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A STUDY FOR COMPUTATIONAL COST OPTIMIZATION FOR INFLUENZA FLU INCLUDING VACCINATION'S IMPACT

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Abstract. *This work proposes a mathematical formulation of epidemics caused by influenza viruses and a numerical solution method to retrieve the solution. In particular, we study the propagation of the influenza virus considering the impact of vaccination campaigns in the disease dynamics and also the loss of efficiency of the vaccine. The numerical solution of the proposed model is found by means of a finite difference method and a numerical optimization procedure is applied to minimize the computational cost of solving the nonlinear ordinary differential equations that define the model. This procedure makes use of a grid refinement framework which, in turn, utilizes some properties of linearly converging algorithms to generate an optimal sequence of approximate models that converges to the true model. Such a sequence is optimal with respect to the total computational cost and minimizes the computational time to find a solution to the proposed model. As a result, such a framework can result in significant computational savings, speeding up the solution procedure.*

1 INTRODUCTION

Epidemiological models are widely used to study the behavior of cyclic diseases, which return periodically over the years, such as the H1N1 flu. This form of disease spreads so rapidly that in 2009 it was classified as pandemic by the World Health Organization. Therefore, it is of the utmost importance that models and tools that assist in the understanding of the dynamics and in the proposal of control mechanisms for the H1N1 flu are developed. This paper proposes a mathematical model based on differential equations and applies it to study the dynamics of the H1N1 flu.

Problems involving differential equations find application in different areas of knowledge and require, as a result, a multidisciplinary approach that combines the knowledge in the areas of transport phenomena, control systems, numerical modeling and computing, among others. These kind of problems can be found in many fields, but we are particularly interested in the public health sector. In particular, this paper addresses the development of numerical simulators aimed at solving problems of spreading diseases with the optimization of the computational cost.

More specifically, we address in this paper a mathematical formulation comprising a set of ordinary differential equations based on the so-called Susceptible - Infected - Removed (SIR) model. This model, proposed by Kermack and McKendric (1927) [12] is comprised of a non-linear system of equations that are common to each of the subgroups included in the model: the susceptibles, which are individuals vulnerable to the disease; the infected, those that actually had acontact with it and may infect others; and the removed, which comprises two groups of individuals, those already recovered and considered immune to the disease thereafter and those who died from the disease.

In this paper, we present a model for the propagation of the influenza virus considering the impact of vaccination campaigns, also the loss of efficiency of the vaccine and the possibility of reinfection. The equations can be solved iteratively by linearly convergent algorithms. However, since this is a continuous problem, the exact solution may not be found in finite time. A typical approach to circumvent this problem is to set up a tolerance a priori and solve an approximate discrete problem whose solution is within the prescribed tolerance of the exact solution of the continuous problem. That makes finding a discrete approximation to the original problem part of the formulation. However, often the definition of a discrete approximation is arbitrary. We define the search for an approximate solution within a tolerance of the original solution as an optimization problem whose objective is to minimize the computational effort (computing time) required to achieve the desired solution. In order to solve the proposed problem, we make use of the results of Almudevar and Arruda (2012) [2], who show that the optimal rate of refinement of an approximate linearly convergent algorithm is constant and numerically equal to the rate of convergence of the original (exact) algorithm. Hence, to make use of that result we need to have an estimate of the convergence rate of the exact algorithm. In this paper, this rate is estimated as the error between any two consecutive iterations that employ

different approximate models.

2 THE VACCINATION

According to Yang [23] the importance of the use of vaccination as a protection against disease may be based on two components: a decrease in the number of new cases (morbidity) and the low cost of the vaccine in relation to the treatment of disease (monetary). The goal is to induce a protection against the pathogen not only to save individuals alone against serious forms of the disease, but also to control the disease in the community.

Therefore, a thorough understanding of the effects of vaccination on the community requires more than pure biological knowledge. To attain it, one should consider the proper way of vaccinating people so that the chain of disease transmission is interrupted. In that context, mathematical models can be very useful, providing contributions to the understanding of the underlying dynamics. Such models describe the phenomenon of disease transmission and allow the generation of scenarios from different vaccination strategies, anticipating the effects of an eventual vaccination [23].

