A Program for the Simulation of Multiple Dosage Regimens on an Analog Computer

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Summary. Small general purpose analog computers are not usually equipped for iterative computation. Since multiple dosage problems are often encountered in pharmacokinetic studies an approximating program is proposed for rapid estimation and curve fitting. The program produces an input function simulating a staircase by integration only of the positive differentials of a sequence of rectangular impulses. The program is used to compute the maximum and minimum concentration factors of Sparteine and Quinidine as examples of two substances obeying first order kinetics. It is apparent from the results that the choice of dosage schedules is restricted both by the pharmacological and the pharmacokinetic properties of the drugs.

During the last ten years analog computers have been widely used in pharmacokinetic studies (Dost & Repges; Garrett; Randall; Röpke & Riemann). The main advantages of these electronic tools lie in the fact that theoretical models can be transformed directly into programs, and that the solution of their descriptive simultaneous differential equations need not be known; Many theoretical models can be tested in a short time for their comparability with real-life situations. If a model is accepted as accurate, different biological situations can be simulated, and probable predictions made.

This paper deals with the simulation of a repetitive dosage regimen with the aim of predicting the range of blood concentrations of a drug during saturation. From the predicted data, the clinical pharmacologist can decide whether or not a substance can be used safely in routine therapy.

Dengler et al. have demonstrated that the pharmacokinetic behaviour of Spartein after intravenous injection can be described with great accuracy by a one compartment model of the first order. The differential equation is

\[ \frac{dy}{dt} = -k_2 y \]

with the solution

\[ y = y_0 e^{-k_2 t} \]

where \( y \) is the blood concentration of the drug at the time \( t \), \( y_0 \) is defined as the level dependent on the dose at zero time of injection, \( k_2 \) signifies the elimination constant and \( e \) is the base of natural logarithms.

The blood concentration after oral administration corresponds to two first order compartments. \( k_i \) signifies the rate constant of invasion from the intestine, and \( y_t \) the amount not yet absorbed.

\[ \frac{dy_n}{dt} = -k_2 y_n + k_1 y_i \]

\[ \frac{dy_i}{dt} = -k_1 y_i \]

This system of differential equations can be solved in an analog computer by the program shown in Fig. 1. The blood levels dependent on time are shown in Curve 2.

In this program the dose administered, or, more accurately, the dose absorbed can be introduced as the initial condition (IC) at the integrator corresponding to the compartment in question. A further possibility for simulating dosage consists in the application of a step function at a summator within the closed loop representing the enteric compartment. Two such summators are necessary because of the sign conversion inherent in every operational amplifier. This method permits simulation of repeated doses; the computer is set to “hold” condition after the dosage interval, and the setting of the potentiometer \( D \) is increased by the desired dose (Röpke & Riemann).

* This paper is dedicated to Professor Dr. F.H. Dost on occasion of his 60th birthday on July 11, 1970.
This procedure is tedious if curve fitting shall be undertaken.

The difficulty of finding a program for continuous computation of multiple dose effects arises from the need for an input function simulating a staircase. This can be achieved in an analog computer with provision for individual state setting of at least two integrating amplifiers. As this storage technique is not practicable on most of the smaller instruments, an approximating program has been designed.

Program description

Fig. 2 displays the principle of the program. The numbers refer to the patch panel of a Telefunken RA 742, which, though, permits the use of storage techniques. Potentiometers for scaling purposes are omitted.

A sine wave generator (01, 02, 03) activates a relay (K 1) with a frequency corresponding to the dosage interval, thus generating a sequence of rectangular impulses of an amplitude set by the potentiometer (3). The onset and duration of the impulses depend on the activation point set by (4). This sequence is interconnected to the input of a differentiating closed loop, consisting of a high gain amplifier (04), a sign converter (16) and an integrator (05). The feedback potentiometer (5) prevents overload and introduces a small error, as the time constant of the integrator (05) does. The differential of the original rectangular impulses consists of a series of alternating positive and negative needle functions, approximated by e-functions, that can be controlled so as to avoid overload (Giloi & Herschel).

The second relay in the comparator (K 1) connects the output of (16) to an integrator (06) only, when positive differentials are generated. The circuit is disconnected again when the differential is at zero. Thus, at the output of (06), the desired staircase is available as the integral of a series of the positive differentials of a sequence of rectangular impulses. Because of the error introduced by the feedback potentiometer (5), the staircase must be calibrated at the output of (6).

Time scaling:

Dengler et al. furnished the essential data for Spartein: Absorption after intestinal administration occurs at a rate of \( k_1 = 0.0582 \pm 0.0204 \text{ min}^{-1} \); elimination from the blood at a rate of \( k_2 = 0.0060 \pm 0.0008 \text{ min}^{-1} \) (mean \( \pm \) standard deviation). From these values it is expected that during repetitive dosage “steady-state saturation” will be reached within 24 h, which is taken therefore as the duration of the problem. Since simultaneous recording of the curves on a x-y recorder (Hewlett-Packard) is planned, the time for computation is set to 60 sec. This introduces a time scaling factor of \( q = 1/24 \text{ sec/min} \).

Amplitude scaling follows from the number of doses administered during one computing cycle. A single dose of 0.1 units proved satisfactory in the problem. The scaling factor has the dimension of ml of distribution volume per dose.

The frequency \( \omega_2 \) of the sine wave generator is set at the coefficient potentiometer (1) following the equation

\[
\omega_2 = \left( \frac{2 \pi}{T} \right)^2
\]

where \( T \) is the scaled dosage interval.

Numerical evaluation:

The numerical value of \( y_B \) at any time can be read on a digital voltmeter connected to the output of (11). The readings are made while the computer is in the “hold” condition.

“Hold” setting for minimum blood concentrations: a relay (K 2) is activated by the dosage-timing sine wave, and connects ground to the “hold” socket on the patch panel at the end of the dosage interval, if a manual switch is set after the last but one dose.

“Hold” setting for maximum blood levels: curve extremes are characterized by the fact that the first differential of the curve becomes zero. Since relays are activated by zero volts, the first differential of the blood concentration curve will activate (K 2) to set the computer to the “hold” condition, when a maximum is reached. Again a manual switch is needed. The differential may be obtained either as the sum of the inputs of the integrator (11), or by a separate differentiating circuit such as the one enclosed in the above program.

Results

In Fig. 3, a graphic presentation of the concentration time course of Spartein is given for dosage intervals of two and six hours. It is apparent from the graph