

Stochastic modeling of the transmission of respiratory syncytial virus (RSV) in the region of Valencia, Spain

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ABSTRACT

In this paper, we study the dynamics of the transmission of respiratory syncytial virus (RSV) in the population using stochastic models. The stochastic models are developed introducing stochastic perturbations on the demographic parameter as well as on the transmission rate of the RSV. Numerical simulations of the deterministic and stochastic models are performed in order to understand the effect of fluctuating birth rate and transmission rate of the RSV on the population dynamics. The numerical solutions of stochastic models are calculated using Euler-Maruyama and Milstein schemes, and confidence intervals for stochastic solutions are given using Monte-Carlo method. Analysis of the numerical results reveals that perturbations on the transmission rate are more decisive in the dynamics of RSV than perturbations on demographic parameters. In addition, the stochastic models show the advantage of reproducing more effectively the noisy RSV hospitalization data. It is concluded that these stochastic models are a viable option to provide a realistic modeling of the RSV dynamics on the population.

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1. Introduction

The respiratory syncytial virus (RSV) is the cause of acute respiratory infections in children younger than 2 years old, mainly bronchiolitis and pneumonia. This virus is known since 1957, but recently the adult pathology has been established and it is the cause of the 18% of the hospitalizations due to pneumonia in adults older than 65 (Hall, 1992). RSV is a seasonal epidemic with minor variations each year and coincides in time with other infections as influenza or rotavirus, producing a high number of hospitalizations and, consequently, a saturation of the Public Health Systems. Moreover, its transmission is very easy and the nosocomial infections are frequent. Respiratory syncytial virus RSV is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year.

RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems (CDC, 2007). RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur

when infectious material contacts mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough. In temperate climates, RSV infections usually occur during annual community outbreaks, often lasting 4–6 months, during the late fall, winter, or early spring months. The timing and severity of outbreaks in a community vary from year to year.

In Spain, there are 15,000–20,000 attentions in medical primary services due to RSV each year. In the Spanish region of Valencia, 1500 children require each year hospitalization by bronchiolitis caused by RSV, that is, an incidence of 400 cases each 100,000 children younger than a year, and six hospitalization days as average (Domingo et al., 2006). The cost for the Public Health System is about 3.5 millions of euros per year, only for pediatric hospitalizations. Therefore, the research in RSV and other viruses and the developing of strategies to control epidemics are very important.

The mathematical models have been revealed as a powerful tool to analyze the epidemiology of the infectious illness, to understand its behavior, to predict its impact and to find out how external factors change the impact (Zaman et al., 2008). Mathematical models for RSV at population level have been developed previously (Weber et al., 2001; White et al., 2005, 2007). One goal of this paper is to model the transmission of virus RSV in the population, but also to understand the mechanisms of the RSV spread. However, the previous developed models do not incorporate environmental fluctuation based upon the hypothesis that in case of large populations, stochastic deviations are small enough to be ignored. Models nor-

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mally take the average birth rate to be constant, implicitly ignoring the possibility that slow changes in this parameter could be a major driving force for dynamical transitions (Earn et al., 2000).

Stochastic differential equation models play a significant role to describe the temporal evolution of several diseases because they have ability to provide some additional degree of realism when compared with their deterministic counterparts (Saha and Bandyopadhyay, 2008; Renshaw, 1991). In addition, environment stochasticity is a driving force that may change deterministic dynamics of models (Rand and Wilson, 1991; Keeling et al., 2001). Several stochastic models have been applied to several issues including epidemics, for instance (Sarkar, 2004; Saha and Bandyopadhyay, 2008, 2004; Tuckwell and Toubiana, 2007; Dalal et al., 2008; Carletti, 2002).

Environmental fluctuation is one of the most important components for real world systems. A large part of natural phenomena do not follow the deterministic law exactly, rather oscillate randomly around some average value (Saha and Bandyopadhyay, 2004). Continuous fluctuation in environment, demographic and all other parameters involved with the model system exhibit random fluctuation to a greater or lesser extent and as a result the equilibrium population distribution never attains a steady value, fluctuates randomly around some average value (May, 2001). Moreover, the parameters of the model can be assumed equal to an average value plus a time fluctuating term and these term follows a normal distribution with mean zero. Therefore, in this paper stochasticity is introduced in a mathematical model proposed in (Weber et al., 2001) using Gaussian distribution having zero mean and unit spectral density, to understand the interactions between the deterministic dynamics and the realistic noisy fluctuating environment.

