences at adult emergence for larvae reared under the same environmental conditions correspond mostly to random (individual) variability. In particular, we mean that body-size depends weakly on the relative time of emergence (early or late in the cohort).

We will put these predictions to test in the coming sections using new data obtained for *Ae. ae.* We intend to show that, at the present level of knowledge, there is no reason compelling us to drop the model or even suggesting that the model is wrong.

4. Experimental exploration of the development of *Aedes aegypti* at constant temperature and food levels

A laboratory experiment was designed to test the model and the insight produced by it. Larvae were bred at different densities of food (yeast) in water. The density was kept nearly constant by replacing the media with a new preparation daily, while the temperature as well as the photo-period were kept constant. In such conditions, we expect to decouple the environmental dynamics from the development of the larvae. This method contrasts with previous experiments where food was offered only at the onset of the experiment (Gilpin and McClelland, 1979; Maciá, 2009) or was added daily (Rueda et al., 1990) at a constant rate. In the present experiment, the aquatic environment containing food available to the larvae is substantially large (more than 25 ml per larva) and it is renewed daily. Hence, the food media is kept almost constant, i.e., with only little variations, during the full process. When, in contrast, food (or properly said, food precursors) is administered as in previous protocols, the reproduction of micro-organisms cannot be controlled. Also, in experiments in which initial food per larvae is controlled by changing the number of larvae, the feeding of the larvae changes the food density as a function of time. The consequence in all cases is that food is not constant over time. Such variability has to be accounted for without available experimental information, i.e., it is accounted by a hidden guess such as "food dynamics is not relevant" or by adding more fitting parameters through a dynamical model for food (hence degrading the quality of the model by making it less *simple*; see Popper (1959) for a discussion of the concept of *simple* in science). An alternative to our protocol would be monitoring daily the density of yeast cells available for larval feeding. Notice that yeast cells and other micro-organisms are notorious for reproducing at different rates for different temperatures (Richards, 1928; Zwietering et al., 1991, 1994), hence when no control is kept in micro-organism reproduction, the contributions of food dynamics to the developmental dynamics of mosquito larvae may be wrongly attributed to other variables.

4.1. Experimental design

Larvae of *Ae. ae.* were raised in the laboratory from just hatched up to emergence as adult, under constant conditions of food-density, day-light and temperature.

Ae. ae. eggs were collected with ovitraps in Buenos Aires city during November 2012, and stored at room temperature and saturated humidity conditions until the beginning of the experiment in December of the same year, when they were induced to hatch by immersion in water. The experiment was performed under controlled photo-period (12:12 light-dark) and temperature conditions (mean 26.1 °C, standard deviation 0.73 °C, measured in water with a HOBO (TM) data logger, recording temperature every 30 min). Recently hatched larvae (less than 12 h old) were separated in six cohorts of 30 larvae. Each cohort was transferred to a plastic recipient (cylindrical 1000 ml model made by Tecnilin, diameter 105 mm, height 125.5 mm), filled with 800 ml of dechlorinated water, and randomly assigned to a treatment. The breeding environment consisted in $150 \times 4^{1-j}$ mg ($j = 1 \cdots 6$) of dried yeast diluted in 800 ml of water, and prepared 24 h earlier to stabilize temperature variations (recipients for each treatment will be referred from here on as Recipient j). The environment was renewed every day restoring the food density conditions. After the beginning of the experiment, each recipient was inspected daily, larvae were counted and their larval instar recorded. In each opportunity, larvae were transferred to a new recipient containing the previously prepared daily ration of food. Pupae were transferred individually to containers conditioned for adult emergence. These consisted of a small plastic cap containing 1 ml of water and one pupa, placed in a larger container (a cylindrical acrylic tube,

Table 1
Estimation of larval mortality under the different treatments. j corresponds to the food in $150 \times 4^{1-j}$ mg/800 ml The interval represents the 95% confidence interval for the probability of death before reaching pupation. Confidence bands for binomial deviates were computed as described in the appendix of Otero et al. (2008).

j	1	2	3	4	5	6
Food (mg/ml)	0.1875	0.0468	0.0117	0.0029	0.00073	0.00018
Mortality	0.0–0.11	0.0–0.11	0.01–0.17	0.01–0.17	0.27–0.61	0.62–0.90

diameter 39 mm, height 55 mm), covered by a nylon mesh to prevent escape of the adult mosquito. For each individual, time of pupation and emergence of the adult, and sex were recorded.

Both wings were removed from each individual, and measured (from the alular notch to the distal margin excluding the fringe scales) to the nearest 0.001 mm using a dissecting microscope equipped with a digital camera. Measurements were performed on digital photographs with the Leica Application Suite V 4.0.0. Only the length of the left wings was used in Section 5.

4.2. Mortality results

The covered experimental range of $150 \times (1 : 4^{-5})$mg/800 ml food-density values gave two qualitatively different responses. We will therefore distinguish these responses in the subsequent analysis. We call *food-deficit range*, (although food may be near optimal for the highest concentration) the one corresponding to food-densities $150 \times (1 : 4^{-3})$mg/800 ml, $(j = 1, \ldots, 4)$. In this range, the effect of reduced food density is a delay in pupation, and an increase in the variability of emergence times among individuals, whereas mortality was not observed to depend on food. The treatments with density $150 \times (4^{-4} : 4^{-5})$mg/800 ml, $(j=5,6)$, are called *food-deprivation range.* Here, a substantial increase of mortality relative to the cohorts reared in the food-deficit range is observed.

This qualitative difference in response to the experiment has been recognized previously. Indeed, in *Drosophila melanogaster* it has been observed (Sang, 1956) that when the number of larvae sharing the same resources is increased, two different situations arise. The first reaction of the organisms when incrementing the number of larvae from an optimal feeding situation is to delay pupation. However, after a critical value is reached, mortality begins to increase as well. The same qualitative responses to increments in crowding have been observed in *Ae. ae.* (Maciá, 2009).

The estimations of mortality under the different treatments are shown in Table 1.

In Fig. 3 we show the cumulative probability of death as a function of time for the two treatments in the food-deprivation range. It can be observed that the onset of mortality presents a delay in time. A time-interval of several days separates the first surge of mortality and the second one. Most mortality cases correspond to *larvae 3* (*moulting*) *stage.*

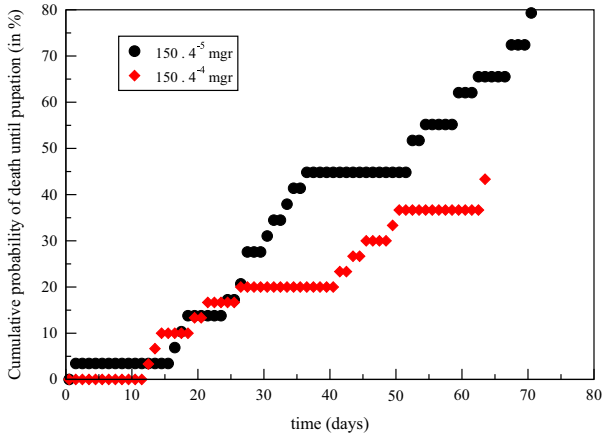

Fig. 3. Cumulative probability of death as a function of time in the food deprivation regime. Rombs, food density 150×4^{-4} mg/800 ml. Circles: 150×4^{-5} mg/800 ml.

