A SEIR Epidemic Model with Infectious Population Measurement

M. De la Sen, S. Alonso-Quesada and A. Ibeas

***Abstract*- This paper is devoted to the design of a vaccination strategy for a SEIR model with incomplete knowledge about the populations. The design is oriented towards the measurement and use of the infectious population in the design of the vaccination rule with the eventual incorporation of an observer to deal with uncertain model state knowledge. The observer is not necessarily parameterized with the exact known parameters of the epidemic model.**

***Keywords*- Epidemic models, SEIR epidemic model, Observer, Vaccination**

I. INTRODUCTION

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. 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 follows: a) SI- models where not removed- by – immunity population is assumed. In other words, only susceptible and infected populations are assumed,.b) SIR models, which include susceptible plus infected plus removed- by –immunity populations, c)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 : constant [8], impulsive [12], discrete – time etc., incorporating point or distributed delays [12-13], oscillatory behaviours [14-18] etc. . On the other hand, variants of such models become considerably simpler for the illness transmission among plants [6-7]. It is assumed that SEIR – model is of the true-mass action type.

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M. De la Sen and S. Alonso-Quesada are with the Institute of Research and Development of Processes, Campus of Leioa , Bizkaia , Aptdo. 644-Bilbao. Spain (e-mail: manuel.delasen@ehu.es). A. Ibeas is with Escola Tecnica Superior dç Enginyeria, Universitat Autonoma de Barcelona, Cerdanyola del Valles, Barcelona, Spain(e-mail: Asier.Ibeasu@ab.cat).

II .THE 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 true-mass action SEIR-type epidemic model:

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

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

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

$$\dot{R}(t)=-(\mu+\omega)R(t)+\gamma(1-\rho)I(t)+\nu N(t)V(t) \quad (4)$$

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 $V:\boldsymbol{R}_{0+}\to\boldsymbol{R}_{0+}$. In the above SEIR – model, N is the total population, μ is the rate of deaths from causes unrelated to the infection, $\rho\in[0,1]$ takes into account the number of deaths due to the infection, ω is the rate of losing immunity, β is the transmission constant (with the total number of infections per unity of time at time t being $\beta\frac{S(t)I(t)}{N(t)}$), σ^{-1} and γ^{-1} are, respectively, the average durations of the latent and infective periods. If $\nu=\mu$ then neither the natural increase of the population nor the loss of maternal lost of immunity of the newborns is taken into account. If $\nu>\mu$ such a lost of immunity is considered. All the above parameters are nonnegative. Note the following:

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a) $\sigma > 0$ since, otherwise, the average duration of the latent period is infinity and the infectious are unrelated to the infected from (3)

b) $\gamma > 0$ since, otherwise, the average duration of the infectious period is infinity and the whole immune population is not dynamically coupled to the infectious one.

c) If $\mu = 0$ then the mortality by causes unrelated to the disease is not taken into account. If $\nu = \mu$ then neither the loss of maternal immunity of the newborns nor the natural increase of the population are considered. If $\rho = 0$ then it is assumed that there is no mortality directly caused by the disease.

d) It is nonsense to eventually fix to zero the disease transmission constant β since this would decouple the infected dynamics from the susceptible one.

e) Some particular modelling variants (so- called pseudo mass-action type models) fix to unity the whole population N(t) in (1)- (4). This modelling strategy does not consider that the disease transmission of few susceptible and infected among large population numbers moderates the disease evolution as the SEIR- model (1)-(4) (so called mass action – type models) does. The mass action models are based of the mass action principle from Chemical kinetics following Guldberg and Waage (1864) which reads as follows: *"For a homogeneous system, the rate of the chemical reaction is proportional to the active masses of the reacting substances"* , [15].

The total population is $N(t) = S(t) + E(t) + I(t) + R(t)$; $\forall t \in \boldsymbol{R}_{0+}$. By summing up both sides of (1)-(4), one gets:

$$\dot{N}(t) = (\nu - \mu) N(t) - \rho \gamma I(t) \qquad (5)$$

If $\rho = \nu - \mu = 0$ then the population is considered to remain constant through time; i.e. $N(t) = N(0)$; $\forall t \in \boldsymbol{R}_{0+}$ so that:

$$\dot{S}(t) + \dot{E}(t) + \dot{I}(t) + \dot{R}(t) = \dot{S}(0) + \dot{E}(0) + \dot{I}(0) + \dot{R}(0) = 0$$

$\forall t \in \boldsymbol{R}_{0+}$ .The next result establishes that if the infection collapses after a finite time then the whole susceptible plus immune populations converge asymptotically to the whole population even in the event that this one has not a finite limit.

