University of Trento

Quantitative and Computational Biology

Network Modelling and Simulations

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

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Contents

1 Introduction

Respiratory Syncytial Virus, also known as RSV, is a common virus that affects the respiratory system without inducing severe symptoms in most cases. RSV is spread through transmission of respiratory secretions when in close contact with infected individuals and the severity of symptoms varies each year. Young children and older adults are, respectively, the first and second highest risk groups to develop a harsher outcome making additional studies necessary. Two vaccines are currently available: Arexvy (GSK) and Abrysvo (Pfizer) of which the latter can be administered to pregnant women as well. Another option for immunization consists in the injection of the RSV antibody especially for infants and toddlers.

As the name itself suggests, the virus is able to form syncytia through cell-to-cell fusion which allows viruses to reach other cells and to evade the host immune system [1]. Syncytia seems to be created thanks to viral envelope proteins which work together with host proteins that maintain membrane integrity, adhesion and cell mobility. One study suggested that RhoA, a host small GTPase, plays a role in the formation of syncytia, but further investigations are needed to define the exact step at which the protein directly acts [1].

Each year 15,000 to 20,000 cases of RSV have been reported in Spain with 400 out of 100,000 children younger than a year hospitalized with consequently high costs for the Spanish public healthcare system [2].

Some scientists have found possible implications of Covid-19 on RSV diffusion. An increase in off-season cases of RSV infections, as well as a shift towards older children, was noticed during the first year of SARS-CoV-2 pandemics firstly in Australia [3]. A possible hypothesis lies in the induced immune dysregulation caused by Covid-19 with downregulation of CD19 in B-cells [4].

Mathematical models are a significant tool to improve our knowledge about how diseases behave in time and should provide a better understanding of how they spread among individuals. Moreover they acquire a major importance when realizing that not only usual environmental factors, but other diseases as well (e.g. Covid-19) might play crucial roles in RSV transmission.

Here, the main aim is to determine how external factors influence the overall dynamics of RSV diffusion taking into account stochastic terms as well to better mimic environmental fluctuations.

The analyzed paper deals with the model proposed in Weber et al. [5] to determine the effects of perturbations on specific parameters of the RSV model. RSV varies in timing and severity each year suggesting that several factors such as temperature, humidity, pollution and others might play a role in shaping RSV dynamics [5].

2 Methods and Models

2.1 Mathematical modeling

Modeling enables a more accurate and comprehensive understanding of complex phenomena. Most system are well described by deterministic models, which have a good balance between their descriptive power and simplicity, though they can be too superficial in capturing inherited variability of real-world events. In such cases stochastic modeling better express complex system unpredictability. In the paper both deterministic and stochastic models are built, the latter, in particular, is used to study the system evolution under the perturbation of demographic parameters.

The authors point out how the stochastic setting is best suited in this case, since real hospitalization data contains noise. Fundamental in this case is to assess if these perturbations are significant and if, instead, the deterministic model could be a better option.

2.1.1 Deterministic Model

The deterministic model is the well known SIRS system, where the population is divided in three compartments: Susceptibles S(t), Infected I(t) and Recovered R(t).
The main assumptions are the following:

1. recovered patients gain a temporal immunity, reentering the susceptible class at the end of it;
2. birth and death rate (μ) are equal, thus the total population is constant;

3. ν is the recovery rate, while γ is the immunization rate;

4. the transmission coefficient is described by the function $\beta(t)$, which is a continuous T-periodic function, we approximated it by the sinusoidal function $\beta(t) = b_0(1 + b_1 * cos(2\pi * t + \Phi))$[5]. b_0 is the baseline transmission rate, $0 < b_1 < 1$ measures the amplitude of the seasonal variation in transmission and $0 < \Phi < 2\pi$ is the phase angle normalized.

The final model is written as follows:

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

The transmission parameters are missing, so the model is fitted to real hospitalization data of children younger than 4 years old retrieved from Valencia databases, the period span from January 2001 to December 2004. The model is fitted through least-squares, using the mean square error function in Mathematica. The error function is minimized through the Nelder-Mead algorithm (Fig. 1).

