

1 **1. Introduction**

2 *Main contribution and its relevance.*

3 *Background.*

4 *Vaccine development.*

5 *Problem setup.*

6 *Litterature review.*

7 *Papaer structure.*

8 **2. Covid-19 spread dynamics**

9 *Uncontrolled dynamics.* We split a given population of size N in the base SEIR
10 structure with segregation infected classes according to the manifestation of
11 symptoms. Let $L, S, E, I_S, I_A, H, R, D$ respectively denote the class of an indi-
12 vidual according to its current state, namely

13 **Lockdown (L)** All individuals that has low or null mobility and that remains
14 under isolation. Thus individual in this class reduce its probability of
15 contagious.

16 **Suceptible (S)** Individual under risk

17 **Exposed (E)** Population fraction that host SARS-CoV-2 but cannot infect

18 **Infected-Symptomatic (I_S)** Population infected fraction with symptoms and
19 reported as confirmed case

20 **Infected-Asymptomatic (I_A)** Infected individual whit transitory or null symp-
21 toms and unreported

22 **Hospitalized (H)** Infected population that requires hospitalization or inten-
23 sive care.

24 **Recover or removed (R)** Population that recovers from infection and devel-
25 ops partial immunity

26 **Death (D)** Population fraction that death by COVID-19

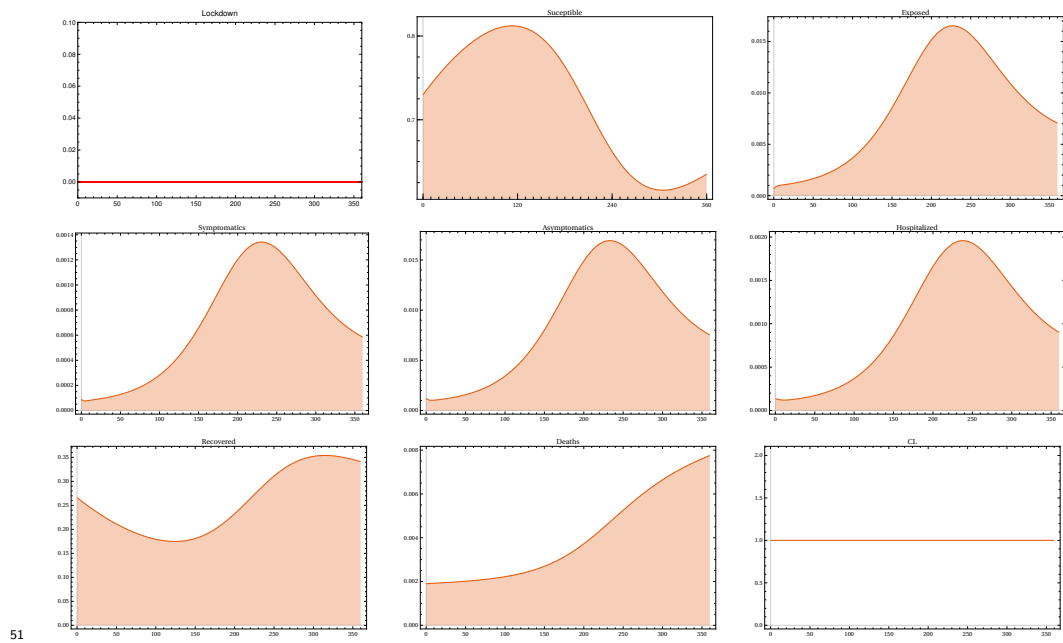
27 To fit data of cumulative reported symptomatic cases, we postulated the counter
28 state Y_{I_S} and made the following hypothesis.

29 **Hypothesis 1.** According to above compartment description, we made the fol-
30 lowing hypothesis.