Assertion 1. Assume that $I(t) = \dot{I}(t) = 0; \forall t \geq t_0$. Then, $E(t) = \dot{E}(t) = 0$; $\forall t \geq t_0$ and $S(t) + R(t) \to N(t) \to 0$ as $t \to \infty$ and $N(t)$ is uniformly bounded for all time if $\mu > \nu$. If furthermore $\nu = \mu$ then $\lim_{t \to \infty} (S(t) + R(t)) = N = N(t_0)$. If $\gamma \rho = 0$ then, irrespective of the initial conditions, the overall population is constant if $\nu = \mu$, the overall population diverges if $\nu > \mu$ and the overall population asymptotically converges to zero if $\nu < \mu$.

Proof: It follows that $E(t) = \dot{E}(t) = 0$; $\forall t \geq t_0$ for some finite t_0 from (3) and (2) so that one gets from (1) and (4):

$$\dot{S}(t_0) + \dot{R}(t_0) = -\mu (S(t_0) + R(t_0)) + \nu N(t_0)$$

$$\Rightarrow S(t) + R(t) =$$

$$e^{-\mu(t-t_0)} (S(t_0) + R(t_0)) + \nu \int_{t_0}^{t} e^{-\mu(t-\tau)} N(\tau) d\tau$$

$$\to \nu \int_{t_0}^{t} e^{-\mu(t-\tau)} N(\tau) d\tau \quad (\text{as } t \to \infty)$$

$$= \nu \int_{t_0}^{t} e^{-\mu(t-\tau)} e^{(\nu-\mu)(\tau - t_0)} N(t_0) d\tau$$

$$\to N(t) = e^{-(\mu-\nu)(t-t_0) - g_0} N(t_0) \text{ as } t \to \infty$$

so that, if $\mu > \nu$, then

$S(t) + R(t) \to N(t) \to 0$ as $t \to \infty$ and $N(t)$ is uniformly bounded for all time since it is a continuous function which is the unique time-differentiable solution of an ordinary differential equation which cannot possess finite escape times.

$S(t) + R(t) \to N(t) \to N(t_0)$ as $t \to \infty$ if $\mu = \nu$ and $N(t)$ is uniformly bounded for all time

$S(t) + R(t) \to N(t) \to \infty$ as $t \to \infty$ if $\nu > \mu$

If, in addition, $\gamma \rho = 0$ then $\dot{N}(t) = (\nu - \mu) N(t)$ and the overall population is constant if $\nu = \mu$ diverges if $\nu > \mu$ and converges to zero if $\nu < \mu$ irrespective of the initial conditions. □

The following result extend Assertion 1 to the case when I (t) vanishes asymptotically.

Assertion 2. Assume that $I(t) = \dot{I}(t) \to 0$ as $t \to \infty$. If $\sigma > 0$ then, $E(t) \to 0$ and $S(t) + R(t) \to N(t)$ as $t \to \infty$.

Proof: The solution of (3) satisfies

$$I(t) = e^{-(\mu+\gamma)t} I(0) + \sigma \int_0^t e^{-(\mu+\gamma)(t-\tau)} E(\tau) d\tau$$

$$\geq \sigma \int_0^t e^{-(\mu+\gamma)(t-\tau)} E(\tau) d\tau \; ; \; t \geq 0$$

