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Biological system interactions

(modeling/delayed effects/coupled equations and coupled systems/oscillations and anharmonic oscillators/cellular or population growth)

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ABSTRACT **Mathematical modeling of cellular population growth, interconnected subsystems of the body, blood flow, and numerous other complex biological systems problems involves nonlinearities and generally randomness as well. Such problems have been dealt with by mathematical methods often changing the actual model to make it tractable. The method presented in this paper (and referenced works) allows much more physically realistic solutions.**

Modeling and analysis of a number of biological problems involving interactions of physiological systems, such as those between the respiratory system and the cardiovascular system, can benefit significantly from new advances in mathematical methodology (1), which allow solution of dynamical systems involving coupled systems (2), anharmonic oscillators (3), nonlinear ordinary or partial differential equations (4, 5), and delay equations (6). Very general oscillators that have been studied (3) can be applied to blood pressure oscillations and cardiac and neural problems. Cardiac pacemakers, for example, involve stimulation of a regular biological rhythm with an external oscillator and can be modeled by coupled anharmonic oscillators with time delays. All dynamical problems are basically nonlinear; commonly used mathematical approaches that involve some form of linearization are too limited in scope and involve gross and unsatisfactory approximations changing essentially the nonlinear nature of the actual system being analyzed. Thus, the mathematical system actually solved is quite different from the original nonlinear model. Commonly used nonlinear least squares analysis for data analysis (such as the Gauss–Newton method) involves the same serious deficiency that can now be circumvented (7).

Randomness is, of course, another factor present in real systems due to a variety of causes. This can be randomness or fluctuations either in parameters of an individual system or in equations involving variations from one individual to another. Compartment analysis is used to model interconnected subsystems (respiratory system, cardiovascular system, etc., or possibly organs—liver, heart, etc.). This leads to differential equations that realistically are both nonlinear and stochastic. This randomness can manifest itself in coefficients of differential operators, in inputs, or in initial or boundary conditions.

Randomness, or stochasticity, in physical (or biological) systems, like nonlinearity, is generally dealt with by perturbative methods, averagings which are not generally valid, or other specialized and restrictive assumptions that do not realistically represent fluctuations, especially if fluctuations are not relatively negligible. We emphasize that the methods used here do not require assumption of small nonlinearity or small randomness, linearization, or closure approximations.

Finally, the methods (1) can handle extremely complex initial or boundary conditions that may be nonlinear, random, or coupled, as well as integral boundary conditions as in the von Foerster problem arising in cellular population growth modeling (8, 9) and other biological problems (7). Neural networks, for example, in their processing and transmission of information display nonlinearity as an essential feature as well as couplings and fluctuation.

When the analytical methodology makes the mathematical solution deviate significantly from the model whose solution was sought, it will convey a false sense of understanding that will be unjustified by experimental results or actual observations. The simplifications are of course made in the name of tractability and the use of well-known mathematics, but they neglect intrinsic nonlinear and stochastic behavior and mean simply that the problem has been changed to a different one than intended.

The decomposition method (1) is also an approximation method, but all modeling is approximation and this methodology approximates (accurately and in an easily computable manner) the solution of the real nonlinear and possibly stochastic problem rather than a grossly simplified linearized or averaged problem.

