# Drug Input Optimization: Bioavailability-Effected Time-Optimal Control of Multiple, Simultaneous, Pharmacological Effects and Their Interrelationships

VICTOR F. SMOLEN*▲, BRUCE D. TURRIE†, and WILLIAM A. WEIGAND†

**Abstract** □ Engineering control systems analysis and optimization techniques are developed, applied, and described with respect to their potential for providing rational approaches and quantitive criteria for such centrally important pharmaceutical problems as: (*a*) the evaluation and time-optimal, dynamic control of the therapeutic performance of drugs, drug products, and interacting drug combinations; (*b*) the optimal design of the dynamic drug release behavior of drug dosage forms; and (*c*) patient-individualized determination of optimal drug dosage regimens. A functional analysis approach is exemplified by the computation of a time-optimal drug input, which could be achieved by an appropriate mode of drug administration, which elicits optimally controlled time variations of drug-induced multiple, simultaneously occurring, pharmacological effects. A computer simulation is performed to exemplify the manner in which an ideally sought level of therapeutic response intensity may be achieved as rapidly as possible without exceeding predetermined safe and tolerable levels of adverse drug effects. The significance and manner of determination of "single-dose" dose–effect relationships are exemplified, and their significance with respect to patient-individualized drug dosage regimens is discussed. The manner in which time variations of drug effects can be interrelated with themselves and plasma drug levels is elucidated.

**Keyphrases** □ Drug input dynamics—relationship of input functions to time variations of multiple pharmacological effects, computer simulation □ Optimal drug input functions—relationship to time variations of multiple pharmacological effects, computer simulation □ Computer simulation—time-optimal control of drug input □ Pharmacokinetics—drug input optimization, computer simulation

It can occur that a drug is completely available to the systemic circulation yet is entirely ineffective with respect to the induction of therapeutic effects; this phenomenon is a consequence of an inadequate access of the drug to location(s) in the body, called the biophase, that contains the site(s) of action for the drug. These considerations emphasize the importance of the concept of "biophasic drug availability" (1–9) as contrasted to systemic or "physiological drug availability" (10). Therefore, a principally important consideration in the selection of routes of administration, dosage regimens, and drug release characteristics of dosage forms, all of which largely determine the time course of drug input into the system, is the manner in which the resulting drug input *versus* time profile influences the biophasic drug level *versus* time profiles; these, in turn, determine the time variation of the intensities of drug responses. The profound influence of drug inputs (*i.e.*, cumulative amounts absorbed *versus* time profiles) on drug disposition and pharmacological response–time profiles has been demonstrated (5). All of a drug's response characteristics, including the time of onset of drug action, the duration of effect, maximal response intensity, time of maximal response, duration of maximal effect, rate of dissipation of effect, and dose–response efficiency (defined as the area under a response–time curve normalized to unit dose), are affected by the manner in which the drug becomes bioavailable.

Drugs seldom produce singularly sought specific therapeutic effects but, instead, generate simultaneously occurring multiple pharmacological responses. Although a drug input may closely induce an ideally sought time variation of a therapeutic response, it may concomitantly induce magnitudes of adverse drug responses which are intolerable. Taking into account this consideration, an optimal drug input may be defined as: "a time variation of cumulatively administered drug that produces a response *versus* time profile which approaches a preselected ideally sought therapeutic response–time profile as closely as possible without exceeding predetermined, safely allowable limits of any concomitantly occurring adverse drug reactions." This type of pharmacological response behavior may be defined as maximally therapeutically efficient. Drug standards in the form of ideal response *versus* time profiles and the limits of safe toleration of adverse effects may, of course, best be prescribed for any particular drug by a pharmacokineticist, pharmacologist, toxicologist, and clinician team having a background of knowledge and experience with the particular drug of interest.

The present report describes a typical time-optimal control of drug input problem, which was studied through simulation using the CDC 6500 digital computer. The problem may be stated as follows: "Determine the cumulative drug input dynamics required to obtain an 80% of maximal therapeutic response, designated *A*, in a minimal time without exceeding toxic response intensities of 50, 40, and 20% for responses *B*, *C*, and *D*, respectively." There were not sufficient multiple pharmacological response data available for any single drug to illustrate this drug input optimization for maximal therapeutic efficiency problem for an actual drug. However, the procedure was exemplified by synthesizing a hypothetical drug system using four different experimental pharmacological response results previously observed with three different drugs; it was assumed that the hypothetical drug produced these responses simultaneously. One response, *A*, was arbitrarily selected to be the sought therapeutic response to be brought up to and maintained at 80% of its maximal intensity in as short a time as possible without exceeding what was arbitrarily designated as three other toxic responses at levels of 50, 40, and 20%. The system, as well as the therapeutic and toxic levels of response intensity, was chosen almost entirely at random so as not to bias the successful or unsuccessful application of the approach. The parameters describing the dynamics and drug response behavior of the hypothetical system are based on values obtained experimentally in this labora-

tory; therefore, such dynamic and drug response behavior could well be obtained in actual practice with a real drug system.

## THEORETICAL

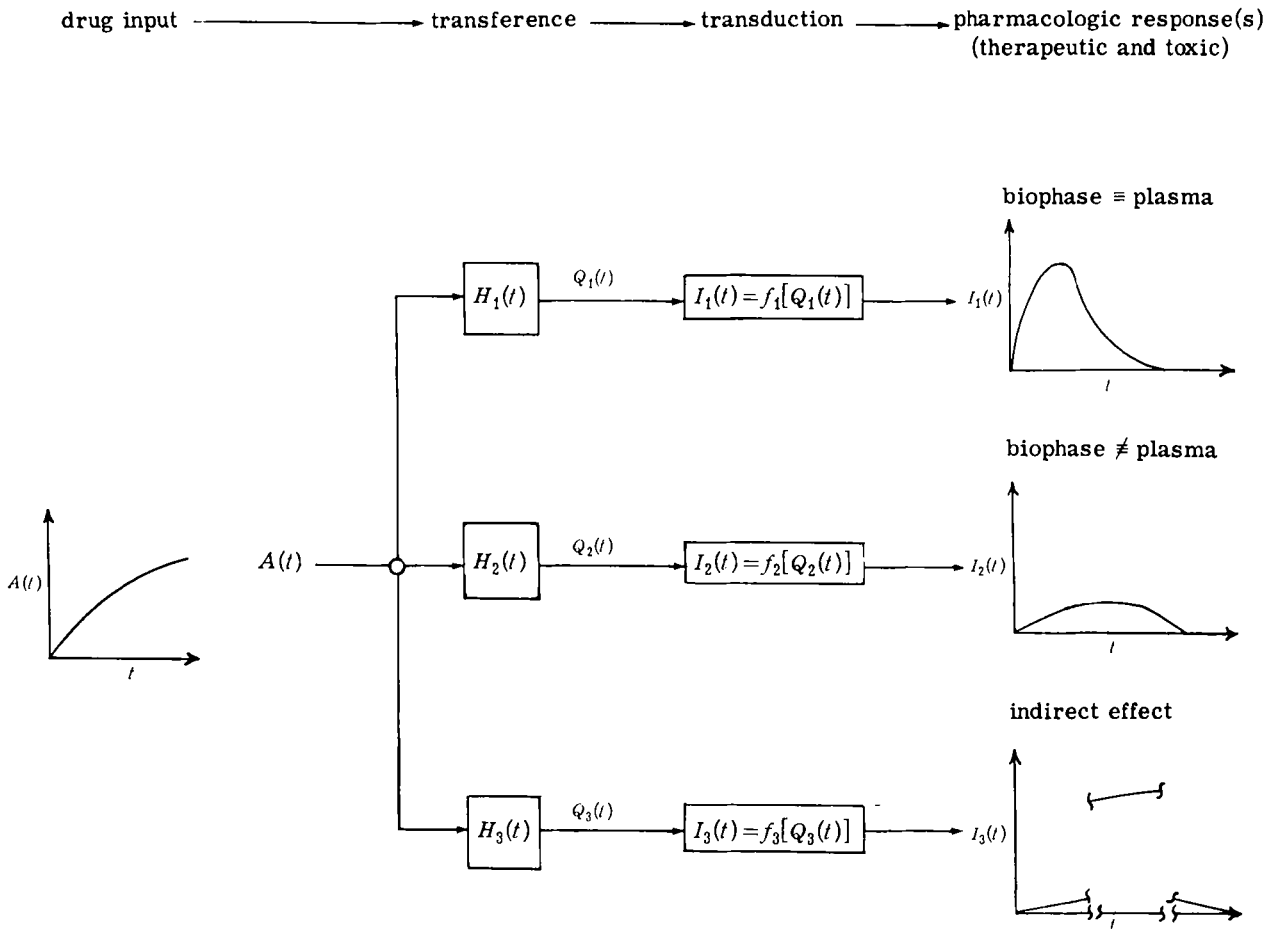
The principal objective of pharmacokinetic research concerns the development of mathematical model descriptions of the dynamics of drug transference and drug effects in pharmacologically responding systems. For such developments to be of maximal pragmatic value to the development of drug products of optimal quality and the computation of drug dosage regimens, the elucidation of the pharmacokinetic systems behavior must allow the prediction of the time course of drug-induced biological response(s) as a function of the manner in which the drug is made available to the biological system.

There are basically two approaches to effecting a measure of control over the biological response behavior of a drug. One conceivable approach may be to attempt to control the disposition of the drug in the body or to modulate the physiological activity of the drug after it is introduced into the system (11). However, except in certain instances where the metabolism, excretion, or activity of the drug can be affected by administering other agents, the disposition of the drug once it has entered the systemic circulation or other body locations is determined by the innate dynamic properties of the biological system and cannot readily be altered in a necessarily routine, predictable fashion. The alternative approach presents the only generally practical means of controlling drug response behavior. The manner in which a drug enters the system can obviously always be controlled by the size of the dose, the dosage regimen, the route and manner in which the drug is administered, and the drug release characteristics of the dosage form.

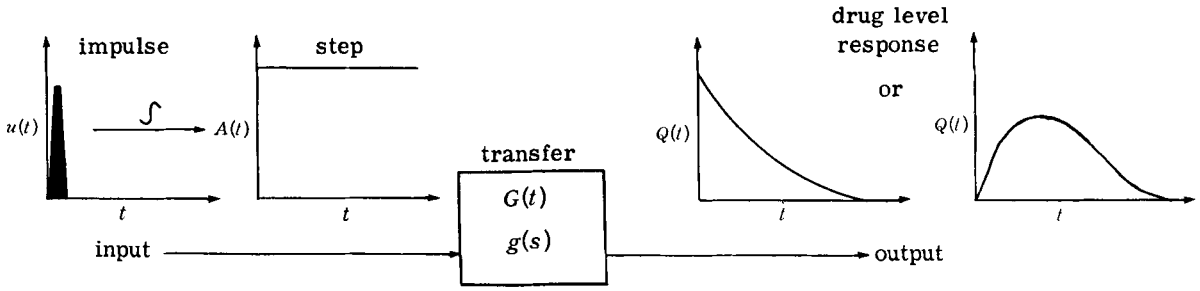
The problem of obtaining drug response behavior that is maximally therapeutically efficient generally transforms into the pharmacokinetic problem of computing optimal drug input *versus* time profiles. An optimal systemic drug input profile can almost always be closely approximated by a programmed intravenous injection of the drug. For other routes of administration, the therapeutic efficiency depends upon how closely the *in vivo* drug availability properties of the dosage form reproduce the time course of optimal drug input.