The main aim of the present paper is to analyze the effects of small perturbations on some parameters involved with the RSV dynamics. At first, we estimate the seasonality parameters for the specific case of the region of Valencia, fitting the deterministic mathematical model proposed in (Weber et al., 2001) to real hospitalization data. RSV is an illness that the timing and severity of outbreaks in a community vary from year to year (Weber et al., 2001). Therefore, one possible explanation to this fact is a noisy environment due to several factors as temperature, humidity, pollution, transport, population and others. In this way, we assume perturbations on the average transmission rate parameter of RSV. Additionally, as pointed out previously it is very natural to consider birth rate varying each month or year, therefore a time varying birth rate is considered using stochastic perturbations. One of the final objectives of this work is to study if these perturbations can produce significant dynamical changes. Moreover, these stochastic models may be useful if we want to investigate the effects of introducing other perturbations, such as prophylactic vaccination.

This paper is organized as follows. In Section 2, the deterministic model is presented and fitted to real data. The stochastic models are developed in order to investigate the effect of stochastic perturbations on the RSV at population level. In Section 3, the deterministic model is fitted to hospitalizations data from Valencia and numerical simulations with deterministic and stochastic model are done. Finally, in Section 4 discussion and conclusions are presented.

2. Mathematical Models

In this section, the deterministic model is presented. Additionally, the stochastic models are constructed as an alternative to the deterministic modeling. Since the real hospitalization data seems to contain noise, the stochastic model is a viable option or a first approach to describe the dynamics of RSV in the population.

2.1. The Deterministic Model

One goal of this paper besides the previously mentioned one is to model and to obtain future behavior of the transmission of virus RSV in the population, but also to understand the mechanisms of the RSV spread. Mathematical models, simpler than the reality, allow to understand the global dynamical behavior of the RSV in the population and to establish sustainable public health programs for the prevention of the childhood infections. In this way, a mathematical model based on a system of first order ordinary differential equations was proposed in (Weber et al., 2001), which has several parameters that need to be estimated fitting the model to medical data. The model is a classical SIRS (susceptibles, infected, recovered and susceptibles), of the following form

$$\begin{aligned}\dot{S}(t) &= \mu - \mu S(t) - \beta(t)S(t)I(t) + \gamma R(t), \quad S(0) = S_0 > 0 \\ \dot{I}(t) &= \beta(t)S(t)I(t) - \nu I(t) - \mu I(t), \quad I(0) = I_0 > 0 \\ \dot{R}(t) &= \nu I(t) - \gamma R(t) - \mu R(t), \quad R(0) = R_0 > 0,\end{aligned}\quad (1)$$

under the hypothesis:

- (1) The population is divided in three classes: Susceptibles $S(t)$, who are all individuals that have not the virus, Infected $I(t)$ are all individuals with the virus and able to transmit the illness and Recovered $R(t)$ who are all the healthy individuals with a temporary immunity.
- (2) The birth rate $\mu > 0$ and death rate are assumed equals. This means that $\dot{S}(t) + \dot{I}(t) + \dot{R}(t) = 0$. Thus total population is constant and $S(t) + I(t) + R(t) = 1$.
- (3) The transmission coefficient function $\beta(t)$ between classes $S(t)$ and $I(t)$ is a continuous T -periodic function, called the transmission rate. Periodicity of the $\beta(t)$ is a way to incorporate the seasonality of the spread in the environment. It is very usual to approximate these seasonality by a cosinusoidal function $\beta(t) = b_0(1 + b_1 \cos(2\pi/T(t + \varphi)))$ where $b_0 > 0$ is the baseline transmission parameter, $0 < b_1 \leq 1$ measures the amplitude of the seasonal variation in transmission and $0 \leq \varphi \leq 2\pi$ is the phase angle normalized (Weber et al., 2001).
- (4) The per capita rate of leaving the infective class $I(t)$ is called ν and the per capita rate of recovered class $R(t)$ is γ .