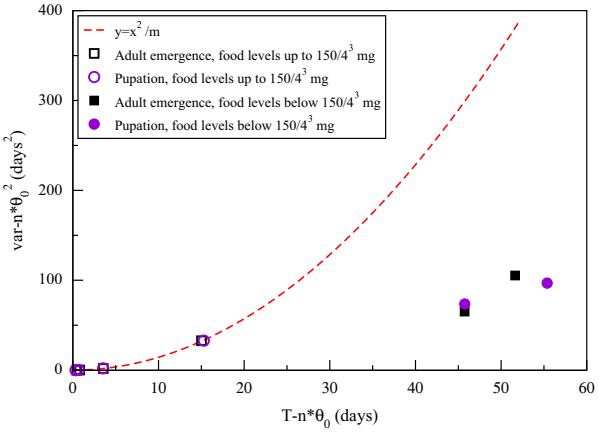

Fig. 4. Variance as a function of average time for different food-density levels. Results for pupae and adults are shown. The line corresponds to Eq. (10) using the values tabulated in Table 2. The data points correspond to all individuals (not separated by gender).

5. Relation of the model to the experimental results

5.1. The statistics of developmental times

Our first task is to show under which conditions the simple model can account for the changes in developmental times as a function of food-density. The relation 9 is shown in Fig. 4.

The relation (9) is acceptable in the food-deficit region but it breaks down when extended to the food-deprivation region. In what follows, we will center our attention in the food-deficit region. There are several reasons for this decision: first, the food-deprivation regime is more complex as it requires to find the relative position of the stages with increased mortality; second, the increment in mortality and concurrently the pupation and emergence data are substantially scarcer for each food condition in the food-deprivation regime than in the food-deficit region; and third, less food conditions are available (there are only two treatments in the food-deprivation regime).

The relation (9) allows for an estimation of the total number of stages, the number of stages with rates that depend on the food density, and the value of the food independent rates.

We first fix the integers $n_P > 0$, $n_A > n_P$, $m > 0$ and from the relation for the mean, $T = n\tau_0 + m\tau_F$ (cf. Eq. (9)), we derive the estimates

$$\tau_j = (\overline{T}_{Pj}^{Exp} + \overline{T}_{Aj}^{Exp} - (n_P + n_A)\tau_0)/(2\,m) \tag{12}$$

$$\tau_0 = 0.25\sum_j (\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp})/(n_A - n_P) \tag{13}$$

where $n_P\,(n_A)$ denote the number of food-independent stages until pupation (adult emergence) and $\overline{T}_{Xj}$ indicates the average of the time of pupation ($X=P$) or adult emergence ($X=A$) over all samples in the food treatment $j = 1, \ldots, 4$. τ_j is then a direct estimate of the time-span τ_F of the food-dependent steps, while τ_0 is obtained from the average time spent as pupae (which the model considers constant). We note that these estimates from Eqs. (12) and (13) minimize

$$\text{Error}_T = \sum_j (\overline{T}_P^{Exp} - (n_P\tau_0 + m\tau_j))^2 + (\overline{T}_A^{Exp} - (n_A\tau_0 + m\tau_j))^2. \tag{14}$$

Substituting Eqs. (12) and (13) into Eq. (14), we obtain $\text{Error}_T = 2\{0.25\sum_j (\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp})^2 - (0.25\sum_j (\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp}))^2\} = 2\{\langle (\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp})^2\rangle - \langle (\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp})\rangle^2\}$, independent of (n_A, n_P, m), which is twice the variance of $(\overline{T}_{Aj}^{Exp} - \overline{T}_{Pj}^{Exp})$ over the four treatments.

Next, the square of the difference between experimental and theoretical variance weighted with the reciprocal of the average time

$$\text{Error}_V = \sum_j (Var_P^{Exp} - (n_P\tau_0^2 + m\tau_j^2))^2/\overline{T}_{Pj} + (Var_A^{Exp} - (n_A\tau_0^2 + m\tau_j^2))^2/\overline{T}_{Aj} \tag{15}$$

is minimized over the integers $n_P > 0$, $n_A > n_P$, $m > 0$ to obtain the parameter estimates of Table 2. The rationale for the weights in the computation of Error_V is to weight possible biases in the measurement of times on an equal footing in all treatments. The values of $(n_P,\ n_A)$ depend on the election of weights but m is robust. We refer to Appendix B for confidence intervals of the estimated parameters. Under the hypothesis that the theory is correct, the p-value associated to the fulfillment of the relation (10) is of $p = 0.666$ (see Appendix B).

Table 2
Parameter values for the simple developmental model. *P* indicates pupation times and *A* emergence times of the adults.

	n	m	$\tau_0 = 1/r_0$	$\tau_1 = 1/r_1$	$\tau_2 = 1/r_2$	$\tau_3 = 1/r_3$	$\tau_4 = 1/r_4$
P	50	7	0.0724	0.0556	0.108	0.506	2.165
A	74	7					

5.2. Goodness of fit

Having obtained (rough) estimates for the parameters involved in the proposed theoretical distributions of pupation and emergence times, Eq. (11), we will try to asses the quality of the fit and the contributions of the theory (see results in Table 3). We leave the comparison with previous theories for the discussion section.

From the experimental data we consider the estimate of the cumulative distribution function

$$P_{Ex}(s < t; j) = N_p^j(s < t)/N_p^j(s < \infty) \tag{16}$$

where $N_p^j(s < t)$ is the number of larvae that have pupated at time t in the experimental conditions j. P_{Ex} is a step function since our measuring protocol is not continuous.

We use the following tests:

1. The Kolmogorov–Smirnov estimator (von Mises, 1964; Conover, 1965) $(D = \sup_d |P_{Th}(s < d) - P_{Ex}(s < d)|)$ for discontinuous distribution functions (Conover, 1972; Gleser, 1985) (p-value p_{KS}).
2. The same Kolmogorov–Smirnov estimator with samples restricted (conditioned) to those deviates that satisfy the conditions: $(Var - Var^{Th})^2 \le (Var^{Exp} - Var^{Th})^2$ and $(T - T^{Th}) \le (T^{Exp} - T^{Th})^2$, where $\{T, Var\}$ stand for the media and variance of the random-deviate, i.e., samples of the proposed distribution function that satisfy a condition stronger than the condition used for fitting the parameters, Eq. (14), (15) (p-value: p_{KS}^*).
3. The estimator $\chi = \sum_i (n_i - Np_i)^2/(Np_i))$ under the above constraint, where the summation runs over the days of observations and n_i are the number of new pupae or new adults counted the i-day, $N = \sum_i n_i$. This test is a χ^2 test in the large N-limit, p_χ^*.
4. The $R2$ estimator: $R2 = 1 - \sum_{i=1}^{L} (n_i - Np_i)^2/\sum_{i=1}^{L} (n_i - N/L)^2)$ where L is the day of the last event observation.

In all cases, due to the smallness of $N \approx 30$, we used Monte-Carlo simulations to assign the p-value.

To assign an overall goodness of fit to the theory we compute the geometrical average of the p-values which result in $p_{KS} = 0.597$; $p_{KS}^* = 0.199$; $p_\chi^* = 0.273$; $R2 = 0.837$.

