Optimal Epidemic Intervention of HIV Spread Using the Cross-Entropy Method

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EXTENDED ABSTRACT

The spread of the human immunodeficiency virus (HIV) depends prominently on the migration of people between different regions. An important consequence of this population mobility is that HIV control strategies that are optimal in a regional sense may not be optimal in a national sense. The question is how the local governments can, individually and collectively, make better use of their budgets to reduce the number of new cases of HIV infection taking into account that people travel among regions. We formulate the problem of epidemic intervention as an *optimal control* problem, finding control sequences (functions) that optimize a given objective function. The mobility of people among regions is modelled via a transition graph as shown in Figure 1

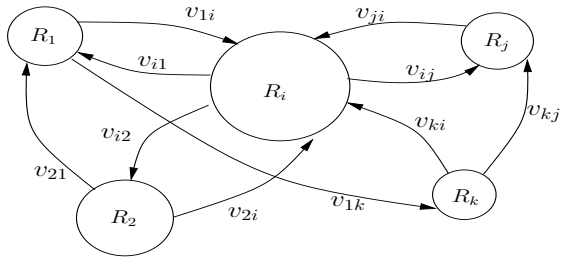


Figure 1. The scheme for the mobility of people among patches. The size of a circle corresponds to the total population size in that patch.

Since heterosexual contact is the primary mode of HIV infection worldwide, we consider only sexually-active populations in the regions. The transmission of the disease is schematically depicted in Figure 2

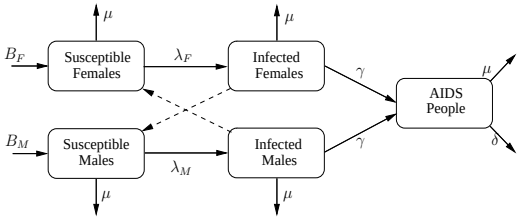


Figure 2. The scheme of the model. Susceptible females (males) are infected by infected males(females) via sexual contact only, indicated by the dashed lines.

We assume that the infection rates in patch r decrease as the function of the amount of budget applied. We formulate various mathematical control problems for the HIV spread in mobile heterosexual populations, and show how optimal regional control strategies can be obtained that minimize the national spread of HIV.

We apply the *Cross-Entropy* method to solve these highly multi-modal and non-linear optimization problems, as an alternative to Nonlinear Programming and Dynamic Programming. A gentle tutorial of the Cross-Entropy method can be found in Kroese *et al.* (2006) or one can visit http//www.cemethod.org. We demonstrate the effectiveness of the method via a range of experiments, and illustrate how the form of the optimal control function depends on the mathematical model used for the HIV spread.

In particular, for the patches that are initially infectives free, the first part of the control function is concave, starting and ending at zero (for the patch where the infectives are initially concentrated is linearly decreasing), the second part is zero (no control), and the third part is linearly increasing, an example is depicted in Figure 3

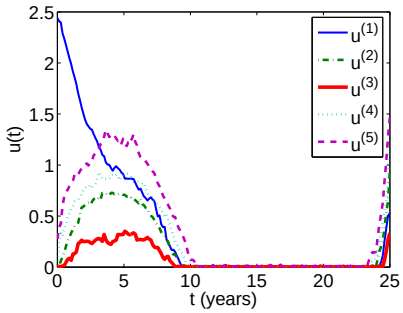


Figure 3. The optimal functions $u^{(r)}$ for five patches obtained via the Cross-Entropy method.

However, quantitatively the control functions (i.e., which part the budget should be concentrated) depend significantly on the form of the model used.

1 INTRODUCTION

The control of infectious diseases such as Acquired Immune Deficiency Syndrome (AIDS), which is caused by HIV, is a challenging public health problem. As the awareness of AIDS increases and the urgency to control it becomes crucial to many nations, more and more local and national governments provide funding to combat the disease. In Indonesia, for example, where a high population mobility among its regions seems to have a high risk for the spread of the epidemic (e.g. Hugo 2001, Woods 2004), many local governments have planned and allocated funds and resources to control the spread of HIV in their regions. However, as the people travel among regions, it is not clear whether an allocation of funds that is optimal for local regions is also optimal for the nation as a whole. The main goal on a country level is to find regional control strategies that minimize the total number of new infectives in the country as a whole, without using more than the allocated budget in each individual region.

