Volume 9 • Number 2 • 2006
VALUE IN HEALTH

A Primer on Dynamic Optimization and Optimal Control in Pharmacoeconomics

John A. Vernon, PhD,[1] W. Keener Hughen, PhD[2]

[1]Department of Finance and Center for Healthcare and Insurance Studies, Graduate School of Business, The University of Connecticut and the National Bureau of Economic Research (NBER), Storrs, CT, USA; [2]Department of Finance, Haas School of Business, The University of California at Berkeley, Berkeley, CA, USA

ABSTRACT

Pharmacoeconomic analyses employ a wide range of techniques and methods to help societies allocate scarce health-care resources wisely, fairly, and efficiently. Techniques such as dynamic optimization and optimal control, however, have yet to be exploited by this field. Although control theory has a long history in mathematical biology and disease management, its application to economic costs in these disciplines has not yet been explored. Pharmacoeconomics therefore may offer a particularly promising starting point because of the emphasis this field places on the economic perspective. Although challenges may exist to implementing these techniques in practice (at least in some settings), there will nevertheless be value to considering the dynamic perspective these techniques offer, which requires thinking more critically about the optimal allocation of scare health-care resources over time. Therefore, our article serves as a primer to introduce this dynamic perspective from an economic standpoint within the context of two examples of treating of hyperlipidemia.

Keywords: control theory, dynamic optimization, hyperlipidemia, pharmacoeconomics.

Introduction

The field of pharmacoeconomics has evolved rapidly over the past two decades and the methodological rigor and sophistication found in contemporary pharmacoeconomic analyses are remarkable. Nevertheless, there still remain some useful analytic methods and tools that have not yet been adopted or fully considered, techniques that may be particularly well suited for this field. One promising method is optimal control, which is an analytic method for solving dynamic optimization problems. Indeed, optimal control has a long history in such fields as mathematical biology [1,2], disease management [3–6], economics [7], and, of course, mathematics [8,9]. Nevertheless, to our knowledge, this technique, and the dynamic optimality perspective more generally, has not been taken advantage of in pharmacoeconomic research.

Therefore, the purpose of this article is to present this perspective and offer suggestions for how optimal control, and dynamic optimization more generally, might be used to guide and/or inform clinical prescribing decisions and the allocation of scarce health-care resources over time. The nature of this article is to serve as a primer for future research and analyses.

The second section provides a brief and heuristic introduction to dynamic optimization and optimal control and discusses when these methods may be appropriate for use in pharmacoeconomic analyses; and if appropriate, how the methods might offer practical value for decision makers and/or analysts. Nevertheless, in order not to detract from the principle objective of this article (i.e., to introduce the perspective and method and to provide suggestions for suitable applications), several complexities are suppressed; ample references therefore are provided for the interested reader. The third section illustrates the optimal control method within the context of a simple model of treating hyperlipidemia. Because it is necessary to impose several restrictions on how the dynamic optimization problem is formulated to use control theory, there may be limits on the general applicability of this technique in practice, as is the case for many nonengineering applications of control theory. Therefore, we provide a second example of how dynamic optimization can be used within the context of treating hyperlipidemia. Although this example does not use optimal control and is different from the first example in several fundamental ways, it originates from the same economic problem and illustrates the importance of considering the dynamic perspective. In this section we also discuss how the second example could be

Address correspondence to: John A. Vernon, Department of Finance and Center for Healthcare and Insurance Studies, Graduate School of Business, The University of Connecticut and the National Bureau of Economic Research (NBER), 2100 Hillside Road., Storrs, CT 06269, USA. E-mail: jvernon@business.uconn.edu

10.1111/j.1524-4733.2006.00088.x

  1098-3015/06/106 106–113

expanded and implemented in practice. Finally, the last section concludes with a brief discussion of other potential applications for optimal control and dynamic optimization in pharmacoeconomic analyses. Limitations of the optimal control method for some applications are also discussed.

The Method of Optimal Control

Intuitively, optimal control may be characterized as the dynamic counterpart to static optimization, which is typically solved using differential calculus. Unlike static optimization, however, which is concerned with finding a point, x, such that a function, $f(x)$, achieves an extreme value (e.g., a minimum value), the method of optimal control is used to obtain a trajectory of x, $x(t)$, over a fixed interval of time, $t_0 \le t \le t_1$, such that a *functional*, Z, obtains an extreme value. The classic optimal control problem may be expressed as follows:

$$\underset{u(t)}{Optimize} \quad Z = \int_{t_0}^{t_1} C(x(t), u(t), t)dt \tag{1}$$

subject to

$$\dot{x}(t) = g(x(t), u(t), t) \tag{2}$$

with endpoint conditions

$$x(t_0) = a \text{ and } x(t_1) = b \tag{3}$$

The variable $u(t)$ in Equations 1 and 2 is referred to as the *control*, which is the choice (or decision) variable used to influence (i.e., control) the *state* variable, $x(t)$, at each point in time (dynamically) from time t_0 until t_1. The way in which $u(t)$ controls the state variable $x(t)$ is determined by the ordinary differential Equation 2.

