Feedback linearization-based vaccination control strategies for true-mass action type SEIR epidemic models

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Abstract. This paper presents a feedback linearization-based control strategy for a SEIR (susceptible plus infected plus infectious plus removed populations) propagation disease model. The model takes into account the total population amounts as a refrain for the illness transmission since its increase makes more difficult contacts among susceptible and infected. The control objective is novel in the sense that the asymptotically tracking of the removed-by-immunity population to the total population while achieving simultaneously the remaining population (i.e. susceptible plus infected plus infectious) to asymptotically converge to zero. The vaccination policy is firstly designed on the above proposed tracking objective. Then, it is proven that identical vaccination rules might be found based on a general feedback linearization technique. Such a formal technique is very useful in control theory which provides a general method to generate families of vaccination policies with sound technical background which include those proposed in the former sections of the paper. The output zero dynamics of the normal canonical form in the theoretical feedback linearization analysis is identified with that of the removed-by-immunity population. The various proposed vaccination feedback rules involved one of more of the partial populations and there is a certain flexibility in their designs since some control parameters being multiplicative coefficients of the various populations may be zeroed. The basic properties of stability and positivity of the solutions are investigated in a joint way. The equilibrium points and their stability properties as well as the positivity of the solutions are also investigated.

Keywords: epidemic models, control, SEIR epidemic models, positivity, stability.

1 Introduction, brief description of some previous background work, objectives and organization

Important control problems nowadays related to life sciences are the control of ecological models like, for instance, those of population evolution (Beverton–Holt model, Hassell

model, Ricker model etc.) via the online adjustment of the species environment carrying capacity, that of the population growth or that of the regulated harvesting quota as well as the disease propagation via vaccination control. In a set of papers, several variants and generalizations of the Beverton–Holt model (standard time-invariant, time-varying parameterized, generalized model or modified generalized model) have been investigated at the levels of stability, cycle-oscillatory behavior, permanence and control through the manipulation of the carrying capacity (see, for instance, [1–5]). The design of related control actions has been proved to be important in those papers at the levels, for instance, of aquaculture exploitation or plague fighting. On the other hand, the literature about epidemic mathematical models is exhaustive in many books and papers. The classic background literature on the subject classifies the epidemic models in various types according to the partial populations included and the couplings of dynamics among them which clearly influence when the disease starts up and propagates. A non-exhaustive list of references is given in this manuscript, cf. [6–14] (see also the references listed therein). The sets of models include the most basic ones, [6, 7] as it is now described for potential readers being not very familiar with the subject:

- SI models where not removed-by-immunity population is assumed. In other words, only susceptible and infected populations are assumed.
- SIR models, which include susceptible plus infected plus removed-by-immunity populations.
- SEIR models where the infected populations is split into two ones (namely, the "infected" which incubate the disease but do not still have any disease symptoms and the "infectious" or "infective" which do have the external disease symptoms).

Those models have also two major variants, namely, the so-called "pseudo-mass action models", where the total population is not taken into account as a relevant disease contagious factor and the so-called "true-mass action models", where the total population is more realistically considered as an inverse factor of the disease transmission rates). There are many variants of the above models, for instance, including vaccination of different kinds as follows: constant [8], impulsive [12], discrete-time etc., incorporating point or distributed delays [12, 13], oscillatory behaviours [14] etc. On the other hand, variants of such models become considerably simpler for the illness transmission among plants [6, 7]. More recent bibliography has considered more sophisticated problems, sometimes involving much richer dynamics and investigation of positivity of solutions and the stability properties as a non-separable tandem of properties. *Note that in the same way that the stability property is a minimum requirement for control problems, positivity is also a minimum requirement for properly dealing with models involving populations (as, for instance, epidemic models) so as to have a better chance to adjust the model solutions to the real and foreseen evolution of the partial populations.* Note that the positivity of the state-trajectory solution of the epidemic model is guaranteed in the vaccination-free case for any nonnegative initial conditions but the property does not hold for any designed potential vaccination rule. This can be performed independently of the initial conditions, the current values of the partial populations through time, the particular illness under study and the species being involved. A major property is that

the boundedness of the total population for all time together with the positivity of the solution guarantees the boundedness, then the stability, of the whole model. In [21], a very general SEIR type model is considered with dynamics mixed point and distributed, in general time-varying, delays and combined regular and impulsive vaccination. Thresholds of infected/infectious which cannot be eventually removed are also incorporated to the epidemic model. A general SVEIRS model is investigated in [23] which incorporates the presence of a vaccinated population to the standard populations of SEIR models. The disease-free and endemic equilibrium points and the positivity of the solutions are investigated. Both regular and impulsive vaccination rules are proposed, discussed and analyzed. In particular, impulsive vaccination can be used to concentrate a vaccination effort in very short periods of time when necessary. The positivity, stability and equilibrium points and their stability properties are also investigated. A dynamic observer is incorporated in [24] to estimate the partial populations towards the vaccination programming under feedback control rules. The main reason is that while the infectious and total populations are directly known or measurable in many cases and the infected population with a certain delay is close to the currently infectious one, the susceptible and removed-by-immunity populations are more difficult to know and sometimes they have to be estimated. In [21] and [23] time-varying epidemic models are considered which take into account the loss of immunity of newborns, the mortality due to the disease and the possible presence of external infected populations. In [25], carrier-dependent infectious diseases (like cholera, measles etc.) are considered. The effect on the vaccination on the spread of the carrier is incorporated to the model by assuming a generalized logistic model which governs the growth of carrier population. In [26], a predator-prey model with a constant delay due to gestation is considered. The proposed model considers that the disease can be transmitted by contacts spreads among the prey only. In [27], a SIR epidemic model with an asymptotically homogeneous transmission function is proposed and discussed. The stability of both the disease-free and the endemic equilibrium points is addressed. It is found, in particular, that the spread of the disease decreases as the social or psychological protective measures for the infective population become increased in spite that the reproduction number is independent of the transmission constant. In [28], a predator-prey model which incorporates a prey refuge and disease in the prey population is proposed. It is assumed that the predator population prefers only infected prey population for their diet as those are more vulnerable. The properties of boundedness, stability and permanence are investigated and the maximum delay size preserving stability is estimated. A compartmental-type epidemic model is proposed in [29]. Such a model incorporates a nonlinear incidence rate and an imperfect preventive vaccine for the susceptible population. A bifurcation analysis is also performed.

In this paper, a feedback control linearization technique is used to obtain a family of vaccination policies capable of asymptotically making the complete population become removed-by-immunity (immune). *That is the proposed vaccination strategies make the immune population to asymptotically "track" the total one what is established as the control design objective and what practically translates into the removal of the disease.* Initially, two of these vaccination policies are proposed and studied in detail. In a second stage, the general formalism is introduced to show the rationale behind the vaccination

policies and how they fit into the general method. Feedback-linearization techniques, [17, 18], are successfully applied in control systems design for nonlinear problems, such as electrical machines, [19], or robotics [20]. However, its use in epidemic model control has been rather limited. It is assumed that the total population remains constant through time, so that the illness transmission is not critical, and the SEIR model is of the above mentioned true-mass action type. The paper is organized as follows. Subsection 1.1 below contains notation notes. Section 2 is devoted to the true-mass action type epidemic model dealt with in the paper which can incorporate a vaccination effort through time and which considers the total population to be constant, i.e. there is no mortality associated will the disease and the loose of immunity of new-borns is not considered either. Sections 3 and 4 are, respectively, devoted to the positivity properties and the equilibrium analysis of the mathematical model. The more involved mathematical proofs are given in Appendix A. The positivity of the solutions is a very important property since it guarantees the global stability if the whole population is bounded even in epidemic time-varying models. Therefore, it deserves some discussion in this paper. The main related proofs are located in Appendix B in order not to disturb the potential reading of the main body of the manuscript to potential readers being not very familiar with its formalism. Section 4 presents also some vaccination laws based on feedback under the knowledge of some of the partial populations. The main control objective is the asymptotic tracking of the whole population by the removed-by-immunity one. Section 5 presents a theoretical study of the feedback linearization method by using the normal canonical form and the zero dynamics of the model. It is seen that the general method leads to the particular vaccination control laws proposed and discussed in the previous section. Section 6 contains numerical simulation and associated brief discussion of the obtained results. Section 7 relies on the discussion of the disease-free equilibrium point in the vaccination-free case, under vaccination effort being identically equal to unit for all time and under the proposed vaccination laws. In the first case, it is seen that depending on the basic reproduction number value, which depends on the model parameters, the disease propagates even under small numbers of infectious for a sufficiently large transmission constant. For a sufficiently small value of such a disease transmission constant the disease becomes easily removed asymptotically without any vaccination action. However, the design of the proposed vaccination rules may remove asymptotically the disease irrespective of the reproduction number. Finally, the concluding remarks end the paper. In order to keep a good readability of the paper, some results with involved equations concerning positivity and stability are placed in appendices.

1.1 Notation

$\mathbb{R}_+^n$ is the first open n-real orthant and $\mathbb{R}_{0+}^n$ is the first closed n-real orthant.

$m \in \mathbb{R}_{0+}^n$ is a positive real n-vector in the usual sense that all its components are nonnegative. In the same way, $M \in \mathbb{R}_{0+}^{n\times n}$ is a positive real n-matrix in the usual sense that all its entries are nonnegative. The notations $\mathbb{R}_+^n$ and $\mathbb{R}_+^{n\times n}$ refer to the stronger properties that all the respective components or entries are positive.

$C^{(q)}(Do; Im)$ is the set of real functions of class q of domain *Do* and image *Im*. $PC^{(q)}(Do; Im)$ is the set of real functions of class $(q-1)$ of domain *Do* and image *Im*

whose q-th derivative exits but it is not necessarily everywhere continuous on its definition domain.

2 SEIR epidemic model

Let $S(t)$ be the "susceptible" population of infection at time t, $E(t)$ the "infected" (i.e. those which incubate the illness but do not still have any symptoms) at time t, $I(t)$ is the "infectious" (or "infective") population at time t, and $R(t)$ is the "removed-by-immunity" (or "immune") population at time t. Consider the SEIR type epidemic model:

$$\dot{S}(t) = -\mu S(t) + \omega R(t) - \beta \frac{S(t)I(t)}{N} + \mu N\big(1 - V(t)\big), \tag{1}$$

$$\dot{E}(t) = \beta \frac{S(t)I(t)}{N} - (\mu + \sigma)E(t), \tag{2}$$

$$\dot{I}(t) = -(\mu + \gamma)I(t) + \sigma E(t), \tag{3}$$

$$\dot{R}(t) = -(\mu + \omega)R(t) + \gamma I(t) + \mu N V(t) \tag{4}$$

subject to initial conditions $S_0 = S(0) \geq 0$, $E_0 = E(0) \geq 0$, $I_0 = I(0) \geq 0$ and $R_0 = R(0) \geq 0$ under the vaccination constraint $V\colon \mathbb{R}_{0+} \to \mathbb{R}_{0+}$. In the above SEIR model, N is the total population, μ is the rate of deaths from causes unrelated to the infection, ω is the rate of losing immunity, β is the transmission constant (with the total number of infections per unit of time at time t being $\beta \frac{S(t)I(t)}{N}$), σ^{-1} and γ^{-1} are, respectively, the average durations of the latent and infective periods. All the above parameters are assumed to be nonnegative.

3 About the positivity of the SEIR epidemic model (1)–(4)

The vaccination strategy has to be implemented so that the SEIR model be positive in the usual sense that none of the populations, namely, susceptible, infected, infectious and immune be negative for any time instant. This requirement follows directly from the nature of the problem at hand. This section investigates conditions for positivity of the SEIR model (1)–(4). The constant population constraint:

$$N = N(0) = S(t) + E(t) + I(t) + R(t) = S(0) + E(0) + I(0) + R(0) \quad \forall t \in \mathbb{R}_{0+} \tag{5}$$

implying directly:

$$\dot{S}(t) + \dot{E}(t) + \dot{I}(t) + \dot{R}(t) = \dot{S}(0) + \dot{E}(0) + \dot{I}(0) + \dot{R}(0) = 0 \quad \forall t \in \mathbb{R}_{0+} \tag{6}$$

holds directly in (1)–(4) since summing-up the four right-sides yields zero for all time.

The following assumption is made:

Assumption 1. The following constraints are assumed on the SEIR model (1)–(4): $\min(S(0), I(0), R(0)) \geq 0$ and $E(0) > \frac{\mu+\gamma}{\sigma} I(0)$ with $\frac{\beta S(0) I(0)}{(\mu+\sigma)N} > E(0)$ if $I(0) \neq 0$.

