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DERIVATION AND COMPUTATION OF DISCRETE-DELAY AND CONTINUOUS-DELAY SDES IN MATHEMATICAL BIOLOGY

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Abstract. Stochastic versions of several discrete-delay and continuous-delay differential equations, useful in mathematical biology, are derived from basic principles carefully taking into account the demographic, environmental, or physiological randomness in the dynamic processes. In particular, stochastic delay differential equation (SDDE) models are derived and studied for Nicholson's blowflies equation, Hutchinson's equation, an SIS epidemic model with delay, bacteria/phage dynamics, and glucose/insulin levels. Computational methods for approximating the SDDE models are described. Comparisons between computational solutions of the SDDEs and independently formulated Monte Carlo calculations support the accuracy of the derivations and of the computational methods.

1. **Introduction.** Many deterministic delay differential equation models in mathematical biology have been developed, analyzed, and analytically or computationally solved. (See, e.g., [6, 11, 14, 19, 21, 27, 33].) As these biological dynamical systems are randomly varying, it important to derive and examine stochastic differential equation models for these delay systems.

In the present investigation, stochastic versions of several discrete-delay and continuous-delay (or distributed-delay) differential equation models, useful in mathematical biology, are derived from basic principles carefully taking into account the demographic, environmental, or physiological randomness in the processes. By demographic randomness, it is meant the variability inherent in the population processes, such as births, deaths, migrations, and infections. Environmental randomness differs from demographic randomness and the effects of environmental randomness are considered collectively and are due to the variability, for example, in the weather, in plant growth, and in populations of predators, prey, and competitors. Physiological randomness is due to variability in bodily functions, e.g., sensory, response, or regulation, and is introduced in this paper. Physiological randomness, as suggested here, is due to organs responding to incremental and not continuous changes in levels. For example, it is well-known that there exist an auditory threshold and a renal threshold, which are, respectively, the smallest perceptible sound and the concentration in the blood above which the kidneys begin

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to eliminate the material in the urine [35]. These threshold levels of perception or of response result in randomly varying processes as illustrated later for the dynamics of glucose-insulin levels. Specifically, as a simplifying approximation to a complex process, it is hypothesized in the present investigation that glucose and insulin concentrations occur at discrete levels and, as a result, this hypothesis leads to a randomly varying process.

Stochastic delay differential equation (SDDE) models, which include demographic, environmental, or physiological variability, are derived and studied for Nicholson's blowflies equation, Hutchinson's equation, an SIS epidemic model with delay, bacteria/phage dynamics, and glucose/insulin levels. Specifically, environmental variability is studied for bacteria/phage dynamics, because demographic variability appears to be low due to the generally high densities of bacteria cells and virions. Physiological variability is studied for the dynamics of glucose-insulin levels. Computational methods for approximating the delay SDE models are described. Comparisons between computational solutions of the delay SDEs and independently formulated Monte Carlo calculations support the accuracy of the derivations and of the proposed computational methods.

The purpose of this investigation is to examine and illustrate the derivation of stochastic differential equation models for randomly-varying biological delay problems. Care is is taken in deriving the stochastic terms in a biologically meaningful manner. Indeed, deterministic differential equation models are simultaneously derived along with the stochastic differential equation models, in particular, when demographic, environmental, or physiological noise is present.

Before deriving the stochastic differential equations, it is useful to consider a few properties of Brownian sheets [2, 12, 46]. The Brownian sheet $W(x,t)$ satisfies:

$$\int_t^{t+\Delta t}\int_x^{x+\Delta x}\frac{\partial^2 W(x',t')}{\partial t'\partial x'}\,dx'\,dt' \sim N(0,\Delta x\Delta t). \tag{1}$$

That is, the Brownian sheet is independent and normally distributed over rectangular regions. In addition, if $x_i = i\Delta x$ for $i = 0,1,\ldots,I$, where $\Delta x = x_{max}/I$, then the Brownian sheet defines for $i = 1,2,\ldots I$, the standard Wiener processes, $W_i(t)$, where

$$\frac{dW_i(t)}{dt} = \frac{1}{\sqrt{\Delta x}}\int_{x_i}^{x_{i+1}}\frac{\partial^2 W(x,t)}{\partial t\partial x}\,dx. \tag{2}$$

In particular, notice that if $t_j = j\Delta t$ for $j = 0,1,\ldots,J$, then

$$\int_{t_{j-1}}^{t_j} dW_i(t) = \sqrt{\Delta t}\,\eta_{i,j} \tag{3}$$

where $\eta_{i,j} \sim N(0,1)$ for each $i = 1,2,\ldots I$ and $j = 1,2,\ldots J$. In addition, a double stochastic integral is defined in an analogous way as the Itô integral for measurable, mean-square integrable functions. Specifically,

$$\begin{aligned}&\int_0^a\int_0^b f(x,t)\frac{\partial^2 W(x,t)}{\partial t\partial x}\,dxdt = \\ &= \lim_{I,J\to\infty}\sum_{i=0}^{I-1}\sum_{j=0}^{J-1} f(x_i,t_j)\int_{x_i}^{x_{i+1}}\int_{t_j}^{t_{j+1}}\frac{\partial^2 W(x,t)}{\partial t\partial x}\,dxdt\end{aligned} \tag{4}$$

where $x_i = i\Delta x$ for $i = 0,\ldots,I$, $t_j = j\Delta t$ for $j = 0,\ldots,J$ with $\Delta x = a/I$ and $\Delta t = b/J$ and the limit is taken in the mean square sense [17, 26].

In the next section, demographic variability is investigated for several common delay models in mathematical biology. In the following two sections, environmental variability is studied for a bacteria-bacteriophage model and physiological randomness is considered in a model for glucose and insulin levels.

2. Derivation Of delay SDEs for populations with demographic variability.

2.1. Nicholson's blowflies equation.

A well-known delay model originally developed to explain blowfly population data is Nicholson's blowflies equation [10, 20, 22, 24, 41]:

$$\frac{du(t)}{dt} = -\delta u(t) + pu(t-\tau)\exp(-au(t-\tau)) \tag{5}$$

where $u(t)$ is the number of adult blowflies at time t, p is the maximum per capita daily egg production, $1/a$ is the population size at which the blowflies reproduce at maximum rate, δ is the per capita death rate, and τ is the time for larvae to develop into adults. To include demographic stochasticity in this model, a discrete stochastic model is first derived from the possible changes in the population for a small time interval Δt taking into account the randomness in the processes. The discrete stochastic model then leads to a certain Itô SDE model using a widely known modeling procedure, a variant of which was first used by Langevin [30] and then later proposed or applied by other investigators [3, 4, 5, 18, 28]. Using this procedure, the probability densities of solutions of the discrete stochastic model and of solutions of the stochastic differential equation model will be similar.

A discrete stochastic model is defined from the changes that occur in the randomly varying system for a small time interval. Let $\Delta u(t)$ be the change in the number of adults at time t for small time interval Δt. Based on the assumptions for the blowfly model, the changes in $u(t)$ with corresponding probabilities for small time interval Δt satisfy the values in the Table 1. The discrete stochastic model

Change $\Delta u(t)$	Probability
-1	$\delta u(t)\Delta t$
$+1$	$pu(t-\tau)\exp(-au(t-\tau))\Delta t$

TABLE 1. Changes and probabilities for time interval Δt define a discrete stochastic model for (5)

of Table 1 implies a certain SDE model which has approximately the same mean changes and covariance matrix of changes for small Δt. Table 1 leads to the Itô delay SDE model given by

$$\begin{aligned} du(t) =& (-\delta u(t) + pu(t-\tau)\exp(-au(t-\tau)))\, dt + \sqrt{\delta u(t)}\, dW_1(t) \\ &+ \sqrt{pu(t-\tau)\exp(-au(t-\tau))}\, dW_2(t) \end{aligned} \tag{6}$$

where $W_1(t)$ and $W_2(t)$ are independent Wiener processes.

The discrete-delay blowfly SDDE model agrees well in computational comparisons with Monte Carlo calculations. In the Monte Carlo calculations, the populations are computationally followed for the specified time and unit adjustments are made in the population levels for each small time step Δt, applying the probabilities in Table 1. Monte Carlo and SDDE calculations are performed using $\delta = 0.3$,

$p = 10$, $\tau = 2$, $a = 1/15$, and $y(t) = 40$ for $-\tau \leq t \leq 0$. The results of the calculations are given in Table 2 and are illustrated in Figure 1. For this problem, as time increases, the oscillations in the mean path decrease in magnitude with the individual sample paths continuing to randomly vary about the mean. An inter-

Time	Mean	Standard Deviation
$t = 4$	64.06 (SDDE) 63.71 (MC)	7.16(SDDE) 6.85 (MC)
$t = 25$	54.03(SDDE) 53.82(MC)	8.35(SDDE) 8.03(MC)

