An Introduction to Optimal Control Applied to Disease Models

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Example

$x(t)$ Number of cancer cells at time t
(exponential growth) **State**

$u(t)$ Drug concentration **Control**

$$\frac{dx}{dt} = \alpha x(t) - u(t)$$

$x(0) = x_0$ known initial data

minimize $\left\{ x(T) + \int_0^T u^2(t)\, dt \right\}$

where the first term represents number of cancer cells and the second term represents harmful effects of drug on body.

Optimal Control

Adjust controls in a system to achieve a goal

System:

- Ordinary differential equations
- Partial differential equations
- Discrete equations
- Stochastic differential equations
- Integro-difference equations

Deterministic Optimal Control

Control of Ordinary Differential Equations (DE)

$u(t)$ control

$x(t)$ state

State function satisfies DE

Control affects DE

$$x'(t) = g(t, x(t), u(t))$$

$u(t), x(t) \rightarrow$ Goal (objective functional)

Basic Idea

System of ODEs modeling situation

Decide on format and bounds on the controls

Design an appropriate objective functional

Derive necessary conditions for the optimal control

Compute the optimal control numerically

Design an appropriate objective functional

–balancing opposing factors in functional

–include (or not) terms at the final time

Big Idea

In optimal control theory, after formulating a problem appropriate to the scenario, there are several basic problems :

(a) to prove the existence of an optimal control,

(b) to characterize the optimal control,

(c) to prove the uniqueness of the control,

(d) to compute the optimal control numerically,

(e) to investigate how the optimal control depends on various parameters in the model.

Deterministic Optimal Control- ODEs

Find piecewise continuous control $u(t)$ and associated state variable $x(t)$ to maximize

$$\max \int_0^T f(t, x(t), u(t))\, dt$$

subject to

$$x'(t) = g(t, x(t), u(t))$$

$x(0) = x_0$ and $x(T)$ $free$

Contd.

- Optimal Control $u^*(t)$ achieves the maximum
- Put $u^*(t)$ into state DE and obtain $x^*(t)$
- $x^*(t)$ corresponding optimal state
- $u^*(t)$, $x^*(t)$ optimal pair

Necessary, Sufficient Conditions

Necessary Conditions

If $u^*(t)$, $x^*(t)$ are optimal, then the following conditions hold

$\vdots$

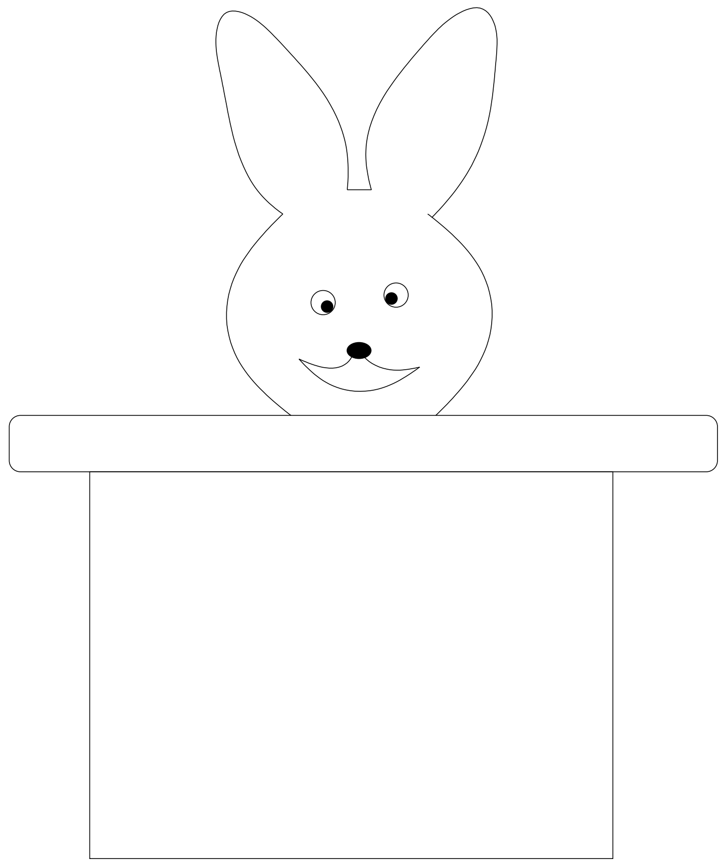
Sufficient Conditions

If $u^*(t)$, $x^*(t)$ and λ (adjoint) satisfy the conditions

$\vdots$

then $u^*(t)$, $x^*(t)$ are optimal.