Remark 1. The physical interpretation of Assumption 1 is that the time origin of interest to fix initial conditions in the SEIR model is the time instant at which the disease starts to be infectious. The growing rate of infectious at the time origin is positive, i.e. $\dot{I}(0) > 0$, even under zero initial condition $I(0) = 0$ so that $E(0) > 0$ and $\dot{E}(0) < 0$ for both the infected and infectious populations. Also, the infected population and its growing rate at the time origin are positive, i.e. $\min(E(0), \dot{E}(0)) > 0$ if $I(0) = 0$ and a third consequence of Assumption 1 is that:

- $\dot{E}(0) + \dot{I}(0) \leq 0$ if $\frac{I(0)}{E(0)} \leq \frac{\mu N}{\beta S(0) - (\mu+\gamma)N}$, $N \geq S(0) \geq \frac{\mu+\gamma}{\beta} N$ or, equivalently, if $N \geq S(0) \geq \frac{\mu+\gamma}{N-\mu-\gamma}(E(0) + I(0) + R(0))$ requiring $\beta \geq \mu + \gamma$;
- $\dot{E}(0) + \dot{I}(0) > 0$ if $\frac{I(0)}{E(0)} > \frac{\mu N}{\beta S(0) - (\mu+\gamma)N}$, $N \geq S(0) \geq \frac{\mu+\gamma}{\beta} N$ requiring $\beta \geq \mu + \gamma$;

so that $\dot{E}(0) + \dot{I}(0) \leq 0$ if $I(0) = 0$. Thus, if $I(0) = 0$ and $\dot{I}(0) > 0$ ($\dot{I}(0) \geq 0$) then $\dot{E}(0) < 0$ ($\dot{E}(0) \leq 0$).

Remark 2. Note that Assumption 1 implies from (3) that:

- $\dot{I}(0) > 0$;
- $S(0) < N - R(0) - (1 + \frac{\mu+\gamma}{\sigma})I(0)$ and $S(0) > \frac{(\mu+\gamma)(\mu+\sigma)N}{\sigma\beta}$ if $I(0) \neq 0$;
- $\beta > \beta_0 := (\mu + \gamma)(1 + \frac{\mu}{\sigma})$ if $I(0) \neq 0$ (since $S(0) < N$).

The parametrical condition $\beta > \beta_0$ is of interest even if $I(0) = 0$ in order to make the SEIR model parameters independent of any set of admissible initial conditions.

Theorem 1. *Assume a vaccination function $V \in PC^{(0)}(\mathbb{R}_{0+}; [0, 1])$ and that the initial conditions satisfy Assumption* 1. *Then, all the solutions of the SEIR model* (1)–(4) *satisfy $S(t), E(t), I(t), R(t) \in [0, N]$ $\forall t \in \mathbb{R}_{0+}$.*

Proof. The constant population constraint (5) is used in (1), (3)–(4) to eliminate the infected population $E(t)$ leading to:

$$\dot{S}(t) = -(\mu + \alpha)S(t) + \omega R(t) + \left(\alpha - \beta\frac{I(t)}{N}\right)S(t) + \mu N\big(1 - V(t)\big), \tag{7}$$

$$\dot{I}(t) = -(\mu + \gamma + \sigma)I(t) + \sigma\big(N - S(t) - R(t)\big), \tag{8}$$

$$\dot{R}(t) = -(\mu + \omega)R(t) + \gamma I(t) + \mu N V(t) \tag{9}$$

for any given real constant $\alpha \geq (\beta/N)\sup_{t\geq 0}(I(t))$. Such a constraint is guaranteed with $\alpha \geq \alpha_0 := \beta$ if $0 \leq I(t) \leq N$ for all $t \geq 0$. It is possible to rewrite (7)–(9) in a compact form as a dynamic system of state $x(t) = (S(t), I(t), R(t))^{\mathrm{T}}$, output $y(t) = S(t) + R(t)$ and whose input is appropriately related to the vaccination function as $u(t) =$

$(1-V(t),V(t))^{\mathrm{T}}$. This leads to the following set of identities:

$$\dot{x}(t)=\bar{A}(\alpha)x(t)+\mu N\bar{E}_{13}u(t)+\left(\left(\alpha-\beta\frac{I(t)}{N}\right)E_1x(t)+\sigma Ne_2\right), \tag{10a}$$

$$=A(\alpha)x(t)+\mu N\bar{E}_{13}u(t)+\left(\left[\left(\alpha-\beta\frac{I(t)}{N}\right)E_1-\sigma E_{13}\right]x(t)+\sigma Ne_2\right), \tag{10b}$$

$$=A(\alpha)x(t)+\mu N\bar{E}_{13}u(t)+\left(\left(\alpha-\beta\frac{I(t)}{N}\right)E_1x(t)+\sigma\big(N-y(t)\big)e_2\right), \tag{10c}$$

$$=A(\alpha)x(t)+\mu Ne_3V(t)+\left(\left(\alpha-\beta\frac{I(t)}{N}\right)E_1x(t)+\sigma\big(E(t)+I(t)\big)e_2 +\mu Ne_1\big(1-V(t)\big)\right), \tag{10d}$$

$$y(t)=e_{13}^{\mathrm{T}}x(t), \tag{11}$$

where e_i is the i-th unit Euclidean column vector in $\mathbb{R}^3$ with its i-th component being equal to one and the other two components being zero, e_{ij} having the i-th and j-th components being one and the remaining one being zero, so that $e_{13}^{\mathrm{T}}=(1,0,1)$, and

$$\bar{A}(\alpha):=A(\alpha)-\sigma E_{13},\quad A(\alpha):=\begin{bmatrix}-(\mu+\alpha) & 0 & \omega\\ 0 & -(\mu+\gamma+\sigma) & 0\\ 0 & \gamma & -(\mu+\omega)\end{bmatrix}, \tag{12}$$

$$E_{13}:=\begin{bmatrix}0^{\mathrm{T}}\\ e_{13}^{\mathrm{T}}\\ 0^{\mathrm{T}}\end{bmatrix}=\begin{bmatrix}0&0&0\\1&0&1\\0&0&0\end{bmatrix},\quad \bar{E}_{13}:=[e_1,e_3]=\begin{bmatrix}1&0\\0&0\\0&1\end{bmatrix},$$
$$E_1:=\begin{bmatrix}e_1^T\\0^T\\0^T\end{bmatrix}=\begin{bmatrix}1&0&0\\0&0&0\\0&0&0\end{bmatrix}. \tag{13}$$

Note that: (i) $A(\alpha)$ is a Metzler matrix [4, 5] for any given $\alpha\in\mathbb{R}_{0+}$ so that the C_0 – semigroup $\Phi\in L(R^3,R^3)$ of infinitesimal generator $A(\alpha)$ can also be represented as a fundamental positive real matrix function $\Psi:=(\Phi x)(t)\in PC^{(1)}(\mathbb{R}_{0+},\mathbb{R}_{0+}^{3\times3})$ for $x\in Do(\Phi)\subset\mathbb{R}^3$of solutions of (7)–(9) as a result defined by $\Psi(\alpha,t)=e^{A(\alpha)t}\,\forall t\geq0$. In addition, since $\Psi(\alpha,t)$ is a fundamental matrix, it is nonsingular so that $(\Psi(\alpha,t)x)\in\mathbb{R}_+^3$ $\forall x\in\mathbb{R}_{0+}^3$.

(ii) $\min(\sigma,\mu)\geq0$, $\alpha\geq\beta\frac{I(t)}{N}$, $V(t)\in[0,1]\;\forall t\in R_{0+}$; $e_1,e_2,e_3,e_{13}\in\mathbb{R}_{0+}^3$; $E_1\in R_{0+}^{3\times3}$.

(iii) From Assumption 1 (see also Remark 1, $E(0)+I(0)\geq0$ and $\dot{E}(0)+\dot{I}(0)>0$ if $\frac{I(0)}{E(0)}>\frac{\mu N}{\beta S(0)-(\mu+\gamma)N}$, $N\geq S(0)\geq\frac{\mu+\gamma}{\beta}N$ provided that $\beta\geq\mu+\gamma$. From continuity of any solution of (1)–(4), it exists $t_1>0$ such that $E(t)+I(t)>0\;\forall t\in(0,t_1)$. Also, $\dot{E}(0)+\dot{I}(0)\leq0$ if $\frac{I(0)}{E(0)}\leq\frac{\mu N}{\beta S(0)-(\mu+\gamma)N}$ and $N\geq S(0)\geq\frac{\mu+\gamma}{\beta}N$ requiring $\beta\geq\mu+\gamma$. Thus, if $I(0)=0$, $\dot{I}(0)>0$ and $N\geq S(0)\geq\frac{\mu+\gamma}{\beta}N$ then $\dot{E}(0)+\dot{I}(0)\leq0$

$\Rightarrow \dot{E}(0) < 0$. Again from continuity arguments, it exists $t_1 > 0$ such that $E(t) < E(0)$ $\forall t \in (0, t_1)$. Then, one has from (10d) that for any admissible initial condition $x(0) = (S(0), I(0), R(0))^{\mathrm{T}}$, the unique solution on $[0, t_1)$ of (7)–(9) is:

$$\mathbb{R}^3_+ \ni x(t) = e^{A(\alpha)t}\left(x(0) + \int_0^t e^{-A(\alpha)\tau} m(\tau)\,\mathrm{d}\tau\right) \quad \forall t \in [0, t_1] \tag{14}$$

since $\mathbb{R}^3_+ \ni x(t) = e^{A(\alpha)t}x(0)\ \forall x(0) \in \mathbb{R}^3_{0+}$, and since $x(t) \in \mathbb{R}^3_+$ on $[0, t_1)$ implies that

$$\mathbb{R}^3_+ \ni E(t) = e^{-(\mu+\sigma)t}\left(E(0) + \frac{\beta}{N} e_1^{\mathrm{T}}\left(\int_0^t e^{(\mu+\sigma)\tau} x(\tau) x^{\mathrm{T}}(\tau)\,\mathrm{d}\tau\right) e_2\right);$$
$$\forall t \in [0, t_1], \tag{15}$$

$$\mathbb{R}^3_{0+} \ni m(t) := \mu N e_3 V(t) + \left(\left(\alpha - \beta\frac{I(t)}{N}\right) E_1 x(t) + \sigma\big(E(t) + I(t)\big)e_2 + \mu N e_1\big(1 - V(t)\big)\right)$$
$$= m_1(t) + \sigma\big(E(t) + e_2^T x(t)\big)e_2 \quad \forall t \in [0, t_1] \tag{16}$$

where $\mathbb{R}^3_{0+} \ni m_1(t) := m(t) - \sigma(E(t) + e_2^{\mathrm{T}} x(t))e_2$ and $(\sigma(E(t) + e_2^{\mathrm{T}} x(t))e_2) \in \mathbb{R}^3_{0+}$. Since $x(t_1) \in \mathbb{R}^3_+$ and $e^{-(\mu+\sigma)t}E(0) \in \mathbb{R}_+\ \forall t \in \mathbb{R}_{0+}$, it exists $t_2 > t_1$ such that $E(t) \in \mathbb{R}_+$, $m(t) \in \mathbb{R}^3_+$, $x(t) \in \mathbb{R}^3_+$ (so that $S(t), I(t), R(t) \in \mathbb{R}_{0+}$) $\forall t \in [0, t_2]$. The above properties extend to $t \in \mathbb{R}_{0+}$ from the structures of (14)–(16). Furthermore, $(\liminf_{t\to\infty} x(t)) \in \mathbb{R}^3_{0+}$ and $(\liminf_{t\to\infty} E(t)) \in \mathbb{R}_{0+}$. Those relations also imply from (5) that $\max(S(t), E(t), I(t), R(t)) \le N\ \forall t \in \mathbb{R}_{0+}$. □

Remark 3. Note that the SEIR model is not guaranteed to be positive according to Theorem 1 in the sense of [15, 16] since Assumption 1 establishes constraints on the initial conditions.

Corollary 1. *Theorem* 1 *still holds if* $V(t) \in [0, 1 + (\alpha - \beta\frac{I(t)}{N})\frac{S(t)}{\mu N}]$, $t \in \mathbb{R}_{0+}$.

Proof. It follows from the proof of Theorem 1 since $m(t) \in \mathbb{R}_{0+}\ \forall t \in \mathbb{R}_{0+}$ from (10d) and (12)–(13) under this modified vaccination constraint. □

4 Equilibrium points, stability, instability and immunity tracking of the whole population via vaccination rules

This section is concerned with vaccination designs so that stability or instability are guaranteed. It is also discussed how the vaccination might be synthesized so that the whole population is matched via vaccination strategies by the immune population so that the susceptible, infected and infectious are zeroed. An important point to deal with these issues is to ensure that all the partial populations (i.e. susceptible, infected, infectious and

immune) are nonnegative for all time so that the boundedness of the whole population guarantees that of the individual ones. For this purpose, the positivity of the models is an important property to be guaranteed by the choice of the vaccination control in $[0, 1]$. Initially, the vaccination policies are introduced being its effects analyzed while in the following Section 5, the general frame (based-on feedback linearization) will be commented.