- 31 (H-1) We suppose that at least 30% of the population is under lock-down and
 32 that eventually a fraction of this class move to the susceptible compart-
 33 ment at rate δ_L .
- 34 (H-2) Force infection is defined as the probability of acquire COVID-19 given
 35 the contact with a symptomatic or asympotomatic individual. Thus we
 36 normalize under live population N^*
- 37 (H-3) Susceptible individuals become exposed—but not infectious—when they
 38 are in contact with asymptomatic or symptomatic individuals. Thus β_S ,
 39 β_A denote probability of infectious given the contact with a symptomatic
 40 or asymptomatic infectious individuals.
- 41 (H-4) After a period of latency of $1/\kappa = 5.1$ days, an exposed individual became
 42 infected. Being p the probability of develop symptoms and $(1 - p)$ the
 43 probability of became infectious but asymptomatic. Thus $p\kappa E$ denotes
 44 the event of become infectious and develop symptoms given that the
 45 individual has been exposed
- 46 (H-5) Asymptomatic individuals not die or get in a Hospital
- 47 (H-6) A fraction μ_H of symptomatic individuals die by COVID-19 without hos-
 48 pitalization

49 Thus we formulate the following Ordinary Differential Equation (ODE)

$$\begin{aligned}
 L' &= \theta\mu N^* - \epsilon\lambda L - \delta_L L - \mu L, \\
 S' &= (1 - \theta)\mu N^* + \delta_L L + \delta_R R - (\lambda + \mu)S, \\
 E' &= \lambda(\epsilon L + S) - (\kappa + \mu)E, \\
 I_S' &= p\kappa E - (\gamma_S + \delta_H + \underline{\mu_{I_S}}^{\text{SDIV}} + \mu)I_S, \\
 I_A' &= (1 - p)\kappa E - (\gamma_A + \mu)I_A, \\
 H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu)H, \\
 R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu)R, \\
 D' &= \underline{\mu_{I_S}}^{\text{SDIV}} + \mu_H H, \\
 \frac{dY_{I_S}}{dt} &= p\kappa E, \\
 \lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}, \\
 N^*(t) &= L + S + E + I_S + I_A + H + R.
 \end{aligned} \tag{1}$$



See Table 1 for notation and references values. Put here the flow diagram [SDIV 1] use WPS

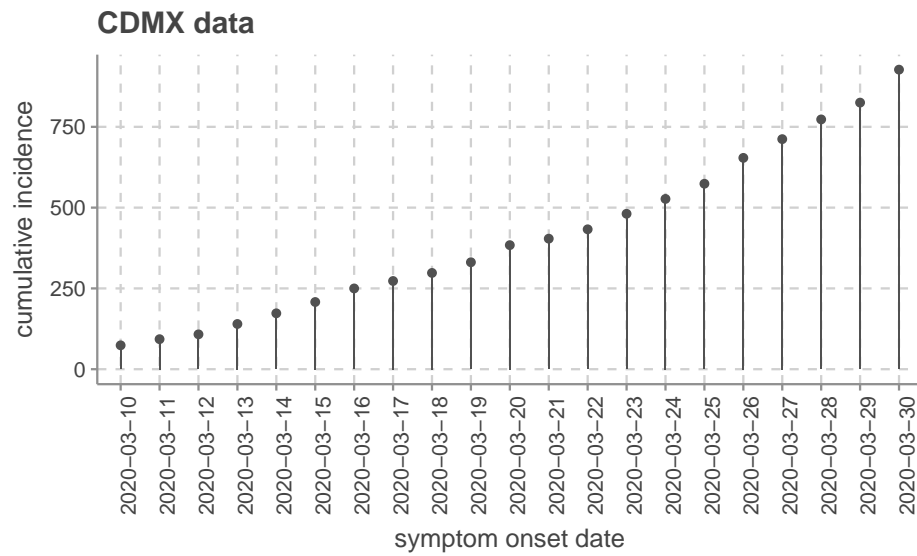


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

Parameter	Description
μ	Death rate
β_S	Infection rate between susceptible and symptomatic infected
β_A	Infection rate between susceptible and asymptomatic infected
λ_V	Vaccination rate
δ_V^{-1}	Vaccine-induced immunity
ε	Vaccine efficacy
κ^{-1}	Average incubation time
p	New asymptomatic generation proportion
θ	Proportion of individuals under lockdown
γ_S^{-1}	Average time of symptomatic recovery
γ_A^{-1}	Recovery average time of asymptomatic individuals
γ_H^{-1}	Recovery average time by hospitalization
δ_R^{-1}	Natural immunity
δ_H	Infected symptomatic hospitalization rate

Table 1: Parameters definition of model in Equation (1).

