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ORIGINAL ARTICLE

Parameter Estimation of Some Epidemic Models. The Case of Recurrent Epidemics Caused by Respiratory Syncytial Virus

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Abstract The research presented in this paper addresses the problem of fitting a mathematical model to epidemic data. We propose an implementation of the Landweber iteration to solve locally the arising parameter estimation problem. The epidemic models considered consist of suitable systems of ordinary differential equations. The results presented suggest that the inverse problem approach is a reliable method to solve the fitting problem. The predictive capabilities of this approach are demonstrated by comparing simulations based on estimation of parameters against real data sets for the case of recurrent epidemics caused by the respiratory syncytial virus in children.

Keywords Seasonal epidemics · Epidemic models · Parameter estimation · Numerical methods

1. Introduction

In this paper, we are concerned with the problem of parameter estimation in ordinary differential equations (ODE). We shall focus on susceptible-infected-recovered-susceptible epidemic models (generally known as SIRS models). These mathematical models, among others, have been intensively studied aiming to understand spread and control of infectious diseases. It is known that the qualitative model behavior is strongly influenced by the way in which the model embodies infection incidence rate. Both forced and non-forced SIRS models with nonlinear incidence rate have rich dynamics and are adequate to model seasonal epidemics.

Qualitative analysis of dynamical systems is a well established and active research area. And the mathematical modeling of key features of epidemics, such as infection

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transmission, has a growing importance as a tool to gain insight into the dynamics of epidemics. To complement this analysis, our aim is to provide a tool for prediction and simulation of epidemics. Consequently, estimation of the parameters in the epidemic models is required. Thus, our purpose is to develop a method to estimate parameters in ODE from incomplete knowledge of the solution. We shall test our method by recovering parameters of the incidence rate (4), (6) from seasonal epidemic data caused by respiratory syncytial virus (RSV) in children from Gambia and Finland. The data that we use is provided in Weber et al. (2001).

There is plenty of research on qualitative analysis of dynamical systems modeling infectious diseases. In the context of incidence rate, Capasso and Serio (1978), Gomes et al. (2005), Hethcote et al. (1989), Hethcote and van den Driessche (1991), Kyrychko and Blyuss (2005), Li and Muldowney (1995), Ruan and Wang (2003), van den Driessche and Watmough (2000), Wang (2006) and Xiao and Ruan (2007) among others, have studied and biologically interpreted epidemic models with nonlinear incidence rates departing from standard incidence rate. Korobeinikov and Maini (2005) established stability theorems for generalized incidence rates under standard biological hypotheses. Alexander and Moghadas (2004, 2006) studied SIRS models for a class of generalized incidence rates and showed analytically that these models undergo several types of Hopf bifurcations.

Other efforts to model recurrent epidemics used forced SIR or SIRS models to take into account the seasonality of transmission. Weber et al. (2001) added a sinusoidal term to the contact rate, while Greenhalgh and Moneim (2003) studied a model with a general periodic function that forces the contact rate. It has been established that these models undergo a period-doubling bifurcation as the amplitude of the oscillating term in the contact rate increases. The problem is far from settled, research is active on both forced and non-forced epidemic models in order to describe the complex dynamics of recurrent epidemics.

Recently, the problem of parameter estimation in mathematical models of biological systems has received a great deal of attention. In the context of infectious diseases, Alioum et al. (2005) have estimated the incidence rate for the human immunodeficiency virus. Closely related to our work, Pourabbas et al. (2001) estimated the incidence of communicable diseases under seasonal fluctuations. The work presented by Brunet and Struchiner (1996) also addresses the problem of rate estimation in epidemic models. It is apparent that the parameter estimation problem is relevant in other biological systems; noteworthy is the work of Banks et al. (2007). Therein, a methodology for estimating dynamic rate parameters in insect populations is presented.

Parameter estimation problems are ubiquitous in science. A common approach is to formulate an appropriate constrained optimization problem. The objective function is a least squares like functional. See Biegler and Grossmann (2004) for a review on numerical methods applied to problems of this sort.

In this paper, we use some of the SIRS models mentioned above as a framework to solve the problem of estimating the parameters of the generalized incidence rate from seasonal epidemic data. The formulation is classical; we pose an optimization problem constrained to a system of ordinary differential equations. It will become apparent that our method is applicable to other physical systems modeled by ODE.

