Controlling infectious diseases: the decisive phase effect on a seasonal vaccination strategy

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Abstract

The study of epidemiological systems has generated deep interest in exploring the dynamical complexity of common infectious diseases driven by seasonally varying contact rates. Mathematical modeling and field observations have shown that, under seasonal variation, the incidence rates of some endemic infectious diseases fluctuate dramatically and the dynamics is often characterized by chaotic oscillations in the absence of specific vaccination programs. In fact, the existence of chaotic behavior has been precisely stated in the literature as a noticeable feature in the dynamics of the classical Susceptible-Infected-Recovered (SIR) seasonally forced epidemic model. However, in the context of epidemiology, chaos is often regarded as an undesirable phenomenon associated with the unpredictability of infectious diseases. As a consequence, the problem of converting chaotic motions into regular motions becomes particularly relevant. In this article, we consider the phase control technique applied to the seasonally forced SIR epidemic model to suppress chaos. Interestingly, this method of controlling chaos takes on a clear meaning as a weak perturbation on a seasonal vaccination strategy. Numerical simulations show that the phase difference between the two periodic forces - contact rate and vaccination - plays a very important role in controlling chaos.

Key words: Infectious diseases, Seasonally forced SIR model, Vaccination strategy, Phase control

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1 Introduction

The outbreaks and spread of infectious diseases are a threat to public health and a source of serious problems to the economic and social development of our society. The research in epidemic dynamics is, without doubt, critical to any attempt to prevent or minimize the transmission of diseases. In particular, we have all witnessed a remarkable intensification of this work in the present days given the quantity of infected people worldwide due to the dissemination of a new virus, referred to as COVID-19 (Coronavirus disease 2019), an infectious disease emerged from China in November 2019 [2].

The use of mathematical models has contributed greatly to our better understanding of the underlying mechanisms that influence the spread of diseases and has suggested control strategies, which may have significant management implications [3]. More precisely, these models are truly significant in different fields, such as policy making, risk assessment, emergency planning and definition of health-economic control-programs. The mechanism of transmission of infections is now known for most diseases. Generally, diseases transmitted by viral agents (such as measles, influenza, rubella and chickenpox) confer immunity against reinfection, while diseases transmitted by bacteria (such as meningitis and tuberculosis) confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human but by vectors (usually insects). The goal of mathematical epidemiology has been the development of mathematical models for the spread of disease as well as tools for their analysis.

The first mathematical model describing an infectious disease was proposed by Bernoulli, in 1760, to study the spread of smallpox, which was prevalent at the time [4]. An early recognition of the importance of mathematical modeling came in 1911 when Ronald Ross won the Nobel Prize in Physiology or Medicine, for his demonstration of the dynamics of the transmission of malaria between mosquitoes and humans (using models formulated with differential equations) [5]. Recent studies in epidemiology are particularly focused on modeling the previously mentioned COVID-19 and high impact recurrent epidemics, best exemplified by childhood infectious diseases such as measles, chickenpox, mumps, whooping cough and rubella, but also including hepatitis, different types of influenza (see [6] and references therein).

One of the questions that first attracts the attention of scientists interested in the study of the spread of communicable diseases is how severe will an epidemic be. This question may be interpreted in a variety of ways and studied with the aid of models. To formulate dynamic models predicting the behavior of outbreaks and the transmission of infectious diseases, compartmental models are usually considered, with the population in a given region subdivided
into several distinct groups or compartments, depending upon their experience with respect to disease, whose sizes change with time. These compartments, which are mutually exclusive categories based on infection status, were initially proposed by William O. Kermack and Anderson G. McKendrick in 1927 with their mathematical epidemic nonlinear system of differential equations, called the Susceptible-Infected-Recovered (SIR) model \([7]\). In the context of this prominent model, of great historical importance in research of epidemics, the population being studied is labeled into three classes: the susceptible compartment refers to individuals who have never come into contact with the disease at time \(t\), but they could catch it, i.e., they are vulnerable to exposure with infectious people. Infected individuals, assumed infectious and capable of spreading the disease to those in the susceptible category, and remain in the infectious compartment until their recovery. The recovered class refers to individuals who have been infected and then recovered from the disease. The recovered individuals are immune for life and are not able to transmit the infection to others. They are essentially removed from the population and play no further role in the dynamics. These models can include, among other aspects, time-dependent parameters to represent the effects of seasonality and human demographics by adopting birth and death rates. In practice, given a model, its parameters must be determined to represent a particular epidemic context. In formulating models as systems of differential equations, we are assuming that the epidemic process is deterministic, that is, the behavior of a population is determined completely by its history and by the rules which describe the model. Particularly, in the present study, we will consider a SIR model representing a class of seasonally forced epidemic models with vital dynamics (birth and death rates) and constant population.