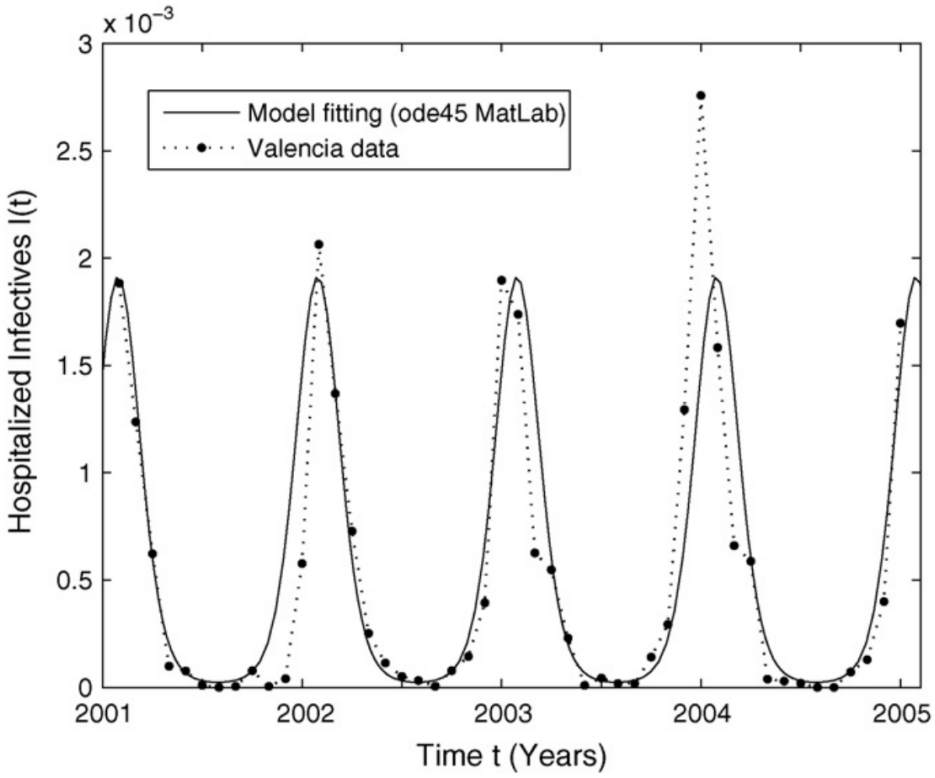


Figure 1: Parameter estimation of the deterministic model using RSV hospitalization data. The authors point out how the behaviour of the real data is not periodic as in the deterministic model.

In the end the function is minimized by the following parameters: $\{b_0, b_1, \Phi, s\} = \{36.4, 0.38, 1.07, 220000\}$, where s is the proportion of infected that is not hospitalized. The other missing parameters are not directly specified in the paper, consequently we choose them from the literature [5], eventually we selected $\{\mu, \nu, \gamma\}=\{0.009, 36, 1{,}8\}$.
The initial conditions for S(t), I(t) and R(t) are the same in all simulations, with values 0.9988, 0.0012 and 0 respectively.

2.1.2 Stochastic Models

Fluctuations in the environment can greatly effect a model dynamics, and the effect is much visible the smaller the population. In this article perturbations are added to the birth rate and on the baseline

transmission parameter, resulting in two different *Itô* type stochastic differential system, where each equation contains a deterministic part and a stochastic part defined by a standard Wiener process W(t). The selected parameter exhibits random oscillations around the mean value employed in the deterministic model. These parameter perturbations are characterized by an average value augmented by a time-varying term, adhering to a normal distribution with a mean of zero. Biologically these fluctuations can be explained by natural variability in births, social conditions and weather.
The perturbed birth parameter and the resulting stochastic system take the form:

$$\begin{aligned} \widetilde{\mu} &= \mu + \alpha \dot{W}(t) \\ \dot{S}(t) &= [\mu - \mu S(t) - \beta(t) S(t) I(t) + \gamma R(t)]\ dt + \alpha(1 - S(t))\ dW(t) \\ \dot{I}(t) &= [\beta(t) S(t) I(t) - \nu I(t) - \mu I(t)]\ dt - \alpha I(t)\ dW(t) \\ \dot{R}(t) &= [\nu I(t) - \mu R(t) - \gamma R(t)]\ dt - \alpha R(t)\ dW(t) \end{aligned} \tag{2}$$

