2021 60th IEEE Conference on Decision and Control (CDC)
December 13-15, 2021. Austin, Texas

Generalized epidemiological compartmental models: guaranteed bounds via optimal control

Franco Blanchini [a], Paolo Bolzern [b], Patrizio Colaneri [b], Giuseppe De Nicolao [c], Giulia Giordano [d]

***Abstract*—We consider a class of epidemiological models in which a compartmental linear system, including various categories of infected individuals (e.g. asymptomatic, symptomatic, quarantined), is fed back by a positive feedback, representing contagion. The positive feedback gain decreases (in a sort of negative feedback) as the epidemic evolves, due to the decrease in the number of susceptible individuals. We first propose a convergence result based on a special copositive Lyapunov function. Then, we address a major problem for this class of systems: the deep uncertainty affecting parameter values. We face the problem adopting techniques from optimal and robust control theory to assess the sensitivity of the model. For this class of systems, the optimal control solution has a peculiar decoupling property that no shooting procedure is required. Finally, we exploit the obtained bounds to assess the effectiveness of possible epidemic control strategies, including intermittent restrictions adopted during the COVID-19 pandemic.**

I. Introduction

We consider a general class of epidemiological models that include a compartmental linear system, representing several infection stages within a population, fed back by the dynamics of the susceptible individuals $S(t)$. This general class includes, besides the standard SIR (Susceptible, Infected, Recovered) model [14], several epidemiological models that describe the spread of infectious diseases [5], [8], [9], [11], [13], [17], [24]. Epidemiological models have been studied with a control perspective for a long time [2], [26], [25], [20], [19], [21], [10], [15], [27], [28], [6] and have been intensively reconsidered after the outburst of the COVID-19 pandemic [3], [11], [16], [23], [18], which has evidenced their importance to understand, predict and control epidemics; a comprehensive survey is proposed in [1]. In our setup, the infection spread is modeled as a linear positive system whose state variables correspond to different categories of infected (e.g., diagnosed and quarantined, non-diagnosed, asymptomatic, pauci-symptomatic, symptomatic) as well as recovered and deceased, which is fed back by a term representing contagion, i.e., the flow of newly infected people caused by contacts between susceptible and infected individuals. A major problem, when applying these models to real situations, is the deep uncertainty affecting parameter values. It has been shown [11] that the sensitivity of different parameters varies a lot. Typically, the pandemic evolution is extremely sensitive to the contagion parameters, which directly influence the growth of the infected population and can be altered to control the epidemic evolution by introducing suitable restrictions and non-pharmaceutical interventions, while it is less sensitive to parameters describing the transitions among different categories of infected.

We prove that both the sensitivity analysis and the control of these epidemiological models can be solved via the same technique: the optimal control of a compartmental system. We show that mid-term predictions, sensitivity analysis and containment plans under uncertainties can be tackled with the same approach and the solution can be effectively achieved by exploiting the special system structure. Our contributions can be summarized as follows.

- We consider general SIR-like models, whose parameters are uncertain, but bounded within given intervals.
- We analyze the class of models and we give a general formula for the reproduction number R_0, which turns out to be the H_∞ norm (equal to the L_1 norm in this case) of the linear part of the system.
- We show how to compute lower and upper bounds for the uncertain system evolution.
- We show that the same methodology can be adopted when considering an optimal control problem aimed at minimizing a linear integral cost with final weight.
- We prove that the computation does not require the shooting approach (often necessary to implement optimal control), if we can rely on a reasonable mid-term prediction of the susceptible population evolution.
- We show that the technique can be adopted to robustly compute periodic open-close mitigation strategies.

II. Class of models

Consider the class of systems described by

$$\dot{x}(t) = F(p)x(t) + S(t)bc(v)^\top x(t) \quad (1)$$

$$\dot{S}(t) = -S(t)c(v)^\top x(t) \quad (2)$$

with $x(t) \in \mathbb{R}^n$, $S(t) \in \mathbb{R}$. We assume that the parameter sets $\mathcal{P}$ and $\mathcal{V}$ have the hyper-rectangular form

$$\mathcal{P} = \{p : 0 < p^- \leq p \leq p^+\}, \quad (3)$$

$$\mathcal{V} = \{v : 0 < v^- \leq v \leq v^+\}, \quad (4)$$

[a] Dipartimento di Matematica, Informatica e Fisica, Università degli Studi di Udine, Udine, Italy. blanchini@uniud.it
[b] Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milano Italy. {paolo.bolzern,patrizio.colaneri}@polimi.it
[c] Department of Computer and System Science, Università degli Studi di Pavia. giuseppe.denicolao@unipv.it
[d] Department of Industrial Engineering, University of Trento, Italy. giulia.giordano@unitn.it

and $F(p)$ is a Metzler matrix, decomposable as the sum of rank-one matrices (BDC-decomposition [7], [12]):

$$F(p) = \sum_{k=1}^{m} f_k g_k^\top \ p_k, \tag{5}$$

where f_k and g_k are vectors in $\mathbb{R}^n$. Henceforth, $>$ and $<$, used with vectors, denote the component-wise strict inequalities.