The article is organized as follows. Immediately after the present Section I, where an introduction to our study is provided, Section II gives essential preliminaries about the model, as well as the control procedure used. Section III is devoted to a diagnosis of the existence of chaos in the system. We exhibit different dynamical interactions between the densities of the susceptible and the infected individuals varying the degree (or amplitude) of seasonality, \(\varepsilon\). Revealing insights about the chaotic dynamics of the SIR model, incorporating seasonal fluctuation, are gained through the computation of bifurcation diagrams and the largest Lyapunov exponent. In Section IV, the phase control technique is applied in order to suppress chaos. A clear biological meaning is assigned to this method of controlling chaos as a weak/small perturbation on a seasonal vaccination strategy. Finally, our last considerations are devoted to significative conclusions.
2 Description of the model

In the literature, and as far as the description of the model is concerned, two related sets of time-dependent variables have been considered in the epidemic modeling process. The first set of dependent variables counts the number of people in each of the groups, each as a function of time. Considering that the population size ($N$) is defined as $N = \tilde{S} + \tilde{I} + \tilde{R}$, the dynamical behavior of a homogeneously mixing population is described using the compartmental forced $\tilde{S}\tilde{I}\tilde{R}$ model [8], with vital dynamics (birth and death rates), given by

$$
\begin{align*}
\frac{d\tilde{S}}{dt} &= \sigma - \mu\tilde{S} - \beta(t)\frac{\tilde{S}\tilde{I}}{N} \\
\frac{d\tilde{I}}{dt} &= \beta(t)\frac{\tilde{S}\tilde{I}}{N} - (\gamma + \mu)\tilde{I} \\
\frac{d\tilde{R}}{dt} &= \gamma\tilde{I} - \mu\tilde{R}
\end{align*}
$$

(1)

The second set of dependent variables represent a fraction of the total population in each of the three categories. So, being $N$ the previous total population, we have

$$
S = \frac{\tilde{S}(t)}{N}, \text{ the susceptible fraction of the population,}
$$

(2)

$$
I = \frac{\tilde{I}(t)}{N}, \text{ the infected fraction of the population,}
$$

$$
R = \frac{\tilde{R}(t)}{N}, \text{ the recovered fraction of the population,}
$$

verifying $S + I + R = 1$. The two sets of dependent variables are proportional to each other, giving the same information about the progress of the epidemic. The independent variable is time $t$, measured in a specific unit according to the epidemic context (such as days, years, etc.). Although it may seem more natural to work with the populations counts, some of our calculations will be simpler if we use the fractions instead. As a consequence, we are going to consider the $SIR$ model with vital dynamics and constant population ($\forall t$, $\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$), such that $S + I + R = 1$,

$$
\begin{align*}
\frac{dS}{dt} &= \sigma - \mu S - \beta(t)\frac{SI}{N} \\
\frac{dI}{dt} &= \beta(t)\frac{SI}{N} - (\gamma + \mu)I \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{align*}
$$

(3)

with time $t$ scaled in unit of years. The parameters of the model (3) and respective meaning are presented in the following table (for more details, please see [3], [9], [10] and references therein).
Table 1. Description of the parameters of model (3)

| Parameter (year)$^{-1}$ | Description                  |
|-------------------------|------------------------------|
| $\sigma$               | Birth rate                   |
| $\mu$                  | Natural death rate           |
| $\gamma$               | Recovery rate                |
| $\beta(t)$             | Contact or transmission rate |

