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)  \( \text{State} \)

\( u(t) \) Drug concentration  \( \text{Control} \)

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

\( x(0) = x_0 \) 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)

\[ u(t) \quad \text{control} \]
\[ x(t) \quad \text{state} \]

State function satisfies DE
Control affects DE

\[ x'(t) = g(t, x(t), u(t)) \]
\[ u(t), x(t) \rightarrow \quad \text{Goal (objective functional)} \]
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
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

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

$$x(0) = x_0 \text{ and } x(T) \text{ free}$$
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 Conditions
If $u^*(t), x^*(t)$ are optimal, then the following conditions hold:

Sufficient Conditions
If $u^*(t), x^*(t)$ and $\lambda$ (adjoint) satisfy the conditions:
then $u^*(t), x^*(t)$ are optimal.
like Lagrange multipliers to attach DE to objective functional.
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

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

$$x(0) = x_0 \text{ and } x(T) \text{ free}$$
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 $u^* + ah$,

$$\frac{dy(t, a)}{dt} = g(t, y(t, a), (u^* + ah)(t))$$
At \( t = 0 \), \( y(0, a) = x_0 \)

all trajectories start at same position

\[ y(t, 0) = x^*(t) \quad \text{when } a = 0, \quad \text{control } u^* \]

\[ J(a) = \int_0^T f(t, y(t, a), u^*(t) + ah(t)) \, dt \]

Maximum of \( J \) w.r.t. \( a \) occurs at \( a = 0 \).
\[
\frac{dJ(a)}{da} \bigg|_{a=0} = 0
\]

\[
\int_0^T \frac{d}{dt} (\lambda(t)y(t, a)) \ dt = \lambda(T)y(T, a) - \lambda(0)y(0, a)
\]

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

Adding 0 to our \( J(a) \) gives
\[ J(a) = \int_0^T \left[ f(t, y(t, a), u^* + ah) + \frac{d}{dt} (\lambda(t)y(t, a)) \right] \, dt \\
+ \lambda(0)y(0, a) - \lambda(T)y(T, a) \\
= \int_0^T \left[ f(t, y(t, a), u^* + ah) + \lambda'(t)y(t, a) \\
+ \lambda(t)g(t, y, u^* + ah) \right] \, dt + \lambda(0)x_0 - \lambda(T)y(T, a) \]

here we used product rule and \( g = dy/dt. \)
\[
\frac{dJ}{da} = \int_0^T \left[ f_x \frac{\partial y}{\partial a} + f_u \frac{\partial (u^* + ah)}{\partial a} + \lambda'(t) \frac{\partial y}{\partial a} \\
+ \lambda(t) \left( g_x \frac{\partial y}{\partial a} + g_u \frac{\partial (u^* + ah)}{\partial a} \right) \right] dt - \lambda(T) \frac{\partial y}{\partial a}(T, a).
\]

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

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

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

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

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

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

$h(t)$ arbitrary variation

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

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 $\lambda$ (like a Lagrange multiplier)

Three unknowns $u^*$, $x^*$ and $\lambda$

$H$ nonlinear w.r.t. $u$

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

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

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

$$\lambda(T') = 0 \quad \text{transversality condition}$$
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: \( H = 2u + \lambda u + x - \lambda x^2 \)

\[ \frac{\partial H}{\partial u} = 2 + \lambda \not= 0 \quad \text{cannot solve for } u \]

\( H \) 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 \( x'(t) = x(t) + u(t), \quad x(0) = i \)

What optimal control is expected?
Example 1 worked

\[
\min \int_0^1 u^2(t) \, dt
\]
\[
x' = x + u, \quad x(0) = 1
\]
\[
H = \text{integrand} + \lambda \ \text{RHS of DE} = u^2 + \lambda(x + u)
\]
\[
\frac{\partial H}{\partial u} = 2u + \lambda = 0 \implies u^* = -\frac{\lambda}{2} \quad \text{at } u^*
\]
\[
\frac{\partial^2 H}{\partial u^2} = 2
\]
\[
\lambda' = -\frac{\partial H}{\partial x} = -\lambda \quad \lambda(1) = 0
\]
\[
\lambda = \lambda_0 e^{-t} \rightarrow 0 = \lambda_0 e^{-1} \implies \lambda_0 = 0
\]
\[
\lambda \equiv 0, u^* \equiv 0, x^* = e^t
\]
Example 2

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

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

What optimal control is expected?
Hamiltonian

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

The adjoint equation and transversality condition give

\[ \lambda'(t) = -\frac{\partial H}{\partial x} = -1 - \lambda, \quad \lambda(2) = 0 \quad \Rightarrow \quad \lambda(t) = e^{2-t} - 1, \]
Example 2 continued

and the optimality condition leads to

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

The associated state is

\[ x^*(t) = \frac{1}{2}e^{2-t} - 1. \]
Example 2.2

Graphs, Example 2

- State
- Adjoint
- Control
Example 3

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

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

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

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

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

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

\[ x' = x + \frac{x + \lambda}{2} \]
\[ x' = \frac{3}{2}x + \frac{\lambda}{2} \]
\[ \lambda' = \frac{3}{2}x - \frac{3}{2}\lambda \]
\[ x(1) = 2, \quad \lambda(5) = 0 \]

Solve for \( x^* \), \( \lambda \) 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

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

\[
x' = 1 - u^2, \quad x(0) = 1, \quad u \text{ control.} \quad H =
\]

\[
\frac{\partial H}{\partial u} = 0
\]

\[
\lambda' =
\]

\[
\lambda =
\]

\[
\lambda(1) =
\]

\[
u^* =
\]

\[
x^* =
\]
\[
\text{max } \int_0^1 (x + u) \, dt
\]

\[
x' = 1 - u^2, \quad x(0) = 1 \quad \text{u control}
\]

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

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

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

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

\[
x^*(t) = t - 1/4(1 - t) + 5/4, \quad u^*(t) = 1/2(1 - t).
\]
There is not an "Optimal Control" in this case.

Want finite maximum.

Here unbounded optimal state
unbounded OC
Opening Example

\[ x(t) \quad \text{Number of cancer cells at time } t \]
(exponential growth) \textbf{State}

\[ u(t) \quad \text{Drug concentration } \textbf{Control} \]

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

\[ x(0) = x_0 \quad \text{known initial data} \]

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
See my homepage www.math.utk.edu/~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