System (1)–(2) generalizes epidemiological model such as [11]. Variable $S(t)$ corresponds to the fraction of susceptible individuals, vector $x(t)$ corresponds to infected individuals at various disease stages (e.g. asymptomatic, diagnosed, hospitalized, recovered) and the term $S(t)bc(v)^\top x(t)$ accounts for contagion; typically, $b = [1\,0\ldots 0]^\top$. The entries of v are the contagion parameters, while the parameter p is associated with transition flows among different infection stages. Note that $F(p)$ is a generic Metzler matrix, not necessarily a compartmental matrix[1].

Assumption 1. *Vector $c(v)$ is nonnegative and linear in the parameters. Vector $c(v)$ is a linear increasing function of its parameters v_k: $\mathbf{0} < c(v^-) \leq c(v) \leq c(v^+)$. Vector b and vectors g_k are nonnegative, while matrix $F(p)$ is Hurwitz for all parameter values. Matrix $F(p) + Sbc(v)^\top$ is irreducible for all positive values of S.*

Checking the Hurwitz property of $F(p)$ is easy based on its decomposition (5).

Proposition 1. *Matrix $F(p)$ is Hurwitz if and only if (a) $F(\hat{p})$ is Hurwitz for an arbitrary positive parameter vector $\hat{p}$ and (b) $\det[-F(\hat{p})] > 0$ for all parameter vectors $\hat{p}$ taken on the vertices $\hat{\mathcal{P}} = \{\hat{p} : \hat{p}_k \in \{p_k^-, p_k^+\},\ \forall k = 1,\ldots,m\}$.*

Proof: Condition (b) is equivalent to $\det[-F(p)] > 0$ for all $p \in \mathcal{P}$ [12]. This condition is clearly necessary because $\det[-F(p)]$ is the constant term of the characteristic polynomial. Hence (a) and (b) are necessary. Conversely, assume that (a) holds and that $F(\tilde{p})$ is not Hurwitz, with $\tilde{p}$ strictly positive. Take $p(\alpha) = \hat{p}(1-\alpha) + \tilde{p}\alpha$, $\alpha \in [0,1]$. Since $F(\hat{p})$ is Metzler and has a real dominant eigenvalue, there must be some α^* in the interval for which $F(p(\alpha^*))$ has a zero eigenvalue, hence $\det[-F(p(\alpha^*))] = 0$, in contradiction with non-singularity in (b). ∎

In the sequel we will consider parameter vectors p and v that are time-varying in $\mathcal{P}$ and $\mathcal{V}$, respectively. In this case, we need to assume robust stability of the open loop system $\dot{x} = F(p(t))x$. A sufficient condition is given by the existence of a common copositive Lyapunov function $q^\top x$.

Assumption 2. *There exists a vector $q > 0$, with $q^\top b > 0$, such that $q^\top F(p)x \leq 0$ for all $p \in \mathcal{P}$ and all $x > 0$.*

Remark 1. *If one of such vectors q has the form $q^\top = \mathbf{1}^\top = [1\ 1\ \ldots\ 1]$, $F(p)$ is a compartmental matrix.*

The next proposition holds

[1]A compartmental is a Metzler matrix with negative diagonal elements and column diagonally dominant

Proposition 2. *Assumption 2 implies boundedness (even with time-varying parameters) of the overall nonlinear system (1)-(2).*

Proof: It is enough to take $V(x,S) = q^\top x + (q^\top b)S$ and compute its Lyapunov derivative $\dot{V} = q^\top F(p)x + q^\top bSc(v)^\top(p)x + q^\top b\dot{S} = q^\top F(p)x \leq 0$. ∎

Example 1. *Consider a simple infection model with three compartments: susceptible $S(t)$, asymptomatic infected $x_1(t)$, symptomatic infected $x_2(t)$, hospitalized $x_3(t)$. The compartmental matrix $F(p)$ and vectors b and $c(v)$ are*

$$F(\alpha,\beta,\gamma,\delta) = \begin{bmatrix} -\alpha & 0 & 0 \\ \alpha & -(\beta+\gamma) & 0 \\ 0 & \beta & -\delta \end{bmatrix}$$

$$b = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}^\top,\ c(\varphi,\mu,\nu)^\top = \begin{bmatrix} \varphi & \mu & \nu \end{bmatrix}.$$

The contagion parameters are φ, μ, ν, while α, β, γ, δ are internal "flow" parameters. Closing the loop, we get

$$\dot{x}(t) = (F(p) + bS(t)c(v)^\top)x(t) \tag{6}$$

Vector q required in Assumption 2 is $q = \mathbf{1}$. Note that $q^\top F(p)x$ is not strictly negative: for $x = [1\ 0\ 0]^\top$, $\dot{V} = 0$. Still, in this case convergence to zero is ensured since there are no trajectories included in the subspace generated by $x = [1\ 0\ 0]^\top$ if $\alpha \neq 0$.