The literature on optimal control for the spread of HIV is not extensive. One of the reasons is that the mathematical models used to describe the dynamics of the HIV spread tend to be quite complex. For example, the disease can be transmitted in many different ways — via sexual contact, blood transfusions, birthing and infected syringes; and the migration of people among subgroups has significant consequences for the dynamics of the epidemic spread (Mode *et al.* 2000, Schinazi 2002). As a consequence, mathematical models involving complex HIV transmission mechanisms usually do not lend themselves to conventional mathematical control techniques such as dynamic programming and convex optimization.

Sani *et al.* (2007) introduced several epidemic models for the spread of HIV in a mobile population. There, the infection rates were considered to be fixed for all times. In this paper we formulate various mathematical control models for the spread of HIV by assuming that the infection rates for all patches can vary; see also, Whitaker *et al.* (2004). The problem is to minimize the number of new infectives over a finite time horizon. These control models turn out to be highly non-linear, and are infeasible to solve via standard (convex) optimization procedures. The optimal control function is derived via the Cross-Entropy (CE) method (Rubinstein *et al.* 2004); to our knowledge this is the first application of CE to optimal control, as an alternative to *Nonlinear Programming* (NLP) and *Dynamic Programming* (DP), both of which suffer from the "curse of dimensionality" (e.g. Bertsekas 2002, Sniedovich 1992).

The mathematical control problems in the present paper are mostly motivated by the papers in (e.g. Blount *et al.* 1997, Brandeau *et al.* 2003, Richter *et al.* 1999), which is shown that it is not generally possible to derive the optimal solution of such complex problem in a closed form and therefore one needs resort to approximation techniques. For a more recent application of mathematical control theory to some other simple disease models, see for example Clancy *et al.* (2005).

2 EPIDEMIC OPTIMAL CONTROL FORMULATION

Let $s_F^{(r)}(t), i_F^{(r)}(t), s_M^{(r)}(t), i_M^{(r)}(t), z^{(r)}(t)$ denote the proportion of susceptible and infected females, susceptible and infected males, and AIDS cases in patch r at time t, respectively, relative to a scaling parameter V, see Sani *et al.* (2007). For the case of constant population sizes, the scaling parameter V is equal to the total population of all patches $N = \sum_{r=1}^{R} N^{(r)}$, where $N^{(r)} = N_F^{(r)} + N_M^{(r)}$ is the population size of patch r, with $N_F^{(r)}$ the size of female subpopulation and $N_M^{(r)}$ the size of male subpopulation. The population sizes $N^{(r)}, r = 1, \ldots, R$ need not be the same. For the case of varying population sizes, the scaling parameter $V = \frac{2B}{\mu}$, where B is the rate at which new susceptible females or males enter their corresponding subpopulation in each patch, for simplicity it is assumed to be a constant, and μ is the natural death rate of individuals.

Models with the Force of Infection

For the case of constant population size, all individuals that leave the system are replaced (balanced) by an inflow of susceptibles, at a proportion ξ for females and $1 - \xi$ for males. Thus, the inflow rates for susceptible females and males are given by $B_F = \xi\,(\mu\, c^{(r)} + \delta\, z^{(r)})$ and $B_M = (1-\xi)\,(\mu\, c^{(r)} + \delta\, z^{(r)})$ respectively, where $z^{(r)} = c^{(r)} - n_F^{(r)} - n_M^{(r)}$ with $c^{(r)} = N^{(r)}/N$, $n_F^{(r)} = N_F^{(r)}/N$, and $n_M^{(r)} = N^{(r)}/N$.

The evolution of susceptibles and infectives among patches for both cases is governed by the following system of differential equations:

$$
\begin{aligned}
\frac{ds_F^{(r)}}{dt} &= B_F - \sum_{j=1}^{R} \beta_{jr}\, \frac{i_M^{(j)}}{n_M^{(j)}}\; s_F^{(r)} - \mu\, s_F^{(r)}, \\
\frac{di_F^{(r)}}{dt} &= \sum_{j=1}^{R} \beta_{jr}\, \frac{i_M^{(j)}}{n_M^{(j)}}\; s_F^{(r)} - (\mu+\gamma)\, i_F^{(r)}, \\
\frac{ds_M^{(r)}}{dt} &= B_M - \sum_{j=1}^{R} \beta_{jr}\, \frac{i_F^{(j)}}{n_F^{(j)}}\; s_M^{(r)} - \mu\, s_M^{(r)}, \\
\frac{di_M^{(r)}}{dt} &= \sum_{j=1}^{R} \beta_{jr}\, \frac{i_F^{(j)}}{n_F^{(j)}}\; s_M^{(r)} - (\mu+\gamma)\; i_M^{(r)},
\end{aligned}
\tag{1}
$$

