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MATHEMATICAL MODELS IN MEDICINE: A DIAGNOSIS

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DISCLAIMER

"A sheet of stiff paper makes an even
simpler model."

-- D'Arcy Thompson

"But the procedure proved singularly
sterile as long as the only deliberate
aim was the design of images and models."

-- Hermann Weyl

INTRODUCTION

To the casual observer or the prospective user of mathematical models in medicine, the present state of the application of mathematics to biological problems may offer an exciting, even intoxicating outlook. A sober examination of the situation reveals, however, that with few exceptions only a small and elementary part of mathematics has been brought to bear on the problems of biology, and even those considerations have been marred frequently by ill-conceived and illogically pursued applications. Further, there is an evident tendency to suppress in the treatment of a problem all biological knowledge which cannot be compressed into a few familiar mathematical recipes. Each mathematical model has its strengths and weaknesses, and too often will an ill-considered approach result in exploitation of the weaknesses. Too often are the mathematical model and the computer siezed upon as a substitute for thought. Such need not be the case in medical applications of mathematical models, provided that each model considered is deeply considered, and provided that each model brims with biology.

In the mathematical community, the growing awareness of the shortcomings of many biological applications unfortunately outstrips recognition of the profound difficulties facing the biologist or medical worker in this area. In the medical community, awareness of those shortcomings is unfortunately exceeded by neglect of the difficulties.

The following collection of remarks indicates some of the notions, attitudes, and, rarely, methods which I consider important and basic to the design and use of mathematical models. The discussion will refer not to mathematics nor to biology, but rather to a vague, partly philosophical area between the two, where both medical worker and mathematician must meet. That their meeting can be fruitful, I doubt not. However, their success must not be left to chance.

IMAGERY AND REALITY

The classical scientific method is to proceed by the testing of hypotheses or conjectures, often called models. In medicine, our hypotheses are usually tentative explanations of biological situations or phenomena, such as the mechanism of muscular contraction or the kinetics of leukocytes. Also traditional in science is attention to quantity, leading to quantitative hypotheses or numerical models. The formulation and testing of such hypotheses naturally involves the use of mathematics, and the hypothesis expressed in formal mathematical terms is called a mathematical model. (In a probably futile attempt to avoid wearisome repetition, I shall customarily refer to a mathematical model simply as a model).

The theory of mathematical models is but little developed, and there is no practical theory of the construction of mathematical models. Their construction must proceed rather by artful means, and the art and skill of both the medical worker and the mathematician are usually required in the design and formulation of a fruitful model. In this effort, it is the task of the medical worker to present biology, and it is the task of the mathematician to find the precisely correct, formal expression. I believe these roles ought not be confused, although sharp questioning on both sides can be only beneficial.

The mathematical model comes only indirectly from the real situation, since there is an important, intermediate step. This intermediate process consists in the construction of an abstraction of the real situation. The abstraction I have named imagery (Nooney, 1963), and the construction of imagery is a necessary prelude to the mathematical model. It is in imagery where the governing features of the real situation are identified and abstracted and where their essential relationships are formulated. The world of imagery contains, then, quantities and their known, measured or conjectured relationships, perhaps even in the form of graphs, tables, or flow charts. The mathematical model is a translation of a part or all of imagery into formal mathematical terms. The quality of the reflection of reality by the mathematical model thus depends on the correspondence between reality and imagery and on the characteristics of the translation.

It is the affair of the medical worker to ensure adequate correspondence between reality and imagery, and that can be surely accomplished only on the foundation of deep understanding of the underlying biological phenomena. Understanding is not sufficient, however: the medical worker must provide also an imaginative, interpretive, rather poetical synthesis. Thus, in a sense, the construction of imagery requires a poet to interpret nature quantitatively.