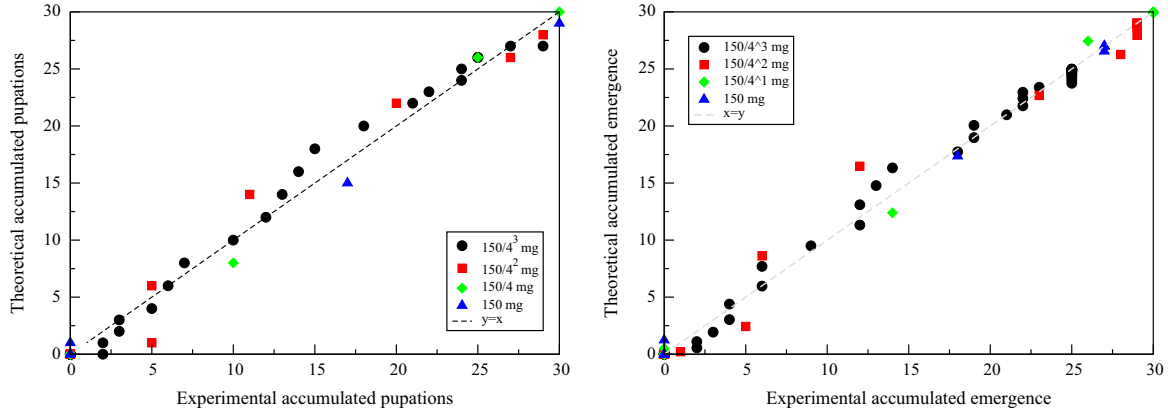

Fig. 5. Theoretical and experimental cumulative functions for pupae (left) and adults (right) including all food treatments in the food-deficit regime. The pairs $(P_{Th}(s < d),\ P_{Ex}(s < d))$ are plotted for all the days d.

Table 3
Goodness of fit. N is the total number of surviving pupae or adults in the experimental arrangement, D is the Kolmogorov–Smirnov (KS) discriminant. Index j indicates food treatments, with food levels given in mg/ml. We show results for the KS tests, p_{KS}; KS with the universe of samples restricted (see text), p^*_{KS}; restricted χ-test, p^*_χ (see text) and R-square statistic, $R2$, as a function of the food treatment for pupae (left) and adults (right). The overall quality of the theory is gauged by the geometrically averaged values $(\Pi_k p_k)^{1/8}$ with k running through all the eight sets.

j	Pupae				Adult				Average
	1	2	3	4	1	2	3	4	
Food	0.1875	0.0468	0.0117	0.0029	0.1875	0.0468	0.0117	0.0029	
N	30	30	29	29	27	30	29	25	–
D	0.06	0.07	0.05	0.11	0.12	0.04	0.08	0.08	–
p_{KS}	0.64	0.67	0.77	0.54	0.21	0.89	0.56	0.87	0.597
p^*_{KS}	0.35	0.17	0.38	0.13	0.03	0.55	0.09	0.56	0.199
p^*_χ	0.27	0.3	0.22	0.73	0.09	0.29	0.10	0.91	0.273
$R2$	0.98	0.94	0.95	0.56	0.93	0.96	0.92	0.60	0.837

A visual presentation for all the data is achieved plotting the pairs $(P_{Th}(s<d),\ P_{Ex}(s<d))$ for all the days, d, of the experiment. Departure from the diagonal indicates discrepancies (statistical or other), see Fig. 5.

We close this subsection showing that, visually, $P_{Th}(s<t)$ (Eq. (11)) does not differ substantially from a Gamma distribution with an effective number of stages given by

$$E_{eff} \sim T^2/var = \frac{T^2}{n\tau_0^2 + (T-n\tau_0)^2/m}, \tag{17}$$

which monotonically decreases from $E_{eff}=(n+m)$ to $E_{eff}=m$ when T goes from $T=(n+m)\tau_0$ to $T=\infty$. This observation illustrates why it was possible to fit the published data of Section 2 (Figs. 1 and 2) with Gamma distributions. In Fig. 6 we show more examples of this property.

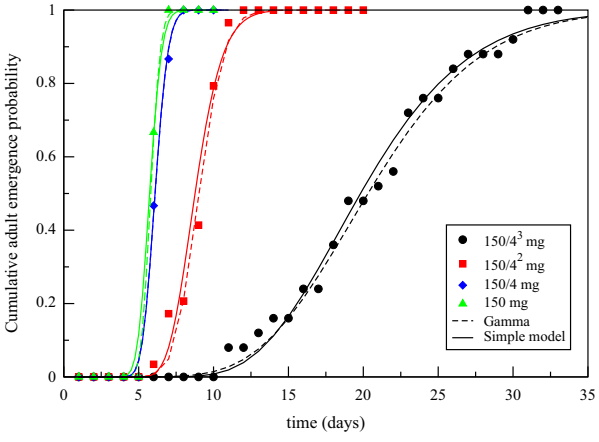

Fig. 6. Experimental and theoretical cumulative distribution approximate by a Gamma-distribution of a number of stages E_{eff}, Eq. (17) and the proposed distribution (11).

5.3. The statistics of adult body-size

We use the cube of wing length as an indicator of the adult size of emerging adults. When adult weight and wing length are considered within a group of larvae reared under the same conditions, the body weight is roughly proportional to the cube of the wing-length (Christophers, 1960; Heuvel, 1963).

The final (average) body-size of *Ae. ae.* depends on the food available being larger for the treatments with larger density of available food (see Table 4).

Additionally, we compare the fraction of the cumulative biomass B_C produced by the day d, $B_C(d)/B_C(\infty)$, with the corresponding fraction of the total number of individuals produced,

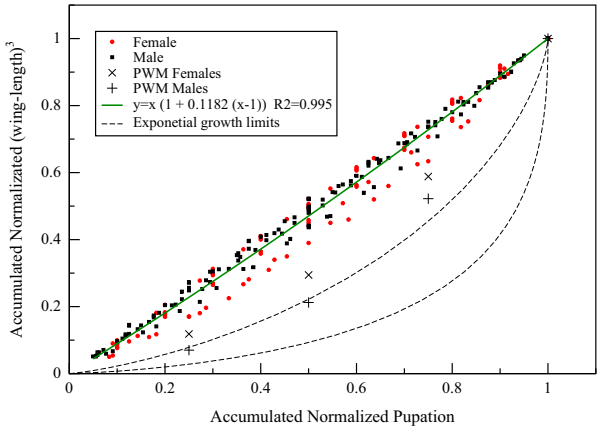

Fig. 7. Fraction of total biomass (wing-length)^3 plotted against the fraction of the total number of individuals (18). The crosses and plus signs indicate the values expected for the WM according to the tables in Magori et al. (2009) for optimal feeding. The solid line corresponds to a least-squares fit, the root mean square error is 0.11 while $\max_x|y(x)-x| \simeq 0.1182/4$. According to an exponential model for growth all the points should lie in the region demarcated by the dashed lines.

Table 4
Average body-size for the different experimental conditions. We indicate the average length of the left wing and the SD for females (*Fe*) and males (*Ma*). Not all wings could be successfully measured.

