EXISTENCE, CHARACTERIZATION AND SIMULATION OF OPTIMAL POLICIES IN A FAMILY OF EPIDEMIC MODELS

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Introduction

Speckled monster and control

By the end of the Middle Ages, smallpox cut down the population in centers of Europe and Asia.
This “monster” represents the first documented disease against which a specific control intervention was available: the inoculation.

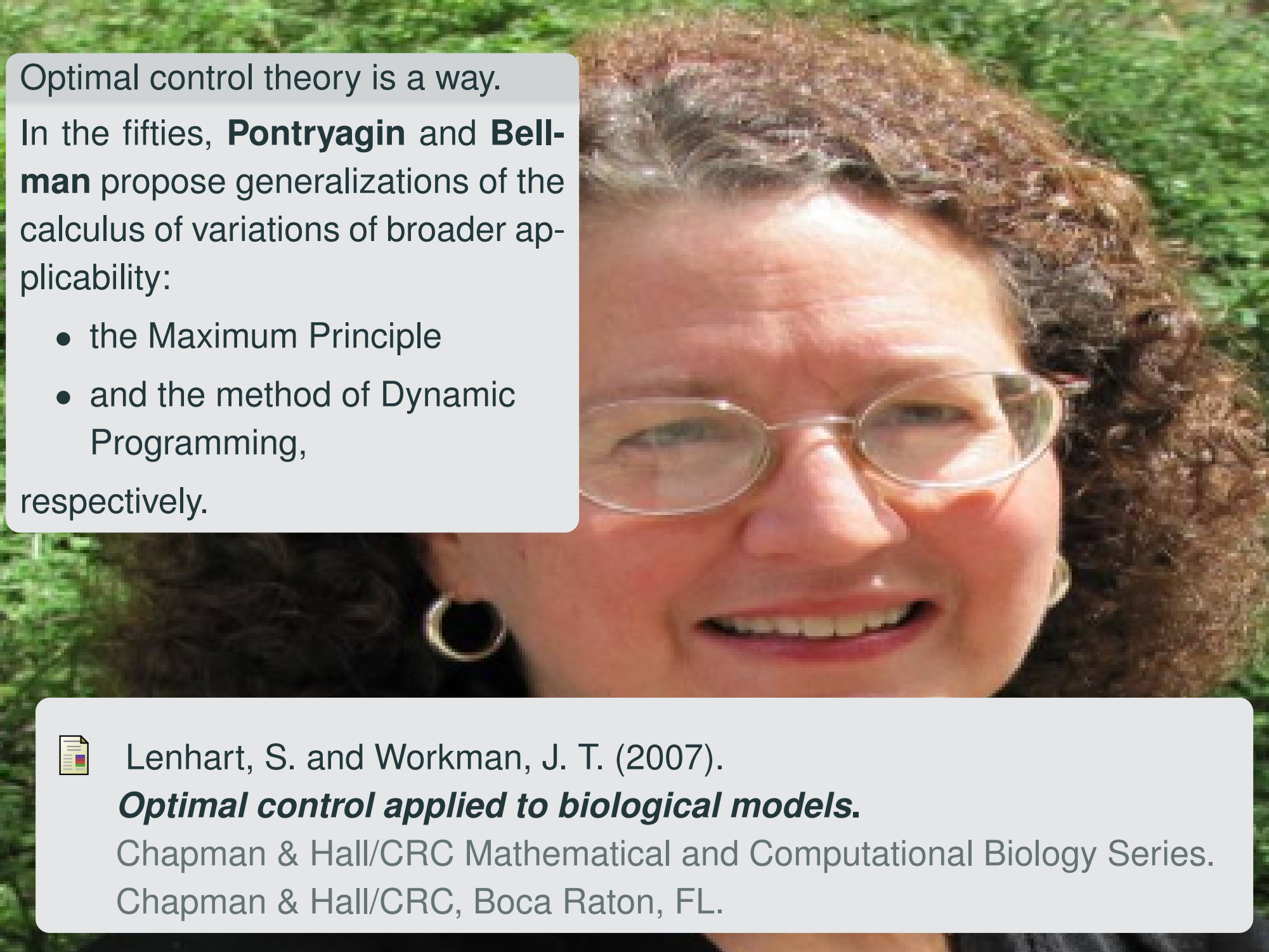

Bradley, L., Bernoulli, D., and d’Alembert, J. L. R. (1971). ***Smallpox inoculation: an eighteenth century mathematical controversy*.** Continuing Education Press.