2.2. Source RSV Data and Model Fitting

The data used in this paper to adjust the model is from RSV hospitalizations of children younger than 4 years old during the period January 2001 to December 2004 from CMBD (Basic Minimum Data Set) database of the Spanish region of Valencia. This data is processed to obtain monthly hospitalizations of children in age between 0 and 4 years old and are shown in Table 1. The deterministic model is fitted to real hospitalizations data through least squares to estimate some unknown parameters of the model.

Table 1

Data from Spanish region of Valencia of children between 0–4 years old hospitalized during 2001–2004.

Month	2001	2002	2003	2004
January	414	454	382	348
February	272	301	138	145
March	137	160	120	129
April	22	55	50	9
May	17	25	2	6
June	2	11	10	4
July	0	7	4	0
August	1	1	4	0
September	17	17	31	15
October	1	32	64	28
November	9	86	284	88
December	127	417	607	373

Other aspect that should be mentioned is that data are referred to hospitalizations, not to infected people. This means that only a proportion of infected are hospitalized and this proportion should be estimated in the model data fitting. It is important to remark that some data have been censored, since they have uncertainties due to human measurement as it is expected in these kinds of works.

First of all, it is important to mention that the unknown parameters of model (1) are $b_0 > 0$, $0 < b_1 \leq 1$ and $0 \leq \varphi \leq 2\pi$. Moreover, the scale parameter s of the proportion of the infected that are not hospitalized is unknown. Additionally, the initial condition data is also unknown. To overcome this problem we fit the model after the model is stabilized. For the least-squares fitting procedure, we implemented in *Mathematica* package, the mean square error function \mathbb{F} using the hospitalization data (Table 1). Function \mathbb{F} takes values in a subset $D = \{(b_0, b_1, \varphi, s) \in \mathbb{R}^4\}$ and returns a positive real number. Hence, we can try to minimize this function using Nelder–Mead algorithm (Nelder and Mead, 1964; Press et al., 1986), that does not need the computation of any derivative or gradient.

Based on realistic data and in order to find a global minimum in a feasible chosen domain, we divide it in disjoint subdomains where, in each one, Nelder–Mead algorithm is applied. We stored all the minima obtained and the resulting parameter estimates of b_0 , b_1 , φ and s that minimize the mean square error function \mathbb{F} in the domain D are

- (1) $b_0 = 36.4$,
- (2) $b_1 = 0.38$,
- (3) $\varphi = 1.07$,
- (4) $s = 220,000$,

and the value of the function in the global minimum, that is, the mean square error, is 0.00157261. The graphical representation of the model fitting can be seen in Fig. 1. As it can be seen, the epidemic model (1) agrees well with the observed epidemic data. It is important to notice that hospitalization data is not exactly periodic as the deterministic model predicts (Arenas et al., 2008). Fitting model to epidemic data to estimate parameters are widely applied, for instance in (Chowell et al., 2006) a well-documented approach was developed to a influenza model at population level.

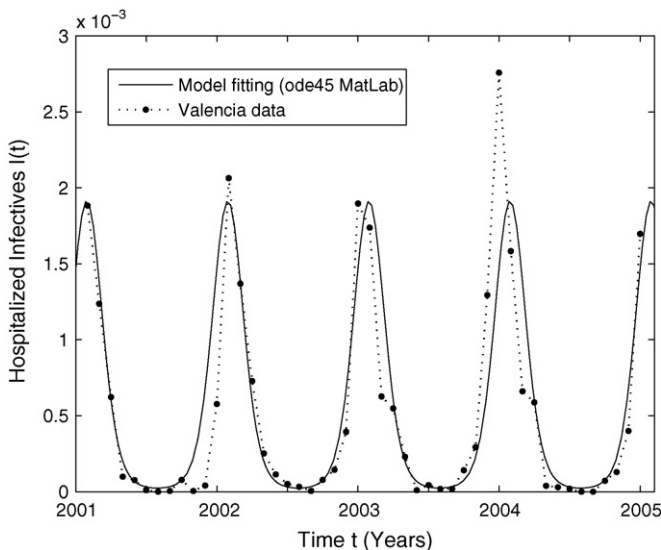


Fig. 1. Fitting of deterministic model (1) to data of RSV hospitalizations in the region of Valencia.