TABLE 2. Calculated results for 1000 sample paths using SDDE (5) and Monte Carlo

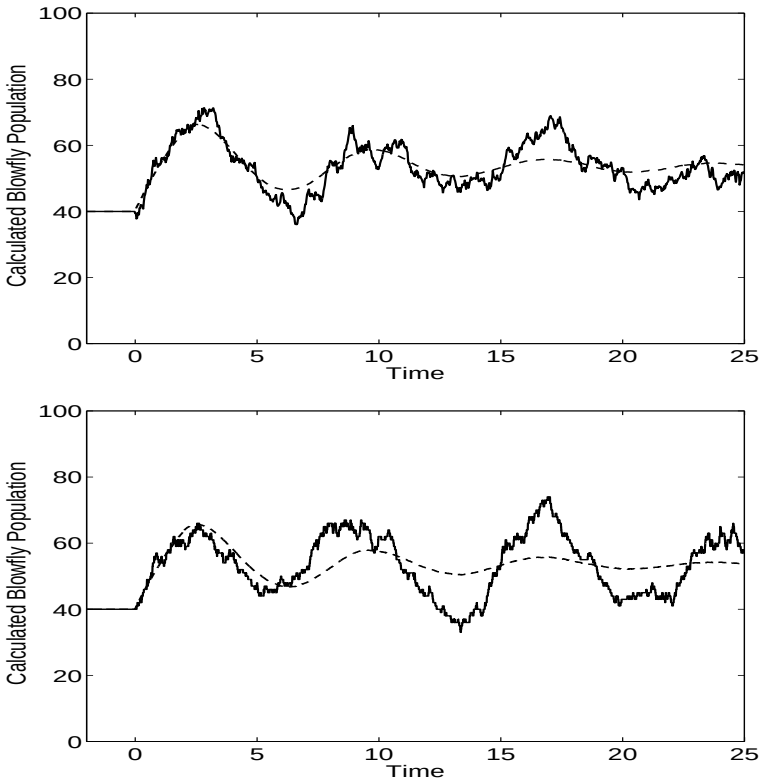

FIGURE 1. Computed mean and one sample path for SDDE (5) (upper) and Monte Carlo (lower)

esting distributed infinite-delay modification to (5) has been studied for modeling single species growth with diffusion [20]. The distributed delay equation without diffusion has the form:

$$\frac{du(t)}{dt} = -\delta u(t) + p\left(\int_{-\infty}^{t} f(t-s)u(s)\,ds\right)\exp\left(-a\int_{-\infty}^{t} f(t-s)u(s)\,ds\right) \qquad (7)$$

where the kernel $f(t) \geq 0$ satisfies $\int_0^\infty f(t)\,dt = 1$. As for (5), the first and second terms on the right-hand side of (7) model death and reproduction rates, respectively.

The values in Table 1 can be correspondingly modified for this distributed delay equation. The resulting SDDE model for (7) has the form:

$$\begin{aligned} du(t) = &\left(-\delta u(t) + p\left(\int_{-\infty}^{t} f(t-s)u(s)\,ds\right)\exp\left(-a\int_{-\infty}^{t} f(t-s)u(s)\,ds\right)\right)\,dt \\ &+\sqrt{\delta u(t) + p\left(\int_{-\infty}^{t} f(t-s)u(s)\,ds\right)\exp\left(-a\int_{-\infty}^{t} f(t-s)u(s)\,ds\right)}\,dW(t). \end{aligned} \tag{8}$$

2.2. **A stage-structured delay model.** Demographic stochasticity is briefly considered for a stage-structured delay model studied in [1, 7] where the two stages are both explicitly considered. The deterministic form of this model is:

$$\begin{aligned} \frac{dN_i(t)}{dt} =& \alpha N_m(t) - \gamma N_i(t) - \alpha\exp(-\gamma\tau)N_m(t-\tau) \\ \frac{dN_m(t)}{dt} =& \alpha\exp(-\gamma\tau)N_m(t-\tau) - \beta N_m^2(t) \end{aligned} \tag{9}$$

where $N_i(t)$ and $N_m(t)$ are the numbers of immature and mature individuals, α is the per capita birth rate, γ is the per capita death rate of immature individuals, and $\beta N_m(t)$ is the death rate of mature individuals. A fixed proportion, $\exp(-\gamma\tau)$, of immature individuals born at time $t-\tau$ survive to time t and exit from the immature population and enter the mature population. Let $\Delta\vec{N}(t)$ be the change in the number of immature and mature populations at time t for small time interval Δt. Based on the assumptions for the model, the changes in $\vec{N}(t)$ with corresponding probabilities for small time interval Δt satisfy the values in the Table 3. The discrete

Change $\Delta\vec{N}(t)$	Probability
$[1,0]^T$	$\alpha N_m(t)\Delta t$
$[-1,0]^T$	$\gamma N_i(t)\Delta t$
$[-e^{-\gamma\tau}, e^{-\gamma\tau}]^T$	$\alpha N_m(t-\tau)\Delta t$
$[0,-1]^T$	$\beta N_m^2(t)\Delta t$

TABLE 3. Changes and probabilities for time interval Δt define a discrete stochastic model for (9)

stochastic model of Table 3 implies a certain Itô delay SDE model given by

$$\begin{aligned} dN_i(t) =& (\alpha N_m(t) - \gamma N_i(t) - \alpha\exp(-\gamma\tau)N_m(t-\tau))\,dt + \sqrt{\alpha N_m(t)}\,dW_1(t) \\ &-\sqrt{\gamma N_i(t)}\,dW_2(t) - \exp(-\gamma\tau)\sqrt{\alpha N_m(t-\tau)}\,dW_1(t-\tau) \\ dN_m(t) =& (\alpha\exp(-\gamma\tau)N_m(t-\tau) - \beta N_m^2(t))\,dt \\ &+\exp(-\gamma\tau)\sqrt{\alpha N_m(t-\tau)}\,dW_1(t-\tau) - \sqrt{\beta N_m^2(t)}\,dW_3(t) \end{aligned} \tag{10}$$

where $W_1(t), W_2(t)$, and $W_3(t)$ are independent Wiener processes. Notice that $W_1(t-\tau)$ occurs in both equations and the survival proportion of immature individuals, $\exp(-\gamma\tau)$, is assumed to be constant but depends on delay time τ.

2.3. **Hutchinson-Wright equation.** A delay differential equation for a single population may have the form of a delay logistic equation which is sometimes referred to as Hutchinson's equation or the Hutchinson-Wright equation [6, 14, 37]:

$$\frac{dy(t)}{dt} = ry(t)(1 - y(t-\tau)/K) \tag{11}$$

with a discrete delay τ or for a continuous delay

$$\frac{dy(t)}{dt} = ry(t)\left(1 - \frac{1}{K\tau}\int_{t-\tau}^{t} h(s)y(s)ds\right) \tag{12}$$

where it is assumed that $y(t)$ is given for $-\tau \leq t \leq 0$. Equation (11) or (12) may model, for example, the population of a species such as *Daphnia* where the clutch size may depend on the amount of food available when the eggs were forming [37].

To derive a stochastic differential equation model for logistic population growth with delay it is useful to consider the demographic terms in an explicit manner. Let $y(t)$ be the population size at time t with birth terms associated with birth rate parameters b_1 and b_2 and death terms associated with death rate parameters d_1 and d_2. Then, a logistic delay equation for a single population may have the general form

$$\frac{dy(t)}{dt} = b_1 y(t) + b_2 y(t-\tau_b) - d_1 y(t) - d_2 y(t)y(t-\tau_d) \tag{13}$$

with discrete delays τ_b and τ_d or for continuous delays it may have the form

$$\frac{dy(t)}{dt} = b_1 y(t) + b_2 \int_{t-\tau_b}^{t} h_b(s)y(s)ds - d_1 y(t) - d_2 y(t)\int_{t-\tau_d}^{t} h_d(s)y(s)ds. \tag{14}$$

A discrete stochastic model is now developed from the possible changes in the population for a small time interval Δt taking into account the randomness in the demographic (birth and death) processes. As previously stated, the discrete stochastic model then leads to a certain Itô SDE model using a widely known modeling procedure, a variant of which was first used by Langevin [30] and then later proposed or applied by other investigators [3, 4, 5, 18, 28].

First, for determining changes and probabilities for the continuous-delay case (14), it is useful to approximate the integrals in (14) using a rectangular rule approximation with N intervals. In effect, this modification produces a delay equation with $2N$ discrete delays. Later, N will be allowed to go to infinity. Hence, in particular, (14) is replaced with

$$\begin{aligned}\frac{dy(t)}{dt} =& b_1 y(t) + b_2 \sum_{j=1}^{N} h_b(t-\tau_{b,j})y(t-\tau_{b,j})(\Delta s)_b - d_1 y(t) \\ & - d_2 y(t)\sum_{j=1}^{N} h_d(t-\tau_{d,j})y(t-\tau_{d,j})(\Delta s)_d.\end{aligned} \tag{15}$$

where the continuous delays are replaced with $2N$ discrete delays $\tau_{b,j} = \tau_b(1 - (j-1)/N)$ and $\tau_{d,j} = \tau_d(1-(j-1)/N)$ for $j = 1, \ldots, N$, with $(\Delta s)_b = \tau_b/N$ and $(\Delta s)_d = \tau_d/N$, and the integrals are approximated with sums. The demographic changes and probabilities for a small time interval are listed in Tables 4 and 5 for the two cases. The discrete stochastic models of Tables 4 and 5 imply certain SDE

Change $\Delta y(t)$	Probability
$+1$	$b_1 y(t)\Delta t$
$+1$	$b_2 y(t-\tau_b)\Delta t$
-1	$d_1 y(t)\Delta t$
-1	$d_2 y(t) y(t-\tau_d)\Delta t$

TABLE 4. Changes and probabilities for time interval Δt define a discrete stochastic model for (13)

Change $\Delta y(t)$	Probability
$+1$	$b_1 y(t)\Delta t$
$+1$	$b_2 h_b(t-\tau_{b,j}) y(t-\tau_{b,j})(\Delta s)_b \Delta t$ for $j=1$ to N
-1	$d_1 y(t)\Delta t$
-1	$d_2 y(t) h_d(t-\tau_{d,j}) y(t-\tau_{b,j})(\Delta s)_d \Delta t$ for $j=1$ to N

TABLE 5. Changes and probabilities for time interval Δt define a discrete stochastic model for (14)

models. With discrete delays τ_b and τ_d, Table 4 leads to the Itô delay SDE model given by

$$\begin{aligned} dy(t) =&(b_1 y(t) + b_2 y(t-\tau_b) - d_1 y(t) - d_2 y(t) y(t-\tau_d))\, dt \\ &+\sqrt{b_1 y(t) + b_2 y(t-\tau_b) + d_1 y(t) + d_2 y(t) y(t-\tau_d)}\, dW(t). \end{aligned} \tag{16}$$