Foppa, I. M. (2016). ***A Historical Introduction to Mathematical Modeling of Infectious Diseases. Seminal Papers in Epidemiology*.** Academic Press, 1 edition.

Then Bernoulli naturally sets a question like this: What happens if everybody were inoculated? Here, we address the question: **How to inoculate in an optimal way?**

Lev Semenovich Pontryagin (1908-1988)

- Soviet mathematician. He was born in Moscow and lost his eyesight due to a primus stove explosion when he was 14.
- He was able to become one of the greatest mathematicians of the 20th century, partially with the help of his mother Tatyana Andreevna who read mathematical books and papers (notably those of Heinz Hopf, J. H. C. Whitehead, and Hassler Whitney) to him.
- He made major discoveries in a number of fields of mathematics, including algebraic topology and differential topology.



Optimal control theory is a way.

In the fifties, **Pontryagin** and **Bellman** propose generalizations of the calculus of variations of broader applicability:

- the Maximum Principle
- and the method of Dynamic Programming,

respectively.

Lenhart, S. and Workman, J. T. (2007).
***Optimal control applied to biological models*.**
Chapman & Hall/CRC Mathematical and Computational Biology Series.
Chapman & Hall/CRC, Boca Raton, FL.

Contents

Control policies in epidemics

Control policies

Optimal control theory is a way.

- We require a **model** to describe the spreading of an uncontrolled disease, and whose transitions generate a **cost or reward**.
- Continuous **control action** that modify changes between states.
- A **functional** which describes **cost-reward**.

Optimal control theory is a way.

- A rule that prescribes which control operation to use at each time, is a **control policy**.
- **closed-loop** or **feedback** control.
- **open-loop** policy.

We consider control policies that affect the bounded rates at which population moves from one class (e.g., infected) to another (e.g., recovered).


Wickwire, K. (1977).
Mathematical models for the control of pests and infectious diseases: A survey.
Theoretical Population Biology, 11(2):182 – 238.

SARS: isolation and quarantine

If an disease lacks of a rapid diagnostic test, therapy or vaccine, then isolation and quarantine .
Gumel et. al model this strategies for (SARS).


Gumel, A. B., Ruan, S., Day, T., Watmough, J., Brauer, F., van den Driessche, P., Gabrielson, D., Bowman, C., Alexander, M. E., Ardal, S., Wu, J., and Sahai, B. M. (2004).
Modelling strategies for controlling sars outbreaks.
Proceedings of the Royal Society of London B: Biological Sciences, 271(1554):2223–2232.

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Based in the work of Gumel et. al., Yan and Zou report a control epidemic model for SARS. They use quarantine and isolation as mitigation controls.


Yan, X. and Zou, Y. (2008).
Optimal and sub-optimal quarantine and isolation control in sars epidemics.
Mathematical and Computer Modelling, 47(1):235 – 245.

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$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{S(\beta I + \mathscr{E}_E \beta E + \mathscr{E}_Q \beta Q + \mathscr{E}_J \beta J)}{N} - \mu S, \\
\frac{dE}{dt} &= p + \frac{\beta S(\beta I + \mathscr{E}_E \beta E + \mathscr{E}_Q \beta Q + \mathscr{E}_J \beta J)}{N} - (k_1 + \mu + \gamma_1)E, \\
\frac{dQ}{dt} &= \gamma_1 E - (k_2 + \mu)Q, \\
\frac{dI}{dt} &= k_1 E - (\gamma_2 + d_1 + \sigma_1 + \mu)I, \\
\frac{dJ}{dt} &= \gamma_2 I + k_2 Q - (d_2 + \sigma_2 + \mu)J, \\
\frac{dR}{dt} &= \sigma_1 I + \sigma_2 J - \mu R.
\end{aligned}
$$

SARS: isolation and quarantine

$$\min_{u\in U}\int_0^{t_f}\left[B_1E(t)+B_2Q(t)+B_3I(t)+B_4J(t)+\frac{C_1}{2}u_1^2(t)+\frac{C_2}{2}u_2^2(t)\right]dt.$$