**Application of Engineering Control Theory and Optimization Methods**—Engineering dynamic systems analysis techniques can be directly applied to describe the pharmacokinetic processes that determine the quantitative nature of drug effects. In this context, drug flow and drug response signals can be considered in a manner analogous to the transfer of electric current, fluids, or forces in electrical, hydrodynamic, or mechanical systems. This simple realization allows the powerful techniques of engineering control theory, signal processing, and optimization to be directly applied to the treatment of pharmaceutical problems.

Pharmacologically responding living systems receiving an input of a drug may be described as analogous to an open loop control system producing multiple responses to the drug input signal. These processes are illustrated by the block diagram in Scheme I, which depicts the consecutive processes of drug input and transference to the sites of action in the biophase. Here the biophasic drug levels are transduced into either therapeutic or toxic pharmacological responses. Three types of commonly occurring drug response profiles are shown. The upper response *versus* time profile is characterized by a relatively rapid appearance of a peak; it typifies the case where the biophase and plasma compartment are kinetically identical. For example, if the response is an antibiotic-induced antibacterial activity of the plasma, it may be expected to be described by the top curve. However, if the activity of the antibiotic is intended to be directed against a deep-seated tissue infection, then the antibacterial response *versus* time profile may appear as given by the middle curve. The lower curve is typical of an indirect effect as elicited by, for example, reserpine on blood pressure or warfarin




*Scheme I—Block diagram characterization of the dynamics of drug response*




*Scheme II—Drug input–drug level response relationships for a rapidly injected,* u(t) *(impulse function), drug input to the drug transfer system,* i.e., *the body. The drug level* versus *time profile represents the impulse response [weighting function,* G(t), *in the time domain or transfer function,* g(s), *in the frequency domain of the system]. Subsequently, the cumulative amounts of drug input to the system at any time,* A(t), *following dosing by other modes of administration are computed as the convolution of the reciprocal of the integral of* G(t) *and their corresponding observed drug level response,* Q(t): i.e., $A(t) = \left[\int_0^t G(t)\right]^{-1} * Q(t)$.

on prothrombin complex activity where the response may be prolonged even beyond the time the dose of drug has been effectively cleared from the plasma. In any event, the response is a causal consequence of the time variation of biophasic drug levels; although the relationship may not always be immediately apparent, the response intensity, $I$, can generally be functionally related to the biophasic drug level(s), $Q(t)$, responsible for its induction.

**Transductive Interrelation between $I(t)$ and $Q(t)$**—Work in this laboratory (1–9) has shown that the functional relationship between the pharmacological response intensity, $I(t)$, and corresponding biophasic drug levels, $Q(t)$, are provided by dose–effect curves or, more completely, by dose–effect–time surfaces. The verity of the relationship in any instance can be rigorously determined from the observed pharmacological data alone (1–4, 7); the method obviates any determination of tissue or corporeal fluid drug levels by chemical or radiological assay and, therefore, can be readily applied where methods for the detection of the drug by direct assay are difficult or nonexistent. A rigorous mathematical basis for the utilization of dose–effect curves to relate biophasic drug levels reciprocally to their corresponding pharmacological response intensities was reported earlier (7).

**Linear Systems Analysis of Drug Disposition**—Except for the transduction between biophasic drug levels and drug response, the majority of drug transference systems are well described by compartment models (12) and, therefore, behave linearly or at least are piecewise linear over an operational range of interest. The objective of the present linear systems analysis is to compute drug input functions that are optimal in producing pharmacological responses of maximal therapeutic efficiency. In engineering terms, this reduces to an input discovery or optimization problem. Scheme II shows the manner by which the drug transference dynamics of the system can be characterized by determining the relationship between drug input and output in terms of biophasic drug levels for a rapidly injected unit dose of drug. Such an injection constitutes a unit impulse function drug input. If the time course of pharmacological response is observed following a rapidly injected dose, its transformation into the time course of biophasic drug levels directly provides the unit impulse response or transfer function for the system. The integral of the unit impulse response then gives the unit step function response required to compute drug inputs corresponding to any desired drug output response profile (13, 14).

**Functional Analysis Approach to Pharmacokinetic Problems**—A new and powerful functional analysis approach, previously described (15–18) and further developed by the authors, has been implemented to achieve the time-optimal control of drug response behavior described in the present report. Functional analysis is a branch of mathematics which generalizes the concepts of classical analysis (including calculus), algebra, and geometry from variables that are real and complex numbers to more general kinds of variables. Relationships that deal with point functions, *i.e.*, $y = f(x)$, are replaced by more general types of functions, called functionals or operators, wherein the function depends upon another function rather than on point values. Functional analysis provides a unified framework for considering problems in which variables are not just numbers but are time functions. It is particularly well suited for open loop, programmed control of dynamic systems through application of appropriately optimal, input time functions. As such, functional analysis is ideal for application to pharmacokinetic problems such as those presently described which relate to the time-optimal control of drug response dynamics.

Although ideally suited for pharmacokinetic purposes, the presently described functional analysis approach has not previously been suggested for application to pharmacokinetic problems. This particular approach to the time-optimal control of multiple pharmacological response dynamics possesses several important advantages relative to other less general mathematical techniques which have been more commonly applied to control engineering optimization problems (19–26). In addition to relative computational and theoretical simplicity, the approach possesses the following advantages:

1. The capability to accommodate multiple inputs. This feature is important in that it will permit the quantitative treatment of multiple pharmacological response or drug level *versus* time data resulting from the simultaneous administration of the same or different drugs by different or the same routes and modes of administration. The significance of this capability to the simulation and prediction of the pharmacological and/or drug level response behavior elicited from acute and chronic administration of a single drug or interacting drug combinations is apparent.
2. The capability to treat system behavior using transfer functions of up to seventh or higher order (*i.e.*, models possessing seven or more compartments for each pharmacological or drug level response can be readily constructed). This capability is certainly more than sufficient for the treatment of the dynamic systems behavior normally encountered with pharmacokinetic problems.
3. The capability to treat adaptive system nonlinearities that can mechanistically arise in drug responding living systems from the occurrence of threshold and saturation phenomena affecting drug plasma and tissue binding, drug transport and metabolic processes, and dose–effect relationships. Drug-interaction-induced time variations in dynamic model parameters resulting from the coadministration of drugs in combination can also be effectively managed.

## EXPERIMENTAL

**Determination of Dose–Effect Curves**—Figure 1 depicts intravenous dose–effect curves for each pharmacological response included in the present simulation of a hypothetical system. These curves provide the relationships necessary to transduce relative biophasic drug levels into their corresponding pharmacological response intensities, or vice versa. The *A* curve in actuality describes the mydriatic response of tropicamide (6), the *B* curve is the miotic response curve for carbachol, the *C* curve is the intraocular pressure response for carbachol, and the *D* curve represents the mydriatic response for tridihexethyl chloride (1). The *A* and *D* dose–effect curves are based on previously reported results (1, 2), where the details of the measurement of the mydriatic response intensity were provided. The miotic response to carbachol was measured similarly. The relative intraocular pressure changes induced by carbachol were determined using a applanation tonometer[1]. Rabbits were the test animals in every case. The dose–effect curves shown in Fig. 1 are plots of the maximum response intensity ob-

[1] Tonomat, Ocular Instruments Inc., Cle Elum, Wash.

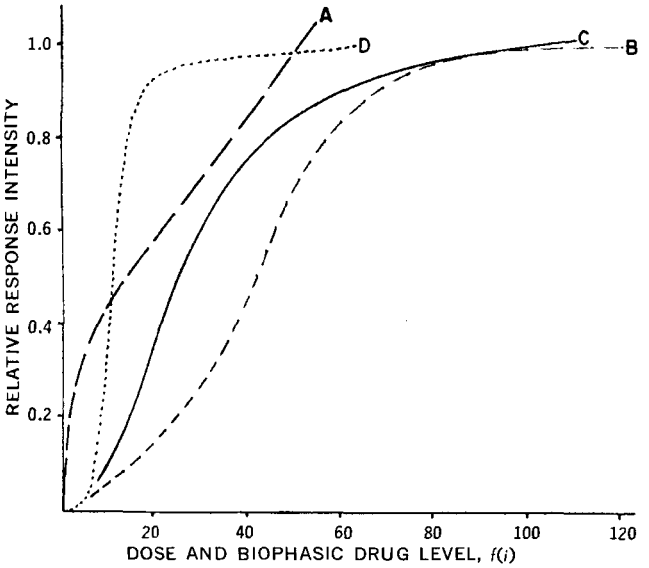



**Figure 1**—*Intravenous dose–effect curves for rabbits. Key: A, mydriatic response of tropicamide; B, miotic response to carbachol; C, intraocular pressure response to carbachol; and D, mydriatic response to tridihexethyl chloride. The curves define the functional relationship between the intensity of drug effect and relative biophasic drug levels.*

served following rapid intravenous dosing with the drugs. A minimum of six different doses administered to at least three rabbits was employed for each response. The dose–effect curves represent curvilinear least-squares regression fits to the averages (9). The details of the studies with carbachol will be presented in subsequent reports.

The tropicamide plasma levels used to construct the "single-dose" dose–effect curve in Fig. 2 were obtained by periodically sampling blood taken from the marginal ear vein of the rabbits used as test animals. The levels of tritiated tropicamide[2] were determined using standard techniques of liquid scintillation counting[3] (9). The method of intravenous infusion was described previously (2).

**Transfer Function Parameters**—The values of transfer function parameters were obtained from the results of weighted, least-squares, multiexponential, computerized fits to the mean time variations of dose-normalized relative biophasic drug levels; these results were obtained by computerized transduction of observed time variations of drug response intensities following impulse drug inputs, *i.e.*, rapid intravenous bolus dosing. The curves presented in Fig. 1 were employed for transduction. Multifit, a previously developed (1, 9) digital computer program which employs an iterative systematized search method, was used to accomplish the weighted least-squares fitting required to obtain the transfer function parameters. This and the programs used to compute the time-optimal control (24, 25) were implemented on a computer[4].

## RESULTS

**Mathematical Approach to Time-Optimal Control of Multiple Pharmacological Response Behavior**—The utility of the proposed pharmacokinetic control systems analysis resides in its ultimate application to simulating drug response behavior and the computation of drug input functions which are optimally consistent with maximizing sought therapeutic responses to drugs and drug combinations while maintaining the intensities of toxic drug effects constrained within predetermined safe, allowable limits. In this manner, a new rational approach to designing the formulation and evaluation of drug products and determining their optimal mode of administration may be attainable. An example is presented below for a hypothetical system.

One type of feasible objective for an optimal drug input is to achieve a desired biophasic drug level and corresponding response intensity in the minimum time subject to the condition that proscribed "toxiphasic" drug levels and response intensities are not exceeded. The following hypothetical system is considered where a drug produces a therapeutic effect, *A*, in the biophase while preselected levels of toxic effects resulting from "toxiphasic" drug levels at the sites of action, *B*, *C*, and *D*, are not exceeded.

