NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.
A NUMERICAL APPROACH TO THE CONVOLUTION EQUATIONS OF A MATHEMATICAL MODEL OF CHEMOTHERAPY

Richard Bellman and Bella Kotkin

PREPARED FOR:
NATIONAL INSTITUTES OF HEALTH

The RAND Corporation
SANTA MONICA • CALIFORNIA
MEMORANDUM
RM-3716-NIH
JULY 1963

A NUMERICAL APPROACH TO
THE CONVOLUTION EQUATIONS OF
A MATHEMATICAL MODEL OF CHEMOTHERAPY
Richard Bellman and Bella Kotkin

This investigation was supported in part by Public Health Service Research Grant Number RG-9608, from the Division of General Medical Sciences, National Institutes of Health.
PREFACE

The physical assumption of laminar flow in the large blood vessels further complicates the mathematical model of drug distribution in the body by introducing convolution terms which are difficult computationally. This Memorandum tackles the new equations of the chemotherapy model and presents a method suitable for programming this model as well as other biological systems involving equations of this type.
SUMMARY

The new model of drug distribution in the body incorporates the exchange between the stationary and flowing phases in the large blood vessels. This introduces computationally difficult convolution terms. The method of differential approximation applied to the convolution equations reduces this model to a system of differential–difference equations which can be solved computationally.
CONTENTS

PREFACE............................................................... iii
SUMMARY............................................................. v

Section
1. INTRODUCTION..................................................... 1
2. THE EQUATIONS OF THE MODEL................................. 2
3. DIFFERENTIAL APPROXIMATION................................. 3
4. REDUCTION TO A SYSTEM OF DIFFERENTIAL–DIFFERENCE EQUATIONS................................. 6

REFERENCES............................................................11
A NUMERICAL APPROACH TO THE CONVOLUTION EQUATIONS OF
A MATHEMATICAL MODEL OF CHEMOTHERAPY

1. INTRODUCTION

Mathematical models of drug distribution presented in previous papers [1 - 5] involved the physical assumption of volume displacement flow in the large blood vessels and led to a system of differential-difference equations with time delays arising from the non-zero recirculation time of the blood. These time lags together with the parameters involving the heart as a mixing pot compensated for the assumption of "slug" flow with no mixing in the arteries and veins. This model initiated continuing research on the numerical solution of differential-difference equations (see [7,8,9]).

The work of Cooper and Jacquez incorporates the exchange between the stationary and flowing phases in the large blood vessels using some results of Landahl (see [6],[10]). These assumptions lead to a set of differential equations together with some equations containing convolution terms, an additional complication. The problem of obtaining a numerical solution of equations of this nature has in turn stimulated considerable research on various approximation techniques since convolution terms introduce significant time and storage problems. We shall apply here some recent results on differential approximation (see [11]) to the equations of our model and obtain thereby a new set of differential-difference equations which can be solved by means of the
techniques described in the foregoing references. Further
details will be presented in a subsequent paper describing
the digital computer program.

2. THE EQUATIONS OF THE MODEL

The equations (see [4],[10]) of our two organ model
consist of a set of 16 first order differential equations
for the functions $u_j, v_j, w_j, z_j, j=1, 2, m=2, 3, ..., 6,$
and the following 3 convolution equations for the functions
$u_{1,1}, u_{2,1}, U_L$ (unless otherwise specified these functions
are functions of $t$):

(1) $u_{1,1}' = H_1 + d_1 \int_0^{t-s} u_L(q)g(t-s-q)dq$

(2) $u_{2,1}' = H_2 + d_2 \int_0^{t-s} u_L(q)g(t-s-q)dq$

(3) $U_L' = H_3 + d_3 \int_0^{t-s} u_{1,6}(q)g(t-s-q)dq$

$+ d_4 \int_0^{t-s} u_{2,6}(q)g(t-s-q)dq$

Here $s = \ell v_I/c$, with time dimension,

$a = e^{-(\kappa \ell/c)}, \quad b = \kappa^2 \ell / v_S c, \quad h = \kappa / v_S$