III. General properties of the model

Define the parametric reproduction number $\mathcal{R}_0(p,v)$ as the H_∞ norm of the positive system $(F(p), b, c(v)^\top)$ [11], which for positive systems is equal to the L_1 norm:

$$\mathcal{R}_0(p,v) = -c(v)^\top F(p)^{-1} b. \tag{7}$$

Then, the stability of any equilibrium with susceptible population $\bar{S}$ is equivalent to

$$\mathcal{R}_0(p,v)\bar{S} < 1.$$

Example 2. *For Example 1, the parametric reproduction number is $\mathcal{R}_0(p,v) = \frac{\varphi}{\alpha} + \frac{\mu}{\beta+\gamma} + \frac{\nu\beta}{\delta(\beta+\gamma)}$.*

For the nonlinear system, the following properties hold.

Theorem 1. *If $p(t) = \bar{p}$ and $v(t) = \bar{v}$, for $t \geq \bar{t}$, then*

$$\begin{aligned} &\log\frac{S(\bar{t})}{S(t)} - \mathcal{R}_0(\bar{p},\bar{v})(S(\bar{t}) - S(t)) \\ = \ & c(\bar{v})^\top F(\bar{p})^{-1}(x(t) - x(\bar{t})), \quad t \geq \bar{t} \end{aligned} \tag{8}$$

$$\lim_{t\to\infty} x(t) = 0 \tag{9}$$

$$\lim_{t\to\infty} S(t) = \bar{S} < \frac{1}{\mathcal{R}_0(\bar{p},\bar{v})} \tag{10}$$

Proof: Equation (8) results from integrating $\dot{x} = Fx - b\dot{S}$ and taking into account that $\dot{S}/S = -c(\bar{v})^\top x$. Take now $\bar{S}$ as the only point $S > 0$ satisfying (8) with $x(\infty) = 0$

$$\log\frac{S(\bar{t})}{\bar{S}} - \mathcal{R}_0(\bar{p},\bar{v})(S(\bar{t}) - \bar{S}) = -c(\bar{v})^\top F(\bar{p})^{-1}x(\bar{t}) > 0$$

The left hand side tends to ∞ for $\bar{S} \to 0$ and is 0 for $\bar{S} = S(\bar{t})$. Moreover, its derivative w.r.t. $\bar{S}$ is $\mathcal{R}_0 - 1/\bar{S}$. The only equilibrium point is such that $\bar{S} < 1/\mathcal{R}_0$ and $S(\bar{t}) - \bar{S} \geq 0$. Moreover, take $\bar{q} > 0$ such that $\bar{q}^\top F(\bar{p}) \doteq -\bar{r} < 0$ and set

$$V(x, S) = \bar{q}^\top x + \bar{q}^\top b(S - \bar{S}) \tag{11}$$

It follows that

$$\begin{aligned} \dot{V}(x,S) &= \bar{q}^\top [F(p) + \bar{q}^\top b S(t) c(\bar{v})^\top] x + \bar{q}^\top b \dot{S} = \\ &- \bar{r}^\top x + (\bar{q}^\top b - \bar{q}^\top b) S c(\bar{v})^\top x = -\bar{r}^\top x < 0 \end{aligned}$$

for $x \neq 0$. This justifies claims (9), (10). ∎

Remark 2. *The Lyapunov function* (11) *provides an interesting interpretation. The variables x_i can be increasing; however, if we consider their sum weighted by the components of vector q, the increase of this quantity is compensated by the decreasing susceptible variable $S(t)$. For a compartmental matrix $F(p)$, we can take $q = \mathbf{1}$ and, if $b = [1\ 0\ \dots\ 0]^\top$ (x_1 associated with the earliest infection stage), $(S(t) - \bar{S}) + \sum_k x_k(t)$ is always decreasing.*

The following is a consequence of Theorem 1.

Proposition 3. *Assuming constant parameters $\bar{p}$ and $\bar{v}$ for $t \geq \bar{t}$, at the equilibrium we have*

$$\log \frac{S(\bar{t})}{\bar{S}} - \mathcal{R}_0(\bar{p}, \bar{v})(S(\bar{t}) - \bar{S}) = -c(\bar{v})^\top F(\bar{p})^{-1} x(\bar{t}) > 0$$

A. Stability analysis

A general property of epidemiological models is that, being of the compartmental type, their linear part is stable even under time-varying parameters [22]. This is not always true for the general model (1)–(2), where $F(p)$ is a generic Metzler matrix. In this regard, we can state the following results, assuming that parameters p and v are bounded and time-varying.