Adjoint



like Lagrange multipliers to attach DE to objective functional.

Deterministic Optimal Control- ODEs

Find piecewise continuous control $u(t)$ and associated state variable $x(t)$ to maximize

$$\max \int_0^T f(t, x(t), u(t))\, dt$$

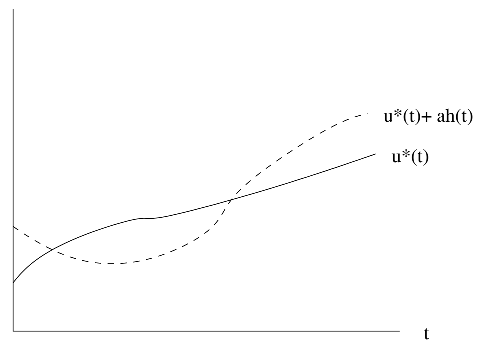
subject to

$$x'(t) = g(t, x(t), u(t))$$

$x(0) = x_0$ and $x(T)\ free$

Quick Derivation of Necessary Condition

Suppose u^* is an optimal control and x^* corresponding state. $h(t)$ variation function, $a \in \mathbb{R}$.

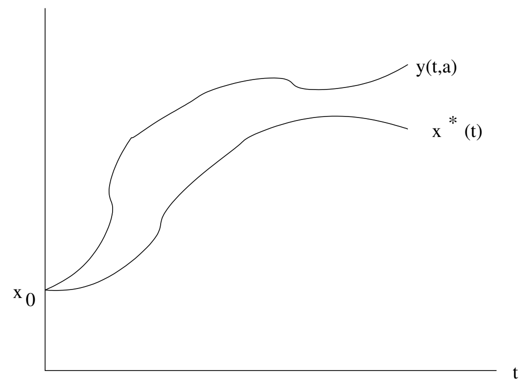


$u^*(t) + ah(t)$ another control.
$y(t,a)$ state corresponding to $u^* + ah$,

$$\frac{dy(t,a)}{dt} = g\left(t, y(t,a), (u^* + ah)(t)\right)$$

Contd.

At $t = 0$, $y(0, a) = x_0$



all trajectories start at same position

$$y(t, 0) = x^*(t) \qquad \text{when } a = 0, \text{ control } u^*$$

$$J(a) = \int_0^T f\left(t, y(t, a), u^*(t) + ah(t)\right) \, dt$$

Maximum of J w.r.t. a occurs at $a = 0$.

Contd.

$$\left.\frac{dJ(a)}{da}\right|_{a=0} = 0$$

$$\int_0^T \frac{d}{dt}\left(\lambda(t)y(t,a)\right)\,dt = \lambda(T)y(T,a) - \lambda(0)y(0,a)$$

$$\Rightarrow \int_0^T \frac{d}{dt}\left(\lambda(t)y(t,a)\right)\,dt + \lambda(0)y(0,a) - \lambda(T)y(T,a) = 0.$$

Adding 0 to our $J(a)$ gives

Contd.

$$
\begin{aligned}
J(a) = \int_0^T &\left[f(t, y(t,a), u^* + ah) + \frac{d}{dt}\left(\lambda(t) y(t,a)\right) \right] dt \\
&+ \lambda(0) y(0,a) - \lambda(T) y(T,a) \\
= \int_0^T &[f(t, y(t,a), u^* + ah) + \lambda'(t) y(t,a) \\
&\quad + \lambda(t) g(t, y, u^* + ah)]\, dt + \lambda(0) x_0 - \lambda(T) y(T,a)
\end{aligned}
$$

here we used product rule and $g = dy/dt$.

Contd.

$$\frac{dJ}{da} = \int_0^T \left[f_x \frac{\partial y}{\partial a} + f_u \frac{\partial (u^* + ah)}{\partial a} + \lambda'(t) \frac{\partial y}{\partial a} \right.$$

$$\left. + \lambda(t) \left(g_x \frac{\partial y}{\partial a} + g_u \frac{\partial (u^* + ah)}{\partial a} \right) \right] dt - \lambda(T) \frac{\partial}{\partial a} y(T, a).$$

Arguments of f, g terms are $(t, y(t, a), u^* + ah(t))$.

$$0 = \frac{dJ}{da}(0) = \int_0^T \left[(f_x + \lambda g_x + \lambda') \left. \frac{dy}{da} \right|_{a=0} + (f_u + \lambda g_u)\, h \right] dt$$

$$- \lambda(T) \frac{\partial y}{\partial a}(T, 0).$$

Arguments of f, g terms are $(t, x^*(t), u^*(t))$.