where β_{jr} is the rate (force) of infection in patch r from patch j and $B_F = B_M = \frac{\mu}{2}$ for varying population size. The force of infection in each patch r is described by the term $\sum_{j=1}^{R} \beta_{jr} \frac{i_M^{(j)}}{n_M^{(j)}}$ for susceptible females and $\sum_{j=1}^{R} \beta_{jr} \frac{i_F^{(j)}}{n_F^{(j)}}$ for susceptible males.

Model with Actual Mobility

Unlike in the previous models, we assume in this model that people physically visit other patches and the force of infection is only from within a patch. Let $n^{(r)} = n_F^{(r)} + n_M^{(r)}$ and $\nu^{(r)}$ denote the population size and the migration rate of patch r, respectively, relative to a scaling parameter $V = \frac{2B}{\mu}$. The evolution of the state variables in this model is described by the following system of ODEs:

$$\begin{aligned}
\frac{ds_F^{(r)}}{dt} &= \frac{\mu}{2} - \beta^{(r)} \frac{i_M^{(r)}}{n_M^{(r)}} s_F^{(r)} - \mu s_F^{(r)} + \sum_{j=1}^{R} \frac{v_{rj}}{n^{(j)}} s_F^{(j)} - \frac{\nu^{(r)}}{n^{(r)}} s_F^{(r)}, \\
\frac{di_F^{(r)}}{dt} &= \beta^{(r)} \frac{i_M^{(r)}}{n_M^{(r)}} s_F^{(r)} - (\mu+\gamma) i_F^{(r)} + \sum_{j=1}^{R} \frac{v_{rj}}{n^{(j)}} i_F^{(j)} - \frac{\nu^{(r)}}{n^{(r)}} i_F^{(r)}, \\
\frac{ds_M^{(r)}}{dt} &= \frac{\mu}{2} - \beta^{(r)} \frac{i_F^{(r)}}{n_F^{(r)}} s_M^{(r)} - \mu s_M^{(r)} + \sum_{j=1}^{R} \frac{v_{rj}}{n^{(j)}} s_M^{(j)} - \frac{\nu^{(r)}}{n^{(r)}} s_M^{(r)}, \\
\frac{di_M^{(r)}}{dt} &= \beta^{(r)} \frac{i_F^{(r)}}{n_F^{(r)}} s_M^{(r)} - (\mu+\gamma) i_M^{(r)} + \sum_{j=1}^{R} \frac{v_{rj}}{n^{(j)}} i_M^{(j)} - \frac{\nu^{(r)}}{n^{(r)}} i_M^{(r)},
\end{aligned} \tag{2}$$

with $v_{rj} = \rho_{rj}\, \nu^{(r)}$, where ρ_{rj} is the probability to visit patch j from patch r. Note that all variables, such as $s_F^{(r)}$ and $i_F^{(r)}$, are relative to the parameter V. The dynamic behavior of these models is discussed in Sani *et al.* (2007).

The epidemic control problem is formulated as follows. Suppose each patch r has a fixed budget, say $K^{(r)}$, for $r = 1, \ldots, R$, which needs to be spent over a finite time horizon $[0, T]$. Let $u^{(r)} = u^{(r)}(t)$ denote the control function, which is to be interpreted as the amount of budget spent per unit time in patch r. Suppose the infection rate in patch r, denoted $\beta^{(r)} = \beta(u^{(r)})$, is a decreasing function with respect to the control function $u^{(r)}$. The function $\beta^{(r)}$ can be, for example, of following form:

$$\beta_1 = \beta(u) = \beta_{\max} - c_1\, u\,, \tag{3}$$

or

$$\beta_2 = \beta(u) = \frac{\beta_{\max}}{1 + c_2\, u}, \tag{4}$$

for some constants $c_1, c_2 \in \mathbb{R}$. In this study, we use the form β_2 which is frequently used in epidemic control, see for example Blount *et al.* (1997).