Treatment j	1	2	3	4	5	6
Food (mg/ml)	0.1875	0.0468	0.0117	0.0029	0.00073	0.00018
Fe wing length (mm)	2.96	2.83	2.56	2.22	1.99	1.84
SD	0.04	0.11	0.13	0.26	0.17	NA
Number of *Fe*	10	10	10	12	8	1
Ma wing length (mm)	2.24	2.15	1.95	1.74	1.62	1.58
SD	0.04	0.07	0.076	0.11	0.06	0.09
Number of *Ma*	16	17	17	11	8	2

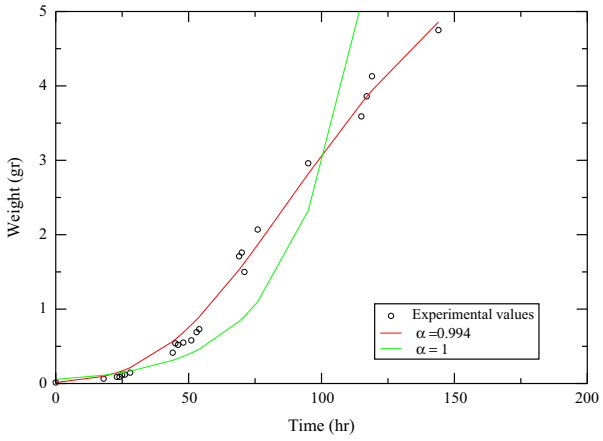

Fig. 8. Larval average weight as a function of time and the model (5) with $B(0)=0.0137$ and the fitted values $B(\infty)=6.629$ mg, $b=3.430\ \mathrm{hr}^{-1}$ and $\alpha=0.994$. For comparison a fitted exponential ($\alpha=1$) is also plotted. The data was taken from Christophers (1960) for larvae fed under optimal conditions.

$N(d)/N(\infty)$. With

$$N(d)=\sum_{0\le i\le d} n(i)$$

$$B_C(d)=\sum_{0\le i\le d}\ \sum_{0\le j\le n(i)} B_{ij} \tag{18}$$

where $n(i)$ is the number of adults emerged in day i and B_{ij} is the weight of the j-adult emerged in day i. In Fig. 7 we show the experimental relation between $N(d)$ and $B_C(d)$ where a small deviation from the identity is observed, indicating that early emerged individuals present an almost negligible smaller weight than those emerging later. Regarding the fit in the Figure, note that the points $(0,0)$ and $(1,1)$ belong in the graph exactly and therefore any proposed fit has to comply this constraint. We tested the nonlinear polynomial of lowest degree satisfying the constraint.

According to Eq. (6) the average weight will grow with a characteristic time of $1/(a-b)$ for $\alpha=1$ (exponential growth), while in the case of $\alpha<1$ an asymptotic body-size is reached. In the first case, we expect the body-size of late emerged adults to be significantly larger than the body-size of those early emerged. We remind the reader that the body size at pupation is the adult size as well since pupae do not eat. Indeed, according to the growth model (von Bertalanffy, 1960) presented in Section 3 and adopting $\alpha=1$ in Eq. (5), the weight variation *TWV* along the period of pupation estimated as the ratio of the biomass accumulated in the second half of the period of pupation relative to the biomass accumulated in the first half of the period is $TWV\sim\exp((a-b)\sigma)\ \sim\exp((a-b)T/\sqrt{E_{eff}})=U^{1/\sqrt{E_{eff}}}$, where U is the growth factor from egg to pupa, $B(T)=U\,B(0)$. In the present situation we have $m\le E_{eff}\le m+n$, or $0.38>1/\sqrt{E_{eff}}>0.13$. The factor U reported in Christophers (1960) for *optimal* food conditions is 234 (males) and 358 (females). Hence, we may estimate $(234(1.74/2.24)^3)^{0.38}\ =5.96>TWV_F>2.15=(358)^{0.13}$ for exponential growth (in the left side of the inequality, Christopher's data is corrected for food scarcity, as reported in Table 4), while we obtain $TWV\lesssim y'(x=1)/y'(x=0)=1.27$ from Fig. 7. The data points are therefore incompatible both with exponential growth and with the expectations of the WM (shown in the graph). When the cumulative probability of pupation is approximated by a gamma distribution of *shape parameter* $E_{eff}\sim T^2/var=(n\tau_0+m\tau_F)^2/n\tau_0^2+m\tau_F^2$ and *scale factor* $\tau_{eff}=(n\tau_0+n\tau_F)/E_{eff}$ the cumulative distribution function corresponds to a gamma distribution as well, with *shape parameter* E_{eff} and *scale factor* $\tau_B=(\tau_{eff}/(1+\tau_{eff}(a-b))$, being the average growth factor $U\simeq(1-((a-b)/\tau_{eff})^{E_{eff}})^{-1}$. These relations allow to produce the exponential growth estimations of Fig. 7 using $(a-b)=(1-U^{-1/E_{eff}})/\tau_{eff}$.

This result indicates that there is little relation between body-size and relative time of emergence. Hence, $\alpha<1$ must be concluded. Direct examination of the data presented in Christophers (1960) indicate as well a value of $\alpha<1$ since saturation effects are visible. Christophers data are plotted in Fig. 8 to facilitate the discussion.

6. Discussion

The Coefficient of variation, CV, for developmental time of adults in the experiment progresses as 0.08, 0.12, 0.17 and 0.28 when we go from high food (recipient 1) to low food (recipient 4). Compared to the coefficient of variation in Rueda et al. (1990) and Southwood et al. (1972), we see that Rueda's 0.07 ranks in the well-fed lot while Southwood's 0.33 pertains to the other extreme.

Performance of the window model: The performance of the WM is uneven. The mean time at the experiment temperature was of $r(26.1\ ^\circ\mathrm{C})^{-1}=7.68$ days while all the well-fed cohorts pupated completely before 7.5 days, indicating a systematic difference that could represent differences between the local strain of the mosquito and the strain used by Rueda et al. (1990). When the observed statistical mean was used as the inverse of the rate $r(Te)$, a good agreement ($R2=0.99$) was found with the proposed distribution in Eq. (3), meaning that the window in physiological time for the emergence of adults was correctly estimated. In sharp contrast, the dispersion in body weight for females increases when going from optimal feeding towards less favourable conditions, contrary to the predictions of the multiple WM; the dispersion of the body-size for males stays approximately constant, again in contrast with the prediction of the WM (see Table 4), despite the fact that the physiological time in the experiment corresponds to the range 0.95:4.98. In the same direction, the data corresponding to the relation between biomass and number of individuals (Fig. 7) show that there is very little deviation towards smaller body-sizes at the beginning of the emergence process relative to body-sizes at the end of the process. This is to say that the lower frame of the WM is not providing a qualitatively satisfactory description of the dispersion in weight. In conclusion, the WM has to be considered only as a statistical relation qualitatively derived from the facts that the average time spent in the preimaginal stages is monotonically decreasing with the food density and that the body-size is monotonically increasing with food density, both of them on average. It follows that average body-size monotonically decreases with the *average* time spent in the preimaginal stages. But the relation does not hold at the individual level within the same food-treatment group.

In contrast with the WM, the model outlined in this work shows weights that are rather insensitive to the fluctuations of adult emergence time within the cohort, in agreement with the experimental results. It should be noted however, that body-size should also be considered a random variable and Eq. (5) should be replaced by a stochastic process if fluctuations in body-size are considered relevant.

Difficulties: We will comment next some difficulties encountered along the work.

The sensitivity of the fit of Eq. (15) is far from being equal for each parameter. While m accounts for the effects that the dependence with food of the time to pupation has on the variance, n_P and n_A account for the minimal variance which is substantially affected by the decision of measuring once a day. This uncertainty in the measurement protocol strongly influences the minimal variance since all within-day effects are wiped away. In Table 2 we reported that the stages not depending on food, τ_0, are longer that the food-dependent stages in treatment 1, τ_1 (presumed to be close to optimal feeding). However, when the fit is repeated

enforcing $\tau_1 = \tau_0$, the errors (14), (15) do not deteriorate significantly, yielding $\tau_0 = \tau_1 = 0.060$, $n_P = 60$, $n_A = 89$, while the rest of the parameters display no significant changes. Hence, the thesis that $\tau_0 = \tau_1$ cannot be rejected and lies within the confidence intervals for the parameters (see Appendix B).