The vaccine production process for a novel flu strain requires at least 6 months for virus identification, vaccine invention, and then mass production using a long-standing egg-based technology [14]. According to the Brazilian government, egg allergy is the single counter indication of this manufacturing technology. In any case, in addition to side effects, there are other factors which are critical to the effectiveness of vaccination strategies. It is understood that the vaccine may fail in two levels. Firstly, it may not induce immunity in the individual, typically as a result of some failure in the manufacturing process or of some deficiency in the individual's immune system. Failure may also occur when the level of vaccination immunity is low, therefore resulting in immunity loss in a short time span [23]. This illustrates the importance of incorporating the possibility of reinfection in a dynamic vaccination model.

To understand the role of vaccination in the eradication of a disease, we must define two basic concepts in epidemiology. The first is called force of infection, which corresponds to a per capita disease incidence or incidence of new cases divided by the number of susceptible individuals in a population. The force of infection could determine not only the extent of spread but also the amount of the effort to combat the disease. The second concept is the most important parameter in epidemiology, the reproductive number R_0, defined as the average number of new infections caused by a typical infectious individual in a fully susceptible population. If $R_0 < 1$ the disease will be extinguished, while if $R_0 \geq 1$ the disease is endemic in state, its severity increasing with the value of R_0 [23]. The reproductive number can be determined depending on the strength of infection. For example, in the 2009 epidemic in Mexico R_0 was estimated to range between 1.4 and 1.6 [14].

When vaccination is introduced in a population, a decrease in the force of infection is expected. Thus, susceptible individuals become immune without going through the infectious state. As a consequence, there is a decrease in secondary cases generated by infected individuals, thus reducing R_0. As vaccine-induced immunity weakens over time, it is necessary to consider also the possibility of reinfection. This paper introduces a SIR model that views vaccination as a mechanism of disease control, and studies its effect on influenza transmission. The model also accounts for reinfection, to emulate the effect of weakened immunity some time after vaccination.

3 MODELLING

Influenza is a directly transmitted disease, i.e., its spread occurs following the contact of susceptible individuals (who have not had contact with the virus) and infected individuals (who have non-negligible concentration of virus in their bodies). The mathematical formulation consists of a set of ordinary differential equations that describe the so-called Susceptible - Infected - Removed (SIR) model. This model, proposed by Kermack and McKendric [12] consists of a non-linear system of equations that are common to each of the subgroups included in the model: the susceptible; the infected; and the removed, which comprise two groups of individuals, those already recovered and considered immune to the disease thereafter and those who died from the disease. Considering only the temporal evolution, the model can be described as follows:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1}$$

where S is the number of susceptible individuals at time t, I is the number of infected individuals at time t , R is the number of removed individuals at time t, β is the infection rate, and γ is the removal rate. To solve the system we need initial values S_0, I_0 and R_0, at time t_0, for susceptible, infected and recovered individuals, respectively.

The compartmentalized model, widely used to study the transmission dynamics of infectious diseases, including H1N1 flu [9], assumes that an individual may successively visit stages of susceptibility, infection and recovery. It also assumes that immunity is permanent (for life). Normally, the model does not consider the latency period during which the virus replicates in the cells of the individual. That is, it does not consider infected but not infectious individuals. Additionally, the rates of birth and death are equal, which implies that the population is kept constant as time evolves. The model also has the limitation of

considering that individuals are evenly spread in space. However, this assumption makes sense if one wishes to describe the spread of a disease in a population spatially distributed by means of differential equations.

According to Larson and Teytelman [14] *the public policy consensus has been to first vaccinate high-risk groups, including pregnant women, health-care workers, and those at risk of complications from influenza. Some authors, however, claim that in the event that large stockpiles of vaccine are available, the vaccines should be distributed to the drivers of infection, such as schoolchildren and other high-activity individuals.* In any case, consideration of a mixed population without targeting the susceptible and infected groups in activity levels, which influences the understanding of disease progression, is common and may be considered appropriate when the model is applied to large regions.

In this study we consider two improvements in the SIR model given by Equation (1): firstly, we consider that part of the susceptible population has been vaccinated and is partially protected from the complications arising from the disease; secondly, we consider that the vaccine has limited effect and that after a period of time there is a possibility of reinfection. To attain the first improvement, we consider the model originally proposed by Zhou and Guo [25] as follows:

$$\begin{aligned}
\tfrac{dS}{dt} &= \alpha - \beta(I+\eta E)S - (\phi+\mu)S \\
\tfrac{dV}{dt} &= \phi S - (1-\sigma)\beta(1+\eta E)V - \mu V \\
\tfrac{dE}{dt} &= \beta(I+\eta E)S + (1-\sigma)\beta(1+\eta E)V - kE - \mu E \\
\tfrac{dI}{dt} &= kE - \delta_1 I - \delta_2 I - \mu I \\
\tfrac{dR}{dt} &= \delta_2 I - \mu R,
\end{aligned} \tag{2}$$

where V is the number of susceptible individuals vaccinated at time t, E is the number of exposed or latent individuals at time t , R is now the number of recovered individuals at time t, with initial values V_0, E_0 and R_0, at time t_0, for vaccinated, latent and recovered individuals, respectively.