With continuous delays with N discrete delays considered first, Table 5 leads to the SDE system

$$\begin{aligned} \frac{dy(t)}{dt} =& b_1 y(t) + \sqrt{b_1 y(t)}\, \frac{dW_b(t)}{dt} + b_2 \sum_{j=1}^{N} h(t-\tau_{b,j}) y(t-\tau_{b,j})(\Delta s)_b \\ &- d_1 y(t) - \sqrt{d_1 y}\, \frac{dW_d(t)}{dt} - d_2 y(t) \sum_{j=1}^{N} h(t-\tau_{d,j}) y(t-\tau_{d,j})(\Delta s)_d \\ &+ \sum_{j=1}^{N} \sqrt{b_2 h(t-\tau_{b,j}) y(t-\tau_{b,j})(\Delta s)_b}\, \frac{dW_j(t)}{dt} \\ &- \sum_{j=1}^{N} \sqrt{d_2 y(t) h(t-\tau_{d,j}) y(t-\tau_{d,j})\, (\Delta s)_d}\, \frac{d\hat{W}_j(t)}{dt}. \end{aligned} \tag{17}$$

Continuing from (14), (15), and (17), there are several possible approaches. In the first approach, equivalent expressions for the Wiener processes in terms of Brownian sheets are substituted into (17). In a second approach, the changes and probabilities for time interval Δt are reconsidered for (14) leading to an alternate but equivalent model. This approach is discussed later. Using the first approach and referring to (17), substitutions are made letting, for example,

$$\frac{dW_j(t)}{dt} = \frac{1}{\sqrt{(\Delta s)_b}} \int_{(s_j)_b}^{(s_j)_b + (\Delta s)_b} \frac{\partial^2 W(s,t)}{\partial t \partial s}\, ds \quad \text{where} \quad (s_j)_b = t - \tau_{b,j}.$$

It follows that (17) becomes

$$\begin{aligned}\frac{dy(t)}{dt} =& b_1 y(t) + \sqrt{b_1 y(t)}\,\frac{dW(t)}{dt} + b_2 \sum_{j=1}^{N} h(t-\tau_{b,j}) y(t-\tau_{b,j})(\Delta s)_b \\ & - d_1 y(t) - \sqrt{d_1 y}\,\frac{d\hat{W}(t)}{dt} - d_2 y(t) \sum_{j=1}^{N} h(t-\tau_{d,j}) y(t-\tau_{d,j})(\Delta s)_d \\ & + \sum_{j=1}^{N} \int_{(s_j)_b}^{(s_j)_b+(\Delta s)_b} \sqrt{b_2 h(t-\tau_{b,j}) y(t-\tau_{b,j})}\,\frac{\partial^2 W(s,t)}{\partial t \partial s}\,ds \\ & - \sum_{j=1}^{N} \int_{(s_j)_d}^{(s_j)_d+(\Delta s)_d} \sqrt{d_2 y(t) h(t-\tau_{d,j}) y(t-\tau_{d,j})}\,\frac{\partial^2 \hat{W}(s,t)}{\partial t \partial s}\,ds\end{aligned} \tag{18}$$

where $\dfrac{\partial^2 W(s,t)}{\partial t \partial s}$ and $\dfrac{\partial^2 \hat{W}(s,t)}{\partial t \partial s}$ are independent Brownian sheets. Letting N go to infinity in (18), the continuous-delay SDDE is implied of the form

$$\begin{aligned}\frac{dy(t)}{dt} =& b_1 y(t) + b_2 \int_{t-\tau_b}^{t} h_b(s) y(s) ds - d_1 y(t) - d_2 y(t) \int_{t-\tau_d}^{t} h_d(s) y(s)\,ds \\ & + \sqrt{b_1 y(t)}\,\frac{dW(t)}{dt} + \int_{t-\tau_b}^{t} \sqrt{b_2 h_b(s) y(s)}\,\frac{\partial^2 W(s,t)}{\partial t \partial s}\,ds \\ & - \sqrt{d_1 y(t)}\,\frac{d\hat{W}(t)}{dt} - \int_{t-\tau_d}^{t} \sqrt{d_2 y(t) h_d(s) y(s)}\,\frac{\partial^2 \hat{W}(s,t)}{\partial t \partial s}\,ds.\end{aligned} \tag{19}$$

Interestingly in (19), Brownian sheets appear in the SDDE system when continuous delays are present.

In the second alternate approach, an equivalent SDE model to (19) is derived from (14) without applying Brownian sheets. Both approaches are described in the present investigation as for a given problem it may be that the first procedure, using Brownian sheets, is more easily applied than the second procedure. In the second procedure, the changes and probabilities for the continuous delay case are reconsidered and listed in Table 6. Notice that the problem is not approximated by N discrete delays. The changes and probabilities given by the discrete stochastic

Change $\Delta y(t)$	Probability
$+1$	$b_1 y(t)\Delta t$
$+1$	$b_2 \int_{t-\tau_b}^{t} h_b(s) y(s) ds \Delta t$
-1	$d_1 y(t)\Delta t$
-1	$d_2 y(t) \int_{t-\tau_d}^{t} h_d(s) y(s) ds \Delta t$

TABLE 6. Changes and probabilities for time interval Δt define a discrete stochastic model for (14)

model of Table 6 directly imply the Itô delay SDE model for (16) given by

$$\begin{aligned} dy(t) = &\left(b_2 \int_{t-\tau_b}^{t} h_b(s)y(s)ds - d_1 y(t) - d_2 y(t) \int_{t-\tau_d}^{t} h_d(s)y(s)\, ds \right) dt \\ &+ b_1 y(t)\, dt + \sqrt{b_1 y(t)}\, dW(t) + \sqrt{\int_{t-\tau_b}^{t} b_2 h_b(s)y(s)\, ds}\;\; dW_b(t) \\ &- \sqrt{d_1 y(t)}\, d\hat{W}(t) - \sqrt{\int_{t-\tau_d}^{t} d_2 y(t) h_d(s)y(s)\, ds}\, dW_d(t). \end{aligned} \tag{20}$$

where $W(t), \hat{W}(t), W_b(t)$ and $W_d(t)$ are independent Wiener processes. Equations (19) and (20) are equivalent SDE models for (14). Finally, it is pointed out that only demographic stochasticity has been considered in deriving (16), (19), and (20).

The randomness due to environmental variability has been ignored up to now in this section. To include environmental stochasticity for (13) and (14), it is reasonable to assume that environmental changes have the effect of causing the individual parameters in the model to vary randomly about average values, such as described by mean-reverting Ornstein-Uhlenbeck processes [3]. In other words, it is reasonable to suppose that the environment induces noise in the parameters of the differential equation models. For example, the influence of the environment is likely to cause the parameters b_1, b_2, d_1, d_2 in (13) to vary randomly. For example, $b_1 = b_1(t)$ in (13) or (16) may be modeled using the mean-reverting process

$$db_1(t) = \alpha_1(b_{e,1} - b_1(t))dt + \alpha_2\, dW_1(t)$$

for which, for a fixed value of t, $b_1(t)$ is nearly normally distributed with mean value $b_{e,1}$ and variance $(\alpha_2)^2/(2\alpha_1)$.

Finally, it is useful to suggest how the delay SDE models can be computationally solved using approximations based on the Euler-Maruyama approximation [25, 26]. For discrete delays for (16), the following computational method is suggested where $y_i \approx y(t_i)$ satisfies

$$\begin{aligned} y_{i+1} = &y_i + b_1 y_i \Delta t + b_2 y_{i-m_b}\Delta t - d_1 y_i \Delta t - d_2 y_i y_{i-m_d}\Delta t \\ &+ \sqrt{(b_1 y_i + d_1 y_i + b_2 y_{i-m_b} + d_2 y_i y_{i-m_d})\Delta t}\;\eta_i \end{aligned} \tag{21}$$

assuming that $m_b = \tau_b/\Delta t$ and $m_d = \tau_d/\Delta t$ are integers. In addition, the value η_i for each i is a random number normally distributed with zero mean and unit variance.

For continuous delays for (19), the following computational method is suggested where $y_i \approx y(t_i)$ satisfies

$$\begin{aligned} y_{i+1} = &y_i + b_1 y_i \Delta t - d_1 y_i \Delta t + \sqrt{b_1 y_i \Delta t}\,\eta_i - \sqrt{d_1 y_i \Delta t}\,\hat{\eta}_i \\ &+ \sum_{j=i-m_b+1}^{i} b_2 h_b(t_j) y_j (\Delta t)^2 + \sum_{j=i-m_b+1}^{i} \sqrt{b_2 h_b(t_j) y_j (\Delta t)^2}\eta_{j,i} \\ &- \sum_{j=i-m_d+1}^{i} d_2 y_i h_d(t_j) y_j (\Delta t)^2 - \sum_{j=i-m_d+1}^{i} \sqrt{d_2 y_i h_d(t_j) y_j (\Delta t)^2}\,\hat{\eta}_{j,i}. \end{aligned} \tag{22}$$

The values $\eta_i, \eta_{j,i}, \hat{\eta}_i, \hat{\eta}_{j,i}$ are random numbers normally distributed with zero mean and unit variance for each i and j. For continuous delays using (20), the following

computational method is suggested where $y_i \approx y(t_i)$ satisfies

$$\begin{aligned} y_{i+1} =& y_i + b_1 y_i \Delta t - d_1 y_i \Delta t + \sqrt{b_1 y_i \Delta t}\,\eta_i - \sqrt{d_1 y_i \Delta t}\,\hat{\eta}_i \\ &+ \sum_{j=i-m_b+1}^{i} b_2 h_b(t_j) y_j (\Delta t)^2 + \sqrt{\sum_{j=i-m_b+1}^{i} b_2 h_b(t_j) y_j (\Delta t)^2}\,\eta_i^b \\ &- \sum_{j=i-m_d+1}^{i} d_2 y_i h_d(t_j) y_j (\Delta t)^2 - \sqrt{\sum_{j=i-m_d+1}^{i} d_2 y_i h_d(t_j) y_j (\Delta t)^2}\,\hat{\eta}_i^d \end{aligned} \tag{23}$$

and where $\eta_i, \eta_i^b, \hat{\eta}_i, \hat{\eta}_i^d$ are random numbers normally distributed with zero mean and unit variance.