The solution to the optimal control problem described in Equations 1–3 above is found by solving a set of partial differential equations, called the Hamilton-Jacobi equations [10,11]. There are a host of existence and uniqueness issues associated with solutions to partial differential equations, and in general the Hamilton-Jacobi equations are difficult to solve. Nevertheless, in the special case where Equation 2 may be inverted to solve for the control u(t) in terms of the state $x(t)$ and its time derivative $\dot{x}(t)$, the optimal control problem may be expressed as the classical calculus of variations problem:

$$\underset{x(t)}{Optimize} \quad Z = \int_{t_0}^{t_1} C(t, x(t), \dot{x}(t))dt$$
$$subject\ to\text{: } x(t_0) = a,\ x(t_1) = b \tag{4}$$

The solution $x^*(t)$ is the trajectory that optimizes the functional Z among all curves subject to the condition that $x(t_0) = a$ and $x(t_1) = b$ for given values of a and b. If one assumes that C satisfies certain properties, $x^*(t)$ may be found by solving the first order necessary condition known as the Euler-Lagrange equation:

$$\frac{\partial C}{\partial x} - \frac{d}{dt}\frac{\partial C}{\partial \dot{x}} \tag{5}$$

Equation 5 is a second-order ordinary differential equation whose integral curves $x(t)$ are the extremals of Z, for different boundary endpoints. Ordinary differential equations are much better behaved than partial differential equations; for example, under mild technical conditions, ordinary differential equations always have unique solutions up to constants of integration. Thus, using the fixed endpoint conditions to define the constants of integration, a unique extremal, $x^*(t)$, may be found that optimizes the functional Z. In fact, finding an extremal that satisfies the Euler-Lagrange equation is only a necessary condition for $x^*(t)$ to optimize the functional Z. Several secondary, sufficiency conditions must also be satisfied, for example the Jacobi condition. These conditions, however, will not be discussed here.

The distinction between static and dynamic optimization is illustrated geometrically in Figure 1. Panel A depicts the static case whereas panel B depicts the dynamic case; it is assumed for illustrative purposes that the extremum and extremal are minimums. In the static case, the value of x that optimizes f is determined by the usual first order conditions:

$$f(x^*) \le f(x) \leftrightarrow \left.\frac{df}{dx}\right|_{x^*} = 0 \tag{6}$$

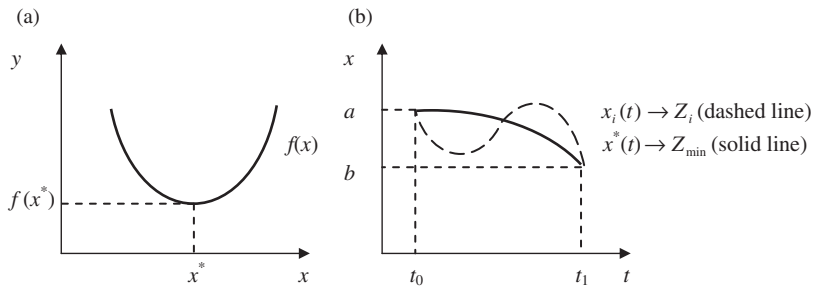

Figure 1 A geometric interpretation of static and dynamic optimization.

In the dynamic case, the trajectory $x(t)$ that optimizes Z is determined by the Euler-Lagrange Equation 5:

$$Z(x^*(t)) \leq Z(x(t)) \leftrightarrow \frac{\partial C}{\partial x} - \frac{d}{dt}\frac{\partial C}{\partial \dot{x}}\bigg|_{x^*} = 0 \qquad (7)$$

An efficient allocation of health-care resources is one that generates a given therapeutic benefit (specified a priori) at minimum economic cost. With respect to Figure 1a, $f(x)$ may be viewed as the cost of attaining some health benefit, with x being the sole input (or vector of inputs) into the generation of the benefit. Thus, the locus of points, $[x, f(x)]$, defines the set of feasible input-cost combinations that generate the given health benefit; clearly, the cost-minimizing, or efficient, ordered pair is $[x^*, f(x^*)]$. Indeed, cost-minimization analyses (CMA) are ubiquitous throughout the pharmacoeconomics literature, and are one of the four major types of analyses in this field [12–14]. The other three categories of pharmacoeconomic analyses are, of course, cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-benefit analyses (CBA). Nevertheless, these CMA studies typically focus explicitly on static cost minimization (as depicted in Fig. 1a), and ignore the issue of dynamic cost minimization, or assume implicitly that dynamic cost minimization characterizes treatment over time.