Proceed by contradiction by assuming that the claim $E(t) \to 0$ as $t \to \infty$ is false. Then, since E(t) is everywhere continuous in $\boldsymbol{R}_{0+}$ because it satisfies the differential equation (2), one has that for any given $t \geq 0$, there exist some real constants $\varepsilon = \varepsilon(t) > 0$, $\delta = \delta(\varepsilon, t) > 0$, $T_1 = T_1(\varepsilon, t) > 0$ and $T_2 = T_2(\varepsilon, \delta, t) \geq T_1 + \delta$ such that $E(t) \geq \varepsilon$; $\forall \tau \in [t + T_1, t + T_2)$ for the given $t \geq 0$ so that:

$$I(t + T_2) \geq \sigma \int_{t+T_1}^{t+T_2} e^{-(\mu+\gamma)(t+T_2-\tau)} E(\tau) d\tau$$

$$= \sigma \int_0^{T_2 - T_1} e^{-(\mu+\gamma)(T_2 - T_1 - \tau)} E(t + \tau + T_1) d\tau$$

$$\geq m(t, \varepsilon, T_1, T_2) := \frac{\sigma \varepsilon}{\mu + \gamma} \left(1 - e^{-(\mu+\gamma)(T_2 - T_1)}\right) > 0$$

which contradicts $I(t) \to 0$ as $t \to \infty$ from Assertion 1 so that $E(t) \to 0$ as $t \to \infty$,since $S(t) + R(t) \to N(t)$ as $t \to \infty$, from Assertion 1. □

It has been proven in previous papers (see, for instance, [16]) that the vaccination control law has to take values in $[0, 1]$ for all time in order to ensure that the SEIR – model (1)-(4) is a positive dynamic system in the sense that for any set of nonnegative initial conditions all the components of the trajectory solution of (1) – (4) are nonnegative for all time. This has to be accomplished with for coherency of the mathematical problem with the real problem at hand. On the other hand, it is assumed that the whole set of parameters parameterizing the SEIR – model (1) –(4) is not known then

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they should be estimated online to synthesize the vaccination law $V: \boldsymbol{R}_{0+} \to [0,1]$ based on those estimations. Assertions 1-2 dictate that if the infection collapses in some way then the whole population of susceptible plus immune asymptotically converge to the whole population even if that one has not a finite limit as time tends to infinity. This feature motivates fixing the adaptive control objective as to synthesize a vaccination law such that the infectious population is asymptotically regulated to zero to achieve the sum of the susceptible plus the immune asymptotically track the whole population as a result.

III. STABILITY AND POSITIVITY RESULTS

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 at any time. This requirement follows directly from the nature of the problem at hand. This section investigates conditions for positivity of the SEIR model (1)-(4). First , assume the constant population constraint (5) with $\nu = \mu$, $\rho = 0$ implying directly:

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

is used in (1), (3)-(4) to eliminate the infected population E(t) leading to:

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

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

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

for any given real constant $\alpha \geq (\beta/N)\sup_{t\geq 0}(I(t))$. It is possible to rewrite (7)-(9) in a compact form as a dynamic system of state $x(t) = (S(t), I(t), R(t))^T$, output $y(t) = S(t) + R(t)$ and whose input is appropriately related to the vaccination function as $u(t) = (1 - V(t), V(t))^T$. This leads to:

$$\dot{x}(t) = \bar{A}(\alpha)x(t) + \mu N \bar{E}_{13} u(t)$$

$$+ \left(\left(\alpha - \beta\frac{I(t)}{N} \right) E_1 x(t) + \sigma N e_2 \right) \tag{10.a}$$

$$= A(\alpha)x(t) + \mu N \bar{E}_{13} u(t) +$$

$$+ \left(\left[\left(\alpha - \beta\frac{I(t)}{N} \right) E_1 - \sigma E_{13} \right] x(t) + \sigma N e_2 \right) \tag{10.b}$$

$$= A(\alpha)x(t) + \mu N \bar{E}_{13} u(t)$$

$$+ \left(\left(\alpha - \beta\frac{I(t)}{N} \right) E_1 x(t) + \sigma (N - y(t)) e_2 \right) \tag{10.c}$$

$$= A(\alpha)x(t) + \mu N e_3 V(t)$$

$$+ \left(\left(\alpha - \beta\frac{I(t)}{N} \right) E_1 x(t) + \sigma (N - y(t)) e_2 + \mu N e_1 (1 - V(t)) \right) \tag{10.d}$$

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

where e_i is the i-th unit Euclidean column vector in $\boldsymbol{R}^3$ 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 $e_{13}^T = (1, 0, 1)$, and

$$\bar{A}(\alpha) := A(\alpha) - \sigma E_{13}$$

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

$$E_{13} := \begin{bmatrix} 0^T \\ e_{13}^T \\ 0^T \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix} \ ; \qquad \bar{E}_{13} := [e_1, e_3] = \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{bmatrix}$$

$$E_1 := \begin{bmatrix} e_1^T \\ 0^T \\ 0^T \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{13}$$