In (2), α is the rate of birth or immigration; β is the rate at which susceptible individuals become infected by those who are infectious; $\eta \in [0,1]$ is a modification parameter to account for the assumed increase in the relative infectiousness of population in the I classes in comparison to those in the corresponding exposed classes E; ϕ is the rate of vaccination for susceptible individuals; μ is the natural death rate; $\sigma \in [0,1]$ is the factor

infection reduction by vaccination, $\sigma = 1$ meaning that the vaccine is completely effective in preventing infection, while $\sigma = 0$ means that the vaccine is utterly ineffective; k is the rate at which the exposed individuals become infectious; δ_1 is the rate of disease-induced death; δ_2 is the rate of recovery from the disease. The dynamics of the proposed model is depicted in Figure 1.

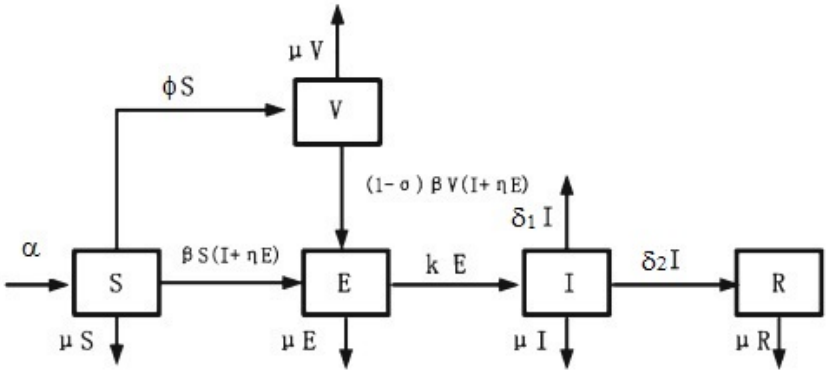

Figure 1: Transfer diagram of the influenza A (H1N1) epidemic model by Zhou and Guo [25].

Note that $S + V + E + I + R = N(t)$, where $N(t)$ is the total population considered. Note that $\frac{1}{k}$ is the average length of the latent period, and $\frac{1}{\delta_2}$ is the mean length of the infectious period before recovery [15].

As vaccine-induced immunity weakens over time, it is necessary to consider the rate of immunity loss π [23], where $\pi = 0$ means that one has perennial immunity. To take into account the possibility of reinfection, the model in Eq. (2) is modified to that in Eq. (3), illustrated in Figure 2:

$$\begin{aligned}
\frac{dS}{dt} &= \alpha + \pi R - \beta(I + \eta E)S - (\phi + \mu)S \\
\frac{dV}{dt} &= \phi S - (1 - \sigma)\beta(1 + \eta E)V - \mu V \\
\frac{dE}{dt} &= \beta(I + \eta E)S + (1 - \sigma)\beta(1 + \eta E)V - kE - \mu E \\
\frac{dI}{dt} &= kE - \delta_1 I - \delta_2 I - \mu I \\
\frac{dR}{dt} &= \delta_2 I - \pi R - \mu R
\end{aligned} \tag{3}$$

The SIR equations can be solved iteratively by linearly convergent algorithms. However, since this is a continuous problem, the exact solution may not be found in finite time.

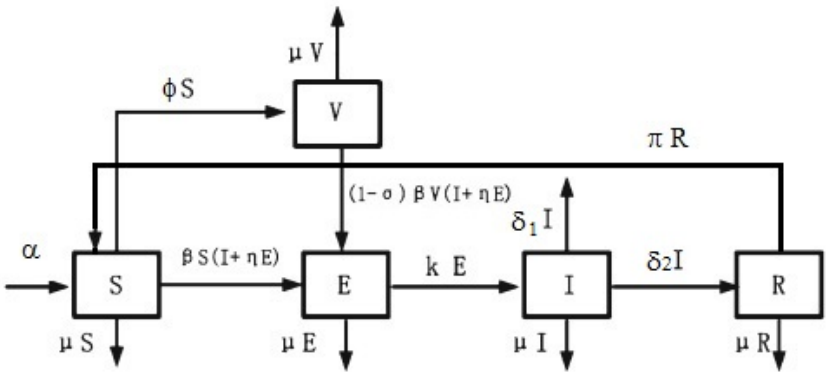

Figure 2: Transfer diagram of the influenza A (H1N1) epidemic model with Reinfection.