It is important to note that the mathematical model is limited by imagery and can deal only with quantities from imagery in terms derived from imagery. Why, then, not remain in imagery, saving the trouble of the step into formal mathematical expression? There are three main reasons for resorting to the mathematical model. The first reason relates to notation and communication, for mathematics offers a concise notation for quantitative matters which is admirably suited to precise expression. The second reason relates to inclusiveness and generality, for the brevity of mathematical notation permits simultaneous consideration of a broad array of variables and their relations, and the purely abstract nature of mathematics permits an unsurpassed generality of expression and manipulation. The third reason relates to the large body of existing, applicable mathematical formalism, for when a problem is once expressed mathematically, it is subject to the vast collection of theorems and methods comprising mathematics. If we wish to deal with an assortment of complex, quantitative relations, mathematics furnishes us a concise mode of expression able to embrace many variables and relations and provides, in addition, explicit methods by which to combine or analyze those relations. Handling involved quantitative relations only in imagery, without formal mathematics, would be very awkward, if not impossible. Handling involved, quantitative conjectures only in reality; that is, by experiment would be even more nearly impossible. The mathematical model furnishes a relatively easy means of assessing quantitative conjectures, narrowing the range of decision for which experiment may be necessary.

MODEL AND EXPERIMENT

The object in considering a mathematical model is to draw conclusions about reality. However, a proof within a mathematical model proves nothing in biology, and the model cannot be thought even to comment directly on the real world. Each result obtained within the model must first be translated back into imagery, and then that translation must be interpreted in reality. Should all results be compatible, when interpreted, with all established knowledge in reality, we would term the model valid. Should a translated or interpreted result conflict with verified knowledge in imagery or reality, then the conjecture would be untenable: the model would be invalid. To this notion of validity we must add some necessarily vague criterion of relevency, to ensure that the model is indeed pertinent to the real situation modelled Thus, each new experiment, representing an addition to knowledge of the real situation, is a new and possibly vital test for the model. Conversely, each new consequence of the model ought, in principle, to be tested by a thorough examination of its compatibility with all of imagery and by a new experiment if imagery does not already contain the appropriately decisive abstraction. If there has accrued a great weight of evidence confirming the validity of a model, then newly discovered consequences of the model which are presently beyond experimental test are often accepted as true comments about the real world. This is the state to which we hope to bring each model in biology.

It is sometimes difficult to judge the compatibility of model and reality as known through experiment. For we observe, alack, that experimenters are fallible, and we recognize, alas, that experiments contain error. Since experimental error is often random, it is clear that statistical techniques may be necessary before a compatibility judgment can be rendered. A usual procedure is to make certain assumptions about the statistical nature of the experimental errors and then by means more or less esoteric to estimate how likely could be the experimental results if reality were perfectly described by the model. If, on that basis, the experimental results are very likely, then the model is nearly valid, and we continue its use. If the experimental results are unlikely; that is, could almost never occur were the model valid, then the model must be judged invalid, and it must be modified or discarded. The question of compatibility of model and experiment, as we see, cannot be stated as a dichotomy; we must be concerned, rather, with how nearly valid is the model or with what probability is the model valid. The goal is to obtain a model which reflects reality sufficiently well to be useful, and the question of perfect representation of reality is an irrelevant metaphysical question. That an approximate description of reality is all that one can expect is demonstrated by the fact that a comprehensible, manipulable model can refer only to a severely restricted niche of reality. It is not possible, however, to strictly isolate a portion of biological reality without severing multitudinous interconnections with other portions, thus making of the isolated portion a mere approximation to reality. The notion of inherent error or lack of absolute validity is contained in our very definition of the model as a conjecture. A recent mathematical development (Nooney, 1965) explicitly accounts for the possible error in a model and allocates to model and to experiment any discrepancy between them. This method permits a quantitative and objective evaluation of the trust to be placed in the model relative to experiment.

The random nature of experimental error introduces statistical procedures into most models, by way of an assessment of validity, but statistical considerations may enter a model more directly, as when the real situation is thought to contain elements of chance or degrees of randomness. Then the model may include these explicitly. In other cases, being ignorant of a great number of supposedly deterministic real processes, we may choose to assign a probabilistic behavior to nature, hoping in that way to compensate for our lack of knowledge. It might be added that the inclusion of these stochastic elements in the model tends to exacerbate the difficulty of a judgment of compatibility with experiment.

Far from being dismayed by ignorance, we sometimes flaunt it in the parametric model, a model which contains unspecified (because unknown) numbers. Experimental data are employed with the parametric model not only in compatibility tests, but also in determining the unknown numbers. Usually those parameters are so determined as to make the model as nearly valid as possible. Strangely enough, the parametric model could be, in principle, a perfect description of reality for certain values of the unknown parameters, but due to experimental error their practical specification results in a model which is only more or less valid. The parametric model serves a deeper purpose, however, and this is to provide a degree of generality and flexibility. Thus, a general model of a disease, say, might include parameters the value of which reflect certain variations in symptoms for individuals. Laboratory tests might suffice to specify the parameters, and the explicit model so determined might be used to project the course of the disease, which would then vary with individuals.