Remark 4. The equilibrium points in the vaccination-free case, which are discussed in Appendix A, are not suitable since one of them is concerned with the whole population being susceptible while the other is concerned with not all the population being asymptotically converging to the removed-by-immunity, in general. Therefore, a suitable vaccination strategy is necessary. The ideal vaccination mechanism objective is to reduce to zero the numbers of susceptible, infected and infectious independent of their initial numbers so that the total population becomes equal to the removed-by-immunity population after a certain time. After inspecting (1) and (4), it becomes obvious that the constraint $V\colon \mathbb{R}_{0+} \to \mathbb{R}_+$ is necessary to decrease the time variation of the susceptible and to increase simultaneously that of the removed-by-immunity.

The following elementary result follows from the SEIR mathematical model (1)–(4)

Assertion 1. *The SEIR model* (1)–(4) *fulfils the constant population through time constraint* $N(t) := S(t) + E(t) + I(t) + R(t) = N(0) = N_0 = N > 0$ *irrespective of the vaccination strategy.*

Proof. It follows immediately by summing-up both sides of (1) and (4) what leads to:

$$\dot{N}(t) = \dot{S}(t)+\dot{E}(t)+\dot{I}(t)+\dot{R}(t) = \mu\big(N(t)-S(t)-E(t)-I(t)-R(t)\big) = 0 \quad \forall t \in \mathbb{R}_{0+}$$

so that $N(0) = S(0)+E(0)+I(0)+R(0) = N_0 \;\Rightarrow\; N(t) = S(t)+E(t)+I(t)+R(t) = N_0 = N$ for all $t \geq 0$.

Remark 5. Note that Assertion 1 proves that the constant population through time is independent of the vaccination strategy so that it is independent of the ideal vaccination objective constraint $V\colon \mathbb{R}_{0+} \to \mathbb{R}_+$ as a result. For instance, in a biological war, the objective would be to increase the numbers of the infected plus infectious population for all time. For that purpose, the appropriate vaccination strategy is negative.

An auxiliary control function may be defined in several ways involving the vaccination function which is really the manipulated variable. For instance, one might define the infected/removed-by-immunity coupling term $z(t)$ and control $u(t)$ as follows:

$$z(t) = \omega R(t) - \sigma E(t), \tag{17}$$

$$u(t) = z(t) - \mu N V(t). \tag{18}$$

Note that any required control u(t) can be achieved using a vaccination strategy

$$V(t) = \frac{z(t) - u(t)}{\mu N} = \frac{\omega R(t) - \sigma E(t) - u(t)}{\mu N}. \tag{19}$$

Then, one gets from (1)–(4) and (19):

$$\dot{E}(t)+\dot{I}(t)=-\mu\big(E(t)+I(t)\big)+\left(\beta\frac{S(t)}{N}-\gamma\right)I(t), \tag{20}$$

$$\begin{aligned}\dot{S}(t)+\dot{E}(t)&=-\mu\big(S(t)+E(t)\big)+\mu N+u(t) &\text{(21a)}\\ &=\mu\big(I(t)+R(t)\big)+u(t), &\text{(21b)}\end{aligned}$$

$$\dot{I}(t)+\dot{R}(t)=-\mu\big(I(t)+R(t)\big)-u(t)=-\big(\dot{S}(t)+\dot{E}(t)\big), \tag{22}$$

$$\begin{aligned}\dot{S}(t)+\dot{R}(t)&=-\mu\big(S(t)+R(t)\big)+\left(\gamma-\frac{\beta S(t)}{N}\right)I(t)+\mu N &\text{(23a)}\\ &=\mu\big(E(t)+I(t)\big)+\left(\gamma-\frac{\beta S(t)}{N}\right)I(t) &\text{(23b)}\\ &=\mu E(t)+\left(\mu+\gamma-\frac{\beta S(t)}{N}\right)I(t)=-\big(\dot{E}(t)+\dot{I}(t)\big), &\text{(23c)}\end{aligned}$$

$$\begin{aligned}\dot{S}(t)+\dot{E}(t)+\dot{I}(t)&=-\mu\big(S(t)+E(t)+I(t)\big)+\omega R(t)-\gamma I(t)\\ &\quad+\mu N\big(1-V(t)\big) &\text{(24a)}\\ &=\mu R(t)+\sigma E(t)-\gamma I(t)+u(t), &\text{(24b)}\end{aligned}$$

$$\begin{aligned}\dot{R}(t)&=-(\mu+\omega)R(t)+\gamma I(t)+\mu NV(t) &\text{(25a)}\\ &=-\mu R(t)-\sigma E(t)+\gamma I(t)-u(t) &\text{(25b)}\\ &=-\big(\dot{S}(t)+\dot{E}(t)+\dot{I}(t)\big). &\text{(25c)}\end{aligned}$$

Remarks 6. (i) Note from Eqs. (1) and (4) that a vaccination strategy applied on a time interval makes the susceptible population to decrease and the removed-by-immunity population to increase in a parallel fashion. From (2), the infected growing rate decreases as the susceptible numbers decrease.

(ii) Eqs. (21)–(22) show that for a certain control associated with a vaccination strategy if the growing rate of joined susceptible plus infected population decreases then that of the infectious plus removed-by-immunity increases and conversely.

The fact that the total population of the SEIR model (1)–(4) remains constant (Assertion 1 makes it both uncontrollable- to-the origin and unreachable. Such a constraint is atypical in most of control problems since the role of the vaccination is to decrease to zero the numbers of susceptible, infected and infectious to make the removed-by-immunity population to asymptotically converge to the total population.

Assertion 2. *The SEIR model* (1)–(4) *is unreachable and uncontrollable to the origin via any vaccination strategy.*

Proof. Proceed by contradiction. Fix any desired final state $x^* := (S(t^*), E(t^*), I(t^*), R(t^*))^{\mathrm{T}}$ at arbitrary finite time $t = t^*$ fulfilling the constraint $S(t^*) + E(t^*) + I(t^*) + R(t^*) > N$. From Assertion 1, the population remains constant equal to N so that x^* is unreachable for any given finite time instant $t*$. Thus, the SEIR model is unreachable. It is always trivially uncontrollable-to-the origin for arbitrary initial conditions for the total population. □

A simple way of defining an useful control function is one with the goal of decreasing appropriately the numbers of susceptible while including the nonlinear term involving the product $S(t)I(t)$ of susceptible and infectious in (1). The following result is concerned with this matter. A subsequent linear feedback vaccination strategy, being proportional to the susceptible for all time is discussed.

Theorem 2. *The following properties hold*:

(i) *Assume that the feedback control and its associated vaccination strategy are generated as follows*:

$$u(t) = -gS(t), \quad g \geq 0, \tag{26a}$$

$$V(t) = \frac{1}{\mu N}\left(\omega R(t) + \left(g - \frac{\beta I(t)}{N}\right)S(t) + \mu N\right), \tag{26b}$$

$\gamma \neq \sigma$, $g \neq \sigma$ and $g \neq \gamma$. Then the whole population becomes asymptotically removed-by-immunity at an exponential rate. Furthermore, $\exists \lim_{t\to\infty} V(t) := 1 + \frac{\omega}{\mu}$.

(ii) *Assume that the feedback control and its associated vaccination strategy accordingly are generated as follows*:

$$u(t) = -g\big(S(t) + E(t)\big), \quad g \geq 0 \tag{27a}$$

$$V(t) = \frac{1}{\mu N}\big(gS(t) + (g - \sigma)E(t) + \omega R(t)\big) \tag{27b}$$

$$= \frac{1}{\mu N}\big(g\big(N - I(t)\big) - \sigma E(t) + (\omega - g)R(t)\big). \tag{27c}$$

Then $\lim_{t\to\infty}(S(t) + E(t)) = \frac{\mu N}{\mu+g}$ *and* $\lim_{t\to\infty}(I(t) + R(t)) = \frac{gN}{\mu+g}$ *at an exponential rate if* $0 \leq g < \mu$ *and, furthermore,*

$$\exists \lim_{t\to\infty}\left(V(t) + \frac{\sigma E(t) - \omega R(t)}{\mu N}\right) = \frac{g}{\mu + g} < 1$$

with $\lim_{t\to\infty} V(t) = \lim_{t\to\infty} E(t) = \lim_{t\to\infty} I(t) = \lim_{t\to\infty} R(t) = 0$ *at exponential rates if* $g = 0$. *In particular, the whole population becomes asymptotically susceptible at an exponential rate if* $0 = g < \mu$ *for the corresponding vaccination law*:

$$V(t) = \frac{1}{\mu N}\big(\omega R(t) - \sigma E(t)\big)$$

while all the other partial populations converge asymptotically to zero at an exponential rate.

Proof. (i) Rewrite (1) in the equivalent form:

$$\dot{S}(t) = -\mu S(t) + u(t) \tag{28}$$

with an auxiliary control $u(t)$ being defined and generated as follows:

$$u(t) = \omega R(t) - \frac{\beta}{N} S(t) I(t) + \mu N\big(1 - V(t)\big) := -gS(t) \tag{29}$$

through the vaccination function $V(t)$ given by (21b). Note that the open-loop solution of (28) is

$$S(t) = e^{-\mu t}\left(S(0) + \int_0^t e^{\mu\tau} u(\tau)\,\mathrm{d}\tau\right). \tag{30}$$

One gets from (28)–(29):

$$\dot{S}(t) = -(\mu + g)S(t) \;\Rightarrow\; S(t) = e^{-(\mu+g)t} S(0) \to S(\infty) = 0 \quad \text{as } t \to \infty, \tag{31}$$

$$u(t) = -gS(t) = -ge^{-(\mu+g)t} S(0) \to 0 \quad \text{as } t \to \infty. \tag{32}$$

Also, one gets from (31)–(32) into (29) that $\limsup_{t\to\infty}(V(t) - \frac{\omega}{\mu}\frac{R(t)}{N}) = 1$ implying that $V(t) \le 1 + \frac{\omega}{\mu}\frac{R(t)}{N} + \varepsilon\ \forall t \ge T = T(\varepsilon)$ (finite) and any arbitrary prefixed $\varepsilon \in \mathbb{R}_+$. On the other hand, one gets from (2) subject to (31):

$$\dot{E}(t) = -(\mu + \sigma)E(t) + \frac{\beta}{N} e^{-(\mu+g)t} S(0) I(t)$$

what leads to

$$\begin{aligned} E(t) &= e^{-(\mu+\sigma)t} E(0) + \frac{\beta S(0)}{N} e^{-(\mu+\sigma)t} \int_0^t e^{-(g-\sigma)\tau} I(\tau)\,\mathrm{d}\tau \\ &\le e^{-(\mu+\sigma)t} E(0) + \beta N \frac{e^{-(\mu+g)t} - e^{-(\mu+\sigma)t}}{\sigma - g} \to 0 \end{aligned}$$

exponentially fast as $t \to \infty$at a rate of at most $\mu + \min(\sigma, g)$ as $t \to \infty$ since $\min(\mu, \sigma) > 0$ and $g \ge 0$. Combining this result with (3) and within the above solution expression for $E(t)$, one obtains:

$$\begin{aligned} I(t) &= e^{-(\mu+\gamma)t} I(0) + \sigma \int_0^t e^{-(\mu+\gamma)(t-\tau)} E(\tau)\,\mathrm{d}\tau \\ &\le e^{-(\mu+\gamma)t} I(0) \\ &\quad + \sigma e^{-(\mu+\gamma)t} \int_0^t e^{(\mu+\gamma)\tau}\left(e^{-(\mu+\sigma)\tau} E(0) + \beta N \frac{e^{-(\mu+g)\tau} - e^{-(\mu+\sigma)\tau}}{\sigma - g}\right)\mathrm{d}\tau \end{aligned}$$

$$
\begin{aligned}
&= e^{-(\mu+\gamma)t}I(0) + \frac{\sigma E(0)}{\gamma-\sigma}\big(e^{-(\mu+\sigma)t} - e^{-(\mu+\gamma)t}\big) \\
&\quad + \frac{\sigma\beta N}{(\sigma-g)(\gamma-g)}\big(e^{-(\mu+g)t} - e^{-(\mu+\gamma)t}\big) - \frac{\sigma\beta N}{(\sigma-g)(\gamma-\sigma)}\big(e^{-(\mu+\sigma)t} - e^{-(\mu+\gamma)t}\big) \\
&= e^{-(\mu+\gamma)t}I(0) + \frac{\sigma((\sigma-g)E(0)-\beta N)}{(\gamma-\sigma)(\sigma-g)}e^{-(\mu+\sigma)t} \\
&\quad + \frac{\sigma(\beta N-(\gamma-g)E(0))}{(\gamma-\sigma)(\gamma-g)}e^{-(\mu+\gamma)t} + \frac{\sigma\beta N}{(\gamma-g)(\sigma-g)}e^{-(\mu+g)t} \to 0
\end{aligned}
$$

exponentially fast as $t \to \infty$ provided that $\gamma \neq \sigma$, $g \neq \sigma$ and $g \neq \gamma$ and $g > \max(-\mu, -\sigma, -\gamma)$, which is guaranteed since $g \geq 0$, so that $R(t) = (N-(S(t)+E(t)+I(t)) \to N$ exponentially fast as $t \to \infty$. Furthermore, from (26b), $\limsup_{t\to\infty}(V(t) - \frac{\omega}{\mu}\frac{R(t)}{N}) = 1 \;\Rightarrow\; \exists \lim_{t\to\infty} V(t) = 1 + \frac{\omega}{\mu}$ since $R(t) \to N$ as $t \to \infty$. Property (i) has been proven.