The discrete-delay and the continuous-delay SDE models agree well in computational comparisons with Monte Carlo calculations. In the Monte Carlo calculations, the populations are computationally followed for the specified time and unit adjustments are made in the population levels for each small time step Δt, applying the probabilities in Tables 5 and 6. Monte Carlo and SDDE calculations are made using $b_1 = 1$, $b_2 = 0$, $d_1 = 0$, $d_2 = 0.01$, $h_d(t) = 1.0$, $\tau_d = 1$, and $y(t) = 110$ for $-\tau_d \le t \le 0$. The results of the calculations are given in Tables 7 and 8 and are illustrated in Figures 2 and 3.

Time	Mean	Standard Deviation
$t = 1$	99.65(SDDE) 99.27(MC)	15.17(SDDE) 12.68(MC)
$t = 9$	99.20(SDDE) 99.44(MC)	17.75(SDDE) 16.38(MC)

TABLE 7. Results for 1000 sample paths calculated using logistic SDDE (16) and Monte Carlo

Time	Mean	Standard Deviation
$t = 0.5$	105.20(SDE) 105.12(MC)	9.99(SDE) 8.85(MC)
$t = 9$	98.32(SDE) 99.35(MC)	12.29(SDE) 11.11(MC)

TABLE 8. Computations for 1000 sample paths calculated using logistic SDDE (19) and Monte Carlo

2.4. **A delay SIS model.** Consider a population of susceptible, S, and infected, I, with a delay in recovery of the infected individuals. Standard deterministic models [6] have the following forms with a discrete or a continuous delay, respectively,

$$\frac{dS(t)}{dt} = -\beta I(t) S(t) + \gamma I(t-\tau) \tag{24}$$

$$\frac{dI(t)}{dt} = \beta I(t) S(t) - \gamma I(t-\tau) \tag{25}$$

$$\frac{dS(t)}{dt} = -\beta I(t) S(t) + \gamma \int_{t-\tau}^{t} h(s) I(s)\, ds \tag{26}$$

$$\frac{dI(t)}{dt} = \beta I(t) S(t) - \gamma \int_{t-\tau}^{t} h(s) I(s)\, ds. \tag{27}$$

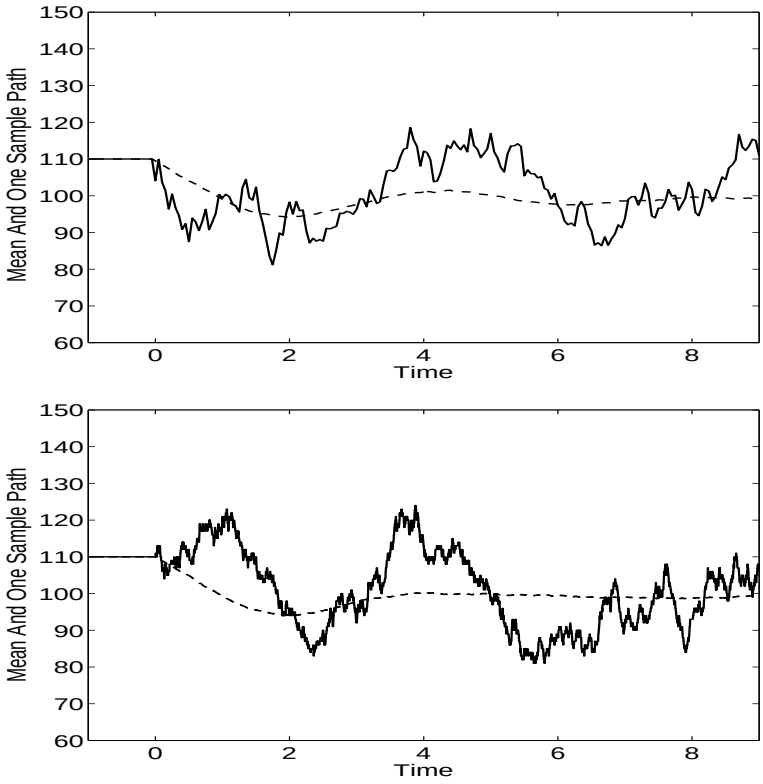

FIGURE 2. Computational results for SDDE (16) (upper) and Monte Carlo (lower)

To obtain a discrete stochastic model, it is convenient, as in the previous section, to replace the continuous delay SIS model with N discrete delays. In effect, the integrals in the SIS model are replaced using a rectangular rule approximation with N intervals which produces a model with N discrete delays. Later, N will be allowed to go to infinity. Hence, the continuous delay is replaced with N discrete delays $\tau_j = \tau(1-(j-1)/N)$ for $j = 1, \ldots, N$ and where $\Delta s = \tau/N$. Then, the integrals are replaced with sums, and so, (26) and (27) become

$$\frac{dS(t)}{dt} = -\beta I(t)S(t) + \gamma \sum_{j=1}^{N} h(t-\tau_j)I(t-\tau_j)\,\Delta s \tag{28}$$

$$\frac{dI(t)}{dt} = \beta I(t)S(t) - \gamma \sum_{j=1}^{N} h(t-\tau_j)I(t-\tau_j)\,\Delta s. \tag{29}$$

The changes and probabilities in a small time interval Δt define discrete stochastic SIS models. These changes and probabilities are listed in Tables 9 and 10, respectively, for the discrete and continuous delay SIS models. The stochastic models defined by Tables 9 and 10 lead to certain SDE models whose solutions have similar probability densities as the discrete stochastic models. With a discrete

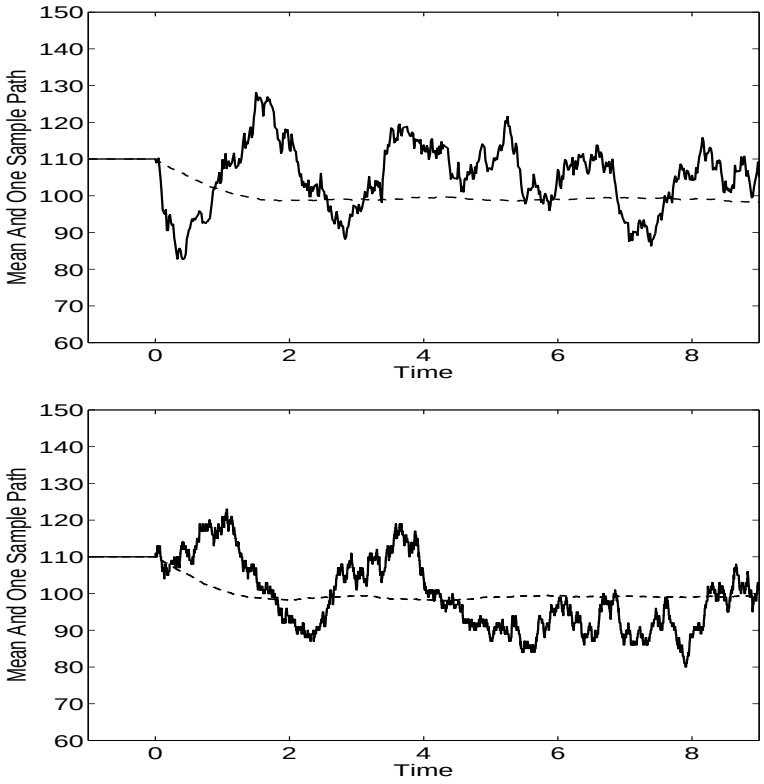

FIGURE 3. Computational results for SDDE (19) (upper) and Monte Carlo (lower)

Change $\Delta[S(t), I(t)]$	Probability
$[-1, +1]$	$\beta S(t)I(t)\Delta t$
$[+1, -1]$	$\gamma I(t-\tau)\Delta t$

TABLE 9. Changes and probabilities for a time interval Δt define a discrete stochastic SIS model for (24) and (25)

Change $\Delta[S(t), I(t)]$	Probability
$[-1, +1]$	$\beta S(t)I(t)\Delta t$
$[+1, -1]$	$\gamma h(t-\tau_j)I(t-\tau_j)\Delta s\Delta t$ for $j = 1$ to N

TABLE 10. Changes and probabilities for a time interval Δt define a discrete SIS stochastic model for (28) and (29)

delay τ, the stochastic versions of (24) and (25) are

$$\begin{aligned} dS(t) = &-\beta I(t)S(t)\,dt - \sqrt{\beta I(t)S(t)}dW_1(t) \\ &+\gamma I(t-\tau)\,dt + \sqrt{\gamma I(t-\tau))}\,dW_2(t) \end{aligned} \tag{30}$$

$$\begin{aligned} dI(t) =&\beta I(t)S(t)\,dt + \sqrt{\beta I(t)S(t)}dW_1(t) \\ &-\gamma I(t-\tau))\,dt - \sqrt{\gamma I(t-\tau))}\,dW_2(t). \end{aligned} \tag{31}$$