An analogous procedure is applied to the baseline-transmission rate perturbed system, resulting in the set of equations below:

$$\begin{aligned} \widetilde{b_0} &= b_0 + \alpha \dot{W}(t) \\ \dot{S}(t) &= [\mu - \mu S(t) - \beta(t) S(t) I(t) + \gamma R(t)]\ dt - \frac{\alpha \beta(t)}{b_0} S(t) I(t)\ dW(t) \\ \dot{I}(t) &= [\beta(t) S(t) I(t) - \nu I(t) - \mu I(t)]\ dt - \frac{\alpha \beta(t)}{b_0} S(t) I(t)\ dW(t) \\ \dot{R}(t) &= [\nu I(t) - \mu R(t) - \gamma R(t)]\ dt \end{aligned} \tag{3}$$

2.2 Simulation Algorithms

2.2.1 The function *solve_ivp*(Initial Value Problem)

`solve_ivp` is a function within the `scipy.integrate` module, designed for solving initial value problems associated with a system of ordinary differential equations (ODEs) [6]. It accommodates various integration methods, domains, and events, and is capable of handling complex-valued problems and vectorized functions. Following a brief description of the primary arguments:

- `fun`: A callable function that computes the derivative of the state vector `y` at time `t`. It should have the signature `fun(t, y, *args)`, where `t` is a scalar, `y` is an array, and `args` are optional extra arguments.
- `t_span`: A 2-tuple of floats specifying the integration interval `(t0, tf)`. The solver initiates at `t=t0` and integrates until `t=tf`.
- `y0`: An array containing the initial condition for `y` at `t0`.
- `method`: A string or an `OdeSolver` object specifying the integration method.

The argument `method` allows you to decide the algorithm, in our implementation we used the `'RK45'`, an explicit Runge-Kutta of order 5(4)[7]. The error is controlled assuming accuracy of the fourth-order method accuracy, but steps are taken using the fifth-order accurate formula (local extrapolation is done)[6].

2.2.2 Euler–Maruyama method for SDEs

The Euler–Maruyama method (also called the Euler method) is a method for the approximate numerical solution of a stochastic differential equation (SDEs)[8]. It is an extension of the Euler method for ordinary differential equations to stochastic differential equations, named after Leonhard Euler and Gisiro Maruyama.

The authors of the article used the Euler-Maruyama and Milstein algorithms to simulate their system of SDEs. Since the results between the two methods are interchangeable we decided to implement only the Euler-Maruyama framework in Python, both for the birth rate and transmission rate perturbation. Each model is simulated 10 times to account for the intrinsic variability of stochastic

systems. The resulting scripts also allow for the possibility of changing the parameters' values from user's inputs.
The pseudo-code for the Euler-Maruyama algorithm is as follows:

***Inputs**: initial time, final time, number of steps, number of iterations.*
***Outputs**: vectors of time points and variables dynamic.*

1. *Define the dW function, which sample a random number from a normal distribution with mean zero and variance dt;*
2. *define the time step dt;*
3. *initialize model parameters;*
4. *initialize the initial conditions for each variable at time t=0;*
5. *for* $1 < t < number\ of\ steps + 1$*:*
   update each variable state according to the model equations;
   update simulation time t=t+dt;
6. *iterate the process for the specified number of iterations.*

3 Results

This section presents the numerical simulations of the stochastic and deterministic differential models for RSV from the articles and from our own simulations. We aimed to replicate the results of the article and build our own implementation using the popular language python instead of Matlab. The aim of the authors was to explore how small variations of the birth and RSV transmission rates can affect the RSV dynamics in the population and see the main consequences on the infected I(t). The deterministic ordinary differential equations (ODEs) are solved with ode45 by the authors and with *solve_ivp* in our implementation. The stochastic differential equation (SDEs) systems are solved using Euler-Maruyama and Milstein methods. We only implemented our version of the Euler-Maruyama, since the Milstein method, both in the authors and our results, didn't show substantial differences. After a brief part about the deterministic simulation the authors concentrate on two different stochastic scenarios. The first one considers the stochastic fluctuations of the birth rate parameter shown by the system of SDEs 2. The second scenario considers the stochastic fluctuations of the transmission rate parameter implemented in system 3. The authors have employed Monte Carlo techniques to calculate statistical measures such as mean and confidence intervals shown in the graphs. However, the specific details regarding the implementation of this technique have not been explicitly provided by the authors themselves.