(ii) Eqs. (15) together with (1)–(2) lead to:

$$
\dot{S}(t) + \dot{E}(t) = -\mu\big(S(t)+E(t)\big) + \mu N + u(t) = -(\mu+g)\big(S(t)+E(t)\big) + \mu N, \quad (33)
$$

whose solution is subject to

$$
\begin{aligned}
&S(t)+E(t) = e^{-(\mu+g)t}\left(S(0)+E(0)+\mu N\int_0^t e^{(\mu+g)\tau}\,\mathrm{d}\tau\right) \to \frac{\mu N}{\mu+g} \\
&\quad \text{as } t \to \infty
\end{aligned} \quad (34)
$$

satisfies $(I(t)+R(t)) \to \frac{gN}{\mu+g}$ as $t \to \infty$. As a result, $S(t)+E(t) \to N$ and $I(t), R(t) \to 0$ as $t \to \infty$at exponential rate if $g = 0$, that is if the vaccination law is $V(t) = \frac{1}{\mu N}(\omega R(t) - \sigma E(t))$, since the SEIR model (1)–(4) is a positive dynamic system if $g < \mu$ and $V(t) \in [0,1]\ \forall t \in \mathbb{R}_{0+}$ as it is proven in Appendix B. Then, all the partial populations are nonnegative for all time. From (2), $\exists\ \lim_{t\to\infty}(V(t) + \frac{\sigma E(t)-\omega R(t)}{\mu N}) := \frac{g}{\mu+g} < 1$. Also, $I(t) \to 0$ as $t \to \infty \;\Rightarrow\; E(t) \to 0$ as $t \to \infty$ for $g = 0$ so that $S(t) \to N$, since $I(t) \to 0$, $E(t) \to 0$ and $R(t) \to 0$ as $t \to \infty$ as $t \to \infty$ and $\lim_{t\to\infty} V(t) = 0$ from (27b) or from (27c). □

A more convenient vaccination strategy because of its properties and because of its implementation issues, based on measuring the immune and total populations instead of the susceptible one, is proposed in the subsequent result:

Theorem 3. *Assume that the control and its associated vaccination strategy are as follows*:

$$
u(t) = -gR(t) + g_1 N, \quad g > -(\mu+\omega), \quad (35)
$$

$$
V(t) = \frac{1}{\mu N}\big(g_1 N - gR(t) - \gamma I(t)\big). \quad (36)
$$

The above vaccination strategy implies that the removed-by-immunity population equalizes asymptotically the total population at exponential rate while the sum of the infected, infectious and susceptible populations converge asymptotically to zero at exponential decay rates according to:

$$R(\infty) = \frac{g_1 N}{\mu + \omega + g}, \quad S(\infty) + E(\infty) + I(\infty) = \frac{(\mu + \omega + g - g_1)N}{\mu + \omega + g}, \tag{37}$$

$$\lim_{t\to\infty} \int_0^t e^{-\mu(t-\tau)}(\omega + g)R(\tau)\,\mathrm{d}\tau = \left(\frac{g_1}{\mu} - \frac{g_1}{\mu + \omega + g}\right)N = \frac{g_1(\omega + g)}{\mu(\mu + \omega + g)}N \tag{38}$$

irrespective of the initial conditions and if, in particular, $g_1 = \mu + \omega + g$ *then*

$$R(\infty) = N, \quad S(\infty) + E(\infty) + I(\infty) = 0,$$

$$\lim_{t\to\infty} \int_0^t e^{-\mu(t-\tau)}(\omega + g)R(\tau)\,\mathrm{d}\tau = \frac{(\omega + g)N}{\mu} = \frac{(g_1 - \mu)N}{\mu}.$$

The vaccination effort is nonnegative for all time if $g_1 \geq \gamma$ *or if* $g \geq 0$ *and* $\gamma = \mu + \omega$ *provided that the SEIR model supplies nonnegative populations.*

Proof. Combining (23)–(24) yields a control action:

$$u(t) = \gamma I(t) + \mu N V(t) = -gR(t) + g_1 N \tag{39}$$

so that (4) becomes:

$$\dot{R}(t) = -(\mu + \omega)R(t) + u(t) = -(\mu + \omega + g)R(t) + g_1 N \tag{40}$$

so that if $g > -(\mu + \omega)$ then

$$R(t) \to R(\infty) := \lim_{t\to\infty} R(t) = \frac{g_1 N}{\mu + \omega + g} \quad \text{as } t \to \infty \tag{41}$$

at exponential rate according to an absolute upper-bound of exponential order of (41) being equal to $-(\mu + \omega + g) < 0$ and $S(\infty) + E(\infty) + I(\infty) = \frac{(\mu+\omega+g-g_1)N}{\mu+\omega+g}$. Also, $R(\infty) = N$ if $g_1 = \mu + \omega + g$ as a result. From Assertion 1, (41) with $g_1 = \mu + \omega + g$ implies also that $S(\infty) + E(\infty) + I(\infty) = 0$. On the other hand, the vaccination function is nonnegative from (36) for all time if $g_1 \geq \gamma$ since

$$\begin{aligned} &g_1 N - gR - \gamma I \\ &\quad = g_1(R + S + E + I) - gR - \gamma I = (g_1 - g)R + (g_1 - \gamma)I + g_1(S + E) \\ &\quad = (\mu + \omega)R + (g_1 - \gamma)I + g_1(S + E) \geq 0. \end{aligned}$$

If the constraint $g_1 \geq \gamma$ is changed to $g \geq 0$ and $\gamma = \mu + \omega$ then $g_1 - g = \gamma = \mu + \omega$, equivalently $g_1 - \gamma = g \geq 0$, and the vaccination function is also nonnegative for all time since the above expression becomes:

$$g_1 N - gR - \gamma I = (\mu + \omega)R + gI + g_1(S + E) \geq 0.$$

□

Remark 7. Note that Theorem 3 holds in particular if $g = 0$ in (35)–(36) so that the vaccination strategy is adopted on the basis of taking into account the total population only. Summing-up (1) and (2) and using (39) yields:

$$\begin{aligned}&\dot{S}(t) + \dot{E}(t)\\&\quad = -\mu\big(S(t) + E(t)\big) + \omega R(t) - \sigma E(t) + \mu N(1 - V(t))\\&\quad = -\mu\big(S(t) + E(t)\big) + (\omega + g)R(t) + \gamma I(t) - \sigma E(t) + (\mu - g_1)N\end{aligned} \tag{42}$$

which combined with (3) yields:

$$\begin{aligned}&\dot{S}(t) + \dot{E}(t) + \dot{I}(t)\\&\quad = -\mu\big(S(t) + E(t)\big) + \omega R(t) - (\mu + \gamma)I(t) + \mu N\big(1 - V(t)\big)\\&\quad = -\mu\big(S(t) + E(t) + I(t)\big) + (\omega + g)R(t) + (\mu - g_1)N\end{aligned} \tag{43}$$

leading to the following solution of susceptible plus infected plus infectious populations:

$$\begin{aligned}&S(t) + E(t) + I(t)\\&\quad = e^{-\mu t}\left(N - R(0) + \int_0^t e^{\mu\tau}\big((\omega + g)R(\tau) + (\mu - g_1)N\big)\,\mathrm{d}\tau\right) = N - R(t)\end{aligned} \tag{44}$$

after using Assertion 1so that one gets (38) from (40) as $t \to \infty$ which leads to

$$\lim_{t\to\infty} \int_0^t e^{-\mu(t-\tau)}(\omega + g)R(\tau)\,\mathrm{d}\tau = \frac{(g_1 - \mu)N}{\mu} \tag{45}$$

if $g_1 = \mu + \omega + g$ (implying that $S(\infty) = I(\infty) = R(\infty) = 0$and $R(\infty) = N$). Finally, since $R(t) \le N$ for all time and since $g_1 - g = \mu + \omega$ from (35), one gets from (36) for all time:

$$V(t) \ge 0 \;\Rightarrow\; I(t) \le \frac{(g_1 - g)N}{\gamma} = \frac{(\mu + \omega)N}{\gamma} \le \frac{g_1 N - gR(t)}{\gamma}$$

which is guaranteed for arbitrary initial conditions of (1)–(4) from Assertion 1 if $g_1 \ge \sigma$ and, in particular, if $\sigma = \mu + \omega$ and $g \ge 0$.

A further result for nonnegative vaccination being guaranteed for all time for the vaccination strategy of Theorem 3 is the following:

Corollary 2. *The vaccination strategy of Theorem* 3 *is nonnegative for all time if*

$$\min\left(1, \frac{\sigma\beta}{(\mu + \sigma)(\mu + \gamma)}\right) \ge \frac{\mu + \omega}{\gamma}.$$

Proof. Note $I(t) = \frac{\sigma E(t)}{\mu+\gamma}$ yields $\dot{I}(t) = 0$ from (3) so that a maximum or minimum of the infectious population is reached depending on the infected $E(t)$. A potential maximum is reached for $I(t) = \frac{\sigma E(t)}{\mu+\gamma}$ with $E(t) \neq 0$. Thus, $I(t) \leq I_{max} := \max(I(t)\colon t \geq 0) \leq \frac{\sigma E_{max}}{\mu+\gamma}$ where $E_{max} := \max(E(t)\colon t \geq 0)$, is reached for $\dot{E}(t) = 0$ in (2) so that $\beta \frac{S_{max} I_{max}}{N} \geq (\mu+\sigma)E_{max}$, where $S_{max} := \max(S(t)\colon t \geq 0)$. Combining the two relations yields the proof by using Assertion 1 since one has for all time:

$$I(t) \leq I_{\max} \leq \frac{\sigma E_{\max}}{\mu+\gamma} \leq \frac{\sigma\beta S_{\max} I_{\max}}{(\mu+\sigma)(\mu+\gamma)N} \leq \frac{\sigma\beta N}{(\mu+\sigma)(\mu+\gamma)}$$

$$\Rightarrow \quad I(t) \leq I_{\max} \leq \min\left(1, \frac{\sigma\beta}{(\mu+\sigma)(\mu+\gamma)}\right) N. \qquad \square$$

Remark 8. An important problem to validate the SEIR model (1)–(4) under vaccination for practical application is the design of a vaccination strategy such that the obtained model is a positive system, as the real problem it describes is, in the sense that none of the populations $S(t)$, $E(t)$, $I(t)$ and $R(t)$ becomes negative at any time. It is proven in Appendix B (Theorem B.1) that if the vaccination strategy is constrained to the real interval $[0, 1]$ for all time then none of those populations is negative for any time instant provided that all of them are nonnegative at $t = 0$. Conditions to maintain its value under the positive unit are discussed in the following.

Theorem 4. *Consider the vaccination strategy* (35)–(36) *of Theorem* 3 *subject to*:

$$g_1 = \mu + \omega + g, \quad g < 0, \ \ \mu \geq |g| - \omega + \max\big(\gamma, |g|\big) \geq \max\big(\gamma, |g|\big). \tag{46}$$

Thus, if all the partial populations of susceptible, infected, infectious and immune have nonnegative initial conditions then the vaccination function fulfills $V\colon \mathbb{R}_{0+} \to [0, 1]$ *provided that* $(|g| - \omega)$ *is sufficiently large. Also, all the values taken by any of those populations in the mathematical SEIR model are nonnegative for all time.*

Proof. Since $\mu + \omega \geq |g| + \max(\gamma, |g|)$ then $g_1 = \mu + \omega + g \geq \max(\gamma, |g|) > 0$. Thus,

$$\begin{aligned} &g_1 N - gR - \gamma I \\ &\quad = g_1 R + g_1 I + g_1(S+E) - gR - \gamma I = (g_1 - g)R + (g_1 - \gamma)I + g_1(S+E) \\ &\quad \geq \min(g_1 - g, g_1 - \gamma, g_1)(R+I+S+E) = \min\big(g_1 + |g|, g_1 - \gamma, g_1\big)N \geq 0 \end{aligned} \tag{47}$$

and $V(t) \geq 0$ for all time from (36). The third constraint of (46) implies $\omega \leq |g|$ so that $V(t) > 1$ for some time t if

$$g_1 N + |g| R(t) - \gamma I(t) > \mu N$$

that is if

$$-\big(|g| - \omega\big)N + |g| R(t) - \gamma I(t) > 0$$

what is impossible for sufficiently large $(|g| - \omega)$. Since $V\colon \mathbb{R}_{0+} \to [0, 1]$ then all the populations of the SEIR model are guaranteed to be nonnegative for all time from Theorem B.1. $\square$

5 Feedback linearization techniques in vaccination control design

The vaccination control laws proposed and analyzed in Theorems 2 and 3 can be regarded as special cases of a general design methodology called feedback linearization, [17, 18]. Feedback linearization is a general design methodology which has been successfully used in many non-linear control problems, [17–20]. The objective of this section is to frame the control laws introduced in the previous sections applied to the nonlinear epidemic model (1)–(4) into the feedback linearization formalism in order to present the rationale behind the proposed vaccination control laws, discuss some technical details concerning them and present the complete technique to be used in different epidemic models or vaccination control design. Thus, the general formalism presented, for instance, in [17,18] is applied to the nonlinear system (1)–(4). The method requires us to follow a number of steps, [18] as follows:

(i) Initially, the relative degree of the system has to be obtained.