A typical approach consists in setting up a tolerance a priori and solving an approximate discrete problem whose solution is within the prescribed tolerance of the exact solution of the continuous problem. That makes finding a discrete approximation to the original problem part of the formulation. However, often the definition of a discrete approximation is arbitrary. For instance, a discrete model is appropriate for analyzing a weekly or monthly disease progression (time step = 1 week or 1 month).

4 Optimization Strategy to Finite Difference Mesh Refinement

To solve the system of equations described in the previous section we make use of numerical methods. Such methods provide approximate solutions for problems that, in general, have no analytical solution or whose analytical solution is too hard to obtain. Derivative approximations are employed by the Finite Difference Method - FDM [8].

The FDM approximates the derivatives making use of the difference between function evaluations in successive points of the discrete solution. The approximate solutions are obtained by means of Taylor series expansion [6].
Let $x_0 \in \Re$ and set $h \in \Re$ as the step of a regular mesh, so that $x_i = x_0 \pm ih,\ i = 1, \ldots, n$. That is, the domain is discretized into a set of n points x_i defined by a mesh of step h, which is used to approximate the derivative of the function.

Consider the Taylor's series,

$$P_n(x) = y(x) + y'(x)(x - x_0) + \frac{y''(x)}{2!}(x - x_0)^2 + \frac{y'''(x)}{3!}(x - x_0)^3 + ... + \frac{y^n(x)}{n!}(x - x_0)^n. \quad (4)$$

It can be rewritten as:

$$y(x + h) = y(x) + hy'(x) + \frac{h^2 y''(x)}{2!} + ... + \frac{h^n y^n(x)}{n!}. \quad (5)$$

Considering a linear approximation ($n = 1$) and dropping the terms of higher order error in the series, so that:

$$y(x+h) = y(x) + hy'(x) + \frac{h^2 y''(\xi)}{2!}, \quad x \leq \xi \leq x+h, \tag{6}$$

we obtain,

$$y'(x) = \frac{y(x+h) - y(x)}{h} - \frac{hy''(\xi)}{2}, \quad x \leq \xi \leq x+h. \tag{7}$$

This approximation of the derivative $y'(x)$ is known as forward difference for the discretization of the derivative of $y(x)$ [6].

On the other hand, Eq. (4) can also be rewritten as:

$$y(x-h) = y(x) - hy'(x) + \frac{h^2 y''(x)}{2!} - ... + \frac{h^n y^n(x)}{n!}. \tag{8}$$

Proceeding in a similar way to the previous case, we can reach the following result:

$$y'(x) = \frac{y(x) - y(x-h)}{h} + \frac{hy''(\xi)}{2}, \quad x-h \leq \xi \leq x. \tag{9}$$

The equation is known as backward difference of $y'(x)$. In both cases, (7) and (9), the last term corresponds to the error which is of order $O(h)$.

Adding one more term ($n = 2$) to the Taylor's series, we have:

$$y(x+h) = y(x) + hy'(x) + \frac{h^2 y''(x)}{2!} + \frac{h^3 y'''(\xi_1)}{3!}, \quad x \leq \xi_1 \leq x+h \tag{10}$$

$$y(x-h) = y(x) - hy'(x) + \frac{h^2 y''(x)}{2!} - \frac{h^3 y'''(\xi_2)}{3!}, \quad x-h \leq \xi_2 \leq x \tag{11}$$

Subtracting the above two equations, we have:

$$y'(x) = \frac{y(x+h) - y(x-h)}{2h} - \frac{h^2 y'''(\xi)}{3!}, \quad x-h \leq \xi \leq x+h. \tag{12}$$

Note that in the equation above, the error in the approximation is of order $O(h^2)$. The expression (12) is known as centered differences.

In order to obtain a desired accuracy, optimizing at the same time the computational cost (computation time), this paper proposes the use of an adaptive mesh refinement strategy x_i. This strategy iteratively refines the mesh step, in order to make better use of the computational resources.