The dynamic optimization technique employed in this work requires the dynamic equations for the systems *A*, *B*, *C*, and *D* and bounds on the input functions for these systems. The dynamic equations were first obtained in terms of transfer functions by the least-squares, multiexponential, computerized fits described previously. Bounds on the input functions are then determined by using the dose–effect curves relating response intensities, relative biophasic and toxiphasic drug levels, and the final value theorem of Laplace transforms. The optimization technique employed here, *i.e.*, the necessary conditions and input functions as derived by the use of some theorems of functional analysis, requires the dynamic system equations to be represented in state variable notation. This is accomplished by the technique of direct programming. A transformation is then performed that casts the system equations into a form with symmetrically constrained inputs. The form of the optimal input function and the subsidiary problem which determines the number and time of the input switchings are derived in the *Appendix*. The solution to the subsidiary problem is accomplished by an iterative numerical technique (24, 25).

The transfer functions relating relative drug levels and cumulative drugs inputs are given by Eqs. 1, 2, 3, and 4 for sites of action *A*, *B*, *C*, and *D*, respectively. The transfer function parameters are evaluated from the results of multiexponential fits to the biophasic drug level response to impulse (bolus injection) or step (zero-order

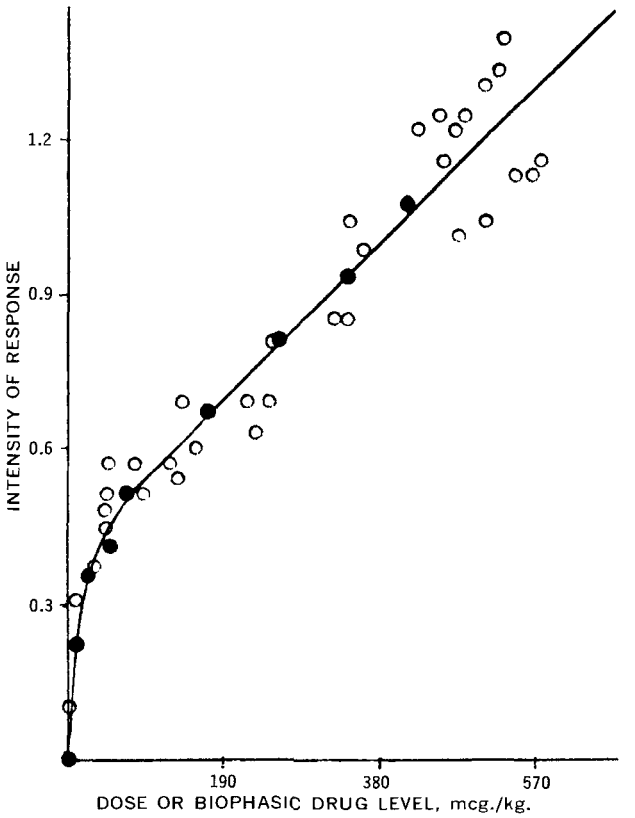



**Figure 2**—*Comparison of multiple bolus intravenous dose–effect curve (●) with a single-dose dose–effect curve (○) obtained by simultaneously monitoring the time course of tritiated tropicamide plasma levels and the mydriatic response intensity during and following the slow intravenous infusion of the drug to rabbits. The curve is a weighted least-squares fit to the "multiple-dose" average values obtained from replications performed with four rabbits.*

[2] Supplied by Alcon Laboratories, Fort Worth, Tex., and New England Nuclear, Boston, Mass.
[3] Performed with a Packard Instrument Co. (La Grange, Ill.) Tri-Carb model 314X counter.
[4] CDC 6500.

intravenous infusion) function drug inputs:

$$\frac{f_A(I_A)(s)}{A(s)} = \frac{\gamma_{1A}s + \gamma_{2A}}{\alpha_{1A}s + \alpha_{2A} + (\alpha_{3A}/s)} \quad \text{(Eq. 1)}$$

$$\frac{f_B(T_B)(s)}{A(s)} = \frac{\gamma_{1B}s + \gamma_{2B}}{\alpha_{1B}s^2 + \alpha_{2B}s + \alpha_{3B} + (\alpha_{4B}/s)} \quad \text{(Eq. 2)}$$

$$\frac{f_C(T_C)(s)}{A(s)} = \frac{\gamma_{1C}}{\alpha_{1C}s + \alpha_{2C} + (\alpha_{3C}/s)} \quad \text{(Eq. 3)}$$

$$\frac{f_D(T_D)(s)}{A(s)} = \frac{\gamma_{1D}s + \gamma_{2D}}{\alpha_{1D}s^2 + \alpha_{2D}s + \alpha_{3D} + (\alpha_{4D}/s)} \quad \text{(Eq. 4)}$$

When considering the time-optimal drug input problem, it is convenient to work with the instantaneous drug input, $u(t)$. Since the cumulative drug input is simply the time integral of $u(t)$, the transfer function relating the outputs $f_A(s)$, $f_B(s)$, $f_C(s)$, and $f_D(s)$ and $u(s)$ are given by Eqs. 1–4 with $A(s)$ replaced by $u(s)/s$. For the particular hypothetical system under consideration the transfer function parameters were determined as $\gamma_{1A} = 1.004$, $\gamma_{2A} = 0.28968$, $\alpha_{1A} = 1.0$, $\alpha_{2A} = 0.5452$, and $\alpha_{3A} = 0.040748$; $\gamma_{1B} = 2.2$, $\gamma_{2B} = 0.674$, $\alpha_{1B} = 1.0$, $\alpha_{2B} = 1.40718$, $\alpha_{3B} = 0.63710$, and $\alpha_{4B} = 0.0937$; $\gamma_{1C} = 0.224$, $\alpha_{1C} = 1.0$, $\alpha_{2C} = 0.3538$, and $\alpha_{3C} = 0.022388$; and $\gamma_{1D} = 0.31842$, $\gamma_{2D} = 0.0049169$, $\alpha_{1D} = 1.0$, $\alpha_{2D} = 0.28734$, $\alpha_{3D} = 0.00761311$, and $\alpha_{4D} = 0.0000525598$.

Considering a specific example, it may be desired to reach 80% of the maximal therapeutic effect at site $A$ while not exceeding the 50, 40, and 20% maximally obtainable toxic response levels for responses $B$, $C$, and $D$, respectively. The therapeutic intensity and toxic intensities are related to the relative biophasic and toxiphasic drug levels by the dose–effect curves shown in Fig. 1. For example, the 80% level at site $A$ corresponds to $f_A(I) = 0.330$, where $f_A(I)$ is the relative biophasic drug level. Once values for the relative biophasic drug levels are obtained, the corresponding values of instantaneous drug input required to maintain these levels are obtained by use of the final value theorem of Laplace transforms, *i.e.*:

$$f_A(I_A)_\infty = \lim_{t\to\infty} f_A(I_A)(t) = \lim_{s\to 0} sf_A(I_A)(s) = \text{steady-state value of } f_A(I_A)(t) \quad \text{(Eq. 5)}$$

For a constant value of instantaneous input, *i.e.*, $u(t) = M$, one obtains from Eq. 1, with $A(s)$ replaced by $u(s)/s$:

$$f_A(I_A)_\infty = \lim_{s\to 0} s\,\frac{M}{s}\,\frac{(\gamma_{1A}s + \gamma_{2A})}{\alpha_{1A}s^2 + \alpha_{2A}s + \alpha_{3A}} \quad \text{(Eq. 6a)}$$

$$f_A(I_A)_\infty = M\frac{\gamma_{2A}}{\alpha_{3A}} \quad \text{(Eq. 6b)}$$

or:

$$M = \frac{\alpha_{3A}}{\gamma_{2A}} f_A(I_A)_\infty \quad \text{(Eq. 6c)}$$

For the 80% level at site $A$, one obtains:

$$M = \frac{0.040748\,(0.330)}{0.28968} = 0.046421 \quad \text{(Eq. 7)}$$

Applying the final value theorem for each site of action, the results found in Table I are obtained.

Here one notes that the limiting toxiphasic drug level in Compartment $D$ requires a sustained drug input, which is 1.86 times that required to maintain the desired therapeutic effect in Compartment $A$. It, therefore, is seen that one can drive the drug level in Compartment $A$ to its final value much faster if the instantaneous drug input is put up to the value of 0.08632, then switched to zero at the appropriate time, held at zero until $f_A(I) = 0.330$, and then switched to the value needed to maintain the desired effect, in this case 0.046421. This, in essence, is the procedure followed for time-optimal control when the instantaneous inputs are constrained in amplitude. The problem then resolves into finding the switching time that yields the minimum time to reach the desired final state. In general, this requires calculation of up to $(n - 1)$ switching times for an $n$th-order system.

**Table I**—Results Used in the Computation of the Time-Optimal Drug Input

| Drug Effect | Percent of $I_{max}$ or $T_{max}$ | $f(I)$ or $f(T)$[a] | $M$[b] |
|---|---|---|---|
| A | 80 | 0.33 | 0.046421 |
| B | 50 | 42.0 | 4.91 |
| C | 40 | 22.0 | 2.20 |
| D | 20 | 8.0 | 0.08632 |

[a] $T$ denotes toxic intensity, and $f(T)$ refers to drug levels in biophasic compartments $B$, $C$, and $D$ containing sites of action for toxic effects, *i.e.*, "toxiphasic" drug levels. [b] $M$ refers to instantaneous step input values, corresponding to the sought level of $I$ and maximally allowable levels of $T$ obtained from application of the final value theorem.

For the particular example considered here, examination of the constants for the transfer functions for sites $A$ and $D$ reveals that $D$ is much slower. Therefore, one can first set the instantaneous rate to a value of 0.10 and be assured that the level at site $D$ will not approach the 20% limit while the level at $A$ is increased to 80%.