53 2.1. Parameter calibration

54 *Bayesian estimation.* We calibrate parameters of our base dynamics in (1) via
55 Multichain Montecarlo (MCMC). To this end, we assume that the cumulative
56 incidence of new infected symptomatic cases CI_S follows a Poisson distribution
57 with mean $\lambda_t = IC_s(t)$. Further, following [] we postulate priors for p and κ

$$\begin{aligned}
Y_t &\sim \text{Poisson}(\lambda_t), \\
\lambda_t &= \int_0^t p \delta_e E, \\
p &\sim \text{Uniform}(0.3, 0.8), \\
\kappa &\sim \text{Gamma}(10, 50).
\end{aligned} \tag{2}$$

Using the reproductive number definition of Van DenDrishe [CITE], and defining $R_1 = \epsilon\theta - \theta + 1$, $R_2 = \mu + \delta_H + \gamma_S + \mu_{I_s}$ we obtain

$$R_0 := \frac{\kappa}{\kappa + \mu} (\mu R_1 + \delta_L) \left[\frac{p\beta_S}{R_2} + \frac{(1-p)\beta_A}{\gamma_A + \mu} \right].$$

[SDIV 2]
Review this
 R_0 calcu-
lation with
Gabriel

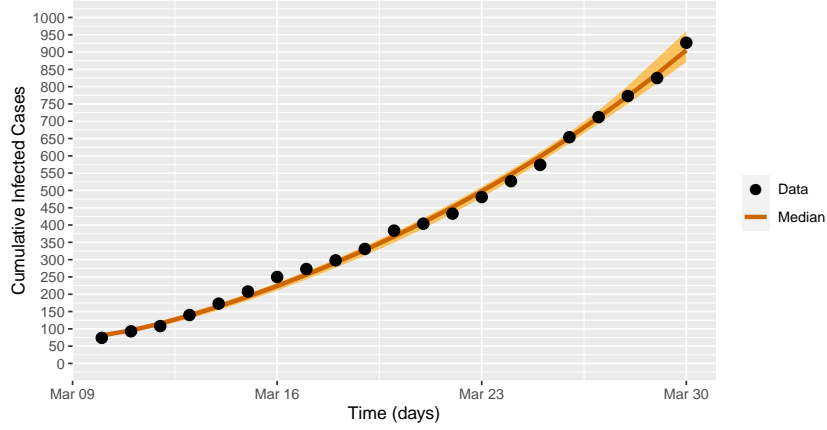


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

Figure 2 displays data of coumulative confirmed cases of COVID-19 of Mexico city, and Figure 2 displays the fitt of our model in Equations (1) and (2). Table 2 enclose fixed and estimated parameters to this setting.

3. Imperfect-preventive COVID-19 vaccination

Preventive vaccines.

Efficacy and vaccine-induced immunity.

Actual vaccine stage development.

Vaccination reproductive number.

Vaccination rate λ_V estimate.

Feasibility regions according to efficacy and vaccination rate.

Hypothesis 2. According to COVID-19 dynamics in model in Equation (1), we made the following modeling hypotheses about the regarding vaccine.

(VH-1) Vaccine is preventive and only reduce susceptibility. Justify this hypothesis cite

(VH-2) The vaccination camping omits testing to detect seroprevalence. Thus Expoxed, Infected Asymptomatics and Recovered Asymptomatic individuals are undetected but would obtain a vaccine dose —which in these model represent a waste of resources