Simple inspection of (10)-(13) yields the following positivity result by taking into account that $E(t) \geq 0$ if the reduced system (7)-(9) is positive by direct calculation of the solution of (2) for $0 \leq \nu \leq \mu$, $\rho\gamma \geq 0$:

Theorem 1. Assume that $min(\omega, \gamma, \sigma, \alpha - \beta) \geq 0$ and that a vaccination function $V \in PC^{(0)}(R_{0+}, [0,1])$ is used. Then, all the solutions of the SEIR model (1)-(4) satisfy $S(t), E(t), I(t), R(t) \in [0, N]$; $\forall t \in \boldsymbol{R}_{0+}$ if $\gamma\rho = 0$ and $\nu = \mu \geq 0$ or if $0 \leq \nu < \mu$ and $\gamma\rho \geq 0$. Furthermore, either $N(t), S(t), E(t), I(t), R(t) \to 0$ as $t \to \infty$ (i.e. the total population asymptotically extinguishes) with all the populations being uniformly bounded or all the partial and total populations are bounded and the infection does not asymptotically vanishes in the second cased with $0 \leq \nu < \mu$ and $\gamma\rho > 0$.

Proof: Note that matrix A in (12) is a Metzler under the given constraints. Then, the dynamic system (10) is positive with $N(t) = N(0) = N = S(0) + E(0) + I(0) + R(0)$; $\forall t \in \boldsymbol{R}_{0+}$ if $\gamma\rho = 0$ and $\nu = \mu \geq 0$ or if $0 \leq \nu < \mu$ and $\gamma\rho \geq 0$. Then, $0 \leq \max(S(t) + E(t) + I(t)) < \infty$; $\forall t \in \boldsymbol{R}_{0+}$. Now, from (4), $R(t) \in \boldsymbol{R}_{0+}$; $\forall t \in \boldsymbol{R}_{0+}$. This implies $S(t), E(t), I(t), R(t) \in [0, N]$; $\forall t \in \boldsymbol{R}_{0+}$ since $N = N(0) = S(t) + E(t) + I(t) + R(t)$; $\forall t \in \boldsymbol{R}_{0+}$. If $0 \leq \nu < \mu$ and $\gamma\rho \geq 0$ then $\dot{N}(t) \leq 0$ and the proof remains valid with the changes $N(t) = S(t) + E(t) + I(t) + R(t)$, $\forall t \in \boldsymbol{R}_{0+}$ and $S(t), E(t), I(t), R(t) \in [0, N(t)]$; $\forall t \in \boldsymbol{R}_{0+}$. The last part is proven by contradiction. Assume that $I(t) > 0$; $\forall t \in \boldsymbol{R}_{0+}$ with $0 \leq \nu < \mu$ and $\gamma\rho > 0$. Then $\dot{N}(t) \leq -\gamma\rho I(t) < 0$; $\forall t \in \boldsymbol{R}_{0+}$ if $I(t) > 0$ so that $N(t), S(t), E(t), R(t) \to 0$ as $t \to \infty$ with (12) being a positive system since $R(t) \in \boldsymbol{R}_{0+}$. Then $I(t) \to 0$ as

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$t \to \infty$ (since $N(t), S(t), E(t), R(t) \to 0$ as $t \to \infty$) contradicting the assumption that $I(t) > 0$; $\forall t \in \boldsymbol{R}_{0+}$. □

Remark 1. The positivity property is an essential tool to discuss the stability of the SEIR- model since all the partial populations are upper-bounded by the total population N(t) for all time. It is also essential for appropriate description of the real problem through the mathematical model. □

Corollary 1. Assume that $\nu \leq \mu$. Then, the SEIR-model (1)-(4) is stable.