Clinical trials, for example, form the basis for much of the data used in pharmacoeconomic analyses. Although these trials may involve long time horizons, they are not designed to consider the dynamic economic properties that are the focus of this article. Cost analyses across various drug products or procedures may identify the least costly treatment in terms of present value total costs, which considers direct, indirect, and opportunity costs, but this is a different question from the one raised in this article, and it implicitly assumes that the clinical-trial mandated treatment algorithm is optimal; thus, analyses based on such trials, even though they may be trials over many years, are not dynamic analyses in the sense we adopt in this article.

Figure 1b depicts two trajectories—from an infinite set of trajectories—with the trajectory, $x^*(t)$, depicting the optimal (i.e., cost minimizing) time path of x, and with $x_i(t)$ corresponding to some other, feasible time path for x such that $Z_i > Z_{\min}$. It is worth noting that in Figure 1a there is a geometrically observable solution to the static optimization problem: where the function $f(x)$ takes on its minimum value. This is not the case for the dynamic solution illustrated in Figure 1b. In this panel we are simply showing that among all feasible trajectories of the state variable, there exists a single trajectory, $x^*(t)$, which corresponds to the optimal value of the functional Z (e.g., that minimizes Z). For this reason the two panels have geometric interpretations that are not analogous.

The issue of dynamic cost minimization directly impinges on CEA, CUA, and CBA. This will be especially true for analyses and studies that involve long time horizons. For example, if a two-armed clinical trial is designed to measure the marginal cost-effectiveness of one drug therapy relative to another, and the protocol-driven titration algorithm specified in the study deviates significantly from the cost-minimizing titration algorithm (recall that costs are *economic* costs which include both monetary and nonmonetary costs), the results could potentially be misleading. This is because the present value difference in economic costs between the two treatments arms may be a function of the treatment trajectory selected. For example, this difference may increase the greater that trajectories deviate from the optimal treatment trajectory. Although this scenario may or may not be likely, the point being made is that there are benefits to *explicitly* considering, if also not evaluating, the dynamic properties from an economic perspective of pharmacological treatment regimes. It seems plausible therefore that such investigations could provide important insights and expand the information set available to decision makers whose responsibility it is to allocate scare health-care resources over time.

Examples of Dynamic Cost Minimization: Treating Hyperlipidemia

This section presents two simple, hypothetical examples of how the methods of dynamic optimization may be used to study hyperlipidemia treatment protocols. The first example uses the previously discussed method of optimal control to solve for the cost-minimizing treatment path associated with lowering an individual patient's cholesterol. The second example is very different in nature, and considers the treatment of a population of patients with high cholesterol. Although this example does not use control theory, it does formulate a dynamic optimization problem, one that could be readily implemented in practice with a few extensions and the necessary data. This being said, it is important to emphasize that both examples are intended only to illustrate the potential usefulness of dynamic optimization and the perspective it offers within the context of pharmacotherapeutic treatment regimens.

Example 1

Consider a hypothetical patient with hyperlipidemia. The treatment objective is to efficiently (i.e., at minimum cost) bring her low-density lipoprotein cholesterol (LDL-C) level to the level recommended by the National Cholesterol Education Program (NCEP) in 1 year's time. Let $\lambda(t)$ denote the patient's *excess* LDL-C level at time t. If her LDL-C level is initially L units too high, then the endpoint conditions are:

$$\lambda(0) = L \text{ and } \lambda(1) = 0 \tag{8}$$

The patient's LDL-C level is managed by the administration of a certain medication (statin). Let $\delta(t)$ be the statin dosage administered at time t. The rate of change of her LDL-C level will be a function of both her current LDL-C level and the dosage administered:

$$\dot{\lambda}(t) = \Gamma(\lambda(t), \delta(t)) \tag{9}$$

Let C be the total cost per unit time incurred during treatment over the course of the year. In general, C will be a function of both λ and δ as we explain in more detail below. The optimal control problem to be solved is therefore the following:

$$\underset{\delta(t)}{Minimize} \int_0^1 (C(\lambda(t), \delta(t)))e^{-rt}\, dt \tag{10}$$

subject to

$$\dot{\lambda}(t) = \Gamma(\lambda(t), \delta(t)) \tag{11}$$

with endpoint conditions

$$\lambda(0) = L,\ \lambda(1) = 0 \tag{12}$$

The exponential term in the objective function accounts for the discounting of costs at the rate r.