3.1 Deterministic Model

The deterministic model, illustrated in system 1 and implemented by the authors using the standard ode45 function in Matlab, resulted in the production of Figure 1. On our end, as said before, we employed the use of *solve_ivp*, from Scipy [6] with default parameters, in python and obtained a comparable result as shown in Figure 2. Due to the deterministic nature of the simulation we didn't perform multiple runs.

3.2 Stochastic Model with perturbation on the birth rate

The simulations done by the authors regarding system 2 and taking into account a possible birth rate perturbation, are shown in Figure 3.

In the same figure we can see the 95% confidence interval and anticipated trajectory for the infected sub population I(t) are depicted through Monte-Carlo simulations. Despite the substantial magnitude of these environmental stochastic perturbations, the infected population exhibits a nearly identical periodic behavior compared to the deterministic model presented before.

Similar results were obtained by our implementation as shown in Figure 4, where it is evident that even after multiple simulations there is not much change from the deterministic model.

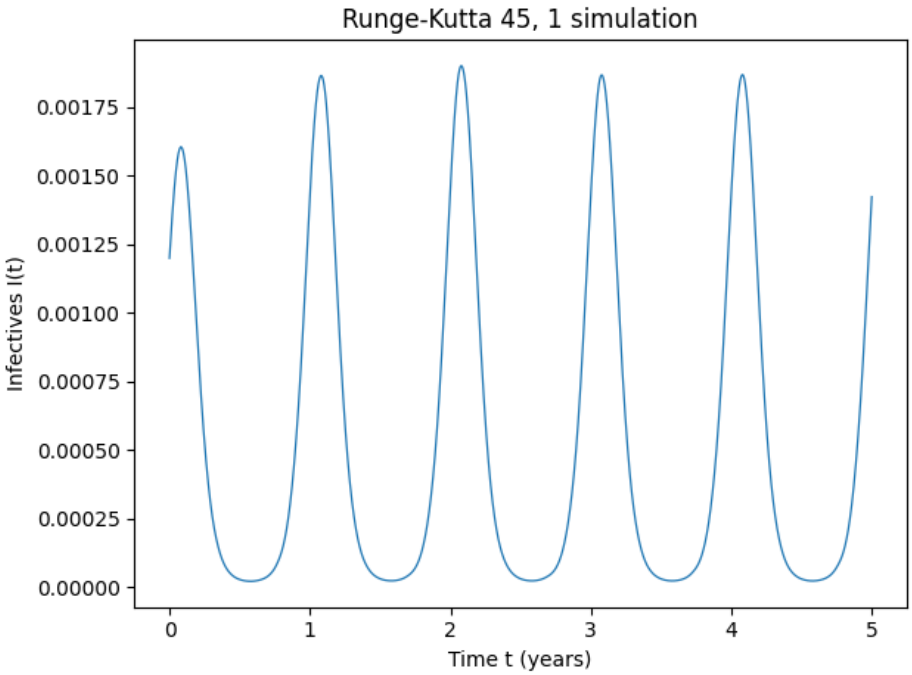
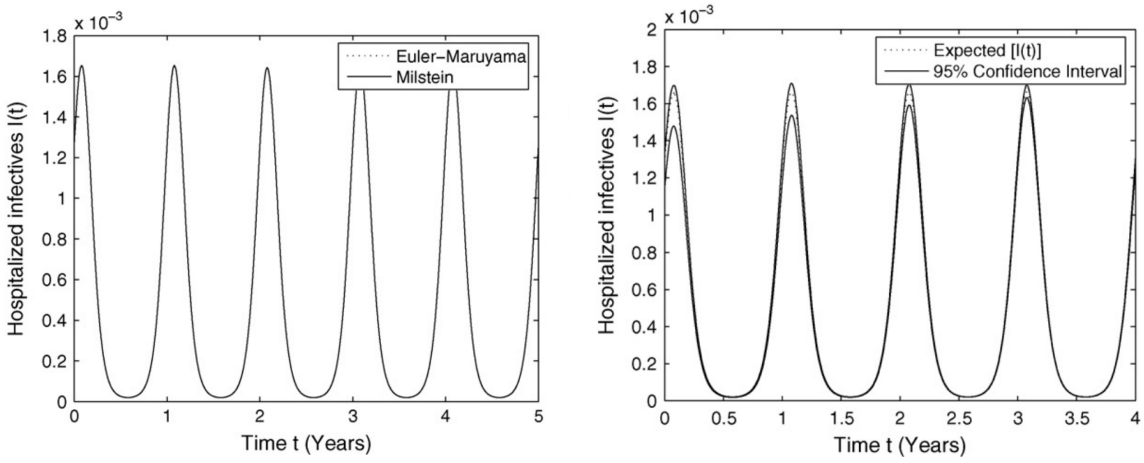