Male and female larvae apparently develop at different rates and differences in pupation times and body-size have been reported (Padmanabha et al., 2011). Our analysis makes no distinction between them because of two reasons: (a) previously presented data and models do not make such a distinction and (b) separating by sexes substantially weakens our statistics.

7. Conclusions

The main qualitative and quantitative aspects of the development of *Aedes* (*Stegomyia*) *aegypti* in different environments characterized by different availability of food are an increase in the average pupation time, an increase in the time-dispersion of pupation (emergence) events and a decrease of body-size for decreasing levels of available food. Only when food is extremely scarce, an important increase in mortality is observed.

We have shown that individuals hatched as a result of the same wetting stimulus and reared under the same conditions do not pupate or emerge synchronously, but rather present relatively large coefficients of variation. Synchronous pupation/emergence can be observed in the laboratory under optimal feeding conditions but it is unlikely to be observed in the wild.

We have shown that the available data correspond well with development thought of as a sequence of compartments (stages) with exponentially distributed times and that Gamma distributions can be fitted to the data. In particular, the egg-hatching time in *Ae. ae.* is exponentially distributed. The effective number of developmental stages (17) depends on the available food and decreases as food-deficit increases. We conjecture that what the data are evidencing is that the transition rates for only a few developmental stages are affected by food availability while most stages are not affected. As the total developmental time becomes dominated by the slow transitions (smaller rates) the apparent number of stages decreases. When only two different values of rates are allowed (food independent and food dependent), we have shown that the expected relation between variance and mean is quadratic; the precise shape of this relationship is the only property of the theory that was optimized to obtain a description. This functional relation between time for adult emergence and cohort dispersion in time means that both phenomena are not independent, but rather different aspects of the same process. This idea supports the view of intrinsic stochasticity, as opposed to the paradigm of "determinism plus noise" for emergence and dispersion (meaning that the biological information is contained exclusively in one value, usually represented by the average, while deviations from average correspond to uncontrollable nuisance factors that should be averaged out without further analysis). Rewritten in terms of body-size and physiological development, the results can be read as: at a few places in the process of physiological development, the process has to wait until body-size/reserves have been accumulated, before proceeding.

We carried out an experiment to test the insight produced by the theory, rearing *Ae. ae.* larvae at different constant food levels and constant temperature. A region of food-deficit with a dynamic range of food-density of $150 \times (1 : 4^{-3})$mg/800 ml was identified, as well as a food-deprivation regime with range $150 \times (4^{-4} : 4^{-5})$ mg/800 ml. The food-deprivation regime is characterized by high mortality and the food-deficit regime corresponds to low mortality. The existence of these two regimes has been previously proposed on the basis of modeling consistency (Romeo et al., 2013). The simple development theory proposed here corresponds to the food-deficit region.

The experimental data obtained are consistent with the theoretical predictions (Section 3.2). Let us repeat them:

1. A quadratic relation such as (10) will be observed between the variance and the mean value of the developmental time, be it pupation time or adult emergence time.
2. The total number of stages, of any particular class, from hatching to pupation is smaller or equal than the total number of steps, of the same class, from hatching to adult emergence. We define class as the set of compartments (stages) having the same developmental rate. Our model has two classes: food-dependent compartments and food-independent compartments.
3. The null hypothesis "the data are distributed according to the probability distributions resulting from the simple model (11) using the estimated parameters" cannot be rejected using standard statistical tests.
4. The body-size, B, follows a growth-law with $\alpha < 1$ contrary to what is conjectured in von Bertalanffy (1960), namely $\alpha = 1$ for insects.
5. Body-size differences at adult emergence for larvae reared under the same environmental conditions correspond mostly to random (individual) variability.

In addition, once parameters are adjusted to the data, the phenomenological model indicates that the rates of the stages between pupation and adult emergence do not depend on the available food.

Body-size was described in the standard form proposed by von Bertalanffy (1960). The exponent for gain, consistent with existing data, appears to be close to $\alpha = 1$, as suggested in general for insects in von Bertalanffy (1960)); yet, saturation effects (meaning $\alpha < 1$) can be readily seen both in pre-existing data and in the relation between biomass produced and number of individual emerged after d-days. The emerging picture is that larvae continue to grow until pupation but pupation takes place when the growing has slowed down substantially, a conclusion agreeing with those reached in Padmanabha et al. (2012). The data present no evidence for body-size being a requirement for pupation as proposed earlier (Gilpin and McClelland, 1979). The WM appears to be limited to the statistical level (regression) but not linked to individual variability. In contrast, early-emerged individuals are slightly smaller than late-emerged ones as explained by the present model.

The model introduced in this work makes no separation between maturation and weight gain. Both processes are treated in a unified way, being both consequences of the interplay of genetic (manifested in basic physiological parameters) and environmental conditions (such as temperature and available food). Both dispersion in body weight and dispersion in adult emergence time increase for suboptimal feeding conditions and are part of an unified picture.

Acknowledgements

We acknowledge support from the Universidad de Buenos Aires under grant 20020100100734. We thank the Grupo de Estudio de Mosquitos monitoring program (FCEN-UBA) for providing the *Ae. ae.* eggs used in the experiment. M.N. acknowledges a grant from *Vetenskapsrädet*.

Appendix A. Derivation of $A(t)$ from the assumptions in Section 3

A general derivation of $A(t)$ in a population context was given elsewhere (Solari and Natiello, 2014). In this Appendix we re-

derive that expression in the simpler context of considering the fate of one larva, since the derivation contributes to gain some insight into the process. We comment below on the corresponding procedure for the case with mortality, referring again to Solari and Natiello (2014) for the complete calculation.

A.1. Case without mortality

The individual process in this case consists of a larva in stage 0 at $t=0$ as initial condition, subject to a Markov process with the following properties:

- The probability of a transition $j\to j+1$ during a short time-interval Δt is $r\Delta t+o(\Delta t)$. Here, $o(\Delta t)$ is a quantity that goes to zero with Δt faster than linearly (i.e., even $o(\Delta t)/\Delta t$ goes to zero with Δt).
- The probability of no transition during Δt is $1-r\Delta t+o(\Delta t)$.
- The probability of more than one transition occurring during time-interval Δt is $o(\Delta t)$.
- The larva evolves through stages 0 to $E-1$, exiting the system at stage E as a pupa (or adult). The final stage is an absorbing state (no further transitions occur).
- There are no transitions $k\to(k-1)$. This is a biological constraint, maturation processes are irreversible.

