SOLUTION OF THE MARCHUK MODEL OF INFECTIOUS DISEASE AND IMMUNE RESPONSE

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Abstract—The decomposition method of Adomian is applied to solve the Marchuk model of infectious disease and immune system response.

A mathematical model of infectious disease based on immunological assumptions has been proposed by Marchuk (1975) and Belykh (1981)[1]. The model involves a system of four coupled nonlinear differential-delay equations in $V(t)$, $F(t)$, $C(t)$ and $m(t)$, where V is the concentration of viruses (pathogenic multiplying antigens), F is the concentration of antibodies (immune substrates neutralizing the viruses). C is the concentration of plasma cells (antibody producers) and m refers to the characteristics of an organ (mass or area) damaged by viruses. The model is given by

$$\begin{aligned} V' &= \beta V - \gamma FV, \\ F' &= \rho C - \eta\gamma FV - \mu_f F, \\ C' &= \xi(m)\alpha V(t-\tau)F(t-\tau)H(t-\tau) - \mu_c(C - C^*), \\ m' &= \zeta V - \mu_m m. \end{aligned} \tag{1}$$

$\xi(m)$ is a continuous function describing immune system failure due to damage of an organ, varying from zero for an entirely damaged organ to unity for a healthy organ, and $H(t-\tau)$ is the Heaviside function (unity if $t \geq \tau$, and zero otherwise). Initial conditions $V(0) \geq 0$, $F(0) > 0$, $V(0) \geq 0$, $C(0) \geq 0$ and $m(0) \geq 0$ are specified. According to this model, the disease process as described by Marchuk and Belykh is the following. The initial virus population at $t = 0$ starts to multiply and injure organ cells. Collision of viruses in the blood with the receptors of immunocompetent cells (antibodies) causes immune system stimulation, and after a time τ, antibody production begins, and the outcome of the disease depends on whether the virus damages the organ so that immune system failure takes place. The immunological status through the parameters α, β, . . . determines whether the disease is acute, chronic or lethal, and the effects of therapy.

This paper discusses only a new methodology which will yield a realistic solution of the system (1), not equally important questions of validation of the model, identification

and measurement of the parameters $\alpha, \beta, \ldots$ and questions of optimal treatment. However, we point out that the methodology used here—the decomposition method (Adomian[2–11])—is independent of the model and can be applied even if the parameters are not constants in each patient but time-varying, stochastic or nonlinear functions of the independent variables. This method solves wide classes of equations—algebraic, differential, differential-delay, integro-differential, partial differential equations or systems of such equations as shown particularly in [3]. It solves *nonlinear* equations: it does not first linearize the equations thereby solving a *different* problem. It avoids the cumbersome integrations of the Picard method and solves problems involving radicals and composite nonlinearities which cannot be done by Picard or iterative methods. Finally, if parameters are stochastic, neither perturbation nor closure approximations are required, i.e. fluctuations need not be small, and it is not necessary to assume unrealistic delta-correlated processes. Thus when nonlinear and stochastic effects are not "small," solutions by decomposition are necessarily more realistic, while the usual solutions, by virtue of the assumption and methods used, deviate from the actual physical solution[2, 3]. Basically the decomposition method assumes the desired solution is decomposed into components to be determined, e.g. $y = \sum_{n=0}^{\infty} y_n$, and any nonlinear term $N[y] = f(y)$ is written as $\sum_{n=0}^{\infty} A_n$, where the A_n are Adomian's polynomials[2–11] generated for the specific nonlinearity. The y_0 term is very easily found in terms of the initial (or boundary) conditions, the forcing function and a trivially invertible part of the linear operator. All other components are determined in terms of preceding components in rapidly converging series. The most valuable feature perhaps is the computability of the terms.

Writing $L = \mathrm{d}/\mathrm{d}t$, (1) becomes

$$\begin{aligned} LV &= \beta V - \gamma FV, \\ LF &= \rho C - \eta\gamma FV - \mu_f F, \\ LC &= \xi(m)\alpha V(t-\tau)\, F(t-\tau)\, H(t-\tau) - \mu_c(C - C^*), \\ Lm &= \zeta V - \mu_m m. \end{aligned} \tag{2}$$

Operating on both sides of all four equations by $L^{-1} = \int_0^t [\cdot]\, \mathrm{d}t \ldots$ the result is [3, 4]

$$\begin{aligned} V &= V(0) + L^{-1}\beta V - L^{-1}\gamma FV, \\ F &= F(0) + L^{-1}\rho C - L^{-1}\eta\gamma FV - L^{-1}\mu_f F, \\ C &= C(0) + L^{-1}\xi(m)\alpha V(t-\tau)F(t-\tau)H(t-\tau) - L^{-1}\mu_c(C - C^*), \\ m &= m(0) + L^{-1}\zeta V - L^{-1}\mu_m m. \end{aligned} \tag{3}$$

