

1. Introduction

Main contribution and its relevance.

Background.

Piecewise optimal policies. Comment about the solution of the underlying Optimal Control Problem

One of the main features of our model is that we consider piecewise constant control policies instead of general measurable control policies. General control policies are difficult to implement since the authority has to make different choices every instant. The optimal policies we find are constant in each interval of time and hence these policies are easier to implement.

Optimal control problems with piecewise constant policies have been widely studied: solution method [1], convergence [2].

However, to the best of our knowledge, this is the first application of such policies in epidemics control.

Vaccine development.

Problem setup.

Litterature review.

Papaer structure.

2. Covid-19 spread dynamics

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

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

Suceptible (S) Individual under risk

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

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

Infected-Asymptomatic (I_A) Infected individual whit transitory or null symptoms and unreported

Hospitalized (H) Infected population that requires hospitalization or intensive care.

[SDIV 1]
David

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

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

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

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

42 (H-1) We suppose that at least 30 % of the population is under lock-down and
43 that eventually a fraction of this class move to the susceptible compart-
44 ment at rate δ_L .

45 (H-2) Force infection is defined as the probability of acquire COVID-19 given
46 the contact with a symptomatic or asymptomatic individual. Thus we
47 normalize under live population N^*

48 (H-3) Susceptible individuals become exposed—but not infectious—when they
49 are in contact with asymptomatic or symptomatic individuals. Thus β_S ,
50 β_A denote probability of infectious given the contact with a symptomatic
51 or asymptomatic infectious individuals.

52 (H-4) After a period of latency of $1/\kappa = 5.1$ days, an exposed individual became
53 infected. Being p the probability of develop symptoms and $(1 - p)$ the
54 probability of became infectious but asymptomatic. Thus $p\kappa E$ denotes
55 the event of become infectious and develop symptoms given that the
56 individual has been exposed

57 (H-5) Asymptomatic individuals not die or get in a Hospital

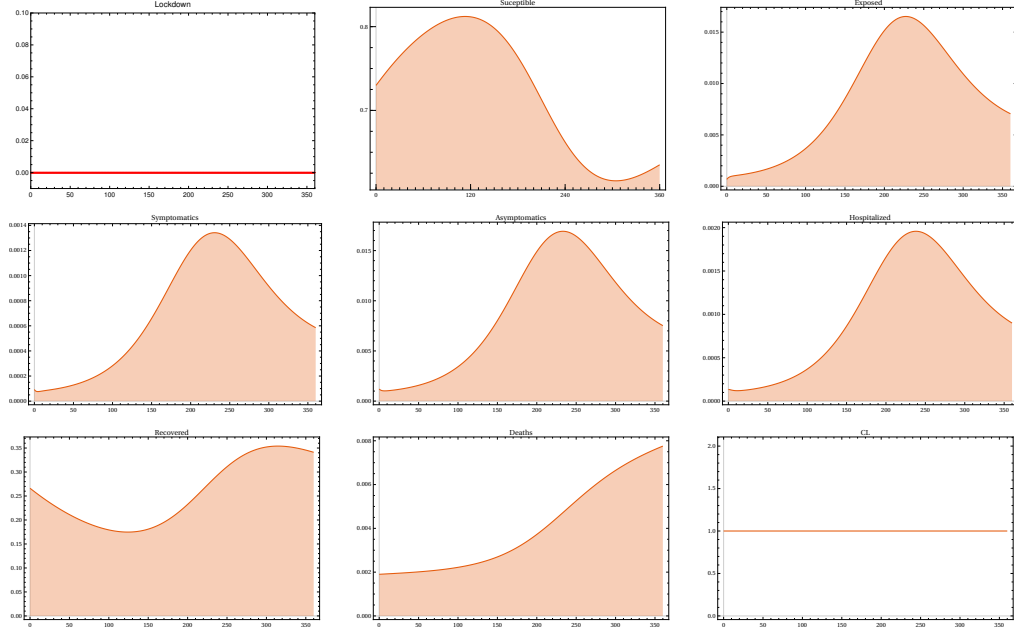
58 (H-6) A fraction μ_H of symptomatic individuals die by COVID-19 without hos-
59 pitalization

60

Thus we formulate the following Ordinary Differential Equation (ODE)

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

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62

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See Table 1 for notation and references values. Put here the flow diagram

[SDIV 2]
use WPS

64

2.1. Parameter calibration

65

Bayesian estimation. We calibrate parameters of our base dynamics in (1) via

66

Multichain Montecarlo (MCMC). To this end, we assume that the cumulative

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).