Some general approaches to deal with the problem of parameter estimation in ODE are also the works of Ramsay et al. (2007) and Li et al. (2005). In the former, a method that

uses noisy measurements of a subset of variables is described. The method is based on a data fitting functional complemented with a smoothing technique. The method requires the selection of a parameter regulating the smoothing term; this selection is heuristic. In the latter, the method of least squares is used to define the objective function. The constraint is a difference equation associated to the ODE. An important feature is the numerical technique developed for implementation. We remark that our method also handles incomplete and noisy data, and unlike the method in Li et al. (2005), it works with the continuous ODE as a constraint. We initialize the method with an efficient global search for local minima.

The paper is organized as follows. In Section 2, we gather appropriate models to solve the parameter estimation problem. First, in Section 2.1, we use some results of Alexander and Moghadas (2006) to contextualize a nonforced model with a generalized incidence rate that admits periodic solutions. In Section 2.2, we write an autonomous model which is equivalent to the forced SIRS model used by Weber et al. (2001). In Section 3, we discuss the inverse problem of recovering the parameters of the incidence rate from seasonal epidemic data, and propose in Section 3.1 a general implementation of the Landweber iteration aimed at solving the inverse problem. Numerical results are shown in Section 4. The numerical experiments are conducted using data from Weber et al. (2001). We use MATCONT of Dhooge et al. (2003) to numerically find and examine bifurcation points near the estimated parameters. Finally, in Section 5, we summarize this paper.

2. Mathematical modeling of seasonal epidemics

The following standard assumptions are made in order to define the epidemic models. Individuals are either susceptible $S(t)$, infective $I(t)$, or recovered $R(t)$. It is assumed that the population is uniformly mixed and there is deterministic transfer between epidemiological classes with exponentially distributed waiting time. Since the annual infection rate is considerably bigger than the population growth, birth and mortality rates are assumed equal. Dimensionless state variables are used by dividing the number of individuals in each class by the total population $s(t) = S(t)/N$, $i(t) = I(t)/N$, and $r(t) = R(t)/N$. μ is the combined birth and mortality rate, γ is the rate of loss of immunity, and ν is the rate of loss of infectiousness. Clinical values of μ, γ, ν, and N are available for RSV; see, for instance, Weber et al. (2001) and references therein.

2.1. Nonforced model

We consider the SIRS model

$$\frac{ds}{dt} = \mu - \mu s - \beta(1 + \alpha i)is + \gamma r, \tag{1}$$

$$\frac{di}{dt} = \beta(1 + \alpha i)is - (\nu + \mu)i, \tag{2}$$

$$\frac{dr}{dt} = \nu i - (\mu + \gamma)r. \tag{3}$$

Here, β and α are constant. The incidence rate

$$\beta(1 + \alpha i)is, \tag{4}$$

models simple and double contacts between susceptible and infective individuals over a short period of time, new infective individuals arise from double exposures at a rate $\beta\alpha i^2 s$, while single contacts lead to infection at rate $\beta i s$; see van den Driessche and Watmough (2000). Incidence rate (4) is an example of the class of generalized incidence rates studied by Alexander and Moghadas. Therefore, their stability, threshold, and bifurcation results hold for models (1)–(3). This model admits periodic solutions.

The basic reproductive number R_0 defined according to van den Driessche and Watmough (2002)

$$R_0 = \frac{\beta}{\mu + \gamma} \tag{5}$$

is independent of the functional form of $\beta(1 + \alpha i)is$. According to Alexander and Moghadas (2006), model (1)–(3) has a unique and asymptotically stable endemic equilibrium if $R_0 > 1$, and there is none, one, or two endemic equilibria, otherwise. Also, they established that varying α near the endemic equilibrium leads to a point of Hopf bifurcation. If the first Lyapunov coefficient of the normal form of (1)–(3) is not zero, a supercritical (backward supercritical) Hopf bifurcation leads to the appearance (disappearance) of a stable or unstable limit cycle when α passes through a critical value α_c.

In Section 4, the first Lyapunov coefficient of (1)–(3) is computed numerically to investigate the behavior of the ensuing bifurcation points near the parameters that correspond to real data of RSV epidemics. Bifurcation diagrams around the system equilibria are numerically constructed with MATCONT of Dhooge et al. (2003) in order to formulate our conclusions.