(VH-3) Individuals under Lockdown also would be vaccinated

Parameter	Median	Reference
q_r, ϵ	0.4, 0.3, 0.1	this study
β_S	$q_r \times 8.690483 \times 10^{-1}$	this study
β_A	$q_r \times 7.738431 \times 10^{-1}$	this study
κ	0.19607843	*
p	0.1213	*
θ	0.2,	this study
δ_L	0.04	postulated
δ_H	0.2	*
δ_V	0.0027397260273972603	$\delta_V^{-1} = 2$ years CanSinoBIO
δ_R	0.00555556	$\delta_R^{-1} \approx 180$ days
μ	3.913894×10^{-5}	**
μ_{I_S}	0.0	
μ_H	0.01632	[FENG]
γ_S	0.09250694	*
γ_A	0.16750419	*
γ_H	5.079869×10^{-1}	*
λ_V	0.00061135	
ε	0.7, 0.80, 0.9, 0.95	[PRESS RELESASES]
N	26446435	**
L_0	0.26626009702112796	
S_0	0.463606046009872	
E_0	0.00067033	*
I_{S_0}	9.283×10^{-5}	* * *
I_{A_0}	0.00120986	*
H_0	$1.34157969 \times 10^{-4}$	**
R_0	$2.66125939 \times 10^{-1}$	
D_0	0.00190074	**
X_{vac}^0	0.0	
V_0	0.0	
$Y_{I_S}^0$	0.12258164	
B	0.0003592166581242425	9500 beds/ N
a_{I_S}	0.0020127755438256486	DALY def
a_H	0.001411888738103725, or $a_H(x) := 0.001411888738103725 \log(\frac{1}{B-\kappa I_S})$	DALY def [Jo 2020]
a_D	7.25	DALY def

Table 2: Model parameters. Values based mainly in [FNEG]

77 (VH-4) The vaccine is leaky and with efficacy $\epsilon \in [0.6, .975]$

$$\begin{aligned}
L' &= \theta \mu N^* - (\epsilon \lambda + \delta_L + \lambda_V + \mu) L \\
S' &= (1 - \theta) \mu N^* + \delta_L L + \delta_V V + \delta_R R \\
&\quad - (\lambda + \lambda_V + \mu) S \\
E' &= \lambda (\epsilon L + (1 - \epsilon) V + S) - (\kappa + \mu) E \\
I_S' &= p \kappa E - (\delta_H + \gamma_S + \mu_{I_S} + \mu) I_S \\
I_A' &= (1 - p) \kappa E - (\gamma_A + \mu) I_A \\
H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\
R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\
D' &= \mu_{I_S} I_S + \mu_H H \\
V' &= \lambda_V (S + L) - [(1 - \epsilon) \lambda + \delta_V + \mu] V
\end{aligned}$$

$$\begin{aligned}
\frac{dX_{vac}}{dt} &= (u_V(t) + \lambda_V) [L + S + E + I_A + R] \\
\frac{dY_{I_S}}{dt} &= p \kappa E \\
\lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}
\end{aligned} \tag{3}$$

$$\begin{aligned}
L(0) &= L_0, \quad S(0) = S_0, \quad E(0) = E_0, \\
I_S(0) &= I_{S_0}, \quad I_A(0) = I_{A_0}, \quad H(0) = H_0, \\
R(0) &= R_0, \quad D(0) = D_0, \\
V(0) &= 0, \quad X_{vac}(0) = 0, \\
X_{vac}(T) &= x_{coverage}, \\
N^*(t) &= L + S + E + I_S + I_A + H + R + V.
\end{aligned}$$

78 4. Vaccination reproductive number

79 R_0 definition.

80 No vaccine reproductive number.

81 Vaccine reproductive number.

82 Efficacy, coverage and vaccination rate.

83 Here Gabriel's R not calculations.^{SDIV}

Define $T_1 = \delta_L + \lambda_V + \mu$, $T_2 = \mu + \lambda_V + \delta_V$, then

$$R_{v0} := \frac{\mu(\delta_L + R_1 T_2) + \delta_V \delta_L + \lambda_V((1 - \epsilon) + \delta_V)}{T_1 T_2 (\delta_L + \mu R_1)} R_0$$

84

[SDIV 3]
Here counter
plots figure
as function
of efficacy
and vaccina-
tion rate