67 incidence of new infected symptomatic cases CI_S follows a Poisson distribution
68 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

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

[SDIV 3]
Review this
 R_0 calculation with
Gabriel

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

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]

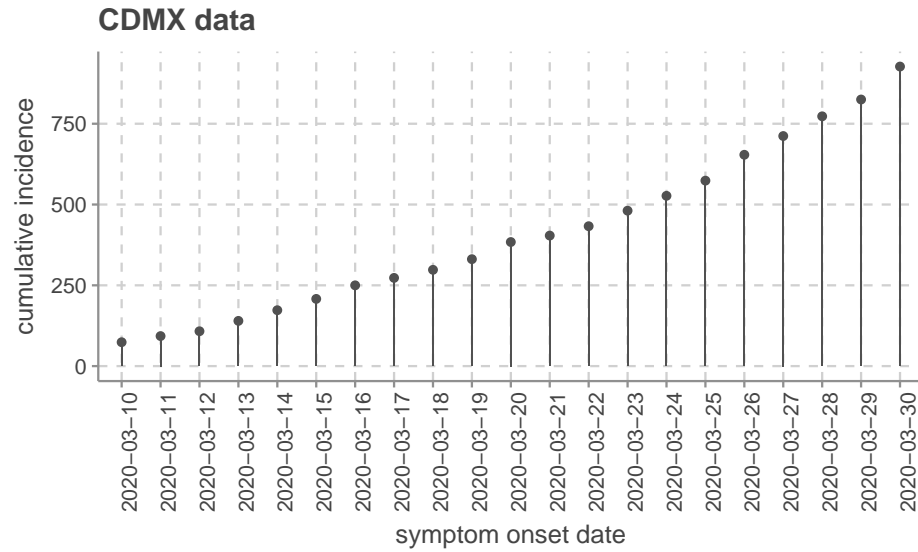


Figure 1: Cumulative new symptomatic and confirmed COVID19 reported cases from Ciudad de Mexico and Valle de Mexico [CITE] between March, 10, to March 30 of 2020.

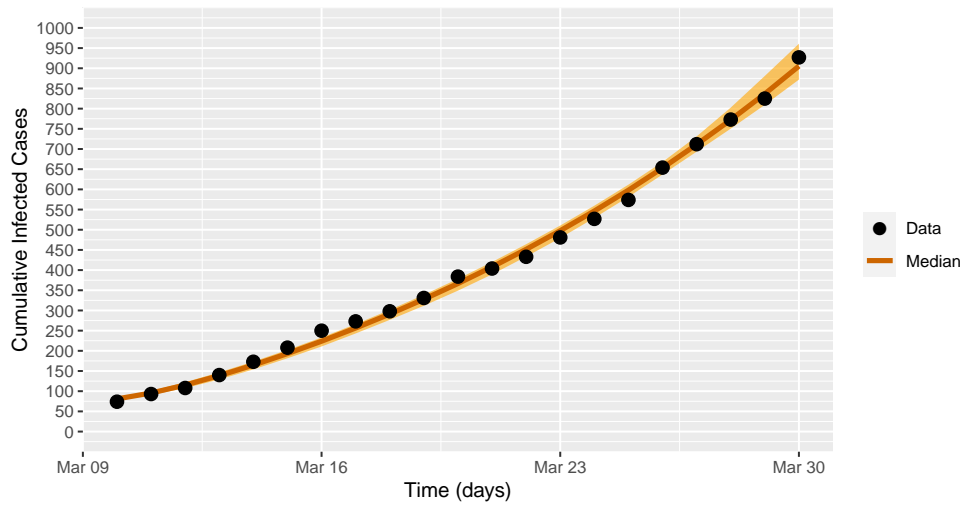


Figure 2: Fit of diary new cases of Mexico city during exponential growth.

72 **3. Imperfect-preventive COVID-19 vaccination**

73 *Preventive vaccines.*

74 *Efficacy and vaccine-induced immunity.*

75 *Actual vaccine stage development.*

76 *Vaccination reproductive number.*

77 *Vaccination rate λ_V estimate.*

78 *Feasibility regions according to efficacy and vaccination rate.*

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

81 (VH-1) Vaccine is preventive and only reduce susceptibility. Justify this hy-
82 pothesis cite

83 (VH-2) The vaccination campaign omits testing to detect seroprevalence. Thus
84 Exposed, Infected Asymptomatics and Recovered Asymptomatic indi-
85 viduals are undetected but would obtain a vaccine dose —which in these
86 model represent a waste of resources