Adequate modeling of blood flow in the human cardiovascular system and ability to solve the resulting very complex nonlinear equations would contribute materially to better understandings of pathogenesis of arterial disease and the design of artificial hearts. Such a solution would depend on solving the general Navier–Stokes equations without resort to linearization and assumptions of "smallness." These equations model fluid flow and occur in a wide variety of physical applications affecting design of aircraft engines, shapes of airfoils in aerodynamics, and internal waves in the ocean and have therefore been intensively studied by physicists. Despite this, however, the solutions indeed leave much to be desired. For example, the ocean dealt with in hydrodynamics studies is a mathematized ocean, not the real ocean in which pressure, density, and velocity are fluctuating or stochastic variables. Nonlinearities are linearized and complex terms are dropped in order to get a solution and the flow is assumed to be laminar since turbulence has not been tractable to mathematical analysis. Turbulence is a strongly nonlinear and stochastic phenomenon and the existing mathematics that can only deal with linearized and perturbative cases is not adequate. The blood flow problem is modeled by these same equations as well as by boundary conditions that may be even more complicated. We are dealing with flow of a complex fluid through an elastic or viscoelastic vessel with branches, organs, prosthetic devices or natural heart valves, and tubes of varying diameter with possible motion of the walls under pulsatile flow because of elasticity. Detailed analysis of arterial flow should consider unsteady viscous flow and retain all the nonlinear terms. The assumptions of smallness—e.g., in wall motions—are unrealistic since such motions may have a significant effect on flow—as in the aorta. The objective is to determine the velocity, knowing quantities such as pressure. Then it is possible to estimate stresses on the walls and possible wall damage or filtration, thrombus growth, or the behavior in an artificial heart. To be able

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to describe mathematically the flow of blood through prosthetic or natural heart valves or the flow about any obstacle in a vessel, or the analytical description of flow under conditions where it becomes nonlaminar, could help diagnoses and design of prosthetic devices. Finally, we must be able to handle another hitherto unsolved problem—that of nonlinear boundary conditions as a result of nonlinear changes of area with pressure changes.

An interesting area of problems also arises in cellular systems and aging models. Cellular population growth models can involve time lags, coupled equations, nonlinearities, and possibly stochastic parameters as well as boundary conditions that can be random, nonlinear, or coupled (9–11).

Consider for example, the Pearl–Verhulst equation (1)

$$\frac{dN(t)}{dt} = kN(t) - (k/N_c)N^2(t), \qquad [1]$$

where $N(t)$ is the number of cells at time t given initial conditions that at t_0, we had N_0 cells, $k = \lambda - \mu$ is the net rate of increase or decrease of population (λ is birth rate; μ is death rate), and N_c is the largest population that the environment can support. Let us write this as

$$\frac{dN(t)}{dt} - kN(t) + gN^2(t) = 0 \qquad [2]$$

and define the operator $L = d/dt$. Equations in this general form have been solved (2) even if k and g are stochastic processes, if L involves higher derivatives, and for large classes of nonlinearities more difficult than the quadratic nonlinearity. Here, we take k, g as constants and write

$$\begin{aligned} LN(t) &= kN(t) - gN^2(t) \\ L^{-1}LN(t) &= N(t) - N(0) \\ &= L^{-1}kN(t) - L^{-1}gN^2(t). \end{aligned}$$

Consequently,

$$N(t) = N(0) = kL^{-1}N(t) - gL^{-1}N^2(t). \qquad [3]$$

Writing $N^2(t) = \Sigma_{n=0}^{\infty} A_n$, where the A_n are a special class of polynomials discussed elsewhere (1), then

$$N(t) = N(0) + kL^{-1}N(t) - gL^{-1}\sum_{n=0}^{\infty} A_n. \qquad [4]$$

Let $N(t)$ be decomposed into components $\Sigma_{n=0}^{\infty} N_n(t)$, which are to be determined taking N_0 as $N(0)$ in this case. If an inhomogeneous term existed here, it would be included in N_0. We can now identify

$$\begin{aligned} N_1 &= kL^{-1}N_0 - gL^{-1}A_0 \\ N_2 &= kL^{-1}N_1 - gL^{-1}A_1 \\ &\vdots \\ N_n &= kL^{-1}N_{n-1} - gL^{-1}A_{n-1}. \end{aligned} \qquad [5]$$

Thus, when the A_n are evaluated, all the N_n are completely determinable in terms of *preceding* components so we can get $N(t) = N_0 + \Sigma_{n=1}^{\infty} N_n$. Calculation of the A_n has been discussed elsewhere (1). We list here for this particular nonlinearity $N^2(t)$

$$\begin{aligned} A_0 &= N_0^2 \\ A_1 &= 2N_0N_1 \\ A_2 &= N_1^2 + 2N_0N_2 \\ A_3 &= 2(N_1N_2 + N_0N_3) \\ &\vdots \end{aligned} \qquad [6]$$