(ii) Then, the nonlinear system (1)–(4) is to be re-written in a normal canonical form.

(iii) Next, the zero dynamics of the system are needed to be calculated and proved to be stable. This is a technical requirement on the system in order to guarantee that the control law is well-posed.

(iv) Once the zero dynamics are proved to be stable, the design of the control law is direct from the canonical normal form. These steps are developed with detail in the following sections.

5.1 Relative degree and normal canonical form

The starting point is the epidemic model given by equations (1)–(4), re-written for convenience as:

$$\dot{x}(t) = f(x,t) + h(x)V(t) \tag{48}$$

with $x(t)^{\mathrm{T}} = [S(t)\, E(t)\, I(t)\, R(t)]$, $\beta' = \beta/N$ (which is a number since N is a constant) and

$$f(x) = \begin{bmatrix} -\mu S(t) + \omega R(t) - \beta' S(t) I(t) + \mu N \\ \beta' S(t) I(t) - (\mu+\sigma) E(t) \\ -(\mu+\gamma) I(t) + \sigma E(t) \\ -(\mu+\omega) R(t) + \gamma I(t) \end{bmatrix}, \quad h(x) = \mu N \begin{bmatrix} -1 \\ 0 \\ 0 \\ 1 \end{bmatrix}. \tag{49}$$

Along with state-space system (48)–(49), we also need to consider an output $y(t)$. The choice of different outputs for the system (48)–(49) leads to different control laws. This is an important fact for this method: a collection of control laws can be generated within this frame by just selecting different outputs $y(t)$. To illustrate the nature of the method, the output is selected as:

$$y \equiv R. \tag{50}$$

The next step is to calculate the relative degree of system (48)–(50). The relative degree can be defined as the number of times the output has to be derived until the input $V(t)$ appears in the derivative.

Thus, we can now derive the output equation (50):

$$\dot{y}(t) = \dot{R}(t) = -(\mu + \omega)R(t) + \gamma I(t) + \mu NV. \tag{51}$$

It can be appreciated in Eq. (51) that the input $V(t)$ appears in the first derivative of $y(t)$. Thus, the system possesses relative degree unit since the first derivative is enough to obtain the input. Furthermore, since $\mu N \neq 0$, the relative degree of system (48)–(50) is well defined in the complete state-space. The relative degree knowledge allows us to obtain a normal form for the original system. The normal form is a change of coordinates in the state-space that will permit the design of the feedback control law. The basic objective of the coordinates transformation is to obtain a nonlinear system with the input $V(t)$ appearing in just one equation. According to [18], the first coordinate of the transformation is defined directly as the output:

$$z_1 \equiv y \equiv R \tag{52}$$

while the remaining variables, $\{z_i(t)\}_{i=2}^4$, are selected to satisfy the condition:

$$\left(\frac{\partial z_i(t)}{\partial x}\right)^{\mathrm{T}} h(x) = \mu N \frac{\partial z_i(t)}{\partial S} - \mu N \frac{\partial z_i(t)}{\partial R} = 0 \tag{53}$$

for $i = 2, 3, 4$. Equation (53) becomes:

$$\frac{\partial z_i(t)}{\partial S} = \frac{\partial z_i(t)}{\partial R} \tag{54}$$

whose solution is given by:

$$z_i(t) = \lambda\big(E(t), I(t)\big)\big(S(t) + R(t)\big), \quad i = 2, 3, 4, \tag{55}$$

where $\lambda(E, I)$ is an arbitrary differentiable function of (E, I). For the sake of simplicity, take $\lambda(E, I) = 1$, being the variable z_2 defined as:

$$z_2 \equiv S + R. \tag{56}$$

The remaining variables should be selected to satisfy Eq. (54) while being linearly independent with (56). Fortunately, the seek of linearly independent solutions to (54) is not necessary in this case since Eqs. (2) for $\dot{E}$ and (3) for $\dot{I}$ are not already directly dependent on the input, which is the objective we wanted to fulfill. Hence, it is made:

$$z_3 \equiv E, \quad z_4 \equiv I. \tag{57}$$

The coordinates transformation (52), (56), (57) defines a global diffeomorphism in the state-space since the Jacobian determinant below is nonzero:

$$\det\left(\frac{\partial(S, E, I, R)(t)}{\partial(z_1, z_2, z_3, z_4)(t)}\right) = -1 \neq 0$$

and, therefore, the transformation is well-defined. This coordinates transformation converts the original system (49)–(50) into the system in normal form:

$$\dot{z}_1(t) = -(\mu+\omega)z_1(t) + \gamma z_4(t) + \mu N V(t), \tag{58}$$

$$\dot{z}_2(t) = -\mu z_2(t) + \gamma z_4(t) - \beta'\big(z_2(t) - z_1(t)\big)z_4(t) + \mu N, \tag{59}$$

$$\dot{z}_3(t) = \beta'\big(z_2(t) - z_1(t)\big)z_4(t) - (\mu+\sigma)z_3(t), \tag{60}$$

$$\dot{z}_4(t) = -(\mu+\gamma)z_4(t) + \sigma z_3(t), \tag{61}$$

$$y(t) = z_1(t). \tag{62}$$

Notice that the input only appears in the first equation of the system (58)–(61). This fact allows the design of the vaccination control. The next step is to analyze the zero dynamics of system (58)–(62).

5.2 Zero-dynamics of the normal system

This section analyzes the zero dynamics of system (58)–(62) which corresponds to the second step in the general process. The stability of the zero dynamics is crucial to ensure the applicability and stability of the vaccination strategy. The zero-dynamics can be regarded as the nonlinear counterpart of the zeros of a linear system and they are defined based on the output zeroing problem. This problem consist in finding an input signal which renders $z_1(t) = \dot{z}_1(t) = 0$ for all $t \geq 0$. Thus, from Eq. (58), such an input is defined by $V(t) = -\frac{\gamma}{\mu N} z_4(t)$ which converts the first equation into the trivial one $0 = 0$. As far as the rest of variables, $z_2(t)$, $z_3(t)$, $z_4(t)$ are concerned, the system of Eqs. (59)–(61) becomes:

$$\dot{z}_2(t) = -\mu z_2(t) + \gamma z_4(t) - \beta' z_2(t) z_4(t) + \mu N, \tag{63}$$

$$\dot{z}_3(t) = \beta' z_2(t) z_4(t) - (\mu+\sigma)z_3(t), \tag{64}$$

$$\dot{z}_4(t) = -(\mu+\gamma)z_4(t) + \sigma z_3(t). \tag{65}$$

The set of equation (63)–(65) is said to be the *zero dynamics* of the nonlinear epidemic system (59)–(61). The stability of this set of equation is an *a priori* condition to design the control law. Thus, the following result holds:

Lemma 1. *The zero dynamics of system* (59)–(61) *are stable, and thus, all variables* $z_2(t)$*,* $z_3(t)$*,* $z_4(t)$ *are bounded for all time.*

Proof. The zero dynamics are defined by equations (63)–(65). Thus, summing up both sides of these equations:

$$\dot{N}(t) = \dot{z}_1(t) + \dot{z}_2(t) + \dot{z}_3(t) + \dot{z}_4(t) = \dot{z}_2(t) + \dot{z}_3(t) + \dot{z}_4(t) = 0 \tag{66}$$

implying that $z_2(t) + z_3(t) + z_4(t) = C$ (constant). In addition, it can be directly proved using similar arguments as those employed in Theorem B.1 that $z_i(t) \geq 0$ for $i = 2, 3, 4$ and all $t \geq 0$ (i.e. the zero-dynamics are positive). Consequently, $0 \leq z_i(t) \leq C$ for $i = 2, 3, 4$ and all $t \geq 0$ and the Lemma 1 is proved. □

In this way, the technical condition to guarantee the employment of feedback linearization control laws is satisfied and we are ready to design the vaccination strategy.

5.3 Feedback control design

The feedback control law $V(t)$ is now designed by taking Eq. (58) and designing $V(t)$ to cancel the dynamics of the right-hand terms of the equations in the form:

$$V(t) = \frac{1}{\mu N}\big((\mu+\omega)z_1(t) - \gamma z_4(t) + \eta(t)\big). \tag{67}$$

Thus, the substitution of (67) into (58) yields:

$$\dot{z}_1(t) = \eta(t)$$

since all the terms appearing in Eq. (58) disappear due to the feedback control law (67). This cancellation plays the same role as the pole-zero cancellation in linear-systems which requires the stability of the zeros. The nonlinear counterpart of the linear zeros is the zero-dynamics whose stability has been verified to be stable in Subsection 5.2 and thus, the feedback control makes the nonlinear system have no stability problems. Now, the signal $\eta(t)$ is used to govern the dynamics of $\dot{z}_1(t)$. A possible selection is:

$$\eta(t) = -g' z_1(t) + g_1 N \tag{68}$$

with $g', g_1 \geq 0$ aimed at making the immune match the total population, N. Thus, the complete control law (undoing the change of coordinates) becomes:

$$\begin{aligned} V(t) &= \frac{1}{\mu N}\big((\mu+\omega)z_1(t) - \gamma z_4(t) - g' z_1(t) + g_1 N\big) \\ &= \frac{1}{\mu N}\big((\mu+\omega-g')R(t) - \gamma I(t) + g_1 N\big) \\ &= \frac{1}{\mu N}\big(g_1 N - gR(t) - \gamma I(t)\big) \end{aligned} \tag{69}$$

which is exactly the vaccination law (36). Thus, the feedback linearization method is the analytical frame containing the presented control laws. A different choice for the output $y(t)$ would lead to different vaccination strategies. For instance, the choice $y(t) = S(t)$ would lead to the vaccination law (26), but any other choice for the output could lead to an admissible vaccination policy. Thus, the general frame can generate a family of vaccination policies by selecting different choices for the output. The complete analysis of control law (69) has been performed in Section 4. However, the introduction of the general frame allows to obtain an in-depth background of the method and provides with techniques and methods to be applied to generate families of vaccination policies not only for the SEIR but also to other types of models. It is worthwhile to note that despite being a well-known control design method for nonlinear systems, its application in epidemics has been rather limited.

6 Simulation results

This section contains some numerical examples concerning the vaccination policies introduced in Section 4 by Theorems 2 and 3. The model parameters are $\frac{1}{\mu} = 70$ years $= 25550$ days; $\beta = 1.8$ day $^{-1}$; $\frac{1}{\sigma} = \frac{1}{\gamma} = 1.75$ days; $\frac{1}{\omega} = 12$ days. The total population is $N = 10^5$ individuals while the initial values for each individual populations are given by $S(0) = 98000$, $E(0) = 1500$, $I(0) = 450$ and $R(0) = 50$. The simulation examples are split into one describing the free evolution of the system in the absence of vaccination and another one related to the vaccination policies been given by (26) and (36). Finally, the influence of the feedback gain g in the epidemic evolution is analyzed.

6.1 Epidemic evolution in the vaccination-free case

Initially, the dynamics without vaccination is considered (i.e. $V(t) = 0$). The epidemic evolution is depicted in Fig. 1.

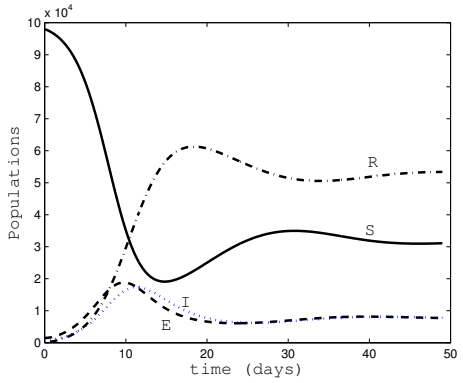

Fig. 1. Time-evolution of the populations without vaccination.