For continuous delays with N discrete delays considered first, then the stochastic versions of (28) and (29) are

$$\begin{aligned} \frac{dS(t)}{dt} =& -\beta I(t)S(t) + \gamma \sum_{j=1}^{N} h(t-\tau_j)I(t-\tau_j)\,\Delta s \\ &-\sqrt{\beta I(t)S(t)}\,\frac{dW(t)}{dt} + \sum_{j=1}^{N}\sqrt{\gamma h(t-\tau_j)I(t-\tau_j)\Delta s}\,\frac{dW_j(t)}{dt} \end{aligned} \tag{32}$$

$$\begin{aligned} \frac{dI(t)}{dt} =&\beta I(t)S(t) - \gamma \sum_{j=1}^{N} h(t-\tau_j)I(t-\tau_j)\,\Delta s \\ &+\sqrt{\beta I(t)S(t)}\,\frac{dW(t)}{dt} - \sum_{j=1}^{N}\sqrt{\gamma h(t-\tau_j)I(t-\tau_j)\Delta s}\,\frac{dW_j(t)}{dt}. \end{aligned} \tag{33}$$

Substituting into (32) and (33) the relation

$$\frac{dW_j(t)}{dt} = \frac{1}{\sqrt{\Delta s}}\int_{s_j}^{s_j+\Delta s}\frac{\partial^2 W(s,t)}{\partial t\partial s}\,ds \quad \text{where} \quad s_j = t-\tau_j,$$

similarly as for the logistic problem in the previous section, and letting N go to infinity, the continuous delay SDE is implied of the form

$$\begin{aligned} \frac{dS(t)}{dt} =& -\beta I(t)S(t) + \gamma\int_{t-\tau}^{t} h(s)I(s)\,ds \\ &-\sqrt{\beta I(t)S(t)}\,\frac{dW(t)}{dt} + \int_{t-\tau}^{t}\sqrt{\gamma h(s)I(s)}\,\frac{\partial^2 W(s,t)}{\partial t\partial s}\,ds \end{aligned} \tag{34}$$

$$\begin{aligned} \frac{dI(t)}{dt} =&\beta I(t)S(t) - \gamma\int_{t-\tau}^{t} h(s)I(s)\,ds \\ &+\sqrt{\beta I(t)S(t)}\,\frac{dW(t)}{dt} - \int_{t-\tau}^{t}\sqrt{\gamma h(s)I(s)}\,\frac{\partial^2 W(s,t)}{\partial t\partial s}\,ds. \end{aligned} \tag{35}$$

The continuous delay SDDE model is interesting as, unexpectedly, a Brownian sheet appears in the stochastic differential equations. An equivalent stochastic system to (34) and (35) is readily derived, as explained in the first section for the logistic equation. This system has the form

$$\begin{aligned} dS(t) =& \left(-\beta I(t)S(t) + \gamma\int_{t-\tau}^{t} h(s)I(s)\,ds\right)dt \\ &-\sqrt{\beta I(t)S(t)}\,W(t) + \sqrt{\int_{t-\tau}^{t}\gamma h(s)I(s)\,ds}\,d\hat{W}(t) \end{aligned} \tag{36}$$

$$\begin{aligned} dI(t) =& \left(\beta I(t)S(t) - \gamma\int_{t-\tau}^{t} h(s)I(s)\,ds\right)dt \\ &+\sqrt{\beta I(t)S(t)}\,dW(t) - \sqrt{\int_{t-\tau}^{t}\gamma h(s)I(s)\,ds}\,d\hat{W}(t). \end{aligned} \tag{37}$$

where $W(t)$ and $\hat{W}(t)$ are independent Wiener processes.

A variation of an Euler-Maruyama approximation is suggested in the present investigation for computational solution of the delay stochastic SIS models. In particular, for (30) and (31), $S_i \approx S(t_i)$ and $I_i \approx I(t_i)$ satisfy

$$S_{i+1} = S_i + (\gamma I_{i-m} - \beta I_i S_i)\Delta t - \sqrt{\beta I_i S_i \Delta t}\,\eta_{1,i} + \sqrt{\gamma I_{i-m}\Delta t}\,\eta_{2,i} \tag{38}$$

$$I_{i+1} = I_i + (\beta I_i S_i - \gamma I_{i-m})\Delta t + \sqrt{\beta I_i S_i \Delta t}\,\eta_{1,i} - \sqrt{\gamma I_{i-m}\Delta t}\,\eta_{2,i} \tag{39}$$

where $\eta_{1,i}$ and $\eta_{2,i}$ are independent normally distributed numbers with zero mean and unit variance for each i and where $m = \tau/\Delta t$. For continuous delay equations (34) and (35), $S_i \approx S(t_i)$ and $I_i \approx I(t_i)$ satisfy

$$\begin{aligned} S_{i+1} =& S_i - \beta I_i S_i \Delta t + \sum_{j=i-m+1}^{i} \gamma h(t_j) I_j (\Delta t)^2 - \sqrt{\beta I_i S_i \Delta t}\,\eta_i \\ &+ \sum_{j=i-m+1}^{i} \sqrt{\gamma h(t_j) I_j (\Delta t)^2}\,\eta_{j,i} \end{aligned} \tag{40}$$

$$\begin{aligned} I_{i+1} =& I_i + \beta I_i S_i \Delta t - \sum_{j=i-m+1}^{i} \gamma h(t_j) I_j (\Delta t)^2 + \sqrt{\beta I_i S_i \Delta t}\,\eta_i \\ &- \sum_{j=i-m+1}^{i} \sqrt{\gamma h(t_j) I_j (\Delta t)^2}\,\eta_{j,i} \end{aligned} \tag{41}$$

where η_i and $\eta_{j,i}$ for each i and j are normally distributed numbers with zero mean and unit variance.

The discrete-delay and the continuous-delay stochastic SIS models agree well with Monte Carlo calculations. In the Monte Carlo calculations, the populations are followed computationally for a specified time where unit changes are made in the population levels for each small time step Δt applying the probabilities in Table 9 or 10. Monte Carlo and SDDE calculations were made using $\beta = 0.01$, $\gamma = 0.5$, $h(t) = 1$, and $\tau = 1$, where $S(t) = 100$ and $I(t) = 50$ for $-\tau \le t \le 0$. The results of the calculations are given in Table 11 and in Figure 4 for the continuous-delay problem. Notice that the SIS SDDE model and the Monte Carlo calculations agree well.

Time	Mean of S(t)	Standard Deviation of S(t)
$t = 0.5$	86.19(SDE) 86.26(MC)	5.93(SDE) 6.64(MC)
$t = 9$	50.15(SDE) 50.97(MC)	6.92(SDE) 7.72(MC)

TABLE 11. A comparison of results for 1000 sample paths using the stochastic SIS model (34)-(35) and Monte Carlo

3. **Delay SDES for marine bacteria/bacteriophage dynamics.** An environmentally important specific time-delay problem involves the population dynamics of bacteria and the viruses that infect them, bacteriophages, commonly referred to as phages. In particular, virulent phage virions are infectious particles that inject genetic material into bacteria cells where they replicate. Then, the cells eventually burst (cell lysis) releasing new phage particles. Over 5,000 phages have been described and in the ocean alone there are estimated to be more than 10^{30} phage

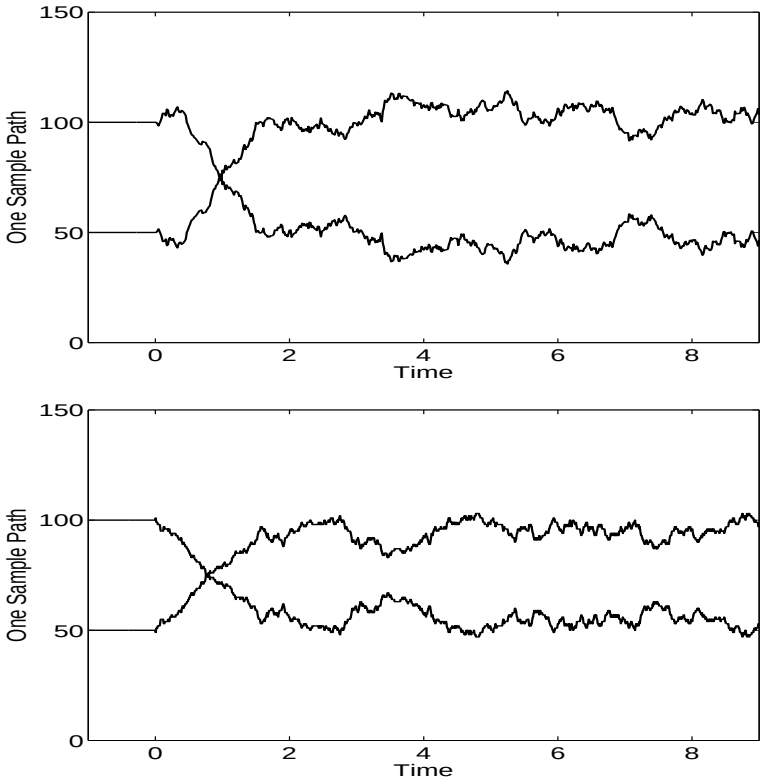

FIGURE 4. SIS SDDE (34)-(35) (upper) and Monte Carlo (lower) results

particles [15, 29, 36]. Bacteriophage is considered the most abundant form of biological entity on the Earth and tailed bacteriophages are possibly the most abundant biological entities in marine environments [15, 34, 36]. In spite of their small size (about 20nm to 200nm in length), marine bacteriophages are an important part of marine ecosystems. They influence many biogeochemical processes and impact population sizes of marine bacteria [16, 44]. Indeed, the number of phage virions to bacteria cells may range from five to twenty-five [15, 16, 36]. See, for example, [16, 29, 42] for a discussion of the biology and for electron micrographs of phage.