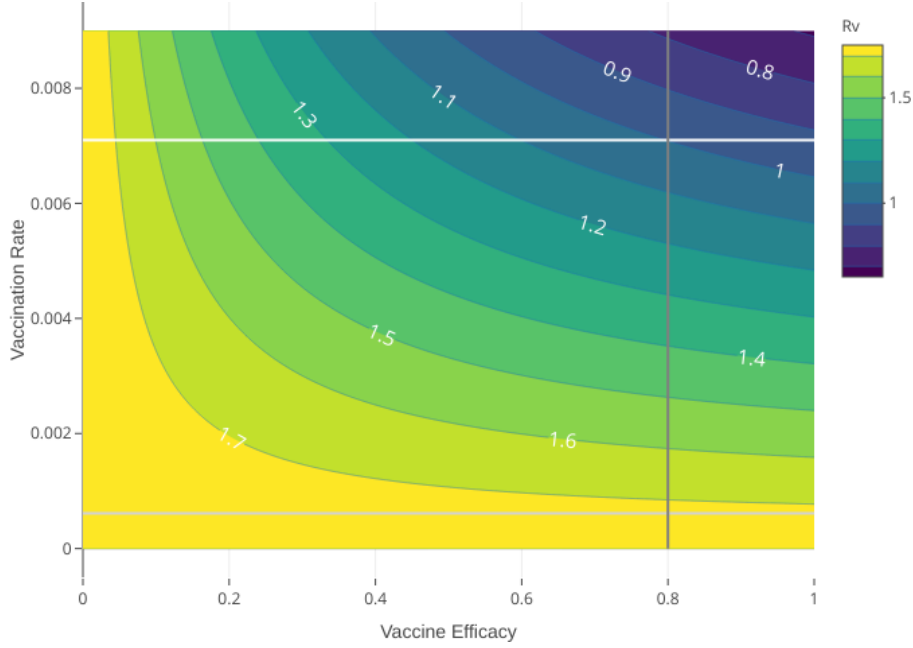


Figure 3: R_v contour plot as function of efficacy and vaccination rate.

5. Optimal controlled version

Controlled Model. Now we model vaccination, treatment and lockdown as a optimal control problem. According to dynamics in Equation (1), we modulate the vaccination rate with a time-dependent control signal $u_V(t)$. We add compartment X_{vac} to count all the vaccine applications of susceptible, exposed, asymptomatic and recovered individuals. This process is modeled by

$$X'(t) = (\lambda_V + u_V(t))(S + E + I_A + R) \quad (4)$$

and describes the number of applied vaccines at time t . Consider

$$x(t) := (L, S, E, I_S, I_A, H, R, D, V, X_{vac})^\top(t)$$

and control signal $u_v(\cdot)$. We quantify the cost and reward of a vaccine strategy policy via the penalization functional

$$J(u_L, u_V) := \int_0^T a_S I_S + a_d D + \frac{1}{2} (c_L u_L^2 + c_V u_V^2) ds. \quad (5)$$

In other words, we assume in functional J that pandemic cost is proportional to the symptomatic and death reported cases and that a vaccination policy implies quadratic consumption of resources.

Further, since we aim to simulate vaccination policies at different coverage scenarios, we impose the vaccination counter state's final time condition $X(T)$

$$\begin{aligned} x(T) &= (\cdot, \cdot, \cdot, \cdot, X_{vac}(T))^\top, \in \Omega \\ X_{vac}(T) &= x_{coverage}, \\ x_{coverage} &\in \{\text{Low}(0.2), \text{Mid}(0.5), \text{High}(0.8)\}. \end{aligned} \tag{6}$$

Thus, given the time horizon T , we impose that the last fraction of vaccinated populations corresponds to 20%, 50% or 80%, and the rest of final states as free. We also impose the path constraint

$$\Phi(x, t) := \kappa I_S(t) \leq B, \quad \forall t \in [0, T], \tag{7}$$

to ensure that healthcare services will not be overloaded. Here κ denotes hospitalization rate, and B is the load capacity of a health system.