Consider an iterative algorithm in linear form,

$$V_{k+1}(x) = TV_k(x),\ x \in S, \tag{13}$$

with $|S|$ defined as the cardinality of the set states and V_0 as the starting point. In order to simplify the calculation of the above system, it is possible to reset the algorithm in the form:

$$V_{k+1}(x) = \tilde{T}_k V_k(x),\ x \in S, \tag{14}$$

wherein the operator $\tilde{T}_k, k \geq 0$, is an approximation of the operator T, such that,

$$\|TV_k(x) - \tilde{T}_k V_k(x)\| < u_k. \tag{15}$$

Note that $\tilde{T}_k$ is an approximate operator whose application generates computational savings with respect to the operator T. The price of this economy is the inclusion of an error, bounded above by the sequence $u_k,\ k \geq 0$. To generate computational savings, the operator $\tilde{T}_k$ can use, for example, a more spaced mesh in the case of a system of differential equations.

Note that the accuracy of the equations is defined by the mesh step value h. Consequently, these can be simplified when using a mesh with fewer points (bigger h), which generates computational economy at the expense of an increased error. Thus, approximations in the form of (14) can be used in the computational calculation of the equations of SIR model discussed in this work. Naturally, one may want to control the accuracy of the approximation and vary it with the iteration count, in such a way that the computational cost in obtaining the desired accuracy is minimized .

With respect to the application of operators in the form of equation (14) for linearly convergent algorithms, it was demonstrated by Almudevar and Arruda [2] that the best way to decrease the sequence of errors limited from above by sequence u_k with respect to the computational cost, is by making:

$$u_{k+1} \propto ru_k, \tag{16}$$

where r is the rate of convergence of the linear algorithm. With this decrease, the approximate algorithm converges to the exact solution of the problem optimally with respect to the computational cost.

This work employs the results of Almudevar and Arruda [2] to the problem of solving the equations of the SIR model by means of the finite difference method. The objective is to minimize the computational cost of solving the system up to a prescribed accuracy. The results described in [2] are used directly in models of progressive and regressive differences, which are linear. In the centered differences method, we use $u_{k+1} \propto \sqrt{r}u_k$. The square root is used to adapt the methods, since the original results were derived for linear algorithms.

The rate of convergence in (14) is estimated, for our problem, as the residue between two successive mesh solutions. Whenever the residue is greater than the tolerance, we continue to refine the mesh. Thus, for the k-th iteration of the methods of progressive and regressive differences, a step mesh h_k will be applied, so that:

$$h_{k+1} = r_k h_k,$$

with $h_0 = h_{\max}$ and $r_0 \triangleq \frac{1}{2}$. Note that $h_{\max}$ is a parameter of the algorithm and $r_k,\ k > 0$, is the residue of the corresponding solutions at the mesh steps h_k and h_{k-1}. For the method of centered differences, of order 2, we use:

$$h_{k+1} = \sqrt{r_k} h_k,$$

with $h_0 = h_{\max}$ and $r_0 = \frac{1}{4}$.

5 NUMERICAL EXPERIMENTS

We performed two studies considering or not immunity loss. First we analyze the effect of vaccination with the following initial values: $S(0) = 1000$; $V(0) = 0$; $E(0) = 0$; $I(0) = 1$ and $R(0) = 0$. Table 1 presents the values of the parameters adopted.

Table 1: Parameters [25].

Rate of birth or immigration	α	15/day
Rate at which susceptible individuals become infected	β	0.00018
Modification parameter	η	0.3
Rate of vaccination for susceptible individuals	ϕ	0.01
Natural death	μ	0.0000548/day
Factor of reducing infection by vaccination	σ	0.15/day
Reduction due to development of clinical symptoms	k	0.2/day
Rate of disease-induced death	δ_1	0.001/day
Rate of recovery from the disease	δ_2	0.14/day
Rate of loss of immunity	π	-
Time	t	365 days

For this experiment, there is no immunity loss, hence $\pi = 0$. Figure 3 shows the results for the experiment without reinfection.

Figure 4 shows results with low rate of reinfection ($\pi = 0.01/day$). It is observed that even with a low re-infection rate the increase in the susceptible population is notorious.

Figure 5 shows results with a high rate of reinfection ($\pi = 0.2/day$), which also depicts a significant increase in the susceptible population.