For example, *Prochlorococcus* is a genus of small (600nm) marine cyanobacteria. These bacteria are possibly the most abundant photosynthetic organisms and the most plentiful species on Earth: a single milliliter of surface seawater may contain more than 10^5 cells [13]. Members of this genus are among the primary producers of oxygen in the ocean and of organic matter on the Earth. [23]. Several different types of bacteriophage have been identified that infect *Prochlorococcus* [43].

The population dynamics of phage and bacteria can be modeled with a delay induced by viral reproduction. The delay is the period of time from the moment when a phage particle injects its genetic material into a bacterium cell until new phage particles burst from the cell. Several deterministic models have been developed for the dynamics of bacteria and phage such as described in [8, 9, 21, 32]. One

biologically reasonable bacteria-phage deterministic model has the form [21]:

$$\frac{dS(t)}{dt} = \alpha S(t)(1 - S(t)/\gamma) - KS(t)P(t) \tag{42}$$

$$\begin{aligned}\frac{dP(t)}{dt} =& -\mu_p P(t) - mP^2(t) - KS(t)P(t) \\ &+ bKe^{-\mu_i \tau} S(t-\tau)P(t-\tau)\end{aligned} \tag{43}$$

where $S(t)$ and $P(t)$ are population sizes of bacteria and phage, respectively, K is an infection rate, τ is the delay until cell bursting, μ_i is the natural death rate of infected bacteria, and b is the burst size. Deaths of phage are accounted for by the rates $-\mu_p P(t)$ and $-mP^2(t)$ which are assumed here to be independent, and $\alpha S(t)$ and $-\alpha S^2(t)/\gamma$ are assumed to be birth and death rates, respectively, for the bacteria.

It is straightforward using the procedure described in the two previous sections to incorporate demographic stochasticity into the population dynamics of (42) and (43). This yields a delay SDE for the bacteriophage-bacteria dynamics of the form:

$$\begin{aligned}\frac{dS(t)}{dt} =& \alpha S(t)(1 - S(t)/\gamma) - KS(t)P(t) + \sqrt{\alpha S(t)}\,\frac{dW_1(t)}{dt} \\ &- \sqrt{\alpha S^2(t)/\gamma}\,\frac{dW_2(t)}{dt} - \sqrt{KS(t)P(t)}\,\frac{dW_3(t)}{dt}\end{aligned} \tag{44}$$

$$\begin{aligned}\frac{dP(t)}{dt} =& -\mu_p P(t) - mP^2(t) - KS(t)P(t) + bKe^{-\mu_i \tau} S(t-\tau)P(t-\tau) \\ &- \sqrt{\mu_p P(t)}\,\frac{dW_4(t)}{dt} - \sqrt{mP^2(t)}\,\frac{dW_5(t)}{dt} - \sqrt{KS(t)P(t)}\,\frac{dW_3(t)}{dt} \\ &+ be^{-\mu_i \tau}\sqrt{KS(t-\tau)P(t-\tau)}\,\frac{dW_3(t-\tau)}{dt}\end{aligned} \tag{45}$$

where $W_i(t)$, $i = 1, 2, \ldots, 5$ are independent Wiener processes. Notice that $W_3(t)$ appears in one term in (45) with delay τ where it is assumed that the phage due to bursting, $be^{-\mu_i \tau}$, is constant but depends on the delay time τ.

To illustrate the dynamics of bacteria and bacteriophage, population sizes are calculated for 1 ml of seawater for which it is assumed that the bacteria cells and the virions are distributed homogeneously. Reasonable values of the parameters are $\alpha = 1.34$/day, $K = 6.70 \times 10^{-8}$/(virions day), $\gamma = 2 \times 10^6$ virions, $\mu_p = 2.00$/day, $m = 6.70 \times 10^{-9}$/(virions day), $b = 75$, $\mu_i = 0.20$/day, and $\tau = 2.24$ days [21, 32]. Calculations are performed up to 72.36 days using the stochastic model (44)-(45). Initial numbers of bacteria cells and phage particles are taken as 6×10^5 and 2×10^6, respectively, in the 1 ml of seawater. The results are listed in Table 12 and displayed in Figure 5. The calculations indicate that the high population densities of the bacteria and phage result in low demographic stochasticity. Environmental stochasticity was then studied for the bacteria-phage dynamics. In performing this study, it was hypothesized that the parameters in the model were individually influenced by the environment. Each parameter was individually assumed to satisfy a mean-reverting Ornstein-Uhlenbeck process with standard deviation 1/5 of the deterministic value. For example, for parameter α

$$d\alpha(t) = (\alpha_e - \alpha(t))\,dt + \sqrt{2\alpha_e^2/25}\,dW(t) \quad \text{with} \quad \alpha(0) = \alpha_e, \tag{46}$$

where for large t, $\alpha(t)$ is approximately normally distributed about mean α_e with variance $\alpha_e^2/25$ where $\alpha_e = 1.34$/day. The effects on bacteria and phage populations, $S(t)$ and $P(t)$, were studied as each parameter, α, K, γ, μ_p, m, b, μ_i, τ, individually

Time	Mean of S(t)	Standard Deviation of S(t)
$t = 1.12$	1.20×10^6	1.36×10^3
$t = 72.36$	5.81×10^6	3.37×10^3
Time	Mean of P(t)	Standard Deviation of P(t)
$t = 1.12$	1.87×10^6	9.89×10^2
$t = 72.36$	1.56×10^7	5.28×10^4

TABLE 12. Calculational results of 1000 sample paths for bacteria and bacteriophage with demographic variability

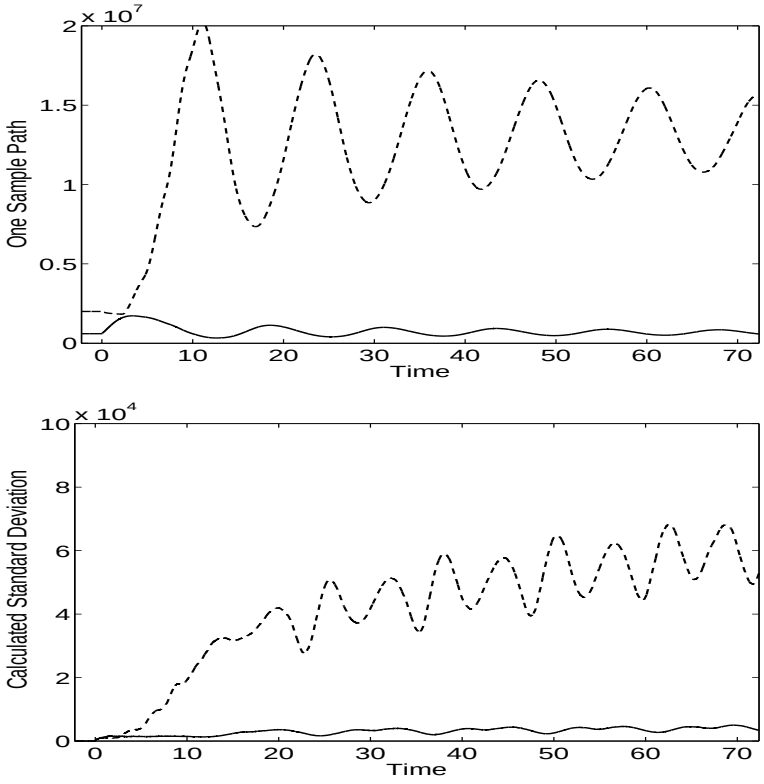

FIGURE 5. Bacteria (solid) and bacteriophage (dashed) SDE results with demographic variability

randomly varied with the environment. This calculational study gave the results listed in Table 13. The dynamics in the population levels are most sensitive to environmental variability in the parameter K. In particular, Figure 6 illustrates the results specifically when K is chosen as the variable influenced by the environment. This figure should be compared with the earlier Figure 5 which shows the populations influenced purely by demographic variability. Figure 6 clearly indicates that the population sizes may be sensitive to the environment through variability induced in the parameter values.

Parameter	Mean of $S(t_f)$	Std. Dev. of $S(t_f)$
α	7.76×10^5	3.16×10^5
K	8.00×10^5	4.64×10^5
γ	7.35×10^5	2.14×10^5
μ_p	7.99×10^5	3.06×10^5
m	5.93×10^5	1.38×10^4
b	7.74×10^5	2.95×10^5
μ_i	6.68×10^5	1.23×10^5
τ	7.57×10^7	3.25×10^5
Parameter	Mean of $P(t_f)$	Std. Dev. of $P(t_f)$
α	1.26×10^7	4.30×10^6
K	1.22×10^7	6.19×10^6
γ	1.31×10^7	3.24×10^6
μ_p	1.24×10^7	4.03×10^6
m	1.55×10^7	2.18×10^5
b	1.27×10^7	4.67×10^6
μ_i	1.44×10^7	2.00×10^6
τ	1.48×10^7	1.85×10^6

TABLE 13. Calculational results of 1000 sample paths for bacteria and phage with demographic and environmental variability at final time $t_f = 72.36$ days

4. **Delay SDEs for insulin-glucose levels.** An interesting physiological stochastic delay problem is estimation of glucose and insulin levels [31, 33, 40, 45]. Understanding interactions that occur between insulin and glucose levels is aided through computation of stochastic delay models. Two time delays exist in the glucose-insulin regulatory system, a time delay in insulin production stimulated by an elevated glucose concentration and a time delay for insulin to inhibit glucose production of the liver. To model insulin levels with time lags, Sturis [40] proposed a deterministic ODE model. Modifications of this model were subsequently investigated [31, 33, 45].