As it can be appreciated in Fig. 1, the system tends to an equilibrium point characterized by a nonzero number of infected and infectious. In particular, $E(\infty) = 7717$ and $I(\infty) = 7804$ individuals which, jointly, correspond to the 15% of the total population. Furthermore, a high percentage of susceptible, (31%), still remain in the population. This means that the illness is not naturally eradicated and a suitable control action, via vaccination, should be taken. The next sections show the application of the vaccination policies introduced in Theorem 2 (vaccination control law 1) and Theorem 3 (vaccination control law 2) and its usefulness in illness control and eradication.

6.2 Epidemic evolution with vaccination given by control law 1

The feedback control law given by Eq. (26b) in Theorem 2(i) is now applied to the system with $g = 0.15$. The results are depicted in Fig. 2.

This case is quite different from the vaccination-free one pictured in Fig. 1. Firstly, the populations of infected and infectious vanish through time instead of converging to a nonzero equilibrium point. In fact, the illness is eradicated in over 30 days. Furthermore, susceptible also converges to zero while the immune population converge to the total population as the closing relation $S(t)+E(t)+I(t)+R(t) = S(0)+E(0)+I(0)+R(0) = N$ for all t implies. This property is shown in Fig. 3 where the convergence of the immune population to the total one is depicted.

Fig. 4 shows the time evolution of the vaccination effort $\mu NV(t)$ applied via Eq. (26b) as vaccination policy. As expected, the vaccination effort increases at the beginning of the illness spreading. In conclusion, the presented vaccination law is capable of eradicating the illness.

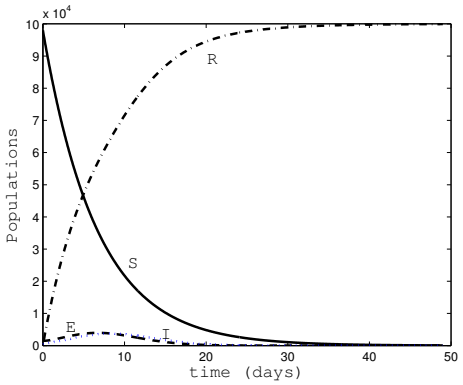

Fig. 2. Time evolution of the populations when vaccination policy (26) is applied with $g = 0.15$.

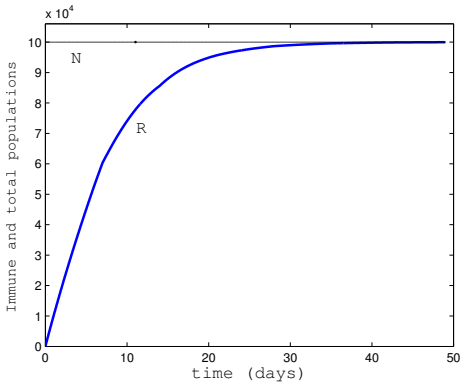

Fig. 3. Convergence of the immune population to the total population.

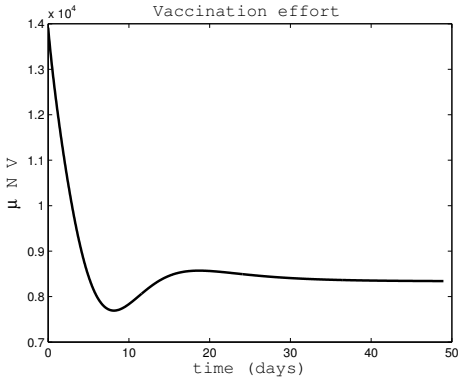

Fig. 4. Time evolution of the vaccination effort.

6.3 Epidemic evolution with vaccination given by control law 2

The vaccination policy given by Eq. (36) can be applied as an alternative to the vaccination law described by equation (26). The following Fig. 5 shows the evolution of the population when vaccination (36) is applied with $g = 0.15$ and $g_1 = \mu + \omega + g$:

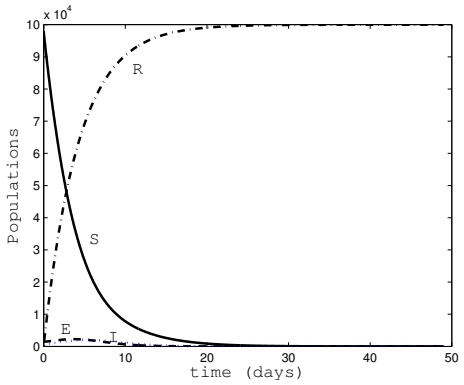

Fig. 5. Time evolution of the populations under the vaccination policy (36) with $g = 0.15$ and $g_1 = \mu + \omega + g$.

As before, the vaccination law is able to eradicate the illness in, approximately, 30 days. The vaccination effort related to this control law is pictured in Fig. 6.

Comparing Figs. 4 and 6 it can be appreciated that the vaccination effort is larger when vaccination policy (36) is applied than when vaccination policy (26) is. However, Fig. 7 points out that the extra vaccination effort required by Eq. (36) is inverted in making the immune to reach the total population in a faster way.

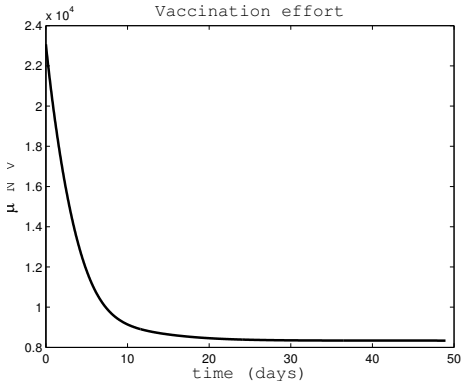

Fig. 6. Vaccination effort corresponding to the control law given by Eq. (36).

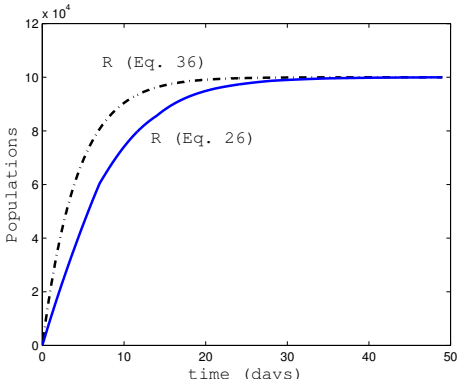

Fig. 7. Immune convergence to the total population for both vaccination laws.

6.4 Influence of the feedback gain g in the convergence rate of the immune to the total population

The influence of the g-gain of the vaccination controller in the convergence rate of the immune to the total population is studied for control law 1. Fig. 8 shows the time evolution of the immune versus the feedback gain, g.

As Fig. 8 shows, the larger gain g is, the faster the immune tends the total population. However, the price it has to be paid to achieve such a fast convergence rate is the increase in the vaccination effort, as depicted in Fig. 9. Thus, Fig. 9 shows that the vaccination enlarges as the convergence rate increases.

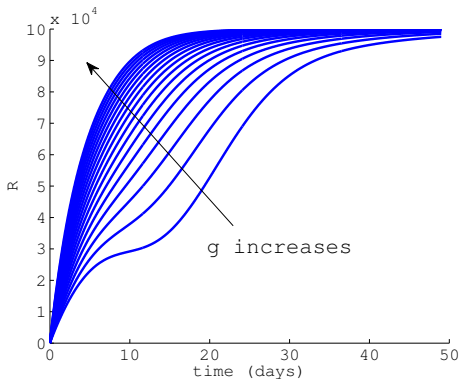

Fig. 8. Convergence rate variation due to changes in the gain g.

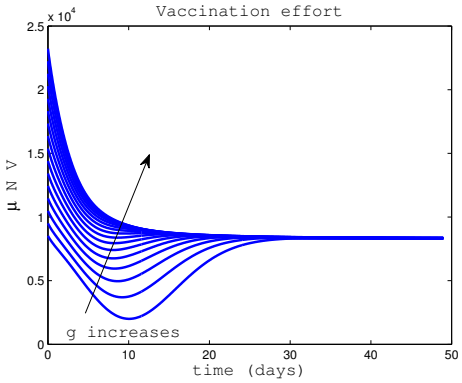

Fig. 9. Vaccination effort variation due to changes in the gain g.

The same evidence is found when the vaccination control law 2 is applied. In general, a larger feedback gain implies a faster convergence to the total population which is related with a higher vaccination effort. Thus, simulation examples have corroborated the usefulness of the designed control laws in the illness control and eradication.

7 Interpretation of some elementary relations between basic reproduction number, disease transmission constant, disease-free equilibrium point and initial infectious population rate

It is found in Theorem A.1 (which is stated and proven in Appendix A) that the basic reproduction number R_0 characterizing the disease propagation is defined by $R_0 := \frac{\sigma\beta}{(\mu+\sigma)^2}$ for $\sigma = \gamma$ in the vaccination-free case, i.e. when $V \equiv 0$. That means that if $R_0 < 1$ the disease-free equilibrium point $x_1^* = (N, 0, 0, 0)^{\mathrm{T}}$ is locally stable and the disease can be removed for a small number of initial infectious population even without using vaccination efforts. Contrarily if $R_0 > 1$, such a point is locally unstable and the disease-free can propagate reaching the endemic equilibrium point if no vaccination action is made. If the vaccination is constant equal to one; i.e. $V \equiv 1$ a similar consideration

to that of the Appendix A for the disease-free equilibrium point concludes that the new disease-free equilibrium point will be $x_1^* = (\frac{\omega N}{\mu+\omega}, 0, 0, \frac{\mu N}{\mu+\omega})^{\mathrm{T}}$. The interpretation is that the disease-free equilibrium point populations are split into the susceptible population and the removed-by-immunity one. The proposed vaccination laws of this paper using control tools to generate the vaccination function lead to a globally asymptotically stable disease-free equilibrium point $x_1^* = (0, 0, 0, N)^{\mathrm{T}}$ where all the population becomes asymptotically to be removed-by-immunity. This is a consequence of the global stabilization procedure associated with the proposed vaccination methods which ensure at the same time the positivity of the model. We emphasize again that the positivity leads automatically to the global stability property since all the partial populations are non-negative, as the real situation dictates, while the total population is constant. This implies that no partial population can result to be unbounded through time. In particular, it can be found that $R_0 < 1$ is equivalent to the constraint $\beta < \frac{(\mu+\sigma)^2}{\sigma}$ for $\sigma = \gamma$ what damps the infection avoiding its propagation. However, $\beta > \frac{(\mu+\sigma)^2}{\sigma}$ leads to the infection propagation. It is not difficult to find that if $\sigma \neq \gamma$ then the respective above conditions become, respectively, $\beta < \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma}$ (i.e. the disease becomes damped) and $\beta > \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma}$ (i.e. the disease propagates). The reproduction number for the case $\sigma \neq \gamma$ is found to be $R_0 := \frac{\sigma\beta}{(\mu+\gamma)(\mu+\sigma)}$. It is now seen that the above conditions taken from the eigenvalues of the linearized system about the disease-free equilibrium have a parallel physical interpretation from the model equations as follows in terms of the first-time derivative of the infectious population being negative for the reproduction number being less than one and, respectively, positive for such a number exceeding one at $t = 0$. In this context, note from Eqs. (2)–(3) that:

$$\dot{E}(0) = 0 \;\Rightarrow\; \frac{E(0)}{I(0)} = \beta \frac{S(0)}{(\mu+\sigma)N}, \tag{70}$$

$$\frac{\dot{I}(0)}{I(0)} = -(\mu+\gamma) + \sigma\frac{E(0)}{I(0)} = -(\mu+\gamma) + \frac{\sigma\beta}{\mu+\sigma}\frac{S(0)}{N}. \tag{71}$$

If $S(0) = N - \varepsilon$ (almost all the population is susceptible at $t = 0$) and $I(0) = \varepsilon$ for a small $\varepsilon > 0$ then $\dot{I}(0) = -(\mu+\gamma)I(0) + \frac{\sigma\beta I(0)}{\mu+\sigma}(1 - \varepsilon/N)$ so that $\dot{I}(0)/I(0) \cong -(\mu+\gamma) + \frac{\sigma\beta}{\mu+\sigma} < 0$ if $\beta < \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma}$, equivalently, if $R_0 < 1$ and $\dot{I}(0)/I(0) \cong -(\mu+\gamma) + \frac{\sigma\beta}{\mu+\sigma} > 0$, since $0 < \varepsilon << N$, if $\beta > \frac{(\mu+\gamma)(\mu+\sigma)}{\sigma}$, equivalently, if $R_0 > 1$.