The problem we are interested in is to determine the shape of the control function $u^{(r)}$ for each patch r, such that the total number of new infectives in all of the patches over the time horizon is minimized. Let $\mathbf{u} = \{u^{(r)}, r = 1, \ldots, R\}$. Then, our epidemic intervention problems are formulated as follows:

For the models with a force of infection

$$\min_{\mathbf{u}} J(\mathbf{u}) = \min_{\mathbf{u}} \int_0^T \sum_{r=1}^{R} \sum_{j=1}^{R} \beta_{jr} \left[\frac{i_M^{(j)}}{n_M^{(j)}} s_F^{(r)} + \frac{i_F^{(j)}}{n_F^{(j)}} s_M^{(r)} \right] dt, \tag{5}$$

subject to the dynamic constraint (1) and the following integral constraints:

$$\int_0^T u^{(r)}\, dt = K^{(r)},\ 0 \le u^{(r)} \le K^{(r)},\ r = 1, \ldots, R. \tag{6}$$

For the model with actual mobility

$$\min_{\mathbf{u}} J(\mathbf{u}) = \min_{\mathbf{u}} \int_0^T \sum_{r=1}^{R} \beta^{(r)} \left[\frac{i_M^{(r)}}{n_M^{(r)}} s_F^{(r)} + \frac{i_F^{(r)}}{n_F^{(r)}} s_M^{(r)} \right] dt \tag{7}$$

subject to the dynamic constraint (2) and the integral constraints (6).

The terms inside the integral in the objective functions describe the rate at which new infectives are generated. For the case of the constant population size, $J(\mathbf{u})$ is the proportion of new infective cases relative to the total population size N in the R patches. For the case of the varying population size, $J(\mathbf{u})$ is the proportion of new infective cases relative to the scaling parameter $V = \frac{2B}{\mu}$.

Finding the optimal solution in a closed form via standard control theory is not feasible due to the high non-linearity and multi-dimensionality of the problem. As the number of control functions and *state* equations increases, these two approaches (NLP and DP) become inefficient to solve such problems (Sniedovich 1992) due to high computational effort. We introduce an alternative method by employing a *Cross-Entropy* (CE) technique to solve the problem numerically.

3 CE METHOD FOR OPTIMAL CONTROL

The *cross-entropy* (CE) method (Rubinstein *et al.* 2004) is a recent Monte Carlo method that has proven to be very successful in solving a wide range of difficult optimization and estimation problems.

Main Procedure. Suppose, we wish to minimize some objective, or performance, function $J(\mathbf{u})$, over some set $\mathcal{U}$ of continuous functions $\mathbf{u} = \{u^{(r)}(t), r = 1, \ldots, R,\ t \in [0, T]\}$, for some finite time T. We can think of $\mathcal{U}$ as a subset of functions in $C^R[0, T]$, the set of continuous functions from $[0, T]$ to $\mathbb{R}^R$, that satisfy certain integral and/or dynamic constraints, such as discussed in the previous section. Let us denote the minimum by γ^*, assuming it exists. Thus,

$$\gamma^* = J(\mathbf{u}^*) = \min_{\mathbf{u} \in \mathcal{U}} J(\mathbf{u}). \tag{8}$$

Instead of solving this *functional* optimization program directly, we consider a related *parametric* optimization program, namely

$$\min_{\mathbf{c} \in \mathcal{C}} J(\mathbf{u}_\mathbf{c}),$$

where $\mathbf{u_c}$ is a function in $\mathcal{U}$ that is parameterized by some *control vector* $\mathbf{c} \in \mathbb{R}^m$, for some m, and $\mathcal{C} \subset \mathbb{R}^m$ is the collection of such control vectors. Clearly, if the collection $\{\mathbf{u_c}, \mathbf{c} \in \mathcal{C}\}$ is chosen large enough, the solution to the parametric problem should approximate that of the original problem. In particular, let $\mathbf{c}^*$ be the optimal control vector and $\gamma_{\mathbf{c}^*}$ the corresponding optimal value, that is,

$$\gamma_{\mathbf{c}^*} = J(\mathbf{u}_{\mathbf{c}^*}) = \min_{\mathbf{c}\in\mathcal{C}} J(\mathbf{u_c}), \tag{9}$$

then $\gamma^* \approx \gamma_{\mathbf{c}^*}$ and $\mathbf{u}^* \approx \mathbf{u}_{\mathbf{c}^*}$, if the set of parametric control functions can approximate $\mathcal{U}$ well enough.