Figure 2: Adaptive step size Runge Kutta simulation obtained from the function *solve_ivp* of the python library scipy



(a) (b)

Figure 3: (a)Comparison between the Milstein and Euler-Maruyama stochastic scheme in regard to the infected sub population I(t) over a single simulation with birth rate perturbation.(b) Confidence intervals and expected behavior for the infected sub population I(t) when the birth rate is perturbed at 100% ($\alpha = 0.009$).

3.3 Stochastic Model with perturbation on the transmission rate

To keep investigating the qualitative transformation in the dynamic patterns of the SDEs, the authors conducted another simulation, this time keeping the transmission rate under varying degrees of environmental perturbation in system 3. However they claim that, due to the significant impact of environmental perturbation on the model dynamics of RSV, they limited the perturbation range to a smaller extent compared to that of the birth rate shown in the previous simulations as we can see in Figure 5.

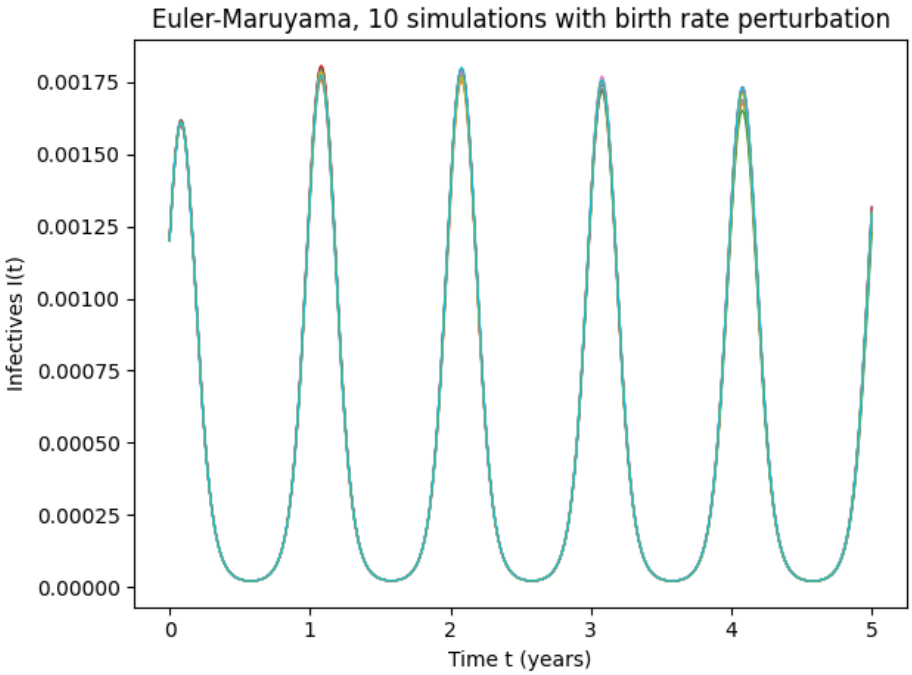
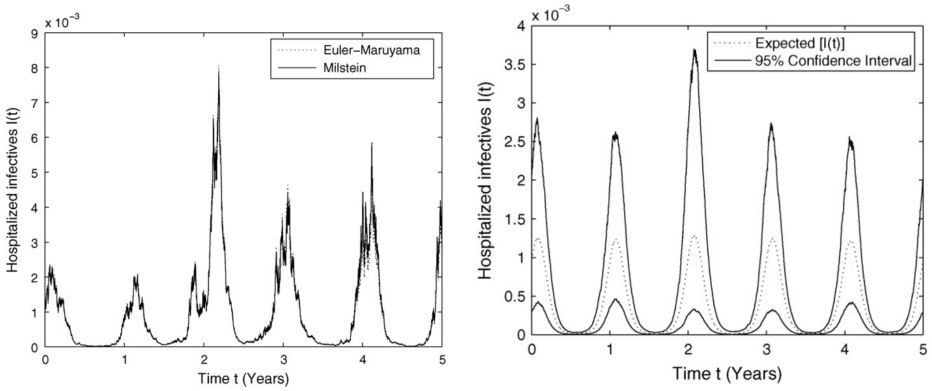