The possibility of experiment simultaneously determining and testing a model, as with the parametric model, relates to a significant connection between the model and experiment. This connection underlies the continual, cyclic process of modelling. As we shall see, the main business of a model is to furnish predictions about reality, and the typical modelling process follows the path: abstraction, translation, prediction, verification by experiment, refinement of imagery, then again translation, and so on through the cycle. We have already dwelt on the effect of experiment on the model; the verification part of the modelling cycle suggests the effect of the model on experiment. By providing predictions, the model demands experiments for verification, and the model consequently stimulates new experimentation, possibly in directions other than those indicated by experiment alone.

DESCRIPTIVE AND EXPLICATIVE MODELS

The truly significant model must provide more than a description of the real situation: it must provide also an explanation. The descriptive model merely disguises the enigmas of nature and often permits a purely arithmetic connection between cause and effect to masquerade as biological fact. Tending to regard biological processes as occurring in a black box, in electronics jargon, the descriptive model directs attention solely to entrances and exits of the black box. This type of model can, at best, reproduce an experiment or, possibly, a series of experiments, and in the strictest sense, its use must be confined to those experiments on which it is based. Even minor pathological deviations in further experiments are beyond the range of description of such a model. The descriptive model often appears as a parametric model in which the parameters have been introduced somewhat whimsically in futile compensation for neglect of biology. It may be a convenience to have a concise, elegant summary or reproduction of experiment, such as a descriptive model might provide, but that convenience is quite unrelated to biological discovery or to increasing knowledge of reality.

Upon closer examination, it is usually found that the black boxes of biology are actually of various hues of gray: much is known about many, if not most, biological processes. Including this knowledge in imagery and then in the model itself allows the possibility of explaining the biological process by the formulation of an explicative model. Such explanation, based on sound biology, often accounts for pathological variations in the process involved and may even lead to correct and accurate predictions by the model about the process. No such prediction can be expected from the descriptive model. The descriptive model, at best, summarizes the past; the explicative model is capable of projection into the future.

The ability to provide predictions is an important characteristic of a model, distinguishing the fertile from the sterile model. Each prediction must be regarded only as a conjecture, of course, but conjectures are precisely the means by which we explore reality. A final distinction may be drawn between descriptive and explicative models. The descriptive model can only portray responses or actions; the explicative model not only portrays these, but attempts also to imitate mathematically the process by which they arise. Therefore, the explicative model displays an unexpected vitality and a close bond with living processes.

SIMULATIVE MODELS

The imitation of a process by means other than those the process employs is called simulation. According to the discussion of the preceding section, it is precisely the explicative model which may offer the possibility of simulation, and in simulation, the mathematical model most clearly reflects the process modelled and most closely approaches reality. Were we in possession of an adequate model and a sufficiency of varied experimental data, we would have no need for simultation except for illustrative purposes. However, it may be said with little exaggeration that we never have quite enough and sufficiently varied data, so that a choice among several competing models is often not possible on the sole basis of direct computation. If the competing models are imitative or simulative models, it may be possible to allow each to simulate the real situation involved, then to choose for continued attention the model which best imitates both qualitatively and quantitatively. The parametric model contains a whole class of models, each defined by a particular value of the parameter, and the choice of the correct parameter value is frequently made on the basis of the simulative procedure described. This procedure has value even when specific schemes are available for the calculation of the correct parameter value, for usually the calculation must start with a reasonably accurate estimate of the correct value, and this may easily be supplied by a few applications of the simulation procedure.

The simulative model is particularly appropriate in the representation and analysis of stochastic processes, those embodying elements of chance or randomness. Direct computation with models of such processes are unwieldy at best, unless the model is designed to provide information about averages only. For information about process effects on individual elements of the system modelled, we turn to the simulative model which may allow us to follow individuals through the process and to observe the influences of chance at each stage. A summary of the experiences of many individuals, of course, yields the average behavior described by the non-imitative model.