A simple way to parameterize the problem is to partition the interval $[0, T]$ into n subintervals $[t_0, t_1], \ldots, [t_{n-1}, t_n]$, and let $\mathbf{c} = \{c_i^{(r)}, r = 1, \ldots, R;\ i = 0, \ldots, n\}$ be a vector of *control points*, and then define each function $u_{\mathbf{c}}^{(r)}$ via some interpolation of the points $\{(t_i, c_i^{(r)})\}$. The interpolation could, for example, be based on the *finite element method* (FEM) (Zienkiewicz *et al.* 2000), in which case each $u_{\mathbf{c}}^{(r)}$ is of the form

$$u_{\mathbf{c}}^{(r)}(t) = \sum_{i=0}^{n} c_i^{(r)}\, v_i(t), \tag{10}$$

where

$$v_i(t) = \begin{cases} \frac{t-t_{i-1}}{t_i - t_{i-1}}, & \text{for } t \in [t_{i-1},\, t_i], \\ \frac{t_{i+1}-t}{t_{i+1}-t_i}, & \text{for } t \in [t_i,\, t_{i+1}], \\ 0, & \text{otherwise.} \end{cases} \tag{11}$$

This is illustrated in Figure 4.

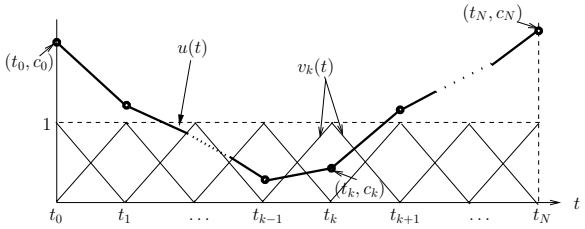


Figure 4. A piecewise linear function $u_{\mathbf{c}}(t)$ that passes through the points $\{(t_0, c_0), \ldots, (t_n, c_n)\}$ using linear FEM.

Remark 3.1 Instead of linear FEM, one can use many different types of *spline* function, such as the popular cubic *B-Spline*, to represent the control functions, or one can apply the Lagrange interpolating polynomial.

For a given control function $\mathbf{u_c}$, the performance value $J(\mathbf{u_c})$ can be evaluated directly by solving numerically the ODE system which describes the dynamic (state) constraints, e.g., via *Runge-Kutta* (RK) techniques. The CE method is employed to find the optimal control vector $\mathbf{c}^* = \{c_i^{(r)*}, r = 1, \ldots, R;\ i = 0, \ldots, n\}$. The idea is to generate each control point $c_i^{(r)}$ *randomly* from a Gaussian distribution with mean $\mu_i^{(r)}$ and standard deviation $\sigma_i^{(r)}$, and to update these parameters via CE to produce better performing control vectors in the next iteration (De Boer *et al.* 2005). We summarize the approach in the following algorithm.

Main Algorithm

1. **Initialize:** Choose $\boldsymbol{\mu}_0 = \{\mu_{i0}^{(r)}, r = 1, \ldots, R;\ i = 0, \ldots, n\}$ and $\boldsymbol{\sigma}_0 = \{\sigma_{i0}^{(r)}, r = 1, \ldots, R;\ i = 0, \ldots, n\}$. Set $k := 1$.

2. **Draw:** Generate a random sample $\mathbf{C}_1, \ldots, \mathbf{C}_N \sim \mathsf{N}(\boldsymbol{\mu}_{\mathsf{k}-1}, \boldsymbol{\sigma}_{\mathsf{k}-1}^2)$ with $\mathbf{C}_m = \{C_{mi}^{(r)}, r = 1, \ldots, R; i = 0, 1, \ldots, n\}$.

3. **Evaluate:** For each control vector $\mathbf{C}_m$ evaluate the objective function $J(\mathbf{u}_{\mathbf{C}_m})$, e.g., by solving the ODE system using RK techniques.

4. **Select:** Find the N^{e} best performing (=elite) samples, based on the values $\{J(u_{\mathbf{C}_m})\}$. Let $\mathcal{I}$ be the corresponding set of indices.