3. Stochastic Model

Continuous fluctuation in environment, demographic and all other parameters of the model system exhibit random fluctuation to a greater or lesser extent and as a result the equilibrium population distribution never attains a steady value, fluctuates randomly around some average value (May, 2001). In addition, as was shown in previous section, real hospitalization data is not exactly periodic as the deterministic model predicts. Therefore, is natural to introduce stochasticity in the previous deterministic mathematical model due to continuous fluctuations of the environment and birth rate. In this section, two models are introduced using stochastic perturbations on some parameters as in (Dalal et al., 2008; Sarkar, 2004; Saha and Bandyopadhyay, 2008). The first stochastic model considers perturbations on the birth rate and the second one the baseline transmission parameter b_0 . For both cases, the Itô type stochastic differential system is

$$\begin{aligned} dX(t) &= f(t, X(t))dt + g(t, X(t))dW(t), \\ X(t_0) &= X_0, \quad t \in [t_0, t_f], \end{aligned} \quad (2)$$

where $X(t) = (S(t), I(t), R(t))^T$ and the solution $\{X(t), t \in [t_0, t_f]\}$ is an Itô process, f is the continuous deterministic component, g is the continuous random component (Kloeden and Platen, 1995). $W(t)$ is a m -dimensional stochastic process having scalar Wiener process components (Carletti et al., 2004). For our particular models, $m = 1$ and $d = 3$.

3.1. Model with Perturbation on the Birth Rate

RSV is an illness that the timing and severity of outbreaks in a community vary from year to year (Weber et al., 2001). Therefore, one possible explanation to this fact is varying population. As pointed out previously it is natural to consider birth rate varying each month or year. In this way, we investigate the effect of birth rate perturbations on the dynamics of the RSV model. One main aim of this work is to study if these small changes can produce significant dynamical changes. Thus, birth rate perturbation is introduced in the following form,

$$\tilde{\mu} = \mu + \alpha \dot{W}(t), \quad (3)$$

where $\alpha \in \mathbb{R}$ and $W(t)$ is a standard Wiener process. Therefore, the birth rate is assumed changing over the time in small values. As a result the equilibrium population distribution never attains a steady value, fluctuates randomly around some average value. The birth rate parameter of the model is equal to an average value plus a time fluctuating term and these term follows a normal distribution with mean zero. The magnitude of these fluctuations need to be estimated using real data regarding the RSV hospitalizations.

The stochastic differential system model with perturbation on the birth rate takes the form,

$$\begin{aligned} dS(t) &= [(\mu - \mu S(t) - \beta(t)S(t)I(t) + \gamma R(t))]dt + \alpha(1 - S(t))dW(t), \\ dI(t) &= [(\beta(t)S(t)I(t) - \nu I(t) - \mu I(t))]dt - \alpha I(t)dW(t), \\ dR(t) &= [(\nu I(t) - \mu R(t) - \gamma R(t))]dt - \alpha R(t)dW(t). \end{aligned} \quad (4)$$

Remark 1. In Eq. (3), we assume that the birth rate μ oscillate randomly around the constant average value assumed in the deterministic model. Biologically, we translate Eq. (3), in that the birth parameter fluctuates randomly around some constant average value assumed in the deterministic model and these fluctuations may be due to several factors such weather, economic conditions and others.

