Optimal Control Applied in Coupled Within-Host and Between-Host Models

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As our motivating scenario for linking within-host and between-host models, we use HIV.

We present a draft of a simple model for HIV.

HIV is transmitted from one person to another through specific body fluids such as blood, semen, genital fluids and breast milk.

The life cycle of HIV infection consists of six stages: binding and fusion, reverse transcription, integration, transcription, assembly and budding.
Goals

1. Use the coupled model to capture the impact on the epidemic of giving treatment to individuals

2. Obtain novel mathematical and optimal control results: investigate mathematically such a coupled ODE/PDE system (well-posedness and optimal control)
Immuno-epidemiology combines individual and population-oriented approaches to create new perspectives.

Translates individual characteristics such as immune status and pathogen load to population level and traces their epidemiological significance.

Possible linking mechanisms:
- Link through a structural variable
- Link through coefficients

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Within-Host Dynamics

1. $\tau$ time since start of infection
2. $x(\tau)$ density of healthy $CD4^+$ T-cells at time $\tau$
3. $y(\tau)$ density of infected $CD4^+$ T-cells at time $\tau$
4. $V(\tau)$ density of free virus at time $\tau$

Within-Host Model

\[
\begin{align*}
\frac{dx}{d\tau} &= r - \beta_1 V(\tau)x(\tau) - \mu x(\tau) \\
\frac{dy}{d\tau} &= \beta_1 V(\tau)x(\tau) - d_1 y(\tau) \\
\frac{dV}{d\tau} &= \nu_1 d_1 y(\tau) - (\delta_1 + s_1)V(\tau) - \hat{\beta}_1 V(\tau)x(\tau)
\end{align*}
\]
Between-Host Model

1. $\tau$ age since infection
2. $S(t)$ density of susceptible individuals at time $t$
3. $i(\tau, t)$ density of infected individuals at time $t$ and age-of-infection $\tau$

\[
\frac{dS}{dt} = \Lambda - \frac{S(t)}{N(t)} \int_0^A c_1 s_1 V(\tau) i(\tau, t) d\tau - m_0 S
\]

\[
\frac{\partial i(\tau, t)}{\partial t} + \frac{\partial i(\tau, t)}{\partial \tau} = -m(V(\tau)) i(\tau, t) \quad S(0) = S_0
\]

\[
i(0, t) = \frac{S(t)}{N(t)} \int_0^A c_1 s_1 V(\tau) i(\tau, t) d\tau
\]

\[
N(t) = S(t) + \int_0^A i(\tau, t) d\tau, \quad i(\tau, 0) = i^0(\tau).
\]
Mathematical Formulation and Analysis

1. Boundedness of within-host state variables
2. Find a representation formulation through the method of characteristics for the solution to the between-host system:

\[ S(t) = L_1(S, i)(t), \quad \text{and} \quad i(\tau, t) = L_2(S, i)(\tau, t). \]

Solution Space

The solution space is

\[ X = \left\{ (S, i) \in L^\infty(0, T) \times L^\infty(0, T; L^1(0, A)) \middle| \right. \]

\[ \sup_{0 \leq t \leq T} \int_0^A |i(\tau, t)| d\tau < \infty, \quad \sup_{0 \leq t \leq T} |S(t)| < \infty \quad \text{a.e. } t \}. \]
Assumptions

1. $S_0, m_0, \Lambda, c_1$ and $s_1$ are positive constants
2. $m(s) \geq 0$ a.e., and is a Lipschitz continuous function
3. $\int_0^A |i^0(\tau, t)| d\tau \leq M$, and $0 < S_0 \leq M$

Theorem (Existence and Uniqueness)

Given $V$, there exists a unique solution $(S, i)$ to the between-host state system.