We further assume there are two principle cost categories associated with treatment, C_1 and C_2 costs. The first category, C_1, consists of the costs of medications, office visits, diagnostic testing, adjunctive therapy (e.g., to treat side-effects), and other related costs. The second category, C_2, consists of the costs of cardiovascular events associated with hyperlipidemia, such as the cost of treating a myocardial infarction (MI), unstable angina, or stroke. If a cardiovascular event occurs, the costs incurred might include hospitalization costs, the cost of required surgical procedures after the event, such as a coronary artery bypass graft (CABG) or a percutaneous transluminal coronary angioplasty (PTCA), the cost of additional medications, and possibly the indirect costs associated time lost from work. The critical distinction between the two categories of costs is the following: a more aggressive treatment regime increases C_1 costs, and decreasing C_2 costs because of a reduced risk of cardiovascular events; a less aggressive treatment regime, on the other hand, will have lower C_1 costs but higher C_2 costs. For example, through more expensive, higher-dose statin treatment, greater monitoring costs associated with such high-dose drug therapy, a higher frequency of treatment side-effects, and thus costs, etc. Geometrically, we illustrate this important tradeoff in Figure 2:

For a specific example, suppose that the cost of medications is proportional to the dosage and the cost of office visits and lipid-level testing is proportional to

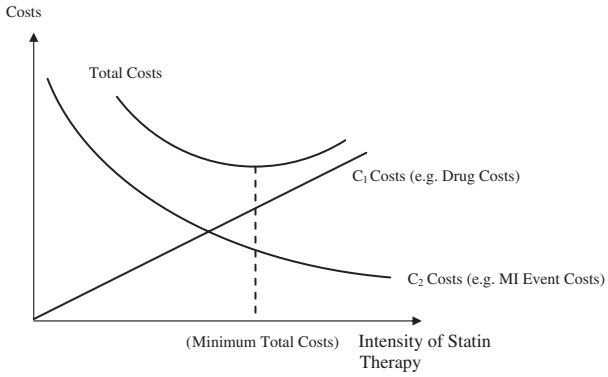

Figure 2 A geometric interpretation of the dynamic minimization problem and solution. MI, myocardial infarction.

the excess LDL-C level, so that C_1 costs accrue at rate $c_1\,\delta(t) + c_2\,\lambda(t)$. Also, suppose the cost of cardiovascular events accrue at a rate proportional to the square of $\lambda(t)$. Thus, the total cost accrues at rate:

$$C(\lambda(t), \delta(t)) = c_1\delta(t) + c_2\lambda(t) + c_3\lambda^2(t) \tag{13}$$

For a specific example of the "response function" Γ, which describes how the LDL-C level responds to dosage, consider the response model:

$$\dot{\lambda}(t) = a(L - \lambda(t)) - b\sqrt{\delta(t)} \tag{14}$$

where a and b are constants such that $aL < b\sqrt{\delta_{Max}}$ for the maximum available dosage δ_{Max}.

This specification has several features:

1. LDL-C level depends on the cumulative amount of drug taken.
2. LDL-C level has a mean-reverting component, which is consistent with the notion that the drug dissipates in the body at a rate proportional to the amount of drug in the body.
3. For a given time t, as the dosage increases the LDL-C level decreases, but at an increasing rate (slower rate of decrease), that is, $\lambda'(\delta) < 0$, $\lambda''(\delta) > 0$.

These features may be verified by direct examination of the solution to Equation 14:

$$\lambda(t) = e^{-at}\left(L + \int_0^1 e^{as}\left(aL - b\sqrt{\delta(s)}\right)ds\right) \tag{15}$$

Note that given an excess LDL-C level trajectory, the response model may be solved for the dosage:

$$\delta(t) = \frac{1}{b^2}\left(a^2(L - \lambda(t))^2 - 2a(L - \lambda(t))\dot{\lambda}(t) + \dot{\lambda}^2(t)\right) \tag{16}$$