We assume that the newborns are susceptible and that the birth and death rates are balanced, $\sigma = \mu$. As we will exemplify with particular values of the parameters, the average time to recover from infection can be derived from $\gamma$ and given by $1/\gamma$. The contact or transmission rate of the infection (the coefficient of infectivity) $\beta(t)$ represents the number of contacts with other individuals per infective per unit of time. More intensive research on seasonally-forced epidemic models did not begin until the 1970s ([11], [12]). With the purpose of expressing seasonality, a commonly used scheme for the contact rate $\beta(t)$ takes the form

$$\beta(t) = \beta_0 (1 + \varepsilon \varphi(t)),$$  \hspace{1cm} (4)

where $\beta_0$ gives the mean contact rate; parameter $\varepsilon$, with $0 \leq \varepsilon \leq 1$, represents the strength of the seasonal forcing (measuring the degree of seasonality); $\varphi$ is a $T$-periodic function of zero mean and $t$ is scaled in units of years. Modelers often incorporate seasonality by making the contact rate $\beta(t)$ a sinusoidal function of time $\beta_0 \cos(t) = \beta_0 (1 + \varepsilon \cos(2\pi t))$. With this procedure, a seasonally-varying transmission rate yields oscillations at periods that are integer multiples of the period of forcing.

As recently proposed in [13], and inspired by the developed arguments, we are going to consider in our epidemiological study yearly periodic Kot-type functions. Particularly, the previously mentioned function $\beta(t)$ is given by

$$\beta(t) = \beta_0 \left(1 + \varepsilon \left(\frac{\frac{2}{3} + \cos(2\pi t)}{1 + \frac{2}{3} \cos(2\pi t)}\right)\right).$$  \hspace{1cm} (5)

In order to point out the main features of the adopted type of periodic functions, we compare in Fig. 1 a sinusoidal-type periodic function with the periodic Kot-type function $\beta(t)$. Differently from the periodic sinusoidal-type function, the Kot-type function gives asymmetrical weights to the seasonal regimes, stressing the relative maxima of the contact rate. This is an eye-catching and noteworthy feature that has been pointed out as more realistic.

An exposure of a susceptible to an infectious is an encounter in which the
infection is transmitted. In this context, the contact rate, $\beta(t)$, is the average density of susceptible in a given population contacted per infectious individuals per unit of time. Therefore, $\beta(t)S(t)$ denotes the rate of the total density of susceptible infected by one infectious and $\beta(t)S(t)I(t)$ represents the rate of infection of the susceptible by all infectious.

It is well known that seasonal forces, including climatic factors and human phenomena (such as school schedules), are a primary factor responsible for the transmission and dynamical behavior of most recurrent infectious diseases [14,15,16,17,18,19,20]. As a consequence, it becomes natural to model these diseases as periodically forced nonlinear systems ([18,21,22,23,24]). Seasonal forces in these systems shape the spread of the infectious disease and many studies have stated that intense seasonality can lead to strong erratic patterns with the presence of chaotic oscillations ([1] and [22]). The chaotic behavior of the simple SIR model with seasonality has deep biological consequences. The sensitive dependence on the initial conditions, in the final epidemic outcome, is one of the main concerns. It is important to notice that this rich dynamical scenario is a direct consequence of seasonality, which makes any vaccination strategy difficult to design. In fact, the inclusion of seasonality increases the complexity of the models at several levels, making a complete comprehension of its influence a non-trivial and challenging task. In this context, chaos is regarded as an unwanted feature and, as a consequence, control schemes (considered as methods of controlling chaos, suppressing chaos, or taming chaos) play a prominent/decisive role. In any case, the explicit aim of all the procedures is to obtain stable periodic orbits from chaotic ones by applying a small/weak, and carefully chosen, perturbation to the system.