Simulation is valuable also in providing the non-mathematician with a broad view of the consequences of the model in easily recognizable form. Should the simulation occur before the very eyes of the medical worker, he may readily sense any false tones and immediately make corrective adjustments in the model. This may be most important in reference to the necessarily restricted scope of any model and the impossibility of isolating the biological situation considered Through simulation, the medical worker may quickly assess the impact of impinging, non-modelled reality on various areas of the model. Such assessment very likely entails new conjectures or modifications, enhancing the fertility of the model. In these ways, the simulative model permits controlling participation by the biologist on ground most familiar to him. Further, the simulative model offers the opportunity for the formulation of qualitative judgments on the model's reflection of reality and often furnishes the means for injecting qualitative considerations into an analysis of the model.

MODEL AND COMPUTER

The pure (and simple) mathematician might maintain that any connection between mathematical models and computers is only incidental. Such a position would be correct if, contrary to the spirit of this discussion, one restricts attention to completed models, ignoring the genesis and design of the model. For should computation be ultimately necessary, it ought to be done with the help of those instruments which are appropriate and available: pad and pencil, slide rule, desk calculator, or possibly big electronic computer. In general, the computation proceeds most effectively if those instruments are used in the order given, with the earliest practicable halt in the progression. Almost invariably, a successful, quick application of the larger computing machines requires, in the words of C. Thompkins, luck, prayer, or further thought. It is obvious that consistent reliance can be placed only in the last.

The principal influence on mathematical models by the computer, and here I refer to the digital computer, is in the domain of design. The availability of computers and their adaptability to simulation has tended to emphasize the simulative model and has made possible stimulation beyond the capability of lesser instruments. The implementation of simulative models may even have become too easy, resulting in simulation by many ill-fated models, obviously inappropriate to reality. Errors in abstraction or translation can never be remedied by the use of a computer, however powerful, and there is a serious risk of burying those errors under heaps of meaningless output of computers.

Classical mathematical analysis draws much of its strength from the continuity of the objects with which it deals, and the tools applicable to continuous variables and functions are among the most powerful in mathematics. The digital computer, however, can operate only with discrete quantities, and this leads to the mathematical discretization of continuous models prior to computation. Such a procedure usually involves only more or less inconvenience in the analysis of a continuous model, depending on how well are known the errors introduced by discretization, but this procedure may sometimes significantly depreciate the model. In such cases, a return to imagery is indicated, in the hope of constructing a new model by translation in discrete terms. This may be feasible even when dealing with continuous, real phenomena, and one then obtains a discrete model which is an approximation to continuous reality rather than a discrete model which is merely an approximation to a continuous model. Nonetheless, the continuous model of continuous reality should first be investigated, and one should bravely attack continuous phenomena with the powerful mathematical weapons of continuity, for their effectiveness may avoid the need for digital comp computation. Thus, discretization is not always the better part of valor, but discretion must be exercised in the use of computers.

I shall add the obvious remark that the availability of big computing machines has opened the way for the numerical analysis of very large and complex models, referring to comparatively broad areas of biological reality. (A necessary condition for this was, of course, the increased participation of mathematicians, as well). In this connection, my old refrain of careful structuring of imagery assumes additional poignancy, since if the poetic foundations of a very large model are insecure, then the consequent computational wastage and biological deception may be very great.

CONCLUSION

Biology and medicine are fields in which even quantitative considerations have not yet led to the formulation of many laws susceptible to mathematical expression. Since conjectural structures in these fields must rest on observed or postulated laws, it is natural that few biological or medical problems have been stated adequately in mathematical terms. Without such statement, the construction of mathematical models is impossible, and, at present, mathematics is inapplicable, even irrelevant to most of biology. This state of affairs is due partly to ignorance of the basic mechanisms of biology and partly to the rigidity and tradition of mathematics The remedy seems to lie in a deeper understanding and analytical development of biological phenomena, since there is no sign of the creation of a new, biologically directed mathematics. ("Biomathematics does not exist" -- Stanislaw Ulam).

I believe that mathematics can be useful to biology in acquiring that deeper understanding, but its use must be firmly based in areas where profound knowledge of biology has been confirmed, and the purview of the mathematical application must be narrowly constricted. Such use will tend to broaden gradually, but certainly, those enclaves of established knowledge. When applied to present mathematical efforts in biology and medicine, the term, mathematical model, has too pretentious an air: I bow to current usage and employ the term, but I have in mind a smaller, firmer object than that usually connoted.

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