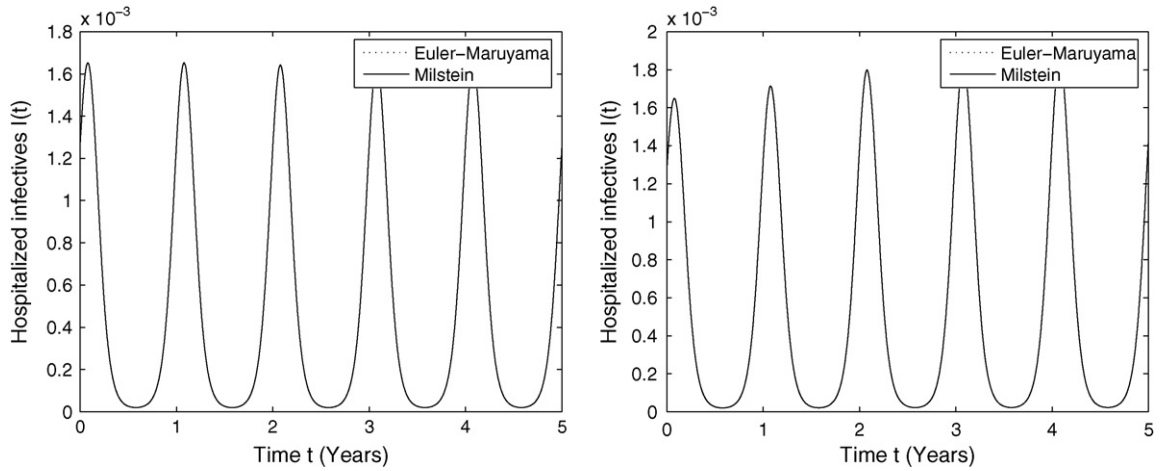


Fig. 2. Comparison between the Milstein and Euler-Maruyama stochastic schemes in regard to the infected subpopulation $I(t)$, using time step sizes $h = 0.001$ (left) and $h = 0.001$ (right), when the birth rate is perturbed in a range of 100%.

3.2. Model with Perturbation of the Transmission Rate of RSV

RSV is a disease that is affected by weather conditions, then the timing and severity of outbreaks in a community vary from year to year (Weber et al., 2001). Thus, as a second case, stochastic perturbations are introduced on the baseline transmission parameter b_0 , due to the fact that this parameter is always affected inevitably by some time varying environment disturbance, such as temperature, humidity, pollution, precipitation, transport, population and others. Thus, we consider the deterministic model (1) for the transmission of RSV in the region of Valencia with random perturbation on the baseline transmission parameter b_0 of the form,

$$\tilde{b}_0 = b_0 + \alpha W(t), \quad (5)$$

where $\alpha \in \mathbb{R}$ and $W(t)$ is a standard Wiener process. Then, we obtain the following stochastic differential system with perturbation of the transmission rate of RSV,

$$\begin{aligned} dS(t) &= (\mu - \mu S(t) - \beta(t)S(t)I(t) + \gamma R(t))dt - \frac{\alpha\beta(t)}{b_0}S(t)I(t)dW(t), \\ dI(t) &= (\beta(t)S(t)I(t) - \nu I(t) - \mu I(t))dt + \frac{\alpha\beta(t)}{b_0}S(t)I(t)dW(t), \\ dR(t) &= (\nu I(t) - \mu R(t) - \gamma R(t))dt. \end{aligned} \quad (6)$$

Remark 2. In Eq. (5), we assume that the baseline transmission parameter b_0 is equal to a constant average value plus a time fluctuating term and these term follows a normal distribution with mean zero. Biologically, we translate Eq. (5), in that the transmission parameter b_0 fluctuates randomly around some constant average value due to time varying environment disturbance.

4. Numerical Simulations

In this section, numerical simulations results of the stochastic differential models of RSV are developed, in order to investigate if small changes of the birth and RSV transmission rates, can produce significant dynamical changes on the dynamics of the RSV at the population. Numerical solutions of the stochastic differential equation systems are obtained with help of Euler-Maruyama and Milstein numerical schemes. At first we consider the stochastic environmental perturbations on the birth rate demographic parameter. The numerical simulation analysis is based upon the stochastic differential model systems (4) and (6). In addition, statistics such

mean and confidence intervals are computed using Monte-Carlo method (Kloeden and Platen, 1995).

4.1. Simulation of RSV Model under Perturbation on the Birth Rate

At first, let us compute the numerical solution of one realization of the stochastic differential equation system (4) with the Euler-Maruyama and Milstein numerical schemes and a environmental perturbation of the birth rate in a range of 100% ($\alpha = 0.009$). It is well known that the Milstein scheme (strong order 1) is more precise than Euler-Maruyama scheme (strong order 0.5). However, as it can be seen in Fig. 2, both numerical schemes show similar results for small time step sizes satisfying that $h < 0.001$. Therefore, in order to save computational time Euler-Maruyama scheme is applied through the following Monte-Carlo simulations and step sizes are chosen such that $h < 0.001$.