The controlling methods have been traditionally classified into two general categories: feedback methods and nonfeedback methods, based on their interaction with the system’s dynamics. Feedback methods attempt to suppress chaos by stabilizing orbits already existing in the chaotic attractor. Nonfeedback methods have been essentially used to stabilize periodically driven chaotic dynamical systems. Typically, they make stable solutions to appear by applying small driving forces directly to some of the parameters of the system or as an additional forcing. It has been shown in the literature (for instance, in

\[ \beta(t) = \beta_0 \cos(t) \]
papers [25,26,27,28,29], and references therein) that a phase difference $\phi$, between the main driving and the perturbation, influences profoundly the global dynamics of the system.

As we will see in the following lines, given the nature of the forced SIR epidemic model, it is specifically a nonfeedback procedure, that makes use of the property where $\phi$ acts as a control parameter, that stands out to be particularly useful in controlling chaotic behavior. Acting as a positive/beneficial biological consequence, this nonfeedback scheme called phase control of chaos makes a vaccination strategy clearly easier to design.

Following the previous considerations, the particular system we are going to consider in this article is

\[
\begin{align*}
\frac{dS}{dt} & = \sigma - \mu S - \beta(t)SI - v(t)S \\
\frac{dI}{dt} & = \beta(t)SI - (\gamma + \mu)I \\
\frac{dR}{dt} & = \gamma I - \mu R + v(t)S
\end{align*}
\]

where the first periodic force, the contact rate $\beta(t)$, drives the system to the chaotic state, while the second one, the vaccination rate $v(t)$, is a weak periodic perturbation sensitively modifying the system’s dynamics. We assume that the vaccination rate $v(t)$ is defined by the Kot-type function

\[
v(t) = v_0 + \alpha \left( \frac{\frac{2}{3} + \cos (2\pi rt + \phi)}{1 + \frac{2}{3} \cos (2\pi rt + \phi)} \right),
\]

where $v_0$ gives the mean vaccination rate, $\phi$ is the phase difference between the applied perturbation $v(t)$ and the driving force $\beta(t)$, a key parameter for our control scheme. Parameter $r$ is the ratio of the frequency of those forces and $\alpha$, with $\alpha << 1$, measures the degree (or amplitude) of the seasonality of $v(t)$. Once vaccinated, the individuals are no more susceptible (fact represented by the term $-v(t)S$ in the first equation of the model) and the vaccinated individuals are added to the recovered class (fact represented by the term $+v(t)S$ in the third equation of the model).

The vaccination switches individuals directly from the susceptible state ($S$) to the immune state ($R$). We suppose that infection transmission rate $\beta(t)$ is subjected to an environmental periodic forcing and management imposes a countercycle control strategy through $v(t)$. The rationale underpinning a vaccination policy is to ensure that the proportion of susceptible individuals in the population would stay below a certain threshold. We display in Fig. 2 a joint representation of the yearly periodic functions $\beta(t)$ and $v(t)$. Notice that, for $\phi > 0$, the qualitative behavior of $v(t)$ anticipates the qualitative behavior of $\beta(t)$. In Section III, we will see how this behavior influences drastically the
dynamics, acting as a controller to suppress chaos. Figure 2 also suggests that this decisive effect of the phase difference will be achieved with just a small perturbation, an observable fact reflected by the scale differences between $\beta(t)$ and $v(t)$ ($v(t) \ll \beta(t)$).

![Graph](image)

Fig. 2. Comparison between the contact rate Kot-type function $\beta(t)$ (Black) and the vaccination Kot-type function $v(t)$ (Red) ($\varepsilon = 0.138$, $\alpha = 0.009$, $r = 2$ and $\phi = \frac{2\pi}{5}$).

The model is clearly understood when $\beta(t) = \beta_0$ and $v(t) = 0$. For this case of constant contact rate, and in the absence of a vaccination strategy, the dynamical system (6) has two equilibrium points:

(i) The Disease-Free Equilibrium (DFE)

$$(S_0^*, I_0^*, R_0^*) = \left( \frac{\sigma}{\mu}, 0, 0 \right),$$

corresponding to a population with no infected individuals;