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

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

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

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

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

89 4. Vaccination reproductive number

90 R_0 definition.

91 No vaccine reproductive number.

92 Vaccine reproductive number.

93 Efficacy, coverage and vaccination rate. [Here Gabriel's R not calculations.](#)^{SDIV}

$$R_{v0} := \left[1 - \frac{\epsilon \lambda_V}{\mu + \lambda_V + \delta_V} - \frac{\theta \mu (1 - \epsilon)}{\mu + \delta_L + \lambda_V} \right] (\mu R_1 + \delta_L) R_0$$

[SDIV 4]
Here countor
plots figure
as function
of efficacy
and vaccina-
tion rate

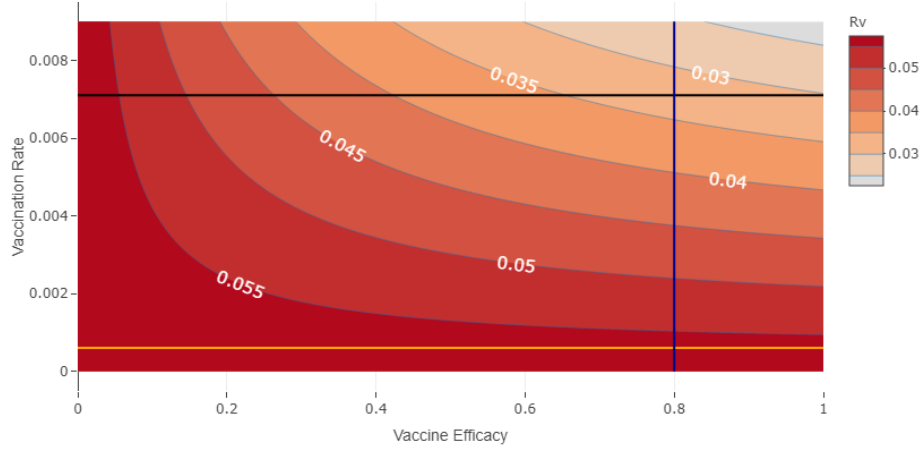


Figure 3: R not contour plot as function of efficacy and vaccination rate.

5. Optimal controlled version

Controlled Model. Now we model vaccination, treatment and lockdown as an 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 $X(T)$

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

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

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

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

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

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

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

121 Our objective is minimize the cost functional (5)—over an appropriated func-
 122 tional space—subject to the dynamics in equations (1) and (4), boundary con-
 123 ditions, and the path constrain in (7). That is, we search for vaccination policies

¹²⁴ $u_V(\cdot)$, which solve the following optimal control problem (OCP).

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

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

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

¹²⁵ **6. Numerical Experiments**

¹²⁶

[SDIV 5]
Aquí va tu descripción Frank.

Initial condition

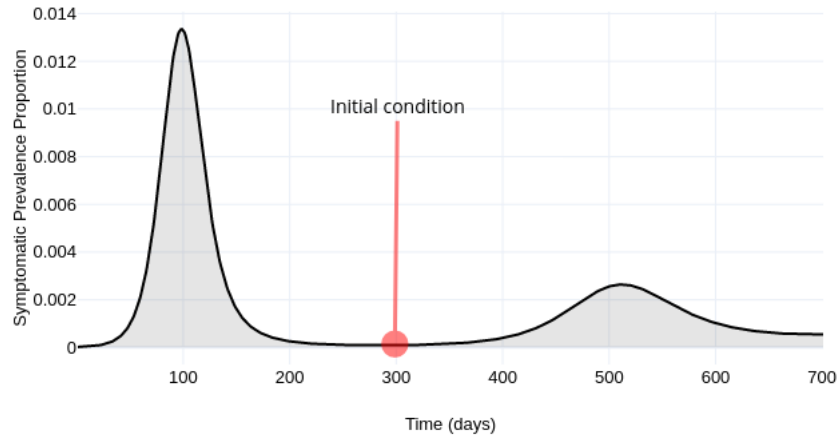


Figure 4: Initial condition scheme. We assume a positive prevalence. For reference, at the date of write this manuscript, prevalence in CDMX is around 16 000 cases, see <https://plotly.com/sauld/36/> to display a electronic viewer.