Proof (Idea): Define a map $L : X \to X$, where

$L(S, i) = (L_1(S, i), L_2(S, i))$ and define an iterative process

$L(S^{n+1}(t), i^{n+1}(\tau, t)) = (L_1(S^n(t), i^n(\tau, t)), L_2(S^n(t), i^n(\tau, t)))$

- Establish convergence of the sequence $(S^n(t), i^n(\tau, t))$ in $X$, for all $n \geq 1$
- Establish uniqueness of limit of the sequence $(S^n(t), i^n(\tau, t))$. 
The basic reproduction number of the epidemiological model is

\[ R_0 = \int_0^A c_1 s_1 V(\tau) e^{-\int_0^\tau m(V(s))ds} d\tau. \]

The steady states of the epidemiological model are \((\frac{\Lambda}{m_0}, 0)\) and

\[ \left( \frac{\Lambda \xi}{R_0 - 1 + m_0 \xi}, \frac{\Lambda(R_0 - 1)e^{-\int_0^\tau m(V_1(s))ds}}{R_0 - 1 + m_0 \xi} \right), \]

where \(\xi = \int_0^A e^{-\int_0^\tau m(V(s))ds} d\tau.\)

**Theorem**

1. The DFE is locally asymptotically stable if \(R_0 < 1\).
2. If \(R_0 < 1\), the DFE is globally stable.
3. The endemic equilibrium is locally asymptotically stable if \(R_0 > 1\) and the maximal age of infection is small.
1. We investigate optimal control in a coupled system of within-host and between-host models.
2. Solutions of first-order PDEs are less regular than solutions of parabolic PDEs.
3. Method used in characterizing optimal control of first-order PDEs is different from method used for parabolic PDEs.
4. Use Ekeland’s variational principle to get the existence of optimal control.
Within-Host Model with Controls

- Control functions $u_1$ and $u_2$ represent rates resulting from transmission and viral production suppressing drugs, respectively.

\[
\begin{align*}
\frac{dx}{d\tau} &= r - \beta_1 (1 - u_1(\tau)) V(\tau) x(\tau) - \mu x(\tau) \\
\frac{dy}{d\tau} &= \beta_1 (1 - u_1(\tau)) V(\tau) x(\tau) - d_1 y(\tau) \\
\frac{dV}{d\tau} &= \nu_1 (1 - u_2(\tau)) d_1 y(\tau) - (\delta_1 + s_1) V(\tau) \\
&\quad - \beta_1 (1 - u_1(\tau)) V(\tau) x(\tau)
\end{align*}
\]
Objective Functional

\[ J(u_1, u_2) = \int_0^T \int_0^A A_1 i(\tau, t) V(\tau) d\tau dt \]
\[ + \int_0^T \int_0^A \gamma_1 i(\tau, t)(c_1 u_1(\tau) + c_2 u_2(\tau)) d\tau dt \]
\[ + \int_0^A B(u_1(\tau)^2 + u_2(\tau)^2) d\tau \]

- We seek to minimize free virus, infected individuals and toxicity cost.
Objectives

1. We seek to find optimal controls $u_1^*$ and $u_2^*$ in the set

$$\mathcal{U} = \{(u_1, u_2) \in (L^\infty(0, A))^2 | u_1 : (0, A) \to [0, \bar{u}_1], u_2 : (0, A) \to [0, \bar{u}_2]\},$$

such that

$$J(u_1^*, u_2^*) = \min_{(u_1, u_2) \in \mathcal{U}} J(u_1, u_2),$$

with objective functional $J$.

2. Differentiate the maps

- Control to state: $(u_1, u_2) \mapsto \text{state variables}$
- Control to objective functional: $(u_1, u_2) \mapsto J(u_1, u_2)$
Sensitivities

1. Start with state system and obtain sensitivities
2. The map

\[(u_1, u_2) \mapsto \text{state variables}\]

is differentiable in the following sense (for one component):

\[
\frac{x(u_1 + \varepsilon l_1, u_2 + \varepsilon l_2) - x(u_1, u_2)}{\varepsilon} \rightarrow \psi \quad \text{in} \quad L^\infty(0, A)
\]

with \(x^\varepsilon = x(u_1 + \varepsilon l_1, u_2 + \varepsilon l_2),\ u_1^\varepsilon = u_1 + \varepsilon l_1,\ l_1, l_2 \in L^\infty(0, A),\ u_1 + \varepsilon l_1, u_2 + \varepsilon l_2, u_1, u_2 \in \mathcal{U}.\)
Sensitivity Equations

1. The state equations corresponding to controls $u_1$ and $u_1^\varepsilon$ are

$$\frac{dx}{d\tau} = r - \beta_1 (1 - u_1(\tau)) V(\tau) x(\tau) - \mu x(\tau)$$

$$\frac{dx^\varepsilon}{d\tau} = r - \beta_1 (1 - u_1^\varepsilon(\tau)) V^\varepsilon(\tau) x^\varepsilon(\tau) - \mu x^\varepsilon(\tau)$$