To study the qualitative change in dynamical behavior of the stochastic differential equation system (4) with the increasing magnitude of environmental perturbation of the birth rate, we simulate the stochastic model system for different values of α . Based on numerical simulations, it is possible to construct different confidence intervals for each subpopulation of the stochastic differential equation system (4). In Fig. 3, it can be observed confidence intervals of 95% and expected behavior for the infected subpopulation $I(t)$ using the Monte-Carlo method, when the birth rate is perturbed in a range of 100% and 500%. Despite the magnitude of these environmental stochastic perturbations are huge, the infected population follows almost the same periodic behavior as in the deterministic model. On the other hand, the width of the confidence interval depends on the size of the stochastic environmental perturbation, as it can be observed in Fig. 3.

4.2. Simulation of RSV Model under Perturbation on the Transmission Rate

In order to investigate briefly which stochastic numerical scheme to use in the Monte-Carlo method, let us first compute the numerical solution of one realization of the stochastic differential equation system (6) with the Euler-Maruyama and Milstein numerical schemes and a environmental perturbation of the transmission rate in a range of 5%. As it can be seen in Fig. 4, both numerical schemes show similar results for small time step sizes satisfying that $h < 0.001$. Therefore, in order to save computational time Euler-Maruyama scheme is applied in the following Monte-Carlo simulations and step sizes are chosen such that $h < 0.001$.

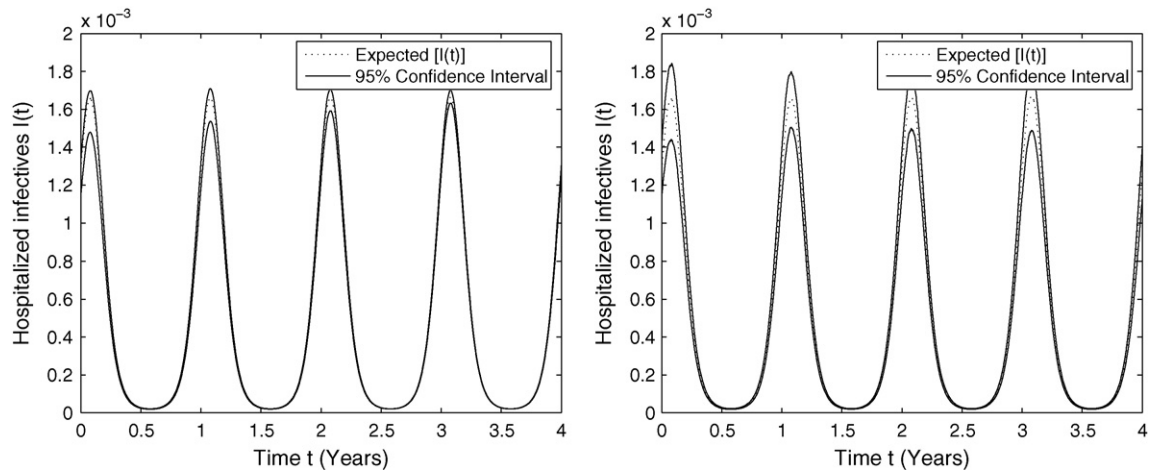


Fig. 3. Confidence intervals and expected behavior for the infected subpopulation $I(t)$ when the birth rate is perturbed in a range of 100% (left) and 500% (right), using Monte-Carlo method.

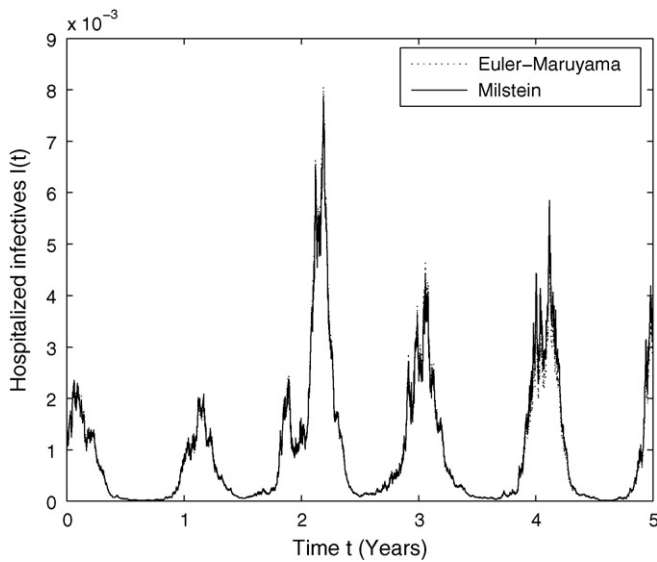


Fig. 4. Comparison between the Milstein and Euler-Maruyama stochastic schemes in regard to the infected subpopulation $I(t)$, using time step size $h = 0.001$, when the RSV baseline transmission rate is perturbed in a range of 5%.