(ii) The Endemic Equilibrium (EE)

$$(S_1^*, I_1^*, R_1^*) = \left( \frac{\gamma + \mu}{\beta_0}, \frac{\mu}{\beta_0} (R_0 - 1), \frac{\gamma}{\beta_0} (R_0 - 1) \right),$$

corresponding to the case in which there is a significant group of infectious individuals, where

$$R_0 = \frac{\beta \sigma}{\mu (\mu + \gamma)} \quad \text{(i.e., } R_0 = \frac{\beta}{\mu + \gamma}, \text{ for } \sigma = \mu)$$

is a derived basic reproduction number (or basic reproductive number) with threshold properties. The basic reproduction number of an infection, $R_0$, is a measure of the potential for the disease to spread in a population. Heuristically, $R_0$ may be read as the expected number of secondary infections directly generated by a single infectious individual in a wholly susceptible population. The number $R_0$ is not a biological constant for a pathogen as it is also affected by other factors such as the behavior of the infected population and environmental conditions. It can also be modified by physical distancing and
other public policy or social interventions. $R_0$ values are usually estimated from mathematical models, and the estimated values are dependent on the model used and values of other parameters. Therefore, values given in the literature only make sense in the given context and it is recommended not to compare directly values based on different models. The most important uses of $R_0$ are determining if an emerging infectious disease can spread in a population and determining what proportion of the population should be immunized through vaccination in order to eradicate a disease. Generally speaking, and independently from biologically meaningful initial values, this means that:

(a) If $R_0 < 1$, the epidemic cannot maintain itself, since each infected individual on average infects less than one member of the population. The EE point $(S^*_1, I^*_1, R^*_1)$ is then unstable, while DFE $(S^*_0, I^*_0, R^*_0)$ is locally stable and the disease goes extinct;

(b) If $R_0 > 1$, each infected individual infects more than one other member of the population and a self-sustaining group of infectious individuals will propagate. In this case, the EE point $(S^*_1, I^*_1, R^*_1)$ is locally stable, while the DFE point $(S^*_0, I^*_0, R^*_0)$ is unstable. The disease will remain permanently endemic in the population.

Mathematical modeling in epidemiology provides understanding of the underlying mechanisms that influence the spread of the disease and, in the process, it suggests control strategies. One of the significant results in mathematical epidemiology is that the majority of mathematical epidemic models, including those that have a high degree of heterogeneity, usually exhibit threshold behavior. In epidemiological terms, this can be stated as follows: If the average number of secondary infections caused by an average infectious, the previously called basic reproduction number, is less than one a disease will die out, while if it exceeds one there will be an epidemic. In the context of differential equation models (or, more generally, evolution equation models), $R_0$ arises as a dimensionless number of transmission. Throughout this work, we will use our parameters following previous studies in the literature (see [3], [9], [10] and references therein). As a prior notice, it is important to emphasize that, in the framework of our study, the main qualitative features of the dynamics are not sensitive to the precise values of certain parameters. With the time measured in units of years, the values of the parameters, corresponding to an infectious disease, are listed in the following table.
Table 2. List of the parameter values.

| Parameter | Value |
|-----------|-------|
| $\sigma = \mu = 0.01 \text{ (year)}^{-1}$ | $\frac{1}{\mu} = 100 \text{ years}$ (mean lifetime of the host) |
| $\gamma = 50 \text{ (year)}^{-1}$ | $\frac{1}{\gamma} = 0.02 \text{ year} \approx 1 \text{ week}$ (mean infectious period) |
| $\beta_0 = 1505 \text{ (year)}^{-1}$ | $\frac{1505}{365} \approx 4 \text{ (day)}^{-1}$ (mean number of contacts per day) |
| $R_0 \approx \frac{\beta_0}{\mu + \gamma}$ | $\approx 30$ (average number of secondary infections) |

Within proper meaningful contexts, the degree of seasonality $\varepsilon$, of the main force $\beta(t)$, as well as parameters $v_0$, $\alpha$ and $\phi$ of the vaccination rate (the added small perturbation that will act as a control component), will be taken as control parameters.

At this moment, it is also critical to stress that, throughout our study, a close attention will be focused, not on the phase control method per se, but on its biological significance and on its consequences in an epidemiological context.