Hence, the probability of reaching an intermediate stage k at time $t+\Delta t$ is

$$P(k,t+\Delta t)=P(k-1,t)r\Delta t+P(k,t)(1-r\Delta t)+o(\Delta t)$$

rearranging the terms we have,

$$\frac{P(k,t+\Delta t)-P(k,t)}{\Delta t}=(P(k-1,t)-P(k,t))r+\frac{o(\Delta t)}{\Delta t}$$

taking the limit for $\Delta t\to 0^+$ we obtain,

$$\dot{P}(k,t)=(P(k-1,t)-P(k,t))r.$$

For the case $k=0$, one has $\dot{P}(0,t)=-rP(0,t)$ while the final maturation stage responds to the equation $\dot{P}(E,t)=rP(E-1,t)$. We will first solve the equations for the intermediate stages $0\le k\le E-1$, and subsequently compute $P(E,t)$ by direct integration. Rearranging the intermediate stage probabilities in a column vector $P(t)=(P(0,t),P(1,t),\ldots,P(E-1,t))^T$, the problem can be recasted as the matrix equation

$$\dot{P}=GP,$$

where the $E\times E$ matrix G satisfies $G=-rI+rJ_1$, and matrix J_1 has ones in the first lower sub-diagonal and zeroes elsewhere (in general, $J_k=J_1^k$ has ones in the lower k-th sub-diagonal and zeroes elsewhere, for $0\le k<E$, while J_E is the zero matrix). The solution is computed straightforwardly as $P(t)=e^{tG}P(0)$, where

$$e^{tG}=e^{-rt}I\cdot\left(I+\sum_{k=1}^{E-1}\frac{r^kt^k}{k!}J_k\right).$$

Inserting the natural initial condition for this problem, i.e., $P(0)=(1,0,\ldots,0)^T$, the probability of the larva being at stage $E-1$ at time t is,

$$P(E-1,t)=\frac{r^{E-1}t^{E-1}}{(E-1)!}e^{-rt}.$$

Finally, the probability of having reached pupation stage E can now be obtained by direct integration of the final equation $\dot{P}(E,t)=rP(E-1,t)$:

$$A(t)=P(E,t)=\frac{r^E}{(E-1)!}\int_0^t e^{-r\tau}\tau^{E-1}d\tau=\frac{1}{(E-1)!}\int_0^{rt}e^{-s}s^{E-1}ds=\Gamma(E,rt).$$

A.2. Case with mortality

Introducing death events at each intermediate stage, the possible evolution of a larva in stage j is either dying at that stage or evolving to the stage $j+1$. We call q and r the rates corresponding to one or the other event. The probability of reaching an intermediate stage k at time $t+\Delta t$ modifies to

$$P(k,t+\Delta t)=P(k-1,t)r\Delta t+P(k,t)(1-(q+r)\Delta t)+o(\Delta t)$$

while the differential equations for the intermediate stages now read

$$\dot{P}(k,t)=rP(k-1,t)-(q+r)P(k,t),\quad \dot{P}(0,t)=-(q+r)P(0,t).$$

The final equation for reaching pupal stage E remains unmodified. The previous procedure can be reproduced straightforwardly, if now matrix G reads: $G=-(q+r)I+rJ_1$. Finally, we obtain

$$P(E,t)=\frac{r^E}{(E-1)!}\int_0^t e^{-(q+r)\tau}\tau^{E-1}d\tau=\left(\frac{r}{q+r}\right)^E\frac{1}{(E-1)!}\int_0^{(q+r)t}e^{-s}s^{E-1}\,ds.$$

Appendix B. Confidence intervals for the estimated parameters

Confidence intervals for the estimated parameters have been calculated using the statistical method known as bootstrap (Efron and Tibshirani, 1993; Chernick, 2008). We start discussing how bootstrap relates to the distinction between theory and description.

As stated in the introduction, the present work is an attempt to produce a theory of aspects of the development process of the larvae of *Ae. ae.* concerning mostly the time spent as larvae until achieving pupation and the time spent as larvae and pupae until emerging as adult. While theories are produced by a process of abstraction and abduction (Burks, 1946) resulting in (tentative) universal statements after removing the particular properties that distinguish any particular realization of the theory, experiments are (at most) realizations of the theory which are subject to particular circumstances in each situation. In the case of our experiment, the number of larvae used for each treatment and the decision to sample with one-day intervals are perhaps the most relevant circumstances. They are also the outcome of a compromise between resources and the adaptation to biological times. The experimental data then reflects not the theory but a particular experiment. In addition to these decisions there are undetected errors and unavoidable uncertainties that will have an effect on the measurements, at some level of precision. For the sequel, let P_0 denote the true distribution for the process, while $\tilde{P}_0$ is the distribution of the data from the actual experiment.

The method of bootstrap (Beran, 1986; Romano, 1988) concerns $\tilde{P}_0$ and the space Ω of *descriptions* compatible with the underlying theory, along with a procedure Θ to pick a description from Ω. Let $\hat{P}$ denote the chosen description. We have $\Theta(data)=\hat{P}\in\Omega$. The procedure Θ usually minimizes some weighted error between the data and the corresponding quantities in the description. The only constraint for Θ at this point is that if $pdata(P_0)$ is any set of pseudo-data obtained with random deviates from the distribution P_0, then, $\Theta(pdata(P_0))=P_0$ Romano (1988). The method proceeds by generating pseudo data and recalculating the description via Θ.

There are two bootstrap "flavours", characterized by the equations $\Theta(pdata(\tilde{P}_0))=\tilde{P}_0$, and $\Theta(pdata(\hat{P}))=\hat{P}$. In the first one, the pseudo data are taken from the actual experimental distribution $\tilde{P}_0$ while in the other – called *parametric bootstrap* – the pseudo data come from the chosen description $\hat{P}$ (Section 5). If $\tilde{P}_0\in\Omega$, these equations are equivalent in the limit (for a sufficiently large amount of bootstrap replications). However, these equations will never be satisfied exactly. Instead, the computation of confidence

intervals over the bootstrap replications is used. Since we compute a finite amount of replications and we are never in the limit, the choice of Θ, the number of replications, the experimental nuisance, etc., will to some extent influence the results, as it is in any statistical appraisal.

Note that none of the bootstrap flavours uses P_0. Whether $P_0 \in \Omega$ is an issue that bootstrap takes for granted, being unable to decide about it Beran (1986), Romano (1988), Efron and Tibshirani (1993), Chernick (2008). Therefore, bootstrap does not belong in the appraisal of the theory, but rather it is involved in the estimation of the accuracy of the description. Its proper place is among the tests discussed in Section 5, or rather *after* them since the bootstrap procedure in itself does not care (Hjorth, 1994) about the fulfillment of the hypothesis $P_0 \in \Omega$.

If $\hat{P}$ is within the resulting confidence intervals, we may be confident that Θ did not introduce important systematic errors or bias. Because of the limitations of the experimental protocol discussed above, it is advisable in this work to perform parametric bootstrap, analysing $\Theta(pdata(\hat{P}))$. Θ, as described in Section 5, is not a projector in the space of models for the experiment but rather a projector in the space of theories.

For the present experimental situation, the pupation times are independent of each other (according to the theory, Eq. (9), $T_j = n_P\tau_0 + m\tau_j$, where j runs over food-treatments). Further, the theory expects $T_{asP} = (n_A - n_P)\tau_0$, the time spent between pupation and emergence, to be independent of the treatment. Finally the integer parameters in the theory can be recasted as $(n_P, n_{asP} = n_A - n_P, m)$ being thus asymptotically independent of each other and of the above times. The confidence intervals obtained assuming normal deviates of the parameters and percentiles over 2000 realizations of the ideal experiment are reported below in terms of these quantities. Values reported under the label *C* were computed forcing the pseudo-data into the experimental protocol of one-day measurements (this is expected to closely mimic $\tilde{P}_0$) while the values with label *R* were computed as given by $\hat{P}$, which is free from experimental limitations.