Given a fixed time horizon and vaccine efficiency, we estimate the constant vaccination rate as the solution of

$$x_{coverage} = 1 - \exp(-\lambda_V T). \tag{8}$$

That is, λ_v denotes the constant rate to cover a fraction $x_{coverage}$ in time horizon T . Thus, according to this vaccination rate, we postulate a policy u_v that modulates vaccination rate according to λ_V as a baseline. That is, optimal vaccination amplifies or attenuates the estimated baseline λ_V in a interval $[\lambda_v^{\min}, \lambda_v^{\max}]$ to optimize functional $J(\cdot)$ —minimizing symptomatic, death reported cases and optimizing resources.

Our objective is minimize the cost functional (5)—over an appropriated functional space—subject to the dynamics in equations (1) and (4), boundary conditions, and the path constrain in (7). That is, we search for vaccination policies

114 $u_V(\cdot)$, which solve the following optimal control problem (OCP).

$$\begin{aligned}
\min_{u \in \mathcal{U}} J(u) &:= \int_0^T [(a_D \mu_s + a_H \delta_H) I_S(r) + a_{I_S} p \kappa E(r)] dr \\
\text{s. t.} \\
L' &= \theta \mu N^* - \epsilon \lambda L - u_L(t) L - \mu L \\
S' &= (1 - \theta) \mu N^* + u_L(t) L + \delta_v V + \delta_R R \\
&\quad - [\lambda + (\lambda_V + u_V(t)) + \mu] S \\
E' &= \lambda(\epsilon L + (1 - \epsilon) V + S) - (\kappa + \mu) E \\
I_S' &= p \kappa E - (\gamma_S + \mu_{I_S} + \delta_H + \mu) I_S \\
I_A' &= (1 - p) \kappa E - (\gamma_A + \mu) I_A \\
H' &= \delta_H I_S - (\gamma_H + \mu_H + \mu) H \\
R' &= \gamma_S I_S + \gamma_A I_A + \gamma_H H - (\delta_R + \mu) R \\
D' &= \mu_{I_S} I_S + \mu_H H \\
V' &= (\lambda_V + u_V(t)) S - [(1 - \epsilon) \lambda + \delta_V + \mu] V
\end{aligned} \tag{9}$$

$$\begin{aligned}
\frac{dX_{vac}}{dt} &= (u_V(t) + \lambda_V) [L + S + E + I_A + R] \\
\frac{dY_{I_S}}{dt} &= p \kappa E \\
\lambda &:= \frac{\beta_A I_A + \beta_S I_S}{N^*}
\end{aligned}$$

$$\begin{aligned}
L(0) &= L_0, \quad S(0) = S_0, \quad E(0) = E_0, \quad I_S(0) = I_{S_0}, \\
I_A(0) &= I_{A_0}, \quad H(0) = H_0, \quad R(0) = R_0, \quad D(0) = D_0, \\
V(0) &= 0, \quad X_{vac}(0) = 0, \quad u_V(\cdot) \in [u_{\min}, u^{\max}], \\
X_{vac}(T) &= x_{coverage}, \quad \kappa I_S(t) \leq B, \quad \forall t \in [0, T], \\
N^*(t) &= L + S + E + I_S + I_A + H + R + V
\end{aligned}$$

115 6. Numerical Results

116 Changes (compact)

117 **Author: anonymous**

118 No changes.

119 **Author: SDIV**

120 Added 2

121 Deleted 2

122 Commented 3

123

Initial condition

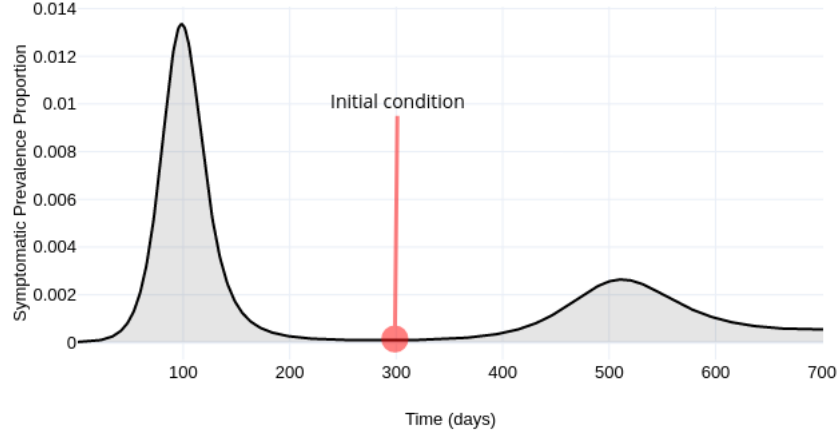


Figure 4: Initial condition scheme. We assume a positive prevalence. For reference, at the date of write this manuscript, prevalence in CDMX is aroundn 16 000 cases, see <https://plotly.com/sauld/36/> to display a electronic viewer.