2.2. *Forced model*

Other approaches to modeling recurrent epidemics take into account the seasonal nature of transmission through an oscillating contact rate. Weber et al. (2001) and Greenhalgh and Moneim (2003) used a SIRS model with incidence rate

$$b_0\big(1 + b_1 \cos(2\pi t + b_3)\big)is \tag{6}$$

which models annual forcing of the contact rate. It is natural to take b_1 as the bifurcation parameter. It is known that both the SIR and SIRS models with incidence rate (6) undergo period doubling bifurcations as b_1 increases. Also, it is known that the model has solutions of period 1, 2, 3, and 4 years.

For the sake of using the Landweber iteration, as described in Section 3, to estimate the model parameters, we use the equivalent autonomous model

$$\frac{ds}{dt} = \mu - \mu s - b_0(1 + b_1 x)is + \gamma r, \tag{7}$$

$$\frac{di}{dt} = b_0(1 + b_1 x)is - (\nu + \mu)i, \tag{8}$$

$$\frac{dr}{dt} = \nu i - (\mu + \gamma)r, \tag{9}$$

$$\frac{dx}{dt} = -My, \tag{10}$$

$$\frac{dy}{dt} = Mx. \tag{11}$$

Model (7)–(11) is a classical SIRS model coupled with an undamped harmonic oscillator. If we introduce the variable $\tau = Mt$, it follows that the model approaches a classical SIRS model as $M \to 0$ and approaches an undamped harmonic oscillator in the variable τ when $1 \ll M$. It is common to fix $M = 2\pi$ beforehand to model annual forcing of the contact rate. It is interesting to study the coupling of the SIRS model with various oscillators in order to study recurrent epidemics; see Greenhalgh and Moneim (2003).

3. Parameter estimation of the epidemic model

There is no a priori information about how accurately can models (1)–(3) or (7)–(11) predict given seasonal epidemic data. Moreover, even for the correct set of parameters there may be discrepancy between the model prediction and data due to measurement errors or model errors. For a model error, we understand an error due to the fact that the assumptions which led to the model are not fulfilled. For instance, the subpopulations are likely not uniformly mixed.

In this paper, we use classical theory of inverse problems for the parameter estimation problem and propose an iterative method to solve this problem locally. Writing $x(t) = (s(t), i(t), r(t))^t \in (L^2([0,T]))^3$ and $p = (\beta, \alpha) \in \mathbb{R}^2$ in model (1)–(3) or $p = (b_0, b_1, b_2) \in \mathbb{R}^3$ in model (7)–(11) we have

$$\dot{x} = \varphi(x, p), \tag{12}$$

$$x(0) = x_0, \tag{13}$$

where φ is the right-hand side of the SIRS model. Problem (12)–(13) define a mapping $\Phi(p) = x$ from parameters p to state variables x, where $\Phi : \mathbb{R}^m \to (L^2([0,T]))^n$. In this paper, we assume that Φ is Fréchet differentiable and injective, thus the direct problem (12)–(13) has a unique solution x for a given p. The Fréchet derivative of Φ is a mapping $\Phi'(p) : \mathbb{R}^m \to (L^2([0,T]))^n$.

Usually the data consists of measurements of the state variables at a discrete set of points $t_1, \ldots, t_k$, and only a subset of the state variables are measurable, e.g., data of the RSV epidemics consists of monthly measurements of the number of infected individuals. This defines a linear observation mapping from state variables to data $\Psi : (L^2([0,T]))^n :\to \mathbb{R}^{s\times k}$, where $s \le n$ is the number of observed variables and k is the number of sample points. In the case of RSV epidemics, $\Psi(x) = (i(t_1), \ldots, i(t_k)) \in \mathbb{R}^{1\times k}$. Let $F : \mathbb{R}^m \to \mathbb{R}^{s\times k}$ be defined by $F(p) = \Psi(\Phi(p))$. The inverse problem is formulated as a standard optimization problem

$$\min_{p\in\mathbb{R}^m} \frac{1}{2} \left\| F(p) - z_\delta \right\|^2 \tag{14}$$

where $z_\delta \in \mathbb{R}^{s\times k}$ is the data and has error measurements of size δ. Equivalently, the inverse problem can be formulated as

$$\min_{p\in\mathbb{R}^m} \frac{1}{2} \left\| \Psi(x) - z_\delta \right\|^2 \tag{15}$$

such that

$$\dot{x} = \varphi(x, p), \tag{16}$$

$$x(0) = x_0. \tag{17}$$

In the following subsection, we propose an implementation of the Landweber iteration with an a posteriori stopping criterion to solve problem (15)–(17).