The intervals CI of Table B1 represent the 90% tightest confidence intervals achievable with an ideal experiment following 30 larva in each treatment. Additionally we compared the error given by Θ for each bootstrap replicate with the error for $\hat{P}$, finding $P(Error_B > Error_{\hat{P}}) = 0.666$, which means that the experimental data satisfies the relation predicted by the theory and reflected in Eq. (10) as much as it can be expected. It also means that the restricted KS test of Section 5 ($p^*_{KS} = 0.20$) is a more demanding test than $P(Error_B > Error_{\hat{P}})$, being both fair tests.

Appendix C. Symbols table

Table C1.

Table B1

Outcome of bootstrap analysis. *Data* corresponds to the experimentally recorded average times. *Description* corresponds to $\hat{P}$, the computed parameters in Section 5, while *Average* correspond to the mean after 2000 replicas of the experiment (*C* is computed grouping event times in one-day intervals and *R* is without grouping). *CI* displays confidence intervals for the respective bootstrap averages, assuming normal deviations (*N*) and as 5–95% percentiles.

Parameter	T_1	T_2	T_3	T_4	T_{asP}	n_P	n_{asP}	m
Data	3.93	4.33	7.16	18.91	1.74	–	–	–
Description	4.01	4.38	7.16	18.78	1.74	50	24	7
Average R	4.02	4.38	7.15	18.79	1.74	~57	~30	~8
Average C	4.01	4.38	7.16	18.80	1.74	~50	~27	~8
CI(*NR*)	3.85–4.18	4.20–4.57	6.72–7.59	17.03–20.56	1.69–1.79	37–77	18–42	4–11
CI(*R*)	3.85–4.19	4.19–4.56	6.74–7.60	17.08–20.63	1.69–1.79	33–70	18–40	5–11
CI(*NC*)	3.83–4.19	4.19–4.57	6.74–7.59	17.02–20.58	1.66–1.82	28–72	13–40	4–11
CI(*C*)	3.83–4.19	4.19–4.57	6.74–7.59	17.05–20.63	1.66–1.82	30–70	16–40	5–11

Table C1

Table of the main symbols used in this work.

Symbol	Meaning
T_{ph}	Physiological time
T_B	Time to reach a target body-mass
T	Mean developmental time
Te	Temperature
E	Gamma *shape parameter* (number of steps)
τ_0	Food-independent Gamma *scale factor*
τ_F	Food-dependent Gamma *scale factor*
r	Gamma *rate* ($r = 1/\tau$)
B	Body-size (weight)
a	Coefficient of anabolic process (gain) in Eq. (5)
b	Coefficient of catabolic process (loss) in Eq. (5)
α	Exponent for body-size gain in Eq. (5)
E_{eff}	Effective number of steps (*shape parameter* for a one-gamma model)
D_i	Death rate in stage i
W_i	Transition rate from stage i to $i+1$
B_C	Cumulative biomass
$A(t)$	Probability to have matured at time t
n (n_P, n_A)	Number of food-independent steps (*P*: pupation, *A*: emergence)
m	Number of food-dependent steps

References

Arrivillaga, J., Barrera, R., 2004. Food as a limiting factor for *Aedes aegypti* in water-storage containers. J. Vector Ecol. 29, 11–20.

Bar-Zeev, M., 1958. The effect of temperature on the growth rate and survival of the immature stages of *Aedes aegypti*. Bull. Entomol. Res. 49, 157–163.

Barrera, Roberto, 1996. Competition and Resistance to Starvation in Larvae of Container-Inhabiting Aedes Mosquitoes. Ecol. Entomol. 21, 1 17–127.

Barrera, Roberto, Amador, Manuel, Clark, Gary G., 2006. Ecological factors influencing Aedes aegypti (Diptera: Culicidae) productivity in artificial containers in Salinas, Puerto Rico. J. Med. Entomol. 43 (3), 484–492.

Beran, R., 1986. Simulated power functions. Ann. Stat. 14, 151–173.

Bocharov, Gennadii A., Rihan, Fathalla, A., 2000. Numerical modelling in biosciences using delay differential equations. J. Comput. Appl. Math. 125 (1), 183–199.

Burks, A.W., 1946. Peirce's Theory of Abduction. Philos. Sci. 1, 301–306.

Carpenter, Stephen R., 1984. Experimental test of the pupation window model for development of detritivorous insects. Ecol. Model. 23 (3), 257–264.

Chernick, M.R., 2008. Bootstrap Methods—A Guide for Practitioners and Researchers, Second ed. Wiley, Hoboken, N.J.

Chowell, G., Diaz-Dueñas, P., Miller, J.C., Alcazar-Velazco, A., Hyman, J.M., Fenimore, P.W., Castillo-Chavez, C., 2007. Estimation of the reproduction number of dengue fever from spatial epidemic. Math. Biosci. 208, 571–589.

Chowell, Gerardo, Fuentes R., Olea, A., Aguilera, X., Nesse, H., Hyman, J.M., 2013. The basic reproduction number R0 and effectiveness of reactive interventions during dengue epidemics: the 2002 dengue outbreak in Easter Island Chile. Math. Biosci. Eng. 10 (5-6), 1455–1474.

Christophers, R., 1960. *Aedes aegypti* L. the Yellow Fever Mosquito. Cambridge University Press, Cambridge.

Conlan, Andrew J.K., Rohani, Pejman Lloyd, Alun, L., Keeling, Mathew, Bryan, Grenfell, 2010. Resolving the impact of waiting time distributions on the persistence of measles. J. R. Soc. Interface 7 (45), 623–640.

Conover, W.J., 1965. Several k-sample Kolmogorov–Smirnov tests. Ann. Math. Stat. 36 (3), 1019–1026.

Conover, William J., 1972. A Kolmogorov goodness-of-fit test for discontinuous distributions. J. Am. Stat. Assoc. 67 (339), 591–596.

Durrett, R., 2001. Essentials of Stochastic Processes. Springer Verlag, New York.

Dye, C., 1982. Intraspecific competition amongst larval *Aedes aegypti*: food exploitation or chemical interference. Ecol. Entomol. 7, 39–46.

Dégallier, P.N., Hervé, J.P., Rosa, A.F.A., Travassos, D., Sa, G.C., 1988. *Aedes aegypti* (L.): importance de Sa Bioéologie dans la transmission de la dengue et des Autres Arbobirus. Bull. Soc. Pathol. Exot. 81, 97–110.

Efron, B., Tibshirani, R., 1993. An Introduction to the Bootstrap. Chapman and Hall, New York.

Ellis, Alicia M., Garcia, Andres J., Focks, Dana A., Morrison, Amy C., Scott, Thomas W., 2011. Parameterization and sensitivity analysis of a complex simulation model for mosquito population dynamics dengue transmission and their control. Am. J. Trop. Med. Hyg. 85 (2), 257–264.

Ethier, S.N., Kurtz, T.G., 1986. Markov Processes. John Wiley and Sons, New York.

Focks, D.A., Haile, D.C., Daniels, E., Moun, G.A., 1993. Dynamics life table model for *Aedes aegypti*: analysis of the literature and model development. J. Med. Entomol. 30, 1003–1018.

Gilpin, Michael E., McClelland, G.A.H., 1979. Systems analysis of the yellow fever mosquito Aedes aegypti. Fortschr. Zool. 25, 355–388.

Gimnig, John E., Ombok, Maurice, Otieno, Samson, Kaufman, Michael G., Vulule, John M., Walker, Edward D., 2002. Density-dependent development of Anopheles gambiae (Diptera: Culicidae) larvae in artificial habitats. J. Med. Entomol. 39 (1), 162–172.