Thus,

$$\begin{aligned} N_1 &= kL^{-1}N_0 - gL^{-1}N_0^2 \\ N_2 &= kL^{-1}N_1 - 2gL^{-1}N_0N_1 \\ N_3 &= kL^{-1}N_2 - gL^{-1}[N_1^2 + 2N_0N_2] \\ &\vdots \end{aligned} \qquad [7]$$

Consequently, since $N_0 = N(0)$

$$\begin{aligned} N_1 &= kL^{-1}N(0) - gN(0)^2t \\ N_2 &= kL^{-1}[kL^{-1}N(0) - gN(0)^2t] \\ &\quad - 2gL^{-1}N_0[kL^{-1}N(0) - gN(0)^2t] \\ &= \frac{k^2N(0)t^2}{2} - \frac{kgN(0)^2t^2}{2} \\ &\quad - \frac{2kgN(0)^2t^2}{2} + \frac{2g^2N(0)^3t^2}{2} \\ &= \frac{t^2}{2}[k^2N(0) - 2kgN(0)^2 + g^2N(0)^3], \end{aligned}$$

etc.

Clearly, all terms are easily calculated.

Mathematical modeling must represent behavior realistically, as well as being computable. An analytic solution of a model that deviates significantly from the actual physical problem being modeled can convey a false sense of understanding unjustified by experimental or actual results. These simplifications, made, of course, for tractability of equations and the use of well-understood mathematical methods, neglect quite seriously the essentially nonlinear and stochastic nature of physical and biological phenomena. Linearity is a special case and linearization of nonlinear phenomena can change the problem to a different problem. It may be adequate if the nonlinearity is "weak" so perturbative methods become adequate. If we can deal with "strong" nonlinearities—as we can—then the "weakly nonlinear" or the "linear" cases derive from the same theory as well. Random fluctuations are always present in real phenomena and perturbative or hierarchy methods and their various adaptations will be adequate only when randomness is relatively insignificant. We wish, therefore, to deal with "strongly" stochastic cases and to derive the special cases as well without the averaging procedures, closure approximations and truncations, or assumptions of special nature for the processes such as Markov or Gaussian white noise, etc. In some problems exact linearization is possible by clever transformations of variables. It is, however, only rarely possible and not a method for general use. These problems have been discussed in many mathematical papers and particularly in a recent book that deals with Adomian's decomposition method (1) for solving such problems.

While still an "approximation" method, it is not to be viewed as less accurate than a so-called "exact" method. All modeling is an approximation and if we change a nonlinear stochastic problem by linearizing it or assuming δ-correlated or small magnitude fluctuations or by making closure approximations, then an exact solution of this grossly simplified and different model may be, and generally is, very much less accurate than an approximate solution of the real problem if it can be done. It is to be noted too that once we realize we are less limited by the mathematics, we can develop more realistic and sophisticated models, since modeling physical phenomena involves retention of essential features while striving for simplicity so resulting equations can be solved. Modeling is always a compromise between realistic representation and mathematical tractability. With fewer limitations imposed to achieve tractability, we can make models more realistic. We are now able to include delayed effects (3, 4) rather than assuming changes take place instantaneously and can make these delays constant, time-dependent, or random. We can deal with coupled nonlinear equations (5), random initial or boundary conditions, and systems of nonlinear differential equations (6, 7). The results are easily obtained and accurate.

This new methodology is developing very rapidly indeed and can meet the difficulties raised. The equations are treated as very general operator equations and the solution is written as an assumed decomposition into components to be found with expansion of nonlinearities in terms of specially generated sets of polynomials defined by Adomian (1) for the particular nonlinearities. The components can be found successively without closure approximations, assumptions of weak nonlinearities, "small" fluctuations, etc., and in a *computable* manner with as much accuracy as required.

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