3 Existence of chaos: epidemics with a seasonal contact rate and constant vaccination

The complexity of the dynamics increases considerably with the introduction of the seasonal contact rate. In this section, we will examine the long-term behavior of the three-dimensional chaotic attractors arising in the forced SIR system (6), with a seasonal transmission rate component and under a constant vaccination strategy. The time series, displayed in Fig. 3 (Lower panel), govern the population dynamics of the susceptible and infected. They were obtained using two different, but close, initial conditions.

In this paragraph, the Lyapunov exponents of the SIR model (6) with the seasonal component $\beta(t)$ and $v(t) = v_0$, receive our attention as a framework to diagnose chaos in the system. A discussion about the Lyapunov exponents as a quantitative measure of the rate of separation of infinitesimally close trajectories, as well as a computation method, can be found in [30]. The characteristic Lyapunov exponents measure the typical rate of the exponential divergence of nearby trajectories in phase space, i.e., they give us information on the rate of growth of a very small error on the initial state of the system.
Fig. 3. Global noticeable features of the dynamics of the SIR system (6) considering a constant vaccination strategy, $v(t) = v_0 = 0.071$ and $\alpha = 0$. Increasing values of the degree of seasonality of the contact rate, $\varepsilon$, bring the dynamics to a chaotic regime. Upper panel: bifurcation diagrams of the dynamical variables $S$ and $I$, taking $\varepsilon$ as control parameter ($0.134 \leq \varepsilon \leq 0.14$). Middle panel: variation of the largest Lyapunov exponent, $\lambda_1$, with $\varepsilon$ ($0.134 \leq \varepsilon \leq 0.14$). Lower panel: corresponding time series of the dynamical variables $S$ and $I$, obtained using two different (but close) initial conditions displayed in red and green ($\varepsilon = 0.138$, value for which the system is chaotic).

A positive Lyapunov exponent is commonly taken as an indicator of chaotic behavior. In Fig. 3, taking $\varepsilon$ as a control parameter, we present the variation of the largest Lyapunov exponent $\lambda_1$ (Middle panel) and two bifurcation diagrams (Upper panel) regarding the dynamical variables $S$ and $I$. In agreement with the represented bifurcation diagrams, the largest Lyapunov exponent, $\lambda_1$, is positive in the chaotic regime and $\lambda_1 \approx 0$ in the periodic windows (precisely in agreement with the theory for 3D systems). When this Lyapunov exponent is positive, it indicates the region where the system is chaotic. Increasing the degree of seasonality $\varepsilon$ results in the complexity of the dynamics at higher values. This way, the actual existence of chaos is numerically recognized, with the seasonal transmission function $\beta(t)$ as the force driving the system to the chaotic state. In particular, for the choice of parameters $\beta_0 = 1505$, $\varepsilon = 0.138$ of the contact rate $\beta(t)$ and $v(t) = v_0 = 0.071$, the system is chaotic and the largest Lyapunov exponent is $\lambda_1 \approx 0.1$. From now on, we keep the parameter values ($\beta_0 = 1505$, $\varepsilon = 0.138$ and $v_0 = 0.071$) all throughout our study.
4 Suppressing chaos: the phase effect on a seasonal vaccination strategy

As we have just stated, intense seasonality of the periodically varying contact rate induces chaotic dynamics in the epidemic system under a conventional constant vaccination strategy. However, in the context of epidemiology, chaos is often regarded as an undesirable phenomenon associated with the erratic permanence of infectious diseases. As a consequence, the aim of the present section is to provide a comprehensive study of the forced epidemic system in terms of the implementation of the phase control, as a control technique to suppress the chaotic behavior.

Inspired by the importance of vaccination for the elimination of infectious diseases (please see [31]), this procedure is introduced as a biologically meaningful weak perturbation on a seasonal vaccination strategy. More specifically, with the parameters $\beta_0 = 1505$, $\varepsilon = 0.138$ and $v_0 = 0.071$ already tailored in such a way that the asymptotic state of system (6), under a constant vaccination strategy ($v(t) = v_0$), is chaotic, our aim here is to analyze the effects of the phase $\phi$ in the chaotic regime, when an additive perturbation to $v_0$, given by (7), is included. For this purpose, the amplitude of the perturbation $\alpha$ is assumed to be very small, i.e., $\alpha << 1$.