Contd.

Choose $\lambda(t)$ s.t.

$$\lambda'(t) = -\left[f_x(t, x^*, u^*) + \lambda(t) g_x(t, x^*, u^*)\right] \quad \text{adjoint equation}$$

$$\lambda(T) = 0 \quad \text{transversality condition}$$

$$0 = \int_0^T (f_u + \lambda g_u)\; h(t)\, dt$$

$h(t)$ arbitrary variation

$$\Rightarrow f_u(t, x^*, u^*) + \lambda(t) g_u(t, x^*, u^*) = 0 \quad \text{for all } 0 \le t \le T.$$

Optimality condition.

Using Hamiltonian

Generate these Necessary conditions from Hamiltonian

$$H(t,x,u,\lambda) = f(t,x,u) + \lambda g(t,x,u)$$

integrand $+$ (adjoint) (RHS of DE)

maximize H w.r.t. u at u^*

$$\frac{\partial H}{\partial u} = 0 \Rightarrow f_u + \lambda g_u = 0 \quad \text{optimality eq.}$$

$$\lambda' = -\frac{\partial H}{\partial x} \Rightarrow \lambda' = -(f_x + \lambda g_x) \quad \text{adjoint eq.}$$

$$\lambda(T) = 0 \quad \text{transversality condition}$$

Converted problem of finding control to maximize objective functional subject to DE, IC to using Hamiltonian pointwise.

For maximization

$$\frac{\partial^2 H}{\partial u^2} \leq 0 \quad \text{at } u^* \quad \bigcap H(u) \quad \text{as a function of } u$$

For minimization

$$\frac{\partial^2 H}{\partial u^2} \geq 0 \quad \text{at } u^* \quad \bigcup H(u) \quad \text{as a function of } u$$

Two unknowns u^* and x^*
introduce adjoint λ (like a Lagrange multiplier)

Three unknowns u^*, x^* and λ

H nonlinear w.r.t. u

Eliminate u^* by setting $H_u = 0$
and solve for u^* in terms of x^* and λ

Two unknowns x^* and λ
with 2 ODEs (2 point BVP)
+ 2 boundary conditions.

Pontryagin Maximum Principle

If $u^*(t)$ and $x^*(t)$ are optimal for above problem, then there exists adjoint variable $\lambda(t)$ s.t.

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)),$$

at each time, where Hamiltonian H is defined by

$$H(t, x(t), u(t), \lambda(t)) = f(t, x(t), u(t)) + \lambda g(t, x(t), u(t)).$$

and

$$\lambda'(t) = -\frac{\partial H(t, x(t), u(t), \lambda(t))}{\partial x}$$

$$\lambda(T) = 0 \qquad \text{transversality condition}$$

Hamiltonian

$$H = f(t, x, u) + \lambda(t) f(t, x, u)$$

u^* maximizes H w.r.t. u, H is linear w.r.t. u

$$H = h(t, x, \lambda)u(t) + k(t, x, \lambda)$$

bounded controls, $a \leq u(t) \leq b$.
Bang-bang control or singular control

Example: $H = 2u + \lambda u + x - \lambda x^2$

$$\frac{\partial H}{\partial u} = 2 + \lambda \stackrel{?}{=} 0 \quad \text{cannot solve for } u$$

H is nonlinear w.r.t. u, set $H_u = 0$ and solve for u^*
optimality equation.

Example 1

$$\min_u \int_0^1 u(t)^2\,dt$$

subject to $\quad x'(t) = x(t) + u(t),\ x(0) = i$

What optimal control is expected?