3.1. Implementation of the Landweber iteration

Let us consider the Lagrangian

$$\mathcal{L}(x, p, \lambda) = \frac{1}{2}\left\|\Psi(x) - i_\delta\right\|^2_{\mathbb{R}^m} + \left\langle \dot{x} - \varphi(x, p), \lambda\right\rangle_{(L^2([0,T]))^n}. \tag{18}$$

Integrating by parts $\langle \dot{x}, \lambda\rangle_{(L^2([0,T]))^n}$ in the second term of (18) and letting $\lambda(T) = 0$, we obtain

$$\mathcal{L}(x, p, \lambda) = \frac{1}{2}\left\|\Psi(x) - i_\delta\right\|^2_{\mathbb{R}^m} - \left\langle x, \dot{\lambda}\right\rangle_{(L^2([0,T]))^n} - \left\langle \varphi(x, p), \lambda\right\rangle_{(L^2([0,T]))^n}. \tag{19}$$

The derivative of (19) with respect to x and p is, respectively,

$$\begin{aligned}\mathcal{L}_x(x, p, \lambda)\xi &= \left\langle \Psi(\xi), \Psi(x) - i_\delta\right\rangle_{\mathbb{R}^m} - \left\langle \xi, \dot{\lambda}\right\rangle_{(L^2([0,T]))^n} \\ &\quad - \left\langle \varphi_x(x, p)\xi, \lambda\right\rangle_{(L^2([0,T]))^n}, \end{aligned} \tag{20}$$

$$\begin{aligned}\mathcal{L}_p(x, p, \lambda)\eta &= -\left\langle \varphi_p(x, p)\eta, \lambda\right\rangle_{(L^2([0,T]))^n} \\ &= -\left\langle \eta, \varphi_p(x, p)^*\lambda\right\rangle_{\mathbb{R}^m}, \end{aligned} \tag{21}$$

where $\varphi_p(x, p)^*\lambda = \int_0^T \varphi_p(x(t), p)^*\lambda(t)\,dt$ in (21).

Let $x = \Phi(p)$ be solution of the initial value problem (12)–(13). Consequently, $\mathcal{L}(x(p), p, \lambda) = \frac{1}{2}\|F(p) - i_\delta\|^2_{\mathbb{R}^m}$. Let us denote $y = \Phi'(p)q$ and $\mathcal{L}'(x(p), p, \lambda)$ the Fréchet derivative with respect to p. Using identities (20) and (21), and the chain rule, we obtain

$$\begin{aligned}\mathcal{L}'\big(x(p), p, \lambda\big)(q) &= \left\langle \Psi(y), \Psi(x) - i_\delta\right\rangle_{\mathbb{R}^m} - \left\langle y, \dot{\lambda}\right\rangle_{(L^2([0,T]))^n} \\ &\quad - \left\langle \varphi_x(x, p)y, \lambda\right\rangle_{(L^2([0,T]))^n} - \left\langle \varphi_p(x, p)q, \lambda\right\rangle_{(L^2([0,T]))^n}. \end{aligned} \tag{22}$$

Equivalently,

$$\begin{aligned}\mathcal{L}'\big(x(p), p, \lambda\big)(q) &= \left\langle \Psi^*\big(\Psi(x) - i_\delta\big) - \varphi_x(x, p)^*\lambda - \dot{\lambda}, y\right\rangle_{(L^2([0,T]))^n} \\ &\quad - \left\langle \varphi_p(x, p)^*\lambda, q\right\rangle_{\mathbb{R}^m}. \end{aligned} \tag{23}$$

The following theorem holds.