In order to visualize the effect of the phase $\phi$, combined with the variation of $\alpha$, we have displayed in Fig. 4 density plots. The color scale corresponds to the computation of the largest Lyapunov exponent over the parameter region characterized by $0 \leq \phi \leq 2\pi$ and $0.001 \leq \alpha \leq 0.01$, fixing $r = 2$. In Fig. 4, we distinguish two dynamical regimes. The chaotic regime, corresponding to $\lambda_1 > 0$, represented by the colored region (Blue: $0 < \lambda_1 \leq 0.015$; Green: $0.005 < \lambda_1 \leq 0.01$; Yellow: $0.001 < \lambda_1 < 0.005$; Navy blue: $\lambda_1 \leq 0.001$).

We distinguish two dynamical regimes: the chaotic regime, corresponding to $\lambda_1 > 0$ (colored region) and the regular regime, represented by the white region.

Fig. 4. Density plots for the largest Lyapunov exponent corresponding to $r = 2$, in the $(\phi, \alpha)$-parameter region. Left: $0 \leq \phi \leq 2\pi$ and $0.001 \leq \alpha \leq 0.01$; Right: zoom in of the previous density plot considering $\pi \leq \phi \leq 2\pi$ and $0.001 \leq \alpha \leq 0.01$. We distinguish two dynamical regimes: the chaotic regime, corresponding to $\lambda_1 > 0$ (colored region) and the regular regime, represented by the white region.
Fig. 5. Upper panel: bifurcation diagrams for $S$ and $I$ when $\alpha = 0.009$, taking $\phi$ as control parameter ($\pi \leq \phi \leq 2\pi$); Middle panel: variation of the largest Lyapunov exponent, with $\alpha = 0.009$ and $\pi \leq \phi \leq 2\pi$; Lower panel: time series for the dynamical variables $S$ and $I$, for $\alpha = 0.009$ and $\phi = \frac{7}{9}\pi$ (a couple of parameter values marks the beginning of a transition from chaotic to regular behavior).

$\lambda_1 \leq 0.01$; Red: $0.01 < \lambda_1 \leq 0.015$; Orange: $\lambda_1 > 0.015$) and the regular regime, represented by the white region. Taking $r = 2$, we are able to obtain a clear transition from chaotic to regular behavior increasing $\phi$. In a biological context, this choice of $r$ guarantees a frequency of the vaccination within one year. With these density plots, we can better appreciate the structure of the chaotic region (colored) and periodic region (white). In our numerical exploration, the choice of such small values for the perturbation parameter $\alpha$ allows us to demonstrate the effectiveness of the phase control. The density plot (right-hand side of Fig. 4), is precisely a zoom in of the previous density plot (left-hand side of Fig. 4), which clearly exhibits the suppression of chaos, increasing the values of $\phi$, when $\pi \leq \phi \leq 2\pi$. In particular, the striking characteristics of the phase control - the key role of the phase $\phi$ in selecting the final state of the system successfully, combined with tiny values of $\alpha$ to suppress chaos - are present in this density plot (right-hand side of Fig. 4). In order to continue illustrating this primary role of the phase $\phi$ we show, in Fig. 5 (upper panel), bifurcation diagrams for $S$ and $I$, fixing $\alpha = 0.009$ and taking $\phi$ as control parameter, with $\pi \leq \phi \leq 2\pi$ and the corresponding variation of the largest Lyapunov exponent (Middle panel). In fact, we have found a wide range of phase values producing regular motion, in which the system leaves the chaotic region to periodic motion via inverse period doubling. A
remarkable feature is that for values of $\alpha$, such that $\alpha \gtrsim 0.003$, chaos is entirely wiped out in this phase region after having achieved a certain threshold of the phase $\phi$ (density plot of Fig. 4, right-hand side). In particular, for $\alpha = 0.009$, the periodic state is obtained when $\phi \approx \frac{7}{5}\pi$. This observation indicates that the phase $\phi$ is a sensitive parameter for the system bifurcation, i.e., the distribution of regular and chaotic regions strongly depends on the phase difference (please, visit again Fig. 2, and see the representation of $v(t)$ precisely for $\phi \approx \frac{7}{5}\pi$). It is extremely interesting that the weak additive force makes the vaccination strategy seasonal and its phase term (with $\phi > 0$) ensures that the vaccination $v(t)$ anticipates the seasonality of the transmission rate $\beta(t)$. Therefore, the phase control method for suppressing chaos takes on a clear meaning, where the phase difference between the two central driven forces: (i) a transmission rate and (ii) a vaccination strategy, stand out to be a key perturbation parameter with immediate and beneficial biological consequences - the control of a given infectious disease.