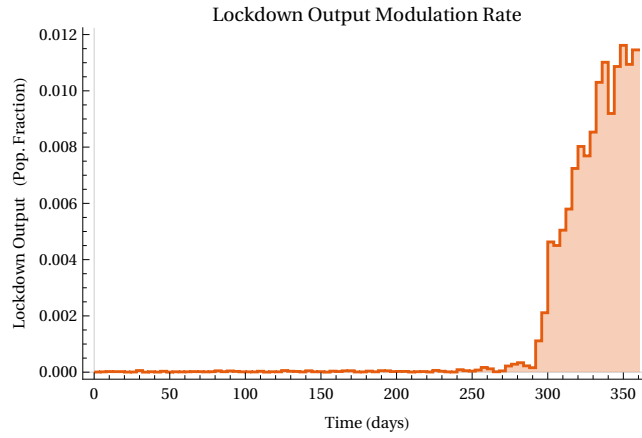


Figure 5: Lockdown modulation signal.

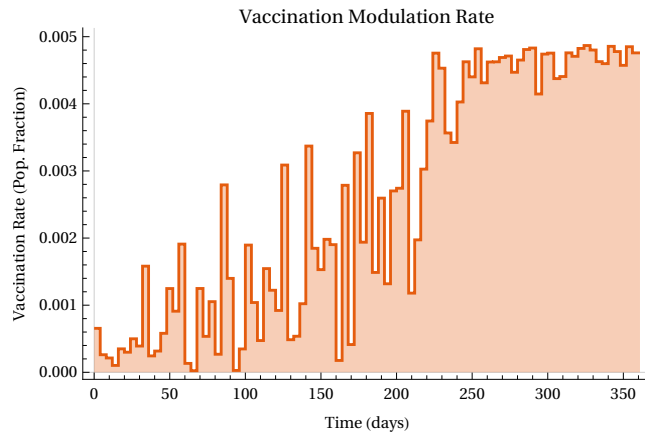


Figure 6: Vaccination rate modulation.

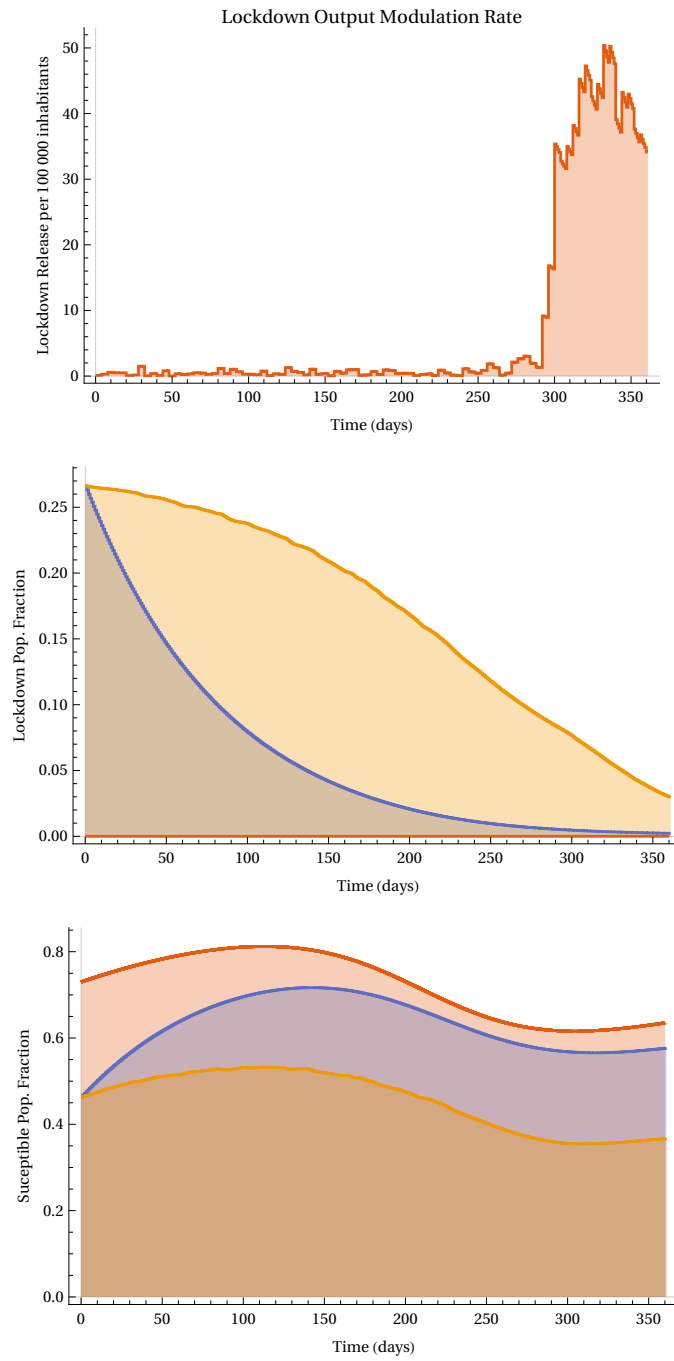


Figure 7: Modulation lock down release.