$d_1 = c_1 a (nc_1/R_{p1}), \quad d_2 = c_1 a (nc_2/R_{p2}), \quad d_3 = c_1 a c_1, \quad d_4 = c_1 a c_2,$
\[ H_1 = \frac{nc_1}{R_{p1}} \left[ g_1 a U_L(t-s) - u_1,1 \right] - \frac{k e_{e1}}{R_{p1}} \left[ u_1,1 - v_1 \right] \]
\[ H_2 = \frac{nc_2}{R_{p2}} \left[ f_2(t) + g_1 a U_L(t-s) - u_2,1 \right] - \frac{k e_{e2}}{R_{p2}} \left[ u_2,1 - v_2 \right] \]
\[ H_3 = \frac{c}{\sqrt{\pi}} \left[ g_1 a c_1 u_1,6(t-s) + c_2 u_2,6(t-s) \right] + g_2 f_1(t) - U_L \]
\[ g(x) = e^{-hx} \frac{d(I_0(2\sqrt{b}x))}{dx} = e^{-hx} \sqrt{b/x} I_1(2\sqrt{b}x) \]

where \( I_1 \) is the 1-st modified Bessel function of the first kind. It should be pointed out that the 19 functions in this system of equations are zero for \( t < 0 \).

For simplicity the model assumes the same length \( l \) for the large blood vessels leading to and from organs 1 and 2. This leads to differential–difference equations involving one time lag, \( s \). We can, however, handle different commensurate time lags (see [12]). This, of course, increases time and storage requirements.

We will proceed to replace each of the three convolution equations by a set of differential–difference equations using a procedure described in the sections that follow.

3. DIFFERENTIAL APPROXIMATION

The method of differential approximation (see [11]) permits us to obtain a set of coefficients, \( a_i, i = 1, \ldots, N \), so that \( g^{(N)}(x) + \sum_{i=1}^{N} a_i g^{(N-1)}(x) \equiv 0 \), in the mean square sense. We proceed as follows.
The modified Bessel function of the first kind satisfies the second order differential equation

\[ I_1''(z) + \frac{1}{z} I_1'(z) - (1 + \frac{1}{z^2}) I_1(z) = 0. \]

From this it follows that

\[ xG''(x) + G'(x)(2hx+2) + G(x)(h^2x+2h-b) = 0. \]

By repeated differentiation we obtain

\[ xG^{(N+1)}(x) + (2hx+N+1)G^{(N)} + (2hN+h^2x-b)G^{(N-1)} + h^2(N-1)G^{(N-2)} = 0. \]

Let \( G_1(x) = G^{(1)}(x) \) and consider the \( N+1 \) differential equations

\[
\begin{cases}
\frac{dG_i}{dx} = G_{i+1}, & i = 0, 1, \ldots, N-1 \\
\frac{dG_N}{dx} = \frac{1}{x} \left((2hx+N+1)G_N + (2hN+h^2x-b)G_{N-1} + h^2(N-1)G_{N-2}\right)
\end{cases}
\]

The initial conditions \( G_1(0) \) can be obtained from the known series expansion for \( I_1(x) \), namely

\[ G(x) = e^{-hx} \left(b + \frac{b^2x^2}{2} + \frac{b^3x^2}{3(2)!^2} + \ldots + \frac{b(n+1)x^n}{(n+1)(n!)^2} + \ldots \right). \]
We wish to determine the coefficients $a_1$ so that over a suitable range $T$ we obtain the minimum

$$M = \min_{a_1} \int_0^T \left[ a_N(x) + \sum_{i=1}^N a_i G(x) \left( N-1 \right) \right] dx .$$

Setting the partial derivatives of $M$ with respect to $a_1$ equal to zero, we obtain the linear system

$$\sum_{j=1}^N a_j \int_0^T G_{N-1} G_{N-j} dx = \int_0^T G_{N-1} G_N , \quad i = 1, N .$$

Let

$$P_{k,q} = \int_0^T G_k G_q dx , \quad k, q = 0, \ldots, N - 1$$

$$Q_k = \int_0^T G_k G_N dx , \quad k = 0, \ldots, N - 1 .$$

To the set of equations (4), add the following differential equations

$$\begin{cases}
\frac{dP_{k,q}}{dx} = G_k G_q , & P_{k,q}(0) = 0, k,q = 0,\ldots, N - 1 \\
\frac{dQ_k}{dx} = -G_k G_N , & Q_k(0) = 0, k = 0, \ldots, N - 1 .
\end{cases}$$
Integrating the combined set of equations (4) and (5) and taking the final values of $P_{k,q}$ and $Q_k$ at $x = T$, we solve the following system of $N$ linear equations in $N$ unknowns $a_{N-q}, \quad q = 0, \ldots, N - 1$,

$$
\sum_{q=0}^{N-1} a_{N-q} P_k, q(T) = Q_k(T), \quad k = 0, \ldots, N - 1 .
$$

The solution gives us $a_N, a_{N-1}, \ldots, a_1$.

