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PHARMACEUTICAL TECHNOLOGY

Analog Computer Program for Simulating Variable Dosing Regimens

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Abstract □ Based on a single-compartment model, an analog computer program was developed which utilizes both analog and logic components of a general-purpose hybrid computer. The program permits the simulation of the blood and urine levels that would be obtained following the administration of an initial dose followed by a series of additional doses. The magnitude of the doses, as well as the time period between doses, may be varied independently. The program can be used to aid the formulator in establishing the amount of drug that should be released during selected time periods from a timed-release dosage form to provide uniform blood levels.

Keyphrases □ Computer program, analog—simulation of variable dosing regimens □ Simulation of variable dosing regimens—analog computer program □ Timed-release dosage formulation—use of computer simulated blood and urine levels □ Dosing regimens, variable—simulation of blood and urine levels

The use of the analog computer for simulating drug distribution in the body has been widely accepted (1–5). Many of the reported analog computer programs have been limited to simulating drug levels after single-dose administration (6–14). Several authors have reported simulations based on multiple-dose administrations that were achieved by either digital computer techniques (15–17) or manual manipulation of analog computer components (18–21). At best, the manual methods are cumbersome and there is a possible loss of accuracy due to time-dependent manual manipulation. In addition, digital computer simulation does not permit the instantaneous observation of the effect of parameter modification on the drug level in a particular compartment.

This paper discusses how digital logic components (22), which have recently been made available as an integral part of general-purpose analog computers, can be used in the simulation of variable dose sequencing regimens. Such components permit manipulation, in microseconds, of operations that were previously performed manually. With the aid of the logic components, programs can be prepared that change parameter values automatically and make decisions based on either timing considerations or other arbitrary conditions inherent in the problem to be simulated.

The flexible analog computer program described here permits the simulation of a variety of dosing regimens and has many applications in pharmacokinetic research. It has the feature of simulating the administration of an initial dose followed by a sequence of doses of variable size where the time periods between the administration of doses may be varied independently.

EXPERIMENTAL

The program is based on the single-compartment model:

$$G \xrightarrow{k_a} B \xrightarrow{k_{el}} U \qquad \text{(Eq. 1)}$$

where G = amount of drug in the gut, B = amount of drug in the blood, U = cumulative urinary excretion level, k_a = first-order rate constant of absorption, and k_{el} = first-order rate constant of excretion.

The model is described by the following differential equations:

$$\frac{dG}{dt} = -k_a G \qquad \text{(Eq. 2a)}$$

$$\frac{dB}{dt} = k_a G - k_{el} B \qquad \text{(Eq. 2b)}$$

$$\frac{dU}{dt} = k_{el} B \qquad \text{(Eq. 2c)}$$

Although the single-compartment model was chosen for demonstration purposes, the program can be easily modified to represent almost any pharmacokinetic model.

Table I—Key to Analog Computation Symbology[a]