Thus, we may recast our optimal control problem in this example as the calculus of variations problem:

$$\underset{\lambda(t)}{Min}\int_0^1 \frac{c_1}{b^2}\Big[\Big(a^2(L-\lambda(t))^2 - 2a(L-\lambda(t))\dot{\lambda}(t) + \dot{\lambda}^2(t)\Big) + c_2\lambda(t) + c_3\lambda^2(t)\Big]e^{-rt}\,dt \quad (17)$$

subject to

$$\lambda(0) = L,\ \lambda(1) = 0 \quad (18)$$

The Euler-Lagrange equation associated with Equation 17 is the following nonhomogeneous second order linear differential equation:

$$\ddot{\lambda} - r\dot{\lambda} - k_1\lambda + k_2 = 0 \quad (19)$$

where

$$k_1 = a(a+r) + \frac{b^2c_3}{c_1},\ k_2 = a(a+r) - \frac{b^2c_2}{2c_1}. \quad (20)$$

The solution to Equation 19 with boundary conditions $\lambda(0) = L$, $\lambda(1) = 0$ is the optimal trajectory, and is found to be the following:

$$\lambda = \lambda^*(t) = A_1e^{\frac{r-\rho}{2}t} + A_2e^{\frac{r+\rho}{2}t} + \frac{k_2}{k_1} \quad (21)$$

where

$$A_1 = \frac{L + \frac{k_2}{k_1}\left(e^{\frac{-\rho-r}{2}-1}\right)}{1-e^{-\rho}},\ A_2 = \frac{L + \frac{k_2}{k_1}\left(e^{\frac{\rho-r}{2}-1}\right)}{1-e^{-\rho}},\ \rho = \sqrt{r^2+4k_1} \quad (22)$$

Given this optimal trajectory $\lambda^*(t)$ for the excess LDL-C level, it is then straightforward to use Equation 16 to find the dosage regimen $\delta^*(t)$ that steers the excess LDL-C level along $\lambda^*(t)$.

In general, the specific choice of model for the response function Γ will depend on the individual patient and the therapeutic used for treatment. In actual applications of the optimal control technique described in the previous example, experts in pharmacokinetics would need to be consulted to ensure that the functional form is pharmacologically accurate. It may also be difficult to identify or approximate a problem's cost functional. Standard econometric methods could be used in some cases, assuming data availability and a willingness and comfort on behalf of the researcher to make assumptions about the functional form of the model's cost functional.

Finally, although we believe the functional forms for the response function Γ and cost rate C used in the previous example to be reasonable, we admit we selected them to guarantee the Euler-Lagrange equation could be solved analytically. If instead C_2 costs accrue, for instance, at a rate proportional to $\lambda^{3/2}$ in the previous example, then the resulting Euler-Lagrange equation is much more difficult to solve. Nevertheless, given the functional forms for C and Γ, numeric solutions for the Euler-Lagrange equation can always be obtained. Numeric techniques for solving ordinary differential equations are ubiquitous in the literature and can be found in many textbooks [15–17].

In the next example we consider the treatment of a population of patients—maybe enrollees in a particular health plan—with high cholesterol. This example will formulate the dynamic optimization problem in a very different way. Although this example will not use control theory, it will still focus on the intertemporal balance between the two types of costs (C_1 and C_2 costs) discussed in the previous example, and illustrated in Figure 2. Moreover, the construction of this example establishes a framework that may be readily applied (with some extensions) to a real-world study using actual data. We make suggestions for how this could be done following the example; doing so in the current article, however, is beyond the scope of our objectives.

Example 2

Suppose there are two LDL-C states: high (H) and low (L), and there are M statin doses $\delta_1 < \delta_2 < \ldots < \delta_M$ available for treating hyperlipidemia. Patients are examined and prescribed dosages once a month, and the total treatment period is N months. To keep things as simple as possible, we assume each patient has a minimal dosage at which their LDL-C level switches from H to L, and this switch in LDL-C level occurs just before the following examination. That is, the patient spends the month in state H but will spend the next month and all subsequent months in state L, assuming continued statin therapy at this minimal dosage. Thus, there are only two outcomes at month n + 1 for a given dosage prescribed at month n to a patient in state H: either the patient remains in state H (and will continue to be in state H unless the dosage is increased), or the patient will switch to state L. Furthermore, once in state L, the minimal dosage is required for the duration to remain in that state. This minimal dosage is a priori unknown for each patient, but the fraction of patients F_m who have minimal dosage greater than or equal to δ_m is known for $m = 1, \ldots, M$, where $0 < F_1 < \ldots < F_M = 1$.