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\frac{dS}{dt} &= \Lambda-\frac{S(\beta I+\mathscr{E}_E\beta E+\mathscr{E}_Q\beta Q+\mathscr{E}_J\beta J)}{N}-\mu S,\\
\frac{dE}{dt} &= p+\frac{\beta S(\beta I+\mathscr{E}_E\beta E+\mathscr{E}_Q\beta Q+\mathscr{E}_J\beta J)}{N}-(u_1(t)+k_1+\mu)E,\\
\frac{dQ}{dt} &= u_1(t)E-(k_2+\mu)Q,\\
\frac{dI}{dt} &= k_1E-(u_2(t)+d_1+\sigma_1+\mu)I,\\
\frac{dJ}{dt} &= u_2(t)I+k_2Q-(d_2+\sigma_2+\mu)J,\\
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$$\min_{u\in U}\int_0^{t_f}\left[B_1E(t)+B_2Q(t)+B_3I(t)+B_4J(t)+\frac{C_1}{2}u_1^2(t)+\frac{C_2}{2}u_2^2(t)\right]dt.$$

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\frac{dR}{dt} &= \sigma_1I+\sigma_2J-\mu R.
\end{aligned}$$

Existence and characterization of optimal policies

Existence and characterization of optimal policies

The non controlled epidemic model described above is of the form

$$\begin{aligned}\dot{X} &= AX + \begin{bmatrix} X^\top B^{(1)} \\ \vdots \\ X^\top B^{(n)} \end{bmatrix} X + k \\ &= \left(A + [X^\top \cdots X^\top] \begin{bmatrix} B^{(1)} \\ \vdots \\ B^{(n)} \end{bmatrix} \right) X + k\end{aligned}$$

where the matrix A represents the linear part of the system, each matrix $B^{(j)}$, $j = 1, \ldots, n$, gives the *interaction* part as a quadratic form, and k is a constant vector.

Thus the j-th row of the above system takes the form

$$\dot{X}_j = r_j(A)X + X^\top B^{(j)} X + k_j.$$

A family of control systems

Let $\mathbf{X} \subset \mathbb{R}^n$ and $\mathbf{U} \subset \mathbb{R}^m$ be nonempty and compact sets. The sets $\mathbf{X}$ and $\mathbf{U}$ are respectively called the *state space* and the *control space*. The vectors in X have non-negative entries, in particular we assume that $0 \in X$. The control set $\mathbf{U}$ is convex. We consider the following control system, for $j = 1, \ldots, n$,

$$\dot{X}_j = [r_j(A) + u^\top C^{(j)}]X + X^\top \begin{bmatrix} r_1(B^{(j)}) + u^\top D^{(j1)} \\ \vdots \\ r_n(B^{(j)}) + u^\top D^{(jn)} \end{bmatrix} X + k_j$$

where $A \in \mathbb{R}^{n \times n}$, $B^{(j)} \in \mathbb{R}^{n \times n}$, $C^{(j)} \in \mathbb{R}^{m \times n}$, and $D^{(jl)} \in \mathbb{R}^{m \times n}$ for $l = 1, \ldots, n$.

$$\dot{X}_j = [r_j(A) + u^\top C^{(j)}]X + X^\top \begin{bmatrix} r_1(B^{(j)}) + u^\top D^{(j1)} \\ \vdots \\ r_n(B^{(j)}) + u^\top D^{(jn)} \end{bmatrix} X + k_j, \quad j = 1, \ldots, n.$$

Theorem

For each measurable function $u : [0, T] \to \mathbf{U}$ and each initial condition $x_0 \in X$, there exists a unique absolutely continuous function $X_u : [0, T] \to \mathbb{R}^n$ that satisfies the the system almost everywhere.

Existence of optimal policies.

Consider the *cost functional* of an admissible control u, given the initial state x_0,

$$V(u, x_0) := \int_0^T g(X(t), u(t)) \, , dt, \tag{1}$$

where $g : \mathbf{X} \times \mathbf{U} \to \mathbb{R}$ is continuous. The *optimal control problem* (OCP) consists of finding an admissible control u^* such that

$$V(u^*, x_0) = \inf\{ V(u, x_0) \mid u \in \mathbb{U}_B \}.$$

If there exists such a control u^*, then it is called an *optimal policy* or *optimal control*. The pair (u^*, X^*), where X^* is given by the above Theorem, is an *optimal pair*.