Many of the mathematical models of glucose-insulin dynamics use certain functions to model specific physiological processes. These functions and processes are briefly described: G_{in} is the source of glucose from food ingestion, $f_1(G) = R_m/(1 + \exp((C_1 - G/V_g)/a_1))$ models insulin production stimulated by glucose level, $f_2(G) = U_b(1 - \exp(-G/(C_2V_g)))$ models insulin-independent glucose utilization, $f_3(G)f_4(I) = [G/(C_3V_g)][U_0 + (U_m - U_0)/S]$ where $S = 1 + \exp(S_0)$, $S_0 = -\beta \log((1/V_i + 1/(Et_i))I/C_4)$, and $f_3(G)f_4(I)$ models insulin-dependent glucose utilization, $f_5(I) = R_g/(1 + \exp(\alpha((I/V_p) - C_5)))$ models glucose production controlled by insulin concentration, d_i models insulin degradation or clearance rate, τ_1 is the time delay in insulin production stimulated by elevated glucose concentration, and τ_2 is the time delay for insulin to inhibit hepatic glucose production. See, for example, [31] or [40] for more detailed explanations of these functions.

Using these functions and discrete time delays, insulin and glucose may be deterministically modeled [31] with the delay differential equation system

$$\frac{dG(t)}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t - \tau_2)) \tag{47}$$

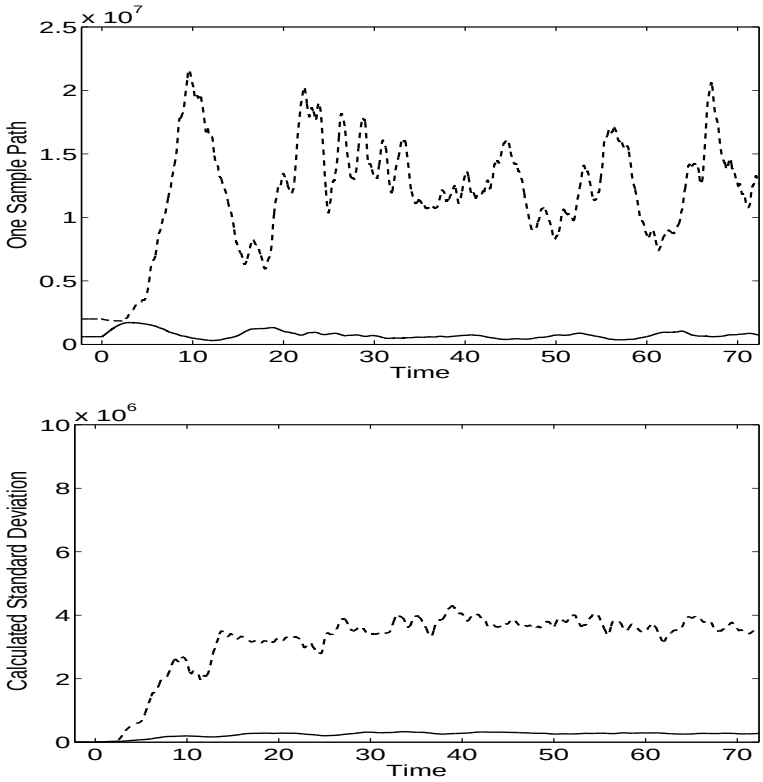

FIGURE 6. Bacteria-bacteriophage SDE calculational results with environmental variability in K

$$\frac{dI(t)}{dt} = f_1(G(t-\tau_1)) - d_i I(t). \tag{48}$$

assuming a constant input rate of glucose G_{in}.

Given the rates of change implied by the functions and the differential equation model (47)-(48), an SDE model could be readily derived if the glucose and insulin levels changed by discrete amounts as, for example, population levels that change by unit amounts. If the body organs sense and respond to infinitesimal changes in glucose and insulin levels, calculated variability in glucose and insulin levels would be exceedingly low and deterministic models would be accurate. However, actual insulin and glucose levels appear to have a noticeable random component [38, 39, 40] suggesting that the body may not detect or respond to minute changes in glucose and insulin levels. It is therefore hypothesized in the present investigation that there exist threshold changes in glucose concentrations and insulin concentrations to which the body senses and responds. To model this effect in an approximate manner, it is assumed that insulin and glucose concentrations occur at discrete levels in the body. Of course, this is a simplification of a complex phenomenon. Let λ_G and λ_I be the incremental changes, respectively, in glucose and insulin levels to which it is assumed that the body detects.

Now, assuming that λ_G and λ_I define the discrete change levels in the body, a discrete stochastic model is straightforward to derive. The changes and the corresponding probabilities for a small time Δt are given in Table 14 assuming that the rate processes are independent. This discrete stochastic model, defined by Table

Change $\Delta[G(t), I(t)]$	Probability
$[-\lambda_G, 0]$	$f_2(G(t))\Delta t/\lambda_G$
$[-\lambda_G, 0]$	$f_3(G(t))f_4(I(t))\Delta t/\lambda_G$
$[\lambda_G, 0]$	$f_5(I(t-\tau_2)\Delta t/\lambda_G$
$[0, \lambda_I]$	$f_1(G(t-\tau_1))\Delta t/\lambda_I$
$[0, -\lambda_I]$	$d_i I(t)\Delta t/\lambda_I$

TABLE 14. Changes and probabilities for time interval Δt define a discrete stochastic glucose-insulin model

14, leads directly to the SDE system:

$$\begin{aligned}\frac{dG(t)}{dt} =& G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2)) \\ & - \sqrt{\lambda_G f_2(G(t))}\,\frac{dW_1(t)}{dt} - \sqrt{\lambda_G f_3(G(t))f_4(I(t))}\,\frac{dW_2(t)}{dt} \\ & + \sqrt{\lambda_G f_5(I(t-\tau_2))}\,\frac{dW_3(t)}{dt}\end{aligned} \tag{49}$$

$$\begin{aligned}\frac{dI(t)}{dt} =& f_1(G(t-\tau_1)) - d_i I(t) + \sqrt{\lambda_I f_1(G(t-\tau_1))}\,\frac{dW_4(t)}{dt} \\ & - \sqrt{\lambda_I d_i I(t)}\,\frac{dW_5(t)}{dt}\end{aligned} \tag{50}$$

where λ_G and λ_I are incremental changes in glucose and insulin levels.

A computational approach is readily suggested for equations (49) and (50) analogous to the computational methods described for the SDDEs in the previous sections. Computations were performed for these models using the parameter values considered in [31]. Specifically, for plasma volume $V_p = 3000$ml and volume of glucose space $V_g = 100$dl, let $\tau_1 = 7$min, $\tau_2 = 12$min, $G_{in} = 108$mg/min, $G(0) = 10000$mg, $I(0) = 100$mU, $d_i = 0.06$/min, $\lambda_1 = G(0)/1000 = 10$mg, $\lambda_2 = I(0)/1000 = 0.1$mU, $R_m = 210$mU/min, $C_1 = 2000$mg/l, $a_1 = 300$mg/l, $U_b = 72$mg/min, $C_2 = 144$mg/l, $C_3 = 1000$mg/l, $U_0 = 40$mg/min, $U_m = 940$mg/min, $\beta = 1.77$, $C_4 = 80$mU/l, $E = .2$l/min, $R_g = 180$mg/min, $\alpha = .29$l/mU, $C_5 = 26$mU/l, with final time = 488min. For these parameter values in (49) and (50), the units of insulin, $I(t)$, and the unit of glucose, $G(t)$, are mg and mU, respectively. To determine concentrations of insulin and glucose, the concentrations are calculated as $G(t)/V_g$ in units of mg/dl and $1000I(t)/V_p$ in units of μU/ml. The values $\lambda_G = 10$mg and $\lambda_I = 0.1$mU are assumed in the present investigation and are about 1/1000 of the average deterministic values of total glucose mass $G(t)$ and total insulin mass $I(t)$, respectively. In particular, $\lambda_G = 10$mg corresponds to a hypothesized incremental change level of 0.01mg/dl in glucose concentration and $\lambda_I = 0.1$mU corresponds to a hypothesized incremental change level of 0.033μU/ml in insulin concentration.

When $\lambda_G = \lambda_I = 0$, the calculations are deterministic and glucose and insulin levels show a smooth oscillatory behavior indicated in the upper two graphs of

Figure 7 and as, for example, previously demonstrated computationally in [31]. However, when the incremental changes, λ_G and λ_I, are nonzero, as in the lower two graphs of Figure 7 where $\lambda_G = 10$mg and $\lambda_I = 0.1$mU, a random variability is introduced into the levels similar to the random variability seen in actual glucose and insulin levels. See, for example, the insulin and glucose levels of experimental subjects presented in [38], [39], and [40]. This agreement between experiment and computation supports the hypothesis that the body may not respond in a perfect continuous manner to glucose and insulin concentration levels, i.e., microscopic changes in insulin and glucose levels may not result in microscopic adjustments in insulin and glucose production or utilization.