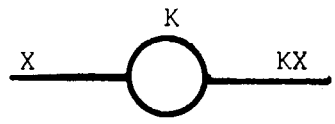
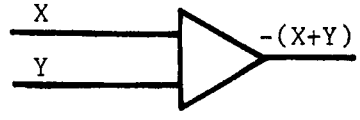
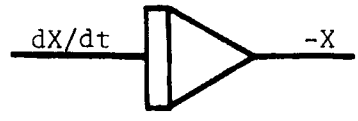
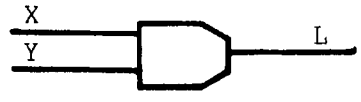
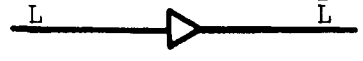
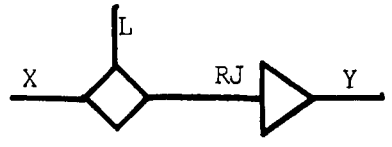
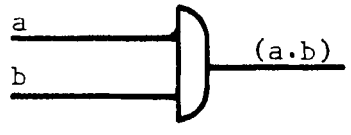
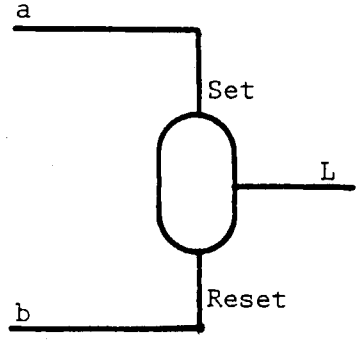
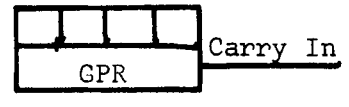
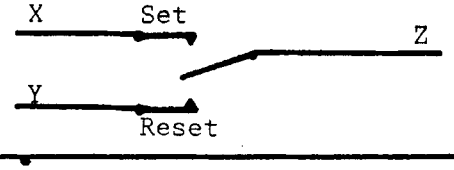
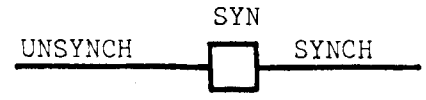
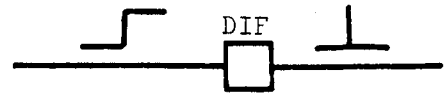
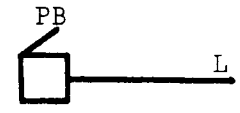
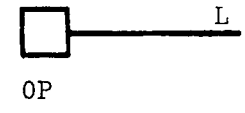
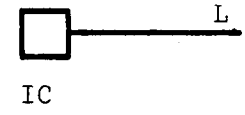
Component	Symbol	Remarks
Potentiometer		
Inverter		
Summer		
Integrator		
Comparator		L = high if (X + Y) = positive low if (X + Y) = negative
Logic inverter		
Electronic switch		Y = X if L = high 0 if L = low
AND gate		
Flip-flop		
General-purpose register		
Function relay		Z = X if switch is Set Y if switch is Reset

Table I—(*Continued*)

Component	Symbol	Remarks
Synch		Synchronizes asynchronous events in accordance with an internal timer
Differentiator		Output is a pulse of 1-μsec. duration when input changes from low to high
Logic push button		L = high if PB is Set low if PB is Reset
Operate bus line		L = high if computer is operating low if computer is in IC
IC bus line		L = low if computer is operating high if computer is in IC

[a] X, Y, and Z are analog signals; a, b, and L are logic signals.

The analog computer[1] program (Fig. 1 and Table I) can be visualized as being divided into three interdependent subprograms: timing, switching, and analog simulation. The basic portion is the analog simulation subprogram, which solves the differential equations describing the pharmacokinetic model. For the analog computer program to simulate the administration of a variable dose regimen, doses must be introduced into the analog simulation subprogram at preselected time intervals. The program section that causes doses to be entered into the analog simulation portion will be called the switching subprogram, and the program portion that controls the time at which these doses are switched into the analog subprogram will be called the timing subprogram. The key aspect of the program is the simulation of drug disposition in the gut compartment after the administration of repetitive doses. Since doses may only be added to integrators in the initial conditions (IC) mode, the simulation is accomplished by using two integrators operating in tandem to follow the amount of drug present in the gut. The modes of the two integrators are complementary when the program is operating; when a new dose is being added to one integrator, which is in the IC mode, the other integrator is integrating the previous dose. A more detailed description of the operations of the three subprograms follows.

Timing Subprogram—The timing subprogram is used to control the time at which the individual doses are switched into the analog simulation and to synchronize the operations of the switching and analog subprograms. To accomplish these tasks, the timing subprogram generates repetitive logic signals of variable frequency.