Proof: $\dot{N}(t) \leq 0$; $\forall t \in \boldsymbol{R}_{0+}$ from (5) so that N(t) is monotone decreasing then it is uniformly bounded $N(t) \leq N(0)$; $\forall t \in \boldsymbol{R}_{0+}$. □

Define indicator binary functions $i_{-+}: \boldsymbol{R}_{0+} \to [0,1]$ defined as $i_+(t) := 1 - i_-(t) = \begin{cases} 1 & if \quad \dot{N}(t) > 0 \\ 0 & otherwise \end{cases}$ and $i_-(t) = \begin{cases} 1 & if \quad \dot{N}(t) \leq 0 \\ 0 & otherwise \end{cases}$.

Thus, Corollary 1 extends directly as follows:

Corollary 2. Assume that $\limsup_{t \to \infty} \int_0^t \left(\left| \dot{N}(\tau) \right| i_-(\tau) - \dot{N}(\tau)\, i_+(\tau) \right) d\tau < \infty$. Then, the SEIR-model (1)-(4) is stable. □

IV. VACCINATION RULES

An useful vaccination control function is one with the goal of decreasing appropriately the numbers of susceptible, infected and infectious while including the nonlinear term involving the product S(t)I(t) of susceptible and infectious in (1) . One has to cope with two major practical problems, namely:

1. The parameters of the SEIR model (1)-(4) are not usually known precisely even if the model is considered valid for a particular study.
2. The only populations being directly measurable with a certain accuracy degree for any time are the total population N (t) and the infectious one I (t). For the remaining populations what it can be said is that $S(t) + E(t) + R(t) = N(t) - I(t)$ at any time. It could be calculated from the differential system (1)-(4) in the case that the model parameters and the initial conditions are fully known. Otherwise, they could be estimated from parameter and initial condition estimated.

The general SEIR- model (1)-(4) may be compacted as the following dynamic system of state $\boldsymbol{x}(t) := (S(t), E(t), I(t), R(t))^T$ and measurable output being the infectious population , i.e. $\boldsymbol{y}(t) := I(t)$:

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \boldsymbol{\omega}(t) \quad ; \quad \boldsymbol{y}(t) = \boldsymbol{e}_3^T \boldsymbol{x}(t) \tag{14}$$

where

$$\boldsymbol{e}_3 := (0,0,1,0)^T$$

$$\boldsymbol{\omega}(t) := \left(\nu N(t)(1 - V(t)) - \beta \frac{S(t)I(t)}{N(t)},\ \beta \frac{S(t)I(t)}{N(t)}, 0,\ \nu N(t) V(t) \right)^T \tag{15}$$

and

$$\boldsymbol{A} := \begin{bmatrix} -\mu & 0 & 0 & \omega \\ 0 & -(\mu + \sigma) & 0 & 0 \\ 0 & \sigma & -(\mu + \gamma) & 0 \\ 0 & 0 & \gamma(1-\rho) & -(\mu + \omega) \end{bmatrix} \tag{16}$$

Using the time-derivative operator $D := d/dt$ in (14) , it may be more compactly rewritten as

$$\boldsymbol{x}(t) = (D\boldsymbol{I} - \boldsymbol{A})^{-1} \boldsymbol{\omega}(t)$$
$$\boldsymbol{y}(t) = I(t) = e_3^T \boldsymbol{x}(t) = e_3^T (D\boldsymbol{I} - \boldsymbol{A})^{-1} \boldsymbol{\omega}(t) \tag{17}$$

subject to $\boldsymbol{x}(0) := (S(0), E(0), I(0), R(0))^T$ with $\boldsymbol{I}$ being the 4×4 identity matrix. Since

$$e_3^T (D\boldsymbol{I} - \boldsymbol{A})^{-1} \boldsymbol{\omega}(t) = \frac{e_3^T Adj(D\boldsymbol{I} - \boldsymbol{A}) \boldsymbol{\omega}(t)}{Det(D\boldsymbol{I} - \boldsymbol{A})} = \frac{N_{I0}(D,t)}{M_0(D)}$$
; $\forall t \in R_{\boldsymbol{0}+}$ (18)