Sufficient conditions for optimality

Consider the Hamiltonian $\mathscr{H} : \mathbf{X} \times \mathbf{U} \times \mathbb{R}^n \to \mathbb{R}$, defined as

$$\mathscr{H}(x, u, \lambda) := g(x, u) + \lambda^\top f(x, u),$$

and

$$\mathscr{H}^*(x, \lambda) := \inf_{u \in \mathbf{U}} \mathscr{H}(x, u, \lambda),$$

where g determines the cost functional and f is given by the right-hand side of the control system.

The function $\lambda : [0, T] \to \mathbb{R}^n$ and the admissible pair (u, X) satisfy the necessary conditions of the *Maximum Principle* (MP) if they solves *adjoint equation*

$$\dot{\lambda}(t) = -\mathscr{H}_x(X(t), u(t), \lambda(t))^\top, \quad \lambda(T) = 0,$$

and satisfy the *optimality condition*

$$\mathscr{H}^*(X(t), \lambda(t)) = \mathscr{H}(X(t), u(t), \lambda(t)).$$

Definition

The function w from $[0, T]$ to some Euclidean space is *piecewise continuous* if

(i) w is continuous on $[0, T]$ except at a finite number of points, and

(ii) if w is discontinuous at t, then

$$\lim_{s \to t^-} w(s) \text{ and } \lim_{s \to t^+} w(s)$$

are finite.

Pontryagin MP

Optimality condition

$$\mathscr{H}(x,u,\lambda) := g(x,u) + \lambda^\top f(x,u),$$
$$\mathscr{H}^*(x,\lambda) := \inf_{u\in\mathbf{U}} \mathscr{H}(x,u,\lambda),$$
$$\mathscr{H}^*(X(t),\lambda(t)) = \mathscr{H}(X(t),u(t),\lambda(t)).$$

adjoint equation

$$\dot{\lambda}(t) = -\mathscr{H}_x(X(t),u(t),\lambda(t))^\top,$$
$$\lambda(T) = 0.$$

Theorem

Let $\lambda : [0,T] \to \mathbb{R}^n$ be a continuous function and let (u^*, X^*) be an admissible pair such that

(i) *u^* is piecewise continuous,*

(ii) *$\dot{X}^*$ exists and is piecewise continuous,*

(iii) *(λ, u^*, X^*) satisfies the optimality condition, and,*

(iv) *except at the points of discontinuity of u^*, the adjoint equation holds.*

If, for each t, the function $\mathscr{H}^*(\cdot,\lambda(t))$ is convex on $\mathbf{X}$, then (u^*, X^*) is an optimal pair.

Example HIV

Consider the uncontrolled HIV model reported in (Butler 1997)

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_1 T + rT\left(1 - \frac{T+T_i}{T_{max}}\right) - k_1 VT$$
$$\frac{dT_i}{dt} = k_1 VT - \mu_2 T_i$$
$$\frac{dV}{dt} = N\mu_2 T_i - \mu_3 V$$


Butler, S., Kirschner, D., and Lenhart, S. (1997). **Optimal control of chemotherapy affecting the infectivity of hiv.** *Ann Arbor*, 1001:48109–0620.

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\frac{dV}{dt} &= N\mu_2 T_i - \mu_3 V
\end{aligned}$$

If $u(t)$ describes a treatment which modifies the T-cells, then the problem reads

$$\max_u \int_{t_i}^{t_f} \left[AT(t) - (1-u(t))^2\right] dt,$$

subject to $(\star)$.

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$$\frac{dT_i}{dt} = u(t)k_1 VT - \mu_2 T_i \qquad (\star)$$
$$\frac{dV}{dt} = N\mu_2 T_i - \mu_3 V$$

$$H(t,x,u,\lambda) = AT - (1-u)^2 + \langle \lambda, f \rangle,$$
$$\dot{\lambda}(t) = -\mathscr{H}_x(X(t),u(t),\lambda(t))^\top,\ \lambda(T) = 0$$

$$\dot{\lambda}_T = -A + \lambda_T\left[\mu_1 - r\left(1 - \frac{T_i}{T_{max}}\right)\right] - \lambda_{T_i} ukV$$
$$\dot{\lambda}_{T_i} = \lambda_T \frac{rT}{T_{max}} + \lambda_{T_i}\mu_2 - \lambda_V N\mu_2$$
$$\dot{\lambda}_V = \lambda_T\left(\frac{s}{(1+V)^2} + ukT\right) - \lambda_{T_i} ukT + \lambda_V \mu_3$$

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Numerical analysis

Indirect Methods

Since we can transform the problem of optimal control into the two-point boundary ODE problem:

$$\dot{x}(t) = f(x(t), u(t)), \qquad x(0) = x_0$$
$$\dot{\lambda}(t) = -\mathscr{H}_x(x(t), u(t), \lambda(t))^\top, \quad \lambda(T) = 0$$

methods designed to solve boundary value problem are applicable.