Theorem 2. *Assume that the linear time-varying system $\dot{x}(t) = F(p(t))x(t)$ is exponentially stable. Then the nonlinear feedback system (1)-(2) is exponentially convergent.*

Proof: In the interval $[0, T]$, take the backward solution of $\dot{q}^\top + q^\top F(p) + l^\top = 0$, with $q(T) = 0$, and the functional $V(x(\cdot), S(\cdot), t) = q(t)^\top x - \int_t^T q(\tau)^\top b \dot{S}(\tau) d\tau$. For any $T > 0$, we have that $\dot{V} = -l^\top x \leq 0$. The assumption and the fact that $\dot{S} \leq 0$ imply that for $T \to \infty$ we have $x \to 0$ and $S \to \hat{S}$, has limit $\hat{S} \geq 0$ depending on $p(\cdot)$ and $v(\cdot)$. ∎

The next theorem provides a testable condition for the robust convergence of the overall system, under uncertain time-varying parameters.

Theorem 3. *Assume that the linear time-varying system $\dot{x}(t) = F(p(t))x(t)$ admits a copositive Lyapunov function $W(x) = q^\top x$, for some $q > 0$, i.e. $q^\top F(p) < 0$ for all $p \in \mathcal{P}$. Then, the nonlinear feedback system is robustly convergent.*

Proof: Take $V = q^\top (x + bS)$. Then $\dot{V} = q^\top F(p) x < 0$ for all $x \neq 0$. ∎

Example 3. *In Example 1, let $\alpha = 0.3$, $\beta = 0.1$, $\gamma = 0.1$, $\delta = 0.2$, $\mu = 0.2$, $\nu = 0.1$, $\varphi(t) = 0.5 + 0.5\sin(t)$. The reproduction number $\mathcal{R}_0$ is periodic with mean 2.919. The time evolution of $x_i(t)$ and $S(t)$ is shown in Figure 1. The asymptotic value of S is $\hat{S} = 0.0633$.*

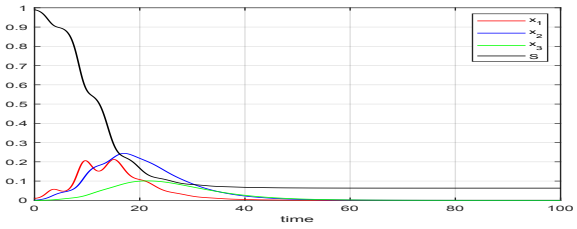

Figure 1: Time evolution of S, x_1, x_2, x_3 for periodic $\mathcal{R}_0$.

IV. Guaranteed bounds and control

In this section we consider

- The sensitivity analysis problem: the parameters are uncertain within given bounds and cannot be decided. In this case we are considering the problem of estimating an uncertain evolution.
- The control case: the parameters are control variables, constrained within their bounds.

As we will see soon, the two problems can be faced as one. Indeed, given any integral performance index, possibly with final cost, the two problems require either the maximization or the minimization of this functional. In the following, we will show that we can take advantage of the system positivity and the fact that its linear part admits a BDC-decomposition, namely it is the sum of rank-one matrices having a special structure [7], [12]. Consider the cost

$$J = h^\top x(T) + \int_0^T l^\top x(t) dt \tag{12}$$

formally $J = J(x(\cdot))$, and the problem of its maximization or minimization w.r.t. the system parameters. Before proceeding further we describe some important cases.

- For $l = 0$ and $h = e_k$, the kth vector of the canonical basis, we are estimating the maximum or the minimum value of $x_k(t)$ at time T. This can be, for instance, important to estimate the casualties at time T.
- For $l = e_k$ and $h = 0$, we are estimating the integral of $x_k(t)$ and this can be useful to estimate, for instance, the overall Intensive Care Unit occupancy in the interval $[0, T]$.

We work under the simplifying assumption, typically satisfied in epidemiological models as long as mid-term predictions are considered, that the susceptible population fraction $S(t)$ over the prediction horizon is unknown but bounded as

$$S^- \leq S(t) \leq S^+ \quad 0 \leq t \leq T. \tag{13}$$

Remark 3. *Although this seems a drastic simplification, which is technically equivalent to excluding the nonlinear*

part of the system and considering a linear differential inclusion, it is a reasonable assumption in practice, because: (a) the number of susceptible people S is slowly time-varying in most of the cases; the infection dynamics is much faster; (b) S can be quite accurately statistically estimated (e.g. through serological studies) and predicted. This estimation can be deemed more accurate than that of other quantities, such as the infection parameters, the fatality rate, the number of infected people; (c) S can be also controlled by means of a vaccination campaign although the process can be very slow.

From our assumptions, we can derive the following.

