On the Use of Quantitative Modeling to Help Understand Prostate-Specific Antigen Dynamics and Other Medical Problems

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DOI: 10.1092/U77TQ20DVQ0CLMJA

An article in the current issue of the Journal[1] provides the opportunity to reflect on and discuss the role of mathematical modeling in the biomedical sciences. During the past 20 years, the application of mathematical modeling in the biomedical sciences has made substantial contributions to our understanding of a wide spectrum of problems such as wound healing, cancer growth, and the control of epidemics. The literature of applications is now large (see Murray[2] and the large number of references cited therein). There is a fundamental difference between what the theoretician and the medical scientist mean by a "model," although their goals in the use of models are the same. The latter usually considers a model to be, in the case of cancer research for example, an animal injected with cancer cells and the animal's and the cancer's progress monitored over time. Quantitative or mathematical modeling refers to the use of mathematics to construct an equation (or, more typically, equations) that reflects in quantitative terms what are considered by the experimentalist or clinician to be the key biological processes that govern the process under study: we give specific examples here. The aim is to try to understand and, ideally, determine what these underlying biological mechanisms are. Once a model (mathematical) has been agreed on as a starting point, it then can be solved, compared with the extant data, and, if in agreement, importantly, it can be used as a predictive tool.

Let us consider an example in which this scenario has resulted in an increased understanding of an anomaly in prostate cancer research. It generally is believed that an enlarged prostate implies an increased serum prostate-specific antigen (PSA) level and that it is a quantitative marker of prostate cancer growth. In the specific problem studied,[3] the clinical model was a xenograft rat model. The theoretical model uses the basic pieces of biological information and quantifies them in a simple equation that can be written in words as follows:

Rate of Change of Serum PSA = Production of Serum PSA by Benign Prostate Cells
+ Production of Serum PSA by Malignant Prostate Cells
– Loss of Serum PSA From the Body

These words then are translated mathematically to an equation like the following:

$$\frac{dp}{dt} = \text{beta}_h V_h + \text{beta}_c V_c - \text{gamma } p$$

where p, shorthand for p(t), is the serum PSA level at time t; V_h and V_c are the volumes of benign and cancerous PSA-producing cells, respectively, and PSA is produced by benign and cancer cells at the rates beta_h and beta_c, respectively. Basically the math equation is simply a shorthand way of writing the word equation, but with the important proviso that assumptions are made about PSA production and loss. It is at this stage that the biology plays a critical role. The form of the *loss* term implies an assumption of exponential loss with the parameter gamma equal to the reciprocal of the half-life of circulating PSA. The *production* terms reflect the assumption that PSA from benign and malignant prostate cells simply increases linearly with tissue volume. As more is learned about the biological processes, these assumptions are replaced by terms that reflect what is found. For example, if it were suggested by experiment that production was governed by first-order kinetics, each of the production terms would be multiplied by p: this would have a major effect on the solutions and their prediction. The whole process of constructing a mathematical model is that it must reflect what is considered to be essential biologically. It is relatively easy for a theoretician to write an equation that could give qualitative agreement by judicious choice of parameters. The art of good

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modeling involves making the model reflect as closely as possible what is going on biologically and, most important, being able to estimate parameter values from the experiment. Without the latter, the model is of much less use because with a sufficiently large number of parameters and/or equations, it is possible to match any data set.

This mathematical model was applied successfully to the xenograft prostate cancer data.[3] In this case, we were able to estimate the parameters from the experiment. Clearly this quantitative model is simple and neglects a wide variety of complicating factors. However, this basic model was successful not only in fitting observed data, but also in suggesting a new and clinically relevant interpretation of those data, thereby leading to a better understanding of serum PSA dynamics.

A major point about mathematical modeling is that if the preliminary model equation or equation system gives solutions that are not in agreement with the biology of the process, the biological input may not be correct. This situation necessitates reexamination of the biology. This iterative process can have a useful role in studies that are genuinely interdisciplinary. It is this iterative aspect that has been so important in a variety of applications.[2] A particularly good medical example of this converging modeling process is given by Connor et al.[4,5] This model addressed lactate metabolism in man and resulted in a new clinical way of determining appropriate medication levels.