Figure 4: Euler-Maruyama stochastic graph in regard to the infected sub population I(t) with birth rate perturbation over multiple simulations.



(a) (b)

Figure 5: (a)Comparison between the Milstein and Euler-Maruyama stochastic scheme in regard to the infected sub population I(t) over a single simulation with transmission rate perturbation of 5%. (b)Confidence intervals and expected behavior for the infected sub population I(t) when the RSV baseline transmission rate is perturbed of 1%

Our implementation of the simulation shows a similar behaviour in Figure 6. We can notice how in the span of ours ten simulation we can clearly see the stochasticity of the system, as our simulations are confined in the confidence interval delineated by the authors except for one simulation (red line). This perturbation moves the system far away from the deterministic model and the birth perturbation model showing how the dynamics of infected population I(t) is greatly modified in response to such a small perturbation of 1%.

Through the same simulations, they also computed the confidence intervals for each sub population within the stochastic system. They notice how the recovered R(t) and susceptible S(t), shown in Figure 7, are expressing a peculiar behaviour. The degree of variation in the R(t) and S(t) sub populations, amplifies with an escalation in transmission rate perturbation. This intensification occurs even though

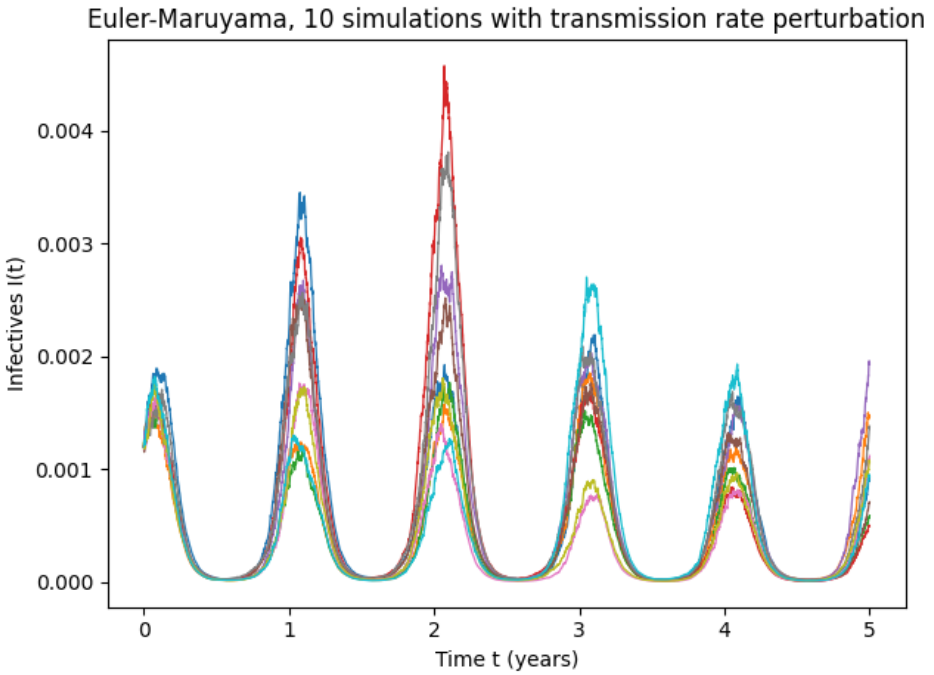
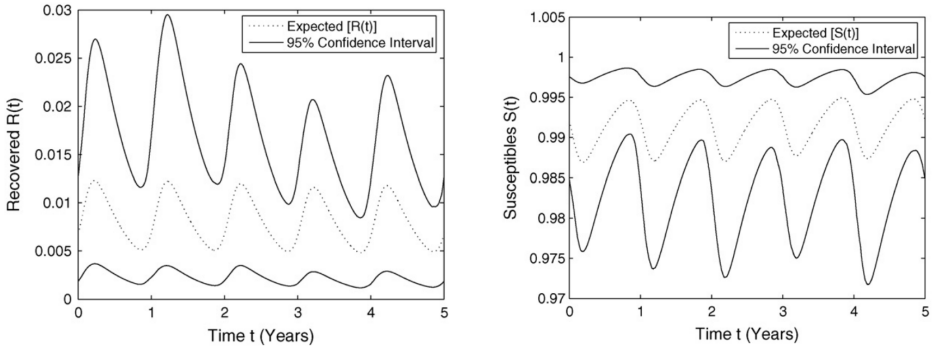