Various techniques can be used to solve the minimum time problem with amplitude constraints, *e.g.*, the minimum principle of Pontryagin (19) and the calculus of variations (26). In the present case, a method developed *via* the use of certain theorems of functional analysis (15–18) will be used. In any case, all of the above-mentioned techniques require the system to be represented in state space notation. The transformation of the dynamics, as expressed by transfer functions, to the state domain can be achieved in various ways. The method used here is known as direct programming. For example, consider the transfer function given by Eq. 1 with $A(s) = u(s)/s$:

$$G_A(s) = \frac{f_A(I_A)(s)}{u(s)} = \frac{\gamma_{1A}s + \gamma_{2A}}{\alpha_{1A}s^2 + \alpha_{2A}s + \alpha_{3A}} \quad \text{(Eq. 8)}$$

Proceeding with the method, one divides both the numerator and the denominator by $\alpha_{1A}s^2$ to obtain:

$$\frac{f_A(I_A)(s)}{u(s)} = \frac{(\gamma_{1A}/\alpha_{1A})s^{-1} + (\gamma_{2A}/\alpha_{1A})s^{-2}}{1 + (\alpha_{2A}/\alpha_{1A})s^{-1} + (\alpha_{3A}/\alpha_{1A})s^{-2}} \quad \text{(Eq. 9a)}$$

Now define the variable $E(s)$ as:

$$E(s) = \frac{u(s)}{1 + (\alpha_{2A}/\alpha_{1A})s^{-1} + (\alpha_{3A}/\alpha_{1A})s^{-2}} \quad \text{(Eq. 9b)}$$

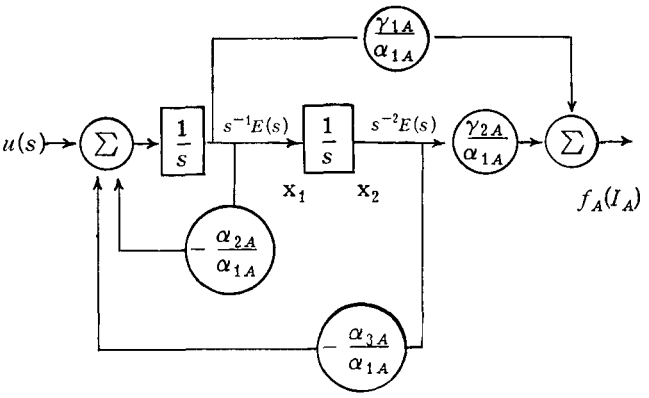
By rearranging Eq. 9b, Eq. 9c is readily obtained:

$$E(s) = -\frac{\alpha_{2A}}{\alpha_{1A}}s^{-1}E(s) - \frac{\alpha_{3A}}{\alpha_{1A}}s^{-2}E(s) + u(s) \quad \text{(Eq. 9c)}$$

Also, Eqs. 9a and 9b yield:

$$f_A(I_A)(s) = \frac{\gamma_{1A}}{\alpha_{1A}}s^{-1}E(s) + \frac{\gamma_{2A}}{\alpha_{1A}}s^{-2}E(s) \quad \text{(Eq. 9d)}$$

Equations 9c and 9d are diagramed in Scheme III.




*Scheme III—Diagram of Eqs. 9c and 9d*

Now define the output of one integrator as $x_2$ and the output of the other as $x_1$. From Scheme III, write:

$$\dot{x}_1 = -\frac{\alpha_{2A}}{\alpha_{1A}} x_1 - \frac{\alpha_{3A}}{\alpha_{1A}} x_2 + u(t) \quad \text{(Eq. 10a)}$$

$$\dot{x}_2 = x_1 \quad \text{(Eq. 10b)}$$

$$f_A(t) = \frac{\gamma_{1A}}{\alpha_{1A}} x_1 + \frac{\gamma_{2A}}{\alpha_{1A}} x_2 \quad \text{(Eq. 10c)}$$

or in vector-matrix notation:

$$\dot{\mathbf{x}} = A\mathbf{x} + b\mathbf{u} \quad \text{(Eq. 11a)}$$

$$\mathbf{x}(0) = \mathbf{x}_0 = \mathbf{0} \quad \text{(Eq. 11b)}$$

$$f_A(t) = \mathbf{d}^T\mathbf{x} \quad \text{(Eq. 11c)}$$

$$f_A(T_f) = 0.33 = \text{desired value of } f_A = f_{A_d} \quad \text{(Eq. 11d)}$$

$$0 \leq u \leq M_D = 0.10 \quad \text{(Eq. 11e)}$$

where:

$$\mathbf{x} = \begin{Bmatrix} x_1 \\ x_2 \end{Bmatrix} \qquad \mathbf{b} = \begin{Bmatrix} 1 \\ 0 \end{Bmatrix}$$

$$A = \begin{bmatrix} -\alpha_{2A}/\alpha_{1A} & -\alpha_{3A}/\alpha_{1A} \\ 1 & 0 \end{bmatrix}$$

$$\mathbf{d}^T = \begin{Bmatrix} \frac{\gamma_{1A}}{\alpha_{1A}} & \frac{\gamma_{2A}}{\alpha_{1A}} \end{Bmatrix}$$

The minimum time problem can now be stated as follows: Given a system described by Eqs. 11*a* and 11*c* with some initial state $\mathbf{x}(0) = \mathbf{x}_0$ and desired state $\mathbf{x}(t) = \mathbf{x}_d$, with the input constrained by $0 \leq u(t) \leq M_D$, find the input function $u(t)$ so that the desired state is reached in the minimum time $T_f^0$.

The particular technique used here, *i.e.*, the functional analysis approach, requires the input to be constrained symmetrically, *i.e.*, $-B \leq u(t) \leq B$, or $|u(t)| \leq B$. Therefore, before one can proceed, a transformation of variables must be made to achieve this type of constraint. In the present case, simply define $u' = u - (M_D/2)$. Then Eq. 11*e* leads to:

$$-\frac{M_D}{2} \leq u' \leq \frac{M_D}{2} \quad \text{(Eq. 12a)}$$

If one also lets $z_1 = x_1$ and:

$$z_2 = x_2 - \frac{M_D}{2}\frac{\alpha_{1A}}{\alpha_{3A}} \quad \text{(Eq. 12b)}$$

one obtains, after substituting into Eqs. 11*a*–11*e*:

$$\dot{z}_1 = -\frac{\alpha_{2A}}{\alpha_{1A}} z_1 - \frac{\alpha_{3A}}{\alpha_{1A}} z_2 + u' \quad \text{(Eq. 12c)}$$

$$\dot{z}_2 = z_1 \quad \text{(Eq. 12d)}$$

$$f_A(t) = \frac{\gamma_{1A}}{\alpha_{1A}} z_1 + \frac{\gamma_{2A}}{\alpha_{1A}} z_2 + \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2} \quad \text{(Eq. 12e)}$$

or:

$$\dot{\mathbf{z}} = A\mathbf{z} + \mathbf{b}u' \quad \text{(Eq. 13a)}$$

$$f_A(t) = \mathbf{d}^T\mathbf{z} + \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2} \quad \text{(Eq. 13b)}$$

$$|u'| \leq \frac{M_D}{2} \quad \text{(Eq. 13c)}$$

$$\mathbf{z}^T(0) = \begin{Bmatrix} 0 - \frac{M_D}{2}\frac{\alpha_{1A}}{\alpha_{3A}} \end{Bmatrix} \quad \text{(Eq. 13d)}$$

where the quantities $A$, $\mathbf{b}$, and $\mathbf{d}^T$ are defined as before. The final desired relative drug level, in terms of $z_1$ and $z_2$, is given by:

$$f_{A_d} = \frac{\gamma_{1A}}{\alpha_{1A}} z_1(T_f) + \frac{\gamma_{2A}}{\alpha_{1A}} z_2(T_f) + \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2} = 0.33 \quad \text{(Eq. 13e)}$$

or:

$$\frac{\gamma_{1A}}{\alpha_{1A}} z_1(T_f) + \frac{\gamma_{2A}}{\alpha_{1A}} z_2(T_f) = f_{A_d} - \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2} \quad \text{(Eq. 13f)}$$

Therefore, $z_1(T_f)$ and $z_2(T_f)$ are constrained by Eq. 13*e*. One can write:

$$z_2(T_f) = \frac{\alpha_{1A}}{\gamma_{2A}}\left[f_{A_d} - \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2} - \frac{\gamma_{1A}}{\alpha_{1A}} z_1(T_f)\right] \quad \text{(Eq. 13g)}$$

Therefore:

$$\mathbf{z}_d^T(T_f) = \{z_{1_d}(T_f) z_{2_d}(T_f)\} \quad \text{(Eq. 13h)}$$

where $z_{2_d}(T_f)$ is given by Eq. 13*g*.

One sees that there is an infinite number of combinations of $z_1(T_f)$ and $z_2(T_f)$ that will satisfy Eq. 13*e*. This means that the final desired value of $f_A(I_A)$ is achieved by any member of the target set formed by Eq. 13*e*. In general (20), there is one combination of $z_1(T_f)$ and $z_2(T_f)$ of the target set that yields the smallest value of $T_f$ corresponding to the initial conditions given by Eq. 13*d*. The solution to the minimum time problem can then be found by repeated calculation using a simple search technique, *i.e.*, a value for $z_1(T_f)$ is chosen, the value of $z_2(T_f)$ is then given by Eq. 13*g*, and the $T_f$ for this pair is found. The procedure is repeated until the $z_1$ yielding the smallest value of $T_f$ is found.

The problem can then be stated as follows: Given the system described by Eqs. 13*a* and 13*b* with the initial condition given by Eq. 13*d* and input constrained by Eq. 13*c*, drive the system to the desired final state, Eq. 13*h*, where $z_1$ and $z_2$ are constrained by Eq. 13*e*, in the minimum time possible.

As stated previously, the solution can be obtained by the application of various theorems of functional analysis. The details of the derivation were given by Kranc and Sarachik (16), Sarachik and Kranc (17), and Kreindler (18). The particular results obtained by this technique are used here because they can be easily applied to systems with multiple inputs, although an example with only a single input is considered here. Systems with multiple inputs will be considered in subsequent reports. A version of the derivation of the solution using the approach of Kreindler (18) is presented in the *Appendix*. The time-optimal control function for the specific example considered here, the case of a second-order system with a scalar input and output, is given by Eq. A35 of the *Appendix*. It is:

$$u'^0(t) = \frac{M_D}{2}\,\text{sgn}\left\{\lambda_1\phi_{11}(T_f^0 - t) + \left[\frac{1.0 - \lambda_1 z_1^d(T_f^0)}{z_2^d(T_f^0)}\right]\phi_{21}(T_f^0 - t)\right\} \quad \text{(Eq. 14)}$$

where sgn is the signum function defined in the *Appendix*.

Therefore, one sees that Eq. 14 defines an input function that switches from $(M_D/2)$ to $-(M_D/2)$ as the argument of sgn changes from positive to negative. Included in the argument of sgn is the parameter $\lambda_1$. It is when $\lambda_1$ has been properly specified that there is a time-optimal solution; $\lambda_1$ can, in turn, be found from Eq. A34 derived in the *Appendix*. It is:

$$1 = \min_{\boldsymbol{\lambda}\cdot\mathbf{z}^d(T_f)=1} \int_0^{T_f} \frac{M_D}{2}\left|\lambda_1\phi_{11}(t-\tau) + \left(\frac{1.0 - \lambda_1 z_1^d(T_f)}{z_2^d(T_f)}\right)\phi_{21}(t-\tau)\right| d\tau \quad \text{(Eq. 15)}$$

*i.e.*, $\lambda_1$ is selected such that the minimum value of the integral is equal to unity while $T_f$, the upper limit of integration, is the minimum time $T_f^0$. All of the terms in the integrand of Eq. 15 except $\lambda_1$ and $T_f$ are known functions of time or given constants. Therefore, once a value for $T_f$ is chosen, the value of the integral depends only upon the value of $\lambda_1$. By searching over values of $\lambda_1$, the minimum value of the right-hand side of Eq. 15 is found. If the value of the

integral is not equal to unity, a new value for $T_f$ is chosen and the minimization with respect to $\lambda_1$ is repeated. This process is continued until a pair, $T_f$ and $\lambda_1$, that satisfies Eq. 15 is found. One then has the minimum time, $T_f^0$, and the value of $\lambda_1$ that produce the correct switch in the control function, Eq. 14. A program was developed for this purpose (24, 25). The quantities $\mathbf{z}^a(T_f)$, $\lambda$, $\phi_{11}$, and $\phi_{21}$ are defined in the *Appendix*, by Eq. 9*a*, by Footnote 8, and by Eq. A31*a*, respectively.