Gleser, Leon Jay, 1985. Exact power of goodness-of-fit tests of Kolmogorov type for discontinuous distributions. J. Am. Stat. Assoc. 80 (392), 954–958.

Heuvel, M.J., 1963. The effect of rearing temperature on the wing length thorax length, leg length, and ovariole number of the adult mosquito, Aedes aegypti (L.). Trans. R. Entomol. Soc. Lond. 115 (7), 197–216.

Hjorth, J.S.U., 1994. Computer Intensive Statistical Methods: Validation, Model Selection, and Bootstrap. Chapman & Hall, London.

Honěk, Alois, 1993. Intraspecific variation in body size and fecundity in insects: a general relationship. Oikos 66, 483–492.

Huang, Yunxin, Magori, Krisztian, Lloyd, Alun L, Gould, Fred, 2007. Introducing transgenes into insect populations using combined gene-drive strategies: modeling and analysis. Insect Biochem. Mol. Biol. 37 (10), 1054–1063.

Jirakanjanakit, Nuananong, Leemingsawat, Somjai, Dujardin, Jean Pierre, 2008. The geometry of the wing of Aedes (Stegomyia) aegypti in isofemale lines through successive generations. Infect. Genet. Evol. 8 (4), 414–421.

Keeling, M.J., Grenfell, B.T., 1997. Disease extinction and community size: modeling the persistence of measles. Science 275, 65–67.

Kuhn, Thomas S., 1962. The Structure of Scientific Revolutions. University of Chicago Press, Chicago.

Legros, Mathieu, Lloyd, Alun L., Huang, Yunxin, Gould, Fred, 2009. Density-dependent intraspecific competition in the larval stage of Aedes aegypti (Diptera: Culicidae): revisiting the current paradigm. J. Med. Entomol. 46 (3), 409.

Lloyd, Alun L., 2001. Realistic distributions of infectious periods in epidemic models: changing patterns of persistence and dynamics. Theor. Popul. Biol. 60 (1), 59–71.

Maciá, A., 2009. Effects of larval crowding on development time, survival and weight at metamorphosis in *Aedes aegypti* (Diptera: Culicidae). Rev. Soc. Entomol. Argent. 68 (1–2), 107–114.

Magori, Krisztian, Legros, Mathieu, Puente, Molly E., Focks, Dana A., Scott, Thomas W., Lloyd, Alun L., Gould, Fred, 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), e508.

Manetsch, Thomas J., 1976. Time-Varying distributed delays and their use in aggregative models of large systems. IEEE Trans. Syst. Man Cybern. SMC-6, 547–553.

Mittler, John E., Sulzer, Bernhard, Neumann, Avidan U., Perelson, Alan S., 1998. Influence of delayed viral production on viral dynamics in HIV-1 infected patients. Math. Biosci. 152 (2), 143–163.

Otero, M., Schweigmann, N., Solari, H.G., 2008. A stochastic spatial dynamical model for *Aedes aegypti*. Bull. Math. Biol. 70, 1297–1325.

Padmanabha, H., Bolker, B., Lord, C.C., Rubio, C., Lounibos, L.P., 2011. Food availability alters the effects of larval temperature on Aedes aegypti growth. J. Med. Entomol. 48 (5), 974–984.

Padmanabha, Harish, Correa, Fabio, Legros, Mathieu, Nijhout, H. Fredrick, Lord, Cynthia, Lounibos, L. Philip, 2012. An eco-physiological model of the impact of temperature on Aedes aegypti life history traits. J. Insect Physiol. 58, 1597–1608.

Plato. 360 BC. Timaeus. Guthemberg project. ⟨http://www.gutenberg.org/ebooks/1572⟩. 2014.

Popper, Karl, 1959. The Logic of Scientific Discovery, first ed. 1934 Routledge, London.

Richards, O.W., 1928. The rate of the multiplication of yeast at different temperatures. J. Phys. Chem. 32, 1865–1871.

Romano, Joseph P., 1988. A bootstrap revival of some parametric distance tests. J. Am. Stat. Assoc. 83, 698–708.

Romeo, Aznar V., Otero, M.J., de Majo, M.S., Fischer, S., Solari, H.G., 2013. Modelling the complex hatching and development of *Aedes aegypti* in temperated climates. Ecol. Model. 253, 44–55 ⟨http://dx.doi.org/10.1016/j.ecolmodel.2012.12.004⟩.

Rueda, L.M., Patel, K.J., Axtell, R.C., Stinner, R.E., 1990. Temperature-dependent development and survival rates of *Culex quinquefasciatus* and *Aedes aegypti* (Diptera: Culicidae). J. Med. Entomol. 27, 892–898.

Salmon, W.C., 1990. The appraisal of theories: Kuhn meets Bayes. PSA: Proceedings of the Biennial Meeting of the Philosophy of Science Association, vol. 2: Symposia and Invited Papers, pp. 325–332.

Sang, James H., 1956. The quantitative nutritional requirements of drosophila melanogaster. J. Exp. Biol. 33, 45–72.

Sharpe, P.J.H., DeMichele, D.W., 1977. Reaction kinetics of poikilotherm development. J. Theor. Biol. 64, 649–670.

Solari, H.G., Natiello M.A. 2014. Linear processes in stochastic population dynamics: Theory and application to insect development, Scientific World J. 2014, 873624. http://dx.doi.org/10.1155/2014/873624.

Southwood, T.R.E., Murdie, G., Yasuno, M., Tonn, R.J., Reader, P.M., 1972. Studies on the life budget of *Aedes aegypti* in Wat Samphaya Bangkok Thailand. Bull. World Health Organ. 46, 211–226.

Stinner, R.E., Butler, G.D., Bacheler, J.S., Tuttle, C., 1975. Simulation of temperature-dependent development in population dynamics models. Can. Entomol. 107 (11), 1167–1174.

Subra, R., Mouchet, J., 1984. The regulation of preimaginal populations of *Aedes aegypti* (L.) (Diptera: Culicidae) on the Kenya Coast. II. Food as a main regulatory factor. Ann. Trop. Med. Parasitol. 78, 63–70.

von Bertalanffy, L., 1960. Principles and theories of growth. In: Nowinski, W. (ed), Fundamental Aspects of Normal and Malignant Growth. Elsevier.

von Mises, R., 1964. Mathematical Theory of Probability and Statistics. Academic Press, New York, London.

Walker, Thomas, Johnson, P.H., Moreira, L.A., Iturbe-Ormaetxe, Inaki, Frentiu, F.D., McMeniman, C.J., Leong, Yi. San, Dong, Y., Axford, Jason, Kriesner, P., Lloyd, Alund, Ritchie, S.A., O'Neill, S.L., Hoffmann, A.A., 2011. The wMel Wolbachia strain blocks dengue and invades caged Aedes aegypti populations. Nature 476 (7361), 450–453.

Wolkowicz, Gail S.K., Xia, Huaxing, Ruan, Shigui, 1997. Competition in the chemostat: a distributed delay model and its global asymptotic behavior. SIAM J. Appl. Math. 57 (5), 1281–1310.

Zwietering, M.H., de Koos, J.T., Hasenack, B.E., de Witt, J.C., van 't Riet, K., 1991. Modeling of bacterial growth as a function of temperature. Appl. Environ. Microbiol. 57 (4), 1094–1101.

Zwietering, M.H., de Wit, J.C., Cuppers, H.G., van 't Riet, K., 1994. Modeling of bacterial growth with shifts in temperature. Appl. Environ. Microbiol. 60 (1), 204–213.