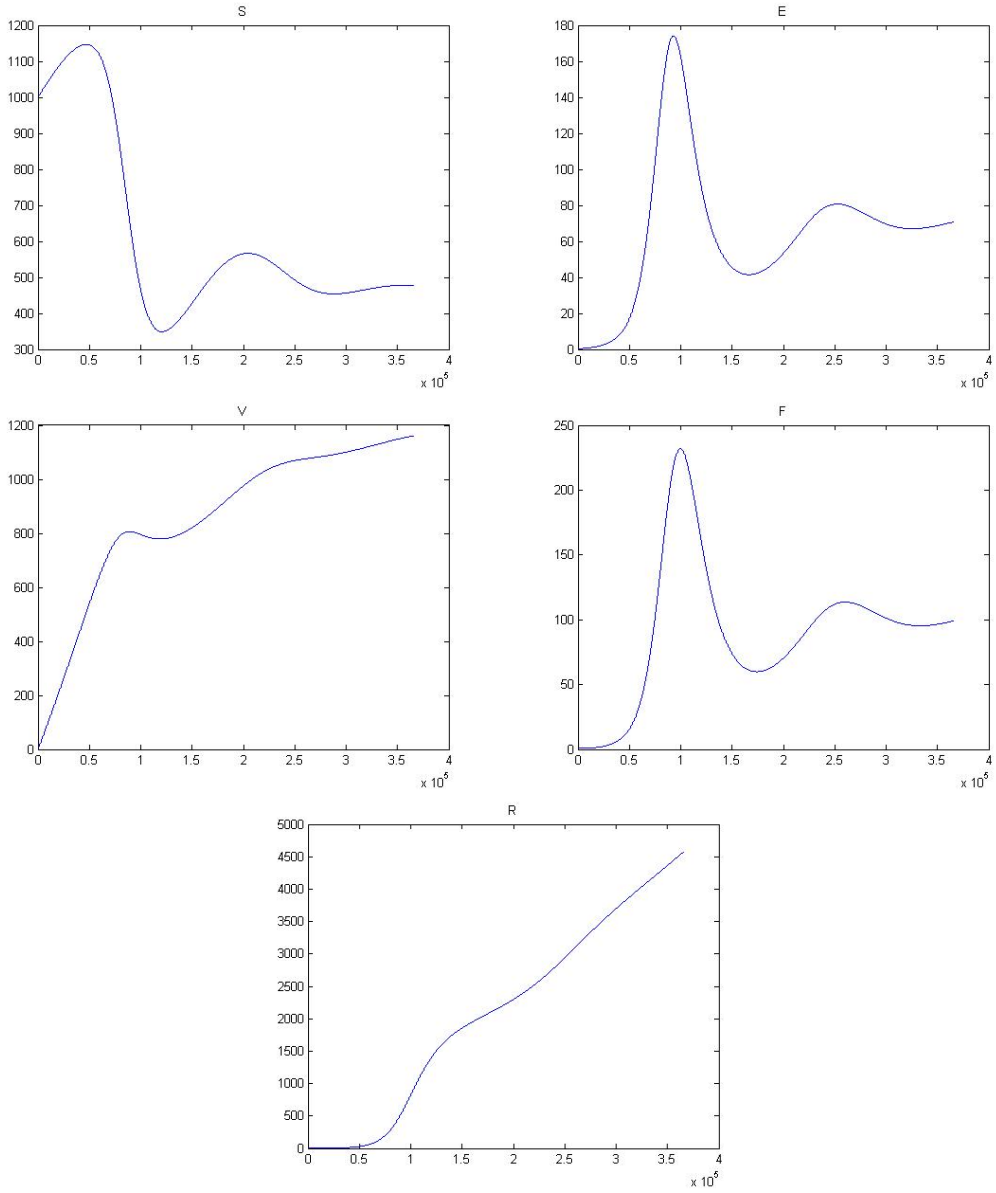

Figure 3: Numerical Experiments with Vaccination.

Regarding the computational economy, the main objective of this study, let us build a first method using FDM with progressive differences and the following refinement strategy. We assume that $h_{max} = h_0$. Furthermore, $h > h_{min}$. So, while the residue (difference between the current and previous solution), r is bigger than a tolerance, we make $h_{k+1} = 0.5\, h_k$, where k being the current iteration. This method was not chosen at random. This is an efficient method in terms of worst-case computational complexity for a stochastic optimization problem, implemented in practice in many adaptive algorithms