5. **Update:** for all $r = 1, \ldots, R;\ i = 0, 1, \ldots, n$, let

$$\begin{aligned} \widetilde{\mu}_{ki}^{(r)} &:= \frac{1}{N^{\mathrm{e}}} \sum_{m\in\mathcal{I}} C_{mi}^{(r)} \quad \text{and} \\ \tilde{\sigma}_{ki}^{(r)\,2} &:= \frac{1}{N^{\mathrm{e}}} \sum_{m\in\mathcal{I}} \left(C_{mi}^{(r)} - \mu_{ki}^{(r)}\right). \end{aligned}$$

6. **Smooth:** For a fixed smoothing parameter $0 < \alpha \leq 1$, let

$$\begin{aligned} \hat{\boldsymbol{\mu}}_k &:= \alpha\widetilde{\boldsymbol{\mu}}_k + (1-\alpha)\hat{\boldsymbol{\mu}}_{k-1} \quad \text{and} \\ \hat{\boldsymbol{\sigma}}_k &:= \alpha\widetilde{\boldsymbol{\sigma}}_k + (1-\alpha)\hat{\boldsymbol{\sigma}}_{k-1}. \end{aligned}$$

7. **Stop:** Repeat 2–6 until $\max_i \sigma_{ki} < \varepsilon$. Let L be the final iteration number. Return $\boldsymbol{\mu}_L$ as an estimate of the optimal control parameter $\mathbf{c}^*$.

4 NUMERICAL EXPERIMENTS

In this section, we apply our CE procedure to solve the epidemic control problems introduced in Section 2. For simplicity, we refer to these epidemic intervention problems as; *Problem I*: the case with a force of infection and constant population size; *Problem II*: the case with a force of infection and varying population size, and *Problem III*: the case with actual mobility.

In the numerical experiments we choose the number of patches $R = 5$ and the initial values for the female and male susceptibles are set to be 50,000. We assume

that 100 male infectives are initially concentrated in patch 1 only, and no infectives in other patches at time $t = 0$; The available budgets for the patches are $K^{(1)} = 10$, $K^{(2)} = 5$, $K^{(3)} = 2$, $K^{(4)} = 7$, $K^{(5)} = 10$, and the time horizon is fixed at $T = 25$ years. The infection rate is of the form β_2 in (4), with $\beta_{\max} = 0.5$ and $c_2 = 1$ for all patches. We assume that the sizes of patches are all equal (except patch 1 where the disease is initially concentrated) and the parameters, $\mu = 0.02$, $\nu^{(r)} = 10$, $\rho_{ij} = 0.25$ for $i \neq j = 1, \ldots, 5$, are set to be equal for all patches.

Problem I

We study Problem I first under a *uniform strategy* (U1 or U2). Then, we compare the results to those obtained via the CE technique. Here, in the case of multiple patches, the U1 scenario means that $u(t)^{(r)} = K^{(r)}/t_a$ for $t \in [0, t_a]$ and $u(t)^{(r)} = 0$ for $t \in (t_a, T]$, and U2 means $u(t)^{(r)} = 0$ for $t \in [0, T - t_a]$ and $u(t)^{(r)} = K^{(r)}/t_a$ for $t \in [T - t_a, T]$.

Uniform Strategy. To see the optimal strategy for U1 and U2, we vary the variable t_a and solve the corresponding control problem. Figure 5 provides an example how the values of objective function (5) (the new infective cases relative to the total population size of whole patches) vary for these two scenarios. As can be seen from the graphs in Figure 5, policy U1 is always better than U2 for this case. And the best U1 policy is the one with $t_a \approx 9.5$ (i.e., spend all budget uniformly and simultaneously in the first 9.5 years for all patches).

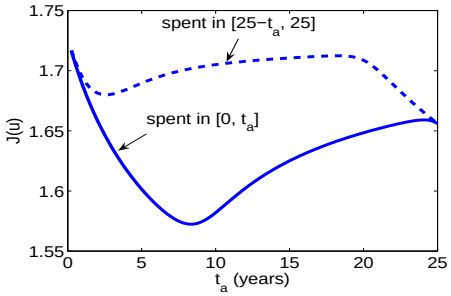


Figure 5. The value of the objective function for the two uniform strategies, as a function of t_a. The *solid* line corresponds to U1 and the *dashed* line to U2.

Solution via CE. The shapes of optimal control functions obtained via CE are quite different from the uniform bang-bang solution. Indeed, the functions have a "parabolic" shape for all patches (except patch 1 which seems to be "linearly" decreasing) in the interval $[0, 10]$, and *zero* on $[10, 23]$, followed by a linearly increasing part in $[23, 25]$, see Figure 6.