Figure 6: Euler-Maruyama stochastic schemes in regard to the infected sub population I(t) over multiple simulations with transmission rate perturbation at 1% ($\alpha = 0.364$).

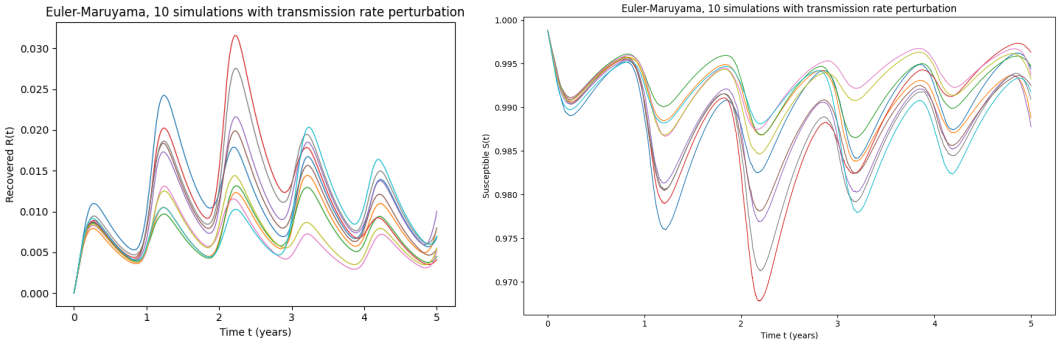


(a) (b)

Figure 7: Confidence intervals and expected behavior for the recovered R(t)(a) and susceptible S(t)(b) sub populations, when the RSV baseline transmission rate is perturbed.

the SDEs governing the two variables do not explicitly include a noisy seasonally forced cosinusoidal functions. Our results in Figure 8 conform with the simulations of the article except for one simulation (red line).

We can observe that, the introduction of a noise term in the equations produces an impact that allows the expression of the fundamental oscillatory nature of those sub populations.



(a) (b)

Figure 8: Euler-Maruyama stochastic graphs of recovered R(t)(a) and susceptible S(t)(b) sub populations over multiple simulations with transmission rate perturbation.

4 Discussion

Deterministic and stochastic approaches can serve different purposes in understanding how biological system works through mathematical models. Here, stochastic models proved to better interpolate the intrinsic variability of data and environmental factors compared to deterministic models which might be used when the environment does not substantially influence the simulation.

The authors tries two different perturbation ranges (100% and 5%), but do not provide any information on the reasons that led them to choose those specific values. They also state that small perturbations, e.g. 2%, result in a drastic decrease of the infected population, showing that even small changes can limit the spread of RSV. For these reasons we suggest a sensitivity analysis to better determine the role of these perturbations on the simulation, a fundamental aspect for governments to apply effective healthcare policies.

While performing the stochastic simulation we also noticed that a value for parameter α is given only for the version with perturbation on the birth rate, whereas the one for the perturbation on the transmission rate is missing. In this last case, the only information provided is the perturbation range of 5% without a specific value. Therefore, we hypothesize that α represents a fraction of the parameter, defining fluctuations above and below the reference parameter value by the specified alpha factor.

Since the transmission rate seems to be highly sensitive to perturbations, we suggest that health policies should act on it to ensure an effective management of epidemics. Moreover, the increasing amount of people moving across different countries and the exacerbation of meteorological conditions in the last years might seriously affect the spread of disease, making modelling studies essential.

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