The most popular

Algorithm 2 Forward Backward Sweep

Input: $t_0, t_f, x_0, h, \text{tol}, \lambda_f$
Output: x^*, u^*, λ

procedure FORWARD_BACKWARD_SWEEP($g, \lambda_{\text{function}}, u, x_0, \lambda_f, h, n_{max}$)
  while $\epsilon > \text{tol}$ **do**
    $u_{\text{old}} \leftarrow u$
    $x_{\text{old}} \leftarrow x$
    $x \leftarrow$ RUNGE_KUTTA_FORWARD(g, u, x_0, h)
    $\lambda_{\text{old}} \leftarrow \lambda$
    $\lambda \leftarrow$ RUNGE_KUTTA_BACKWARD$(\lambda_{\text{function}}, x, \lambda_f, h)$
    $u_1 \leftarrow$ OPTIMALITY_CONDITION(u, x, λ)
    $u \leftarrow \alpha u_1 + (1-\alpha)u_{old}, \qquad \alpha \in [0,1]$ ▷ convex combination
    $\epsilon_u \leftarrow \dfrac{||u - u_{\text{old}}||}{||u||}$
    $\epsilon_x \leftarrow \dfrac{||x - x_{\text{old}}||}{||x||}$ ▷ relative error
    $\epsilon_\lambda \leftarrow \dfrac{||\lambda - \lambda_{\text{old}}||}{||\lambda||}$
    $\epsilon \leftarrow \max\{\epsilon_u, \epsilon_x, \epsilon_\lambda\}$
  end while
  return x^*, u^*, λ ▷ Optimal pair
end procedure

SARS: isolation and quarantine

$$\min_{u\in U}\int_0^{t_f}\left[B_1E(t)+B_2Q(t)+B_3I(t)+B_4J(t)+\frac{C_1}{2}u_1^2(t)+\frac{C_2}{2}u_2^2(t)\right]dt.$$