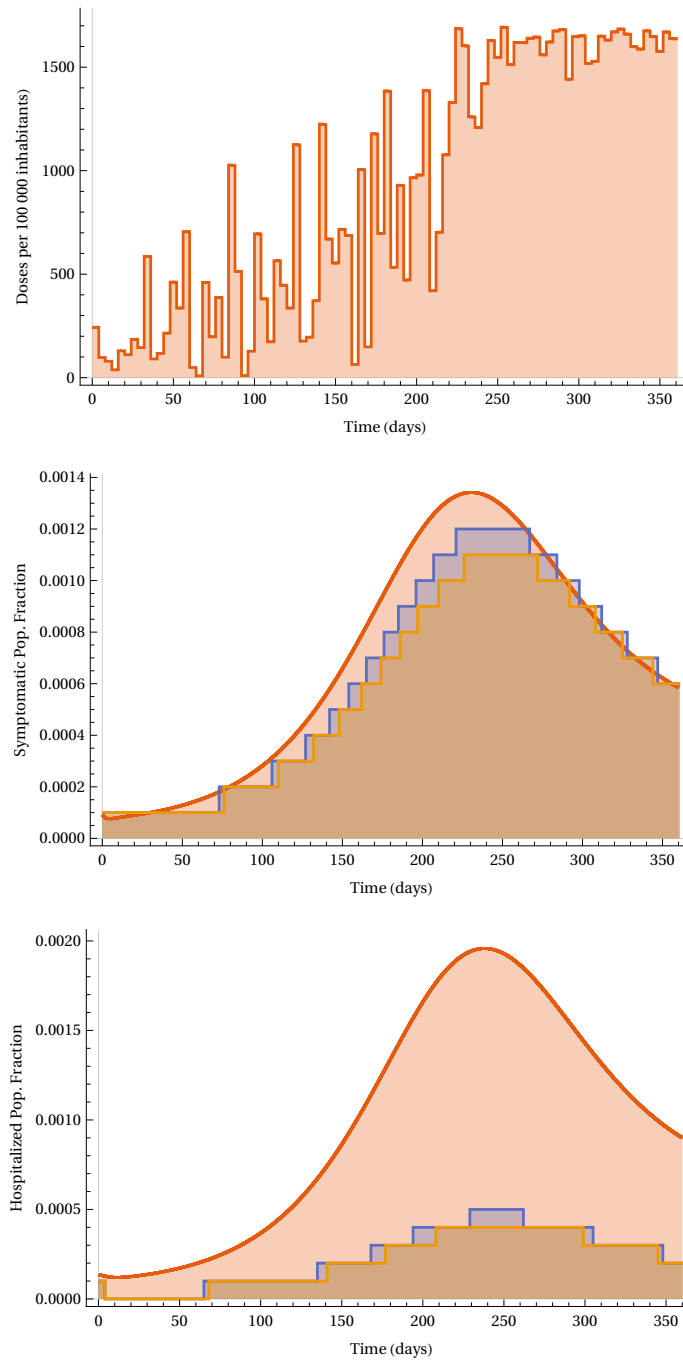


Figure 8: Symptomatic Prevalence and Hospitalization.

127 **Changes (compact)**

128 **Author: anonymous**

129 No changes.

130 **Author: SDIV**

131 Added 2

132 Deleted 2

133 Commented 5

134

135 **Appendix A. Existence of optimal policies**

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

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

139 subject to the dynamics

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

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

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

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

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

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

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

148 By Assumption (A-1), the system

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

149 has a unique solution $\tilde{X}_0(t; x_0, a_0)$ which is continuous in (x_0, a_0) . Next, put
150 $x_1 := \tilde{X}_0(t_1; x_0, a_0)$ 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

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

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

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

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

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

155 By Assumption (A-2), the mapping

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

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

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

162 References

- 163 [1] K. R. Aida-zade and A. B. Rahimov. Optimal control of a concentrated
 164 system on the class of piecewise constant functions under uncertainty in the
 165 parameters and initial conditions. *Cybernet. Systems Anal.*, 48(3):397–405,
 166 2012. Translation of Kibernet. Sistem. Anal. **2012**, no. 3, 91–100.
- 167 [2] Loïc Bourdin and Emmanuel Trélat. Linear-quadratic optimal sampled-
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 169 *J. IFAC*, 79:273–281, 2017.