Theorem 1. *The Landweber iteration*

$$p_{k+1} = p_k + F'(p_k)^*\big(F(p_k) - i_\delta\big) \tag{24}$$

can be written

$$p_{k+1} = p_k - \int_0^T \varphi_p\big(x_k(t),\, p_k\big)^* \lambda(t)\, dt \tag{25}$$

where $x_k = \Phi(p_k)$ *and* $\lambda \in (L^2([0,T]))^n$ *is solution of the adjoint problem*

$$\dot{\lambda} = -\varphi_x(x_k,\, p_k)^*\lambda + \Psi^*\big(\Psi(x_k) - i_\delta\big), \tag{26}$$

$$\lambda(T) = 0. \tag{27}$$

Remark 1. *An approximate solution* p_k *can be refined evaluating* $\Phi(p_k)$, $F(p_k)$, *solving the adjoint problem* (26)–(27) *and updating the approximate solution according to* (25).

The least squares functional (14) does not depend continuously on the parameters p. The data is polluted with noise. Therefore, early iterations of the Landweber iteration improve the approximate solution but it leads to an unstable solution if it is arbitrarily continued. The Landweber iteration yields a regularized solution of problem (15)–(17) if it is stopped at an appropriate step k_{final}. In Section 4, we use the following a posteriori stopping condition, known as the discrepancy principle, to select k_{final}

$$\big\|F(p_{k_{\text{final}}}) - i_\delta\big\| \le \tau\delta \le \big\|F(p_k) - i_\delta\big\|, \quad 0 \le k \le k_{\text{final}},\ \tau > 2. \tag{28}$$

The discrepancy principle (28) was introduced by Hanke et al. (1995).

4. Numerical results

In the examples shown below, the initial guess p_0 for the Landweber iteration is constructed starting the Nelder–Mead algorithm simultaneously at an array of random points p for the objective function (14). This gives rise to an array of local solutions. We choose p_0 such that it minimizes the objective function over the array of local solutions. The initial value for the unknown state variables is estimated similarly. We choose the Nelder–Mead algorithm since it is well suited for low dimensional problems. See Lagarias et al. (1998) for convergence results of the Nelder–Mead algorithm in low dimensional problems. To stop the iteration, we use the discrepancy principle (28) with $\tau = 2.5$, although τ should be chosen as described in detail in Hanke et al. (1995). We remark that the computation of τ with the theory described in Hanke et al. (1995) is not simple and constitutes the subject of further research. We guess the noise size $\delta = 0.1$. We show the parameter estimation for two different cases. Data corresponds to epidemics caused by syncytial respiratory virus (RSV) in children under 5 years old from Gambia and Finland. The data sets are taken from Weber et al. (2001).

4.1. Gambia

Figures 1a and 1b show the results of fitting the nonforced and forced models, respectively, to the data set from Gambia.

Starting at the estimated parameter values $\beta = 59.614152$ and $\alpha = 5.266016$ for the nonforced model (1)–(3) and the data set from Gambia, we explore numerically the bifurcation behavior around stationary points. Taking α as the parameter of bifurcation, we find that the system has Hopf bifurcations at $\alpha_1 = 4.565891$ and $\alpha_2 = 223.606757$. The continuation of stationary points for $\alpha \in [0, 230]$ is shown in Fig. 2. The Hopf points are denoted by H. The numerical computation of the first Lyapunov coefficient yields $\lambda_1 = -7.957588$ and $\lambda_2 = -1493.439$ at α_1 and α_2, respectively. Therefore, a family of stable limit cycles bifurcates from the stationary points that correspond to α_1 and α_2. We conduct continuation of the limit cycles that bifurcate from the Hopf points taking β and α as free parameters. Plots of the arising limit cycles are shown in Fig. 2 for selected values of α. This bifurcation diagram is in agreement with the analysis of Alexander and Moghadas (2006).

The forced model (7)–(11) has no stationary points for $b_1 \neq 0$. The estimated parameters $b_0 = 55.3645$, $b_1 = 0.3942$ correspond to a limit cycle.