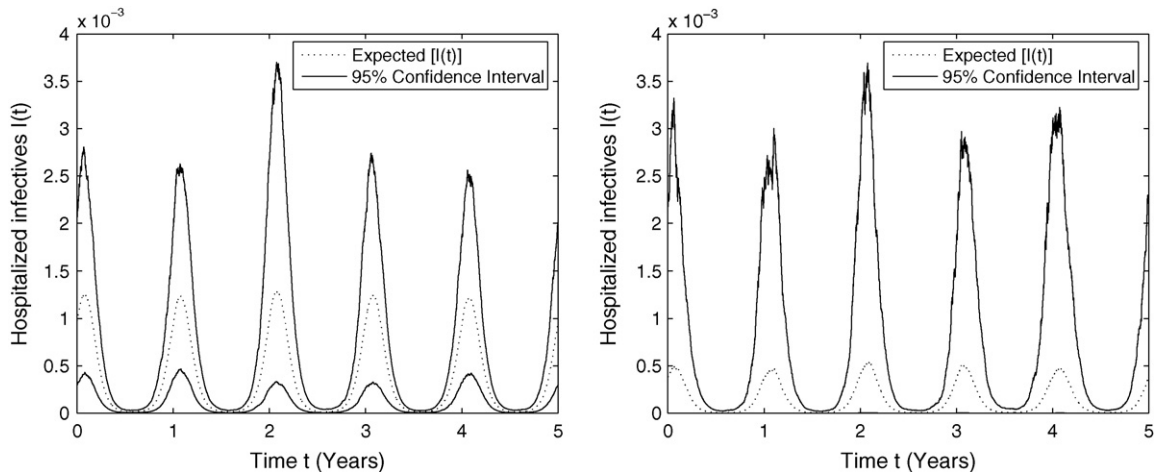


Fig. 5. Confidence intervals and expected behavior for the infected subpopulation $I(t)$ when the RSV baseline transmission rate is perturbed in a range of 1% (left) and 2% (right), using Monte-Carlo method.

To study the qualitative change in dynamical behavior of the stochastic differential equation system (6) with the increasing magnitude of environmental perturbation on the transmission rate, we simulate the stochastic model system for different values of α . However, since the environmental perturbation of the transmission rate affects strongly the model dynamic of RSV, this perturbation was done in a smaller range than in the birth rate case. Based on numerical simulations, it is possible to construct different confidence intervals for each subpopulation of the stochastic system of differential Eq. (6). In Fig. 5, it can be observed confidence intervals of 95% and expected behavior for the infected subpopulation $I(t)$ using the Monte-Carlo method, when the transmission rate is perturbed in a range of 1% and 2%. Despite the magnitude of these environmental stochastic perturbations are small, the dynamics of infected population $I(t)$ is modified greatly with respect to the deterministic model. As it is illustrated in Fig. 5, the width of the interval is wider than when the model is perturbed on the birth rate. Moreover, the confidence interval with environment perturbation in a range of 2%, leads to very low limits for the infected population. Therefore, extinction of the RSV is a realistic option for small environment perturbations, since infected population may become extinct.

At this position we want to remark that this previous result means that the underlying deterministic model is more sensitive to environment perturbations on the transmission rate than on demographic parameters. It is quite interesting to note in Fig. 6,