5 Concluding remarks

For decades, mathematical models have been proposed to evaluate the spread and control of infectious diseases. Recently, for the last entire year, the world has been experiencing the intensification of the research in epidemic dynamics generated by the dissemination of COVID-19 ([32],[33],[34],[35] and [36]). The year 2020 has seen significant advances taking place, to build the infrastructures to keep up with this coronavirus. SARS-CoV-2, the virus which causes COVID-19, is constantly evolving and mutating, as do all similar virus. The pressure on the virus to evolve is increased by the fact that so many millions of people have now been infected. Such identified changes since it emerged in 2019, in a RNA virus that exists as a cloud of genetic variants known as quasispecies, are completely to be expected to occur and have been useful in understanding the worldwide spread as well as the transmission patterns. The majority of the mutations will not be significant or cause for concern, but some may give the virus an evolutionary advantage which may lead to higher transmission. More specifically, a new genetic variant of the virus has emerged and is spreading in many parts of the UK and across the world. This efficient transmission among people is usually associated to a modeling process with a higher basic reproduction number, $R_0$.

It is precisely in this context of controlling infectious diseases with $R_0 >> 1$, that we have successfully applied the phase control method of suppressing chaos to the continuous periodically driven SIR epidemic model with a seasonal transmission rate and under a conventional constant vaccination strategy. A close attention has been devoted, not to the phase control procedure per se, but to its biological significance and to its consequences within the frame-
work of epidemiology. We have provided detailed/revealing insights about the role played by the phase difference of the two periodically driven forces - the seasonal transmission function $\beta(t)$ and a vaccination component $v(t)$. Having started with the analysis of the existence of chaos, the transmission rate function $\beta(t)$ has been identified as the main force driving the system to the chaotic regime under a classical constant vaccination strategy. With the computation of the largest Lyapunov exponent, values of the parameters of $\beta(t)$ have been tailored within the chaotic region.

Motivated by the fact that, in an epidemiological context, chaotic behavior is often associated with the erratic permanence of infectious diseases and a vaccination strategy is associated with their efficient elimination. Thus, an idea emerged - to introduce the control procedure as a biologically meaningful weak perturbation on a seasonal vaccination function $v(t)$. Given the importance of controlling the chaotic behavior, i.e., the necessity of having predictable densities for the epidemic populations, we have applied the mentioned periodic control signal $v(t)$, including the phase difference with respect to the periodic forcing of the initial system, which has acted as an effective control strategy. More precisely, the chaotic epidemic outbreaks, that appeared as a result of the seasonal variations in the contact rate, have been suppressed by the used vaccination control scheme. Indeed, the crucial role of the phase term, in the seasonal component of $v(t)$, was evidenced by using numerical simulations that allowed us to clearly identify dynamical transitions from a chaotic regime to a regular behavior, which is biologically associated with the control of a given infectious disease.

This study provides another illustration of how an integrated approach, involving numerical evidences and theoretical reasoning, within the theory of dynamical systems, can contribute to our understanding of important biological models and provide a trustworthy explanation of complex phenomena witnessed in biological systems.

Above all, the recent appearance of COVID-19 is a reminder that there is still so much to learn about a pandemic dynamics. The pace of the research effort in the past year has been extraordinary. However, there is no room for complacency. We have to be humble and mostly be prepared to adapt and respond to new and continued changes.

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