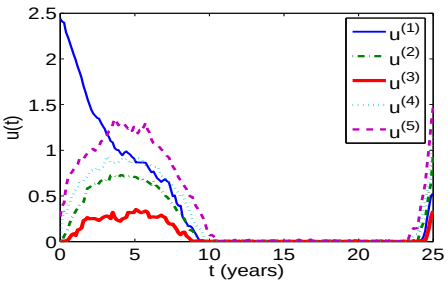


Figure 6. The optimal control functions $u^{(r)}$ of Problem I for patch $r = 1, \ldots, 5$ obtained via CE.

Although a little funding should be allocated in the last 2 years, the numerical results via CE suggest that most budget should be concentrated in the first 10 years. This is in accordance with the best uniform strategy. However, the CE strategy suggest to spend only a very small portion of the budget in the first one or two years, whereas in the U1 strategy a significant amount of budget for all patches has been allocated in the beginning. This CE result seems reasonable since it might not be worth spending much budget in the first one or two years when no or only a few infectives might be present, except in patch 1. The control strategy obtained via CE gives quantitatively a better solution, which is $J(\mathbf{u}) \approx 1.5543$, than that using the uniform strategy ($J(\mathbf{u}) \approx 1.5724$).

Varying the time horizon T. It is interesting to examine how the shape of the control function changes under the uniform policies if one varies the time period T, while keeping other parameters unchanged. Figure 7 shows that the graphs of the performance function $J(\mathbf{u})$ (given by (5)) are qualitatively quite different.

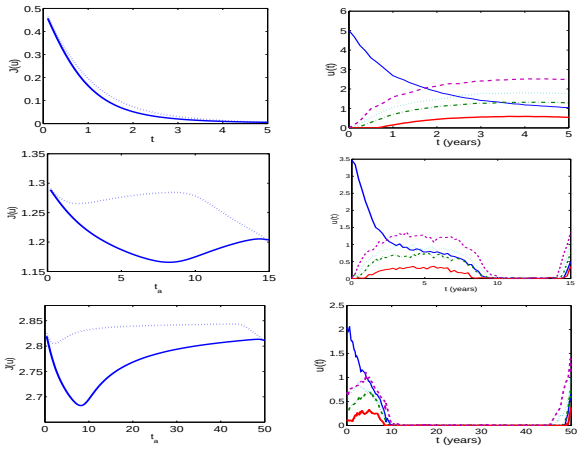


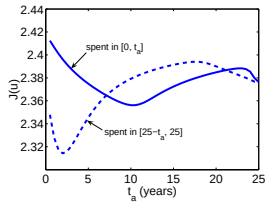
Figure 7. The *first* column of figures represent the values of objective function $J(\mathbf{u})$ with the strategies U1 (*solid* lines) and U2 (*dashed* lines), for three different time horizons $T = 5, 15$, and 50. The *second* column of figures represent the optimal trajectory $\mathbf{u}$ of Problem I via the CE method as the time horizon T is varied. The other parameters remain unchanged.

However, the numerical results also indicate that the optimal uniform control strategy remains the same, namely to spend the whole budget in all patches simultaneously up to 9.5 years, and if $T \leq 9.5$, to spend all budget uniformly in $[0, T]$. As shown in Figure 7, the optimal solutions via CE also behave similar to those in the uniform strategies, when varying the time horizon T. For $T \leq 10$, all budget is spent almost uniformly in the interval $[0, T]$ and for $T > 10$, the optimal solution has a similar structure to that in Figure 6.

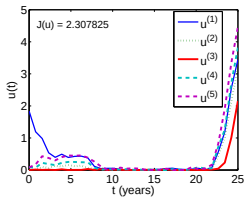
Problem II

The numerical experiments of Problem II use the same initial values and parameters as for Problem I.

Uniform Strategy. In contrast to Problem I, the minimum number of new infective cases is achieved by employing the U2 policy; specifically, with $t_a \approx 3$ years; see Figure 8(a). Varying the time horizon T or the budget K for the uniform strategies gives quite similar results as in Problem I.



(a) The values of objective functions for U1 and U2.



(b) The optimal control function via CE.

Figure 8. Numerical results of Problem II for $T = 25$.

Solution via CE. The optimal solution via CE method suggests a similar result to the second uniform strategy, where most budget is concentrated in the last 3 years. As in Problem I, the numerical experiments also indicate that some portion of the budget should be spent approximately in the first 9.5 years for all patches. Moreover, the control functions in $[0, 9]$ have again a "parabolic" shape, except for patch 1 where the infectives are initially concentrated. The best strategy is to allocate the budget in the first 9.5 years, with "parabolic" control functions for all patches except for patch 1 which has a "linearly" decreasing control function, spend nothing for the next 13 years, and spend the rest of budget in the last 2.5 years in a linearly increasing way, for all patches.