The particular example presented here demonstrates the interesting case of a plant with numerator dynamics as seen by Eq. 8. Systems with numerator dynamics lead to the situation where the desired final output, $f_{A_d}$, given by Eq. 13*e*, can be reached by any pair of state variables, $z_1$ and $z_2$, that satisfies Eq. 13*e*. As stated previously, one then has a target set rather than a target point. Therefore, with the initial state fixed by Eq. 13*d*, many combinations of $z_1$ and $z_2$ will give $f_{A_d} = 0.33$. For example, one pair of values for $z_1$ and $z_2$ which satisfies Eq. 13*e* is $z_1 = 0$ and:

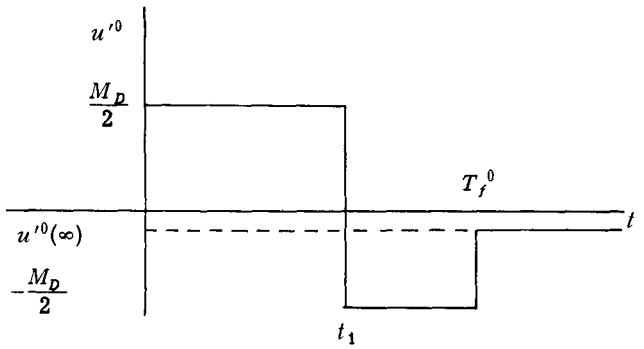
$$z_2(T_f) = \frac{\alpha_{1A}}{\gamma_{2A}}\left(f_{A_d} - \frac{\gamma_{2A}}{\alpha_{3A}}\frac{M_D}{2}\right) \qquad \text{(Eq. 16)}$$

*i.e.*, $z_1(T_f)$ is equal to its initial value and $z_2(T_f)$ is prescribed by Eq. 13*e*. This pair corresponds to the original state variables, Eqs. 10*a*–10*c*, with values of $x_1(T_f) = 0$ and:

$$x_2(T_f) = f_{A_d}\frac{\alpha_{1A}}{\gamma_{2A}} \qquad \text{(Eq. 17)}$$

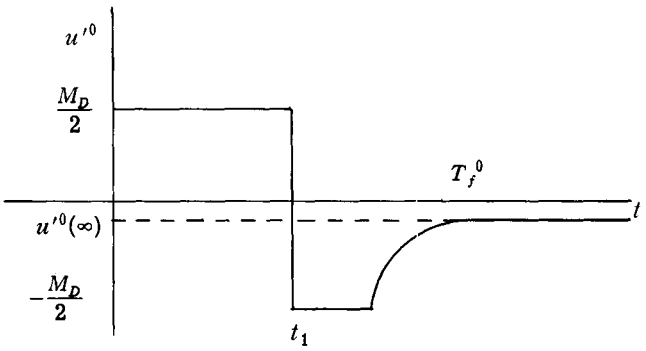
However, whenever there exists a target set, in this case a straight line, there is an infinite number of $z_1$ and $z_2$ pairs that will yield $f_{A_d}$, but only one pair will achieve $f_{A_d}$ in the minimum time. The minimum is then found by the iterative approach explained after Eqs. 13*a*–13*h*. In addition, the type of function that produces the minimum time response depends on the optimal point on the target set. In general, depending on the initial conditions as given by Eq. 13*d* and the desired value of the system output $f_{A_d}$, one has three types of optimal control functions, satisfying condition 13*c*, for a second-order system. They are pictured in Schemes IV–VI in terms of the transformed input $u'^0$.

Scheme IV illustrates a case where a single switch at time $t_1$ and a

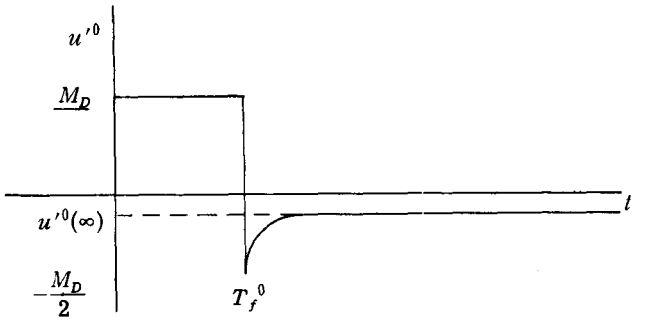



*Scheme IV—Control at both upper and lower bounds with no singular region*

switch to $u'^0 = 0$ at $t = T_f^0$ yield the optimal time. This corresponds to the case where Eq. 13*e* is satisfied by values of $z_1(T_f)$ and $z_2(T_f)$, which remain constant after time greater than $T_f^0$ and yet maintain the output at its desired value, $f_{A_d}$. In general, this will not be the case for a system with numerator dynamics and the usual form of the control function is given by either Scheme V or Scheme VI. Scheme V indicates a situation where one still has a switch to $u'^0 = -(M_D/2)$ at $t = t_2$, but the target set is reached at values of $z_1(T_f^0)$ and $z_2(T_f^0)$ which do not maintain the output at $f_{A_d}$ for times greater than $T_f^0$. Consequently, an exponential type decay for $u'^0(t)$ from $u'^0 = -(M_D/2)$ to $u'^0 = -0.003579$ is required until $z_1$ and $z_2$ adjust to the values which do maintain the output at its desired constant value. Scheme VI indicates a situation where the control is never switched to its lower limit to achieve $f_{A_d}$ in the minimum time. One notes in Scheme VI that the required exponential decay appears as it did in Scheme V but that it does not in general begin from $u'^0 = -(M_D/2)$. To picture the optimal drug input in terms of $u'^0$, one simply transforms Schemes IV–VI by the addition of $(M_D/2)$




*Scheme V—Control at both upper and lower bounds with a singular region*




*Scheme VI—Control only at upper bound with a singular region*

to the values of $u'^0$ on each plot. Equations 14 and 15 will then permit calculation of the form of the control function up to time $T_f^0$. The form of the exponential decay required for the cases of Schemes V and VI are then calculated from the system equations. For the particular example considered, it happens that the optimal control is given by the form shown in Scheme VI. The decaying portion of $u'^0$ is known as the region of singular control, and it is found from the simultaneous consideration of Eq. 13*e* and the condition that $f_A$ remains constant at the desired value for times greater than $T_f^0$. This condition requires the derivative of Eq. 12*e* to be zero, *i.e.*:

$$\frac{df_A}{dt} = \frac{\gamma_{1A}}{\alpha_{1A}}\dot{z}_1(t) + \frac{\gamma_{2A}}{\alpha_{1A}}\dot{z}_2(t) = 0 \qquad t \geq T_f^0 \qquad \text{(Eq. 18)}$$

Substituting for $\dot{z}_1$ and $\dot{z}_2$ in Eq. 18 from Eqs. 12*c* and 12*d*, one obtains:

$$\left(\gamma_{2A} - \frac{\gamma_{1A}\alpha_{2A}}{\alpha_{1A}}\right)z_1(t) - \frac{\gamma_{1A}\alpha_{3A}}{\alpha_{1A}}z_2(t) + \gamma_{1A}u'^0(t) = 0 \qquad \text{(Eq. 19)}$$

Now $t = T_f^0$ will be the first time when Eqs. 13*e* and 18 (and, therefore, also Eq. 19) will be simultaneously satisfied. By substituting for $\dot{z}_2(t)$ from Eq. 12*d* into Eq. 18, one obtains:

$$\gamma_{1A}\dot{z}_1(t) + \gamma_{2A}z_1(t) = 0 \qquad \text{(Eq. 20)}$$

The solution to Eq. 20 for $t \geq T_f^0$ is:

$$z_1(t) = z_1(T_f^0)\exp\left[-\frac{\gamma_{2A}}{\gamma_{1A}}(t - T_f^0)\right] \qquad \text{(Eq. 21)}$$

By substituting Eq. 21 into Eq. 12*d*, one obtains:

$$\dot{z}_2 = z_1(T_f^0)\exp\left[-\frac{\gamma_{2A}}{\gamma_{1A}}(t - T_f^0)\right] \qquad t \geq T_f^0 \qquad \text{(Eq. 22)}$$

By integrating Eq. 22 and using the condition of $z_2(T_f^0)$, one obtains for $t \geq T_f^0$:

$$z_2(t) = z_2(T_f^0) + \frac{\gamma_{1A}}{\gamma_{2A}}z_1(T_f^0)\left\{1 - \exp\left[-\frac{\gamma_{2A}}{\gamma_{1A}}(t - T_f^0)\right]\right\} \qquad \text{(Eq. 23)}$$

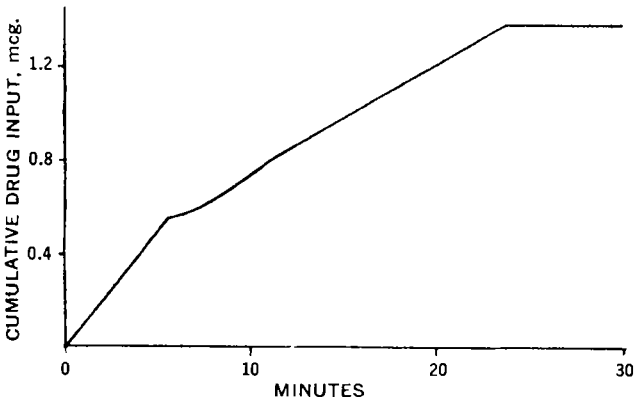



**Figure 3**—*Time-optimal drug input profile.*

Now, substituting Eqs. 21 and 23 into Eq. 19 and rearranging yield:

$$u'^0(t) = \frac{\alpha_{3A}}{\alpha_{1A}}\left[\frac{\gamma_{1A}}{\gamma_{2A}}z_1(T_f^0) + z_2(T_f^0)\right] + \left(\frac{\alpha_{2A}}{\alpha_{1A}} - \frac{\gamma_{2A}}{\gamma_{1A}} - \frac{\gamma_{1A}}{\alpha_{1A}}\frac{\alpha_{3A}}{\gamma_{2A}}\right)z_1(T_f^0)\exp\left[-\frac{\gamma_{2A}}{\gamma_{1A}}(t - T_f^0)\right] \quad \text{(Eq. 24)}$$

for $t \geq T_f^0$.

From Eqs. 11*e*, 21, 23, and 24, the definition of $u'$ proceeding Eq. 12*a*, and the value of $u(\infty)$ given in Table I, one sees that as $t \to \infty$:

$$z_1(\infty) = 0 \quad \text{(Eq. 25}a\text{)}$$

$$z_2(\infty) = \frac{\gamma_{1A}}{\gamma_{2A}}z_1(T_f^0) + z_2(T_f^0) \quad \text{(Eq. 25}b\text{)}$$

and:

$$u'^0(\infty) = \frac{\alpha_{3A}}{\alpha_{1A}}\left(\frac{\gamma_{1A}}{\gamma_{2A}}z_1(T_f^0) + z_2(T_f^0)\right) = -0.003579 \quad \text{(Eq. 25}c\text{)}$$

Or, in terms of the state variables and control function given by Eq. 10:

$$x_1(\infty) = 0 \quad \text{(Eq. 26}a\text{)}$$

$$x_2(\infty) = z_1(\infty) + \frac{M_D}{2}\frac{\alpha_{1A}}{\alpha_{3A}} \quad \text{(Eq. 26}b\text{)}$$

$$u^0(\infty) = 0.046421 \quad \text{(Eq. 26}c\text{)}$$

The actual results obtained for the systems given by Eqs. 1–4 are presented in Figs. 3 and 4. Figure 3 represents the cumulative drug input [simply the integral of $u^0(t)$] to achieve an 80% therapeutic effect in minimum time for the system given by Eq. 1. The first phase of the input is described by a relatively rapid zero-order input having a rate of 0.1 mcg./min. given for 5.56 min., the minimum time for this example. The cumulative drug input is then the integral of the exponential portion of the instantaneous input, $u^0(t)$. The exponential portion dissipates after about 12.0 min., and the cumulative input then follows a zero-order input of 0.0464 mcg./min. which maintains the therapeutic response intensity at a level of 80%.