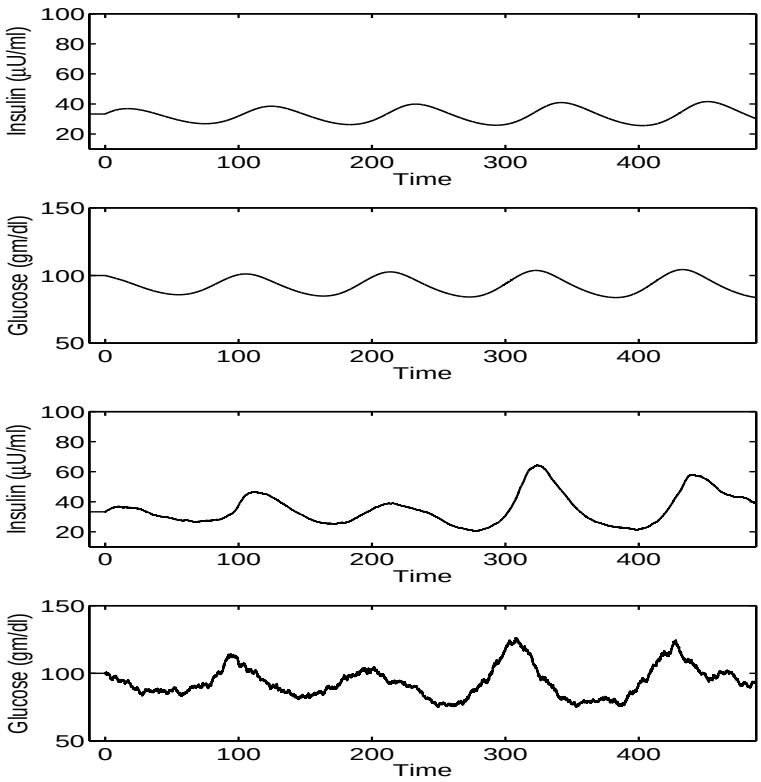

FIGURE 7. Deterministic results (upper two graphs) with $\lambda_G = 0.0, \lambda_I = 0.0$, and stochastic results (lower two graphs) with $\lambda_G = 10$mg, $\lambda_I = 0.1$mU

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REFERENCES

[1] W. Aiello and H. Freedman, A time-delay model of single-species growth with stage structure, *Mathematical Biosciences*, **101** (1990), 139–153.

[2] E. Allen, S. Novosel and Z. Zhang, Finite element and difference approximation of some linear stochastic partial differential equations, *Stochastics and Stochastics Reports*, **64** (1998), 117–142.
[3] E. Allen, *Modeling With Itô Stochastic Differential Equations*, Springer, Dordrecht, 2007.
[4] E. Allen, L. Allen, A. Arciniega and P. Greenwood, Construction of equivalent stochastic differential equation models, *Stoch. Anal. Appl.*, **26** (2008), 274–297.
[5] L. Allen, *An Introduction to Stochastic Processes with Applications to Biology*, 2nd edition, CRC Press, Boca Raton, 2010.
[6] L. Allen, *An Introduction to Mathematical Biology*, Prentice Hall, Upper Saddle River, 2007.
[7] J. Al-Omari and A. Tallafha, Modelling and analysis of stage-structured population model with state-dependent maturation delay and harvesting, *Int. Journal of Math. Analysis*, **1** (2007), 391–407.
[8] E. Beretta and Y. Kuang, Modeling and analysis of a marine bacteriophage infection, *Mathematical Biosciences*, **149** (1998), 57–76.
[9] E. Beretta and Y. Kuang, Modeling and analysis of a marine bacteriophage infection with latency period, *Nonlinear Anal. Real World Appl.*, **2** (2001), 35–74.
[10] L. Berezansky, E. Braverman and L. Idels, Nicholson's blowflies differential equations revisited: Main results and open problems, *Appl. Math. Modell.*, **34** (2010), 1405–1417.
[11] G. Bocharov and F. Rihan, Numerical modeling in biosciences using delay differential equations, *Journal of Computational and Applied Mathematics*, **125** (2000), 183–199.
[12] E. Cabaña, The vibrating string forced by white noise, *Zeitschrift für Wahrscheinlichkeitstheorie und verwandte Gebiete*, **15** (1970), 111–130.
[13] S. Chisholm, S. Frankel, R. Goericke, R. Olson, B. Palenik, J. Waterbury, L. West-Johnsrud and E. Zettler, Prochlorococcus-marinus nov gen-nov sp - an oxyphototrophic marine prokaryote containing divinyl chlorophyll-a and chlorophyll-B, *Archives of Microbiology*, **157** (1992), 297–300.
[14] J. Cushing, *Integrodifferential Equations and Delay Models in Population Dynamics*, Lecture Notes in Biomathematics 20, Springer, Berlin, Heidelberg, New York, 1977.
[15] J. Filée, F. Tétart, C. Suttle and H. Krisch, Marine T4-type bacteriophages, a ubiquitous component of the dark matter of the biosphere, *Proc. Nat. Acad. Sci.*, **102** (2005), 12471–12476.
[16] J. Fuhrman, Marine viruses and their biogeochemical and ecological effects, *Nature*, **399** (1999), 541–548.
[17] T. Gard, *Introduction to Stochastic Differential Equations*, Marcel Decker, New York, 1987.
[18] D. Gillespie, Exact stochastic simulation of coupled chemical reactions, *The Journal of Physical Chemistry*, **81** (1977), 2340–2361.
[19] K. Gopalsamy, *Stability and Oscillations in Delay Differential Equations of Population Dynamics*, Kluweer Academic Publishers, Dordrecht, The Netherlands, 1992.
[20] S. Gourley and S. Ruan, Dynamics of the diffusive Nicholson's blowfies equation with distributed delay, *Proceedings of the Royal Society of Edinburgh*, **130** (2000), 1275–1291.
[21] S. Gourley and Y. Kuang, A delay reaction-diffusion model of the spread of bacteriophage infection, *SIAM J. Appl. Math.*, **65** (2005), 550–566.
[22] W. Gurney, S. Blythe and R. Nisbet, Nicholson's blowflies revisited, *Nature*, **287** (1980), 17–21.
[23] T. Hilleman, *Environmental Biology*, Science Publishers, Enfield, New Hampshire, 2009.
[24] V. Jansen, R. Nisbet and W. Gurney, Generation cycles in stage structured populations, *Bulletin of Mathematical Biology*, **52** (1990), 375–396.
[25] P. Kloeden and E. Platen, *Numerical Solution of Stochastic Differential Equations*, Springer-Verlag, New York, 1992.
[26] P. Kloeden, E. Platen and H. Schurz, *Numerical Solution of SDE Through Computer Experiments*, Springer, Berlin, 1994.
[27] Y. Kuang, *Delay Differential Equations: With Applications in Population Dynamics*, Academic Press, San Diego, 1993.
[28] T. Kurtz, Limit theorems for sequences of jump Markov processes approximating ordinary differential equations, *Journal of Applied Probability*, **8** (1971), 344–356.
[29] E. Kutter and A. Sulakvelidze, *Bacteriophages: Biology and Applications*, CRC Press, Boca Raton, Florida, 2004.
[30] P. Langevin, Sur la théorie du mouvement brownien, *Comptes-rendus de l'Académie des Sciences*, **146** (1908), 530–533.

[31] J. Li, Y. Kuang and C. Mason, Modeling the glucose-insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays, *J. Theor. Biol.*, **242** (2006), 722–735.
[32] S. Liu, Z. Liu and J. Tang, A delayed marine bacteriophage infection model, *Applied Mathematics Letters*, **20** (2007), 702–706.
[33] A. Makroglou, I. Karaoustas, J. Li and Y. Kuang, Delay differential equation models in diabetes modeling: A review, in *EOLSS encyclopedia,* (eds. A. de Gaetano, P. Palumbo), 2011.
[34] C. Munn, *Marine Microbiology: Ecology and Applications*, 2nd edition, Garland Science, Taylor and Francis Group, New York, 2011.
[35] D. Oreopoulos, R. Lindeman, D. VanderJagt, A. Tzamaloukas, H. Bhagavan and P. Garry, Renal excretion of ascorbic acid: Effect of age and sex, *Journal of the American Collge of Nutrition*, **12** (1993), 537–542.
[36] J. Paul, M. Sullivan, A. Segall and F. Rohwer, Marine phage genomics, *Comparative Biochemistry and Physiology Part B*, **133** (2002), 463–476.
[37] S. Ruan, Delay differential equations in single species dynamics, in *Delay Differential Equations and Applications,* (eds. O. Arino, M. Hbid and E. Ait Dads), Springer, Berlin, 2006, 477–517.
[38] E. Shapiro, H. Tillil, K. Polonsky, V. Fang, A. Rubenstein and E. Van Cauter, Oscillations in insulin secretion during constant glucose infusion in normal man: Relationship to changes in plasma glucose, *The Journal of Clinical Endocrinology & Metabolism*, **67** (1988), 307–314.
[39] C. Simon, G. Brandenberger and M. Follenius, Ultradian oscillations of plasma glucose, insulin, and C-peptide in man during continuous enteral nutrition, *The Journal of Clinical Endocrinology & Metabolism*, **64** (1987), 669–674.
[40] J. Sturis, K. Polonsky, E. Mosekilde and E. Van Cauter, Computer-model for mechanisms underlying ultradian oscillations of insulin and glucose, *Am. J. of Physiol. Endocrinol. Metab.*, **260** (1991), E801–E809.
[41] Y. Su, J. Wei and J. Shi, Bifurcation analysis in a delayed diffusive Nicholson's blowflies equation, *Nonlinear Analysis: Real World Applications*, **11** (2010), 1692–1703.
[42] M. Sullivan, J. Waterbury and S. Chisholm, Cyanophages infecting the oceanic cyanobacterium Prochlorococcus, *Nature*, **424** (2003), 1047–1051.
[43] M. Sullivan, M. Coleman, P. Weigele, F. Rohwer and S. Chisholm, Three Prochlorococcus Cyanophage genomes: Signature features and ecological interpretations, *PLoS Biology*, **3** (2005), 790–806.
[44] C. Suttle, Marine viruses major players in the global ecosystem, *Nature Reviews Microbiology*, **5** (2007), 801–812.
[45] I. Tolic, E. Mosekilde and J. Sturis, Modeling the insulin-glucose feedback system: The significance of pulsatile insulin secretion, *J. Theor. Biol.*, **207** (2000), 361–375.
[46] J. Walsh, An introduction to stochastic partial differential equations, in *Notes in Mathematics,*, Volume 1180, (eds. A. Dold and B. Eckmann), Springer-Verlag, Berlin, 1986, 265–439.

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