124 Appendix A. Existence of optimal policies

125 In this appendix, we show the existence of optimal policies in the class of
 126 *piecewise constant policies*. Consider the following cost functional that we want
 127 to minimize

$$\int_0^T C(X(t), u(t)) dt \quad (\text{A.1})$$

128 subject to the dynamics

$$\dot{X}(t) = f(X(t), u(t)), \quad 0 \leq t \leq T, \quad (\text{A.2})$$

129 and the initial state $X(0) = x_0$. The functions $u : [0, T] \rightarrow U$ are called *control*
 130 *policies*, where U is a subset of some Euclidean space. Let $t_0 < t_1 < \dots < t_n$,
 131 with $t_0 = 0$ and $t_n = T$, be a partition of the interval $[0, T]$. We consider
 132 piecewise constant policies \tilde{u} of the form

$$\tilde{u}(t) = a_j \quad t_j \leq t < t_{j+1} \quad (\text{A.3})$$

133 for $j = 0, \dots, n-1$.

134 **Assumptions 1.** We made the following assumptions.

135 (A-1) The function f in the dynamics (A.2) is of class C^1 .

136 (A-2) The cost function C in (A.1) is continuous and the set U is compact.

137 By Assumption (A-1), the system

$$\dot{X}(t) = f(X(t), a_0), \quad X(0) = x_0, \quad 0 \leq t \leq t_1,$$

138 has a unique solution $\tilde{X}_0(t; x_0, a_0)$ which is continuous in (x_0, a_0) . Next, put
139 $x_1 := \tilde{X}_0(t_1; x_0, a_0)$ and consider the system

$$\dot{X}(t) = f(X(t), a_1), \quad X(t_1) = x_1, \quad t_1 \leq t \leq t_2,$$

Again, by Assumption (A-1), the latter system has a unique solution $\tilde{X}_1(t; x_1, a_1)$ which is continuous in (x_1, a_1) . By following this procedure, we end up having a recursive solution

$$\begin{aligned} \tilde{X}_{n-1}(t; x_{n-1}, a_{n-1}), \quad t_{n-1} \leq t \leq T, \\ x_{n-1} := \tilde{X}_{n-2}(t_{n-1}; x_{n-2}, a_{n-1}), \end{aligned}$$

140 where \tilde{X}_{n-1} is continuous in (x_{n-1}, a_{n-1}) .

141 For a control \tilde{u} of the form (A.3) and the corresponding solution path \tilde{X} ,
142 we have

$$\int_0^T C(\tilde{X}(t), \tilde{u}(t)) dt = \sum_{j=0}^{n-1} \int_{t_j}^{t_{j+1}} C(\tilde{X}_j(t), a_j) dt.$$

143 Notice that each \tilde{X}_j is a continuous function of (a_0, \dots, a_j) and x_0 .

144 By Assumption (A-2), the mapping

$$(a_0, \dots, a_{n-1}) \mapsto \sum_{j=0}^{n-1} \int_{t_j}^{t_{j+1}} C(\tilde{X}_j(t), a_j) dt$$

145 is continuous. Since each piecewise constant policy \tilde{u} of the form (A.3) can be
146 identified with the vector (a_0, \dots, a_{n-1}) in the compact set $U \times \dots \times U$, the
147 functional (A.1) attains its minimum in the class of piecewise constant policies.

148 The cost functional (5) and the dynamics (9) are particular cases of (A.1)
149 and (A.2), respectively, and satisfy Assumptions (A-1) and (A-2). Then there
150 exists an optimal vaccination policy of the form (A.3).

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