## DISCUSSION

**Optimized Drug Input**—The cumulative drug input profile depicted in Fig. 3 could in practice be precisely achieved by a programmed slow intravenous infusion or be obtained less precisely by a properly designed oral dosage form. If the time-optimal input was not used and the zero-order drug input rate was simply set to the rate required to maintain the 80% steady-state level of the therapeutic, *A*, response, it would have required 50 min. to achieve a level within 1% of the desired 80% of maximal response intensity. The time-optimal input achieved the 80% level in 5.56 min. The time-optimal drug input, therefore, allowed the desired level of therapeutic effect to be achieved nine times faster than could be attained by simple intravenous infusion of the drug at a constant rate. Computational schemes for optimizing first-order drug inputs which are more common and can more readily be achieved in practice by administration routes other than intravenous are presently being further developed.

**Time-Optimal Drug Response Dynamics**—Figure 4 presents the time-optimal therapeutic response intensity, *A*, and the corresponding toxic response intensities produced at sites *B*, *C*, and *D* as a function of time. One notes from Fig. 4 that the minimum toxic intensities are well within the prescribed limits of 50, 40, and 20% for *B*, *C*, and *D*, respectively, while the desired therapeutic effect of 80% at *A* is achieved in 5.56 min. The time coordinate for response *D* in Fig. 4 was contracted by a factor $^1/_4$, *i.e.*, 10 min. is actually 40 min. It can be seen that the toxic *D* response results from the presence of the drug in an apparent kinetic compartment into which it enters and is eliminated slowly. After chronic administration of the drug at uncontrolled drug inputs, the level of the drug can be expected to build up to induce a serious toxic effect which would have a prolonged duration. On the other hand, if *D* was a sought therapeutic effect, it can be seen that a rapidly absorbed single dose of drug would be relatively very ineffective in producing a response. It can, therefore, occur that potentially useful drugs are discarded whereas appropriate adjustment to their dosing requirements would have allowed them to exhibit their activity. Such considerations again emphasize the importance of controlling drug inputs and thinking in terms of biophasic drug availability rather than systemic bioavailability.

For any drug the actual selection of an allowable intensity for any particular toxic drug effect would obviously depend upon the severity of its morbific character. A drug that does not elicit acceptable levels of toxic effects is generally not a useful drug. However, in some instances, depending upon the drug's transference dynamics, it is still quite conceivable that the toxic response behavior could be substantially minimized by appropriately programming the drug input.

**Interrelationship of Plasma Drug Levels and Multiple Pharmacological Effects**—The recording of multiple drug effects simultaneously with plasma drug levels permits the establishment of single-dose dose-effect curves for each response. The interrelationships which exist between drug responses and drug levels, *e.g.*, as determined directly by chemical or radiological assay techniques, become apparent when it is considered that in addition to the occurrence of sometimes complex feedback control mechanisms, which can function to cause interactions between drug-induced changes in physiological processes, each drug effect may be related to any other by virtue of the consideration that it occurs as a consequence of the distribution of the drug(s) in a system of interconnecting compartments. For a linear system, the relationship between any two drug effects can be established; an effect can be subsequently predicted from the results of recording another by computing the transfer functions that describe the kinetics of the drug(s) passage between biophasic compartments. Such transfer

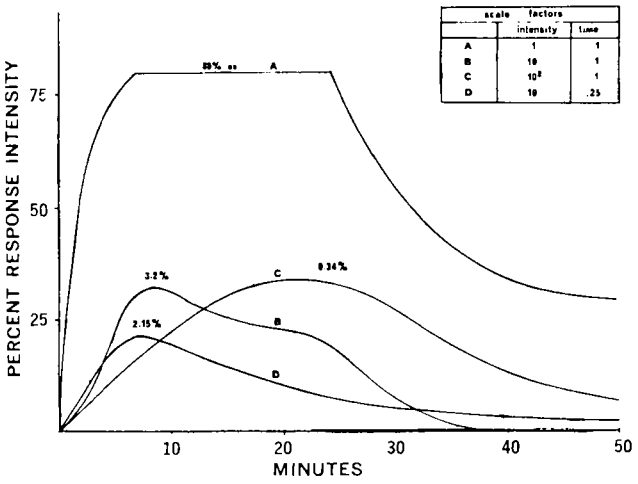
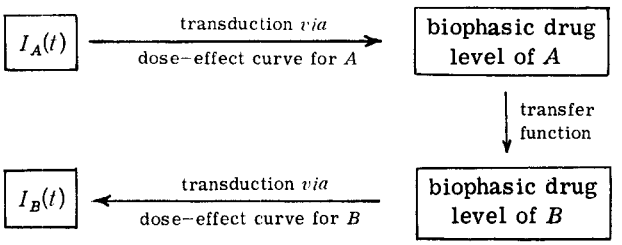



**Figure 4**—*Time variation of therapeutic, A, and toxic, B, C, and D, simultaneously elicited pharmacological response intensities corresponding to a time-optimal controlled drug input.*

functions can be computed from the results of recording the simultaneous drug effects that occur in response to any drug input. The time course of drug response $A$, *i.e.*, $I_A(t)$, can be transformed into a time course of response $B$, $I_B(t)$, by the process shown in Scheme VII. The authors implemented the above approach[5] to the determination of the time course of the intraocular pressure response, following ophthalmic dosing of carbachol, from the results of monitoring the time course of the drug's miotic activity. In this case the approach had the advantage of providing the intraocular pressure results of interest without disturbing the kinetics of the transcorneal transport processes by which the drug penetrates to its sites of action within the eye; the direct tonometric recording of intraocular pressure requires contact with the eye, while the miotic response can be monitored, *e.g.*, using a vernier calipers, without touching the cornea through which the drug is being absorbed.




*Scheme VII*

**"Single-Dose" Dose–Effect Curves and Patient-Individualized Dosage Regimen Optimization**—It is well known that following the administration of a "standard dose" of a drug to different patients, the peak blood levels, for example, may vary as much as 40-fold between patients; pharmacological responses can range from inefficacy to acute toxicity. An individual patient may vacillate in such extremes for appreciable periods of time prior to the establishment of an optimal dosage schedule by trial and error. If the drug transference dynamics and appropriate transduction functions (as defined by dose–effect relationships) were known for a patient, an optimal dosing regimen could be computed and initiated with the first introduction of the drug into the patient's system. However, such information may be expected to be quite rarely available and, due to pathologies that can profoundly influence the dynamics of a drug's absorption, distribution, and elimination, it would become rapidly obsolete. However, it is quite conceivable that for appropriate drugs such information may be approximated from monitoring the results of administering an initial standard dose (or a dose which the physician would normally prescribe) and utilizing the data to compute a subsequent dose and dosing regimen optimal for the particular patient. In this manner the time required to achieve an optimal therapeutic response behavior is minimized. An apparent difficulty in this approach is the multiple dose–response data required to construct the dose–effect curves necessary to transduce observed time variations of pharmacological response intensities into their corresponding biophasic drug levels, which are subsequently utilized to obtain the necessary transfer functions; these relate drug inputs to biophasic drug level *versus* time profiles. In effect, what is required to circumvent the impracticality of determining multiple-dose dose–effect curves is the ability to construct a dose–effect curve from the results of a single dose. An indication that this may be a feasible objective is suggested by the preliminary result represented by the two dose–effect curves for the mydriatic response of tropicamide shown in Fig. 2.

## SUMMARY AND CONCLUSIONS

The presently described approaches represent the first known attempt to relate quantitatively the factors which determine drug input functions (*i.e.*, mode of administration and drug release properties of dosage forms) to the corresponding time variations of multiple pharmacological effects which they determine. The development of the computational capability to optimize drug inputs is salutary to three centrally important problem areas of pharmaceutical science. These include: (*a*) the rational design of the drug release properties of new drug dosage forms, (*b*) the evaluation of the therapeutic performance of existing drug products, and (*c*) computation of time-optimal, patient-individualized, and automated drug dosage regimens.

In order for a product developer to apply his skill to developing an optimal drug product, he must have criteria on which to judge the success of his efforts at any stage of the development. When applicable, the concepts of optimal drug inputs and therapeutic efficiency of the product provide the most rational criteria. The computation of optimized drug inputs also provides a rational basis for the selection of drug products already available—as well as the routes and time schedule for their administration—which will allow an optimal therapeutic efficiency to be attained as closely as practicable.

The theoretical basis for the computation of optimal drug inputs planned to be further developed and expanded is also fundamental and salutary to the eventual development of controllers and servomechanisms for the automated administration of potent drugs (such as anesthetics, cardiac stimulants, and depressants) to patients in response to feedback signals which originate from continuously monitoring and computer processing of, for example, electroencephalographic, electrocardiographic, and other cardiovascular–pulmonary drug-effected changes (27–31). In this manner, drug inputs can be continually observed to maintain biophasic drug levels which are constantly consistent with maintaining a maximal therapeutic efficiency of a drug's responses. The feasibility of a similar approach to the operation of an electroencephalographically innervated, automated, anesthetic administration apparatus has already been described (32, 33).

In principle, elucidation of the dynamics of a pharmacologically responding system's dynamic behavior will permit the computation of time-optimal drug inputs as well as the interrelation and computation of the time variation of any drug effect or plasma drug level from the results of monitoring any other. The fidelity of these theoretical relationships and their potential clinical usefulness are the subject of present research efforts by the authors.

## APPENDIX: DERIVATION OF TIME-OPTIMAL INPUT

A version of the derivation of the solution using the approach presented by Kreindler (18) is presented here.