Thus, although the optimal strategies suggested via CE for Problem I and Problem II are quantitatively different (i.e., the amount of budget is concentrated in different time intervals), the shapes of control functions in both models look similar, that is a parabolic-like function in the first 10 years, a zero function for the next 13 years, and followed by an linearly increasing function in the last 2 years.

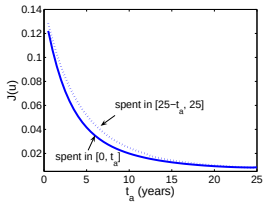
When varying the time horizon T in Problem II, the optimal trajectories $\mathbf{u}$ obtained via CE also behave much similar to those in Problem I.

Our numerical results suggest that allowing for some reallocation of resources over the time horizon of the problem, rather than allocating resources just once at the beginning (or at the last) of the time horizon, can qualitatively lead to significant decreases in the number of new infectives.

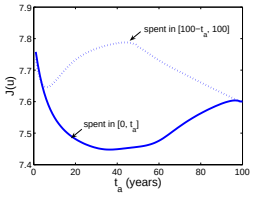
Problem III

We set the same migration rate, $v^{(r)} = 10$ per unit time, for all patches, $r = 1, \ldots, 5$. We assume that the probability that an individual leaving a patch i visits patch j is equal for all patches, so that $\rho_{ij} = \frac{1}{R-1} = 0.25$, $i \neq j$. Thus, the rate at which individuals leaving a patch i visit patch j is $\nu_{ij} = \rho_{ij}\, v^{(i)} = 2.5$. Initial values and other parameters remain the same as specified in the previous simulations for Problems I and II.

Uniform Strategy. As shown in Figure 9 (a) for the time horizon $T = 25$ years, Problem III appears to have a different structure of the optimal trajectory to those in Problems I and II for the uniform strategies. The best uniform strategy is to spend the budget evenly (uniformly) over the entire time period. However, if we extend the time scale, say $T = 100$, see Figure 9 (b), we obtain a similar structure as in the previous problems.



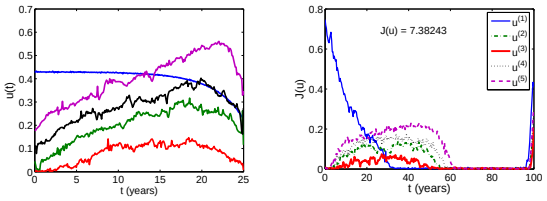
(a) The optimal control function $\mathbf{u}$ for $T = 25$.



(b) The optimal control function $\mathbf{u}$ for $T = 100$.

Figure 9. The values for the objective function $J(u)$ for several uniform control scenarios.

Solution via CE. Solving the problem via CE gives a quite similar result to the U1 strategy over the interval $[0, 25]$, see Figure 10. Note, however, that the optimal curves are, except for patch 1, significantly lower at the beginning and end of the time period. The optimal value $J(u)$ obtained via CE turns out to be very close to that of the uniformly distributed strategy with a bang-bang structure solution $u^{(r)} = K^{(r)}/T, r = 1, \ldots, 5$. By varying T, see Figure 10, or K we obtain a significant different structure of the solution.



(a) The opt. control function $\mathbf{u}$ for $T = 25$.

(b) The opt. control function $\mathbf{u}$ for $T = 100$.

Figure 10. The optimal control function $\mathbf{u}$ of Problem III for 5 patches obtained via CE.

5 CONCLUSIONS

In this paper, we have formulated various epidemic intervention models for the spread of HIV in multiple populations and introduced a new CE technique to solve these problems. The numerical results indicate that the shapes of the control functions for the different models are qualitatively similar. In particular, for the patches that are initially infectives free, the first part of the control function is concave, starting and ending at zero, the second part is zero (no control), and the third part is linearly increasing. However, quantitatively the control functions depend significantly on the form of the model used. For example, in the model with a force of infection and a fixed population size, most budget is concentrated in the first part, whereas in the model with a force of infection and a varying population size most budget is concentrated in the last part. This notable difference can also be observed when applying "uniform" strategies, where the budget is spent at a constant rate in either the first or the last part of the time interval.

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