The timing subprogram functions as a triangular and square wave oscillator where the comparator, by switching, controls its own bias voltage. The triangular wave is the output of integrator 14, and the square wave is the output of the comparator. The frequency of oscillation is controlled by the gain of integrator 14. Examples of the outputs of the comparator and integrator 14 are illustrated in Fig. 2.

At time zero, the program is in the IC mode and the logic signal from the IC bus line is high[2], while the logic signal from the operate (OP) bus line and the output of AND gate 9 are low and the electronic digital/analog (D/A) switch 1 is open. The outputs of summer 13 and integrator 14 have values of −1.0 machine unit[3], so the output of the comparator is low.

When the program is put into OP, the logic level of the OP bus line goes high, the logic level of the IC bus line goes low, and the states of the comparator, AND gate 9, and D/A switch 1 remain unchanged. The output of summer 13 remains at −1.0 mu while integrator 14 integrates from −1.0 to +1.0 mu in time $2T$ at the rate of $1/T$, where T is the time required for integrator 14 to integrate from 0.0 to +1.0 mu. When the output of integrator 14 attains a value of +1.0 mu, the negative bias on the comparator is overcome, forcing the output of the comparator high. The change of state of the comparator drives the output of AND gate 9 high, which closes D/A switch 1. The output of summer 13 changes from −1.0 to +1.0 mu; therefore, integrator 14 integrates from +1.0 to −1.0 mu during the time period from $2T$ to $4T$. At time $4T$, the cycle repeats itself. The output of integrator 14 is a triangular wave of period $4T$, and the output of the comparator is a square wave which is low from $0T$ to $2T$ and is high from $2T$ to $4T$. The square wave output of the comparator is routed to the differentiator in the switching subprogram and to AND gates 10 and 11, which control the modes of integrators 1 and 2 in the analog subprogram.

Switching Subprogram—The switching subprogram controls the administration of the doses so that only the dose desired is switched into the analog subprogram. In operation, it accepts timing pulses from the timing subprogram and switches the selected dose, which is set on a potentiometer, so that the dose is routed to integrator 1 in the analog subprogram.

The values of the doses are set on potentiometers (pots) 7–11, which are connected to amplifier 12 through D/A switches controlled by logic signals. A D/A switch is open when the gate is logic low and is closed when the gate is logic high. To control the switching of the doses by the timing subprogram, the output of the comparator is put through a differentiator (DIF). The output of the DIF is a pulse of 1-μsec. duration when its input signal changes from low to high. Therefore, for each period of the comparator, one pulse is generated by the DIF.

The general-purpose register (GPR) counts pulses and its combined output, in this case a grouping of four logic levels, can be used to designate a number in binary form. The AND gates 2–7 are used to decode specific binary numbers, and their outputs go high when the number they are programmed to detect is loaded in the

[1] An Electronic Associates Inc., fully expanded, 380 analog/hybrid computing system, equipped with a series 1140 Variplotter recorder, was used throughout.

[2] "High" denotes a logic signal of +5 v. "Low" denotes a logic signal of 0 v.

[3] One machine unit equals 10 v. and is designated mu.