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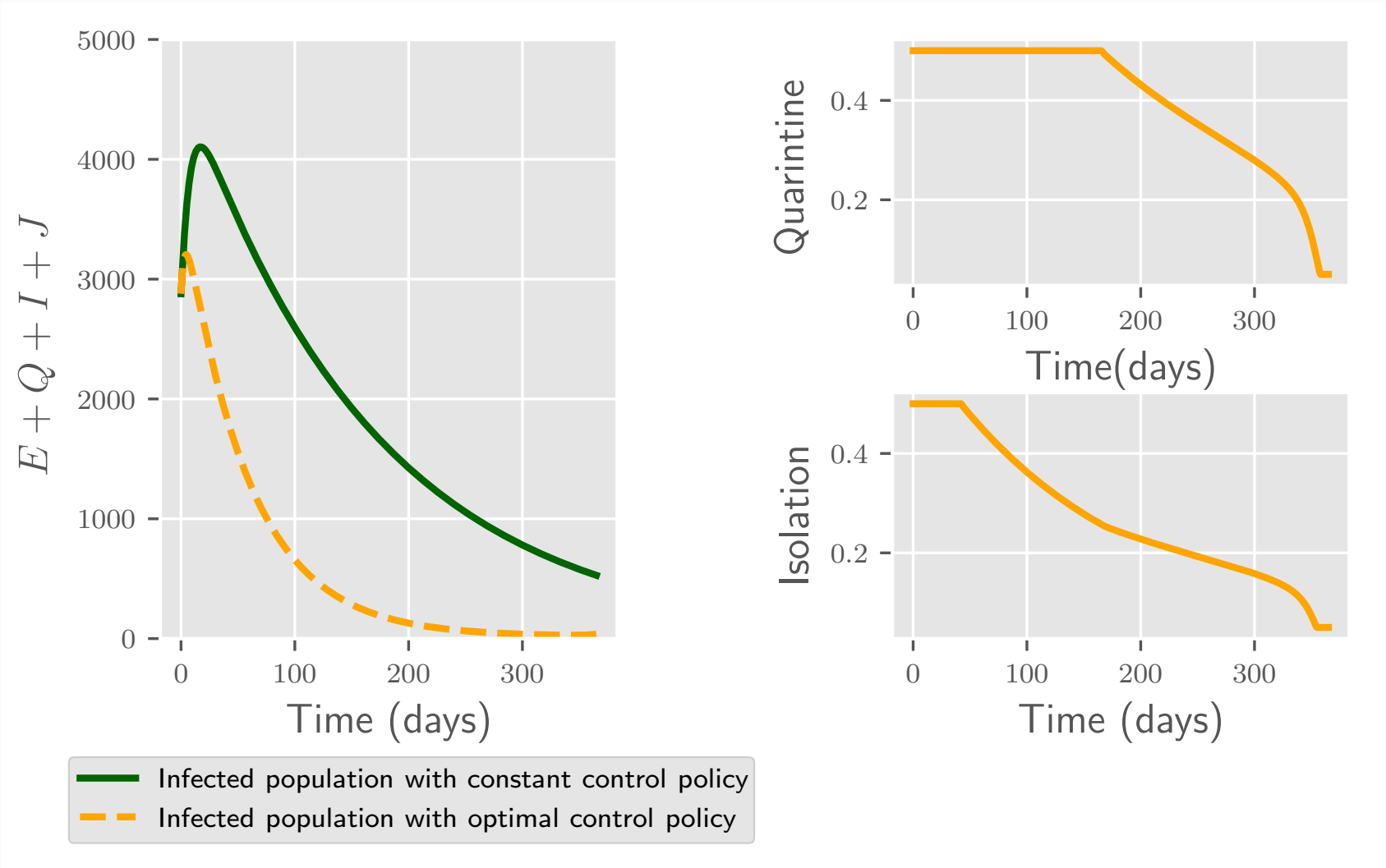
\frac{dJ}{dt} &= u_2(t)I+k_2Q-(d_2+\sigma_2+\mu)J,\\
\frac{dR}{dt} &= \sigma_1I+\sigma_2J-\mu R.
\end{aligned}$$