The problem is set up in this way because it broadly corresponds to the information set available to prescribing physicians, with F_m being the cumulative distribution function (c.d.f.) for patients reaching state L on dose m. If state L is, for example, a patient's NCEP LDL-C goal, and if we are considering a homogenous patient population (except with respect to their response to statin therapy), then this formulation may be quite reasonable. Clinical data are readily available on the probability distribution functions for percentage reductions in LDL-C for different statin doses [18]. For example, clinical data have shown that the LDL-C

response to Lipitor (atorvastatin) 10 mg is normally distributed with a mean reduction in LDL-C of 39% and standard deviation of 10%. Thus, for a homogenous patient population with an initial LDL-C of 200 mg/dL and an LDL-C goal of 140 mg/dL, for example, it is straightforward to determine F_m for $m = 1, \ldots, M$.

Consider three costs associated with treatment: the cost of office visits, drug costs, and the cost of coronary events (which are higher for patients in state H). Patients have monthly office visits until it is determined that they have switched to state L, and the cost of each office visit is c; the monthly cost of dose δ_m is p_m; and the expected cost of a coronary event is e_H (or e_L) for a patient in state H (or L).

Let S be the set of dosage sequence regimens for which the entire population reaches goal (i.e., switches to state L) by the end of the N-month treatment period (the problem could also, of course, be formulated such that the objective was to bring x percent of the population to goal, where $x < 100$). The elements of S are sequences of dosages $\{\delta^{(1)}, \ldots, \delta^{(N)}\}$, where $\delta^{(n)}$ is the dosage prescribed at month n to the patients who have not yet reached goal. By our assumptions, for each n, $\delta^{(n)} = \delta_m$ for some $m \in \{1, \ldots, M\}$, and $\delta^{(n)} < \delta^{(n+1)}$, unless all patients are at goal by month n + 1 (in which case we set $\delta^{(n+1)} = \delta^{(n+2)} = \ldots = \delta^{(N)} = 0$). The problem is to find the dosage sequence regimen in S that minimizes total cost over the N-month treatment period.

The timing in which costs are incurred is as follows. All patients are examined in month 1 and are prescribed dose $\delta^{(1)}$; the month-1 cost for each patient is thus: $c + p^{(1)} + e_H$. All patients are reexamined in month 2 and on average a fraction, $F^{(1)}$, are found to be at goal and $1 - F^{(1)}$ are not at goal; thus, the expected total cost in month 2 is $c + F^{(1)}(p^{(1)} + e_L) + (1 - F^{(1)})(p^{(1)} + e_H)$. In month 3 only the fraction $1 - F^{(1)}$ are examined, and of these, on average, $F^{(2)}$ are found to be at goal and $1 - F^{(2)}$ are not at goal. Thus, the expected total cost in month 3 is

$$(1 - F^{(1)})c + F^{(1)}(p^{(1)} + e_L) + F^{(2)}(1 - F^{(1)})(p^{(2)} + e_L) + (1 - F^{(2)})(1 - F^{(1)})(p^{(3)} + e_H) \quad (21)$$

and so on for the remaining months. Note that all patients will reach goal by some month $N' \leq N$, and that the monthly cost will then be constant for $N' \leq n \leq N$. For example, if everyone is given the maximum dosage at the first examination (this corresponds to the dosage sequence $\{\delta_M, 0, \ldots, 0\}$), so that $F^{(1)} = 1$, then the total expected cost (with discounting at rate r) is:

$$c + P_M + e_H + \frac{c}{1+r} + \sum_{n=1}^{N} \frac{P_M + e_L}{(1+r)^n} \quad (22)$$

To find the optimal dosage sequence, we first determine the set S by running through all dosage sequences and eliminating those that fail to bring all patients to goal by the required time. Then we compute the total, expected present value cost for each dosage sequence in S; the optimal dosage sequence is the one with lowest total expected cost. This combinatorial problem is conceptually straightforward (albeit cumbersome).

Table I Monthly cost and effectiveness by dose

Dose	F_m (%)	Monthly price ($)
1	10.0	0.00
2	50.0	100.00
3	80.0	150.00
4	100.0	250.00

For a specific example, consider a time period of 6 months and assume there are only 4 dosages available for treatment; we assume the first dose is no dose at all, but rather a diet and exercise regimen). The cost of an office visit is $200, and the expected costs of coronary events are $0 and $500, for patients at goal and not at goal, respectively. These expected event costs might correspond to, for example, a 1% or 0% risk of a coronary event that costs $50,000. The c.d.f. for treatment success, along with the corresponding monthly price of each available dose, is given in Table 1:

Because the time period is only 6 months, we assume a zero discount rate for convenience.