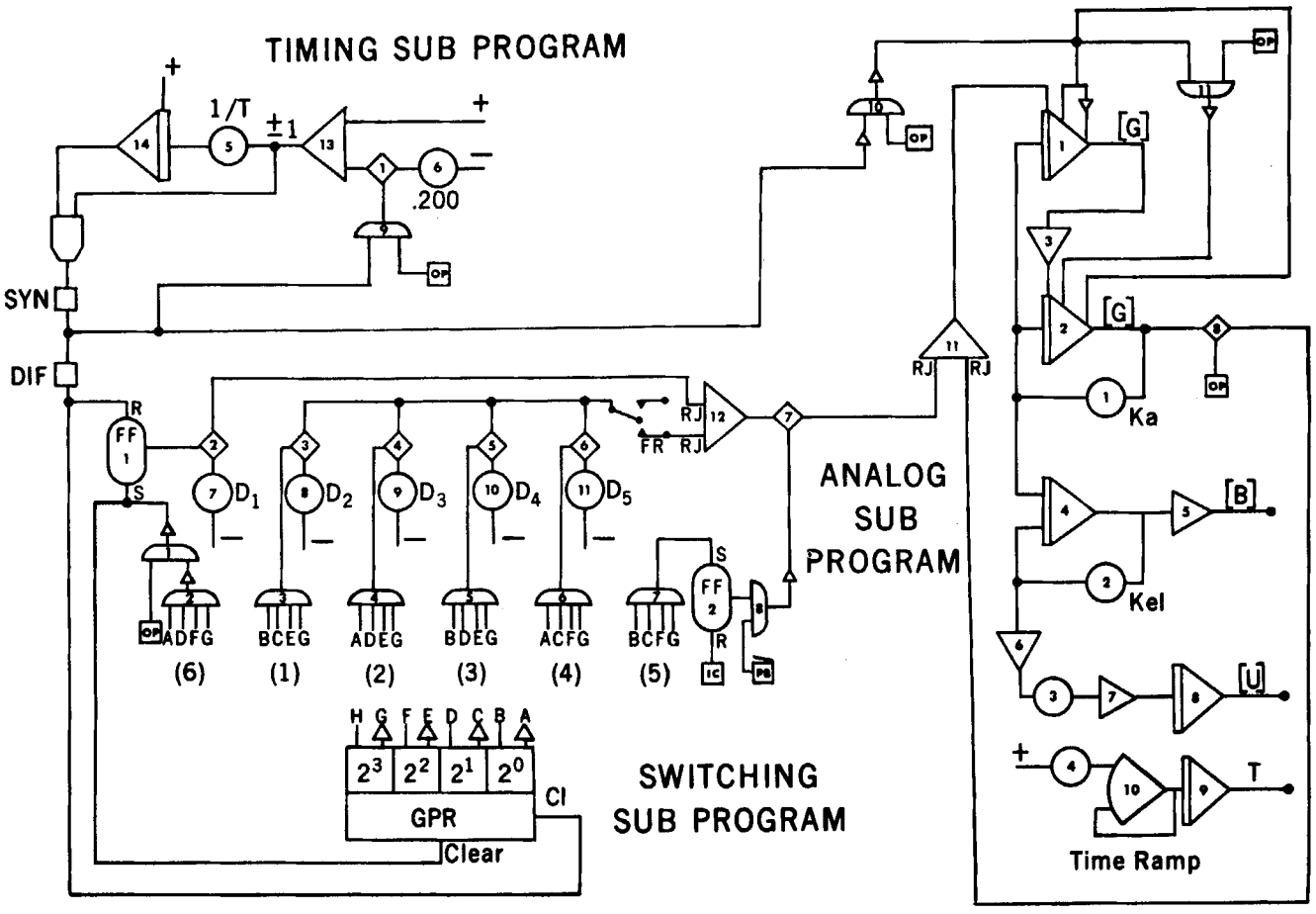


Figure 1—*Analog computer program.*

GPR. When the output of one of these AND gates goes high, the appropriate D/A switch is closed and the corresponding dose is routed through amplifiers 12 and 11 to the IC input of integrator 1 in the analog subprogram. Dose 1 (D1), which is set on pot 7, is connected when either the computer is in the IC mode or the output of AND gate 2 is high.

The GPR is programmed to clear whenever the computer is in the IC mode or AND gate 2 is high. Thus, the cycle of dose administrations is automatically repeated. The repetitive dosing feature of the program can be eliminated by manually depressing a push button (PB) causing a logic level high to be transmitted to AND gate 8. If the PB is high, D/A switch 7 opens after dose 5 is administered, disconnecting all of the doses from the analog portion of the program. However, if the output of the PB is low, the sequence of doses is repeated when the number loaded into the GPR equals the value set on AND gate 2. For single-dose administration, the function relay (FR) switch is opened, disconnecting doses 2–5.