The story of PSA dynamics is clearly more complicated than this simple model: for example, prostate cancer of different grades produces different amounts of PSA. But modeling like that described in the preceding text can suggest much about PSA dynamics. In the previous example, analysis of the mathematical model revealed that an elevated serum PSA level did not necessarily result from a large tumor volume.[3] In fact, the model predicts (and the data support) the hypothesis that rapidly growing tumors can maintain relatively low serum PSA levels until the tumor is large compared with slowly growing tumors with similar serum PSA levels. This result suggests that PSA may well be a useful marker of tumor growth. However, care must be taken in interpreting single serum PSA values without reference to the prostate size. Clearly, before we can understand prostate cancer and the concomitant PSA production, we need to understand the mechanisms underlying these processes. These mechanisms can naturally be studied via mathematical modeling.

The Use and Abuse of Mathematical Modeling

We should keep in mind what a truly scientific model must try to do. It is essential to (1) start with a real biological situation and try to isolate the key steps in a process, (2) try to construct a model mechanism (equations) that reflects these key elements and involves real biological quantities, (3) investigate the theoretical model mathematically and obtain solutions with biologically realistic boundary and initial conditions, and, most important, (4) on the basis of the theoretical results, return to the biology with predictions, comments, and suggestions for illuminating experiments that will help elucidate the underlying biological processes. If the results do not agree with the known biology, the iterative process must be repeated. The most notable successes are those in which the experimentalist and theoretician work on the model and interpretation together. If the use of a model stimulates experiments, even if the model subsequently is shown to be wrong, it has been successful. Models also can be useful for summarizing, interpreting, and interpolating real data. There are many such illustrative modeling examples in which the biology, models, and subsequent experiments are described in detail.[2]

The increasing use of mathematics in biology is inevitable as biology becomes more quantitative. The complexity of the biological sciences makes interdisciplinary involvement essential. For the biologist, mathematical modeling offers another research tool commensurate with a new powerful laboratory technique but *only* if used appropriately and with recognition of limitations. As has been said before,[2] use of esoteric mathematics arrogantly applied to biological problems by mathematicians who know little about the real biology, together with unsubstantiated claims as to how important such theories are, not only does little to promote interdisciplinary involvement, which is so essential, it does measurable harm. The theoretical literature abounds with many such articles.

Other Examples of Useful Modeling

PSA Half-Life

The need for proper, albeit simple, quantitative modeling can be illustrated by the example of trying to determine the half-life of PSA following radical prostatectomy. A search on MEDLINE reveals at least a dozen articles on the topic (eg, Bjork et al,[6] Haab et al,[7] Lein et al,[8] Partin et al,[9] Ravery et al,[10] Richardson et al,[11] Semjonow et al,[12] and van Straalen et al[13]). In these articles, we find that the calculated half-life of PSA can range from minutes to days. Clearly, this range cannot reflect the same process. Closer examination of these articles reveals that each group of investigators fits the serum dynamics of PSA after surgery to a different curve. Some assume a fit to an exponentially decaying function [$p(t) = A \exp(-at)$], others suggest a biexponential fit [$p(t) = A$

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exp(–at) + B exp(–bt)], where the a, b, A, and B are constant parameters to be chosen to get a good fit. Focusing on the exponential and biexponential forms, a wide variety of decay rates (a, b) are published. Although in some cases accurate nonlinear regression techniques are used to fit the biexponential equation to the data, others use visual estimates of the cutoff from one exponential to another and fit the first portion of the data to the A exp(–at) form and the second portion of the data to B exp(–bt). The mathematical problem with this is that the decay parameters a and b are highly sensitive to changes in the choice of cutoff values, which can predispose to erroneous estimates of half-lives. Although simple mathematics (nonlinear regression) can be used to correct these errors, this example demonstrates that curve fitting is not a model in the sense that the investigators make no attempt to describe the actual biological process that is giving rise to these curves. With their philosophy of curve fitting, why not choose 3 or 4 exponentials? In fact, each of their assumptions implies a background mathematical model, even though the biological relevance of the model may be nonexistent. One has to start with a biologically based model and then derive the function describing the concentration of PSA as a function of time.