Proposition 4. *The maximum (resp. the minimum) of* (12)*, under* (1) *and* (13)*, is always achieved for $S = S^+$ (resp. $S = S^-$) and for $v = v^+$ (resp. $v = v^-$).*

Proof: It follows immediately from the fact that b and c are positive vectors and $c(v)$ is an increasing function. ■

Henceforth we always assume that S and c are both fixed to their maximum or minimum. It is not difficult to show that, considering all parameters p and v, the maximization (resp. minimization) problem, given $x(0)$, has the form

$$\max_{p_k^- \le p_k(t) \le p_k^+} \quad h^\top x(T) + \int_0^T l^\top x(t)dt \tag{14}$$

s.t.

$$\begin{aligned} \dot{x}(t) &= \sum_{k=1}^{m} f_k g_k^\top p_k(t) x(t) + bSc(v)^\top x(t) \\ &= \sum_{k=0}^{m} f_k g_k^\top p_k(t) x(t) \end{aligned} \tag{15}$$

where we take $f_0 = b$, $g_0 = c$, $p_0(t) = S(t)$. Then we take

$$f_0 g_0^\top = bc(v^+)^\top \quad \text{and} \quad p_0 = S^+$$

in the maximization case and

$$f_0 g_0^\top = bc(v^-)^\top \quad \text{and} \quad p_0 = S^-$$

in the minimization case. Finding p is a control problem, faced via Pontryagin theory and usually requires a shooting approach. Shooting is not necessary for this problem in view of its special structure that makes it easy to solve.

The Hamiltonian is

$$H(x, \xi, p) = \xi^\top \left[\sum_{k=0}^{m} f_k g_k^\top p_k \right] x + h^\top x$$

The maximum is achieved componentwise by solving

$$\max_{p_k^- \le p_k \le p_k^+} \xi^\top f_k g_k^\top x p_k$$

Since $g_k^\top x > 0$, the pointwise maximizer p_k^* is

$$p_k^*(\xi) \in \arg \max_{p_k^- \le p_k \le p_k^+} (\xi^\top f_k p_k)$$

namely

$$p_k^*(\xi) = \begin{cases} p_k^- & \text{if} \quad \xi^\top f_k < 0 \\ p_k^+ & \text{if} \quad \xi^\top f_k \ge 0 \end{cases}$$

and *does not depend on* x. The adjoint equation

$$-\dot{\xi}(t)^\top = \xi(t)^\top \left[\sum_{k=0}^{m} f_k g_k^\top p_k^*(\xi(t)) \right] + l^\top, \quad \xi(T)^\top = h^\top \tag{16}$$

can be solved independently of x to determine the optimal control p^*, after a single integration backward in time with final condition h. This means that the problem can be solved without resorting to shooting, requiring multiple trials involving integration.

Proposition 5. *The optimal control problem* (14)-(15) *can be solved with a single backward integration of* (16)*.*

Example 4. *Consider the elementary case*

$$F(\alpha, \beta) = \begin{bmatrix} -\alpha & 0 \\ \alpha & -\beta \end{bmatrix}$$

with $c = 0$ (i.e. no infection), and the cost weights $h^\top = [0 \ 1]$ and $l = 0$. With this purely academic example we wish to pose a question: is the worst (maximum) or best (minimum) case achieved for constant values of the parameters? The answer is no, even without the infection term. The differential equation (16) *is*

$$-\begin{bmatrix} \dot{\xi}_1 & \dot{\xi}_2 \end{bmatrix} = \begin{bmatrix} \xi_1 & \xi_2 \end{bmatrix} \begin{bmatrix} -\alpha & 0 \\ \alpha & -\beta \end{bmatrix}, \quad \begin{bmatrix} \xi_1(T) \\ \xi_2(T) \end{bmatrix}^\top = \begin{bmatrix} 0 \\ 1 \end{bmatrix}^\top$$

and the maximizing parameters are

$$\begin{aligned} [\alpha^*, \beta^*]^\top &= \arg\max_{\alpha,\beta} \ [\xi_1, \xi_2] \begin{bmatrix} -\alpha & 0 \\ \alpha & -\beta \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \\ &= \arg\max_{\alpha,\beta} \ x_1(\xi_2 - \xi_1)\alpha - \beta x_2 \xi_2 \end{aligned}$$

Take $\alpha \in [1, 4]$, $\beta \in [2, 3]$ and $T = 1$. As shown in Fig. 2, upper panel (minimizer functions α, β) and middle panel (maximizer functions α, β), while β does not switch, α does at some point. The lower panel reports the bounds and a set of randomly generated curves; it is important to notice that the bounds are valid at the final time $t = T$.

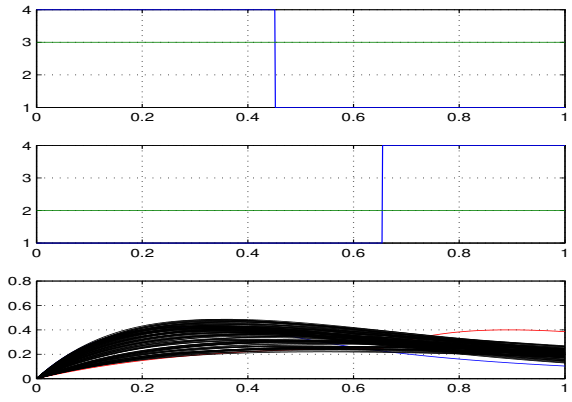

Figure 2: Time evolution of: the minimizer functions $\alpha(t)$, blue, and $\beta(t)$, green (upper panel); the maximizer functions $\alpha(t)$, blue, and $\beta(t)$, green (middle panel); the lower- (blue) and upper- (red) bounding curves for $x_2(T)$, along with a set of randomly generated curves (lower panel). It is important to note that the bounds only hold at the final time T.