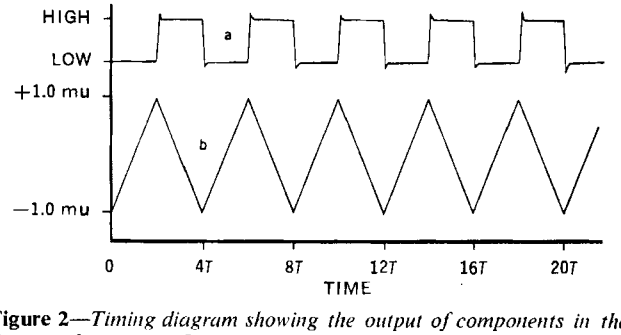


Figure 2—*Timing diagram showing the output of components in the timing subprogram. Curves a and b represent the outputs of the comparator and integrator 14 with time. The value of* T *is variable and is equal to the time needed for integrator 14 to integrate from 0 to +1.0 mu.*

Analog Subprogram—The differential equations, which describe the pharmacokinetic model, are solved by the analog subprogram. Values for initial conditions can only be set on integrators when they are in the IC mode. To simulate the administration of multiple doses, the gut integrator is returned to the IC mode each time a dose is given while the remaining integrators are operating. If only a single integrator was used to simulate the disposition of the drug in the gut, and if the new dose was entered into the gut integrator before the previous dose had been completely dissipated, then the amount of drug remaining in the gut would be lost from the simulation at the instant the integrator went into the IC mode. To prevent such losses, a two-integrator system was developed, where integrators 1 and 2 simulate the disposition of the drug in the gut. The integrators act in tandem and are in complementary modes (when one integrator is in the IC mode, the other integrator is in the OP

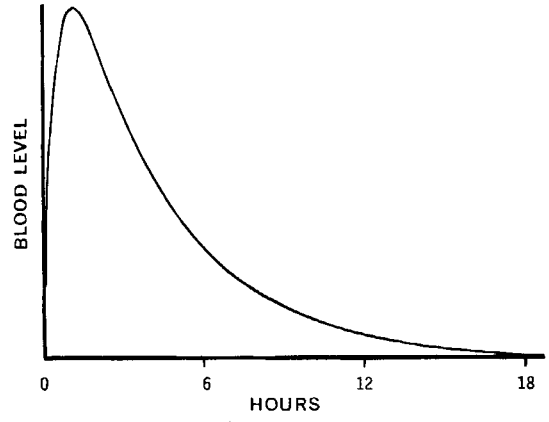


Figure 3—*Projected blood level curve from a single 50.0-mg. administration of the hypothetical drug* (k_a = *2.0 hr.*$^{-1}$, k_{el} = *0.30 hr.*$^{-1}$).

Table II—Pharmacokinetic Parameters

Parameter	Value
Dose	50.0 mg.
k_a	2.00 hr.$^{-1}$
k_{el}	0.30 hr.$^{-1}$

mode) at all times, except when the computer is in the IC mode.

The two integrators are interconnected so that the output of one integrator is the IC input of the other. When an integrator is in the IC mode, its output is equal to its IC input; therefore, if its IC input is a changing value, the integrator tracks this value. Amplifier 11 sums the new dose and any residual drug that is left in the gut and its output is connected to the IC input of integrator 1. When integrator 1 is in the IC mode, its output is equal to the sum of [G] plus the new dose; when it goes into the OP mode, it integrates from that value. When integrator 1 goes into the OP mode, integrator 2 goes into the IC mode and tracks the output of integrator 1. When either integrator is in the IC mode, the value of the amount of drug remaining in the gut is being tracked, so this value is never lost.