Example 1 worked

$$\min \int_0^1 u^2(t)\,dt$$

$$x' = x + u, \quad x(0) = 1$$

$$H = \text{ integrand } + \lambda \text{ RHS of DE } = u^2 + \lambda(x+u)$$

$$\frac{\partial H}{\partial u} = 2u + \lambda = 0 \Rightarrow u^* = -\frac{\lambda}{2} \quad \text{at } u^*$$

$$\frac{\partial^2 H}{\partial u^2} = 2$$

$$\lambda' = -\frac{\partial H}{\partial x} = -\lambda \quad \lambda(1) = 0$$

$$\lambda = \lambda_0 e^{-t} \to 0 = \lambda_0 e^{-1} \Rightarrow \lambda_0 = 0$$

$$\lambda \equiv 0, u^* \equiv 0, x^* = e^t$$

Example 2

$$\min_u \int_0^2 x(t) + \frac{1}{2}u(t)^2 \, dt$$

subject to $\quad x'(t) = x(t) + u(t),\ x(0) = \frac{1}{2}e^2 - 1.$

What optimal control is expected?

Hamiltonian

$$H = x + \frac{1}{2}u^2 + \lambda(x+u)$$

The adjoint equation and transversality condition give

$$\lambda'(t) = -\frac{\partial H}{\partial x} = -1-\lambda,\ \lambda(2) = 0 \ \Rightarrow \ \lambda(t) = e^{2-t}-1,$$

Example 2 continued

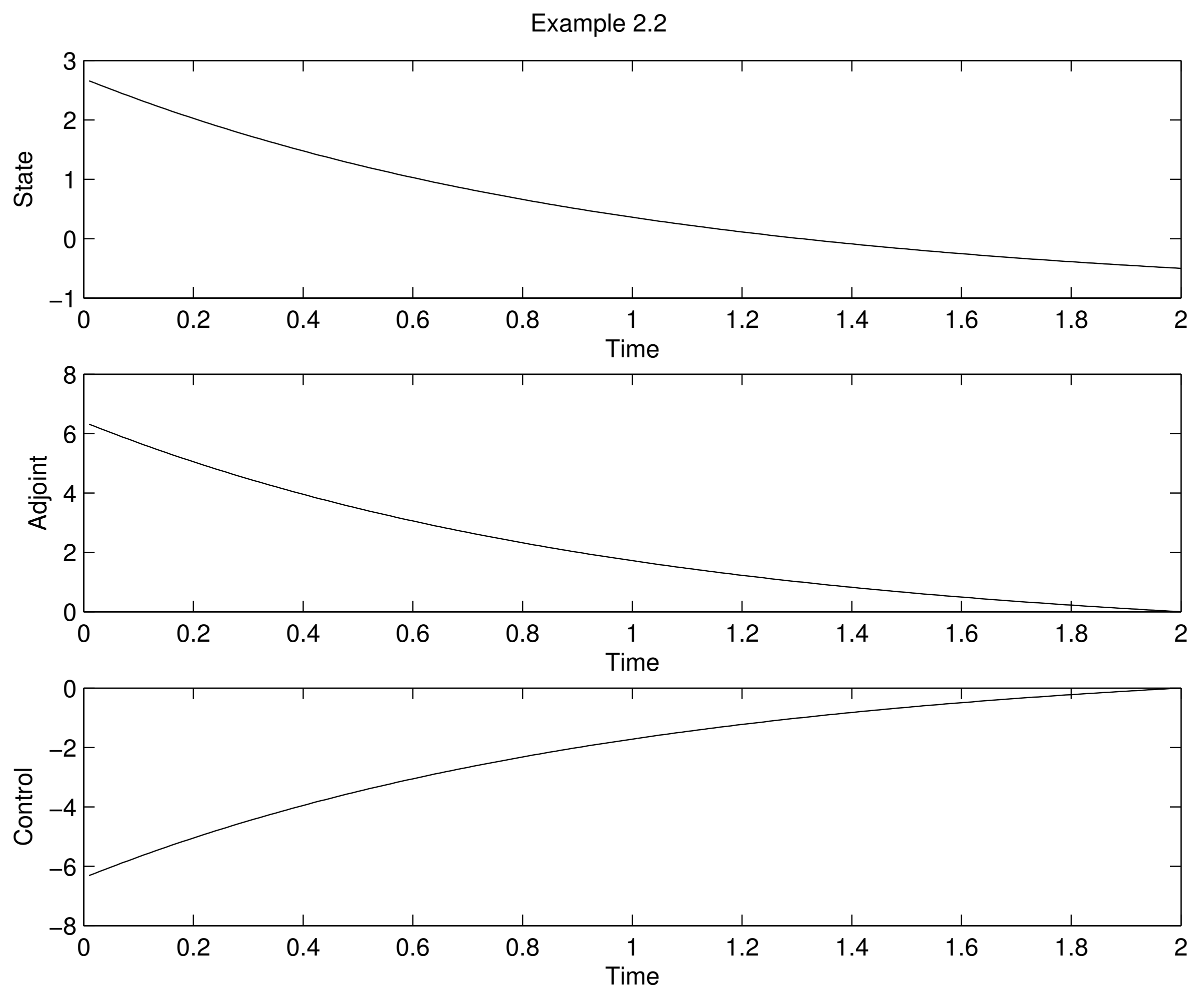
and the optimality condition leads to

$$0 = \frac{\partial H}{\partial u} = u + \lambda \;\Rightarrow\; u^*(t) = -\lambda = 1 - e^{2-t}.$$