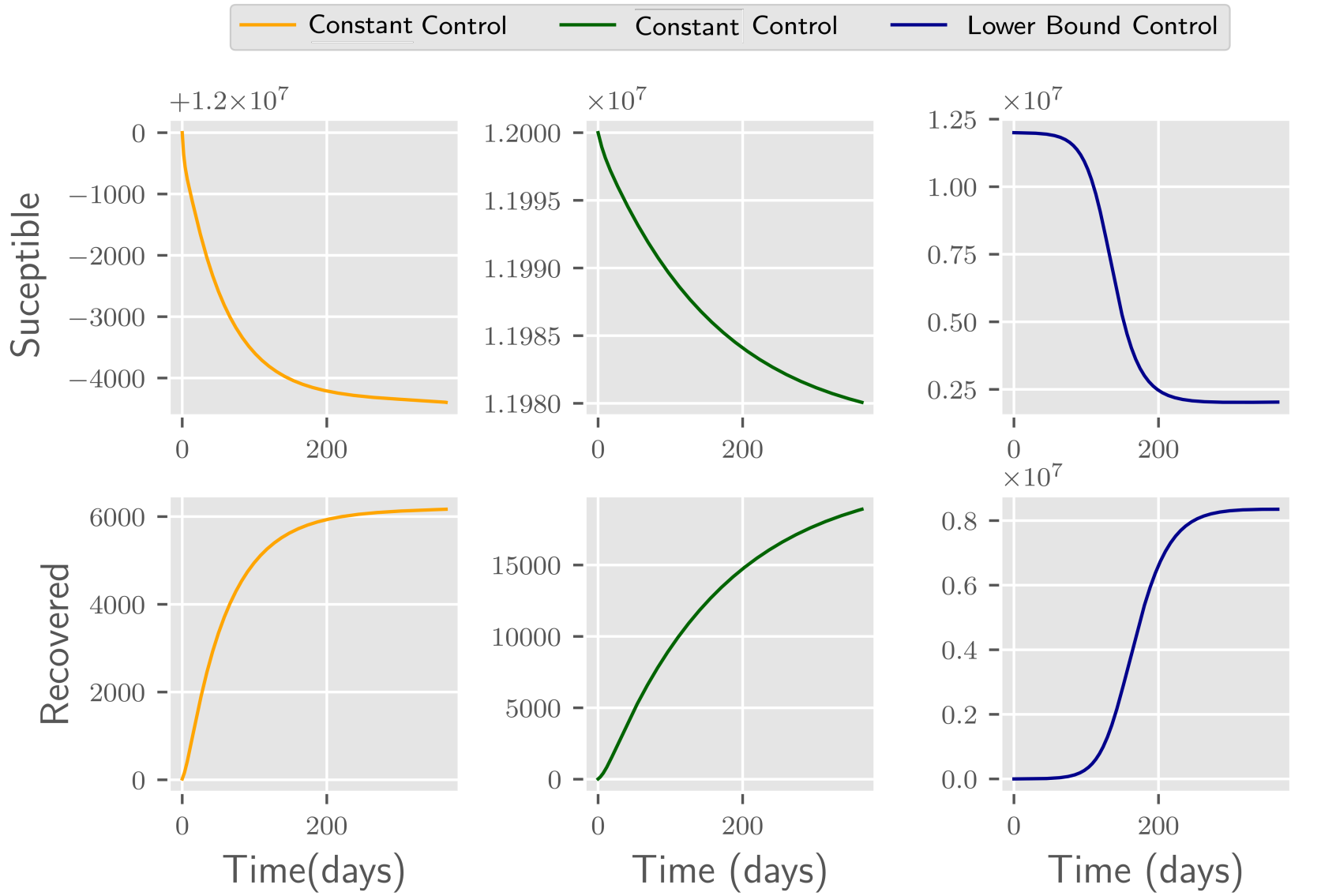
Parameters values

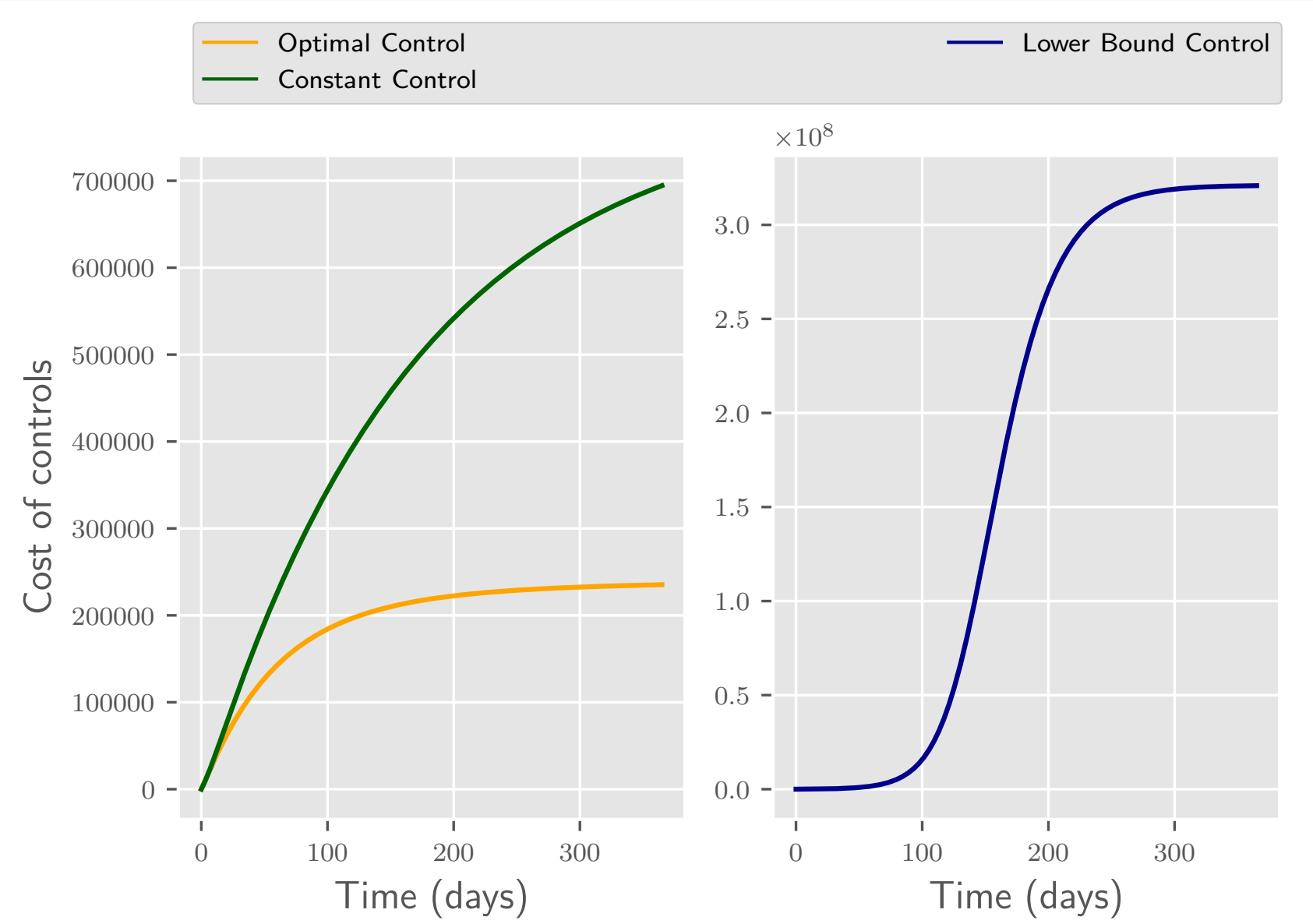
β	0.2	d_1, d_2	0.0079, 0.0337
ε_E, ε_Q, ε_J	0.3, 0.0, 0.1	k_1, k_2	0.1, 0.125
μ	0.000 034		
Λ	μN		
p	0.0		
σ_1, σ_2	0.0337, 0.0386		
t_f	1.0 year		
Step size	$dt = 1.0$ day		
u_i bounds	0.05, 0.5		
B_1, B_2, B_3, B_4	1.0, 1.0, 1.0, 1.0		
C_1, C_2	300, 600		