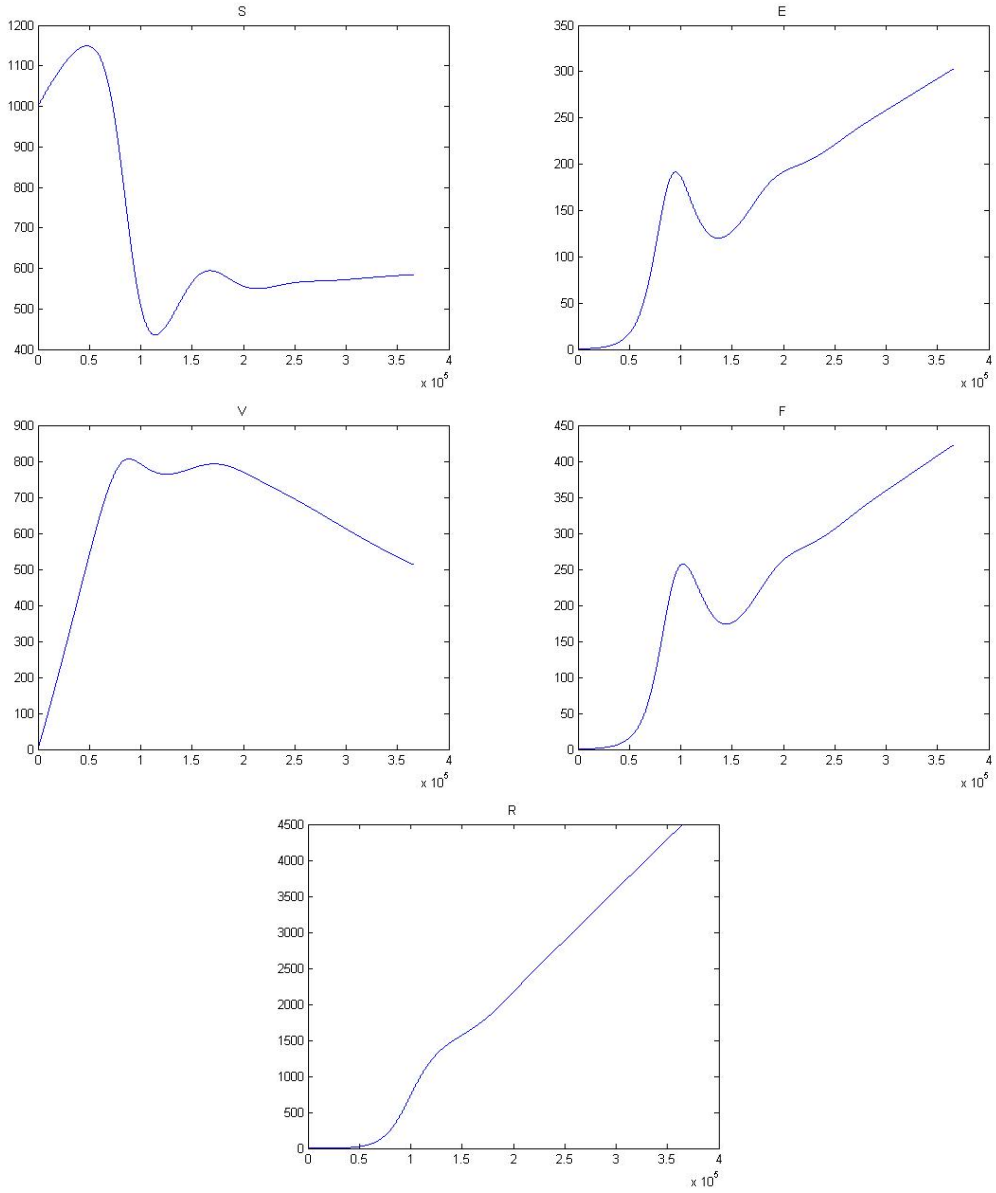

Figure 4: Numerical Experiments with loss of immunity with $\pi = 0.01/day$.

for the solution of partial differential equations models.

It was observed that in the experiment with refinement $h_{k+1} = 0.5\,h_k$ we needed to generate 10 different meshes up to convergence. Moreover, the refinement based on the proposed control strategy needed only 4 meshes to converge. In the course of the algorithm, the first strategy evaluated each of the populations 7.460.600 times, while the optimal strategy evaluated the same populations 14.600 times, which features savings of about 99.80% of the number of operations required. If compared with the non adaptive