The nonlinear term FV can be expanded in terms of Adomian's A_n polynomials*; however, for this simple product nonlinearity, it is not really necessary. The function $\xi(m)$ described as a continuous nonincreasing function varying from 1 to 0 requires an analytical or explicit form—it can be approximated by polynomials, Fourier terms or by a simple function, for example. Assuming we have such a form, we generate the A_n polynomials for the $\xi(m)$ function or series, and we will simply write now $\xi(m) = \sum_{n=0}^{\infty} A_n$, where the A_n are the appropriate polynomials exactly representing $\xi(m)$. The $V(t-\tau)$, $F(t-\tau)$

* These polynomials, generated for any specific nonlinearity in an equation, are discussed in numerous references (see particularly [2–11]) and need not be discussed again here.

and $H(t-\tau)$ can be written in terms of the delay operation D defined by $Dy(t) = y(t-\tau)$. We now have

$$\begin{aligned} V &= V(0) + L^{-1}\beta V - L^{-1}\gamma FV, \\ F &= F(0) + L^{-1}\rho C - L^{-1}\eta\gamma FV - L^{-1}\mu_f F \\ C &= C(0) + L^{-1}\xi(m)\alpha\, DVDFDH - L^{-1}\mu_c(C - C^*), \\ m &= m(0) + L^{-1}\xi V - L^{-1}\mu_m m. \end{aligned} \tag{4}$$

The quantities in the left are decomposed into components to be determined, $V = \sum_{n=0}^{\infty} V_n$, $F = \sum_{n=0}^{\infty} F_n$, $C = \sum_{n=0}^{\infty} C_n$ and $m = \sum_{n=0}^{\infty} m_n$, with $V_0 = V(0)$, $F_0 = F(0)$, $C_0 = C(0)$ and $m_0 = m(0)$. Then

$$\begin{aligned} V &= V_0 + L^{-1}\beta \sum_{n=0}^{\infty} V_n - L^{-1}\gamma \sum_{n=0}^{\infty} F_n \sum_{n=0}^{\infty} V_n, \\ F &= F_0 + L^{-1}\rho \sum_{n=0}^{\infty} C_n - L^{-1}\eta\gamma \sum_{n=0}^{\infty} F_n \sum_{n=0}^{\infty} V_n - L^{-1}\mu_f \sum_{n=0}^{\infty} F_n, \\ C &= C_0 + L^{-1} \sum_{n=0}^{\infty} A_n\alpha\, DVDFDH - L^{-1}\mu_c \left(\sum_{n=0}^{\infty} C_n - C^* \right), \\ m &= m_0 + L^{-1}\xi \sum_{n=0}^{\infty} V_n - L^{-1}\mu_m \sum_{n=0}^{\infty} m_n. \end{aligned} \tag{5}$$

In the decomposition series for V, F, C and m, the V_0, F_0, C_0 and m_0 have been identified as the initial values. Consider the first equation of (5). On the left side we have $\sum_{n=0}^{\infty} V_n = V_0 + V_1 + \cdots$. On the right we have $V_0 + L^{-1}\beta \sum_{n=0}^{\infty} V_n - L^{-1}\gamma \sum_{n=0}^{\infty} F_n \sum_{n=0}^{\infty} V_n$. Thus V_1 is equated to the first term after V_0 or $L^{-1}\beta B_0 - L^{-1}\gamma F_0 V_0$. The other equations are dealt with in exactly the same manner. Then, since V_0, C_0, F_0 and m_0 are known, the four terms with subscript 1 can be calculated from the terms with subscript 0. Higher terms are similarly calculated in terms of preceding terms. (If forcing terms are included in the equations, they must be accounted for in the V_0, F_0, C_0 and m_0 terms as well[2–4].) The following terms can be identified now as

$$\begin{aligned} V_1 &= L^{-1}\beta V_0 - L^{-1}\gamma F_0 V_0, \\ F_1 &= L^{-1}\rho C_0 - L^{-1}\eta\gamma F_0 V_0 - L^{-1}\mu_f F_0, \\ C_1 &= L^{-1}A_0\alpha\, DV_0DF_0DH - L^{-1}\mu_c(C_0 - C^*), \\ m_1 &= L^{-1}\xi V_0 - L^{-1}\mu_m m_0. \end{aligned} \tag{6}$$