Remark 4. Consistency verification *The strong assumption of the knowledge of bounds* (13) *can be verified a posteriori. Having the minimizer or maximizer trajectory $x^*(t)$, one can integrate starting from the initial conditions $x(0)$ and $S(0)$ to compute $S(T)$ by means of*

$$\log \frac{S(T)}{S(0)} = -\int_0^T c(v)^\top x^*(t)dt$$

and check if the final value $S(T) \geq S^-$. Note that, in a controlled epidemic event, the infected population $x(t)$ is orders of magnitude smaller than the susceptible population, therefore the relative variation of $S(t)$ is in general very small in the medium term (3-4 months). In the long run, more sophisticated techniques should be considered.

V. Open-close control

We consider an on-off switching control consisting of a sequence alternating periods in which restrictions are enforced and periods in which these are released. Now the model (1) has the form

$$\dot{x}(t) = F(p)x(t) + Sbc(v)^\top x(t)\,, \tag{17}$$

where $v \in \{v^-, v^+\}$ is now considered a switching decision variable (a control): v^- is the "closing value" while v^+ is the "opening value". During the closing regime the contagion parameters are at their lowest level, while during the opening regime contagion parameters are at their highest level. We consider S again as an uncertain parameter bounded as in (13) and, to establish safety bounds, we assume $S = S^+$. We consider two regions

$$\mathcal{S}_L = \{x : q^\top x \leq \theta_L\}, \quad \mathcal{S}_H = \{x : q^\top x \leq \theta_H\} \tag{18}$$

with $q > 0$ and

$$\theta_L \leq \theta_H. \tag{19}$$

In the closing period, the goal is to safely reach $\mathcal{S}_L$. In the opening period, we must not leave region $\mathcal{S}_H$.

To have boundedness of the setup, we need the following assumption.

Assumption 3. *The "closing" configuration*

$$\dot{x} = [F(p) + S^+bc(v^-)^\top]x(t)$$

is asymptotically stable: there exists $q > 0$ such that

$$\mathbf{q}^\top \left[F(p) + S^+bc(v^-)^\top\right] < 0$$

The opening-closing sequences can be then robustly determined as follows.

Set $k = 0$ and $x(0) = x_0$ (given). Then

1) **Close:** Given the initial state x_0 determine the smallest closure interval $T_c^k > 0$ such that at the end
$$\mathbf{q}^\top x(T_c^k) \leq \theta_L \tag{20}$$
and apply v^- in this interval.
2) **Open:** Given $x(T_c)$, determine the largest opening interval $T_o^k > 0$ such that, at the end,
$$\mathbf{q}^\top x(T_c^k + T_o^k) = \theta_H, \tag{21}$$
and apply v^+ in this interval.
3) Set $k := k + 1$, $x_0 = x(T_c^k + T_o^k)$ and go to 1).

The problem of determining the two intervals T_c^k and T_o^k can be robustly solved by adopting the techniques suggested in the previous section, even under time-varying parameter uncertainties.

The sequences T_c^k and T_o^k depend on $x(0) = x_0$ and they are not constant (there is no periodicity). To compute strictly periodic sequences $\{T_c,\ T_o,\ T_c,\ T_o\ \ldots\}$, we can slightly change the approach by assuming regions of the form

$$\mathcal{B}_L = \{x : 0 \leq x \leq \bar{x}_L\}, \quad \mathcal{B}_H = \{x : 0 \leq x \leq \bar{x}_H\} \tag{22}$$

with $0 < \bar{x}_L < \bar{x}_H$. Then we proceed as follows.

1) **Closing interval:** Take $x(0) = \bar{x}_H$, determine T_c as the smallest T such that, at the end, $x(T) \in \mathcal{B}_L$. **Opening interval:** Take $x(0) = \bar{x}_L$, determine T_o as the largest T such that, at the end, $x(T) \in \mathcal{B}_H$ (necessarily on the boundary).

In view of monotonicity, trajectories starting from any initial condition in $\mathcal{B}_L$ will end up in $\mathcal{B}_H$ at time T_o and, conversely, from any initial condition in $\mathcal{B}_H$ trajectories will end up in $\mathcal{B}_L$ at time T_c.

Remark 5. *The two vectors $\bar{x}_L$ and $\bar{x}_H$ can can be arbitrary positive vectors. As a good choice, if a nominal value $\bar{p}$ is known for p, we could take the right Frobenius eigenvectors of $F(p) + S^+bc(v)^\top$ corresponding to v^- and v^+.*

Note that the condition $x(T_o) \leq \bar{x}_H$ holds for the final state of the opening period, but might be violated immediately after the commutation to the closure period. To ensure that the safety barrier is never violated, we may seek the positive invariance of $\mathcal{S}_H$ for the closure dynamics.