2. The equation satisfied by the difference quotient $\frac{x^\varepsilon - x}{\varepsilon}$ is

$$\frac{d}{d\tau} \left( \frac{x^\varepsilon - x}{\varepsilon} \right) = -\beta_1 \left( \frac{V^\varepsilon x^\varepsilon - V x}{\varepsilon} \right) + \beta_1 \left( \frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 V x}{\varepsilon} \right)$$

$$- \mu \left( \frac{x^\varepsilon - x}{\varepsilon} \right)$$
Sensitivity Equations

The equation satisfied by the difference quotient for $S$ is

$$
\frac{d}{dt} \left( \frac{S^\varepsilon - S}{\varepsilon} \right) = -m_0 \left( \frac{S^\varepsilon - S}{\varepsilon} \right) - c_1 s_1 \int_0^A \left( \frac{S^\varepsilon(t)V^\varepsilon(\tau)i^\varepsilon(\tau,t)}{\varepsilon N^\varepsilon(t)} - \frac{S(t)V(\tau)i(\tau,t)}{\varepsilon N(t)} \right) d\tau
$$

$$
\frac{d\theta}{dt} = \frac{c_1 s_1 S(t)}{N(t)^2} \int_0^A i(\tau,t)V(\tau) \int_0^A \omega(h,t) dh d\tau - \frac{c_1 s_1}{N(t)} \left( 1 - \frac{S(t)}{N(t)} \right) \theta(t) \int_0^A i(\tau,t)V(\tau) d\tau - m_0 \theta(t) + \frac{S(t)}{N(t)} \int_0^A \left[ V(\tau)\omega(\tau,t) + i(\tau,t)\phi(\tau) \right] d\tau, \text{ as } \varepsilon \to 0.
$$
Sensitivity Equations

1. The state equations corresponding to controls $u_1$ and $u_1^\varepsilon$ are

$$\frac{dx}{d\tau} = r - \beta_1 (1 - u_1(\tau)) V(\tau) x(\tau) - \mu x(\tau)$$

$$\frac{dx^\varepsilon}{d\tau} = r - \beta_1 (1 - u_1^\varepsilon(\tau)) V^\varepsilon(\tau) x^\varepsilon(\tau) - \mu x^\varepsilon(\tau)$$

2. The equation satisfied by the difference quotient $\frac{x^\varepsilon - x}{\varepsilon}$ is

$$\frac{d}{d\tau} \left( \frac{x^\varepsilon - x}{\varepsilon} \right) = -\beta_1 \left( \frac{V^\varepsilon x^\varepsilon - V x}{\varepsilon} \right) + \beta_1 \left( \frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 V x}{\varepsilon} \right) - \mu \left( \frac{x^\varepsilon - x}{\varepsilon} \right)$$

$$\frac{d\psi}{d\tau} = -\beta_1 (1 - u_1) V \psi - \beta_1 (1 - u_1) x_1 \phi - \mu \psi + \beta_1 h V_1 x_1$$
Sensitivity Operators

1. Sensitivity operators on five components

\[
\mathcal{L}_1 \begin{bmatrix}
\psi \\
\varphi \\
\phi
\end{bmatrix} = \begin{bmatrix}
\beta_1 l_1 V x \\
-\beta_1 l_1 V x \\
\hat{\beta}_1 l_1 V x - \nu_1 d_1 b_2 y
\end{bmatrix},
\]

\[
\mathcal{L}_2 \theta = 0 \quad \text{and} \quad \mathcal{L}_3 \omega = 0.
\]

2. The sensitivity functions satisfy linearized version of state equations
Sensitivity and Adjoint Operators

\[ \langle \text{adjoints}, \mathcal{L}(\text{states}) \rangle = \langle \mathcal{L}^*(\text{adjoints}), \text{states} \rangle \]

\[
\int_0^A \begin{pmatrix} \lambda \\ \xi \\ \eta \end{pmatrix}^T \mathcal{L}_1 \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix} d\tau + \int_0^T p \mathcal{L}_2 \theta dt + \int_0^T \int_0^A q \mathcal{L}_3 \omega d\tau dt
\]

\[
= \int_0^A \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix}^T \mathcal{L}_1^* \begin{pmatrix} \lambda \\ \xi \\ \eta \end{pmatrix} d\tau + \int_0^T \theta \mathcal{L}_2^* p dt + \int_0^T \int_0^A \omega_1 \mathcal{L}_3^* q d\tau dt
\]