The modes of integrators 1 and 2 are controlled by AND gates 10 and 11 which, in turn, are controlled by the output of the comparator. When the program is in the IC mode, both integrators are in IC. At this time the outputs of both integrators equal the value of dose 1. When the program is put into the OP mode, integrator 1 goes into OP and integrator 2 remains in IC. The output of integrator 1 is the value of the amount of drug in the gut, [G], and since integrator 2 tracks the output of integrator 1, its output is also equal to [G]. At time $2T$, integrator 1 goes into IC and integrator 2 goes into OP. Integrator 2 integrates from the last value of [G], while the output of integrator 1 becomes [G] plus the value of dose 2. At time $4T$, integrator 1 goes into OP and integrator 2 into IC and the cycle is repeated. The value of the output of integrator 2 is always equal to [G], the amount of drug in the gut.

As stated previously, the single-compartment model was used only for demonstration purposes. Almost any pharmacokinetic model can be programmed utilizing the "two integrator" system.

RESULTS AND DISCUSSION

Once kinetic parameters have been determined from an immediate-release dosage form, the variable dose program can be used to project blood and urine levels for various pharmacokinetic problems. Additionally, it would not be difficult to proceed to a more complex model since the subprograms that control the administration of doses, namely the timing and switching subprograms, are model independent.

For demonstration purposes, a hypothetical situation based on the single-compartment model will be used to illustrate one application of this program. The situation selected is one where it is desired to formulate a timed-release dosage form and where the single-compartment pharmacokinetic constants have been previously determined (in this case they will be arbitrarily assigned). The goal is to determine what the release pattern of the active from the dosage form should be so that the most uniform blood level above the therapeutic level is produced. The assumption made is that the drug is released in bursts (at periodic intervals, portions of the drug are released instantaneously).

The arbitrarily selected pharmacokinetic parameters (Table II) describe the distribution of a 50-mg. immediate-release dose of a drug with rapid absorption and moderately fast elimination. As illustrated in Fig. 3, the drug is eliminated rapidly from the body, making it a good candidate for a timed-release preparation.

Assuming it is desired to formulate a 150-mg. product that would maintain therapeutic and uniform blood levels for 12 hr., the variable dose program can be used to predict the amount of drug that should be released from a timed-release formulation at given periods. For this situation, one can simulate bursts of drug being released at the beginning of each time interval. Since both the amount of drug administered and the interval between administrations can be controlled, the optimized blood level curve can be rapidly obtained. The effect of manipulating the sizes of the doses and the time interval between doses may be visualized directly on either an oscilloscope or a graphic plotter. To predict the "stacking" effect, the program was designed so that the sequence of dose

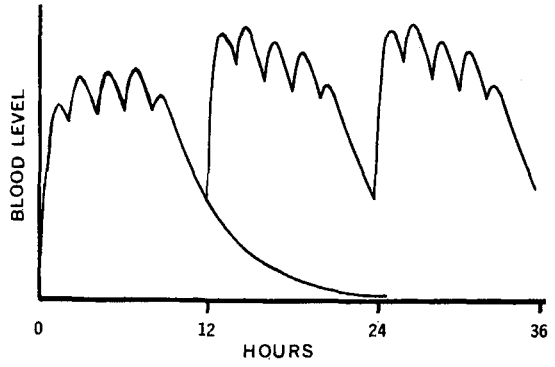


Figure 4—*Projected blood level curve depicting the timing sequence that produced the most uniform blood level curve* (k_a = *2.0 hr.*$^{-1}$, k_{el} = *0.30 hr.*$^{-1}$). *The administration of doses is as follows: 60.0, 25.0, 25.0, 25.0, and 15.0 mg. at 0, 2, 4, 6, and 8 hr., respectively. The regimen was repeated every 12 hr.*

administrations may be repeated continually. The results of these trials, including the repeated dose sequences, and the selected dose regimen are shown in Fig. 4. Since the basic assumption in this case was that the dose is released in bursts at these time intervals, it would be suggested that the formulator prepare an oral dosage form that would provide an *in vitro* release pattern in accordance with this regimen.

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