The associated state is

$$x^*(t) = \frac{1}{2}e^{2-t} - 1.$$

Graphs, Example 2



Example 3

$$\int_1^5 (ux - u^2 - x^2)\,dt$$

$$x' = x + u, \quad x(1) = 2$$

$$H = ux - u^2 - x^2 + \lambda(x + u)$$

$$\frac{\partial H}{\partial u} = x - 2u + \lambda = 0 \quad \text{at } u^* \Rightarrow u^* = \frac{x + \lambda}{2}$$

$$\lambda' = -\frac{\partial H}{\partial x} = -(u - 2x + \lambda), \quad \lambda(5) = 0$$

$$\lambda' = -\left(\frac{x + \lambda}{2} - 2x + \lambda\right)$$

$$x' = x + \frac{x + \lambda}{2}$$

Contd.

$$
\begin{aligned}
x' &= \frac{3}{2}x + \frac{\lambda}{2} \\
\lambda' &= \frac{3}{2}x - \frac{3}{2}\lambda \\
x(1) &= 2, \quad \lambda(5) = 0
\end{aligned}
$$

Solve for x^*, λ and then get u^*.

Do numerically with Matlab or by hand

$$
\begin{pmatrix} x \\ \lambda \end{pmatrix} = C_1 \begin{pmatrix} 1 \\ 2\sqrt{3}-3 \end{pmatrix} e^{\sqrt{3}t} + C_2 \begin{pmatrix} 1 \\ -2\sqrt{3}-3 \end{pmatrix} e^{-\sqrt{3}t}
$$

Exercise

$$\max_u \int_0^1 (x+u)\,dt$$

$x' = 1 - u^2, \quad x(0) = 1, \quad u$ control. $\quad H =$

$$\frac{\partial H}{\partial u} = 0$$

$\lambda' =$ $\qquad\qquad$ $\lambda =$

$\lambda(1) =$

$u^* =$ $\qquad\qquad$ $x^* =$

Exercise completed

$$\max_u \int_0^1 (x+u)\,dt$$

$x' = 1 - u^2, \quad x(0) = 1 \quad u$ control

$$H(t,x,u,\lambda) = x + u + \lambda(1-u^2)$$

$$\frac{\partial H}{\partial u} = 1 - 2\lambda u = 0 \quad \Rightarrow u = \frac{1}{2\lambda} \quad \& H_{uu} = -2\lambda \leq 0,$$

$$\lambda' = -\frac{\partial H}{\partial x} = -1, \quad \lambda(1) = 0, \quad \Rightarrow \lambda = 1 - t$$

$$x' = 1 - u^2 = 1 - \frac{1}{4(1-t)^2}$$

$$x^*(t) = t - 1/4(1-t) + 5/4, \quad u^*(t) = 1/2(1-t).$$

Contd.

$$\int_0^1 [x^*(t) + u^*(t)]\, dt = \infty$$

There is not an “Optimal Control" in this case.

Want finite maximum.

Here unbounded optimal state
unbounded OC

Opening Example

$x(t)$ Number of cancer cells at time t (exponential growth) **State**

$u(t)$ Drug concentration **Control**

$$\frac{dx}{dt} = \alpha x(t) - u(t)$$

$x(0) = x_0$ known initial data

minimize $\left\{ x(T) + \int_0^T u^2(t)\,dt \right\}$

See need for bounds on the control. See salvage term.

Further topics to be covered

Interpretation of the adjoint
Salvage term
Numerical algorithms
Systems case
Linear in the control case

Discrete models

more info

See my homepage www.math.utk.edu$\setminus$ $\sim$lenhart
Optimal Control Theory in Application to Biology
short course lectures and lab notes
Book: Optimal Control applied to Biological Models
CRC Press, 2007, Lenhart and J. Workman