**Integral Representation of Linear System**—Equation 13*a*, the linear system to be controlled, will be referred to as the *plant*. The solution to Eq. 13*a* can be expressed in the well-known form (21):

$$\mathbf{z}(t) = \Phi(t,t_0)\mathbf{z}(0) + \int_0^t \Phi(t,\tau)\mathbf{b}(\tau)u'(\tau)\,d\tau \qquad \text{(Eq. A1)}$$

where $\mathbf{z}(t)$ is the state vector and where $\Phi(t,\tau)$ is the state transition matrix. Equation A1 can be written as:

$$\mathbf{z}(t) = \mathbf{z}_0(t) + \int_0^t \mathbf{h}(t,\tau)u'(\tau)\,d\tau \qquad \text{(Eq. A2)}$$

where $\mathbf{z}_0(t)$ expresses the effect on $\mathbf{z}(t)$ of the initial conditions and $h(t,\tau)$ can be interpreted as the response $\mathbf{z}(t)$ to an impulse $u(t) = \delta(t - \tau)$ applied at $t = \tau$. The functions $h_i(t,\tau)$, $i = 1, 2, \ldots, n$, will be considered arbitrary, except for the following conditions:

1. $h_i(t,\tau)$ is bound on finite intervals of $t$ and $\tau$, continuous in $t$, and piecewise continuous in $\tau$ [for plants described by an equation, *i.e.*, 13*a*, with constant coefficients, $h_i(t)$ is continuous]. If $h(t,\tau)$ is the impulse response, then $h_i(t,\tau) = 0$ for $t \leq \tau$ and may be discontinuous at $t = \tau$. This condition implies that the control $u$ and discontinuities (if any) of the plant's parameters affect the output $\mathbf{z}(t)$ only through dynamic elements.

2. The functions $h_i(t,\tau)$ are linearly independent on all intervals of $0 \leq \tau \leq t$. That is, for every nonzero $n$-vector $\lambda$, the inner product:

$$\lambda \cdot \mathbf{h}(t,\tau) = \sum_{i=1}^{n} \lambda_i h_i(t,\tau) \not\equiv 0 \quad \text{on} \quad 0 \leq \tau \leq t \qquad \text{(Eq. A3)}$$

This condition is equivalent (21) to the statement that the plant can

[5] To be published.

be brought, by a suitable control $u$, from any initial condition at $t = 0$ to any output $\mathbf{z}(T_f)$ at $t = T_f$ (both finite) on an arbitrary finite interval of time $0 \leq t \leq T_f$. This property of the plant will be called *total controllability*.

It is important to observe that condition A3 allows $\lambda \cdot h(t,\tau) \equiv 0$ on proper subintervals of $0 \leq \tau \leq t$ provided that, for each $t$, there is some $f$ finite interval $t_1 \leq \tau \leq t_1$, where $\lambda \cdot \mathbf{h} \not\equiv 0$. If $\lambda \cdot \mathbf{h}(t,\tau)$ can vanish only on a set of isolated points, the plant is called *normal* (21).

**Constraints on $u'$**—Usually, $u'$ is constrained in some manner. The most common constraints are the amplitude constraint $|u'(t)| \leq C$, the "area" constraint $\int_0^{T_f} |u'(t)|\, dt \leq C_1$, and the energy constraint $\int_0^{T_f} |u'(t)|^2\, dt \leq C_2{}^2$. These constraints may be unified by:

$$\left( \int_0^{T_f} |u'(t)|^p dt \right)^{1/p} \leq C_p \qquad 1 \leq p \leq \infty \qquad \text{(Eq. A4)}$$

For $p = \infty$ and piecewise continuous $u'$, Eq. A4 reduces to the amplitude constraint:

$$\max_{0 \leq t \leq T_f} |u'(t)| \leq C \qquad \text{(Eq. A5}a\text{)}$$

A control $u'$ satisfying Eq. A4 will be called *admissible;* the collection of all admissible controls is called the *admissible set.*

If the wider class of all *measurable* controls satisfying condition A4 are considered, the integration is then in the Lebesque sense (22). Then, for a given $p$, each control becomes a member of the function and the admissible set is the closed $C_p$ – sphere in $L_p$. In the example considered here, only the amplitude constraint, condition A5, is used, but the future application of the area constraint would correspond to a limit on the cumulative drug in the system.

**The Control Problem**—As stated previously, the objective is to cause $\mathbf{z}(t)$ to coincide with Eq. 13*h* and thereby cause Eq. 13*e* to be satisfied, in the minimum time, using an admissible control. Forming the difference: $\mathbf{z}^d(t) = \mathbf{z}_d(t) - \mathbf{z}_0(t)$, and referring back to Eq. A2, the problem may be formulated as follows:

Given $\mathbf{z}^d(t)$, find an admissible control $u'$ so that:

$$\int_0^t \mathbf{h}(t,\tau) u'(\tau)\, d\tau = \mathbf{z}^d(t) \qquad \text{(Eq. A5}b\text{)}$$

at the *minimal time*, $t = T_f{}^0$.

**The Reachable Region**—The output $\mathbf{z}(t)$ can be viewed as a continuously moving point in an $n$-dimensional Cartesian space $Z$, the output space. Consider the plant, A2, at rest at $t = 0$ [$\mathbf{z}_0(t) = 0$]. The set of the points $\mathbf{z}(T_f)$ in $Z$, reached by using all $u$ in an admissible set, will be called the reachable region and denoted by $R(0,T_f)$; $R$ depends on $p$ and $C_p$.

The general properties of $R(0,T_f)$ can be expressed by the following theorem.

*Theorem 1*—The reachable region, $R(0,T_f)$, is a closed, bound, and convex body[6], symmetrical with respect to (and centered on) the origin $\mathbf{z} = \mathbf{0}$ and continuous in $T_f$. (The proofs of the theorems to be presented can be found in *Reference 18.*)

The control process can now be *visualized* (for $n \leq 3$) as follows. In the output space, there are the continuously changing region $R(0,T_f)$ and the continuously moving "target" point $\mathbf{z}^d(t)$. By definition, $\mathbf{z}^d(t)$ can be reached if and only if, for some finite time $T_f$, $\mathbf{z}^d(T_f)$ is in $R(0,T_f)$. Because of the continuity of $R(0,T_f)$, it is clear that the first contact of $\mathbf{z}^d(t)$ with $R(0,t)$ must be at the boundary of $R(0,t)$, determining the minimal time $t = T_f{}^0$. This leads to the following theorem.

*Theorem 2*—If for some terminal time $T_f = T_{f1}$, $\mathbf{z}^d(T_{f1})$ is in $R(0, T_{f1})$, then the optimal time $T_f{}^0, T_f{}^0 \leq T_{f1}$, exists; $T_f{}^0$ is such that $z^d(T_f{}^0)$ is in the boundary of $R(0,T_f{}^0)$, and, for $T_f < T_f{}^0$, $\mathbf{z}^d(T_f)$ is not in $R(0,T_f)$.

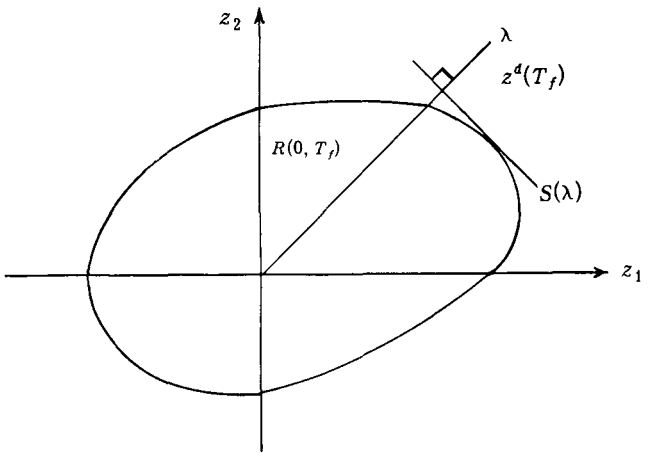
The validity of Theorem 2 is the main reason for Conditions 1 and 2 imposed on $h_i(t,\tau)$. Unless Condition 1 holds, $R(0,t)$ and/or $\mathbf{z}_0(t)$ and $\mathbf{z}^d(t)$ may be discontinuous and the first contact of $\mathbf{z}^d(t)$ may be at the interior of $R(0,t)$. The same may happen if $R(0,T_f)$ degenerates to be confined in a linear subspace[7] of $Z$, because Eq. A3 of Condition 2 fails for $\tau = 0$ and some $t = T_f$.

According to Theorem 2, it is necessary to seek the controls that lead to boundary points in $R(0,T_f)$; such a control will be called an *optimal control* $u'^0$.

**Necessary and Sufficient Conditions for an Optimal Control**—*Theorem 3*—An admissible control can be optimal only if it satisfies Eq. A4 with an *equality* sign.

This result *by itself* does not imply a bang-bang control for the amplitude constraint; it merely implies, according to Eq. A5, that $|u'(t)| = C_\infty$ for at least one point on the interval $0 \leq t \leq T_f$.

Since $R$ is convex, each point in the boundary of $R$ can be contained in a supporting hyperplane[8] to $R$, $S(\lambda)$. The points in the intersection of the supporting plane and the boundary of $R$ are the farthest points in $R$ in the direction of $\lambda$. An illustration of a hyperplane $S(\lambda)$ supporting an $R(0,T_f)$ at $\mathbf{z}^d(T_f)$ is shown in Scheme VIII for a space of dimension 2.




*Scheme VIII—Reachable region with the supporting hyperplane*

The preceding yields the following theorem.

*Theorem 4*—A *necessary* and *sufficient* condition for an admissible control to be optimal, that is, for reaching all points in the intersection between $s(\lambda)$ and the boundary of $R(0,T_f)$, is that $u'$ *maximize:*

$$\lambda \cdot \mathbf{z}(T_f) = \int_0^{T_f} \lambda \cdot \mathbf{h}(T,\tau) u'(\tau)\, d\tau \qquad \text{(Eq. A6)}$$

*Proof:* For a given admissible $u'$, the right side of Eq. A6 is a constant, say $C$, and $\mathbf{z}(T_f)$ is then in the hyperplane $\lambda \cdot \mathbf{z} = C$. By the definition of the supporting hyperplane, and by the convexity of $R(0,T_f)$, $\lambda \cdot \mathbf{z}(T_f)$ is maximized if and only if $\mathbf{z}(T_f)$ is in the intersection of $S(\lambda)$ and the boundary of $R(0,T_f)$. Since $R$ is closed, all points in this intersection must be reached.

The maximization of Eq. A6 yields an optimal control $u'^0$ as a function of time, with $\lambda$, $T_f{}^0$, and $C_p$ as parameters. The value of $C_p$ (see Eq. A4) will be prescribed by physical considerations. The problem now is to find $T_f{}^0$ and $\lambda$.

For this, one uses the following theorem.

*Theorem 5*—A *necessary* and *sufficient* condition for the point $\mathbf{z}^d(t)$ to be in the boundary of $R(0,t)$ at time $t = T_f$ is that:

$$\max \left. \frac{\lambda \cdot \mathbf{z}^d(t)}{\int_0^{T_f} \lambda \cdot \mathbf{h}(t,\tau) u'^0(\tau;\lambda,t,C_p)\, d\tau} \right|_{t=T_f} = 1 \qquad \text{(Eq. A7)}$$

There are *no local maxima* of Eq. A7. As $t$ is increased from 0, the first $T_f$ that satisfies Eq. A7, for $\lambda = \lambda^0$, is the optimal terminal time $T_f{}^0$, and $\lambda_0$ is such that $\mathbf{z}^d(T_f{}^0)$ is in the intersection of $S(\lambda^0)$ and the boundary of $R(0,T_f{}^0)$.

**Formulas for Optimal Control**—The maximization of Eq. A6 subject to constraint A4 is easily solved using Hölder's inequality

[6] Closed means a region that includes its boundary, and convex means a region with no holes, *i.e.*, all points within the region boundary belong to the region.