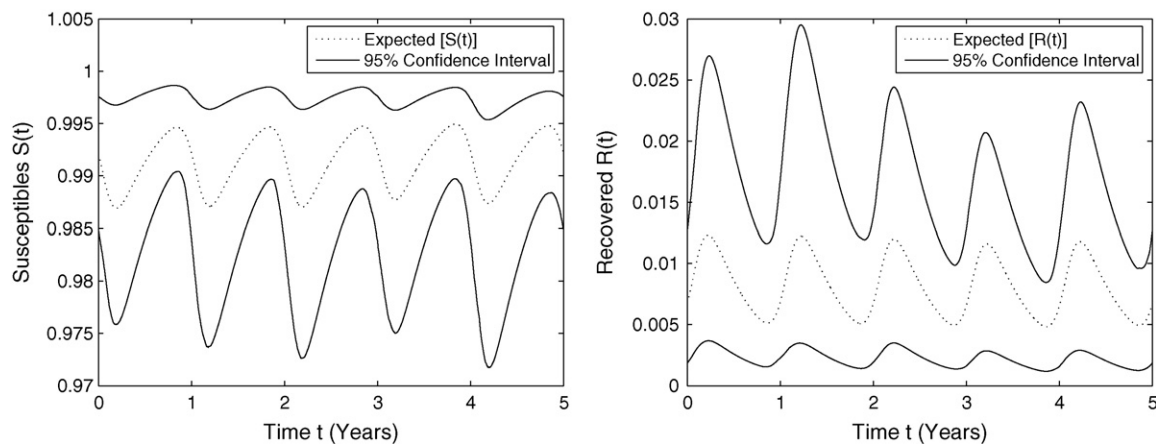


Fig. 6. Confidence intervals and expected behavior for the susceptible $S(t)$ and recovered $R(t)$ subpopulations, when the RSV baseline transmission rate is perturbed in a range of 1% using Monte-Carlo method.

that the intensity of fluctuation on the recovered subpopulation $R(t)$ increases when the environmental perturbation on the transmission rate increases, despite the noisy seasonally forced cosinusoidal function does not appear in the equation related to the variation of $R(t)$. As the noise term is introduced in the susceptibles and infected subpopulations, is logical that these populations should be affected significantly in regard to their basic oscillatory nature and their span of oscillation.

5. Discussion and Conclusions

The influence of environmental noise on nonlinear models has received a considerable amount of attention recently, since almost every real model evolves in the presence of noisy environmental driving forces. However, it is often assumed that the environmental noise has negligible contribution on the evolution of population, since it is argued that noises are relatively small compared to the size of population under consideration. But introduction of noise terms in the models may change the deterministic dynamics radically. Deterministic modeling approach is a suitable choice for a particular model system if the basic evolutionary pattern remains unaltered in the presence of stochastic fluctuation in the demographic parameters (Bandyopadhyay, 2008).

In this paper, we have considered two stochastic models describing the transmission of the respiratory syncytial virus RSV in the population of the region of Valencia, Spain. The underlying deterministic model is fitted to real data in order to estimate some unknown parameters related to the transmission of RSV in Valencia. After adjusting the underlying deterministic model using least squares, the stochasticity is introduced by the parameter perturbation technique, using Gaussian white noise. Environment perturbations were made at first on the birth rate population and afterwards on the transmission rate of RSV. The effect of environment fluctuations of the birth rate of the population and transmission rate of the virus is analyzed using stochastic models, based on systems of stochastic ordinary differential equations. In order to obtain numerical solutions of these stochastic ordinary differential equations the well-known Euler-Maruyama and Milstein schemes were used. However, in order to save computational time and simplicity, solutions were computed using Euler-Maruyama numerical stochastic scheme with small step size.

With the help of Monte-Carlo method confidence intervals for the dynamics of the subpopulations were constructed in order to investigate the dynamics of RSV under environment small perturbations. It is important to remark that based on the numerical results presented in this paper, we can establish that the underlying

deterministic model is more sensitive to environment perturbations on the transmission rate than in demographic parameters and extinction of the infected population $I(t)$ may be challenged by the intensity of environmental perturbations. Therefore, public health policies should focus on the transmission rate parameter, in order to reduce the incidence of RSV. Moreover, the model allows to introduce a perturbation such a prophylactic vaccine and simulate the results on the population dynamics in regard to RSV.

Based on these results we are able to establish the fact that the dynamics of the deterministic model varies significantly in the presence of environmental fluctuation and extinction of the infected population $I(t)$ may be challenged by the intensity of environmental perturbations.

Finally, this paper shows that stochastic environments are more suitable to model RSV in the population, since the real data is not exactly periodic as his counterpart deterministic model predicts. Furthermore, numerical simulations show that stochastic differential equations are useful to analyze viral dynamics. Simulations of the stochastic model as discussed here add another dimension to model RSV dynamics, since most real world problems are not deterministic, the introduction of stochastic effects into the model give us a more realistic way of modeling RSV dynamics.

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