8 Concluding remarks and potential related future work

This paper has considered a SEIR true-mass action type of epidemic model. The main objective of the manuscript has been the design and analysis of feedback vaccination control laws based on the partial populations so that the removed-by-immunity population be able to track the whole population which is assumed to be constant. The positivity of the model has been discussed so that the stability can be guaranteed in the sense that there is uniform boundedness through time of all the partial populations which is guaranteed from the positivity of the solution and the boundedness of the total population. The disease-free and endemic equilibrium points and the stability properties are also discussed

in the Appendices as well as the relation of the stability with the value of the basic reproduction number. We agree that if all are susceptible then there is no infection. In case of infective illnesses with no associate mortality, that situation is asymptotically reached with no vaccination effort. However, such a situation normally describes the starting infective process of a new potential infective cycle. There is no infection if either the total population equalizes the sum of the susceptible plus the removed-by-immunity populations or if the total population becomes removed-by-immunity. In fact, any of the three objectives could be the vaccination control objective expressed in terms of tracking the total population. It seems that if the whole population becomes removed-by-immunity, a certain prevention against the disease can be achieved for a new potential real next disease cycle in some cases. All the three asymptotic tracking control objectives implying the removal of the disease could be mutually compared in a future related research to elucidate for which of them the infection might be practically removed with the achievement of sufficiently small numbers of infected plus infectious populations in a shorter time period.

A Appendix. Equilibrium points and their stability properties

A.1 Equilibrium points of the uncontrolled system

Assume for discussion simplicity of the equilibrium points that in the SEIR model (1)–(4). The equilibrium points $x^* = (S^*, E^*, I^*, R^*)^{\mathrm{T}}$ of (1)–(4) under identically zero vaccination strategy satisfy the set of constraints:

$$\mu S^* - \omega R^* + \beta \frac{S^* I^*}{N} = \mu N, \tag{A.1}$$

$$\beta \frac{S^* I^*}{N} = (\mu + \sigma) E^*, \tag{A.2}$$

$$(\mu + \sigma) I^* = \sigma E^*, \tag{A.3}$$

$$(\mu + \omega) R^* = \sigma I^*. \tag{A.4}$$

An equilibrium point is $x_1^* = (N, 0, 0, 0)^{\mathrm{T}}$. Another one is calculated as follows:

The combination of (A.2)–(A.3) yields:

$$\beta \frac{S^* I^*}{N} = \frac{(\mu + \sigma)^2 I^*}{\sigma} \;\Rightarrow\; S^* = \frac{(\mu + \sigma)^2}{\sigma \beta} N \quad \text{if } I^* \neq 0. \tag{A.5}$$

This constraint can be explored to obtain a new equilibrium point if $\frac{(\mu+\sigma)^2}{\sigma\beta} \leq 1$ guaranteeing the necessary model constraint $S^* \leq N$ from Assertion 1. If $\frac{(\mu+\sigma)^2}{\sigma\beta} \geq 1$ then the only equilibrium point is x_1^* since $\frac{(\mu+\sigma)^2}{\sigma\beta} = 1 \Rightarrow S^* = N$. Thus, assume that $\frac{(\mu+\sigma)^2}{\sigma\beta} < 1$ and (A.5) holds. Then one gets from (A.1) and (A.4) that:

$$\left[\frac{(\mu + \sigma)^2 (\mu + \omega)}{\sigma^2} - \omega \right] R^* = \mu N \left(1 - \frac{(\mu + \sigma)^2}{\sigma \beta} \right) \tag{A.6}$$

provided that $\mu > 0$ implying that $\frac{(\mu+\sigma)^2(\mu+\omega)}{\sigma^2} > \omega$. If $\mu = 0$ implying that $\frac{(\mu+\sigma)^2(\mu+\omega)}{\sigma^2} = \omega$ then the equilibrium points are x_1^* and $x_{20}^* = (\frac{\sigma N}{\beta}, \frac{(\beta-\sigma)\omega N}{\beta(2\omega+\sigma)}, \frac{(\beta-\sigma)\omega N}{\beta(2\omega+\sigma)}, \frac{(\beta-\sigma)\sigma N}{\beta(2\omega+\sigma)})^{\mathrm{T}}$. Eq. (A.6) is equivalent to

$$R^* = \frac{\sigma(\sigma\beta - (\mu+\sigma)^2)}{\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}N \tag{A.7}$$

for $\mu > 0$ which implies $R^* \geq 0$ if $\frac{(\mu+\sigma)^2}{\sigma\beta} \leq 1$. From (A.4) and (A.7), one gets if $\sigma \neq 0$ that

$$I^* = \frac{\mu+\omega}{\sigma}R^* = \frac{(\mu+\omega)(\sigma\beta - (\mu+\sigma)^2)}{\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))^N}. \tag{A.8}$$

Now, combining (A.3) and (A.8) yields:

$$E^* = \left(1 + \frac{\mu}{\sigma}\right)I^* = \frac{(\mu+\omega)(\mu+\sigma)}{\sigma^2}R^* = \frac{(\mu+\omega)(\mu+\sigma)(\sigma\beta - (\mu+\sigma)^2)}{\sigma\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}N. \tag{A.9}$$

Thus,

$$\begin{aligned} x_2^* = \Bigg(& \frac{(\mu+\sigma)^2}{\sigma\beta}N,\ \frac{(\mu+\omega)(\mu+\sigma)(\sigma\beta - (\mu+\sigma)^2)}{\sigma\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}N, \\ & \frac{(\mu+\omega)(\sigma\beta - (\mu+\sigma)^2)}{\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}N,\ \frac{\sigma(\sigma\beta - (\mu+\sigma)^2)}{\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}N\Bigg)^{\mathrm{T}} \end{aligned} \tag{A.10}$$

is an equilibrium point of (1)–(4) provided that none of its components exceeds N and $\frac{(\mu+\sigma)^2}{\sigma\beta} < 1$ holds, that is if

$$\frac{\sigma\beta - (\mu+\sigma)^2}{\beta((\mu+\sigma)^2 + \omega(\mu+2\sigma))}\max\left(\sigma, \left(1 + \frac{\mu}{\sigma}\right)(\mu+\omega)\right) \leq 1. \tag{A.11}$$

Remark A.1. Note that $\frac{(\mu+\sigma)^2}{\sigma\beta} = 1$ then an equilibrium point $x_{21}^* = x_1^*$ exists as a particular case of (A.10). Also, $(N, 0, 0, 0)^{\mathrm{T}}$ is a disease-free equilibrium point if $\mu = 0$ and $\beta = \sigma$ and x_{20}^* is an equilibrium point if $\mu = 0$ and $\sigma < \beta$ both being particular cases of (A.10). Note also that both constraints of (A.11) are guaranteed in particular for sufficiently small positive parameters $\sigma = \gamma$ and μ after fixing ω, β.

A.2 Stability of the linearized model about the equilibrium points

The linearized model (1)–(4) about its equilibrium points is:

$$\begin{bmatrix} \Delta\dot{S}(t) \\ \Delta\dot{E}(t) \\ \Delta\dot{I}(t) \\ \Delta\dot{R}(t) \end{bmatrix} = \begin{bmatrix} -\mu - \beta\frac{I^*}{N} & 0 & -\beta\frac{S^*}{N} & \omega \\ \beta\frac{I^*}{N} & -(\mu+\sigma) & \beta\frac{S^*}{N} & 0 \\ 0 & \sigma & -(\mu+\sigma) & 0 \\ 0 & 0 & \sigma & -(\mu+\omega) \end{bmatrix} \begin{bmatrix} \Delta S(t) \\ \Delta E(t) \\ \Delta I(t) \\ \Delta R(t) \end{bmatrix}. \tag{A.12}$$

At the equilibrium point x_1^*, the linearized system (A.12) becomes:

$$\begin{bmatrix} \Delta\dot{S}(t) \\ \Delta\dot{E}(t) \\ \Delta\dot{I}(t) \\ \Delta\dot{R}(t) \end{bmatrix} = \begin{bmatrix} -\mu & 0 & -\beta & \omega \\ 0 & -(\mu+\sigma) & \beta & 0 \\ 0 & \sigma & -(\mu+\sigma) & 0 \\ 0 & 0 & \sigma & -(\mu+\omega) \end{bmatrix} \begin{bmatrix} \Delta S(t) \\ \Delta E(t) \\ \Delta I(t) \\ \Delta R(t) \end{bmatrix} \tag{A.13}$$

whose characteristic equation is

$$\begin{aligned} p(s) &= (s+\mu)\left[(s+\mu+\omega)(s+\mu+\sigma)^2 + \beta \det\left(\begin{bmatrix} -\sigma & 0 \\ 0 & s+\mu+\omega \end{bmatrix}\right)\right] \\ &= (s+\mu)(s+\mu+\omega)\big((s+\mu+\sigma)^2 - \sigma\beta\big) = 0. \end{aligned}$$

The characteristic zeros are $-\mu$, $-(\mu+\omega)$ and $-(\mu+\sigma\pm\sqrt{\sigma\beta})$. As a result, the disease-free equilibrium point x_1^* of (A.13) is locally asymptotically Lyapunov stable if $\mu > 0$, $\omega > -\mu$ and $0 \le \beta < \frac{(\mu+\sigma)^2}{\sigma}$. Define the basic reproduction number as $R_0 := \frac{\sigma\beta}{(\mu+\sigma)^2}$. If such a number is less than one, then the equilibrium point $x_1^*$is locally stable since all the eigenvalues of the matrix of dynamics of the linearized system in (A.13) are negative. If it exceeds one then the equilibrium point x_1^* is locally unstable. For the equilibrium point x_2^*, the linearized system (A.12) has a characteristic equation

$$\begin{aligned} p(s) &= \left(s+\mu+\beta\frac{I^*}{N}\right)\det\left(\begin{bmatrix} s+\mu+\sigma & -\beta\frac{S^*}{N} & 0 \\ -\sigma & s+\mu+\sigma & 0 \\ 0 & -\sigma & s+\mu+\omega \end{bmatrix}\right) \\ &\quad + \omega\det\left(\begin{bmatrix} -\beta\frac{I^*}{N} & s+\mu+\sigma & -\beta\frac{S^*}{N} \\ 0 & -\sigma & s+\mu+\sigma \\ 0 & 0 & -\sigma \end{bmatrix}\right) + \beta^2\sigma(s+\mu+\omega)\frac{S^*I^*}{N^2} \\ &= \left(s+\mu+\beta\frac{I^*}{N}\right)(s+\mu+\omega)\left((s+\mu+\sigma)^2 - \beta\sigma\frac{S^*}{N}\right) \\ &\quad + \beta^2\sigma(s+\mu+\omega)\frac{S^*I^*}{N^2} - \beta\omega\sigma^2\frac{I^*}{N} \\ &= p_0(s) + \beta\tilde{p}(s) = p_0(s)\left(1 + \frac{\beta\tilde{p}(s)}{p_0(s)}\right) = 0 \end{aligned} \tag{A.14}$$

where

$$\begin{aligned} p_0(s) &:= (s+\mu)(s+\mu+\sigma)^2(s+\mu+\omega), \\ \tilde{p}(s) &:= \frac{I^*}{N}\big((s+\mu+\sigma)^2(s+\mu+\omega) - \omega\sigma^2\big) - \sigma\frac{S^*}{N}(s+\mu)(s+\mu+\omega) \end{aligned} \tag{A.15}$$

evaluated at (A.10). From the root locus technique in (A.14), the zeros of $p(s)$ converge to those of $p_0(s)$, namely, $s=-\mu$, $s=-(\mu+\sigma)$ (double), $s=-(\mu+\omega)$ as $\beta\to 0$. As a result, the eigenvalues of the linearized system (A.12) about x_2^* are all stable from the continuity of the root locus for $|\beta|$ not exceeding some sufficiently small threshold value for any

given values of the remaining parameters of (1)–(4). Equivalently, that property holds if

$$\left\| \frac{\tilde{p}(s)}{p_0(s)} \right\|_\infty := \max_{\omega \in \mathbb{R}_{0+}} \left| \frac{\tilde{p}(i\omega)}{p_0(i\omega)} \right| < \frac{1}{\beta}$$

where $\|.\|_\infty$ is the RH_∞-norm of strictly stable transfer functions and $i = \sqrt{-1}$ is the complex unit. This follows since $p_0(s)$ being a Hurwitz polynomial implies that $p(s)$ is Hurwitz if $|\beta\tilde{p}(i\omega)| < |p_0(i\omega)| \; \forall \; \omega \in \mathbb{R}_{0+}$ from Rouché theorem of number of zeros within a closed set applied to the complex half-plane $\operatorname{Re} s < 0$. Note that the global Lyapunov stability is automatically guaranteed for the SEIR model (1)–(4) since the total population is assumed to be constant for all time. The summarized local stability result around the equilibrium points is as follows:

Theorem A.1. *The vaccination-free SEIR model* (1)–(4) *is locally stable about* x_1^* *in the vaccination-free case if the basic reproduction number satisfies* $R_0 := \frac{\sigma\beta}{(\mu+\sigma)^2} < 1$*, that is if the transmission constant is small enough satisfying* $\beta < \frac{(\mu+\sigma)^2}{\sigma}$ *provided that* $\gamma = \sigma$*. Contrarily,* x_1^* *is locally unstable and the disease propagates in the vaccination-free case if the transmission constant is large enough satisfying* $\beta > \frac{(\mu+\sigma)^2}{\sigma}$ *so that* $R_0 > 1$*. The vaccination-free SEIR model* (1)–(4) *is locally stable about* x_2^* *if* $\|\frac{\tilde{p}(s)}{p_0(s)}\|_\infty < \frac{1}{\beta}$.