4. REDUCTION TO A SYSTEM OF DIFFERENTIAL–DIFFERENCE EQUATIONS

For simplicity of presentation, let us assume $N = 3$ for the order of the differential approximation. Let us define

$$
X(t) = \int_0^t u_L(q) G(t-q) dq,
$$

$$
Y(t) = \int_0^t u_{1, G}(q) G(t-q) dq,
$$

$$
Z(t) = \int_0^t u_{2, G}(q) G(t-q) dq ,
$$

and

$$
X_1 = X^{(1)}, \quad Y_1 = Y^{(1)}, \quad Z_1 = Z^{(1)} .
$$

The 3 convolution equations become
(6) \[ u_{1,1} = h_1 + d_1 x(t-s) \]

(7) \[ u_{2,1} = h_2 + d_2 x(t-s) \]

(8) \[ u_L' = h_3 + d_3 y(t-s) + d_4 z(t-s) \]

To these equations adjoin the following set:

\[
\begin{cases}
    x' = x_1, & x(0) = 0 \\
    x_1' = x_2, & x_1(0) = 0 \\
    x_2' = h_4(x_1, x_2, u_L, u_L', u_L''), & x_2(0) = 0 \\
    y' = y_1, & y(0) = 0 \\
    y_1' = y_2, & y_1(0) = 0 \\
    y_2' = h_4(y_1, y_2, u_1, c, u_1', c, u_1'', c), & y_2(0) = 0 \\
    z' = z_1, & z(0) = 0 \\
    z_1' = z_2, & z_1(0) = 0 \\
    z_2' = h_5(z_1, z_2, u_2, c, u_2', c, u_2'', c), & z_2(0) = 0 \\
\end{cases}
\]

The function \( h_i \) and the initial conditions are obtained as follows: Illustrating with \( X(t) \), by using Leibniz's rule repeatedly, we get

(10) \[ X'(t) = g(0) u_L''(t) + \int_0^t g'(t-q) u_L(q) dq \]

(11) \[ X''(t) = g(0) u_L'(t) + g'(0) u_L(t) + \int_0^t g''(t-q) u_L(q) dq \]
(12) \[ x''(t) = g(0)u''_L(t) + g'(0)u'_L(t) + g''(0)u_L(t) \]
\[ + \int_0^t g''(t-q)u_L(q)\,dq. \]

Combining these together with the 3 coefficients \( a_1 \) of our differential approximation, we obtain

\[ x'' + a_1 x'' + a_2 x' + a_3 x = g(0)u''_L(t) + g'(0)u'_L(t) + g''(0)u_L(t) \]
\[ + a_1 (g(0)u'_L(t) + g'(0)u_L(t)) + a_2 g(0)u_L(t) \]
\[ + \int u_L(q)(g''(t-q) + a_1 g''(t-q) + a_2 g'(t-q) + a_3 g(t-q))\,dq. \]

By a change of variable and the result of Sec. 3, the integrand in the last term vanishes. The function \( H_4 \) by virtue of (13) is given by

\[ H_4(x, x_1, x_2, u_L, u'_L, u''_L) = -a_3 x - a_2 x_1 - a_1 x_2 \]
\[ + [g''(0) + a_1 g'(0) + a_2 g(0)]u'_L + [g'(0) + a_1 g(0)]u''_L + g(0)u''_L. \]

By going back to the equations of the model (see [4], [10]) the derivative terms \( u'_L, u''_L, u'_{j6}, u''_{j6}, j=1,2 \), in the function \( H_4 \), can be expressed in terms of the original functions of our set of 28 differential–difference equations, for a
two organ model with a third order differential approximation for \( G(x) \). Differential approximation of order \( k \) involves a system of \( 19 + 3k \) equations.
REFERENCES