[7] For $n = 3$, a linear subspace could be either a plane or a line. For $n = 2$, a linear subspace could be a line.

[8] A hyperplane, $\lambda \cdot \mathbf{z} = C$, where $C \geq 0$ and $\lambda$ is a nonzero fixed-length vector in $Z$, is the generalization to $n$-space of a plane in 3-space; it is an $(n-1)$-dimensional subspace.

(23) for integrals. It is:

$$\int_a^b |x(t)v(t)|dt \leq \left[\int_a^b |x(t)|^p\, dt\right]^{(1/p)} \left[\int_a^b |v(t)|^q\, dt\right]^{(1/q)} \quad \text{(Eq. A8)}$$

where $1 \leq p \leq \infty$ and $(1/p) + (1/q) = 1$, and which, for $1 < p < \infty$ is satisfied with an equality if and only if $|x(t)|^p = K_1\,|y(t)|^q$, where $K_1$ is a positive real constant.

By the definition of a hyperplane, $\lambda \cdot \mathbf{z}(T_f) > 0$ and, therefore:

$$\lambda \cdot \mathbf{z}(T_f) \leq \left[\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right]^{(1/q)} \times \left[\int_0^{T_f} |u'(\tau)|^p\, d\tau\right]^{(1/p)}, \quad \frac{1}{p} + \frac{1}{q} = 1 \quad \text{(Eq. A9)}$$

By using Hölder's inequality, A8, on the right-hand side of Eq. A9, one obtains:

$$\lambda \cdot \mathbf{z}(T_f) \leq \left[\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right]^{(1/q)} \times \left[\int_0^{T_f} |u'(\tau)|^p\, d\tau\right]^{(1/p)}, \quad \frac{1}{p} + \frac{1}{q} = 1 \quad \text{(Eq. A10)}$$

By Theorem 3, a necessary condition for the maximum of $\lambda \cdot \mathbf{z}(T_f)$ is that:

$$\left[\int_0^{T_f} |u'(\tau)|^p\, d\tau\right]^{(1/p)} = C_p \quad \text{(Eq. A11)}$$

By substituting Eq. A11 into Eq. A10, one obtains:

$$\lambda \cdot \mathbf{z}(T_f) \leq \left[\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right]^{(1/q)} C_p \quad \text{(Eq. A12)}$$

Obviously, the maximum of $\lambda \cdot \mathbf{z}(T_f)$ is obtained if and only if Eq. A12 satisfies the *equality* sign. Now, the inequality in Eq. A9 is satisfied with an equality if and only if:

$$\operatorname{sgn} u'(\tau) = \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)] \quad \text{(Eq. A13)}^9$$

Also, Eq. A10 is satisfied with an equality if and only if, for $1 < p < \infty$:

$$|u'(\tau)| = K_1^{1/p} |\lambda \cdot \mathbf{h}(T_f,\tau)|^{(q/p)} \quad \text{(Eq. A14}a\text{)}$$

or:

$$|u'(\tau)| = K|\lambda \cdot \mathbf{h}(T_f,\tau)|^{(q/p)} \qquad K > 0 \quad \text{(Eq. A14}b\text{)}$$

Considering the definition of the signum function, one can write $u'(\tau)$ as:

$$u'(\tau) = |u'(\tau)| \operatorname{sgn} |u'(\tau)| \quad \text{(Eq. A15)}$$

To have condition A10 be satisfied with the equality, one must apply Eq. A14*b* to Eq. A15. One obtains:

$$u'(\tau) = K|\lambda \cdot \mathbf{h}(T_f,\tau)|^{(q/p)} \operatorname{sgn} |u'(\tau)| \quad \text{(Eq. A16)}$$

Also, to have condition A9 be satisfied with the equality, one must apply Eq. A13 to Eq. A16. This yields:

$$u'(\tau) = K|\lambda \cdot \mathbf{h}(T_f,\tau)|^{(q/p)} \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)] \qquad 1 < p < \infty \quad \text{(Eq. A17)}$$

Now $u'(\tau)$ must also satisfy Eq. A11. This can be done by adjusting $K$; *i.e.*, substituting Eq. A17 into Eq. A11 yields $K$ so that Eq. A11 is satisfied.

[9] sgn is the signum function described by $\operatorname{sgn} x = \begin{cases} -1 & x < 0 \\ +1 & x > 0 \end{cases}$

Proceeding, one has:

$$\left(\int_0^{T_f} K^p |\lambda \cdot \mathbf{h}(T_f,\tau)|^q \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)]|^p\, d\tau\right)^{(1/p)} = C_p \quad \text{(Eq. A18)}$$

or, moving $K^p$ out of the integral and rearranging, one obtains:

$$K = \frac{C_p}{\displaystyle\int_0^{T_f} (|\lambda \cdot \mathbf{h}(T_f,\tau)|^q \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)]|^p\, d\tau)^{(1/p)}} \quad \text{(Eq. A19)}$$

Recalling the definition of the signum function, one can write:

$$|\operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)]|^p = |(\pm 1)|^p = 1 \quad \text{(Eq. A20)}$$

where $p$ is some integer value, $1 \leq p \leq \infty$.

Also since $(1/p) + (1/q) = 1$, one can write:

$$\frac{1}{p} = \frac{q-1}{q} \quad \text{(Eq. A21)}$$

and:

$$\frac{q}{p} = q - 1 \quad \text{(Eq. A22)}$$

Substituting Eqs. A20 and A21 into Eq. A19, one obtains:

$$K = \frac{C_p}{(\pm 1)\left(\displaystyle\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right)^{(q-1/q)}} \quad \text{(Eq. A23)}$$

Therefore, substituting Eqs. A23 and A22 into Eq. A17 results in the following theorem.

*Theorem 6*—An admissible control is optimal *if and only if:*

$$u'^0(t) = \frac{C_p |\lambda \cdot \mathbf{h}(T_f,\tau)|^{q-1} \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)]}{\left(\displaystyle\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right)^{(q-1/q)}} \qquad 1 < p < \infty \quad \text{(Eq. A24)}$$

For $p = \infty, q = 1$ (the amplitude constraint), Eq. A24 becomes:

$$u'^0(t) = C \operatorname{sgn} \lambda \cdot \mathbf{h}(T_f,t) \quad \text{(Eq. A25)}$$

which is *necessary and sufficient* for *equalities* in Eqs. A9 and A10.

With $u'^0(t)$ given by Eq. A24, Eq. A7 becomes:

$$\max_{\lambda} \left. \frac{\lambda \cdot \mathbf{z}^d(t)}{\displaystyle\int_0^{T_f} \lambda \cdot \mathbf{h}(T_f,\tau) C_p |\lambda \cdot \mathbf{h}(T_f,\tau)|^{q-1} \operatorname{sgn} [\lambda \cdot \mathbf{h}(T_f,\tau)]\, d\tau \Big/ \left(\displaystyle\int_0^{T_f} |\lambda \cdot \mathbf{h}(T_f,\tau)|^q\, d\tau\right)^{(q-1/q)}} \right|_{t=T_f} = 1 \quad \text{(Eq. A26)}$$

Once again, by recalling the definition of the signum function, Eq. A26 becomes:

$$\max_{\lambda} \left. \frac{\lambda \cdot \mathbf{z}^d(t)}{\left(\displaystyle\int_0^{t} |\lambda \cdot \mathbf{h}(t,\tau)|^q\, d\tau\right)^{(1/q)}} \right|_{t=T_f} = C_p \quad \text{(Eq. A27)}$$

The length of $\lambda$ is arbitrary (only the direction of $\lambda$ being significant): therefore, it can be adjusted so that $\lambda \cdot \mathbf{z}^d(t) = 1.0$. Equation A27 becomes:

$$\min_{\lambda} \left. \left(\int_0^{t} |\lambda \cdot \mathbf{h}(t,\tau)|^q\, d\tau\right)^{(-1/q)} \right|_{t=T_f} = C_p, \lambda \cdot \mathbf{z}^d(t) \Big|_{t=T_f} = 1 \quad \text{(Eq. A28)}$$

for the amplitude constraint, and a system described by an equation (*i.e.*, A9) with constraint coefficients, $p = \infty$ and $q = 1$, Eq. A28 can be arranged to yield:

$$1 = \min_{\lambda} \int_0^{T_f} C_\infty |\lambda \cdot \mathbf{h}(t-\tau)|\, d\tau \qquad \text{(Eq. A29)}$$

$$\lambda \cdot \mathbf{z}^d(T_f) = 1$$

For this particular system, as described by Eq. A9, one has:

$$\mathbf{z}^d(T_f) = \mathbf{z}_d(T_f) - \mathbf{z}(0) = \begin{Bmatrix} z_{d_1}(T_f) \\ z_{d_2}(T_f) + \frac{M_D}{2}\frac{\alpha_{1A}}{\alpha_{3A}} \end{Bmatrix} = \begin{Bmatrix} z_1{}^d(T_f) \\ z_2{}^d(T_f) \end{Bmatrix} \qquad \text{(Eq. A30)}$$

Therefore:

$$\lambda \cdot \mathbf{z}^d(T_f) = \lambda_1 z_1{}^d(T_f) + \lambda_2 z_2{}^d(T_f) = 1.0 \qquad \text{(Eq. A31}a\text{)}$$

and:

$$\lambda \cdot \mathbf{h}(t-\tau) = \lambda \cdot \left\| \Phi(t-\tau) b = \lambda_1 \phi_{11}(t-\tau) + \lambda_2 \phi_{21}(t-\tau) \right. \qquad \text{(Eq. A31}b\text{)}$$

where:

$$\left\| \Phi(t-\tau) = \begin{pmatrix} \phi_{11}(t-\tau) & \phi_{12}(t-\tau) \\ \phi_{21}(t-\tau) & \phi_{22}(t-\tau) \end{pmatrix} \right. \qquad \text{(Eq. A31}c\text{)}$$

$\Phi(t)$ was defined in Eq. A1.

From Eq. A31*a*, one obtains:

$$\lambda_2 = \frac{1}{z_2{}^d(T_f)} [1.0 - \lambda_1 z_1{}^d(T_f)] \qquad \text{(Eq. A32)}$$

Also:

$$C_\infty = \frac{M_D}{2} \qquad \text{(Eq. A33)}$$

Substituting Eqs. A31*b*, A32, and A33 into Eq. A29, one obtains:

$$1 = \min_{\lambda} \int_0^{T_f} \frac{M_D}{2} \left| \lambda_1 \phi_{11}(t-\tau) + \frac{1.0 - \lambda_1 z_1{}^d(T_f)}{z_2{}^d(T_f)} \phi_{21}(t-\tau) \right| d\tau \qquad \text{(Eq. A34)}$$

$$\lambda \cdot \mathbf{z}^d(T_f) = 1$$

and the control Eq. A25 becomes:

$$u'^0(t) = \frac{M_D}{2} \operatorname{sgn} \left\{ \lambda_1 \phi_{11}(T_f{}^0 - t) + \frac{[1.0 - \lambda_1 z_1{}^d(T_f{}^0)]}{z_2{}^d(T_f{}^0)} \phi_{21}(T_f{}^0 - t) \right\} \qquad \text{(Eq. A35)}$$

where $\lambda_1$ is found by the minimization of Eq. A34.

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▲ To whom inquiries should be directed.