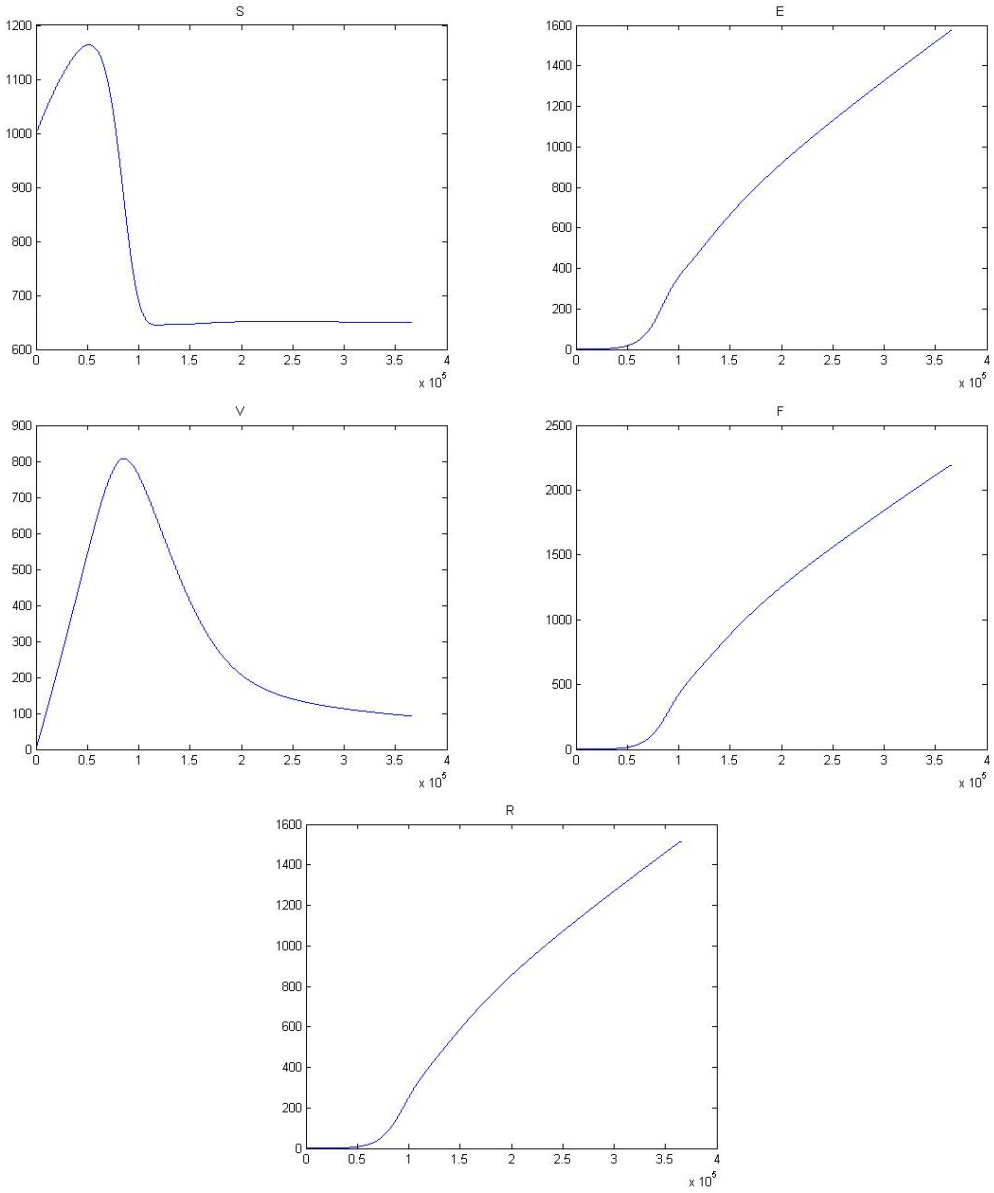

Figure 5: Numerical Experiments with loss of immunity with $\pi = 0.2/day$.

algorithm, which needs around 365.000 operations to attain the same precision, the FDM refinement strategy is responsible for savings of about 96 % of the number of operations required.

6 CONCLUSIONS

It is known that naturally created immunity for infection and immunity induced by vaccination are not permanent. They reduce over time causing a significant impact on

immunization programs. We employ a model that takes into account the immunity loss over time.

Vaccines can be used to control or eradicate a disease. If the goal is the eradication is necessary to know the period that the vaccine protects the individual immunized. Thus, eradication strategies based on vaccination will only be effective if the protection time is long enough [23]. Specifically regarding Influenza, that poses a great challenge.

As a natural extensions of the present work, one could analyze the effects of immunization with respect to the age of vaccinated individuals to propose a vaccination strategy. The resulting strategy could be compared with optimal vaccination strategies whose purpose is to minimize both the infected population and the vaccination costs [4].

This paper also presents an optimal adaptive strategy of simple implementation based on the calculation of the residue between successive solutions to the spread of the H1N1 flu. For the examples presented, the results proved efficient, preserving the quality of the solutions and presenting significant savings in computational cost (about 99%). This is an interesting strategy that preserves the quality of the solution while minimizing the computational time needed to evaluate the equations.

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