Initial conditions

$S(0) = 12 \times 10^6$, $E(0) = 1565$,
$Q(0) = 292$, $I(0) = 695$,
$J(0) = 326$, $R(0) = 20$


5000
4000
3000
2000
1000
0
$E + Q + I + J$
0
100
200
300
Time (days)
Infected population with constant control policy
Infected population with optimal control policy
Quarintine
0.4
0.2
0
100
200
300
Time(days)
Isolation
0.4
0.2
0
100
200
300
Time (days)


Constant Control
Constant Control
Lower Bound Control
Suceptible
Recovered
Time(days)
Time (days)
Time (days)


Optimal Control
Constant Control
Lower Bound Control
Cost of controls
700000
600000
500000
400000
300000
200000
100000
0
0
100
200
300
Time (days)
$\times 10^8$
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
100
200
300
Time (days)

Concluding remarks

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Uniqueness of optimal policy. The proof of the uniqueness of the state path X_u, given a policy u, is fairly standard. However, the uniqueness of an *optimal policy* is not trivial and it can be established on some small enough interval.

Numerical schemes. According with the forward-backward-sweep, the schemes needs a ODE solver one of its steps. However some times this solver generates spurious solutions as resulting of numeric instability. We see an opportunity to apply nonstandard numerical schemes which are consistent with the underlying conservation laws.

Direct methods

Maximum principle vs. Dynamic programming. The same approach is followed in almost all the related literature on optimal control of epidemics/diseases.

As an alternative, the so-called Dynamic programming approach can be used to analyze this kind of problems. With the Maximum principle we need to solve a system of ordinary differential equations (ODEs) whereas in Dynamic programming a partial differential equation (PDE) arises. In addition, both approaches involve an optimization problem.

By following the DP approach, the optimal policies are obtained in *feedback* (or *Markov*) form, i.e., the control policy is a function of the state of the system. Thus DP is a natural approach to solve stochastic models.

References

Complete list of references:
https://www.overleaf.com/read/vnvgjdqkmznc

Python code:

 Saúl Díaz-Infante, Francisco Peñuñuri, and David González-Sánchez, *Python implementation of the forward-backward-sweep method for epidemic models*, `https://github.com/SaulDiazInfante/PythonLenhartCode`, 2018, Accessed: Aug-15-2018.