There are eight possible dosage sequences, and all are expected to bring the patient population to goal within the 6-month period, because there are more time periods than available dosages. In Table 2 we list these dosage sequences and their corresponding expected costs for an initial patient population of 1000:

As may be seen in Table 2, the cost-minimizing strategy involves initiating the patient population on the third dose, and then titrating up to the fourth dose those patients not reaching goal at dose 3. The total cost of this strategy is $2,040,000. Observe that the strategy of starting patients off at the lowest available dose and then titrating up gradually (those not yet at goal), is approximately 30% more costly than the optimal sequence in the current example.

Some of the treatment strategies in Table 2 may seem somewhat unconventional within the context of treating hyperlipidemia in practice, which typically involves titrating patients up in a sequential fashion. Figure 3 considers only these strategies, and bares a striking resemblance to the theoretical depiction of total costs illustrated in Figure 2.

The current example, both the generalized and numeric version, is, of course, a vast simplification of reality. In a more comprehensive analysis one would want to consider such things as adverse events to lipid therapy, which should increase with dosage, using established cardiovascular risk equations (e.g., one of

Table 2 Costs by category and dosage sequence

Dosage sequence (strategy)	CHD event costs ($)	Office visit costs ($)	Drug costs ($)	Total costs ($)	% Deviation from optimal sequence
$\{\delta_1,\delta_2,\delta_3,\delta_4,0,0\}$	1,300,000	720,000	610,000	2,630,000	28.9
$\{\delta_1,\delta_2,\delta_4,0,0,0\}$	1,175,000	670,000	585,000	2,430,000	19.1
$\{\delta_1,\delta_3,\delta_4,0,0,0\}$	1,040,000	616,000	443,000	2,099,000	2.9
$\{\delta_1,\delta_4,0,0,0,0\}$	950,000	580,000	1,125,000	2,655,000	30.1
$\{\delta_2,\delta_3,\delta_4,0,0,0\}$	850,000	540,000	805,000	2,195,000	7.6
$\{\delta_2,\delta_4,0,0,0,0\}$	750,000	500,000	975,000	2,225,000	9.1
$\{\delta_3,\delta_4,0,0,0,0\}$	600,000	440,000	1,000,000	2,040,000	0.0
$\{\delta_4,0,0,0,0,0\}$	500,000	400,000	1,500,000	2,400,000	17.6

CHD, coronary heart disease.

the Framingham risk equations) to model event risk as a function of LDL-C level, currently available statin doses and their respective prices, and any other costs relevant to the treatment of hyperlipidimia. Although a comprehensive analysis considering these factors is beyond the scope and objectives of the current article, such an analysis could be undertaken using the general framework outlined in this section. We emphasize that our approach demonstrates the potential value associated with considering the costs of different pharmacologic treatment strategies within a dynamic context.

Conclusions

In the preceding section we provided two simple, hypothetical examples of how dynamic cost minimization could be used to inform prescribing algorithms for treating hyperlipidemia. There are a multitude of other settings for which these techniques might be used. Potential examples include the treatment of obesity (weight loss), the management of diabetes, and the treatment of hypertension. All of these examples involve dynamic treatment paths and the management of a state variable (weight, Hb1C levels, and blood pressure, respectively) over time. Of course, there are a number of limitations to implementing these techniques in practice, especially optimal control theory. For example, it may be difficult to identify or approximate an optimal control problem's cost functionals. Standard econometric methods could be used in some cases, assuming data availability and a willingness (and comfort) on behalf of the researcher to make assumptions about the functional forms of a model's cost functional. It may also be difficult to treat along the optimal trajectory once one is identified; as a result of possible uncertainty in the response-to-therapy function (Γ from Section III), there may be a discrepancy between the specified and actual response of a patient. Thus, although optimal control theory may be of great value in highlighting the critical nature of the dynamic perspective, it may be challenging to implement in practice within some settings. Nevertheless, these caveats being mentioned, this is also the case for many applications of control theory falling outside the domain of the engineering sciences. The fact that optimal control may be difficult to apply in practice was the impetus for our second example in this article, which examined the issue of dynamic cost minimization using a very different formulation of the problem. Despite the fact that our second example was simple and also employed a number of restrictive assumptions, it did illustrate how the dynamic perspective could more easily be employed in practice, and thus inform intertemporal treatment decisions for hyperlipidemia.