then

$$I(t) = \frac{e_3^T Adj(D\boldsymbol{I} - \boldsymbol{A})\, \boldsymbol{\omega}(t)}{Det(DI - \boldsymbol{A})} =$$
$$\frac{1}{Det(DI - \boldsymbol{A})} \left(\sum_{i=1}^{4} (Adj(D\boldsymbol{I} - \boldsymbol{A}))_{3i}\ \boldsymbol{\omega}_i(t) \right)$$
$$= \frac{1}{Det(DI - \boldsymbol{A})}$$
$$\left(\sum_{i=1}^{4} (Adj(D\boldsymbol{I} - \boldsymbol{A}))_3 \left(-\beta \frac{S(t)I(t)}{N(t)} + \nu N(t)(1 - V(t)),\ \beta \frac{S(t)I(t)}{N(t)},\ 0,\ \nu N(t) V(t) \right)^T \right) \tag{19}$$

with

$$M_0(D) := Det(D\boldsymbol{I} - \boldsymbol{A})$$
$$= (D + \mu)(D + \mu + \sigma)(D + \mu + \gamma)(D + \mu + \omega)$$

Since the calculation of the adjoint matrix involves matrix transposition then the third column of $(D\boldsymbol{I} - \boldsymbol{A})$ has to be checked in view of (19) as follows;(a) the (3,1) transpose, i.e. the (1,3)- adjoint determinant of $(D\boldsymbol{I} - \boldsymbol{A})$ is zero by inspecting (16); (b) the (2,3) adjoint determinant of $(D\boldsymbol{I} - \boldsymbol{A})$ is $\sigma(D + \mu)(D + \mu + \omega)$ and (c) the (4,3) – adjoint determinant is zero. The (3,3) adjoint has not to be calculated since $\boldsymbol{\omega}_3(t) = 0$ for all time. Thus, one gets from (19):

$$M_0(D) I(t) = N_{I0}(D) \left(\frac{S(t) I(t)}{N(t)} \right);\ \forall t \in R_{0+} \tag{20}$$

where $N_{I0}(D) = \beta\sigma(D + \mu)(D + \mu + \omega)$

Since $\frac{N_{I0}(D)}{M_0(D)} = \frac{N_I(D)}{M(D)} := \frac{\sigma\beta}{(D + \mu + \sigma)(D + \mu + \gamma)}$ after removing the stable polynomial cancellation $(D + \mu)(D + \mu + \omega)$, Eq. 20 is equivalent to

$$M(D)(I(t) - v_I(x(0), t)) = N_I(D) \left(\frac{S(t) I(t)}{N(t)} \right) \tag{21}$$

where $v_I(t) = c_{1I} e^{-\mu t} + c_{2I} e^{-(\mu + \omega)t}$ is a real function which takes into account the contribution to the solution of (21) from nonzero initial conditions of (20) which has been

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neglected by the zero-pole cancellation $\frac{N_{I0}(D)}{M_0(D)} = \frac{N_I(D)}{M(D)}$ which vanishes exponentially as $t \to \infty$ with $c_{iI} = c_{iI}(x(0))$ for i=1,2 being two real constants subject to $c_{1I} + c_{2I} = v_I(0)$ (i =1,2).

The vaccination control below is nonnegative for all time if it belongs to the interval $[0,1]$ for all time

$$V(t) = \frac{1}{\hat{\mu} N}\left(k_1 \hat{S}(t) + k_3 \hat{I}(t) + k_4 \hat{R}(t) + k_5 \hat{S}(t)\hat{I}(t) + g N\right) \tag{22}$$

The above hat superscripts on the various populations denote their estimates through some available observer in the case when the population amounts are not perfectly known. The following vaccination nonnegative control combined of (9) and (22) may be used when the positivity of the observer and the saturation of the vaccination to unity are not imposed:

$$V(t) = \begin{cases} \bar{V}(t) & \text{if} \quad 1 \geq \bar{V}(t) \geq 0 \\ \frac{1}{\hat{\mu} N}\left(k_1 \hat{S}(t) + k_4 \hat{R}(t) + k_5 \hat{S}(t)\hat{I}(t) + g N\right) & \text{, otherwise} \end{cases} \tag{23}$$

$$\bar{V}(t) := \frac{1}{\hat{\mu} N}\left(k_1 \hat{S}(t) + k_2 \hat{E}(t) + k_3 \hat{I}(t) + k_4 \hat{R}(t) + k_5 \hat{S}(t)\hat{I}(t) + g N\right) \tag{24}$$

Simulations results about the above vaccination laws are in progress and seem to be promising. It seems to be, in general, promising the potential application of some control theory techniques, [17-21] to epidemic models to design the vaccination rules.

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