HIV: Modeling Combination Drug Therapy

Ho et al[14] proposed a very basic model for HIV. The model consisted of a simple linear equation that accounted for viral production and viral decline via first-order kinetics. In words the equation is written as follows:

Rate of Change of HIV (V) = Production of Serum HIV – Viral Decline

which translates into the (differential) equation

$$\frac{dV}{dt} = P - cV$$

where P represents a source of viral peptides and c is the viral clearance rate. While many factors have a role in the clearance of viral peptides, such as immune cells, fluid flow, and absorption into other cells, c did not distinguish between these factors. After introduction of the protease inhibitor (the specific type of drug used to treat patients), it was assumed that the drug would be completely effective, or, in other words, the drug would block all viral production after being introduced. Hence P = 0, and we are left with the simple equation

$$\frac{dV}{dt} = -cV$$

which has the solution

$$V(t) = V_0 e^{-ct}$$

where V_0 is measured as the mean viral concentration in the plasma before treatment. Plotting ln(V) against t and using linear regression to determine the slope gave an estimate for c and, hence, for the half-life of the virus in the plasma, namely, $t_{1/2} = \ln(2)/c$. The mean for the half-life was $t_{1/2} = 2.1 \pm 0.4$ days (see Ho et al[14] for the complete data). The experimentalists then assumed that the patients were in a quasi-steady state before treatment, that is, the levels of viral load measured in the plasma remained fairly constant. With this assumption, and knowing the value for c and the initial viral concentration, V_0, they were able to compute the viral production before therapy by solving P = cV. While these results were minimal estimates, based on the assumption of a perfect drug (with no delays), they still provided an estimate of more than 1 billion viral particles being produced daily. This important result was contrary to the universally held belief that the viral dynamics during this latent period were close to dormant. This is an excellent example of how even simple, mathematically trivial models can be immensely important in extracting crucial information about the disease from patient data.

Brain Tumors: Modeling Spatiotemporal Growth and Invasion of Gliomas

The examples we have illustrated thus far relate to the temporal dynamics of biomedical variables, eg, PSA, lactate, and HIV. Mathematical modeling also can be used to analyze spatiotemporal problems. A specific example of such modeling is in the study of the most common brain tumors, gliomas. Because these lesions diffusely invade the local tissue well beyond the portion of the lesion visible on imaging, Swanson et al[15,16] developed a mathematical model to describe the growth and invasion of the tumor cells throughout the brain parenchyma. The mathematical model portrays the growth and extension of theoretical glioma cells throughout the brain and assumes that only 2 factors need be considered: net growth rate and infiltrative ability. The model not only provides illustrations of theoretical gliomas that closely resemble the imaging results and autopsy specimens of actual patients[16] but also suggests new experiments to further elucidate gliomas.

Some Concluding Remarks

Murray et al[17] in part summarized our philosophy on the use of mathematical models in the biomedical sciences:

> *Why use mathematics to study something as intrinsically complicated and ill-understood as development, tumor growth, angiogenesis, wound healing, interacting population dynamics, regulatory networks, marital interaction and so on? We suggest that mathematics, rather theoretical modeling, must be used if we ever hope to genuinely and realistically convert an understanding of the underlying mechanisms into a predictive science. Mathematics is required*

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to bridge the gap between the level on which most of our knowledge is accumulating (in developmental biology it is cellular and below) and the macroscopic level of the patterns we see. In wound healing and scar formation, for example, a mathematical approach lets us explore the logic of the repair process. Even if the mechanisms were well understood—and they certainly are far from it at this stage—mathematics would be required to explore the consequences of manipulating the various parameters associated with any particular scenario. In the case of such things as wound healing—and now in angiogenesis with its relation to possible cancer therapy—the number of options that are fast becoming available to wound and cancer managers will become overwhelming unless we can find a way to simulate particular treatment protocols before applying them in practice….

The very process of constructing a mathematical model can be useful in its own right. Not only must we commit to a particular mechanism, but we are also forced to consider what is truly essential to the process, the central players (variables) and mechanisms by which they evolve. We are thus involved in constructing frameworks on which we can hang our understanding. The model equations, the mathematical analysis and the numerical simulations that follow serve to reveal quantitatively as well as qualitatively the consequences of that logical structure.

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DOI: 10.1092/U77TQ20DVQ0CLMJA