Proposition 6. *Set $\mathcal{S}_H$ is positively invariant for the closure dynamics with $v = v^-$ if and only if, for all p,*

$$[F(p) + S^+bc(v^-)^\top]\bar{x}_H < 0 \tag{23}$$

Proof. Condition (23) is necessary and sufficient for the positive invariance of $\mathcal{S}_H$ for $\dot{x} = [F(p) + S^+bc(v^-)^\top]x$ [4]. It can be checked via linear programming because it can be equivalently written as $[F(p^i)+S^+bc(v^-)^\top]x_H < 0$, $i = 1, \ldots, n_p$, where $p^i \in \hat{\mathcal{P}}$, the set of vertices of $\mathcal{P}$. □

Vector $\bar{x}_H$ (if any) can be found via linear programming.

VI. Example

Consider the system in Example 1 with $1 \leq \alpha, \beta, \gamma, \delta \leq 2$, and $c^\top = [1\ 0.2\ 0.1]v$, where $v = 0.5$ in the closing regime and $v = 1.3$ in the opening regime. Starting from the initial condition $x(0) = [10^{-4}\ 0\ 0]$, meaning that 0.01% of the population is infected, with no symptomatic or hospitalized, an opening-closing sequence has been computed. The worst case values of $\mathcal{R}_0$, computed with (7), are 0.6 (closing) and 1.495 (opening). We consider the threshold function $\mathbf{q}^\top x(t)$ with

$$\mathbf{q}^\top = [\ 0.2547\ \ 0.1898\ \ 0.5554\ ]$$

This is the left unit-sum Frobenius eigenvector of the "worst case opening dynamics". The rationale is that the region $\mathbf{q}^\top x \leq \theta_H$ is invariant for the closure dynamics.

The upper and lower thresholds are $\theta_L = 0.5 \cdot 10^{-4}$ and $\theta_H = 1 \cdot 10^{-4}$. The first six periods of the epidemic evolution are reported in Fig. 3, which shows possible realizations corresponding to randomly generated (constant) parameters (black), along with their upper (red) and lower (blue) bounds. Numerically, we observe that the sequences "tend to periodicity" after a while.

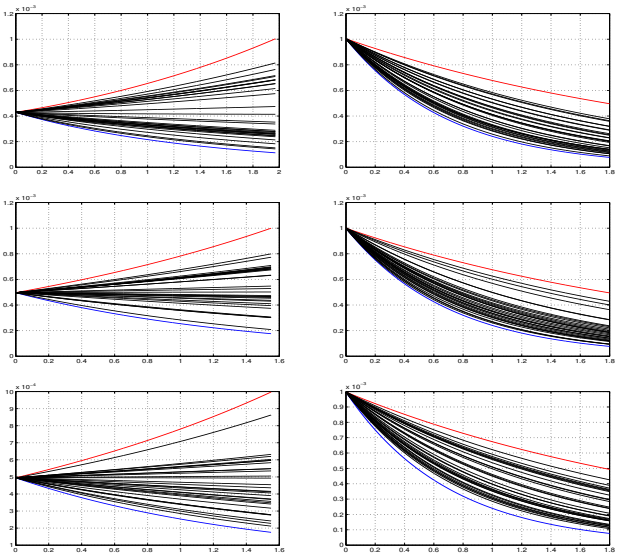

Figure 3: The sequence of opening and closing periods: $T_o^1 = 1.97$, $T_c^1 = 1.8$, $T_o^2 = 1.55$ $T_c^2 = 1.8$, $T_o^3 = 1.55$ $T_c^3 = 1.8$. The upper and lower bounds are reported in red and blue, respectively; black curves are possible realizations with randomly generated parameters.

VII. Conclusions

We have considered a general model of infection dynamics in which a compartmental uncertain system is coupled with nonlinear infection dynamics due to the time-varying susceptible fraction of the population. We have provided general properties, including some exact relations between the compartmental state and the susceptible population. We have then considered a sensitivity analysis, formulated as an optimal control problem and found a solution which does not involve shooting if we can assume the knowledge of bounds on the number of susceptible individuals. Removing this assumption is left to future work.

Acknowledgment: The authors thank the reviewers, in particular one of them who made a great proofreading work!

References

[1] T. Alamo, D. G. Reina, P. M. Gata, V. M. Preciado, G. Giordano, "Data-Driven Methods for Present and Future Pandemics: Monitoring, Modelling and Managing", Arxiv, https://arxiv.org/pdf/2102.13130.pdf

[2] J. Arino, F. Brauer, P. van den Driessche, J. Wu J. Watmough "A final size relation for epidemic models", Volume 4, Number 2, April 2007

[3] M. Bin, P. Y. K. Cheung, E. Crisostomi, P. Ferraro, H. Lhachemi, R. Murray-Smith, C. Myant, T. Parisini, R. Shorten, S. Stein, L. Stone, "Post-lockdown abatement of COVID-19 by fast periodic switching", *PLoS Computational Biology*, 17(1), 2021.