Thus V_1, F_1, C_1 and m_1 are computable, since V_0, F_0, C_0 and m_0 are known. Now

$$\begin{aligned} V_2 &= L^{-1}\beta V_1 - L^{-1}\gamma(F_0V_1 + F_1V_0), \\ F_2 &= L^{-1}\rho C_1 - L^{-1}\eta\gamma(F_0V_1 + F_1V_0) - L^{-1}\mu_f F_1, \\ C_2 &= L^{-1}A_1\alpha[DV_0DF_1 + DV_1DF_0]DH - L^{-1}\mu_c(C_1 - C^*), \\ m_2 &= L^{-1}\xi V_1 - L^{-1}\mu_m m_1. \end{aligned} \tag{7}$$

Note what happens to the nonlinear term FV. This is equivalent to generating A_n polynomials for FV. We write products of components such the sum of subscripts is always less by 1 than the subscript on the left side. This is not a heuristic procedure. The polynomials can be derived by procedures given in [2–4], and the methodology is fully discussed in the referenced papers and it would be redundant to repeat it in each application. Our objective here is only to show the Marchuk model can be solved accurately and realistically. We add that if random initial conditions are important to consider as they well might be because of patient-to-patient variations or imprecisely determined initial concentrations, or some of the constants are randomly fluctuating in time, the expressions in (7) are random, and when we have computed enough components, we can simply derive the appropriate expectation, variance or covariance without any closure approximations, perturbation theory or restrictive assumptions[2, 3]. It needs to be emphasized that the decomposition method is *new*; it is not a Picard method or a perturbation or iteration[2].

Note again that V_2, F_2, C_2 and m_2 are determinable from the already determined components. We proceed in the same way up to V_n, F_n, C_n and m_n for some reasonable n:

$$
\begin{aligned}
V_3 &= L^{-1}\beta V_2 - L^{-1}\gamma(F_0V_2 + F_1V_1 + F_2V_0),\\
F_3 &= L^{-1}\rho C_2 - L^{-1}\eta\gamma(F_0V_2 + F_1V_1 + F_2V_0) - L^{-1}\mu_f F_2,\\
C_3 &= L^{-1}A_2\alpha[DV_0DF_2 + DV_1DF_1 + DV_2DF_0]DH - L^{-1}\mu(C_2 - C^*),\\
m_3 &= L^{-1}\xi V_2 - L^{-1}\mu_m m_2,\\
&\vdots\\
V_{n-1} &= L^{-1}\beta V_{n-2} - L^{-1}\gamma(F_0V_{n-2} + F_1V_{n-3} + \cdots + F_{n-2}V_0),\\
F_{n-1} &= L^{-1}\rho C_{n-2} - L^{-1}\eta\gamma(F_0V_{n-2} + F_1V_{n-3} + \cdots + F_{n-2}V_0) - L^{-1}\mu_f F_{n-2},\\
C_{n-1} &= L^{-1}A_{n-1}\alpha[DV_0DF_{n-2} + DV_1DF_{n-3} + \cdots + DV_{n-2}DF_0]DH\\
&\quad - L^{-1}\mu(C_{n-2} - C^*),\\
m_{n-1} &= L^{-1}\xi V_{n-2} - L^{-1}\mu_m m_{n-2}.
\end{aligned}
$$

Adding components with subscripts running from 0 to $n-1$ results in n-term approximations for V, F, C and m.

The expressions

$$\sum_{i=0}^{n-1} V_i, \quad \sum_{i=0}^{n-1} F_i, \quad \sum_{i=0}^{n-1} C_i, \quad \sum_{i=0}^{n-1} m_i$$

are *n-term approximations* to the desired quantities, which are easily obtained once initial conditions are specified. Convergence holds[3, 9] and is extremely rapid as well. The successive components are readily calculable hence the accuracy can be carried to any necessary point.

With the proposed solutions, one can consider various conditions and parameters and reach biological/medical conclusions regarding the course of the disease and its treatment. Of course, it is not only possible but likely that the model of Marchuk may need further modification to consider stochasticity or delayed effects—both within the scope of the theory[2, 3]. This should be determinable with research on the values of the parameters with many individuals, after which detailed computer calculations can follow. Since this method requires no smallness assumptions or linearizations or discretizations, the solu-

tions should correspond closely to physically observed results. Solutions which linearize also change the problem and can be expected to deviate from a nonlinear solution. Comparison of observed and calculated results in clinical trials can follow.

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