2 The transversality conditions are:

\[ \lambda(A) = 0, \quad \xi(A) = 0, \quad \eta(A) = 0, \quad p(T) = 0 \]

\[ q(\tau, T) = 0, \quad \forall \tau \in \Omega \quad \text{and} \quad q(A, t) = 0, \quad \forall t \in (0, T) \]
Adjoint Operators

The adjoint operators on five components are

\[ \mathcal{L}^*_1 \begin{bmatrix} \lambda \\ \xi \\ \eta \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ \int_0^T A_1 i(\tau, t) \, dt \end{bmatrix} \]

\[ \mathcal{L}^* \begin{bmatrix} p \\ q \end{bmatrix} = \begin{bmatrix} 0 \\ A_1 V + \gamma_1 (c_1 u_1 + c_2 u_2) \end{bmatrix}, \]

where

\[ \mathcal{L}^* \begin{bmatrix} p \\ q \end{bmatrix} = \begin{bmatrix} \mathcal{L}_2^* p \\ \mathcal{L}_3^* q \end{bmatrix}. \]
Characterization of Optimal Control Pair

1. Solutions of first-order partial differential equations are less regular than those of parabolic PDEs
2. Use Ekeland’s Variational Principle to characterize optimal control of first-order PDEs
3. Embed the objective functional $J$ in the space $L^1(\Omega) \times L^1(Q)$ by defining

$$J(u_1, u_2) = \begin{cases} J(u_1, u_2) & \text{if } (u_1, u_2) \in U \\ +\infty & \text{if } (u_1, u_2) \notin U. \end{cases}$$
Theorem (Characterization of Optimal Control Pair)

If \((u_1^*, u_2^*) \in U\) is an optimal control pair minimizing \(J\), and 
\((x^*, y^*, V^*, S^*, i^*)\) and \((\lambda, \xi, \eta, p, q)\) are the corresponding state and adjoint solutions, then

\[
\begin{align*}
    u_1^*(\tau) &= \mathcal{F}_1 \left( \frac{\beta_1 V^* x^* (\xi - \lambda) - \hat{\beta}_1 V^* x^* \eta - c_1 \gamma_1 \int_0^T i^*(\tau, t) dt}{2B} \right), \\
    u_2^*(\tau) &= \mathcal{F}_2 \left( \frac{\nu_1 d_1 \eta_1 y^* - c_2 \gamma_1 \int_0^T i^*(\tau, t) dt}{2B} \right) \quad \text{a.e. in } L^1(\Omega),
\end{align*}
\]

where

\[
\mathcal{F}_j(x) = \begin{cases} 
    0, & x < 0 \\
    x, & 0 \leq x \leq \tilde{u}_j \\
    \tilde{u}_j, & x > \tilde{u}_j
\end{cases} \quad \text{for } j = 1, 2.
\]
1. Ekeland’s Principle is used to construct an approximate functional, $J_\varepsilon$, and a minimizing pair, $(u_1^\varepsilon, u_2^\varepsilon)$ for $J_\varepsilon$

2. The functional $J$ is lower semi-continuous

3. There exists a unique optimal control pair $(u_1^*, u_2^*) \in U$ minimizing the objective functional $J$. 
Numerical Simulation (forward-backward sweep iterative method)

1. Establish initial guess for control variable
2. Solve the state system forward in time
3. Solve the adjoint system backward in time
4. Update control pairs using the control characterizations
5. Repeat until convergence condition is met.
Preliminary Figures

Individuals w/ control

- 3D plots showing the impact of control on individuals over time and age.
- Line graphs illustrating the number of individuals without and with control over time.
- Additional graphs depicting the time evolution of different variables with and without control.
1. More numerical results will be completed
2. This work is being done in collaboration with Drs. Lenhart, Martcheva and Bhattacharya.
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References


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THANK YOU