B Appendix. Positive solutions of the SEIR model (1)–(4)

The following result holds:

Theorem B.1 (Positivity)**.** *Assume the SEIR model* (1)–(4) *with* $N = N(0) = S(0) + E(0) + I(0) + R(0) > 0$ *and* $\min(S(0), E(0), I(0), R(0)) \geq 0$ *under any vaccination strategy* $V\colon \mathbb{R}_{0+} \to [0, 1]$*. Then,* $\min(S(t), E(t), I(t), R(t)) \geq 0 \; \forall t \in \mathbb{R}_{0+}$.

Proof. Let eventually exist finite time instants $t_S, t_E, t_I, t_R \in \mathbb{R}_{0+}$ with $t^* := \min(t_S, t_E, t_I, t_R)$ be such that:

if $t^* = t_S$ then $S(t_S) = 0$, $\min(S(t), E(t), I(t), R(t)) \geq 0 \; \forall t \in [0, t_S]$;
if $t^* = t_E$ then $E(t_E) = 0$, $\min(S(t), E(t), I(t), R(t)) \geq 0 \; \forall t \in [0, t_E]$;
if $t^* = t_I$ then $I(t_I) = 0$, $\min(S(t), E(t), I(t), R(t)) \geq 0 \; \forall t \in [0, t_I]$;
if $t^* = t_R$ then $R(t_R) = 0$, $\min(S(t), E(t), I(t), R(t)) \geq 0 \; \forall t \in [0, t_R]$.

Note that either t^* does not exist or it is the first eventual finite time instant where some of the partial populations of the SEIR model reaches a zero value and can be coincident with at most three of its arguments since the total population being N is incompatible with the four partial populations being zero. The remaining of the proof is split into four parts as follows:

1. Proceed by contradiction by assuming that there exists a finite $t^* = t_S \geq 0$ such that $S(t) \geq 0 \; \forall t \in [0, t_S)$, $S(t_S) = 0$ and $S(t_S^+) < 0$, meaning with abbreviate notation that $S(t) < 0 \; \forall t \in (t_S + \varepsilon_1, t_S + \varepsilon_1 + \varepsilon_2)$, with $\min(E(t), I(t), R(t)) \geq 0$ $\forall t \in [0, t_S]$. Thus, $\dot{S}(t_S) = \omega R(t_S) + \mu N(1 - V(t_S)) \geq 0$ from (1) since $V(t) \in [0, 1] \; \forall t \in \mathbb{R}_{0+}$. Since $S(t_S) = 0$ and $\dot{S}(t_S) \geq 0$ then $S(t_S^+) \geq 0$, meaning

with abbreviate notation that $S(t) > 0\ \forall t \in (t_S + \varepsilon_1, t_S + \varepsilon_1 + \varepsilon_2)$, since the solution of the SEIR model (1)–(4) is continuous for all time, contradicting the assumption $S(t_S^+) < 0$ so that such a time instant $t^* = t_S \geq 0$ does not exist.

2. Proceed by contradiction by assuming that there exists a finite $t^* = t_E \geq 0$ such that $E(t) \geq 0\ \forall t \in [0, t_E)$, $E(t_E) = 0$ and $E(t_E^+) < 0$ with $\min(S(t), I(t), R(t)) \geq 0\ \forall t \in [0, t_E]$. Thus, $\dot{E}(t_E) = \frac{\beta S(t_E) I(t_E)}{N} \geq 0$ from (2) $\forall t \in \mathbb{R}_{0+}$. Since $E(t_E) = 0$ and $\dot{E}(t_E) \geq 0$ then $E(t_E^+) \geq 0$, since the solution of the SEIR model (1)–(4) is continuous for all time, contradicting the assumption $E(t_E^+) < 0$ so that such a $t^* = t_E \geq 0$ does not exist.

3. Proceed by contradiction by assuming that there exists a finite $t^* = t_I \geq 0$ such that $I(t) \geq 0\ \forall t \in [0, t_I)$, $I(t_I) = 0$ and $I(t_I^+) < 0$ with $\min(S(t), E(t), R(t)) \geq 0\ \forall t \in [0, t_I]$. Thus, $\dot{I}(t_I) = \sigma E(t_I) \geq 0$ from (3) $\forall t \in \mathbb{R}_{0+}$. Since $I(t_I) = 0$ and $\dot{I}(t_I) \geq 0$ then $I(t_I^+) \geq 0$, since the solution of the SEIR model (1)–(4) is continuous for all time, contradicting the assumption $I(t_I^+) < 0$ so that such a $t^* = t_I \geq 0$ does not exist.

4. Proceed by contradiction by assuming that there exists a finite $t^* = t_R \geq 0$ such that $R(t) \geq 0\ \forall t \in [0, t_R)$, $R(t_R) = 0$ and $R(t_R^+) < 0$ with $\min(S(t), E(t), I(t)) \geq 0\ \forall t \in [0, t_R]$. Thus, $\dot{R}(t_R) = \gamma I(t_R) + \mu N V(t_R) \geq 0$ from (4) since $V(t) \in [0, 1]\ \forall t \in \mathbb{R}_{0+}$. Since $R(t_R) = 0$ and $\dot{R}(t_R) \geq 0$ then $R(t_R^+) \geq 0$, since the solution of the SEIR model (1)–(4) is continuous for all time, contradicting the assumption $R(t_R^+) < 0$ so that such a time instant $t^* = t_R \geq 0$ does not exist.

If such a finite time instant t^* does not exist then the above result follows directly. As a result, $\min(S(0), E(0), I(0), R(0)) \geq 0 \ \Rightarrow\ \min(S(t), E(t), I(t), R(t)) \geq 0\ \forall t \in \mathbb{R}_{0+}$ since there is no time instant $t^* \geq 0$ for which any of the four partial populations reaches a zero value with its first time-derivative being simultaneously negative at such a time instant.

The stability is directly guaranteed from Theorem B.1 as follows:

Theorem B.2 (Stability)**.** *If Theorem* B.1 *holds then all the partial populations are uniformly bounded through time for any vaccination law fulfilling the positivity constraint.*

Proof. It is direct since the total population is constant and finite and all the partial populations are non-negative so they are uniformly bounded for all time. □

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References

1. M. De la Sen, S. Alonso-Quesada, A Control theory point of view on Beverton–Holt equation in population dynamics and some of its generalizations, *Appl. Math. Comput.*, **199**(2), pp. 464–481, 2008.
2. M. De la Sen, S. Alonso-Quesada, Control issues for the Beverton–Holt equation in population in ecology by locally monitoring the environment carrying capacity: Non-adaptive and adaptive cases, *Appl. Math. Comput.*, **215**(7), pp. 2616–2633, 2009.
3. M. De la Sen, S. Alonso-Quesada, Model-matching-based control of the Beverton–Holt equation in ecology, *Discrete Dyn. Nat. Soc.*, **2008**, Article ID 793512, 2008, doi:10.1155/2008/793512.
4. M. De la Sen, About the properties of a modified generalized Beveron–Holt equation in ecology models, *Discrete Dyn. Nat. Soc.*, **2008**, Article ID 592950, 2008, doi:10.1155/2008/592950.
5. M. De la Sen, The generalized Beverton–Holt equation and the control of populations, *Appl. Math. Model.*, **32**(11), pp. 2312–2328, 2008.
6. D. Mollison (Ed.), *Epidemic Models: Their Structure and Relation to Data*, Publications of the Newton Institute, Cambridge Univ. Press, 2003.
7. M.J. Keeling, P. Rohani, *Modeling Infectious Diseases in Humans and Animals*, Princeton Univ. Press, Princeton, NJ, 2008.
8. A. Yildirim, Y. Cherruault, Analytical approximate solution of a SIR epidemic model with constant vaccination strategy by homotopy perturbation method, *Kybernetes*, **38**(9), pp. 1566–1575, 2009.
9. V.S. Erturk, S. Momani, Solutions to the problem of prey and predator and the epidemic model via differential transform method, *Kybernetes*, **37**(8), pp. 1180–1188, 2008.
10. N. Ortega, L.C. Barros, E. Massad, Fuzzy gradual rules in epidemiology, *Kybernetes*, **32**(3–4), pp. 460–477, 2003.
11. H. Khan, R.N. Mohapatra, K. Varajvelu, S.J. Liao, The explicit series solution of SIR and SIS epidemic models, *Appl. Math. Comput.*, **215**(2), pp. 653–669, 2009.
12. X.Y. Song, Y. Jiang, H.M. Wei, Analysis of a saturation incidence SVEIRS epidemic model with pulse and two time delays, *Appl. Math. Comput.*, **214**(2), pp. 381–390, 2009.
13. T.L. Zhang, J.L. Liu, Z.D. Teng, Dynamic behaviour for a nonautonomous SIRS epidemic model with distributed delays, *Appl. Math. Comput.*, **214**(2), pp. 624–631, 2009.
14. B. Mukhopadhyay, R. Bhattacharyya, Existence of epidemic waves in a disease transmission model with two-habitat population, *Int. J. Syst. Sci.*, **38**(9), pp. 699–707, 2007.
15. M. De la Sen, On excitable dynamic systems with delays, *Kybernetes*, **38**(9), pp. 1576–1598, 2009.
16. M. De la Sen, On positivity of singular regular linear time-delay time-invariant systems subject to multiple internal and external incommensurate point delays, *Appl. Math. Comput.*, **190**(1), pp. 382–401, 2007.

17. S. Sastry, *Nonlinear Systems: Analysis, Stability and Control*, Springer-Verlag, 1999.

18. A. Isidori, *Nonlinear Control Systems*, 3rd edition, Springer-Verlag, 2001.

19. E. De Tuglie, S.M. Iannone, F. Torelli, Feedback-linearization and feedback-feedforward decentralized control for multipower system, *Electric Pow. Sys. Res.*, **78**(3), pp. 382–391, 2008.

20. K. Shojaei, A.M. Shahri, A. Tarakameh, Adaptive feedback linearizing control of nonholonomic wheeled mobile robots in presence of parametric and nonparametric uncertainties, *Robotics and Computer-Integrated Manufacturing*, **27**(1), pp. 194–204, 2011.

21. M. De la Sen, R.P. Agarwal, A. Ibeas, S. Alonso-Quesada, On a generalized time-varying SEIR epidemic model with mixed point and distributed time-varying delays and combined regular and impulsive controls, *Adv. Differ. Equ.*, **2010**, Article ID 281612, 2010, doi:10.1155/2010/281612.

22. M. De la Sen, S. Alonso-Quesada, On vaccination controls tools for a general SEIR epidemic model, in: *Proceedings of the 18th Mediterranean Conference on Control and Automation*, **1**, pp. 1322–1328, 2010, doi:10.1109/MED.2010.5547865.

23. M. De la Sen, R.P. Agarwal, A. Ibeas, S. Alonso-Quesada, On the existence of equilibrium points, boundedness, oscillating behavior and positivity of a SVEIRS epidemic model under constant and impulsive vaccination, *Adv. Differ. Equ.*, **2011**, Article ID 748608, 2011, doi:10.1155/2011/748608.

24. M. De la Sen, S. Alonso-Quesada, A. Ibeas, An observer-based vaccination law for a SEIR epidemic model, in: *Proceedings of International Conference on Database and Data Mining (ICDDM 2011)*, Vol. 1, pp. 1–5, 2011.

25. R. Naresh, S. Pandey, A.K. Misra, Analysis of a vaccination model for carrier dependent infectious diseases with environmental effects, *Nonlinear Anal. Model. Control*, **13**(3), pp. 331–350, 2008.

26. G.P. Samanta, Analysis of a delay nonautonomous predator-prey system with disease in the prey, *Nonlinear Anal. Model. Control*, **15**(1), pp. 97–108, 2010.

27. S. Pathak, A. Maiti, G.P. Samanta, Rich dynamics on an SIOR epidemic model, *Nonlinear Anal. Model. Control*, **15**(1), pp. 71–81, 2010.

28. A.K. Pal, G.P. Samanta, Stability analysis of an eco-epidemiological model incorporating a prey refuge, *Nonlinear Anal. Model. Control*, **15**(4), pp. 473–491, 2010.

29. B. Buonomo, D. Lacitignola, On the backward bifurcation of a vaccination model with nonlinear incidence, *Nonlinear Anal. Model. Control*, **16**(1), pp. 30–46, 2011.