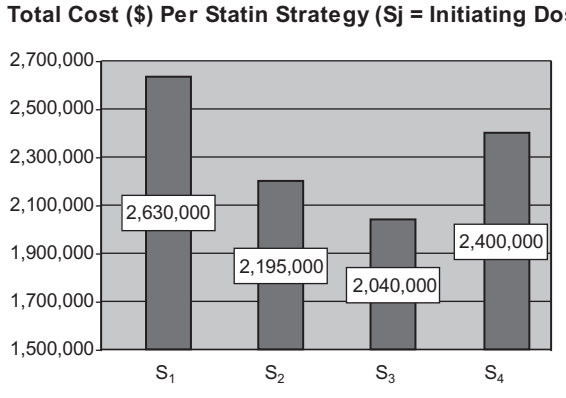

Figure 3 Total costs over 6 months.

The practical limitations to optimal control aside, we argue that the process of formulating and setting up the dynamic optimization problem, as well as obtaining a solution, may shed important light on the relative costs and tradeoffs involved in various health-care and medical treatment trajectories over time. Insight into the dynamic economic properties of the various treatment regimens may therefore be of considerable value to decision-makers who are responsible for the efficient allocation of scarce health-care resources. Moreover, there may be ways to improve dynamic treatment paths even when control theory is not used; other methods of dynamic optimization may be of use here.

In summary, the primary purpose of this article is to introduce dynamic cost minimization and optimal control theory. The hope is that the perspectives they offer and the techniques they employ may enrich, or simply

support, certain types of pharmacoeconomic analyses. Our objective is to draw attention to the fact that dynamic considerations may warrant more attention in the future. Hopefully, this primer will be successful in raising researchers' awareness to these issues and possibly aiding future research.

We are grateful to the following individuals for their helpful comments and suggestions on this article: Henry Grabowski and John M. Vernon of the Department of Economics, and Robert Bryant of the Department of Mathematics, at Duke University; and Mike Grossman of the NBER. We are also indebted to Gordon Liu, Coeditor of this journal, and three anonymous reviewers for their extremely helpful guidance in improving this article from an earlier version.

Source of financial support: None

References

1 Perelson AS. Applications of optimal control theory to immunology. In: Mohler RR, Ruberti A, eds., Recent Developments in Variable Structure Systems, Economics and Biology. New York: Springer-Verlag, 1978.
2 Perelson AS, DeLisi C. Optimal strategies in immunology. J Math Biol 1980;10:209–56.
3 Swan GW. Applications of Optimal Control Theory in Biomedicine. New York: Marcel Dekker, Inc., 1984.
4 Kirschner D, Lenhart S, Serbin S. Optimal control of chemotherapy of HIV. J Math Biol 1997;35:775–92.
5 Stengel RF, Ghigliazza R. Stochastic optimal therapy for enhanced immune response. Math Biosci 2004; 191:123–42.
6 Wein LM, D'Amato RM, Perelson AS. Mathematical analysis of antiretroviral therapy aimed at HIV-1 eradication or maintenance low viral loads. J Theor Biol 1998;192:81–98.
7 Dorfman R. An economic interpretation of optimal control theory. Am Econ Rev 1969;59:817–31.
8 Bellman R. Dynamic Programming. Princeton, NJ: Princeton University Press, 1975.
9 Pontryagin LS, Boltyansky VG, Gamkrelidze RV, Mishchenko EF. The Mathematical Theory of Optimal Processes. New York: Wiley, 1962.
10 Silberberg E. The Structure of Economics: A Mathematical Analysis (2nd ed.). New York: McGraw-Hill Co, 1990.
11 Intriligator M. Mathematical Optimization and Economic Theory. Englewood Cliffs, NJ: Prentice Hall Inc, 1971.
12 Bootman L, Townsend R, McGhan W. Principles of Pharmacoeconomics (3rd ed.). Cincinnati, OH: W. Harvey. Whitney Books Co, 2005.
13 Rascati K, Gagnon JP. Report of a panel discussion: pharmacoeconomic education, managed care, and the pharmaceutical industry. Am J Pharm Educ 1999;63: 449–53.
14 Venturini F, Johnson K. Introduction to Pharmacoeconomic Principles and Applications in Pharmacy Practice. Available from: http://www.continuingeducation.com/pharmacy/principles/types.html. [Accessed July 29, 2005].
15 Hirsch M, Smale S. Differential Equations, Dynamical Systems, and Linear Algebra. New York: Academic Press, 1974.
16 Bertsekas D. Dynamic Programming and Optimal Control (2nd ed.). New York: Athena Scientific, 2000.
17 Weinstock R. Calculus of Variations with Applications to Physics and Engineering. New York: Dover, 1974.
18 Delea T. Use of surrogate measures in cost-effectiveness analyses of lipid-lowering therapies. Value Health 1998;1:175–86.