[4] F. Blanchini, P. Colaneri, M. E. Valcher, "Switched Linear Positive Systems", *Foundations and Trends in Systems and Control*, 2(2):101-273. 2016.

[5] M. Bloem, T. Alpcan, T. Basar, "Optimal and robust epidemic response for multiple networks", *Control Engineering Practice*, 17:525–533, 2009.

[6] E. H. Bussell, C. E. Dangerfield, C. A. Gilligan, N. J. Cunniffe, "Applying optimal control theory to complex epidemiological models to inform real-world disease management", *Philosophical Transactions of the Royal Society B*, 374:20180284, 2019.

[7] F. Blanchini and G. Giordano, "Piecewise-linear Lyapunov functions for structural stability of biochemical networks", *Automatica*, 50(10):2482–2493, 2014.

[8] F. Brauer and C. Castillo-Chavez. *Mathematical Models in Population Biology and Epidemiology*. 2nd ed., Springer, 2012.

[9] O. Diekmann and J. A. P. Heesterbeek. *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, Wiley, 2000.

[10] G. A. Forster and C. A. Gilligan, "Optimizing the control of disease infestations at the landscape scale", *Proceedings of the National Academy of Sciences*, 104:4984–4989, 2007.

[11] G. Giordano, F. Blanchini, R. Bruno, P. Colaneri, A. Di Filippo, A. Di Matteo, M. Colaneri, "Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy", *Nature Medicine*, 26:855–860, 2020.

[12] G. Giordano, C. Cuba Samaniego, E. Franco, F. Blanchini, "Computing the structural influence matrix for biological systems", *Journal of Mathematical Biology*, 72(7):1927–1958, 2016.

[13] A. B. Gumel et al. "Modelling strategies for controlling SARS outbreaks", *Proc. R. Soc. B Biol. Sci.*, 271(1554):2223-32, 2004.

[14] W. O. Kermack and A. G. McKendrick, "A contribution to the mathematical theory of epidemics", *Proc. R. Soc. Lond.*, 115:700–721, 1927.

[15] E. Hansen and T. Day, "Optimal control of epidemics with limited resources", *Journal of Mathematical Biology*, 62:423–451, 2011.

[16] M. Hayhoe, F. Barreras, V. Preciado, "Data-driven control of the COVID-19 outbreak via non-pharmaceutical interventions: A geometric programming approach", arXiv preprintarXiv:2011.01392, 2020.

[17] H. W. Hethcote, "The mathematics of infectious diseases", *SIAM Rev.* 42:599–653, 2000.

[18] J. Köhler, L. Schwenkel, A. Koch, J. Berberich, P. Pauli, F. Allgöwer, "Robust and optimal predictive control of the COVID-19 outbreak" Annual Reviews in Control 51 (2021) 525–53.

[19] C. S. Lee and G. Leitmann, "Control strategies for an en- demic disease in the presence of uncertainty", in: R. P. Agarwal (Ed.), Recent Trends in Optimization Theory and Applications, pp. 221–238, 1994.

[20] G. Leitmann, "The use of screening for the control of anendemic disease", in: Variational Calculus, Optimal Control and Applications. volume 124 of International Series of Numerical Mathematics, Birkhauser, pp. 291–300, 1998.

[21] S. Lenhart and J. T. Workman. *Optimal control applied to biological models*. Chapman & Hall/CRC, 2007.

[22] H. Maeda, S. Kodama, Y. Ohta, "Asymptotic behavior of nonlinear compartmental systems: Nonoscillation and stability", *IEEE Transactions on Circuits and Systems*, 25(6):372–378, 1978.

[23] M. Mandal, S. Jana, S. K. Nandi, A. Khatua, S. Adak, T. Kar, "A model based study on the dynamics of COVID-19: Prediction and control", *Chaos, Solitons & Fractals*, 136:109889, 2020.

[24] M. Martcheva. *An Introduction to Mathematical Epidemiology*, Springer Science and Business Media LLC, 2015.

[25] R. Morton and K. H. Wickwire, "On the optimal control of a deterministic epidemic", *Advances in Applied Probability*, 6:622–635, 1974.

[26] R. E. Rowthorn, R. Laxminarayan, C. A. Gilligan. "Optimal control of epidemics in metapopulations", *Journal of the Royal Society Interface*, 6:1135–1144, 2009.

[27] O. Sharomi and T. Malik, "Optimal control in epidemiology", *Annals of Operations Research*, 251:55–71, 2017.

[28] A. Swierniak, U. Ledzewicz, H. Schättler "Optimal Control for a Class of. Compartmental Models in Cancer Chemotherapy", *Int. J. Appl. Math. Comput. Sci.*, 13(3):357–368, 2003.