4.2. Finland

Figure 3a and 3b show the results of fitting the nonforced and forced models to the data set from Finland. We examine numerically the bifurcation behavior of the nonforced model in a neighborhood of the parameters corresponding to Fig. 3a. Similarly to Section 4.1, the

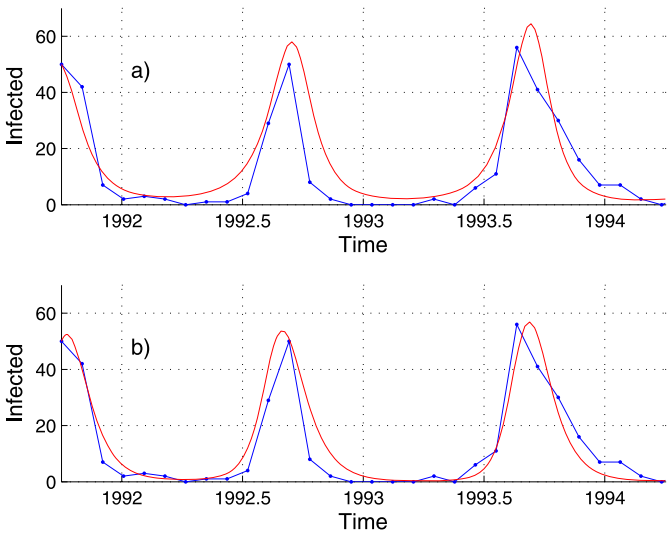

Fig. 1 Part (a) shows the fitting of the nonforced model to the data set from Gambia. The blue line with dots is the clinical data. The continuous red line is the simulation based on parameter estimation. The time is scaled in years. Part (b) shows the corresponding fitting of the forced model to the data set. (Color figure online.)

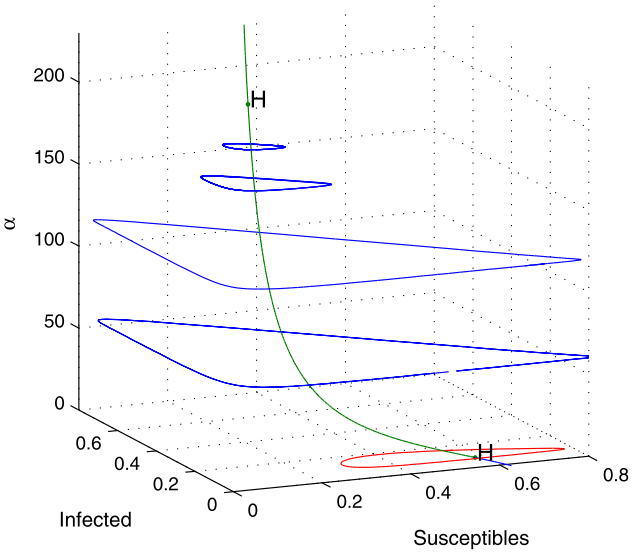

Fig. 2 The green line is the numerical continuation of the stationary points of the nonforced model. The system undergoes two supercritical Hopf bifurcations, which are denoted by H in this figure. A family of stable limit cycles bifurcates from these points. Limit cycles in the susceptible-infected plane are plotted in blue for selected values of α. The red line is the simulation with the estimated parameters. (Color figure online.)

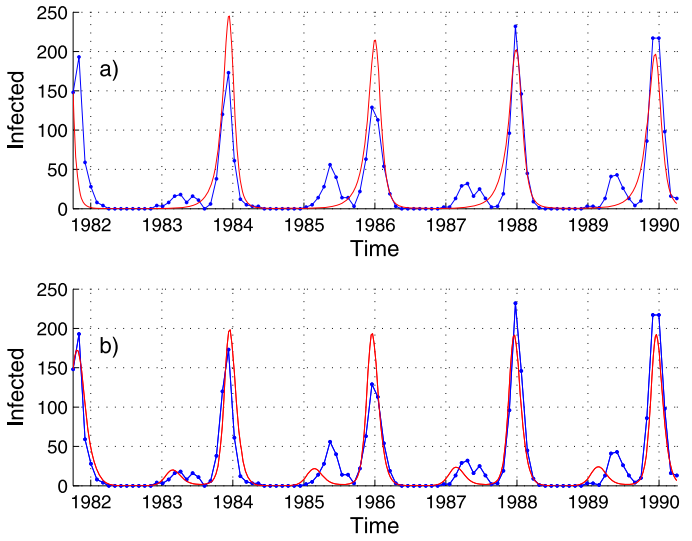

Fig. 3 Part (a) shows the fitting of the nonforced model to the data set from Finland. The blue line with dots is the clinical data. The continuous red line is the simulation based on parameter estimation. The time is scaled in years. Part (b) shows the corresponding fitting of the forced model to the data set. The nonforced model fails to predict the data accurately. (Color figure online.)

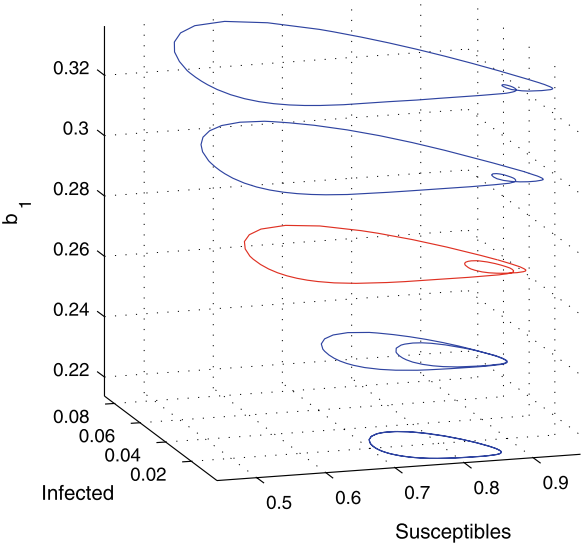

Fig. 4 Some plots in the susceptible-infected plane are plotted in blue at selected values of b_1. It is numerically exhibited that the limit cycle undergoes a period doubling bifurcation as the amplitude of the forcing term increases. The red line is the simulation with the estimated parameters. (Color figure online.)

model has Hopf bifurcations at $\alpha_1 = 6.135971$ and $\alpha_2 = 327.717954$. The computation of the first Lyapunov coefficient yields $\lambda_1 = -5.588314$ and $\lambda_2 = -1600.410$, respectively. Therefore, a family of stable limit cycles bifurcates from the Hopf points. This is an interpretation of why the nonforced model fails to predict the smaller peak in the number of infected individuals seen every other year in the data set from Finland.

Simulations of the forced model at selected values of the parameter b_1 are shown in Fig. 4. This figure shows the occurrence of the period doubling bifurcation of a limit cycle. The red line is the simulation with the forced model and the estimated parameters.

Apparently (7)–(11) is a better model to estimate the underlying transmission model structure from data. Further research is necessary in order to gain insight on how the seasonal pattern of transmission varies between host populations and climates. However, we consider that the parameter estimation technique described in this paper may represent a useful tool for this task.

5. Conclusions

In this paper, we propose an implementation of the Landweber iteration together with a standard stopping condition as a method to solve locally the problem of estimating the parameters in a system of ODE. The proposed method is capable of handling incomplete and noisy data, although an estimate of the noise level is required in order to stop the iterations in a timely manner. The predictive capabilities of the proposed method are demonstrated

by comparing simulations based on estimation of parameters against real data sets for the case of recurrent epidemics caused by respiratory syncytial virus in children. In particular, our results suggest that among the two models considered, the forced model is more appropriate to explain recurrent epidemics.

The method proposed in this paper is a suitable choice to conduct parameter estimation in ODE. For the sake of comparison, let us comment further on some other methods. For noisy data, a successful method is that of Ramsay et al. (2005). As pointed out before, the method of Ramsay is a combination of estimation and smoothing. The latter requires the choice of a smoothing parameter. The authors apply their method to two examples, the FitzHugh–Nagumo equations and the tank reactor equations. The necessary smoothing parameter for their algorithm is chosen based on numerical and visual heuristics. This parameter selection method poses the risk of not always choosing the best value of the regularization parameter. It is interesting to study the method of Ramsay under the theory of regularization of inverse problems. From the numerical point of view, the method introduced in Li et al. (2005) is appealing. Therein, the ODE is discretized, and consequently a constrained optimization problem is posed. A nontrivial algorithm is developed for the optimization, which might be a challenge to implement. We take the continuous version of the optimization as a better solution to the problem, where the mathematical analysis can be carried out leaving discretization as a final step.

One weakness of the proposed method is that it requires many iterations to reach a regularized solution. The results of this paper may be generalized to an improved version of the Landweber iteration, or another method of higher order of convergence, but that constitutes the subject of further research.

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